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Addition of Allylmagnesium Bromide to Bromonitriles as a Key Step in the Synthesis of Iminosugars

Thesis submitted for the degree of Doctor of Philosophy in Chemistry in the Institute of Organic Chemistry PAS

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Abstract

The main purpose of this dissertation was to study the feasibility of the addition of allylmagnesium bromide to *ω*-bromonitriles as a tool for the synthesis of polyhydroxylated derivatives of piperidine and pyrrolidine, compounds that can be regarded as iminosugars. The subject of the Thesis belongs to a relatively unexplored field, having a very limited number of literature precedents.

The first chapter of the Thesis, entitled *Introduction*, covers the general information about iminosugars and the addition of Grignard reagents to nitriles. In the context of these considerations, the detailed goals of the research project are depicted.

The second chapter, *Literature review*, consists of two sections. The first one is focused on the modern approaches to the synthesis of iminosugars, whereas the second one covers the subject of the addition of Grignard reagents to *ω*-bromonitriles. The closing conclusions and a brief summary of the chapter are included.

The third chapter, *Results and discussion*, covers the original research and is divided into two sections. The first one describes the synthesis of polyhydroxylated *ω*-bromonitriles from the chiral pool and their use as substrates in the reaction with allylmagnesium bromide. The discussion of the stereochemical course of the studied transformation is included. The second section is focused on the attempts to obtain the bicyclic iminosugars based on quinolizidine, indolizidine, and 6-azaspiro[4.5]decane scaffolds from the previously obtained building blocks. The following reactions were used, among others, in the course of these synthetic routes: ring-closing metathesis (RCM), palladium-catalyzed allylic C-H oxidation, and one-pot RCM/*syn*-dihydroxy-lation with the reuse of a ruthenium catalyst. The closing conclusions and a summary are included in the end of the chapter. The possible future investigations are also outlined.

The fourth chapter, *Experimental procedures*, covers the procedures of all experiments described in the previous chapter. Each procedure is followed by the characterization data of the obtained compound.

In the last chapter, entitled *Bibliography*, all cited literature is listed.

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Streszczenie

Głównym celem niniejszej pracy było zbadanie, czy addycja bromku allilomagnezowego do *ω*-bromonitryli może być wydajnym narzędziem w syntezie polihydroksylowych pochodnych piperydyny i pirolidyny, związków należących do grupy iminocukrów. W literaturze można znaleźć jedynie kilka publikacji, w których opisywane są podobne przemiany.

Pierwszy rozdział, zatytułowany *Wstęp*, podaje ogólne informacje na temat iminocukrów oraz addycji odczynników Grignarda do nitryli. W świetle tychże rozważań sformułowane zostały, w sposób szczegółowy, cele badań.

Drugi rozdział, *Przegląd literatury*, składa się z dwóch części. Pierwsza z nich opisuje nowoczesne metody syntezy iminocukrów, podczas gdy w drugiej znaleźć można opis dotychczasowych badań na temat addycji odczynników Grignarda do *ω*-bromonitryli. Rozdział kończą krótkie podsumowanie oraz wnioski.

W trzecim rozdziale, zatytułowanym *Badania własne*, opisane zostały wyniki własnych prac laboratoryjnych. W pierwszej części rozdziału opisana została synteza *ω*-bromonitryli z substratów pochodzenia naturalnego. Następnie, otrzymane związki były badane pod kątem tytułowej addycji, a rezultaty eksperymentów zostały opisane i skomentowane. W części tej zawarto również dyskusję dotyczącą konfiguracji nowopowstałych centrów stereogenicznych. W drugiej części rozdziału opisano syntezę bicyklicznych pochodnych chinolizydyny, indolizydyny oraz 6-azaspiro[4.5]-dekanu z otrzymanych wcześniej bloków budulcowych. W ścieżkach syntetycznych prowadzących do tych związków wykorzystano, między innymi, następujące przemiany: metatezę olefin z zamknięciem pierścienia, katalizowane palladem utlenianie pozycji allilowej oraz przemianę typu *one-pot* metateza olefin/*syn*-dihydroksylacja z powtórnym wykorzystaniem katalizatora rutenowego. Rozdział kończy podsumowanie oraz wnioski końcowe. Możliwe dalsze kierunki rozwoju przedstawionej ścieżki badawczej są również opisane.

Czwarty rozdział, zatytułowany jako *Procedury eksperymentalne*, zawiera szczegółowy opis przeprowadzonych eksperymentów. Każdy z otrzymanych związków został wyczerpująco scharakteryzowany.

Niniejszą pracę doktorską kończy spis cytowanej literatury.

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Preface

All experiments, that I have described in this work, were conducted by me between 2011 and 2015, when I was a graduate student in the Institute of Organic Chemistry of the Polish Academy of Sciences, under the supervision of Prof. Sławomir Jarosz. I have already published most of the results presented in this Thesis in the following articles:

- Malik, M.; Witkowski, G.; Ceborska, M.; Jarosz, S. *Org. Lett.* **2013**, 15, 6214-6217.
- Malik, M.; Witkowski, G.; Jarosz, S. *Org. Lett.* **2014**, 16, 3816-3819.
- Malik, M.; Ceborska, M.; Witkowski, G.; Jarosz, S. *Tetrahedron: Asymmetry* **2015**, 26, 29-34.

I have participated in several international and local conferences, presenting my research during the poster sessions:

- 14th Tetrahedron Symposium, Vienna, 25-28.06.2013,
- 18th European Symposium on Organic Chemistry, Marseille, 07-12.07.2013,
- FloHet 15, Gainesville, FL, USA, 01-04.03.2014,
- 16th Tetrahedron Symposium, London, 16-19.06.2014,
- Balticum Organicum Syntheticum, Vilnius, 06-09.07.2014,
- 57th Meeting of PTChem and SITPChem, Częstochowa, 14-18.09.2014,
- 19th European Symposium on Organic Chemistry, Lisbon, 12-16.07.2015.

I have also delivered an oral communication during the symposium *Chemia organiczna wczoraj i dziś*, taking place in Warsaw on 12-13.11.2014.

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Acknowledgments

First of all, I would like to thank Prof. Sławomir Jarosz for his kind supervision and a willingness to discuss thoroughly any arising problems. I owe him words of gratitude for giving me a significant dose of independence in my experimental work, a fact that I particularly appreciate.

Secondly, I would like to thank all the colleagues for making my stay in the Group a very pleasant experience. Especially, I would like to thank Grzegorz Witkowski who inspired a significant part of my research. His thought-provoking comments and questions allowed me to reshape many experiments, some of which turned out to be very important for my Thesis. Moreover, I would like to thank those with whom I shared the laboratory space - Marta Magdycz, Mykhaylo Potopnyk, Michał Kowalski, Kinga Kuczyńska, and Bartosz Chaciak - for creating an exceptionally friendly atmosphere.

Finally, I would like to acknowledge the financial support from the Grant: POIG.01.01.02-14-102/09 (part-financed by the European Union within the European Regional Development Fund), entitled *Sugars as Raw Materials in the Synthesis of the Products with High-Added Value*.

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Abbreviations

BQ – benzoquinone

CPME – cyclopentyl methyl ether

CTAB – cetyltrimethylammonium bromide

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

2,2-DMP – 2,2-dimethoxypropane

DMP – Dess-Martin periodinane

DMPU – 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DNJ – deoxynojirimycin

DPPA – diphenylphosphoryl azide

HFIP – hexafluoroispropanol

HMPA – hexamethylphosphoramide

MTBE – methyl *t*-butyl ether

NMO – *N*-methylmorpholine-*N*-oxide

PMB – *p*-methoxybenzyl group

RCM – ring-closing metathesis

L-Selectride – lithium tri-*sec*-butylborohydride

TBDPS – *t*-butyl-diphenylsilyl group

TBDMS – *t*-butyl-dimethylsilyl group

TCDI – 1,1'-thiocarbonyldiimidazole

TFA – trifluoroacetic acid

TFAA – trifluoroacetic anhydride

Tr – triphenylmethyl group

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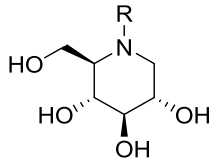
1. Introduction

1.1. The importance of iminosugars

Iminosugars represent a vast group of organic compounds and are, as the name suggests, closely related to carbohydrates. As such, they are heterocyclic, polyhydroxylated compounds which are widely abundant in Nature. But most of all, a member of the iminosugar family is easily recognized by the fact, that instead of an endocyclic oxygen, one of its rings contains a nitrogen atom.[1] Bearing in mind their resemblance to carbohydrates, it is not surprising that iminosugars possess very interesting biological properties.[2,3] For example, *Miglitol* is widely used as anti-diabetic drug,[4] whereas *Miglustat* is applied against type 1 Gaucher disease.[5] Both of these compounds are analogs of deoxynojirimycin (DNJ) (Fig. 1.0), probably the most recognizable iminosugar.[6]



Miglitol: R = CH_2CH_2OH
Miglustat: R = *n*-butyl
DNJ: R = H

Fig. 1.0. Deoxynojirimycin (DNJ) and its well-known analogs.

The synthesis of DNJ was reported for the first time in 1966 by Paulsen.[7] A decade later, it was isolated from *Bacillus* bacteria and its potential as an anti-diabetic drug was recognized by the scientists from the Bayer company.[8] The emerging field of iminosugars started to gain more importance. Soon, bicyclic iminosugars, such as (+)-castanospermine were isolated from natural sources[9] and were proven to possess strong anti-glycosidase[10] and anti-tumour activity.[11,12]

The parallel rapid progress in the art of the total synthesis enabled the development of numerous synthetic routes leading to naturally occurring iminosugars.[13,14] The creativity of researchers led also to many novel structures, not

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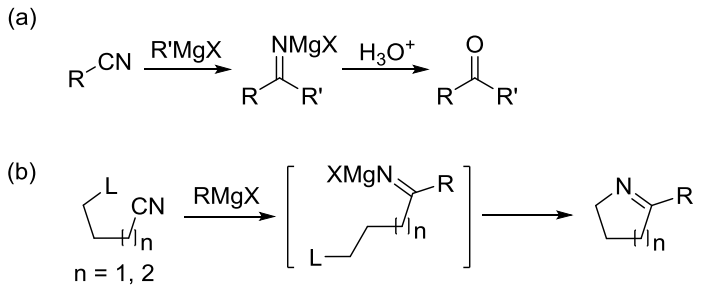
occurring in Nature.[15,16] I will discuss some of the most important approaches in the following chapter. Even in the light of this progress, members of the iminosugar family still represent a challenging synthetic target.

1.2. Aim of the research

The Grignard reaction is one of the most useful tools for the construction of carbon-carbon bonds. It is usually associated with the addition of an alkyl, alkenyl, or aryl magnesium halide to a C=O bond.[17] However, this reaction is not limited only to this particular functional group. For example, it is also well-established, that the addition of a Grignard reagent to a nitrile group results in a formation of an imine salt, which, upon hydrolysis, yields a ketone (Scheme 1.0a).[18,19,20] However, if a good leaving group, for example a halide or a mesyl ester, is present in the molecule, the reaction can proceed via a different route. Namely, an intramolecular S_N2 reaction takes place and a cyclic imine is formed (Scheme 1.0b).[21,22]



Scheme. 1.0. Addition of Grignard reagents to nitriles: (a) general course of the addition; (b) a special case, in which a leaving group (L) is present in the molecule.

Despite the simplicity and the synthetic potential of the latter approach, there are only few reports on its application to the synthesis of nitrogen heterocycles. I will briefly summarize all of them in the following chapter. Moreover, to the best of my knowledge, there is no literature precedence for the above-described process, in which allylmagnesium halide is used. However, taking into account the versatility of the allyl group, it is evident, that such transformation would be very useful in the synthesis of important natural products, *e.g.* iminosugars.

Therefore, in my research, I plan to develop a methodology enabling the cascade transformation which would consist in the addition of an allylmagnesium

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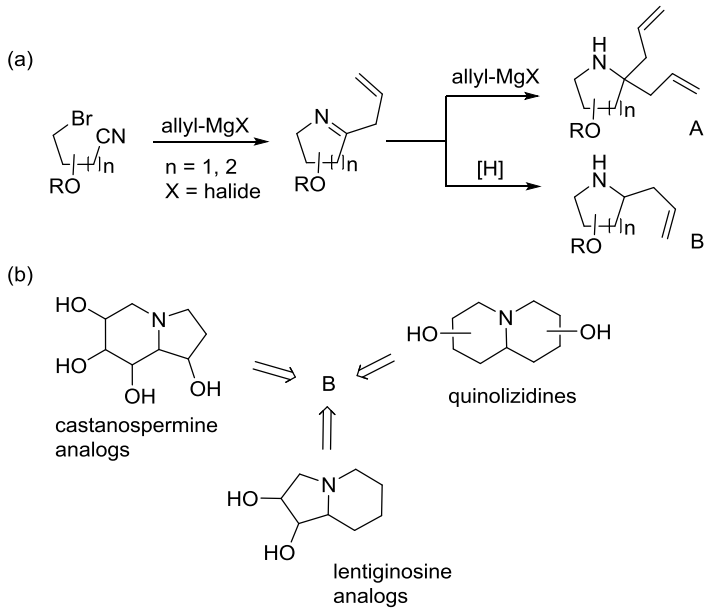
halide to the nitrile group, followed by an intramolecular displacement of a leaving group (Scheme 1.1a). The resulting imine would be, most likely, unstable. Therefore, I would either treat it *in situ* with another equivalent of allylmagnesium halide in order to obtain derivative of type A, or reduce it to derivative of type B.



Scheme 1.1. The main goals of my Thesis: (a) the planned addition of allylmagnesium halide to sugar-derived bromonitriles followed by an intramolecular S_N2 cyclization and then either *in situ* addition of another equivalent of allylmagnesium halide or reduction of the transitional cyclic imine; (b) the intended total syntheses.

As substrates, I would like to use carbohydrate-derived halonitriles. In this way, I will be able to transform A- and B-type compounds into iminosugar-like structures. To complete my research, I plan to perform the total syntheses of diastereoisomers of some well-known, naturally-occurring iminosugars: (+)-castanospermine and (-)-lentiginosine (Scheme 1.1b). Moreover, I also plan to perform the synthesis of iminosugars based on the quinolizidine scaffold.

The methodology, that I plan to develop, would enable, in just one step, a rapid increase in the structure complexity, an attribute highly appreciated by the synthetic organic chemists. One-pot, cascade transformations are not only elegant, but also appealing from the economical point of view.[23,24]

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2. Literature Background

2.1. Synthesis of iminosugars

The aim of this section is to familiarize the Reader with the synthetic methodologies leading to iminosugars. There are at least two approaches, by which the existing literature can be categorized. The most straightforward and intuitive way would be to sort it by the type of the alkaloid group, to which the target compound belongs. In this way, one would obtain, for example, the following categories: indolizidines, quinolizidines, pyrrolizidines, piperidines, and pyrrolidines. However, from a purely synthetic point of view, it is more interesting to learn at first glance *how* the target compound was obtained, rather than the nature of the final structure itself. Therefore, I decided to sort the collected material basing on the type of the reaction leading to the desired iminosugar scaffold. Despite the fact, that such an organization gives rise to some ambiguities, I believe that it also allows for an easier discussion and simplifies the orientation in the presented material, especially for a synthetic organic chemist.

The following categories cover the vast majority of the existing literature concerning the synthesis of iminosugars: S_N2-type cyclizations, reactions of cyclic imines (including reductive aminations), reactions of cyclic nitrones, and ring-closing metathesis (RCM). Finally, I have included some other interesting approaches, not fitting into any of these categories. Those include the aza-Achmatowicz reaction and cycloadditions. Moreover, for the purpose of brevity, only the recent examples[i] are covered in details, whereas the older ones serve only as a historical background. In the part dedicated to the reactions of cyclic imines, I deliberately have not included the methodology consisting in the addition of Grignard reagents to ω-halonitriles. Since it represents the core of my Thesis, I have dedicated an entire section to this particular transformation.

[i] I have chosen the papers published from 2005 onwards.

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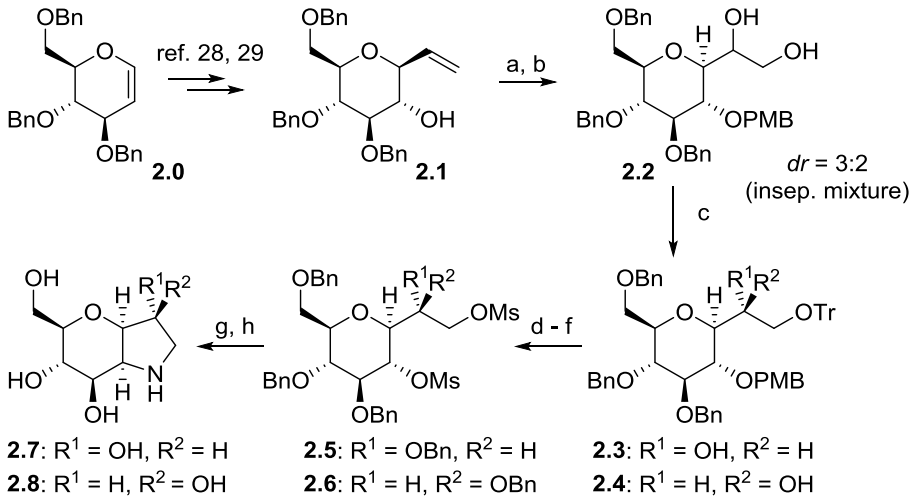
I have focused on the methodologies beginning from the chiral pool, since, taking into account a high availability and low price of natural substrates, this is the most popular starting point when undertaking a total synthesis of natural compounds. Nonetheless, some papers based on the less common *de novo* asymmetric approach (*i.e.* starting from achiral substrates) are also included.

2.1.1. S_N2 cyclizations

The S_N2-type cyclizations are among the most common methodologies leading to iminosugars. The earliest total syntheses of mono- and bicyclic compounds of this class were often accomplished by means of an intramolecular displacement of a leaving group by a nitrogen nucleophile,[25] as, for example, in the first total synthesis of (+)-castanospermine.[26] Due to the reliability of this approach, many novel iminosugars are still synthesized this way.

The synthetic routes involving this methodology are usually long, since they require tedious manipulations with protecting groups, a major drawback of this approach. This is not always the case, though, as I will present in some of the following examples.

Vankar's group reported the synthesis of a novel family of bicyclic iminosugars, which can be regarded as conformatically locked pyrrolidines (Scheme 2.0).[27]



Scheme 2.0. Reagents and conditions: (a) PMBCl, DMF, NaH, 0 °C to rt, 4 h, 93%; (b) OsO_4 (0.4 mol%), NMO·H_2O, acetone/H_2O/*t*-BuOH, rt, 48 h, 89%; (c) TrCl, DCM, Et_3N, rt, 8 h, 51% (**2.3**), 35% (**2.4**); (d) BnCl, DMF, NaH, 0 °C to rt, 4 h; (e) $TrBF_4$, DCM, rt, 30 min; (f) MsCl, DMAP, Et_3N, DMAP, 0 °C to rt, 2 h, 56% (**2.5**) or 62% (**2.6**) (3 steps); (g) $BnNH_2$, 120 °C, 18 h; (h) H_2, $Pd(OH)_2$/C, EtOH, rt, 35 h, 75% (**2.7**) or 76% (**2.8**) (2 steps).

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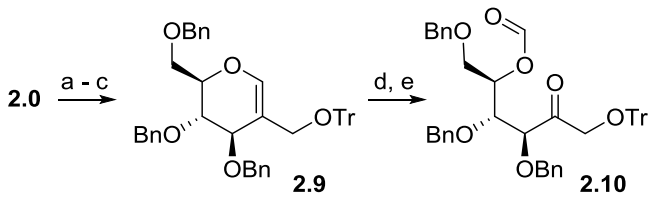
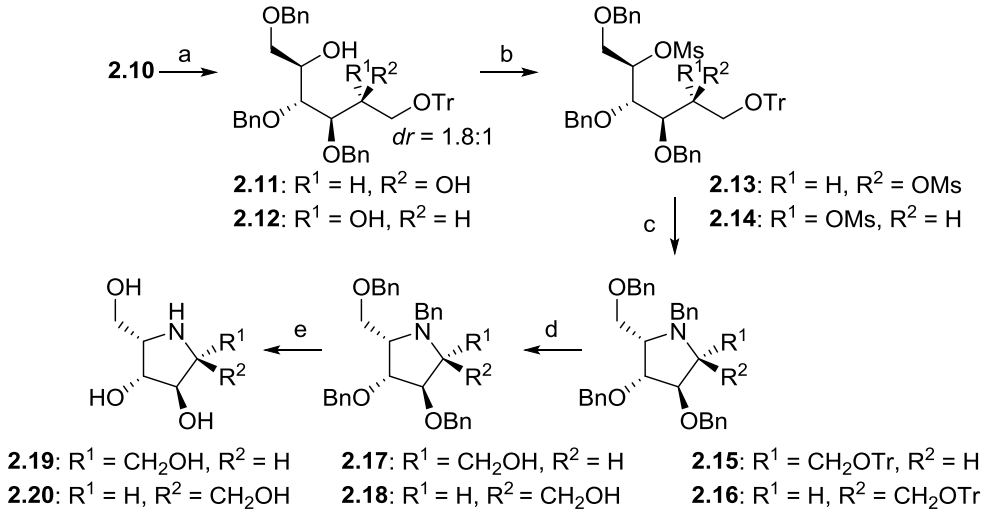
The synthesis was initiated from known derivative of tri-*O*-benzyl-D-glucal **2.1**.[28,29] It was *syn*-dihydroxylated to give diol **2.2** as an inseparable mixture of isomers (*dr* = 3:2). The following tritylation gave derivatives **2.3** and **2.4**, which were easily separated by chromatography. Further steps, performed separately on **2.3** and **2.4**, led to the final bicyclic derivatives **2.7** and **2.8**. Enzyme inhibition activity tests showed that both derivatives are good inhibitors of α-galactosidase ($IC_{50} \approx 1$ mM).

In a more recent paper, Vankar and Ansari presented an approach to dihydroxymethyl dihydroxypiperidines, starting from protected D-glucal **2.0**.[30] They transformed it, *via* formylation, reduction, and tritylation into derivative **2.9**. Subsequent oxidative cleavage of the double bond led to dicarbonyl compound **2.10** (Scheme 2.1), which was reduced with $NaBH_4$ providing diastereomeric diols **2.11** and **2.12** (Scheme 2.2).



Scheme 2.1. Reagents and conditions: (a) $POCl_3$, DMF, 0 °C to rt, overnight, 45%; (b) $NaBH_4$, MeOH, 0 °C to rt, 15 min, 86%; (c) TrCl, Et_3N, DMAP, DCM, rt, 3 h, 92%; (d) OsO_4, NMO, acetone/H_2O/*t*-BuOH, rt, overnight; (e) $NaIO_4$, $NaHCO_3$, MeCN/H_2O, rt, 5 h, 74% (2 steps).



Scheme 2.2. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 48% (**2.11**), 34% (**2.12**); (b) MsCl, Et_3N, DMAP, DCM, 0 °C to rt, 1 h, 89% (**2.13**) or 92% (**2.14**); (c) $BnNH_2$, 140 °C, 6 h, 78% (**2.15**) or 76% (**2.16**); (d) TFA, DCM, 0 °C, 1 h, 85% (**2.17**) or 88% (**2.18**); (e) H_2, $Pd(OH)_2$, MeOH, HCl, rt, 48 h, 62% (**2.19**) or 68% (**2.20**).

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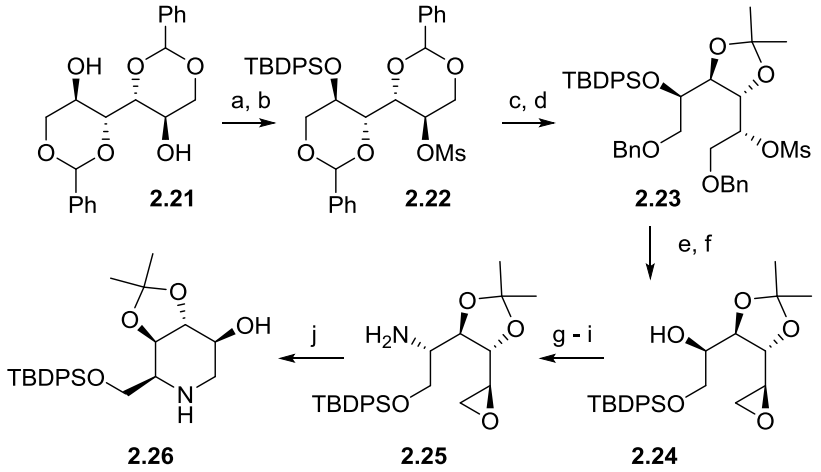
Both compounds, after mesylation, were transformed into the corresponding pyrrolidines by means of S_N2 cyclization with $BnNH_2$. After detritylation and hydrogenolysis, the final products, namely **2.19** and **2.20**, were obtained. They showed good inhibitory activity against some glycosidases, *e.g.* α- and β-glucosidases (0.02 mM < IC_{50} < 0.15 mM).

Baskaran and co-workers devised a synthetic strategy towards a piperidine iminosugar **2.28** (Scheme 2.4),[31] a potent anticancer agent. Starting from protected D-mannitol **2.21**, they obtained mesyl ester **2.22** (Scheme 2.3). Then, reductive, regioselective cleavage of benzylidene acetals and the following protection with 2,2-dimethoxypropane led to derivative **2.23**. Next, the benzyl groups were removed and the resulting diol was subjected to basic conditions, under which oxirane formation proceeded, along with silyl ether migration, resulting in the formation of **2.24**. Subsequently, they transformed it, *via* azide, into a linear amine **2.25**, which, upon refluxing in MeOH, cyclized to piperidine **2.26**. Reductive amination with *n*-pentanal, followed by the removal of protecting groups yielded the final iminosugar **2.28** (Scheme 2.4).



Scheme 2.3. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, 24 h, 69%; (b) MsCl, Et_3N, DCM, 0 °C to rt, 30 min, 94%; (c) $BF_3{\cdot}Et_2O$, Et_3SiH, DCM, 0 °C, 30 min, 85%; (d) 2,2-DMP, acetone, CSA (cat.), rt, 6 h, 80%; (e) H_2, Pd/C, EtOH, rt, 3 d, 95%; (f) K_2CO_3, MeOH, rt, 1 h, 60%; (g) Tf_2O, py, 0 °C to rt, 30 min; (h) NaN_3, DMF, rt, 30 min 90% (2 steps); (i) H_2, $Pd/CaCO_3$, MeOH, 2 h, 87%; (j) MeOH, reflux, 93%.

In yet another example, Behr's group reported a new synthetic route leading to analogs of natural alkaloid (-)-codonopsinine (Scheme 2.5).[32] This approach is quite concise and involves a highly diastereoselective Grignard addition of two different

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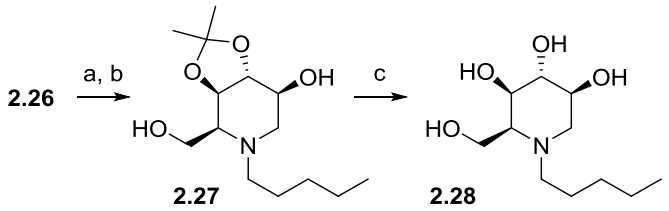
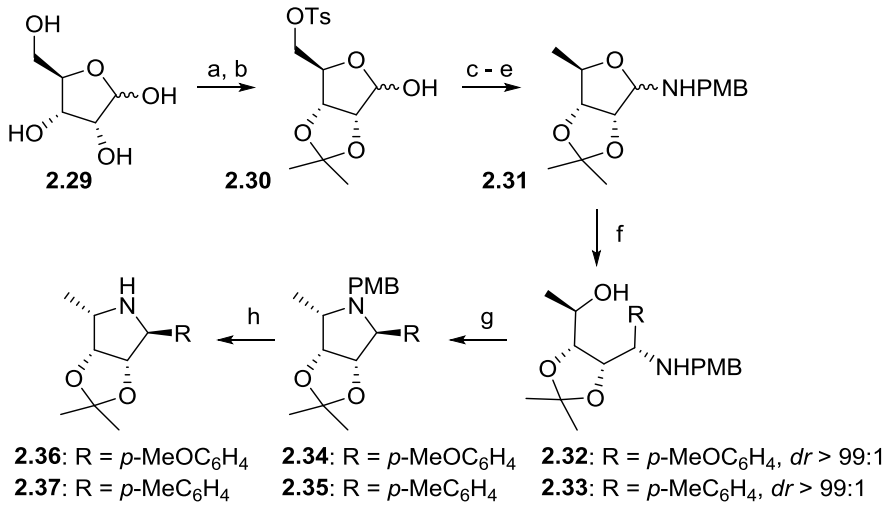
arylmagnesium chlorides to a D-ribose-derived hemiaminal **2.31** to give either **2.32** or **2.33** (for both products *dr* > 99:1), followed by the S_N2 cyclization.



Scheme 2.4. Reagents and conditions: (a) *n*-pentanal, $NaBH_3CN$, AcOH (cat.), MeOH, rt, 3 h, 81%; (b) TBAF, THF, rt, 6 h, 95%; (c) DOWEX 50WX8-100H^+, MeOH, reflux, 4 h, 90%.



Scheme 2.5. Reagents and conditions: (a) acetone, H_2SO_4, rt, 1.5 h; (b) TsCl, py, rt, 16 h, 80% (two steps); (c) NaI, dioxane/DMF, 80 °C, 3 h, 82%; (d) H_2, Pd/C, Et_3N, EtOH, 90%; (e) $PMBNH_2$, MS 4 Å, DCM, rt, 24 h, not purified; (f) RMgCl, THF, 0 °C to rt, 7 h, 52% (**2.32**) or 52% (**2.33**); (g) MsCl, py, 0 °C to rt, 16 h, 63% (**2.34**) or 78% (**2.35**); (h) H_2, Pd/C, MeOH, 48 h, 46% (**2.36**) or 46% (**2.37**).

Thus, pyrrolidines **2.34** and **2.35** were obtained, which, after partial deprotection, gave free amines **2.36** and **2.37**. Then, both compounds were fully deprotected (Scheme 2.6), and the final products were tested against α-L-fucosidase.

In addition, **2.36** was also (prior to deprotection) *N*-methylated under Eschweiler-Clarke conditions, which gave derivative **2.40**. All these products, namely **2.38**, **2.39** and **2.40**, turned out to be very potent inhibitors ($IC_{50} \approx 6$ μM for **2.40** and as low as 6 nM for **2.38** and **2.39**) of α-fucosidase. Derivatives **2.38** and **2.39** are among the most potent α-fucosidase inhibitors ever reported.

Very recently, an exceptionally concise *de novo* asymmetric approach to pyrrolidine-based iminosugars was presented by Britton and co-workers.[33] Starting

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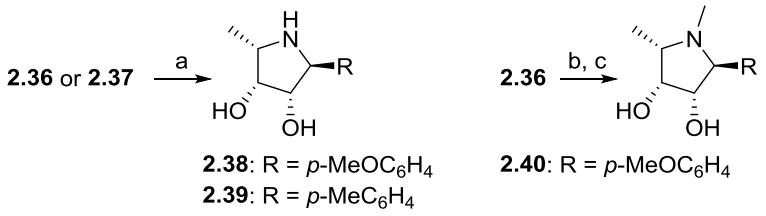
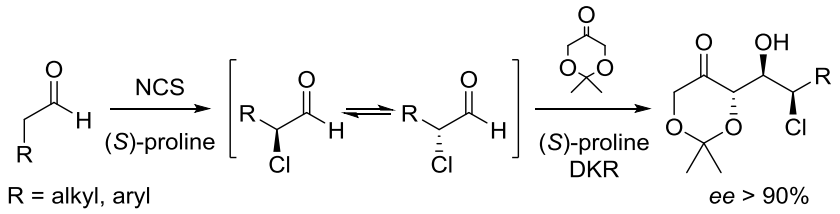
from a wide range of acetaldehyde derivatives, they used a tandem α-chlorination/DKR aldol reaction catalyzed by (*S*)-proline to obtain linear γ-haloketones in good yields and high *ee* values (Scheme 2.7).



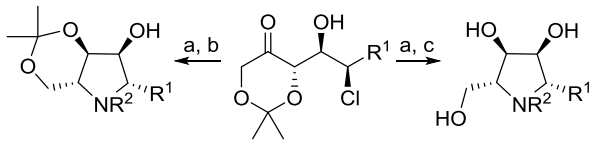
Scheme 2.6. Reagents and conditions: (a) 1M aq. HCl, rt, 24 h, then DOWEX 50WX8, aq. NH_3 (eluent), 73% (**2.38**) or 73% (**2.39**); (b) HCOOH, HCHO, 80 °C, 64%; (c) 1M aq. HCl, rt, 24 h, then DOWEX 50WX8, aq. NH_3 (eluent), 75%.



Scheme 2.7. General course of the tandem (*S*)-proline-catalyzed α-chlorination/DKR aldol reaction leading to linear γ-haloketones.

Then, by means of a reductive amination, followed by an intramolecular S_N2 reaction, a family of variously substituted, polyhydroxylated pyrrolidines was synthesized (Table 2.0).

Table 2.0. Scope of the transformation of γ-haloketones to pyrrolidines.



(a) R^2NH_2, AcOH, MS 4 Å, THF, then $NaCNBH_3$, rt; (b) $NaHCO_3$, toluene, 105 °C
(c) MeOH, 120 °C, microwaves

entry	R^1	R^2	conditions	isolated yield (%)	*ee* (%)
1	methyl	benzyl	a, b	74	95
2	*n*-propyl	benzyl	a, b	98	94
3	*n*-propyl	benzyl	a, c	84	94
4	allyl	benzyl	a, b	92	92
5	allyl	benzyl	a, c	76	92
7	allyl	allyl	a, c	69	92

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Especially interesting is the fact that, depending on the conditions employed, not only fully deprotected derivatives can be obtained, but also partially protected compounds are available. Finally, some of the obtained pyrrolidines were transformed into the bicyclic analogs of (+)-hyacinthacine and (-)-steviamine (not shown). The wide range of the compounds obtained, in addition to the high diastereo- and enantioselectivity of the developed process, makes the whole methodology presented by Britton very well suited for the development of large libraries of iminosugars.

2.1.2. Reactions of cyclic imines

Another general approach towards iminosugars involves the formation of cyclic imines and their subsequent reactions. The versatility of imines is reflected by the number of possible transformations they can undergo: reduction to amines,[34] nucleophilic addition,[35,36] and aza-Diels-Alder cycloadditions[37] are among the most common.

Generally, some of the most important methods of the synthesis of imines involve: condensation of amines with carbonyl compounds,[38,39] dehydrohalogenation of *N*-halogenoamines,[40,41] and reduction of nitrones.[42]

Especially useful in the context of the synthesis of iminosugar are cyclic imines derived from the chiral pool. However, they are usually unstable and have to be used without any purification. Therefore, once synthesized, they should be used immediately, preferentially in a one-pot procedure. Among the transformations involving cyclic imines, the most known and straightforward is reductive amination. This classical approach, over the years, led to many naturally occurring iminosugars and their analogs. For example, the first, famous synthesis of DNJ was accomplished *via* a reductive amination.[7]

The approach is also not rare in the recent literature. For example, Majewski and Palyam presented an organocatalytic approach towards derivatives of DNJ, which were prepared in a reaction of dioxanone **2.41**, in the presence of (*S*)-proline, with (*S*)-isoserinal hydrate **2.42** (Scheme 2.8).[43] In this way, linear ketone **2.43** was obtained, which, upon one-pot hydrogenolysis of the Cbz group, followed by a reductive amination under acidic conditions, gave the *N*-isopropyl-L-ido-DNJ **2.44**.

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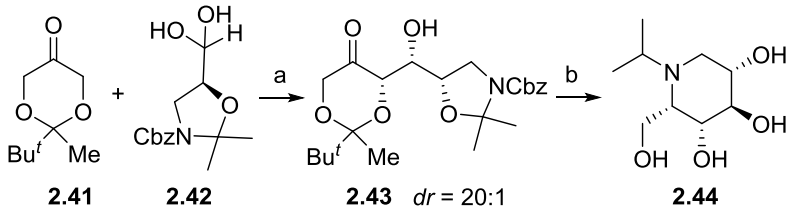
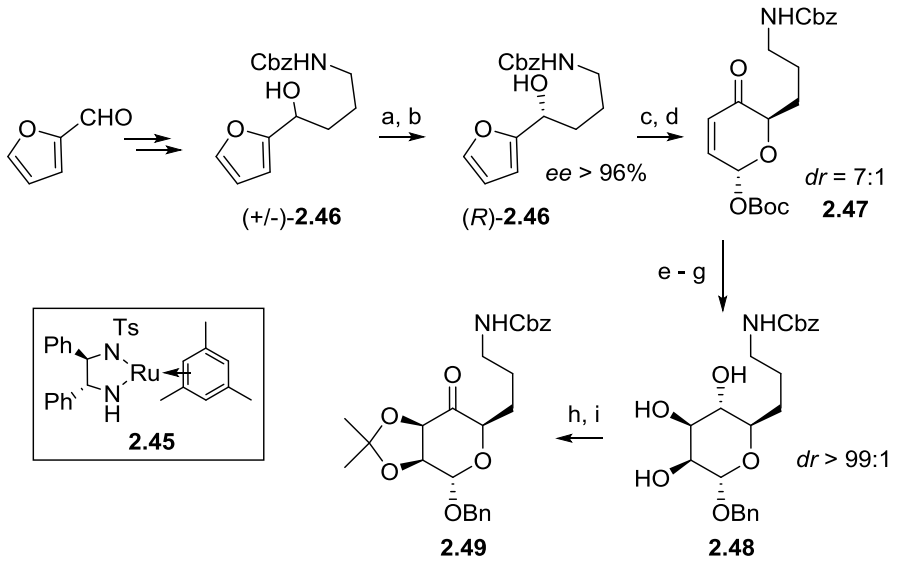


Scheme 2.8. Reagents and conditions: (a) (*S*)-proline, DMSO, LiCl, 5 °C, 48 h, 69%; (b) H_2, Pd/C, MeOH, HCl, 12 h, 82%.

O'Doherty's group, in turn, reported on the *de novo* asymmetric synthesis of 8a-*epi*-swainsonine.[44] The key step of this approach consisted in a one-pot procedure, in which the removal of protecting groups was followed by two consecutive reductive amination reactions (Scheme 2.10). Starting from furfural, after several straightforward steps, they obtained racemic alcohol (+/-)-**2.46**. This compound, after oxidation to a ketone, was reduced in the presence of Noyori's asymmetric catalyst **2.45** to yield alcohol (*R*)-**2.46** with very high optical purity (*ee* > 96%). Subsequent Achmatowicz reaction and protection of the free hydroxyl group with Boc gave predominantly diastereoisomer **2.47**.



Scheme 2.9. Reagents and conditions: (a) MnO_2, THF, rt, 12 h, 90%; (b) cat. **2.45** (2 mol%), HCOOH, Et_3N, rt, 24 h, 91%; (c) NBS, AcONa, THF/H_2O, 0 °C, 30 min, 92%; (d) Boc_2O, DCM, DMAP (cat.), -78 °C, 14 h, 80%; (e) $Pd_2DBA_3{\cdot}CHCl_3$ (2.5 mol%), BnOH, DCM, Ph_3P (5 mol%), 0 °C to rt, 2 h, 88%; (f) $NaBH_4$, MeOH, DCM, $CeCl_3$, -78 °C, 87%; (g) OsO_4 (1 mol%), *t*-BuOH/acetone, NMO·H_2O, 0 °C, 24 h, 89%; (h) *p*-TsOH·H_2O, 2,2-DMP, acetone, 0 °C, 30 min, 87%; (i) Swern ox., 92%.

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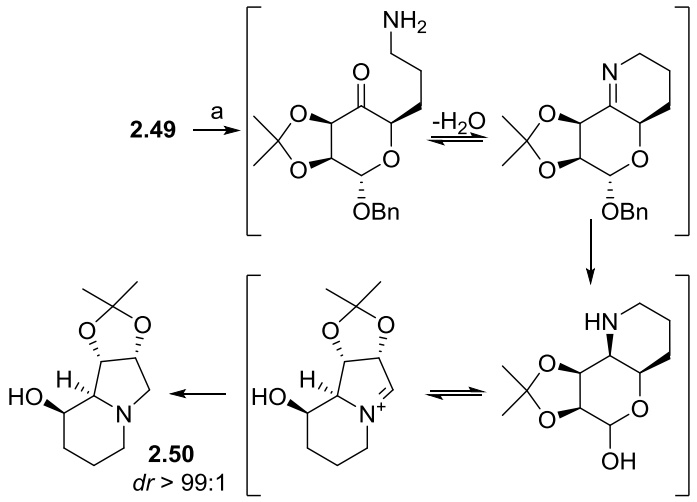
This derivative was then transformed, in a synthetic route consisting of Tsuji-Trost reaction with BnOH, followed by Luche reduction and Os-mediated *syn*-dihydroxylation, into triol **2.48** (practically one isomer, *dr* > 99:1 in each step). This derivative was further transformed, after protection with 2,2-DMP and Swern oxidation, into ketone **2.49**. Subsequently, this compound was subjected to reductive conditions, under which the desired bicyclic scaffold **2.50** was formed (Scheme 2.10 presents a probable route of this transformation). Finally, removal of the isopropylidene group under acidic conditions gave the final product.



Scheme 2.10. Reagents and conditions: (a) H_2, $Pd(OH)_2$/C, EtOH/THF, rt, 3 d, 76%.

In a similar approach, O'Doherty obtained another diastereoisomer of swainsonine.[45] This time, the synthesis started from furan, which was transformed into ketone **2.51** and subsequently reduced, in an enantioselective manner, to the respective alcohol, again with the use of catalyst **2.45** (*ee* > 95%) (Scheme 2.11). Then, Achmatowicz reaction followed by protection of the hydroxyl group with Boc led to unsaturated ketone **2.52** with good diastereoselectivity (*dr* = 8:1). The subsequent several, straightforward steps gave azide **2.56**. This compound was then subjected to reductive conditions, under which it gave the desired indolizidine scaffold **2.57**. The mechanism of this transformation involves a removal of the benzyl group, reduction of the azide moiety and subsequent reductive amination (Scheme 2.12 presents the probable course of the reaction).

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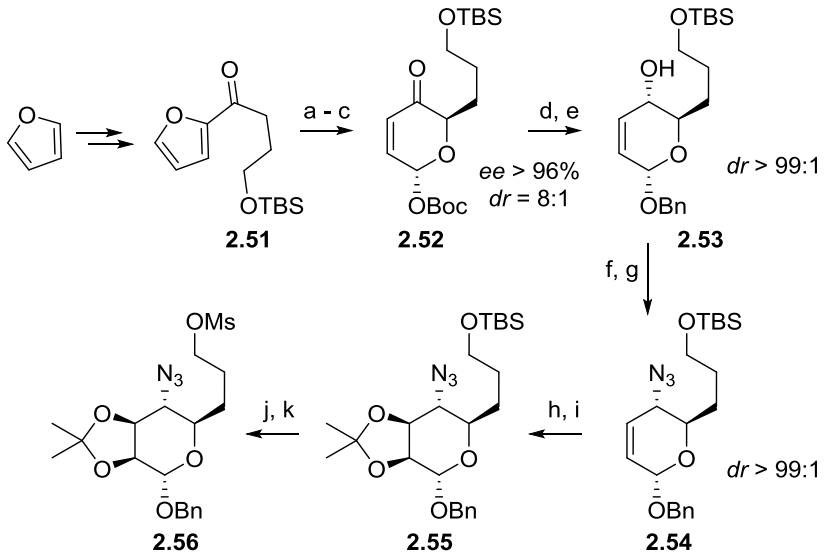
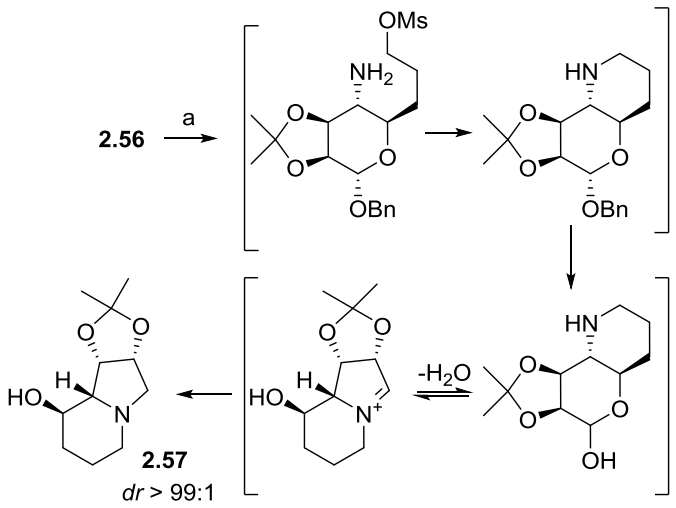


Scheme 2.11. Reagents and conditions: (a) cat. **2.45** (0.5 mol%), CTAB, HCO_2Na, 95%; (b) NBS, H_2O, 0 °C, 84%; (c) Boc_2O, DMAP, -78 °C, 85%; (d) Pd(0) (2.5 mol%), Ph_3P (5 mol%), BnOH, 88%; (e) $NaBH_4$, $CeCl_3$, -78 °C, 94%; (f) CH_3OCOCl, DMAP, py, 96%; (g) $(Pd(allyl)Cl)_2$/dppb, $TMSN_3$, 91%; (h) OsO_4, NMO, 92%; (i) 2,2-DMP, *p*-TsOH, 97%; (j) TBAF, THF, 98%; (k) MsCl, Et_3N, 99%.



Scheme 2.12. Reagents and conditions: (a) H_2, $Pd(OH)_2$/C, EtOH/THF, rt, 7 d, 85%.

Apart from the previously mentioned approaches, the synthesis of cyclic imines can be also accomplished by means of a Staudinger/aza-Wittig transformation.[46] It consists in the addition of a phosphine, usually Ph_3P, to an azide group, followed by extrusion of N_2. The resulting iminophosphorane is unstable and can be easily hydrolysed to an amine or it can react with a carbonyl group to yield an imine. The utility of this approach was proven, for example, by Chattopadhyay and co-workers,

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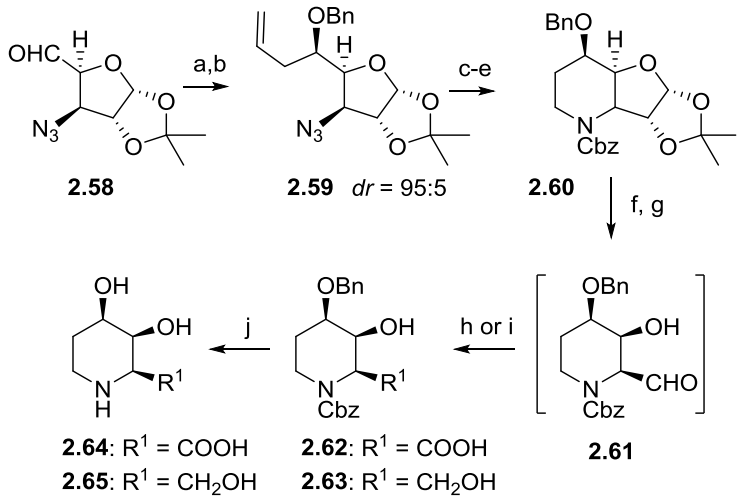
who devised a divergent approach towards the analogs of fagomine and hydroxypipecolic acid (Scheme 2.13).[47] The authors initiated the synthesis from aldehyde **2.58**, which was obtained from D-glucose according to known procedures.[48]



Scheme 2.13. Reagents and conditions: (a) allyl bromide, Zn, THF, 0 °C to rt, 7 h, 61%; (b) BnBr, NaH, THF, 0 °C to rt, 4 h, 76%; (c) O_3, DCM, -78 °C, then Ph_3P, -78 °C to rt, 12 h; (d) $NaBH_3CN$, AcOH (cat.), rt; (e) CbzCl, $NaHCO_3$, MeOH, 0 °C to rt, 4 h, 25% (3 steps); (f) TFA/H_2O, 0 °C, 1 h; (g) $NaIO_4$, acetone/H_2O, 0 °C, 30 min; (h) NaH_2PO_4, $NaClO_2$, 30% H_2O_2, MeCN, 0 °C to rt, 7 h, 67% (**2.62**) (3 steps from **2.60**); (i) $NaBH_4$, MeOH/H_2O, 0 °C, 20 min, 40% (**2.63**) (3 steps from **2.60**); (j) H_2, Pd/C, MeOH, 25 °C, 12 h, 92% (**2.64**) or 93% (**2.65**).

Then, using Barbier reaction with allyl bromide, they introduced an allyl side chain in a highly diastereoselective manner (*dr* = 95:5). Further, the newly formed hydroxyl group was benzylated to give a protected derivative **2.59**. Ozonolysis of the double bond followed by treatment with Ph_3P gave cyclic imine (product of the aza-Wittig reaction), which was reduced with $NaBH_3CN$ to yield, after protection with Cbz, the desired piperidine derivative **2.60**. This compound was further transformed, *via* aldehyde **2.61**, either into pipecolic acid analog **2.64** or fagomine analog **2.65**.

The group of Blèriot used a Staudinger/aza-Wittig tandem process to transform azide **2.66**, in a reaction with solid-supported Ph_3P, into seven-membered derivative **2.67**, which was isolated in its more stable, bicyclic form (Scheme 2.14).[49]

The addition of various Grignard reagents to **2.67** provided a wide range of polyhydroxylated azepanes, *e.g.* the allyl derivative **2.68** (Scheme 2.15). This compound can be easily converted into interesting piperidine scaffold, such as **2.72**.

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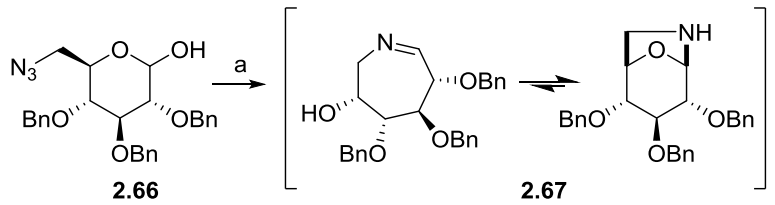
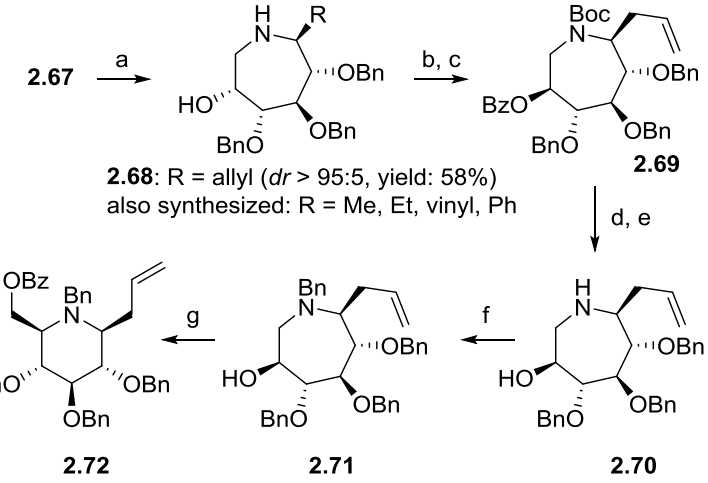


2.66 2.67

Scheme 2.14. Reagents and conditions: (a) supp. Ph_3P, THF, 40 °C, overnight, 62%.



Scheme 2.15. Reagents and conditions: (a) R-MgBr, THF, 0 °C to rt, 1 h; (b) Boc_2O, AcOEt, H_2O, 4 h, rt, 83%; (c) DEAD, Ph_3P, *p*-nitrobenzoic acid, THF, 0 °C, 3 h, 93%; (d) K_2CO_3, THF/MeOH, rt, 5 h, 93%; (e) TFA, DCM, rt, 6 h; (f) DMF, BnBr, K_2CO_3, rt, 14 h, 82% (2 steps); (g) DEAD, Ph_3P, *p*-nitrobenzoic acid, THF, 0 °C, 2 h, 77%.

As I have mentioned previously, a useful approach towards the synthesis of cyclic amines consists in the *N*-halogenation of a cyclic amine, followed by dehydrohalogenation. This methodology poses a serious problem, since it may lead to a mixture of regioisomeric imines. Therefore, *C*-2 symmetrical precursors are usually preferred in this transformation.

Recently, Yang and Shao have exploited this methodology in the synthesis of lentiginosine and steviamine analogs.[50] Starting from the chiral pool, they obtained a family of various five-membered cyclic aldimines (Scheme 2.16). In order to overcome the regioselectivity problem, they used either *C*-2 symmetrical *N*-chloroamines or took advantage of the directing influence of Boc group. These compounds were subsequently subjected to ytterbium(III) triflate-catalyzed aza-Diels-Alder reaction with Danishefsky's diene (Table 2.1), giving a family of polyhydroxylated indolizidines.

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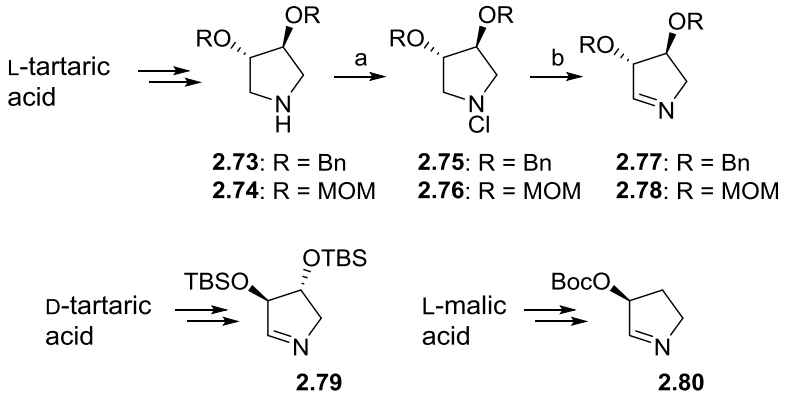
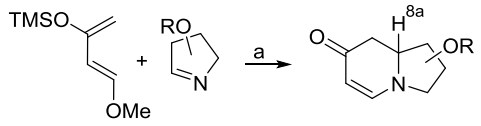


Scheme 2.16. Reagents and conditions: (a) NCS, Et_2O, rt, 30 min, 90% (**2.75**) or 88% (**2.76**) (b) DBU, Et_2O, rt, 4 h, 78% (**2.77**) or 75% (**2.78**).

Some of them were easily transformed into iminosugars: (+)- and (-)-lentiginosine, and (-)-2-*epi*-steviamine (only the synthesis of the first one is shown) (Scheme 2.17). The six-membered ring in the bicyclic derivative **2.81** was reduced to amine **2.85** which, after deprotection, gave the desired indolizidine alkaloid.

Table 2.1. Application of cyclic imines in the synthesis of indolizidine alkaloids by means of aza-Diels-Alder reaction.



(a) $Yb(OTf)_3$, DCM, -40 °C to 0 °C, 3 h

entry	imine	isolated yield (%)	*dr* (8a-*R* : 8a-*S*)
1	**2.77**	65	1:10
2	**2.78**	62	1:5
3	**2.79**	71	10:1
4	**2.80**	73	> 99:1

Another, a somehow less exploited possibility for the synthesis of cyclic imines consists in a partial reduction of a lactam group. Usually, reduction of amides is achieved by employing aluminum or boron hydrides.[51] Such harsh and hard to control conditions eventually lead to amines. However, some novel protocols were reported, in which aldimines and ketimines were obtained from the corresponding amides in good yields by using Tf_2O/Et_3SiH[52] or the Schwartz's reagent.[53]

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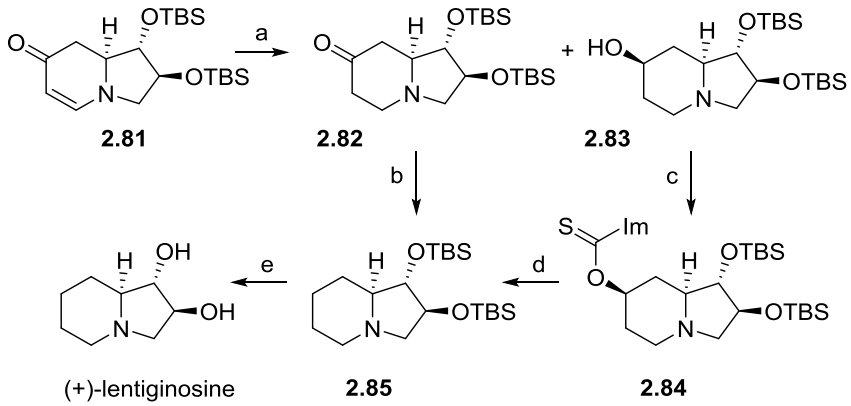
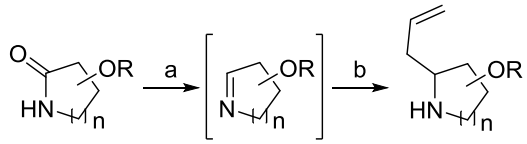


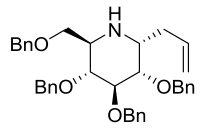
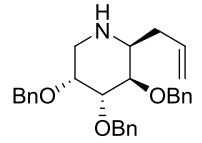
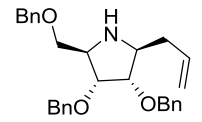
Scheme 2.17. Reagents and conditions: (a) H_2, Pd/C, AcOEt, 35 °C, 3 h, 15% (**2.82**), 68% (**2.83**); (b) $TsNHNH_2$, MeOH, MS 4 Å, reflux, 3 h, 55%; (c) TCDI, THF, reflux, 6 h, 88%; (d) *n*-Bu_3Sn, AIBN, toluene, reflux, 3 h, 75%; (e) MeCN, aq. HCl, rt, 3 h, then Dowex OH, 80%.

Furman and co-workers used the latter reagent to obtain a series of sugar-derived five- and six-membered imines and transformed them, *via* nucleophilic addition of *n*-Bu_3Sn-allyl, in a one-pot procedure, into various pyrrolidine and piperidine iminosugars (Table 2.2).[54]

Table 2.2. One pot reduction of lactams to imines by Schwartz's reagent, followed by allylation with *n*-Bu_3Sn-allyl.



(a) $Cp_2Zr(H)Cl$, THF, -25 °C to rt
(b) *n*-Bu_3Sn-allyl, $Yb(OTf)_3$, THF, -25 °C to rt

entry	major product	isolated yield (%)	*dr*
1		84	90:10
2		55	60:40
3		69	81:19

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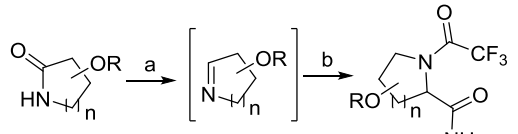
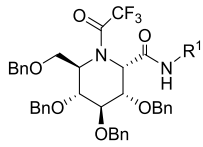
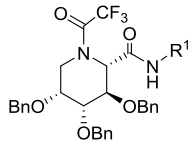
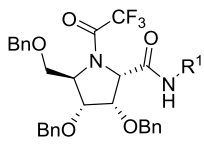
The reaction is high-yielding, whereas the diastereoselectivities range from poor to excellent. Furman reported also, that other nucleophiles, such as TMSCN, PhMgBr or silyl enol ethers react similarly, providing variously substituted iminosugars. They described yet another one-pot procedure, in which the cyclic imine was reacted *in situ* with Danishefsky's diene.[55] In this way, they obtained a series of bicyclic iminosugars, similarly to the already shown approach by Yang and Shao (see Table 2.1).

Finally, in their most recent paper,[56] they presented an elegant methodology for the synthesis of peptidomimetics (Table 2.3). In this approach, the reduction of lactams with Schwartz's reagent was followed, in a one-pot manner, by Joullié-Ugi reaction. All in all, despite the versatility of Furman's approach, the whole methodology suffers from the necessity of the stoichiometric use of zirconium-based Schwartz's complex, a relatively expensive reagent.

Table 2.3. One pot reduction of lactams to imines by Schwartz's reagent, followed by Joullié-Ugi reaction.



(a) $Cp_2Zr(H)Cl$, THF, -25 °C to rt
(b) TFA, isocyanide, -78 °C to rt

entry	major product	R^1	isolated yield (%)	*dr*
1		*t*-Bu	69	> 95:5
		Cy	74	> 95:5
		PMP	86	> 95:5
2		*t*-Bu	76	75:25
		Cy	84	80:20
		PMP	68	59:41
3		*t*-Bu	72	84:16
		Cy	63	> 95:5

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2.1.3. Reactions of cyclic nitrones

Nitrones can undergo various, synthetically useful reactions: 1,3-dipolar cycloaddition with alkenes and alkynes to give isoxazolidines,[57] nucleophilic addition to give hydroxylamines,[58] or even SmI_2-mediated cross couplings with carbonyl compounds to give vicinal amino alcohols[59] (Fig. 2.1). Recently, a special attention is focused on the synthesis and application of optically pure cyclic nitrones, compounds of great utility in the synthesis of biologically important molecules.[60]

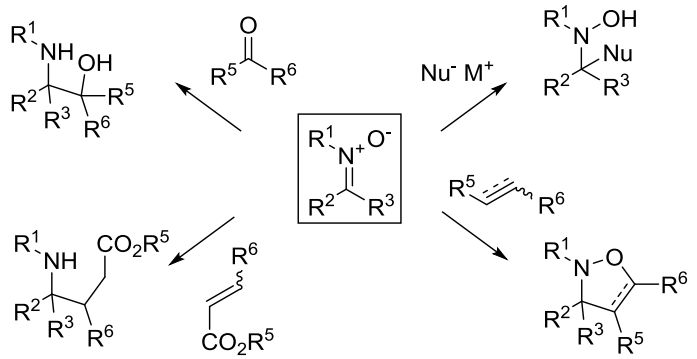

Fig. 2.1. The synthetic application of nitrones: nucleophilic addition, 1,3-dipolar cycloaddition and various cross-couplings are possible.

In addition to this high synthetic versatility, cyclic nitrones are relatively easy to obtain, even from complex, sugar-derived substrates, since protected hydroxyl groups are usually tolerated (Fig. 2.2).

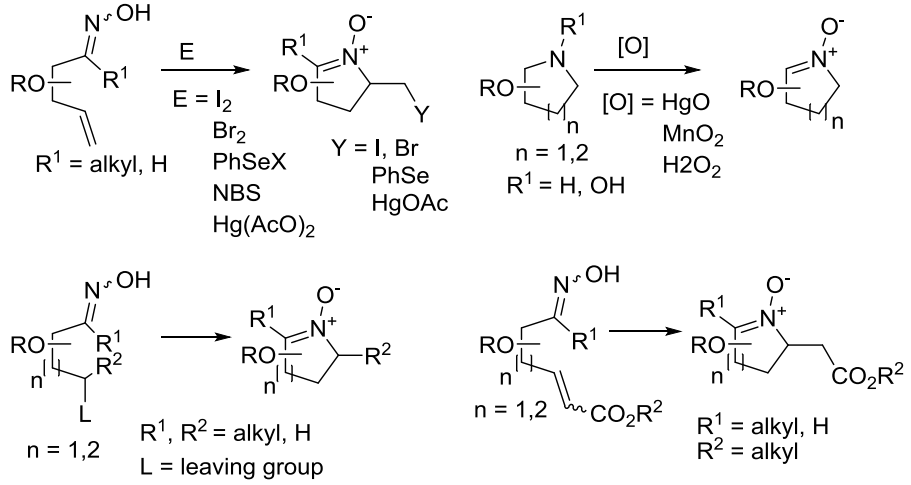

Fig. 2.2. Various approaches to the synthesis of five- and six-membered, cyclic nitrones from optically pure substrates. Protected hydroxyl groups are tolerated.

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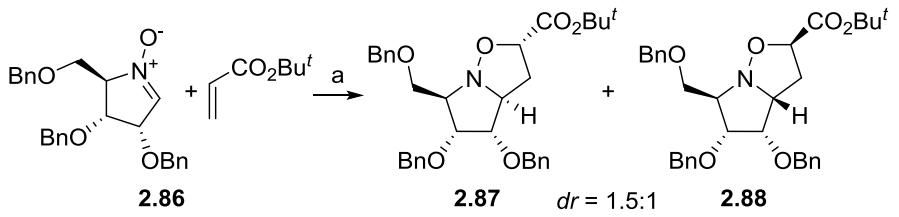
The first possibility consists in the oxidation of hydoxylamines, imines or amines.[61] Although straightforward, this approach lacks regioselectivity. Another way to obtain cyclic nitrones is through an intramolecular S_N2 *N*-alkylation of oximes.[60] This is probably the easiest access to polyhydroxylated, cyclic (*i.e*. sugar-like) nitrones.

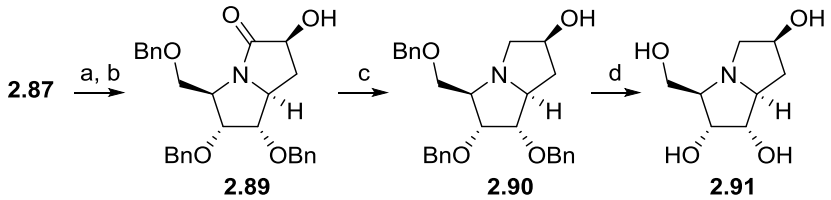
In the light of these facts, it would be reasonable to attempt the synthesis of iminosugars *via* cyclic nitrones. Indeed, there are plethora of reports in the recent literature.

For example, Goti and Cardona presented a route towards (+)-hyacinthacine A_1 and its analogs.[62] In their approach, D-ribofuranose-derived nitrone **2.86** was subjected to a 1,3-dipolar cycloaddition with *t*-butylacrylate to give a mixture of diastereomeric oxazolidines **2.87** and **2.88** (*dr* = 1.5:1) (Scheme 2.18).



Scheme 2.18. Reagents and conditions: (a) DCM, rt, 3 d, 88%.

The subsequent one-pot cleavage of the N-O bond in **2.87**, followed by a ring-closure gave lactam **2.89** in very good yield (90%). The following, straightforward steps, namely $LiAlH_4$ reduction of the lactam moiety and removal of the benzyl groups, led to the desired bicyclic compound **2.91** (Scheme 2.19). Analogous route was applied to the oxazolidine **2.88**.



Scheme 2.19. Reagents and conditions: (a) Zn, AcOH/H_2O, reflux, 3 d; (b) Ambersep 900 OH, MeOH, rt, 10 h, 90% (2 steps); (c) $LiAlH_4$, THF, reflux, 2 h, 82%; (d) H_2, Pd/C, MeOH, HCl, rt, 3 d, then DOWEX-50WX8-200, quant.

Yu and co-workers presented an approach towards (-)-hyacinthacine C_5, which was based on a nucleophilic addition of 2-lithio-1,3-dithiane derivative **2.92** to a

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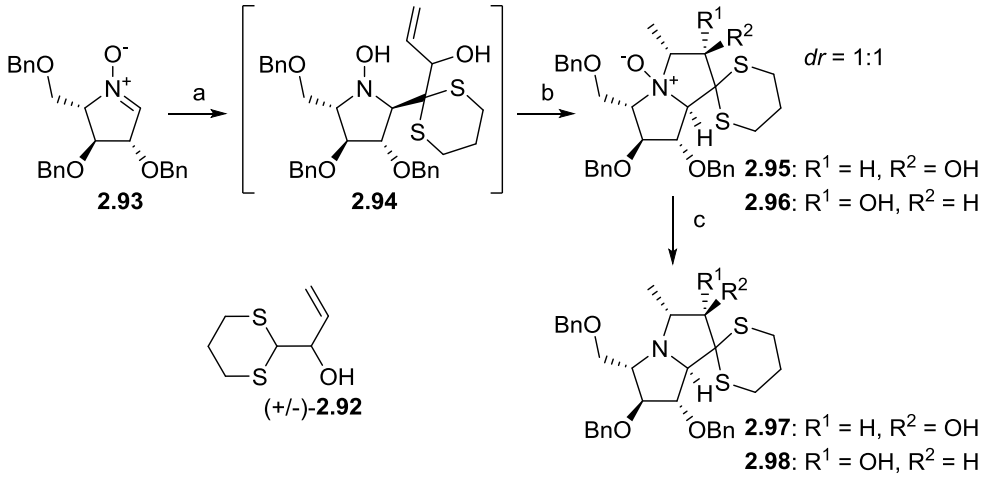
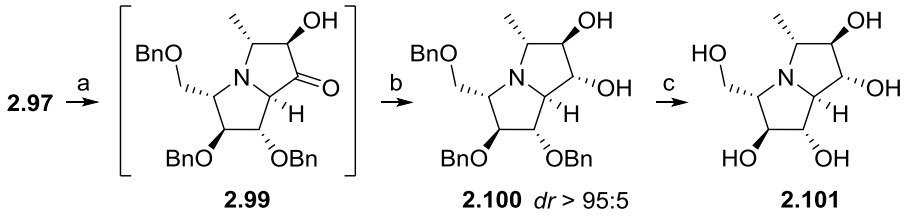
cyclic, sugar-derived nitrone **2.93**, followed by a Cope-House cyclization which provided derivatives **2.95** and **2.96** as a separable mixture of diastereoisomers (*dr* = 1:1) (Scheme 2.20).[63] The reduction with Zn/AcOH gave thioacetals **2.97** and **2.98**. The subsequent removal of the dithiane moiety in **2.97**, followed *in situ* by a stereoselective reduction of the carbonyl group in **2.99**, gave diol **2.100** in a highly diastereoselective manner (*dr* > 95:5), albeit in moderate yield (31% over 2 steps) (Scheme 2.21). Then, after deprotection, the desired iminosugar **2.101** was obtained. An analogous route was applied to derivative **2.98**.



Scheme 2.20. Reagents and conditions: (a) first **2.92**, *n*-BuLi, TMEDA, THF, -30 °C, 1 h then **2.93**, -30 °C, 1 h; (b) $CHCl_3$, rt, 2 h, 27% (**2.95**), 28% (**2.96**) (2 steps); (c) Zn, AcOH, rt, 1 h, **2.97** (98%) or **2.98** (98%).



Scheme 2.21. Reagents and conditions: (a) NBS, $AgNO_3$, $MeCN/H_2O$, rt, 1 h; (b) $NaBH_4$, MeOH, rt, 30 min, 31 % (2 steps); (c) H_2, Pd/C, MeOH, HCl, rt, 16 h, 93%.

Very recently, Michalak and co-workers have reported the nucleophilic addition of variously monosubstituted acetylenes to optically pure nitrones catalyzed by NHC-Cu(I) complexes (Table 2.4).[64] The presented methodology, leading to a family of 2-propargyl-hydroxylamines, is both high-yielding and very diastereoselective (in most cases, *dr* > 95:5). Usually, such transformations require the

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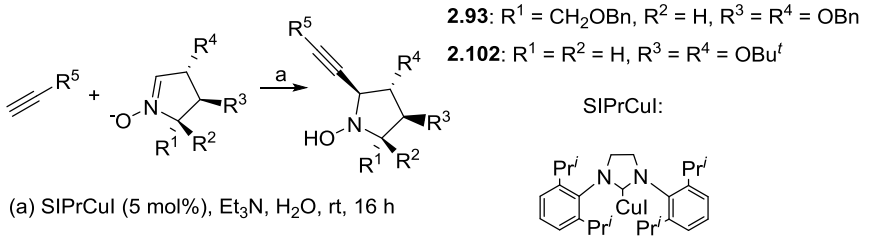
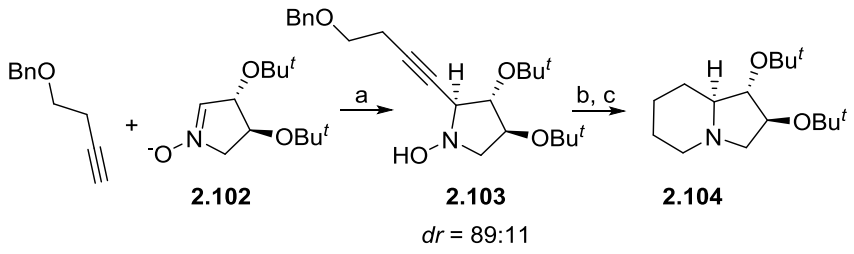
use of stoichiometric amounts of organometallic species under strictly anhydrous conditions. However, the authors presented a methodology, in which water is not only tolerable, but is also a preferred solvent. Interestingly, this is an unprecedented behaviour of Cu(I) acetylides in the combination with nitrones, since, usually, under such conditions, the Kinugasa reaction takes place.[65]

Table 2.4. NHC-Cu(I)-catalyzed, nucleophilic addition of terminal alkynes to cyclic, sugar-derived nitrones. All products were obtained as practically single diastereoisomers (*dr* > 95:5).



entry	nitrone	R^5	isolated yield (%)
1	**2.93**	phenyl	94
2	**2.93**	*p*-F-phenyl	98
3	**2.93**	*p*-MeO-phenyl	97
4	**2.93**	*p*-NO_2-phenyl	0
5	**2.93**	*p*-NMe_2-phenyl	73
7	**2.93**	$BnOCH_2$-	62
8	**2.93**	$PhCH_2$-	79
9	**2.102**	$Cl(CH_2)_2CH_2$-	63
10	**2.102**	phenyl	96

Finally, Michalak and co-workers used their novel methodology to obtain (-)-lentiginosine scaffold **2.104** (Scheme 2.22).



Scheme 2.22. Reagents and conditions: (a) SIPrCuI (10 mol%), TMG, H_2O, 50 °C, 16 h, 66%; (b) H_2, Pd/C, EtOH, rt, 16 h; (c) Ph_3P (polymer-bound), CCl_4, DCM, rt, 16 h, 65% (2 steps).

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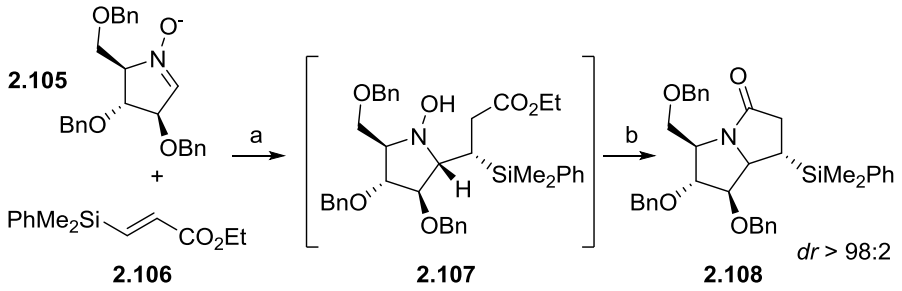
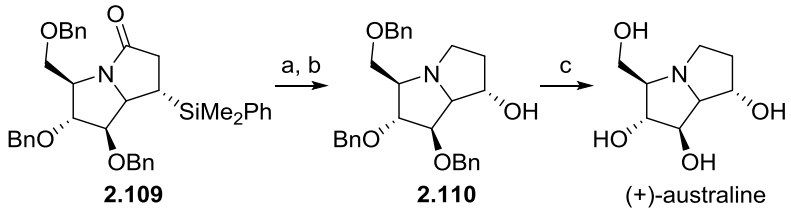
Recently, Py and Gilles presented the total synthesis of (+)-australine.[66] The key step consisted in a SmI_2-mediated cross-coupling between sugar-derived cyclic nitrone **2.105** and β-silyl ethyl acrylate **2.106** to give hydroxylamine **2.107** (not isolated) (Scheme 2.23). The following reduction/cyclization sequence gave lactam **2.108**, isolated as practically single diastereoisomer. The subsequent reduction of the lactam group, followed by Tamao-Fleming oxidation and deprotection, allowed to obtain the final alkaloid (Scheme 2.24).



Scheme 2.23. Reagents and conditions: (a) SmI_2, HFIP, LiBr, THF, -78 °C to -30 °C, 5 min; (b) Zn, AcOH, 80 °C,))), 64% (2 steps).



Scheme 2.24. Reagents and conditions: (a) $BH_3 \cdot Me_2S$, THF, reflux, 1 h, 73%; (b) *t*-BuOOH, KH, TBAF, DMF, rt, 40 h, 89%; (c) H_2, Pd/C, HCl, THF/MeOH, rt, 6 h, quant.

In another paper, Py and co-workers presented a route to 2,2-disubstituted piperidines by means of a highly selective, stereodivergent nucleophilic addition of vinylmagnesium bromide to L-sorbose-derived nitrone **2.111** (Scheme 2.25).[67] The obtained mixture of hydroxylamines **2.112** and **2.113** was, without purification, reduced to the mixture of separable amines **2.114** and **2.115**. Subsequently, they obtained *N*-allyl-substituted piperidines **2.116** and **2.117**, which were then transformed into a series of bicyclic derivatives, for example **2.119** and **2.121** (Scheme 2.26). These compounds turned out to be quite potent inhibitors of α-glucosidase ($IC_{50} \approx 0.05$ μM for **2.119** and 1.5 μM for **2.121**).

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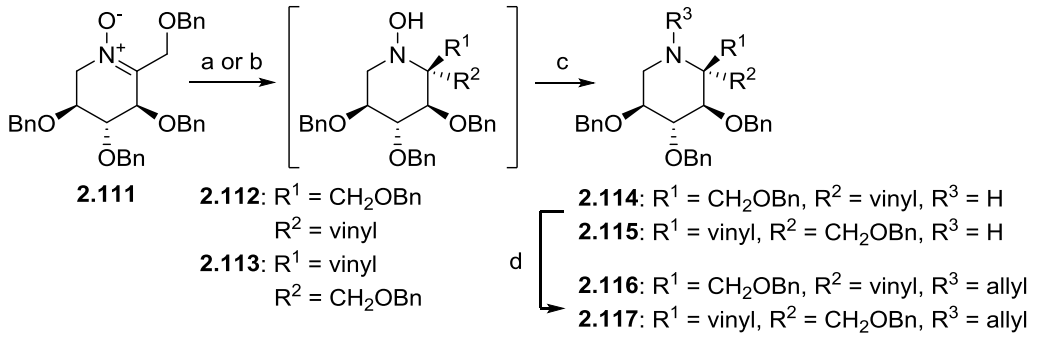
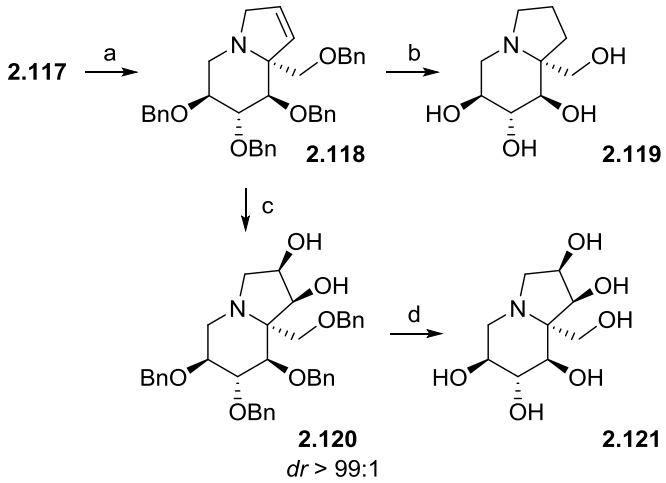


Scheme 2.25. Reagents and conditions: (a) vinyl-MgBr, DCM, -78 °C; (b) vinyl-MgBr, $ZnCl_2$, DCM, -78 °C; (c) Zn, AcOH/EtOH, 80 °C,))), (**2.114** : **2.115** = 15:85), 91% (route (a)) or (**2.114** : **2.115** = 98:2), 86% (route (b)); (d) allyl-Br, MeCN, K_2CO_3, KI, reflux, 6 h, 82% (**2.116**) or 81% (**2.117**).



Scheme 2.26. Reagents and conditions: (a) cat. **2.123** (5 mol%), DCM, 40 °C, 3 h, 93%; (b) H_2, $Pd(OH)_2/C$, HCl, MeOH, rt, overnight, 89%; (c) OsO_4, TMEDA, DCM, -78 °C to -20 °C, 3 h, then ethylene diamine, rt, 16 h, then $NaHSO_3$, rt, 16 h, 62%; (d) H_2, $Pd(OH)_2/C$, HCl, MeOH, rt, overnight, 91%.

2.1.4. Ring-closing metathesis

Soon after its discovery, the ruthenium-based olefin metathesis became widely applied in organic synthesis. This potent, versatile reaction offers an atom-economy approach, relatively stable catalysts and the ease of use.[68] Structures of some of the commonly used catalysts are depicted on Fig. 2.3.

Not surprisingly, the olefin metathesis, in its ring-closing variant (RCM), was also used with much success in total syntheses of iminosugars.[69] This approach was

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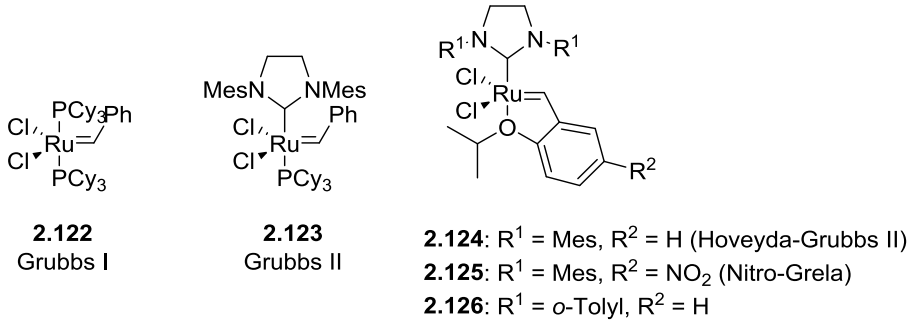
proven in numerous examples to be fast (at least in terms of number of synthetic steps involved) and reliable.



2.122
Grubbs I

2.123
Grubbs II

2.124: R^1 = Mes, R^2 = H (Hoveyda-Grubbs II)
2.125: R^1 = Mes, R^2 = NO_2 (Nitro-Grela)
2.126: R^1 = *o*-Tolyl, R^2 = H

Fig. 2.3. Some of the most commonly used Ru catalyst for olefin metathesis.

However, the RCM methodology has also its drawbacks. First of all one has to be aware, that the basic amino group in the substrate, if present, deactivates the catalyst.[70] Therefore, before the reaction, it should be reversibly masked as, for example, a carbamate, amide, or ammonium salt. Secondly, the metathesis catalysts are still very expensive – a fact, that cannot be ignored when planning the synthesis on a larger scale. Moreover, the pollution of the products with ruthenium, even many steps after the metathesis, is usually significant. This poses serious problems in drug development, where the use of heavy metals is highly avoided.[71]

In the first example, Madsen's approach to nine-membered nitrogen heterocycle **2.133**, in which the key step consisted in the RCM of diene **2.131** (Scheme 2.27), is presented.[72] First, they obtained iodo-derivative **2.128**, which was then subjected to the Vasella reaction. Thus obtained aldehyde **2.129** was reacted with homoallylamine to give, after the reduction of the transitional imine, amine **2.130**. The protection with trifluoroacetyl group gave derivative **2.131**. The optimization of the ring-closing step revealed, that the reaction had to be performed at elevated temperatures (refluxing toluene or benzene), under highly dilute conditions (< 1 mM). The catalyst screening showed, that only complexes with an *N*-heterocyclic carbene ligand give good results, most notably catalyst **2.126**. As a by-product, the eight-membered derivative **2.132** was isolated in significant amounts in each run (*ca.* 10%). It is most likely formed as a result of isomerization of the terminal double bond followed by the elimination of propene during the ring closure step. In the final sequence, Madsen and co-workers transformed the heterocycle **2.133**, via intramolecular epoxide ring opening, into (+)-castanospermine (Scheme 2.28).

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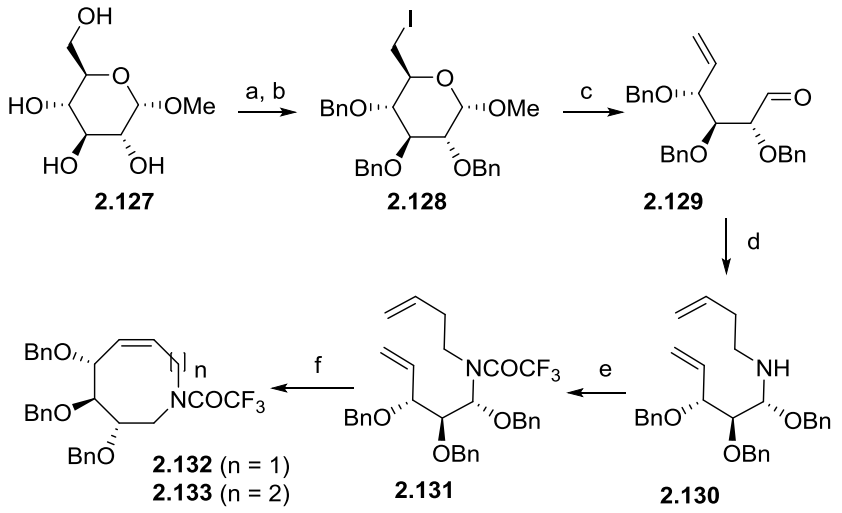
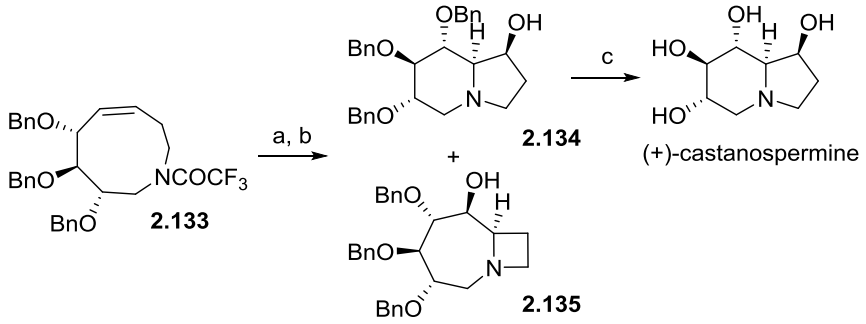


Scheme 2.27. Reagents and conditions: (a) I_2, Ph_3P, imidazole, THF, 65 °C, 87%; (b) $BnOC(NH)CCl_3$, TfOH, dioxane, rt, 90%; (c) Zn, THF/H_2O,))), 40 °C, 1 h, 99%; (d) homoallylamine, MS 4 Å, AcOH/THF, $NaCNBH_3$, 0 °C to rt, 14 h, 89%; (e) TFAA, Et_3N, DCM, 0 °C, 0.5 h, 93%; (f) cat. **2.126** (30 mol%), toluene, 80 °C, 24 h, 78% (**2.133**), 7% (**2.132**) .



Scheme 2.28. Reagents and conditions: (a) CF_3COCH_3, Oxone, $NaHCO_3$, Na_2EDTA, MeCN/H_2O, -10 °C to 0 °C, 4 h; (b) *t*-BuOK, Et_2O, H_2O, 0 °C to rt, 10 h, 44% (**2.134**), 15% (**2.135**) (2 steps); (c) H_2, Pd/C, HCl, MeOH, rt, 48 h, then Amberlite IRA-400 (OH), MeOH, 2 h, rt, 94% (2 steps).

In the next example, the Poisson's group used the RCM in the *de novo* asymmetric total synthesis of (+)-DNJ (Scheme 2.29).[73] Sharpless asymmetric epoxidation of alcohol **2.136** gave oxirane **2.137** with excellent enantioselectivity (*ee* > 99%). Then, oxazolidinone **2.138** was synthesized and subsequently transformed into benzylidene acetal **2.139**. Alkylation of the latter with allyl iodide **2.140** gave diene **2.141**. With this compound in hands, they started to optimize the one-pot metathesis/hydroboration-oxidation sequence. After optimization of the reaction conditions, the RCM step was carried out in refluxing toluene in the presence of benzoquinone,

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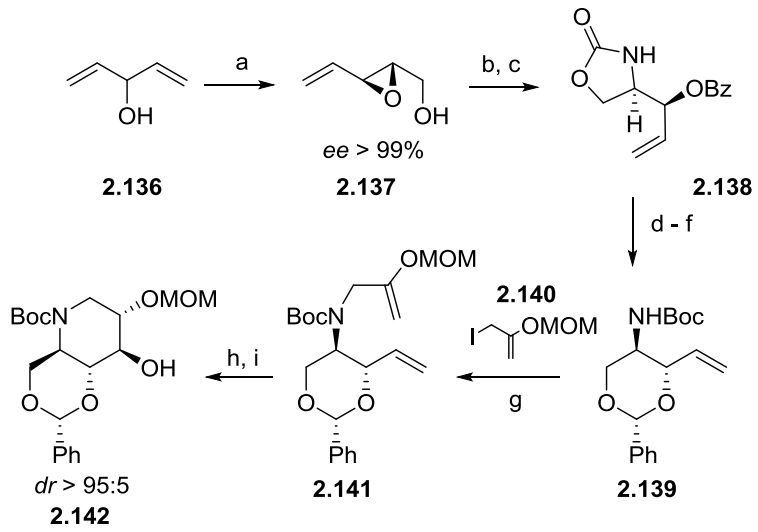
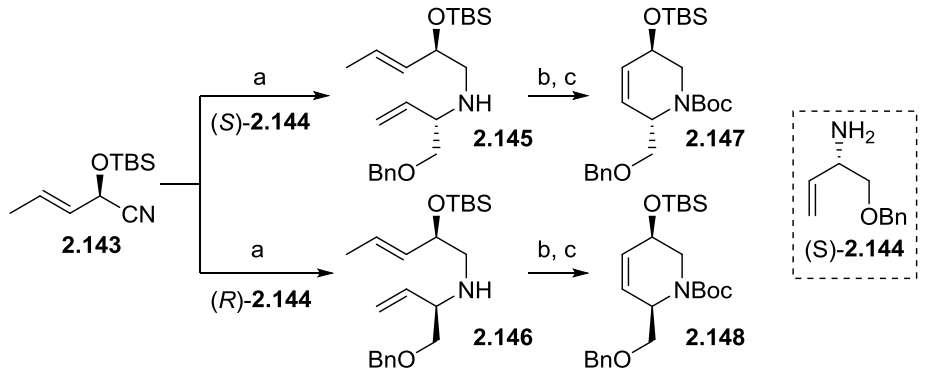
with Hoveyda-Grubbs II (**2.124**) as catalyst. Subsequently, hydroboration-oxidation was performed in a one-pot manner to yield derivative **2.142**, which, upon treatment with HCl, gave the final compound.



Scheme 2.29. Reagents and conditions: (a) Sharpless asymmetric epoxidation; (b) BzNCO, Et_2O, 0 °C to rt, 2 h, 96%; (c) K_2CO_3, DCM/H_2O, $C_{12}H_{25}NMe_3Cl^+$ (cat.), rt, 16 h, 80%; (d) i. Boc_2O, Et_3N, DMAP, DCM, rt, 1.5 h, 91%; (e) EtONa, EtOH, 0 °C to rt, 2 h, 93%; (f) $PhCH(OMe)_2$, CSA, DCM, rt, 6 h, 91%; (g) **2.140**, NaH, DMF, 0 °C to rt, 1 h, 82%; (h) cat. 2.124 (10 mol%), BQ (10 mol%), toluene, reflux, 4.5 h; (i) $BH_3 \cdot Me_2S$, THF, 0 °C to rt, 20 h, then $NaBO_3 \cdot 4H_2O$, rt, 18 h, 70% (2 steps).

In another approach, starting from enantiomerically pure TBS-protected cyanohydrin **2.143** (obtained earlier by enzyme-catalyzed hydrocyanation of crotonaldehyde), the Overkleeft group prepared derivatives of DNJ (Scheme 2.30).[74]



Scheme 2.30. Reagents and conditions: (a) DIBAL-H, Et_2O, -78 °C to 10 °C, then MeOH, (*S*)- or (*R*)-**2.144**, -90 °C to rt, overnight, then $NaBH_4$, 0 °C to rt, 2 h, 80% (**2.145**) or 78% (**2.146**); (b) Boc_2O, THF, TEA, 50 °C, overnight; (c) **2.122** (3.5 mol%), DCM, reflux, 48 h, 99% (**2.147**) or 95% (**2.148**) (2 steps).

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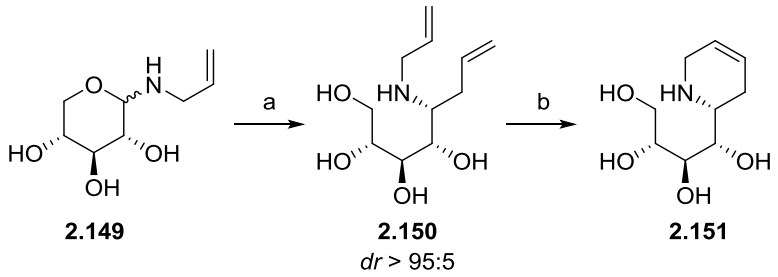
In the first step, they performed a sequence of a DIBAL-H reduction followed by reductive amination with amines (*S*)-**2.144** and (*R*)-**2.144** (synthesized earlier by Ellman's[75] methodology). This way, they obtained dienes **2.145** and **2.146**, respectively. Once the amine moieties had been protected with Boc groups, the RCM step was performed with Grubbs I catalyst (**2.122**) in refluxing DCM to give piperidine derivatives **2.147** and **2.148**. The subsequent *syn*-dihydroxylation and deprotection gave the final iminosugars.

Very interesting approach to iminosugars was presented by Behr and co-workers.[76] Using an indium-mediated allylation of carbonyl group on unprotected pentosylamines, such as **2.149**, they prepared linear diene **2.150** with very high diastereoselectivity (*dr* > 95:5) (Scheme 2.31). The latter compound was then *in situ* protected with *p*-toluenesulfonic acid to yield an ammonium salt and subjected to RCM with Hoveyda-Grubbs II catalyst (**2.124**). Thus, the piperidine derivative **2.151** with a long, polyhydroxylated side-chain was obtained.



Scheme 2.31. Reagents and conditions: (a) In, allyl bromide, MeOH, rt, 16 h, 79%; (b) TsOH, DCM, cat. **2.124** (2.5 mol%), 40 °C, 16 h, 55%.

2.1.5. Miscellaneous approaches

Apart from the previously described, well-established methodologies, few different, less common approaches were also reported.

For example, Aggarwal and Bi reasoned,[77] that the hemiaminal **2.155** can be synthesized from amine **2.154** (derived itself from protected D-glycaeraldehyde) by means of aza-Achmatowicz reaction (Scheme 2.32). The obtained heterocyclic derivative **2.155** was transformed, under acidic conditions, into acetal and then, the carbonyl group was reduced under the Luche conditions providing derivative **2.156** as practically single isomer. Subsequently, in a single step with H_2 and Pd/C, the Cbz group and *N*,*O*-acetal were cleaved, and the double bond was reduced to give

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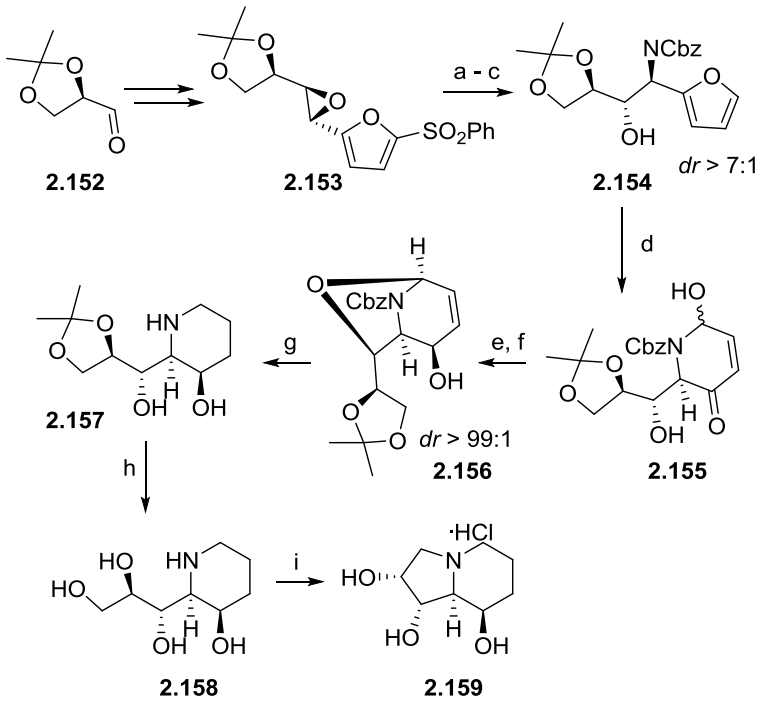
piperidine **2.157**. This compound was then easily transformed into 8a-*epi*-swainsonine **2.159**.

Although the aza variant of the Achmatowicz reaction is well established in the context of the synthesis of nitrogen heterocycles,[78] its application in the field of iminosugars is still limited, especially in the recent literature. However, some earlier reports can be found.[79,80,81]



Scheme 2.32. Reagents and conditions: (a) aq. NH_3, MeOH, rt, 24 h, 79%; (b) Na/Hg, MeOH, K_2HPO4, rt, 20 min, 92%; (c) CbzCl, DCM/H_2O, $NaHCO_3$, 0 °C to rt, 20 min, 98%; (d) *m*-CPBA (anh.), DCM, rt, 20 h, 72%; (e) *p*-TsOH·H_2O, toluene, MS 4 Å, rt, 1.5 h, 80%; (f) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, rt, 25 min, 95%; (g) H_2, Pd/C, MeOH, rt, 12 h, 67%; (h) *p*-TsOH·H_2O, MeOH, rt, 12 h, 93%; (i) DMF, Ph_3P, CCl_4, Et_3N, 80%.

Another less common approach towards bicyclic iminosugars was presented by Jarosz and Magdycz.[82] They used D-glucose-derived (*E*)-dienoaldehyde **2.160** to obtain oxime **2.161**, which was supposed, as they expected, to undergo intramolecular aza-Diels-Alder reaction to [5.6.0]-bicyclic hydroxylamine (Scheme 2.33). Instead, however, they obtained the vinyl-substituted [5.5.0]-bicyclic oxazolidine **2.162**, a product of a 1,3-dipolar cycloaddition. This compound, obtained as practically one isomer, was then transformed, *via* RCM with Grubbs I catalyst (**2.122**), to olefin **2.163**. The following *syn*-dihydroxylation with OsO_4 gave **2.164** as practically one isomer. Subsequent cleavage of the N-O bond with Zn/NH_4Cl, and debenzylation with sodium

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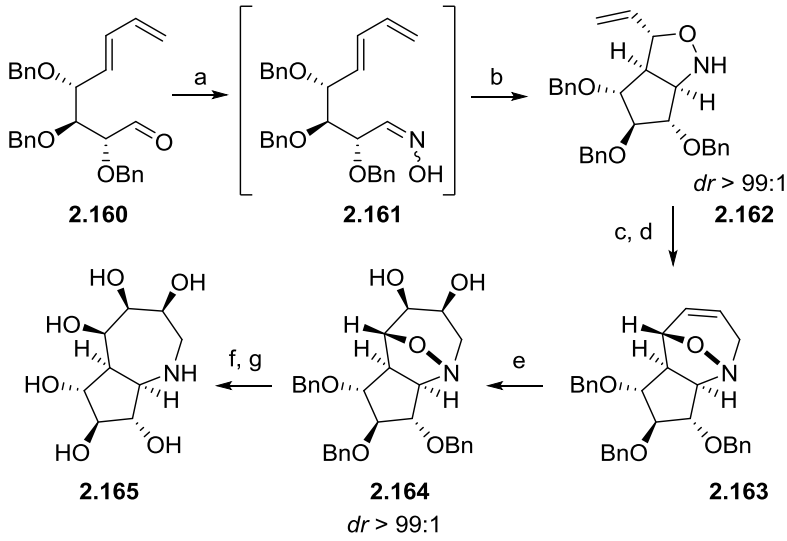
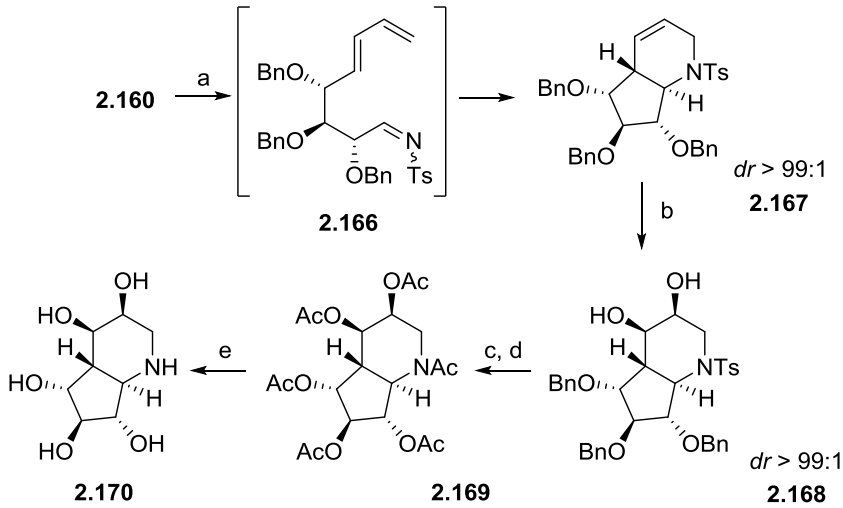
in liquid ammonia (since hydrogenolysis failed) yielded [5.7.0]-bicylic derivative **2.165**.



Scheme 2.33. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, EtOH/py, rt, 3 h; (b) benzene/toluene, rt, 10 kbar, 10 h, 99% (2 steps); (c) allyl-Br, DMF, K_2CO_3, reflux, 24 h, 65%; (d) cat. **2.122** (10 mol%), DCM, reflux, 6 h, 97%; (e) OsO_4, $NMO{\cdot}H_2O$, THF/*t*-BuOH/H_2O, rt, 24 h, 70%; (f) MeOH, NH_4Cl, Zn, 40 °C, 1 h, 70%; (g) Na/NH_3, THF, -78 °C, 5 h, 80%.

In another, similar approach, Jarosz and Magdycz transformed dienoaldehyde **2.160** into *N*-tosyl imine **2.166** (Scheme 2.34). [83]



Scheme 2.34. Reagents and conditions: (a) $TsNH_2$, *p*-TsOH, DCM, rt, 1 h, 66%; (b) OsO_4, $NMO{\cdot}H_2O$, THF/*t*-BuOH/H_2O, rt, 24 h, 85%; (c) Na/NH_3, THF, -78 °C, 5 h; (d) Ac_2O, py, rt, 10 h, 57% (2 steps); (e) MeOH, aq. NaOH, then Dowex H, quant.

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They were unable to isolate this transitional product, since it spontaneously cyclized, *via* aza-Diels-Alder reaction, to the desired [5.6.0]-bicylic compound **2.167** in a highly diastereoselective manner (*dr* > 99:1). It was then *syn*-dihydroxylated to give diol **2.168**, also as virtually one diastereoisomer. The following steps, namely deprotection with sodium in liquid ammonia (hydrogenolysis failed), acetylation and deacetylation gave polyol **2.170**. In a similar manner, starting from **2.167**, *anti*-diols were obtained by means of epoxidation/oxirane ring opening sequence.

2.2. Addition of Grignard reagents to *ω*-halonitriles

In this section, I summarize all literature reports on the addition of Grignard reagents to *ω*-halonitriles (as depicted on Scheme 1.0b). As a result of this cascade transformation, cyclic imines – compounds of great synthetic utility – are formed. I have found only five papers addressing the subject, so the research potential lying within this field is evident. The fact, that the transformation has not found any widespread application yet, may be attributed to the susceptibility of nitriles to undergo α-deprotonation under basic conditions,[84,85] which, in turn, may lead to significant amounts of side-products.

In one of the papers presented below,[86] a mesyl ester is used as a leaving group instead of a halide. In fact, the reported transformation is of the same type as those described in the other papers.

Finally, I would like to point out, that only one of the papers examines the possibility of employing allylmagnesium halide - with no success, though.[21] Given the fact, that an allyl group is a highly versatile moiety, studies towards the use of this particular reagent in the context of the described cascade transformation are still necessary.

2.2.1. Seminal works of Fry and Dieter

It was not until 1994 that the potential of the addition of Grignard reagents to *ω*-halonitriles was recognized.[21] In that paper, Fry and Dieter described the addition of alkyl, vinyl, and phenyl magnesium halides to simple *ω*-bromonitriles (Table 2.5). A typical procedure involved the addition of a solution of a Grignard reagent in diethyl ether to a solution of a substrate in benzene. According to this report, five-membered

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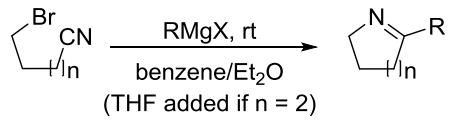
imines are obtained easily (Table 2.5, entries 1-4), whereas six-membered rings are formed much slower (entries 8-11).

Table 2.5. Synthesis of cyclic imines from ω-bromonitriles by the addition of Grignard reagent/cyclization cascade.



entry	n	R	X	isolated yield (%)
1	**1**	*n*-butyl	Cl	84
2	**1**	phenyl	Br	90
3	**1**	*s*-butyl	Cl	55
4	**1**	benzyl	Cl	72
5	**1**	*t*-butyl	Cl	<10
6[a]	**1**	vinyl	Br	0
7[b]	**1**	allyl	Cl	0
8	**2**	*n*-butyl	Cl	75
9	**2**	phenyl	Br	85
10	**2**	*s*-butyl	Cl	58
11	**2**	benzyl	Cl	64
12[c]	**3**	phenyl	Br	0

[a] Most of the starting material recovered. [b] Diallyl piperidine isolated (17%). [c] Acyclic bromoimine isolated.

As it turned out, in the latter case, the addition of THF was crucial to obtain products with good yields. The authors were not able, however, to obtain seven-membered imines (entry 12). It should be pointed out, that the addition of allylmagnesium chloride to ω-bromonitriles was unsuccessful – the desired imine was not isolated (entry 7). Instead, the authors reported on the formation of diallylpiperidine in 17% yield, resulting from the addition of the second equivalent of the Grignard reagent to the transitional cyclic imine. The reactions with vinylmagnesium bromide (entry 6) and *t*-butyl magnesium chloride (entry 5) were also unsuccessful. The former gave a complicated mixture of products, whereas the latter left the starting material almost intact.

Nonetheless, encouraged by the generally promising results, Fry and Dieter continued their work in this field. In the following paper,[22] they broadened the

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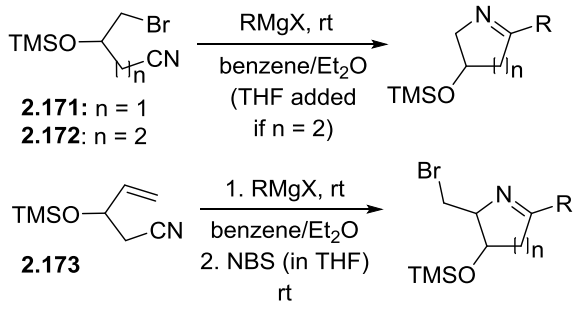
substrate scope by using trimethylsilyloxy-substituted ω-bromonitriles (Table 2.6, entries 1-7).

Moreover, in order to study a NBS-induced cyclization, they prepared also trimethylsilyloxy-substituted γ,δ-unsaturated nitriles (entries 8-10). It turned out, however, that only phenylmagnesium bromide performs well in this transformation, whereas the addition of alkyl Grignard reagents leads to complicated mixtures of products. Therefore, the cyclization of ω-bromonitriles is a much more reliable process.

Table 2.6. The synthesis of cyclic imines from trimethylsilyloxy ω-bromonitriles and γ, δ-unsaturated nitriles (X = Br or Cl) by the addition of Grignard reagent/cyclization cascade.



entry	substrate	R	isolated yield (%)
1	**2.171**	*n*-butyl	49
2	**2.171**	Ph	69
3	**2.171**	benzyl	57
4	**2.172**	*n*-butyl	81
5	**2.172**	Ph	85
6	**2.172**	benzyl	63
7	**2.172**	*n*-propyl	74
8	**2.173**	Ph	58
9	**2.173**	*n*-butyl	0
10	**2.173**	benzyl	0

In the same paper, Fry and Dieter proved the synthetic utility of their newly developed cascade reaction by accomplishing the total synthesis of (+/-)-pseudo-conhydrine (Table 2.7). Interestingly, the choice of the reduction conditions was crucial for the relative position of the substituents in the product. Namely, the reduction with H_2 on Pt gave mainly the *syn* product, whereas employing $LiAlH_4$ gave predominantly the *anti* isomer.

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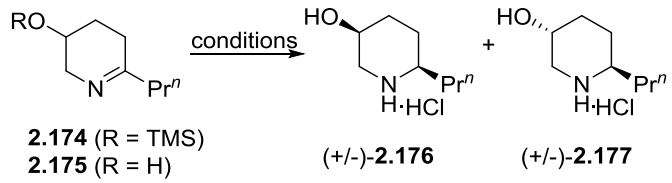
Table 2.7. Grignard addition-cyclization in the synthesis of (+/-)-pseudoconhydrine.



2.174 (R = TMS)
2.175 (R = H)

(+/-)-**2.176**

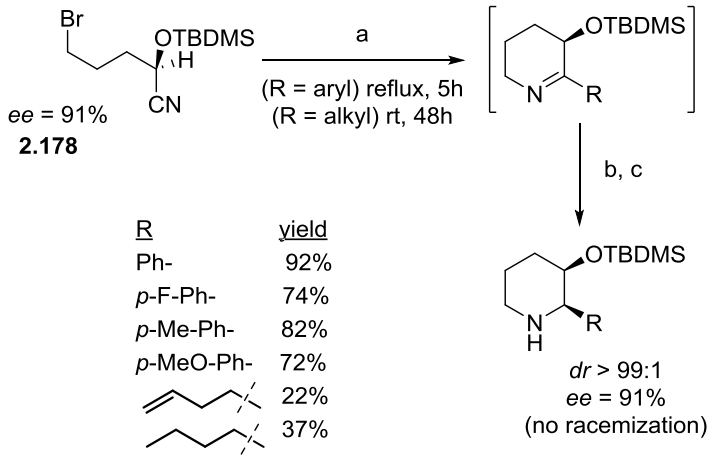
(+/-)-**2.177**

entry	substrate	conditions	isolated yield (%)	ratio 2.176/2.177
1	**2.174**	i. H_2/Pt, EtOH, ii. conc. HCl	>95	90/10
2	**2.175**	i. H_2/Pt, EtOAc, ii. conc. HCl	95	60/40
3	**2.175**	i. LAH, THF, reflux ii. conc. HCl	86	5/95

2.2.2. Further application in the total synthesis

Apart from the previously mentioned synthesis of (+/-)-pseudoconhydrine, I have found only three more examples of the use of the discussed cascade transformation in total synthesis. All of them were inspired by the pioneering papers by Fry and Dieter.

In the first of those papers,[87] authors used optically pure 5-bromo-2-hydroxy-pentanenitrile silyl ether **2.178** as substrate (Scheme 2.35).



Scheme 2.35. Reagents and conditions: (a) RMgBr, THF; (b) $NaBH_4$, MeOH, rt, 12 h; (c) CbzCl, DCM/H_2O, Na_2CO_3, 0 °C to rt, 4 h, yields in table (over 3 steps).

Subsequently, it was treated with several various arylmagnesium bromides to afford, after reduction with $NaBH_4$ (the transitional cyclic imine was unstable, so it had

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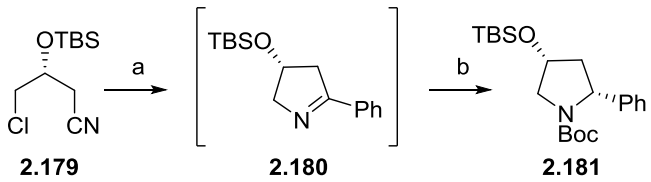
to be reduced *in situ*), the desired piperidine derivatives as practically single diastereoisomers.

The aliphatic Grignard reagents, namely butyl- and butenylmagnesium halides, were also tested, but the products were obtained only with moderate yields. As I mentioned before, nitriles are susceptible towards α-deprotonation.[84,85] Therefore, the loss of enantiomeric purity in the products was expected by the authors. However, as indicated by HPLC studies on chiral columns, no racemization occurred – the *ee* of the products was the same as in the substrate **2.178**. It should be noted, that the conditions applied for the addition of a Grignard reagent differed quite significantly from those described by Fry and Dieter. Namely, the authors carried out the reactions in refluxing THF, instead of using benzene/diethyl ether mixture at ambient temperature. However, they do not comment on this fact.

In the next report, the Maeda's group described an approach to the synthesis of 3,5-disubstituted pyrrolidine **2.181** (Scheme 2.36).[88] A moiety of this type is found in some carbapenem antibiotics, *e.g.* in meropenem. The synthesis started from readily obtainable chloronitrile **2.179**,[ii] to which PhMgBr was added. In order to ensure a successful addition to the nitrile group, a relatively non-polar MTBE had to be used as a solvent. However, for the cyclization step, addition of more polar THF or DME was crucial. The resulting cyclic imine, without purification, was subsequently hydrogenated to afford the desired pyrrolidine scaffold. After protection with Boc group, compound **2.181** was obtained.



2.179 **2.180** **2.181**

Scheme 2.36. Reagents and conditions: (a) PhMgBr, MTBE, 0 °C to rt, 15 min, then THF or DME, rt, 5 min; (b) H_2, Pt/C, rt, 18 h, then Boc_2O, rt, 5 h, 89% (3 steps).

The most recent paper comes from the Behr's group.[86] The authors attempted to develop a methodology leading to analogs of polyhydroxylated ketimines, a family of naturally-occurring unsaturated iminosugars. However, this report differs from those previously described in two ways. First of all, the mesyl ester was used as a leaving

[ii] This compound is synthesized by TBS protection of commercially available (*R*)-(+)-4-chloro-3-hydroxybutyronitrile.

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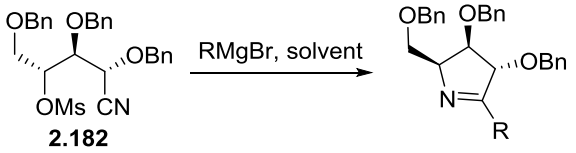
group instead of a halide and, secondly, it was not located at the terminal position (Table 2.8).

Table 2.8. Grignard addition of alkyl- and arylmagnesium bromides to sugar-derived mesyl ester 2.182.



2.182

entry	R	*T* (°C)	solvent	time (h)	conversion (%)	yield (%)
1	methyl	20	THF	24	< 5	0
2	methyl	20	Et_2O	24	< 5	0
3	methyl	20	toluene	24	30	0
4[a]	methyl	20	toluene	24	60	10
5	methyl	70	toluene	1.5	100	55
6[b]	methyl	70	toluene	1.5	35	0
7	phenyl	70	toluene	1.5	100	61
8	*n*-butyl	70	toluene	1.5	100	56
9	*n*-$C_{10}H_{21}$-	70	toluene	1.5	100	38

[a] $LiClO_4$ (1.5 equiv) was added. [b] THF (*ca*. 5%) was added.

After some screening of conditions, they established, that the reaction proceeds best in toluene at elevated temperatures (entries 5 and 7-9). According to their results, the proper selection of a solvent plays a very important role for the successful outcome of the reaction. For example, the process is much slower in the presence of even small amounts (*ca*. 5%) of THF (entry 6).

In order to investigate the tolerance of protecting groups, the authors synthesized some other sugar-like substrates (Scheme 2.37) and performed on them the addition of Grignard reagents. The reaction proceeded well in the presence of isopropylidene moiety, *t*-butyldimethylsilyl ether and trityl group.

Surprisingly, when a derivative **2.185** was used as substrate under the same conditions as **2.183** and **2.184**, only linear products were formed. The addition of THF to the reaction mixture after the Grignard reaction ensured the cyclization to imine **2.189**. In the last step, the obtained ketimines were deprotected with BCl_3 to afford the final products.

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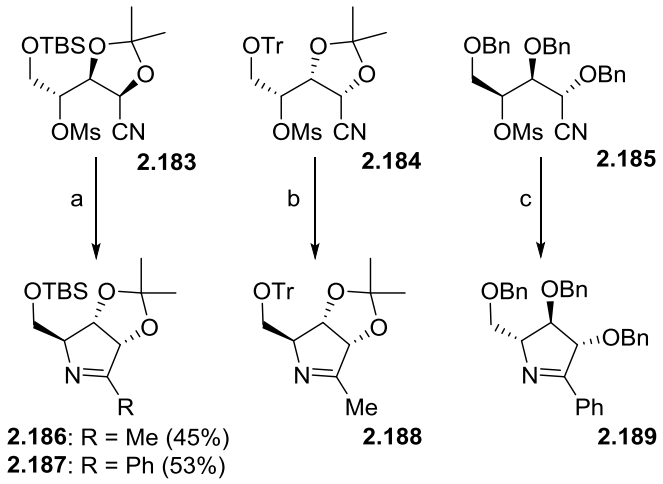

Scheme 2.37. Reagents and conditions: (a) RMgBr, toluene, 70 °C, 1.5 h; (b) MeMgBr, toluene, 70 °C, 1.5 h, 88%; (c) PhMgBr, toluene, 70 °C, 1.5 h, then THF, rt, overnight, 50%.

2.3. Summary

In the first section of this chapter, I have summarized the most recent literature reports concerning the synthesis of iminosugars. Due to the promising biological properties they may possess, these compounds represent an interesting synthetic target and, having usually many stereogenic centers, not a trivial one. Moreover, the total syntheses of iminosugars often serve as a challenging testing ground for the development of new synthetic tools.

Then, in the subsequent section, I have highlighted some other important facts. First of all, the addition of Grignard reagents to ω-halonitriles followed by intramolecular displacement of a halide appears to be a convenient way to obtain five- and six-membered cyclic imines, compounds of high synthetic utility, *e.g.* in the context of total synthesis of iminosugars. However, this approach has not been yet extensively studied - only several reports can be found in the literature. It is not surprising then, that a lot of work is still required to overcome some difficulties. For example, a major shortcoming of this methodology is the lack of a successful use of allyl and vinyl Grignard reagents. Since these organometallic species allow to introduce highly versatile moieties to the molecule, more studies in this area still need to be conducted. Another question can be posed: is it possible to add, in a controlled and predictable manner, a second equivalent of a Grignard reagent to the transition cyclic imine? By this approach, the synthesis of 2,2-disubstituted piperidines and

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pyrrolidines would be possible. Ideally, one should be able to choose between conditions leading to mono- and disubstituted products.

On the basis of the above considerations, I found it reasonable to start studying the problem myself. The results of my work are presented in the following chapter.

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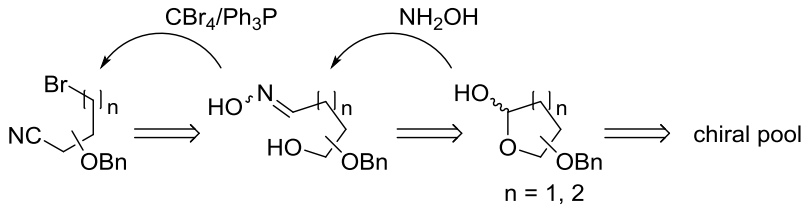
3. Results and Discussion

In this chapter, I have described my attempts to conduct addition of allylmagnesium bromide to various polyhydroxylated *ω*-bromonitriles, followed by an intramolecular displacement of a bromide anion, resulting in five- or six-membered cyclic imines. These compounds could be reduced *in situ* to the corresponding 2-allylsubstituted cyclic amines or they could accept another equivalent of the Grignard reagent to form 2,2-diallylsubstituted cyclic amines (as depicted in Scheme 1.1a in the Introduction). My goal is to be able to control the outcome of the reaction – it should be possible to obtain selectively either mono- or disubstituted products.

Then, in the next part of the chapter, I have reported on my attempts to transform the obtained cyclic amines into bicyclic iminosugars.

3.1. Addition of allylmagnesium bromide to polyhydroxylated *ω*-bromonitriles

I have envisioned, that polyhydroxylated *ω*-bromonitriles can be easily obtained in a two-step sequence from suitably protected carbohydrates. First, the free hemiacetal would be reacted with hydroxylamine to form an oxime and, subsequently, treated with CBr_4/Ph_3P (Appel conditions) (Scheme 3.0). The latter transformation would require the substitution at the terminal hydroxyl group and dehydration of the oxime moiety.



Scheme 3.0. Retrosynthetic analysis of polyhydroxylated bromonitriles.

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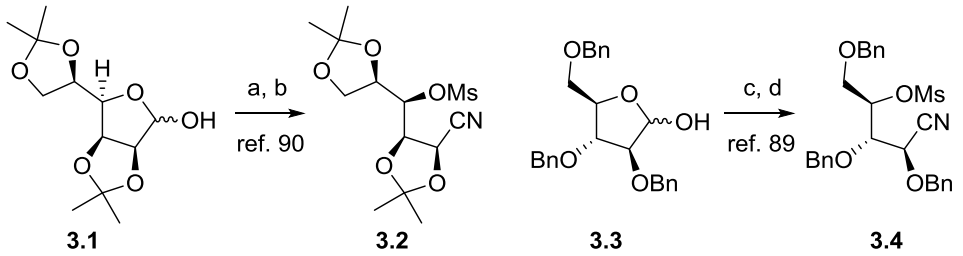
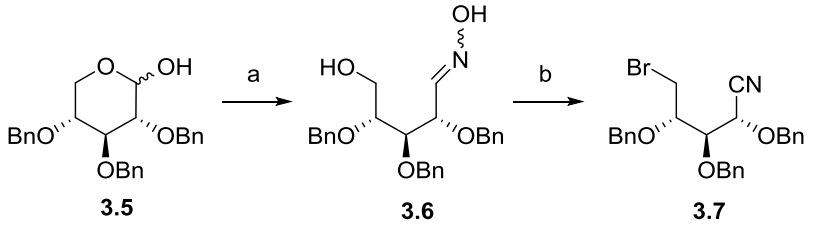
Similar approach was already reported in the synthesis of 5- and 6-*O*-methanesulfonyl-glyconontriles.[89,90] In these reports, mesyl chloride was used to enable dehydration of oximes (Scheme 3.1).



Scheme 3.1. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, $NaHCO_3$, $EtOH/H_2O$, rt, 2h; (b) MsCl, py, 0 °C to rt, 3 h, 49% (2 steps); (c) $NH_2OH{\cdot}HCl$, MeONa, MeOH, rt, 16 h; (d) MsCl, py, -20 °C to rt, overnight, 95% (2 steps).

3.1.1. Initial attempts

As a model substrate to study the addition of allylmagnesium bromide to *ω*-bromonitriles, I have decided to use compound **3.7** (Scheme 3.2). It can be easily obtained, in just two steps, from known[91] tri-*O*-benzyl derivative of D-xylose **3.5**. After treatment of this compound with hydroxylamine, oxime **3.6** was formed which, without purification, I subjected to the reaction with CBr_4/Ph_3P. Under these conditions, the desired **3.7** was formed with very good yield (83% after 2 steps). This approach turned out to be easily scalable and allowed me to obtain multigram quantities of derivative **3.7**.



Scheme 3.2. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, py, rt, 24 h; (b) CBr_4, Ph_3P, MeCN, 0 °C to rt, 1.5 h, 83% (2 steps).

With *ω*-bromonitrile **3.7** in hands, I started to study the title reaction.[92] In my initial attempt, I used the following procedure: allylmagnesium bromide (1 M solution in Et_2O, 1.3 equiv) was added dropwise to a solution of **3.7** in THF at 0 °C. After 75 min, I quenched the reaction with methanol and then I added $NaBH_4$. This approach

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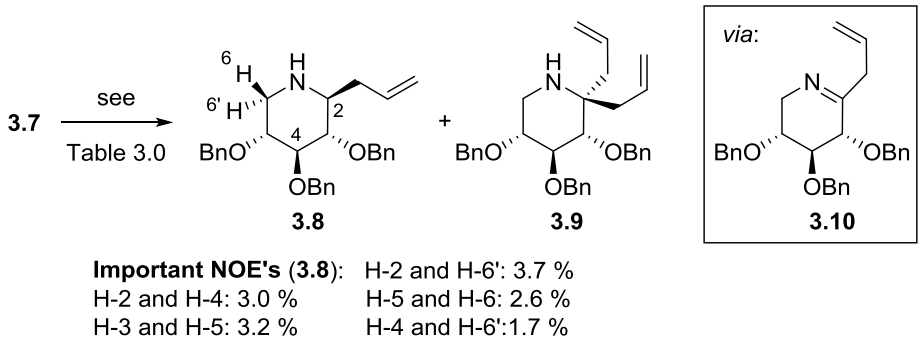
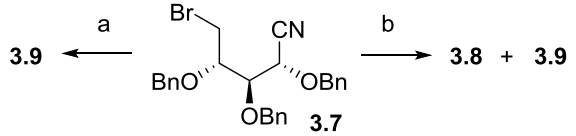
led to a mixture of 2-allylpiperidine **3.8** (28%, *dr* > 99:1) and 2,2-diallylpiperidine **3.9** (13%) (Scheme 3.3).



Scheme 3.3. Addition of allylmagnesium bromide to ω-bromonitrile **3.7**. For detailed reaction conditions see Table 3.0.

Although far from being successful, this attempt proved, that the planned transformation is possible, but an extensive search for suitable reaction conditions should be performed. Therefore, I decided to carry out the reaction in two different ways. The first one, already described, consists in the addition of only slight excess of allyl-MgBr and is followed by the addition of $NaBH_4$. The second approach, which should lead exclusively to 2,2-diallylsubstituted derivatives, relies on the use of a much larger excess of this Grignard reagent (5 equiv). I presented the results of my studies in Table 3.0.[92]

Table 3.0. Search for the optimal conditions for the selective transformations of **3.7**.



(a) allyl-MgBr (5 equiv), solvent, 0 °C, 1.5 h
(b) allyl-MgBr (1.3 equiv), solvent, 0 °C to rt
75 min, then MeOH, $NaBH_4$, rt, 10 min

entry	solvent	conditions	yields[a] 3.8 / 3.9 (%)
1	THF	*a*	n/a / 34
2		*b*	28 / 13
3	toluene	*a*	n/a / 22
4		*b*	74 / 4
5	THF/DMPU (4:1)	*a*	n/a / 70
6	THF/HMPA (4:1)	*a*	n/a / 68
7	methylene chloride	*a*	n/a / 23
8		*b*	55 / 0

[a] Isolated yields. In all cases, conversion > 90%.

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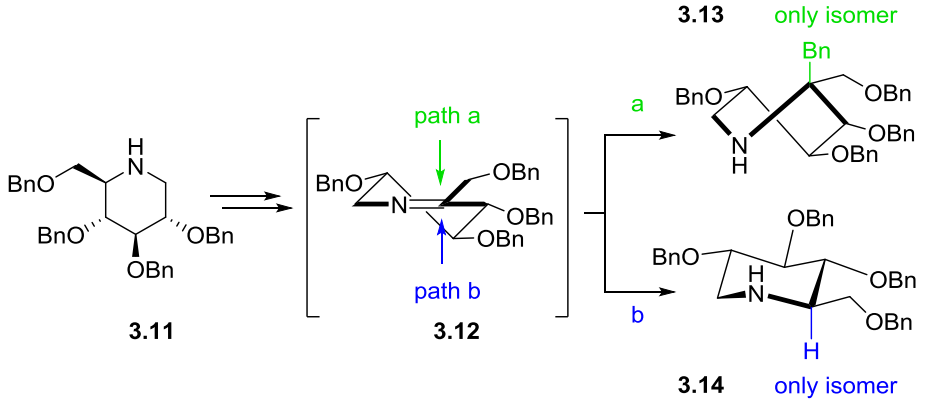
It turned out, that choosing of the proper solvent is crucial for the successful outcome of the reaction. Namely, toluene is a solvent of choice if 2-allylpiperidine **3.8** is the desired product (entry 4, 74%, only 4% of **3.9**), whereas a mixture of THF and DMPU (alternatively THF and HMPA) should be used for the synthesis of 2,2-diallyl-piperidine **3.9** (entries 5 and 6). To sum up, relatively apolar solvents (DCM and toluene) appear to limit the formation of 2,2-diallylsubstituted products, whereas more polar solvent mixtures (THF/DMPU, THF/HMPA) promote the addition of a second equivalent of allyl-MgBr to the transitional cyclic imine **3.10**.

In all cases, I obtained **3.8** as practically single diastereoisomer (*dr* > 99:1). I assigned the configuration of the newly formed stereogenic center based on 1D-NOE experiments (as depicted in Scheme 3.3). Such unusually high diastereoselectivity has been already observed in nucleophilic addition to endocyclic C=N bonds in polyhydroxylated compounds. Davis and co-workers, for example, reported on the reduction of imine **3.12** with $LiAlH_4$ (Scheme 3.4, path b), which afforded piperidine **3.14** as a single diastereoisomer.[93] Interestingly, BnMgCl (much bulkier nucleophile) approached the imine from the opposite site, giving exclusively piperidine **3.13** (path a), although in low yield (19%). Davis proposed, that two different reaction modes may be operating. The first one (path a) is controlled by steric factors, whereas the second one (path b) relies on the strain relief (*via* chair-like transition state). The low yield, in which **3.13** is formed may be attributed to the strain developed during the formation of twisted chair transition state.



Scheme 3.4. Studies of Davis concerning nucleophilic addition to cyclic imine **3.12**. Reagents and conditions: (a) BnMgCl, Et_2O, -78 °C to rt, 12 h, 19% (*dr* > 99:1); (b) $LiAlH_4$, Et_2O, 10 min, 87% (*dr* > 99:1).

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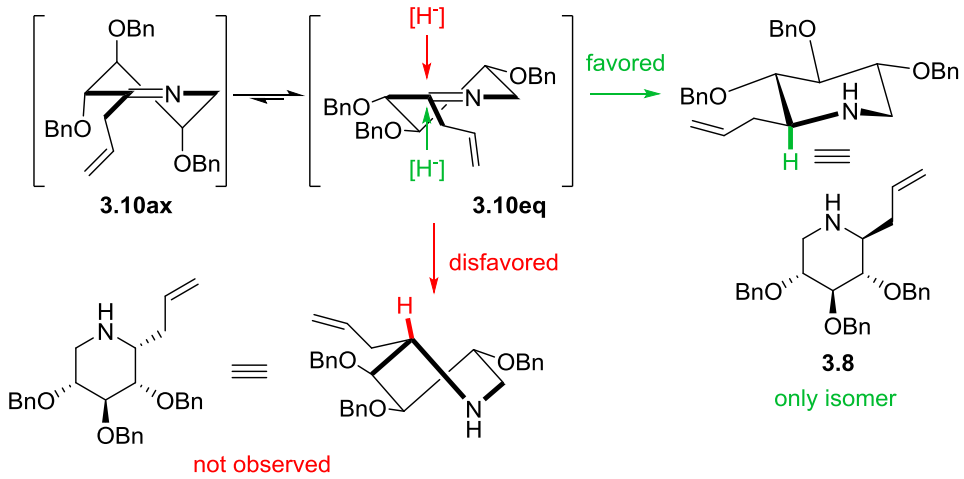
The similar phenomenon was observed by Cheng's group in the studies concerning addition of Grignard reagents to cyclic nitrones.[94] A closely related reaction was also examined by Py and co-workers (already depicted in Scheme 2.25);[67] the obtained results were in accordance with the model proposed by Davis.

I assumed, that in the case of imine **3.10**, the most preferred conformer is the one, in which benzyloxy substituents are placed in pseudo-equatorial positions (**3.10eq**; as in Davis' model) (Scheme 3.5). Although the electronic effects may impose pseudo-axial position at the C-3, C-4, and, as a consequence, at the C-2,[95,96] the 1,3-diaxial interactions probably strongly discourage formation of all-pseudo-axial conformer **3.10ax**.



Scheme 3.5. Possible course of the highly stereoselective reduction of imine **3.10**.

The attack of the hydride anion on the imine moiety proceeds through a much more favored, chair-like transition state rather than *via* twisted-boat conformation.[97] Such phenomenon is also observed in the ring opening of cyclohexene-derived epoxides (known as *trans*-diaxial rule).[98,99]

3.1.2. Broadening the reaction scope

In order to broaden the scope of the studied transformation, I decided to synthesize *ω*-bromonitriles **3.15**, **3.16** (shorter analogs of **3.7**), and **3.17** (in which the halogen atom is attached to the secondary carbon atom) (Scheme 3.6). These compounds would enable me the synthesis of pyrrolidine-based heterocycles, convenient intermediates in the preparation of many bicyclic iminosugars based on indolizidine and pyrrolizidine scaffold.[13,16]

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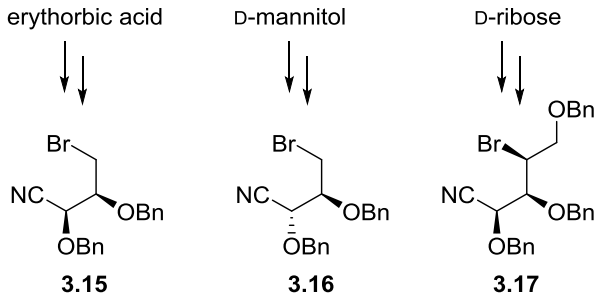
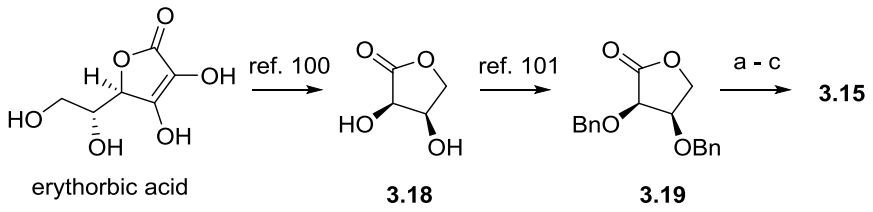


Scheme 3.6. Planned synthesis of polyhydroxylated bromonitriles.

I started the synthesis of compound **3.15** with erythorbic acid, a naturally occurring diastereoisomer of L-ascorbic acid. I transformed it, *via* a known procedure,[100] into D-erythronolactone **3.18** (Scheme 3.7). Then, I subjected this compound, again by using a known procedure,[101] to benzylation under mild, neutral conditions (Ag_2O, BnBr, $CaSO_4$) to get lactone **3.19**. Then, I carried out the reduction of this derivative with DIBAL-H to obtain the corresponding hemiacetal, which I then treated with hydroxylamine to get an oxime and then, finally, with CBr_4/Ph_3P to obtain the desired *ω*-bromonitrile **3.15** in good overall yield (72% over 3 steps). This approach was easily scalable and allowed me to obtain multigram quantities of **3.15**.



Scheme 3.7. Reagents and conditions: (a) DIBAL-H, DCM, -78 °C, 1 h; (b) $NH_2OH{\cdot}HCl$, py, rt, 24 h; (c) CBr_4, Ph_3P, MeCN, rt, 24 h, 72% (3 steps).

On the other hand, I started the synthesis of **3.16** from D-mannitol, which was transformed into 1,2:5,6-di-*O*-isopropylidene **3.20** derivative according to a known procedure (Scheme 3.8).[102] In the next step, I subjected this compound to benzylation *via* a slight modification of a known method.[103] This procedure furnished the fully protected derivative **3.21**. Then, I removed both isopropylidene moieties in a single step, which yielded compound **3.22**. Subsequently, I subjected this tetraol to oxidative cleavage with $NaIO_4$, which was then followed by the reduction of hemiacetal group with $NaBH_4$ to triol **3.23**. Then, I cleaved the 1,2-diol moiety in **3.23**, which allowed me to obtain hemiacetal **3.24**. In the next step, I used this compound in a reaction with

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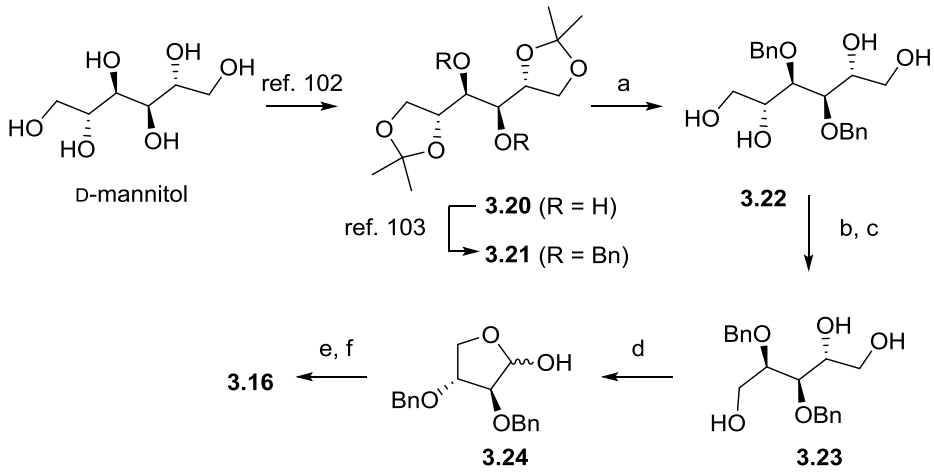
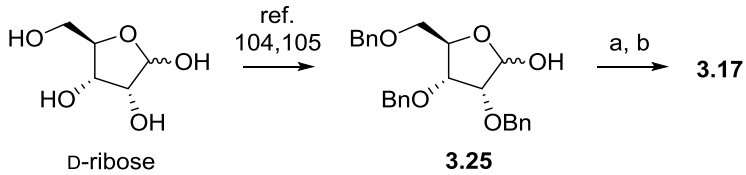
hydroxylamine to obtain oxime, which I subsequently subjected to Appel conditions (CBr_4/Ph_3P). This procedure led to the desired derivative **3.16**. The approach consists of several straightforward, easy to perform steps and enabled me to synthesize multigram quantities of **3.16**.



Scheme 3.8. Reagents and conditions: (a) conc. HCl, MeOH, 65 °C, 1 d; (b) $NaIO_4$, sat. $NaHCO_3$, DCM, rt, 2 h; (c) $NaBH_4$, MeOH, rt, 1 h, 59% (3 steps); (d) $NaIO_4$, sat. $NaHCO_3$, DCM, rt, 48 h; (e) $NH_2OH{\cdot}HCl$, py, rt, 24 h; (f) CBr_4, Ph_3P, MeCN, rt, 24 h, 60% (3 steps).

Finally, I started the synthesis of ω-bromonitrile **3.17** from D-ribose, which I transformed into tri-*O*-benzyl derivative **3.25** by a slight modification of known procedures (Scheme 3.9).[104,105] Then, I reacted this compound with hydroxylamine and subjected the resulting oxime to the Appel conditions (CBr_4/Ph_3P). This straightforward, two-step procedure allowed me to obtain the expected derivative **3.17** in multigram quantities.



Scheme 3.9. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, py, rt, 24 h; (b) CBr_4, Ph_3P, MeCN, 45 °C, 24 h, 53% (2 steps).

With these new ω-bromonitriles (**3.15**, **3.16**, and **3.17**) in hands, I started to study the title reaction. In the initial attempt, I followed the procedure described for the transformation of **3.7** into **3.8**: I added dropwise allylmagnesium bromide solution in Et_2O (1 M, 1.3 equiv) to a solution of **3.16** in toluene at 0 °C. After 75 min of stirring,

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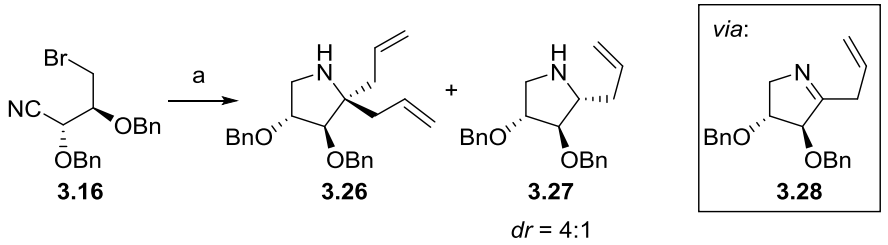
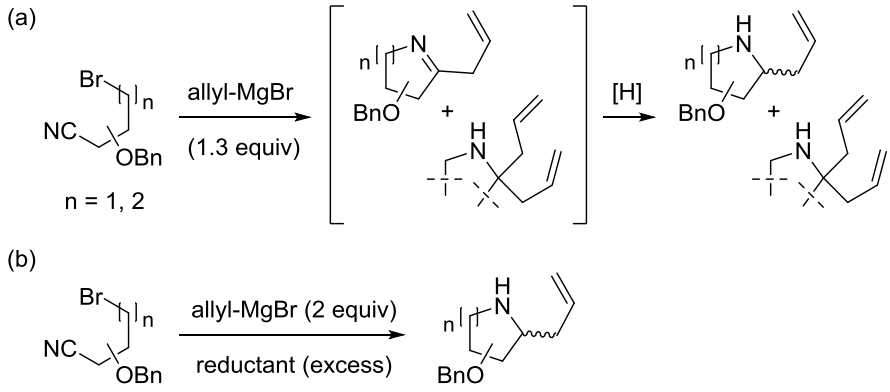
I added methanol and $NaBH_4$ to the reaction mixture. Although I expected an outcome similar to that observed in the case of **3.7** (Table 3.0, entry 4), this approach turned out to be much less selective and provided, unfortunately, a mixture of 2,2-diallyl-pyrrolidine **3.26** (22%) and 2-allylpyrrolidine **3.27** (35%, *dr* = 4:1) (Scheme 3.10).



Scheme 3.10. Reagents and conditions: (a) allyl-MgBr (1.3 equiv), toluene, 0 °C, 75 min, then MeOH, $NaBH_4$, rt, 10 min, 22% (**3.26**), 35% (**3.27**, *dr* = 4:1).

Since imine **3.28** reacts rapidly with the second equivalent of allyl-MgBr even in a relatively apolar toluene, I reasoned, that the reaction should be carried out, right from the beginning, in the presence of the excess of a reducing agent (Scheme 3.11b). This way, the formation of 2,2-diallylsubstituted product could be limited, or even eliminated.



Scheme 3.11. (a) Sequential mode of the reaction: slight excess of allyl-MgBr is first added and then, after the addition, is followed by reductant; this approach suffers from the formation of diallyl derivatives as byproducts. (b) Approach, in which excess of reductant is already present during the addition of allyl-MgBr; the formation of diallyl derivatives can be eliminated.

However, the choice of a suitable reducing agent was a challenging task. First of all, it had to react with the transitional imine **3.28** faster than the second equivalent of allyl-MgBr does. Moreover, it had to be unreactive towards nitriles (which excludes $LiAlH_4$ and DIBAL-H) and compatible with the Grignard reagents. In the light of these considerations, I decided to test the following reductants: $Et_3SiH/BF_3{\cdot}Et_2O$,

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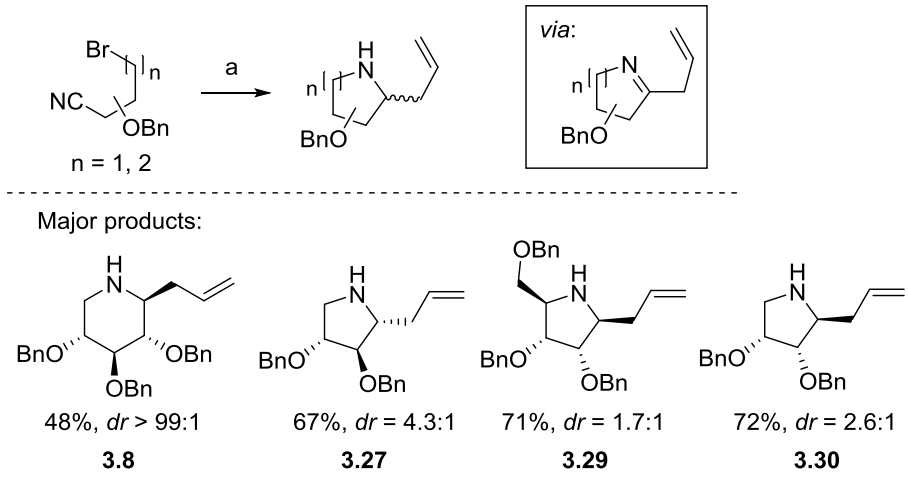
$Et_3SiH/TiCl_4$, $Et_3SiH/SnCl_4$, L-Selectride, $LiBH_4$, $BH_3 \cdot THF$, and $BH_3 \cdot Me_2S$, in various solvents (DCM, Et_2O, THF, toluene) and in a wide range of temperatures (-78 °C to rt). The obtained results were unsatisfying – either complicated mixtures were formed or 2,2-diallylsubstituted derivative was the major product. However, to my satisfaction, when I added the allylmagnesium bromide to the solution of **3.16** in toluene, in the presence of excess of freshly prepared $Zn(BH_4)_2$ (4 equiv), at 0 °C, the yield of 2-allylpyrrolidine **3.27** increased to 67%, with only traces (< 5%) of 2,2-diallylsubstituted **3.26** (Scheme 3.12). Zinc borohydride is known to be a mild reducing agent, soluble in many organic solvents (in opposition to $NaBH_4$).[106] In particular, it has already been successfully applied to the reduction of imines.[107,108]



Scheme 3.12. Reagents and conditions: (a) allyl-MgBr (1 M in Et_2O, 2 equiv), toluene, $Zn(BH)_4$ (4 equiv), 0 °C, 1 h.

Similarly, under these conditions, I converted ω-bromonitriles **3.17** and **3.15** into the corresponding 2-allylpyrrolidines **3.29** and **3.30**. By using this modified procedure, I also obtained piperidine **3.8** in fair yield and excellent diastereoselectivity. In neither case diallyl products were formed in significant amounts (*i.e.* >5%).

On the other hand, when I treated compounds **3.15** and **3.16** (dissolved in a mixture of THF and DMPU) with a larger excess of allyl-MgBr (5 equiv), 2,2-diallylsubstituted products **3.31** and **3.26** were formed in good yields (Scheme 3.13).

Since **3.27** and **3.30** were formed as inseparable mixtures of diastereoisomers, I was not able to determine the configurations at the newly formed stereogenic centers at this point. I assigned them at a later stage, after transformation of these compounds into bicyclic derivatives (see Scheme 3.35 and 3.36). Similarly, **3.29** was also formed

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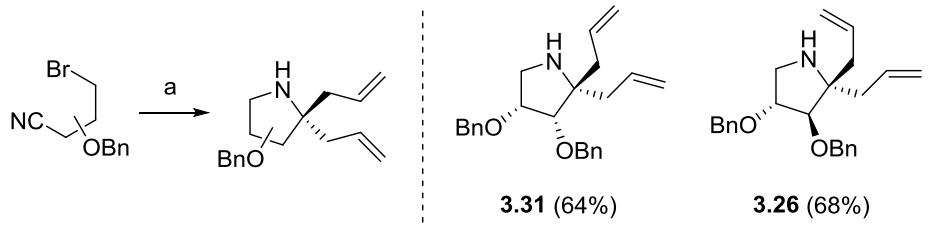
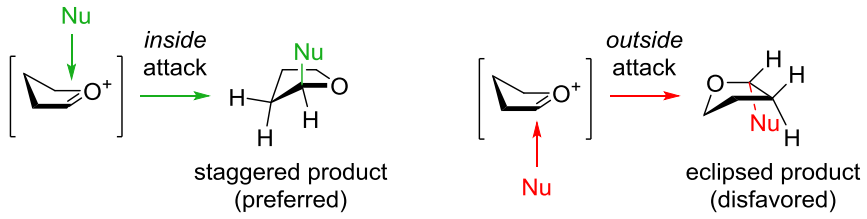
as an inseparable mixture of diastereoisomers; this compound has been, however, already reported in the literature (also as a mixture, but with a much better diastereoselectiviy),[54] so I assigned the stereochemistry by comparison of NMR spectra.



Scheme 3.13. Reagents and conditions: (a) allyl-MgBr (1 M in Et_2O, 5 equiv), THF/DMPU, 0 °C, 1 h.

In the next step, I attempted to explain the stereochemical course of the developed reaction leading to 2-allylpyrrolidines. It has been established by Woerpel and co-workers, that nucleophilic addition to endocyclic oxocarbenium cations in five-membered rings proceeds from the *inside* of the envelope (Scheme 3.14).[109]



Scheme 3.14. Two modes of attack of a nucleophile on endocyclic oxocarbenium ion in five-membere rings.

Moreover, according to their results, the alkoxy substituent at the C-4 is oriented pseudo-axially, preferring the close proximity of a positively charged oxocarbenium cation (Scheme 3.15a).[110] As a result, 2,4-*syn* product is formed predominantly. Although the presence of other groups at the C-3 and C-5 also impacts (to some extent) the direction of the addition, the alkoxy substituent at the C-4 plays the leading role in the process, basically governing the stereochemical outcome of the reaction. However, in the absence of the alkoxy group at the C-4, the substituent at the C-3 directs the addition towards the 2,3-*syn* product (Scheme 3.15b).

Furman and co-workers, in their works concerning the nucleophilic addition to cyclic imines, extended the Woerpel's model to the area of nitrogen heterocycles, in order to explain the stereochemistry of the obtained pyrrolidines and piperidines.[56] It has to be noted, though, that they carried out the reactions with the excess of TFA, so

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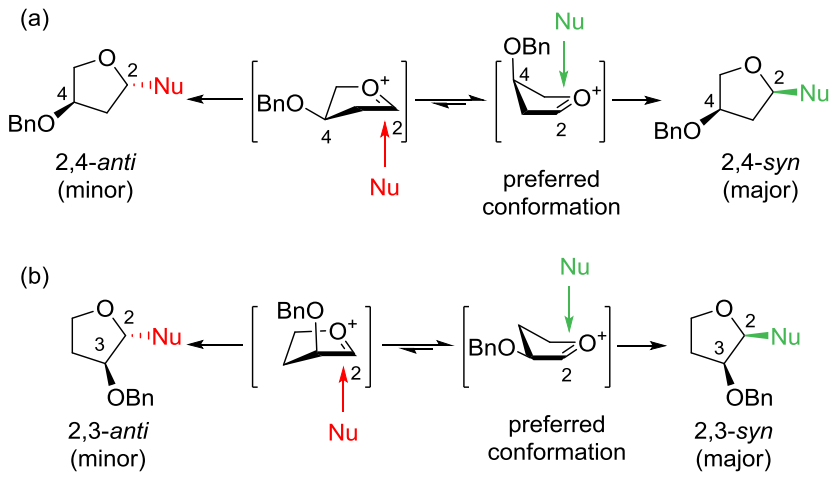
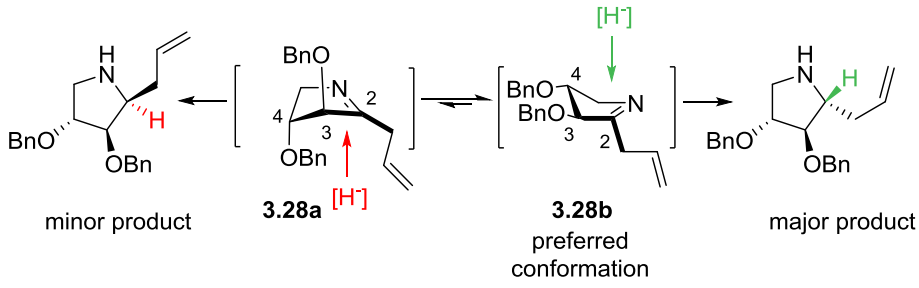
the iminium cations (analogs of oxocarbenium cations) were *de facto* the reactive species.



Scheme 3.15. (a) Pseudo-axial orientation of alkoxy substituent at C-4 is preferred and plays the dominant role even in the presence of other substituents. (b) In the absence of alkoxy group at C-4, the substituent at C-3 governs the diastereoselectivity.

My approach, on the contrary, is carried out under basic conditions, so the stabilizing role of the substituent at C-4 is not justified. As a result, other substituents may impact the diastereoselectivity to a much larger degree than they do in the Woerpel's model.

Indeed, the reduction of imine **3.28** led me to a product, in which the nucleophile (hydride anion) is in *anti* relation to the benzyl group at the C-4 and *syn* to the C-3 positions; the transitional imine is (most likely) attacked from the *inside* of the envelope. Both substituents seem to prefer pseudo-equatorial orientations (conformation **3.28b**, Scheme 3.16).



Scheme 3.16. Pseudo-equatorial orientations at C-3 and C-4 are preferred (in opposition to Woerpel's model, in which C-4 should be axial); the resulting diastereoselectivity is moderate (4.3:1).

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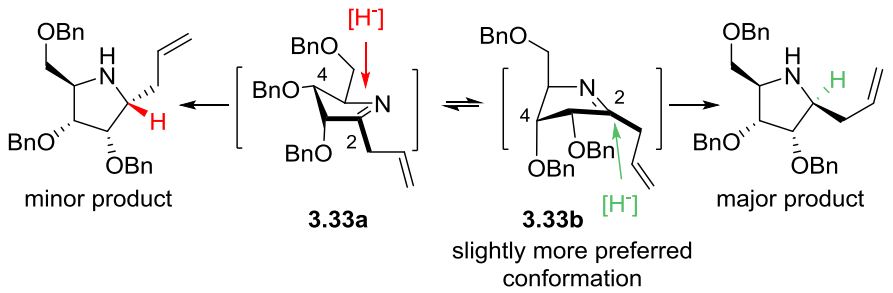
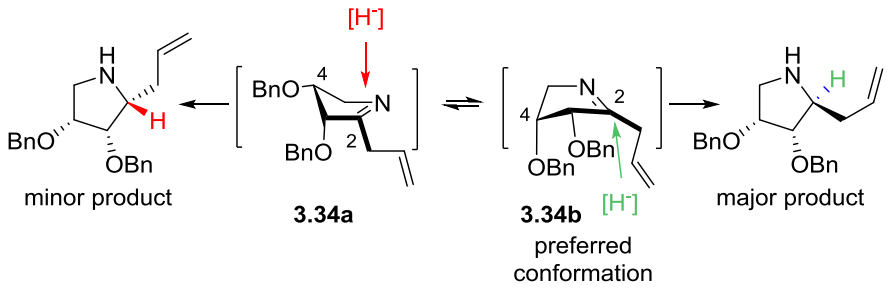
In the case of imine **3.33**, the stereoselectivity was much worse (*dr* = 1.7:1); none of the envelope conformers (3-ax, 4-eq, 5-eq in **3.33a** and 3-eq, 4-ax, 5-ax in **3.33b**) appears to be particularly preferred (Scheme 3.17).

The reduction of imine **3.34** proceeds with a moderate diastereoselectivity (*dr* = 2.6:1) (Scheme 3.18). Conformer **3.34b** seems to be more preferred, so the product, in which the allyl side-chain is in *anti* relation to the benzyl groups at the C-3 and C-4, prevails in the mixture.



Scheme 3.17. The envelope conformation **3.33b** is only slightly more preferred (*dr* = 1.7:1).



Scheme 3.18. The envelope conformation **3.34b** is more preferred; the resulting diastereoselectivity is moderate (*dr* = 2.6:1).

All in all, somewhat contrary to the Woerpel's model (oxocarbenium cations) and observations of Furman (iminium cations), the reduction of imines **3.28**, **3.33**, and **3.34** leads predominantly to products, in which the nucleophile has, before all, a *syn* relationship to the group at the C-3. Its directing role is most strikingly shown in the formation of **3.27** (*dr* = 4.3:1), in which the influence of the substituent at the C-4 appears to be largely neglected. Nonetheless, the directing role of the alkoxy group at the C-3 is not very strong, which results in moderate and poor diastereoselectivities.

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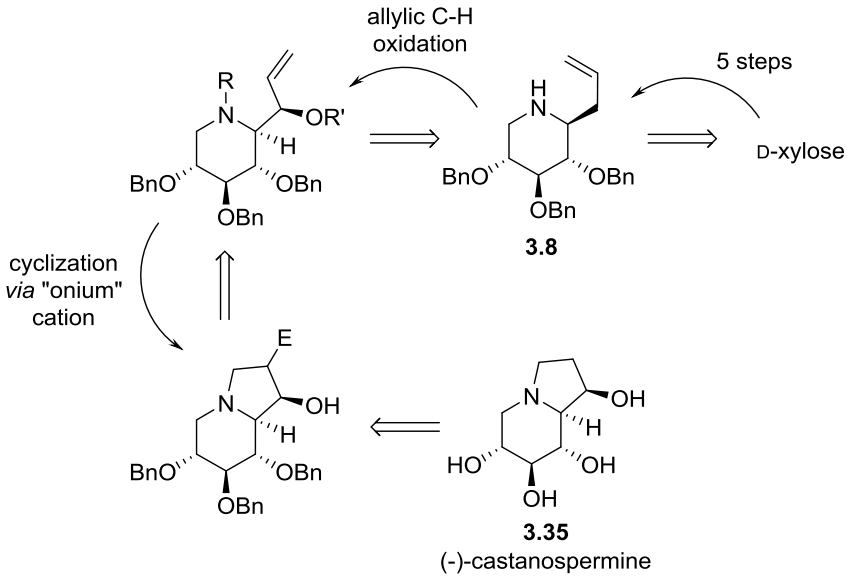
3.2. Synthesis of bicyclic iminosugars

Having established the above described methodology leading to various monocyclic polyhydroxylated scaffolds, I attempted to transform amines **3.8**, **3.9**, **3.27**, and **3.30** into bicyclic iminosugars.

3.2.1. Total synthesis of (-)-castanospermine

In my next synthetic route, I envisaged, that piperidine **3.8** can be transformed into non-natural (-)-castanospermine **3.35** (Scheme 3.19). The first step would involve the oxidation at the allylic position, which would be followed by an electrophile-induced nucleophilic cyclization *via* "onium" cation (iodonium, mercuronium, selenonium, or similar). I would then easily transform the obtained bicyclic compound into the desired alkaloid.



Scheme 3.19. Retrosynthetic analysis of (-)-castanospermine **3.35**.

Usually, an allylic C-H oxidation is achieved by the use of selenium or chromium oxidants.[111] Although some other reagents have been already explored in the context of this reaction,[112,113,114] the first general and robust approach has been proposed only recently by the group of Christina White.[115]

During the last years, her palladium catalyst with bis-sulfoxide ligand (**3.36**) has emerged as a powerful tool for the allylic C-H oxidation (Scheme 3.20).[116] It is known to be able to mediate intramolecular reactions,[117,118,119,120,121] including

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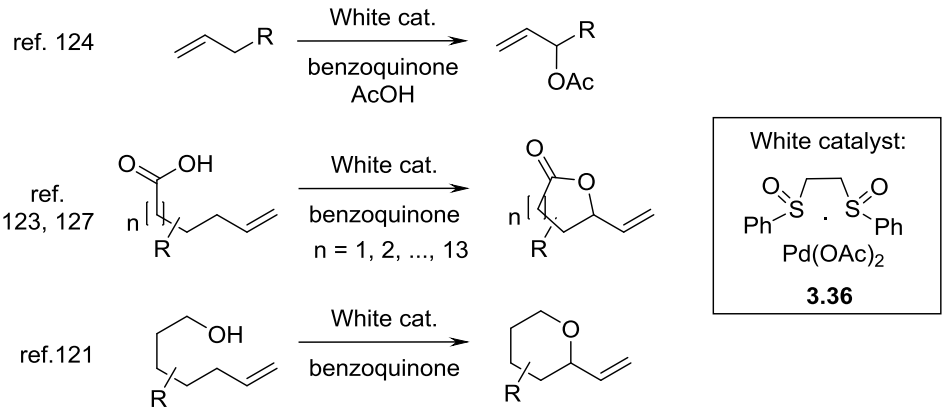
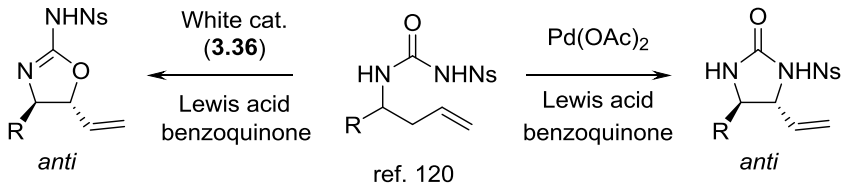
macrocyclizations,[122,123] as well as intermolecular transformations.[124,125,126] The White's approach to the allylic C-H oxidation has been already used with much success, in the synthesis of polyoxygenated compounds.[127,128]

In the light of these encouraging facts, I decided to take advantage of this methodology to oxidize the allylic position in piperidine **3.8**.



Scheme 3.20. White's approach to the allylic C-H oxidation; representative scope of the methodology.

Initially, I opted for the use of White's *N*-nosyl urea methodology (Scheme 3.21).[120] Such intramolecular variant would less likely suffer from a poor diastereoselectivity, since, as White has already noticed, five-membered rings are formed exclusively as the *anti*-isomers.[120,127]



Scheme 3.21. One of the approaches to allylic C-H oxidation by White (*N*-noysl urea moiety serves as internal nucleophile).

However, I was wondering, if the application of *N*-nosyl ureas could be replaced with much more available carbamates, for example Boc or Cbz groups. This approach would be more appealing, not only due to the availability of those carbamates, but also it would eliminate the risk of allylic C-H amination (Scheme 3.22).

As a result of this transformation, I should obtain a synthetically versatile oxazolidinone ring, which can be regarded, for example, as a masked 1,2-aminoalcohol, a group found in many natural products.[129]

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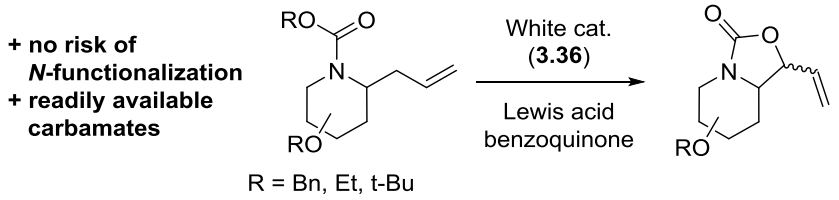
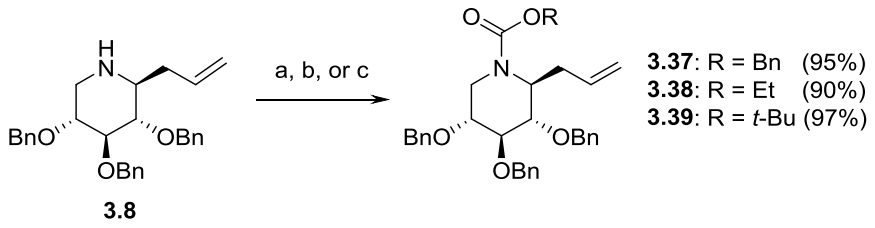


Scheme 3.22. My approach to the allylic C-H oxidation with White catalyst (**3.36**).

A somewhat related transformation, leading to oxazolidinones as well, has been already reported by Shimamoto and Ohfune.[130] In their work, the benzylic cation was generated from derivatives of L-tyrosine by treatment with $K_2S_2O_8/CuSO_4$ and then trapped with the Boc group. The nucleophilicity of the carbonyl oxygen atom of the Boc group is already well-documented. For example, it is used in the combination with standard leaving groups[131,132,133,134] or in Tsuji-Trost-type reactions.[135] On the other hand, I have found no reports on the allylic C-H oxidation, in which the carbonyl oxygen atom of a carbamate group would be used as a nucleophile.

To verify the above-described assumptions, I synthesized carbamates **3.37**, **3.38**, and **3.39** (Scheme 3.23). In the next step, I subjected these compounds to various oxidative conditions (Table 3.1). To my satisfaction, in some cases, the reaction proceeded smoothly and oxazolidinone **3.40** was obtained in good yields.[136]



Scheme 3.23. Reagents and conditions: (a) benzyl chloroformate, MeCN, K_2CO_3, 30 min, rt, 95%; (b) ethyl chloroformate, MeCN, K_2CO_3, 30 min, rt, 90%; (c) Boc_2O, MeCN, K_2CO_3, 24 h, rt, 97%.

As it turned out, the reaction should be preferentially carried out with benzyl carbamate **3.37**, in the presence of $Yb(OTf)_3$ or $Sc(OTf)_3$ (10 mol%) and White's catalyst **3.36** (10 mol%) (entries 1 and 4, respectively). However, when I conducted the reaction with $Zn(OTf)_2$ (10 mol%) (entry 5), the desired product was formed in poor yield (21%). The addition of a Lewis acid was crucial; without its presence, I isolated only traces of **3.40** (entry 6). In the literature, there are many reports on the rare earth metal triflates being promoters of organic reactions.[137]

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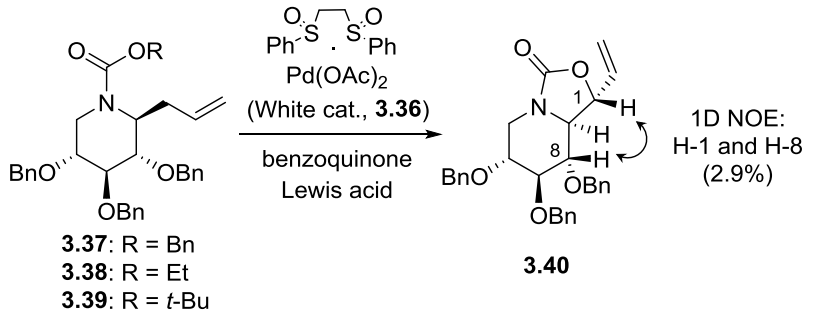
Table 3.1. Conditions screening of the allylic C-H oxidation leading to **3.40**.



3.37: R = Bn
3.38: R = Et
3.39: R = *t*-Bu

3.40

entry	substrate	cat. load. (mol %)	$Yb(OTf)_3$ (mol %)	time (h)	yield[a] (%)
1	**3.37**	10	10	4	71
2[b]	**3.37**	0	50	15	0
3[c]	**3.37**	0	10	8	16
4[d]	**3.37**	10	0	4	69
5[b,e]	**3.37**	10	0	15	21
6[b]	**3.37**	20	0	15	6
7[b,f]	**3.37**	20	20	15	0
8	**3.38**	20	30	20	47
9[c]	**3.38**	0	10	24	29
10[b,f]	**3.38**	20	50	20	0
11	**3.39**	10	10	4	30
12[b,f]	**3.39**	20	20	20	0

All reactions were carried out in dioxane (0.2 M) at 75 °C under air, with 2 equiv of BQ, until total consumption of the starting material, unless otherwise stated. [a] Isolated yields. [b] Full conversion was not achieved. [c] $Pd(OAc)_2$ (10 mol %) was used as a catalyst. [d] $Sc(OTf)_3$ (10 mol %) was used as a promoter. [e] $Zn(OTf)_2$ (10 mol %) was used. [f] Reaction carried out in the presence of molecular sieves 4 Å.

On the other hand, in the absence of the White's Pd catalyst, the desired product was not formed at all (entry 2); I recovered almost quantitatively the starting material. When I used $Pd(OAc)_2$ as a catalyst, I isolated the corresponding methyl ketone as the main product (result of the Wacker oxidation), whereas oxazolidinone **3.40** was formed only in poor yield (16%) (entry 3).

Then, I tested the other two carbamates, namely **3.38** and **3.39**. In the former case, in order to obtain the full conversion, I had to carry out the reaction much longer and in the presence of larger amounts of Lewis acid and Pd catalyst (entry 8). The isolated yield was, however, relatively low (47%). The *t*-Bu carbamate, *i.e.* **3.39**, on the other hand, was consumed as rapidly as carbamate **3.37**, but a complicated mixture

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of products was formed and, eventually, the yield of the desired **3.40** was poor (30%, entry 11).

It should be also noted, that in all cases, in which I used **3.37** as a substrate, benzoquinone monobenzyl ether was formed as a major byproduct (*e.g.* 35% in entry 1).

As 1D-NOE experiments indicate, in all cases, the oxazolidinone **3.40** was formed exclusively as the *anti* isomer (*dr* > 99:1) (Table 3.1). This is in accordance with my previously described expectations.

The mechanism of this allylic C-H oxidation can be partially explained basing on the aspects already discussed by White. The susceptibility of the π-allyl-Pd(BQ) species to undergo the S_N2 reaction can be greatly enhanced by the presence of oxophilic Lewis acid (in my case - $Yb(OTf)_3$ and $Sc(OTf)_3$).[138] As White has already proposed, a Lewis acid molecule binds through a benzoquinone molecule.[125] It is also evident, from the results collected in Table 3.1, that a water molecule is somehow involved in the process, since the reaction does not proceed in the presence of freshly activated molecular sieves 4 Å (entries 7, 10, 12). Its role is to me, at this moment, unclear. It can be somehow involved in the removal of the benzyl moiety, since the preceding steps, *i.e.* C-H oxidation and S_N2-type substitution are known to proceed under the anhydrous conditions. In the light of these considerations, I proposed a possible catalytic cycle leading to oxazolidinone **3.40** (Scheme 3.24).[136]

Interestingly, once my manuscript on this allylic C-H oxidation had been accepted for publication, White and co-workers reported on a similar reaction involving Boc carbamates.[139]

Having established a reliable synthesis of oxazolidinone **3.40**, I turned my attention to the further stages of the planned synthetic route. Methanolysis at elevated temperature (75 °C) led to 1,2-aminoalcohol **3.41** in very good yield (85%) (Scheme 3.25). Then, I treated the obtained compound with phenylselenyl bromide[140,141] to get a separable mixture of bicyclic compounds **3.42** and **3.43** (81%, *dr* = 7:1). This cyclization proceeded through an intermediate phenylselenonium cation, which can be attacked, intramolecularly, by a secondary nitrogen atom, which could result in the formation of four- or five-membered ring. I performed HMBC and 1D-NOE experiments in order to unambiguously prove the proposed structures of derivatives **3.42** and **3.43** (Fig. 3.0).

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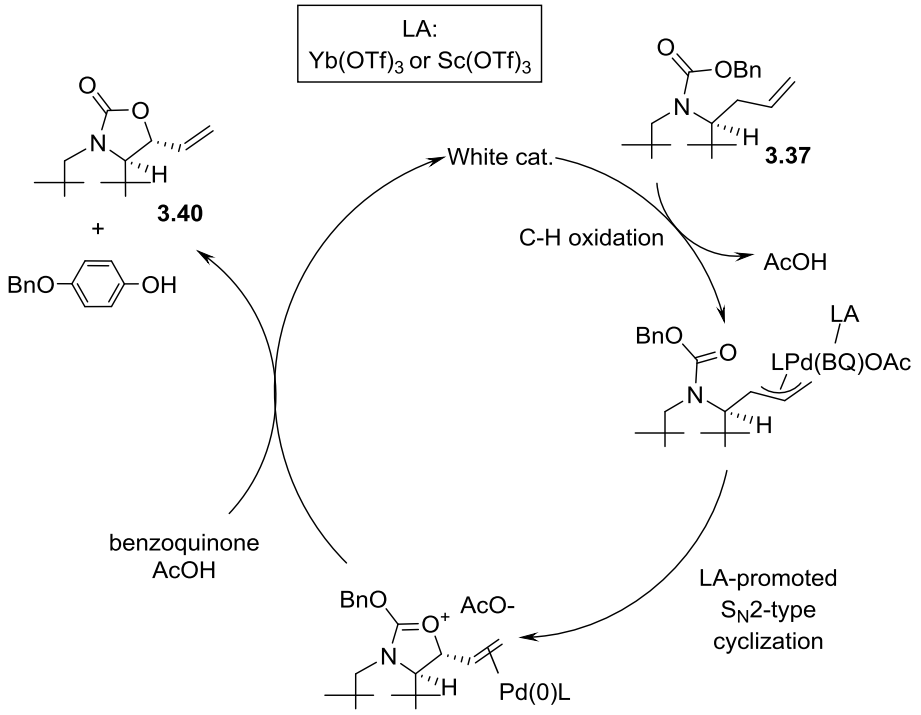
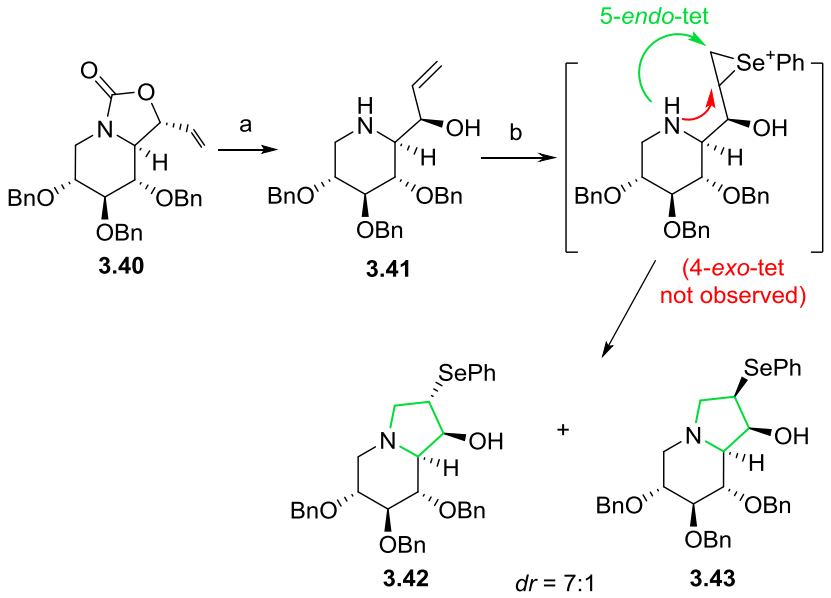


Scheme 3.24. Proposed catalytic cycle for the C-H oxidation of the allylic position in carbamate **3.37**.



Scheme 3.25. Reagents and conditions: (a) KOH, MeOH, 75 °C, 12 h, 85%; (b) PhSeBr, DCM/py, rt, 10 min, 81% (*dr* = 7:1).

The fact, that I did not observe the formation of the four-membered ring stands in contradiction to Baldwin's rules.[142] Such phenomenon is, however, not

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unprecedented in the literature: *onium*-mediated (*e.g.* iodonium, mercuronium) 5-*endo*-tet cyclizations represent exceptional cases to Baldwin original rules.[143,144]

In the next step, I attempted to remove the phenylselenyl group. Unfortunately, the most straightforward approach, involving tin and silicon hydrides under the free radical conditions, failed to furnish the desired product **3.44** (Scheme 3.26).

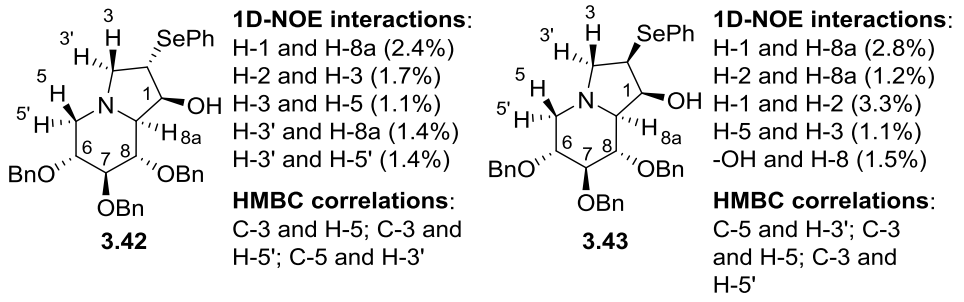
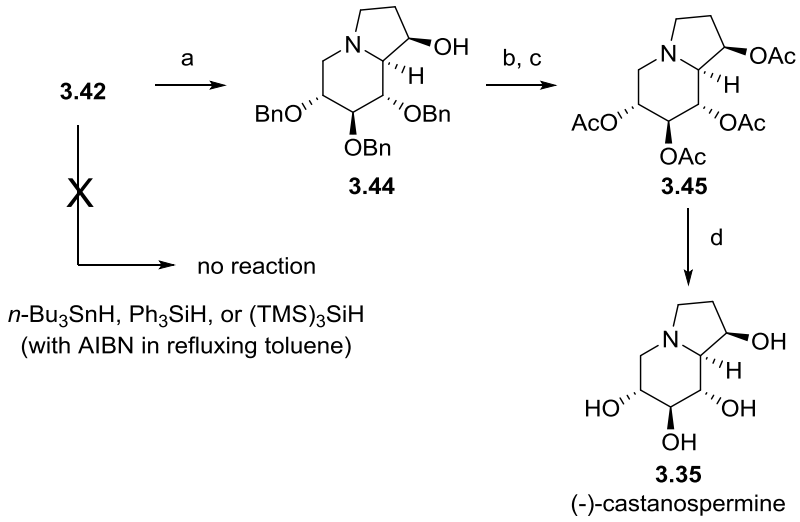


Fig. 3.0. Structures of phenylselenyl-derivatives **3.42** and **3.43**. In both cases, HMBC correlations indicate the formation of five-membered rings.

However, when I treated **3.42** with the *in situ* produced nickel boride,[145,146] deselenylation occurred in fair yield (60%). The subsequent hydrogenation over $Pd(OH)_2/C$, followed by acetylation/deacetylation procedure led to the final compound, (-)-castanospermine (**3.35**).[136]



Scheme 3.26. Reagents and conditions: (a) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH/THF, 0 °C to rt, 2 h, 60%; (b) H_2 (balloon), $Pd(OH)_2/C$, MeOH, 3 d, rt; (c) Ac_2O, DMAP, py, 24 h, rt, 79% (2 steps); (d) MeOH, MeONa, 12 h, rt, then Amberlyst 15, quant.

Alternatively, I subjected oxazolidinone **3.40** to hydroboration/oxidation sequence (Scheme 3.27). My initial attempts to use $BH_3 \cdot THF$ and 9-BBN as hydroborating agents failed, though. In the former case, a complicated mixture of

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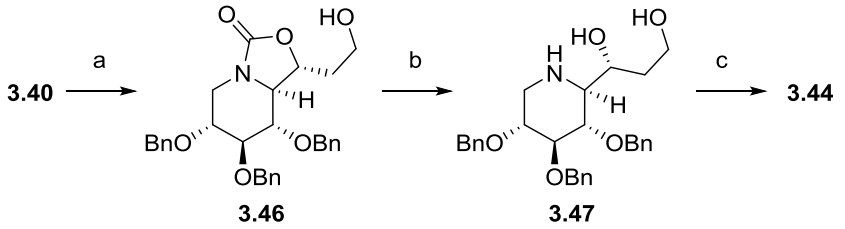
products was formed. In the latter, on the other hand, the conversion of the substrate was very low, even at elevated temperatures. However, the rhodium-catalyzed hydroboration with catecholborane, followed by oxidation with H_2O_2 afforded the desired alcohol **3.46**. Subsequently, standard methanolysis gave derivative **3.47**, which I subsequently subjected to cyclization with the help of DPPA. As a result, bicyclic derivative **3.44** was formed.[136]



Scheme 3.27. Reagents and conditions: (a) catecholborane, $(Ph_3P)_3RhCl$ (Wilkinson cat.), THF, rt, 24 h, then $NaOH_{aq}$, H_2O_2, rt, 24 h, 72%; (b) KOH, MeOH, 75 °C, 12 h, 68%; (c) DPPA, Et_3N, DCM, 12 h, rt, 80%.

3.2.2. Synthesis of polyhydroxylated quinolizidines and decahydropyrido[1,2-*a*]azepines

In my approach to these compounds, I allylated the nitrogen atom in piperidine **3.8** (Scheme 3.28) and subjected the resulting product to the ring-closing metathesis. The initial, most straightforward procedure, failed to give the desired derivative **3.51** in good yield; a high catalyst loading (Grubbs II cat. **2.123**, 3 × 5 mol%), combined with long reaction times (3 days) at elevated temperature (80 °C) led to **3.51** in only 44% yield (conversion *ca*. 60%).[92]

It is not unusual, that the olefin metathesis performed on compounds containing the free amine groups leads to poor results.[70] Although the nature of this particular phenomenon is not fully understood (some amines react, some do not), it is known, that strong donor ligands may competitively bind to ruthenium and disrupt the catalytic cycle.[147] These difficulties, if present, can be sometimes overcome by *in situ* masking the free amine as ammonium salt.[148,149] Therefore, I converted piperidine **3.48** into the corresponding TFA salt, which I then subjected to the RCM with the Grubbs II catalyst (**2.123**, 5 mol%). As a result, the desired bicyclic derivative **3.51** was formed in high yield (81%).

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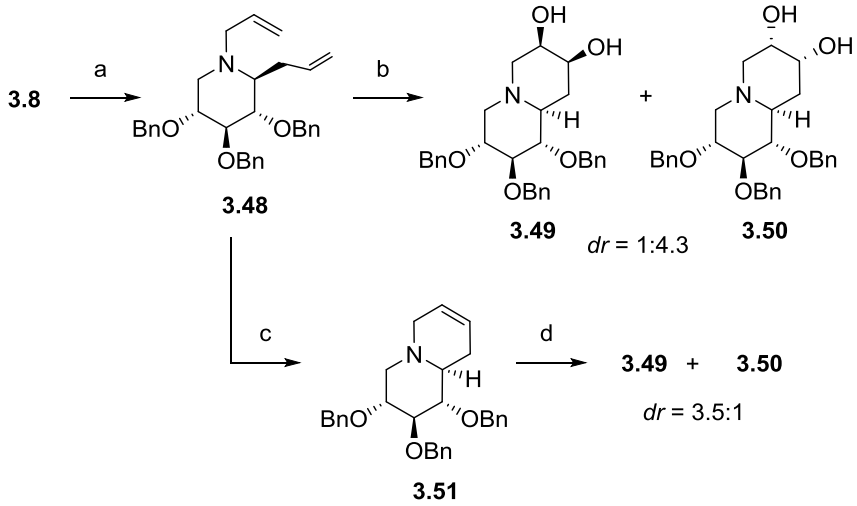

Scheme 3.28. Reagents and conditions: (a) allyl bromide, K_2CO_3, MeCN, 50 °C, 6 h, 89%; (b) Grubbs II cat. (**2.123**, 5 mol%), TFA, toluene/DCM, 70 °C, 4 h, then evaporation, then $NaIO_4$, $CeCl_3 \cdot H_2O$ (20 mol%), MeCN/AcOEt/H_2O, 0 °C, 1 h, 13% (**3.49**), 56% (**3.50**); (c) Grubbs II cat. (**2.123**, 5 mol%), TFA, toluene/DCM, 70 °C, 4 h, 81%; (d) OsO_4 (5 mol%), NMO, THF/*t*-BuOH/ H_2O, 0 °C, 10 h, 53% (**3.49**), 15% (**3.50**).

Then, I focused my attention on the *syn*-dihydroxylation of the double bond in **3.51**. This transformation is usually accomplished with catalytic amounts of osmium species, most commonly OsO_4.[150] Although this approach is very reliable and predictable, some of its drawbacks (significant price and high toxicity) encouraged researchers to develop alternative methodologies.[151] For example, the use of RuO_4 is much safer and cheaper, since it can be easily generated *in situ* from other Ru-species, usually $RuCl_3$, with the combination of other oxidants like $NaIO_4$ or NaOCl.[152] However, due to its high oxidative potential, the use of RuO_4 usually requires a tedious fine-tuning of reaction conditions in order to overcome overoxidation and other selectivity problems.[153,154] Interestingly, the progress in the field of Ru-based olefin metathesis resulted in the development of protocols allowing the reuse of the catalyst in the subsequent *syn*-dihydroxylation step.[155,156,157] Moreover, it was proven, that selectivity issues associated with high reactivity of RuO_4 can be greatly reduced by the use of $NaIO_4$-$CeCl_3$ as a re-oxidation system.[158]

With the above considerations in mind, once the RCM of **3.48** had been completed, I changed the solvent to MeCN/AcOEt/H_2O and oxidized the remains of Grubbs II catalyst with $NaIO_4$ in the presence of $CeCl_3$ (Plietker's conditions).[158] As a result, mixture of **3.49** and **3.50** was formed in good yield (69%, 4.3:1) (Scheme 3.28). I would like to point out, that this methodology is still rarely applied in the total

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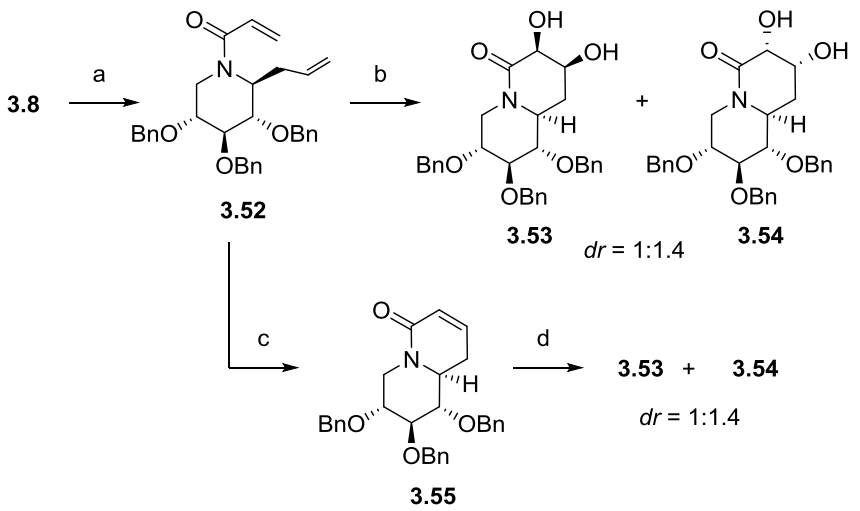
synthesis and, to the best of my knowledge, this is the first example of its use in the synthesis of iminosugars. For comparison, I also performed the OsO_4-mediated dihydroxylation (5 mol%) of **3.51**. Interestingly, **3.49** and **3.50** were also formed in good yield (68%), but in a reversed ratio (3.5:1).[92]

Then, I transformed derivative **3.8** into *N*-acryloyl derivative **3.52** (Scheme 3.29). Subsequently, I subjected this compound to the RCM with Grubbs II cat. (5 mol%), which led to bicyclic lactam **3.55** in excellent yield (95%). The following OsO_4-mediated (5 mol%) oxidation gave the mixture of diols **3.53** and **3.54** (92%, 1:1.4). Alternatively, after the RCM of **3.52**, I changed the solvent to MeCN/AcOEt/H_2O and I oxidized the remains of Grubbs II cat. with $NaIO_4$ in the presence of $CeCl_3$. This transformation proceeded smoothly and afforded a mixture of diols **3.53** and **3.54** (74%, 1:1.4).[92]

I elucidated the configuration of the obtained diols **3.49**, **3.50**, **3.53**, and **3.54** on the basis of 1D-NOE experiments (Fig. 3.1).



Scheme 3.29. Reagents and conditions: (a) acryloyl chloride, Et_3N, DCM, 0 °C to rt, 30 min, 91%; (b) Grubbs II cat. (**2.123**, 5 mol%), toluene, 50 °C, 4 h, then evaporation, then $NaIO_4$, $CeCl_3 \cdot H_2O$ (20 mol%), MeCN/AcOEt/H_2O, 0 °C, 1 h, 31% (**3.53**), 43% (**3.54**); (c) Grubbs II cat. (**2.123**, 5 mol%), toluene, 50 °C, 4 h, 95%; (d) OsO_4 (5 mol%), NMO, THF/*t*-BuOH/ H_2O, rt, 24 h, 39% (**3.53**), 53% (**3.54**).

Then, I reasoned, that oxazolidinone ring in **3.40** can be opened with Grignard reagents. However, reports on the addition of carbon nucleophiles to oxazolidinones are very limited. In the recent literature, I found only few examples of the addition of alkyllithiums[159] and Grignard reagents[160] to such compounds. Nonetheless, I tried to perform the said reaction with allyl- and vinyl-MgBr. If successful, it would allow me

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to obtain further precursors of quinolizidines and polyhydroxylated decahydro-pyrido[1,2-*a*]azepines and (**3.56** and **3.57** respectively) (Scheme 3.30).

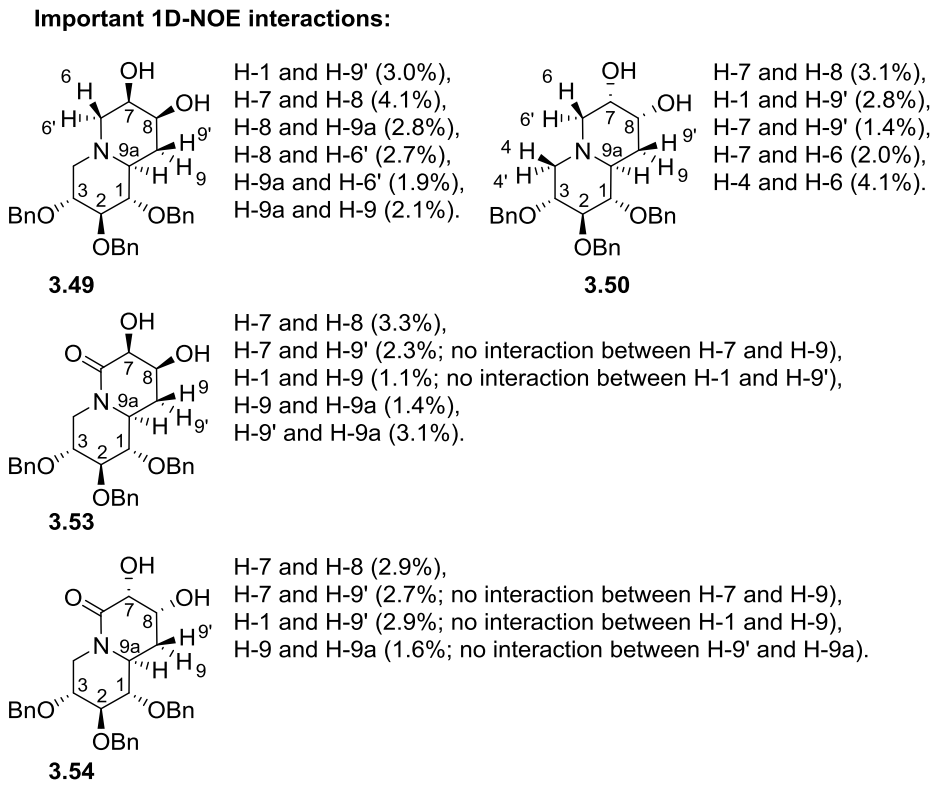

Fig. 3.1. Diagnostic 1D-NOE interactions for bicyclic diols **3.49**, **3.50**, **3.53**, and **3.54**.

It turned out, that the reaction of **3.40** with allylmagnesium bromide proceeded smoothly and afforded the anticipated derivative **3.57** in very good yield (84%). On the other hand, however, addition of vinyl-MgBr did not yield the desired *N*-acryloyl derivative **3.56**. I tested various reaction conditions (many solvents, broad temperature range from (-78 °C to 60 °C), acidic and basic additives), but with no success. Eventually, I obtained the desired **3.56** from **3.41** in fair yield (57%) by reaction with acryloyl chloride. In this approach, unfortunately, significant amounts of diacryloyl derivative **3.58** were also formed (26%).[161]

Subsequently, I subjected both diolefins **3.56** and **3.57** to olefin metathesis with Grubbs II catalyst **2.123** (Scheme 3.31). The reactions proceeded smoothly, furnishing bicyclic derivatives **3.59** and **3.61**, respectively. In the next step, I subjected these compounds to the standard *syn*-dihydroxylation procedure with catalytic amounts of OsO_4 which provided diols **3.60** and **3.62** in good yields as practically single diastereoisomers (*dr* > 99:1).

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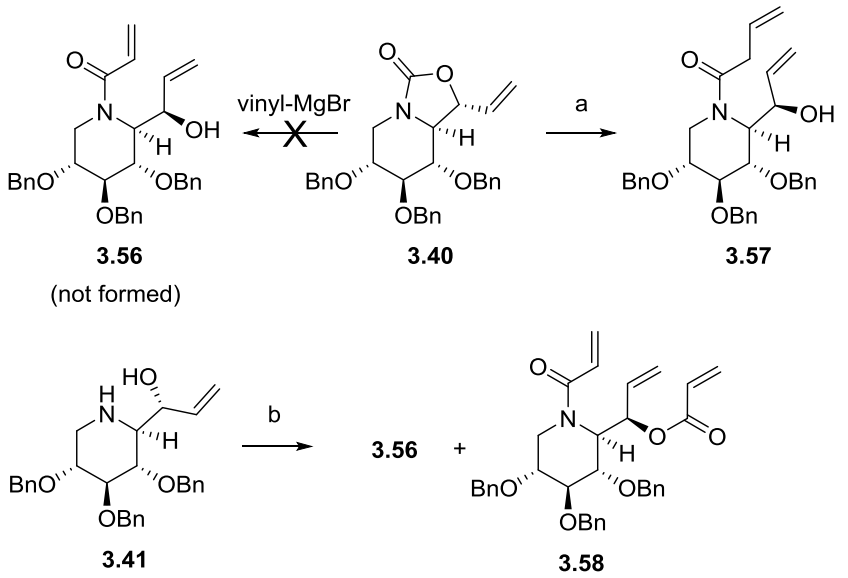
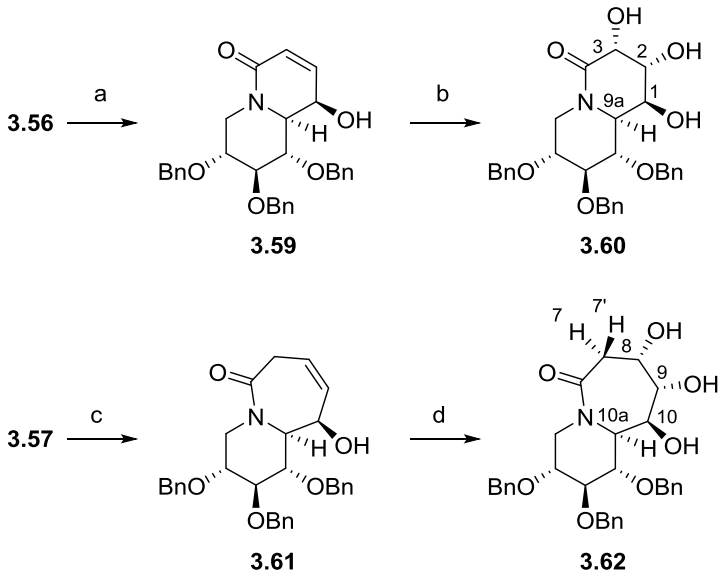


Scheme 3.30. Reagents and conditions: (a) allyl-MgBr, THF, -78 °C, 40 min, 84%; (b) acryloyl chloride, DCM, Et_3N, 0 °C, 15 min, 57% (**3.56**), 26% (**3.58**).



Scheme 3.31. Reagents and conditions: (a) Grubbs II cat. (**2.123**, 5 mol%), toluene, 50 °C, 30 min, 97%; (b) OsO_4 (5 mol%), NMO, THF/*t*-BuOH/H_2O, 0 °C, 6 h, 89% (*dr* > 99:1); (c) Grubbs II cat. (**2.123**, 5 mol%), toluene, 50 °C, 6 h, 83%; (d) OsO_4 (5 mol%), NMO, THF/*t*-BuOH/H_2O, rt, 24 h, 76% (*dr* > 99:1).

I established the configuration of the diol moiety in derivative **3.60** based on 2D-NOESY experiments; in the spectra, no interactions between H-9a and H-2, H-9a and H-3, H-1 and H-3 were seen. The observation, that the newly formed hydroxyl groups are in the *anti* relation to the existing -OH group at C-1, is in accordance with Kishi's empirical rule.[162,163]

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In order to elucidate the configurations at the C-8 and C-9 positions in compound **3.62**, I assigned signals belonging to the H-7 and H-7' protons in the ^{1}H NMR spectrum (strong interaction between H-7 and H-10a in 2D-NOESY). Despite the fact, that coupling constants in 7-membered rings are not as diagnostic and reliable as in the case of 6-membered rings, I assumed, that large *J* values observed for H-7 (13.2 and 11.7 Hz; geminal and vicinal) indicate that H-7 and H-8 have the *anti* relationship. This observation is also in accordance with the Kishi's rule.

Then, I turned my attention to the application of the previously used one-pot RCM/*syn*-dihydroxylation with the reuse of the Ru-catalyst. Therefore, once the metathesis of **3.56** was finished, I applied the Plietker's conditions (MeCN/AcOEt/H_2O, $NaIO_4$, $CeCl_3 \cdot 7H_2O$). Unfortunately, this methodology failed, since a complicated mixture of products was formed. Analogous process applied to diolefin **3.57** was also unsuccessful. Since the proximity of a free hydroxyl group may have a negative effect on this reaction, I decided to mask the -OH groups in **3.56** and **3.57** as acetates (Scheme 3.32). Then, I performed RCM on acetate **3.63** with Grubbs II catalyst **2.123** (5 mol%), which was followed by evaporation of the solvent and application of the Plietker's conditions. As a result, after 20 min at 0 °C, the diol **3.64** was formed in good yield (75%) as practically single diastereoisomer (*dr* > 99:1).[161]

Similarly to **3.60**, 2D-NOESY experiments proved the formation of *anti* product which is in accordance with Kishi's rule (interactions between the H-9a and H-2, H-9a and H-3, H-1 and H-3 were not observed).

I also subjected acetate **3.65** to the RCM with Grubbs-II catalyst. This compound, however, reacted sluggishly and a higher loading of the catalyst (10 mol%) was needed to accomplish the ring closure with full conversion. Next, I changed the solvent to MeCN/AcOEt/H_2O and oxidized the remains of the catalyst with $NaIO_4$ in the presence of $CeCl_3$. After 1 h at 0 °C, diol **3.66** was formed in good yield (66%) as a virtually single diastereoisomer (*dr* > 99:1).

Based on the 2D-NOESY experiments, I was able to assign signals from H-7 and H-7' on ^{1}H-NMR spectrum (interaction between H-7 and H-10a). As in the case of **3.62**, I assumed, that large values of the coupling constants observed for H-7 (13.3 and 11.7 Hz; geminal and vicinal) indicate the existence of *anti* relationship between H-7 and H-8. This assumption, being in accordance with Kishi's rule, was eventually fully confirmed by X-ray analysis of derivative **3.66** (Fig. 3.2).

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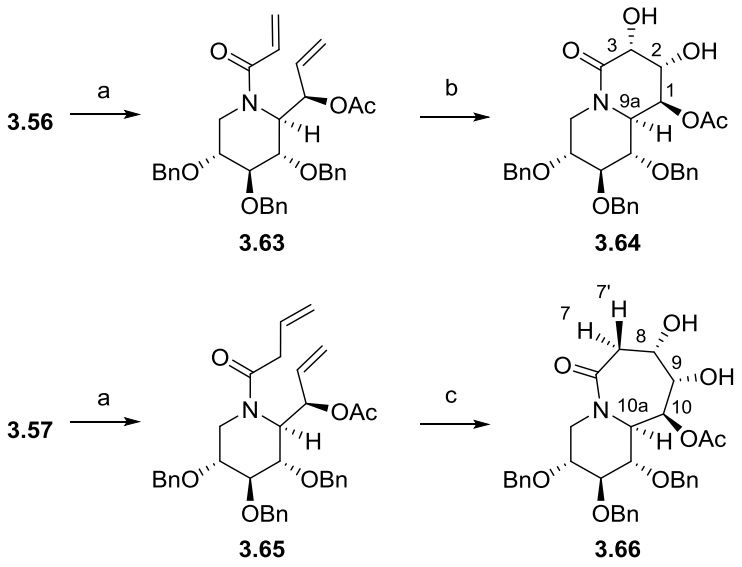

Scheme 3.32. Reagents and conditions: (a) Ac_2O, DMAP, DCM/py, rt, 24 h, 90% (**3.63**) or 92% (**3.65**); (b) Grubbs II cat. (**2.123**, 5 mol%), toluene, 50 °C, 2 h, then evaporation, then $NaIO_4$, $CeCl_3 \cdot H_2O$ (20 mol%), MeCN/AcOEt/H_2O, 0 °C, 20 min, 75%; (c) Grubbs-II cat. (**2.123**, 10 mol%), toluene, 60 °C, 4 h, then evaporation, then $NaIO_4$, $CeCl_3 \cdot H_2O$ (20 mol%), MeCN/AcOEt/H_2O, 0 °C, 1 h, 66%.

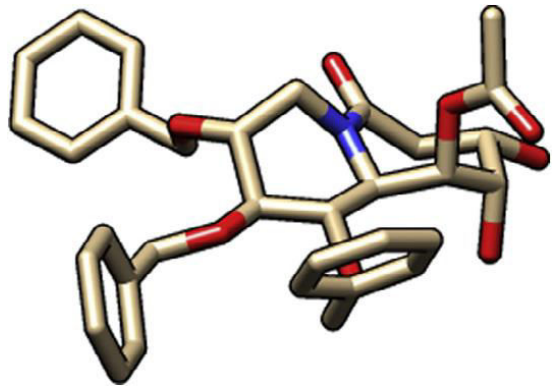

Fig. 3.2. X-ray structure of diol **3.66**. Hydrogen atoms are removed for the sake of clarity.

3.2.3. Synthesis of spirocyclic iminosugars

Spirocyclic scaffolds are abundant among compounds of medicinal importance.[164] Due to the conformational rigidity they impose in three-dimensional space (especially small, three-, four-, and five-membered rings), the pharmaceutical industry is increasingly interested in the development of novel methodologies leading to them.[165]

During my studies on the addition of allylmagnesium bromide to *ω*-bromo-nitriles (earlier in this chapter), I elaborated a methodology enabling the synthesis of 2,2-diallylsubstituted piperidines and pyrrolidines. One of such compounds was

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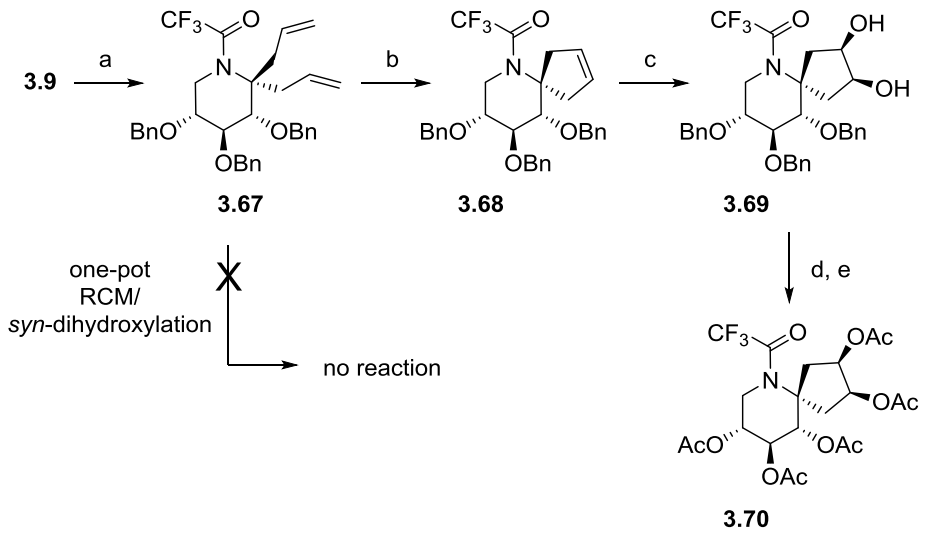
derivative **3.9**. I envisaged, that a successful ring-closing metathesis would yield 6-azaspiro[4.5]decane, a scaffold found in some natural products.[166,167]

In order to prevent possible problems with the RCM (induced by the presence of secondary amine), I decided to install a protecting group on the nitrogen atom. However, reactions with CbzCl, Boc_2O, TsCl, and NsCl failed to give the expected product. Closer inspection of compound **3.9** shows, that the nitrogen atom is situated at the neopentyl-like position which is, most likely, responsible for its reduced reactivity. Fortunately, the reaction of this derivative with trifluoroacetic anhydride (TFAA) proceeded smoothly and furnished the desired protected derivative **3.67** in excellent yield (94%) (Scheme 3.33). I carried out the subsequent RCM with only 1 mol% of Grubbs II catalyst **2.123**, which led to spiro derivative **3.68** in excellent yield (95%). Then, I turned my attention to the *syn*-dihydroxylation of the double bond. Treatment of olefin **3.68** with OsO_4 (5 mol%) and NMO afforded diol **3.69** as practically single diastereoisomer (*dr* > 99:1).[92]



Scheme 3.33. Reagents and conditions: (a) TFAA, DMAP, py, rt, 30 min, 94%; (b) Grubbs II cat. (**2.123**, 1 mol%), DCM, rt, 16 h, 95%; (c) OsO_4 (5 mol%), NMO, THF/*t*-BuOH/H_2O, rt, 2 h, 82%; (d) H_2, Pd/C, MeOH, rt, 72 h; (e) Ac_2O, DMAP, py, rt, 24 h, 83% (2 steps).

At this point, however, I was unable to determine the stereochemistry of **3.69**. Therefore, I performed hydrogenation over Pd/C and subjected the crude product to acetylation. The resulting hexaacetate **3.70** crystallized relatively easily, so the configuration of the diol moiety was determined based on the X-ray analysis (Fig. 3.3).

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I also subjected the olefin **3.67** to the one-pot RCM/*syn*-dihydroxylation. Once the metathesis was completed, I changed the solvent to MeCN/AcOEt/H_2O and added the oxidant ($NaIO_4$/$CeCl_3 \cdot H_2O$). Surprisingly to me, the conversion was very low, even at room temperature.

Then, encouraged by the successful metathesis of TFA salt of **3.48**, I assumed, that amine **3.9**, in the form of ammonium salt, could also undergo RCM. Therefore, I treated this derivative with various Brønsted ($MeSO_3H$, CH_3COOH, CF_3COOH, TsOH, HCOOH, HCl) and Lewis acids ($BF_3 \cdot Et_2O$, $TiCl_4$, $SnCl_4$) and then I tried to perform RCM (Grubbs II, 5 mol%, toluene, from rt to 80°C). It turned out, that only with the addition of HCl (handled as a 3 M anhydrous solution in cyclopentyl methyl ether), I was able to obtain the desired spiro compound **3.71** (Scheme 3.34). The use of the other acids resulted in very low conversion of **3.9**.

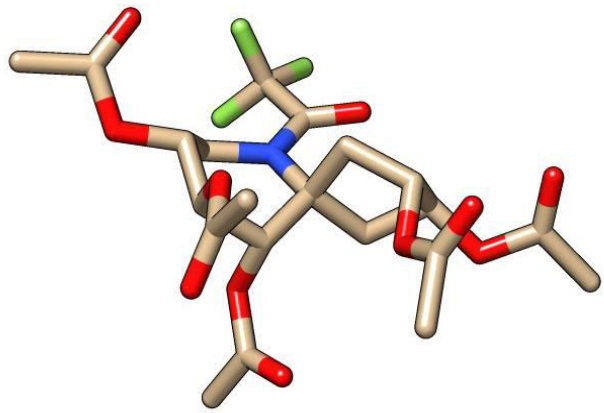

Fig. 3.3. X-ray structure of hexaacetate **3.70**. Hydrogen atoms are removed for the sake of clarity.

Once the conditions of the RCM step were established, I tried to perform the one-pot RCM/*syn*-dihydroxylation on derivative **3.9**. Unfortunately, in this case, a complicated mixture of products was formed. The use of catalytic OsO_4-based approach on this compound failed too; the conversion was very low.

These failures prompted me to perform an equimolar variant of the OsO_4 *syn*-dihydroxylation under Donohoe's conditions (OsO_4, TMEDA),[168] which afforded osmate **3.72** as virtually single diastereoisomer (*dr* > 99:1). This compound was stable enough to survive the standard chromatography procedures. The stability of such compounds is, however, not unprecedented.[169,170] Osmate **3.72** was treated with excess of ethylenediamine, which resulted in the formation of free diol **3.73**. The

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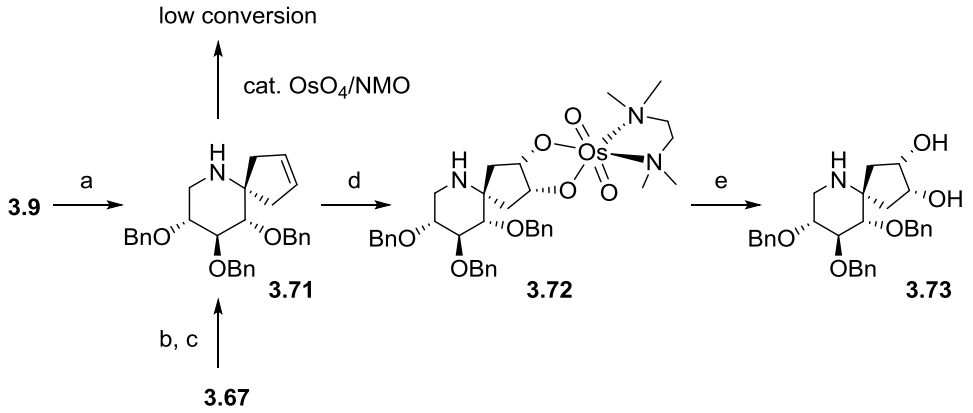
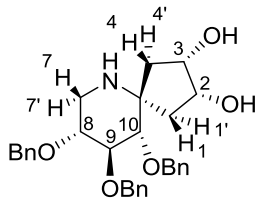
configuration of this compound was determined by the 1D-NOE experiments (Fig. 3.4).



Scheme 3.34. Reagents and conditions: (a) Grubbs II cat. (**2.123**, 10 mol%), HCl, toluene/CPME, 50 °C, 6 h, 87%; (b) Grubbs II cat. (**2.123**, 1 mol%), DCM, rt, 16 h, 95%; (c) K_2CO_3, MeOH, rt, 24 h, 86% (2 steps); (d) OsO_4, TMEDA, DCM/*t*-BuOH, -78 °C to rt, 30 min, 89%; (e) ethylenediamine, DCM, rt, 15 min, 81%.



Important 1D-NOE interactions:
H-1 and H-2 (3.5%),
H-1 and H-9 (1.8%),
H-1 and H-3 (1.2%; no interaction between H-1' and H-3),
H-4 and H-3 (3.1%),
H-4 and H-2 (1.1%; no interaction between H-4' and H-2),
H-1' and H-7' (5.0%; the only interaction between H-7' and a proton from the five-membered ring),
H-10 and H-4 (1.4%).

Fig. 3.4. Diagnostic 1D-NOE interactions for the diol **3.73**.

Interestingly, it turned out, that *syn*-dihydroxylation of **3.71** occurred from the side of the nitrogen atom. It has been already shown,[171,172] that a hydrogen bond donor may act as a directing group in equimolar variant of OsO_4 dihydroxylation (in the presence of TMEDA), yielding the anti-Kishi product. This way, by performing *syn*-dihydroxylation either on protected compound (**3.68**) or on free amine (**3.71**), I was able to obtain, highly stereoselectively, both possible diastereomeric diols.

3.2.4. Total synthesis of (-)-lentiginosine and 2-*epi*-lentiginosine

The obtained 2-allylpyrrolidines **3.27** and **3.30** can serve as precursors for the synthesis of diastereoisomers of alkaloid known as lentiginosine.[173]

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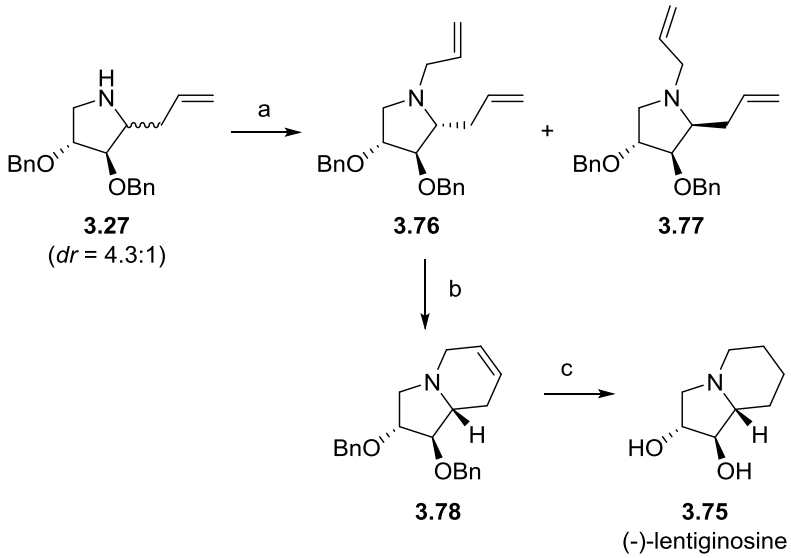
I reasoned, that a protocol consisting in *N*-allylation, ring-closing metathesis and a reduction/deprotection sequence should be sufficient to yield (-)-lentiginosine **3.75** (Scheme 3.35). Indeed, the allylation of **3.27** (as a mixture of diastereoisomers) proceeded smoothly and yielded *N*-allyl derivatives **3.76** and **3.77** as a separable mixture of diastereoisomers.

The subsequent RCM turned out to be more challenging. My initial attempts performed on derivative **3.76** (in the form of HCl ammonium salt) with the use of Grubbs II catalyst **2.123** gave the desired product, but in moderate yield (44%); most of the substrate remained unreacted (conversion 60%).



Scheme 3.35. Reagents and conditions: (a) allyl bromide, MeCN, K_2CO_3, rt, 24 h, 55% (**3.76**), 13% (**3.77**); (b) TFA, Grubbs-Hoveyda II cat. (**2.124**, 5 mol%), toluene, 60 °C, 12 h, 94%; (c) H_2, $Pd(OH)_2$/C, MeOH, rt, 12 h, 91%.

However, the reaction induced by Hoveyda-Grubbs II catalyst **2.124** (5 mol%) led to the desired bicyclic compound **3.78** in excellent yield (94%). In the next step, the reduction of the double bond accompanied by debenzylation gave the first of the title alkaloids, (-)-lentiginosine **3.75**. This way, I was able to unambiguously assign the configuration in **3.27** by comparison of **3.75** with the literature (see Experimental section for details).

Then, I tried to apply the same procedure to compound **3.30** (Scheme 3.36). Unfortunately, I was unable to obtain the *N*-allylated products in good yield; complicated mixtures of products were formed. Therefore, I decided to use a procedure described by Singh.[174] Derivative **3.30** (as a mixture of diastereoisomers) was subjected to the reaction with acryloyl chloride, furnishing compounds **3.79** and **3.80**,

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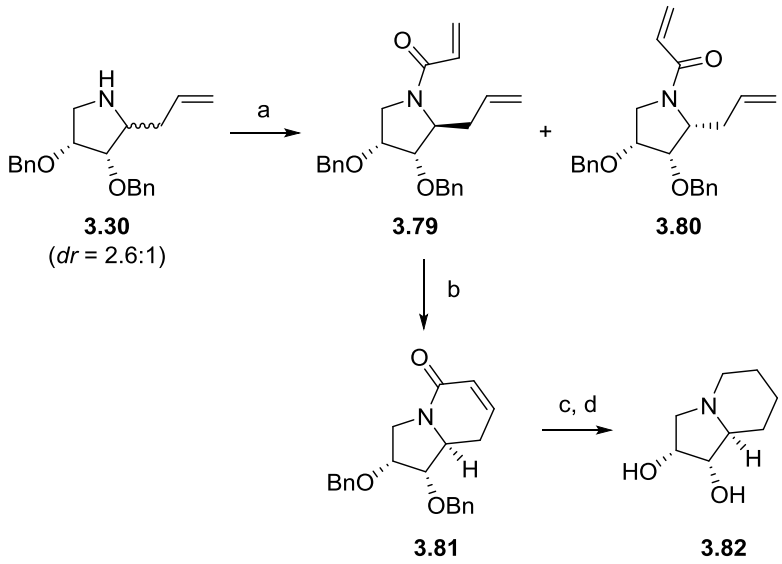
which were easily separated by chromatography. Then, the RCM with Grubbs II catalyst **2.123**, which was performed on the major isomer, gave the bicyclic compound **3.81**, which was subsequently subjected to hydrogenation over $Pd(OH)_2/C$. The reduction of the lactam group gave the final **3.82** (2-epimer of (+)-lentiginosine). This way, I was able to unambiguously assign the configuration in **3.30** by comparison of **3.82** with the literature (see Experimental section for details).



Scheme 3.36. Reagents and conditions: (a) acryloyl chloride, DCM, Et_3N, rt, 30 min, 53% (**3.79**), 21% (**3.80**); (b) Grubbs II cat. (**2.123**, 5 mol%), toluene, 50 °C, 4 h, 83%; (c) H_2, $Pd(OH)_2/C$, MeOH, rt, 12 h; (d) $LiAlH_4$, THF, 60 °C, 1.5 h, 56% (2 steps).

3.3. Summary

In summary, I have developed a novel methodology leading to polyhydroxylated 2-allyl- and 2,2-diallylsubstituted piperidines and pyrrolidines. It consists in the addition of allylmagnesium bromide to *ω*-bromonitriles, which leads, through an intramolecular S_N2 reaction, to cyclic imines. They can be, in turn, reduced *in situ* to form monosubstituted amines or treated with another equivalent of allyl-MgBr to yield disubstituted compounds. Moreover, although the conditions that I have applied are strongly basic, I have not observed the epimerization at the α position.

It has to be noted, that such cascade transformations have not been previously reported in the literature. In general, the addition of organometallic reagents to *ω*-halonitriles is still not well explored.

The route leading to 2-allylsubstituted derivatives can be carried out in two ways. The first one, a sequential approach, consists in the addition of slight excess (1.3

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equiv) of allyl-MgBr to ω-bromonitriles (dissolved in apolar solvents), which is followed by methanol and $NaBH_4$. This mode of reaction is not reliable and usually leads to a mixture of 2-allyl- and 2,2-diallylsubstituted products. As a matter of fact, I was only able to obtain piperidine **3.8** in good yield by using this method. However, I obtained much more consistent results when allyl-MgBr was added to the mixture of ω-bromonitrile and $Zn(BH_4)_2$. This way, 2-allylsubstituted pyrrolidines **3.27**, **3.29**, and **3.30** were formed in good yields, with almost no traces of 2,2-diallysubstituted derivatives. Piperidine **3.8** can be also obtained by using this upgraded methodology.

On the other hand, I carried out the reaction leading to 2,2-diallylsubstituted compounds with large excess of allyl-MgBr (5 equiv), which was added to ω-bromonitriles dissolved in polar solvents (preferably THF/DMPU). This approach led to the desired products **3.9**, **3.26**, and **3.32** in good yields.

Briefly, I am able to control the addition of allylmagnesium bromide to ω-bromonitriles in such way, that either 2-allyl- or 2,2-diallylsubstituted derivatives are formed.

In my opinion, further studies concerning the addition of allylmagnesium bromide to ω-bromonitriles should be conducted. First of all, the substrate scope can be expanded in various directions. For example, other protecting groups can be scanned for compatibility, functional groups tolerance can be extensively tested, and other patterns of substitutions can be used. The transformation I described suffers from inconsistent diastereoselectivities, which are ranging from poor to excellent. Therefore, such conditions should be found, under which better selectivities can be obtained and, preferably, the reaction can proceed in a more predictable manner (with the regard to the stereoselectivity).

In the further steps, I transformed piperidine **3.8** into unnatural (-)-castanospermine **3.35**. The most challenging step in this route involved the Pd-catalyzed allylic C-H oxidation assisted by carbamate group. As a result of this transformation, a versatile oxazolidine **3.40** was formed. I would like to point out, that this variation of the White's methodology was unknown at the time when my article was submitted for publication. I think, that expanding the scope of this reaction to other polyhydroxylated substrates could result in more concise routes to many other iminosugars. However, extensive studies in this direction should be conducted.

Starting from piperidine **3.8**, I also synthesized some quinolizidine derivatives, as well as one [6.7.0]-bicyclic derivative. In these synthetic routes, I focused on the

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methodology consisting in the ring-closing metathesis, followed by the reuse of the Ru catalyst in the *syn*-dihydroxylation step. This is a rarely used approach to the synthesis of polyhydroxylated bicyclic compounds, probably due to the fact, that the osmium-based approach is regarded as a more reliable option. However, the ruthenium-based dihydroxylation is faster and, when combined with olefin metathesis, a safer and a more concise approach. Therefore, in my opinion, it is worth to conduct studies, which would test other various substitution patterns and protecting groups for compatibility.

In yet another approach, I subjected 2,2-diallylsubstituted piperidine **3.9** and its *N*-protected derivative **3.67** to RCM. The resulting spiro compounds **3.71** and **3.68** were then both subjected to the *syn*-dihydroxylation, in either equimolar or catalytic variation, respectively. As a result of this divergent approach, stereoisomeric derivatives **3.73** and **3.69** were obtained in excellent yields and diastereoselectivities.

In the final approach, I used 2-allylsubstituted pyrrolidines **3.27** and **3.30** to synthesize unnatural (-)-lentiginosine **3.75** and an epimer of (+)-lentiginosine, compound **3.82**, respectively.

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4. Experimental Procedures

4.1. General information

NMR spectra were recorded with 600 and 500 MHz apparatus in $CDCl_3$, C_6D_6 or D_2O. Chemical shifts (δ) in ^1H spectra are reported in ppm relative to Me_4Si (δ 0.00) for $CDCl_3$ and C_6D_6; in case of D_2O, chemical shift of the lock solvent was used as a reference. Chemical shifts (δ) in ^{13}C spectra are reported in ppm relative to residual non-deuterated solvents: 77.0 for $CDCl_3$ and 128.1 for C_6D_6; in case of D_2O, chemical shift of the lock solvent was used as a reference. All significant resonances (carbon skeleton) were assigned by COSY (^1H-^1H), HSQC (^1H-^{13}C), and HMBC (^1H-^{13}C) correlations. Relative stereochemistry was assigned based on the 1D-NOE or 2D-NOESY experiments.

Mass spectra were recorded with MALDISynapt G2-S HDMS (*Waters Inc.*). Melting points were measured with a SRS OptiMelt and are uncorrected. Optical rotations were measured in DCM (unless otherwise stated) with Jasco P-1020, using sodium light (c = 1). Elemental analyses were performed with Elementar vario ELIII.

Reagents were purchased from Sigma-Aldrich, Alfa Aesar, and ABCR. Dry solvents were either purchased from Sigma-Aldrich and used as obtained or prepared according to standard procedures. Hexanes (65-80 ˚C fraction from petroleum) and EtOAc, obtained from local suppliers, were purified by distillation. Other solvents were purchased from Sigma-Aldrich and were used without further purification. Thin-layer chromatography was carried out on silica gel 60 F-254 (Merck). TLC staines were developed with Ce-Mo developer or with $KMnO_4$ (for compounds with small molecular weight). Organic solutions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography was performed on Grace Resolv or Grace Reveleris cartridges, using Grace Reveleris X2 system (UV and ELSD detection); linear gradient was usually applied to modulate the solvent strength.

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Diffraction data was collected at 100 K using SuperNova Agilent diffractometer using CuK\α radiation (λ= 1.54184 Å). The data was processed with CrysAlisPro.[175] Structures were solved by direct methods and refined using SHELXL-97.[176] These procedures were carried out by Dr. Magdalena Ceborska from Institute of Physical Chemistry PAS.

4.2. Detailed information

4.2.1. General procedures

A. Synthesis of *ω*-bromonitriles from cyclic hemiacetals

Hemiacetal (10 mmol) was dissolved in dry pyridine (40 mL). Then, hydroxylamine hydrochloride (2.1 g, 30 mmol, 3 equiv) was added in one portion and the resulting mixture was stirred for 48 h at rt. After this time, the solvent was evaporated and the residue was dissolved in a mixture of DCM and Et_2O (1:1 *v*/*v*, 100 mL). The organic solution was washed with H_2SO_4 (1 M, 50 mL), water (50 mL), brine (25 mL), dried and concentrated. The crude oxime (in the form of white solid) was dissolved in MeCN (100 mL) and triphenylphosphine (5.8 g, 21.9 mmol, 2.2 equiv) was added in one portion at rt. When most of the Ph_3P was dissolved (after *ca*. 20 min), tetrabromomethane (7.6 g, 22.9 mmol, 2.3 equiv) was added in several portions over a period of 20 min and the resulting mixture was stirred for 24 h (at rt in the case of reaction leading to **3.7**, **3.15**, and **3.16**; at 45 °C in the case of **3.17**). Then, methanol (100 mL) was added at rt (in one portion) and the mixture was stirred for additional 1 h. Then, silica gel (230-400 mesh, 30 g) was added and the resulting suspension was concentrated. Flash chromatography (100% hexanes to 85:15 hexanes:AcOEt) afforded *ω*-bromonitrile.

B. Preparation of $ZnCl_2$ (*ca*. 1 M ethereal solution)

This procedure was carried out in a flame-dried Schlenk flask, closed with a rubber septum and equipped with a large stirring bar. $ZnCl_2$ (13.6 g, 0.1 mol) was heated to 150 °C (oil bath) and vigorously stirred under reduced pressure (*ca*. 0.5 mbar) for 5 h. Then, the oil bath was removed and the flask was allowed to cool down to room temperature under argon atmosphere. The flask was subsequently filled with dry Et_2O (100 mL); the resulting suspension was vigorously stirred at 30 °C for 24 h. Then, the

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mixture was cooled down to room temperature and the undissolved solids were allowed to sediment. The mixture was stored under argon atmosphere, but no longer than five days; after a week, the solution becomes usually too wet to be used for the preparation of $Zn(BH_4)_2$. The clear solution of $ZnCl_2$ was collected with a syringe and used in the next step.

C. Preparation of $Zn(BH_4)_2$ (*ca*. 0.25 M ethereal solution)

This procedure was carried out in a flame-dried Schlenk flask, closed with a rubber septum and equipped with a large stirring bar. To dry Et_2O (15 mL), under argon atmosphere, $NaBH_4$ (440 mg, 11.6 mmol, powder – as dry as possible) was added. To this mixture, under vigorous stirring, freshly prepared (**procedure B**) solution of $ZnCl_2$ (1 M in Et_2O, 5.4 mL, 5.4 mmol) was added dropwise over a period of 10 min at rt. The resulting mixture was stirred for 24 h. After this time, the solids were allowed to sediment. The clear solution was collected with a syringe and used immediately in the next step.

D. Synthesis of 2-allylsubstituted heterocycles from *ω*-bromonitriles

This procedure was carried out in a flame-dried Schlenk flask, closed with a rubber septum and equipped with a large stirring bar. A freshly prepared (**procedure C**) solution of $Zn(BH_4)_2$ (0.25 M in Et_2O, 16 mL, 4 mmol) was placed, under argon atmosphere and at rt, in a flask. The majority of the solvent (*ca*. 90%) was evaporated under reduced pressure. To the residue, dry toluene (10 mL) was added under argon atmosphere and the resulting mixture was cooled to 0 °C. Under vigorous stirring, solution of the *ω*-bromonitrile (1 mmol) in dry toluene (3 mL) was added dropwise (5 min, syringe pump). Then, allyl-MgBr (1 M in Et_2O, 2 mL, 2 mmol) was added dropwise (1 h, syringe pump). After this time, the reaction was carefully quenched (violent gas evolution) with MeOH (5 mL). Then, after removal of the cooling bath, more MeOH was added (20 mL), followed by silica gel (230-400 mesh, 8 g). Flash chromatography was performed (100% hexanes to 90:10:1 AcOEt/MeOH/Et_3N) to yield the desired product.

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E. Synthesis of 2,2-diallyl-substituted piperidines and pyrrolidines from *ω*-bromonitriles

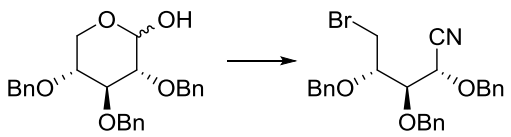
ω-Bromonitrile (1 mmol) was dissolved in dry THF (8 mL), under argon atmosphere. Then, dry DMPU was added (2 mL) and the resulting mixture was cooled to 0 °C. Then, solution of allylmagnesium bromide (1 M in diethyl ether, 5 mL, 5 equiv) was added under vigorous stirring over 60 min (syringe pump). White, thick solid precipitated in the course of addition (large stir bar needed to ensure proper stirring). Stirring was continued at 0 °C for another 30 min. Then, the reaction was quenched with saturated aqueous NH_4Cl (30 mL). Diethyl ether (100 mL) was added, the layers were separated and the aqueous one was washed with diethyl ether (2 × 25 mL). Combined organic solutions were washed with water (2 × 20 mL), brine and dried. Solvent was evaporated and the residue was subjected to flash chromatography (100% hexanes to 100% ethyl acetate).

F. *Syn*-dihydroxylation catalyzed by OsO_4

To a solution of olefin (0.25 mmol), dissolved in THF/water (2.5 mL/0.1 mL), NMO (0.5 mmol, 59 mg) was added at rt. The resulting mixture was stirred until all NMO was dissolved (a biphasic solution was formed at this point). Then, OsO_4 (5 mol%, 0.13 mL, 0.1M in *t*-BuOH) was added and the reaction was continued, under vigorous stirring, until the total disappearance of the starting. Then, sat. aq. Na_2SO_3 was added (2 mL) and the mixture was stirred for another 15 min. Subsequently, ethyl acetate (50 mL) and water (3 mL) were added, the layers were separated, and the aqueous one was washed with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine, dried, and concentrated.

4.2.2. Detailed procedures and characterization of compounds

(2*S*,3*R*,4S)-2,3,4-Tribenzyloxy-5-bromopentanenitrile (3.7):



3.5 **3.7**

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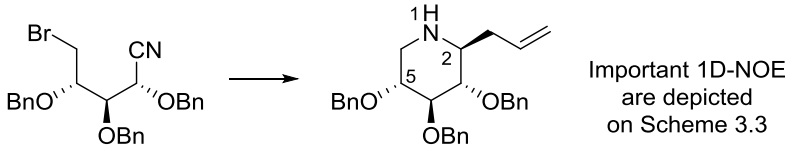
This reaction was carried out according to the **general procedure A**. ω-Bromonitrile **3.7** was obtained as white solid (83%).

HRMS: found: *m/z* = 480.1173; calc. for $C_{26}H_{27}NBrO_3$ (M + H^+): 480.1174; elem. anal.: found: C – 65.03, H – 5.44, N – 2.89, Br – 16.62%; calcd. C – 65.01, H – 5.46, N – 2.92, Br – 16.63%; $[\alpha]_D^{23}$ = 43.8; mp: 111-112 °C; R_f = 0.8 (hexanes:AcOEt 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.32 (m, arom.), 4.85, 4.82, 4.69, 4.65, 4.61, 4.54 (6 × d, 6H, *J* = 11.2÷11.5 Hz, 6 × OC*H*$_2$Ph), 4.44 (d, 1H, *J* = 6.5 Hz, H-2), 4.08 (dd, 1H, *J* = 6.5, 3.4 Hz, H-3), 4.01 (ddd, 1H, *J* = 8.2, 4.8, 3.4 Hz, H-4), 3.52 (dd, 1H, *J* = 10.1, 8.2 Hz, H-5), 3.36 ppm (dd, 1H, *J* = 10.1, 4.8 Hz, H-5'). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.2, 137.1, 135.4 (3 × quat. benzyl), 116.5 (*C*N), 128.7–128.2 (arom.), 78.7 (C-4), 78.0 (C-3), 75.7, 73.7, 73.0 (3 × O*C*H$_2$Ph), 69.5 (C-2), 29.1 ppm (C-5).

(2*S*,3*S*,4*S*,5*R*)-2-Allyl-3,4,5-tribenzyloxypiperidine (3.8):



3.7 **3.8**

(a) To a cooled to 0 °C solution of ω-bromonitrile **3.7**, under argon atmosphere, (260 mg, 0.542 mmol) in dry toluene (5.4 mL), allylmagnesium bromide (1.0 M solution in diethyl ether, 0.7 mL, 1.3 equiv) was added under vigorous stirring (15 min, syringe pump). The stirring was continued at 0 °C for another 45 min. Then, cooling bath was removed and the mixture was allowed to reach rt. Methanol (10 mL) was added, followed by sodium borohydride (30 mg, 1.5 equiv). After 10 min, water (15 mL) and ethyl acetate (50 mL) were added. Layers were separated and the aqueous one was extracted three times with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine and dried. Solvent was evaporated and the residue was chromatographed (flash chromatography, 100% hexanes to 100% ethyl acetate) to yield **3.8** as colorless oil, which solidified upon standing (178 mg, 74%) and **3.9** as thick yellow oil (11 mg, 4%).

(b) This transformation was also carried out according to the **general procedure D**. Piperidine **3.8** was obtained as colorless oil, which solidified upon standing (48%).

HRMS: found: *m/z* = 444.2537; calc. for $C_{29}H_{34}NO_3$ (M + H^+): 444.2539; elem. anal.: found: C – 78.45, H – 7.40, N – 3.22%; calcd. C – 78.52, H – 7.50, N – 3.16%; $[\alpha]_D^{23}$

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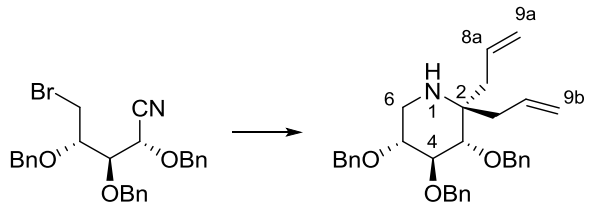
= −17.3; mp: 56-57 °C; R_f = 0.4 (hexanes:AcOEt 2:1). ^{1}H NMR (600 MHz, C_6D_6) δ: 7.18 (m, arom.), 5.66 (dddd, 1H, *J* = 17.0, 10.1, 8.8, 5.6 Hz, H-8), 5.04 (m, 4H, H-9, H-9', 2 × OC$\underline{H_2}$Ph), 4.87 (d, 1H, *J* = 11.3 Hz, OC$\underline{H_2}$Ph), 4.53 (m, 3H, 3 × OC$\underline{H_2}$Ph), 3.59 (~ t, 1H, *J* = 8.8 Hz, H-4), 3.50 (ddd, 1H, *J* = 10.2, 9.0, 5.1 Hz, H-5), 3.11 (~ t, 1H, *J* = 9.1 Hz, H-3), 2.99 (dd, 1H, *J* = 11.5, 5.1 Hz, H-6), 2.63 (m, 1H, H-7), 2.47 (~ td, 1H, *J* = 9.0, 3.0 Hz, H-2), 2.33 (dd, 1H, *J* = 11.5, 10.4 Hz, H-6'), 2.00 ppm (~ dt, 1H, *J* = 13.8, 8.7 Hz, H-7'). ^{13}C NMR (125 MHz, C_6D_6) δ: 140.0, 139.7, 139.6 (3 × quat. benzyl), 136.0 (C-8), 128.6-127.5 (arom.), 117.6 (C-9), 88.2 (C-4), 83.6 (C-3), 81.1 (C-5), 75.6, 75.3, 72.5 (3 × O$\underline{C}$H$_2$Ph), 59.7 (C-2), 48.9 (C-6), 37.2 ppm (C-7).

(3*S*,4*S*,5*R*)-2,2-Diallyl-3,4,5-tribenzyloxypiperidine (3.9):



3.7 **3.9**

Compound **3.7** was subjected to **general procedure E**. As a result, **3.9** was obtained as thick yellow oil (183 mg, 70%), along with the recovered substrate (16 mg).
HRMS: found: *m/z* = 484.2855; calc. for $C_{32}H_{38}NO_3$ (M + H$^+$): 484.2852; elem. anal.: found: C – 79.45, H – 7.68, N – 2.74%; calcd. C – 79.47, H – 7.71, N – 2.90%; $[\alpha]_D^{23}$ = 18.4; R_f = 0.5 (hexanes:AcOEt 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (m, arom.), 5.85 (m, 2H, H-8a, H-8b), 5.14 (m, 2H, H-9a, H-9a'), 5.08 (m, 2H, H-9b, H-9b'), 4.95 (m, 2H, 2 × OC$\underline{H_2}$Ph), 4.76 (d, 1H, *J* = 10.7 Hz, OC$\underline{H_2}$Ph), 4.68 (m, 3H, 3 × OC$\underline{H_2}$Ph), 3.79 (~ t, 1H, *J* = 9.1 Hz, H-4), 3.52 (m, 1H, H-5), 3.41 (d, 1H, *J* = 9.2 Hz, H-3), 3.08 (dd, 1H, *J* = 12.6, 5.5 Hz, H-6), 2.67 (dd, 1H, *J* = 12.5, 10.9 Hz, H-6'), 2.56 (dd, 1H, *J* = 14.6, 7.8 Hz, H-7a), 2.39 (m, 2H, H-7a', H-7b), 2.26 ppm (dd, 1H, *J* = 14.3, 7.1 Hz, H-7b'). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.0, 138.7, 138.4 (3 × quat. benzyl), 133.5 (C-8b), 133.2 (C-8a), 128.4-127.1 (arom.), 119.0 (C-9b), 118.6 (C-9a), 84.2 (C-4), 82.7 (C-3), 81.1 (C-5), 75.6, 75.0, 72.8 (3 × O$\underline{C}$H$_2$Ph), 59.3 (C-2), 42.9 (C-6), 40.7 (C-7b), 34.5 ppm (C-7a).

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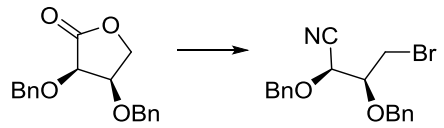
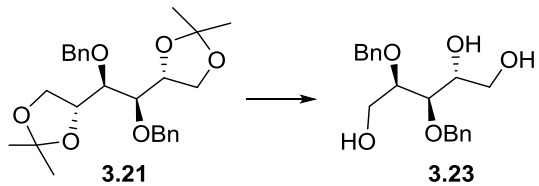
(2*S*,3*S*)-2,3-Dibenzyloxy-4-bromobutanenitrile (3.15):



3.19 **3.15**

Lactone **3.19** (4.8 g, 16.1 mmol) was dissolved in dry DCM (120 mL) under argon atmosphere. Then, the solution was cooled to -78 °C and DIBAL-H (1 M/hexanes, 22 mL, 1.4 equiv) was added (20 min, syringe pump) under vigorous stirring. After stirring for 1 h, mixture of Celite and $Na_2SO_4 \cdot 10H_2O$ (90 g/40 g) was added in several portions over a period of 20 min. The cooling bath was removed and the mixture was allowed to reach rt. After 12 h of vigorous stirring, the mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude product was subjected to **general procedure A**. *ω*-Bromonitrile **3.15** was obtained as colorless oil (72%).
HRMS: found: *m*/*z* = 382.0414; calc. for $C_{18}H_{18}NO_2BrNa$ ($M + Na^+$): 382.0419; elem. anal.: found: C – 60.13, H – 5.12, N – 3.83%; calcd. C – 60.01, H – 5.04, N – 3.89%; $[\alpha]_D^{23}$ = 68.9; R_f = 0.6 (hexanes:AcOEt 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34 (m, arom.), 4.86 (d, 1H, *J* = 11.3 Hz, OC*H*$_2$Ph), 4.75 (d, 1H, *J* = 11.4 Hz, OC*H*$_2$Ph), 4.71 (d, 1H, *J* = 11.4 Hz, OC*H*$_2$Ph), 4.56 (d, 1H, *J* = 11.3 Hz, OC*H*$_2$Ph), 4.34 (d, 1H, *J* = 7.5 Hz, H-2), 3.88 (~dt, 1H, *J* = 7.6, 4.0 Hz, H-3), 3.54 ppm (m, 2H, H-4, H-4'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.5, 135.1 (2 × quat. benzyl), 128.7-128.2 (arom.), 116.8 (*C*N), 76.7 (C-3), 73.2, 73.0 (2 × O*C*H$_2$Ph), 68.9 (C-2), 31.1 ppm (C-4).

(2*R*,3*R*,4*R*)-3,4-Dibenzyloxypentane-1,2,5-triol (3.23):



3.21 **3.23**

To the solution of fully protected mannitol **3.21** (12.5 g, 28.3 mmol) in MeOH (150 mL), at rt, conc. HCl (2 mL) was added and the mixture was heated to 65 °C. After 24 h at this temperature, the solvents were evaporated. Then, toluene (20 mL) was added and the solution was once again concentrated; this procedure was repeated until all residue water was removed. The crude mixture was dissolved in DCM (85 mL) and sat. aq. $NaHCO_3$ was added until slightly basic pH was achieved. Then, $NaIO_4$ (12.6 g,

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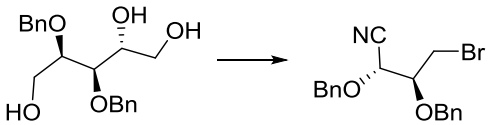
58.3 mmol, 2.1 equiv) was added in several portions over a period of 10 min. The mixture was vigorously stirred for another 2 h. After this time, $MgSO_4$ (10 g) was added and the mixture was stirred for additional 30 min. The solids were filtered off using Celite, after which the filtrate was concentrated. The crude product was dissolved in MeOH (150 mL) and $NaBH_4$ was added, at rt, in several portions over a period of 10 min. After 1 h, sat. aq. NH_4Cl (50 mL) was carefully added and the resulting solution was extracted with AcOEt (3 × 100 mL). Flash chromatography (50:50 hexanes:AcOEt, 40:50:10 hexanes:AcOEt:MeOH, and eventually 90:10 AcOEt:MeOH) yielded the desired triol **3.23** as white solid (59%).

HRMS: found: *m/z* = 355.1523; calc. for $C_{19}H_{24}O_5Na$ ($M + Na^+$): 355.1521; elem. anal.: found: C – 68.59, H – 7.27; calcd. C – 68.66, H – 7.28; $[\alpha]_D^{23}$ = 3.5; mp: 59-60 °C; R_f = 0.3 (hexanes:AcOEt:MeOH 10:10:0.5). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.32 (m, arom.), 4.62 (m, 4H, 4 × OC<u>*H*</u>$_2$Ph), 3.86 (m, 2H, H-5, H-2), 3.80 (dd, 1H, *J* = 11.8, 4.8 Hz, H-5'), 3.74 (m, 2H, H-1, H-4), 3.68 (m, 2H, H-1', H-3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ: 137.5, 137.4 (2 × quat. benzyl), 128.6-128.1 (arom.), 79.3 (C-4), 73.6 (C-3), 72.7 (2 × O<u>*C*</u>H$_2$Ph), 71.5 (C-2), 63.4 (C-1), 60.9 (C-5) ppm.

(2*R*,3*S*)-2,3-Dibenzyloxy-4-bromobutanenitrile (3.16):



3.23 **3.16**

Triol **3.23** (5.5 g, 16.6 mmol) was dissolved in DCM (50 mL) and sat. aq. $NaHCO_3$ (4 mL) was added at rt. Then, $NaIO_4$ (7.1 g, 33.1 mmol, 2 equiv) was added in several portions over a period of 10 min and the resulting mixture was vigorously stirred at room temperature for 48 h. After this time, $MgSO_4$ (5 g) was added and the mixture was stirred for additional 30 min. The solids were filtered off using Celite, after which the filtrate was concentrated. The crude hemiacetal was subjected to **general procedure A**. ω-Bromonitrile **3.16** was obtained as colorless oil (60%).

HRMS: found: *m/z* = 382.0418; calc. for $C_{18}H_{18}NO_2BrNa$ ($M + Na^+$): 382.0419; elem. anal.: found: C – 60.20, H – 5.00, N – 3.85%; calcd. C – 60.01, H – 5.04, N – 3.89%; $[\alpha]_D^{23}$ = -54.7; R_f = 0.6 (hexanes:AcOEt 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34 (m, arom.), 4.87 (d, 1H, *J* = 11.7 Hz, OC<u>*H*</u>$_2$Ph), 4.76 (d, 1H, *J* = 11.7 Hz, OC<u>*H*</u>$_2$Ph), 4.71 (d, 1H, *J* = 11.7 Hz, OC<u>*H*</u>$_2$Ph), 4.54 (d, 1H, *J* = 11.7 Hz, OC<u>*H*</u>$_2$Ph), 4.39 (d, 1H, *J* = 4.3

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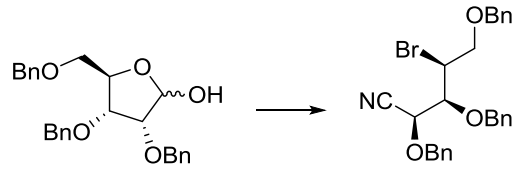
Hz, H-2), 3.86 (ddd, 1H, *J* = 6.1, 6.0, 4.4 Hz, H-3), 3.60 (dd, 1H, *J* = 10.7, 5.8 Hz, H-4), 3.48 (dd, 1H, *J* = 10.7, 6.3 Hz, H-4') ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.7, 136.1 (2 × quat. benzyl), 128.7-128.2 (arom.), 116.1 (*C*N), 78.2 (C-3), 74.1, 72.9 (2 × O*C*H_2Ph), 68.5 (C-2), 29.5 ppm (C-4).

(2*S*,3*S*,4*S*)-4-Bromo-2,3,5-tribenzyloxypentanenitrile (3.17):

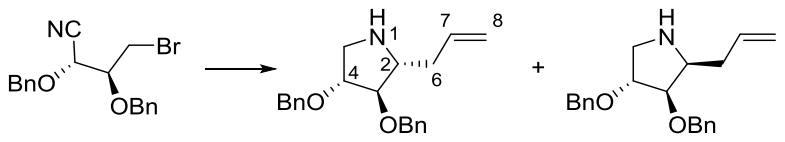


3.25 **3.17**

Compound **3.25** was subjected to **general procedure A**. As a result, *ω*-bromonitrile **3.17** was obtained as colorless oil (53%).

HRMS: found: *m*/*z* = 502.0997; calc. for $C_{26}H_{26}NO_3BrNa$ (M + Na^+): 502.0994; elem. anal.: found: C – 64.99, H – 5.46, N – 2.77%; calcd. C – 65.01, H – 5.46, N – 2.92%; $[\alpha]_D^{23}$ = 67.8; R_f = 0.7 (hexanes:AcOEt 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33 (m, arom.), 4.96 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.86 (d, 1H, *J* = 11.1 Hz, OC*H*$_2$Ph), 4.65 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.57 (d, 1H, *J* = 11.1 Hz, OC*H*$_2$Ph), 4.49 (d, 1H, *J* = 11.8 Hz, OC*H*$_2$Ph), 4.42 (m, 2H, OC*H*$_2$Ph, H-2), 4.37 (ddd, 1H, *J* = 9.5, 5.5, 2.0 Hz, H-4), 4.11 (dd, 1H, *J* = 8.7, 2.0 Hz, H-3), 3.76 (~t, 1H, *J* = 9.7 Hz, H-5), 3.70 ppm (dd, 1H, *J* = 9.8, 5.6 Hz, H-5'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 137.2, 136.9, 136.1 (3 × quat. benzyl), 128.7-128.2 (arom.), 117.7 (*C*N), 76.5 (C-3), 75.5, 73.2, 73.0 (3 × O*C*H_2Ph), 69.8 (C-5), 69.4 (C-2), 50.7 ppm (C-4).

2-Allylpyrrolidines 3.27:



3.16 **3.27**
dr = 4.3:1

Compound **3.16** was subjected to **general procedure D**. As a result, 2-allylpyrrolidine **3.27** was obtained as dark orange oil (67%, *dr* = 4.3:1).

HRMS: found: *m*/*z* = 324.1959; calc. for $C_{21}H_{27}NO_2$ (M + H^+): 324.1964; elem. anal.: found: C – 77.82, H – 7.99, N – 4.25%; calcd. C – 77.99, H – 7.79, N – 4.33%; R_f =

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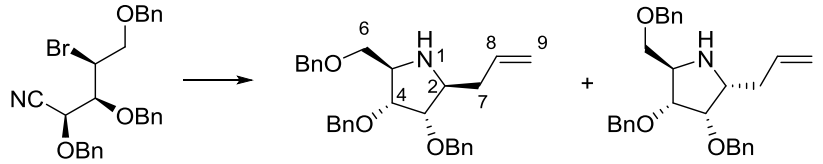
0.3 (DCM:MeOH 10:1). ^{1}H NMR (600 MHz, major isomer, $CDCl_3$) δ: 7.32 (m, arom.), 5.82 (m, H-7), 5.07 (m, H-8, H-8'), 4.52 (m, 4 × OC<u>*H*</u>$_2$Ph), 3.98 (ddd, 1H, *J* = 4.6, 1.8, 1.8 Hz, H-3), 3.66 (m, 1H, H-4) 3.06 (m, H-2, H-5, H-5'), 2.39 (m, H-6), 2.31 ppm (m, 1H, H-6'). ^{13}C NMR (150 MHz, major isomer, $CDCl_3$) δ: 138.0 (2 × quat. benzyl), 135.2 (C-7), 128.4-127.5 (arom.), 117.1 (C-8), 88.3 (C-4), 84.3 (C-3), 71.8, 71.0 (2 × O<u>*C*</u>H$_2$Ph), 63.9 (C-2), 51.0 (C-5), 37.8 ppm (C-6). ^{1}H NMR (600 MHz, minor isomer, selected signals, $CDCl_3$) δ: 4.01 (dd, 1H, *J* = 5.9, 3.0 Hz, H-4), 3.81 (d, 1H, *J* = 3.9 Hz, H-3), 3.42 (dd, 1H, *J* = 12.4, 6.3 Hz, H-5), 3.19 (m, 1H, H-2), 2.88 (dd, 1H, *J* = 12.4, 2.8 Hz, H-5') ppm. ^{13}C NMR (150 MHz, minor isomer, selected signals, $CDCl_3$) δ: 83.3 (C-3), 82.9 (C-4), 61.2 (C-2), 51.4 (C-5), 33.1 (C-6) ppm.

2-Allylpyrrolidines 3.29:



Compound **3.17** was subjected to **general procedure D**. As a result, 2-allylpyrrolidine **3.29** was obtained as dark orange oil (71%, *dr* = 1.7:1). NMR spectra of this mixture was in agreement with the literature.[54]

HRMS: found: *m/z* = 444.2545; calc. for $C_{29}H_{34}NO_3$ (M + H^+): 444.2539; elem. anal.: found: C – 78.53, H – 7.59, N – 3.12%; calcd. C – 78.52, H – 7.50, N – 3.16%; R_f = 0.6 (DCM:MeOH 20:1). ^{1}H NMR (600 MHz, major isomer, $CDCl_3$) δ: 7.31 (m, arom.), 5.77 (m, H-8), 5.05 (m, H-9), 4.53 (m, 6 × OC<u>*H*</u>$_2$Ph), 3.74 (~t, 1H, *J* = 5.2 Hz, H-4), 3.47 (m, H-3, H-5, H-6, H-6'), 3.33 (m, 1H, H-2), 2.38 (m, H-7), 2.09 ppm (m, 1H, H-7'). ^{13}C NMR (150 MHz, major isomer, $CDCl_3$) δ: 138.3, 138.25, 138.20 (3 × quat. benzyl), 135.2 (C-8), 128.3-127.5 (arom.), 117.1 (C-9), 81.3 (C-3), 78.2 (C-4), 73.2, 71.8, 71.6 (3 × O<u>*C*</u>H$_2$Ph), 71.1 (C-6), 61.6 (C-5), 60.6 (C-2), 38.4 ppm (C-7). ^{1}H NMR (600 MHz, minor isomer, selected signals, $CDCl_3$) δ: 3.89 (m, 2H, H-3, H-4), 3.18 ppm (ddd, 1H, *J* = 7.2, 7.1, 3.8 Hz). ^{13}C NMR (150 MHz, minor isomer, selected signals, $CDCl_3$) δ: 82.0 (C-3), 78.6 (C-4), 60.1 (C-5), 59.5 (C-2), 34.6 ppm (C-7).

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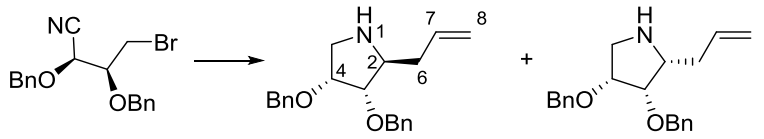
2-Allylpyrrolidines 3.30:

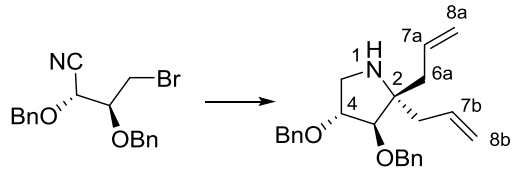


3.15 **3.30**
dr = 2.6:1

Compound **3.15** was subjected to **general procedure D**. As a result, 2-allylpyrrolidine **3.30** was obtained as dark orange oil (72%, *dr* = 2.6:1).

HRMS: found: *m/z* = 324.1963; calc. for $C_{21}H_{27}NO_2$ (M + H^+): 324.1964; R_f = 0.4 (DCM:MeOH 10:1). ^{1}H NMR (600 MHz, major isomer, $CDCl_3$) δ: 7.31 (m, arom.), 5.78 (m, H-7), 5.07 (m, H-8, H-8'), 4.57 (m, 4 × OC*H*$_2$Ph), 3.93 (dd, 1H, *J* = 9.0, 4.7 Hz, H-4), 3.52 (~dd, 1H, *J* = 7.0, 4.9 Hz, H-3), 3.36 (~td, 1H, *J* = 7.4, 5.1 Hz, H-2), 3.15 (m, H-5, H-5'), 2.39 (m, H-6), 2.16 ppm (m, 1H, H-6'). ^{13}C NMR (150 MHz, major isomer, $CDCl_3$) δ: 138.1 (2 × quat. benzyl), 135.0 (C-7), 128.4-127.5 (arom.), 117.3 (C-8), 82.6 (C-3), 76.6 (C-4), 72.2, 71.5 (2 × O*C*H$_2$Ph), 60.3 (C-2), 49.3 (C-5), 38.1 ppm (C-6). ^{1}H NMR (600 MHz, minor isomer, selected signals, $CDCl_3$) δ: 4.09 (~td, 1H, *J* = 6.6, 4.1 Hz, H-3), 3.90 (~t, 1H, *J* = 4.2 Hz, H-4), 3.18 (m, 1H, H-2), 2.49 (m, 1H, H-6) ppm. ^{13}C NMR (150 MHz, minor isomer, selected signals, $CDCl_3$) δ: 80.2 (C-3), 78.4 (C-4), 60.0 (C-2), 48.2 (C-5), 34.0 (C-6) ppm.

(3*R*,4*R*)-2,2-Diallyl-3,4-dibenzyloxypyrrolidine (3.26):



3.16 **3.26**

Compound **3.16** was subjected to **general procedure E**. Diallyl derivative was obtained as orange oil (68%).

Elem. anal.: found: C – 79.12, H – 8.04, N – 3.92%; calcd. C – 79.30, H – 8.04, N – 3.85%; $[\alpha]_D^{23}$ = -20.6; R_f = 0.4 (DCM:MeOH 20:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31 (m, arom.), 5.86 (m, 2H, H-7a, H-7b), 5.08 (m, 4H, H-8a, H-8a', H-8b, H-8b'), 4.61 (d, 1H, *J* = 11.7 Hz, 1 × OC*H*$_2$Ph), 4.50 (m, 3H, 3 × OC*H*$_2$Ph), 4.05 (m, 1H, H-4), 3.76 (d, 1H, *J* = 3.1 Hz, H-3), 3.27 (dd, 1H, *J* = 12.2, 6.7 Hz, H-5), 2.89 (dd, 1H, *J* = 12.2, 4.4 Hz, H-5'), 2.29 ppm (m, 4H, H-6a, H-6a', H-6b, H-6b'). ^{13}C NMR (125

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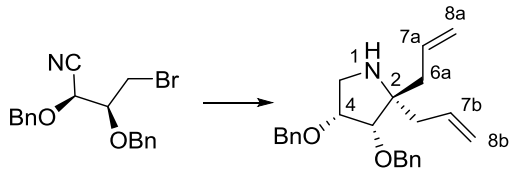
MHz, $CDCl_3$) δ: 138.4, 138.1 (2 × quat. benzyl), 134.9, 133.9 (C-7a, C-7b), 128.4-127.5 (arom.), 118.2, 117.9 (C-8a, C-8b), 88.5 (C-3), 85.2 (C-4), 71.9, 71.7 (2 × O<u>*C*</u>H_2Ph), 65.3 (C-2), 49.1 (C-5), 42.9, 38.6 ppm (C-6a, C-6b).

(3*S*,4*R*)- 2,2-Diallyl-3,4-dibenzyloxypyrrolidine (3.31):

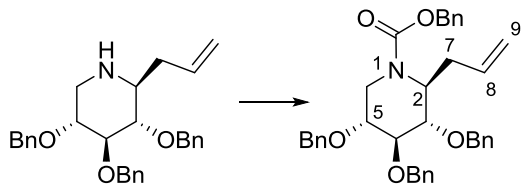


3.15 **3.31**

Compound **3.15** was subjected to **general procedure E**. Diallyl derivative was obtained as orange oil (64%).

HRMS: found: *m/z* = 364.2274; calc. for $C_{24}H_{30}NO_2$ (M + H^+): 364.2277; $[\alpha]_D^{23}$ = -49.9; R_f = 0.4 (DCM:MeOH 20:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.31 (m, arom.), 5.95 (m, 1H, H-7a), 5.75 (m, 1H, H-7b), 5.03 (m, 4H, H-8a, H-8a', H-8b, H-8b'), 4.70 (d, 1H, *J* = 11.8 Hz, 1 × OC<u>*H*</u>$_2$Ph), 4.60 (d, 1H, *J* = 12.1 Hz, 1 × OC<u>*H*</u>$_2$Ph), 4.53 (d, 1H, *J* = 12.1 Hz, 1 × OC<u>*H*</u>$_2$Ph), 4.46 (d, 1H, *J* = 11.8 Hz, 1 × OC<u>*H*</u>$_2$Ph), 3.98 (~td, 1H, *J* = 5.1, 3.3 Hz, H-4), 3.64 (d, 1H, *J* = 5.3 Hz, H-3), 3.04 (dd, 1H, *J* = 12.4, 3.2 Hz, H-5), 2.94 (dd, 1H, *J* = 12.4, 4.9 Hz, H-5'), 2.59 (dd, 1H, *J* = 14.3, 7.6 Hz, H-6a), 2.39 (dd, 1H, *J* = 14.3, 7.3 Hz, H-6a'), 2.19 ppm (m, 2H, H-6b, H-6b'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 138.48, 138.45 (2 × quat. benzyl), 134.9 (C-7a), 134.3 (C-7b), 128.3-127.5 (arom.), 118.1, 117.8 (C-8a, C-8b), 84.0 (C-3), 77.7 (C-4), 72.6, 71.7 (2 × O<u>*C*</u>H_2Ph), 63.7 (C-2), 48.7 (C-5), 42.9 (C-6b), 38.6 ppm (C-6a).

(2*S*,3*S*,4*S*,5*R*)-1-Benzyloxycarbonyl-2-allyl-3,4,5-tribenzyloxypiperidine (3.37):



3.8 **3.37**

To a stirred solution of **3.8** (980 mg, 2.21 mmol) in acetonitrile (50 mL), finely pulverized K_2CO_3 (1.5 g, 4.9 equiv) was added, followed by benzyl chloroformate (0.35 mL, 2.45 mmol, 1.1 equiv). The reaction was stirred for 30 min, the solid was

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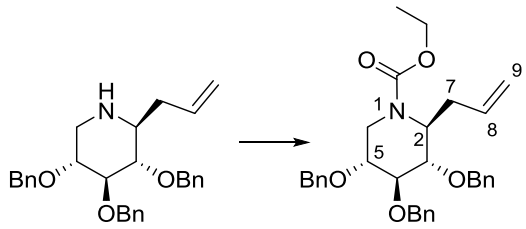
filtered off and the solvent was evaporated. The residue was chromatographed (flash chromatography, 100% hexanes to 100% ethyl acetate) to yield **3.37** as colorless oil (1.22 g, 95%).

LRMS: *m/z*: 600.5 ([M + Na]$^+$); elem. anal.: found: C – 76.69, H –6.86, N – 2.49%; calcd. C – 76.92, H – 6.80, N – 2.42%; $[\alpha]_D^{23} = -7.1$; R_f = 0.6 (hexanes:AcOEt 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.28 (m, arom.), 5.71 (m, 1H, H-8), 5.12 (m, 2H, OC$\underline{H}_2$Ph), 4.98 (m, 2H, H-9, H-9'), 4.57 (m, 6H, OC$\underline{H}_2$Ph), 4.32 (~bs, 1H, H-2), 4.05 (~bs, 1H, H-6), 3.73 (~t, 1H, *J* = 4.2 Hz, H-4), 3.65 (~d, 1H, *J* = 3.3 Hz, H-5), 3.55 (~t, 1H, *J* = 3.7 Hz, H-3), 3.31 (dd, 1H, *J* = 14.1, 3.0 Hz, H-6'), 2.45 ppm (m, 2H, H-7, H-7'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.0 ($\underline{C}$=O), 138.2, 138.0, 136.7 (4 × quat. benzyl), 134.5 (C-8), 128.4-127.5 (arom.), 117.7 (C-9), 79.5 (C-4), 75.9 (C-5), 75.3 (C-3), 72.5, 71.8, 70.7, 67.1 (4 × O$\underline{C}$H$_2$Ph), 54.5 (C-2), 39.7 (C-6), 35.1 ppm (C-7).

(2*S*,3*S*,4*S*,5*R*)-1-Ethoxycarbonyl-2-allyl-3,4,5-tribenzyloxypiperidine (3.38):



3.8 **3.38**

To a stirred solution of **3.8** (500 mg, 1.13 mmol) in acetonitrile (25 mL), finely pulverized K_2CO_3 (0.7 g, 5.1 equiv) was added, followed by ethyl chloroformate (0.24 mL, 2.51 mmol, 2.2 equiv). The reaction was stirred for 30 min, the solid was filtered off and the solvent was evaporated. The residue was chromatographed (flash chromatography, 100% hexanes to 100% ethyl acetate) to yield **3.38** as colorless oil (520 mg, 90%).

LRMS: *m/z*: 538.4 ([M + Na]$^+$); elem. anal.: found: C – 74.36, H – 7.16, N – 2.53%; calcd. C – 74.54, H – 7.23, N – 2.72%; $[\alpha]_D^{23} = -11.1$; R_f = 0.5 (hexanes:AcOEt 4:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.29 (m, arom.), 5.74 (~ddt, 1H, *J* = 17.4, 10.4, 7.2 Hz, H-8), 5.01 (m, 2H, H-9, H-9'), 4.71 (d, 1H, *J* = 11.9 Hz, OC$\underline{H}_2$Ph), 4.61 (m, 2H, OC$\underline{H}_2$Ph), 4.54 (m, 2H, OC$\underline{H}_2$Ph), 4.24 (~bs, 1H, H-2), 4.12 (m, 2H, $CH_3C\underline{H}_2$-), 4.00 (~d, 1H, *J* = 12.0 Hz, H-6), 3.72 (~t, 1H, *J* = 4.4 Hz, H-4), 3.65 (~dd, 1H, *J* = 7.8, 4.2 Hz, H-5), 3.55 (~t, 1H, *J* = 4.2 Hz, H-3), 3.30 (dd, 1H, *J* = 14.1, 3.2 Hz, H-6'), 1.21 ppm (t, 3H, *J* = 7.1 Hz, C$\underline{H}_3$CH$_2$-). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 156.2 ($\underline{C}$=O),

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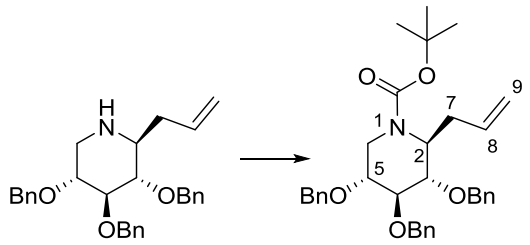
138.23, 138.19, 138.0 (3 × quat. benzyl), 134.6 (C-8), 128.4-127.5 (arom.), 117.6 (C-9), 80.0 (C-4), 76.2 (C-5), 75.5 (C-3), 72.5, 71.9, 70.7 (3 × O<u>*C*</u>H_2Ph), 61.3 (CH_3<u>*C*</u>H_2-), 54.4 (C-2), 39.7 (C-6), 35.2 (C-7), 14.6 ppm (<u>*C*</u>H_3CH_2-).

(2*S*,3*S*,4*S*,5*R*)-1-(*tert*-Butoxycarbonyl)-2-allyl-3,4,5-tribenzyloxypiperidine (3.39):



3.8 **3.39**

To a stirred solution of **3.8** (291 mg, 0.66 mmol) in acetonitrile (5 mL), finely pulverized K_2CO_3 (0.5 g, 5.5 equiv) was added, followed by Boc_2O (2 M in DCM, 0.8 mL, 1.6 mmol, 2.4 equiv). The reaction was stirred for 24 h, the solid was filtered off and the solvent was evaporated. The residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) to yield **3.39** as colorless oil (348 mg, 97%).

LRMS: *m*/*z*: 566.5 ($[M + Na]^+$); elem. anal.: found: C – 74.97, H – 7.62, N – 2.55%; calcd. C – 75.11, H – 7.60, N – 2.58%; $[\alpha]_D^{23} = -10.8$; R_f = 0.5 (hexanes:AcOEt 5:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.29 (m, arom.), 5.75 (~ddt, 1H, *J* = 16.0, 11.1, 7.2 Hz, H-8), 5.01 (m, 2H, H-9, H-9'), 4.73 (d, 1H, *J* = 11.7, OC<u>*H*</u>$_2$Ph), 4.57 (m, 5H, OC<u>*H*</u>$_2$Ph), 4.18 (~bs, 1H, H-2), 3.96 (~d, 1H, H-6), 3.72 (~t, 1H, *J* = 4.5 Hz, H-4), 3.66 (~dd, 1H, *J* = 7.9, 4.3 Hz, H-5), 3.54 (~t, 1H, *J* = 4.5 Hz, H-3), 3.26 (dd, 1H, *J* = 14.1, 3.3 Hz, H-6'), 2.44 (m, 2H, H-7, H-7'), 1.43 ppm (s, 9H, (C<u>*H*</u>$_3$)$_3$C-). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.3 (<u>*C*</u>=O), 138.29, 138.27, 138.1 (3 × quat. benzyl), 134.8 (C-8), 128.4-127.4 (arom.), 117.5 (C-9), 80.8 (C-4), 79.7 ((CH$_3$)$_3$<u>*C*</u>-), 76.7 (C-5), 75.9 (C-3), 72.6, 71.9, 70.6 (3 × O<u>*C*</u>H_2Ph), 54.4 (C-2), 39.6 (C-6), 35.3 (C-7), 28.4 ppm ((<u>*C*</u>H$_3$)$_3$C-).

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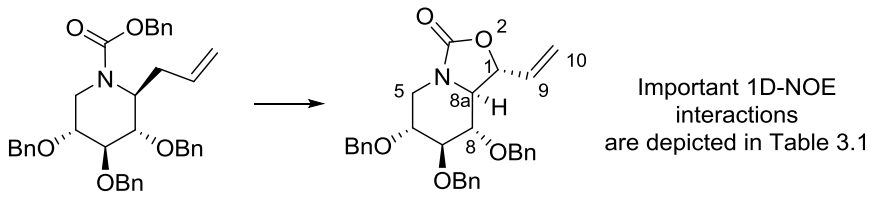
(1*R*,6*R*,7*S*,8*S*,8a*R*)-1-Ethenyl-6,7,8-tribenzyloxyhexahydro[1,3]oxazolo[3,4-*a*]pyridin-3-one (3.40):



No precautions were taken to exclude moisture and air. To a solution of **3.37** (494 mg, 0.86 mmol) in dioxane (4.3 mL), benzoquinone (185 mg, 2 equiv) was added, followed by $Yb(OTf)_3$ (53 mg, 0.1 equiv) and [1,2-bis(phenylsulfinyl) ethane] palladium acetate **3.36** (White catalyst, 43 mg, 0.1 equiv). The flask was sealed with a rubber septum and the mixture was stirred at 75 °C for 4 h. Then, the mixture was cooled down and toluene (5 mL) was added, followed by silica gel (3 g, 230-400 mesh). The solvent was evaporated and the dry residue was loaded on a chromatography column. Flash chromatography (100% hexanes to 100% ethyl acetate) yielded **3.40** (297 mg, 71%) as pale orange oil that solidified upon standing.

HRMS: found: *m/z* = 486.2285; calcd. for $C_{30}H_{32}NO_5$ ($[M + H]^+$): 486.2280; elem. anal.: found: C – 74.21, H – 6.66, N – 2.67%; calcd. C – 74.21, H –6.43 , N – 2.88%; mp = 82 ÷ 84 °C; $[\alpha]_D^{23} = -21.9$; R_f = 0.4 (hexanes: ethyl acetate 3:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (m, arom.), 5.82 (ddd, 1H, *J* = 17.0, 10.6, 5.8 Hz, H-9), 5.33 (m, 1H, H-10), 5.25 (m, 1H, H-10'), 5.00 (d, 1H, *J* = 10.9 Hz, OC$\underline{H_2}$Ph), 4.92 (d, 1H, *J* = 11.4 Hz, OC$\underline{H_2}$Ph), 4.82 (d, 1H, *J* = 10.9 Hz, OC$\underline{H_2}$Ph), 4.67 (m, 3H, OC$\underline{H_2}$Ph), 4.37 (~ddt, 1H, *J* = 5.7, 4.4, 1.3 Hz, H-1), 4.13 (dd, 1H, *J* = 13.2, 5.4 Hz, H-5), 3.56 (m, 2H, H-6, H-7), 3.37 (m, 1H, H-8), 3.28 (dd, 1H, *J* = 9.5, 4.4 Hz, H-8a), 2.74 ppm (dd, 1H, *J* = 13.2, 10.0 Hz, H-5'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.9 (C-3), 138.2, 137.57, 137.56 (3 × quat. benzyl), 134.1 (C-9), 128.5-127.8 (arom.), 118.1 (C-10), 85.7 (C-7), 79.8 (C-8), 77.7 (C-1), 77.4 (C-6), 75.9, 75.1, 73.2 (3 × O$\underline{C}H_2$Ph), 61.8 (C-8a), 42.8 ppm (C-5).

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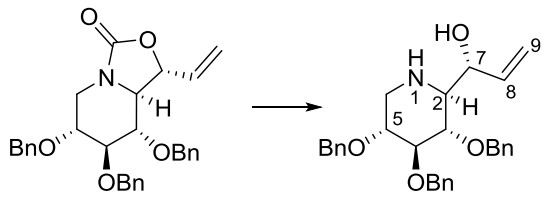
(2*S*,3*S*,4*S*,5*R*)-2-[(1*R*)-1-Hydroxyprop-2-en-1-yl]-3,4,5-tribenzyloxypiperidine (3.41):



3.40 **3.41**

To a stirred solution of **3.40** (503 mg, 1.04 mmol) in methanol (10 mL), KOH (1.1 g, 19 equiv) was added in few portions. The flask was sealed with a rubber septum and the mixture was stirred at 75 °C for 12 h. After cooling down to room temperature, water (20 mL) and ethyl acetate (100 mL) were added. Layers were separated and the aqueous one was washed with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (10 mL) and brine. Then, the mixture was dried and solvent was evaporated. The residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) to yield **3.41** (404 mg, 85%) as a colorless oil.

HRMS: found: *m*/*z* = 460.2488; calcd. for $C_{29}H_{34}NO_4$ ($[M + H]^+$): 460.2488; elem. anal.: found: C – 75.79, H – 7.16, N – 3.01%; calcd. C – 75.79, H – 7.24, N – 3.05%; $[\alpha]_D^{23}$ = 4.6; R_f = 0.3 (hexanes: ethyl acetate 2:3). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (arom.), 5.87 (ddd, 1H, *J* = 17.2, 10.6, 3.9 Hz, H-8), 5.38 (m, 1H, H-9), 5.24 (m, 1H, H-9'), 4.99 (d, 1H, *J* = 11.0 Hz, OC*H*$_2$Ph), 4.95 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.86 (d, 1H, *J* = 11.0 Hz, OC*H*$_2$Ph), 4.70 (m, 2H, OC*H*$_2$Ph), 4.65 (d, 1H, *J* = 11.6 Hz, OC*H*$_2$Ph), 4.47 (dd, 1H, *J* = 3.7, 1.8 Hz, H-7), 3.57 (m, 2H, H-3, H-4), 3.50 (m, 1H, H-5), 3.23 (dd, 1H, *J* = 11.6, 4.9 Hz, H-6), H- 2.57 (m, 1H, H-2), 2.50 ppm (dd, 1H, *J* = 11.3, 10.6 Hz, H-6'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.0 (C-8), 138.8, 138.42, 138.37 (3 × quat. benzyl), 128.4-127.5 (arom.), 115.5 (C-9), 87.1 (C-4), 80.0 (C-5), 78.9 (C-3), 75.5, 75.3, 72.8 (3 × O*C*H$_2$Ph), 69.4 (C-7), 62.5 (C-2), 47.9 ppm (C-6).

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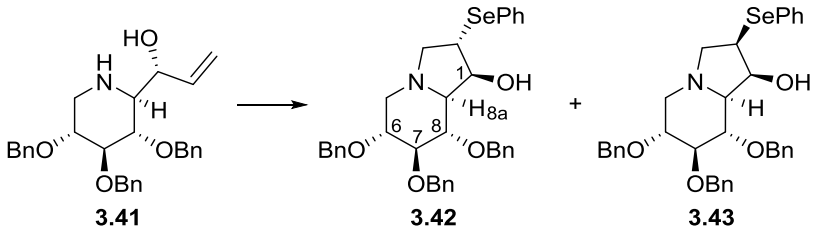
Phenylselenyl bromide-mediated cyclization of 3.41



3.41 **3.42** **3.43**

All 1D-NOE interactions and HMBC correlations are already depicted on Fig. 3.0

To a stirred solution of **3.41** (287 mg, 0.63 mmol) in a mixture of dry DCM (5 mL) and dry pyridine (1 mL), at rt and under argon atmosphere, phenylselenyl bromide (162 mg, 1.1 equiv) was added in one portion. After 10 min, triethylamine was added (1 mL). Then, solvents were evaporated. The residue was redissolved in hot toluene and concentrated again. The process was repeated 2 × times. Column chromatography (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) yielded **3.42** as off-white solid (272 mg, 71%) and **3.43** as off-white solid (38 mg, 10%).

(1*S*,2*S*,6*R*,7*S*,8*S*,8a*R*)-2-(Phenylselenyl)-6,7,8-tribenzyloxyoctahydroindolizine-1-ol (3.42):

LRMS: *m*/*z*: 616.4 ([M + H]$^+$); elem. anal.: found: C – 68.33, H – 5.93, N – 2.17%; calcd. C – 68.40, H – 6.07, N – 2.28%; mp = 95 ÷ 97 °C; $[\alpha]_D^{23} = -81.1$; R_f = 0.4 (hexanes:AcOEt 2:1). ^{1}H NMR (600 MHz, C_6D_6) δ: 7.11 (m, arom.), 5.00 (d, 1H, *J* = 11.2 Hz, OC*H*$_2$Ph), 4.92 (m, 3H, OC*H*$_2$Ph), 4.56 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.50 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.42 (~d, 1H, *J* = 2.9 Hz, H-1), 3.84 (~t, 1H, *J* = 9.2 Hz, H-8), 3.68 (~td, 1H, *J* = 9.6, 5.0 Hz, H-6), 3.60 (~t, 1H, *J* = 8.9 Hz, H-7), 3.51 (~t, 1H, *J* = 7.9 Hz, H-2), 3.18 (dd, 1H, *J* = 9.7, 8.4 Hz, H-3), 2.93 (dd, 1H, *J* = 10.5, 5.0 Hz, H-5), 2.32 (dd, 1H, *J* = 9.5, 3.8 Hz, H-8a), 1.99 (dd, 1H, *J* = 9.8, 7.7 Hz, H-3'), 1.81 ppm (~t, 1H, *J* = 10.4 Hz, H-5'). ^{13}C NMR (150 MHz, C_6D_6) δ: 139.82, 139.81, 139.4 (3 × quat. benzyl), 133.0-127.3 (arom.), 87.4 (C-7), 79.3 (C-6), 78.8 (C-1), 77.7 (C-8), 75.8, 74.6, 72.8 (3 × O*C*H$_2$Ph), 70.2 (C-8a), 59.1 (C-3), 54.3 (C-5), 45.6 ppm (C-2). ^{77}Se NMR (114 MHz, C_6D_6) δ: 358.3 ppm (s, -*Se*Ph).

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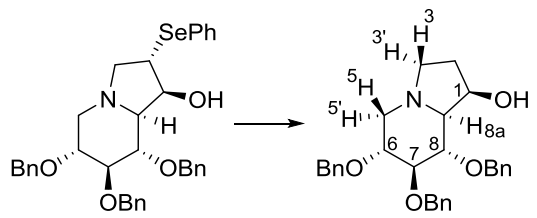
(1*S*,2*R*,6*R*,7*S*,8*S*,8a*R*)-2-(Phenylselenyl)-6,7,8-tribenzyloxyoctahydroindolizine-1-ol (3.43):

LRMS: *m*/*z*: 616.5 ([M + H]$^+$); elem. anal.: found: C – 68.16, H – 6.29, N – 2.13%; calcd. C – 68.40, H – 6.07, N – 2.28%; m.p. = decomp. (>50°C); $[\alpha]_D^{23} = -50.0$; R_f = 0.7 (hexanes:AcOEt 2:1). ^{1}H NMR (600 MHz, C_6D_6) δ: 7.21 (m, arom.), 5.05 (d, 1H, *J* = 11.3 Hz, OC*H*$_2$Ph), 4.96 (m, 3H, OC*H*$_2$Ph), 4.59 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.52 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.13 (m, 1H, H-1), 3.82 (~t, 1H, H-8), 3.62 (m, 1H, H-6), 3.57 (~t, 1H, H-7), 3.51 (ddd, 1H, *J* = 9.7, 5.5, 4.2 Hz, H-2), 2.99 (dd, 1H, *J* = 10.0, 4.1 Hz, H-3), 2.91 (dd, 1H, *J* = 10.4, 5.1 Hz, H-5), 2.44 (d, 1H, *J* = 9.8 Hz, -O*H*), 2.31 (~t, 1H, *J* = 9.8 Hz, H-3'), 1.91 (dd, 1H, *J* = 9.4, 3.1 Hz, H-8a), 1.82 ppm (~t, 1H, *J* = 10.3 Hz, H-5'). ^{13}C NMR (150 MHz, C_6D_6) δ: 140.02, 140.00, 139.5 (3 × quat. benzyl), 133.6-127.4 (arom.), 87.4 (C-7), 79.2 (C-6), 78.4 (C-8), 75.8, 74.8, 72.9 (3 × O*C*H$_2$Ph), 71.9 (C-1), 71.7 (C-8a), 60.3 (C-3), 54.3 (C-5), 47.1 ppm (C-2). ^{77}Se NMR (114 MHz, C_6D_6) δ: 323.8 ppm (s, -*Se*Ph).

(1*R*,6*R*,7*S*,8*S*,8a*S*)-6,7,8-Tribenzyloxyoctahydroindolizine-1-ol (3.44):



Important 2D-NOESY interactions:
H-3' and H-5',
H-3 and H-5,
H-3' and H-8a;
H-1 and H-8a

Important HMBC correlations:
C-5 and H-3',
C-3 and H-5,
C-3 and H-5'

To a stirred solution of **3.42** (108 mg, 0.18 mmol) in MeOH (1.0 mL) and THF (0.3 mL), a solution of $NiCl_2 \cdot 7H_2O$ (90 mg, 2 equiv) in MeOH (0.5 mL) was added. The resulting mixture was cooled to 0 °C and $NaBH_4$ (150 mg, 22 equiv) was added for 1 h in several portions. Then, the mixture was warmed to room temperature and stirred for another 1 h. After this time, the mixture was filtered through a pad of silica gel (3 g, 230-400 mesh), which was then thoroughly washed with ethyl acetate (100 mL). Solvent was evaporated and the residue was chromatographed (flash chromatography, 100% hexanes to 100% ethyl acetate) to yield **3.44** (48 mg, 60%) as pale yellow oil. NMR spectra matched those reported for its enantiomer; [α] value was also in accordance, but with opposite sign.[72]

HRMS: found: *m*/*z* = 460.2492; calcd. for $C_{29}H_{34}NO_4$ (M + H$^+$): 460.2488; elem. anal.: found: C – 75.66, H – 7.12, N – 2.89%; calcd. C – 75.79, H – 7.24, N – 3.05%; $[\alpha]_D^{23}$

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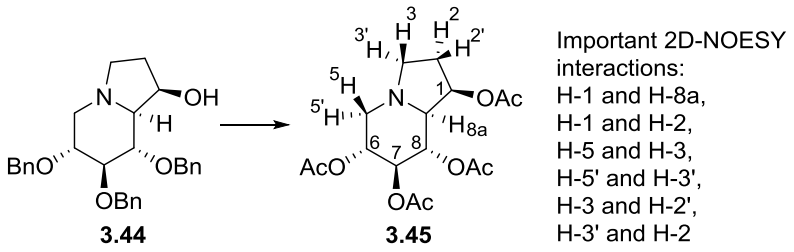
= −38.5; R_f = 0.4 (DCM: methanol 20:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.31 (arom.), 4.97 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.87 (m, 2H, OC*H*$_2$Ph), 4.80 (d, 1H, *J* = 11.3 Hz, OC*H*$_2$Ph), 4.70 (d, 1H, *J* = 11.6 Hz, OC*H*$_2$Ph), 4.65 (d, 1H, *J* = 11.6 Hz, OC*H*$_2$Ph), 4.23 (bs, 1H, H-1), 3.68 (m, 2H, H-8, H-6), 3.56 (~t, 1H, *J* = 9.0 Hz, H-7), 3.25 (dd, 1H, *J* = 10.6, 5.0 Hz, H-5), 3.09 (~td, 1H, *J* = 8.8, 2.5 Hz, H-3), 2.17 (m, 1H, H-2), 2.12 (m, 1H, H-3'), 2.00 (~t, 1H, *J* = 10.4 Hz, H-5'), 1.94 ppm (dd, 1H, *J* = 9.5, 3.6 Hz, H-8a), 1.74 (m, 1H, H-2'). ^{13}C NMR (600 MHz, $CDCl_3$) δ: 138.9, 138.8, 138.4 (3 × quat. benzyl), 128.5-127.5 (arom.), 87.3 (C-7), 79.2, 76.7 (C-6, C-8), 75.6, 74.3, 72.9 (3 × O*C*H$_2$Ph), 71.8 (C-8a), 70.8 (C-1), 54.4 (C-5), 51.6 (C-3), 33.6 ppm (C-2).

(1*R*,6*R*,7*S*,8*S*,8a*S*)-Octahydroindolizine-1,6,7,8-tetrayl tetraacetate (3.45):



To a solution of **3.44** (50 mg, 0.11 mmol) in methanol (1.1 mL), palladium hydroxide on charcoal (20% (dry basis), <50% H_2O, 200 mg) was added under an argon atmosphere. Then, argon was replaced by hydrogen (from a balloon) and the reaction was carried out for 72 h. Then, the suspension was filtered through a pad of Celite and washed repeatedly with methanol. The solvent was evaporated and the residue was dissolved in pyridine (0.8 mL) and Ac_2O (0.2 mL). DMAP was added (1 mg) and the mixture was stirred for 24 h. The solvent was evaporated and the residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate in 30 min) to yield **3.45** as white solid (31 mg, 79%). NMR spectra matched those reported for its enantiomer; [α] value was also in accordance, but with opposite sign.[177,178]

HRMS: found: *m*/*z* = 358.1493; calcd. for $C_{16}H_{24}NO_8$ ($M + H^+$): 358.1502; elem. anal.: found: C – 53.88, H – 6.38, N – 3.75%; calcd. C – 53.78, H – 6.49, N – 3.92%; $[\alpha]_D^{23}$ = −44.9; m. p. = 105 ÷ 110 °C (decomp.); R_f = 0.3 (hexanes: ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.36 (m, 1H, H-1), 5.21 (m, 1H, H-8), 5.08 (m, 2H, H-6, H-7), 3.40 (m, 1H, H-5), 3.22 (~td, 1H, *J* = 9.0, 2.2 Hz, H-3), 2.36 (m, 1H, H-2), 2.33 (dd, 1H, *J* = 9.8, 4.6 Hz, H-8a), 2.24 (m, 1H, H-3'), 2.08 (m, 1H, H-5'), 2.05, 2.03,

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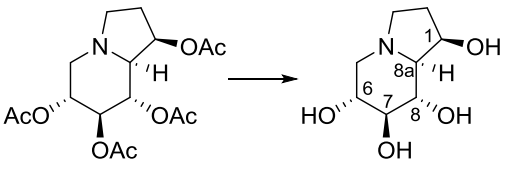
2.02, 1.97 (4 × s, 12H, 4 × C<u>*H*</u>$_3$C(O)O-), 1.86 ppm (~dtd, 1H, *J* = 14.4, 8.8, 1.9 Hz, H-2'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.5, 170.4, 169.9, 169.6 (4 × CH_3<u>*C*</u>(O)O-), 75.1 (C-7), 71.0 (C-1), 70.2 (C-6), 68.5 (C-8a), 68.2 (C-8), 52.9 (C-5), 51.9 (C-3), 31.6 (C-2), 21.0, 20.8, 20.7, 20.6 ppm (4 × <u>*C*</u>H_3C(O)O-).

(1*R*,6*R*,7*S*,8*S*,8a*S*)-Octahydroindolizine-1,6,7,8-tetraol ((−)-castanospermine, 3.35):



3.45 **3.35**

To a solution of **3.45** (20 mg, 0.06 mmol) in dry methanol (1 mL), MeONa (freshly prepared ~1M in MeOH, 50 μL) was added and the resulting mixture was stirred for 12 h at room temperature. Then, Amberlyst-15 (freshly activated with 5% aq. HCl, 0.5 g) was added. The resin was filtered off and washed thoroughly with 25% aq. NH_3. The solvent was evaporated to yield **3.35** ((−)-castanospermine) (10 mg, quant.). This product was characterized without further purification. NMR spectra matched those reported for **3.35**[179] as well as those of its enantiomer;[175] [α] value was also in accordance.

HRMS: found: *m*/*z* = 190.1077; calcd. for $C_8H_{16}NO_4$ ([M + H^+]): 190.1079; $[\alpha]_D^{23}$ = −73.7; ^{1}H NMR (600 MHz, D_2O) δ: 4.40 (m, 1H, H-1), 3.60 (m, 2H, H-6, H-8), 3.31 (~t, 1H, *J* = 9.1 Hz, H-7), 3.16 (dd, 1H, *J* = 10.8, 5.0 Hz, H-5), 3.07 (~td, 1H, *J* = 9.0, 1.7 Hz, H-3), 2.32 (m, 1H, H-2), 2.20 (dd, 1H, *J* = 18.3, 9.2 Hz, H-3'), 2.04 (~t, 1H, *J* = 10.7 Hz, H-5'), 2.01 (dd, 1H, *J* = 9.9, 4.3 Hz, H-8a), 1.70 ppm (m, 1H, H-2'). ^{13}C NMR (150 MHz, D_2O) δ: 81.8 (C-7), 74.2 (C-8a), 72.9 (C-6), 72.4 (C-1), 71.7 (C-8), 58.2 (C-5), 54.3 (C-3), 35.5 ppm (C-2).

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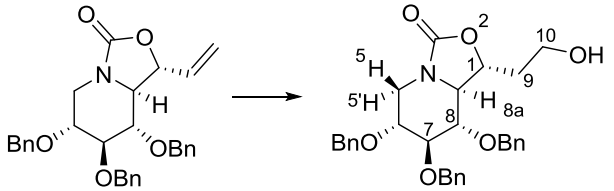
(1*R*,6*R*,7*S*,8*S*,8a*R*)-6,7,8-Tribenzyloxy-1-(2-hydroxyethyl)hexahydro[1,3]oxazolo[3,4-*a*]pyridin-3-one (3.46):



3.40 **3.46**

To a stirred solution of **3.40** (420 mg, 0.87 mmol) in dry THF (5.7 mL), Wilkinson catalyst (40 mg, 5 mol%) was added in one portion. The resulting mixture was cooled to 0 °C and catecholborane (1M in THF, 3.0 mL, 3.4 equiv) was added with a syringe pump (15 min). The cooling bath was removed and the reaction was performed for 24 h at room temperature. Then, the mixture was cooled to 0 °C and NaOH (10% aq., 3 mL) was added dropwise (10 min), followed by H_2O_2 (30% aq., 3 mL). The cooling bath was removed and the mixture was stirred for another 24 h at room temperature. After this time, water (30 mL) was added and the mixture was washed with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (10 mL) and brine. Then, the mixture was dried and solvent was evaporated. The residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) to yield **3.46** (315 mg, 72%) as white solid.

HRMS: found: *m/z* = 526.2211; calcd. for $C_{30}H_{33}NO_6$ ($[M + Na]^+$): 526.2206; elem. anal.: found: C – 71.58, H – 6.64, N – 2.68%; calcd. C – 71.55, H – 6.61, N – 2.78%; mp = 136 ÷ 138 °C; $[\alpha]_D^{23} = -32.9$; R_f = 0.3 (hexanes: ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (m, arom.), 5.01 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.92 (d, 1H, *J* = 11.3 Hz, OC*H*$_2$Ph), 4.82 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.68 (m, 3H), 4.13 (m, 2H, H-1, H-5), 3.66 (m, 2H, H-10,H-10'), 3.56 (m, 2H, H-7, H-8), 3.36 (m, 1H, H-8), 3.30 (dd, 1H, *J* = 9.5, 4.5 Hz, H-8a), 2.75 (dd, 1H, *J* = 13.1, 9.8 Hz, H-5'), 1.87 ppm (m, 2H, H-9, H-9'). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.8 (C-3), 138.1, 137.6, 137.4 (3 × quat. benzyl), 128.7-127.8 (arom.), 85.7 (C-7), 80.2 (C-8), 77.5 (C-6), 76.3 (C-1), 75.9, 75.3, 73.2 (3 × O*C*H$_2$Ph), 61.4 (C-8a), 58.6 (C-10), 42.7 (C-5), 37.7 ppm (C-9).

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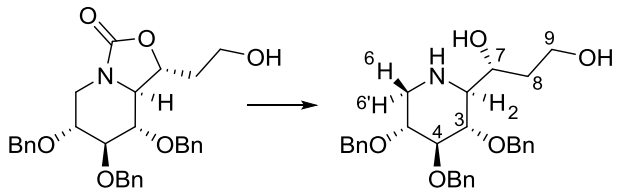
(2*S*,3*S*,4*S*,5*R*)-2-[(1*R*)-1,3-Dihydroxypropyl]-3,4,5-tribenzyloxypiperidine (3.47):

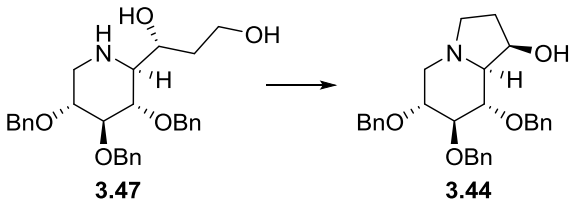


3.46 **3.47**

To a stirred solution of **3.46** (100 mg, 0.20 mmol) in methanol (2.0 mL), KOH (0.5 g, 45 equiv) was added in few portions. The flask was sealed with a rubber septum and the mixture was stirred at 75 °C for 12 h. After cooling down to room temperature, water (10 mL) and DCM (50 mL) were added. Layers were separated and the aqueous one was washed with DCM (2 × 20 mL). The combined organic layers were washed with water (10 mL) and brine. Then, the mixture was dried and solvent was evaporated. The residue was chromatographed (prep. TLC, 1 mm, DCM: MeOH 10:1) to yield **3.47** (65 mg, 68%) as white solid.

HRMS: found: *m*/*z* = 478.2601; calcd. for $C_{29}H_{36}NO_5$ ($[M + H]^+$): 478.2593; elem. anal.: found: C – 72.83, H – 7.51, N – 3.02%; calcd. C – 72.93, H – 7.39, N – 2.93%; mp = 100 ÷ 102 °C; $[\alpha]_D^{23} = -28.8$; R_f = 0.4 (DCM: MeOH 10:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (m., arom.), 4.99 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.94 (d, 1H, *J* = 11.2 Hz, OC*H*$_2$Ph), 4.85 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.68 (m, 3H, OC*H*$_2$Ph), 4.10 (m, 1H, H-7), 3.77 (m, 1H, H-9), 3.65 (ddd, 1H, *J* = 11.2, 5.2, 3.5 Hz, H-9'), 3.59 (~t, 1H, *J* = 9.0 Hz, H-4), 3.45 (m, 2H, H-3, H-5), 3.23 (dd, 1H, *J* = 13.1, 5.1 Hz, H-6), 2.47 (m, 2H, H-2, H-6'), 1.84 (m, 1H, H-8), 1.71 ppm (m, 1H, H-8'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 138.7, 138.3, 138.2 (3 × quat. benzyl), 128.5-127.6 (arom.), 86.9 (C-4), 80.3 (C-5), 78.8 (C-3), 75.6, 75.1, 72.9 (3 × O*C*H$_2$Ph), 68.0 (C-7), 62.5 (C-2), 59.0 (C-9), 47.1 (C-6), 37.2 ppm (C-8).

DPPA-mediated cyclization of 3.47 to 3.44



3.47 **3.44**

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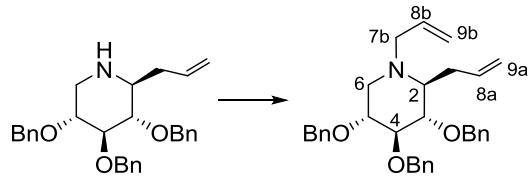
To a stirred solution of **3.47** (42 mg, 0.09 mmol) in dry DCM (1 mL), at room temperature and under argon atmosphere, dry Et_3N (50 µL, 4 equiv) was added, followed by DPPA (diphenylphosphoryl azide, 50 µL, 2.6 equiv). The mixture was stirred for 12 h at room temperature. Then, water (10 mL) and DCM (50 mL) were added. Layers were separated, and the aqueous one was washed with DCM (2 × 20 mL). The combined organic layers were washed with brine. Then, the mixture was dried and solvent was evaporated. The residue was chromatographed (prep. TLC, 0.5 mm, DCM: MeOH 20:1) to yield **3.44** (32 mg, 80%) as a colorless oil. All spectral data matched those reported for compound **3.44**.

(2*S*,3*S*,4*S*,5*R*)-1,2-Diallyl-3,4,5-tribenzyloxypiperidine (3.48):



3.8 **3.48**

Compound **3.8** (104 mg, 0.235 mmol) was dissolved in acetonitrile (2.3 mL). Next, finely pulverized potassium carbonate was added (190 mg, 5.9 equiv), followed by allyl bromide (0.1 mL, 4.9 equiv), and the reaction mixture was vigorously stirred at 50 °C for 6 h. Then, the suspension was filtered through a pad of Celite and repeatedly washed with ethyl acetate. Solvent was evaporated and the residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate in 1 h) to yield **3.48** as thick, pale yellow oil (101 mg, 89%).

HRMS: found: *m/z* = 484.2850; calc. for $C_{32}H_{38}NO_3$ ($M + H^+$): 484.2852; elem. anal.: found: C – 79.42, H – 7.63, N – 2.92%; calcd. C – 79.47, H – 7.71, N – 2.90%; $[\alpha]_D^{23}$ = 7.1; R_f = 0.7 (hexanes:ethyl acetate 3:1). ^{1}H NMR (C_6D_6) δ: 7.17 (m, arom.), 5.97 (m, 1H, H-8b), 5.75 (m, 1H, H-8a), 5.06 (m, 6H, 2 × OC$\underline{H_2}$Ph, 2 × H-9a, 2 × H-9b), 4.85 (d, 1H, *J* = 11.3 Hz, OC$\underline{H_2}$Ph), 4.65 (d, 1H, *J* = 11.4 Hz, OC$\underline{H_2}$Ph), 4.52 (m, 2H, 2 × OC$\underline{H_2}$Ph), 3.64 (m, 1H, H-5), 3.59 (~ t, 1H, *J* = 8.8 Hz, H-4), 3.49 (~ t, 1H, *J* = 9.0 Hz, H-3), 3.26 (m, 1H, H-7a), 3.14 (dd, 1H, *J* = 11.3, 4.6 Hz, H-6), 2.80 (dd, 1H, *J* = 14.3, 7.7 Hz, H-7a'), 2.66 (m, 1H, H-7b), 2.44 (m, 1H, H-7b'), 2.37 (m, 1H, H-2), 2.10 ppm (dd, 1H, *J* = 11.2, 10.4, H-6'). ^{13}C NMR (C_6D_6) δ: 139.9, 139.8, 139.4 (3 × quat. benzyl), 134.93 (C-8b), 134.90 (C-8a), 128.6-127.5 (arom.), 117.7, 117.3 (C-9a, C-9b),

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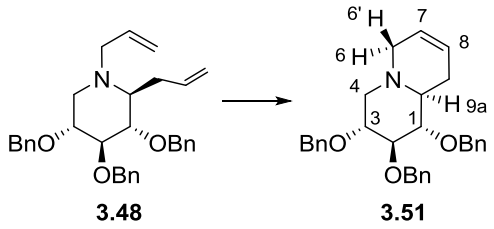
87.9 (C-4), 80.4 (C-3), 79.0 (C-5), 75.4, 75.1, 72.5 (3 × O<u>*C*</u>H$_2$Ph), 63.7 (C-2), 55.4 (C-7a), 54.8 (C-6), 32.1 ppm (C-7b).

(7*R*,8*S*,9*S*,9a*S*)-7,8,9-Tribenzyloxy-1,6,7,8,9,9a-hexahydro-4*H*-quinolizine (3.48):



3.48 **3.51**

Important 1D-NOE interactions:
H-9 and H-7 (1.8%),
H-8 and H-9a (1.4%),
H-8 and H-6' (3.2%),
H-7 and H-6 (1.5%),
H-6' and H-9a (2.6%).

Compound **3.48** (115 mg, 0.238 mmol) was dissolved in dry toluene (1.8 mL), under argon atmosphere, in a flask equipped with a double-surface reflux condenser. Trifluoroacetic acid (*ca*. 1.2 M in DCM, 0.4 mL, 2 equiv) was added and the mixture was stirred for 5 min Then, a solution of Grubbs-II catalyst (10 mg, 5 mol%) in dry toluene (0.2 mL) was added in one portion and the mixture was heated at 70 °C for 4 h; constant argon flushing was maintained throughout the reaction. Then, sat. aq. $NaHCO_3$ was added (3 mL) and the mixture was vigorously stirred for 15 min Subsequently, ethyl acetate (50 mL) was added and layers were separated. The organic one was dried, concentrated, and the residue was chromatographed (preparative TLC, 1 mm, hexanes:ethyl acetate 2:1), yielding **3.51** as a brown solid (87 mg, 81%) and recovered starting material (12 mg).

HRMS: found: *m/z* = 456.2537; calc. for $C_{30}H_{34}NO_3$ ($M + H^+$): 456.2539; elem. anal.: found: C – 79.01, H – 7.42, N – 3.04%; calcd. C – 79.09, H – 7.30, N – 3.07%; $[\alpha]_D^{23}$ = −46.1; mp: 91-93 °C; R_f = 0.3 (hexanes:ethyl acetate 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.31 (m, arom.), 5.73 (m, 1H, H-2), 5.63 (m, 1H, H-3), 4.97 (m, 2H, 2 × OC<u>*H*$_2$</u>Ph), 4.84 (d, 1H, *J* = 10.9 Hz, OC<u>*H*$_2$</u>Ph), 4.71 (m, 2H, 2 × OC<u>*H*$_2$</u>Ph), 4.63 (d, 1H, *J* = 10.9 Hz, OC<u>*H*$_2$</u>Ph), 3.71 (~ td, 1H, *J* = 10.2, 4.6 Hz, H-7), 3.55 (~ t, 1H, *J* = 9.2 Hz, H-8), 3.27 (m, 2H, H-9, H-4), 3.15 (dd, 1H, *J* = 11.3, 4.6 Hz, H-6), 2.77 (m, 1H, H-4'), 2.53 (m, 1H, H-1), 2.24 (m, 1H, H-9a), 2.10 (~ t, 1H, *J* = 11.0 Hz, H-6'), 1.96 ppm (m, 1H, H-1'). ^{13}C NMR ($CDCl_3$) δ: 138.9, 138.42, 138.35 (3 × quat. benzyl), 128.4-127.5 (arom.), 124.0 (C-2), 123.7 (C-3), 86.4 (C-8), 84.4 (C-9), 78.0 (C-7), 75.7, 75.5, 72.9 (3 × O<u>*C*</u>H$_2$Ph), 60.5 (C-9a), 57.8 (C-6), 53.7 (C-4), 30.4 ppm (C-1).

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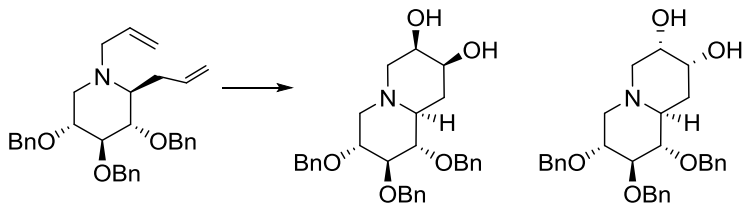
Synthesis of quinolizidines 3.49 and 3.50 *via* one-pot RCM/*syn*-dihydroxylation:



3.48 **3.49** **3.50**

All 1D-NOE interactions
are depicted on Fig. 3.1.

Compound **3.48** (93 mg, 0.192 mmol) was dissolved in dry toluene (1.6 mL), under argon atmosphere, in a flask equipped with a double-surface reflux condenser. Trifluoroacetic acid (*ca*. 1.2 M in DCM, 0.4 mL, 2 equiv) was added and the mixture was stirred for 5 min. Then, a solution of Grubbs-II catalyst (10 mg, 5 mol%) in dry toluene (0.2 mL) was added in one portion and the mixture was heated at 70 °C for 4 h; constant argon flushing was maintained throughout the reaction. Then, solvent was evaporated, the residue was dissolved in ethyl acetate (1.0 mL), and cooled to 0 °C. Parallelly, in a separate vial, $NaIO_4$ (61 mg, 1.5 equiv) and $CeCl_3 \cdot 7H_2O$ (11 mg, 15 mol%) were dissolved in water (0.2 mL) and the mixture was gently heated at 50 °C for a few minutes until it became yellow; then, acetonitrile was added (1.0 mL), the yellow suspension was cooled to 0 °C and added in one portion to the solution of the RCM product. The mixture was vigorously stirred for 1 h at 0 °C. Then, pulverized K_2CO_3 (200 mg), Na_2SO_3 (200 mg), and $MgSO_4$ (100 mg) were added, and stirring was continued for another 15 min at rt. The mixture was filtered through a pad of Celite, repeatedly washed with ethyl acetate and concentrated. The residue was chromatographed (preparative TLC, 1 mm, DCM:methanol 25:1, three times developed) to yield **3.49** as a yellow, thick oil (12 mg, 13%) and **3.50** as white solid (53 mg, 56%).

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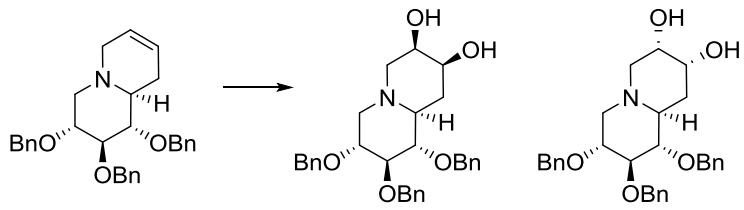
Synthesis of quinolizidines 3.49 and 3.50 *via* OsO_4-mediated *syn*-dihydroxylation:



All 1D-NOE interactions
are depicted on Fig. 3.1.

This reaction was carried out according to the **general procedure F** (at 0 °C, 10 h) to give a crude mixture of **3.49** and **3.50**. Preparative TLC (1 mm, DCM:methanol 25:1, three times developed) yielded **3.49** (65 mg, 53%) and **3.50** (18 mg, 15%).

(1*S*,2*S*,3*R*,7*R*,8*S*,9a*S*)-1,2,3-Tribenzyloxy-octahydro-2*H*-quinolizine-7,8-diol (3.49):

HRMS: found: *m/z* = 490.2594; calc. for $C_{30}H_{36}NO_5$ ($M + H^+$): 490.2593; elem. anal.: found: C – 73.66, H – 7.19, N – 2.88%; calcd. C – 73.60, H – 7.21, N – 2.86%; $[\alpha]_D^{23}$ = −37.4; R_f = 0.51 (DCM:methanol 20:1). ^{1}H NMR ($CDCl_3$) δ: 7.30 (m, arom.), 4.96 (d, 1H, *J* = 11.0 Hz, 1 × OC*H*$_2$Ph), 4.92 (d, 1H, *J* = 10.6 Hz, 1 × OC*H*$_2$Ph), 4.83 (d, 1H, *J* = 11.0 Hz, 1 × OC*H*$_2$Ph), 4.68 (m, 2H, 2 × OC*H*$_2$Ph), 4.61 (d, 1H, *J* = 10.6 Hz, 1 × OC*H*$_2$Ph), 3.82 (bs, 1H, H-7), 3.65 (m, 1H, H-3), 3.53 (ddd, 1H, *J* = 11.6, 5.1, 3.1 Hz, H-8), 3.48 (~ t, 1H, *J* = 9.1 Hz, H-2), 3.20 (~ t, 1H, *J* = 9.2 Hz, H-1), 2.98 (m, 2H, H-4, H-6), 2.31 (m, 1H, H-9), 2.25 (dd, 1H, *J* = 12.2, 0.8 Hz, H-6'), 2.06 (~ t, 1H, *J* = H-4'), 1.94 (m, 1H, H-9a), 1.36 ppm (~ dd, 1H, *J* = 23.9, 11.7 Hz, H-9'). ^{13}C NMR ($CDCl_3$) δ: 138.7, 138.3, 138.1 (3 × quat. benzyl), 128.4-127.6 (arom.), 86.3 (C-2), 82.8 (C-1), 78.1 (C-3), 75.8, 75.5, 72.9 (3 × O*C*H$_2$Ph), 69.1 (C-8), 68.0 (C-7), 62.8 (C-9a), 59.1 (C-6), 57.3 (C-4), 32.4 (C-9).

(1*S*,2*S*,3*R*,7*S*,8*R*,9a*S*)-1,2,3-Tribenzyloxy-octahydro-2*H*-quinolizine-7,8-diol (3.50):

HRMS: found: *m/z* = 490.2599; calc. for $C_{30}H_{36}NO_5$ ($M + H^+$): 490.2593; elem. anal.: found: C – 72.41, H – 7.47, N – 2.88%; calcd. C – 72.27, H – 7.28, N – 2.81% (for $C_{30}H_{35}NO_5 \cdot 0.5H_2O$); $[\alpha]_D^{23}$ = −25.0; mp= 109-111 °C; R_f = 0.49 (DCM:methanol 20:1). ^{1}H NMR ($CDCl_3$) δ: 7.30 (m, arom.), 4.96 (d, 1H, *J* = 10.9 Hz, 1 × OC*H*$_2$Ph),

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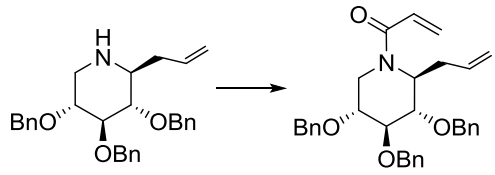
4.92 (d, 1H, J = 10.9 Hz, 1 × OC$\underline{H}_2$Ph), 4.81 (d, 1H, J = 10.9 Hz, 1 × OC$\underline{H}_2$Ph), 4.68 (m, 2H, 2 × OC$\underline{H}_2$Ph), 4.57 (d, 1H, J = 10.9 Hz, 1 × OC$\underline{H}_2$Ph), 3.94 (m, 1H, H-8), 3.71 (m, 1H, H-7), 3.63 (~ td, 1H, J = 10.1, 4.9 Hz, H-3), 3.50 (~ t, 1H, J = 9.1 Hz, H-2), 3.11 (~ t, 1H, J = 9.2 Hz, H-1), 2.97 (dd, 1H, J = 11.3, 4.8 Hz, H-4), 2.69 (dd, 1H, J = 10.6, 5.0 Hz, H-6), 2.30 (m, 2H, H-6', H-9), 2.23 (m, 1H, H-9a), 2.14 (~ t, 1H, J = 10.9 Hz, H-4'), 1.29 ppm (m, 1H, H-9'). ^{13}C NMR ($CDCl_3$) δ: 138.7, 138.34, 138.26 (3 × quat. benzyl), 128.4-127.5 (arom.), 86.7 (C-2), 82.9 (C-1), 78.3 (C-3), 75.5, 75.4, 72.8 (3 × O$\underline{C}$H$_2$Ph), 68.4 (C-7), 66.6 (C-8), 57.74 (C-9a), 57.66 (C-4), 55.0 (C-6), 34.4 ppm (C-9).

(2*S*,3*S*,4*S*,5*R*)-1-Acryloyl-2-allyl-3,4,5-tribenzyloxypiperidine (3.52):



3.8 **3.52**

To a solution of compound **3.8** (126 mg, 0.284 mmol) in dry DCM (2.8 mL), under argon atmosphere, dry triethylamine was added (80 μL, 2.0 equiv). Then, under vigorous stirring, acryloyl chloride (freshly prepared 0.5 M solution in DCM, 0.73 mL, 1.3 equiv) was added at ambient temperature using a syringe pump (15 min). After another 15 min, toluene (2 mL) was added and most volatiles were evaporated under reduced pressure, leaving suspension of white solid in toluene. The solid was filtered off and repeteadly washed with toluene. The combined organic solutions were concentrated and chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate in 1 h) to yield **3.52** as thick pale yellow oil (128 mg, 91%).

HRMS: found: m/z = 498.2645; calc. for $C_{32}H_{36}NO_4$ (M + H$^+$): 498.2644; elem. anal.: found: C – 77.15, H – 6.91, N – 2.75%; calcd. C – 77.24, H – 7.09, N – 2.81%; $[\alpha]_D^{23}$ = −5.4; R_f = 0.6 (hexanes: ethyl acetate 2:1). The NMR spectra of this compound consisted of broaden signals, making the interpretation impossible.

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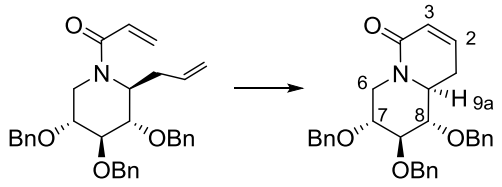
(7*R*,8*S*,9*S*,9a*S*)-7,8,9-Tribenzyloxy-1,6,7,8,9,9a-hexahydro-4*H*-quinolizin-4-one (3.55):

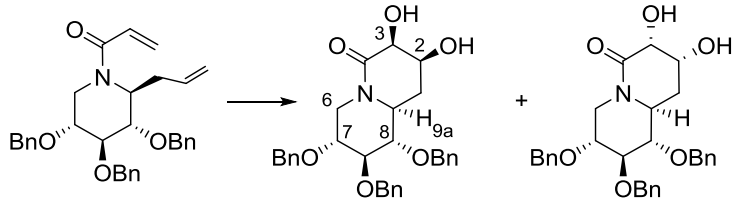


3.52 **3.55**

Compound **3.52** (85 mg, 0.171 mmol) was dissolved in dry toluene (1.5 mL), under argon atmosphere, in a flask equipped with a double-surface reflux condenser. To this solution Grubbs II gen. catalyst (7 mg, 5 mol%) freshly dissolved in dry toluene (0.2 mL) was added in one portion. Reaction was conducted at 50 °C for 3 h under constant argon flushing. The solvent was evaporated and the residue was chromatographed (preparative TLC, 1 mm, hexanes:ethyl acetate 2:1), yielding **3.55** as brown solid (76 mg, 95%).

HRMS: found: *m*/*z* = 470.2325; calc. for $C_{30}H_{32}NO_4$ ($M + H^+$): 470.2331; elem. anal.: found: C – 76.69, H – 6.52, N – 2.85%; calcd. C – 76.73, H – 6.65, N – 2.98%; $[\alpha]_D^{23}$ = −18.1; mp: 113-115 °C; R_f = 0.6 (hexanes:ethyl acetate 1:1). ^{1}H NMR ($CDCl_3$) δ: 7.31 (m, arom.), 6.26 (ddd, 1H, *J* = 9.6, 4.3, 3.5 Hz, H-2), 5.83 (ddd, 1H, *J* = 9.9, 2.1, 1.5 Hz, H-3), 4.98 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.91 (d, 1H, *J* = 11.2 Hz, OC*H*$_2$Ph), 4.77 (m, 3H, 2 × OC*H*$_2$Ph, H-6), 4.67 (d, 1H, *J* = 11.3 Hz, OC*H*$_2$Ph), 4.57 (d, 1H, *J* = 11.2 Hz, OC*H*$_2$Ph), 3.62 (m, 1H, H-8), 3.57 (m, 1H, H-7), 3.38 (m, 2H, H-9, H-9a), 2.61 (m, 1H, H-1), 2.54 (dd, 1H, *J* = 12.9, 10.3 Hz, H-6'), 2.43 ppm (m, 1H, H-1'). ^{13}C NMR ($CDCl_3$) δ: 164.3 (C-4), 138.5 (1 × quat. benzyl), 138.1 (C-2), 137.9, 137.7 (2 × quat. benzyl), 128.5-127.6 (arom.), 123.8 (C-3), 86.7 (C-8), 79.4 (C-9), 77.5 (C-7), 75.4, 75.2, 72.7 (3 × O*C*H$_2$Ph), 56.9 (C-9a), 44.7 (C-6), 24.6 ppm (C-1).

Synthesis of quinolizidinones 3.53 and 3.54 *via* one-pot RCM/*syn*-dihydroxylation:



3.52 **3.53** **3.54**

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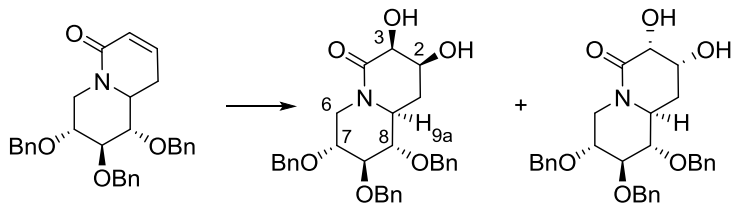
Compound **3.52** (100 mg, 0.201 mmol) was dissolved in dry toluene (1.8 mL) in a flask equipped with a double-surface reflux condenser. To this solution, Grubbs II catalyst (8.5 mg, 5 mol%) freshly dissolved in dry toluene (0.2 mL) was added in one portion. Reaction was conducted at 50 °C for 3 h under constant argon flushing. Then, solvent was evaporated, the residue was dissolved in ethyl acetate (1.0 mL) and cooled to 0 °C. Parallelly, in a separate vial, $NaIO_4$ (65 mg, 1.5 equiv) and $CeCl_3 \cdot 7H_2O$ (11 mg, 15 mol%) were placed in water (0.2 mL) and the mixture was gently heated at 50 °C for a few minutes until it became yellow; then, acetonitrile was added (1.0 mL), the yellow suspension was cooled to 0 °C and added in one portion to the solution of RCM product. The mixture was vigorously stirred for 1 h at 0 °C. Then, pulverized K_2CO_3 (200 mg), Na_2SO_3 (200 mg) and $MgSO_4$ (100 mg) were added, and the stirring continued for 15 min at rt. The mixture was filtered through a pad of Celite and repeatedly washed with ethyl acetate. Solvent was evaporated and the residue was chromatographed (preparative TLC, DCM:methanol 25:1, three times developed) to yield **3.53** as a yellow thick oil (31 mg, 31%) and **3.54** as a white solid (43 mg, 43%).

Synthesis of quinolizidinones 3.53 and 3.54 *via* OsO_4-mediated *syn*-dihydroxylation:



3.55 **3.53** **3.54**

All 1D-NOE interactions are depicted on Fig. 3.1.

This reaction was carried out according to the **general procedure F** (at rt, 24 h). Preparative TLC (1 mm, DCM:methanol 25:1, three times developed) yielded **3.53** (49 mg, 39%) and **3.54** (67 mg, 53%).

(1*S*,2*S*,3*R*,7*S*,8*S*,9a*S*)-1,2,3-Tribenzyloxy-7,8-dihydroxy-octahydro-2*H*-quinolizin-6-one (3.53):

HRMS: found: *m*/*z* = 504.2382; calc. for $C_{30}H_{34}NO_6$ ($M + H^+$): 504.2386; elem. anal.: found: C – 71.58, H – 6.39, N – 2.62%; calcd. C – 71.55, H – 6.61, N – 2.78%; $[\alpha]_D^{23}$ = −49.5; R_f = 0.49 (DCM: methanol 20:1). ^{1}H NMR ($CDCl_3$) δ: 7.30 (m, arom.), 4.96

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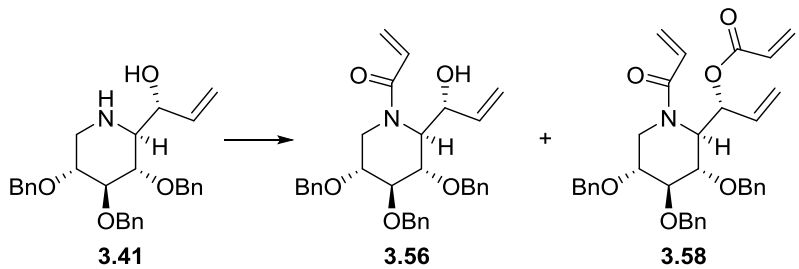
(m, 2H, 2 × OC$\underline{H}_2$Ph), 4.81 (m, 3H, 2 × OC$\underline{H}_2$Ph, H-4), 4.73 (m, 2H, 2 × OC$\underline{H}_2$Ph), 4.31 (~ dd, 1H, *J* = 5.4, 3.6 Hz, H-8), 4.03 (d, 1H, *J* = 3.1 Hz, H-7), 3.97 (dd, 1H, *J* = 10.1, 8.9 Hz, H-1), 3.56 (m, 1H, H-3), 3.51 (~ t, 1H, *J* = 8.8 Hz, H-2), 3.33 (~ dd, 1H, *J* = 10.1, 7.6 Hz, H-9a), 2.61 (~ dd, 1H, *J* = 15.5, 4.0 Hz, H-9), 2.47 (dd, 1H, *J* = 12.3, 11.1 Hz, H-4'), 1.98 ppm (ddd, 1H, *J* = 15.4, 7.5, 1.9 Hz, H-9'). ^{13}C NMR ($CDCl_3$) δ: 169.9 (C-6), 138.6, 138.3, 138.0 (3 × quat. benzyl), 128.5-127.6 (arom.), 87.1 (C-2), 81.4 (C-1), 77.6 (C-3), 75.6, 75.3, 73.0 (3 × O$\underline{C}$H$_2$Ph), 70.0 (C-7), 66.6 (C-8), 57.8 (C-9a), 44.8 (C-4), 24.4 ppm (C-9).

(1*S*,2*S*,3*R*,7*R*,8*R*,9a*S*)-1,2,3-Tribenzyloxy-7,8-dihydroxy-octahydro-2*H*-quinolizin-6-one (3.54):

HRMS: found: *m/z* = 504.2386; calc. for $C_{30}H_{34}NO_6$ (M + H$^+$): 504.2386; elem. anal.: found: C – 70.70, H – 6.75, N – 2.64%; calcd. C – 70.71, H – 6.66, N – 2.75% (for $C_{30}H_{33}NO_6 \cdot 0.33H_2O$); $[\alpha]_D^{23} = -25.4$; mp: 119-121°C; R_f = 0.40 (DCM:methanol 20:1). ^{1}H NMR ($CDCl_3$) δ: 7.31 (m, arom.), 4.97 (m, 2H, 2 × OC$\underline{H}_2$Ph), 4.78 (m, 3H, 2 × OC$\underline{H}_2$Ph, H-4), 4.65 (m, 2H, 2 × OC$\underline{H}_2$Ph), 4.25 (m, 1H, H-8), 3.95 (d, 1H, *J* = 2.3 Hz, H-7), 3.61 (~ t, 1H, *J* = 9.0 Hz, H-2), 3.50 (m, 2H, H-3, H-9a), 3.20 (~ t, 1H, *J* = 9.4 Hz, H-1), 2.64 (~ dt, 1H, *J* = 14.6, 4.9 Hz, H-9), 2.54 (m, 1H, H-4'), 1.48 ppm (~ dd, 1H, *J* = 13.4, 11.3 Hz, H-9'). ^{13}C NMR ($CDCl_3$) δ: 171.4 (C-6), 138.4, 137.82, 137.77 (3 × quat. benzyl), 128.5-127.7 (arom.), 86.0 (C-2), 83.1 (C-1), 77.4 (C-3), 75.7, 75.5, 72.8 (3 × O$\underline{C}$H$_2$Ph), 70.2 (C-7), 65.4 (C-8), 55.8 (C-9a), 43.9 (C-4), 30.0 ppm (C-9).

1-{(2*S*,3*S*,4*S*,5*R*)-3,4,5-Tribenzyloxy-2-[(1*R*)-1-hydroxyprop-2-en-1-yl]piperidin-1-yl}prop-2-en-1-one (3.56):



To a stirred solution of **3.41** (217 mg, 0.47 mmol) in dry DCM (3.7 mL), dry triethylamine (0.1 mL) was added. The solution was cooled to 0 °C and a freshly prepared solution of acryloyl chloride (*ca*. 0.5 M, 1.0 mL, 1.05 equiv.) was added

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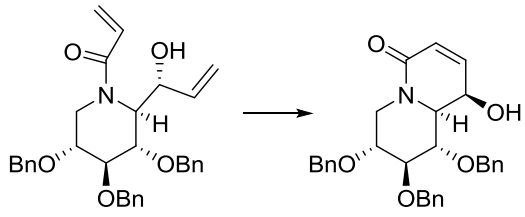
dropwise. Once the addition was completed, toluene (2 mL) was added and the solution was concentrated. The residue was purified by chromatography (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) to yield **3.56** (137 mg, 57%) as colorless oil and the diacryloyl derivative **3.58** (70 mg, 26%) as colorless oil.

3.56: HRMS: found: *m*/*z* = 536.2416; calcd. for $C_{32}H_{35}NO_5Na$ ([M + Na]$^+$): 536.2413. Anal.: found: C – 74.82, H – 6.90, N – 2.64%; calcd. C – 74.83, H – 6.87, N – 2.73% $[\alpha]_D^{23}$ = 16.1 (DCM); R_f = 0.3 (hexanes:ethyl acetate 2:3). ^{1}H NMR and ^{13}C NMR spectra indicate, that this compound exists as a mixture of rotamers, which makes the interpretation very difficult.

3.58: LRMS: *m*/*z* = 590.3 ([M + Na]$^+$). Anal.: found: C – 74.04, H – 6.57, N – 2.48%; calcd. C – 74.05, H – 6.57, N – 2.47%. $[\alpha]_D^{23}$ = 2.3 (DCM); R_f = 0.8 (hexanes: ethyl acetate 2:3). ^{1}H NMR and ^{13}C NMR spectra indicate, that this compound exists as a mixture of rotamers, which makes the interpretation very difficult.

(1*R*,7*R*,8*S*,9*S*,9a*S*)-1-hydroxy-7,8,9-tribenzyloxy-1,6,7,8,9,9a-hexahydro-4*H*-quinolizin-4-one (3…):



3.56 **3.59**

To a solution of **3.56** (49 mg, 0.096 mmol) in dry toluene (1 mL), under argon atmosphere, Grubbs-II cat. (4 mg, 5 mol%) was added and the mixture was heated to 50 °C. After 30 min, the solvent was evaporated and the residue was purified by chromatography (preparative TLC, 1 mm, DCM: MeOH 15:1) to yield **3.59** (45 mg, 97%) as pale brown solid.

LRMS: *m*/*z* = 508.4 ([M + Na]$^+$). Anal.: found: C – 74.04, H – 6.40, N – 2.70%; calcd. C – 74.21, H – 6.43, N – 2.88%. $[\alpha]_D^{23}$ = −111.7 (DCM); m. p. = 135 ÷ 138 °C; R_f = 0.5 (DCM:methanol 20:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.32 (m, arom.), 6.74 (dd, 1H, *J* = 9.7, 5.7 Hz, H-2), 6.02 (d, 1H, *J* = 9.7 Hz, H-3), 4.94, 4.89, 4.78, 4.75, 4.70, 4.60 (6 × d, 6H, *J* = 11.0-11.6 Hz, OC$\underline{H_2}$Ph), 4.36 (ddd, 1H, *J* = 9.4, 5.6, 3.8 Hz, H-1), 4.19 (dd, 1H, *J* = 13.6, 4.0 Hz, H-6), 4.03 (dd, 1H, *J* = 10.4, 8.4 Hz, H-9), 3.73 (dd,

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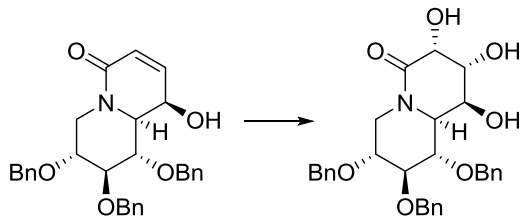
1H, *J* = 8.4, 6.6 Hz, H-8), 3.63 (ddd, 1H, *J* = 8.6, 6.6, 4.1 Hz, H-7), 3.43 (dd, 1H, *J* = 10.4, 3.7 Hz, H-9a), 3.24 (dd, 1H, *J* = 13.6, 8.6 Hz, H-6'), 2.21 ppm (d, 1H, *J* = 9.4 Hz, -O*H*). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.6 (C-4), 139.4 (C-2), 138.13, 138.10, 137.7 (3 × quat. benzyl), 128.6-127.8 (arom.), 126.5 (C-3), 85.2 (C-8), 76.6 (C-9), 75.8 (C-7), 74.9, 74.2, 71.9 (3 × O*C*H_2Ph), 60.8 (C-1), 59.6 (C-9a), 42.1 ppm (C-6).

(1*S*,2*R*,3*R*,7*R*,8*S*,9*S*,9a*R*)-1,2,3-trihydroxy-7,8,9-tribenzyloxyoctahydro-4*H*-quinolizin-4-one (3.60):



3.59 **3.60**

This reaction was carried out according to the **general procedure F** (at 0 °C, 6 h). Crude product was dissolved in hot ethyl acetate and precipitated with hexanes to give 33 mg (89%) of the pure product **3.60**.

HRMS: found: *m/z* = 542.2167; calcd. for $C_{30}H_{33}NO_7Na$ ([M + Na]$^+$): 542.2155. $[\alpha]_D^{23}$ = −0.4 (MeOH); m. p. = 177 ÷ 179 °C; R_f = 0.3 (DCM: methanol 20:1). ^{1}H NMR (600 MHz, CD_3OD:$CDCl_3$, 2:1) δ: 7.31 (m, arom.), 4.98 (d, 1H, *J* = 11.0 Hz, OC*H*$_2$Ph), 4.94 (d, 1H, *J* = 10.7 Hz, OC*H*$_2$Ph), 4.79 (m, 4H, H-6, OC*H*$_2$Ph), 4.67 (d, 1H, *J* = 11.4 Hz, OC*H*$_2$Ph), 4.48 (d, 1H, *J* = 2.9 Hz, H-3), 4.32 (m, 1H, H-1), 4.22 (dd, 1H, *J* = 4.7, 3.1 Hz, H-2), 3.91 (dd, 1H, *J* = 10.3, 9.3 Hz, H-9), 3.65 (~t, 1H, *J* = 9.1 Hz, H-8), 3.55 (dd, 1H, *J* = 10.4, 3.5 Hz, H-9a), 3.49 (ddd, 1H, *J* = 10.9, 9.2, 5.0 Hz, H-7), 2.53 ppm (m, 1H, H-6'). ^{13}C NMR (150 MHz, CD_3OD:$CDCl_3$, 2:1) δ: 172.2 (C-4), 138.1, 138.0, 137.4 (3 × quat. benzyl), 127.8-127.0 (arom.), 85.9 (C-8), 76.4 (C-7), 76.1 (C-9), 75.0, 74.4, 72.1 (3 × O*C*H_2Ph), 70.4 (C-2), 67.0 (C-3), 64.6 (C-1), 59.2 (C-9a), 43.2 ppm (C-6).

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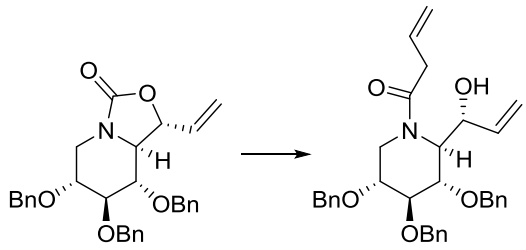
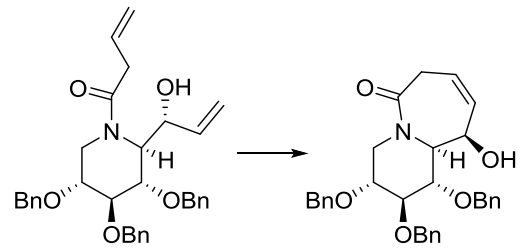
1-{(2*S*,3*S*,4*S*,5*R*)-3,4,5-Tribenzyloxy-2-[(1*R*)-1-hydroxyprop-2-en-1-yl]piperidin-1-yl}but-3-en-1-one (3.57):



3.40 **3.57**

To a stirred and cooled to −78 °C solution of **3.40** (147 mg, 0.30 mmol) in dry THF (1.5 mL), under argon atmosphere, allylmagnesium bromide (0.9 mL, 1M in diethyl ether, 3 equiv) was added via a syringe pump (10 min). After additional 30 min at −78 °C, sat. aq. NH_4Cl (10 mL) was added, followed by water (10 mL) and ethyl acetate (30 mL). Layers were separated and the aqueous one was washed with ethyl acetate (2 × 15 mL). The combined organic solutions were dried, concentrated and the residue was purified by chromatography (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) to yield **3.57** (135 mg, 84%) as colorless oil.
Anal.: found: C – 75.11, H –7.21, N – 2.49%; calcd. C – 75.12, H – 7.07, N – 2.65%.
$[\alpha]_D^{23}$ = 0.9 (DCM); R_f = 0.4 (hexanes:ethyl acetate 1:1). ^{1}H NMR and ^{13}C NMR spectra indicate, that this compound exists as a mixture of rotamers, which makes the interpretation very difficult.

(1*S*,2*S*,3*R*,10*R*,10a*S*)-1,2,3-tribenzyloxy-10-hydroxy-1,3,4,7,10,10a-hexahydropyrido[1,2-*a*]azepin-6(2*H*)-one (3.61):



3.57 **3.61**

To a stirred solution of **3.57** (61 mg, 0.12 mmol) in dry toluene (1.2 mL), Grubbs-II catalyst (5 mg, 5 mol%), under argon atmosphere, was added and the mixture was kept at 50 °C for 6 h. Then it was cooled to ambient temperature, concentrated, and the

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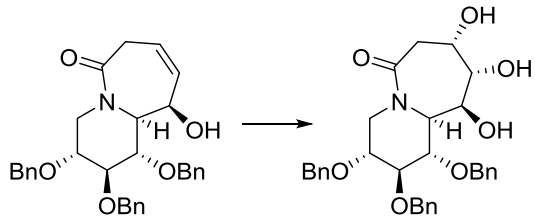
residue was purified by chromatography (preparative TLC, 1 mm, DCM: MeOH 15:1) to yield **3.61** (45 mg, 83%) as pale brown solid (amorphous).

HRMS: found: *m/z* = 522.2256; calcd. for $C_{31}H_{33}NO_5Na$ ([M + Na]$^+$): 522.2256. $[\alpha]_D^{23}$ = − 45.7 (DCM); R_f = 0.2 (hexanes: ethyl acetate 2:3). ^{1}H NMR (600 MHz; $CDCl_3$) δ: 7.31 (m, arom.), 5.80 (ddd, 1H, *J* = 11.3, 4.7, 3.1 Hz, H-9), 5.74 (m, 1H, H-8), 4.99 (d, 1H, *J* = 11.0 Hz, OC*H*$_2$Ph), 4.68 (m, 5H, H-4, OC*H*$_2$Ph), 4.42 (d, 1H, *J* = 11.4 Hz, OC*H*$_2$Ph), 4.29 (m, 1H, H-10), 4.10 (~t, 1H, *J* = 9.3 Hz, H-1), 3.84 (m, 1H, H-3), 3.80 (dd, 1H, *J* = 9.3, 3.5 Hz, H-2), 3.76 (~d, 1H, *J* = 9.0 Hz, H-10a), 3.36 (ddd, 1H, *J* = 16.3, 5.4, 2.6 Hz, H-7), 3.16 (dd, 1H, *J* = 14.5, 3.2 Hz, H-4'), 2.93 (dd, 1H, *J* = 16.6, 8.9 Hz, H-7'), 2.59 ppm (d, 1H, *J* = 9.0 Hz, -O*H*). ^{13}C NMR (600 MHz; $CDCl_3$) δ: 172.3 (C-6), 137.97, 137.96, 137.6 (3 × quat. benzyl), 131.0 (C-9), 128.5-127.7 (arom.), 123.7 (C-8), 84.9 (C-2), 79.8 (C_3), 75.2 (C-1), 75.0, 72.7, 70.5 (3 × O*C*H$_2$Ph), 66.1 (C-10), 60.0 (C-10a), 40.0 (C-4), 35.8 ppm (C-7).

(1*S*,2*S*,3*R*,10*S*,10a*S*)-1,2,3-Tribenzyloxy-8,9,10-trihydroxy-octahydropyrido[1,2-*a*]azepin-6(2*H*)-one (3.62):



3.61 **3.62**

This reaction was carried out according to the **general procedure F** (at rt, 24 h). The crude product was dissolved in hot ethyl acetate and precipitated with hexanes to give triol **3.62** (29 mg; 76%) as a pure compound (white solid).

HRMS: found: *m/z* = 556.2303; calcd. for $C_{31}H_{35}NO_7Na$ ([M + Na]$^+$): 556.2311. $[\alpha]_D^{23}$ = −18.1 (MeOH); m. p. = decomp. (>100 °C); R_f = 0.4 (DCM: MeOH 10:1). ^{1}H NMR (600 MHz, CD_3OD:$CDCl_3$, 5:1) δ: 7.30 (m, arom.), 4.97 (d, 1H, *J* = 11.1 Hz, OC*H*$_2$Ph), 4.66 (m, 5H, OC*H*$_2$Ph, H-4), 4.42 (d, 1H, *J* = 11.3 Hz, OC*H*$_2$Ph), 4.01 (m, 1H, H-8), 4.00 (m, 1H, H-10), 3.98 (m, 1H, H-10a), 3.94 (m, 1H, H-9), 3.86 (~t, 1H, *J* = 9.6 Hz, H-1), 3.83 (m, 1H, H-3), 3.71 (dd, 1H, *J* = 9.7 Hz, 3.5 Hz, H-2), 3.36 (dd, 1H, *J* = 13.2, 11.8 Hz, H-7), 3.07 (dd, 1H, *J* = 14.8, 3.3 Hz, H-4'), 2.26 ppm (m, 1H, H-7'). ^{13}C NMR (150 MHz, CD_3OD:$CDCl_3$, 5:1) δ: 171.9 (C-6), 137.5, 137.3, 137.0 (3 × quat. benzyl), 127.5-126.7 (arom.), 84.1 (C-2), 79.1 (C-3), 75.2 (C-1), 73.8

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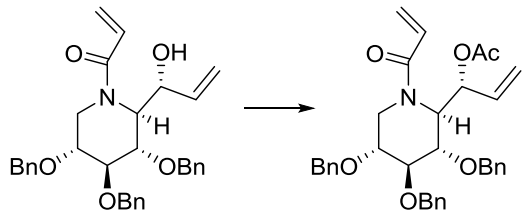
(O<u>*C*</u>H$_2$Ph), 72.7 (C-9), 71.9, 69.4 (2 × O<u>*C*</u>H$_2$Ph), 69.2 (C-10), 64.3 (C-8), 54.7 (C-10a), 39.1 (C-4), 37.5 ppm (C-7).

(1*R*)-1-[(2*R*,3*S*,4*S*,5*R*)-1-acryloyl-3,4,5-tribenzyloxypiperidin-2-yl]prop-2-en-1-yl acetate (3.63):

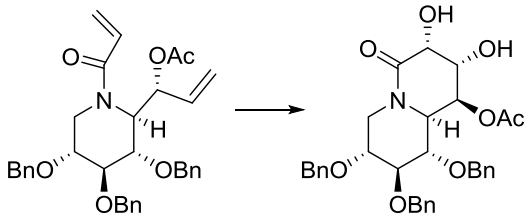


3.56 **3.63**

To a stirred solution of **3.56** (62 mg, 0.12 mmol) in dichloromethane (1 mL), pyridine (0.1 mL) was added, followed by acetic anhydride (0.1 mL) and DMAP (1 mg, 5 mol%). The resulting mixture was stirred at room temperature for 24 h, concentrated, and the residue was purified by chromatography (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) to yield **3.63** (60 mg, 90%) as colorless oil.

HRMS: found: *m*/*z* = 578.2518; calcd. for $C_{34}H_{37}NO_6Na$ ([M + Na]$^+$): 578.2519. $[\alpha]_D^{23}$ = −6.4 (DCM); R_f = 0.3 (hexanes: ethyl acetate 2:1). ^{1}H NMR and ^{13}C NMR spectra indicate, that this compound exists as a mixture of rotamers.

(1*S*,7*R*,8*S*,9*S*,9a*R*)-2,3-dihydroxy-7,8,9-tribenzyloxy-4-oxooctahydro-2*H*-quinolizin-1-yl acetate (3.64):



3.63 **3.64**

To a stirred solution of **3.63** (60 mg, 0.11 mmol) in dry toluene (1.1 mL), Grubbs II catalyst (4.5 mg, 5 mol%) was added and the mixture was kept at 50 °C for 2 h. Then, it was cooled to room temperature, solvent was evaporated, and the residue was dissolved in AcOEt (0.5 mL) and MeCN (0.5 mL). The resulting mixture was cooled to 0 °C. Simultaneously, in a separate vial, $NaIO_4$ (75 mg, 3.1 equiv.) and $CeCl_3 \cdot 7H_2O$ (8 mg, 20 mol%) were suspended in water (0.1 mL) and the mixture was gently heated

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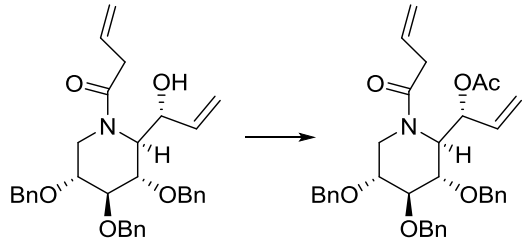
at 50 °C until it turned yellow (1 min); then, MeCN (0.2 mL) was added; the yellow suspension was cooled to 0 °C and added in one portion to the solution of the RCM product. The mixture was vigorously stirred for 20 min at 0 °C. Then, pulverized $MgSO_4$ (250 mg) and Na_2SO_3 (400 mg) were added and stirring was continued for 30 min. After this time, the mixture was filtered through a pad of Celite, which was then repeatedly washed with ethyl acetate. Solvent was evaporated and the residue was purified by chromatography (preparative TLC, 1 mm, DCM: MeOH 15:1) to yield **3.64** (46 mg, 75%) as an off-white solid.

HRMS: found: *m/z* = 584.2263; calcd. for $C_{32}H_{35}NO_8Na$ ($[M + Na]^+$): 584.2260. Anal.: found: C – 68.12, H – 6.11, N – 2.43%; calcd. C – 68.44, H – 6.28 , N – 2.49%. $[\alpha]_D^{23}$ = 1.0 (DCM); m. p. = 140 ÷ 142 °C; R_f = 0.5 (DCM:methanol 20:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (arom.), 5.61 (dd, 1H, *J* = 4.4, 3.7 Hz, H-1), 5.03 (d, 1H, *J* = 10.8 Hz, OC$\underline{H}_2$Ph), 4.95 (d, 1H, *J* = 10.2 Hz, OC$\underline{H}_2$Ph), 4.77 (m, 3H, OC$\underline{H}_2$Ph, H-6), 4.68 (d, 1H, *J* = 11.5 Hz, OC$\underline{H}_2$Ph), 4.39 (m, 1H, H-2), 4.34 (d, 1H, *J* = 10.2 Hz, OC$\underline{H}_2$Ph), 4.19 (d, 1H, *J* = 2.8 Hz, H-3), 3.77 (dd, 1H, *J* = 9.8, 3.5 Hz, H-9a), 3.73 (bs, 1H, -O$\underline{H}$) 3.66 (m, 2H, H-8, H-9), 3.52 (ddd, 1H, *J* = 10.9, 8.8, 5.1 Hz, H-7), 2.83 (bs, 1H, -O$\underline{H}$), 2.59 (dd, 1H, *J* = 12.8, 11.2 Hz, H-6'), 2.08 ppm (s, 3H, C$\underline{H}_3$C(O)O-). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.8 (C-4), 169.0 ($CH_3\underline{C}$(O)O-), 138.2, 137.7, 137.4 (3 × quat. benzyl), 128.5-127.8 (arom.), 86.3 (C-8), 76.8 (C-7), 76.0 (C-9), 75.7, 75.2, 72.7 (3 × O$\underline{C}H_2$Ph), 67.4 (C-3), 66.8 (C-1), 66.6 (C-2), 58.1 (C-9a), 44.0 (C-6), 20.9 ppm ($\underline{C}H_3$C(O)O-).

(1*R*)-1-[(2*R*,3*S*,4*S*,5*R*)-1-(but-3-enoyl)-3,4,5-tribenzyloxypiperidin-2-yl]prop-2-en-1-yl acetate (3.65):



3.57 **3.65**

To a stirred solution of **3.57** (95 mg, 0.18 mmol) in dichloromethane (1.5 mL), pyridine (0.2 mL) was added, followed by acetic anhydride (0.2 mL) and DMAP (1 mg, 5 mol%). The resulting mixture was stirred at room temperature for 24 h. Then, solvent was evaporated and the residue was purified by chromatography (flash

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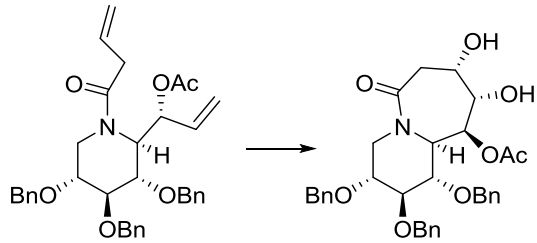
chromatography, linear gradient: 100% hexanes to 100% ethyl acetate) to yield **3.65** (94 mg, 92%) as a colorless oil.

HRMS: found: *m*/*z* = 592.2674; calcd. for $C_{35}H_{39}NO_6Na$ ([M + Na]$^+$): 592.2675. $[\alpha]_D^{23}$ = −6.3 (DCM); R_f = 0.4 (hexanes: ethyl acetate 2:1). ^{1}H NMR and ^{13}C NMR spectra indicate, that this compound exists as a mixture of rotamers, which makes the interpretation very difficult.

(1*S*,2*S*,3*R*,10*S*,10a*R*)-1,2,3-tribenzyloxy-8,9-dihydroxy-6-oxodecahydropyrido[1,2-*a*]azepin-10-yl acetate (3.66):



3.65 **3.66**

To a stirred solution of **3.65** (51 mg, 0.09 mmol) in dry toluene (2 mL), Grubbs II catalyst (7 mg, 10 mol%) was added. The reaction was conducted at 60 °C for 4 h, after which the solvent was evaporated and the residue was dissolved in AcOEt (0.5 mL) and MeCN (0.5 mL). The resulting mixture was cooled to 0 °C. Simultaneously, in a separate vial, $NaIO_4$ (60 mg, 3.1 equiv) and $CeCl_3 \cdot 7H_2O$ (7 mg, 20 mol%) were suspended in water (0.1 mL) and the mixture was heated gently at 50 °C until it turned yellow (1 min); then, MeCN (0.2 mL) was added; the yellow suspension was cooled to 0 °C and added in one portion to the solution of RCM product. The mixture was vigorously stirred for 1 h at 0 °C. Then, pulverized $MgSO_4$ (250 mg) and Na_2SO_3 (400 mg) were added and the stirring was continued for 30 min. After this time, the mixture was filtered through a pad of Celite, which was then repeatedly washed with ethyl acetate. Solvent was evaporated and the residue was purified by chromatography (prep. TLC, 1 mm, DCM: MeOH 15:1) to yield **3.66** (34 mg, 66%) as off-white solid.

CCDC 1020185; HRMS: found: *m*/*z* = 598.2415; calcd. for $C_{33}H_{37}NO_8Na$ ([M + Na]$^+$): 598.2417. Anal.: found: C – 68.86, H – 6.36, N – 2.37%; calcd. C – 68.85, H – 6.48, N – 2.43%. $[\alpha]_D^{23}$ = −11.3 (DCM); R_f = 0.3 (DCM:methanol 20:1); mp = decomp. (>100 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (m, arom.), 5.30 (d, 1H, *J* = 4.5 Hz, H-10), 4.89 (d, 1H, *J* = 10.9 Hz, OC*H*$_2$Ph), 4.71 (d, 1H, *J* = 11.7 Hz, OC*H*$_2$Ph), 4.62 (m, 4H, OC*H*$_2$Ph, H-4), 4.43 (~d, 1H, *J* = 11.7 Hz, OC*H*$_2$Ph), 4.15 (~d, 1H, *J* =

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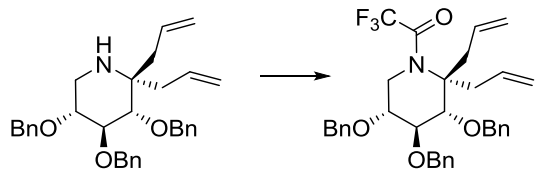
9.0 Hz, H-10a), 4.02 (~bs, 1H, H-9), 3.96 (~d, 1H, *J* = 11.5 Hz, H-8), 3.75 (m, 2H, H-2, H-3), 3.54 (~t, 1H, *J* = 8.8 Hz, H-1), 3.31 (dd, 1H, *J* = 13.3, 11.7 Hz, H-7), 2.98 (dd, 1H, *J* = 14.6, 3.1 Hz, H-4'), 2.42 (~d, 1H, *J* = 13.5 Hz, H-7'), 1.98 ppm (s, 3H, C*H*$_3$C(O)O-). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.3, 169.9 (C-6, CH_3*C*(O)O-), 137.74, 137.71, 137.4 (3 × quat. benzyl), 128.4-127.8 (arom.), 84.6 (C-2), 78.9 (C-3), 75.8 (C-1), 74.6, 72.8 (2 × O*C*H$_2$Ph), 71.0 (C-10), 70.5 (C-9), 70.3 (O*C*H$_2$Ph), 65.6 (C-8), 53.8 (C-10a), 39.4 (C-4), 38.7(C-7), 20.8 ppm (*C*H$_3$C(O)O-).

(3*S*,4*S*,5*R*)-1-Trifluoroacetyl-2,2-diallyl-3,4,5-tribenzyloxypiperidine (3.67):



3.9 **3.67**

Compound **3.9** (117 mg, 0.242 mmol) and DMAP (3 mg, 10 mol%) were dissolved, under argon atmosphere, in dry pyridine (2.4 mL). Then, under vigorous stirring, trifluoroacetic anhydride (0.1 mL, 2.9 equiv) was added dropwise over few minutes. The reaction mixture turned orange during the addition. After another 30 min water (10 mL) was added, followed by ethyl acetate (50 mL). Layers were separated and the aqueous one was extracted twice with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (5 mL), then with brine and dried. Solvent was evaporated and the residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate in 1 h) to yield **3.67** as thick, pale yellow oil (132 mg, 94%).

HRMS: found: *m/z* = 602.2496; calc. for $C_{34}H_{36}NO_4F_3Na$ ($M + Na^+$): 602.2494; elem. anal.: found: C – 70.62, H – 6.05, N – 2.42%; calcd. C – 70.45, H – 6.26, N – 2.42%; $[\alpha]_D^{23}$ = −7.7; R_f = 0.7 (hexanes: ethyl acetate 8:1). ^{1}H NMR ($CDCl_3$) δ: 7.30 (m, arom.), 5.94 (~ ddt, 1H, *J* = 17.2, 10.1, 7.3 Hz, H-8a), 5.65 (~ ddt, 1H, *J* = 17.3, 10.2, 7.3 Hz, H-8b), 5.12 (m, 1H, H-9b), 5.07 (m, 2H, H-9a, H-9b'), 4.99 (m, 1H, H-9a'), 4.88 (d, 1H, *J* = 11.4 Hz, OC*H*$_2$Ph), 4.61 (m, 4H, 4 × OC*H*$_2$Ph), 4.53 (d, 1H, *J* = 11.8 Hz, OC*H*$_2$Ph), 3.99 (dd, 1H, *J* = 7.2, 4.5 Hz, H-4), 3.76 (d, 1H, *J* = 7.2 Hz, H-3), 3.67 (m, 1H, H-5), 3.61 (m, 2H, 2 × H-6), 3.13 (dd, 1H, *J* = 14.3, 7.0 Hz, H-7b), 2.97 (dd, 1H, *J* = 14.7, 7.0 Hz, H-7a), 2.73 ppm (m, 2H, H-7a', H-7b'). ^{13}C NMR ($CDCl_3$) δ: 156.5 (q, *J* = 34.7 Hz, C-10), 137.9, 137.8, 137.5 (3 × quat. benzyl), 134.7 (C-8a),

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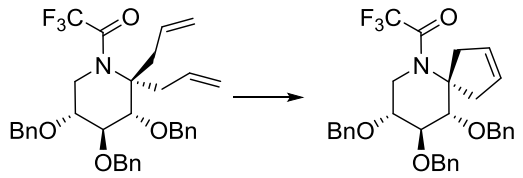
132.9 (C-8b), 128.5-127.4 (arom.), 120.1 (C-9b), 117.8 (C-9a), 116.3 (q, *J* = 290.0 Hz, C-11), 81.8 (C-4), 79.9 (C-3), 78.1 (C-5), 74.6, 73.0, 71.4 (3 × O<u>*C*</u>H_2Ph), 66.7 (C-2), 43.7 (q, *J* = 3.7 Hz, C-6), 37.8 (C-7a), 37.2 ppm (C-7b).

(8*R*,9*S*,10*S*)-6-Trifluoroacetyl-6-azaspiro[4.5]-8,9,10-tribenzyloxydec-2-ene (3.68):



3.67 **3.68**

Compound **3.67** (255 mg, 0.440 mmol) was dissolved in dry dichloromethane (4.0 mL), under argon atmosphere, in a flask equipped with a double-surface reflux condenser. Then, Grubbs II catalyst (3.7 mg, 1 mol%) freshly dissolved in dry dichloromethane (0.4 mL) was added in one portion and the reaction was conducted under constant argon flushing at ambient temperature for 16 h. The solvent was evaporated and the residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate in 1 h), yielding **3.68** as pale yellow, thick oil (230 mg, 95%).

HRMS: found: *m*/*z* = 574.2179; calc. for $C_{32}H_{32}NO_4F_3Na$ ($M + Na^+$): 574.2181; elem. anal.: found: C – 69.75, H – 5.79, N – 2.59%; calcd. C – 69.68, H – 5.85, N – 2.54%; $[\alpha]_D^{23}$ = −13.3; R_f = 0.6 (hexanes:ethyl acetate 8:1). ^{1}H NMR ($CDCl_3$) δ: 7.32 (m, arom.), 5.63 (m, 2H, H-2, H-3), 4.64 (m, 5H, 5 × OC<u>*H*</u>$_2$Ph), 4.45 (d, 1H, *J* = 11.3 Hz, 1 × OC<u>*H*</u>$_2$Ph), 3.89 (dd, 1H, *J* = 5.6, 3.1 Hz, H-9), 3.81 (dd, 1H, *J* = 13.1, 2.8 Hz, H-7), 3.71 (m, 1H, H-8), 3.63 (dd, 1H, *J* = 13.0, 10.3 Hz, H-7'), 3.50 (d, 1H, *J* = 3.1 Hz, H-10), 2.79 (m, 3H, H-1, H-1', H-4), 2.68 ppm (~ d, 1H, *J* = 16.8 Hz, H-4'). ^{13}C NMR ($CDCl_3$) δ: 156.2 (q, *J* = 34.9 Hz, C-11), 137.7, 137.4, 137.2 (3 × quat. benzyl), 128.5-127.4 (arom.), 128.5, 127.8 (C-2, C-3), 116.3 (q, *J* = 289.0 Hz, C-12), 81.7 (C-10), 81.5 (C-9), 78.9 (C-8), 73.3, 72.5, 71.9 (3 × O<u>*C*</u>H_2Ph), 69.0 (C-5), 42.9 (q, *J* = 3.7 Hz, C-7), 41.5, 39.4 ppm (C-1, C-4).

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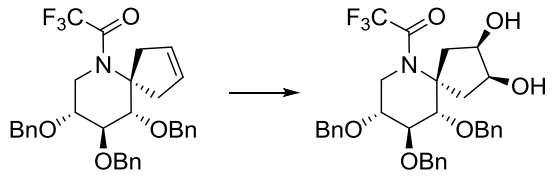
(2*R*,3*S*,5*S*,8*R*,9*S*,10*S*)-6-Trifluoroacetyl-6-azaspiro[4.5]-8,9,10-tribenzyloxydecane-2,3-diol (3.69):

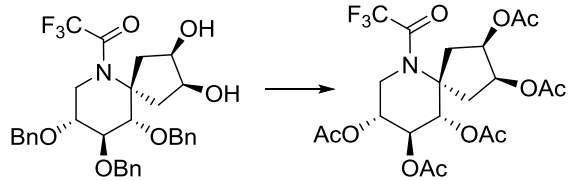


3.68 **3.69**

This reaction was carried out according to the **general procedure F** (at rt, 2 h). Flash chromatography (linear gradient: 100% hexanes to 100% ethyl acetate) yielded **3.69** as pale yellow, thick oil (125 mg, 82%).

HRMS: found: *m/z* = 608.2235; calc. for $C_{32}H_{34}NO_6F_3Na$ ($M + Na^+$): 608.2236; elem. anal.: found: C – 65.66, H – 5.99, N – 2.39%; calcd. C – 65.63, H – 5.85, N – 2.39%; $[\alpha]_D^{23} = -1.1$; R_f = 0.4 (DCM:methanol 20:1). ^{1}H NMR ($CDCl_3$) δ: 7.33 (m, arom.), 4.82 (bd, 1H, *J* = 10.4 Hz, 1 × OC*H*$_2$Ph), 4.69 (d, 1H, *J* = 11.4 Hz, 1 × OC*H*$_2$Ph), 4.58 (m, 4H, 4 × OC*H*$_2$Ph), 4.48 (bs, 1H, H-2), 4.39 (~ dd, 1H, *J* = 10.3, 4.7 Hz, H-3), 3.91 (bs, 1H, H-10), 3.84 (~ t, 1H, *J* = 4.1 Hz, H-9), 3.68 (m, 3H, H-7, H-7', H-8), 2.38 (dd, 1H, *J* = 15.0, 7.0 Hz, H-1), 2.25 (m, 1H, H-4), 2.17 (m, 1H, H-4'), 2.06 ppm (m, 1H, H-1'). ^{13}C NMR ($CDCl_3$) δ: 156.4 (q, *J* = 35.1 Hz, C-11), 137.5, 137.3, 136.5 (3 × quat. benzyl), 128.6-127.7 (arom.), 116.3 (q, *J* = 289.1 Hz, C-12), 81.9 (C-10), 81.4 (C-9), 77.6 (C-8), 74.3 (1 × benzyl), 74.0 (C-3), 73.7 (C-2), 72.0, 71.7 (2 × benzyl), 68.2 (C-5), 43.0 (C-7), 40.8 (C-4), 39.4 ppm (C-1).

(2*R*,3*S*,5*S*,8*R*,9*S*,10*S*)-6-Trifluoroacetyl-6-azaspiro[4.5]-2,3,8,9,10-decanyl pentaacetate (3.70):



3.69 **3.70**

To a solution of **3.69** (61 mg, 0.1 mmol) in methanol (1.0 mL), palladium on charcoal (10%, 60 mg) was added under an argon atmosphere. Then, argon was replaced by hydrogen (from a balloon; three cycles vacuum-hydrogen) and the reaction was carried out for 72 h. Then, the suspension was filtered through a pad of Celite and washed repeteadly with methanol. The solvent was evaporated and the residue was dissolved

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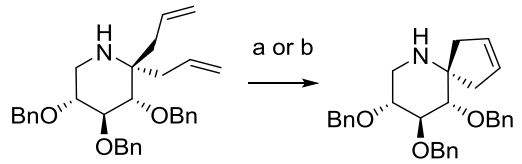
in pyridine (0.8 mL) and Ac_2O (0.2 mL). DMAP was added (1 mg, 8 mol%) and the mixture was stirred for 24 h. The solvent was evaporated and the residue was chromatographed (flash chromatography, linear gradient: 100% hexanes to 100% ethyl acetate in 30 min) to yield **3.70** as white solid (44 mg, 83%).

CCDC: 967856; HRMS: found: *m/z* = 548.1351; calc. for $C_{21}H_{26}NO_{11}F_3Na$ ($M + Na^+$): 548.1356; elem. anal.: found: C – 47.77, H – 5.03, N – 2.60%; calcd. C – 48.00, H – 4.99, N – 2.67%; $[\alpha]_D^{23} = 0.15$; mp: 139-141 °C; $R_f = 0.3$ (hexanes:ethyl acetate 2:1). ^{1}H NMR ($CDCl_3$) δ: 5.71 (~ td, 1H, *J* = 7.4, 4.5 Hz, H-2), 5.58 (m, 1H, H-3), 5.36 (d, 1H, *J* = 2.6 Hz, H-10), 5.08 (dd, 1H, *J* = 5.7, 2.6 Hz, H-9), 4.96 (m, 1H, H-8), 3.89 (dd, 1H, *J* = 13.4, 4.5 Hz, H-7), 3.60 (dd, 1H, *J* = 13.4, 10.9 Hz, H-7'), 2.53 (m, 2H, H-1, H-4), 2.36 (dd, 1H, *J* = 15.0, 3.3 Hz, H-4'), 2.20, 2.11, 2.08, 2.07, 2.02 (5 × s, 5 × 3H, 5 × acetyl), 1.98 ppm (dd, 1H, *J* = 14.7, 7.3 Hz, H-1'). ^{13}C NMR ($CDCl_3$) δ: 169.9-168.9 (5 × $CH_3\underline{C}(O)$-), 156.6 (q, *J* = 36.0 Hz, C-11), 115.9 (q, *J* = 288.8 Hz, C-12), 75.2 (C-10), 74.3 (C-3), 73.4 (C-2), 72.5 (C-9), 70.1 (C-8), 65.9 (C-5), 42.6 (q, *J* = 3.8 Hz, C-7), 37.7 (C-4), 37.0 (C-1), 20.8-20.6 ppm (5 × $\underline{C}H_3C(O)$-).

(8*R*,9*S*,10*S*)-6-Azaspiro[4.5]-8,9,10-tribenzyloxydec-2-ene (3.71):



3.9 **3.71**

(a) Compound **3.9** (95 mg, 0.197 mmol) was dissolved in dry toluene (0.5 mL) in a flask equipped with a double-surface reflux condenser. Then, HCl (0.4 mL, 6.1 equiv, 3 M in cyclopentyl methyl ether) was added dropwise at ambient temperature. Subsequently, the mixture was warmed to 50 °C and Grubbs II catalyst (17 mg, 10 mol%) freshly dissolved in dry toluene (0.3 mL) was added with a syringe pump over 3 h. The reaction was performed for another 3 h at 50 °C (all the time under constant argon flushing). Then, the heating bath was removed and the mixture was allowed to cool down to ambient temperature, after which sat. aq $NaHCO_3$ (3 mL) was added and the mixture was vigorously stirred for another 15 min Then, ethyl acetate (50 mL) was added, layers were separated and the organic one was dried. The solvent was evaporated and the residue was chromatographed (linear gradient: 100% hexanes to 100% ethyl acetate in 1 h) to yield **3.71** as brown, thick oil (78 mg, 87%).

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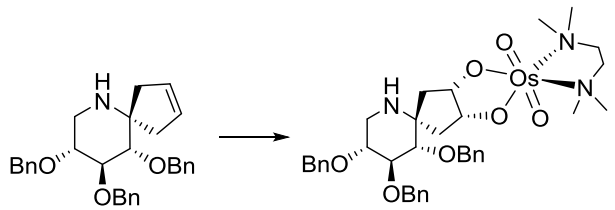
(b) Compound **3.67** (98 mg, 0.169 mmol) was dissolved in dry dichloromethane (1.5 mL) in a flask equipped with a double-surface reflux condenser. Then, Grubbs II catalyst (1.5 mg, 1 mol%) freshly dissolved in dry dichloromethane (0.2 mL) was added in one portion and the reaction was conducted under constant argon flushing at ambient temperature for 16 h. The solvent was evaporated and the residue was dissolved in MeOH (1.7 mL). Then, finely pulverized K_2CO_3 (120 mg, 5.1 equiv) was added in one portion and the mixture was vigorously stirred for 24 h. Subsequently, ethyl acetate (20 mL) was added, the mixture was filtered through a pad of Celite and repeteadly washed with ethyl acetate. Solvent was evaporated and the residue was chromatographed (linear gradient: 100% hexanes to 100% ethyl acetate in 1 h) to yield **3.71** as a yellow, thick oil (66 mg, 86%).

HRMS: found: *m/z* = 456.2542; calc. for $C_{30}H_{34}NO_3$ ($M + H^+$): 456.2539; elem. anal.: found: C – 79.05, H – 7.45, N – 3.19%; calcd. C – 79.09, H – 7.30, N – 3.07%; $[\alpha]_D^{23}$ = 19.9; R_f = 0.6 (DCM:methanol 20:1). ^{1}H NMR ($CDCl_3$) δ: 7.29 (m, arom.), 5.64 (m, 2H, H-2, H-3), 4.98 (d, 1H, *J* = 11.6 Hz, 1 × OC*H*$_2$Ph), 4.92 (d, 1H, *J* = 10.8 Hz, 1 × OC*H*$_2$Ph), 4.79 (d, 1H, *J* = 10.8 Hz, 1 × OC*H*$_2$Ph), 4.69 (m, 3H, 3 × OC*H*$_2$Ph), 3.54 (m, 2H, H-8, H-9), 3.34 (d, 1H, *J* = 9.1 Hz, H-10), 3.06 (dd, 1H, *J* = 12.7, 4.5 Hz, H-7), 2.74 (m, 1H, H-7'), 2.68 (m, 2H, H-1, H-4), 2.34 (m, 1H, H-1'), 2.04 ppm (m, 1H, H-4'). ^{13}C NMR ($CDCl_3$) δ: 139.0, 138.8, 138.5 (3 × quat. benzyl), 129.0, 128.0 (C-2, C-3), 128.4-127.3 (arom.), 85.4 (C-9), 84.0 (C-10), 80.7 (C-8), 75.6, 75.2, 72.9 (3 × O*C*H$_2$Ph), 65.6 (C-5), 45.8 (C-1), 44.1 (C-7), 36.2 ppm (C-4).

Osmate ester (3.72):



3.71 **3.72**

Compound **3.71** (94 mg, 0.207 mmol) was dissolved in dry dichloromethane (2.0 mL) under argon atmosphere. Then, TMEDA was added (60 μL, 1.9 equiv) and the mixture was cooled to −78 °C. Subsequently, osmium tetroxide was added (2.3 mL, 1.1 equiv, 0.1 M in *t*-BuOH) dropwise over 5 min The resulting slurry was stirred for another 15 min, after which the cooling bath was removed and the mixture was allowed to reach

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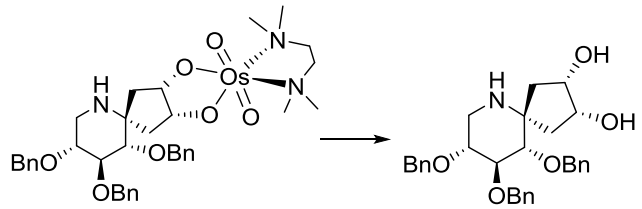
room temperature (15 min). The solvent was evaporated and the residue was chromatographed (preparative TLC, 1 mm, DCM:methanol 10:1) to yield **3.72** as brown, thick oil (152 mg, 89%).

HRMS: found: *m/z* = 828.3257; calc. for $C_{36}H_{50}N_3O_7Os$ (M + H^+): 828.3264; $[\alpha]_D^{23}$ = −232.8; R_f = 0.4 (DCM:methanol 10:1). ^{1}H NMR ($CDCl_3$) δ: 7.28 (m, arom.), 5.02 (d, 1H, *J* = 11.6 Hz, 1 × OC*H*$_2$Ph), 4.90 (d, 1H, *J* = 10.8 Hz, 1 × OC*H*$_2$Ph), 4.79 (m, 1H, H-2), 4.77 (d, 1H, *J* = 10.8 Hz, 1 × OC*H*$_2$Ph), 4.74 (m, 1H, H-3), 4.66 (m, 3H, 3 × OC*H*$_2$Ph), 3.67 (bs, 1H, H-8), 3.46 (~ t, 1H, *J* = 9.2 Hz, H-9), 3.37 (bs, 1H, H-10), 3.08 (m, 5H, H-7, $Me_2NCH_2CH_2NMe_2$), 2.87, 2.84, 2.82, 2.80 (4 × s, 12H, $Me_2NCH_2CH_2NMe_2$), 2.72 (~ t, 1H, *J* = 11.2 Hz, H-7'), 2.56 (dd, 1H, *J* = 14.2, 5.6 Hz, H-4), 2.36 (dd, 1H, *J* = 14.5, 8.3 Hz, H-1), 2.09 ppm (m, 2H, H-1', H-4'). ^{13}C NMR ($CDCl_3$) δ: 139.0, 138.9, 138.6 (3 × quat. benzyl), 128.3-127.2 (arom.), 94.8 (C-2), 93.9 (C-3), 85.7 (C-9), 82.5 (C-10), 79.9 (C-8), 75.6, 75.5, 72.7 (3 × benzyl), 67.1 (C-5), 64.3, 64.2 ($Me_2NCH_2CH_2NMe_2$), 51.8, 51.52, 51.50, 51.3 ($Me_2NCH_2CH_2NMe_2$), 44.5 (C-7), 42.2 (C-4), 33.2 ppm (C-1).

(2*R*,3*S*,5*S*,8*R*,9*S*,10*S*)-6-Azaspiro[4.5]-8,9,10-tribenzyloxydecane-2,3-diol (3.73):



3.72 **3.73**

Compound **3.72** (130 mg, 0.157 mmol) was dissolved in dry DCM (1.6 mL), under argon atmosphere. Then, ethylenediamine (60 µl, 0.90 mmol, 5.7 equiv) was added dropwise over few min at room temperature. The reaction mixture was stirred for 10 min. Then, water (5 mL) was added and the reaction was stirred vigorously for 5 min, after which ethyl acetate (50 mL) was added. Layers were separated and the aqueous one was washed with ethyl acetate (15 mL). The combined organic layers were washed with brine and dried. Solvent was evaporated and the residue was chromatographed (preparative TLC, 1 mm, DCM:MeOH 20:1, three times developed) to yield **3.73** as orange, thick oil (62 mg, 81%).

HRMS: found: *m/z* = 490.2591; calc. for $C_{30}H_{36}NO_5$ (M + H^+): 490.2593; elem. anal.: found: C – 72.09, H – 7.28, N – 2.69%; calcd. C – 72.27, H – 7.28, N – 2.81% (for

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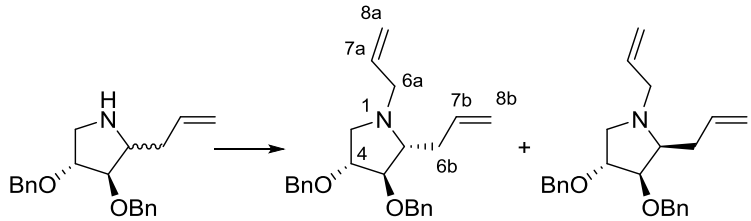
$C_{30}H_{35}NO_5 \cdot 0.5\ H_2O$); $[\alpha]_D^{23} = -7.8$; $R_f = 0.6$ (DCM:methanol 10:1). ^{1}H NMR ($CDCl_3$) δ: 7.28 (m, arom.), 4.97 (d, 1H, J = 11.4 Hz, 1 × OC$\underline{H}_2$Ph), 4.90 (d, 1H, J = 10.8 Hz, 1 × OC$\underline{H}_2$Ph), 4.75 (d, 1H, J = 10.9 Hz, 1 × OC$\underline{H}_2$Ph), 4.69 (d, 1H, J = 11.6 Hz, 1 × OC$\underline{H}_2$Ph), 4.65 (d, 1H, J = 11.6 Hz, 1 × OC$\underline{H}_2$Ph), 4.57 (d, 1H, J = 11.4 Hz, 1 × OC$\underline{H}_2$Ph), 4.07 (~ dt, 1H, J = 6.6, 4.3 Hz, H-2), 4.00 (~ dt, 1H, J = 7.5, 3.9 Hz, H-3), 3.50 (~ t, 1H, J = 8.9 Hz, H-9), 3.44 (m, 1H, H-8), 3.18 (bs, 3H), 3.13 (d, 1H, J = 9.0 Hz, H-10), 3.03 (dd, 1H, J = 13.6, 5.1 Hz, H-7), 2.66 (dd, 1H, J = 13.6, 10.3 Hz, H-7'), 2.15 (dd, 1H, J = 14.0, 6.7 Hz, H-1), 2.09 (dd, 1H, J = 14.2, 6.4 Hz, H-4), 1.72 (dd, 1H, J = 14.0, 3.2 Hz, H-1'), 1.44 ppm (dd, 1H, J = 14.1, 1.8 Hz, H-4'). ^{13}C NMR ($CDCl_3$) δ: 138.5, 138.4, 138.2 (3 × quat. benzyl), 128.4-127.4 (arom.), 84.2 (C-9), 83.1 (C-10), 80.1 (C-8), 75.52, 75.49 (2 × benzyl), 74.8 (C-2), 73.4 (C-3), 72.9 (1 × benzyl), 65.4 (C-5), 43.6 (C-7), 42.8 (C-4), 34.8 ppm (C-1).

Allylation of 3.27:



3.27 **3.76** **3.77**

To a stirred solution of **3.27** (421 mg, 1.3 mmol) in MeCN (13 mL), at room temperature, pulverized K_2CO_3 (1.5 g) was added in one portion. Then, allyl bromide (0.12 mL, 1.4 mmol, 1.1 equiv) and the resulting mixture was vigorously stirred for 24 h. Subsequently, the solids were filtered off using Celite and the filtrate was concentrated. Flash chromatography (100% hexanes to 100% ethyl acetate) gave **3.76** (260 mg, 55%) and **3.77** (61 mg, 13%), both as yellow oils.

(2*S*,3*R*,4*R*)-1,2-Diallyl-3,4-dibenzyloxypyrrolidine (3.76):

HRMS: found: m/z = 364.2277; calc. for $C_{24}H_{30}NO_2$ ($M + H^+$): 364.2277; elem. anal.: found: C – 79.40, H – 8.05, N – 3.98%; calcd. C – 79.30, H – 8.04, N – 3.85%; $[\alpha]_D^{23} = -32.1$; R_f = 0.7 (hexanes:AcOEt 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.31 (m, arom.), 5.89 (m, 2H, H-7a, H-7b), 5.09 (m, 4H, H-8a, H-8a', H-8b, H-8b'), 4.58 (d, 1H, J = 12.3 Hz, 1 × OC$\underline{H}_2$Ph), 4.45 (m, 3H, 3 × OC$\underline{H}_2$Ph), 3.87 (m, 1H, H-4), 3.76 (m, 1H, H-3), 3.48

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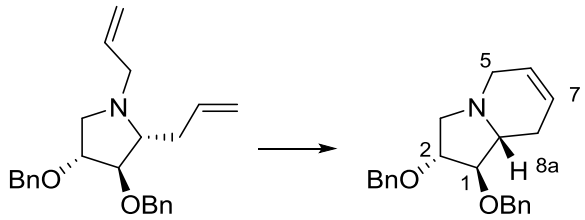
(m, 1H, H-6a), 3.16 (~d, 1H, *J* = 10.8 Hz, H-5), 2.83 (dd, 1H, *J* = 13.4, 7.8 Hz, H-6a'), 2.46 (m, 3H, H-2, H-5', H-6b), 2.31 ppm (~td, 1H, *J* = 14.5, 7.1 Hz, H-6b'). ^{13}C NMR ($CDCl_3$) δ: 138.2, 138.1 (2 × quat. benzyl), 135.3 (C-7a), 135.2 (C-7b), 128.3-127.6 (arom.), 117.3 (C-8a), 116.7 (C-8b), 87.7 (C-3), 81.0 (C-4), 71.6, 71.1 (2 × $\underline{C}H_2$OPh), 68.0 (C-2), 57.0 (C-5), 56.8 (C-6a), 35.7 ppm (C-6b).

(2*R*,3*R*,4*R*)-1,2-Diallyl-3,4-dibenzyloxypyrrolidine (3.77):

HRMS: found: *m*/*z* = 364.2270; calc. for $C_{24}H_{30}NO_2$ (M + H^+): 364.2277; elem. anal.: found: C – 79.12, H – 8.10, N – 3.78%; calcd. C – 79.30, H – 8.04, N – 3.85%; $[\alpha]_D^{23}$ = 38.5; R_f = 0.5 (hexanes:AcOEt 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.28 (m, arom.), 7.31 (m. arom.), 5.92 (m, 1H, H-7a), 5.78 (m, 1H, H-7b), 5.05 (m, 4H, H-8a, H-8a', H-8b, H-8b'), 4.60 (d, 1H, *J* = 11.9 Hz, 1 × OC$\underline{H_2}$Ph), 4.46 (m, 3H, 3 × OC$\underline{H_2}$Ph), 3.98 (m, 1H, H-4), 3.84 (dd, 1H, *J* = 5.2, 1.4 Hz, H-3), 3.50 (m, 2H, H-6a, H-5), 2.85 (dd, 1H, *J* = 13.3, 7.9 Hz, H-6a'), 2.65 (~dt, 1H, *J* = 9.4, 4.7 Hz, H-2), 2.46 (m, 1H, H-6b), 2.32 ppm (m, 2H, H-5', H-6b'). ^{13}C NMR ($CDCl_3$) δ: 138.2, 138.0 (2 × quat. benzyl), 136.1 (C-7b), 135.2 (C-7a), 128.4-127.6 (arom.), 117.3 (C-8a), 116.3 (C-8b), 83.4 (C-3), 81.1 (C-4), 71.7, 71.3 (2 × $\underline{C}H_2$OPh), 66.0 (C-2), 58.0 (C-5), 57.0 (C-6a), 31.8 ppm (C-6b).

(1*R*,2*R*,8a*R*)-1,2-Dibenzyloxy-1,2,3,5,8,8a-hexahydroindolizine (3.78):



3.76 **3.78**

To a solution of **3.76** (65 mg, 0.18 mmol) in dry toluene (1 mL), under argon atmosphere and at room temperature, CF_3CO_2H (30 μL) was added. Then, Grubbs-Hoveyda-II (6 mg, 10 mol%) catalyst was added and the mixture was heated to 60 °C. After 12 h of stirring at this temperature, the reaction was cooled to room temperature and Amberjet 4400 OH (250 mg) was added. After 30 min, the ion-exchange resin was filtered off and the filtrate was concentrated. Preparative TLC (1 mm, hexanes:AcOEt 1:1) yielded the product **3.78** as a yellow oil (56 mg, 94%).

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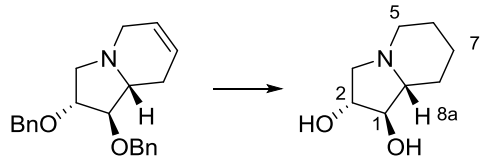
HRMS: found: *m/z* = 336.1964; calc. for $C_{22}H_{26}NO_2$ ($M + H^+$): 336.1964; elem. anal.: found: C – 78.56, H – 7.38, N – 4.40%; calcd. C – 78.77, H – 7.51, N – 4.18%; $[\alpha]_D^{23}$ = 54.5; R_f = 0.4 (hexanes:AcOEt 2:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (m, arom.), 5.73 (ddd, 1H, *J* = 9.4, 5.1, 2.1 Hz, H-7), 5.66 (ddd, 1H, *J* = 10.0, 2.7, 1.6 Hz, H-6), 4.56 (m, 3H, 3 × OC*H*$_2$Ph), 4.46 (d, 1H, *J* = 12.0 Hz, 1 × OC*H*$_2$Ph), 3.96 (m, 1H, H-2), 3.77 (dd, 1H, *J* = 7.0, 2.2 Hz, H-1), 3.41 (m, 1H, H-5), 3.27 (~d, 1H, *J* = 10.5 Hz, H-3), 2.76 (m, H-5'), 2.47 (dd, 1H, *J* = 10.6, 6.3 Hz, H-3'), 2.39 (m, 1H, H-8), 2.27 (m, 1H, H-8a), 2.19 ppm (m, 1H, H-8'). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 138.15, 138.13 (2 × quat. benzyl), 128.3-127.6 (arom.), 124.9 (C-6), 124.6 (C-7), 90.7 (C-1), 81.9 (C-2), 72.0, 71.2 (2 × *C*H$_2$OPh), 63.8 (C-8a), 58.8 (C-3), 52.7 (C-5), 30.8 ppm (C-8).

(1*R*,2*R*,8a*R*)-octahydroindolizine-1,2-diol ((-)-lentiginosine, 3.75):



3.78 **3.75**

To a stirred solution of **3.78** (71 mg, 0.21 mmol) in MeOH, under argon atmosphere and at room temperature, $Pd(OH)_2$/C (250 mg) was added. The argon was replaced with hydrogen (from a balloon) and the reaction was carried out under hydrogen atmosphere for 12 h. After this time, the mixture was filtered through Celite and the filtrate was concentrated to give **3.75** as yellow solid (30 mg, 91%). NMR spectra and [α] were in accordance with the literature.[180]

HRMS: found: *m/z* = 158.1183; calc. for $C_8H_{16}NO_2$ ($M + H^+$): 158.1181; $[\alpha]_D^{23}$ = -2.2 (MeOH); ^{1}H NMR (600 MHz, D_2O) δ: 3.90 (ddd, 1H, *J* = 7.3, 3.7, 1.8 Hz), 3.49 (dd, 1H, *J* = 8.8, 3.8 Hz), 2.85 (~bd, 1H, *J* = 11.2 Hz), 2.73 (m, 1H), 2.62 (~dd, 1H, *J* = 11.5, 7.6 Hz), 2.04 (m, 2H), 1.75 (m, 1H), 1.60 (m, 1H), 1.47 (~bd, 1H, *J* = 14.0 Hz), 1.28 (m, 1H), 1.08 ppm (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 82.6, 75.5, 69.0, 60.2, 52.9, 27.4, 23.9, 23.0 ppm.

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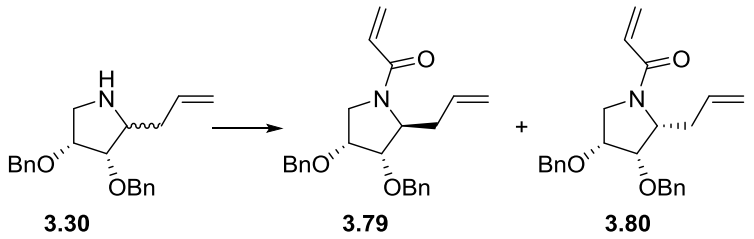
***N*-acryloylation of 3.30**



3.30 **3.79** **3.80**

To a stirred solution of **3.30** (90 mg, 0.28 mmol) in dry DCM (2.8 mL), under argon atmosphere and at room temperature, Et_3N (0.1 mL, 2.6 equiv) was added. Then, acryloyl chloride (80 μL, 3.6 equiv) was added and the resulting mixture was stirred for 15 min. Subsequently, toluene (2 mL) was added and the majority of the solvent was evaporated. As a result, suspension of a $Et_3N{\cdot}HCl$ (white solid) in toluene was obtained. The clear solution was subjected to chromatography (prep. TLC, 1 mm, hexanes:AcOEt 2:3), which gave **3.79** (56 mg, 53%) and **3.80** (22 mg, 21%), both as orange oils.

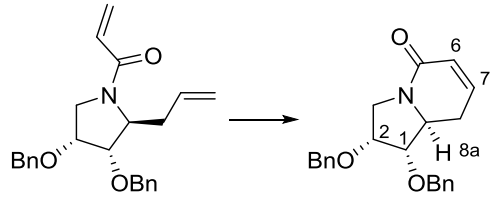
1-[(2*S*,3*S*,4*R*)-3,4-Dibenzyloxy-2-(prop-2-en-1-yl)pyrrolidin-1-yl]prop-2-en-1-one (3.79):

HRMS: found: *m*/*z* = 400.1884; calc. for $C_{24}H_{27}NO_3Na$ (M + Na^+): 400.1889; R_f = 0.4 (hexanes:AcOEt 3:2). NMR spectra indicate, that this compound is formed as a mixture of rotamers, which makes the interpretation very difficult.

1-[(2*R*,3*S*,4*R*)-3,4-Dibenzyloxy-2-(prop-2-en-1-yl)pyrrolidin-1-yl]prop-2-en-1-one (3.80):

HRMS: found: *m*/*z* = 400.1882; calc. for $C_{24}H_{27}NO_3Na$ (M + Na^+): 400.1889; R_f = 0.3 (hexanes:AcOEt 3:2). NMR spectra indicate, that this compound is formed as a mixture of rotamers, which makes the interpretation very difficult.

(1*S*,2*R*,8a*S*)-1,2-Dibenzyloxy-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (3.81):



3.79 **3.81**

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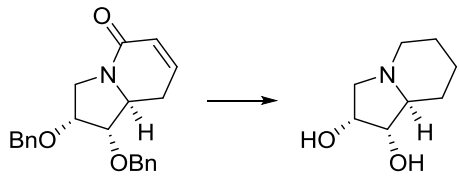
To a stirred solution of **3.79** (45 mg, 0.12 mmol) in dry toluene, under argon atmosphere and at room temperature, Grubbs-II catalyst (5 mg, 5 mol%) was added and the reaction mixture was heated to 50 °C. After 3 h, the solvent was evaporated and the crude product was purified by chromatography (prep. TLC 1 mm, DCM:MeOH 10:1), which gave **3.81** (35 mg, 83%) as orange oil.

HRMS: found: *m*/*z* = 372.1564; calc. for $C_{22}H_{23}NO_3Na$ (M + Na^+): 372.1576; $[\alpha]_D^{23}$ = -144.3; R_f = 0.2 (hexanes:AcOEt 2:3). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (m, arom.), 6.51 (m, 1H, H-7), 5.94 (dd, 1H, *J* = 9.8, 3.0 Hz, H-6), 4.98 (m, 2H, 2 × OC<u>*H*</u>$_2$Ph), 4.54 (d, 1H, *J* = 12.1 Hz, 1 × OC<u>*H*</u>$_2$Ph), 4.46 (d, 1H, *J* = 12.0 Hz, 1 × OC<u>*H*</u>$_2$Ph), 4.20 (~t, 1H, *J* = 4.2 Hz, H-2), 4.00 (ddd, 1H, *J* = 14.2, 9.3, 5.2 Hz, H-8a), 3.85 (~d, 1H, *J* = 13.7 Hz, H-3), 3.65 (dd, 1H, *J* = 9.3, 4.1 Hz, H-1), 3.49 (dd, 1H, *J* = 13.6, 4.3 Hz, H-3'), 3.61 (m, 1H, H-8), 2.07 ppm (m, 1H, H-8'). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.4 (C-5), 138.1 (C-7), 137.5, 137.3 (2 × quat. benzyl), 128.5-127.7 (arom.), 125.8 (C-6), 84.1 (C-1), 72.5 (C-2), 71.8, 71.2 (2 × <u>*C*</u>H_2OPh), 56.3 (C-8a), 47.3 (C-3), 28.6 ppm (C-8).

(1*S*,2*R*,8a*S*)-octahydroindolizine-1,2-diol (3.82):



3.81 **3.82**

To a stirred solution of **3.81** (33 mg, 0.09 mmol) in MeOH, under argon and at rt, $Pd(OH)_2$/C (200 mg) was added. The argon was replaced with hydrogen (from a balloon) and the reaction was carried out under hydrogen atmosphere for 12 h. After this time, the mixture was filtered through Celite and the filtrate was concentrated. The crude product was dissolved in dry THF (0.5 mL) under argon and at rt. $LiAlH_4$ (0.3 mL, 1 M/THF, 3.3 equiv) was added and the resulting mixture was heated to 60 °C. The reaction was carried out at this temperature for 1.5 h. Then, the mixture was cooled to rt and Celite/$Na_2SO_4 \cdot 10H_2O$ (1:1 *w*/*w*) was added in few portions over a period of 10 min. The resulting mixture was stirred for additional 1 h, after which it was filtered through Celite. The filtrate was concentrated and subjected to flash chromatograpy ($CHCl_3$:acetone:MeOH:H_2O 57:20:20:3), which yielded **3.82** (9 mg,

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56%) as yellow solid. NMR spectra and [α] value were in accordance with the literature.[181,182]

HRMS: found: *m/z* = 158.1176; calc. for $C_8H_{16}NO_2$ (M + H^+): 158.1181; $[\alpha]_D^{23}$ = -34.6 (MeOH); R_f = 0.1 ($CHCl_3$:acetone:MeOH:H_2O 57:20:20:3). ^{1}H NMR (500 MHz, D_2O) δ: 4.09 (m, 1H), 3.53 (dd, 1H, *J* = 8.9, 6.9 Hz), 3.36 (dd, 1H, *J* = 11.1, 7.0 Hz), 2.93 (m, 1H), 2.15 (m, 3H), 1.87 (m, 1H), 1.71 (m, 1H), 1.58 (m, 1H), 1.35 (m, 1H), 1.21 (m, 1H), 1.11 ppm (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 75.3, 67.8, 67.2, 60.8, 53.3, 28.3, 25.0, 23.7 ppm.

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