(+)-Batzellaside B, a piperidine alkaloid isolated from a sponge Batzella sp. : Determination of absolute configurations and the first total synthesis

DOCTOR THESIS

(+)-Batzellaside B, a piperidine alkaloid isolated from a sponge *Batzella* sp. – Determination of absolute configurations and the first total synthesis –

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Batzella 属の海綿より単離されたピペリジンアルカロイド (+)-batzellaside B －構造決定と初の全合成－

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大学院自然科学系教育部

光・ナノ物質機能専攻

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Theme

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1. Introduction

1.1 The importance of biologically active natural products in medicinal chemistry

Since ancient times people all over the world have used a wide range of natural products for medicinal purposes. These products obtained from animals or plants were sometimes very effective. However, the mechanism of biological activity and the chemistry of moieties responsible for it were not readily known. Many of these remedies also occurred to be very toxic for human and the lack of information led to their misuse and tragic consequences.

Over the decades, the knowledge about biologically active natural products has significantly evaluated. Nowadays, it is well known that they are products of secondary metabolism synthesized by many living organisms for self-defense against enemies, which were classified as phenolics, terpenoids, steroids and alkaloids. Recently, available techniques allow the isolation and precise determination of their chemical structures and biological activities.

Natural products have historically provided many major new drugs and their importance as a source of bioactive compounds has been recently reviewed.[1] In one of the publications it has been concluded that "in retrospect, the use of natural products has been the single most successful strategy in the discovery of modern medicines".[1e] A number of drugs probably would never be discovered if they were not found in the natural sources. Moreover, natural products can provide templates for future drug design. Structure modifications of the original compound can lead to development of biologically more potent analogues, which can occur to be very effective medicines.

1.2 The importance of total synthesis of natural products

A large majority of biologically active natural products are produced by living organisms in trace amounts and the natural supply is usually not rich enough to provide large scale of the material and allow the commercialization of the potent medicine. Therefore, synthetic approaches toward natural products have been highly desired. Moreover, the synthetic modification of the naturally occurring molecule can provide a number of related compounds with higher biological activity and pharmaceutical potency. From these reasons,

natural products have attracted a great deal of interest from the synthetic community leading to development of large number of concise and stereoselective synthetic approaches.

1.3 Examples of natural products applied as medicines

As mentioned above, natural products have made an enormous contribution to human health due to the fact that many of them were applied as pharmaceutics. The discovery of penicillin G (**Figure 1**), which was isolated from fungi *Penicillium* sp. in 1928 by Alexander Fleming, is the example of historical breakthrough in medicine.[2] This naturally occurring β-lactam was the first drug that was effective against many previously serious diseases, such as syphilis and bacterial infections caused by staphylococci and streptococci. Due to its low toxicity for human and very strong antibacterial activity, it has been much safer than other conventional drugs and has been widely used as antibiotic from 1940's.

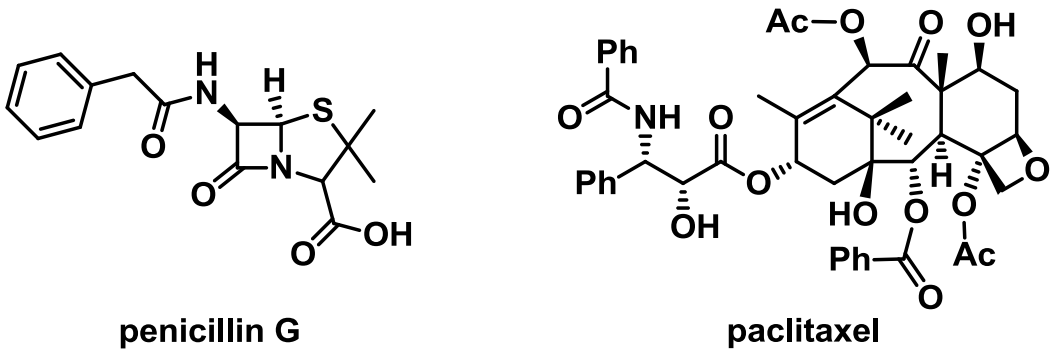


Figure 1. Chemical structures of penicillin G and paclitaxel

Another example of important natural product applied for medicinal use is taxol®, recently known as paclitaxel (**Figure 1**), which is a powerful anticancer agent.[3] This compound was discovered in 1967, when it was isolated from the bark of the Pacific yew tree, *Taxus brevifolia*. The chemical structure of taxol and its biological activity was published by Wall and coworkers in 1971[3a] and excited interests of medicinal community leading to approval of this natural product for the treatment of refractory ovarian cancer (1992) and for refractory or anthracycline-resistant breast cancer (1994). Significantly, the knowledge of action mechanism of taxol and chemical modification of its structure has led to the discovery

of several new natural and synthetic compounds that are either in clinical trial or advanced preclinical development.[3b]

1.4 Alkaloids

Alkaloids are defined as nitrogen-containing molecules, which are secondary metabolites displaying significant physiological activity. They are structurally the most diverse class of biologically active natural products. Currently, over 10000 compounds are known, ranging from relatively simple structures such as coniine to exceedingly complex ones, like neurotoxin batrachotoxin (**Figure 2**).[4]

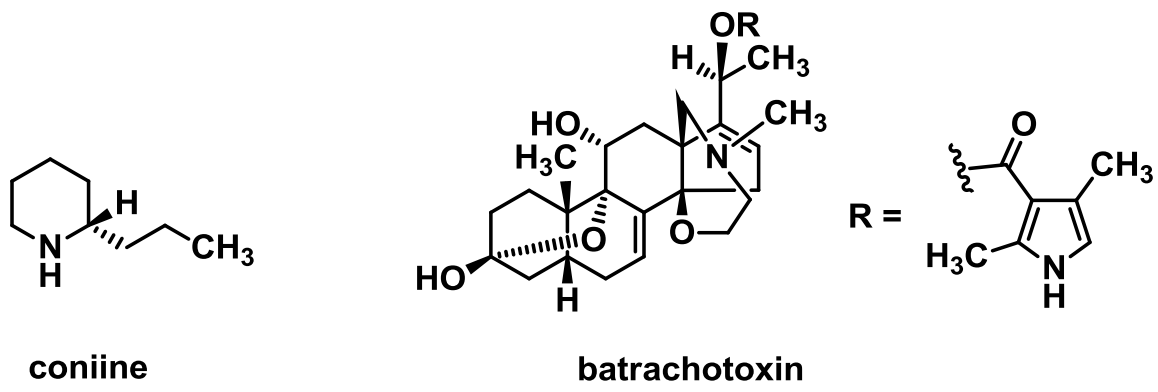


Figure 2. Structural diversity of alkaloids

1.4.1 Examples of alkaloids applied as medicines

Studies of alkaloids began in the 19th century. In 1804 German chemist Friedrich Serütrner has isolated the first active principle from opium plant, known as morphine (**Figure 3**).[5] This compound occurred to be a powerful analgesic agent, which acts directly on the central nervous system to relieve the pain. Due to its strong biological activity morphine has been widely used in medicine, however, the dosing and indication should be strictly controlled due to its well known strong potential for addiction.

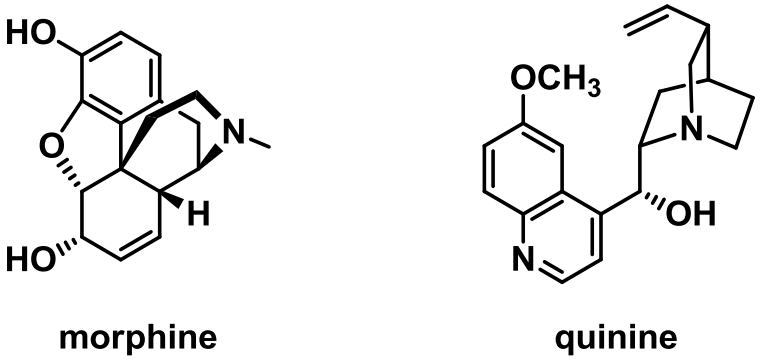
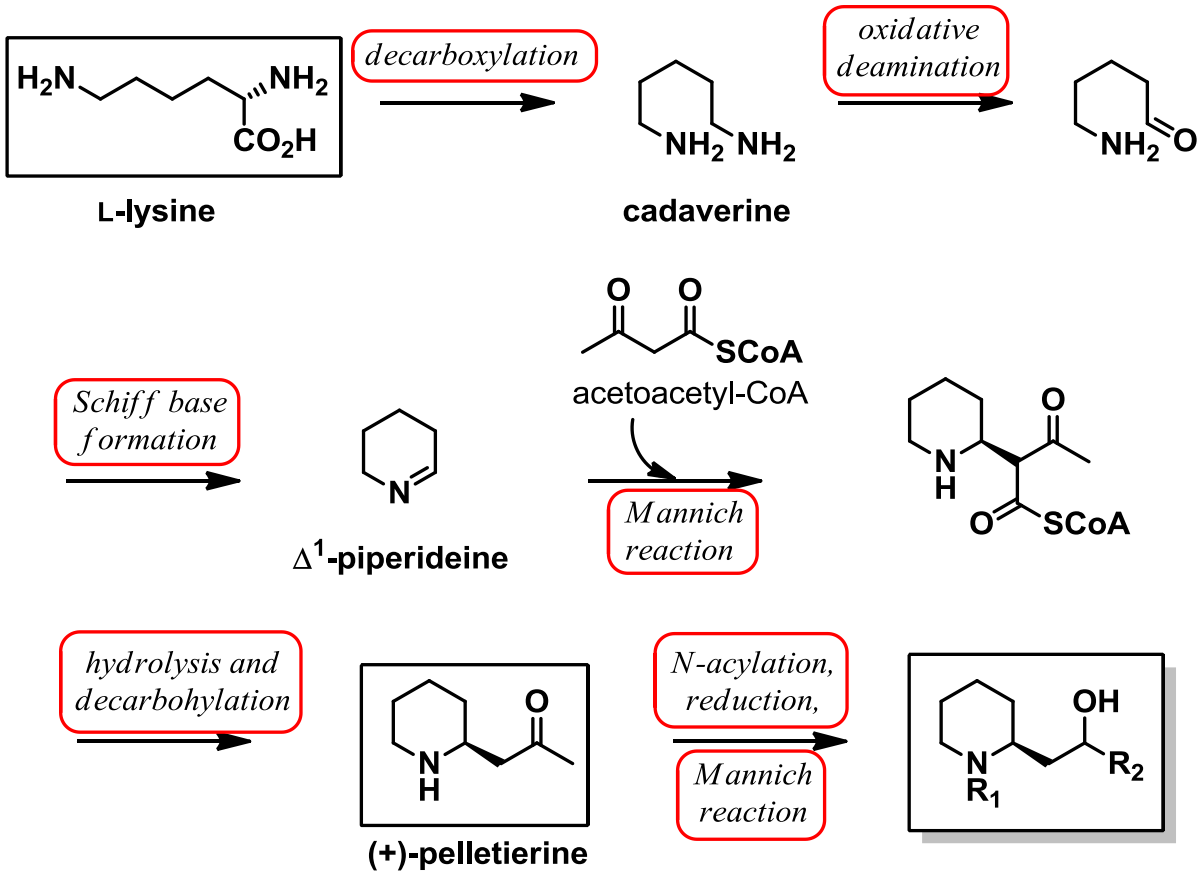


Figure 3. Chemical structures of morphine and quinine

Since the discovery of morphine a large number of alkaloids have been isolated from living organisms and many of them were applied as medicines, such as quinine (**Figure 3**).[6] This natural product was the first effective treatment for malaria, a disease responsible for death of thousands of people. Quinine has been used in unextracted form from 17th century until the successful isolation of the pure product from the bark of the cinchona tree in 1920. Over the years this alkaloid has cured a large number of people and it remained the antimalarial drug of choice until the 1940s, when other medicines with lower side effects replaced it.

1.4.2 Piperidine alkaloids

Piperidine alkaloids are six-membered nitrogen containing heterocyclic compounds and they represent a large important class of natural products from the alkaloid family. They are derived from L-lysine in a metabolic cycle of living organisms as presented on **Scheme 1**.[7] The biosynthesis of piperidine alkaloid starts from decarboxylation of L-lysine to achiral diamine Cadaverine. Oxidative deamination of this compound via diamine oxidase and a subsequent Schiff base formation gives unsaturated heterocycle Δ^1-piperideine, which affords the simplest member of piperidine alkaloid family, (+)-pelletierine, after reaction with acetoacetyl-CoA followed by hydrolysis and decarboxylation. The further elaboration of (+)-pelletierine, such as *N*-acylation, carboxylation or Mannich reaction, provide a variety of related naturally occurring molecules.



Scheme 1. Biosynthetic approach to piperidine alkaloids

Piperidine alkaloids are the most widespread in plants,[8a] but they can also be found in other organisms such as dendrobatid frogs,[8b] myrmicine ants and other insects.[8c] They often exhibit toxic or deterrent activity as illustrated by solenopsin A (**Figure 4**), one of the active component of fire-ant venom,[9] or by coniine (**Figure 2**), from the plant *Conium maculatum*, which is also a powerful insect-paralyzing component.[10]

Figure 4. Chemical structure of solenopsin A

Noteworthy, the piperidine moiety is probably the most common heterocycle occurring in drugs,[11] not only as a scaffold but also contributing to a wide range of

bioactivities, as represented by the antidepressant paroxetine, the anti-parkinsonian agent biperiden, the analgestic fenantyl, the anaesthetic bupivacaine, or the recently patented ani-Alzheimer series of compounds[12] (**Figure 5**).

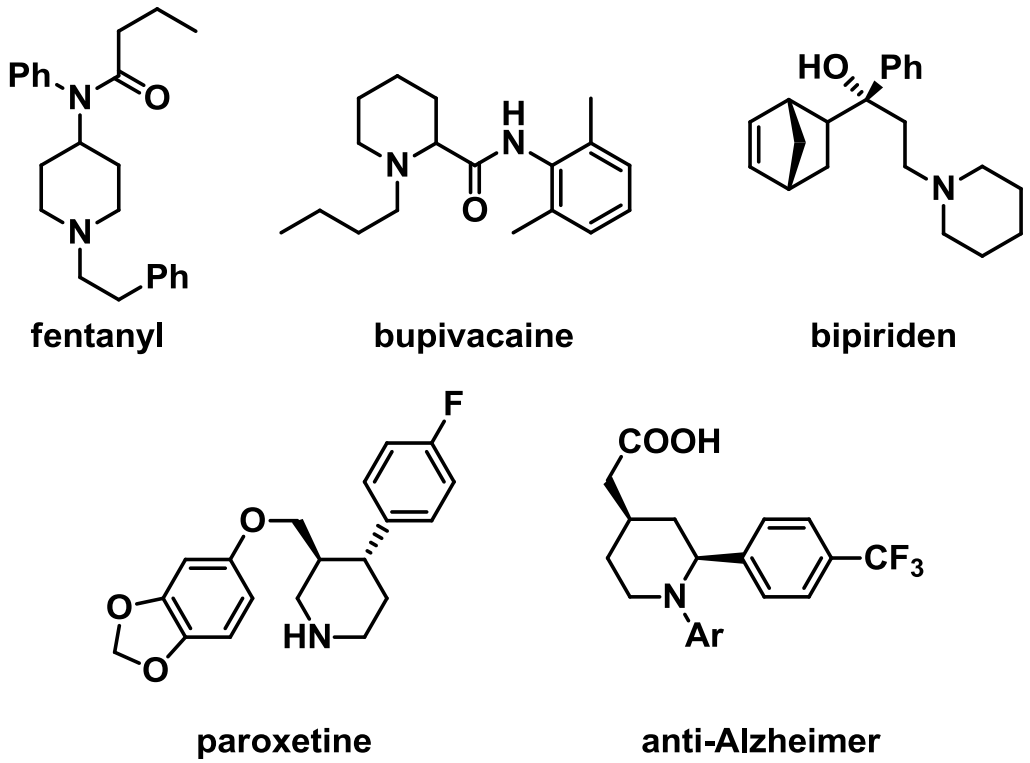


Figure 5. Examples of drugs containing the piperidine moiety

1.4.3 Polyhydroxylated piperidine alkaloids (iminosugars)

Iminosugars are monosaccharide analogues in which the endocyclic oxygen is replaced by a nitrogen atom. They have been found to display a wide spectrum of biological activities, which are ascribed to their ability to mimic sugars and thereby competitively and selectively inhibit glicosidases and glycotransferases.[13] Since the discovery of nojirimycin (**Figure 6**), which has been isolated from *Streptomyces roseochromogenes* R-468 and *S. lavendulae* SF-425 in the 1960s,[14] this class of compounds has attracted a great deal of interest to medicinal community due to their promising pharmaceutical potentials as antidiabetic,[15] antitumor[16] and antiviral agents.[17] The therapeutic applications of polyhydroxylated piperidines has been imparted by the clinical approval of two iminosugar drugs, miglitol[18] and miglustat[19] (**Figure 6**).

Miglitol was developed by Bayer in 1996 and has been used to treat type II diabetes through its strong inhibiting effect against alpha-glucosidase in human body to block the digestion of dietary carbohydrate source into glucose. Miglustat was commercialized by Acetlion for treatment of type I Gaucher's disease and Niemann-Pick type C disease. Its proposed mechanism of action is through inhibition of glucosylceramide synthase, an enzyme responsible for the synthesis of many glycosphingolipids.

Significantly, some other iminosugars has been recently used in a phase II clinical trials such as *iso*-fagomine,[20] migalastat[21] and celgosivir[22] as potent medicines for treatment of type I Gaucher's, Fabrys's disease and Hepatitis C virus (HCV) infection, respectively (**Figure 6**).[23]

Not surprisingly, much effort has been expended by synthetic chemists in order to find efficient and cost effective strategies for the synthesis of this class of natural products.[24]

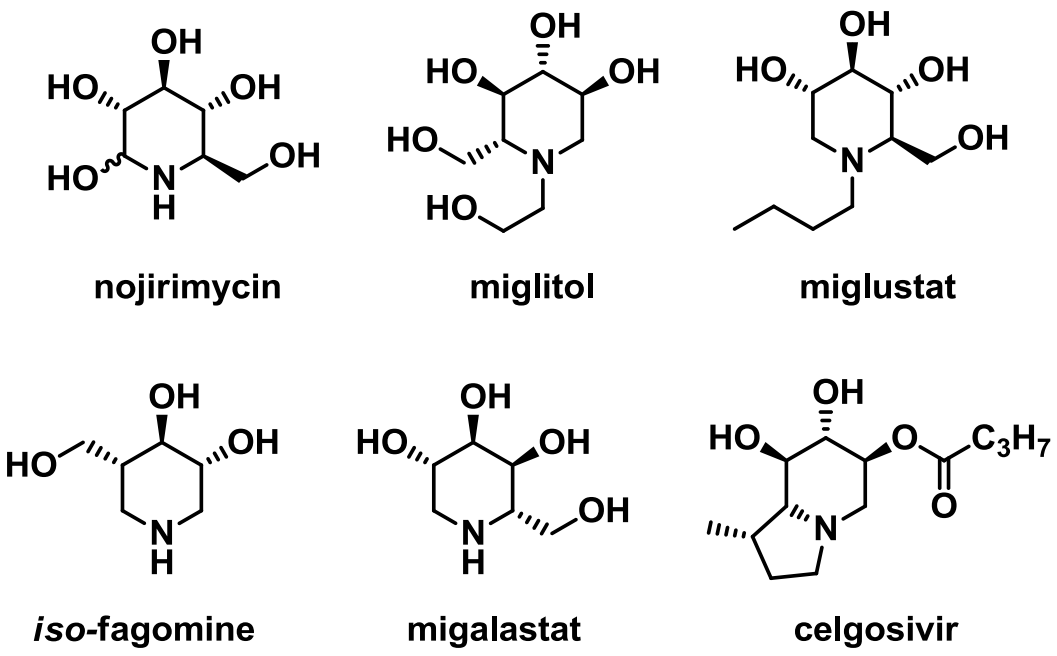
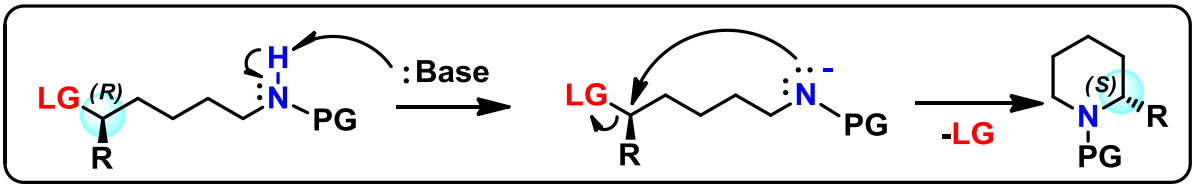


Figure 6. Examples of pharmaceuticaly valuable iminosugars.

1.4.4 Synthesis of iminosugars

The strong therapeutic potential of iminosugars has generated a huge interest in their synthesis and stimulated many groups to develop concise and stereoselective approaches.[24] For the past years, a wide range of methods for the construction of polyhydroxylated piperidine system have been developed using chiral-pool starting materials such as carbohydrates, amino acids and tartaric acids. Several strategies commonly used for the synthesis of this class of compounds will be presented below.

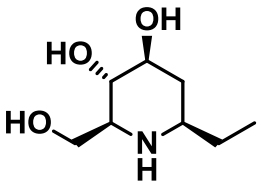
1.4.4.1 Nucleophilic displacement of a leaving group



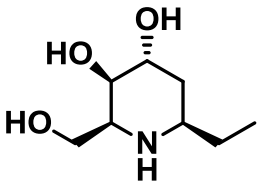
LG = leaving group; **PG** = protecting group

Scheme 2. Intramolecular nucleophilic displacement of a leaving group via S_N2 mechanism

Nucleophilic displacement is a reaction in which a lone pair of electrons on the nucleophile attacks an electrophilic center and bonds to it, displacing a leaving group (**Scheme 2**). The intramolecular variant of this reaction proceeding via S_N2 mechanism is a classical method used for the synthesis of *N*-heterocyclic compounds, which stereospecifically forms the products with an inversed configuration at the electrophilic carbon. Accordingly, a large number of synthetic approaches to iminosugars are based on use of this method and they have been widely reported in literature.[25]



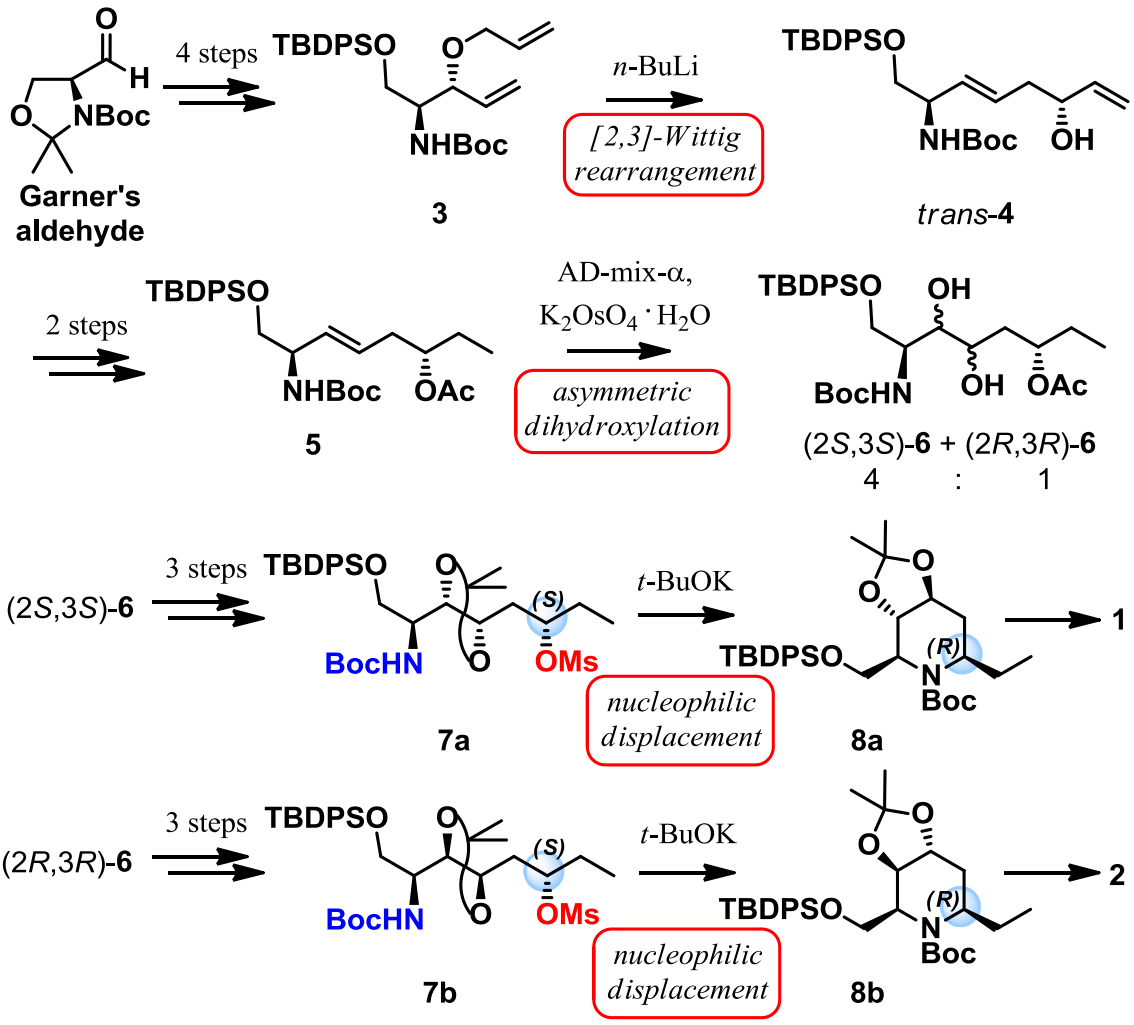
2-*epi*-5-deoxy-adenophorine (1)



5-*epi*-ethylfagomine (2)

Figure 7: The chemical structures of **1** and **2**.

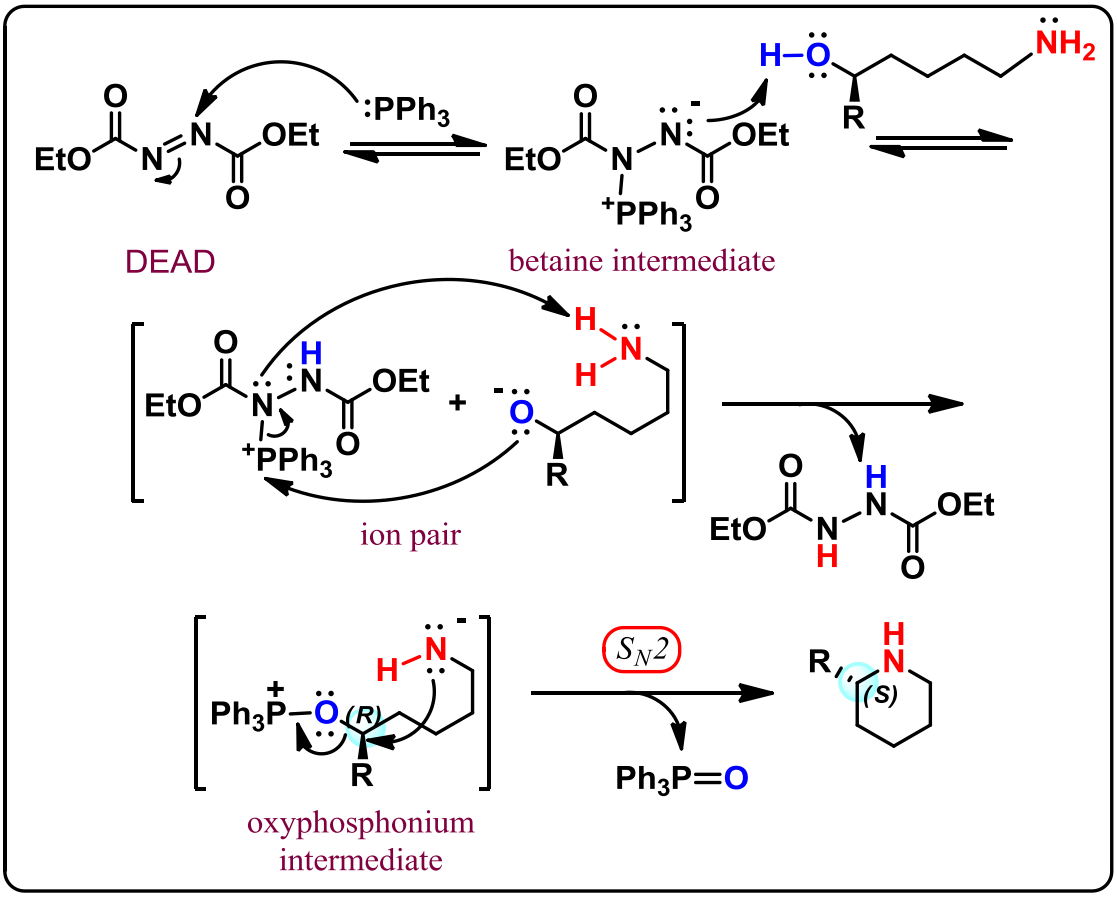
For example, Chandrasekhar and co-workers have used this strategy for the preparation of 2-*epi*-5-deoxy-adenophorine (**1**) and 5-*epi*-ethylfagomine (**2**) (**Figure 7**) from L-serine derived Garner's aldehyde (**Scheme 3**).[25a] The synthesis began with preparation of **3** from Garner's aldehyde by a 4 steps procedure. Treatment of **3** with *n*-butyl lithium (*n*-BuLi) at -78 ^{o}C stereoselectively formed a [2,3]-Wittig rearrangement product *trans*-**4**, which was converted to olefin **5** in 2 steps. This intermediate was next subjected to Sharpless asymmetric dihydroxylation with AD-mix-α providing dieastereomeric mixture of diols (2*S*,3*S*)- and (2*R*,3*R*)-**6** in a 4:1 ratio. After separation of isomers by silica gel column chromatography, both of compounds (2*S*,3*S*)- and (2*R*,3*R*)-**6** were independently converted to **7a** and **7b**, respectively, by using a 3 steps protocol. Intramolecular nucleophilic displacement of mesyl (Ms) leaving group in **7a** and **7b** under basic condition led to formation of cyclized compounds **8a** and **8b**, which gave access to target iminosugars 2-*epi*-5-deoxy-adenophorine (**1**) and 5-*epi*-ethylfagomine (**2**), respectively, after full deprotection.



Scheme 3. Total synthesis of 2-*epi*-5-deoxy-adenophorine (**1**) and 5-*epi*-ethylfagomine (**2**)[25a]

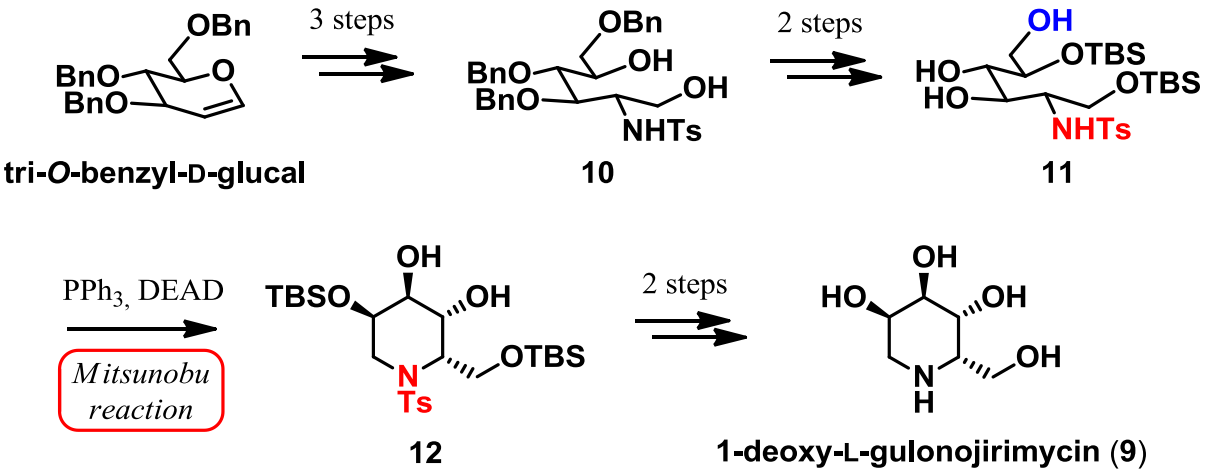
1.4.4.2 Intramolecular Mitsunobu reaction

An intramolecular Mitsunobu reaction of aminoalcohols in the presence of triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD), which is a representative example of the nucleophilic displacement, has been successfully applied for the preparation of iminosugars as reported in the literature.[26] The mechanism of this reaction is fairly complex as illustrated on **Scheme 4**. It starts from the nucleophilic attack of PPh_3 on DEAD producing a betaine intermediate, which subsequently deprotonates the hydroxy moiety of aminoalcohol to give a betaine-alkoxide ion pair. Nucleophilic attack of the alkoxide onto phosphorous atom and subsequent deprotonation of the amine moiety provides an oxyphosphonium intermediate, which undergoes intramolecular nucleophilic substitiution (S_N2) to form a *N*-heterocyclic compound and triphenylphosphine oxide ($Ph_3P=O$). Due to the S_N2 mechanism of the final step Mitsunobu reaction results in inversion of configuration at the hydroxy-substituted carbon.



Scheme 4. Mechanism of the intramolecular Mitsunobu reaction

A total synthesis of naturally occurring 1-deoxy-L-gulonojirimicin (**9**) from tri-*O*-benzyl-D-glucal reported by Ganesan and Ramesh is an example of an application of Mitsunobu cyclization strategy for the synthesis of iminosugars (**Scheme 5**).[26a] The synthesis relied on the use of amido diol **10**, prepared from tri-*O*-benzyl-D-glucal in 3 steps. Protection of the hydroxyl functionalities in **10** as TBS ethers and subsequent cleavage of benzyl groups afforded amino triol intermediate **11** in 2 steps. This compound was subjected to a regioselective intramolecular cyclization under Mitsunobu condition giving the preferable 6-memebered heterocycle **12** as a single product, which was converted to 1-deoxy-L-gulonojirimicin (**9**) by a 2 steps procedure.

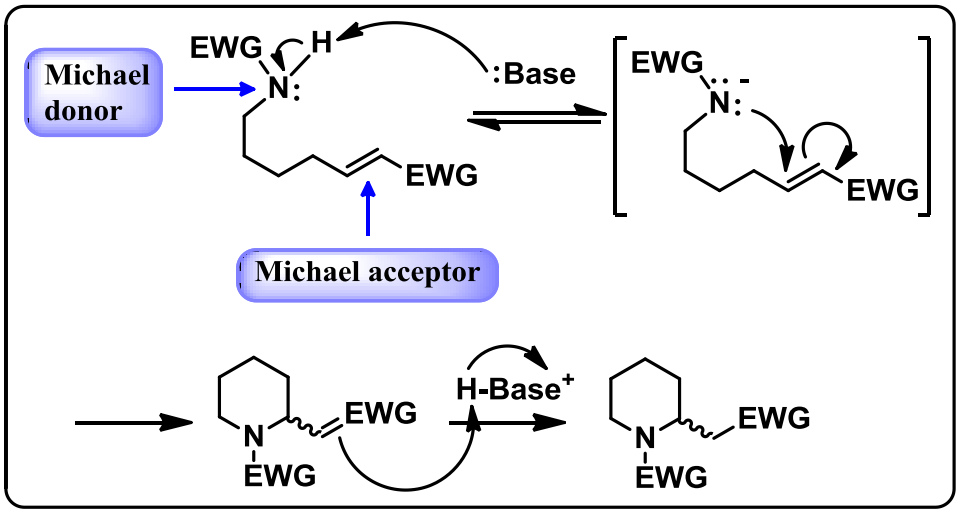


Scheme 5. Total synthesis of 1-deoxy-L-gulonojirimicin (**9**) by Ganesan and Ramesh [26a]

1.4.4.3 Intramolecular aza-Michael reaction (IMAMR)

An aza-Michael reaction is one of the simplest and most straightforward ways to create C-N bonds. It is based on 1,4-addition of a nitrogen-centered nucleophile (called a Michael donor) to an α,β-unsaturated functionality (a Michael acceptor). An intramolecular version of this method is particularly relevant because it allows a direct generation of *N*-heterocycles as presented in **Scheme 6**.

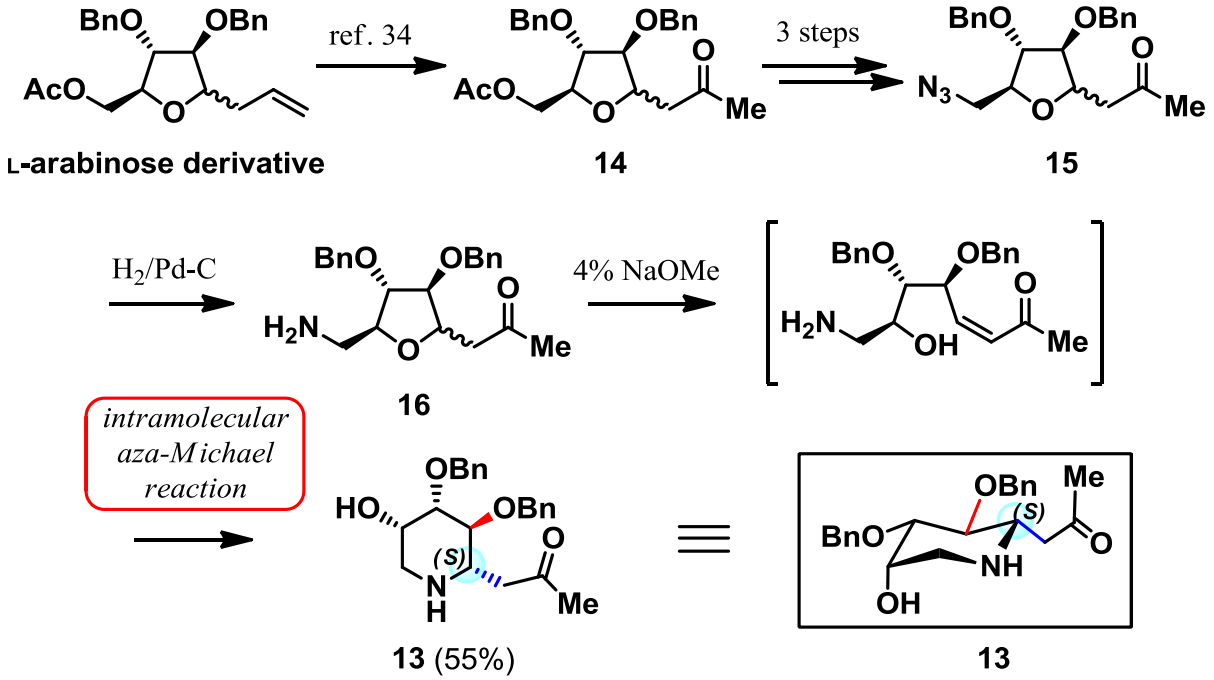
Despite a synthetic potential of the intramolecular aza-Michael reaction (IMAMR), only a small number of reports on the preparation of functionalized piperidines by using this method have been published,[27] and its application in the field of iminosugar synthesis has been even less published.[28]



EWG = Electron withdrawing group

Scheme 6. Mechanism of the intramolecular aza-Michael reaction

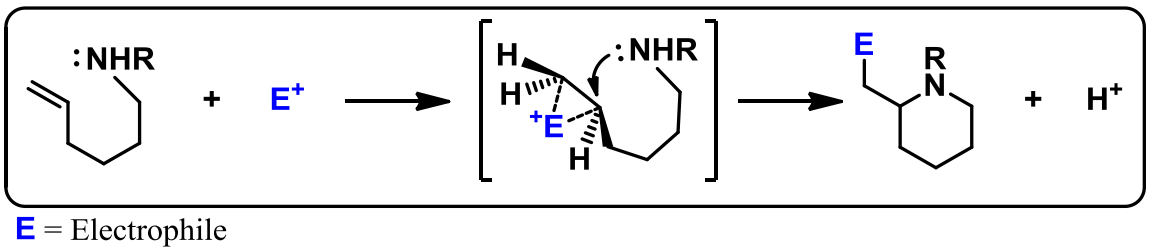
For example the Zou's group have described a stereoselective synthetic approach to azasugar **13** from *C*-allylated L-arabionose derivative (**Scheme 7**).[28a] They began with preparation of ester **14** from the starting material according to the established literature procedure.[29] Removal of the 5-*O*-acetyl functionality in **14** followed by azidation through nucleophilic displacement of introduced mesyl group led to compound **15**, which provided amine **16** after selective palladium-catalyzed hydrogenation of azido group. Treatment of **16** with 4% sodium methoxide (NaOMe) resulted in formation of iminosugar **13** in 55% yield via β-elimination and the subsequent intramolecular aza-Michael reaction of the α,β-unsaturated intermediate. Due to a steric effect of the C2-OBn group the conjugate addition was highly stereoselective to give product (1*S*)-**13** in which the C1-substituent takes a favorable equatorial position, while the moderate yield was the result of competing side reactions such as amidation. A similar stereoselective outcome was also observed when the corresponding D-xylose and D-ribose derivatives were used as starting materials, giving (1*S*)-iminosugars in 45 and 52% yields, respectively, after the intramolecular aza-Michael reaction.



Scheme 7. Total synthesis of **13** by Zou et al.[28a]

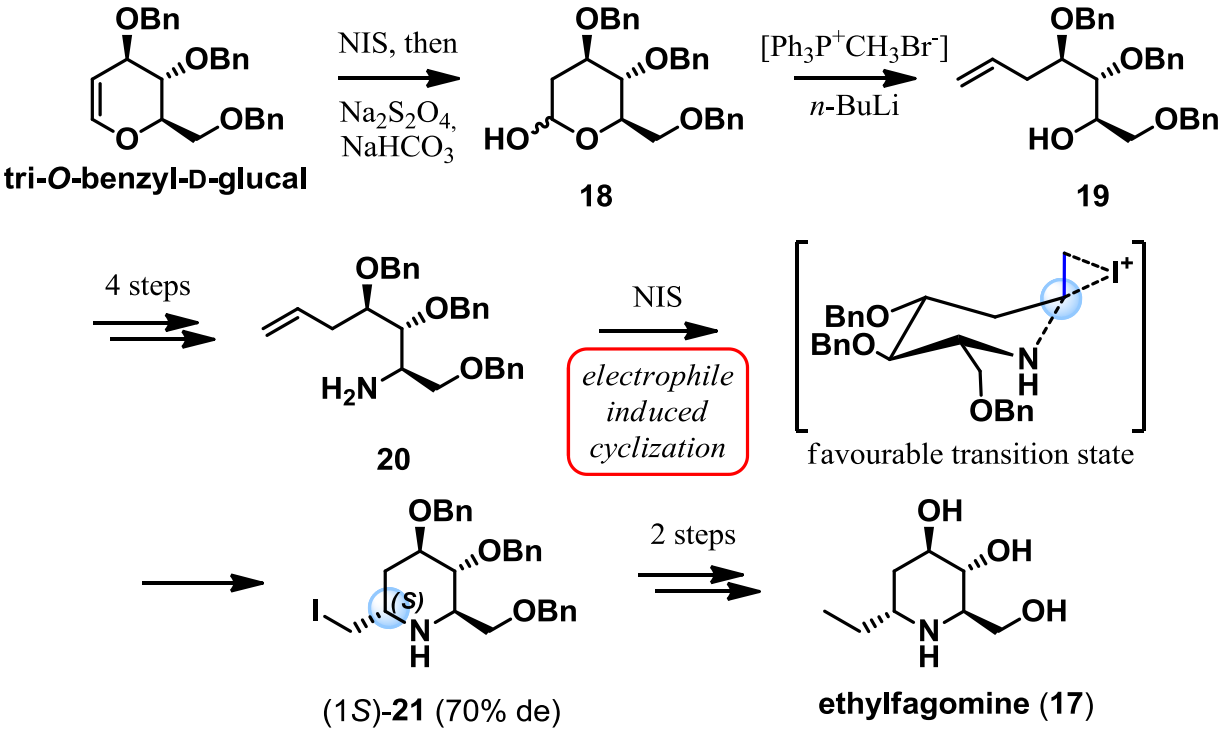
1.4.4.4 Electrophile-induced cyclization of aminoalkene

An electrophile-promoted cyclization of aminoalkenes is a powerful strategy used for the synthesis of *N*-heterocycles. The reaction generally proceeds via intramolecular nucleophilic attack on alkene intermediate activated by electrophiles to form C1-substituted piperidine type compound (**Scheme 8**). The further functionalization at the C1 position, through cleavage of the electrophile-carbon bond may give access to a wide variety of *N*-heterocyclic compounds.



Scheme 8. Mechanism of the electrophile-induced cyclization of amino alkene

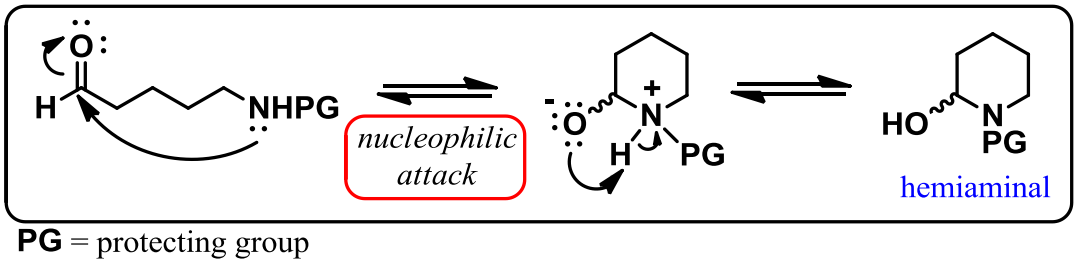
According to the literature,[30] cyclization of aminoalkenes leading to formation of polyhydroxylated piperidines has been usually promoted by *N*-iodosuccinimide (NIS) and mercury(II) or palladium(II) salts. A stereoselective approach to ethylfagomine (**17**) reported by Martin et al. is an example of the application of this strategy in the field of iminosugar synthesis (**Scheme 9**).[30a] In this synthetic pathway, tri-*O*-benzyl-D-glucal was converted to 2-deoxysugar **18** via treatment with NIS followed by removal of the iodide using sodium dithionide ($Na_2S_2O_4$) in a one-pot procedure. Wittig methylenation of **18** afforded unsaturated alcohol **19**, which was subsequently transformed to amino alkene **20** by a 4 steps protocol. Cyclization of this compound promoted by NIS as an electrophile proceeded with expected stereoselectivity to give (1*S*)-iodomethyl derivative **21** with 70% de. After 2 steps from (1*S*)-**21** the authors achieved access to the target iminosugar, ethylfagomine (**17**).



Scheme 9. Total synthesis of ethylfagomine (**17**) by Martin et al.[30a]

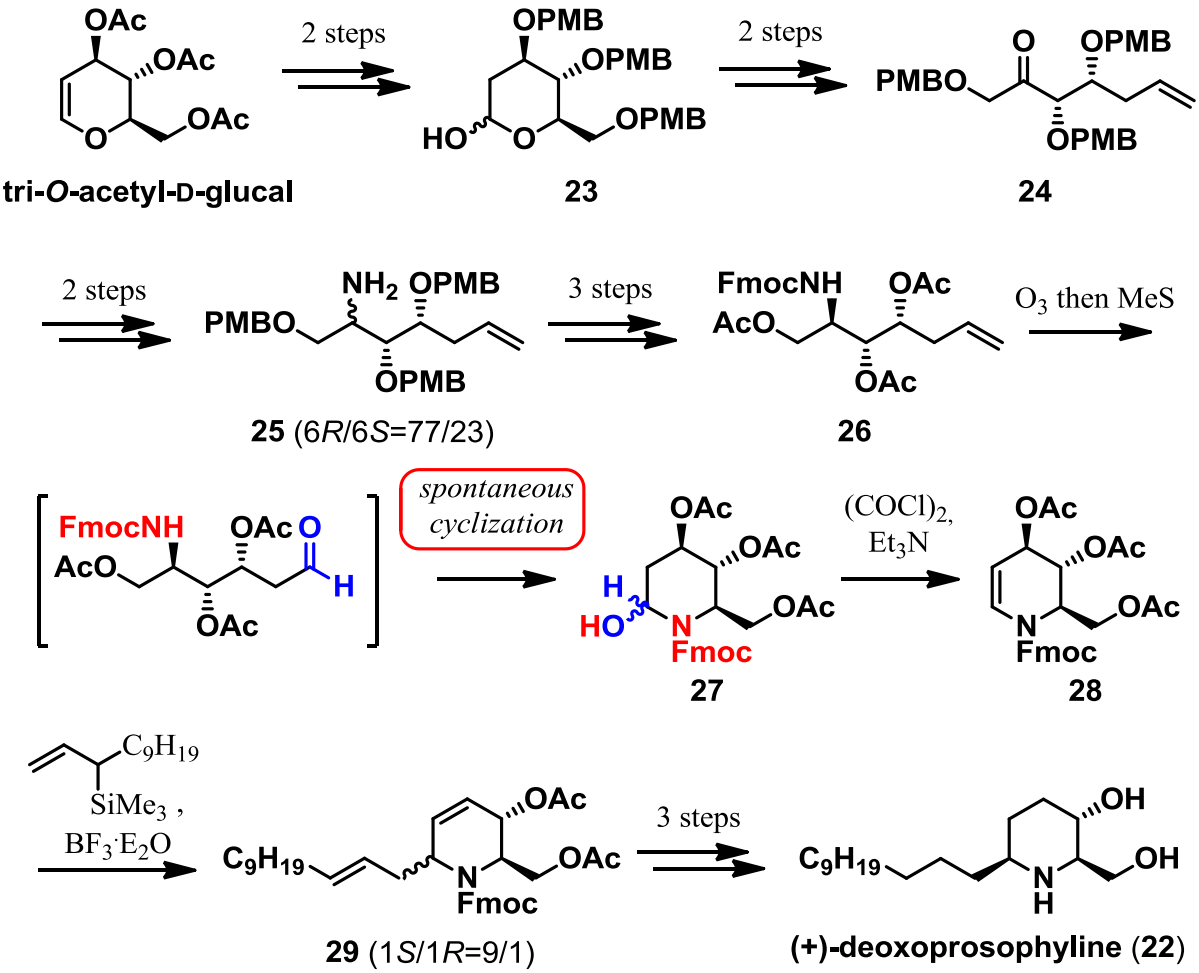
1.4.4.5 Intramolecular cyclization of an aminoaldehyde

Intramolecular cyclization of an aminoaldehyde into a hemiaminal intermediate is a spontaneous process, which has recently found an application in the field of iminosugar synthesis.[31] The mechanism of this strategy is relatively simple and involves nucleophilic attack of the amine group upon aldehyde functionality, which results in cyclization to form heterocyclic hemiaminal as illustrated in **Scheme 10**.



Scheme 10. Mechanism of the intramolecular cyclization of an aminoaldehyde

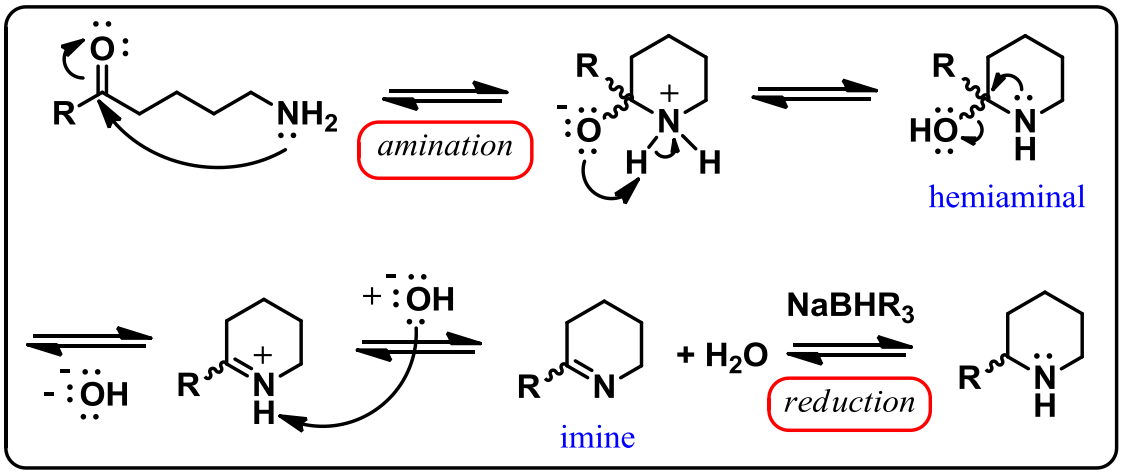
Shipman and co-workers were the pioneer, who used this methodology for the preparation of polyhydroxylated piperidines.[31a-d] For example, they have reported a stereocontrolled synthesis of (+)-deoxoprosophylline (**22**) using tri-*O*-acetyl-D-glucal as a chiral source (**Scheme 11**).[31c] The synthesis began with a preparation of **23** from the starting D-glucal by a 2 steps procedure. Wittig methylenation followed by oxidation of the resulting secondary alcohol provided ketone **24**, which afforded an inseparable diastereomeric mixture of amines (6*R*)- and (6*S*)-**25** (6*R*:6*S* = 77:23) after stereocontrolled reduction of the corresponding oxime. Separation of diastereomers was achieved by preparative MPLC after derivatization of **25** to **26** via 3 steps manipulation of amine and hydroxyl protecting groups. Ozonolytic cleavage of the terminal double bond of diastereomerically pure **26** led to spontaneous cyclization of the resulting aldehyde to produce hemiaminal intermediate **27**. A subsequent dehydration of **27** with oxalyl chloride furnished iminoglucal **28**, which can be a chiral synthon for the preparation of a various C1-substituted iminosugars via C-C bond forming reactions at C1 position. Accordingly, stereoselective addition of 3-(trimethylsilyl)dodec-1-ene to **28** in the presence of $BF_3{\cdot}Et_2O$ furnished a diastereomeric mixture of (1*S*)- and (1*R*)-**29** in a 9:1 ratio, which allowed access to (+)-deoxoprosophylline (**22**) in 3 steps after chromatographic separation of the major isomer.



Scheme 11. Total synthesis of (+)-deoxoprosophylline (**22**) by Shipman et al.[31c]

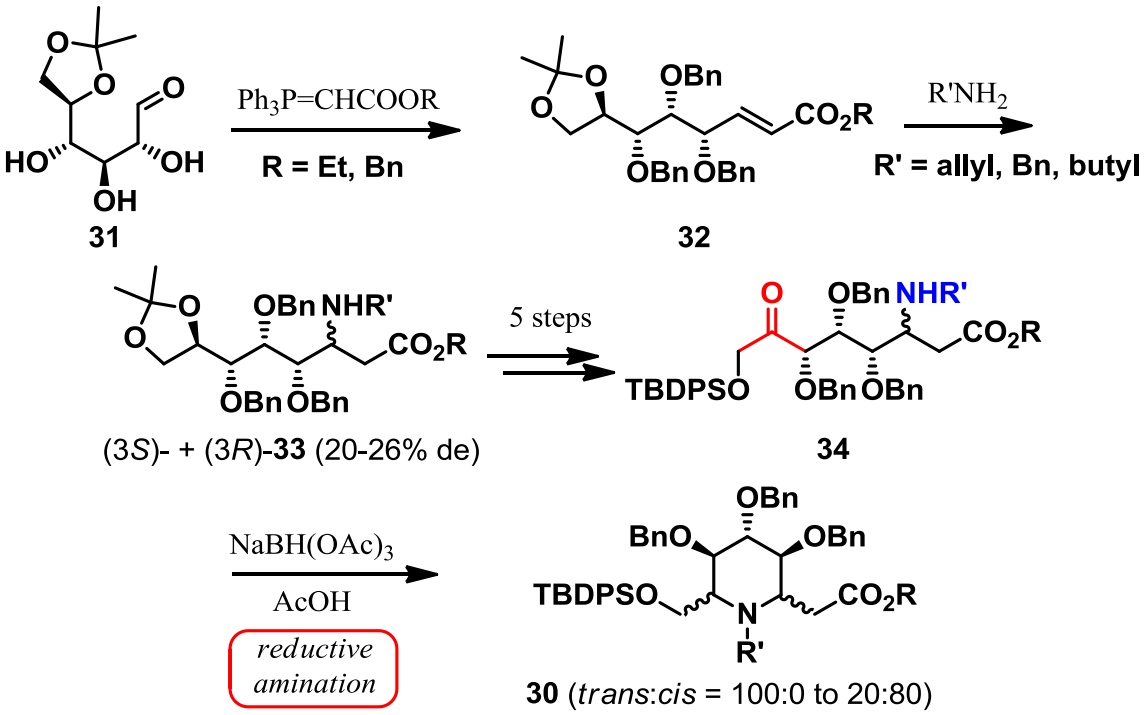
1.4.4.6 Intramolecular direct reductive amination

Intramolecular direct reductive amination of amino carbonyl compound is one of the most common methods used for the formation of piperidine ring system.[32] In this reaction, the amine moiety attacks the carbonyl group to form a hemiaminal intermediate, which is derivatized to imine by loss of one molecule of water (**Scheme 12**). A formation of the piperidine is completed after the hydrogenation of imine with reducing agent such as sodium cyanoborohydride ($NaBH_3CN$) or sodium triacetoxyborohydride ($NaBH(OAc)_3$), which are more reactive toward imine than carbonyl functionality.



Scheme 12. Mechanism of intramolecular reductive amination

An example of the reductive amination applied for the formation of iminosugars was reported by Nicotra et al. for the synthesis of **30** (**Scheme 13**).[32a] The synthetic strategy started with the preparation of α,β-unsaturated esters **32** by treatment of **31**, derived from 2,3,4,6-tetra-*O*-benzyl-D-glucopyrnose, with ylides Ph_3P=CHCOOR in refluxing toluene. The Michael addition of amines R'NH_2 to **32** afforded separable mixture of diastereoisomers (3*S*)- and (3*R*)-**33** with the predominance of (3*S*)-**33** (20-26% de). Since authors were interested in the production of both diastereomers, no efforts has been undertaken to improve the stereoselectivity of this reaction. Intermediates (3*S*)- and (3*R*)-**33** were separated by silica gel column chromatography and next transformed into amino ketones **34** via a 5 steps procedure. Compounds **35** underwent reductive amination by exposure to $NaBH(OAc)_3$ in AcOH to provide polysubstituted piperidines **30** with very good stereocontrol (*trans*:*cis* = 100:1 to 20:80), which can be further derivatized to various iminosugars as potential inhibitors of glycosidase.



Scheme 13. The synthesis of **30** by Nicotra at al.[32a]

1.4.4.7 Ring closing metathesis (RCM)

In the last decade, the ring closing metathesis (RCM) has emerged as an extraordinarily powerful and general method for the construction of nitrogen heterocyclic compounds and has relevant application in the field of iminosugar synthesis.[33] The success of this methodology strongly depends on the development of stable and easy handling commercial catalysts with a wide functional group tolerance. Of the several catalysts described in the literature, the most popular are ruthenium-derived ones developed by Grubbs (**Figure 8**).[34]

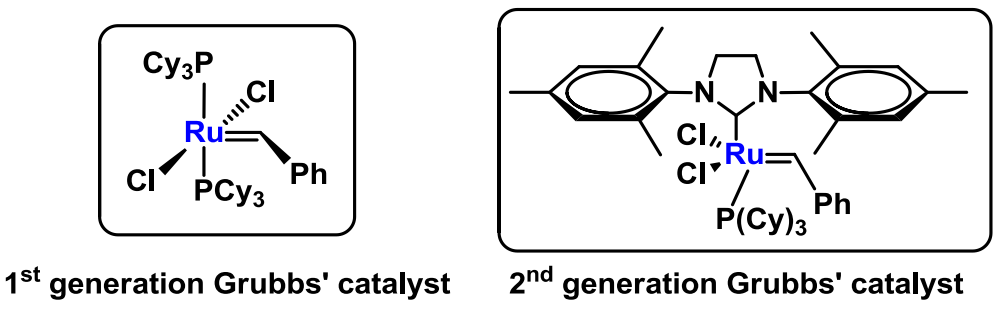
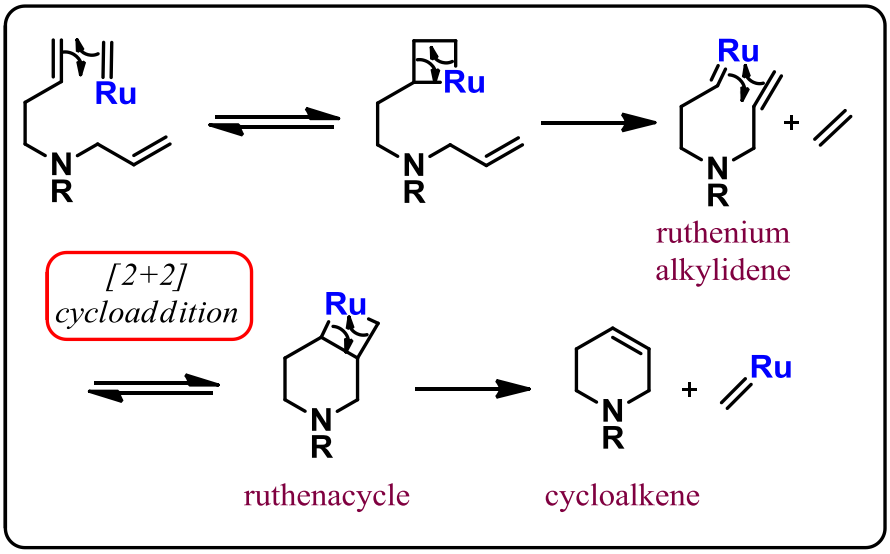


Figure 8: The chemical structures of 1st and 2nd generation Grubbs' catalysts

The ring closing metathesis is an intramolecular reaction of diene, which leads to production of cycloalkene. A reaction mechanism involves [2+2] cycloaddition of an alkene double bond to a ruthenium alkylidene to form a ruthenacycle, which cycloreverts to give either cycloalkene or the starting diene (**Scheme 14**). It should be noted that in most cases of *N*-containing substrates the nitrogen atom must be deactivated as an amide or a carbamate for RCM to be successful.[33b]

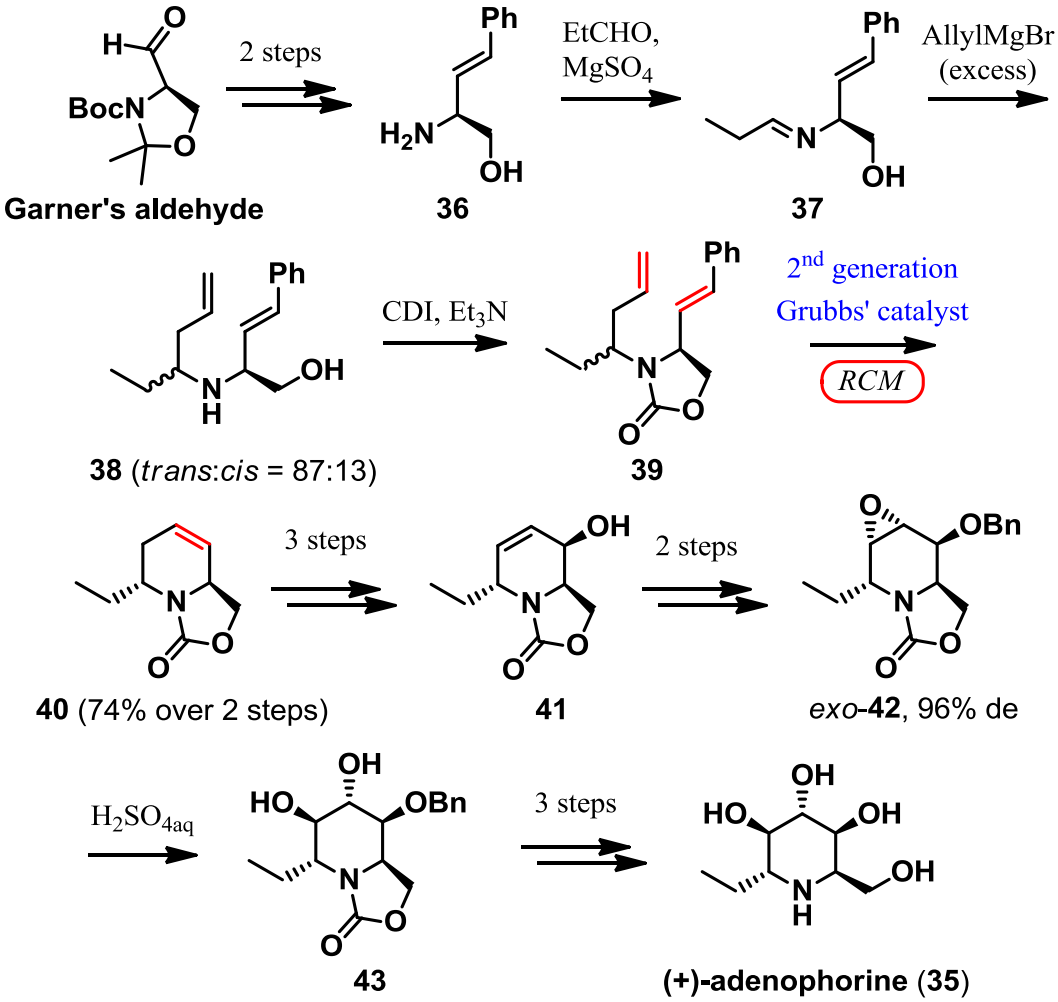
In the field of azasugar synthesis, the newly formed double bond has been found to be well-suited to install either a *cis*- or *trans*-vicinal diol functionality in targets, using a dihydroxylation reaction or an epoxidation reaction followed by subsequent hydrolysis.[33]



Scheme 14. Mechanism of the ring closing metathesis (RCM)

A synthesis of naturally occurring (+)-adenophorine (**35**) from Garner's aldehyde using RCM reaction as a key step was reported by Lebreton et al. (**Scheme 15**).[33a] The authors began with preparation of **36** from Garner's aldehyde by a 2 steps procedure. Condensation of propionaldehyde with **36** afforded imine **37**, which gave an insaparable diastereomeric mixture of **38** (*trans*:*cis* = 87:13) after treatment with excess amount of allylmagnesium bromide. Protection of amino alcohol **38** as an oxazolidinone gave intermediate **39**, which underwent ring closing metathesis by exposure to 2nd generation Grubbs' catalyst to produce enantiomerically enriched tetrahydropyridine **40** with 74% yield for 2 steps. Introduction of hydroxyl group at C2 position of **40** was achieved by a 3 steps protocol involving epoxidation, regioselective opening of the epoxide ring with a "selenium-boron complex" and oxidation

sequence. The resulting intermediate **41** was then stereoselectively converted into epoxide *exo*-**42** (96% de) via a 2 steps procedure of benzylation followed by *m*-CPBA epoxidation. This compound was subjected to reaction with H_2SO_{4aq} to afford diol **43**, which gave access to (+)-adenophorine (**35**) after the following 3 steps.



Scheme 15. Total synthesis of (+)-adenophorine (**35**) by Lebreton et al.[33a]

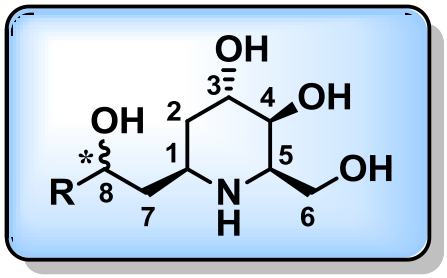
1.4.4.8 Summary

In conclusion, many successful and efficient strategies toward formation of polyhydroxylated piperidine alkaloids have been developed. Although a large number of iminosugars are now accessible by using these common techniques, the continuous discoveries of new compounds provide a challenge for contemporary organic chemistry and entail research on novel practical methods.

1.4.5 Batzellasides

(+)-Batzellasides A-C (**Figure 9**) are a novel class of azasugars isolated in 2005 from *Batzella* sp., a sponge collected off the west coast of Madagascar, which represent a first example of iminosugars from marine organism.[35] These naturally occurring products have been demonstrated to retain remarkably high degree of potency against *Staphylococcus epidermidis* with MICs of ≤6.3 μg/mL, thus serving as new potent antibacterial agents.[35] The structures of sugar mimicking molecules of batzellasides contain long alkyl side chains bearing uncommon C8 stereocenters with unknown absolute configurations. The unique structural properties of batzellasides provide an intriguing extension of the iminosugar frameworks due to the fact that they are biosynthetically related to a variety of plant-derived alkaloids rather than marine-derived ones, thereby attracting attention to the research field of contemporary drug discovery.

Unfortunately, the low natural abundance of batzellasides has limited their availability, further impeding complete understanding of absolute configurations and extensive studies on development of biologically potent analogues. Although it is believed that synthetic approach to these alkaloids would address this supply problem and could open the window for the future drug design, no reports have appeared previously describing successful studies on the synthesis of these compounds. From these reasons, batzellasides became target of my study, while my synthetic efforts have focused on (+)-batzellaside B as a represent member of this new class of natural products.



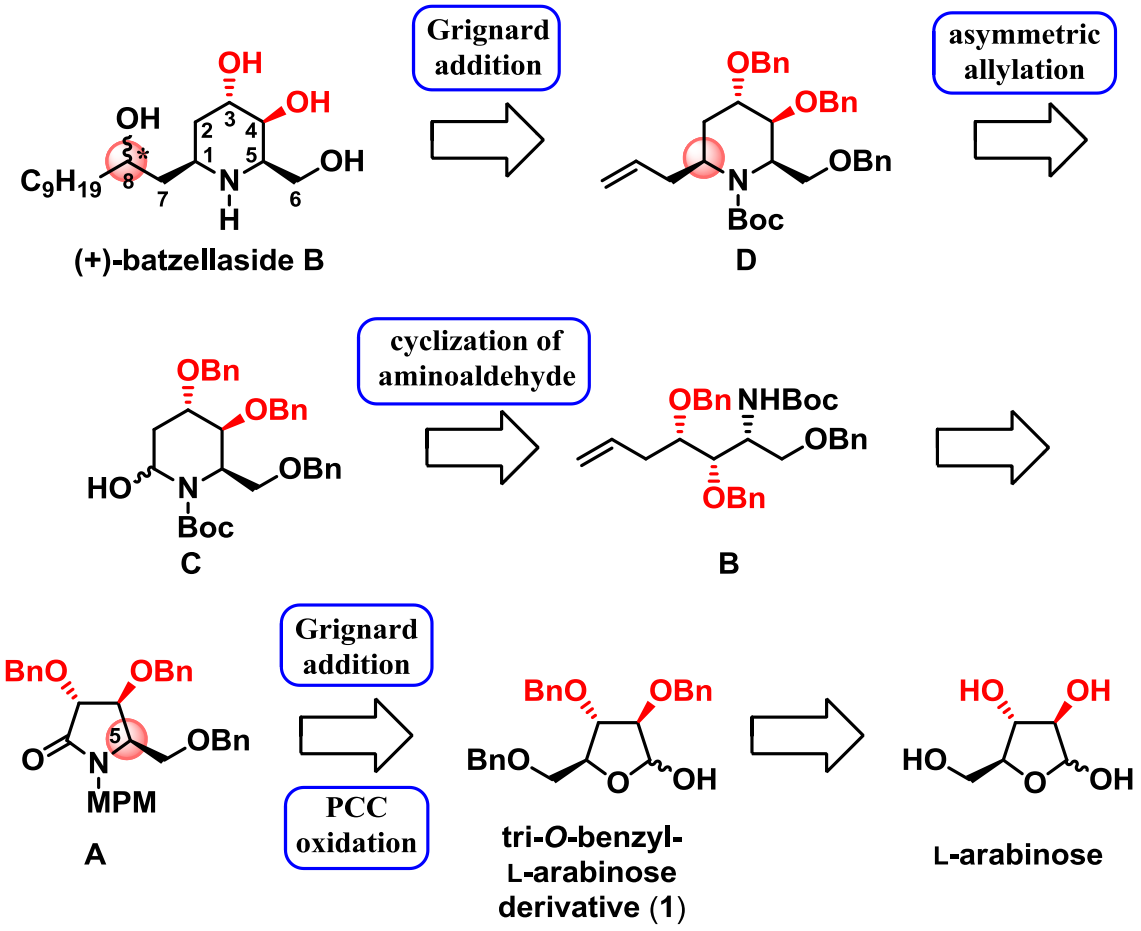
(+)-batzellaside A : R = $C_{10}H_{21}$
B : R = C_9H_{19}
C : R = $C_{11}H_{23}$

Figure 9: The chemical structures of (+)-batzellasides A-C.[35]

2. The first synthetic approach to (+)-batzellaside B from L-arabinose[36]

2.1 Retrosynthetic analysis

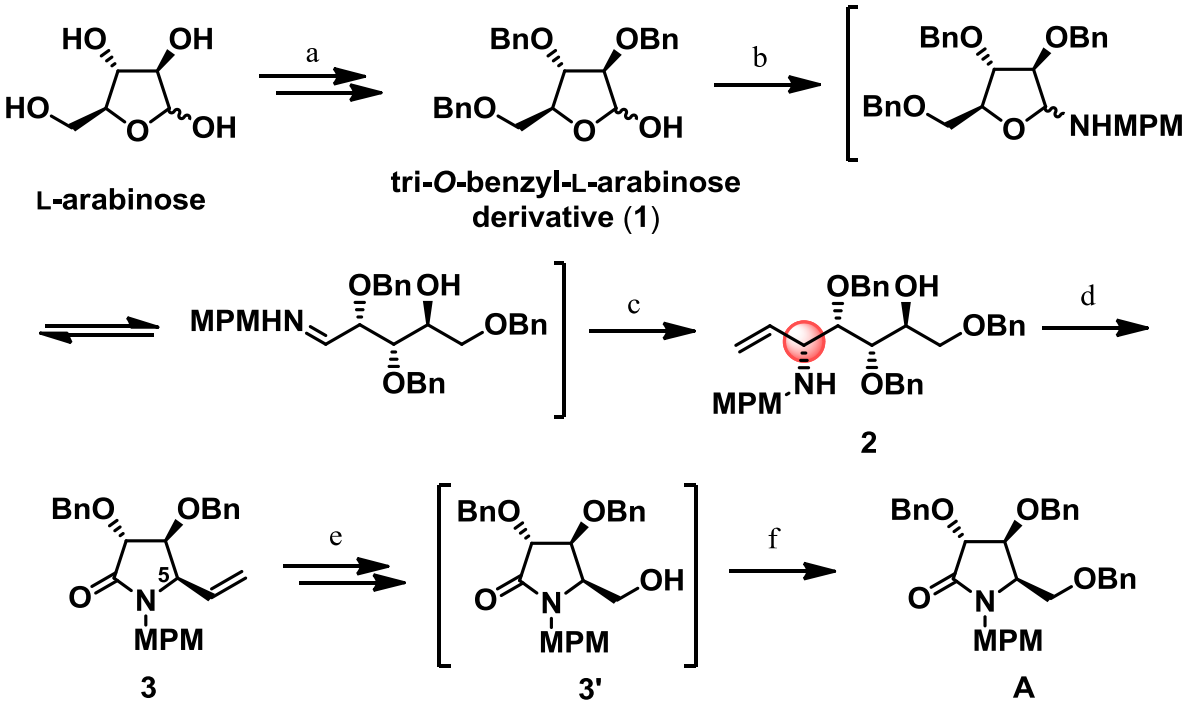
The retrosynthetic analysis of (+)-batzellaside B, outlined in **Scheme 16** is based on the direct employment of the two of the three inherent stereocenters contained in L-arabinose. It was assumed that (+)-batzellaside B can be accessed from piperidine **D** through introduction of the C_9H_{19} chain by Grignard addition. The C1 stereocenter in **D** would be constructed via asymmetric allylation of hemiaminal **C**, prepared from **B** through intramolecular cyclization of an aminoaldehyde intermediate. Olefin **B** can be synthesized from tri-*O*-benzyl-L-arabinose derivative (**1**) via γ-lactam **A**, whereas C5 center would be constructed by Grignard addition to a relevant aminal intermediate followed by PCC oxidation.



Scheme 16. Retrosynthetic analysis of (+)-batzellaside B – the first synthetic approach

2.2 Preparation of γ-lactam **A**

The synthesis began with the preparation of tri-*O*-benzyl-L-arabinose derivative (**1**) by following the published methods (**Scheme 17**).[37] Treatment of **1** with *p*-methoxyphenyl amine ($MPMNH_2$) in refluxing toluene afforded aminal intermediate which would exist in equilibrium with the corresponding γ-hydroxy imine. In agreement with previous findings on similar reactions,[38] this equilibrium can be shifted toward the ring-opened form through Grignard reaction. Thus, the mixture was treated with vinylmagnesium chloride, facilitating the *syn*-selective reaction to give the diastereomerically pure adduct **2** in 81% yield from **1**.



Scheme 17. Preparation of **A**. *Reagents and conditions*: (a) see Ref. 37; (b) $MPMNH_2$, toluene, reflux, 5 h; (c) CH_2=CHMgCl, THF, -78 to 0 °C, 2 h; 81% (2 steps); (d) PCC, MS 4Å, CH_2Cl_2, 0 °C to rt, 1 h; 64%; (e) (i) OsO_4, NMO, acetone, rt, 4 days; (ii) $NaIO_4$, THF–H_2O (1:1), 0 °C to rt, 3 days; (iii) $NaBH_4$, MeOH, 0 °C to rt, 24 h; (f) BnBr, Ag_2O, DMF, rt, 24 h; 90% (4 steps).

The *syn*-selectivity of Grignard addition can be explained by the Cram's chelate model presented in **Figure 10**. This model shows the formation of a five-membered cyclic chelate between the imine functionality, magnesium cation and α-benzyloxy group, which entails the production of *syn*-adduct **2** through attack of the vinyl nucleophile from the less hindered side.

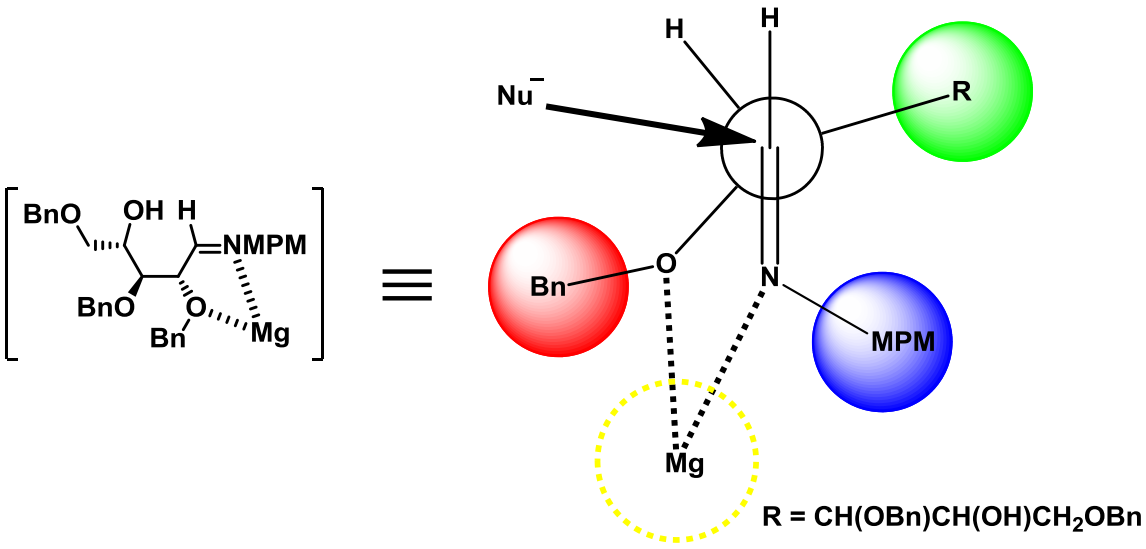


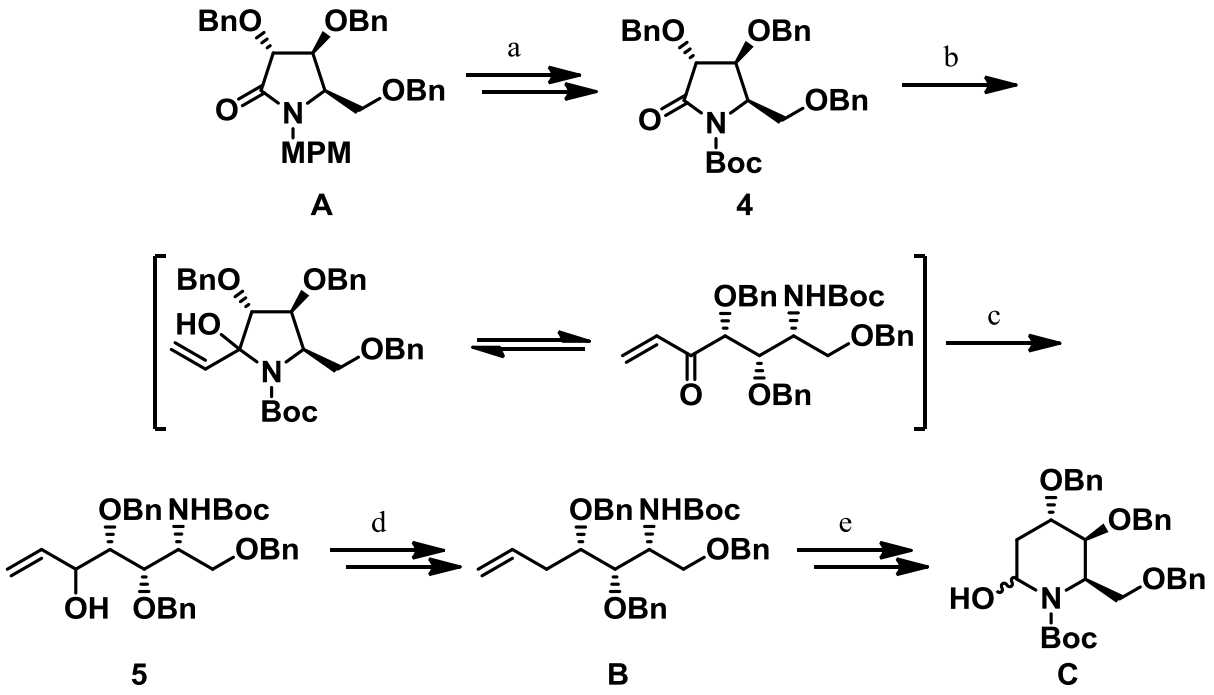
Figure 10: The Cram's chelate model for Grignard addition

In the next step of the synthesis, γ-lactam **3** was prepared from **2** in 64% yield after oxidation with pyridinium chlorochromate (PCC), which resulted in in situ cyclization of the intermediate ketone (**Scheme 17**). The absolute configuration at the newly formed C5 stereocenter of the product was established to be *R* by comparison of ^{13}C NMR spectrum of **3** with the spectral data of its antipode prepared via identical mechanistic sequence from D-antipode of **1**.[38a] Oxidative cleavage of the vinyl group in **3** by a 2 steps procedure of dihydroxylation with osmium tetroxide (OsO_4) in the presence of *N*-methylmorpholine-*N*-oxide (NMO) followed by oxidation with sodium periodate ($NaIO_4$) gave aldehyde, which after reduction with $NaBH_4$ and a subsequent benzyl protection of an intermediate alcohol **3'** afforded the corresponding benzyl ether **A** in 90% over 4 steps.

2.3 Preparation of hemiaminal **C**

At this point, it was envisioned that replacement of the MPM group of **A** with the Boc functionality would offer potential advantages making the lactam carbonyl more reactive in nucleophilic processes due to reduced conjugation of the amide bonding associated with delocalization of the nitrogen electron pair in the second carbonyl system.[39] Accordingly, the MPM group in **A** was removed by treatment with ceric ammonium nitrate (CAN) giving *N*-unsubsituted γ-lactam, which afforded intermediate **4** in 77% for 2 steps after Boc protection (**Scheme 18**). As expected, treatment of **4** with vinylmagnesium chloride resulted in

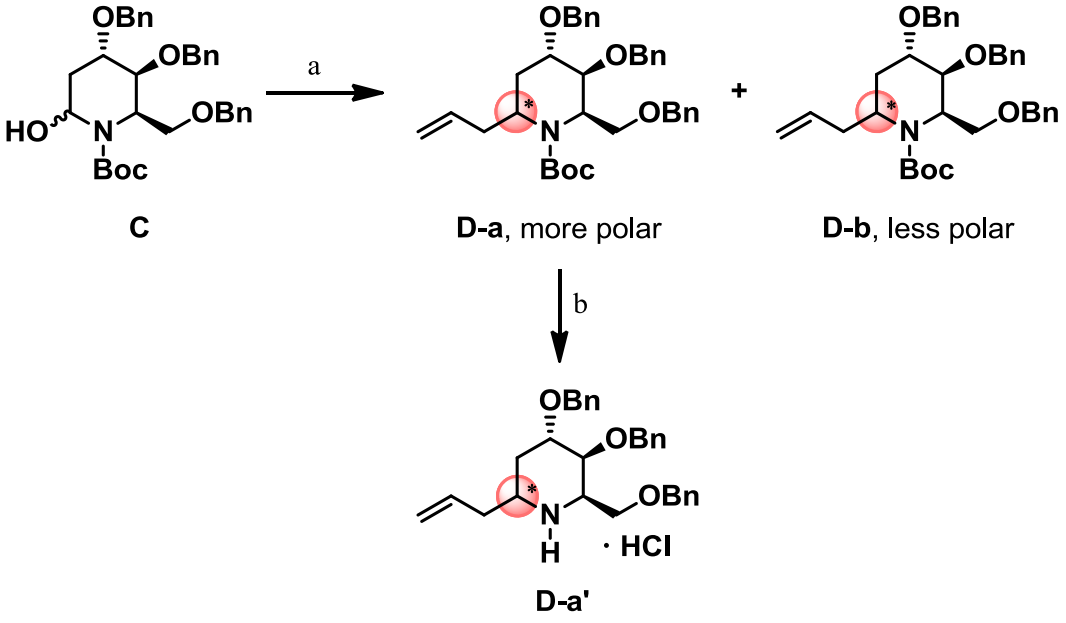
nucleophilic addition to the carbonyl group on the γ-lactam ring to give the corresponding hemiaminal, which further undergoes Luche reduction due to equilibrium with the acyclic enone, giving rise to acyclic allyl alcohol **5** in 81% for 2 steps. Compound **5** was then deoxygenated by a 2 steps transformation into ethyl carbonate followed by catalytic transfer hydrogenolysis using ammonium formate (HCO_2NH_4) and triethylamine (Et_3N) in the presence of tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) to provide acyclic olefin **B** in 86%.[40] The piperidine ring system was next constructed by oxidative cleavage of olefinic endgroup of **B** through the dihydroxylation-oxidation sequence, which resulted in spontaneous cyclization of the intermediate aldehyde to produce the heterocyclic hemiaminal **C** in an excellent yield (98% for 2 steps).



Scheme 18. Preparation of **C**. *Reagents and conditions*: (a) (i) CAN, MeCN–H_2O (9:1), 0 °C to rt, 2.5 h; (ii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; 77% (2 steps); (b) CH_2=CHMgCl, THF, -78 °C, 1.5 h; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 2 h; 81% (2 steps); (d) (i) $ClCO_2Et$, pyridine, 0 °C to rt, 12 h; (ii) $Pd(PPh_3)_4$, HCO_2NH_4, Et_3N, toluene, reflux, 30 min; 86% (2 steps); (e) (i) OsO_4, NMO, acetone, rt, 24 h; (ii) $NaIO_4$, THF–H_2O (1:1), 0 °C to rt, 3.5 h; 98% (2 steps).

2.4 Preparation of **D** and determination of absolute configuration at the C1 stereocenter

Having the hemiaminal intermediate in hand, the next objective was the construction of the C1 stereocenter of the six-membered piperidine ring system (**Scheme 19**). Thus, a Lewis acid mediated allylation of **C** was carried out by using allyltributylstannane ($AllylSnBu_3$) and *tert*-butyldimethylsilyl triflate (TBSOTf) in toluene at -78 °C.[41] Under these conditions, the reaction took place in a stereoselective manner to form a diastereomeric mixture of the C1-allylated products **D-a** and **D-b** in 96% with a 69:31 ratio. After separation of diastereomers by silica gel column chromatography we attempted to determine the absolute configuration of the newly formed stereocenter based on the ^{1}H NMR analysis of the major isomer **D-a**. Unfortunately, the overlapping resonances for the C1 methine proton and protons of the Boc group enabled the precise analysis. Thus, an alternative way was explored involving an *N*-unsubstituted piperidine analogue **D-a'**, which was obtained from **D-a** via HCl treatment in methanol. This compound provided well-separated resonances in the ^{1}H NMR spectrum showing clearly distinguishable multiplicities.



Scheme 19. Preparation of **D**. *Reagents and conditions*: (a) $AllylSnBu_3$, TBSOTf, toluene, -78 °C, 9 h; 66% (**D-a**), 30% (**D-b**); (b) MeOH–HCl, rt, 2 h, 81%.

In aim to provide relevant positions (axial of equatorial) of the all protons in **D-a'**, the obtained *J* coupling constants of $^3J_{H2eq–H3}$ = 2.8 Hz, $^3J_{H2ax–H3}$ = 11.7 Hz, $^3J_{H1–H2eq}$ = 2.8 Hz, and $^3J_{H1–H2ax}$ = 2.7 Hz were compared to the standard vicinal coupling constants values given for

cyclohexane in a chair conformation (**Figure 11**) [42] indicating that the substitution patterns of H_3-H_4, H_{2eq}-H_3, H_{2ax}-H_3, H_1-H_{2eq}, and H_1-H_{2ax} should keep axial-axial, equatorial-axial, axial-axial, equatorial-equatorial, and equatorial-axial relationships, respectively. This allowed for visualization of the three-dimensional structure of the substituted piperidine ring system, demonstrating the desired 1,5-*syn* relative arrangement for the substitution pattern with (*S*)-configuration at the C1 position of **D-a** (**Figure 12**).

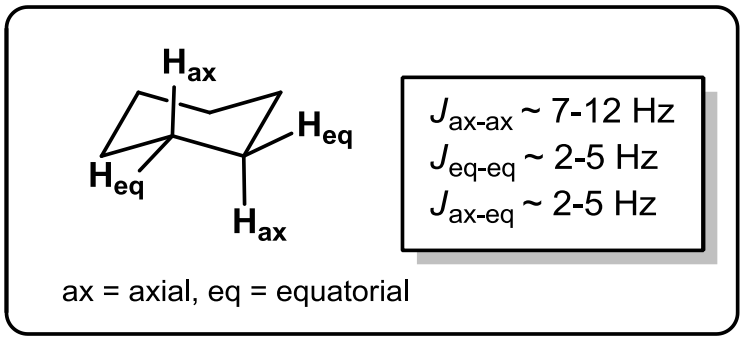


Figure 11. Vicinal coupling constants values of cyclohexane in a chair conformation[42]

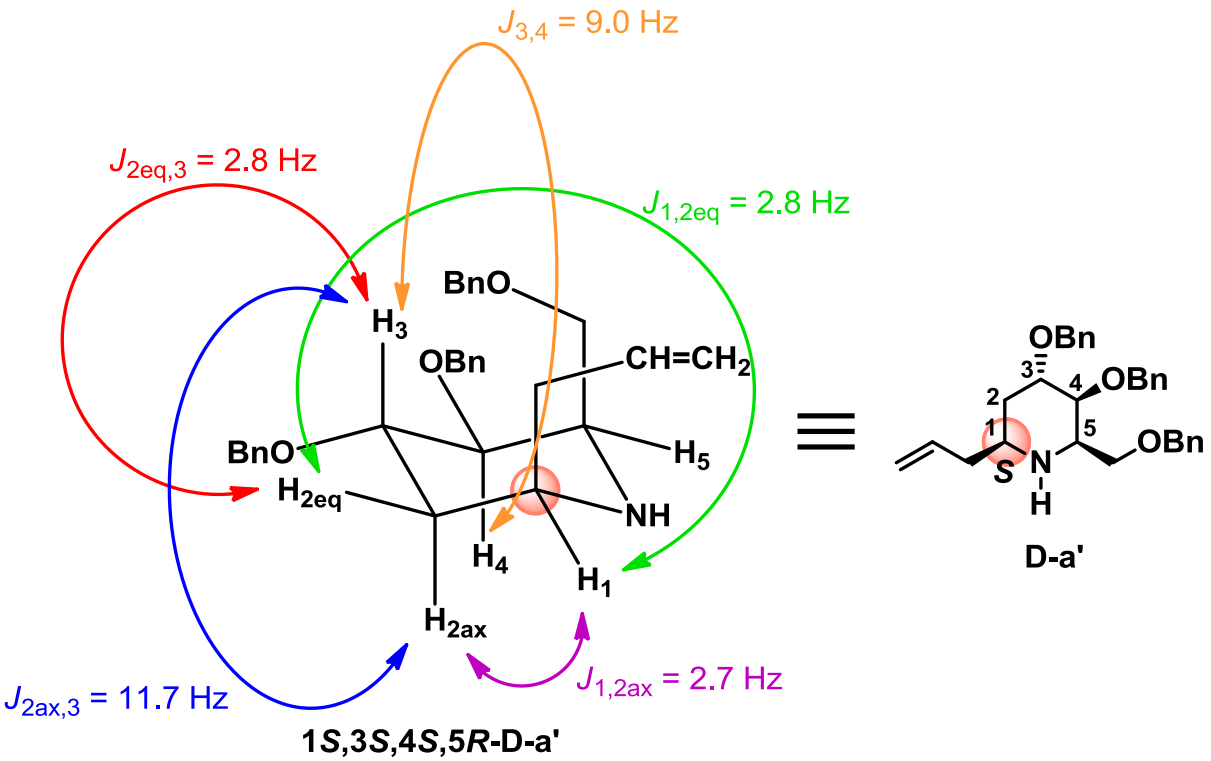
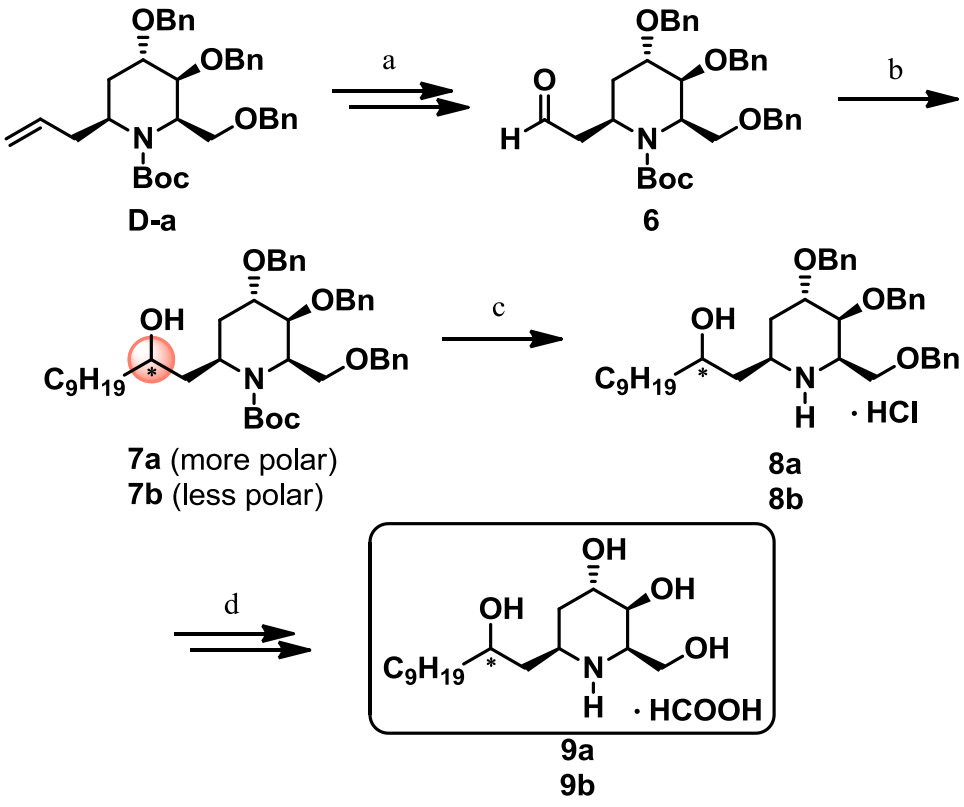


Figure 12. Visualization of a 3D structure of **D-a'**

2.5 Preparation of (+)-batzellaside B and its C8-epimer

In the next step, oxidative cleavage of the olefinic endgroup in **D-a** was performed via dihydroxylation–oxidation sequence to give the corresponding aldehyde **6** in 91% yield for 2 steps (**Scheme 20**). Introduction of the alkyl side chain by Grignard addition furnished a diastereomeric mixture of more and less polar alcohols **7a** and **7b** in 90% yield with a 1:1 ratio. The diastereomers **7a,b** were separated by silica gel column chromatography and independently subjected to an acid-catalyzed removal of the Boc groups affording *N*-unsubstituted piperidine analogues **8a,b** with 84% and 90% yield, respectively. These compounds were then hydrogenated in the presence of 10% Pd/C and HCl under H_2 atmosphere to give HCl salts of the fully deprotected products, which were purified by column chromatography on DOWEX 50W resin (X-8, H+ form, eluent: 0.7 N aqueous NH_3) and subsequently subjected to counterion exchange with formic acid in methanol to afford the corresponding formate salts **9a,b** in 70% and 90% yield, respectively.



Scheme 20. Preparation of (+)-batzellaside B and its C8-epimer. *Reagents and conditions*: (a) (i) OsO_4, NMO, acetone–H_2O (3:2), rt, 24 h; (ii) $NaIO_4$, THF–H_2O (1:1), 0 °C to rt, 4 h; 91% (2 steps); (b) $C_9H_{19}MgBr$, THF, -78 °C to 0 °C, 4.5 h; 45% (**7a**), 45% (**7b**); (c) MeOH–HCl, rt, 12 h; 84% (**8a**), 90%

(**8b**); (d) (i) H_2, Pd/C (10% Pd), MeOH–HCl, rt, 11 days; (ii) HCO_2H, MeOH, rt; 70% (**9a**) (2 steps), 90% (**9b**) (2 steps).

2.6 Comparison of the spectral data of synthetic **9a** and **9b** with natural (+)-batzellasides

Figure 13 shows the ^{1}H NMR spectra of the final products **9a,b** compared with ^{1}H NMR spectrum of natural (+)-batzellaside B given in the literature.[35] Remarkably, the spectral shape observed for **9a** closely matches that for formate salt of (+)-batzellaside B. On the other hand, inspection of the ^{1}H NMR spectrum of **9b** revealed that resonances assignable to the protons at the C2 position (H2 and H2') were significantly shifted downfield relative to those of **9a**, accompanied by noticeable changes in spectral shapes of the H2' and H7 with even less resolved multiplets.

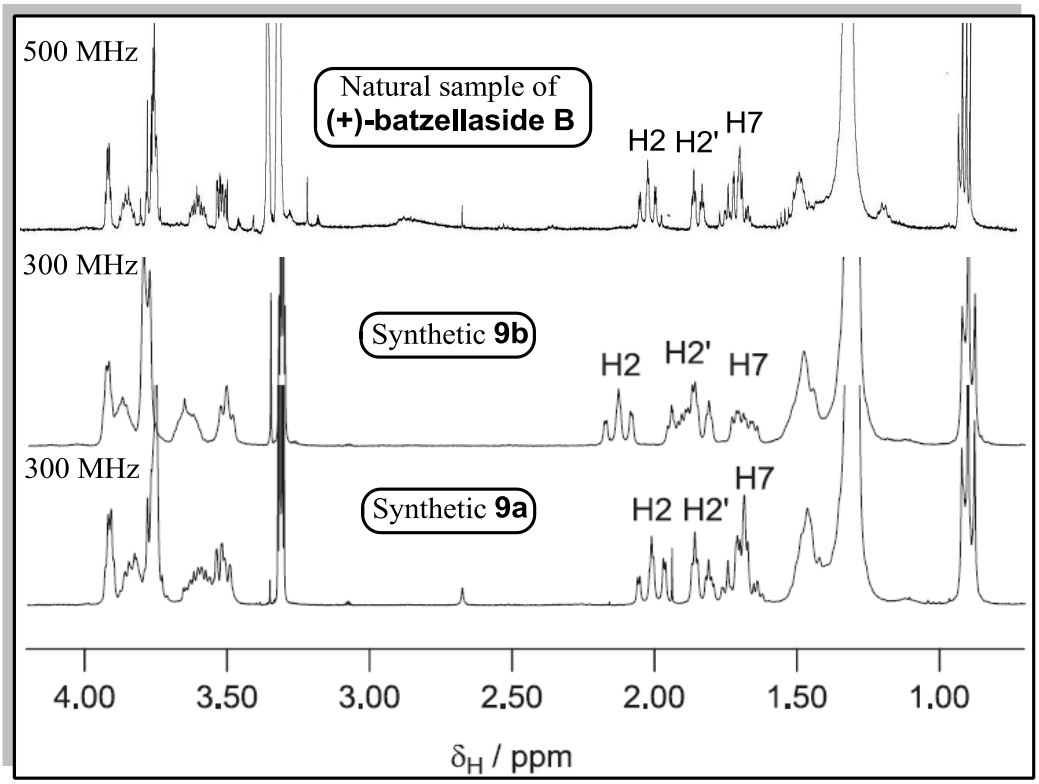


Figure 13. ^{1}H NMR spectra of **9a**, **9b** and natural (+)-batzellaside B[35] in CD_3OD

The ^{13}C NMR analysis also has shown differences in the spectra for **9a**,**b** with downfield shifted C9, C5 and C2 resonances in **9b** relative to those of **9a**. Due to unavailability of ^{13}C NMR spectrum of natural (+)-batzellaside B in the literature, the ^{13}C NMR spectra of synthetic **9a**,**b** were compared with the available data for structurally related (+)-batzellaside A (**Figure 14**).[35]

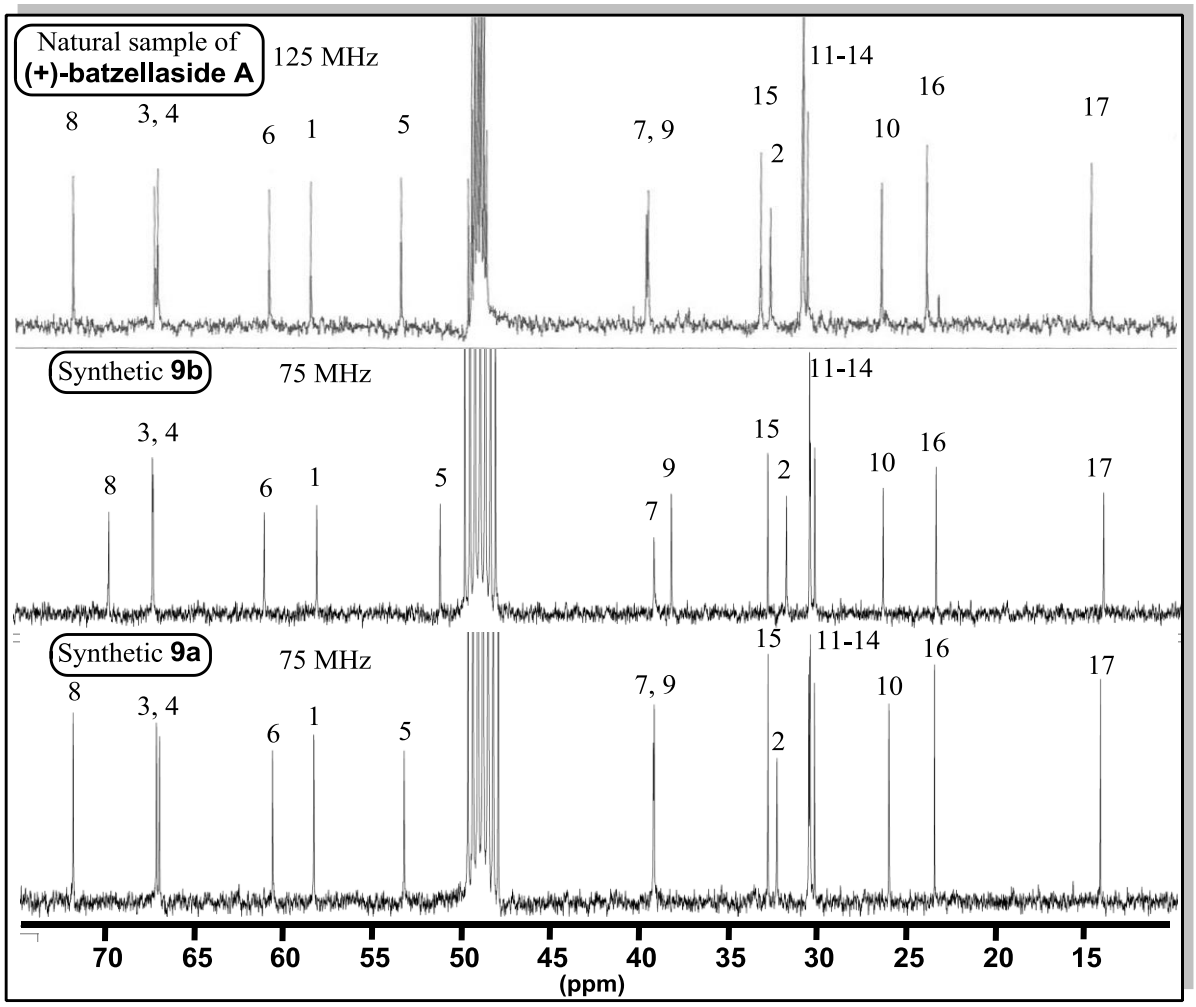
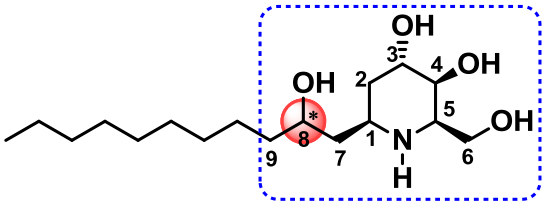


Figure 14. ^{13}C NMR spectra of synthetic **9a**, **9b** and natural (+)-batzellaside A[35] in CD_3OD

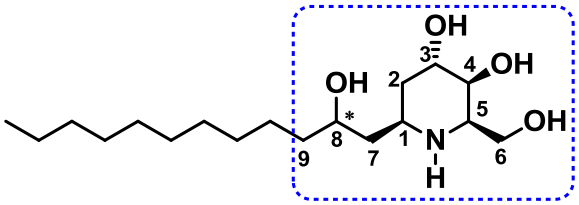
Comparison of the chemical shifts for the related carbons C1-C9 of the analyzed products shows a complete consistence of the corresponding spectral data between **9a** and the natural (+)-batzellaside A, whereas significant differences are evident in the case of **9b** (**Table 1**).

Moreover, comparison of optical rotation values obtained for **9a** ($[\alpha]_D^{23}$ +9.3, *c* 0.5, MeOH) and **9b** ($[\alpha]_D^{23}$ +4.7, *c* 0.2, MeOH)) with the literature data given for (+)-batzellaside B ($[\alpha]_D^{23}$ +10, *c* 0.5, MeOH)[35] also indicates the identity of the absolute configurations of **9a** and the natural sample.

From these observations, it can be assumed that **9a** proved to be a formate salt of (+)-batzellaside B and **9b** should be its C8-epimer. Furthermore, the absolute configurations at C1, C3, C4 and C5 of this natural product could be unambiguously determined to be *S*, *S*, *S*, and *R*, respectively, based on the above analyses.



9a,b·HCOOH



(+)-batzellaside A·HCOOH

	C1	C2	C3	C4	C5	C6	C7	C8	C9
Synthetic[a] (**9a**·HCOOH)	58.6	32.7	67.5	67.3	53.6	61.0	39.6	72.2	39.6
Synthetic[a] (**9b**·HCOOH)	58.2	32.1	67.3	67.3	51.4	61.1	39.5	69.8	38.5
Natural[b] (**(+)-batzellaside A**·HCOOH)	58.6	32.6	67.3	67.2	53.4	60.9	39.6	72.0	39.5

[a]75 MHz CD_3OD. [b]125 MHz CD_3OD.

Table 1. Comparison of ^{13}C NMR spectral data of **9a**, **9b** and natural (+)-batzellaside A

2.7 Determination of the absolute configuration at the C8 stereocenter of (+)-batzellaside B

After the completion of the total synthesis of (+)-batzellaside and its C8-epimer, my next objective was to determine the absolute configuration at the C8 stereocenters of these products, since the assignment by the analysis of the natural sample did not succeed. For this purpose I decided to apply the modified Mosher's method.[43]

2.7.1 Introduction to modified Mosher's method[43]

The modified Mosher's method is a spectroscopic strategy used for the determination of absolute configuration of secondary alcohols, optically active primary amines, β-aminoalcohols and α-aminoacids. It is based on the application of the 1-methoxy-1-phenyl-1-trifluoromethylacetic acid (MTPA) as a chiral supporting moiety which is responsible for the differentiation of chemical shifts in ^1H NMR spectra between its (*R*) and (*S*)-analogues.

In case of secondary alcohols, the compound with unknown stereochemistry is transformed into its relevant (*R*) and (*S*)-MTPA esters through reaction with (*S*)- and (*R*)-

MTPA-Cl, respectively, and the analysis of ^{1}H NMR spectra of the resulting products is performed by following the general rules.

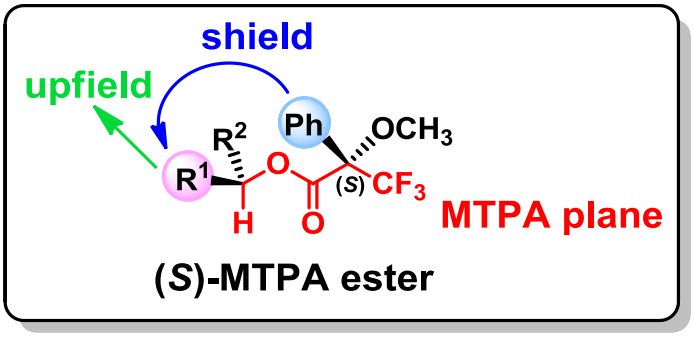


Figure 15. Ideal conformation of (*S*)-MTPA esters of secondary alcohols

Figure 15 depicts the most preferable conformation of an MTPA ester of a secondary alcohol, which is called as an ideal conformation. Due to the diamagnetic effect of the phenyl group, R^1 protons of the (*S*)-MTPA ester should show the ^{1}H NMR signals in upfield magnetic region relative to those of the (*R*)-MTPA ester. The reverse should hold for R^2 protons. Therefore, when $\Delta\delta_{SR} = \delta_S - \delta_R$ (ppm), protons on the right side of the MTPA plane must have positive values ($\Delta\delta_{SR} > 0$) and protons on the left side of the plane must have negative values ($\Delta\delta_{SR} < 0$) as visualized in **Figure 16**. Performing the back step analysis of calculation of the $\Delta\delta_{SR}$ values for the prepared MTPA esters and the construction of the relevant model (**Figure 16**), the absolute configuration of the secondary alcohol could be precisely assigned basing on the visualization of the ideal conformation of the MTPA ester (**Figure 15**).

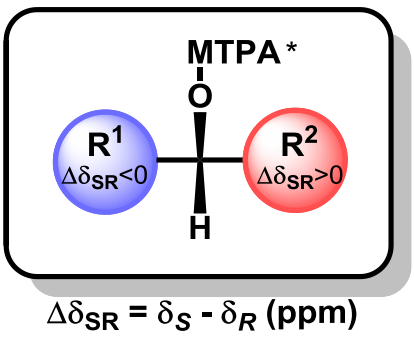
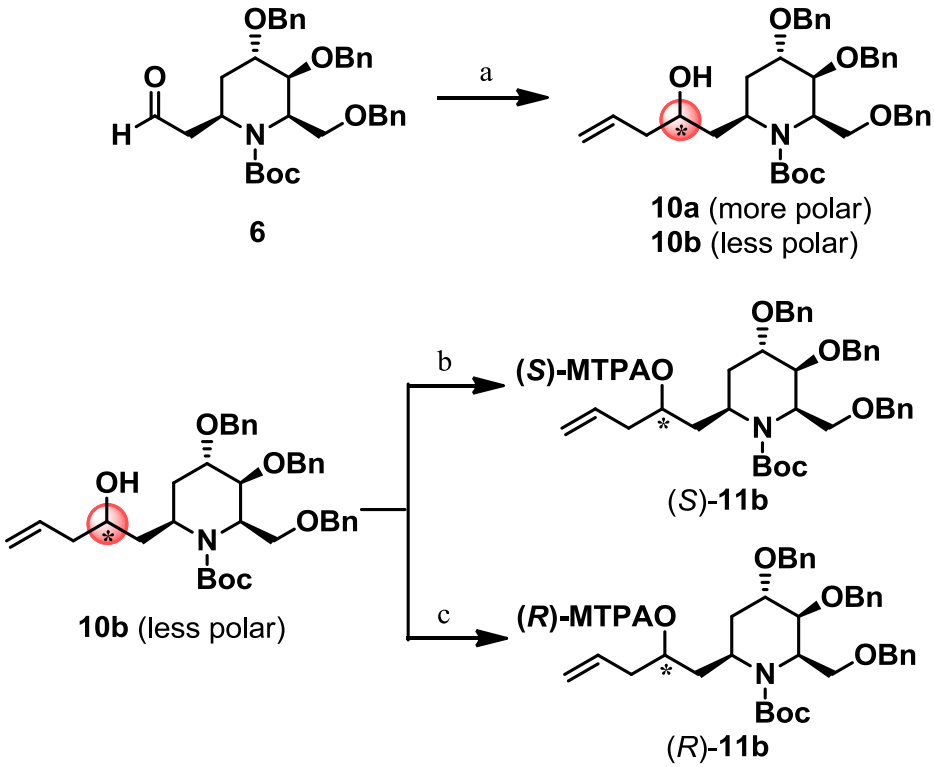


Figure 16. Model used for the determination of configuration

2.7.2 Application of the Mosher's method for the determination of the absolute configuration at the C8 stereocenter of (+)-batzellaside B

The initial attempt for determination of the absolute configuration at the C8 stereocenters of (+)-batzellaside B and its C8-epimer was carried out by direct application of the modified Mosher's method to target products **9a** and **9b**. However, the undistinguishable proton resonances due to the presence of a long side alkyl chain in the structures made the ^{1}H NMR analysis impossible and forced the pursuit of an alternative route.

The employment of structurally simpler analogues of **9a** and **9b** so as to enable the Mosher analysis was considered to be a potentially proper alternative. Accordingly, allylation of the synthetic intermediate **6** was performed by following the Barbier-type protocol[44] to provide a mixture of more and less polar diastereomers **10a** and **10b**, respectively (**Scheme 21**). After separation of each component by silica gel column chromatography, **10b** was subjected to derivatization with (*R*)- and (*S*)-MTPA-Cl to convert into the corresponding MTPA-esters (*S*)- and (*R*)-**11a**, respectively.



Scheme 21. Preparation of (*S*)-**11b** and (*R*)-**11b**. *Reagents and conditions*: (a) AllylBr, Mg, THF, -40 °C, 1 h then -30 °C, 2 h; 27% (**10a**), 58% (**10b**); (b) (*R*)-MTPA-Cl, pyridine, rt, 24 h; 42%; (c) (*S*)-MTPA-Cl, pyridine, rt, 5 days, 81%.

The highly resolved ^{1}H NMR spectra for (*S*)- and (*R*)-**11a** (600 MHz, $CDCl_3$) allowed the precise calculation of $\Delta\delta_{SR}$ values according to above empirical method and construction of the model projection for $\Delta\delta_{SR}$ value distributions (**Figure 17**). This model clearly indicates that the absolute configurations at C8 stereocenters in **11a** and **11b** must be *R* and *S*, respectively.

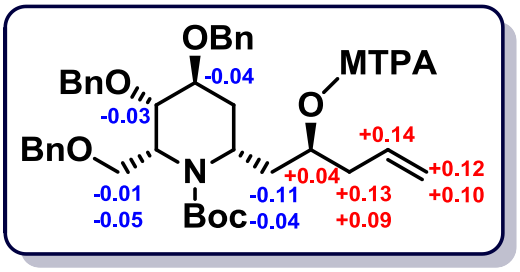
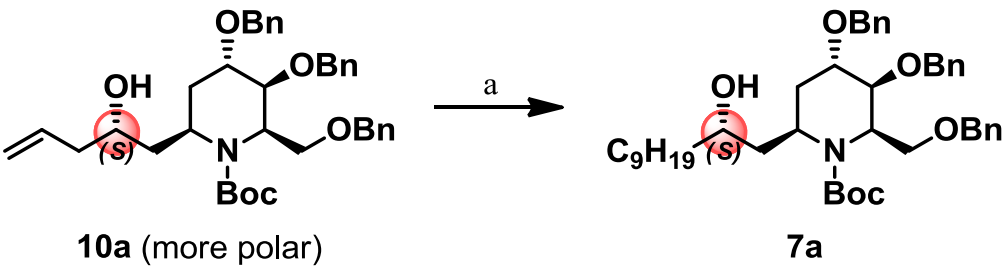


Figure 17. Model projection for the $\Delta\delta_{SR}$ value distributions in ppm (600 MHz, $CDCl_3$)

2.7.3 Transformation of **10a** into **7a**

To accomplish the assignment of absolute configuration of (+)-batzellaside B and its C8-epimer, the above prepared more polar diastereomer **10a** was derivatized to the synthetic intermediate **7a**. Accordingly, **10a** was subjected to cross metathesis with 1-octene in the presence of 2nd generation Grubbs' catalyst to give an internal olefinic intermediate, which exclusively produced **7a** after subsequent hydrogenation (**Scheme 22**). The structural identity of the newly formed product and the previously synthesized intermediate was confirmed by the ^{1}H NMR analysis (**Figure 18**).



10a (more polar) **7a**

Scheme 22. Transformation of **10a** into **7a**. *Reagents and conditions*: (a) (i) 1-octene, Grubbs II complex, toluene, rt, 4.5 h; (ii) H_2, Pd/C(en), MeOH, rt, 12 h; 61% (2 steps).

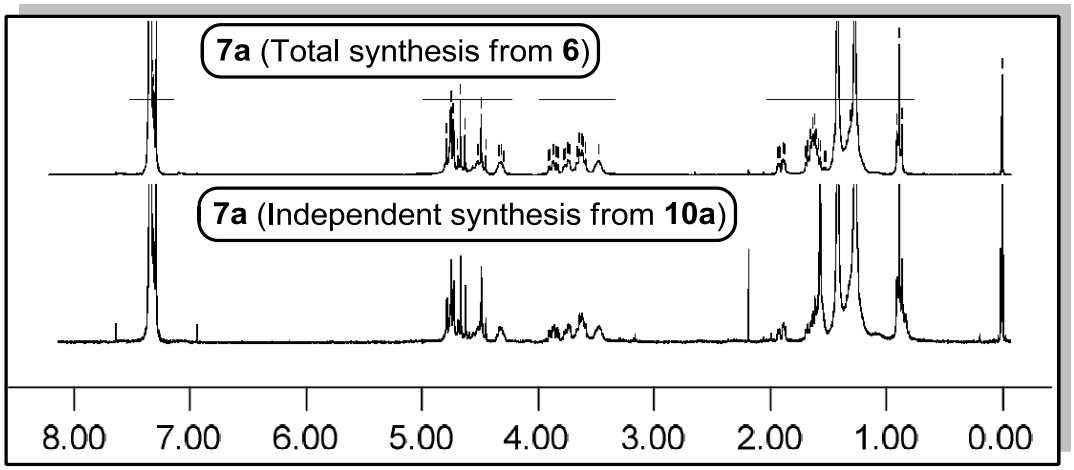


Figure 18. Comparison of ^{1}H NMR spectra of **7a** (300 MHz, $CDCl_3$)

Consequently, the definitive conclusion drawn from the correlation of the above structure/absolute configuration relationship is that the C8 stereochemistries of batzellaside B (**9a**) and its C8-epimer (**9b**) should be *S* and *R*, respectively.

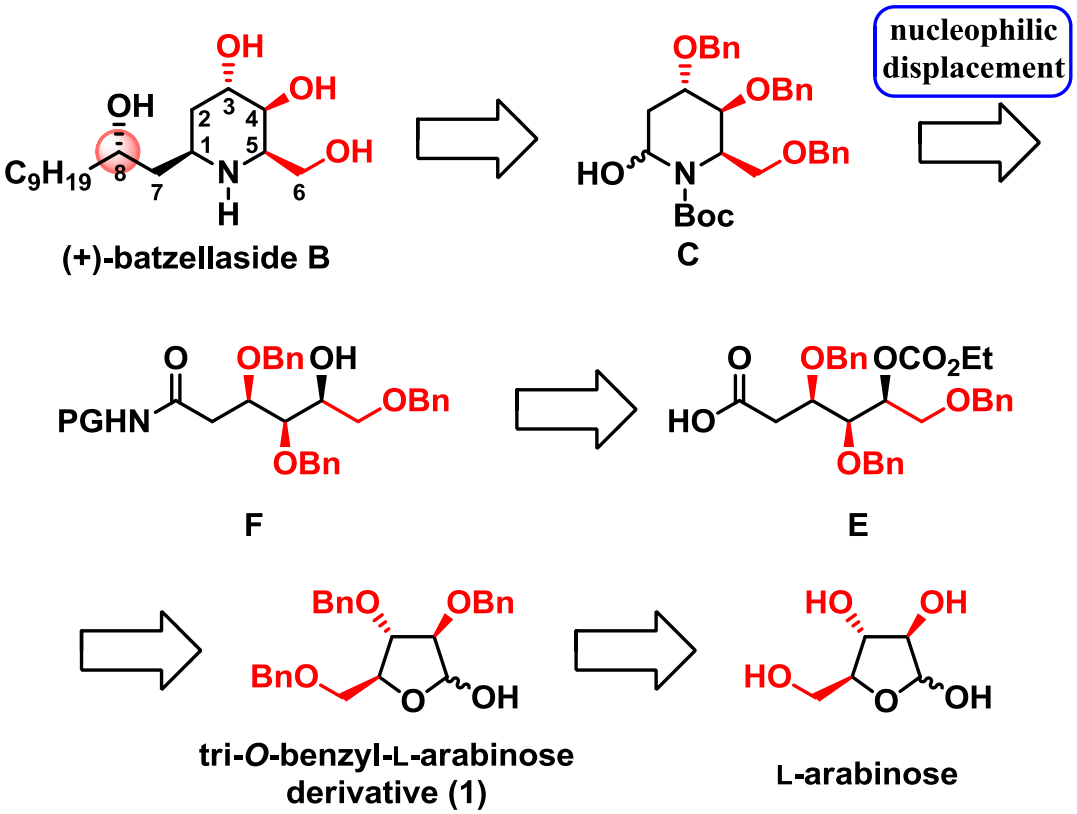
3. Efforts toward development of alternative approaches to (+)-batzellaside B from L-arabinose

Althought the synthetic approach presented in Chapter 2 allows access to (+)-baztellaside B, efforts to provide more concise and efficient routes to this natural product and its analogues have been continued. The potential improvement of the existing pathway could be achieved by development of the strategy, which would directly utilize the three inherent stereocenters contained in the starting L-arabinose. This modification is believed to decrease the number of synthetic steps leading to increase of the overall yield of the target-directed synthesis.

3.1 The first route through cyclization of amide

3.1.1 Retrosynthetic analysis

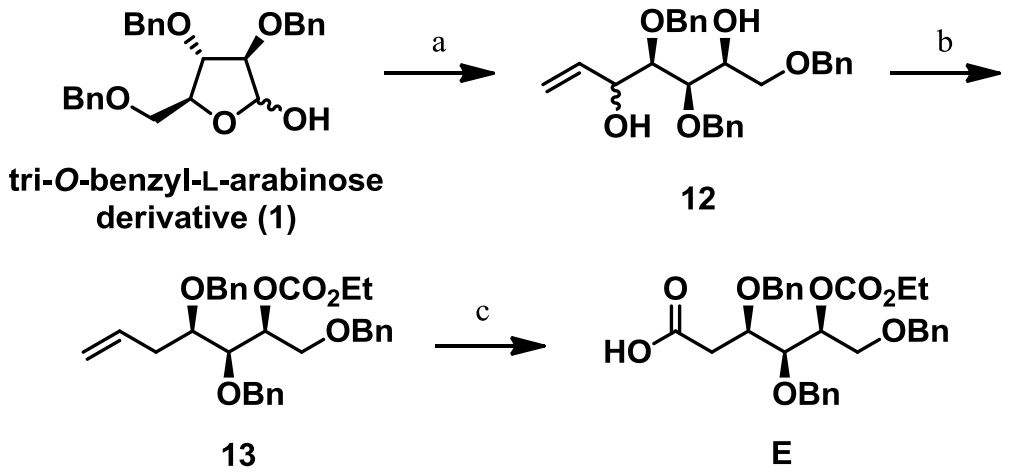
According to the retrosynthetic analysis outlined in **Scheme 23**, (+)-batzellaside B would be synthesized from the common intermediate **C** via already established protocol. The hemiaminal **C** could be formed by cyclization of amide **F**, prepared by functionalization of carboxylic acid **E**. The intermediate **E** might be accessed from L-arabinose as an appropriate chiral source through its 2,3,5-tri-*O*-benzyl derivative (**1**).



Scheme 23. Retrosynthetic analysis

3.1.2 Preparation of **E**

Starting the synthesis, the previously prepared L-arabinose derivative **1** was subjected to ring-opening Grignard addition with vinyl magnesium chloride to form acyclic unsaturated compound **12** in 96% yield (**Scheme 24**). Deoxygenation at α-position of olefin **12** via the above established method involving transformation of the two hydroxyl functionalities into ethyl carbonates and the subsequent Pd(0)-catalyzed hydrogenetaion provided **14** in 94% over 2 steps. Oxidative cleavage of vinyl group in **14** by a dihydroxylation/degradation reaction sequence followed by oxidation of the intermediate aldehyde under Pinnick conditions[45] using 2-methyl-2-butene, sodium dihydrogenorthophosphate ($NaH_2PO_4 \cdot H_2O$) and sodium chlorite ($NaClO_2$) in *tert*-butanol furnished carboxylic acid **E** in 83% over 3 steps.

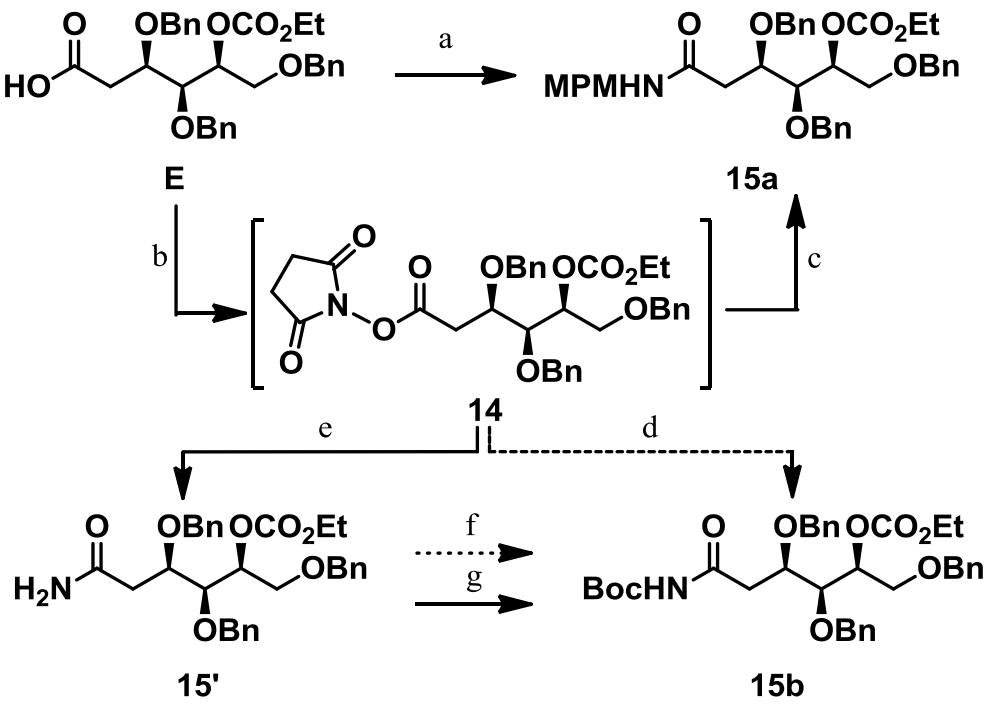


Scheme 24. Preparation of **E**. *Reagents and conditions*: (a) CH_2=CHMgCl, THF, -78 to 0 ^oC, 1 h; 96%; (b) (i) $ClCO_2Et$, DMAP, pyridine, rt, 4.5 h (ii) $Pd(PPh_3)_4$, Et_3N, HCO_2NH_4, toluene, 80 ^oC, 0.5 h; 94% (2 steps); (c) (i) OsO_4, NMO, acetone-H_2O (3:2), rt, 16 h; (ii) $NaIO_4$,THF-H_2O (1:1), 0 ^oC to rt, 2.5 h; (iii) 2-methyl-2-butene, $NaH_2PO_4 \cdot H_2O$, $NaClO_2$, *tert*-BuOH, rt, 22 h; 84% (3 steps).

3.1.3 Preparation of **F** and efforts toward its cyclization

Having intermediate **E** in a hand, the next objective was preparation of mono-protected amides **15**, and study of the effect of amide protecting group on cyclization of **F** to piperidine ring system. Accordingly, **E** was treated with *p*-methoxybenzylamine ($MPMNH_2$) in the presence of dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 to give MPM-mono-protected amide **15a** in 35% yield (**Scheme 25**). Addition of triethylamine or 4-dimethylaminopyridine (DMAP) to the reaction mixture did not improve the efficiency of this reaction. However, activation of the carboxyl group in **E** by coupling with *N*-hydroxysuccinimide (NHS) in the presence of Et_3N and DCC and a subsequent ester aminolysis with $MPMNH_2$ occurred efficiently to give desired MPM-amide **15a** in 78% yield for 2 steps.[46] A similar method was found to be inapplicable for the preparation of Boc-protected intermediate **15b**. Therefore, alternative strategies were examined employing unprotected amide **15'** prepared from **E** in 87% by a 2 steps protocol of activation of carboxylic group as the succinimide ester followed by amination using ammonium formate (HCO_2NH_4) in a two face system, 1,4-dioxane-H_2O (5:3). Initially Boc protection of **15'** was performed via treatment with oxalyl chloride ($(CO)_2Cl_2$) in refluxing dichloroethane and a subsequent treatment with *tert*-butyl alcohol at 0 ^oC.[47] However, this attempt failed due to elimination of β-benzyloxy group and formation of the unsaturated compound as a major product. Finally, the desired amide **15b** was isolated in

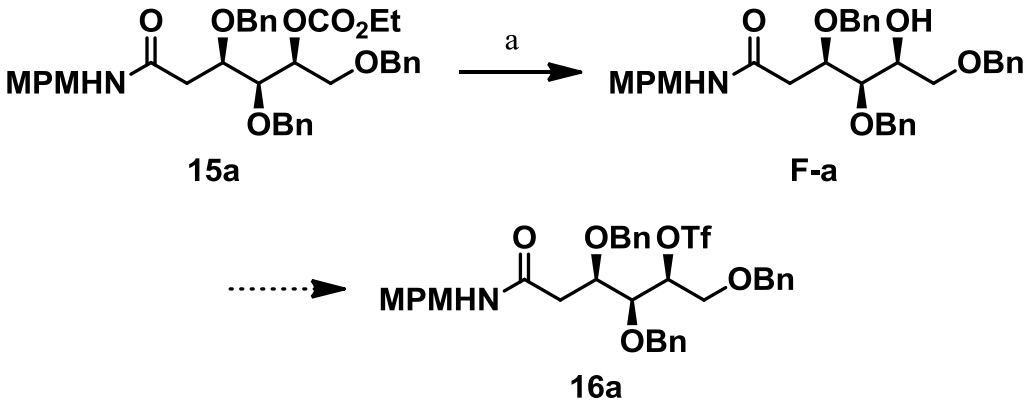
28% yield after a 2 steps reaction sequence of di-Boc protection of **15'** under standard conditions followed by mono-selective cleavage of Boc group using magnesium perchlorate ($Mg(ClO_4)_2$) in acetonitrile at 40 °C.[48]



Scheme 25. Preparation of **15**. *Reagents and conditions*: (a) $MPMNH_2$, DCC, CH_2Cl_2, rt, 3 h; 35% (b) NHS, DCC, Et_3N, CH_2Cl_2, rt, 1.5 h; (c) $MPMNH_2$, CH_2Cl_2, rt; 18 h; 78% (2 steps); (d) $BocNH_2$, *tert*-BuOK, CH_2Cl_2, -78 to rt, 20 h; 0%; (e) NH_4HCO_2, 1,4-dioxane-H_2O (5:3), rt, 41 h; 87% (2 steps from **E**); (f) (i) $(CO)_2Cl_2$, $(CH_2Cl_2)_2$, 0 °C to 85 °C, 1 h; (ii) *tert*-BuOH-$(CH_2Cl_2)_2$ (1:1), 0 °C, 1 h; 0% (2 steps); (g) (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (ii) $Mg(ClO_4)_2$, MeCN, 40 °C, 1.7 h; 28% (2 steps).

In the next step, ethyl carbonate functionality in **15a** was hydrolyzed under basic conditions using sodium carbonate (Na_2CO_3) in methanol to provide secondary alcohol **F-a** in 72% yield (**Scheme 26**). Unfortunately, an attempt to introduce the triflate (TfO) leaving group by treatment of **F-a** with trifluoromethanesulfonic anhydride ($(CF_3SO_2)_2O$) in the presence of pyridine failed due to the high lability observed for β-benzyloxy group, which was shown to be easily eliminated under basic conditions. Formation of the α,β-unsaturated compound most likely took place via E1cB mechanism whereas the neighboring electron withdrawing amide group could stabilize the negative charge of the carboanion center. Considering the fact that the presence of strong base is necessary for the introduction of a

leaving group as well as for the cyclization step by nucleophlic displacement, this strategy was assumed to be unsuitable and should not be further continued.

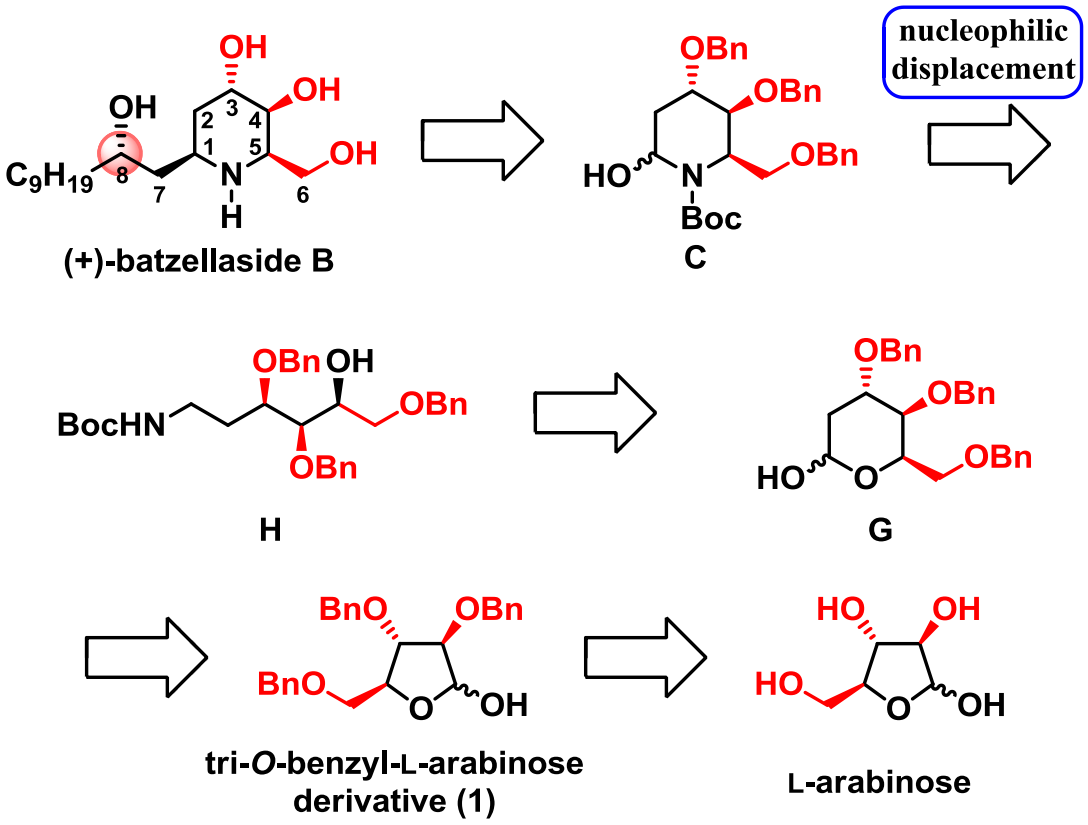


Scheme 26. Preparation of **16a**. *Reagents and conditions*: (a) Na_2CO_3, MeOH, rt, 24 h; 72%.

3.2 The second route through cyclization of amine

3.2.1 Retrosynthetic analysis

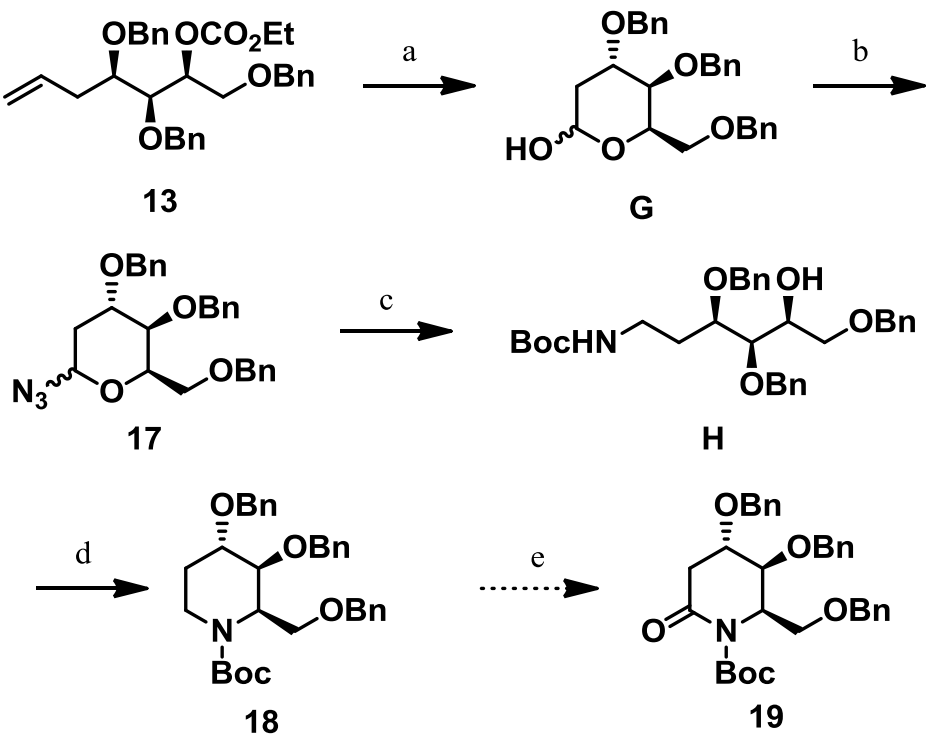
The electron withdrawing effect of the amide group was found to be a crucial factor causing the failure of the previous synthetic strategy. Therefore, in the new retrosynthetic analysis it was assumed that the hemiaminal **C** can be accessed through cyclization of amine **H** by nucleophilic displacement, and a subsequent oxidation at the α-position of a resulting piperidine analogue (**Scheme 27**). Intermediate **H** would be synthesized by functionalization of lactam **G** prepared from L-arabinose derivative **1**.



Scheme 27. Retrosynthetic analysis

3.2.2 Preparation of **19**

The new approach involves the olefinic intermediate **13**, prepared from L-arabinose derivative **1** during the course of the previous synthetic strategy. Hydrolysis of the carbamate group in **13** by treatment with sodium hydroxide (NaOH) in methanol followed by oxidative cleavage of terminal double bond resulted in cyclization of an intermediate hydroxyl aldehyde into lactam **G** to form the product in 88% over 3 steps (**Scheme 28**). This compound was then subjected to azidation with bis(*p*-nitrophenyl) azidophosphonate (*p*-NO_2DPPA) in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in dimethylformamide (DMF) to provide glycosyl azide **17** in 93% yield.[49] The ring opening reduction of **17** by using lithium aluminium hydride ($LiAlH_4$) in THF gave acyclic amine, which afforded intermediate **H** in 88% for 2 steps after Boc protection.



Scheme 28. Preparation of **16**. *Reagents and conditions*: (a) (i) NaOH, MeOH, rt, 20 h; (ii) OsO_4, NMO, acetone-H_2O (3:2), rt, 47 h; (iii) $NaIO_4$, THF-H_2O (1:1), 0 ^oC to rt, 1 h; 88% (3 steps); (b) *p*-NO_2DPPA, DBU, DMF, rt, 16 h; 93%; (c) (i) $LiAlH_4$, THF, rt, 2 h; (ii) Boc_2O, $NaHCO_3$, 1,4-dioxane-H_2O (1:1), rt, 20 h; 82% (2 steps); (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 ^oC to rt, 0.5 h; (ii) *tert*-BuOK, THF, rt, 1 h; 23% (2 steps) (e) RuO_2, 10% $NaIO_{4\ aq}$, AcOEt, rt, 3 h; complex mixture.

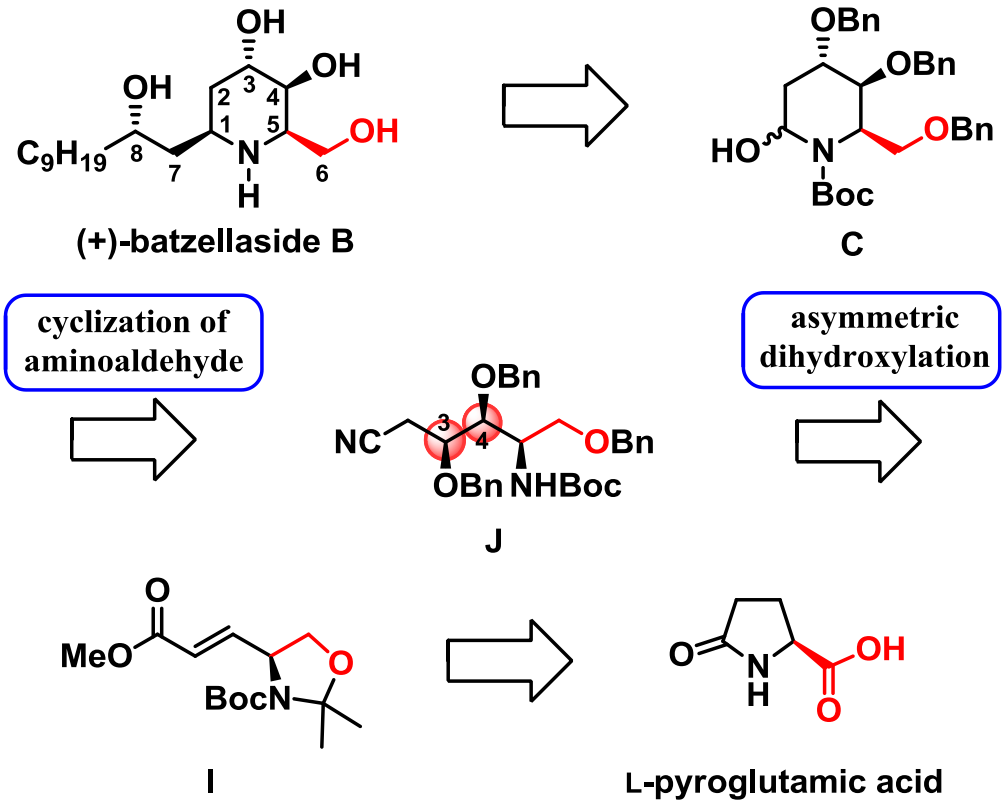
Next, the piperidine ring system was constructed by a 2 steps procedure involving introduction of a mesyl leaving group to **H** using mesyl chloride (MsCl) in the presence of triethylamine and a subsequent S_N2 cyclization by treatment with potassium *tert*-butoxide (*tert*-BuOK) in THF (**Scheme 28**). This transformation furnished a piperidine analog **18** in 23% over 2 steps. Unfortunately, oxidation of **18** with ruthenium(IV) oxide (RuO_2) in the presence of 10% aquaous solution of sodium periodate ($NaIO_4$) in ethyl acetate (AcOEt)[50] did not afforded the desired lactam **19**. The complex mixture produced in this reaction was a result of oxidations of benzyl groups (Bn) in **18** to benzoyl (Bz) functionalities, which were found to be more preferable than oxidation at α-position in piperidine ring. It was considered that this unanticipated reation could be potentially avoided by an exchange of benzyl protecting groups into silyl ones. Howewer, removal of benzyl functionalieties via palladium catalyzed hydrogenation resulted in formation of a complex mixture. Due to these failures the studied synthetic patway was assumed to be unseccessful and has been ceased.

4. Synthetic approach to (+)-batzellaside B from L-pyroglutamic acid[51]

Due to the fact that efforts to provide more efficient and concise synthetic approach to (+)-batzellaside B from L-arabinose failed, an alternative starting material was considered to be employed as a chiral source. L-Pyroglutamic acid, whose rich natural abundance makes it a commercially and economically viable substrate,[52] can be envisaged as a potentially practical starting material allowing efficient and convenient access to the target natural product.

4.1 Retrosynthetic analysis

The retrosynthetic analysis of the new approach to (+)-batzellaside B from L-pyroglutamic acid is outlined in **Scheme 29**. It involves heterocyclic hemiaminal **C**, the common precursor of the target molecule, which would be prepared by the cyclization of an intermediate aldehyde in situ generated from cyanide **J**. This compound can be synthesized from α,β-unsaturated methyl ester **I**, which could be obtained via stepwise functionalization of L-pyroglutamic acid. In this proposed strategy, the key transformation would require Sharpless asymmetric dihydroxylation to install stereoselectively the adjacent hydroxy groups at C3 and C4 positions of the relevant olefinic substrate.

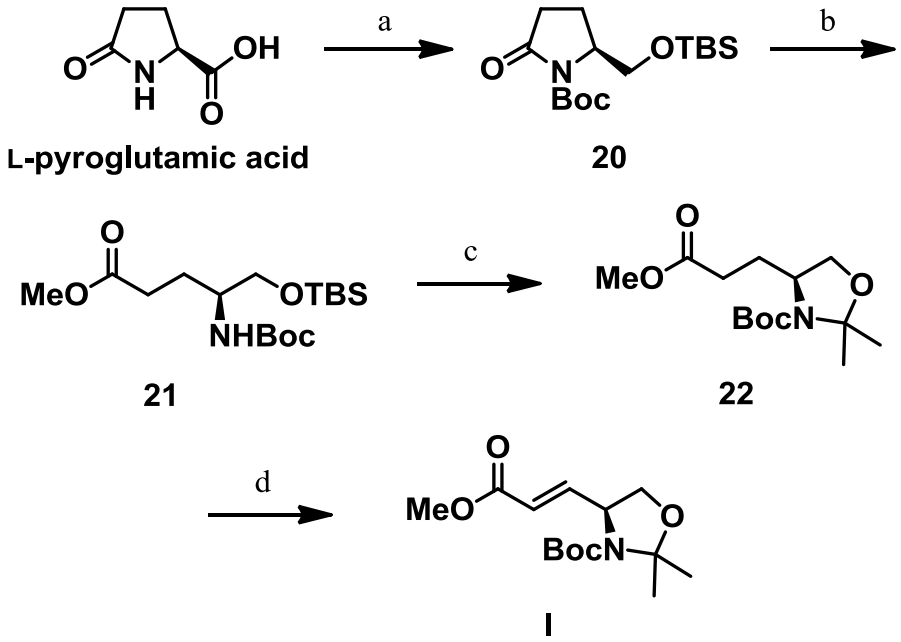


Scheme 29. Retrosynthetic analysis – the synthetic approach from L-pyroglutamic acid

4.2 Preparation of α,β-unsaturated methyl ester **I**

The synthesis began with the preparation of *N*-Boc-protected γ-lactam **20** from L-pyroglutamic acid by following the published synthetic strategy (**Scheme 30**).[53] Accordingly, the starting material was treated with thionyl chloride ($SOCl_2$) in methanol at -20 ^oC to furnish the corresponding methyl ester, which gave compound **20** through reduction to alcohol by $NaBH_4$ and a subsequent protection of hydroxyl and amide groups with TBS and Boc functionalities, respectively. The ring-opening reaction of **20** with sodium methoxide (MeONa) in methanol proceeded smoothly to provide acyclic methyl ester **21** in 98% yield.[54] Exposure of **21** to methanolic *p*-TsOH removed TBS protective group and the resulting alcohol was next converted to *N*,*O*-acetonide **22** in 93% yield for 2 steps by treatment with 2,2-dimethoxypropane (2,2-DMP) in the presence of $BF_3{\cdot}Et_2O$.[55] Olefination of **22** through deprotonation with lithium diisopropyl amine (LDA) followed by addition of phenylselenyl bromide (PhSeBr) and subsequent oxidative elimination of the resulting phenylseleno group

with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded *E*-isomer **I** with quantitative geometric purity in 90% yield for 2 steps.[56]

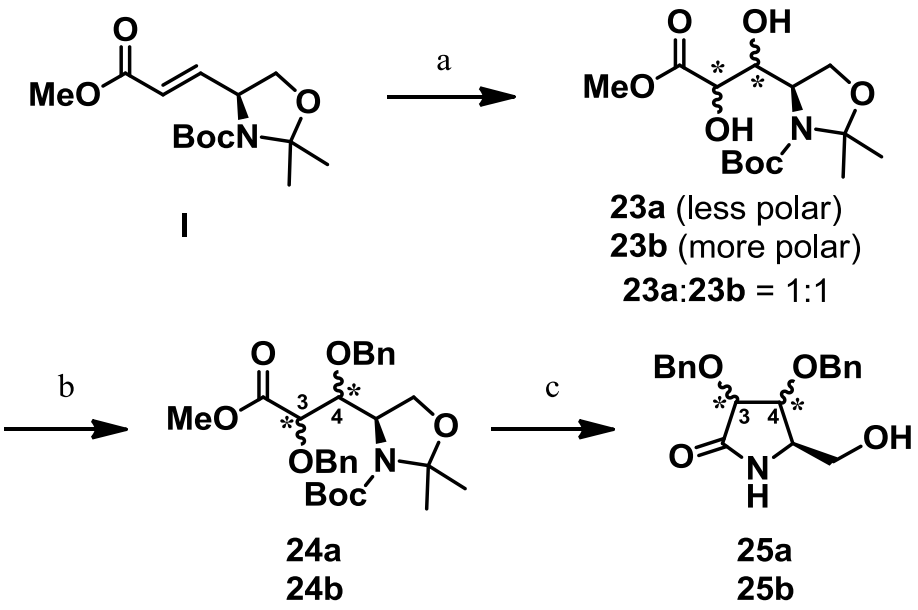


Scheme 30. Preparation of **I**. *Reagents and conditions*: (a) (i) $SOCl_2$, MeOH, -20 °C to rt, 3.5 h; (ii) $NaBH_4$, EtOH, 0 °C to rt, 4 h; (iii) TBSCl, imidazole, DMF, rt, 2.5 h; (iv) Boc_2O, DMAP, CH_2Cl_2, rt, 2 h; 98%; (4 steps) (b) MeONa, MeOH, rt, 10 min; 98%; (c) (i) *p*-TsOH, MeOH, rt, 3 h; (ii) $BF_3{\cdot}Et_2O$, acetone, 2,2-DMP, rt, 30 min; 93% (2 steps); (d) (i) LDA, HMPA, PhSeBr, THF, -78 °C, 3 h; (ii) *m*-CPBA, CH_2Cl_2, -40 °C, 3 h; 90% (2 steps).

4.3 Dihydroxylation of α,β-unsaturated methyl ester **I** and determination of absolute configuration of **23a** and **23b**

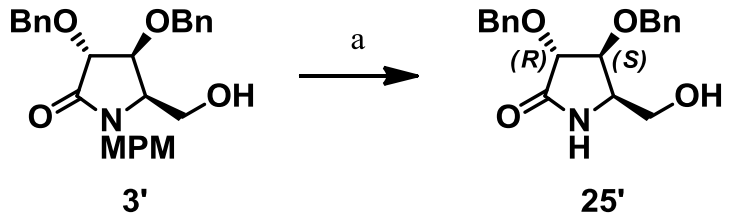
With the olefinic intermediate **I** in a hand, an investigation of dihydroxylation reaction was carried out to selectively install hydroxyl groups at C3 and C4 positions. Initially, **I** was treated with osmium tetroxide (OsO_4) in the presence of *N*-methylmorpholine-*N*-oxide (NMO) to produce diastereomeric mixture of diols **23a,b** in quantitative yield with a 1:1 ratio (**Scheme 31**).[57] These diastereomers were separated by silica gel column chromatography, and then transformed to *trans*-3,4-dibenzyloxy-(5*R*)-hydroxymethyl-substituted γ-lactams, respectively, that allow a precise assignment of the absolute configuration by comparison of

^{13}C NMR spectrum resonances with that of the relative compound with the desired (3*R*,4*S*,5*R*) configuration, derived from the intermediate of the first synthetic approach.[36]



Scheme 31. Dihydroxylation of **I**. *Reagents and conditions*: (a) OsO_4, NMO, *tert*-BuOH-H_2O (2:1), rt, 41 h; 50% (**23a**), 50% (**23b**); (b) BnBr, Ag_2O, AcOEt, rt, 3 days; 11% (**24a**), 46% (**24b**); (c) (i) *p*-TsOH, MeOH, rt, 3 h; (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 2 h; 12% (**25a**) (2 steps), 32% (**25b**) (2 steps).

Accordingly, hydroxyl functionalities in **23a,b** were independently protected as benzyl ethers by exposure to benzyl bromide (BnBr) in the presence of silver oxide (Ag_2O) to give compounds **24a,b** in 11 and 46%, respectively. Cleavage of acetal group in **24a,b** with *p*-TsOH in methanol and a subsequent Boc deprotection using $BF_3{\cdot}Et_2O$ in dichloromethane followed by in situ cyclization of the resulting γ-amino ester[58] gave rise to γ-lactams **25a,b** in 12 and 32% yields for 2 steps, respectively. On the other hand, compound **25'** with the desired (3*R*,4*S*,5*R*) configuration was prepared in 58% yield from **3'** by removal of MPM moiety upon treatment with ceric ammonium nitrate (CAN) (**Scheme 32**) and ^{13}C NMR spectra of the above prepared γ-lactams were next analyzed (**Figure 19**).



Scheme 32. Preparation of **22'**. *Reagents and conditions*: (a) CAN, H_2O-acetonitrile (9:1), rt, 2 h; 58%.

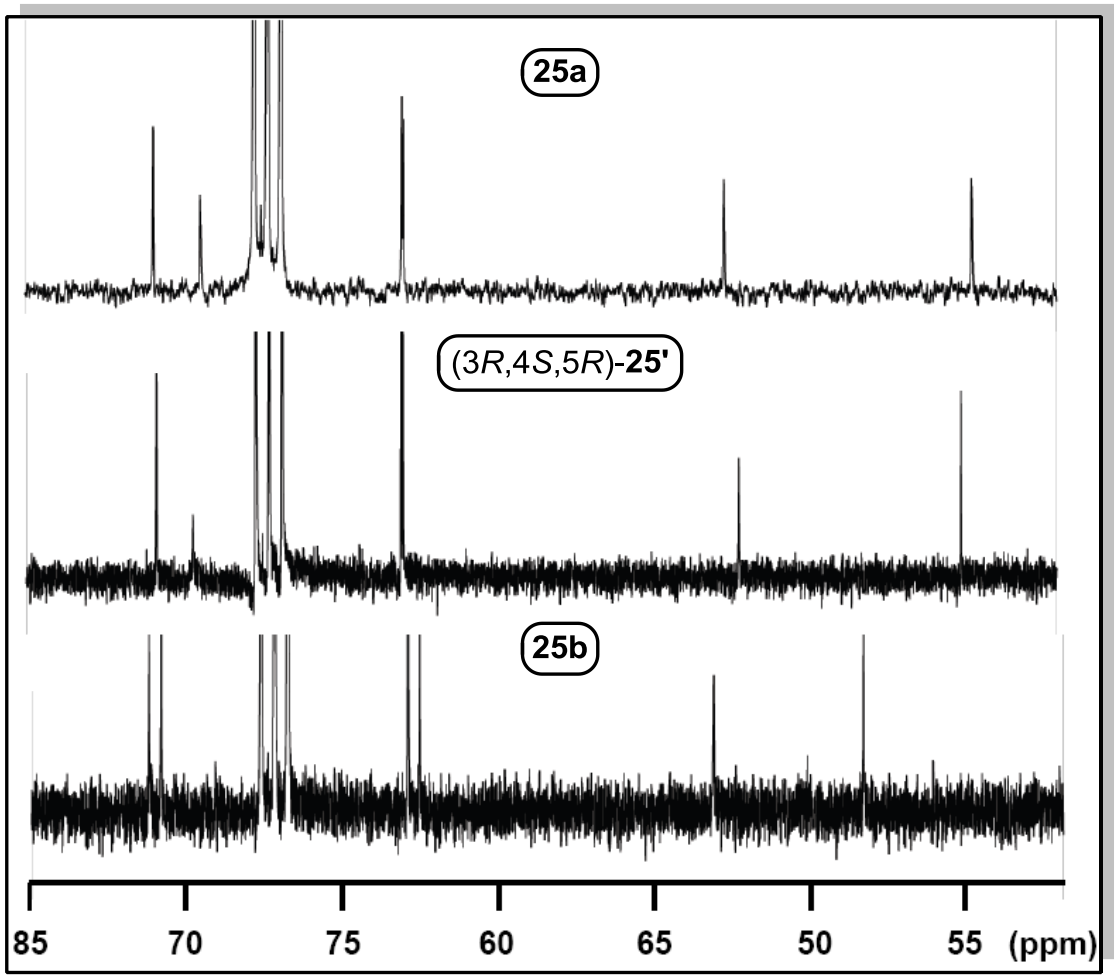


Figure 19. Comparison of ^{13}C NMR spectra of **25a**, **25b** and (3*R*,4*S*,5*R*)-**25'** (75 MHz, $CDCl_3$)

Remarkably, signals resonated in the δ 55-85 ppm range observed for **25a** closely match that for (3*R*,4*S*,5*R*)-**25'**, whereas significant differences are evident in the case of **25b**. From these observations it can be assumed that the absolute configuration of diols **23a** and **23b** should be identified as (3*R*,4*S*) and (3*S*,4*R*), respectively.

In efforts to improve the stereoselectivity for the production of the desired diastereomer **23a**, Sharpless asymmetric dihydroxylation of **I** using AD-mix-α or AD-mix-β

was carried out in *tert*-BuOH-H_2O (1:1) at room temperature.[59] Unfortunately, the reaction did not proceed under these conditions and starting material was recovered intact in both cases. The failure of this methodology can be most likely explained in terms of the effect of α-methyl ester group in the olefinic substrate, which would decrease the reactivity toward dihydroxylation due to its strong electron withdrawing nature, in agreement with previous results reported for the OsO_4-catalyzed reactions.[60] The steric effect of this functionality and the bulky Boc moiety can also play a role, since access of the catalyst to double bond might be significantly hampered as shown in visualization of a molecular modeling for the structure of **l** (**Figure 20**.)

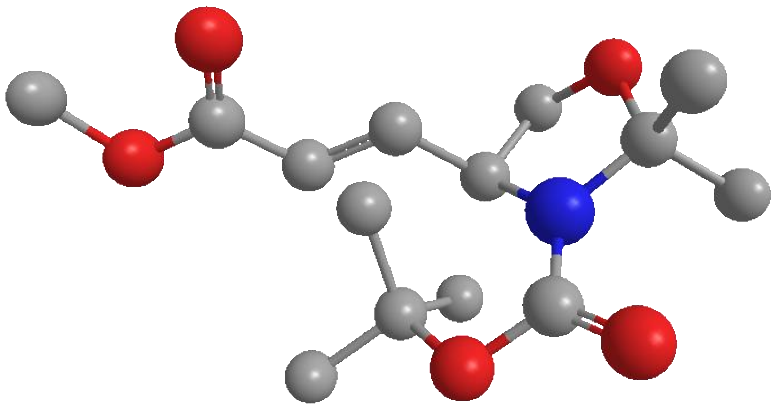
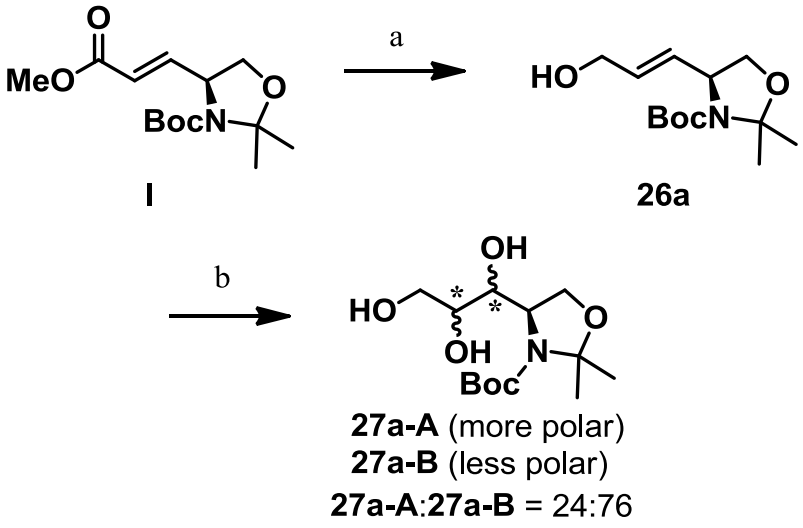


Figure 20. A 3D molecular modeling for **l**

4.4 Dihydroxylation of olefinic alcohol **26a** and determination of absolute configuration of **27a-A** and **-B**.

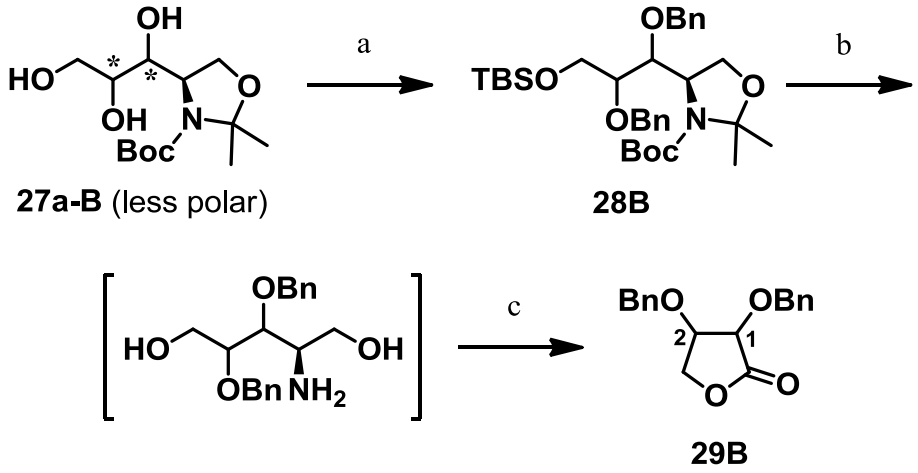
To improve the reactivity of the olefinic substrate toward asymmetric dihydroxylation, chemoselective reduction of **l** with DIBAL-H was carried out in tetrahydrofuran at 0 ^oC to produce α,β-unsaturated alcohol **26a** in 95% yield (**Scheme 33**).[61] This compound was next subjected to dihydroxylation with OsO_4 and NMO in 50% aqueous *tert*-BuOH at room temperature to provide an approximately 1:3 ratio of more and less polar diastereomeric triols **27a-A** and **-B** in 30% yield, respectively. The diastereomers were separated by silica gel column chromatography, and then derivatized to *trans*-1,2-dibenzyloxy-substituted γ-lactone

that allows a precise assignment of the absolute configuration by comparison with the specific optical rotation value.[62]



Scheme 33. Preparation of **27a-A,B**. *Reagents and conditions*: (a) DIBAL-H, THF, 0 °C, 1 h; 95%; (b) OsO_4, NMO, *tert*-BuOH-H_2O (1:1), rt, 24 h; 30%, **27a-A**:**27a-B** = 24:76.

Accordingly, the primary hydroxy group of major isomer **27a-B** was chemoselectively protected as the TBS ether[63] and the remaining diol moiety was then etherified with NaH and benzyl bromide, affording **28B** in 30% for 3 steps (**Scheme 34**). Deprotection of the acetal and TBS groups of this product was carried out by stepwise reactions with *p*-TsOH and TFA to give a dihydroxyamine intermediate, which underwent spontaneous cyclization upon treatment with $NaIO_4$[64] followed by PCC oxidation to form the corresponding *trans*-1,2-dibenzyloxy-substituted γ-lactone **29B** in 30% yield for 3 steps. For comparison, optical rotation measurement was performed on a solution of **29B** in $CHCl_3$ at *c* 0.36. Indeed, this compound exhibited its optical activity with $[\alpha]_D^{24}$ value of -51.6, indicative of opposite sense of the absolute configuration in comparison to the literature data given for (1*S*,2*S*)-**29'** ($[\alpha]_D^{25}$ +60.1, *c* 1.0, $CHCl_3$)[62] (**Figure 21**). From this, it can be concluded that the more polar triol **27a-A** obtained as a minor component of this dihydroxylation process could be identified as (1*S*,2*S*)-isomer that should be supplied to advance the ongoing synthetic strategy, albeit with low yield for its preparation.



Scheme 34. Preparation of **29B**. *Reagents and conditions*: (a) (i) TBSCl, Et_3N, CH_2Cl_2, rt, 24 h; (ii) BnBr, NaH, Bu_4NI, THF, rt, 15 h; 30% (3 steps) (b) (i) *p*-TsOH, MeOH, rt, 2 days; (ii) TFA, CH_2Cl_2, rt, 30 min; (c) (i) $NaIO_4$, Et_2O-H_2O (1:1), rt, 8 h; (ii) PCC, MS 4Å, CH_2Cl_2, rt, 10 min; 30% (3 steps).

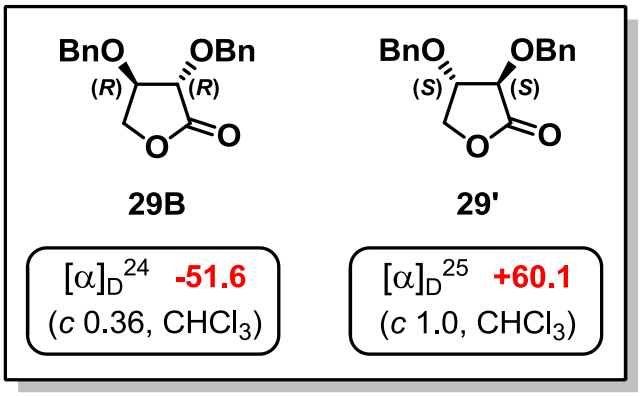
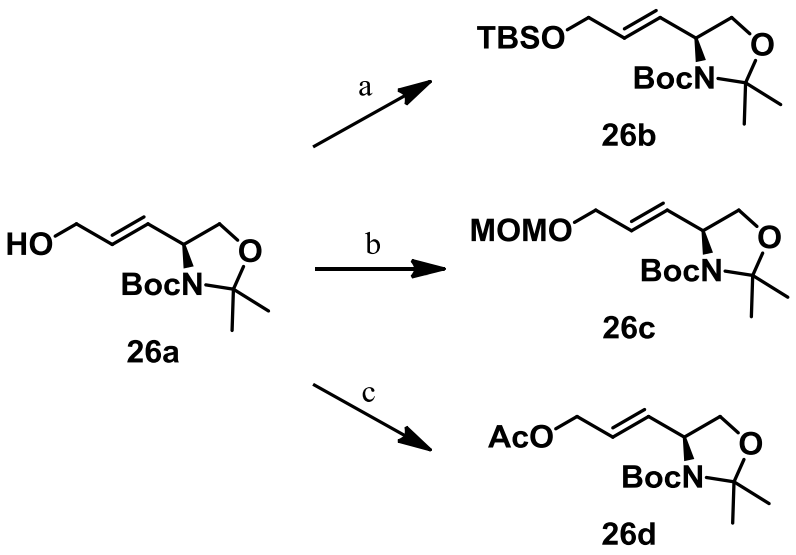


Figure 21. Comparison of optical rotation values of **29B** and (1*S*,2*S*)-**29'**[62]

4.5 Preparation of olefins **26b-d**

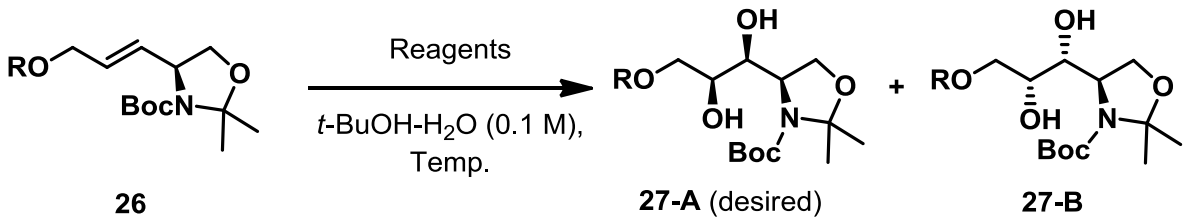
In an effort to improve selectivity of stereogenesis for the dihydroxylation step, three other olefinic substrates, in which the terminal hydroxy group was replaced with various functionalities, were prepared (**Scheme 35**). Accordingly, treatment of **26a** with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole afforded TBS ether **26b** in 77% yield.[65] Reaction of **26a** with methoxymethyl chloride (MOMCl) and sodium hydride (NaH) furnished **26c** in 68%,[66] and acetyl protection of **26a** using acetic anhydride (Ac_2O) in the presence of Et_3N and DMAP provided acetate **26d** in 99% yield.[67]



Scheme 35. Preparation of **26b-d**. *Reagents and conditions*: (a) TBSCl, imidazole, DMF, rt, 1 h; 77%; (b) MOMCl, NaH, THF, rt, 1 h; 68%; (c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 1 h; 99%.

4.6 Asymmetric dihydroxylation of **26a-d**

Having the four different olefinic compounds **26a-d** in hand, an asymmetric technique of dihydroxylation was studied to synthesize the (1*S*,2*S*)-constituent in preference to another (**Table 2**). Indeed, the Sharpless methodology was initially applied to **26a** by carrying out the reactions at room temperature under a standard set of the asymmetric hydroxylation conditions. Using AD-mix-α and -β, mixtures of **27a-A** and **-B** were obtained in 45:55 and 13:87 ratios with isolated yields of 32 and 77%, respectively (entries 1 and 2). Analogously, the asymmetric dihydroxylations of **26b** and **26c** produced predominantly undesired diastereomers **27b-B** and **27c-B** that could be converted through acidic deprotection to **27a-B** (entries 3,4 and 6), while the reaction of **26c** with AD-mix-α afforded a 50:50 mixture of diastereomers (entry 5).



26 **27-A** (desired) **27-B**

Entry	Substrates	R	Reagents (/ mol%)	Temp.	Yields [%][a] (**27A:27B**)[b]
1	26a	H	AD-mix-α (0.5) $MeSO_2NH_2$ (100)	rt	32 (45:55)
2	26a	H	AD-mix-β (0.5) $MeSO_2NH_2$ (100)	rt	77 (13:87)
3	26b	TBS	AD-mix-α (0.5) $MeSO_2NH_2$ (100)	rt	33 (14:86)
4	26b	TBS	AD-mix-β (0.5) $MeSO_2NH_2$ (100)	rt	35 (40:60)
5	26c	MOM	AD-mix-α (0.5) $MeSO_2NH_2$ (100)	rt	52 (50:50)
6	26c	MOM	AD-mix-β (0.5) $MeSO_2NH_2$ (100)	rt	88 (0:100)
7	**26d**	**Ac**	**AD-mix-α (0.5) $MeSO_2NH_2$ (100)**	**rt**	**48 (69:31)**
8	26d	Ac	AD-mix-β (0.5) $MeSO_2NH_2$ (100)	rt	51 (9:91)
9	26d	Ac	AD-mix-α (0.5) $MeSO_2NH_2$ (100)	0 °C	54 (78:22)
10	**26d**	**Ac**	**AD-mix-α (0.5)**	**0 °C**	**52 (84:16)**
11	26d	Ac	AD-mix-α (0.5) $(DHQ)_2PHAL$ (10)	0 °C	53 (83:17)

[a]Isolated yield [b]Diastereomeric ratios were determined by ^1H NMR (300 MHz).

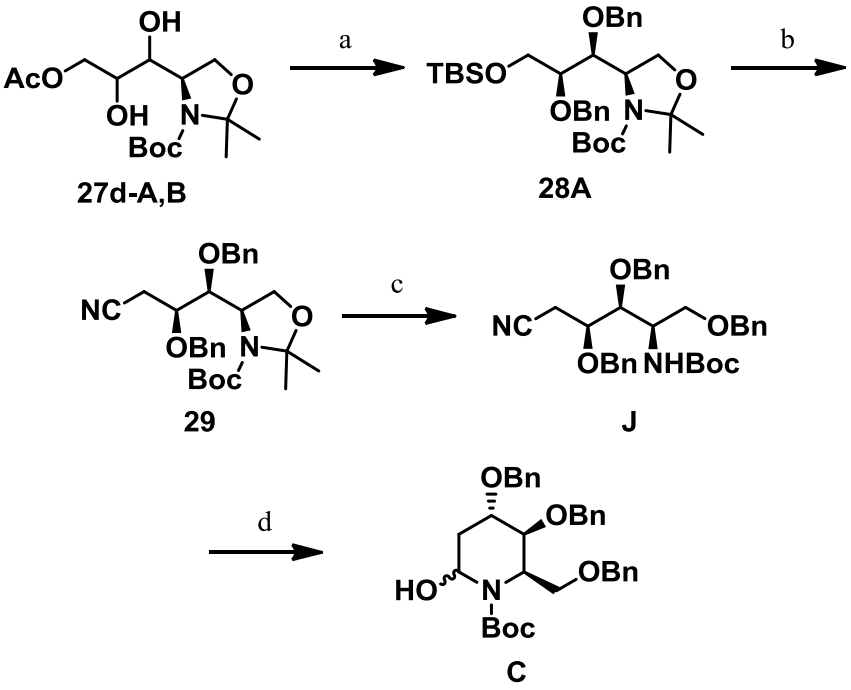
Table 2. Asymmetric dihydroxylation of **26a-d**.

A remarkable change in the product profile occurred when **26d** was used for this reaction. By employing AD-mix-α under the above reaction conditions, **26d** gave rise to a 69:31 mixture of **27d-A** and **-B** in 48% yield, leading to **27a-A** and **-B** through hydrolysis under basic conditions, respectively, whereas the use of AD-mix-β resulted in predominant formation of the undesired diastereomer (entries 7 and 8). The above observations led to explore the AD-mix-α-mediated reaction of **26d** at lower temperatures. When the reaction was performed at 0 ˚C with the same set of the reagents, the product selectivity for **27d-A** was slightly improved (entry 9). Remarkably, **26d** underwent slow reaction in the absence of $MeSO_2NH_2$ to give the product mixture in 52% yield, and the diastereomeric ratio could be

further enriched to 84:16 (entry 10). Additionally, a similar result was obtained by carrying out the reaction using 0.1 equiv of $(DHQ)_2PHAL$ (53%, 83:17 in entry 11).

4.7 Preparation of **C**

Having established the optimized conditions for the preparation of **27d-A**, my next objective was construction of the piperidine ring system. As shown in **Scheme 36**, the acetyl group of **27d-A** and **-B** was removed by exposure to K_2CO_3 in methanol to give the separable mixture of triols **27a-A** and **-B**, respectively.[68] After purification by silica-gel column chromatography, **27a-A** was subjected to the TBS protection-benzylation sequence, as illustrated for the preparation of **28B**, to generate **28A** in 50% yield for 3 steps. In the next step, deprotection of the TBS group with TBAF[65] and subsequent tosylation of the resulting hydroxy group with TsCl in the presence of pyridine were carried out to yield the corresponding tosylate, whose activated sulfonate group could be displaced with NaCN in DMSO to provide cyanide **29** in 80% yield for 3 steps.[69] Then, the *N*,*O*-acetonide group of **29** was cleaved upon treatment with *p*-TsOH in methanol,[70] and the released primary hydroxy group was subsequently protected as the benzyl ether to produce the key intermediate **J** in 67% yield over 2 steps. As expected, conversion of this compound into the heterocyclic hemiaminal **C** was achieved in one pot with DIBAL-H via the formation of aldehyde followed by spontaneous intramolecular cyclization with a yield of 67%. The structural identity of this product was precisely confirmed by ^1H NMR spectroscopic data, which proved to be in good agreement with those on record for intermediate of the first synthetic pathway.[36] Hence, it can be concluded that a formal total synthesis of (+)-batzellasides B was accomplished, considering that the synthetic route from **C** to the target natural product has been established previously.



Scheme 36. Preparation of **C**. *Reagents and conditions*: (a) (i) K_2CO_3, MeOH, rt, 1 h; (ii) TBSCl, Et_3N, CH_2Cl_2, rt, 24 h; (iii) BnBr, NaH, Bu_4NI, THF, rt, 3 days; 50% (3 steps); (b) (i) TBAF, THF, rt, 1.5 h; (ii) TsCl, pyridine, 0 °C to rt, 40 min; (iii) NaCN, $NaHCO_3$, DMSO, 60 °C, 8 h; 80% (3 steps); (c) (i) *p*-TsOH, MeOH, rt, 6 h; (ii) BnBr, Ag_2O, AcOEt, rt, 16 h; 67% (2 steps); (d) DIBAL-H, toluene, -78 °C, 1 h; 67%.

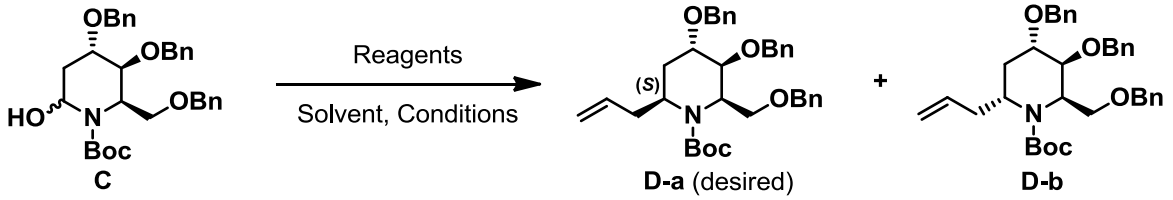
4.8 Study on stereoselective introduction of hydroxyalkyl chain at C1 position of **C**

At this point, it was suggested that the remaining challenge was to improve stereoselectivity of the introduction of hydroxyalkyl chain at C1 position of **C** associated with the construction of C1 and C8 stereocenters of the target molecule.

4.8.1 Investigation on diastereoselective allylation of **C**

In the first approach,[36] the heterocyclic hemiaminal **C** was allylated by following a protocol using allyltributylstannane ($AllylSnBu_3$) and *tert*-butyldimethylsilyl triflate (TBSOTf) at -78 °C in toluene to furnish the product **D** as a 69:31 mixture of diastereomeric isomers in 96% yield (**Table 3**, entry 1). Despite the appealing performance observed in the above synthetic process, low stereoselectivity in this reaction protocol is a major problem

associated with laborious chromatographic separation of the two stereoisomers. From the practical considerations, a more efficient synthetic method for stereoselective allylation of **C** was next explored using appropriate combination of allylic reagent and Lewis acid to produce the desired diastereomer **D-a** preferentially. The initial reaction using indium chloride ($InCl_3$) instead of TBSOTf at 0 °C in dichloromethane resulted in no substantial improvement in the stereoselectivity of the allylation, affording a 44:56 mixture of **D-a** and **D-b** in quantitative yield (entry 2). A much greater preference for the formation of **D-a** was observed in the cases where allyltrimethylsilane (AllylTMS) was used as an allylic reagent (entries 3-5). In fact, the reaction carried out with zinc chloride ($ZnCl_2$) at room temperature in toluene led to exclusive stereoselectivity for **D-a** with 98% de, albeit in low yield (24%, entry 3). Furthermore, the use of TBSOTf as a Lewis acid resulted in significant enhancement of reaction rate to give almost the same stereochemical outcome (98 and 92% de) with slightly and moderately higher yields (29 and 41%) for the periods of 2 and 3 h (entries 4 and 5), respectively. In spite of its increased susceptibility that should be discriminated from those of unsubstituted structural systems,[71] it became apparent that this multiply functionalized hemiaminal **C** is well tolerated to undergo the direct allylation with the silyl reagents. The results of the above investigations provide one particularly successful route that has the potential for allowing access to intermediate **D-a** under precise stereochemical control as well as for circumventing the purification problems related to the diastereomeric impurity in this product.



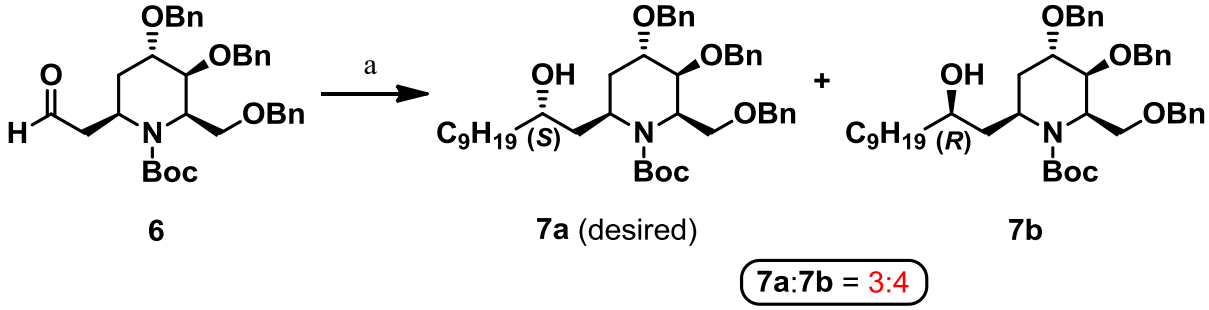
Entry	Reagents (eq.)	Solvent	Conditions	Yield of **D** %[a] (**a**:**b**)[b]
1	$AllylSnBu_3$ (3.0), TBSOTf (1.5)	toluene	-78 °C, 9 h	**96** (69:31)
2	$AllylSnBu_3$ (3.0), InCl (1.5)	CH_2Cl_2	0 °C, 0.75 h	quant. (44:56)
3	AllylTMS (4.0), $ZnCl_2$ (4.0)	toluene	rt, overnight	24 (99:1)
4	AllylTMS (4.0), TBSOTf (2.0)	CH_2Cl_2	-78 °C to -45 °C, 2 h	29 (**99:1**)
5	AllylTMS (10), TBSOTf (1.5)	toluene	-78 °C, 3 h	41 (94:6)

[a] Isolated yield. [b] Determined by ^1H NMR (300 MHz, $CDCl_3$).

Table 3. Asymmetric allylation of **C**

4.8.2 Grignard addition to **6**

In the previous synthetic approach, the C8 stereocenter has been constructed through Grignard addition to aldehyde **6** under the conditions using nonyl magnesium bromide in THF at the temperature of -78 to 0 °C. This reaction proceeded without stereocontrol to afford a 1:1 diastereomeric mixture of (8*S*)-**7a** and (8*R*)-**7b** in 90% yield. In order to improve stereoselectivity for the production of **7a**, a similar reaction in the presence of cerium chloride ($CeCl_3$) was performed (**Scheme 37**).[72] Unfortunately, reaction of **6** under these conditions predominantly formed undesired diastereomer affording mixture of **7a,b** in 63% yield with a 3:4 ratio.



Scheme 37. Grignard addition to **6**. *Reagents and conditions*: (a) $C_9H_{19}MgBr$, $CeCl_3$, THF, -78 °C, 30 min; 27% (**7a**), 36% (**7b**).

4.8.3 An alternative approach for introduction of hydroxyalkyl chain at C1 position of **C**

Due to the fact that the stereoselective construction of C8 chiral center with (*S*) configuration via Grignard reaction failed, an alternative strategy for the introduction of hydroxyalkyl chain at C1 position of **C** was pursued.

Recently, an interesting work has been reported by Kanai and co-workers presenting a highly stereoselective incorporation of ketones to cyclic hemiaminals catalyzed by copper(I)−chiral phosphine complex.[73] The process comprises three distinct steps in one pot, all of which are promoted by the chiral copper(I)-conjugated Brønsted base catalyst. Among a number of ligands examined, the highest

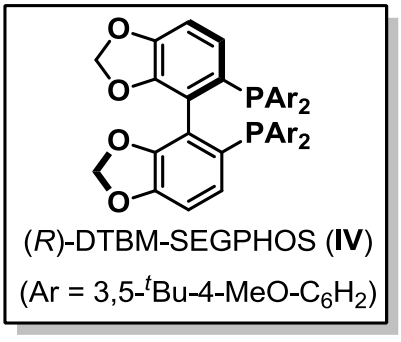
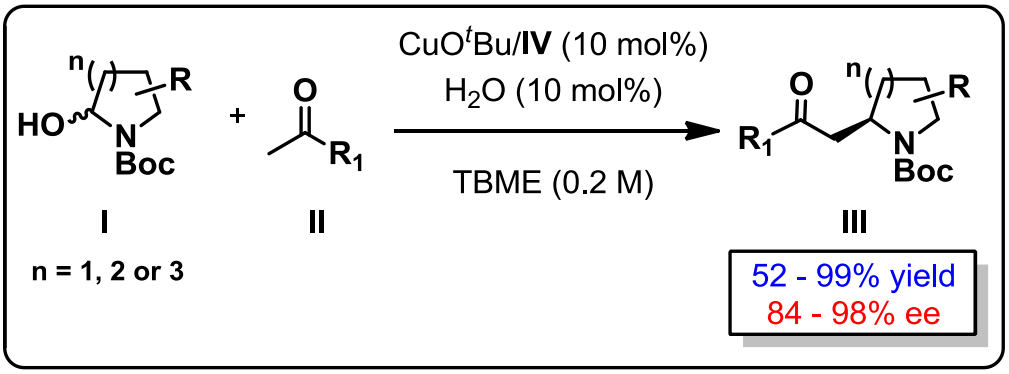


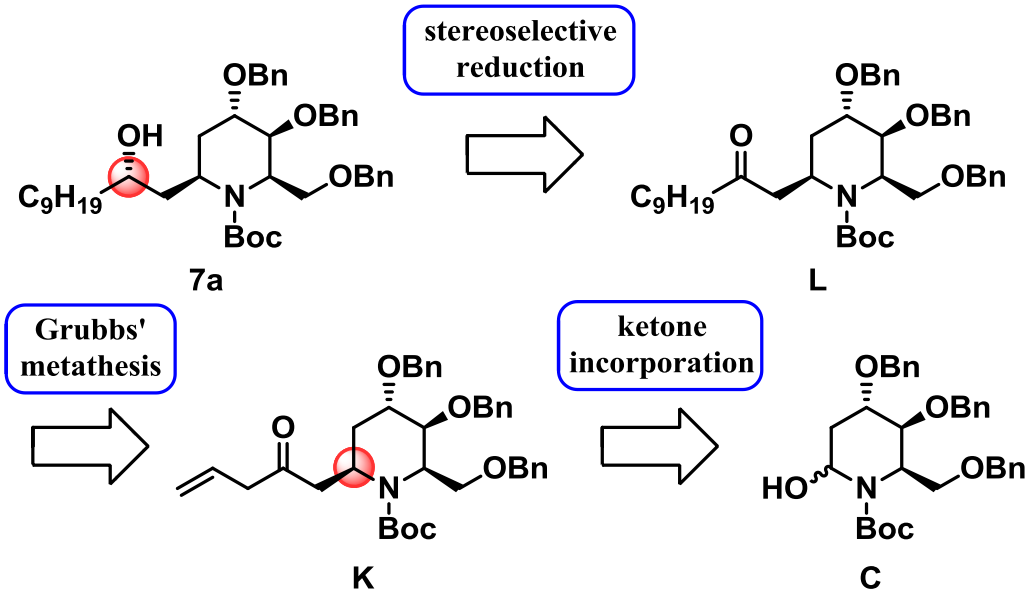
Figure 22.

reactivity and enantioselectivity was observed when (*R*)-DTBM-SEGPHOS (**IV**) (**Figure 22**) was used for this reaction. Treatment of simple *N*-heterocycles **I** bearing differing ring sizes (five-, six-, and seven-membered rings) with ketones **II** under the optimal reaction conditions furnished C1-substituted products **III** in 52-99% yields with excellent enantioselectivity of 84-99% ee (**Scheme 38**).



Scheme 38. Incorporation of ketones to heterocyclic hemiaminals developed by Kanai et al.[73]

The above development became an inspiration to explore a new synthetic strategy to (+)-batzellaside B from heterocyclic hemiaminal **C** as presented in **Scheme 39**.



Scheme 39. Retrosynthetic analysis for the introduction of hydrohyalkyl chain at the C1 position of **C**

In this approach it was assumed that the C8 stereocenter could be constructed via diastereoselective reduction of ketone **L**, which would be prepared from **C** via the above copper(I)-catalyzed reaction. Considering the fact that long-chain carbonyl compounds display lower reactivity than their simple analogues,[74] the incorporation of ketone with unsaturated 6-membered substrate **30** and further enhancement of the side chain in the resulting adduct **K** via Grubbs' metathesis was decided to be explored.

4.8.3.1 Incorporation of ketone to **C** catalyzed by copper(I)−chiral phosphine complex

The reaction of hemiaminal **C**, existing with an equilibrium of its acyclic aldehyde form, with ketone **30** was performed using catalytic complex CuO^{t}Bu (generated in situ from $CuClO_4 \cdot 4CH_3CN$ and *tert*-BuOK)[75]/**IV** in *tert*-butylmethyl ether (TBME) at room temperature (**Table 4**). According to the published procedure,[73] concentration of the aldehyde form of **C**, which undergoes an aldol reaction in the first step of the process, could be increased by addition of 0.5 equivalent of an achiral base, such as cesium carbonate (Cs_2CO_3). The initial experiment was carried out under the reported optimal conditions using 10 mol% of the chiral catalyst. However, instead of the desired C1-substituted piperidine compound **K** a ring-opened derivative **K'** (**Figure 23**) has been isolated in 11% yield along with 78% of the recovered starting material **C** after this reaction (entry 1). A similar results were obtained for the reaction under the conditions using 20 mol% of CuO^{t}Bu/**IV** which afforded **K'** in 18% together with 75% of the hemiaminal **C** (entry 2). Furtermore, preparation of 20 mol% of copper(I)−chiral phosphine complex at 50 ^oC and a subsequent reaction of **C** with ketone **30** at room temperature has not changed the reaction profile, leading only to increase production of **K'** (50% yield), while not forming the desired adduct **K** (entry 3). The formation of **K'** most likely proceeded through elimination of C3-benzoxy group in the intermediate aldol condensation product, which might be favored due to the presence of a powerful electron withdrawing group in the neighborhood.

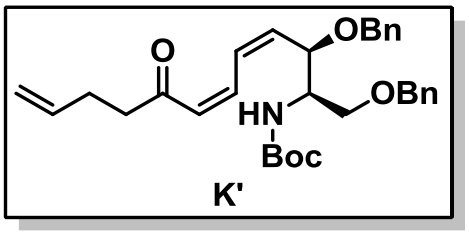
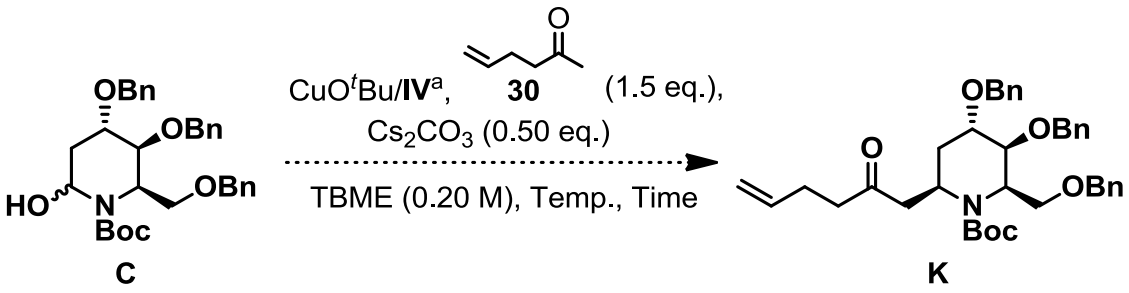


Figure 23.

From this study it can be assumed that this method is not applicable for the formation of the polisubstituted intermediade **K** due to the occurance of side reaction leading to exclusive production of acyclic compound **K'**.



C **K**

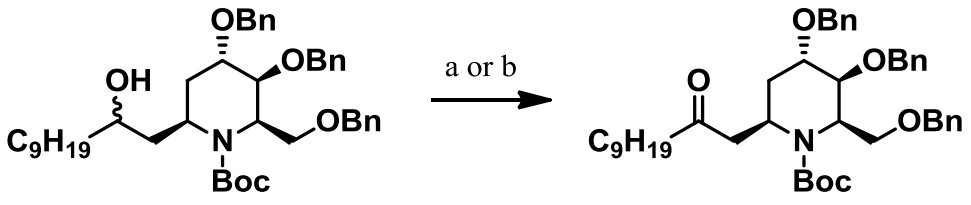
Entry	CuO^{t}Bu (eq.)	**IV** (eq.)	Temp. (°C)	Time (h)	Yield of **K** (%)	Yield of **K'** (%)	Recovery of **C** (%)
1	0.1	0.1	rt	122	0	11	78
2	0.2	0.2	rt	20	0	18	75
3	0.2	0.2	rt^a	120	0	50	> 68

[a] Copper (I)-chiral phosphine complexes were prepared at 50 °C.

Table 4. Ketone incorporation to **C**

4.8.3.2 Alternative preparation of ketone **L** and its diastereoselective reduction

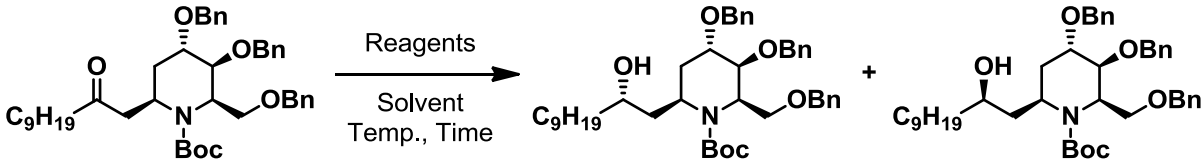
Due to the failure of the above proposed method for the preparation of ketone **L**, an alternative synthetic strategy was decided to be pursued. Oxidation of the racemic mixture of alcohols **7a,b** obtained from **C** via the previously established 4 steps procedure was considered to be the most straightforward approach to **L**. Thus, the diastereomeric mixture of **7a,b** was treated with pyridinium chlorochromate (PCC) in dichloromethane to give ketone **L** in 83% yield (**Scheme 40**).[76] The efficiency of this step was further improved by using tatrapropylammonium perruthenate (TPAP) as an oxidating agent in the presence of NMO and molecular sieves, affording **L** in a quantitative yield.[77]



7a,b (**7a**/**7b** = 1/1) **L**

Scheme 40. Preparation of **L**. *Reagents and conditions*: (a) PCC, MS 4Å, CH_2Cl_2, rt, 4 h; 83%; (b) TPAP, NMO, MS 4Å, CH_2Cl_2, rt, 30 min; quant.

Having the carbonyl compound **L** in hand, the next objective was the examination of reduction of **L** with various reducing agents to determine the optimal conditions for the stereoselective formation of alcohol **7a** (**Table 5**).[78] Accordingly, ketone **L** was reduced with DIBAL-H to provide diastereomers **7a**,**b** in a quantitative yield, with an undesired diastereoselectivity (**7a**:**7b** = 1:2) (entry 1). Remarkably, treatment of **L** with sodium borohydride ($NaBH_4$) in methanol at -20 ^oC resulted in the predominant formation of the desired disatereomer, giving **7a,b** in a quantitative yield with a ratio of 5:1 (entry 2), whereas a reaction under Luche conditions provided a 1.5:1 mixture of alcohols **7a,b** in 96% yield (entry 3). The stereoselectivity for **7a** was further improved by using lithium aluminum hydride ($LiAlH_4$) or lithium triethylborohydride ($LiEt_3BH$) in THF at -78 ^oC affording products **7a,b** with 6.6:1 ratios in 85 and 99% yields, respectively (entries 4 and 5). On the other hand, **7a,b** were obtained in only trace amount when reduction of **L** was carried out with lithium tri-*tert*-butoxy aluminum hydride ($LiAlH(O\text{-}^tBu)_3$) or sodium cyanoborohydride ($NaBH_3CN$) (entries 6 and 7).



L **7a** (desired) **7b**

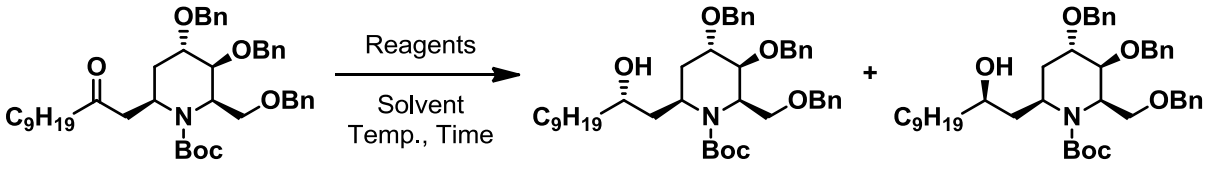
Entry	Reagents (eq.)	Solvent (M)	Temp. (^oC)	Time (h)	Yield of **7a** (%)[a]	Yield of **7b** (%)[a]	Ratio of **7a**:**7b**
1	DIBAL-H (2.0)	THF (0.15)	-78	0.5	34	66	1:2.0
2	$NaBH_4$ (2.0)	MeOH (0.15)	-20	0.5	83	17	5.0:1
3	$NaBH_4$ (1.5), $CeCl_3{\cdot}7H_2O$ (1.5)	MeOH (0.15)	-78	0.5	58	38	1.5/1
4	$LiAlH_4$ (4.0)	THF (0.010)	-78	0.5	74	11	6.6:1
5	$LiEt_3BH$ (2.0)	THF (0.010)	-78	0.1	86	13	6.6:1
6	$LiAlH(O\text{-}tBu)_3$ (6.0)	THF (0.30)	-78 ~ rt	9	trace	trace	-
7	$NaBH_3CN$ (6.0)	MeOH (0.15)	-40 ~ rt	64	trace	trace	-

[a]Isolated yield.

Table 5. Diastereoselective recduction of **L** – screening of reducing agents

After the preliminary investigation of the reducing agents for the reduction of **L** to **7** and finding of those displaying the desired selectivity, the next attempt was determination of the optimal reaction conditions by examining $NaBH_4$, $LiAlH_4$ and $LiEt_3BH$ in various solvents (**Table 6**).[78] The obtained results showed that reductions with $NaBH_4$ in ethanol at -

20 °C or *iso*-propanol at room temperature were less selective than the analogous reaction in methanol giving alcohols **7a,b** in slightly lower yields, with ratios of 3.0:1 and 1.9:1, respectively (entries 2 and 3). Furthermore, when $LiAlH_4$ reduction was carried out in TBME instead of THF at the temperature of -78 °C to rt, a mixture of **7a,b** was isolated in 36% yield (ratio 3.1:1) among with 51% recovery of starting material (entry 5), whereas no reaction was observed when this reaction was performed in toluene (entry 6). Study on the optimal solvent for reduction of **L** with $LiEt_3BH$ showed that replacement of THF with TBME led to increase of selectivity for the production of desired diastereomer, giving alcohols **7a,b** in 99% yield with the a 6.8:1 ratio (entry 8), while reactions in diethyl ether or toluene were less efficient to afford products with 3.4:1 and 4.6:1 ratios, respectively (entries 9 and 10).



L **7a** (desired) **7b**

Entry	Reagents (eq.)	Solvent (M)	Temp. (°C)	Time (h)	Yield of **7a** (%)[a]	Yield of **7b** (%)[a]	Ratio of **7a**:**7b**
1	$NaBH_4$ (2.0)	MeOH (0.15)	-20	0.5	83	17	5.0:1
2	$NaBH_4$ (4.0)	EtOH (0.15)	-20	1.5	71	24	3.0:1
3	$NaBH_4$ (4.0)	*i*-PrOH (0.15)	rt	2.5	47	25	1.9:1
4	$LiAlH_4$ (4.0)	THF (0.010)	-78	0.5	74	11	6.6:1
5[b]	$LiAlH_4$ (4.0)	TBME (0.010)	-78 to rt	23	27	9	3.1:1
6	$LiAlH_4$ (6.0)	toluene (0.010)	-78 to rt	18	N.R.	N.R.	-
7	$LiEt_3BH$ (2.0)	THF (0.010)	-78	0.1	86	13	6.6:1
8	**$LiEt_3BH$ (2.0)**	**TBME (0.010)**	**-78**	**0.1**	**86**	**13**	**6.8:1**
9	$LiEt_3BH$ (2.0)	Et_2O (0.010)	-78	0.1	75	22	3.4:1
10	$LiEt_3BH$ (2.0)	toluene (0.010)	-78	0.1	82	18	4.6:1

[a]Isolated yield. [b]The products were isolated among with the starting material (51%).

Table 6. Diastereoselective recduction of **L** – screening of solvents

4.8.3.3 Possible explanation for stereoselectivity of reduction of **L**

The observed stereoselectivity for the reduction of ketone **L** can not be explained by Cram's model due to lack of chiral α-carbon in the structure. Threfore, other effects such as stereoelectronic or steric effects should be taken under consideration.

Based on the stable chair conformation of the piperidine type precursor as determined previously, the steric effect on reduction of **L** has been studied (**Figure 24**). In this conformation carbonyl oxygen might take various positions due to a free rotation at the α-carbon. However, a conformation in which the oxygen is located in an opposite direction to the bulky C6- benzyloxymethyl group (-CH_2OBn) could be a favourable one, facilitating the access of reducing agent. In the case of ketone **L**, attack of reducing agent from the re face of carbonyl group leads to formation of the desired alcohol **7a**, whereas attack from si face gives **7b**.

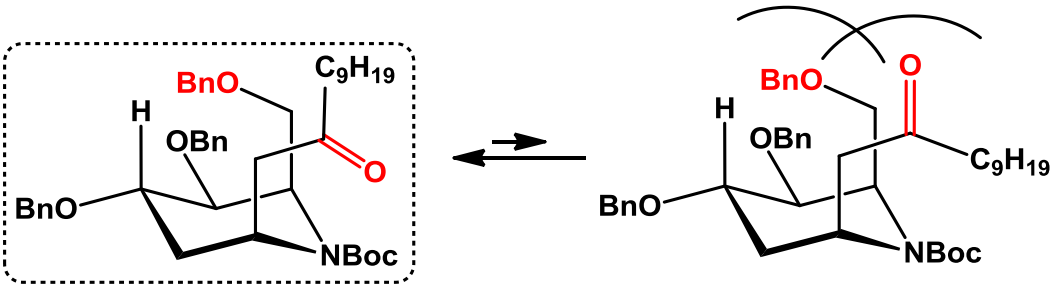


Figure 24. Favourable conformation of ketone **L** for reduction

According to the above presented results, DIBAL-H preferred attack from the si face, while the other reducing agents such as $NaBH_4$, $LiAlH_4$ and $LiEt_3BH$ favored attack from the opposite direction. This behavior could be most likely explained by stereoelectronic effect which is illustrated in **Figure 25**. Due to a high electron density on the re face of **L** associated with the presence of NBoc functionality, the relatively small molecules of $NaBH_4$, $LiAlH_4$ and $LiEt_3BH$ could coordinate to the nitrogen atom of the piperidine ring and consequently facilitate reduction from the re face. On the other hand, analogous coordination of DIBAL-H can be stericaly hindered due to the bulkiness of this reducing agent. Therefore, DIBAL-H favored attack from the less hindered si face of **L** leading to the opposite stereoselectivity than the other reducing agents. A similar behavior has been previously observed by our group in the course of synthesis of lennoxamine.[79]

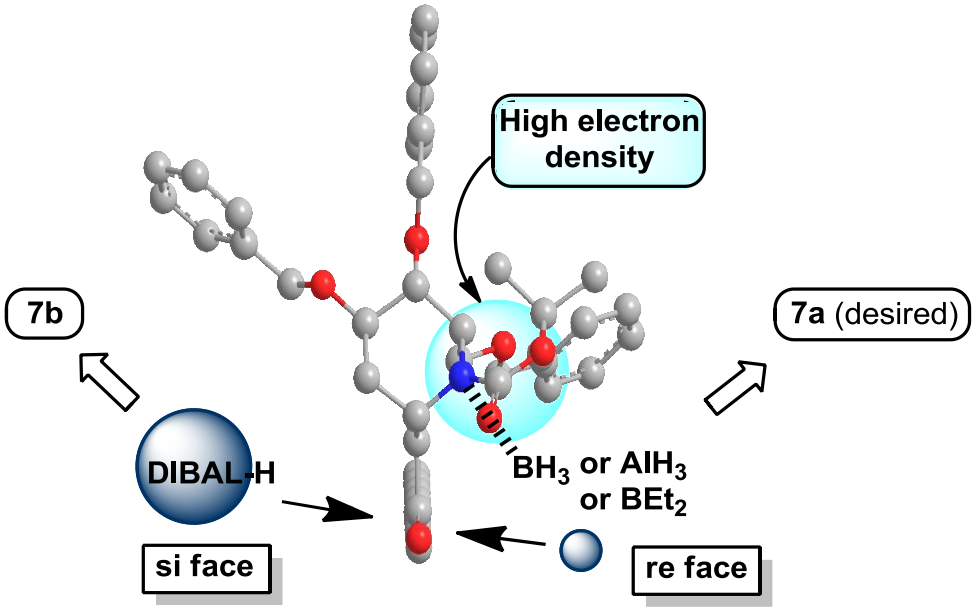
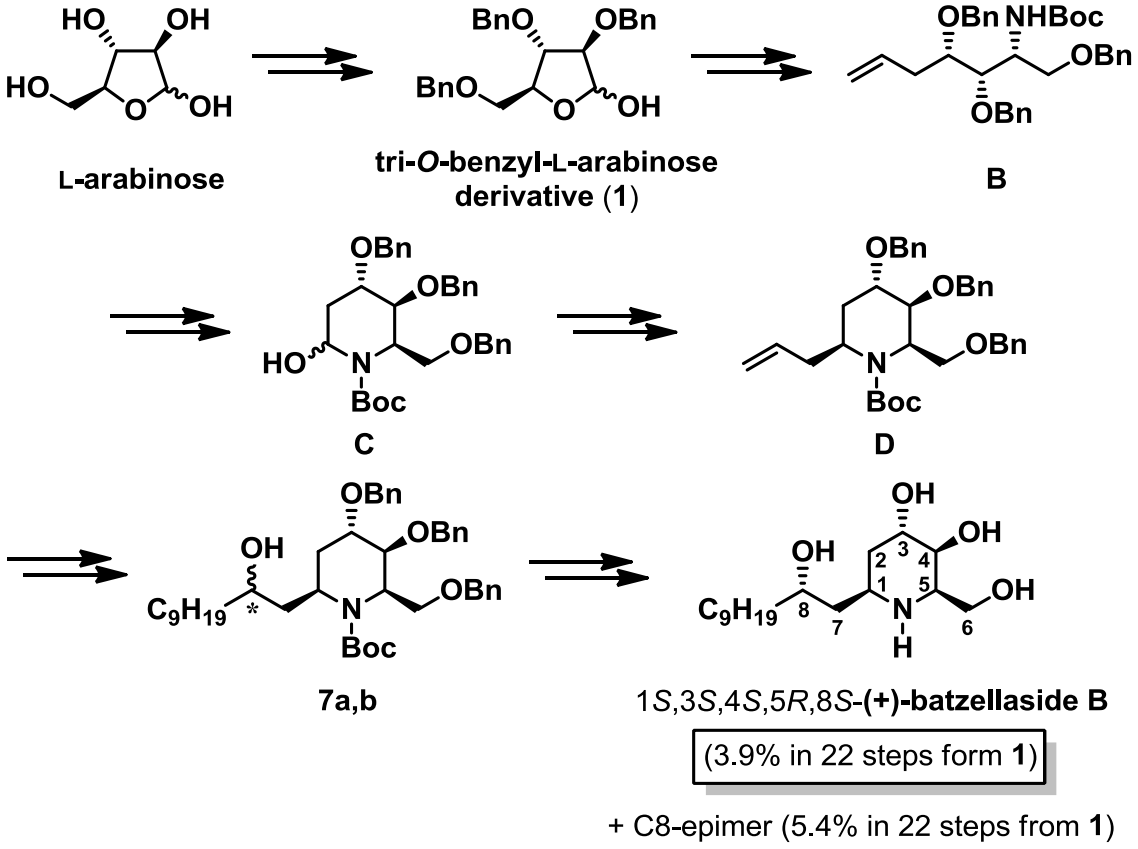


Figure 25. Possible explanation of stereoselectivity with various reducing agents

5. Summary[36, 51, 78]

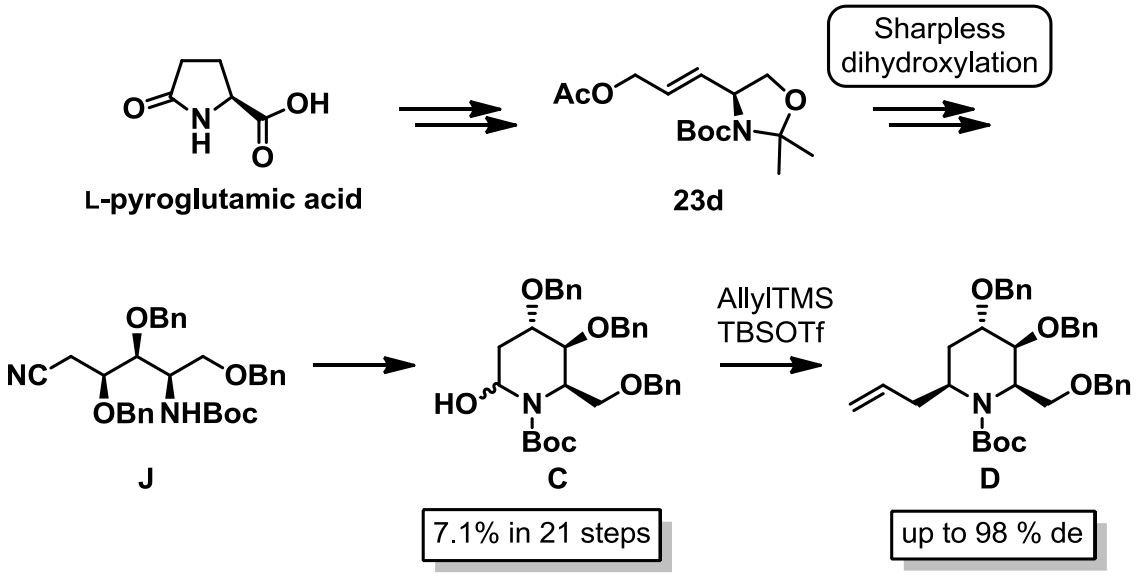
In summary, the first total synthesis of (+)-batzellaside B and its C8-epimer from tri-*O*-benzyl-L-arabinose derivative (**1**) was achieved in 22 steps with overall yields of 3.9% and 5.4%, respectively (**Scheme 41**). In the course of the synthetic studies, the absolute configurations of (+)-batzellaside B also have been unambiguously determined to be 1*S*,3*S*,4*S*,5*R*,8*S* by using spectral data, specific rotation, the modified Mosher's analysis of the synthetic intermediate prepared through the separate route, and coupling constants et al.[36, 78]



Scheme 41. Synthetic approach to (+)-batzellaside B from L-arabinose

Efforts to develop an alternative more concise synthetic pathway toward (+)-batzellaside B from L-arabinose derivative (**1**) have failed due to the side reactions occurred in the course of the synthesis of hemiaminal intermediate **C**. The effect of functional groups such as amide or benzyloxy functionalities contained in the relevant intermediates were a main factor giving rise to the side products.

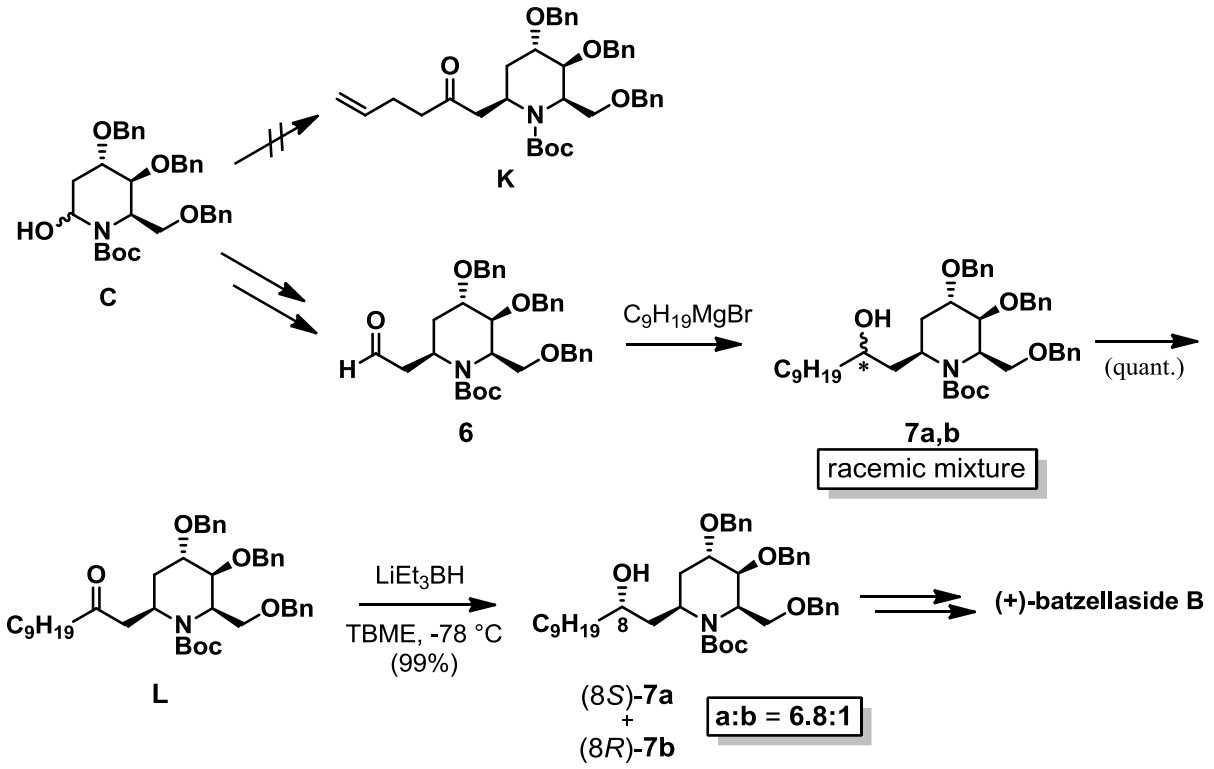
Remarkably, a new synthetic approach to (+)-batzellaside B from L-pyroglutamic acid has been developed (**Scheme 42**). Starting from this chiral material, the formal total synthesis accessible to the heterocyclic hemiaminal **C**, a key intermediate elaborated commonly in the first total synthesis, has been achieved in an efficient 21 steps protocol in 7.1% overall yield. Furthermore, the stereospecificity in the allylation of **C** at C1-position has been exemplified by performing the procedures with AllylTMS and two types of Lewis acids, which allows for simpler synthetic operation with ease of purification of the products.[50, 78]



Scheme 42. Alternative approach to (+)-batzellaside B from L-pyroglutamic acid

Efforts toward construction of C1 stereocenter through incorporation of the relevant ketone to **C** catalyzed by copper(I)−chiral phosphine complex failed to give the acyclic unsaturated ketone instead of the ring-closed product **K** (**Scheme 43**).

The stereoselective production of alcohol (8*S*)-**7a**, however, has been achieved by employing diastereoselective reduction of ketone **L**, which was quantitatively derived through oxidation from the racemic mixture of **7a,b** previously obtained by Grignard addition. The reaction performed under the conditions using $LiEt_3BH$ in TBME at -78 ^oC afforded products **7a,b** in 99% yield with a 6.8:1 ratio, allowing asymmetric access to intermediate **7a** required in the advance stage of the synthesis (**Scheme 40**).[78]



Scheme 43. Introduction of hydroxyalkyl chain at C1 position of **C**

The above studies represent the precursor works on determination of absolute configurations and total synthesis of (+)-batzellaside B,[80] which provided two alternative approaches to this natural product.[36, 51, 78]

6. Experimental section

6.1 Reagents and analytical instruments

6.1.1 Organic starting materials and reagents

Commercially available L-arabinose, *p*-methoxyphenylamine, vinylmagnesium chloride, pyridinium chlorochromate, 4.8 M aqueous solution of *N*-methylmorpholine-*N*-oxide, benzyl bromide, ceric ammonium nitrate, di-*tert*-butyl dicarbonate, triethylamine, 4-dimethylaminopyridine, ethyl chloroformate, allyl tributylstannane, *tert*-butyl dimethylsilyl triflate, nonylmagnesium bromide, (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, allyl bromide, pyridine, 1-octene, Grubbs II complex, 2-methyl-2-butene, dicyclohexylcarbodiimide, *N*-hydroxysuccinimide, *N*-*tert*-butoxycarbonyl-amide, trifluoromethanesulfonic anhydride, bis(*p*-nitrophenyl) azidophosphonate, 1,5-diazabicyclo[5.4.0]undec-5-ene, methanesulfonyl chloride, L-pyroglutamic acid, thionyl chloride, *tert*-butyldimethylsilyl chloride, imidazole, *p*-toluenesulfonic acid monohydrate, trifluoride diethyl ether complex, 2,2-dimethoxypropane, diisoplopylamine, *n*-butyl lithium (1.0 M THF solution), hexamethylphosphoric triamide, phenyl selenyl bromide, *m*-chlorobenzoic acid, AD-mix-α and β, diisobutylaluminium hydride (1.0 M toluene solution), trifluoroacetic acid, methoxymethyl chloride, acetic anhydride, $(DHQ)_2PHAL$, *p*-toluenesulfonyl chloride, allyltrimethylsilane, (*R*)-DTBM-SEGPHOS, 5-hexen-2-one (**30**) and tatrapropylammonium perruthenate were used without purification.

6.1.2 Inorganic reagents

Commercially available osmium tetroxide (0.025 M *tert*-BuOH solution), sodium periodate, sodium hydrogen sulfite, sodium borohydride, silver oxide, cerium(III) chloride heptahydrate, ammonium formate, tetrakis(triphenylphosphine)palladium, concentrated hydrochloric acid, palladium on activated carbon (10% Pd), formic acid, magnesium, palladium-activated carbon ethylenediamine complex (3.5-6.5% Pd), sodium dihydrogen phosphate dihydrate, sodium chlorite, magnesium perchlorate, potassium *tert*-butoxide,

sodium carbonate, sodium hydroxide, lithium aluminium hydride, sodium hydrogen carbonate, ruthenium (IV) oxide, sodium hydride, tetrabutylammonium iodide, methane sulfonamide, potassium carbonate, zinc chloride, cesium carbonate, lithium triethylborohydride (1.0 M THF solution), lithium tri-*tert*-butoxy aluminum hydride and sodium cyanoborohydride were used without purification.

Sodium methoxide (1.0 M in methanol) was prepared by dissolving sodium hydride in methanol.

Cerium(III) chloride ($CeCl_3$) was prepared from cerium(III) chloride heptahydrate by drying it with stirring at 140 ^oC under reduced pressure for 2 h.

Copper(I) acetonitrile perchlorate ($CuClO_4 \cdot 4CH_3CN$) was prepared via reaction of copper(II) perchlorate hexahydrate ($Cu(ClO_4)_2 \cdot 6H_2O$) and powdered copper(0) in acetonitrile according to published procedure.[81]

Sodium cyanide and indium chloride were dried before use by stirring at 120 ^oC under reduced pressure for 2 h.

6.1.3 Organic solvents

Tetrahydrofuran was dried using sodium. Toluene, dichloromethane, dimethylformamide, dimethyl sulfoxide, diethyl ether and *tert*-butyl methyl ether were dried using molecular sieves. Other solvents were used as commercially available.

6.1.4 Other

Silica gel 60N (spherical, neutral) produced by Kanto Chemical Co. was used for silica gel column chromatography. TLC plates Sieselgel $60F_{254}$ produced by Merck were used. DOWEX 50W resin (X-8, H^+ form) was used for ion exchange chromatography.

6.1.5 Analytical instruments

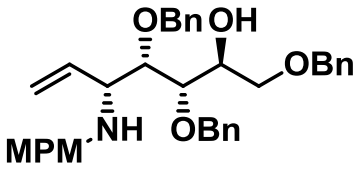
^{1}H NMR	:	JNM-AL300 (300 MHz) (Japan Electronics)
^{13}C NMR	:	JNM-AL300 (75 MHz) (Japan Electronics)
IR	:	FT/IR-4100 (JASCO)
Polarimeter	:	DIP-1000 (JASCO)
Elemental analysis	:	JM-10 (Jay Scence Lab)

6.1.6 Equipment

Low – temperature water bath	:	Science Instruments, Tokyo	PSL-1400
			PSL-1800

6.2 Synthesis of (+)-batzellaside B from L-arabinose derivative (**1**).

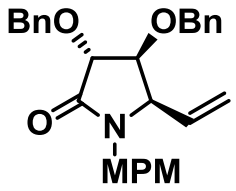
6.2.1 Synthesis and characterization of **2**



2

To a solution of **1** (2.00 g, 4.76 mmol) in toluene (20 mL) was added *p*-methoxyphenylmethylamine ($MPMNH_2$, 0.78 g, 5.66 mmol), and the resulting mixture was refluxed under stirring. After 5 h, the reaction mixture was concentrated and extracted with ethyl acetate (50 mL). The extracts were washed with 3% HCl_{aq} (20 mL) and saturated $NaHCO_{3aq}$ (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude aminal intermediate (2.09 g). To a solution of this material (2.09 g) in THF (16 mL) was added slowly vinylmagnesium chloride (10.8 mL, 14.9 mmol, 1.38 M solution in THF) at -78 °C and the resulting mixture was stirred at this temperature. After 2 h, the reaction was quenched by slow addition of saturated NH_4Cl_{aq} (15 mL) and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1 to 1/1) to yield **2** (2.18 g, 3.84 mmol, 81% for 2 steps): IR (NaCl) 2864 cm^{-1} (C-H), 1070 cm^{-1} (C=O); $[\alpha]_D^{23}$ -3.1 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.29-7.21 (m, 18H, C*H* and N*H*), 6.83 (d, *J* = 8.3 Hz, 2H, C*H*), 5.77 (m, 1H, CH_2=C*H*), 5.24-5.12 (m, 2H, CH_2=CH), 4.65 (d, *J* = 11.4 Hz, CH_2), 4.56-4.46 (m, 4H, CH_2), 4.39 (d, *J* = 11.4 Hz, CH_2), 3.94 (m, 1H, C*H*), 3.84 (m, 1H, C*H*), 3.76 (s, 3H, CH_3), 3.69-3.59 (m, 5H, CH_2 and C*H* and O*H*), 3.65 (d, *J* = 7.7 Hz, 1H, CH_2), 3.44 (d, *J* = 8.4 Hz, 1H, C*H*); ^{13}C NMR ($CDCl_3$) δ 158.9 (*C*), 138.6 (*C*), 138.3 (*C*), 138.2 (*C*H), 138.0 (*C*), 131.2 (*C*), 129.9 (*C*H), 128.4 (*C*H), 128.3 (*C*H), 128.0 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 127.4 (*C*H), 117.5 (CH_2), 113.9 (*C*H), 83.1 (*C*H), 77.1 (*C*H), 77.6 (CH_2), 73.2 (CH_2), 72.7 (CH_2), 71.8 (CH_2), 70.6 (*C*H), 59.1 (*C*H), 55.1 (CH_3), 50.0 (CH_2).

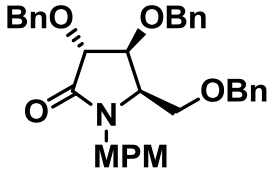
6.2.2 Synthesis and characterization of **3**



3

To a mixture containing **2** (1.61 g, 2.84 mmol) and powdered 4Å molecular sieves (MS4Å, 4.90 g) in CH_2Cl_2 (28 mL) was added pyridinium chlorochromate (PCC, 2.44 g, 11.3 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h, diluted with diethyl ether (60 mL), stirred for additional 12 h and filtrated through a pad of Celite, which was successively washed with diethyl ether (30 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/2) to yield **3** (810 mg, 1.83 mmol, 64%): IR (NaCl) 2856 cm^{-1} (C-H), 1703 cm^{-1} (C=O); $[\alpha]_D^{24}$ +176 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.43-7.23 (m, 10H, C*H*), 7.15 (dt, *J* = 9.0, 2.5 Hz, 2H, C*H*), 6.84 (dt, *J* = 9.0, 2.5 Hz, 2H, C*H*), 5.73 (m, 1H, CH_2=C*H*), 5.37 (d, *J* = 10.2 Hz, CH_2), 5.22 (d, *J* = 16.8 Hz, CH_2), 5.12 (d, *J* = 11.7 Hz, 1H, CH_2), 5.04 (d, *J* = 14.7 Hz, 1H, CH_2), 4.83 (d, *J* = 11.5 Hz, 1H, CH_2), 4.53 (d, *J* = 11.7 Hz, 1H, CH_2), 4.44 (m, *J* = 11.5 Hz, 1H, CH_2), 4.33 (dd, *J* = 7.3, 0.7 Hz, 1H, C*H*), 4.11 (m, 1H, C*H*), 3.94 (m, 1H, C*H*), 3.78 (s, 3H, CH_3), 3.66 (d, *J* = 14.7 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$) δ 170.2 (*C*), 159.2 (*C*), 137.8 (*C*), 137.4 (*C*), 132.6 (*C*H), 129.8 (*C*H), 128.4 (*C*H), 128.4 (*C*), 128.1 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 127.6 (*C*H), 120.4 (*C*H_2), 114.1 (*C*H), 79.9 (*C*H), 79.4 (*C*H), 72.7 (*C*H_2), 71.8 (*C*H_2), 59.4 (*C*H), 55.3 (*C*H_3), 43.5 (*C*H_2). Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 76.15; H, 6.51; N, 3.45.

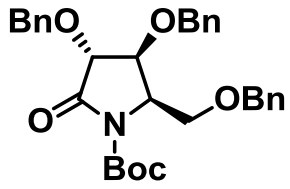
6.2.3 Synthesis and characterization of **A**



A

To a solution of **3** (281 mg, 0.633 mmol) in acetone (0.6 mL) were added *N*-methylmorpholine-*N*-oxide (NMO, 0.26 mL, 1.25 mmol, 4.8 M aqueous solution) and osmium tetroxide (OsO_4, 0.25 mL, 0.00625 mmol, 0.025 M solution in *tert*-BuOH), and the resulting mixture was stirred at room temperature. After 4 days, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude diol intermediate (302 mg). To a solution of this material (302 mg) in a mixture of THF/H_2O (1/1, 2.1 mL) was added sodium periodate ($NaIO_4$, 412 mg, 1.93 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 days, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude aldehyde intermediate (282 mg). To a solution of this material (282 mg) in methanol (3.2 mL) was added sodium borohydride ($NaBH_4$, 71.0 mg, 1.88 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 24 h, concentrated and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude alcohol intermediate (264 mg). To a solution of this material (264 mg) in DMF (0.7 mL) were added silver oxide (Ag_2O, 234 mg, 1.01 mmol) and benzyl bromide (BnBr, 345 mg, 2.02 mmol), and the resulting mixture was stirred at room temperature. After 24 h, the reaction was filtered through a pad of Celite, which was successively washed with ethyl acetate (30 mL). The filtrate was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 3/1 to 0/1) to yield **A** (0.327 g, 0.570 mmol, 90% for 4 steps): IR (NaCl) 2911 cm^{-1} (C-H), 1700 cm^{-1} (C=O); $[\alpha]_D^{24}$ +104 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.44-7.20 (m, 15H, C*H*), 7.13 (d, *J* = 8.4 Hz, 1H, C*H*), 6.82 (m, 2H, C*H*), 5.19 (d, *J* = 11.7 Hz, 1H, CH_2), 4.90 (d, *J* = 14.7 Hz, 1H, CH_2), 4.81 (d, *J* = 11.7 Hz, 1H, CH_2), 4.69-4.37 (m, 5H, CH_2 and C*H*), 4.13 (m, 1H, C*H*), 3.92 (d, *J* = 14.7 Hz, 1H, CH_2), 3.78 (s, 3H, CH_3), 3.57-3.52 (m, 3H, C*H* and CH_2); ^{13}C NMR ($CDCl_3$) δ 171.4 (*C*), 159.2 (*C*), 138.1 (*C*), 138.0 (*C*), 137.8 (*C*), 129.7 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 128.1 (*C*), 127.7 (*C*H), 127.6 (*C*H), 127.5 (*C*H), 114.0 (*C*H), 80.0 (*C*H), 79.4 (*C*H), 73.2 (*C*H_2), 72.7 (*C*H_2), 72.3 (*C*H_2), 66.0 (*C*H_2), 55.8 (*C*H), 55.2 (*C*H_3), 44.0 (*C*H_2).

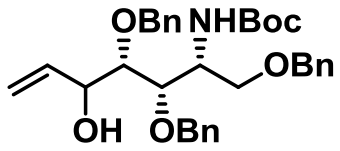
6.2.4 Synthesis and characterization of **4**



4

To a solution of **4** (667 mg, 1.16 mmol) in a mixture of MeCN/H_2O (9/1, 33 mL) was added ceric ammonium nitrate (CAN, 3.20 g, 5.83 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2.5 h, quenched by addition of water (10 mL), filtered through a pad of Celite, which was successively washed with ethyl acetate (30 mL) and extracted. The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1 to 1/2) to provide the crude lactam intermediate (436 mg). To a solution of this material (436 mg) in CH_2Cl_2 (2.6 mL) were added triethylamine (Et_3N, 158 mg, 1.56 mmol), 4-dimethylaminopyridine (DMAP, 13.0 mg, 0.104 mmol), and di-*tert*-butyl dicarbonate (Boc_2O, 454 mg, 2.08 mmol) at 0 °C, and the resulting mixture was stirred at this temperature. After 2 h, the reaction was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to yield **4** (462 mg, 0.893 mmol, 77% for 2 steps): IR (NaCl) 2871 cm^{-1} (C-H), 1717 cm^{-1} (C=O); $[\alpha]_D^{24}$ +54 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40-7.19 (m, 15H, C*H*), 5.15 (d, *J* = 11.4 Hz, 1H, CH_2), 4.75 (d, *J* = 11.4 Hz, 1H, CH_2), 4.70-4.60 (m, 3H, C*H*, CH_2), 4.49 (s, 2H, CH_2), 4.22-4.18 (m, 2H, C*H*), 3.72 (brs, 2H, CH_2), 1.50 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.0 (*C*), 149.7 (*C*), 137.9 (*C*), 137.8 (*C*), 137.7 (*C*), 128.5 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 127.8 (*C*H), 127.6 (*C*H), 127.4 (*C*H), 83.4 (*C*), 80.3 (*C*H), 77.6 (*C*H), 73.2 (*C*H_2), 72.9 (*C*H_2), 72.5 (*C*H_2), 65.3 (*C*H_2), 55.9 (*C*H), 27.9 (*C*H_3). Anal. Calcd for $C_{31}H_{35}NO_6$: C, 71.93; H, 6.82; N, 2.71. Found: C, 71.78; H, 6.71; N, 2.79.

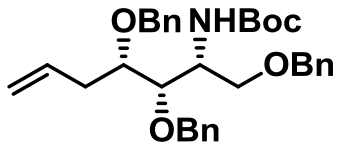
6.2.5 Synthesis and characterization of **5**



5

To a solution of **4** (342 mg, 0.661 mmol) in THF (3.3 mL) was added slowly vinylmagnesium chloride (1.8 ml, 2.64 mmol, 1.46 M solution in THF) at -78 °C, and the resulting mixture was stirred at this temperature. After 1.5 h, reaction was warmed to room temperature, quenched by slow addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) to provide the crude hemiaminal intermediate (301 mg). To a solution of this material (301 mg) and well-ground cerium chloride heptahydrate ($CeCl_3 \cdot 7H_2O$, 309 mg, 0.829 mmol) in methanol (5.5 mL) was added sodium borohydride ($NaBH_4$, 64.0 g, 1.69 mmol) at 0 °C, and the resulting mixture was stirred at this temperature. After 2 h, the reaction was quenched by addition of saturated $NaHCO_{3aq}$ (10 mL), filtered through a pad of Celite, which was successively washed with ethyl acetate (30 mL) and extracted. The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to yield **5** (292 mg, 0.533 mmol, 81% for 2 steps): IR (NaCl) 3444 cm^{-1} (N-H), 2866 cm^{-1} (C-H), 1700 cm^{-1} (C=O); $[\alpha]_D^{25}$ +18 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.30-7.19 (m, 15H, C*H*), 5.96 (m, 1H, CH_2=C*H*), 5.37 (d, *J* = 17.1 Hz, 1H, CH_2=CH), 5.18 (d, *J* = 10.5 Hz, 1H, CH_2=CH), 4.92 (d, *J* = 10.0 Hz, 1H, C*H*), 4.81-4.75 (m, 2H, CH_2), 4.61-4.41 (m, 4H, CH_2), 4.34 (brs, 1H, O*H*), 4.16 (dd, *J* = 10.0 and 8.1 Hz, 1H, C*H*), 4.02 (d, *J* = 8.4 Hz, 1H, C*H*), 3.56 (dd, *J* = 8.1, 2.0 Hz, 1H, C*H*), 3.46-3.42 (m, 2H, CH_2), 1.43 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.8 (*C*), 138.6 (*C*H), 138.4 (*C*), 138.2 (*C*), 138.1 (*C*), 128.4 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 115.7 (*C*H_2), 82.8 (*C*H), 79.6 (*C*), 77.8 (*C*H), 75.2 (*C*H_2), 75.1 (*C*H_2), 72.8 (*C*H_2), 71.9 (*C*H), 69.4 (*C*H_2), 50.0 (*C*H), 28.3 (*C*H_3). Anal. Calcd for $C_{33}H_{41}NO_6$: C, 72.37; H, 7.55; N, 2.56. Found: C, 72.16; H, 7.35; N, 2.94.

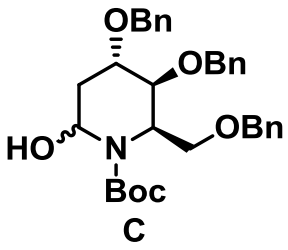
6.2.6 Synthesis and characterization of **B**



B

To a solution of **5** (303 mg, 0.553 mmol) in pyridine (0.6 mL) was added ethyl chloroformate ($ClCO_2Et$, 365 mg, 3.36 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 12 h, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to provide the crude formate ester (343 mg). To a freeze-deaerated solution of this material (73.0 mg, 0.118 mmol) and triethylamine (Et_3N, 33.0 mg, 0.326 mmol) in toluene (1.2 mL) were added well-ground ammonium formate (HCO_2NH_4, 16.6 mg, 0.263 mmol) and tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$, 7.90 mg, 0.00684 mmol) at room temperature. The resulting mixture was refluxed under stirring for 30 min, cooled to room temperature and filtered through a pad of Celite, which was successively washed with ethyl acetate (30 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 15/1) to yield **B** (54.0 g, 0.102 mmol, 86% for 2 steps): IR (NaCl) 3447 cm^{-1} (N-H), 2863 cm^{-1} (C-H), 1718 cm^{-1} (C=O); $[\alpha]_D^{24}$ +11 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32-7.20 (m, 15H, C*H*), 5.91 (m, 1H, CH_2=C*H*), 5.16 (d, *J* = 17.4 Hz, 1H, CH_2=CH), 5.09 (d, *J* = 10.5 Hz, 1H, CH_2=CH), 4.90 (d, *J* = 9.6 Hz, 1H, C*H*), 4.80 (d, *J* = 10.8 Hz, 1H, CH_2), 4.61 (s, 2H, CH_2), 4.51 (d, *J* = 11.7 Hz, 1H, CH_2), 4.47 (d, *J* = 10.8 Hz, 1H, CH_2), 4.41 (d, *J* = 11.7 Hz, 1H, CH_2), 4.10 (m, 1H, C*H*), 3.83 (dd, *J* = 7.8, 1.0 Hz, 1H, C*H*), 3.63 (m, 1H, C*H*), 3.45-3.37 (m, 2H, CH_2), 2.53 (m, 1H, CH_2), 2.31 (m, 1H, CH_2), 1.42 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.5 (*C*), 138.8 (*C*), 138.6 (*C*), 138.3 (*C*), 134.5 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 127.6 (*C*H), 117.5 (CH_2), 80.3 (*C*H), 79.4 (*C*), 78.8 (*C*H), 75.1 (CH_2), 72.9 (CH_2), 72.8 (CH_2), 69.5 (CH_2), 49.6 (*C*H), 35.1 (CH_2), 28.3 (CH_3). Anal. Calcd for $C_{33}H_{41}NO_5$: C, 74.55; H, 7.77; N, 2.63. Found: C, 74.70; H, 7.72; N, 2.98.

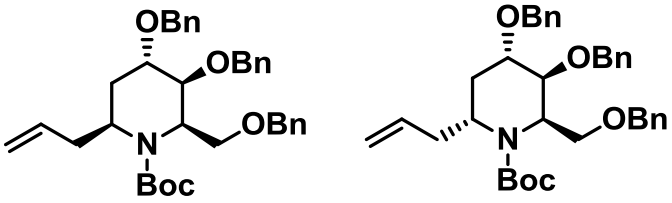
6.2.7 Synthesis and characterization of **C**



C

To a solution of **B** (296 mg, 0.556 mmol) in acetone (0.60 mL) were added *N*-methylmorpholine-*N*-oxide (NMO, 0.17 mL, 0.834 mmol, 4.8 M aqueous solution) and osmium tetroxide (OsO_4, 0.2 mL, 0.00556 mmol, 0.025 M solution in *tert*-BuOH), and the resulting mixture was stirred at room temperature. After 24 h, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude diol intermediate (314 mg). To a solution of this material (314 mg) in a mixture of THF/H_2O (1/1, 16 mL) was added sodium periodate ($NaIO_4$, 359 mg, 1.68 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3.5 h, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1 to 4/1) to yield **C** (291 mg, 0.545 mmol, 98% for 2 steps): ^{1}H NMR ($CDCl_3$) δ 7.31-7.26 (m, 15H), 5.60 (m, 1H), 4.96-4.20 (m, 8H), 3.99 (dd, *J* = 9.9, 3.0 Hz, 1H), 3.64-3.59 (m, 2H), 2.26 (m, 1H), 1.65-1.43 (m, 11H).

6.2.8 Synthesis and characterization of **D-a,b**



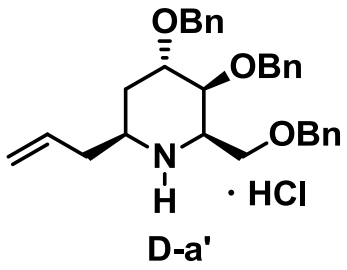
D-a (desired) **D-b**

An oven-dried round-bottom flask was purged with nitrogen and charged with a solution of **C** (94.0 mg, 0.176 mmol) in dry toluene (0.35 mL). To this solution were added allyltributylstannane ($AllylSnBu_3$, 160 mg, 0.483 mmol) and *tert*-butyldimethylsilyl triflate (TBSOTf , 112 mg, 0.424 mmol) at -78 °C, and the resulting mixture was stirred at this temperature. After 9 h, the reaction was quenched by slow addition of saturated $NaHCO_{3aq}$ (10 mL), warmed to room temperature and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was separated in part by column chromatography on silica gel for two times (eluent: hexane/ethyl acetate, 30/1, 20/1, then 15/1) to yield **D-a** (0.038 g, 0.0683 mmol, 39%), **D-b** (0.018 g, 0.0323 mmol, 18%), and a 69:31 mixture of **D-a,b** (0.038 g, 0.0683 mmol, 39%).

D-a: IR (NaCl) 1678 cm^{-1} (C=O); $[\alpha]_D^{30}$ +8.4 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 15H, C*H*), 5.69 (m, 1H, CH_2=C*H*), 4.95 (d, *J* = 9.6 Hz, 1H, CH_2=CH), 4.93 (d, *J* = 12.3 Hz, 1H, CH_2=CH), 4.90-4.43 (m, 6H, CH_2 and C*H*), 4.85 (m, 1H, C*H*), 4.18 (brs, 1H, C*H*), 3.88 (m, 1H, C*H*), 3.78 (dd, *J* = 10.5, 4.5 Hz, 1H, CH_2), 3.61-3.57 (m, 2H, C*H*, CH_2), 2.36 (m, 1H, CH_2), 2.15 (m, 1H, CH_2), 1.99 (dd, *J* = 13.5, 3.1 Hz, 1H, CH_2), 1.58-1.43 (m, 10H, CH_3 and CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3 (*C*), 138.9 (*C*), 138.7 (*C*), 138.5 (*C*), 136.2 (*C*H), 128.4 (*C*H), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.5 (*C*H), 127.4 (*C*H), 116.9 (*C*H_2), 80.9 (*C*H), 80.0 (*C*), 73.0 (*C*H), 72.9 (*C*H_2), 72.9 (*C*H_2), 72.5 (*C*H_2), 69.7 (*C*H_2), 52.5 (*C*H), 50.4 (*C*H), 39.1 (*C*H_2), 31.9 (*C*H_2), 28.3 (*C*H_3). Anal. Calcd for $C_{35}H_{43}NO_5$: C, 75.37; H, 7.77; N, 2.51. Found: C, 75.66; H, 7.94; N, 2.90.

D-b: IR (NaCl) 1684 cm^{-1} (C=O); $[\alpha]_D^{24}$ +50 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 15H, C*H*), 5.76 (m, 1H, CH_2=C*H*), 5.07-5.01 (m, 2H, CH_2=CH), 4.67-4.49 (m, 6H, CH_2), 4.31 (brs, 1H, C*H*), 3.96 (t, *J* = 6.0 Hz, 1H, C*H*), 3.87-3.77 (m, 3H, C*H*, CH_2), 3.66 (dd, *J* = 9.9 and 3.9 Hz, 1H, CH_2), 2.55-2.32 (m, 2H, CH_2), 2.18 (dt, *J* = 14.8, 6.0 Hz, 1H, CH_2), 1.87 (dt, *J* = 14.8, 2.4 Hz, 1H, CH_2), 1.44 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (*C*), 138.9 (*C*), 138.6 (*C*), 136.0 (*C*H), 128.3 (*C*H), 127.6 (*C*H), 127.5 (*C*H), 127.4 (*C*H), 117.2 (*C*H_2), 79.8 (*C*), 79.2 (*C*H), 76.8 (*C*H), 73.0 (*C*H_2), 72.2 (*C*H_2), 71.1 (*C*H_2), 68.5 (*C*H_2), 52.3 (*C*H), 51.0 (*C*H), 39.7 (*C*H_2), 28.4 (*C*H_3), 28.2 (*C*H_2). Anal. Calcd for $C_{35}H_{43}NO_5$: C, 75.37; H, 7.77; N, 2.51. Found: C, 75.38; H, 7.75; N, 2.84.

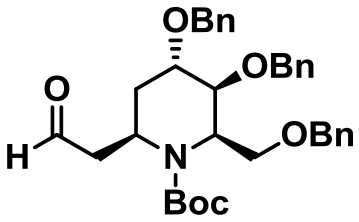
6.2.9 Synthesis and characterization of **D-a'**



D-a'

To a solution of **D-a** (57.3 mg, 0.103 mmol) in methanol (0.50 mL) was added conc HCl (ten drops) at 0 °C, and the resulting mixture was stirred at this temperature. After 2 h, the reaction was filtered through a pad of Celite, which was successively washed with methanol (15 mL) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: $CHCl_3$/methanol, 30/1) to yield **D-a'** (38.0 mg, 0.0833 mmol, 81%): ^{1}H NMR ($CDCl_3$) δ 7.37-7.21 (m, 15H, C*H*), 5.75 (m, 1H, CH_2=C*H*), 5.15-5.03 (m, 2H, CH_2=CH), 4.52-4.36 (m, 6H, CH_2), 3.66 (m, 1H, C*H*), 3.55 (dd, *J* = 8.5, 8.2 Hz, 1H, C*H*), 3.42- 3.28 (m, 3H, C*H* and *CH*$_2$), 2.96 (m, 1H, C*H*), 2.28-2.04 (m, 4H, C*H* and CH_2), 1.79 (t, *J* = 13.8, 2.8 Hz, 1H, CH_2), 1.56 (ddd, *J* = 13.8, 11.7, 2.7 Hz, 1H, CH_2).

6.2.10 Synthesis and characterization of **6**

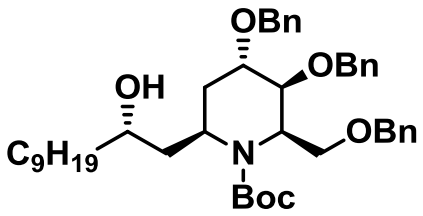


6

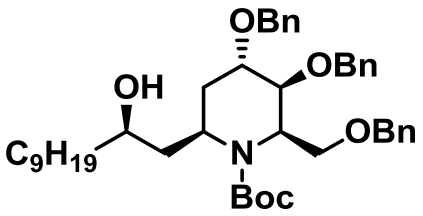
To a solution of **D-a** (68.0 mg, 0.122 mmol) in a mixture of acetone/H_2O (3/2, 0.5 mL) were added *N*-methylmorpholine-*N*-oxide (NMO, 0.080 mL, 0.384 mmol, 4.8 M aqueous solution) and osmium tetroxide (OsO_4, 0.12 mL, 0.00300 mmol, 0.025 M solution in *tert*-BuOH), and the resulting mixture was stirred at room temperature. After 24 h, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered

and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1 to 1/2) to provide the crude diol intermediate (72.0 mg). To a solution of this material (72.0 mg) in a mixture of THF/H_2O (1/1, 3.6 mL) was added sodium periodate ($NaIO_4$, 79.0 mg, 0.369 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 4 h, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/7) to yield **6** (62.0 mg, 0.111 mmol, 91% for 2 steps): ^{1}H NMR ($CDCl_3$) δ 9.66 (t, *J* = 2.0 Hz, 1H, C*H*O), 7.34-7.30 (m, 15H, C*H*), 4.80-4.48 (m, 8H, CH_2 and C*H*), 3.95 (m, 1H, C*H*), 3.73-3.61 (m, 3H, CH_2 and C*H*), 2.83 (ddd, *J* = 16.2, 5.7, 2.0 Hz, 1H, CH_2), 2.54 (ddd, *J* = 16.2, 8.0, 2.0 Hz, 1H, CH_2), 1.88 (m, 1H, CH_2), 1.71 (m, 1H, CH_2), 1.43 (s, 9H, CH_3).

6.2.11 Synthesis and characterization of **7a,b**



7a (desired)



7b

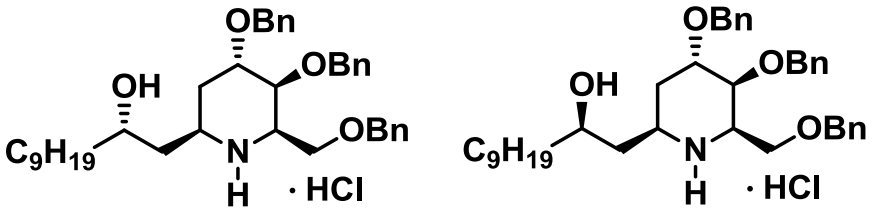
An oven-dried round-bottom flask was purged with nitrogen and charged with a solution of **6** (52.0 mg, 0.0929 mmol) in THF (0.30 mL). To this solution was added slowly nonylmagnesium bromide (0.50 mL, 0.500 mmol, 1.0 M solution in THF) at -78 °C. The resulting mixture was warmed to 0 °C under stirring over a period of 4.5 h, quenched by slow addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **7a** (29.0 mg, 0.0422 mmol, 45%) and **7b** (29.0 mg, 0.0422 mmol, 45%).

7a: IR (NaCl) 2926 cm^{-1} (C-H), 1685 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.32-7.26 (m, 15H, C*H*), 4.77-4.45 (m, 7H, CH_2 and C*H*), 4.30 (m, 1H, C*H*), 3.89-3.57 (m, 4H, CH_2 and C*H*), 3.46 (brs, 1H, C*H*), 1.89 (m, 1H, CH_2), 1.69-1.26 (m, 28H, CH_2 and CH_3), 0.88 (t, *J* = 6.6 Hz,

3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 155.8 (*C*), 138.8 (*C*), 138.6 (*C*), 138.2 (*C*), 128.4 (*C*H), 128.3 (*C*H), 127.9 (*C*H), 127.7 (*C*H), 127.6 (*C*H), 80.8 (*C*H), 80.5 (*C*), 73.2 (*C*H), 73.0 (*C*H$_2$), 72.6 (*C*H$_2$), 70.1 (*C*H), 68.9 (*C*H$_2$), 48.3 (*C*H), 37.9 (*C*H$_2$), 34.1 (*C*H$_2$), 31.8 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.3 (*C*H$_2$), 28.2 (*C*H$_3$), 25.6 (*C*H$_2$), 22.6 (*C*H$_2$), 14.0 (*C*H$_3$).

7b: ^{1}H NMR ($CDCl_3$) δ 7.33-7.25 (m, 15H, C*H*), 4.80-4.45 (m, 8H, C*H*$_2$ and C*H*), 3.89-3.73 (m, 2H, C*H*$_2$, C*H*), 3.60-3.52 (m, 3H, C*H*$_2$ and C*H*), 1.96-1.70 (m, 3H, C*H*$_2$), 1.40-1.24 (m, 26H, C*H*$_2$ and C*H*$_3$), 0.87 (t, *J* = 6.8 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 150 (C) 138.9 (*C*), 138.5 (*C*), 138.3 (*C*), 128.4 (*C*H), 128.3 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 127.6 (*C*H), 127.5 (*C*H), 81.0 (*C*), 80.7 (*C*H), 73.8 (*C*H), 73.3 (*C*H$_2$), 73.0 (*C*H$_2$), 72.4 (*C*H$_2$), 69.4 (*C*H$_2$), 67.2 (*C*H), 53.5 (*C*H), 47.0 (*C*H), 36.8 (*C*H$_2$), 35.0 (*C*H$_2$), 31.8 (*C*H$_2$), 29.8 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.3 (*C*H$_2$), 28.1 (*C*H$_3$), 25.9 (*C*H$_2$), 22.6 (*C*H$_2$), 14.0 (*C*H$_3$). Anal. Calcd for $C_{43}H_{61}NO_6$: C, 75.07; H, 8.94; N, 2.04. Found: C, 75.17; H, 8.63; N, 2.30.

6.2.12 Synthesis and characterization of **8a,b**



8a (desired) **8b**

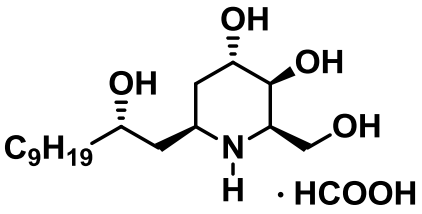
The synthesis of **8b** was achieved by the following synthetic procedures. To a solution of **7b** (22.0 g, 0.0320 mmol) in methanol (0.30 mL) was added conc. HCl (4 drops), and the resulting mixture was stirred at room temperature. After 12 h, the reaction was quenched by addition of saturated $NaHCO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified twice by column chromatography on silica gel (eluent: hexane/chloroform/methanol, 10/8/1) to yield **8b** (17.0 mg, 0.0289 mmol, 90%). Following these procedures with **7a** afforded **8a** (32.0 mg, 0.0544 mmol, 84%).

8a: ^{1}H NMR ($CDCl_3$) δ 7.36-7.20 (m, 15H, C*H*), 4.53-4.41 (m, 6H, C*H*$_2$), 3.81 (m, 1H, C*H*), 3.74 (m, 1H, C*H*), 3.58 (d, *J* = 3.0 Hz, 1H, C*H*), 3.46-3.32 (m, 3H, C*H* and C*H*$_2$), 3.14 (m, 1H, C*H*), 1.69 (dt, *J* = 14.1, 2.5 Hz, 1H, C*H*$_2$), 1.57-1.11 (m, 19H, C*H*$_2$), 0.87 (t, *J* = 6.8 Hz, 3H,

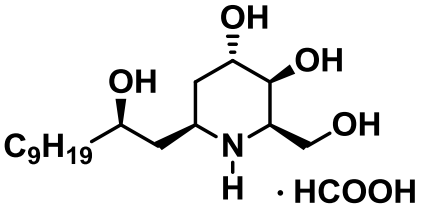
C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 138.6 (*C*), 138.4 (*C*), 138.3 (*C*), 128.4 (*C*H), 127.8 (*C*H), 127.6 (*C*H), 127.5 (*C*H), 73.2 (*C*H$_2$), 73.1 (*C*H), 72.8 (*C*H), 72.6 (*C*H$_2$), 71.6 (*C*H), 71.0 (*C*H$_2$), 69.8 (*C*H$_2$), 53.8 (*C*H), 52.5 (*C*H), 42.0 (*C*H$_2$), 38.0 (*C*H$_2$), 33.6 (*C*H$_2$), 31.8 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.2 (*C*H$_2$), 25.3 (*C*H$_2$), 22.6 (*C*H$_2$), 14.0 (*C*H$_3$).

8b: $[\alpha]_D^{25}$ +13 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35-7.19 (m, 15H, C*H*), 4.60-4.38 (m, 6H, C*H*$_2$), 3.93-3.85 (m, 1H, C*H*), 3.70-3.60 (m, 8H, C*H*$_2$, C*H*, O*H* and N*H*), 1.88-1.25 (m, 20H, C*H*$_2$), 0.87 (t, *J* = 6.6 Hz, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 138.3 (*C*), 138.1 (*C*), 128.5 (*C*H), 128.4 (*C*H), 128.0 (*C*H), 127.9 (*C*H), 127.8 (*C*H), 127.5 (*C*H), 73.4 (*C*H$_2$), 72.6 (*C*H$_2$), 72.1 (*C*H), 71.8 (*C*H), 71.0 (*C*H$_2$), 69.4 (*C*H), 54.2 (*C*H), 48.6 (*C*H), 40.1 (*C*H$_2$), 37.4 (*C*H$_2$), 31.8 (*C*H$_2$), 31.0 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.2 (*C*H$_2$), 25.9 (*C*H$_2$), 22.6 (*C*H$_2$), 14.0 (*C*H$_3$). Anal. Calcd for $C_{38}H_{53}NO_4$: C, 77.64; H, 9.09; N, 2.38. Found: C, 77.53; H, 9.17; N, 2.78.

6.2.13 Synthesis and characterization of (+)-batzellaside B (**9a**) and its C8-epimer **(9b**)



(+)-Batzellaside B (**9a**)



C-8 epimer (**9b**)

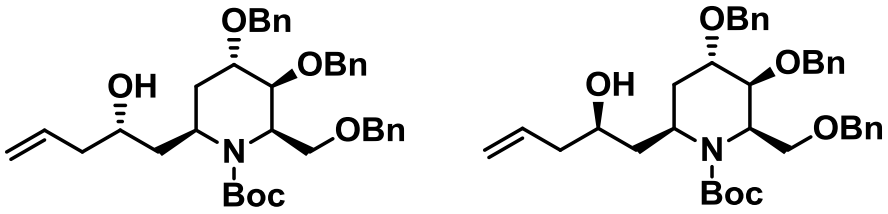
The synthesis of **9b** was achieved by the following synthetic procedures. To a solution of **8b** (39.0 g, 0.0663 mmol) in methanol (2.2 mL) were added conc. HCl (five drops) and 10% palladium-activated carbon (Pd/C, catalytic amount). The resulting mixture was hydrogenated at room temperature for 11 days and filtered through a pad of Celite, which was successively washed with methanol (20 mL). The filtrate was concentrated in vacuo, the residue was purified by column chromatography on DOWEX 50W resin (X-8, H+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with a mixture of 1% v/v formic acid-methanol at room temperature and concentrated in vacuo to yield **9b** (19.0 mg, 0.0599 mmol, 90%). Following these procedures with **8a** afforded **9a** (12.0 mg, 0.0378 mmol, 70%).

9a: $[\alpha]_D^{23}$ +9.3 (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 3.91 (q, *J* = 3.0 Hz, 1H, C*H*), 3.86-3.75 (m, 3H, C*H*$_2$ and C*H*), 3.65-3.49 (m, 2H, C*H*), 2.01 (ddd, *J* = 14.7, 13.5, 2.4 Hz, 1H, C*H*$_2$),

1.83 (dt, *J* = 14.4, 3.0 Hz, 1H, C*H*$_2$), 1.76-1.64 (m, 2H, C*H*$_2$), 1.46 (brs, 2H, C*H*$_2$), 1.30 (brs, 14H, C*H*$_2$), 0.90 (t, *J* = 6.8 Hz, 3H, C*H*$_3$); ^{13}C NMR (CD_3OD) δ 72.2 (*C*H), 67.5 (*C*H), 67.3 (*C*H), 61.0 (*C*H$_2$), 58.6 (*C*H), 53.6 (*C*H), 39.6 (*C*H$_2$), 39.6 (*C*H$_2$), 33.2 (*C*H$_2$), 32.7 (*C*H$_2$), 30.9 (*C*H$_2$), 30.8 (*C*H$_2$), 30.8 (*C*H$_2$), 30.6 (*C*H$_2$), 26.4 (*C*H$_2$), 23.8 (*C*H$_2$), 14.5 (*C*H$_3$). Anal. Calcd for $C_{18}H_{37}NO_6$: C, 59.48; H, 10.26; N, 3.85. Found: C, 59.74; H, 9.97; N, 4.06.

9b: $[\alpha]_D^{23}$ +4.7 (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD) δ 3.92-3.77 (m, 5H, C*H*$_2$ and C*H*), 3.63 (brs, 1H, C*H*), 3.50 (t, *J* = 6.5 Hz, 1H, C*H*), 2.12 (dt, *J* = 13.6, 2.0 Hz, 1H, C*H*$_2$), 1.95-1.81 (m, 2H, C*H*$_2$), 1.68 (m, 1H, C*H*$_2$), 1.47 (brs, 2H, C*H*$_2$), 1.31 (brs, 14H, C*H*$_2$), 0.87 (t, *J* = 6.8 Hz, 3H, C*H*$_3$); ^{13}C NMR (CD_3OD) δ 69.8 (*C*H), 67.3 (*C*H), 61.1 (*C*H$_2$), 58.2 (*C*H), 51.4 (*C*H), 39.5 (*C*H$_2$), 38.5 (*C*H$_2$), 33.2 (*C*H$_2$), 32.1 (*C*H$_2$), 30.9 (*C*H$_2$), 30.8 (*C*H$_2$), 30.6 (*C*H$_2$), 26.8 (*C*H$_2$), 23.8 (*C*H$_2$), 14.5 (*C*H$_3$). Anal. Calcd for $C_{18}H_{37}NO_6$: C, 59.48; H, 10.26; N, 3.85. Found: C, 59.36; H, 9.93; N, 4.20.

6.2.14 Synthesis and characterization of **10a,b**



10a (more polar) **10b** (less polar)

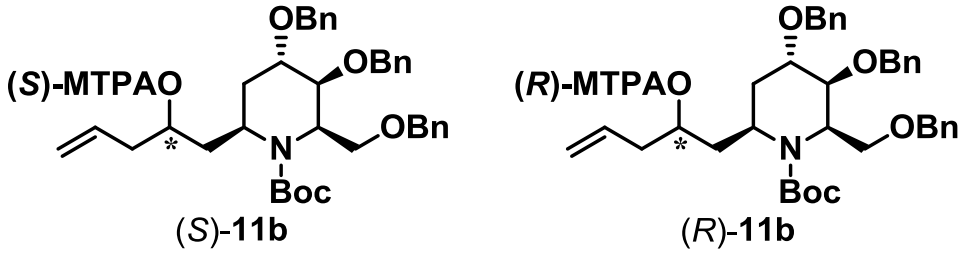
To a solution of **6** (12.5 mg, 0.0208 mmol) and allyl bromide (9.0 μL, 0.104 mmol) in THF (1.0 mL) placed in an oven-dried round-bottom flask, purged with nitrogen, were added magnesium turnings (2.50 mg, 0.104 mmol) at -40 ^{o}C, and the resulting mixture was stirred at this temperature. After 1 h, the reaction was warmed to -30 °C, stirred for additional 2 h, quenched by addition of saturated NH_4Cl_{aq} (5.0 mL) and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to yield **10a** (3.40 mg, 0.00565 mmol, 27%) and **10b** (7.30 mg, 0.0121 mmol, 58%).

10a: ^{1}H NMR ($CDCl_3$) δ 7.35-7.24 (m, 15H, C*H*), 5.74 (m, 1H, C*H*), 5.07-5.02 (m, 2H, C*H*$_2$), 4.78-4.42 (m, 8H, C*H* and C*H*$_2$), 4.33 (m, 1H, C*H*), 3.85 (m, 1H, C*H*), 3.74 (dd, *J* = 10.2, 4.1

Hz, CH_2), 3.66-3.51 (m, 3H, CH_2 and C*H*), 2.19-2.11 (m, 2H, CH_2), 1.70-1.55 (m, 3H, CH_2), 1.41 (s, 9H, CH_3).

10b: ^{1}H NMR ($CDCl_3$) δ 7.36-7.24 (m, 15H, C*H*), 5.78 (m, 1H, C*H*), 5.06-5.00 (m, 2H, CH_2), 4.79-4.44 (m, 8H, C*H* and CH_2), 3.89-3.50 (m, 5H, CH_2 and C*H*), 2.24 (m, 1H, CH_2), 2.11 (m, 1H, CH_2), 1.98-1.69 (m, 3H, CH_2), 1.48-1.25 (m, 10H, CH_2 and CH_3).

6.2.15 Synthesis and characterization of (*S*)- and (*R*)-**11b**



(*S*)-**11b** (*R*)-**11b**

The synthesis of (*S*)-**11b** was achieved by the following synthetic procedures. To a solution of **10b** (3.50 mg, 0.00582 mmol) in pyridine (0.30 mL) was added (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPA-Cl, 40.0 mg, 0.158 mmol), and the resulting mixture was stirred at room temperature. After 24 h, pyridine was removed azeotropically by using toluene (1.0 mL) and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1 to 3/1) to yield (*S*)-**11b** (2.20 mg, 0.00269 mmol, 46%). Following these procedures with **10b** (3.80 mg, 0.00631 mmol) and (*S*)-MTPA-Cl (40.0 mg, 0.158 mmol) afforded (*R*)-**11b** (3.80 mg, 0.00513 mmol, 81%) after the reaction time of 5 days. It is worth noticing that complete conversion of both diastereomers was achieved, thus demonstrating that no kinetic resolution occurred during the reaction. Moreover, it was checked that the composition of the diastereomeric mixture of Mosher esters remains unchanged after the chromatographic purification.

(*S*)-**11b**: ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 2H, C*H*), 7.40-7.23 (m, 18H, C*H*), 5.54 (ddt, *J* = 17.4, 10.0, 7.2 Hz, 1H, C*H*), 5.04 (quint. *J* = 5.9 Hz, C*H*), 4.97-4.90 (m, 2H, CH_2), 4.76-4.23 (m, 8H, C*H* and CH_2), 3.87 (dt, *J* = 6.7, 4.0 Hz, 1H, C*H*), 3.72 (dd, *J* = 10.5, 4.6 Hz, 1H, CH_2), 3.60-3.49 (m, 5H, CH_2, C*H* and CH_3), 2.42-2.24 (m, 2H, CH_2), 2.09 (dd, *J* = 13.6, 4.0 Hz, 1H, CH_2), 1.93-1.18 (m, 2H, CH_2), 1.58 (m, 1H, CH_2), 1.42 (s, 9H, CH_3).

(*R*)-**11b**: ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 2H, C*H*), 7.39-7.25 (m, 18H, C*H*), 5.67 (m, 1H, C*H*),

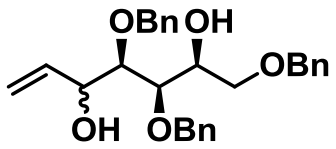
5.11-5.01 (m, 3H, C*H* and CH_2), 4.90-4.56 (m, 5H, C*H* and CH_2), 4.46 (d, *J* = 11.3 Hz, 1H, CH_2), 4.31 (d, *J* = 11.3 Hz, 1H, CH_2), 3.83 (m, 1H, C*H*), 3.70 (dd, *J* = 10.5, 4.7 Hz, 1H, CH_2), 3.56-3.44 (m, 5H, CH_2, C*H* and CH_3), 2.50-2.30 (m, 2H, CH_2), 2.05-1.73 (m, 3H, C*H* and CH_2), 1.59 (m, 1H, CH_2), 1.42 (s, 9H, CH_3).

6.2.16 Transformation of **10a** to **7a**

To a freeze-deaerated solution of **10a** (3.40 mg, 0.00570 mmol) and 1-octene (0.018 mL, 0.115 mmol) in toluene (1.0 mL) was added (benzylidene)bis(tricyclohexylphosphine)ruthenium dichloride (Grubbs II complex, 1.00 mg), and the resulting mixture was stirred at room temperature. After 4.5 h, the reaction mixture was subjected to separation by column chromatography on silica gel for two times (eluent for the first setup: hexane/ethyl acetate, 20/1 to 1/1, eluent for the second setup: hexane/ethyl acetate, 7/1 to 3/1) to provide the crude olefinic intermediate (4.70 mg). To a solution of this material (4.70 mg) in methanol (1.0 mL) was added palladium-activated carbon ethylenediamine complex (Pd/C(en), 3.5-6.5% Pd, 8.00 mg), and the resulting mixture was hydrogenated at room temperature. After 12 h, the reaction was filtered through a pad of Celite, which was successively washed with methanol (10 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 4/1) to yield **7a** (4.70 mg, 0.00349 mmol, 61% for 2 steps). The product identity was unambiguously established, with the same R_f values determined using analytical thin layer chromatography (TLC), by comparison with the ^{1}H NMR spectrum measured for **7a** synthesized during the course of the total synthesis.

6.3 Efforts toward alternative synthesis of (+)-batzellaside B from L-arabinose derivative (**1**).

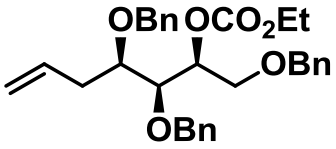
6.3.1 Synthesis and characterization of **12**



12

To a solution of **1** (140 mg, 0.333 mmol) in THF (5.6 mL) was added slowly vinylmagnesium chloride (0.91 mL, 1.33 mmol, 1.38 M solution in THF) at -78 °C. The resulting mixture was warmed to 0 °C under stirring over a period of 1 h, quenched by slow addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) to yield **12** (143 mg, 0.318 mmol, 96%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.20 (m, 15H, C*H*), 5.94 and 5.91 (diastereomers, dq, *J* = 17.1, 5.4 Hz, 1H, C*H*), 5.41 and 5.33 (diastereomers, dt, *J* = 17.1, 1.5 Hz, 1H, CH_2), 5.23 and 5.18 (diastereomers, dt, *J* = 10.5, 1.5 Hz, 1H, CH_2), 4.72-4.48 (m, 6H, CH_2), 4.40 (brs, 1H, C*H*), 4.06 (brs, 1H, O*H*), 3.90-3.50 (m, 4H, C*H* and CH_2), 3.05-2.95 (brs, 2H, C*H* and O*H*).

6.3.2 Synthesis and characterization of **13**

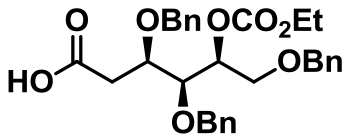


13

To a solution of **12** (313 mg, 0.296 mmol) and 4-dimethylaminopyridine (DMAP, 3.62 mg, 0.0296 mmol) in pyridine (0.85 mL) was added ethyl chloroformate ($ClCO_2Et$, 385 mg, 3.55 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 4.5 h,

quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to provide the crude formate ester (170 mg). To a freeze-deaerated solution of this material (16.7 mg), triethylamine (Et_3N, 8.56 mg, 0.0846 mmol) and well-ground ammonium formate (HCO_2NH_4, 3.90 mg, 0.0620 mmol) in toluene (0.30 mL) was added tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$, 3.30 mg, 0.00282 mmol) and the resulting mixture was stirred at 80 ^oC. After 30 min, the reaction was cooled to room temperature and filtered through a pad of Celite, which was successively washed with ethyl acetate (20 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **13** (13.9 mg, 0.0275 mmol, 94% for 2 steps) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.20 (m, 15H, C*H*), 5.84-5.69 (m, 1H, C*H*), 5.15-5.00 (m, 3H, C*H* and CH_2), 4.73-4.41 (m, 6H, CH_2), 4.16 (dd, *J* = 7.2, 1.8 Hz, 2H, CH_2), 3.88 (dd, *J* = 11.1, 3.0 Hz, 1H, C*H*), 3.83-3.75 (m, 2H, CH_2), 3.63 (dt, *J* = 6.3, 4.2 Hz, 1H, C*H*), 2.43 (t, *J* = 6.6 Hz, 2H, CH_2), 1.28 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9 (*C*), 138.5 (*C*), 138.4 (*C*), 138.3 (*C*), 134.8 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 128.3 (*C*H), 128.3 (*C*H), 127.9 (*C*H), 127.9 (*C*H), 127.8 (*C*H), 127.8 (*C*H), 117.8 (*C*H_2), 79.2 (*C*H), 79.1 (*C*H), 74.6 (*C*H_2), 73.3 (*C*H_2), 72.8 (*C*H_2), 68.6 (*C*H_2), 64.1 (*C*H_2), 35.2 (*C*H_2), 14.3 (*C*H_3).

6.3.3 Synthesis and characterization of **E**

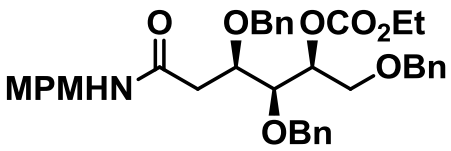


E

To a solution of **13** (293 mg, 0.581 mmol) in a mixture of acetone/H_2O (3/2, 2.5 mL) were added *N*-methylmorpholine-*N*-oxide (NMO, 0.34 mL, 1.63 mmol, 4.8 M aqueous solution) and osmium tetroxide (OsO_4, 0.58 mL, 0.0145 mmol, 0.025 M solution in *tert*-BuOH), and the resulting mixture was stirred at room temperature. After 16 h, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered

and concentrated in vacuo to provide the crude diol intermediate (308 mg). To a solution of this material (72.7 mg) in a mixture of THF/H_2O (1/1, 0.45 mL) was added sodium periodate ($NaIO_4$, 116 mg, 0.540 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 days, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude aldehyde intermediate (67.4 mg). To a solution of this material (67.4 mg), 2-methyl-2-butene (0.067 mL, 1.14 mmol) and sodium dihydrogen phosphate dehydrate ($NaH_2PO_4 \cdot H_2O$, 353 mg, 2.26 mmol) in *tert*-BuOH (1.3 mL) was added sodium chlorite ($NaClO_2$, 109 mg, 1.20 mmol) at 0°C. The resulting mixture was stirred at room temperature for 19 h, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with conc HCl (until pH 3-6), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2) to yield **E** (59.4 mg, 0.114 mmol, 94% for 3 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 15H, C*H*), 5.11 (dt, *J* = 5.4, 3.0 Hz, 1H, C*H*), 4.70-4.38 (m, 6H, CH_2), 4.20-4.08 (m, 3H, C*H* and CH_2), 3.92-3.74 (m, 3H, C*H* and CH_2), 2.17 (d, *J* = 5.7 Hz, 2H, CH_2), 1.26 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3 (*C*), 154.9 (*C*), 138.2 (*C*), 138.0 (*C*), 137.8 (*C*), 128.7 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 128.0 (*C*H), 128.0 (*C*H), 127.9 (*C*H), 78.0 (*C*H), 76.4 (*C*H), 75.8 (*C*H), 74.3 (*C*H_2), 73.4 (*C*H_2), 73.3 (*C*H_2), 68.6 (*C*H_2), 64.3 (*C*H_2), 36.1 (*C*H_2), 14.3 (*C*H_3).

6.3.4 Synthesis and characterization of **15a**

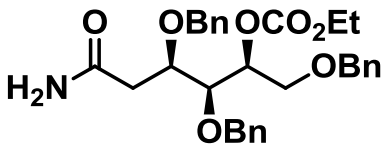


15a

To a solution of **E** (13.0 mg, 0.0249 mmol) and dicyclohexylcarbodiimide (DCC, 6.17 mg, 0.0299 mmol) in dry CH_2Cl_2 were added triethylamine (Et_3N, 2.52 mg, 0.0249 mmol) and *N*-hydroxysuccinimide (NHS, 5.73 mg, 0.0498 mmol), and the resulting mixture was stirred at room temperature. After 1.5 h, the reaction was cooled to 0 °C and filtered through cotton which was successively washed with cooled CH_2Cl_2 (15 mL). The filtrate was washed

with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude activated ester (17.9 mg). To a solution of this material (17.9 mg) in CH_2Cl_2 (0.058 mL) was addend *p*-methoxybenzylamine ($MPMNH_2$, 0.0076 mL, 0.0578 mmol), and the resulting mixture was stirred at room temperature. After 18 h, the reaction was quenched by addition of water (5 mL) and extracted with ethyl acetate (15 mL). The extracts were washed with 3% HCl_{aq} (10 mL) and saturated $NaHCO_{3aq}$ (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) to yield **15a** (12.5 mg, 0.0195 mmol, 78% for 2 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (m, 15H, C*H*), 7.09 (d, *J* = 8.7 Hz, 2H, C*H*), 6.77 (d, *J* = 8.7 Hz, 2H, C*H*), 5.91 (t, *J* = 5.4 Hz, 1H, N*H*), 5.11 (dt, *J* = 5.4, 3.4 Hz, 1H, C*H*), 4.72-4.42 (m, 6H, CH_2), 4.32 (dd, *J* = 14.4, 5.7 Hz, 1H, C*H*), 4.25-4.02 (m, 4H, CH_2), 3.90-3.71 (m, 3H, C*H* and CH_2), 3.78 (s, 3H, CH_3), 2.54 (dd, *J* = 14.7, 4.8 Hz, 1H, CH_2), 2.45 (dd, *J* = 14.7, 7.8 Hz, 1H, CH_2), 1.24 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (*C*), 159.3 (*C*), 154.9 (*C*), 138.2 (*C*), 138.2 (*C*), 138.0 (*C*), 129.5 (*C*), 128.7 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.6 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 128.0 (*C*H), 127.9 (*C*H), 114.2 (*C*H), 78.4 (*C*H), 76.7 (*C*H), 76.5 (*C*H), 74.1 (*C*H_2), 73.5 (*C*H_2), 73.4 (*C*H_2), 68.7 (*C*H_2), 64.3 (*C*H_2), 55.4 (*C*H_3), 43.2 (*C*H_2), 38.6 (*C*H_2), 14.3 (*C*H_3).

6.3.5 Synthesis and characterization of **15'**

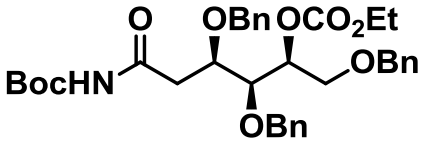


15'

To a solution of **E** (59.4 mg, 0.114 mmol) and dicyclohexylcarbodiimide (DCC, 28.3 mg, 0.137 mmol) in dry CH_2Cl_2 were added triethylamine (Et_3N, 11.5 mg, 0.144 mmol) and *N*-hydroxysuccinimide (NHS, 26.2 mg, 0.228 mmol), and the resulting mixture was stirred at room temperature. After 1.5 h, the reaction mixture was cooled to 0 ^oC and filtered through cotton which was successively washed with cooled CH_2Cl_2 (20 mL). The filtrate was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to

provide the crude activated ester (82.9 mg). To a solution of this material (82.9 mg) in a mixture of 1,4-dioxane/H_2O (5/3, 1.3 mL) was added ammonium formate (NH_4HCO_2, 56.3 mg, 0.670 mmol), and the resulting mixture was stirred at room temperature. After 1.5 h, the reaction was quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1) to yield **15'** (51.8 mg, 0.0993 mmol, 87% for 2 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.17 (m, 15H, C*H*), 5.72 (brs, 1H, NH_2), 5.37 (brs, 1H, NH_2), 5.11 (dt, *J* = 5.4, 3.0 Hz, 1H, C*H*), 4.52-4.49 (m, 6H, CH_2), 4.20-4.07 (m, 3H, C*H* and CH_2), 3.90-3.73 (m, 3H, C*H* and CH_2), 2.65-2.40 (m, 2H, CH_2), 1.26 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (*C*), 154.9 (*C*), 138.2 (*C*), 138.1 (*C*), 138.0 (*C*), 128.7 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 128.1 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 127.9 (*C*H), 78.4 (*C*H), 76.5 (*C*H), 74.2 (*C*H_2), 73.5 (*C*H_2), 73.4 (*C*H_2), 68.7 (*C*H_2), 64.3 (*C*H_2), 37.7 (*C*H_2), 14.3 (*C*H_3).

6.3.6 Synthesis and characterization of **15b**

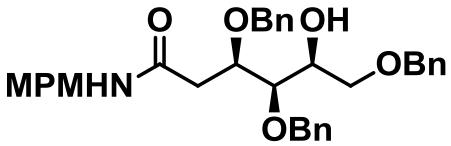


15b

To a solution of **15'** (12.9 mg, 0.0247 mmol) in CH_2Cl_2 (0.1 mL) were added triethylamine (Et_3N, 7.50 mg, 0.0741 mmol), di-*tert*-butyl dicarbonate (Boc_2O, 13.5 mg, 0.0618 mmol) and 4-dimethylaminopyridine (DMAP, 0.300 mg, 0.00247 mmol), and the resulting mixture was stirred at room temperature. After 2 h, reaction was quenched by addition of water (5 mL) and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to provide the crude di-protected intermediate (10.9 mg). To a solution of this material (10.9 mg) in acetonitrile (0.038 mL) was added magnesium perchlorate ($Mg(ClO_4)_2$, 1.69 mg, 0.00755 mmol), and the resulting mixture was stirred at 40 ^{o}C. After 1.7 h, the reaction was quenched by addition of 1 M H_3PO_{4aq} (5 mL) and extracted with ethyl acetate

(15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 4/1) to yield **15b** (4.2 mg, 0.00693 mmol, 46% for 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.18 (m, 15H, C*H*), 5.72 (brs, 1H, N*H*), 5.14 (dt, *J* = 8.4, 3.0 Hz, 1H, C*H*), 4.70-4.43 (m, 6H, CH_2), 4.32-4.22 (m, 1H, C*H*), 4.19-4.07 (m, 2H, CH_2), 3.94-3.90 (m, 1H, C*H*), 3.87 (dd, *J* = 11.4, 2.7 Hz, 1H, CH_2), 3.79 (dd, *J* = 11.1, 5.7 Hz, 1H, CH_2), 3.31 (dd, *J* = 17.4, 7.2 Hz, 1H, CH_2), 3.08 (dd, *J* = 17.4, 4.5 Hz, 1H, CH_2), 1.52 (s, 9H, CH_3), 1.26 (t, *J* = 7.2 Hz, 3H, CH_3).

6.3.7 Synthesis and characterization of **F-a**



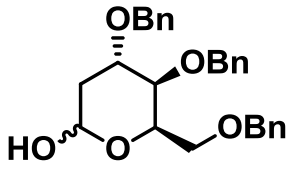
F-a

To a solution of **15a** (21.1 mg, 0.0329 mmol) in methanol (3.3 mL) was added sodium carbonate (Na_2CO_3, 69.7 mg, 0.658 mmol), and the resulting mixture was stirred at room temperature. After 24 h, reaction was quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1) to yield **F-a** (13.5 mg, 0.0237 mmol, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.17 (m, 15H, C*H*), 7.11 (d, *J* = 8.7 Hz, 2H, C*H*), 6.79 (d, *J* = 8.7 Hz, 2H, C*H*), 5.93 (t, *J* = 5.1 Hz, 1H, N*H*), 4.63-4.47 (m, 6H, CH_2), 4.38-4.25 (m, 2H, CH_2), 4.21 (dd, *J* = 14.4, 5.4 Hz, 1H, C*H*), 3.98-3.90 (m, 1H, C*H*), 3.77 (s, 3H, CH_3), 3.69-3.57 (m, 3H, C*H* and CH_2), 3.11 (d, *J* = 5.1 Hz, 1H, O*H*), 2.59 (dd, *J* = 14.4, 4.5 Hz, 1H, CH_2), 2.49 (dd, *J* = 14.4, 7.8 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (*C*), 159.3 (*C*), 138.3 (*C*), 138.1 (*C*), 137.9 (*C*), 130.5 (*C*), 129.5 (*C*H), 128.7 (*C*H), 128.7 (*C*H), 128.7 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 114.3 (*C*H), 78.3 (*C*H), 78.1 (*C*H), 73.7 (*C*H_2), 73.6 (*C*H_2), 73.4 (*C*H_2), 71.3 (*C*H), 71.0 (*C*H_2), 55.4 (*C*H_3), 43.2 (*C*H_2), 38.2 (*C*H_2).

6.3.8 Introduction of a triflate (TfO) group into **F-a**

To a solution of **F-a** (26.1 mg, 0.0458 mmol) in CH_2Cl_2 (0.10 mL) was added trifluoromethanesulfonic anhydride (Tf_2O, 25.8 mg, 0.0916 mmol) at 0 ^oC, and the resulting mixture was stirred at this temperature. After 1 h, reaction was quenched by addition of saturated NH_4Cl_{aq} (10 mL) and extracted with CH_2Cl_2 (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo.

6.3.9 Synthesis and characterization of **G**

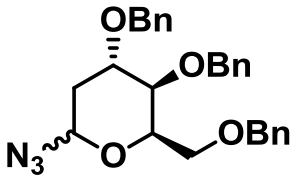


G

To a solution of **13** (309 mg, 0.612 mmol) in methanol (6.1 mL) was added a solution of NaOH in methanol (0.30 M, 6.1 mL), and the resulting mixture was stirred at room temperature. After 20 h, reaction was quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to provide the crude alcohol intermediate (259 mg). To a solution of this material (259 mg) in a mixture of acetone/H_2O (3/2, 2.4 mL) were added *N*-methylmorpholine-*N*-oxide (NMO, 0.39 mL, 1.88 mmol, 4.8 M aqueous solution) and osmium tetroxide (OsO_4, 0.60 mL, 0.0150 mmol, 0.025 M solution in *tert*-BuOH), and the resulting mixture was stirred at room temperature. After 20 h, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2) to provide the crude diol intermediate (268 mg). To a solution of this material (268 mg) in a mixture of THF/H_2O (1/1, 1.9 mL) was added sodium periodate ($NaIO_4$, 491 mg, 2.30 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h, quenched by addition of water (10 mL) and

extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2) to yield **G** (234 mg, 0.538 mmol, 88% for 3 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.10 (m, 15H, C*H*), 5.39 (brs, 1H, C*H*), 4.88 (dd, *J* = 10.8, 5.4 Hz, 1H, C*H*), 4.74-4.45 (m, 6H, CH_2), 4.11-3.97 (m, 1H, C*H*), 3.80-3.55 (m, 2H, CH_2), 3.54-3.41 (m, 1H, C*H*), 3.06 (brs, 1H, O*H*), 2.40-2.20 (m, 1H, CH_2), 1.79-1.42 (m, 1H, CH_2).

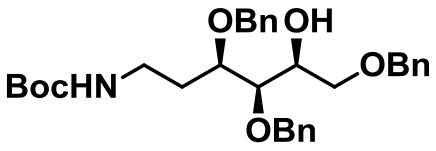
6.3.10 Synthesis and characterization of **17**



17

To a solution of **G** (234 mg, 0.538 mmol) and bis(*p*-nitrophenyl) azidophosphonate (*p*-NO_2DPPA, 394 mg, 1.08 mmol) in dry DMF (5.4 mL) was added 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU, 164 mg, 1.08 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 4/1) to yield **17** (229 mg, 0.499 mmol, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.05 (m, 15H, C*H*), 4.89 (dd, *J* = 10.8 and 2.4 Hz, 1H, C*H*), 4.77-4.23 (m, 6H, CH_2), 3.96-3.40 (m, 5H, C*H* and CH_2), 2.29 (major diastereomer, ddd, *J* = 12.6, 4.8, 2.1 Hz, 1H, CH_2), 2.13 (minor diastereomers, ddd, *J* = 13.2, 4.8, 1.5 Hz, 1H, CH_2), 1.82-1.51 (m, 1H, CH_2).

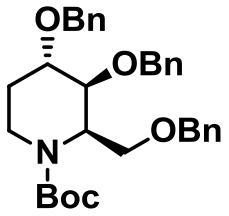
6.3.11 Synthesis and characterization of **H**



H

To a suspension of lithium aluminum hydride ($LiAlH_4$, 36.7 mg, 0.966 mmol) in THF (0.70 mL) was added **17** (148 mg, 0.322 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h, quenched by addition of mixture of THF/H_2O (3/1, 15 mL), filtered through a pad of Celite, which was successively washed with ethyl acetate (30 mL) and extracted. Organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide the crude acyclic amine intermediate (146 mg). To a solution of this material (146 mg) in a mixture of 1,4-dioxane/H_2O (1/1, 0.64 mL) were added sodium hydrogen carbonate ($NaHCO_3$, 59.5 mg, 0.708 mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 70.3 mg, 0.322 mmol), and the resulting mixture was stirred at room temperature. After 20 h, reaction was quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 4/1 to 3/1) to yield **H** (141 mg, 0.262 mmol, 82% for 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.21 (m, 15H, C*H*), 4.65-4.48 (m, 6H, CH_2), 4.45 (brs, 1H, N*H*), 3.97 (dt, *J* = 11.4, 3.9 Hz, 1H, C*H*), 3.73-3.62 (m, 4H, C*H* and CH_2), 3.20-3.05 (m, 3H, CH_2 and O*H*), 1.93-1.67 (m, 2H, CH_2), 1.43 (s, 9H, CH_3).

6.3.12 Synthesis and characterization of **18**



18

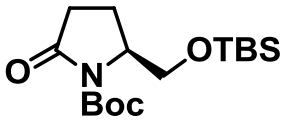
To a solution of **H** (151 mg, 0.282 mmol) and triethylamine (Et_3N, 85.6 mg, 0.846 mmol) in CH_2Cl_2 (0.63 mL) was added methanesulfonyl chloride (MsCl, 86.9 mg, 0.846 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 30 min, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with 3% HCl_{aq} (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 3/1) to provide the crude sulfonate (141 mg). To a solution of this material (141 mg) in THF (2.3 mL) was added potassium *tert*-butoxide (*tert*-BuOK, 129 mg, 1.15 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 1 h, quenched by addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1 to 3/1) to yield **18** (28.5 mg, 0.0551 mmol, 23% for 2 steps): ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.14 (m, 15H, C*H*), 5.10 (brs, 1H, C*H*), 5.01 (t, *J* = 7.5 Hz, 1H, C*H*), 4.85-4.40 (m, 6H, CH_2), 4.39-4.16 (m, 1H, C*H*), 3.98 (d, *J* = 7.5 Hz, 2H, CH_2), 3.40-2.95 (m, 2H, CH_2), 2.13-1.98 (m, 1H, CH_2), 1.98-1.75 (m, 1H, CH_2), 1.41 (s, 9H, CH_3).

6.3.13 Oxidation of **18**

To a solution of **18** (15.2 mg, 0.0294 mmol) in ethyl acetate (0.10 mL) were added ruthenium(IV) oxide (RuO_2, 3.91 mg, 0.0294 mmol) and 10% $NaIO_{4aq}$ (0.29mL), and the resulting mixture was stirred at room temperature. After 2 h, reaction mixture was filtered through a pad of Celite, which was successively washed with ethyl acetate (15 mL) and extracted. Organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo.

6.4 Synthesis of (+)-batzellaside B from L-pyroglutamic acid

6.4.1 Synthesis and characterization of **20**

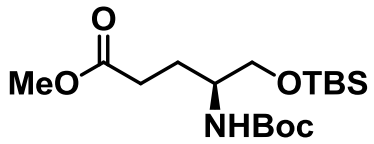


20

To a solution of L-pyroglutamic acid (1.00 g, 7.75 mmol) in methanol (10 mL) was added thionyl chloride ($SOCl_2$, 0.28 mL, 3.87 mmol) at -20 ^oC, and the resulting mixture was stirred at this temperature. After 2.5 h, the mixture was warmed up to room temperature, stirred for additional 1 h and concentrated. The residue was roughly separated by column chromatography (eluent: ethyl acetate/methanol, 1/1) to provide crude methyl ester (1.10 g). To a solution of this material (1.10 g) in ethanol (7.8 mL) was added sodium borohydride (498 mg, 13.2 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 4 h, quenched by addition of acetone (15 mL) and filtered through a pad of Celite, which was successively washed with ethanol (30 mL). The filtrate was concentrated in vacuo and the residue was roughly separated by column chromatography on silica gel (eluent: ethyl acetate/methanol, 5/1) to give the crude alcohol intermediate (892 mg). To a solution of this material (892 mg) in DMF (0.75 mL) were added imidazole (1.06 g, 15.5 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl, 2.34 g, 15.5 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 2.5 h, quenched by addition of water (15 mL) and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to provide the crude protected intermediate (2.56 g). To a solution of this material (2.56 g) in CH_2Cl_2 (0.75 mL) were added triethylamine (Et_3N, 1.57 g, 15.5 mmol), di-*tert*-butyl dicarbonate (Boc_2O, 3.38 g, 15.5 mmol) and 4-dimethylaminopyridine (DMAP, 142 mg, 1.16 mmol), and the resulting mixture was stirred at room temperature. After 2 h, the reaction was quenched by addition water (15 mL) and extracted with AcOEt (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to yield

20 (2.50 g, 7.59 mmol, 98% for 4 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (ddt, *J* = 8.4, 3.9, 2.4 Hz, 1H, C*H*), 3.91 (dd, *J* = 10.3, 3.9 Hz, 1H, CH_2), 3.68 (dd, *J* = 10.3, 2.4 Hz, 1H, CH_2), 2.70 (m, 1H, CH_2), 2.37 (m, 1H, C*H*), 2.20-1.97 (m, 2H, CH_2), 1.56 (s, 9H, CH_3), 0.89 (s, 9H, CH_3), 0.06 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (*C*), 150.0 (*C*), 82.5 (*C*), 64.2 (*C*H_2), 58.8 (*C*H), 32.2 (*C*H_2), 28.0 (*C*H_3), 25.7 (*C*H_3), 21.0 (*C*H_2), 18.0 I, -5.7 (*C*H_3).

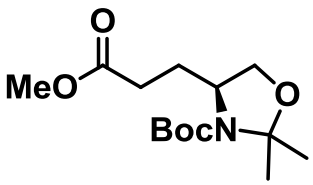
6.4.2 Synthesis and characterization of **21**



21

To a solution of **20** (145 mg, 0.439 mmol) in methanol (0.50 mL) was added a solution of MeONa in methanol (1.0 M, 1.0 mL), and the resulting mixture was stirred at room temperature. After 10 min, the mixture was quenched by addition of saturated NH_4Cl_{aq} (10 mL), concentrated and extracted with ethyl acetate (20 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1) to yield **21** (156 mg, 0.430 mmol, 98%) as a colorless oil: IR ($CHCl_3$) 3450 cm^{-1} (N-H), 1741 cm^{-1} (C=O), 1718 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (brs, 1H, N*H*), 3.56 (s, 3H, CH_3), 3.49 (brs, 3H, CH_2 and C*H*), 2.28 (t, *J* = 7.5 Hz, 2H, CH_2), 1.85-1.57 (m, 2H, CH_2), 1.32 (s, 9H, CH_3), 0.78 (s, 9H, CH_3), 0.06 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (*C*), 155.8 (*C*), 79.0 (*C*), 65.1 (*C*H_2), 51.5 (*C*H_3), 30.7 (*C*H_2), 28.3 (*C*H_3), 27.0 (*C*H_2), 25.8 (*C*H_3), 18.2 I, -5.6 (*C*H_3). Anal. Calcd for $C_{17}H_{35}NO_5Si$: C, 56.47; H, 9.76; N, 3.87. Found: C, 56.85; H, 9.39; N, 3.66.

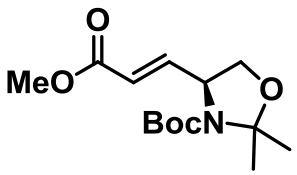
6.4.3 Synthesis and characterization of **22**



22

To a solution of **21** (43.9 mg, 0.122 mmol) in methanol (2.0 mL) was added *p*-toluenesulfonic acid (*p*-TsOH, catalytic amount), and the resulting mixture was stirred at room temperature. After 3 h, the mixture was quenched by addition of saturated $NaHCO_{3aq}$ (30 mL), concentrated and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1) to provide the crude alcohol intermediate (29.3 mg). To a solution of this material (29.3 mg) and 2,2-dimethoxypropane (DMP, 0.13 mL) in acetone (2.5 mL) was added boron trifluoride diethyl ether complex ($BF_3{\cdot}Et_2O$, 1.3 mg, 0.089 mmol), and the resulting mixture was stirred at room temperature. After 30 min, the reaction was quenched by addition of saturated $NaHCO_{3aq}$ (10 mL), concentrated and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1 to 1/1) to yield **22** (32.5 mg, 0.113 mmol, 93% for 2 steps) as a colorless oil: IR ($CHCl_3$) 1732 cm^{-1} (C=O), 1688 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 4.03-3.91 (m, 1H, C*H*$_2$), 3.90-3.80 (brs, 1H, C*H*), 3.72 (d, *J* = 7.8 Hz, 1H, C*H*$_2$), 3.68 (s, 3H, C*H*$_3$), 2.40-2.29 (m, 2H, C*H*$_2$), 2.13-1.76 (m, 2H, C*H*$_2$), 1.60 (s, 3H, C*H*$_3$), 1.56 (s, 3H, C*H*$_3$), 1.48 (s, 9H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (*C*), 152.7 and 152.2 (rotamers, *C*), 94.1 and 93.7 (rotamers, *C*), 80.3 and 80.0 (rotamers, *C*), 67.1 (*C*H_2), 56.9 and 56.6 (rotamers, *C*H), 51.7 (*C*H_3), 30.9 (*C*H_2), 29.1 (*C*H_2), 28.5 (*C*H_3), 27.7 and 26.9 (rotamers, *C*H_3), 24.5 and 23.2 (rotamers, *C*H_3). Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.43; H, 8.51; N, 4.94.

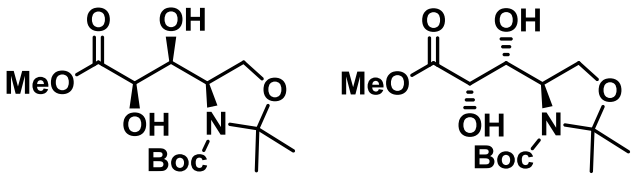
6.4.4 Synthesis and characterization of **I**



I

To a solution of diisopropylamine (1.56 g, 14.5 mmol) in THF (200 mL) was added a solution of *n*-butyl lithium (*n*-BuLi, 1.65 M, 8.5 mL, 14.0 mmol) in hexane at -78 ^{o}C, and the resulting mixture was stirred at this temperature. After 20 min, 1.4 M THF solution of **22** (2.02 g, 7.03 mmol) including hexamethylphosphoramide (HMPA, 3.36 g, 3.28 mmol) was added, and the resulting mixture was stirred. After 30 min, phenylselenyl bromide (PhSeBr, 2.48 g, 10.5 mmol) in THF (5 mL) was added to the reaction mixture, which was stirred at -78 ^{o}C. After 3 h, the mixture was quenched by addition of saturated NH_4Cl_{aq} (20 mL), warmed to room temperature and extracted with ethyl acetate (100 mL). The extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude intermediate (3.94 g). To a solution of this material (3.94 g) in CH_2Cl_2 (140 mL) was added *m*-chloroperoxybenzoic acid (*m*-CPBA, 70%, 3.45 g, 14.0 mmol) at -40 ^{o}C, and the resulting mixture was stirred at this temperature. After 3 h, the reaction was quenched by addition of saturated $NaHCO_{3aq}$ (30 mL), warmed to room temperature and extracted with CH_2Cl_2 (100 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 8/1) to yield **I** (1.83 g, 6.41 mmol, 90% for 2 steps) as a colorless oil: IR ($CHCl_3$) 1714 cm^{-1} (C=O), 1693 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (dd, *J* = 15.0, 7.5 Hz, 1H, C*H*=*CH*), 5.93 (t, *J* = 15.0 Hz, 1H, C*H*=*CH*), 4.64-4.34 (brs, 1H, C*H*), 4.10 (dd, *J* = 9.0, 6.3 Hz, 1H, CH_2), 3.80 (dd, *J* = 9.0, 2.1 Hz, 1H, CH_2), 3.76 (s, 3H, CH_3), 1.80-1.33 (m, 15H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9 (*C*), 152.3 and 151.9 (rotamers, *C*), 146.7 and 146.4 (rotamers, *C*H), 122.2 (*C*H), 94.8 and 94.3 (rotamers, *C*), 81.0 and 80.5 (rotamers, *C*), 67.5 (*C*H_2), 58.2 (*C*H_3), 51.8 (*C*H), 28.5 (*C*H_3), 27.7 and 26.6 (rotamers, *C*H_3), 24.8 and 23.7 (rotamers, *C*H_3). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.64; H, 7.74; N, 4.80.

6.4.5 Synthesis and characterization of **23a,b**



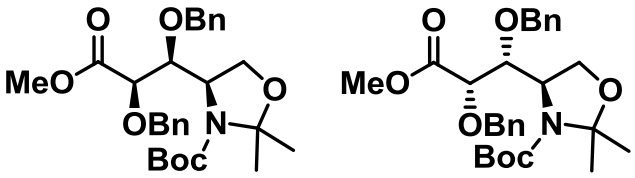
23a (desired) **23b**

To a solution of **I** (238 mg, 0.834 mmol) in a mixture of acetone/H_2O (3/2, 1.6 mL) was added *N*-methylmorpholine-*N*-oxide (NMO, 0.55 mL, 2.63 mmol, 4.8 M aqueous solution) and osmium tetroxide (OsO_4, 0.83 mL, 0.0209 mmol, 0.025 M solution in *tert*-BuOH), and the resulting mixture was stirred at room temperature. After 1 day, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1 to 1/1) to yield **23a** (133mg, 0.417 mmol, 50%) and **23b** (133 mg, 0.417 mmol, 50%) as colorless oil.

23a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (brs, 1H, C*H*), 4.20-4.10 (m, 1H, C*H*), 4.08-3.95 (brs, 2H, CH_2), 3.90-3.80 (m, 4H, C*H* and CH_3), 3.29 (brs, 1H, O*H*), 1.65-1.44 (m, 15H, CH_3).

23b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (brs, 1H, C*H*), 4.25-4.13 (m, 2H, C*H*), 4.08-3.80 (m, 6H, C*H*, CH_2 and CH_3), 2.80 (brs, 1H, O*H*), 1.58-1.44 (m, 15H, CH_3).

6.4.6 Synthesis and characterization of **24a,b**



24a **24b**

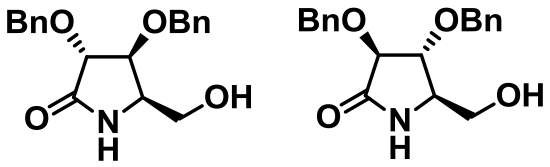
The synthesis of **24a** was achieved by the following synthetic procedures. To a solution of **23a** (226 mg, 0.707 mmol) in ethyl acetate (0.5 mL) were added silver oxide (Ag_2O, 573 mg, 2.47 mmol) and benzyl bromide (BnBr, 484 mg, 2.83 mmol), and the

resulting mixture was stirred at room temperature. After 3 days, the reaction mixture was filtered through a pad of Celite, which was successively washed with ethyl acetate (30 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 10/1 to 6/1) to yield **24a** (40.9 mg, 0.0818 mmol, 11%) as a colorless oil. Following these procedures with **23b** afforded **24b** (3.50 mg, 0.00806 mmol, 46%) as a colorless oil.

24a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.70 (m, 10H, Ar*H*), 4.75-4.00 (m, 8H, C*H* and CH_2), 3.80-3.45 (brs, 1H, C*H*), 3.58-3.48 (brs, 3H, CH_3), 1.75-1.34 (m, 15H, CH_3).

24b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.73 (m, 10H, Ar*H*), 4.75-4.00 (m, 8H, C*H* and CH_2), 3.80-3.45 (brs, 1H, C*H*), 3.63-3.50 (brs, 3H, CH_3), 1.78-1.34 (m, 15H, CH_3).

6.4.7 Synthesis and characterization of **25a,b**



25a **25b**

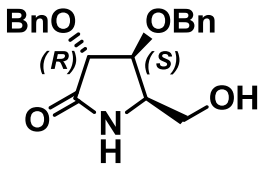
The synthesis of **25b** was achieved by the following synthetic procedures. To a solution of **24b** (42.5 mg, 0.0850 mmol) in methanol (2.0 mL) was added *p*-toluenesulfonic acid (*p*-TsOH, catalytic amount), and the resulting mixture was stirred at room temperature. After 3 h, the mixture was quenched by addition of water (10 mL), concentrated and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2) to provide the crude deprotected intermediate. To a solution of this material in CH_2Cl_2 (0.1 mL) was added boron trifluoride diethyl ether complex (BF_3·Et_2O, catalytic amount) at -5 ^oC. The resulting mixture was stirred at room temperature for 2 h, quenched by addition of saturated $NaHCO_{3aq}$ (10 mL), concentrated and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2) to yield

25b (9.0 mg, 0.0272 mmol, 32% for 2 steps) as a colorless oil. Following these procedures with **24a** afforded **25a** (133 mg, 0.317 mmol, 12%) as a colorless oil.

25a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 10H, Ar*H*), 6.82 (brs, 1H, N*H*), 5.12 (d, *J* = 12.0 Hz, 1H, CH_2), 4.79 (d, *J* = 12.0 Hz, 1H, CH_2), 4.66 (d, *J* = 12.0 Hz, 1H, CH_2), 4.57 (d, *J* = 12.0 Hz, 1H, CH_2), 4.38 (t, *J* = 6.0 Hz, 1H, C*H*), 4.31 (d, *J* = 3.9 Hz, 1H, C*H*), 3.80-3.62 (m, 3H, C*H*) 2.35 (brs, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6 (*C*), 137.1 (*C*), 128.9 (*C*H), 128.8 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 80.9 (*C*H), 79.3 (*C*H), 79.9 (*C*H_2), 79.87 (*C*H_2), 62.8 (*C*H_2), 54.6 (*C*H).

25b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 10H, Ar*H*), 6.82 (brs, H, N*H*), 5.05 (d, *J* = 12.0 Hz, 1H, CH_2), 4.77 (d, *J* = 12.0 Hz, 1H, CH_2), 4.60 (d, *J* = 12.0 Hz, 1H, CH_2), 4.52 (d, *J* = 12.0 Hz, 1H, CH_2), 4.23 (d, *J* = 6.0 Hz, 1H, C*H*), 3.98 (t, *J* = 6.0 Hz, 1H, C*H*), 3.75 (dd, *J* = 11.1, 2.4 Hz, 1H, C*H*), 3.80-3.62 (m, 2H, C*H*) 1.75 (brs, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 (*C*),137.7 (*C*), 137.6 (*C*), 128.8 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.3 (*C*H), 128.2 (*C*H), 128.1 (*C*H), 81.2 (*C*H), 80.9 (*C*H), 73.0 (*C*H_2), 72.6 (*C*H_2), 63.2 (*C*H_2), 58.4 (*C*H).

6.4.8 Synthesis and characterization of (3*R*,4*S*,5*R*)-**25'**

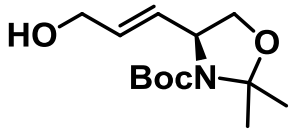


25'

To a solution of **A'** (30 mg, 0.0670 mmol) in a mixture of MeCN/H_2O (9/1, 1.7 mL) was added ceric ammonium nitrate (CAN, 183 mg, 0.335 mmol), and the resulting mixture was was stirred at room temperature. After 2.5 h, the reaction was quenched by addition of water (10 mL), filtered through a pad of Celite, which was successively washed with ethyl acetate (30 mL) and extracted. The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2) to yield **25'** (12 mg, 0.0367 mmol, 58%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 10H, Ar*H*), 6.82 (brs, H, N*H*), 5.06 (d, *J* = 12 Hz, 1H, CH_2), 4.76 (d, *J* = 12 Hz, 1H, CH_2), 4.64 (d, *J* = 12 Hz,

1H, CH_2), 4.57 (d, J = 12 Hz, 1H, CH_2), 4.35 (d, J = 3.0 Hz, 2H, CH_2), 3.90 (brs, 1H, OH), 3.80-3.62 (m, 3H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6 (*C*), 137.1 (*C*), 128.7 (*C*H), 128.5 (*C*H), 128.2 (*C*H), 128.0 (*C*H), 127.9 (*C*H), 80.6 (*C*H), 79.4 (*C*H), 79.8 (*C*H_2), 79.7 (*C*H_2), 61.9 (*C*H_2), 54.7 (*C*H).

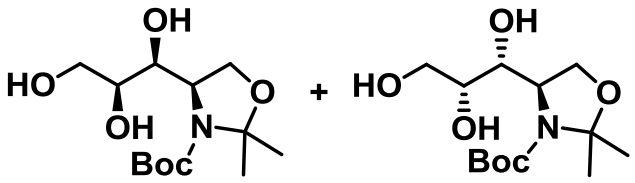
6.4.9 Synthesis and characterization of **26a**



26a

To a solution of **I** (533 mg, 1.87 mmol) in THF (5.1 mL) was added dropwise diisobutylaluminium hydride (DIBAL-H, 1.02 M in toluene, 4.2 mL, 4.3 mmol) at 0 ^{o}C an the resulting mixture was stirred at this temperature. After 1 h, the mixture was poured into methanol (25 mL), followed by addition of a saturated aqueous sodium potassium tartrate (10 mL), water (30 mL) and ethyl acetate (40 mL). The heterogeneous mixture was stirred overnight and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) to yield **26a** (456 mg, 1.77 mmol, 95%) as a colorless oil: IR ($CHCl_3$) 3447 cm^{-1} (O-H), 1686 cm^{-1} (C=O); $[\alpha]_D^{30}$ +13 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88-5.60 (m, 2H, CH=CH), 4.52-4.23 (brs, 1H, CH), 4.15 (d, J = 12 Hz, 2H, CH_2), 4.04 (dd, J = 9.0, 6.3 Hz, 1H, CH_2), 3.74 (dd, J = 9.0, 2.4 Hz, 1H, CH_2), 2.09 (brs, 1H, OH), 1.60 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.47 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4 and 152.3 (rotamers, *C*), 131.4 (*C*H), 130.8 and 130.4 (rotamers, *C*H), 94.2 and 94.0 (rotamers, *C*) 80.5 and 79.9 (rotamers, *C*), 68.2 (*C*H_2), 63.0 (*C*H_2), 58.9 (*C*H), 28.6 (*C*H_3), 27.4 and 26.7 (rotamers, *C*H_3), 24.9 and 23.8 (rotamers, *C*H_3). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.33; H, 8.90; N, 5.53.

6.4.10 Synthesis and characterization of **27a-A,B**



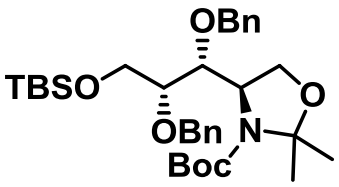
27a-A (desired) **27a-B**

A mixture containing **26a** (52.0 mg, 0.202 mmol), *N*-methylmorpholine-*N*-oxide (NMO, 0.13 mL, 0.606 mmol, 4.8 M aqueous solution) and osmium tetroxide (OsO_4, 0.81 mL, 0.0202 mmol, 0.025 M solution in *tert*-BuOH) was stirred at room temperature. After 1 day, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (3 x 30 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 3/1 to 0/1) to yield a 24:76 mixture of **27a-A** and **-B** (17.7 mg, 0.0607 mmol, 30%). These diastereoisomers were separated by the second column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2 then ethyl acetate/methanol, 1/1) to give pure triols **27a-A** and -**B** as white solids.

27a-A: mp 35-37 ^{o}C; IR (KBr) 3433 cm^{-1} (O-H), 3323 cm^{-1} (O-H), 1703 cm^{-1} (C=O); $[\alpha]_D^{30}$ +33 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 4.40-3.93 (brs, 3H, C*H*$_2$ and C*H*), 3.92-3.53 (brs, 4H, C*H*$_2$ and C*H*), 1.74-1.47 (m, 15H, C*H*$_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 156.3 and 154.3 (rotamers, *C*), 95.5 (*C*), 82.5 and 81.6 (rotamers, *C*), 73.5 and 72.2 (rotamers, *C*H), 71.5 and 70.8 (rotamers, *C*H), 65.6 (*C*H$_2$), 64.7 (*C*H$_2$), 60.8 (*C*H), 28.8 (*C*H$_3$), 27.8 and 27.1 (rotamers, *C*H$_3$), 24.8 and 23.3 (rotamers, *C*H$_3$). Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.46; H, 8.39; N, 4.86.

27a-B: mp 117-121 ^{o}C; IR (KBr) 3406 cm^{-1} (O-H), 3317 cm^{-1} (O-H), 1658 cm^{-1} (C=O); $[\alpha]_D^{30}$ +14 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 4.37-4.12 (brs, 1H, C*H*), 4.11-3.83 (m, 2H, C*H*$_2$), 3.81-3.40 (m, 4H, C*H*$_2$ and C*H*), 1.68-1.25 (m, 15H, C*H*$_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 156.0 (*C*), 95.3 (*C*), 82.8 (*C*), 72.2 (*C*H), 72.0 (*C*H), 66.4 (*C*H$_2$), 64.1 (*C*H$_2$), 60.4 and 60.3 (rotamers, *C*H), 28.8 (*C*H$_3$), 27.9 and 27.4 (rotamers, *C*H$_3$), 24.9 and 24.8 (rotamers, *C*H$_3$). Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.61; H, 8.29; N, 5.01.

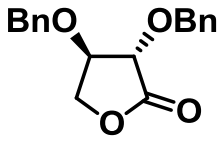
6.4.11 Synthesis and characterization of **28B**



28B

To a solution of **27a-B** (92.7 mg, 0.318 mmol) in CH_2Cl_2 (0.60 mL) were added triethylamine (Et_3N, 96.5 mg, 0.954 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl, 95.4 mg, 0.636 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 day, cooled to 0 °C, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to provide crude TBS protected diol (128 mg). To a solution of this material (128 mg) in THF (2.5 mL) was added sodium hydride (NaH, 55% oil dispersion, 59.4 mg, 1.36 mmol) at 0 °C. After stirring for 20 min at this temperature, tetrabutylammonium iodide (Bu_4NI, 8.38 mg, 0.0227 mmol) and benzyl bromide (BnBr, 110 mg, 0.648 mmol) were added, and the resulting mixture was stirred at room temperature. After 15 h, the reaction was quenched by addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 100/1 to 15/1) to yield **28B** (55.9 mg, 0.0954 mmol, 30% for 3 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.23 (m, 10H, Ar*H*), 4.80-4.50 (m, 4H, PhCH_2), 4.45-4.15 (brs, 2H, C*H*), 4.15-3.67 (m, 3H, C*H* and CH_2), 2.78-2.45 (m, 2H, CH_2), 1.80-1.33 (m, 15H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 and 154.2 (rotamers, *C*), 138.1 (*C*), 137.5 (*C*), 128.8 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 94.4 and 94.2 (rotamers, *C*), 80.8 (*C*H), 78.7 and 78.2 (rotamers, *C*), 77.4 and 76.8 (rotamers, *C*H), 74.1 (*C*H_2), 73.6 (*C*H_2), 64.8 (*C*H_2), 57.1 and 56.8 (rotamers, *C*H), 28.5 (*C*H_3), 27.4 and 27.0 (rotamers, *C*H_3), 24.1 and 22.4 (rotamers, *C*H_3), 20.4 (*C*H_2).

6.4.12 Synthesis and characterization of **29B**

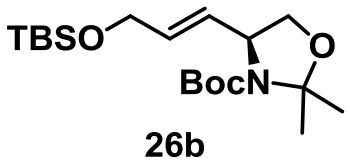


29B

To a solution of **28B** (78.7 mg, 0.134 mmol) in methanol (4.5 mL) was added *p*-toluenesulfonic acid (*p*-TsOH, catalytic amount) and the resulting mixture was stirred at room temperature. After 2 days, the reaction was quenched by addition of water (10 mL), concentrated and extracted with ethyl acetate (30 mL). The extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1) to provide crude deprotected intermediate. To a solution of this material in CH_2Cl_2 (0.30 mL) was added trifluoroacetic acid (TFA, 0.18 mL), and the resulting mixture was stirred at room temperature for 30 min. Then, trifluoroacetic acid was removed azeotropically by using 1,4-dioxane (1.0 mL) to provide the crude deprotected intermediate. To a solution of this material in a mixture of diethyl ether/H_2O (1/1, 2.0 mL) was added dropwise sodium periodate ($NaIO_4$, 34.0 mg, 0.16 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 8 h, diluted with water (10 mL) and extracted with CH_2Cl_2 (20 mL). The extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to provide the crude lactol. To a solution of this material in CH_2Cl_2 (0.40 mL) were added powdered 4Å molecular sieves (MS 4Å, 139 mg), and the mixture was cooled to 0 °C. To this mixture, pyridinium chlorochromate (PCC, 33.7 mg, 0.156 mmol) was added, and the resulting mixture was warmed to room temperature with stirring for additional 10 min. The resulting mixture was diluted with diethyl ether (5.0 mL), stirred for 5 h and filtrated through a pad of Celite, which was successively washed with ethyl acetate (20 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 4/1 to 2/1) to yield **29B** (12.0 mg, 0.0402 mmol, 30% for 3 steps) as a colorless oil: IR ($CHCl_3$) 1793 cm^{-1} (C=O); $[\alpha]_D$ -51.6°(*c* 0.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 10H, Ar*H*), 5.02 (d, *J* = 12.0 Hz, 1H, CH_2), 4.80 (d, *J* = 12.0 Hz, 1H, CH_2), 4.62 (d, *J* = 12.0 Hz, 1H, CH_2), 4.54 (d, *J* = 12.0 Hz, 1H, CH_2), 4.38 (dd, *J* = 21.0, 15.0 Hz, 1H, C*H*), 4.31 (dd, *J* = 12.0, 6.0 Hz, 1H, CH_2), 4.22 (d, 1H, *J* = 6.0 Hz, C*H*), 4.05 (dd, *J* = 9.0, 6.0 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (*C*), 137.2 (*C*), 137.0

(*C*), 128.9 (*C*H), 128.8 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.2 (*C*H), 78.6 (*C*H), 77.6 (*C*H), 72.7 (*C*H_2), 72.5 (*C*H_2), 69.3 (*C*H_2). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08; Found: C, 72.13; H, 6.17.

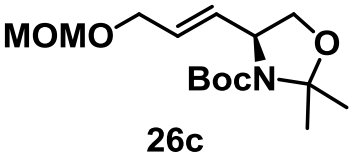
6.4.13 Synthesis and characterization of **26b**



26b

To a solution of **26a** (506 mg, 1.97 mmol) in DMF (0.20 mL) were added imidazole (268 mg, 3.93 mmol) and TBSCl (445 mg, 2.95 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 h, cooled to 0 °C, quenched by addition of water (15 mL) and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to yield **26b** (562 mg, 1.51 mmol, 77%) as a colorless oil: IR ($CHCl_3$) 1687 cm^{-1} (C=O); $[\alpha]_D^{30}$ +19 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85-5.55 (brs, 2H, C*H*=*CH*), 4.48-4.21 (brs, 1H, C*H*), 4.17 (s, 2H, CH_2), 4.01 (dd, *J* = 8.7, 6.0 Hz, 1H, CH_2), 3.73 (dd, *J* = 8.7, 2.1 Hz, 1H, CH_2), 1.59 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.46 (s, 9H, CH_3), 0.89 (s, 9H, CH_3), 0.05 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3 (*C*), 131.6 (*C*H), 129.2 and 129.1 (rotamers, *C*H), 94.0 and 93.7 (rotamers, *C*), 80.1 and 79.7 (rotamers, *C*), 68.4 (*C*H_2), 63.2 (*C*H_2), 58.9 (*C*H), 28.6 (*C*H_3), 27.7 and 26.9 (rotamers, *C*H_3), 26.1 (*C*H_3), 24.7 and 23.9 (rotamers, *C*H_3), 18.5 (*C*), -5.1 (*C*H_3). Anal. Calcd for $C_{19}H_{37}NO_4Si$: C, 61.41; H, 10.04; N, 3.77. Found: C, 61.07; H, 9.65; N, 4.04.

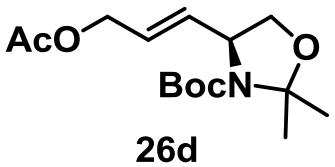
6.4.14 Synthesis and characterization of **26c**



26c

To a solution of NaH (55% oil dispersion, 71.6 mg, 1.64 mmol) in THF (0.40 mL) was added **26a** (301 mg, 1.17 mmol) at 0 °C. After stirring for 20 min at this temperature, methyl chloromethyl ether (MOMCl, 132 mg, 1.64 mmol) was added to this reaction mixture. After stirring at room temperature for 1 h, the reaction was quenched by addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to yield **26c** (241 mg, 0.800 mmol, 68%) as a colorless oil: IR ($CHCl_3$) 1689 cm^{-1} (C=O); $[\alpha]_D^{30}$ +24 (*c* 0.68, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88-5.65 (brs, 2H, C*H*=*CH*), 4.64 (s, 2H, CH_2), 4.53-4.20 (brs, 1H, C*H*), 4.19-3.97 (m, 3H, CH_2), 3.76 (dd, *J* = 8.7, 1.5 Hz, 1H, CH_2), 3.37 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.45 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3 and 152.2 (rotamers, *C*), 132.4 and 132.1 (rotamers, *C*H), 128.3 (*C*H), 95.7 (*C*H_2), 94.2 and 93.9 (rotamers, *C*), 80.3 and 79.8 (rotamers, *C*), 68.3 (*C*H_2), 67.1 (*C*H_2), 58.9 (*C*H), 55.4 (*C*H_3), 28.5 (*C*H_3), 27.6 and 26.7 (rotamers, *C*H_3), 24.9 and 23.8 (rotamers, *C*H_3). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.89; H, 9.42; N, 5.04.

6.4.15 Synthesis and characterization of **26d**



26d

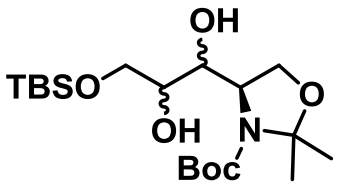
To a solution of **26a** (373 mg, 1.45 mmol) in CH_2Cl_2 (14 mL) were added Et_3N (439 mg, 4.35 mmol), acetic anhydride (Ac_2O, 444 mg, 4.35 mmol) and 4-dimethylaminopyridine (DMAP, 177 mg, 1.45 mmol). The resulting mixture was stirred at room temperature for 1 h and concentrated. The residue was poured into water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **26d** (434 mg, 1.44 mmol, 99%) as a colorless oil: IR ($CHCl_3$) 1734 cm^{-1} (C=O), 1691 cm^{-1} (C=O); $[\alpha]_D^{30}$ +11 (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.85-5.60 (brs, 2H, C*H*=*CH*), 4.57 (m, 2H, CH_2), 4.49-4.19 (brs, 1H, C*H*), 4.05 (dd, *J* = 9.0, 5.7 Hz, 1H, CH_2), 3.75 (dd, *J* = 9.0, 2.1 Hz, 1H, CH_2), 2.07 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.51 (s,

3H, C*H*$_3$), 1.44 (s, 9H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (*C*), 152.5 and 152.2 (rotamers, *C*), 134.0 and 133.5 (rotamers, *C*H), 126.2 (*C*H), 94.3 and 94.1 (rotamers, *C*), 80.5 and 80.0 (rotamers, *C*), 68.1 (*C*H$_2$), 64.4 (*C*H$_2$), 58.8 (*C*H), 28.5 (*C*H$_3$), 27.6 and 26.7 (rotamers, *C*H$_3$), 24.8 and 23.8 (rotamers, *C*H$_3$), 21.0 (*C*H$_3$). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.36; H, 8.18; N, 4.71.

6.4.16 General procedure for asymmetric dihydroxylation of **26a-d** (Table 2, entries 1-9)

To a suspension of AD-mix-α or AD-mix-β in 50% aqueous *tert*-BuOH (0.080 M, 0.50 mol%) were successively added a solution of olefinic substrate **26** in 50% aqueous *tert*-BuOH (0.020 M) and methanesulfonamide (100 mol%) at 0 ^{o}C, and the resulting mixture was stirred at the temperature as indicated in Table 2. Upon completion of the reaction based on TLC analysis, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL), extracted with ethyl acetate (3 x 30 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel to yield the mixtures of **27-A** and **-B** (diastereomeric ratios and combined yields are presented in Table 2).

6.4.17 Characterization of **27b-A,B**

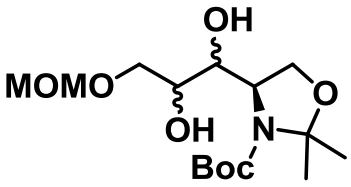


27b-A,B

A mixture of **27b-A** and **27b-B** was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 3/1) and obtained as white solid (Table 2, entries 3-4): mp 92-94 ^{o}C; IR (KBr) 3446 cm^{-1} (O-H), 1656 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60-4.18 (brs, 1H, C*H*), 4.17-4.10 (m, 1H, C*H*$_2$), 4.02-3.89 (m, 1H, C*H*$_2$), 3.84 (dd, *J* = 9.0, 5.7 Hz, 1H, C*H*$_2$), 3.81-3.45 (m, 4H, C*H*$_2$ and C*H* and O*H*), 3.10-2.60 (brs, 1H, O*H*), 1.60 (s, 3H, C*H*$_3$), 1.52 (s, 3H, C*H*$_3$), 1.50 (s, 9H, C*H*$_3$), 0.90 (**27b-A**, s, 9H, C*H*$_3$), 0.89 (**27b-B**, s, 9H, C*H*$_3$),

0.08 (**27b-B**, s, 6H, C*H*$_3$), 0.07 (**27b-A**, s, 6H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7 (**27b-A**, *C*), 154.7 (**27b-B**, *C*), 94.4 and 94.1 (rotamers, *C*), 81.7 (*C*), 73.3 (**27b-A**, *C*H), 71.6 (**27b-A**, *C*H), 71.4 (**27b-B**, *C*H), 69.6 (**27b-B**, *C*H), 66.0 (**27b-B**, *C*H), 65.0 (**27b-A**, *C*H), 64.8 (**27b-A**, *C*H$_2$), 63.8 (**27b-B**, *C*H$_2$), 59.7 (**27b-A**, *C*H$_2$), 59.2 (**27b-B**, *C*H$_2$), 28.5 (**27b-A**, *C*H$_3$), 28.5 (**27b-B**, *C*H$_3$), 27.6 and 27.2 (rotamers, *C*H$_3$), 26.0 (*C*H$_3$), 24.5 and 24.3 (rotamers, *C*H$_3$), 18.4 (**27b-A**, *C*), 18.3 (**27b-B**, *C*), -5.3 (**27b-B**, *C*H$_3$), -5.4 (**27b-A**, *C*H$_3$). Anal. Calcd for $C_{19}H_{39}NO_6Si$: C, 56.26; H, 9.69; N, 3.45. Found: C, 56.29; H, 9.38; N, 3.56.

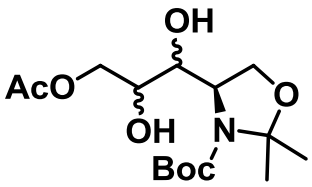
6.4.18 Characterization of **27c-A,B**



27c-A,B

A mixture of **27c-A** and **27c-B** was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/1) and obtained as colorless oil (Table 2, entries 5-6): IR ($CHCl_3$) 3422 cm^{-1} (O-H), 1662 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 2H, C*H*$_2$), 4.51-4.24 (brs, 1H, C*H*), 4.23-4.10 (brs, 1H, CH), 4.07-3.75 (m, 2H, C*H*$_2$), 3.83-3.58 (m, 4H, C*H* and C*H*$_2$ and O*H*), 3.39 (**27c-A**, s, 3H, C*H*$_3$), 3.38 (**27c-B**, s, 3H, C*H*$_3$), 2.91-2.65 (brs, 1H, O*H*), 1.58-1.45 (m, 15H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8 (**27c-A**, *C*), 154.9 (**27c-B**, *C*), 97.3 (**27c-B**, *C*H$_2$), 97.1 (**27c-A**, *C*H$_2$), 94.5 and 94.2 (rotamers, *C*), 82.1 and 81.9 (rotamers, *C*), 74.0 (**27c-A**, *C*H), 72.2 (**27c-B**, *C*H), 70.6 (**27c-A**, *C*H$_2$), 68.9 (**27c-B**, *C*H$_2$), 68.4 (*C*H), 66.0 (**27c-A**, *C*H$_2$), 65.0 (**27c-B**, *C*H$_2$), 59.8 (**27c-A**, CH), 59.2 (**27c-B**, CH), 55.6 (**27c-B**, *C*H$_3$), 55.5 (**27c-A**, *C*H$_3$), 28.5 (*C*H$_3$), 27.7 and 27.2 (rotamers, *C*H$_3$), 24.4 and 24.2 (rotamers, *C*H$_3$). Anal. Calcd for $C_{15}H_{29}NO_7$: C, 53.72; H, 8.72; N, 4.18. Found: C, 53.82; H, 8.35; N, 4.37.

6.4.19 Characterization of **27d-A,B**



27d-A,B

A mixture of **27d-A** and **27d-B** was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) and obtained as white solid (Table 2, entries 7-9): mp 103-105 ^{o}C; IR (KBr) 3373 cm^{-1} (O-H), 3310 cm^{-1} (O-H), 1742 cm^{-1} (C=O), 1656 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91-4.53 (brs, 1H, C*H*), 4.34-4.06 (m, 3H, CH_2 and C*H*), 3.98 (dd, *J* = 9.0, 5.1 Hz, 1H, CH_2), 3.87 (dd, *J* = 9.0, 5.1 Hz, 1H, CH_2), 3.82-3.68 (dd, *J* = 10.8, 6.0 Hz, 1H, C*H*), 3.42 (t, *J* = 10.2 Hz, 1H, O*H*), 3.10-2.64 (brs, 1H, O*H*), 2.09 (**27d-A**, s, 3H, CH_3), 2.08 (**27d-B**, s, 3H, CH_3), 1.57-1.46 (m, 15H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (**27d-A**, *C*), 171.2 (**27d-B**, *C*), 154.8 (*C*), 94.2 (*C*), 82.0 (*C*), 71.6 (*C*H), 67.5 (*C*H), 66.1 (**27d-A**, *C*H_2), 65.9 (**27d-B**, *C*H_2), 59.7 (**27d-A**, *C*H), 59.0 (**27d-B**, *C*H), 28.3 (*C*H_3), 27.7 (*C*H_3), 24.1 (*C*H_3), 20.9 (*C*H_3). Anal. Calcd for $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.20. Found: C, 54.14; H, 7.94; N, 4.60.

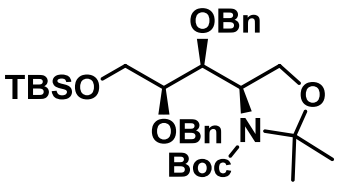
6.4.20 Asymmetric dihydroxylation of **26d** (Table 2, entry 10)

To a suspension of AD-mix-α (294 mg, 0.50 mol%) in 50% aqueous *tert*-BuOH (1.5 mL) was added a solution of **26d** (62.4 mg, 0.208 mmol) in 50% aqueous *tert*-BuOH (0.50 mL) at 0 ^{o}C, and the resulting mixture was stirred at this temperature. After 3 days, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (3 x 30 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) to yield an 84:16 mixture of **27-A** and **-B** (35.8 mg, 0.208 mmol, 52%).

6.4.21 Asymmetric dihydroxylation of **26d** (Table 2, entry 11)

To a suspension of AD-mix-α (133 mg, 0.50 mol%) in 50% aqueous *tert*-BuOH (0.80 mL) were added a solution of **6d** (28.4 mg, 0.0948 mmol) in 50% aqueous *tert*-BuOH (0.20 mL) and hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2PHAL$, 7.38 mg, 9.48 μmol) at 0 ^oC, and the resulting mixture was stirred at this temperature. After 3 days, the reaction was quenched by addition of saturated $NaHSO_{3aq}$ (10 mL) and extracted with ethyl acetate (3 x 30 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) to yield an 83:17 mixture of **27-A** and **-B** (16.3 mg, 0.0497 mmol, 53%).

6.4.22 Synthesis and characterization of **28A**

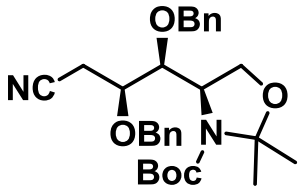


28A

To a solution of a 84:16 mixture of **27d-A** and **-B** (752 mg, 2.26 mmol) in methanol (23 mL) was added potassium carbonate (K_2CO_3, 312 mg, 2.26 mmol), and the resulting mixture was stirred at room temperature. After 1 h, the reaction was quenched by addition of saturated NH_4Cl_{aq} (10 mL), concentrated and extracted with ethyl acetate (3 x 50 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 3/1 to 0/1) to yield an 84:16 mixture of **27a-A** and -**B** (654 mg). These diastereoisomers were separated by the second column chromatography on silica gel (eluent: hexane/ethyl acetate, 1/2 then ethyl acetate/methanol, 1/1) to give pure triols **27a-A** (548 mg) and **27a-B** (104 mg). To a solution of **27a-A** (548 mg) in CH_2Cl_2 (3.8 mL) were added Et_3N (761 mg, 7.52 mmol) and TBSCl (850 mg, 5.64 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 day, cooled to 0 ^oC, quenched by addition of water (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by

column chromatography on silica gel (eluent: hexane/ethyl acetate, 5/1) to provide crude **27b-A** (671 mg). To a solution of this material (671 mg) in THF (17 mL) was added NaH (55% oil dispersion, 722 mg, 16.5 mmol) at 0 °C. After stirring for 20 min at this temperature, tetrabutylammonium iodide (Bu_4NI, 61.0 mg, 0.165 mmol) and BnBr (2.26 g, 13.2 mmol) were added and the resulting mixture was stirred at room temperature. After 3 days, the reaction was quenched by addition of saturated NH_4Cl_{aq} (15 mL) and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 100/1 to 15/1) to yield **28A** (657 mg, 1.12 mmol, 50% for 3 steps) as a white solid: mp 51-53 ^oC; IR (KBr) 1687 cm^{-1} (C=O); $[\alpha]_D^{31}$ +20 (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 10H, Ar*H*), 4.78-4.55 (m, 4H, PhCH_2), 4.47 (d, *J* = 8.4 Hz, C*H*), 4.35-4.05 (brs, 1H, C*H*), 3.90-3.76 (m, 2H, CH_2), 3.75-3.52 (m, 3H, CH and CH_2), 1.75-1.30 (m, 15H, CH_3), 0.86 (s, 9H, CH_3), 0.01 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3 and 153.0 (rotamers, *C*), 139.2 (*C*), 139.0 (*C*), 128.5 (*C*H), 128.0 (*C*H), 127.7 (*C*H), 94.5 and 93.9 (rotamers, *C*), 80.4 and 80.2 (rotamers, *C*), 79.1 (*C*H), 77.4 and 76.7 (rotamers, *C*H), 73.9 (*C*H_2), 73.4 (*C*H_2), 62.7 (*C*H_2), 57.8 and 57.5 (rotamers, *C*H), 28.6 (*C*H_3), 27.6 and 27.0 (rotamers, *C*H_3), 26.0 (*C*H_3), 24.2 and 22.7 (rotamers, *C*H_3). Anal. Calcd for $C_{33}H_{51}NO_6Si$: C, 67.65; H, 8.77; N, 2.39. Found: C, 67.91; H, 8.73; N, 2.39.

6.4.23 Synthesis and characterization of **29**

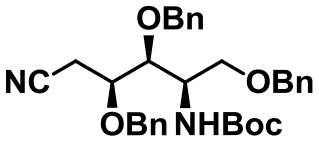


29

To a solution of **28A** (163 mg, 0.278 mmol) in THF (0.93 mL) was added tetra-*n*-butylammonium fluoride (TBAF, 1 M in THF, 0.42 mL, 0.416 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 90 min, cooled to 0 ^oC, quenched by addition of water (15 mL) and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1)

to provide the crude alcohol (128 mg). To a solution of this material (128 mg) in pyridine (0.13 mL) was added *p*-toluenesulfonyl chloride (*p*-TsCl, 155 mg, 0.813 mmol) at 0 °C. The resulting mixture was stirred at this temperature for 40 min, quenched by addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 4/1) to provide the crude intermediate (165 mg). To a solution of this material (165 mg) in dry DMSO (2.6 mL) were added sodium cyanide (NaCN, 129 mg, 2.63 mmol) and $NaHCO_3$ (221 mg, 2.63 mmol) at room temperature. The resulting mixture was stirred at 60 ^oC for 8 h, cooled to room temperature, quenched by addition of saturated NH_4Cl_{aq} (10 mL) and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: toluene/ethyl acetate, 11/1) to yield **29** (106 mg, 0.221 mmol, 80% for 3 steps) as a colorless oil: IR ($CHCl_3$) 2250 cm^{-1} (C-N), 1692 cm^{-1} (C=O); $[\alpha]_D^{30}$ +30 (*c* 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.23 (m, 10H, Ar*H*), 4.80-4.50 (m, 4H, PhCH_2), 4.45-4.15 (brs, 2H, C*H*), 4.15-3.67 (m, 3H, C*H* and CH_2), 2.78-2.45 (m, 2H, CH_2), 1.68 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.49 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 and 154.2 (rotamers, *C*), 138.1 (*C*), 137.5 (*C*), 128.8 (*C*H), 128.6 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 118.3 (*C*), 94.4 and 94.2 (rotamers, *C*), 80.8 (*C*H), 78.7 and 78.2 (rotamers, *C*), 74.4 (*C*H), 74.1 (*C*H_2), 73.6 (*C*H_2), 64.8 (*C*H_2), 57.1 and 56.8 (rotamers, *C*H), 28.5 (*C*H_3), 27.4 and 27.0 (rotamers, *C*H_3), 24.1 and 22.4 (rotamers, *C*H_3), 20.4 (*C*H_2). Anal. Calcd for $C_{28}H_{36}N_2O_5$: C, 69.98; H, 7.55; N, 5.83. Found: C, 70.28; H, 7.36; N, 6.08.

6.4.24 Synthesis and characterization of **J**

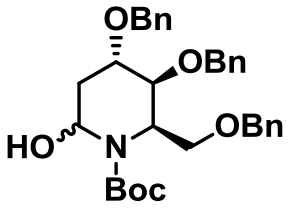


J

To a solution of **29** (38.7 mg, 0.0805 mmol) in methanol (2.7 mL) was added *p*-TsOH (20.8 mg, 0.121 mmol), and the resulting mixture was stirred at room temperature. After 6 h,

the reaction was quenched by addition of saturated $NaHCO_{3aq}$ (10 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was roughly separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 2/1) to yield the crude alcohol intermediate (47.1 mg). To a solution of this material (250 mg, 0.567 mmol) in ethyl acetate (0.57 mL) were added silver oxide (Ag_2O, 657 mg, 2.84 mmol) and BnBr (243 mg, 1.42 mmol), and the resulting mixture was stirred at room temperature. After 16 h, the reaction mixture was filtrated through a pad of Celite, which was successively washed with ethyl acetate (20 mL) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 3/1) to yield **J** (205 mg, 0.386 mmol, 67% for 2 steps) as a colorless oil: IR ($CHCl_3$) 3439 cm^{-1} (N-H), 2251 cm^{-1} (C-N), 1705 cm^{-1} (C=O); $[\alpha]_D^{30}$ +7.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.13 (m, 15H, Ar*H*), 4.86 (d, *J* = 9.1 Hz, 1H, N*H*), 4.75-4.34 (m, 6H, PhCH_2), 4.03 (dd, *J* = 15.0, 9.3 Hz, 1H, C*H*), 3.92-3.71 (m, 2H, C*H*), 3.48-3.26 (m, 2H, CH_2), 2.80-2.50 (m, 2H, CH_2), 1.42 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7 (*C*), 138.1 (*C*), 138.0 (*C*), 137.6 (*C*), 128.8 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.3 (*C*H), 128.1 (*C*H), 118.1 (*C*), 80.2 (*C*), 77.7 (*C*H), 75.9 (*C*H), 75.1 (*C*H_2), 73.7 (*C*H_2), 73.2 (*C*H_2), 69.6 (*C*H_2), 49.3 (*C*H), 28.4 (*C*H_3), 20.1 (*C*H_2). Anal. Calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.53; H, 7.60; N, 5.68.

6.4.25 Synthesis of **C**



C

To a solution of **J** (36.0 mg, 0.0678 mmol) in dry toluene (0.9 mL) was added dropwise diisobutylaluminium hydride (DIBAL-H, 1.04 M in toluene, 0.098 mL, 0.102 mmol) at -78 ^oC, and the resulting mixture was stirred at this temperature. After 1 h, the reaction was quenched by addition of saturated aqueous sodium potassium tartrate (5 mL), warmed up to room temperature and poured into a mixture of water (3 mL) and ethyl acetate

(5 mL). The heterogeneous mixture was stirred overnight and extracted with ethyl acetate (20 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: toluene/ethyl acetate, 6/1) to yield **C** (24.3 mg, 0.0455 mmol, 67%) as a colorless oil. The product identity was unambiguously established by comparison with the ^{1}H NMR spectrum measured for **C** synthesized during the course of the first total synthesis.

6.4.26 General procedure for allylation of **C** (Table 3)

An oven-dried round-bottom flasks were purged with nitrogen and charged sequentially with a solution of **C** (0.1 M), allylic reagent and Lewis acid (solvents, temps, reagents and eqs are given in Table 3). The resulting mixtures were stirred until complete consumption of the starting material, quenched by slow addition of water (10 mL), warmed to room temperature and extracted with ethyl acetate (50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residues were purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 30/1 to 15/1) to yield mixtures of **D-a** and **D-b** as colorless oil (ratios of **D-a** and **D-b** and combined yields are given in Table 3).

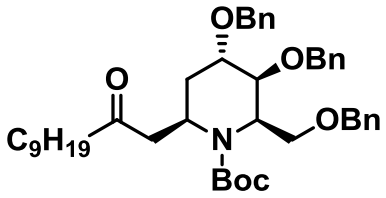
6.4.27 Grignard addition to **6** in the presence of $CeCl_3$

An oven-dried round-bottom flask was purged with nitrogen and charged with a solution of **6** (15.5 mg, 0.0277 mmol) in THF (0.092 mL). To this solution was added cerium(III) chloride ($CeCl_3$, 6.83 mg, 0.0277 mmol) at -78 °C and the resulting mixture was stirred at this temperature. After 30 min, nonylmagnesium bromide (0.14 mL, 0.139 mmol, 1.0 M solution in THF) was slowly added, and the resulting mixture was continuously stirred at -78 ^{o}C. After 30 min, reaction was quenched by slow addition of saturated NH_4Cl_{aq} (5 mL) and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **7a** (5.10 mg, 0.00741 mmol, 27%) and **7b** (6.80 mg, 0.00988 mmol, 36%).

6.4.28 General procedure for incorporation of ketone **30** to **C** (Table 4)

A mixtures containing copper(I) acetonitrile perchlorate ($CuClO_4 \cdot 4CH_3CN$), (*R*)-DTBM-SEGPHOS (**IV**) (mol% of reagents are presented in Table 4) and cesium carbonate (Cs_2CO_3, 0.5 eq.) in TBME (0.20 M) were stirred at room temperature. After 10 min, 5-hexen-2-one (**30**, 1.5 eq.) followed by 1.0 M THF solution of potassium *tert*-butoxide (*tert*-BuOK) were added, and the resulting mixture was stirred at the temperature as indicated in Table 4. After 30 min, a 1.0 M TBME solution of **C** was added, and the resulting mixtures were stirred at room temperature. Upon completion of the reaction based on TLC analysis, the reactions were quenched by addition of saturated NH_4Cl_{aq} (5 mL) and 30% H_2O_{2aq} (3 drops), stirred for additional 10 min and extracted with ethyl acetate (30 mL). The extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 50/1 to 12/1) to yield **K'** and recovered starting material **C** (yields are given in Table 4). **K'**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.24 (m, 10H, C*H*), 7.14 (dd, *J* = 15.9, 10.8 Hz, 1H, CH=C*H*), 6.36 (dd, *J* = 15.0, 10.8 Hz, 1H, CH=C*H*), 6.15 (dd, *J* = 15.3, 6.0 Hz, 1H, CH=C*H*), 5.83 (m, 1H, CH=C*H*), 5.08-4.92 (m, 2H, CH=CH_2), 4.59-4.31 (m, 4H, CH_2), 4.05 (t, *J* = 7.8 Hz, 1H, C*H*), 3.84 (brs, 1H, N*H*), 3.70 (m, 1H, CH_2), 3.53 (dd, *J* = 9.3, 3.6 Hz, 1H, CH_2), 2.66 (t, *J* = 7.5 Hz, 2H, CH_2), 2.38 (dd, *J* = 13.5, 6.3 Hz, 2H, CH_2), 1.56-1.26 (m, 10H, CH_3 and CH_2).

6.4.29 Synthesis and characterization of **L**



L

6.4.29.1 Oxidation of **7a,b** with PCC

To a mixture containing **7a,b** (74.4 mg, 0.108 mmol) and powdered 4Å molecular sieves (MS4Å, 232 mg) in CH_2Cl_2 (5.4 mL) was added pyridinium chlorochromate (PCC, 2.44 g, 11.3 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 4 h, diluted with diethyl ether (11 mL), stirred for additional 16 h and filtered through a pad of Celite, which was successively washed with diethyl ether (30 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **L** (61.5 mg, 0.0897 mmol, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 15H, *H*), 4.79-4.43 (m, 8H, C*H*$_2$ and C*H*), 3.94-3.82 (m, 1H, C*H*), 3.79-3.57 (m, 3H, C*H*$_2$ and C*H*), 2.70-2.47 (m, 2H, C*H*$_2$), 2.32-2.07 (m, 2H, C*H*$_2$), 1.89 (brs, 1H, C*H*$_2$), 1.72-1.60 (m, 1H, C*H*$_2$), 1.42 (s, 9H, C*H*$_3$), 1.42 (s, 14H, C*H*$_2$), 0.88 (t, *J* = 6.6 Hz, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8 (*C*), 155.3 (*C*), 139.1 (*C*), 138.8 (*C*), 138.5 (*C*), 128.7 (*C*H), 128.6 (*C*H), 128.6 (*C*H), 128.1 (*C*H), 127.9 (*C*H), 127.9 (*C*H), 127.8 (*C*H), 127.8 (*C*H), 80.9 (*C*H), 80.4 (*C*), 73.4 (*C*H), 73.4 (*C*H$_2$), 73.3 (*C*H$_2$), 72.5 (*C*H$_2$), 69.3 (*C*H$_2$), 47.2 (*C*H$_2$), 46.5 (*C*H), 43.3 (*C*H$_2$), 33.4 (*C*H$_2$), 32.0 (*C*H$_2$), 29.6 (*C*H$_2$), 29.5 (*C*H$_2$), 29.4 (*C*H$_2$), 29.3 (*C*H$_2$), 28.5 (*C*H$_3$), 23.9 (*C*H$_2$), 22.8 (*C*H$_2$), 14.2 (*C*H$_3$).

6.4.29.2 Oxidation **7a,b** with TPAP

To a solution of **7a,b** (9.40 mg, 0.0137 mmol) in CH_2Cl_2 (0.10 mL) were added powdered 4Å molecular sieves (MS4Å, 232 mg), tatrapropylammonium perruthenate (TPAP, catalytic amount) and *N*-methylmorpholine-*N*-oxide (NMO, 4.81 mg, 1.25 mmol), and the resulting mixture was stirred at room temperature. After 30 min, the reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 8/1) to yield **L** (9.40 mg, 0.0137 mmol, quant.) as a colorless oil.

6.4.30 Reduction of **L** with DIBAL-H (Table 5, entry 1)

To a solution of **L** (12.1 mg, 0.00176 mmol) in THF (0.12 mL) was added dropwise diisobutylaluminium hydride (DIBAL-H, 1.02 M in toluene, 0.035 mL, 0.0352 mmol) at -78 ^{o}C, and the resulting mixture was stirred at this temperature. After 30 min, the mixture was

quenched by addition of a saturated aqueous sodium potassium tartrate (1 mL), warmed up to room temperature and poured into a mixture of water (1.5 mL) and ethyl acetate (1.5 mL). The heterogeneous mixture was stirred overnight and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was separated by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **7a** (4.1 mg, 0.00595 mmol, 34%) and **7b** (8.0 mg, 0.0116 mmol, 66%) as colorless oil.

6.4.31 General procedure for reduction of **L** with $NaBH_4$ (Table 5, entry 2; Table 6, entries 1-3)

To a solutions of **L** (0.15 M) was added sodium borohydride ($NaBH_4$) and the resulting mixtures were stirred until complete consumption of the starting material (solvents, temps, times and eqs of $NaBH_4$ are given in Tables 5 and 6). The reactions were quenched by addition of water (3 mL), warmed to room temperature and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residues were purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **7a** and **7b** as colorless oil (yields and ratios of **7a** and **7b** are given in Tables 5 and 6).

6.4.32 Reduction of **L** under Luche conditions (Table 5, entry 3)

To a solution of **L** (9.60 mg, 0.00140 mmol) in methanol (0.098 mL) was added cerium(III) chloride heptahydrate (8.16 mg, 0.0219 mmol) at -78 ^oC, and the resulting mixture was stirred at this temperature. After 1 h, sodium borohydride ($NaBH_4$ 0.830 mg, 0.0219 mmol) was added, and the resulting mixture was continuously stirred at -78 ^oC. After 30 min, the reaction was quenched by addition of saturated $NaHCO_{3aq}$ (3 mL), warmed to room temperature and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **7a** (5.80 mg, 0.00843 mmol, 58%) and **7b** (3.80 mg, 0.00552 mmol, 38%) as colorless oil.

6.4.33 General procedure for reduction of **L** with $LiAlH_4$ (Table 5, entry 4; Table 6, entries 4-6)

To a suspensions of lithium aluminum hydride ($LiAlH_4$) (0.010 M) was added a 0.02 M solution of **17** at -78 ^oC, and the resulting mixtures were stirred (solvents, temps, times and eqs of $LiAlH_4$ are given in Tables 5 and 6). Upon completion of the reaction based on TLC analysis, the reactions were quenched by addition of a saturated aqueous sodium potassium tartrate (1 mL), warmed up to room temperature and poured into a mixture of water (1.5 mL) and ethyl acetate (1.5 mL). The heterogeneous mixtures were stirred overnight and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residues were purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **7a** and **7b** as colorless oil (yields and ratios of **7a** and **7b** are given in Tables 5 and 6).

6.4.34 General procedure for reduction of **L** with $LiEt_3BH_4$ (Table 5, entry 5; Table 6, entries 7-10)

To solutions of **L** (0.010 M) was added lithium triethylborohydride ($LiEt_3BH$, 2.0 eq., 1.0 M THF solution) at -78 ^oC, and the resulting mixtures were stirred at this temperature (solvents are given in Tables 5 and 6). Upon completion of the reaction based on TLC analysis, the reactions quenched by addition of 3% HCl_{aq} (3 mL), warmed to room temperature and extracted with ethyl acetate (15 mL). The extracts were washed with 2 N $NaOH_{aq}$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residues were purified by column chromatography on silica gel (eluent: hexane/ethyl acetate, 6/1) to yield **7a** and **7b** as colorless oil (yields and ratios of **7a** and **7b** are given in Tables 5 and 6).

6.4.35 Reduction of **L** with $LiAlH(O\text{-}^tBu)_3$ (Table 5, entry 6)

To a solution of **L** (10.1 mg, 0.00147 mmol) in THF (0.049 mL) was added tri-*tert*-butoxy aluminum hydride ($LiAlH(O\text{-}^tBu)_3$, 22.4 mg, 0.0882 mmol) at -78 ^oC. The resulting mixture was warmed to room temperature under stirring over a period of 9 h, quenched by

addition of a saturated aqueous sodium potassium tartrate (1 mL) and poured into a mixture of water (1.5 mL) and ethyl acetate (1.5 mL). The heterogeneous mixture was stirred overnight and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo.

6.4.36 Reduction of **L** with $NaBH_3CN$ (Table 5, entry 7)

To a solution of **L** (14.7 mg, 0.00214 mmol) in methanol (0.14 mL) was added sodium cyanoborohydride ($NaBH_3CN$, 8.1 mg, 0.128 mmol) at -40 ^oC. The resulting mixture was warmed to room temperature under stirring over a period of 64 h, quenched by addition of saturated NH_4Cl_{aq} and extracted with ethyl acetate (15 mL). The extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo.

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