
This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.

Koskinen, Ari M.P.

Conformational control in stereoselective chemical reactions

Published in:
Heterocycles

DOI:
[10.3987/REV-20-SR\(K\)7](https://doi.org/10.3987/REV-20-SR(K)7)

Published: 01/01/2021

Document Version
Peer-reviewed accepted author manuscript, also known as Final accepted manuscript or Post-print

Published under the following license:
CC BY-NC-ND

Please cite the original version:
Koskinen, A. M. P. (2021). Conformational control in stereoselective chemical reactions: From amino acids to iminosugars. *Heterocycles*, 103(2), 609-623. [https://doi.org/10.3987/REV-20-SR\(K\)7](https://doi.org/10.3987/REV-20-SR(K)7)

This material is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of the repository collections is not permitted, except that material may be duplicated by you for your research use or educational purposes in electronic or print form. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone who is not an authorised user.

CONFORMATIONAL CONTROL IN STEREOSELECTIVE CHEMICAL REACTIONS: FROM AMINO ACIDS TO IMINOSUGARS

Ari M. P. Koskinen*

Aalto University School of Chemical Engineering, Department of Chemistry and Materials Science, Kemistintie 1, P.O. Box 16100, 02150 Espoo, Finland. E-mail: ari.koskinen@aalto.fi

This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

Abstract – Two alternative synthetic strategies for the synthesis of vicinal amino alcohols from naturally occurring amino acids have been investigated, viz. one going through diastereoselective addition of organometallic species to an amino aldehyde and one going through α' -chiral α,β -enones and their diastereoselective reduction. Based on these investigations we were able to develop a synthetic strategy towards all diastereomers of deoxynojirimycin starting from naturally occurring serine through a divergent route with a late stage intermediate that can be prepared in large quantities and in enantiomerically pure form.

INTRODUCTION

Currently more than 170 million unique organic or inorganic chemical substances are known, with a vast majority of them being organic molecules. It is impossible to estimate how many of these compounds exist in enantiomerically pure form, but one can safely say that at least for biologically active compounds, such as pharmaceutical agents and agrochemicals, there is an increasing need and emphasis on enantiopure compounds. For the synthesis of enantiopure compounds one can in principle envision three major alternative possibilities.¹ One can use chiral starting materials and utilize the existing chirality of the starting material to multiply that information into new stereocenters. We call this *internal asymmetric induction*. One can also use the chiral information in a molecule in such a way that the stereochemical information is temporarily covalently connected to an achiral starting material. In an ensuing reaction, a second stereocenter is formed with asymmetric induction from the original stereocenter forming diastereomers. The diastereomers can then be separated and the original source of stereochemical

information can be removed to give an enantiopure intermediate. We call this *relayed asymmetric induction*. The third possibility is to utilize the stereochemical information in forming a chiral catalyst which will then induce the chirality to the reacting partners by modifying the transition state in the reaction leading from prochiral starting materials to chiral products. We call this *external asymmetric induction*. In all three cases the original source of stereochemical information is ultimately derived from naturally occurring chiral compounds, the so-called chiral pool.

The origins of stereoselective (diastereoselective or enantioselective) synthesis date back to the early 20th century, but the development of what became to be known as asymmetric synthesis truly gained momentum only starting from the late 1970s and early 1980s. In chemistry Noble prizes the importance of three-dimensional structures for chemical reactions was acknowledged first in 1969 when Sir Derek H.R. Barton and Odd Hassel shared the Nobel Prize in chemistry “for their contributions to the development of the concept of conformation and its application in chemistry”. In 1975 the Nobel Prize in chemistry was awarded jointly to Sir John W. Cornforth “for his work on the stereochemistry of enzyme-catalyzed reactions” and Vladimir Prelog “for his research into the stereochemistry of organic molecules and reactions”. The most recent Nobel Prize in chemistry in this field was awarded in 2001 jointly to Ryoji Noyori, and William S. Knowles and Ryoji Noyori “for their work on chirally catalyzed hydrogenation reactions” and K. Barry Sharpless “for his work on chirally catalyzed oxidation reactions”. In the field of natural product synthesis, currently slightly over 4000 papers are published annually covering the synthesis of natural products, but out of them only about 1/5 covers enantioselective or asymmetric synthesis of the same.²

In this review I wish to describe our three decade long journey in the development of the synthesis strategy leading from readily available natural amino acids to multiply chiral naturally occurring nitrogen heterocycles, especially those of the iminosugar deoxynojirimycin type. Professor Yasuyuki Kita is a prominent figure in many fields, also the asymmetric synthesis of nitrogen containing heterocycles, and it is a privilege to dedicate this paper to him on his 77th birthday.

PROLOGUE

I entered my independent academic career in 1989 at the University of Surrey in the UK. I had decided to investigate the possibilities of utilizing the existing chiral information in simple and inexpensive highly functional amino acids such as proline or serine in order to construct more complex biologically active natural products, in other words, the methodology of internal asymmetric induction. Central in this investigation would be the conformational control of the acyclic stereoselectivity of reactions. Of particular interest to the successful outcome of this research was that we needed to fully understand allylic A^{1,3}-strain and its use in controlling the stereochemistry of reactions.

Vicinal amino alcohols seemed like appropriate target compounds for the development of diastereoselective synthesis methodology. In principle, one could envision two major alternative synthesis strategies starting from naturally occurring amino acids (Figure 1). One could either reduce the carboxylic acid function to an aldehyde function, and then attempt diastereoselective addition of alkyl, alkenyl or alkynyl organometallic species to the aldehyde. In an alternative strategy, one would convert the carboxylic acid function to a β keto phosphonate, then conduct an olefination reaction (for instance Horner-Wadsworth-Emmons type of reaction) to give α' -chiral α,β -enones. Diastereoselective reduction would then offer a route to the target amino alcohols. Both routes seemed attractive although one could also foresee problems in both routes. Because of the larger literature precedent, I initially decided to explore the amino aldehyde route.

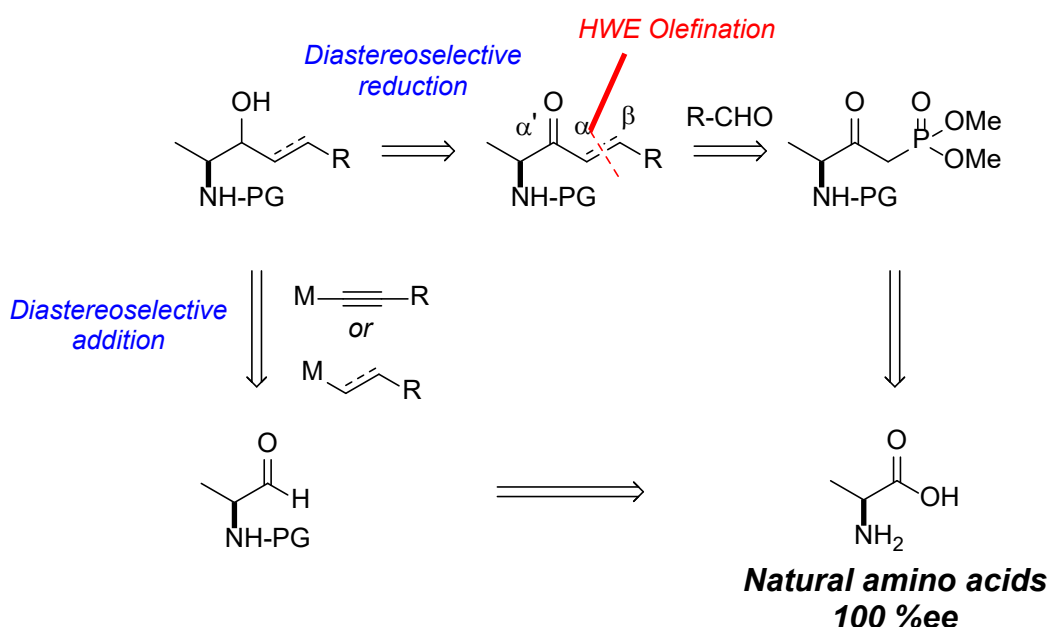
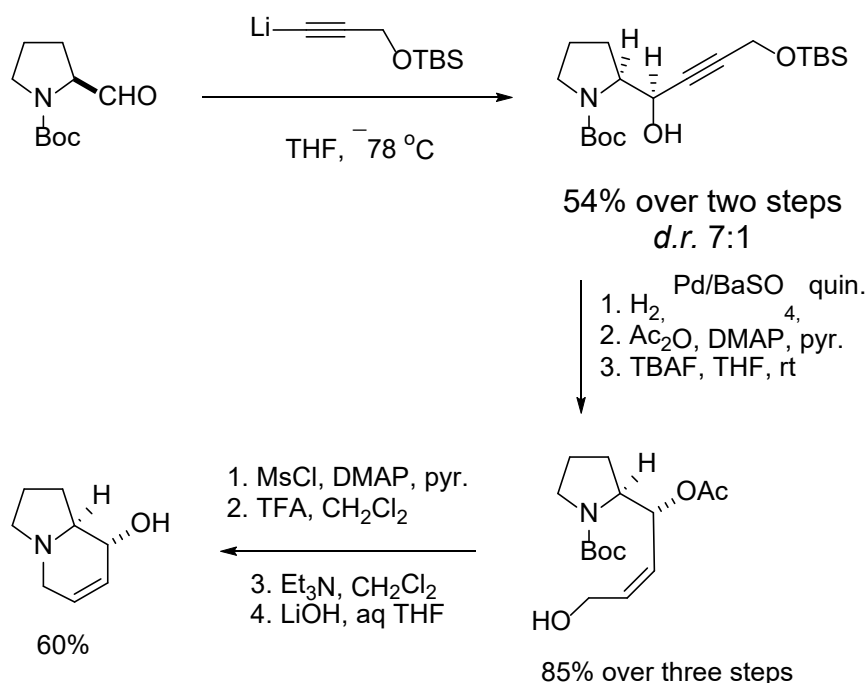


Figure 1. Planned strategies for the synthesis of vicinal amino alcohols.

Diastereoselective Addition to Amino Aldehydes

Because of the prevalent HIV condition in the late 1980's and early 1990's, indolizidine alkaloids started gaining popularity as targets for synthesis. Together with my first undergraduate student, we came up with an idea of trying to synthesize indolizidine alkaloids from proline. Castanospermine, a polyhydroxyindolizidine alkaloid, was one of the first compounds shown to be active against HIV. Today, 77 (poly)hydroxyindolizidines are known, although today the number of publications related to these is more than 1000, by 1989 only 61 papers had been published since isolation of swainsonine, the first polyhydroxyindolizidine alkaloid in 1979.³

Our first results along these lines were thus obtained in connection with a synthesis of an intermediate towards (poly)hydroxyindolizidines (Scheme 1).⁴ Addition of a lithio acetylide onto an α -chiral proinal follows the polar Felkin-Anh model, favouring the *anti*-diastereomer with a diastereomer ratio of 7:1. Conversion of the propargylic alcohol to the first hydroxyindolizidine included reduction of the triple bond to a *Z*-alkene followed by protection of the secondary alcohol as an acetate and cleavage of the TBS protection. Final activation for the cyclization was performed by converting the primary alcohol to a mesylate. Then, liberation of the Boc-protection with TFA and neutralization of the salt with triethylamine effected cyclization. The temporary acetate protection was removed by mild hydrolysis with aqueous LiOH in THF. The final steps from the propargyl alcohol were achieved in 60% overall yield.

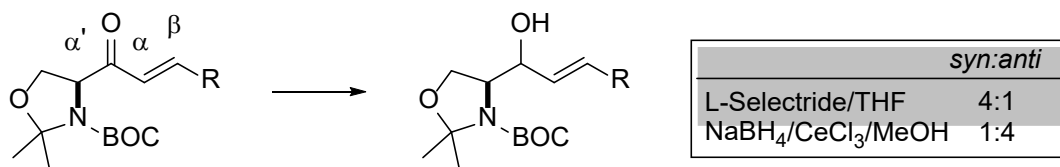


Scheme 1. First diastereoselective addition route to deoxycastanospermine derivative.

Although pleased with the diastereoselectivity, we were concerned with the fact that the chiral starting material was an aldehyde reacting with a basic nucleophile, thus making the original stereocenter vulnerable to epimerization.⁵⁻⁷

Diastereoselective Reduction of α' -chiral α,β -enones

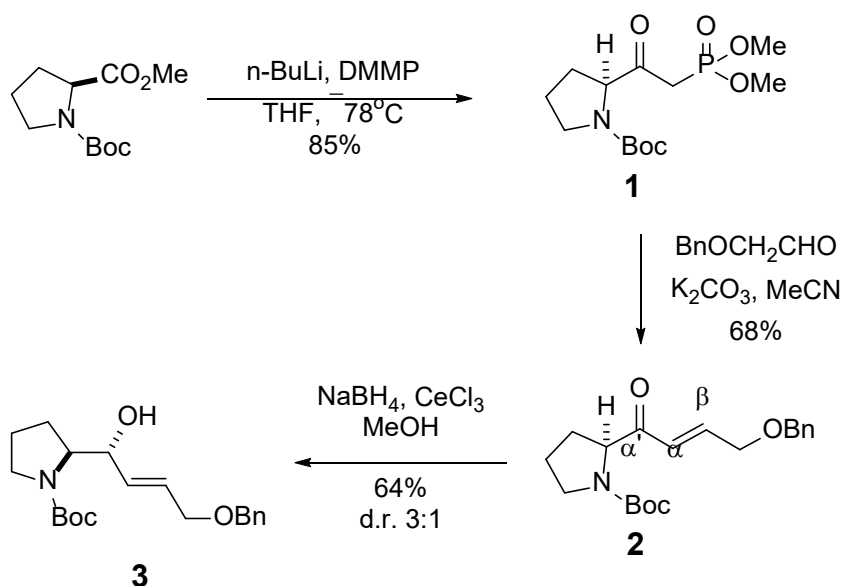
In connection with syntheses of sphingosines and their derivatives, we had earlier examined a number of hydride reduction protocols for the reduction of α' -chiral α,β -enones to allylic alcohols (Scheme 2).⁸ For serine derived enones, reproducible, albeit modest diastereoselectivities were obtained.



Scheme 2. Diastereoselective reductions of α' -chiral α,β -enones.

Although optimal protocols were found for spingosine itself (>20:1 *anti*-selectivity),⁹ the methods were highly sensitive to the nature of the substrate used in the reduction. Thus, in our later syntheses of deoxycastanospermine derivatives (Scheme 3),¹⁰⁻¹¹ the observed diastereoselectivity in the reduction was lower.

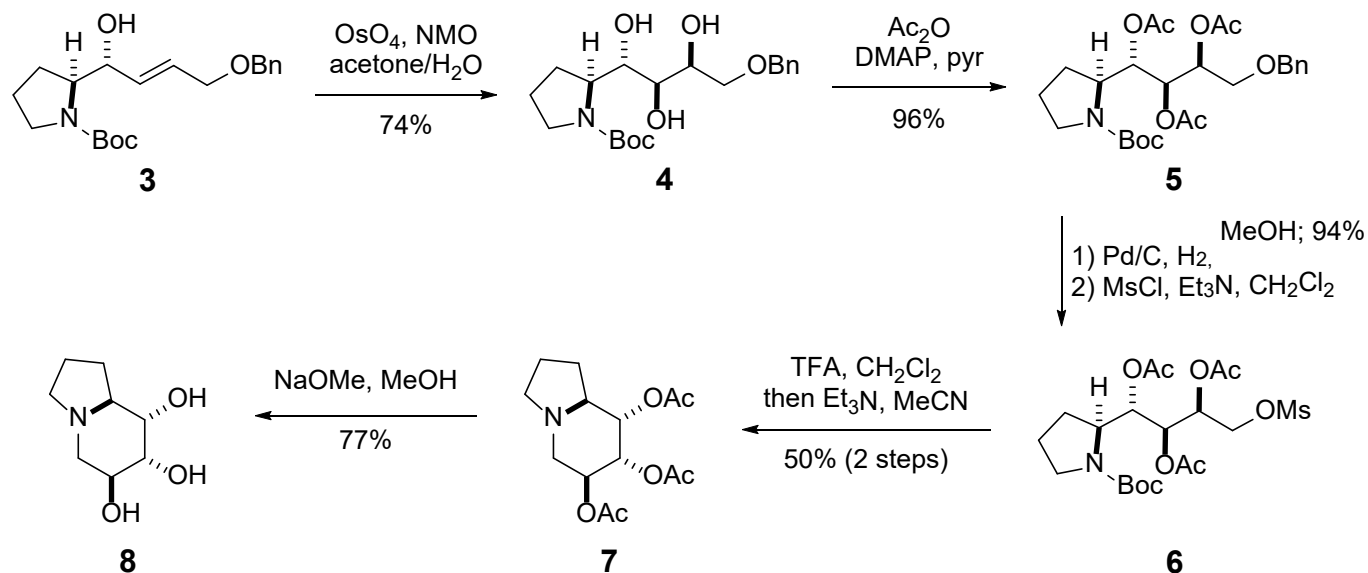
Starting from protected proline, we prepared the β -ketosphonate **1**, and converted that to the unsaturated α' -chiral α,β -unsaturated ketone **2** using a modified Horner-Wadsworth-Emmons protocol, where we used calcined potassium carbonate in acetonitrile to ensure minimal epimerization during the reaction. The key step here is to set up the stereochemistry on reduction of the enone to the amino alcohol **3**. Utilizing just sodium borohydride/cerium chloride (Luche conditions) we obtained a 3:1 ratio favouring the desired *anti*-alcohol.



Scheme 3. Diastereoselective reductions of proline derived α' -chiral α,β -enone.

We were now ready to complete the synthesis of our first deoxycastanospermine analogue following this route (Scheme 4). The *anti*-amino alcohol **3** was subjected to the Kishi-selective Upjohn dihydroxylation, and the product triol **4** was protected as the triacetate **5**. The benzyl protecting group of the primary hydroxyl group was hydrogenolyzed off and replaced with the leaving group mesylate **6**. Sequential treatment with TFA to remove the Boc protecting group followed by treatment with a base effected ring

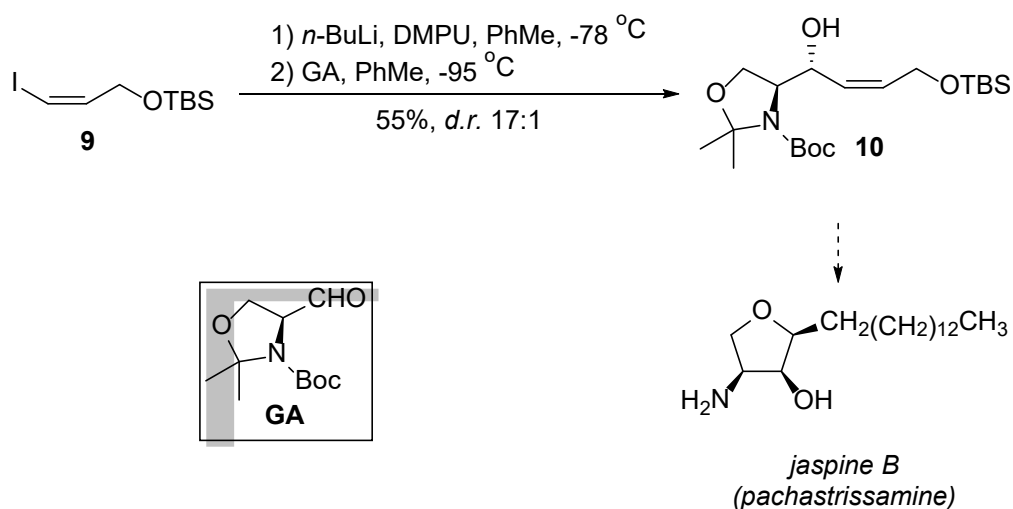
closure to the triacetate **7**. Finally, the acetates were transesterified to provide (6*S*,7*R*,8*S*,8*aS*)-octahydroindolizine-6,7,8-triol **8**.



Scheme 4. Completion of the synthesis of deoxy-*epi*-castanospermine.

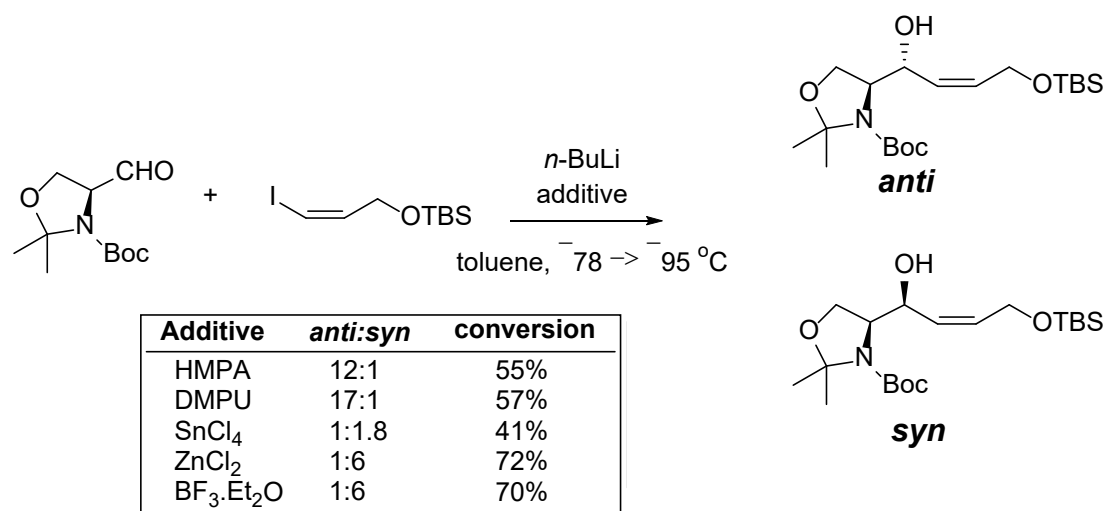
Return to the Diastereoselective Addition to Amino Aldehydes

Disappointed with the poor diastereoselectivity in the reduction of the enones, we decided to return our attention to the addition reactions onto the aldehydes, where we had obtained a 7:1 *anti:syn* ratio with a prolinal derivative. The *gem*-dimethyl group on the five membered ring of Garner's aldehyde (GA), or any similar serine derivatives, restricts the conformational freedom of the Boc protecting group. Both X-ray structures and extensive molecular modeling suggested that the carbonyl oxygen of the carbamate is placed between the *gem*-dimethyl group, thus placing the bulky *tert*-butoxy group in close proximity of the reactive carbonyl group. This effectively shields one face of the carbonyl group, which was expected to lead to improved selectivity. We further felt that increasing the steric bulk of the nucleophile to a vinyl lithium species should further increase the steric bias. This approach was successfully adopted in our synthesis of the C₁₈ anhydrosphingosine jaspine B (pachastrissamine) (Scheme 5).¹² Thus, addition of the *Z*-vinyl lithium nucleophile derived from the vinyl iodide **9** onto GA provided a 17:1 excess of the desired *anti*-product **10** in 55% yield. This was then converted to the natural product in a few efficient steps, including a Pd-mediated ring closure of the tetrahydrofuran followed by a cross metathesis. The overall yield of jaspine from GA was 20%.



Scheme 5. Efficient synthesis of Jaspine B (pachastrissamine).

Having achieved the highest *anti* selectivity so far, we became interested in finding out whether the diastereoselectivity can be inverted. Towards this end, we examined the effects of various additives in the addition reaction (Scheme 6). It turned out that addition of Lewis bases enhances the *anti*-selectivity whereas addition of Lewis acids inverts the selectivity and gives acceptable levels of the *syn* product.¹² Obviously, the role of the Lewis basic additives is to deaggregate the organolithium species, whereas the Lewis acidic additives effectively cause transmetalation to softer nucleophiles.



Scheme 6. Reversal of diastereoselectivity.

IMINOSUGARS

Iminosugars are related to sugars in the sense that the ring oxygen atom is replaced with a nitrogen atom (Figure 2).¹³ Compared to their oxygen containing relatives, these compounds are usually unstable

because of the lower electronegativity of the nitrogen atom, which donates electron density to the anomeric C-O bond, making the bond easier to cleave. One way to make the iminosugars more stable is to remove the anomeric oxygen atom altogether to form a deoxyiminosugar. Iminosugars or iminoglycosides are structural mimics of sugars, and therefore they have found applications as glycosidase inhibitors.

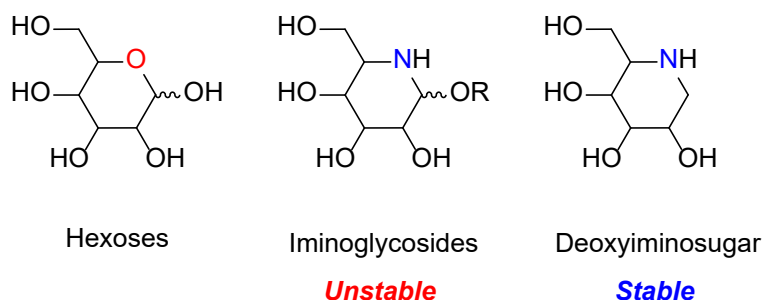


Figure 2. Sugars, iminoglycosides and deoxyiminosugars.

The first syntheses for iminosugars were reported prior to the isolation of these compounds from nature independently by Paulsen, Jones and Hanessian already in the early 1960s (Figure 3).¹⁴⁻¹⁹ Nojirimycin was isolated from *Streptomyces roseochromogenes* species after the first syntheses were reported.²⁰

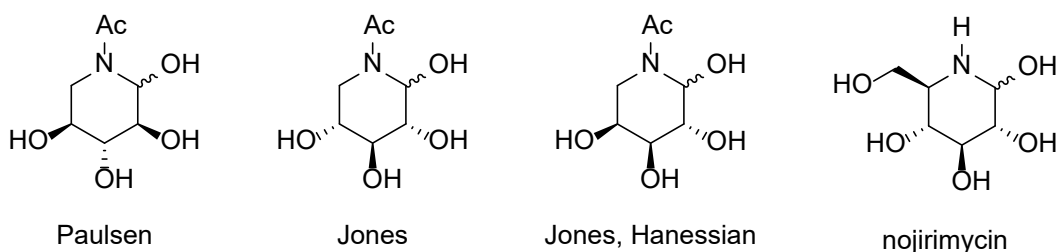


Figure 3. First iminosugars.

The iminosugars of deoxynojirimycin type constitute eight diastereomers plus another eight from the enantiomeric series. We can group the structures into two major groups (Figure 4): the ones where the relative stereochemistry of the hydroxyl group coming from the addition of the nucleophile to the aldehyde function is either *anti* or *syn* relative to the amine containing carbon. Our initial goal was to make all these compounds from serine as the starting material and preferably diverging only at a late stage intermediate.

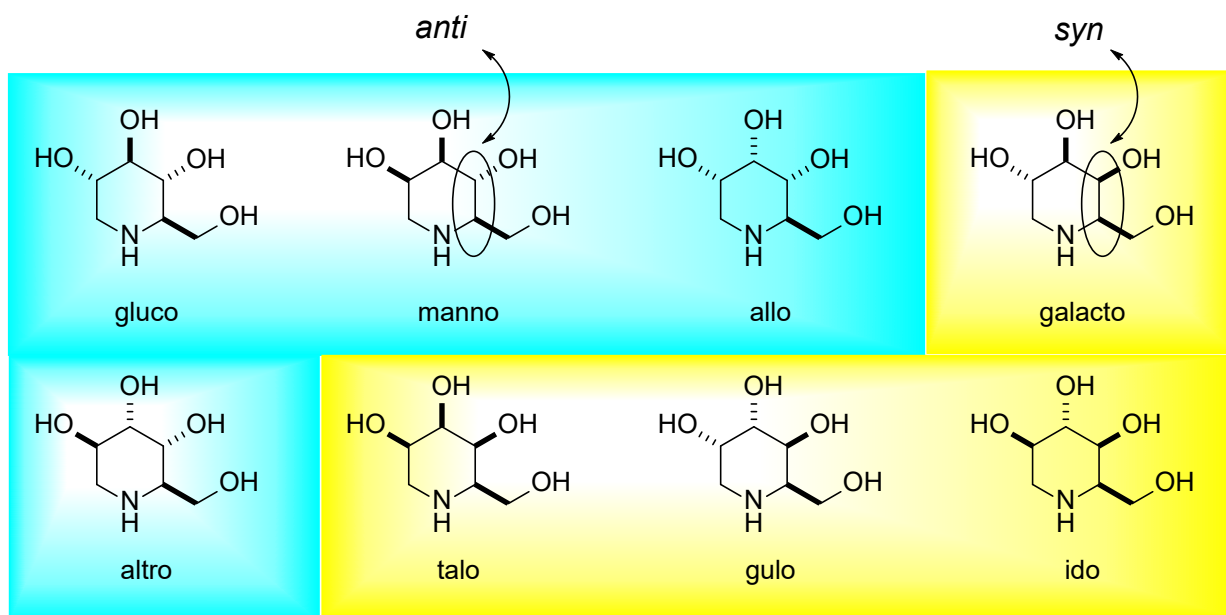
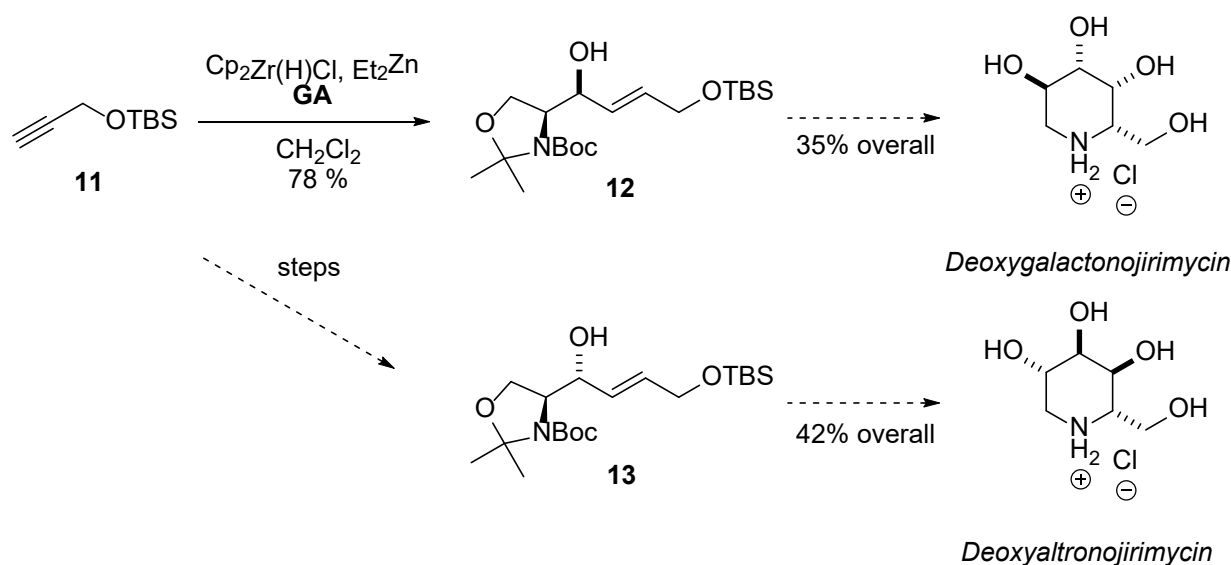


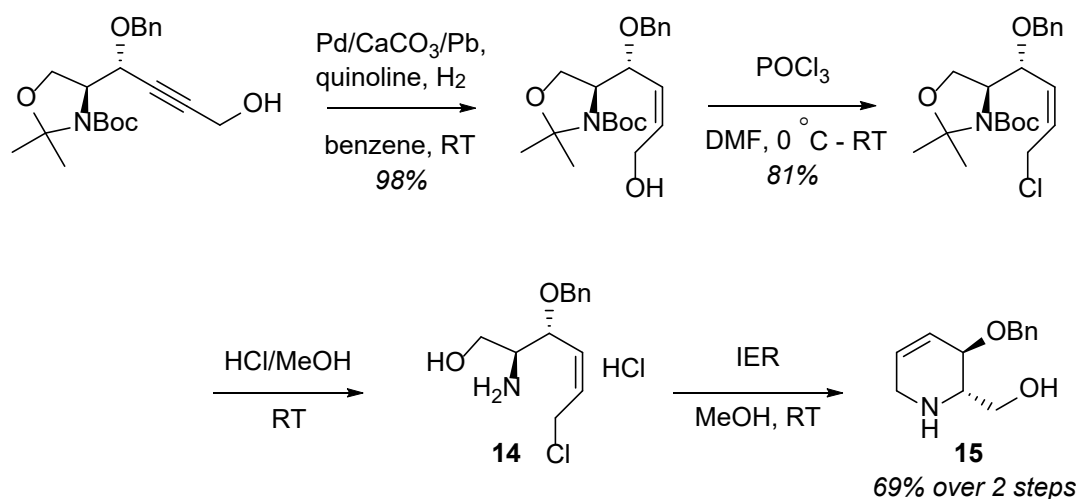
Figure 4. Deoxynojirimycin type eight diastereomers.

An improved procedure for the generation of the vinyl zinc species was sought for, and the hydrozirconation-transmetalation sequence pioneered by Peter Wipf turned out to give excellent results.²¹ Thus (Scheme 7), treatment of the TBS-protected propargyl alcohol **11** with Schwartz's reagent followed by transmetalation with diethyl zinc gave the *E* vinyl zinc species, which added onto the Garner's aldehyde with practically complete diastereoselectivity to give the *syn*-amino alcohol **12**. This high selectivity was utilized in the synthesis of deoxygalactonojirimycin,²² which was achieved in only eight steps and 35% overall yield from Garner's aldehyde. The diastereomeric vicinal amino alcohol **13** could also be obtained using the standard alkynyl lithium chemistry followed by Red-Al reduction of the triple bond to the trans double bond. The *anti*-amino alcohol **13** was efficiently converted to deoxyaltronojirimycin in nine steps with an overall yield of 42%.²³ It is also noteworthy that only two chromatographic separations were needed in this synthesis sequence.



Scheme 7. Synthesis of deoxygalacto- and altronojirimycins.

A further major breakthrough was achieved when we were able to develop an efficient synthesis of the advanced intermediate **15**. In this particular synthesis chromatographies were completely avoided, and the advanced intermediate **15** was obtained in seven steps from Garner's aldehyde in 50% overall yield. A key finding in the final ring closure stage was that instead of using soluble bases the amino alcohol hydrochloride salt **14** could be induced to undergo ring closure simply by passing through a basic ion exchange resin (IER).²⁴ The process was easily scalable two quantities of 10 grams or more.

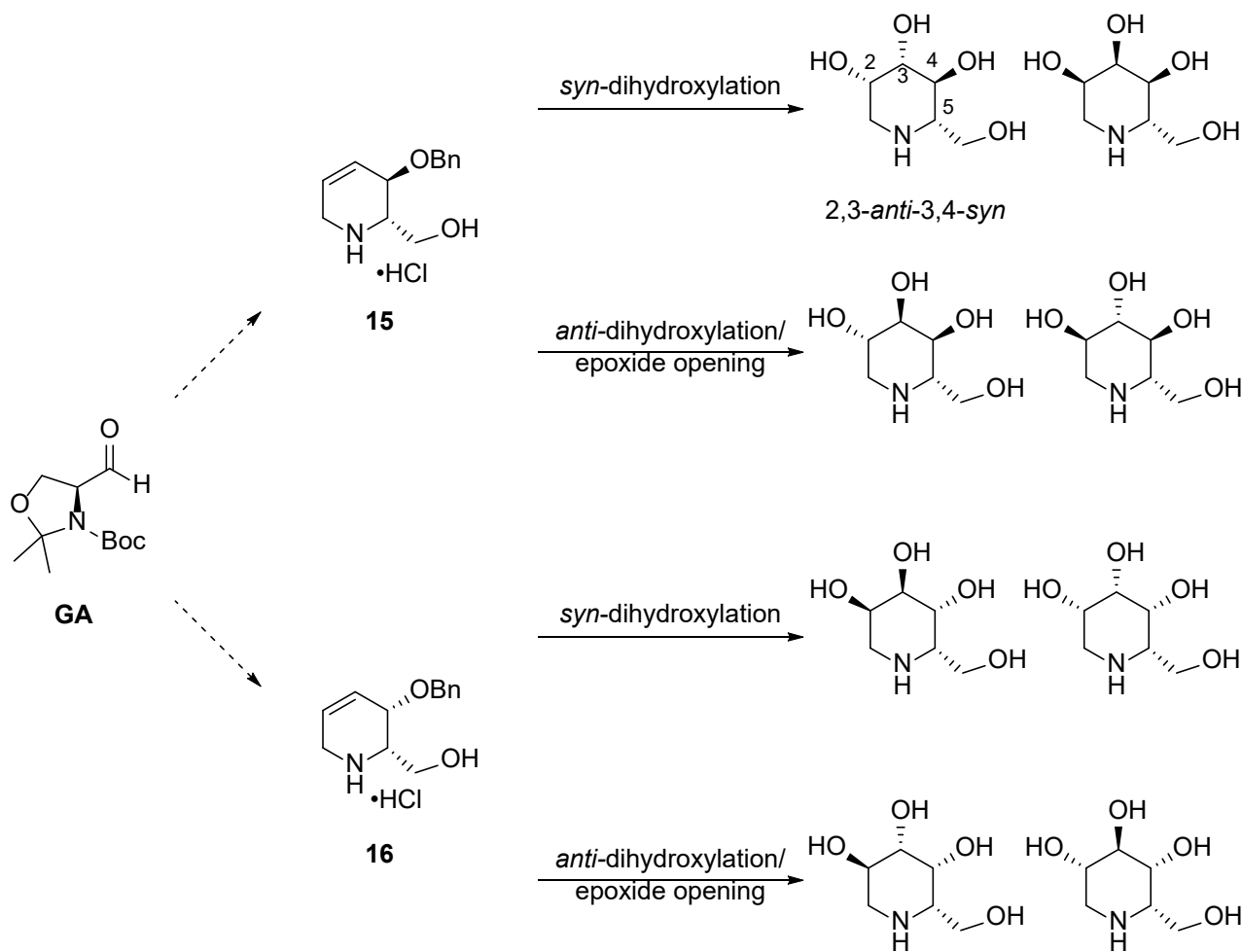


Scheme 8. Scalable synthesis of advanced intermediate **15**.

FINALE: DIVERGENT SYNTHESIS OF THE DEOXYNOJIRIMYCIN DIASTEREOMERS

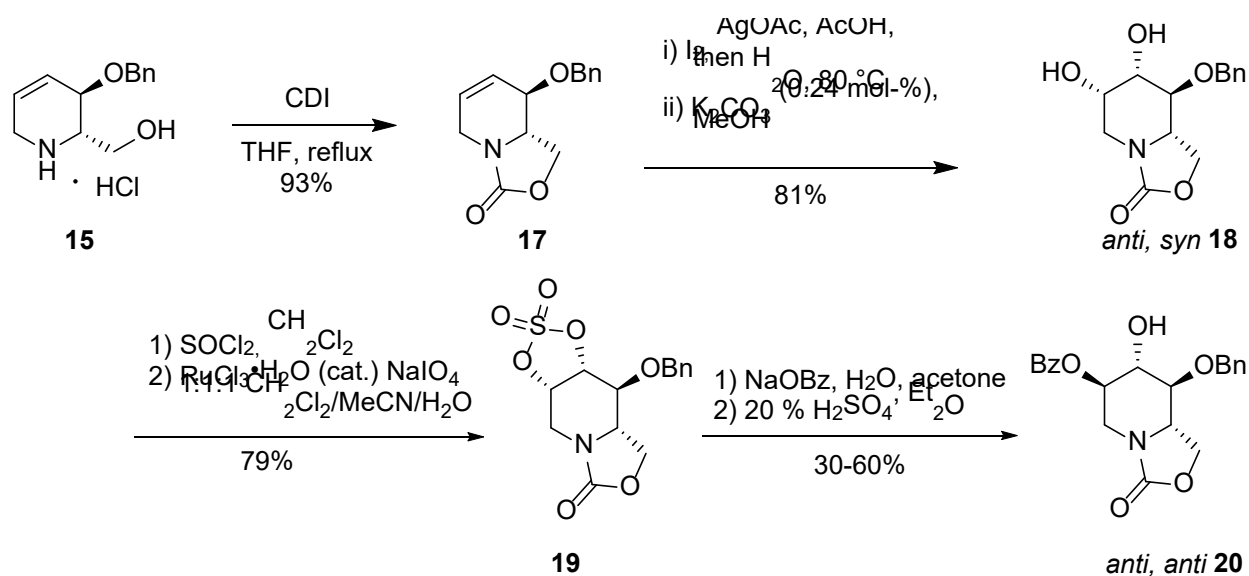
We were now set for developing divergent approaches to the different stereoisomers of the deoxynojirimycins (Scheme 9).²⁵ Starting from the Garner's aldehyde **GA**, one can make either one of the

two diastereomeric intermediates **15** or **16**, which can then be subjected to either *syn*-dihydroxylation of the allylic alcohol either following the Kishi selectivity or the anti-Kishi-selectivity. *anti*-Dihydroxylation reaction, for instance through epoxidation and epoxide opening, would allow access to the remaining four diastereomers. Thus, all eight stereoisomers of the deoxynojirimycins are achievable from the two advanced intermediates **15** and **16**. The remaining eight isomers would be obtainable from D-serine following the same chemistry.



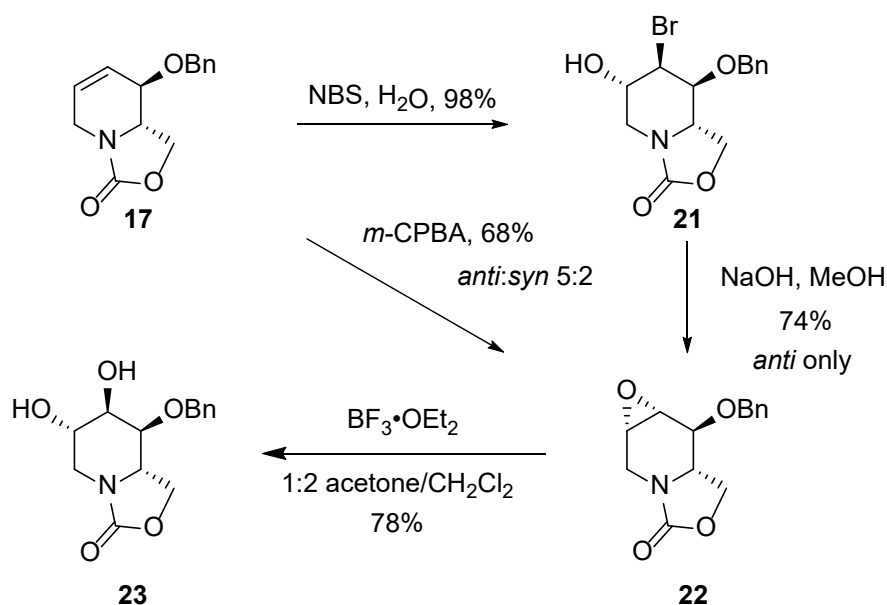
Scheme 9. Divergent route to the deoxynojirimycin diastereomers.

In order to arrive at the *anti*, *syn*- or *anti*, *anti*-series (Scheme 10) we prepared the cyclic carbamate **17** and performed a Prevost oxidation to obtain the Kishi-selective dihydroxylation *anti*, *syn*-product **18**. One of the hydroxy centers could now be inverted by going through the cyclic sulfate **19**, and opening this cyclic sulfate with sodium benzoate revealed the *anti*, *anti*-product **20**.



Scheme 10. *anti, syn*- and *anti, anti*-triols.

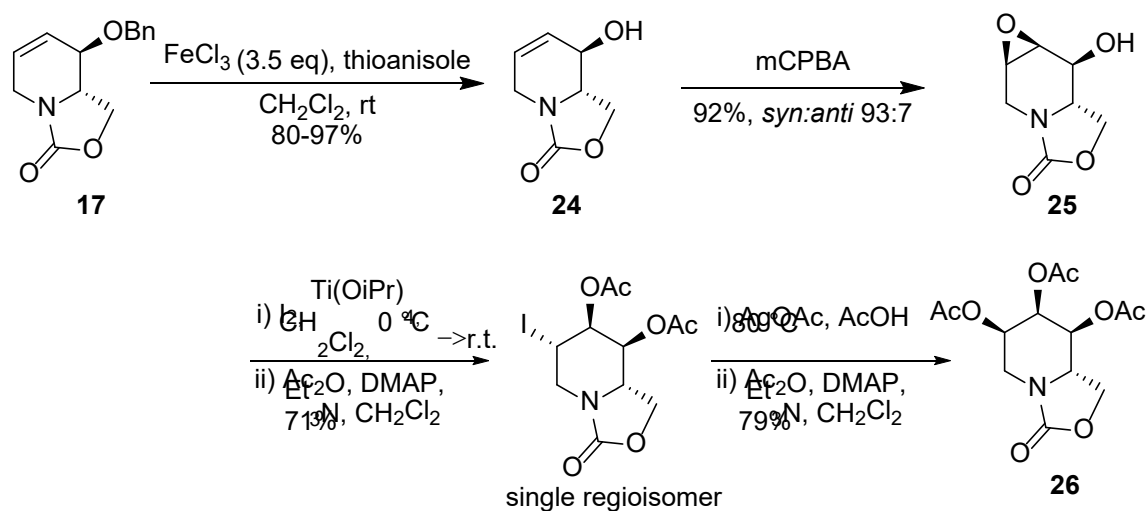
To gain access to the *syn, anti*-series, we started with the same cyclic carbamate **17**. NBS oxidation gave the halohydrin **21** in high yield, which could be ring closed to the epoxide **22** by base treatment. This provided the *anti*-epoxide **22** in 74% yield. Direct epoxidation of the allyl ether **17** with *m*-CPBA gave a poorer yield and a mixture of *anti* and *syn* isomers of the epoxide. When the epoxide **22** was treated with Lewis acid the desired *syn, anti*-diol **23** was obtained in 78% yield.



Scheme 11. *syn, anti*-triol.

Finally, for the remaining the *syn, syn*-diastereomer we needed to have a free allyl alcohol to direct the epoxidation (Scheme 12). Cleavage of the benzyl ether was achieved with ferric chloride.²⁶ The allyl alcohol **24** now underwent a clean hydroxy directed epoxidation to give a 92% yield of a separable 93:7

mixture of the *syn*- (**25**) and *anti*-epoxy alcohols. The epoxide was ring opened with iodide and then in a few steps converted to the triacetate **26**.



Scheme 12. *syn, syn*-triol.

To conclude the syntheses, the cyclic carbamate protecting groups were cleaved by hydrolysis with lithium hydroxide, which also cleaved the acetates, and the benzyl ethers were removed by hydrogenolysis under slightly acidic conditions (H_2 , Pd/C, HCl, MeOH). The corresponding 4,5-*syn*-1-deoxynojirimycin derivatives were obtained through the chelation-controlled addition of the alkynyl zinc species onto the Garner's aldehyde and then following the same protocols as described for the diastereomers in the *anti* series.

CONCLUSIONS

Eventually we had the occasion to investigate both synthetic strategies presented in Figure 1, and we made several important observations which are crucial for the eventual selection of the synthetic route (Figure 5). The amino aldehyde route is certainly disadvantaged by the fact that amino aldehydes are vulnerable to racemization and usually cannot be stored for longer periods of time. The β -keto phosphonate route seemed in this respect to be safer, but one must emphasize that handling of the β -keto phosphonates and the α' -chiral α,β -enones requires special care. It is therefore not exceptional to see enantiopurities <94 %ee. The diastereoselectivities in the reduction reactions of the enones are meager compared to the addition reactions to the aldehydes where with judicious choice of the nucleophilic species one can obtain even excellent results. Taken all these together, we were able to develop a synthetic strategy towards all diastereomers of deoxynojirimycin starting from naturally occurring serine through a divergent route with a late stage intermediate that could be prepared in large quantities and in enantiomerically pure form.

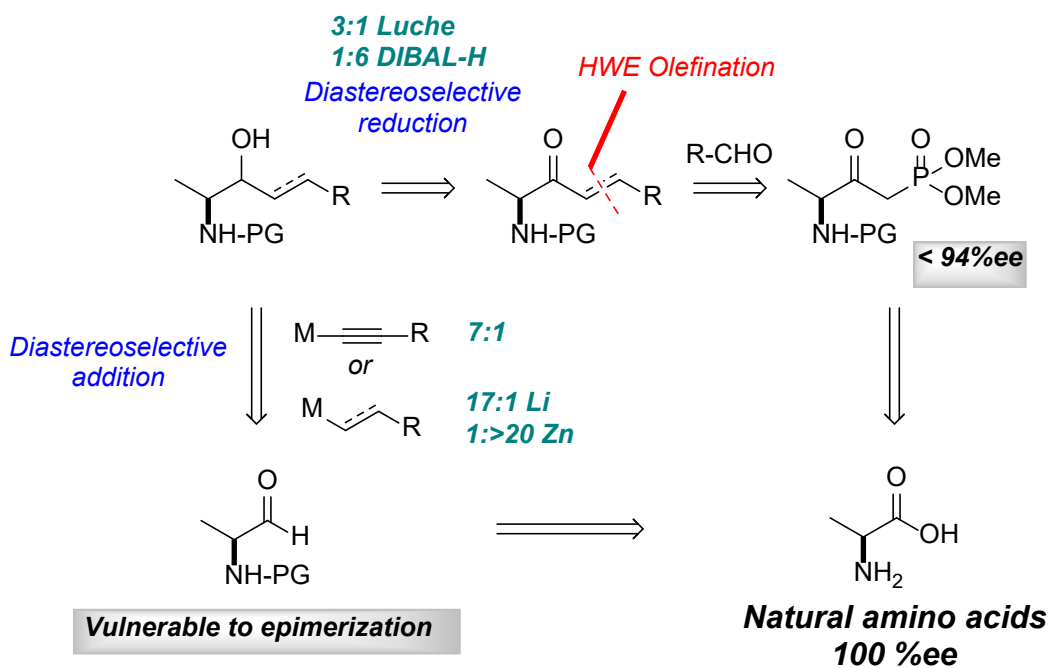


Figure 5. Realized strategies for the synthesis of vicinal amino alcohols.

After a long journey into investigating different ways of synthesizing vicinal amino alcohols from amino carbonyl compounds, we finally succeeded in developing a practical divergent route to all the diastereomers of deoxynojirimycin starting from L- or D-serine. I consider this a testimony to what Victor Hugo said that “perseverance is the secret of all triumphs”. We have had to go back several times to improve the selectivities or to avoid other pitfalls in the synthesis. This attests how true Franklin Delano Roosevelt was when he said “It is common sense to take a method and try it; if it fails, admit it frankly and try another. But above all, try something.”

ACKNOWLEDGEMENTS

The results presented in this review are the product of a large number of students in my group over the years. I wish to thank the able students B.Sc. Jane Paul, Ph.D. Päivi Koskinen, Ph.D. Oili Kallatsa, Ph.D. Mikko Passiniemi, Ph.D. Oskari Karjalainen, and Ph.D. Saara Tiuri for their skilled execution of this research. Skillful technical support for analyses have been provided by Päivi Joensuu (University of Oulu) and Tiia Seppä (Aalto University). For NMR experiments, Dr. Jari Koivisto has been instrumental in providing not only help, but also new pulse sequences. Funding for this project has been generously provided by University of Surrey, U.K., Nuffield Foundation, U.K., University of Oulu, Finland, The Finnish Academy, and Aalto University. Networking opportunities through the European collaboration within the COST framework (CM0804, CM1407) is appreciated.

REFERENCES

1. A. M. P. Koskinen, *Asymmetric Synthesis of Natural Products*, John Wiley & Sons, Ltd., Chichester, 2012, pp. 49-50.
2. Reaxys search 19.11.2020.
3. S. M. Colegate, P. R. Dorling and C. R. Huxtable, *Austr. J. Chem.*, 1979, **32**, 2257.
4. A. M. P. Koskinen and J. M. Paul, *Tetrahedron Lett.*, 1992, **33**, 6853.
5. J. Jurczak and A. Golebiowski, *Chem Rev.*, 1989, **89**, 149.
6. M. Adia, N. Hénaff, and A. Whiting, *Tetrahedron Lett.*, 1997, **38**, 3101.
7. E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.
8. A. M. P. Koskinen and P. M. Koskinen, *Tetrahedron Lett.*, 1993, **34**, 6765.
9. A. M. P. Koskinen and P. M. Koskinen, *Meth. Enzymol.* **1999**, 311, 458.
10. A. M. P. Koskinen and O.A. Kallatsa, *Tetrahedron*, 2003, **59**, 6947.
11. A. M. P. Koskinen, O.A. Kallatsa and M. Nissinen, *Tetrahedron*, 2009, **65**, 9285.
12. M. Passiniemi and A.M.P. Koskinen, *Org. Biomol. Chem.*, 2011, **9**, 1774.
13. *Iminosugars as Glycosidase Inhibitors – Nojirimycin and beyond*. A. E. Stütz (Ed.), Wiley-VCH, Weinheim, 1999, 397 pp.
14. H. Paulsen, *Angew. Chem. Int. Ed.*, 1962, **1**, 454.
15. H. Paulsen, *Angew. Chem. Int. Ed.*, 1962, **1**, 597.
16. J. K. N. Jones and J. C. Turner, *J. Chem. Soc.*, 1962, 4699.
17. J. K. N. Jones and W. A. Szarek, *Can. J. Chem.*, 1963, **41**, 636.
18. S. Hanessian and T. H. Haskell, *J. Org. Chem.*, 1963, **28**, 2604.
19. S. Hanessian *Chem. Commun.*, 1966, 796.
20. T. Nishikawa and N. Ishida, *J. Antibiotics*, 1965, **18**, 132-133.
21. P. Wipf and W. Xu, *Tetrahedron Lett.*, 1994, **35**, 5197.
22. O. K. Karjalainen, M. Passiniemi and A. M. P. Koskinen, *Org. Lett.*, 2010, **12**, 1145.
23. O. K. Karjalainen and A. M. P. Koskinen, *Org. Biomol. Chem.*, 2011, **9**, 1231.
24. O. K. Karjalainen and A. M. P. Koskinen, *Tetrahedron*, 2014, **70**, 2444.
25. S. Tiuri, Ph.D. Thesis, Aalto university, 2019. ISBN: 978-952-60-8787-0.
<http://urn.fi/URN:ISBN:978-952-60-8787-0>
26. R. Rodebaugh, J. S. Debenham and B. Fraser-Reid, B., *Tetrahedron Lett.*, 1996, **37**, 5477.