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Synthesis of polyhydroxylated pyrrolidines from sugar-derived bromonitriles through a cascade addition of allylmagnesium bromide/cyclization/reduction†‡

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The synthesis of polyhydroxylated 2-allylpyrrolidines from sugar-derived bromonitriles in a cascade addition of allylmagnesium bromide/S_N2 cyclization/reduction with $Zn(BH_4)_2$ is described. The stereochemical course of the reduction step is rationalized. Two of the obtained compounds are transformed into stereoisomers of naturally-occurring iminosugar (+)-lentiginosine. In an alternative approach, 2,2-diallylpyrrolidines are obtained from bromonitriles in a cascade addition of allylmagnesium bromide/S_N2 cyclization/addition of another equivalent of allylmagnesium bromide.

Introduction

Iminosugars belong to a vast group of organic compounds closely related to carbohydrates. They are polyhydroxylated heterocycles which, instead of an endocyclic oxygen, contain a nitrogen atom in the ring.[1] Bearing in mind the resemblance to carbohydrates, it is not surprising that iminosugars possess interesting biological properties.[2,3] For example, miglitol is used as an anti-diabetic drug,[4] whereas miglustat is applied against type 1 Gaucher disease.[5] These compounds, based on the piperidine scaffold, are derivatives of deoxynojirimycin, probably the most recognizable representative of the iminosugar family.[4,6]

Pyrrolidine-based monocyclic iminosugars have also gained attention as possible therapeutic agents. For example, derivatives of codonopsinine have been reported to possess inhibitory activity against fucosidase.[7] Recently, a new derivative of L-arabinitol with the *n*-butyl side-chain has been reported to be a potent inhibitor of intestinal maltase, isomaltase, and sucrase.[8] Moreover, polyhydroxylated derivatives of pyrrolidine often serve as precursors in the synthesis of bicyclic iminosugars.[9]

In general, the recent approaches to the synthesis of iminosugars can be categorized into S_N2 cyclizations,[10] reactions of cyclic nitrones,[11] ring-closing metathesis,[12] and cycloadditions.[13] Another methodology, which can be added to this list, relies on the use of polyhydroxylated cyclic imines. The commonly employed methods enabling the synthesis of these compounds are based on dehydrohalogenation of *N*-halogenated amines[14] and the Staudinger/aza-Wittig reaction.[15] Recently, Furman and co-workers have exploited another possibility lying in the reduction of cyclic, polyhydroxylated lactams with the Schwartz's reagent.[16]

Cyclic imines can also be formed as a result of the addition of Grignard reagents to ω-halonitriles.[17] This cascade transformation is rarely used, with only a few examples in the literature.[18] Having recognized the research potential lying in this field, we began to examine it more closely. In our recent paper,[19] we have presented a divergent methodology enabling the synthesis of D-xylose-derived piperidines **3** and **4** (Scheme 1), versatile intermediates in the synthesis of bicyclic iminosugars, including (−)-castanospermine.[20,21]

The transformation consists of the addition of allylmagnesium bromide to ω-bromonitrile **1**, followed by an intramolecular S_N2 cyclization. The transitional imine **2** can be either reduced to 2-allyl-substituted amine **3** or it can accept another equivalent of allylmagnesium bromide to form the 2,2-diallyl-substituted product **4**. To the best of our knowledge, it is the first successful application of an allylmagnesium halide in the context of this transformation. In this paper, we present our further studies in this area, expanding the product scope to polyhydroxylated pyrrolidines.

Results and discussion

Synthesis of bromonitriles from a chiral pool

As we have previously shown,[19] polyhydroxylated ω-bromonitriles can be easily obtained in a two-step sequence from the

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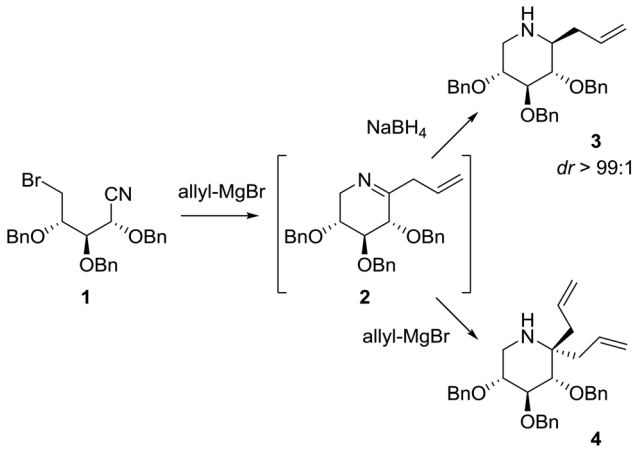
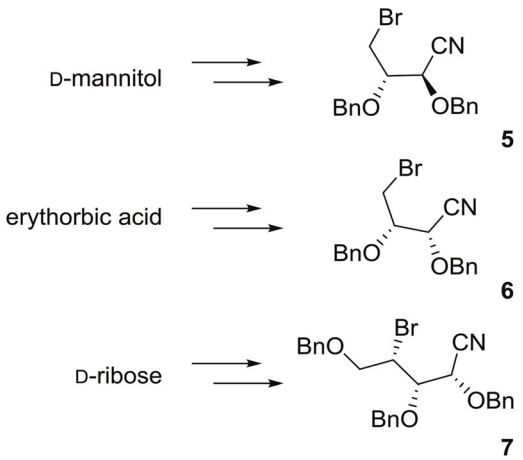
†This paper is dedicated to Professor Janusz Jurczak on the occasion of his 75th birthday.

‡Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c5ob02573g



Scheme 1 Cascade addition of allylmagnesium bromide/cyclization and subsequent reactions.



Scheme 2 Planned synthesis of bromonitriles from natural substrates.

suitably protected carbohydrates. First, the free hemiacetal reacts with hydroxylamine to form an oxime which subsequently is treated with CBr_4/Ph_3P (Appel conditions). The latter transformation results in the substitution of the terminal hydroxyl group and dehydration of the oxime moiety. A similar approach has already been reported in the synthesis of 5- and 6-*O*-methanesulfonylglyconononitriles.[22,23] In these reports, mesyl chloride was used to enable dehydration of oximes.

We envisaged that ω-bromonitriles **5**, **6** (shorter analogs of **1**), and **7** (in which the halogen atom is attached to the secondary carbon atom) can be easily obtained from the chiral pool in a similar way (Scheme 2).

The synthesis of nitrile **5** was initiated from 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene D-mannitol derivative **8** (Scheme 3).[24] Then, both isopropylidene moieties were removed in a single step yielding compound **9**. This product was subjected, without purification, to oxidative cleavage with $NaIO_4$. The resulting hemiacetal was reduced with $NaBH_4$ to afford triol **10** (59% after 3 steps). Then, the cleavage of the 1,2-diol moiety provided hemiacetal **11**, which was reacted with hydroxylamine. The obtained crude oxime was subjected to the Appel conditions (CBr_4/Ph_3P), which yielded the desired derivative **5** in good overall yield (60% after 3 steps). This approach consists of several straightforward, easy to perform steps and enables the synthesis of multigram quantities of **5**.

The synthesis of compound **6** started from erythorbic acid, a naturally occurring diastereoisomer of L-ascorbic acid. It was transformed, *via* known procedures,[25,26] into the protected D-erythronolactone **12** (Scheme 4). The subsequent reduction of this derivative with DIBAL-H led to a hemiacetal, which was converted into an oxime by reaction with hydroxylamine. Treatment of the latter with CBr_4/Ph_3P afforded the desired ω-bromonitrile **6** in good overall yield (72% over 3 steps). This approach is also easily scalable and allows us to obtain multigram quantities of **6**.

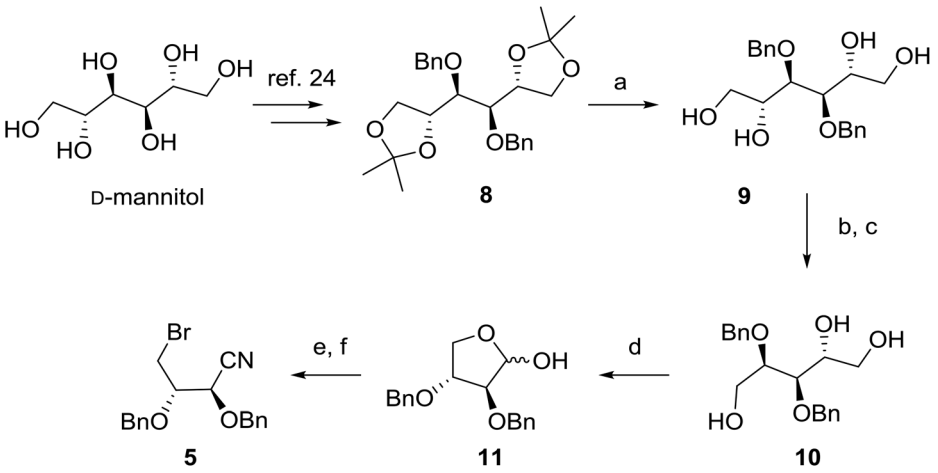
Then, we turned our attention to the synthesis of ω-bromonitrile **7**. This synthetic route started from D-ribose, which was transformed into known tri-*O*-benzyl derivative **13** (Scheme 5).[15c] This compound was reacted with hydroxylamine and the resulting crude oxime was subjected to the Appel conditions (CBr_4/Ph_3P). As a result of this two-step sequence, compound **7** was obtained in good yield (72% after 2 steps) and in multigram quantities.

Addition of allylmagnesium bromide to sugar-derived bromonitriles

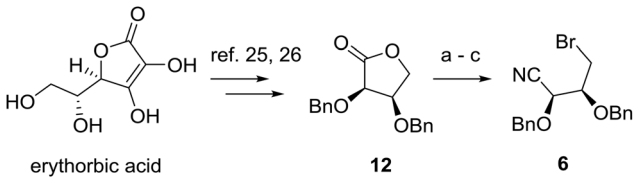
Having established the reliable synthetic routes to ω-bromonitriles **5**, **6**, and **7**, we started to study the title reaction. In the initial attempt, we followed the procedure described for the transformation of **1** into **3** (see Scheme 1).[19] As we have already reported, polar solvents (such as THF) promote the addition of an additional equivalent of allyl-MgBr to the transitional imine **2**, whereas apolar solvents (toluene, DCM) should be used for transformation of **1** into **3**.[19] Most notably, when a solution of bromonitrile **1** in toluene was treated with allyl-MgBr (1.3 equiv.) and subsequently with MeOH/$NaBH_4$, amine **3** was formed in 74% yield (dr > 99 : 1), with only 4% of diallyl derivative **4** as a by-product. Following this procedure, we added allylmagnesium bromide solution in Et_2O (1 M, 1.3 equiv.) to a solution of **5** in toluene at 0 °C. After 75 min of stirring, methanol and $NaBH_4$ were added to the reaction mixture. This approach turned out to be much less selective and provided a mixture of 2,2-diallylpyrrolidine **14** (22%) and 2-allylpyrrolidine **15** (35%, dr = 4 : 1 as based on ^{1}H-NMR) (Scheme 6).

In contrast to our previous observations,[19] imine **16** appears to react rapidly with the second equivalent of allyl-MgBr even in a relatively non-polar solvent such as toluene. Therefore, we reasoned that this reaction should be carried out, right from the beginning, in the presence of the excess of the reducing agent (Scheme 7), which may surpass the formation of a 2,2-diallyl-substituted product.

The choice of a suitable reducing agent was, however, a challenging task. First of all, it had to react with the transi-

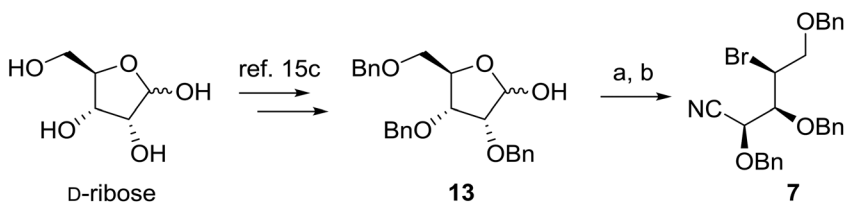


Scheme 3 Reagents and conditions: (a) conc. HCl, MeOH, 65 °C, 1 d; (b) $NaIO_4$, sat. $NaHCO_3$, DCM, rt, 2 h; (c) $NaBH_4$, MeOH, rt, 1 h, 59% (3 steps); (d) $NaIO_4$, sat. $NaHCO_3$, DCM, rt, 48 h; (e) $NH_2OH{\cdot}HCl$, py, rt, 24 h; (f) CBr_4, Ph_3P, MeCN, rt, 24 h, 60% (3 steps).

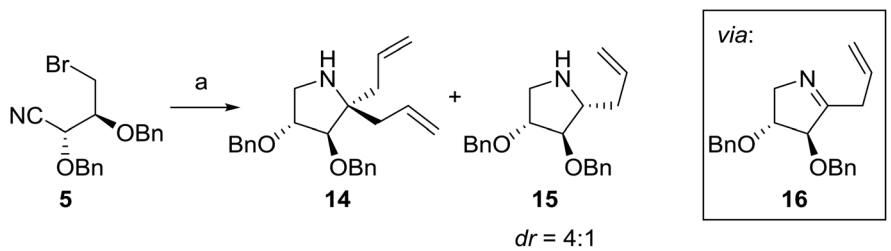


Scheme 4 Reagents and conditions: (a) DIBAL-H, DCM, −78 °C, 1 h; (b) $NH_2OH{\cdot}HCl$, py, rt, 24 h; (c) CBr_4, Ph_3P, MeCN, rt, 24 h, 72% (3 steps).

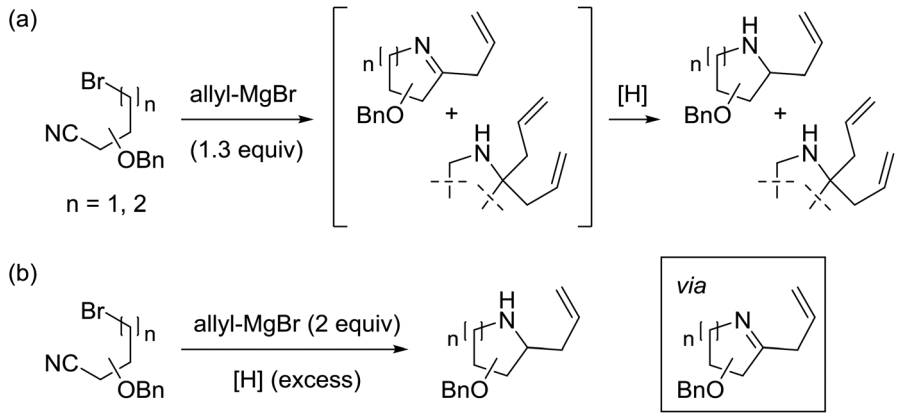
tional imine **16** faster than the second equivalent of allyl-MgBr does. Moreover, it had to be unreactive towards nitriles (which excludes $LiAlH_4$ and DIBAL-H) and compatible with Grignard reagents. In the light of these considerations, we decided to test the following reductants: $Et_3SiH/BF_3{\cdot}Et_2O$, $Et_3SiH/TiCl_4$, $Et_3SiH/SnCl_4$, L-selectride, $LiBH_4$, $BH_3{\cdot}THF$, and $BH_3{\cdot}Me_2S$, in various solvents (DCM, Et_2O, THF, and toluene) and in a wide range of temperatures (−78 °C to rt). The obtained results were unsatisfying, either complicated mixtures were formed or a 2,2-diallyl-substituted derivative was the major product. However, we were pleased to observe that the addition of allylmagnesium bromide to the solution of **5** in toluene, in the presence of the excess of freshly prepared zinc borohydride $[Zn(BH_4)_2]$; 4 equiv.], at 0 °C, yielded 2-allylpyrrolidine **15** in much better yield (67%), with only traces (<5%) of the 2,2-diallyl-substituted derivative **14** (Scheme 8). Zinc borohydride



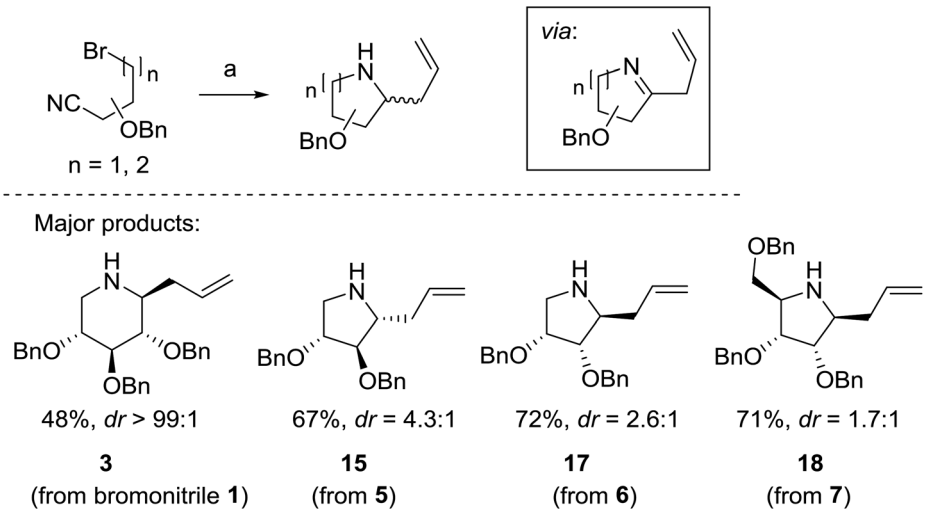
Scheme 5 Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, py, rt, 24 h; (b) CBr_4, Ph_3P, MeCN, 45 °C, 24 h, 53% (2 steps).



Scheme 6 Reagents and conditions: (a) allyl-MgBr (1.3 equiv.), toluene, 0 °C, 75 min, then MeOH, $NaBH_4$, rt, 10 min, 22% (**14**), 35% (**15**, dr = 4 : 1).



Scheme 7 (a) Sequential mode of the reaction: a slight excess of allyl-MgBr is first added and then, once the addition is completed, it is followed by a reductant; this approach suffers from the formation of diallyl derivatives as byproducts. (b) Approach, in which the excess of the reductant is already present during the addition of allyl-MgBr; the formation of diallyl derivatives can be eliminated.



Scheme 8 Diastereoselectivities based on ^{1}H-NMR. Reagents and conditions: (a) allyl-MgBr (1 M solution in Et_2O, 2 equiv.), toluene, $Zn(BH_4)_2$ (4 equiv.), 0 °C, 1 h.

is known to be a mild reducing agent, soluble in many organic solvents (in opposition to $NaBH_4$).[27] In particular, it has already been successfully applied to reduction of imines.[28]

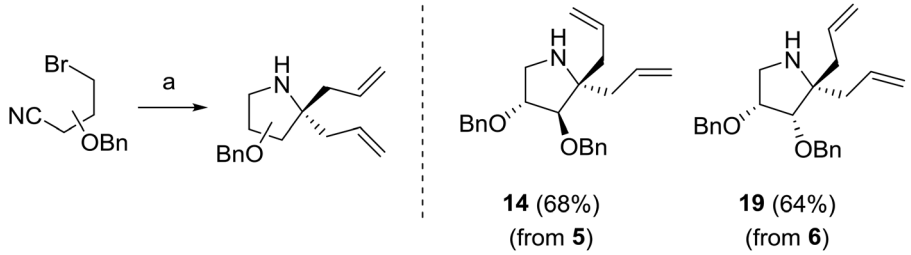
ω-Bromonitriles **6** and **7** were converted similarly into the corresponding 2-allylpyrrolidines **17** and **18** (Scheme 8). By this general procedure, piperidine **3** was also obtained in fair yield and excellent diastereoselectivity. The diallyl products were formed only in minute amounts (less than 5%) in all these reactions.

On the other hand, when compounds **5** and **6** (dissolved in a mixture of THF and DMPU, as previously described for the transformation of **1** into **4**)[19] were treated with a larger excess of allyl-MgBr (5 equiv.), 2,2-diallyl-substituted products **14** and **19** were formed in good yields (Scheme 9).

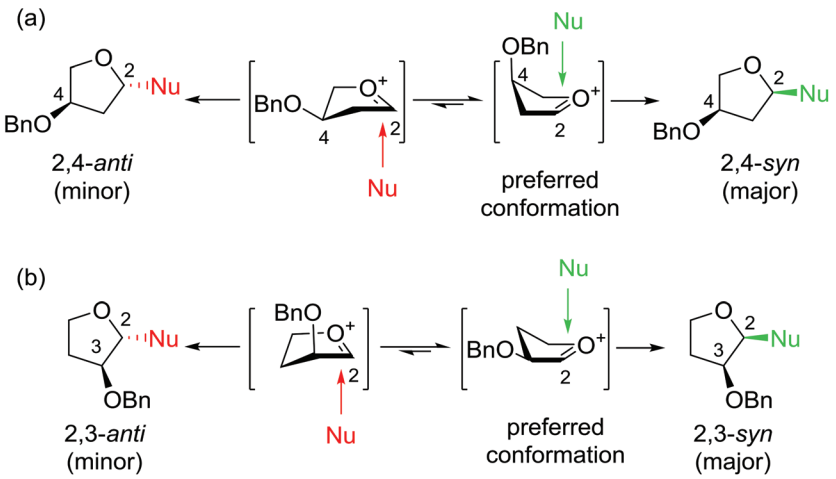
Compounds **15**, **17**, and **18** were formed as inseparable mixtures of diastereoisomers and we were not able to determine the configurations at the newly formed stereogenic centers at this point. In the case of compounds **15** and **17** we assigned them at a later stage, after their transformation into bicyclic derivatives (see Schemes 15 and 16). Derivative **18** was already reported in the literature,[16a] which allowed for the safe assignment of the structure by comparison of the NMR spectra.

Stereochemical course of the reaction

It has been established by Woerpel and co-workers that the nucleophilic addition to the endocyclic oxocarbenium cations in the five-membered rings proceeds from the inside of the envelope (Scheme 10).[29] 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 10a). As a result, the 2,4-*syn* product is formed predominantly. Although the presence of other groups



Scheme 9 Reagents and conditions: (a) allyl-MgBr (1 M in Et_2O, 5 equiv.), THF/DMPU, 0 °C, 1 h.



Scheme 10 Woerpel's observations:[29] (a) Pseudo-axial orientation of the alkoxy substituent at C-4 is preferred and plays the dominant role even in the presence of other substituents. (b) In the absence of the alkoxy group at C-4, the substituent at C-3 governs the diastereoselectivity.

at the C-3 and C-5 centers also has (to some extent) influence on the direction of the addition to multiple substituted substrates, 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 10b).

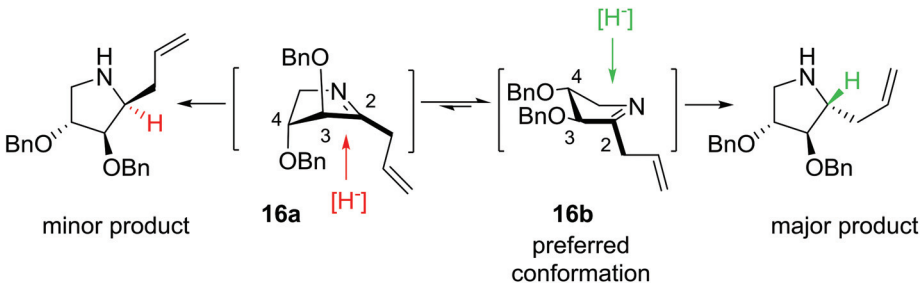
Furman and co-workers,[16c] as well as van der Marel and Codée,[15c] in their work concerning the nucleophilic addition to cyclic imines, extended the Woerpel's model to the area of nitrogen heterocycles, in order to explain the stereochemistry of the obtained pyrrolidines and piperidines. It has to be noted, though, that both groups carried out the reactions with an excess of an acid, so the iminium cations (analogs of oxocarbenium cations) were *de facto* the reactive species. Our approach, on the contrary, is carried out under basic conditions, so the stabilizing role of the substituent at the C-4 is not justified. As a result, other substituents may affect the diastereoselectivity to a much higher degree than they do in the Woerpel's model.

Indeed, the reduction of imine **16** (resulting from the reaction of bromonitrile **5**) led to a product, in which the nucleophile (hydride anion) is in an *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 the pseudo-equatorial orientations (conformation **16b**, Scheme 11).

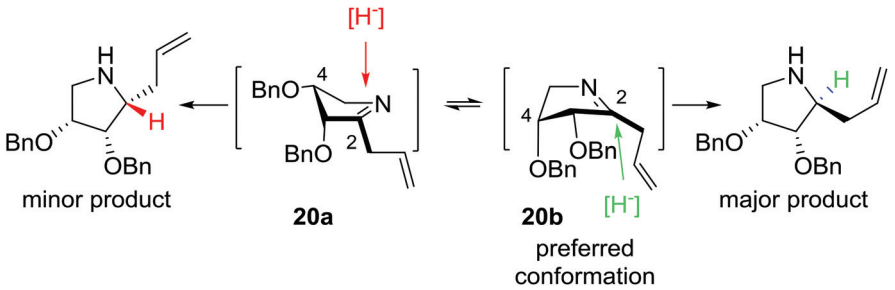
The reduction of imine **20** (resulting from the reaction of bromonitrile **6**) proceeds with a moderate diastereoselectivity (dr = 2.6 : 1) (Scheme 12). Conformer **20b** seems to be preferred, so the product in which the allyl side-chain is in an *anti*-relation to the benzyl groups at the C-3 and C-4, prevails in the mixture.

In the case of imine **21** (resulting from the reaction of bromonitrile **7**), the stereoselectivity was much worse (dr = 1.7 : 1); none of the envelope conformers (3-ax, 4-eq, 5-eq in **21a** and 3-eq, 4-ax, 5-ax in **21b**) appears to be particularly preferred (Scheme 13).

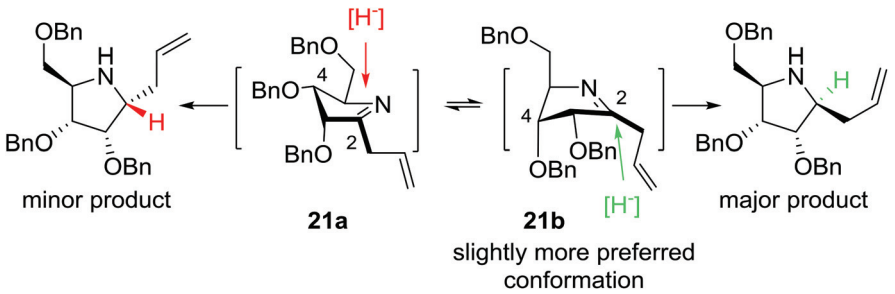
All in all, somewhat contrary to the Woerpel's model (oxocarbenium cations)[29] and observations regarding reactions of iminium cations,[15c,16c] the reduction of imines **16**, **20**, and **21** leads predominantly to the products, in which the nucleophile has consistently the *syn* relationship with the group at the C-3. Its directing role is most strikingly visible in the formation of **15** (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.



Scheme 11 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).



Scheme 12 The envelope conformation **20b** is preferable (dr = 2.6 : 1).



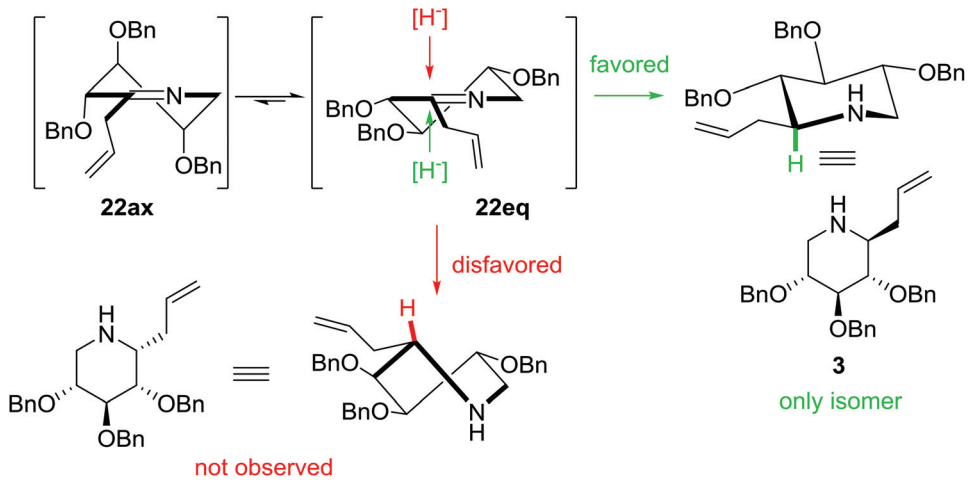
Scheme 13 The envelope conformation **21b** is preferable (dr = 1.7 : 1).

Then, we turned our attention to explain the excellent diastereoselectivity of the transformation of **1** into **3** (dr > 99 : 1, configuration assigned in our previous report;[19] see Scheme 1). Such a high diastereoselectivity has already been observed by Davis in the addition of nucleophiles to the endocyclic C=N bonds in polyhydroxylated compounds.[30] A similar phenomenon was observed by Cheng's group in the study concerning the addition of Grignard reagents to cyclic nitrones;[31] a closely related reaction was also examined by Py and co-workers.[11b] Therefore, we assumed that in the case of imine **22** (resulting from the reaction of bromonitrile **1**), the preferred conformer is the one, in which the benzyloxy substituents are placed in the pseudo-equatorial positions (**22eq**; as in Davis' model)[30] (Scheme 14). Although the electronic effects may impose a pseudo-axial position at the C-3, C-4 and – as a consequence – at the C-2,[32] the 1,3-diaxial interactions probably strongly discourage the formation of the all-pseudo-axial conformer **22ax**.

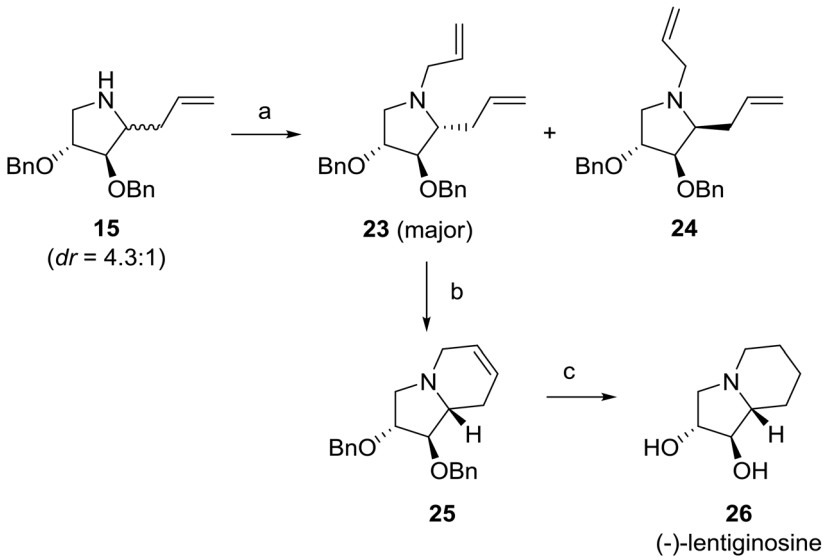
The attack of the hydride anion on the imine moiety proceeds through a much more favored, chair-like transition state rather than *via* a twisted-boat conformation.[33] Such a phenomenon is also observed in the opening of the ring of cyclohexene-derived epoxides (it is known as *trans*-diaxial rule).[34]

Synthesis of lentiginosine

The obtained 2-allylpyrrolidines **15** and **17** can serve as precursors in the synthesis of diastereoisomers of alkaloid lentiginosine.[35] We reasoned that a protocol consisting of an *N*-allylation, ring-closing metathesis, and reduction/deprotection sequence should be sufficient to yield this alkaloid. Indeed, the allylation of **15** (used as a mixture of diastereoisomers) proceeded smoothly and yielded *N*-allyl derivatives



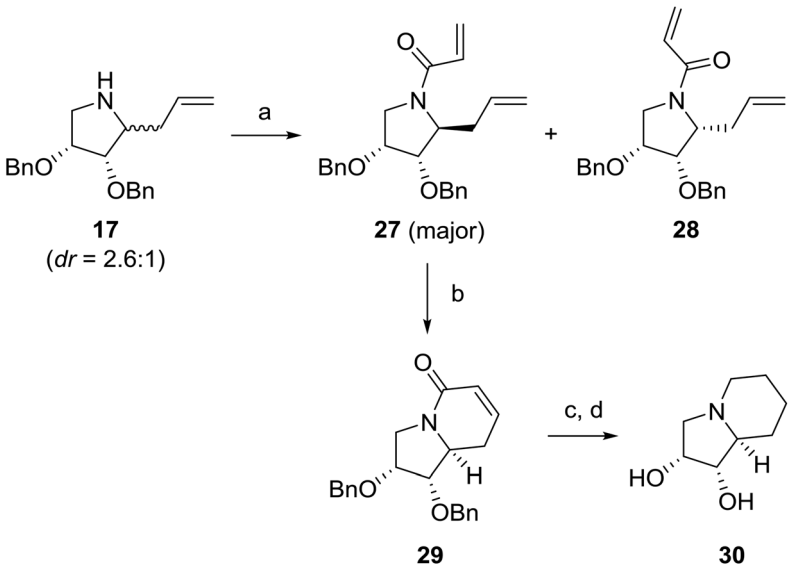
Scheme 14 Possible course of the highly stereoselective reduction of imine **22**.



Scheme 15 Reagents and conditions: (a) allyl bromide, MeCN, K_2CO_3, rt, 24 h, 55% (**23**), 13% (**24**); (b) TFA, Grubbs–Hoveyda II cat. (5 mol%), toluene, 60 °C, 12 h, 94%; (c) H_2, $Pd(OH)_2/C$, MeOH, rt, 12 h, 91%.

23 and **24** as a separable mixture of diastereoisomers (Scheme 15). The subsequent RCM process turned out to be more challenging. Our initial attempts performed on derivative **23** (in the form of TFA ammonium salt) with the use of the Grubbs II catalyst (10 mol%) gave the desired product **25**, but in moderate yield (44%, conversion 60%). It is known that amines are challenging substrates in olefin metathesis.[36] However, the reaction induced by the Hoveyda–Grubbs II catalyst (5 mol%) led to the desired bicyclic compound **25** in excellent yield (94%). In the next step, the reduction of the double bond with simultaneous debenzylation gave (−)-lentiginosine **26**. This way, we were able to unambiguously assign the configuration at the C-2 in **15** by comparison of **26** with the literature data (see Experimental for details).

Then, we tried to apply the same procedure to compound **17** (Scheme 16). Unfortunately, we were unable to obtain the *N*-allylated products in good yields; a complicated mixture of products was formed. Therefore, we decided to use a procedure described by Singh.[37] Derivative **17** (as a mixture of diastereoisomers) was subjected to the reaction with acryloyl chloride, furnishing compounds **27** and **28**, which were easily separated by chromatography. Then, the RCM process with the Grubbs II catalyst (5 mol%) was performed on the major isomer to give the bicyclic compound **29**, which was subsequently subjected to hydrogenation over $Pd(OH)_2/C$. The final reduction of the lactam group with $LiAlH_4$ gave the final target: 2-*epi*-lentiginosine **30**. This way, we were able to unambiguously assign the configuration at the C-2 in **17** by



Scheme 16 Reagents and conditions: (a) acryloyl chloride, DCM, Et_3N, rt, 30 min, 53% (**27**), 21% (**28**); (b) Grubbs II cat. (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).

comparison of **30** with the literature data (see Experimental for details).

Conclusion

In this report, we have demonstrated that the methodology consisting of an addition of allyl-MgBr to sugar-derived bromonitriles can be extended to the synthesis of 2-allyl- and 2,2-diallyl-substituted pyrrolidines. The monosubstituted derivatives are available by modification of our previously reported method.[19] Namely, the solution of allyl-MgBr was added to a mixture of bromonitrile and an excess of $Zn(BH_4)_2$. This methodology, in contrast to the previous one (sequential mode of addition), does not suffer from the formation of disubstituted products. On the other hand, when the excess of allyl-MgBr is added to the solution of bromonitrile in THF/DMPU, disubstituted products are formed in good yields. To sum up, the transformation we have proposed enables, depending on the applied conditions, the synthesis of either 2-allyl or 2,2-diallyl iminosugars.

Experimental

General information

NMR spectra were recorded with 600 and 500 MHz apparatus in $CDCl_3$ or D_2O. The chemical shifts (δ) in the ^1H spectra are reported in ppm relative to Me_4Si (δ 0.00) for $CDCl_3$; in the case of D_2O, the chemical shift of the lock solvent was used as a reference. The chemical shifts (δ) in the ^{13}C spectra are reported in ppm relative to residual non-deuterated solvents: 77.0 for $CDCl_3$; in the case of D_2O, the 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. Mass spectra were recorded with a MALDI Synapt G2-S HDMS (Waters). Melting points were measured with a SRS OptiMelt and are uncorrected. Optical rotations were measured in dichloromethane (unless otherwise stated) with a Jasco P-1020, using sodium light (c = 1). Elemental analyses were performed with an Elementar Vario ELIII. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, and ABCR. Dry solvents were purchased from Sigma-Aldrich and used as obtained. Hexanes (fraction from petroleum) and EtOAc 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 plates were developed with a Ce–Mo developer or with $KMnO_4$ (for compounds with low molecular weight). The 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 the Grace Reveleris X2 system (UV and ELSD detection); a linear gradient was applied to modulate the solvent strength.

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. The flask was subsequently filled with argon, and then dry Et_2O (100 mL) was added; the resulting suspension was vigorously stirred at 30 °C for 24 h. Then, the mixture was cooled to room temperature and undissolved solids were allowed to sediment. The mixture

was stored under an argon atmosphere and used within a week. The clear solution of $ZnCl_2$ was collected with a syringe and used in the next step.

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

This procedure was carried out under an argon atmosphere in a flame-dried Schlenk flask, closed with a rubber septum and equipped with a large stirring bar. To a vigorously stirred suspension of $NaBH_4$ (440 mg, 11.6 mmol, powder – as dry as possible) in dry Et_2O (15 mL), a freshly prepared 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.

Procedure A – synthesis of ω-bromonitriles from cyclic hemiacetals

Hemiacetal (10 mmol) was dissolved in dry pyridine (40 mL) to which 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 1 M H_2SO_4 (50 mL), water (50 mL), brine (25 mL), dried, and concentrated. The crude oxime (in the form of a white solid) was dissolved in MeCN (100 mL) to which 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 the reaction leading to **5** and **6**; at 45 °C in the case of **7**). 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 the desired ω-bromonitrile.

Procedure B – synthesis of 2-allyl-substituted heterocycles from ω-bromonitriles

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

Procedure C – synthesis of the 2,2-diallyl-substituted pyrrolidines from ω-bromonitriles

To a solution of ω-bromonitrile (1 mmol) in dry THF (8 mL), dry DMPU was added (2 mL) under an argon atmosphere, and the resulting mixture was cooled to 0 °C. Then, a solution of allylmagnesium bromide (1 M solution in diethyl ether, 5 mL, 5 equiv.) was added under vigorous stirring over 60 min (syringe pump); a white, thick solid precipitated during addition (a large stirring bar needed to ensure proper stirring). Stirring was continued for another 30 min at 0 °C, and 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). The combined organic solutions were washed with water (2 × 20 mL), brine, dried, and concentrated and the residue was subjected to flash chromatography (100% hexanes to 100% ethyl acetate).

(2*R*,3*R*,4*R*)-3,4-Dibenzyloxypentane-1,2,5-triol (10). To the solution of fully protected mannitol **8** (12.5 g, 28.3 mmol) in MeOH (150 mL), conc. HCl (2 mL) was added at rt, and the mixture was heated to 65 °C for 24 h. Then, the mixture was cooled to rt and concentrated. Toluene (20 mL) was added to the residue and the solution was once again concentrated in order to remove the traces of water; this procedure was repeated 3 times. Crude product **9** was dissolved in DCM (85 mL) and sat. aq. $NaHCO_3$ was added to make it slightly basic pH. Then, $NaIO_4$ (12.6 g, 58.3 mmol, 2.1 equiv.) was added in several portions over a period of 10 min. The mixture was vigorously stirred for 2 h, then $MgSO_4$ (10 g) was added, and the mixture was stirred for additional 30 min. The solids were filtered off through a Celite pad, and the filtrate was concentrated. The crude product was dissolved in MeOH (150 mL) and $NaBH_4$ (1.5 g) 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 **10** as a white solid (5.5 g, 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$\underline{H}_2$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$\underline{C}$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 (5). Triol **10** (5.5 g, 16.6 mmol) was dissolved in DCM (50 mL) to which 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 through a Celite pad, the filtrate was concentrated, and the crude hemiacetal **11** was subjected to general procedure A providing ω-bromonitrile **5** as colorless oil (3.6 g, 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$\underline{H}_2$Ph), 4.76 (d, 1H, J = 11.7 Hz, OC$\underline{H}_2$Ph), 4.71 (d, 1H, J = 11.7 Hz, OC$\underline{H}_2$Ph), 4.54 (d, 1H, J = 11.7 Hz, OC$\underline{H}_2$Ph), 4.39 (d, 1H, J = 4.3 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 ($\underline{C}$N), 78.2 (C-3), 74.1, 72.9 (2 × O$\underline{C}H_2$Ph), 68.5 (C-2), 29.5 ppm (C-4).

(2*S*,3*S*)-2,3-Dibenzyloxy-4-bromobutanenitrile (6). Lactone **12** (4.8 g, 16.1 mmol) was dissolved in dry DCM (120 mL) under an 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. Then, $Na_2SO_4{\cdot}10H_2O$ was deposited on Celite and (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 Celite pad, the filtrate was concentrated, and the crude product was subjected to general procedure A which provided ω-bromonitrile **6** as a colorless oil (4.2 g, 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$\underline{H}_2$Ph), 4.75 (d, 1H, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.71 (d, 1H, J = 11.4 Hz, OC$\underline{H}_2$Ph), 4.56 (d, 1H, J = 11.3 Hz, OC$\underline{H}_2$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 ($\underline{C}$N), 76.7 (C-3), 73.2, 73.0 (2 × O$\underline{C}H_2$Ph), 68.9 (C-2), 31.1 ppm (C-4).

(2*S*,3*S*,4*S*)-4-Bromo-2,3,5-tribenzyloxypentanenitrile (7). This product was obtained as a colorless oil (53%) from compound **13** according to general procedure A. 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$\underline{H}_2$Ph), 4.86 (d, 1H, J = 11.1 Hz, OC$\underline{H}_2$Ph), 4.65 (d, 1H, J = 10.9 Hz, OC$\underline{H}_2$Ph), 4.57 (d, 1H, J = 11.1 Hz, OC$\underline{H}_2$Ph), 4.49 (d, 1H, J = 11.8 Hz, OC$\underline{H}_2$Ph), 4.42 (m, 2H, OC$\underline{H}_2$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 ($\underline{C}$N), 76.5 (C-3), 75.5, 73.2, 73.0 (3 × O$\underline{C}H_2$Ph), 69.8 (C-5), 69.4 (C-2), 50.7 ppm (C-4).

(2*R*,3*R*,4*R*)-2-(Prop-2-en-1-yl)-3,4-dibenzyloxypyrrolidine (15). Bromonitrile **5** was subjected to general procedure B. As a result, 2-allylpyrrolidine **15** 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 = 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$\underline{H}_2$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$\underline{C}H_2$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*S*,3*S*,4*S*,5*R*)-2-Allyl-3,4,5-tribenzyloxypiperidine (3). This transformation was also carried out according to the general procedure B. Piperidine **3** was obtained as colorless oil, which solidified upon standing (48%). The NMR data were in accordance with those we have previously reported.[19]

(2*S*,3*S*,4*R*)-2-(Prop-2-en-1-yl)-3,4-dibenzyloxypyrrolidine (17). Bromonitrile **6** was subjected to general procedure B. As a result, 2-allylpyrrolidine **17** 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$\underline{H}_2$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$\underline{C}H_2$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.

(2*R*,3*R*,4*S*,5*S*)-2-(Hydroxymethyl)-3,4-dibenzyloxy-5-(prop-2-en-1-yl)pyrrolidine (18). Bromonitrile **7** was subjected to general procedure B. As a result, 2-allylpyrrolidine **18** was obtained as dark orange oil (71%, dr = 1.7 : 1). 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$\underline{H}_2$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$\underline{C}$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).

(3*R*,4*R*)-2,2-Diallyl-3,4-dibenzyloxypyrrolidine (14). Bromonitrile **5** was subjected to general procedure C. Diallyl derivative **14** 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$\underline{H}_2$Ph), 4.50 (m, 3H, 3 × OC$\underline{H}_2$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 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$\underline{C}$H$_2$Ph), 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 (19). Bromonitrile **6** was subjected to general procedure C. Diallyl derivative **19** 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$\underline{H}_2$Ph), 4.60 (d, 1H, J = 12.1 Hz, 1 × OC$\underline{H}_2$Ph), 4.53 (d, 1H, J = 12.1 Hz, 1 × OC$\underline{H}_2$Ph), 4.46 (d, 1H, J = 11.8 Hz, 1 × OC$\underline{H}_2$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$\underline{C}$H$_2$Ph), 63.7 (C-2), 48.7 (C-5), 42.9 (C-6b), 38.6 ppm (C-6a).

Allylation of 15. To a stirred solution of **15** (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.) was added 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 **23** (260 mg, 55%) and **24** (61 mg, 13%), both as yellow oils.

(2*S*,3*R*,4*R*)-1,2-Diallyl-3,4-dibenzyloxypyrrolidine (23). 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 (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 (24). 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 (25). To a solution of **23** (65 mg, 0.18 mmol) in dry toluene (1 mL), under an argon atmosphere and at room temperature, CF_3CO_2H (30 μL) was added. Then, the 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 **25** as yellow oil (56 mg, 94%). 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$\underline{H}_2$Ph), 4.46 (d, 1H, J = 12.0 Hz, 1 × OC$\underline{H}_2$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 × $\underline{C}$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, 26). To a stirred solution of **25** (71 mg, 0.21 mmol) in MeOH, under an 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 a hydrogen atmosphere for 12 h. After this time, the mixture was filtered through Celite and the filtrate was concentrated to give **26** as a yellow solid (30 mg, 91%). The NMR spectra and $[\alpha]$ were in accordance with the literature.[38] 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.

***N*-Acryloylation of 17.** To a stirred solution of **17** (90 mg, 0.28 mmol) in dry DCM (2.8 mL), under an 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, a suspension of Et_3N·HCl (white solid) in toluene was obtained. The clear solution was subjected to chromatography (prep. TLC, 1 mm, hexanes : AcOEt 2 : 3), which gave **27** (56 mg, 53%) and **28** (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 (27). 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). The NMR spectra indicate that this compound is formed as a mixture of rotamers (see the ESI‡).

1-[(2*R*,3*S*,4*R*)-3,4-Dibenzyloxy-2-(prop-2-en-1-yl)pyrrolidin-1-yl]prop-2-en-1-one (28). 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). The NMR spectra indicate that this compound is formed as a mixture of rotamers (see the ESI‡).

(1*S*,2*R*,8a*S*)-1,2-Dibenzyloxy-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (29). To a stirred solution of **27** (45 mg, 0.12 mmol) in dry toluene, under an argon atmosphere and at room temperature, the 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 **29** (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$\underline{H}_2$Ph), 4.54 (d, 1H, J = 12.1 Hz, 1 × OC$\underline{H}_2$Ph), 4.46 (d, 1H, J = 12.0 Hz, 1 × OC$\underline{H}_2$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 × $\underline{C}H_2$OPh), 56.3 (C-8a), 47.3 (C-3), 28.6 ppm (C-8).

(1*S*,2*R*,8a*S*)-Octahydroindolizine-1,2-diol (30). To a stirred solution of **29** (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 a 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_4·10H_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 chromatography ($CHCl_3$: acetone : MeOH : H_2O 57 : 20 : 20 : 3), which yielded **30** (9 mg, 56%) as a yellow solid. The NMR spectra and [α] value were in accordance with the literature.[39]

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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