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(+)-Lentiginosine, a Potent and Selective Inhibitor of Amyloglucosidase: Synthetic Efforts and Disputes on Its Absolute Configuration

Francesca Cardona,*[a] Andrea Goti,[a] and Alberto Brandi[a]

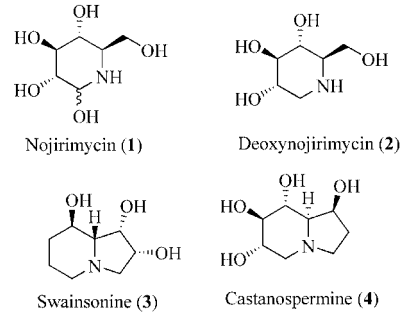
Keywords: Indolizidine / Alkaloids / Imino sugars / Cycloaddition / Molecular dynamics

(+)-Lentiginosine is a powerful and selective inhibitor of amyloglucosidases and has become a reference compound in the field among derivatives related to imino sugars. The present review focuses on the several total syntheses of this alkaloid, which rely on either a chiral pool or on enantioselective approaches that have appeared since its isolation in 1990. A summary of biological assays and molecular dynamic studies which allowed the assignment of the correct absolute configuration of natural (+)-lentiginosine is reported.

Glycosidases are enzymes that are involved in a wide range of anabolic and catabolic processes based on molecular recognition, such as intestinal digestion, post-translational processing of glycoproteins and lysosomal catabolism of glycoconjugates. For this reason, glycosidase inhibitors have received more and more attention as potential therapeutic agents and future new drugs in antidiabetic therapy and for the treatment of several other pathologies such as tumour metastasis, viral infections and genetic disorders.[1–3]

Most glycosidase inhibitors belong to the class of sugar mimics characterised by a polyhydroxylated structure containing a nitrogen atom in the ring, namely polyhydroxylated piperidine, pyrrolidine, pyrrolizidine, indolizidine and nortropane alkaloids. The glycosidase inhibition activity of these compounds is related to their structural resemblance to the sugar moiety of the natural substrate. Exploitation of their enormous potential in the treatment of many diseases has led to increased interest and demand for these compounds.

In the past forty years, more than 100 polyhydroxylated alkaloids have been isolated from plants and microorganisms.[2] Also, great synthetic effort has been carried out to afford several of these natural products and their nonnatural analogues.[4] The development of efficient and general synthetic methods for these compounds is a challenging task due to their complex chemical structures. At the same time, it is a valuable objective in consideration of the poor yield that is usually obtained from natural sources. In addition, the synthesis of nonnatural analogues opens the way to structure–activity relation studies (SAR). In 1966, Inouye and coworkers[5] discovered the first natural polyhydroxylated alkaloid, nojirimycin (**1**). It was isolated from a *Streptomyces* filtrate, and it was shown to inhibit α- and β-glucosidases:[6] it was therefore the first natural glucose mimic (Scheme 1). Compound **1** and other imino sugars bearing a hydroxy group at C-1 were found to be relatively difficult to isolate and handle because of the low stability of the aminal functionality. The first 1-deoxy derivative, 1-deoxynojirimycin (**2**), was synthesised by the same authors through reduction of the anomeric carbon.[7] Only later, deoxynojirimycin (**2**) was isolated from mulberry trees[8] and streptomyces cultures[9] and found to be a potent inhibitor of α-glucosidases and other glycosidases.[10]



Scheme 1.

In regard to indolizidine alkaloids, the first example was swainsonine (**3**), isolated from the leaves of *Swainsona canescens* (Leguminosae) in 1979.[11] Later, it was also found in *Astragalus* spp. (Leguminosae), together with swainsonine *N*-oxide.[12] Swainonine is a potent inhibitor of α-mannosidases.[13]

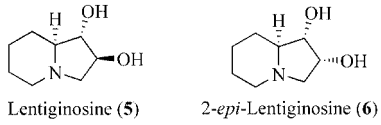
Castanospermine (**4**), a bicyclic analogue of deoxynojirimycin that has an ethylene bridge between the hydroxymethyl group and the nitrogen atom, was isolated from the seeds of *Castanospermum australe*, and its struc-

[a] Dipartimento di Chimica Organica "Ugo Schiff", Laboratorio di Progettazione, Sintesi e Studio di Eterocicli Biologicamente Attivi (HeteroBioLab), Università di Firenze, Polo Scientifico, Via della Lastruccia 13, 50019 Sesto Fiorentino (Firenze), Italy

ture was confirmed by X-ray crystallography.[14] Castanospermine was found to be a potent inhibitor of α-glucosidases (including human glucosidases I and II) and of β-glucosidases.[15]

Lentiginosine (**5**) was isolated in 1990 (Scheme 2).[16] Among imino sugars, it appeared to be the least hydroxylated inhibitor of all the amyloglucosidases,[17] which are enzymes that hydrolyse 1,4- and 1,6-α-glucosidic linkages. Nonetheless, it proved to be a very active and selective compound. It was the first compound to violate the empirical rule stating that at least 3 hydroxy functionalities (β to the nitrogen atom) should be needed for the imino sugar to possess inhibitory properties towards glycosidases.[18] The authors who isolated lentiginosine proposed the absolute configuration (1*S*,2*S*,8a*S*) on the basis of biogenetic considerations.[16] Since 1990, until very recently, numerous syntheses of this molecule and of its structural analogues have been published, which testifies to the fact that the interest of the scientific community in this topic remains undiminished.

The issue of absolute configuration of natural lentiginosine has been the object of recurrent dispute since its discovery. Even recently, the absolute configuration of natural lentiginosine has been questioned,[19] in contrast to the numerous concurring proofs of the initially assigned one. To put an end to this dispute and to dissolve any doubt that has risen around this molecule, and also stimulated by our long-lasting interest in this natural product, we consider the time mature for a comprehensive review analysing the whole story of lentiginosine.



Lentiginosine (**5**) 2-*epi*-Lentiginosine (**6**)

Scheme 2.

The Isolation

The isolation of lentiginosine dates back to 1990 when it was obtained by Elbein and coworkers on fractioning the hot methanol extracts from the leaves of *Astragalus lentiginosus*.[16] Purification through ion-exchange, thin-layer and radial chromatography gave approximately 10 mg of the alkaloid from 1 Kg of dried plant material, together with the major alkaloid swainsonine (**3**), an α-mannosidase inhibitor, and with a second dihydroxyindolizidine, the 2-epimer of lentiginosine (**6**) (Scheme 2).

Francesca Cardona was born in Firenze, Italy, in 1971. She studied at the University of Firenze, where she earned her Laurea in Chemistry in 1995 and her Doctoral degree in Chemistry in 1999, under the supervision of Prof. Alberto Brandi while working on the syntheses and computational studies of glycosidases inhibitors. She joined the group of Prof. Pierre Vogel (University of Lausanne, Switzerland) during the third year of her PhD and continued as a Postdoctoral Fellow (1998, 1999) working on the syntheses of imino-C-disaccharides by cross aldolisation reactions. She was a C.N.R. Postdoctoral Fellow at the Consiglio Nazionale delle Ricerche, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro applicazioni (CSCEA) in Firenze (2000).From 2002 she has worked as a Researcher in the University of Firenze. In 2006 she received the "G. Ciamician" silver medal of the Organic Chemistry Division of the Italian Chemical Society for young Chemists. Her fields of interest are: stereoselective syntheses of polyhydroxylated alkaloids and analogues, new oxidation methods, ionic liquids, kinetic resolutions and parallel kinetic resolutions by 1,3-dipolar cycloaddition reactions.

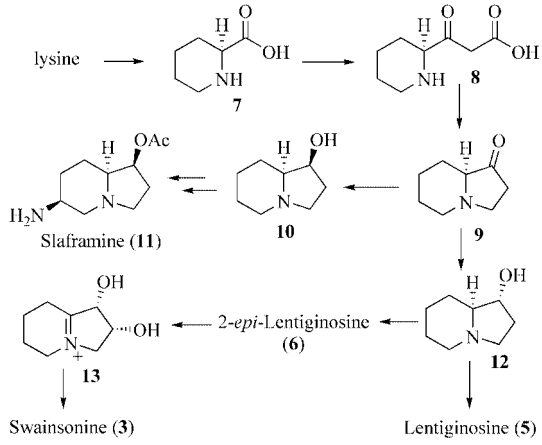
Andrea Goti was born in Firenze, Italy, in 1957. He is currently a full Professor at the University of Firenze, Italy. He studied at the University of Firenze, where he earned his Doctoral degree in Chemistry in 1982, under the supervision of Professor F. De Sarlo. He was a C.N.R. Postdoctoral Fellow at Princeton University with Professor M. F. Semmelhack (1987) and a Vigoni Visiting Researcher at the Georg-August University of Göttingen (Germany) with Professor A. de Meijere (1994). From 1985 to 1998 he was a Researcher at the Consiglio Nazionale delle Ricerche, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni (CSCEA) in Firenze. In 1998 he was appointed Associate Professor at the University of Firenze, and in 2002 he was nominated Full Professor. Since 2006 he is a founding member of the Interdepartmental Laboratory HeteroBioLab of the University of Firenze. His research interests focus on stereoselective organic synthesis, synthesis of biologically active natural and nonnatural products, carbohydrate derivatives and mimetics, synthetic applications of organometallic derivatives, cycloaddition reactions, new oxidation methods and green chemistry.

Alberto Brandi was born in 1951. He received his Doctoral degree in Chemistry in 1975 from the University of Florence. In 1978 he worked as a CNR fellow, and in 1980 he worked at the Ricercatore Universitario in the Department of Organic Chemistry of the University of Florence. From 1982 to 1984 he worked as a NATO fellow with Professor Barry M. Trost at the University of Wisconsin-Madison. He was appointed an Associate Professor at the University of Basilicata-Potenza in 1987. In 1990 he moved back to the University of Florence, and in 1994 he earned the title of Professor of Organic Chemistry in the Faculty of Science, where he now serves as the Head of the Department of Organic Chemistry "U. Schiff". He has received the following awards: 1994, Osaka City University, Japan, Fellowship; 2005, Prix Franco-Italien of the French Chemical Society; 2006, gold medal of the Italian Chemical Society. He is also the author of over 170 original papers and reviews in Chemical Reviews and Topics on Current Chemistry. His recent research interests deal with stereoselective 1,3-dipolar cycloadditions of nitrones for the syntheses of alkaloids and azaheterocycles, asymmetric synthesis of biologically active compounds, glycosidase inhibitors, sugar mimetics and β-lactams, amino acids, synthesis of peptidomimetics and peptides, chemistry of spirocyclopropane heterocycles and the synthesis of organic materials for molecular recognition and photochemical applications.

The crude methanolic extracts of *A. lentiginosus* were found to inhibit fungal amyloglucosidases. After separation by chromatography it clearly emerged that this activity could not be ascribed to the major alkaloid swainsonine, which inhibits α-mannosidase. Further purification of the biologically active fractions led to isolation of the two isomeric dihydroxyindolizidine alkaloids, whose structures were assigned by mass spectrometry and NMR spectroscopy (also by esterification of the free hydroxy groups).

Both of the indolizidine alkaloids were dihydroxylated since acetylation furnished diacetate derivatives. Both their mass spectra showed a parent ion at $m/z = 97$, which indicates the lack of hydroxy substituents in the six-membered ring. Therefore, the new metabolites were stereoisomeric 1,2-dihydroxyindolizidine alkaloids. One of them, the *cis*-diol, (1*S*,2*R*,8a*S*)-1,2-dihydroxyindolizidine or 2-epilentiginosine **6**, was identical to the synthetic compound obtained by Overman shortly before.[20]

The second dihydroxyindolizidine isolated exhibited a large coupling constant ($J = 8.5$ Hz) for H^1,H^{8a} in the ^1H NMR spectrum, which is very similar in magnitude to that of the *cis*-diol ($J = 8.7$ Hz) and indicative of a *trans* configuration between these two protons. This, consequently, required a *trans* relationship for the diol group moiety in the newly isolated diastereomeric alkaloid that was named lentiginosine. The structure of lentiginosine was therefore established as (1*S*,2*S*,8a*S*)-1,2-dihydroxyindolizidine (**5**), or its enantiomer. On the basis of biosynthetic considerations, the authors proposed the (1*S*,2*S*,8a*S*) absolute configuration (structure **5**) as the most likely, which is derived from (*S*)-pipecolic acid **7** (Scheme 3).



Scheme 3.

The Biosynthesis

2-Epilentiginosine was synthesized in its racemic form in 1984 by Colegate et al.[21] as a model compound for swainsonine-type indolizidine alkaloids, and its biological activity was evaluated. It was found to weakly inhibit both acid α-mannosidase and acid α-glucosidase.[21] (1*S*,2*R*,8a*S*)-Enantiomer **6** was later isolated from *Rhizoctonia leguminicola*,[22] the fungus that also produces slaframine (**11**) and swainsonine (**3**), two toxic indolizidine alkaloids. The biosynthesis of slaframine and swainsonine in *Rhizoctonia leguminicola* was extensively studied in the 1970s by Broquist and coworkers,[23] who showed that both alkaloids are formed from L-lysine via L-pipecolic acid (**7**), 1-oxoindolizidine (**9**), and 1-hydroxyindolizidine epimers **10** and **12**, respectively (Scheme 3).

All six carbon atoms of pipecolic acid are incorporated in the final alkaloids, an unusual event in alkaloid biosynthesis. The remaining two carbon atoms of the pyrrolidine ring are provided by malonate, presumably by a Claisen-type condensation to form pipecolyl acetate intermediate **8** (even if direct proof of its involvement is lacking).[23]

Diol **6** was identified as a minor metabolite of the fungus *Rhizoctonia leguminicola*,[22] and strong evidence for its participation in the biosynthetic pathway to **3** was provided by means of isotopic labelling experiments.[22,24] Although **6** and **3** differ in the absolute configuration at C-8a, formation of iminium ion **13**, which accounts for epimerisation at C-8a, has been proved.[24] Diol **6** was also identified as a metabolite of *Astragalus Oxyphysus* by isolation of its diacetate,[25] and the biosynthesis of swainsonine (**3**) in the plant has been shown to follow a pathway very similar to that of the fungus, which suggests that these two groups of organisms use the same biosynthetic scheme, at least in part [the plant does not produce slaframine (**11**), neither does it produce **10** or 1,6-dihydroxyindolizidines, both of which are implicated in slaframine biosynthesis] (Scheme 3).

It is relatively unusual that both microorganisms and higher plants produce the same metabolite. However, 1-deoxynojirimycin (**2**) is another relevant example of this phenomenon. 1-Deoxynojirimycin, also a glycosidase inhibitor, was isolated from mulberry (*Morus*)[26] and from species of *Streptomyces*[27] and *Bacillus*.[28]

On the basis of all of these biological considerations, lentiginosine (**5**), found together with diol **6** and swainsonine (**3**) in *A. lentiginosus*, is thought to be formed by a similar pathway that involves hydroxylation at C-2 *trans* to the existing OH group in **12**, which is derived by diastereoselective reduction of ketone **9**.[16] Therefore, the authors tentatively assigned the absolute configuration (1*S*,2*S*,8a*S*)-1,2-dihydroxyindolizidine to natural lentiginosine.[16]

Some confusion around the absolute configuration of natural lentiginosine arose from the reported value of the optical rotation for the isolated material. As a matter of fact, natural lentiginosine, obtained as a colourless oil with a 95% purity (determined by GC), was reported levorotatory with a value of $[\alpha]_D^{24} = -3.3$ for the optical rotation.[16] However, all the various syntheses of (1*S*,2*S*,8a*S*)-lentiginosine subsequently reported led to samples with small positive rotations. On the basis of biological activity data of both (+)- and (–)-lentiginosine,[17] we argued that the natural product is dextrorotatory and the negative rotation initially reported was due to impurities present in the natural product and also visible in the published NMR spectrum.[16] Most of the troubles experienced with lentiginosine and its assignment of absolute configuration and sign of optical rotation are due to its low value of $[\alpha]_D$, which

then requires accurate measurements carried on very pure samples. The presence of impurities, even in small amounts but highly rotating the polarised plane, may be responsible for inversion of the rotation sign.

Biological Activity

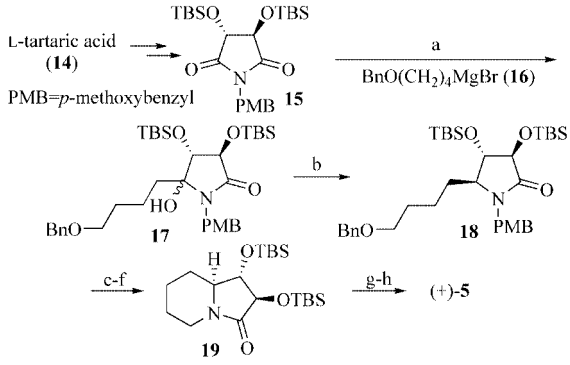
The isolation of lentiginosine was prompted by the initial observation that an inhibitor of amyloglucosidases was present in the methanol extracts of *A. lentiginosus*. Once isolated and purified, it was established that **5** was a good inhibitor of the enzyme, with IC_{50} = 5 μg/mL. Castanospermine (**4**) still remained the most effective inhibitor of amyloglucosidase.[16] Later, we found that synthetic **5** is twice as potent as castanospermine in its inhibition of amyloglucosidase, (IC_{50} = 0.43 μg/L versus IC_{50} = 0.82 μg/L towards amyloglucosidase from *Aspergillus niger*), which makes (+)-lentiginosine the most potent imino sugar type inhibitor towards the enzyme found so far. This discrepancy in the biological result may also be ascribed to the impurities present in the alkaloid extracted from natural sources.

The 2-epimer **6** was completely inactive even when tested at 40 μg/mL. Thus, it immediately emerged that the relative configuration of the two hydroxy groups was crucial for the activity. Compound **5** behaved as a competitive inhibitor of amyloglucosidases and displayed high specificity. In fact, neither lentiginosine nor its epimer **6** inhibit any other glycosidases tested, even at high concentrations (100 μg/mL), including the glycoprotein processing glucosidase I or II, intestinal sucrase, intestinal maltase, yeast α-glucosidase, β-glucosidase, α- or β-galactosidase and α- or β-mannosidase.[16] Overall, the peculiarity of lentiginosine rests in the fact that it is the first potent glycosidase inhibitor bearing only two hydroxy groups. Moreover, it is one of the most selective inhibitors.

Diastereoselective Syntheses of Lentiginosine

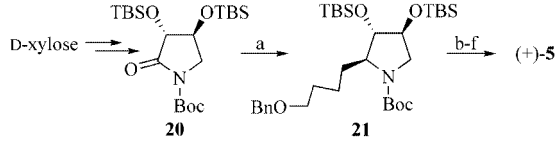
Because of its relevant biological activity and its relatively simple structure, lentiginosine has inspired a lot of synthetic work, mostly based on chiral pool starting materials, and only occasionally relying on enantioselective synthesis. Among the chiral starting materials used, cheap L-tartaric acid is the most widely employed because it allows the straightforward installation of the (1*S*,2*S*) configuration of the target molecule.

The first total synthesis of (1*S*,2*S*,8a*S*)-lentiginosine was achieved by Yoda and coworkers in 1993,[29] who employed L-tartaric acid (**14**) as the starting material and a *trans*-selective asymmetric deoxygenation of a quaternary α-hydroxy lactam as the key step for installation of the required configuration at C-8a (Scheme 4). Imide **15**, obtained in 53% yield from **14**,[30] was treated with Grignard reagent **16** to give labile quaternary α-hydroxy lactam **17**, which underwent reductive deoxygenation with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ to give lactam **18** with 92% *de*. After removal of the nitrogen protecting group of **18**, mesylation of the primary alcohol and cyclisation furnished bicyclic amide **19**, readily transformed into **5** through simple removal of the silyl protecting groups and reduction. The authors measured, for their synthetic lentiginosine, a value of $[a]_D^{23}$ = +0.19 (*c* 6.10, MeOH), and attributed the difference with the value reported for the natural product to the presence of the minor C-8a epimer.



Scheme 4. Reagents and conditions: (a) **16**, THF, –78 °C to 0 °C, 85%; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, 95%; (c) $Ce(NH_4)_2(NO_3)_6$, CH_3CN/H_2O, 0 °C; (d) Pd (black), HCOOH, *i*PrOH, 27% (2 steps); (e) MsCl, TEA, CH_2Cl_2; (f) NaH, THF, 90% (2 steps); (g) HCl, MeOH, 100%; (h) $LiAlH_4$, THF, reflux, 100%.

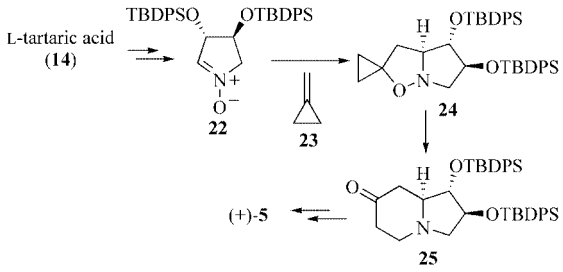
The same authors later reported a novel improved synthesis of lentiginosine based on a similar synthetic strategy using D-xylose as the starting material.[31] Pyrrolidinone **20**, obtained in a few steps from D-xylose, was treated with Grignard reagent **16** (Scheme 5) and the labile quaternary α-hydroxy lactam intermediate was subjected to the described asymmetric deoxygenation to give pyrrolidine **21** with very high diastereoselectivity (98:2 by HPLC). After separation, **21** was readily transformed into lentiginosine (**5**), with $[a]_D^{27}$ = +3.2 (*c* 1.07, MeOH), in agreement with the value reported in the meantime by ourselves (see below).



Scheme 5. Reagents and conditions: (a) **16**, THF, –78 °C; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, 55% (2 steps); (c) Pd (black), HCOOH/MeOH, 40 °C, 90%; (d) TsCl, pyridine, 70%; (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C to 0 °C; (f) KOH, MeOH, 74% (2 steps).

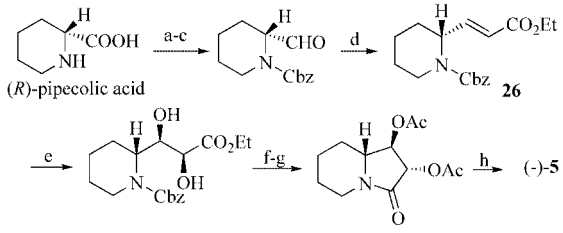
We carried out the second total synthesis of lentiginosine, based on L-tartaric acid derived pyrroline nitrone **22** as the key intermediate and a highly stereoselective cycloaddition with methylenecyclopropane (**23**), followed by thermal rearrangement of adduct **24** into indolizidinone **25** as the key steps (Scheme 6).[32] The specific rotation of our synthesised lentiginosine {$[a]_d$ = +3.2 (*c* 0.27 in MeOH)} was identical in value, but opposite in sign with that reported for the natural compound for which, however, the same (1*S*,2*S*,8a*S*) absolute configuration had been proposed.[16] At this point, the problem of the absolute configuration of

natural lentiginosine was not solved: either the originally measured optical rotation was wrong, or the absolute configuration of natural lentiginosine was opposite to that proposed.



Scheme 6.

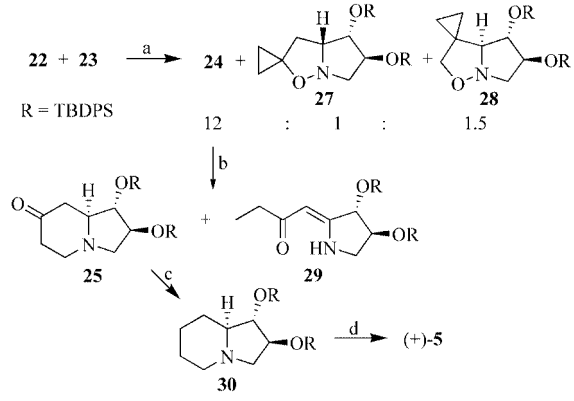
The matter was further complicated by the synthesis of both enantiomers of lentiginosine reported shortly after by Gurjar and coworkers. They seemed to suggest that natural lentiginosine had the (1*R*,2*R*,8a*R*) stereochemistry by assuming that the measured optical rotation value of the natural compound was correct. Indeed, levorotatory lentiginosine (–)-**5** {$[\alpha]_d$ = –2.6 (*c* 1, MeOH)} was obtained from (*R*)-pipecolic acid (Scheme 7), whereas its enantiomer, obtained starting from (*S*)-pipecolic acid, showed $[\alpha]_d$ = +3.2 (*c* 0.33, MeOH).[33] Gurjar's approach is shown in Scheme 7 for (all *R*)-lentiginosine. While (*R*)-pipecolic acid determined the absolute configuration at C-8a, the *trans* (C-1–C-2) diol was introduced through a Sharpless asymmetric dihydroxylation[34] of α,β-unsaturated ester **26**.



Scheme 7. Reagents and conditions: (a) CbzCl, NaOH, room temp., 6 h; (b) BH_3·SMe_2, THF, 0 °C to room temp., 10 h; (c) Py·SO_3, DMSO, 0 °C to room temp., 30 min; (d) Ph_3P=CHCOOEt, C_6H_6, room temp., 10 h; (e) AD-mix-β, *t*BuOH/H_2O, 1:1, room temp., 24 h; (f) 10% Pd-C, NaOAc, MeOH, H_2, 1 atm, 12 h; (g) Ac_2O, Py, room temp., 8 h; (h) BH_3·SMe_2, THF, room temp., 12 h.

The absolute configuration determination of natural lentiginosine was unambiguously assigned as (1*S*,2*S*,8a*S*)-1,2-dihydroxyindolizidine [(+)-**5**] by our synthesis of both enantiomers (+)-**5** and (–)-**5** coupled with their inhibitory activity determination on a series of glycosidic enzymes.[17] Both (+)-**5** and (–)-**5** displayed selective inhibition for amyloglucosidases, and it was inactive toward 17 other glycosidases. Towards amyloglucosidase from *Aspergillus niger*, synthetic (+)-**5** showed an inhibition activity (K_i = 2 μM) that was five times stronger than that reported for natural lentiginosine, and 35 times higher than that reported for (–)-**5**. Surprisingly, synthetic (+)-**5** turned out to be a better inhibitor than castanospermine (**4**); thus, it was revealed that it was the most potent inhibitor of amyloglucosidases found so far among imino sugars and related compounds. Therefore, the evaluation of inhibitory properties of both enantiomers of lentiginosine clearly established that natural lentiginosine is the (1*S*,2*S*,8a*S*) enantiomer; it followed that it is dextrorotatory. This conclusion was reinforced by the trend of optical rotation measured at different wavelengths, which showed a decrease at lower wavelengths for both the natural compound and the synthetic (all *S*)-lentiginosine. These findings should have closed the dispute on the absolute configuration of the natural compound. However, some of the contributions on lentiginosine published later on questioned again this conclusion or stated incorrectly the absolute configuration of the natural compound. We hope that this account will clarify this point definitely.

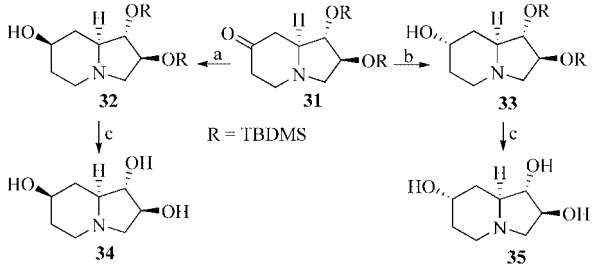
The first approach that our group used to synthesise lentiginosine[32] was the methylenecyclopropane 1,3-dipolar cycloaddition-rearrangement methodology.[35] Nitrone **22** was synthesised from L-tartaric acid **14** by using a modification of a procedure reported by Petrini and coworkers.[36] The cycloaddition to methylenecyclopropane (**23**), carried out in a sealed tube at 35 °C for 8 d with an excess of dipolarophile, gave a 12:1:1.5 mixture of isoxazolidines **24** and **27** and regioisomeric **28** in high yield (Scheme 8). The high diastereoselectivity observed in the cycloaddition was assured by the bulky TBDPS protecting groups on the nitrone, which favoured attack of the dipolarophile *anti* to the vicinal OR group of the nitrone. Thermal rearrangement of **24** in xylene heated at reflux afforded indolizidinone **25** in 45% yield, together with isomeric enone **29** (49% yield). Reduction of **25** with tosylhydrazone gave TBDPS-protected lentiginosine **30** in 45% yield, which was treated with 40% aqueous HF in acetonitrile to give (+)-**5** in high yield as an analytically pure white solid, m.p. 106–107 °C, $[\alpha]_D^{25}$ = + 3.2 (*c* 0.27, MeOH). Its enantiomer (–)-**5** was prepared from the nitrone derived from D-tartaric acid following the same procedure.



Scheme 8. Reagents and conditions: (a) 2 equiv. of **23**, benzene, 35 °C, 8 d, 94%; (b) xylene, reflux, 100 min, 45% of **25**, 49% of **29**; (c) (*p*-toluenesulfonyl)hydrazine, MeOH, then $NaBH_4$, reflux, 3 h, 45%; (d) 7:3 mixture of CH_3CN/aqueous 40% HF, room temp., 46 h, 85%.

By using similar methodology, the synthesis of two new epimeric 7-hydroxylentiginosines, **34** and **35**, was accomplished (Scheme 9).[37] Indolizidinone **31**, obtained by

thermal rearrangement of the corresponding isoxazolidine adduct, was reduced selectively to indolizidinol **32** or **33** by using $NaBH_4$ or the bulkier LS-Selectride (lithium trisiamylborohydride), respectively. A balance of steric and torsional factors was responsible for the observed diastereoselectivity in the reduction. Further deprotection with 40% aqueous HF in CH_3CN afforded trihydroxyindolizidines **34** and **35**.



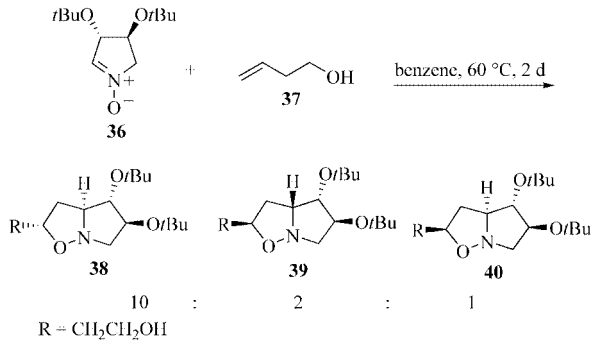
Scheme 9. Reagents and conditions: (a) $NaBH_4$, EtOH, room temp., 1 h, 85%; (b) LS-Selectride, THF, –78 to 0 °C, 51%; (c) 7:3 mixture of CH_3CN/aqueous 40% HF, room temp., 24 h, 75% for **34**, 89% for **35**.

It was found that both compounds are competitive inhibitors of amyloglucosidases with K_i values of ca. 6 and 75 μM, respectively, towards amyloglucosidase from *Aspergillus niger*. Moreover, (7*R*)-hydroxylentiginosine **34** weakly inhibited α-L-fucosidase from bovine epididymis. A model to rationalise the structure–activity relationship of (+)-lentiginosine and the two new compounds towards amyloglucosidases was also proposed, and it will be discussed later.

The activity of these compounds prompted the search to find out a more efficient strategy for their synthesis. The main drawbacks of the described syntheses were the poor regioselectivity of the cycloaddition, the low chemoselectivity of the thermal rearrangement and, regarding the synthesis of lentiginosine (+)-**5**, the low yield of the reduction of ketone **25** to TBDPS-protected lentiginosine **30**.

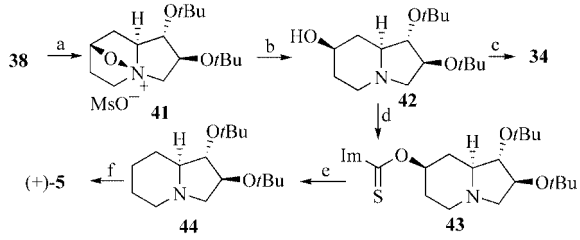
A new synthesis of (+)-lentiginosine (**5**) and of (7*R*)-hydroxylentiginosine **34** afforded yields increased by an order of magnitude (Scheme 10).[38] The new approach involved the use of *tert*-butyl protected nitrone **36** (available from L-tartaric acid by employing a new procedure developed in our group)[39] in a different cycloaddition protocol with 3-buten-1-ol (**37**) as the dipolarophile for the construction of the indolizidine nucleus (Scheme 10). In this case, the cycloaddition was totally regioselective and afforded three diastereomeric 2-substituted isoxazolidines, **38**, **39** and **40**, with high diastereoselectivity in favour of *exo-anti* adduct **38** (79% isolated yield).

Major cycloadduct **38** was transformed, according to Tufariello's protocol,[40] into the corresponding mesylate, which underwent intramolecular S_N2-type attack at the bridgehead nitrogen atom to quantitatively afford salt **41** (Scheme 11). The crude salt was directly hydrogenated at 50 psi in the presence of catalytic Pd on charcoal to give diprotected triol **42**. Deprotection of **42** by trifluoroacetic acid afforded (7*R*)-hydroxylentiginosine **34** in excellent yield. For the synthesis of lentiginosine, a radical deoxygen-



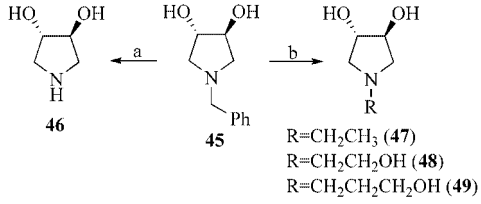
Scheme 10.

ation[41] was performed by formation of thiocarbonylimidazolide **43**, which was subjected to tri(*n*-butyl)tin hydride in refluxing toluene. Diprotected lentiginosine **44**, obtained in 68% yield, was treated with trifluoroacetic acid to afford (+)-**5** (Scheme 11) in 10 steps and 35% overall yield versus nine steps and 2.4% overall yield of our previous syntheses.[17,32]



Scheme 11. Reagents and conditions: (a) MsCl, TEA, CH_2Cl_2; (b) H_2, 50 psi, Pd/C 10%, MeOH, 24 h, 86% (2 steps); (c) CF_3COOH, 24 h, 93%; (d) $Im_2C{=}S$, THF, 68 °C, 2.5 h, 99%; (e) nBu_3SnH (1.5 equiv.), toluene, 110 °C, 16 h, 68%; (f) CF_3COOH, 16 h, 93%.

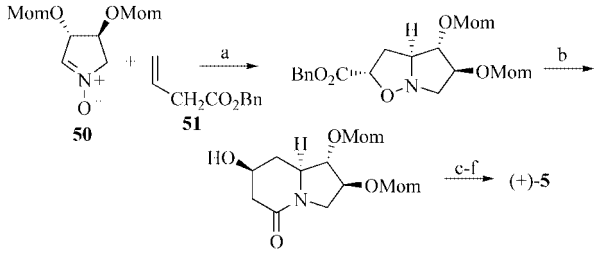
By starting from D-tartaric acid, enantiomeric (–)-**5** and *ent*-**34** were analogously obtained.[42] Because it arose that the enzymatic inhibitory activity of (+)-lentiginosine and of its analogue **34** rested in the 1,2-*trans* dihydroxy substitution, also a series of *N*-substituted-3,4-*trans*-dihydroxypyrrolidines **46**–**49** (Scheme 12) were synthesised as simpler models of glycosidase inhibitors. The enzymatic essays[42] showed that some activity and selectivity is still retained for these simpler analogues, but the rate of inhibition was much lower, which suggests that subtle factors are involved in the recognition by the enzyme.



Scheme 12. Reagents and conditions: (a) H_2, Pd/C, MeOH, 91%; (b) R-Br, heat, then H_2, Pd/C, MeOH, 46% for **47**, 66% for **48**, 80% for **49**.

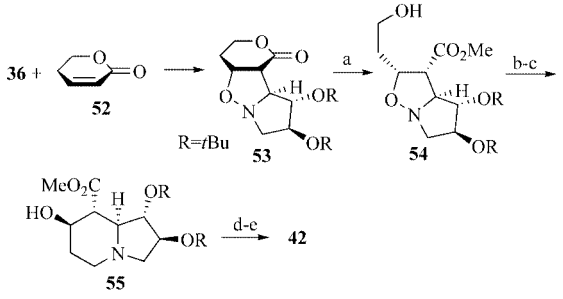
The use of chiral pyrroline nitrones analogous to **22** and **36** as precursors for the dihydroxylated portion of lentiginosine **5** in 1,3-dipolar cycloaddition protocols has been pur-

sued also by other research groups. Wightman and coworkers achieved the synthesis of both enantiomers of **5** by employing nitrone **50** or its enantiomer, available from L- or D-tartaric acids, respectively, as the key intermediate and benzyl but-3-enoate (**51**) as the dipolarophile (Scheme 13).[43]



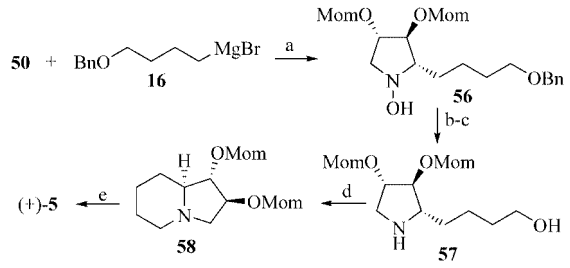
Scheme 13. Reagents and conditions: (a) Toluene, reflux, 44%; (b) Zn, CH_3COOH, 60 °C, 83%; (c) $BH_3{\cdot}SMe_2$, then EtOH, reflux, 95%; (d) $Im_2C{=}S$, CH_2Cl_2, reflux, 83%; (e) Bu_3SnH, AIBN, toluene, reflux, 53%; (f) HCl aq (6 M), 60%.

Cycloaddition of nitrone **36** to lactone **52** was employed in the formal synthesis of (+)-**5** by Chmielewski and coworkers (Scheme 14).[44] The cycloaddition reaction selectively produced lactone **53**,[45] which was easily ring-opened by treatment with K_2CO_3 in MeOH. The terminal hydroxy group in **54** was used for intramolecular alkylation by the nitrogen atom. Decarboxylation of **55** to **42** was achieved by application of Barton's *N*-hydroxythiopyrrolidinone methodology[46] through the corresponding free acid. Compound **42** had been previously transformed into (+)-**5** (see Scheme 11).



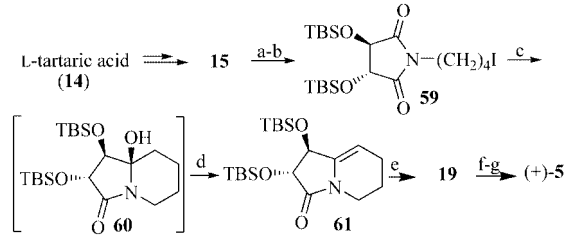
Scheme 14. Reagents and conditions: (a) K_2CO_3, MeOH, 53%; (b) CBr_4, PPh_3; (c) H_2, 70 psi, $Pd(OH)_2$/C 10%, MeOH, 72% (2 steps); (d) LiOH, 89%; (e) *N*-hydroxypyridin-2-thione, DCC, DMAP, CH_3CN, 50 °C, 64%.

Nitrone **50** was used by Petrini and coworkers for the synthesis of (+)-**5** in a different protocol that employs the addition of an organometallic reagent as the key step for the introduction of the correct stereochemistry at C-8a.[47] Attack of (4-benzyloxybutyl)magnesium bromide **16** to **50** produced a 95:5 mixture of two diastereoisomers, with the *trans* isomer **56** prevailing (Scheme 15). Reduction of **56**, debenzylation and cyclisation of amine **57** and deprotection of **58** afforded (+)-**5**.



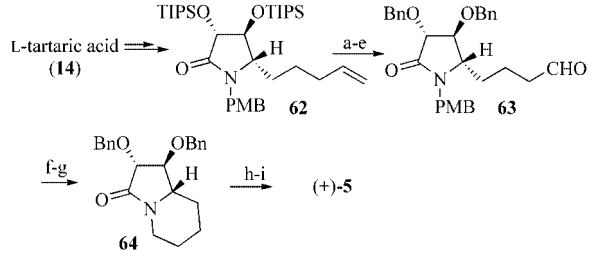
Scheme 15. Reagents and conditions: (a) THF, room temp., 82%; (b) H_2, Ni-Raney; (c) $HCONH_4$, Pd/C, 76% (2 steps); (d) Ph_3P, CCl_4, TEA, DMF, 88%; (e) HCl, MeOH, reflux, 3 h, 91%.

More recently, two other syntheses of (+)-lentiginosine that used chiral cyclic imides derived from L-tartaric acid as the key intermediate and cyclisation methods based on SmI_2 have been reported.[48,49] Ha and coworkers based the construction of pyrrolizidinone, indolizidinone and quinolizinone ring systems on a SmI_2-promoted cyclisation of *N*-(iodoalkyl)-substituted cyclic imides.[50] Imide **15**, prepared from L-tartaric acid,[29,30] was subjected to oxidative removal of the 4-methoxybenzyl group followed by introduction of the iodoalkyl group to provide **59** in 85% yield (Scheme 16). Treatment with SmI_2 in the presence of catalytic amounts of tris(dibenzoylmethido)iron(III)-[$Fe(DBM)_3$] in THF led to cyclisation to corresponding hydroxyindolizidinone **60** that dehydrated to enamide **61** upon treatment with 4 Å molecular sieves and catalytic *p*-TsOH. Further stereoselective reduction to **19**[29] with Et_3SiH/CF_3COOH, followed by desilylation in methanolic HCl and reduction with lithium aluminium hydride afforded (+)-**5**.



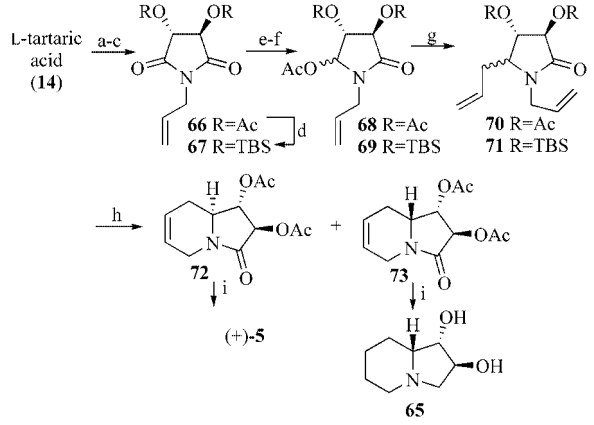
Scheme 16. Reagents and conditions: (a) CAN, CH_3CN; (b) I-$(CH_2)_2$-I, K_2CO_3, 85% (2 steps); (c) SmI_2, tris(dibenzoylmethido)-iron(III) [$Fe(DBM)_3$], THF; (d) 4 Å molecular sieves, *p*-TsOH, CH_2Cl_2, 82% (2 steps); (e) CF_3COOH, Et_3SiH, 93%; (f) HCl, MeOH, 86%; (g) $LiAlH_4$, 83%.

Yoda and coworkers described a nitrogen–carbon coupling reaction between lactams and aldehydes mediated by SmI_2 to afford *N*-α-hydroxyalkylated lactams, and applied this approach to the synthesis of (+)-**5**,[49] as shown in Scheme 17. Lactam **63**, obtained in a few steps from **62**, was subjected to the SmI_2-mediated coupling reaction followed by deoxygenation with Et_3SiH to give indolizidine lactam **64**, which was easily converted into (+)-lentiginosine (**5**).



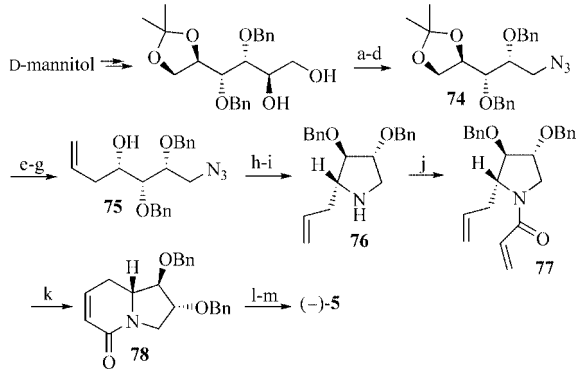
Scheme 17. Reagents and conditions: (a) Bu_4NF, THF, 100%; (b) BnBr, Ag_2O, CH_3COOEt, 63%; (c) CAN, CH_3CN/H_2O, 9:1, 75%; (d) OsO_4, NMO, acetone/H_2O, 1:1, 95%; (e) $NaIO_4$, H_2O/Et_2O, 100%; (f) SmI_2 (3 equiv.), THF, 85%; (g) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –20 °C, 92%; (h) Pd (black), 4.4% HCOOH-MeOH, 90%; (i) $LiAlH_4$, reflux, 100%.

In the last five years, several enantiospecific approaches to lentiginosine took advantage of a ring closing metathesis (RCM) reaction for the cyclisation step. This metal-mediated reaction has been extensively used in the construction of a variety of nitrogen-containing ring systems, including pyrrolizidines, indolizidines and other compounds related to imino sugars.[51] With regards to dihydroxyindolizidines, Paolucci and coworkers firstly reported a RCM-based synthesis of (8a*R*)-*epi*-lentiginosine **65**.[52] Later, Pilli et al. reported a synthesis of both (+)-**5** and **65** from L-tartaric acid as the starting material (Scheme 18).[53] *N*-Allyl lactams **68** or **69**, obtained from *N*-allyl imides **66** or **67**, respectively, were treated with Lewis acids (4.0 equiv.) to ensure in situ formation of the corresponding *N*-acyliminium ion, followed by the addition of allyltrimethylsilane (or tributylallyltin). The addition proceeded with moderate, if any, *anti* preference. Ring closing metathesis on the diastereoisomeric mixture afforded indolizidines **72** and **73**, which could be separated and easily transformed into (+)-**5** and **65**, respectively by treatment with lithium aluminium hydride.



Scheme 18. Reagents and conditions: (a) AcCl, reflux; (b) allylamine, CH_2Cl_2, room temp.; c) AcCl, reflux, 99% (3 steps); (d) AcCl, EtOH, then TBDSCl, imidazole, DMF, 83%; (e) $NaBH_4$, EtOH, –23 °C; (f) Ac_2O, TEA, DMAP, CH_2Cl_2, 76% for **68**, 69% for **69**; (g) allyltrimethylsilane, $BF_3{\cdot}Et_2O$, 89% and 1:1 *cis:trans* ratio for **70**, 95% and 2.5:1 *cis:trans* ratio for **71**; (h) 4 mol-% benzylidene-bis(tricyclohexyl phosphane)-dichlororuthenium (1st generation Grubbs' catalyst), CH_2Cl_2, 44% of **72**, 44% of **73**; (i) $LiAlH_4$, THF, reflux, 82% for **5**, 60% for **65**.

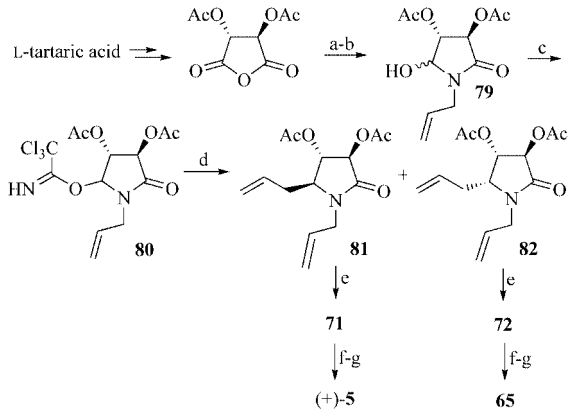
Ring closing metathesis was used as the key step for the construction of the indolizidine skeleton of (–)- and (+)-lentiginosine by Singh and coworkers, who again questioned the assignment of the absolute configuration of natural lentiginosine.[19] As shown in Scheme 19, their approach for the synthesis of (–)-**5** was based on the cyclisation of key intermediate **75**, obtained from D-mannitol, for the installation of the C-8a stereochemistry, and on the RCM with Grubbs' catalyst for the construction of the six-membered ring. Azide **75** was obtained through a diastereoselective addition of allyltributylstannane to the crude aldehyde derive from azide **74**. A formal synthesis of (+)-lentiginosine was also obtained with an analogous approach starting from L-tartaric acid.



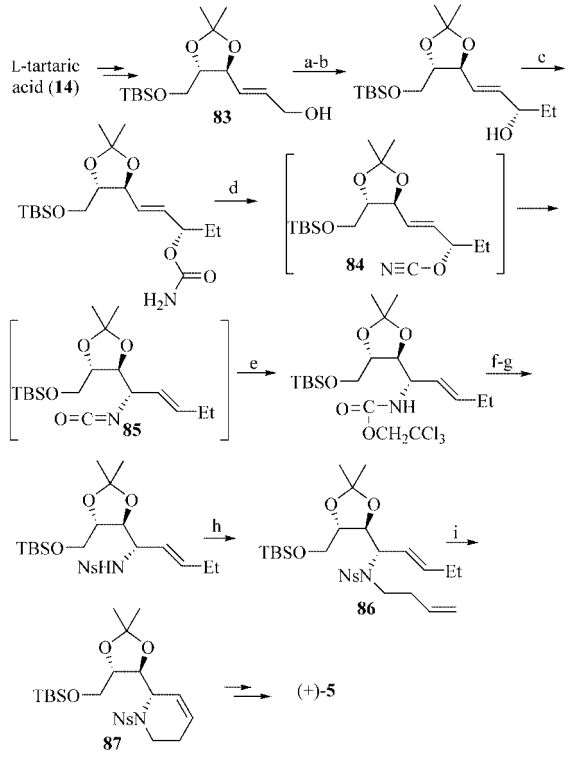
Scheme 19. Reagents and conditions: (a) $Pb(OAc)_4$, CH_2Cl_2, 3 h; (b) $NaBH_4$, EtOH, 3 h; (c) TsCl, TEA, CH_2Cl_2, 12 h; (d) NaN_3, DMF, 80 °C, 8 h, 80% (4 steps); (e) CF_3COOH, THF/H_2O (4:1), 65 °C, 8 h, 97%; (f) $Pb(OAc)_4$, CH_2Cl_2, 3 h; (g) $SnCl_4$, allyltributyl tin, CH_2Cl_2, –78 °C, 1 h, 82% (2 steps); (h) MsCl, TEA, CH_2Cl_2, 6 h, 92%; (i) $LiAlH_4$, THF, reflux, 65 °C, 12 h, 68%; (j) acryloyl chloride, TEA, CH_2Cl_2, 12 h, 85%; (k) 1st generation Grubbs' catalyst (10 mol-%), toluene, reflux, 24 h, 86%; (l) 10% Pd/C, H_2, 24 h; (m) $LiAlH_4$, THF, reflux, 6 h, quantitative yield (2 steps).

Schmidt et al. also used the RCM reaction for the construction of the six-membered ring of (+)-lentiginosine **5** and 8a-*epi*-lentiginosine **65**.[54] Their strategy was based on the transformation of O,N-acetal derivative **79** into corresponding trichloroacetimidate **80**, and its acid-catalysed activation for α-amidoalkylation (Scheme 20). Reaction of **80** with allyltrimethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst afforded quantitatively pyrrolidinones **81** and **82** in 1:1 ratio. After separation by flash chromatography, ring closing metathesis gave, respectively, indolizidinones **71** and **72**, which were transformed into the target molecules via simple steps.

Ichikawa and coworkers reported a synthesis of (+)-lentiginosine from L-tartaric acid (**14**) as the starting material,[55] in which the C-8a stereochemistry was installed by means of an asymmetric diethylzinc addition (Soai protocol) to the aldehyde derived from alcohol **83** (Scheme 21). Subsequent [3,3] sigmatropic rearrangement of allyl cyanate **84** to isocyanate **85** occurred with a high degree of [1,3]-chirality transfer.[56] Further manipulations, including RCM of sulfonylamine **86**, allowed the construction of the tetrahydropyridine ring of **87**. Further chemical transformations eventually gave (+)-**5**.

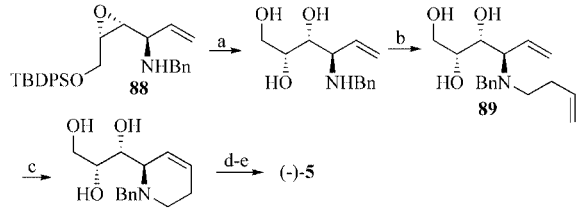


Scheme 20. Reagents and conditions: (a) allylamine, 87%; (b) $NaBH_4$, MeOH, 89%; (c) CCl_3CN, DBU, 75%; (d) allyltrimethylsilane, TMSOTf; (e) 1st generation Grubbs' catalyst, 4 mol-%, CH_2Cl_2, 78%; (f) $LiAlH_4$, THF, reflux, 4 h, 73%; (g) 10% Pd/C, MeOH, 75%.



Scheme 21. Reagents and conditions: (a) *o*-iodoxybenzoic acid, DMSO, 90%; (b) Et_2Zn, (*S*)-diphenyl(1-methylpyrrolidin-2-yl)-methanol, 93:7 *dr*, 91%; (c) CCl_3CONCO, then K_2CO_3, MeOH, H_2O, 95%; (d) PPh_3, CBr_4, TEA, –20 °C to 0 °C; (e) Cl_3CCH_2OH, 86%; (f) Zn, CH_3COOH, THF; (g) NsCl, TEA, 87% (2 steps); (h) 3-buten-1-ol, PPh_3, DEAD, 89%; (i) 1st generation Grubbs'catalyst (6 mol-%), benzene, reflux, 92%.

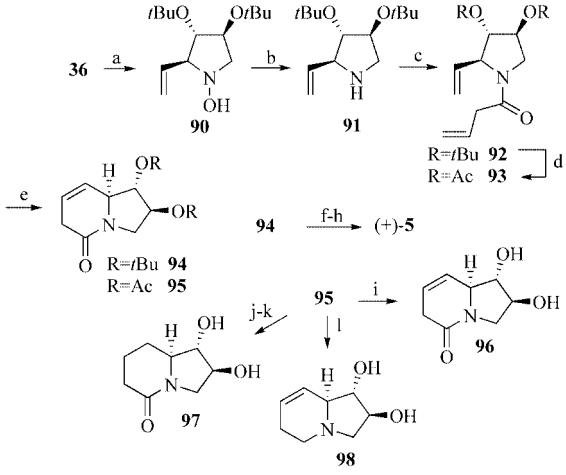
Génisson, Baltas and coworkers also employed the RCM reaction for a straightforward synthesis of (–)-**5** and of its pyrrolizidine analogue[57] starting from chiral *cis*-α,β-epoxyamine **88**, readily available from the corresponding chiral epoxy aldehyde.[58] After regiocontrolled hydrolytic opening of epoxide **88** (Scheme 22), which installed the correct stereochemistry at C-1 and C-2 of the target molecule, a butenyl residue was introduced to afford diene **89**. Treatment with the second generation 1,3-bis(mesityl)-2-imidazolidinylidene substituted ruthenium Grubbs catalyst (Grubbs II) was found to be superior to the classical first generation Grubbs catalyst in the formation of the tetrahydropyridine ring. Catalytic hydrogenation followed by Appel cyclisation gave (–)-**5**.



Scheme 22. Reagents and conditions: (a) H_2SO_4, dioxane, reflux, 70%; (b) 4-butenyltrifluoromethanesulfonate, proton sponge, CH_2Cl_2, room temp., 67%; (c) benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphane)-ruthenium (8 mol-%), toluene, 79 °C, 66%; (d) 12 bar H_2, Pd/C, MeOH, HCl, 90%; (e) PPh_3, CCl_4, TEA, DMF, room temp., 68%.

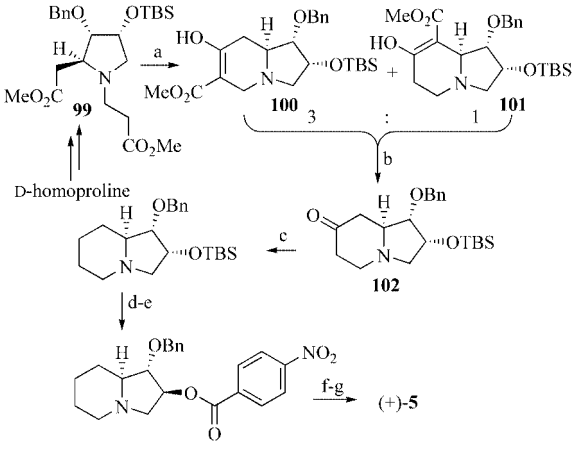
A new concise synthesis of (+)-lentiginosine and some structural analogues based on a highly selective addition of vinylmagnesium bromide to L-tartaric derived nitrone **36**[39] and on a RCM was recently reported by our group.[59] As shown in Scheme 23, addition of 1.2 equiv. of vinylmagnesium bromide in diethyl ether at room temperature afforded **90** as a single diastereoisomer, which was derived from the preferred *anti* attack of the organometallic reagent with respect to the vicinal alkoxy group. Reduction of **90** was undertaken by using recently introduced methodology for the reduction of hydroxylamines to amines,[60] to give pyrrolidine **91** in high yield (84%). Amine **91** was then coupled with but-3-enoic acid to afford amide **92**. The RCM reaction, performed with the first generation Grubbs' catalyst, afforded higher yields with the less bulky acetoxy groups than with the *tert*-butoxy groups (89% yield versus 60% yield). From lactam **94**, (+)-lentiginosine **5** was obtained in few steps. Analogues **96**, **97** and **98** were derived from diacetyl protected lactam **95** in few steps. The study of their inhibitory activity toward 22 commercially available glycosidases showed an interesting selective activity of 7,8-didehydrolentiginosine (**98**) towards amyloglucosidases, albeit weaker than that of **5**, but no activity for dihydroxylactams **96** and **97**. These biological results confirmed that, at least for the inhibition towards amyloglucosidases, a basic nitrogen atom is essential for the activity.

Other total syntheses considered materials from the chiral pool that were different from L-tartaric acid. Chmielewski and coworkers used D-homoproline derivative **99** as the key intermediate which, however, required an inversion of configuration at C-2, and a Dieckmann condensation approach as the key step of the synthesis.[61] The condensation was achieved by treatment with LDA in THF at –78 °C to afford a 3:1 mixture of isomeric keto esters **100** and **101**, which were decarboxylated in DMSO in the presence of catalytic amounts of water and NaCl (Scheme 24). A modified Wolff–Kishner procedure for the reduction of indolizi-



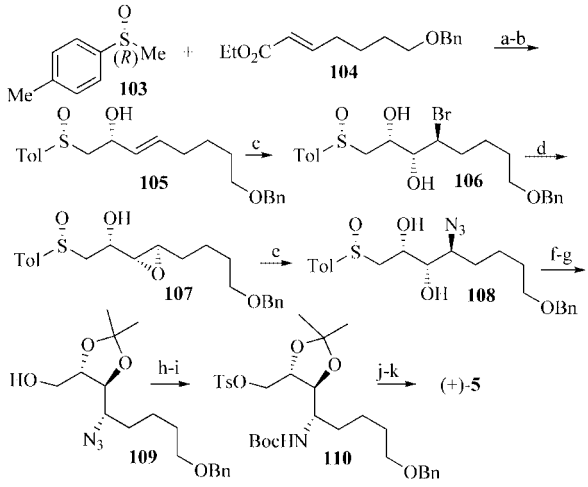
Scheme 23. Reagents and conditions: (a) CH_2=$CHMgBr$, Et_2O, 96%; (b) In (18 mol-%), Zn (4 equiv.), MeOH, NH_4Cl, reflux, 84%; (c) CH_2=$CHCH_2COOH$, HOBt, DCC, 71%; (d) CF_3COOH, then Ac_2O, Py, 65%; (e) $(Cl)_2(Cy_3P)_2RuCHPh$, CH_2Cl_2, 60% for **94**, 89% for **95**; (f) $LiAlH_4$, THF, 62%; (g) H_2, Pd/C, MeOH, 90%; (h) CF_3COOH, 74%; (i) Ambersep 900 OH, 78%; (j) H_2, Pd/C, MeOH, 87%; (k) Ambersep 900 OH, 99%; (l) $LiAlH_4$, THF, 59%.

dinone **102**, followed by desilylation, inversion of configuration at C-2 by a Mitsunobu reaction and final deprotection of the hydroxy groups gave (+)-lentiginosine.



Scheme 24. Reagents and conditions: (a) LDA, THF, –78 °C, 87%; (b) DMSO, cat. H_2O/NaCl, 37%; (c) (*p*-toluenesulfonyl)hydrazine, then $NaBH_3CN$, 89%; (d) TBAF, 96%; (e) PPh_3, THF, DEAD, *p*-nitrobenzoic acid; (f) K_2CO_3, MeOH, 82% (2 steps); (g) liq. NH_3, Na, 78%.

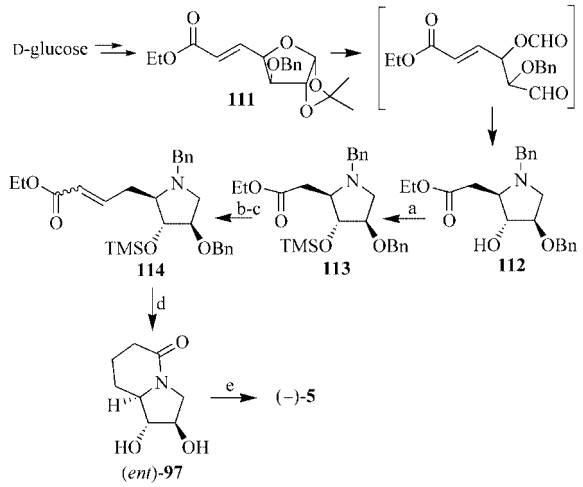
Raghavan et al. reported a stereoselective synthesis of (+)-**5** using (*R*)-(+)-methyl *p*-tolylsulfoxide (**103**) as the starting material (Scheme 25), which served for the transfer of chirality in the formation of the required stereogenic centres.[62] Unsaturated sulfoxide **105** was readily obtained by condensation of ester **104** with the α-lithium derivative of **103**, followed by diastereoselective reduction of the resulting β-ketosulfoxide. Sulfoxide **105** was converted into bromohydrin **106** by regio- and stereoselective methodology developed earlier by the same authors.[63] After transformation of **106** into epoxide **107**, the nitrogen atom was introduced by a regioselective displacement with sodium azide. Protection of diol **108**, treatment under Pummerer reaction conditions followed by in situ hydrolysis and reduction afforded **109**. Subsequent azide reduction of **109** followed by transformation of the terminal hydroxy groups into a suitable leaving group and final double intramolecular nucleophilic displacement afforded (+)-lentiginosine (Scheme 25).



Scheme 25. Reagents and conditions: (a) LDA, THF, –78 °C, 70%; (b) DIBAL, $ZnCl_2$, THF, –78 °C, 91%; (c) NBS, H_2O, toluene, room temp., 85%; (d) K_2CO_3, MeOH, 0 °C, 83%; (e) NaN_3, NH_4Cl, MeOH/H_2O (8:1), reflux, 85%; (f) 2,2-DMP, acetone, CSA (cat.), room temp., 87%; (g) TFAA, TEA, CH_2Cl_2, 0 °C, then aq $NaHCO_3$, $NaBH_4$, 75%; (h) H_2, $Pd(OH)_2$, $(Boc)_2O$, ethanol, room temp., 82%; (i) TsCl, TEA, DMAP (cat.), CH_2Cl_2, 75%; (j) TFA/H_2O (95:5), CH_2Cl_2, 0 °C to room temp.; (k) TEA, CH_2Cl_2, room temp., 70% (2 steps).

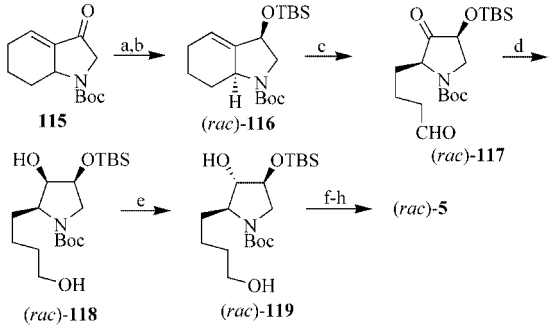
Dhavale and coworkers reported the synthesis of (–)-**5** by using D-glucose as the chiral starting material (Scheme 26).[64] D-Glucose derived α,β-unsaturated ester **111** was transformed into pyrrolidine **112** according to previous reports through opening of the 1,2-acetonide group followed by oxidative cleavage, reductive amination and intramolecular conjugate addition.[65] Protection of the hydroxy group with TMSCl then afforded **113**. Subsequent reduction of the ester group and Wittig olefination led to **114**. Hydrogenation afforded δ-lactam *ent*-**97** through a four step process involving reduction of the double bond, hydrogenolysis of the OBn and NBn groups, desilylation and concomitant cyclisation. Reduction with $LiAlH_4$ finally afforded (–)-lentiginosine.

Worth a brief mention is the synthesis of racemic lentiginosine by Sha and coworkers.[66] They used racemic hexahydro-1*H*-indol-3-one **115** as the key intermediate, which was transformed into compound **116** by Luche reduction followed by TBS protection of the alcohol functionality (Scheme 27). Further ozonolysis of the double bond afforded pyrrolidone **117**, stereoselectively reduced with $LiBH_4$ to give **118**. At this point, the correct relative stereochemistry at C-1 of the final alkaloid was introduced by a



Scheme 26. Reagents and conditions: (a) HMDS, cat. TMSCl, cat. NH_4SCN, CH_2Cl_2, 25 °C, 30 min, 88%; (b) DIBAL-H, CH_2Cl_2, –50 °C, 2.5 h; (c) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, 25 °C, 30 min, 89% (2 steps); (d) $HCOONH_4$, 10% Pd/C, cat. AcOH, MeOH, reflux, 1 h, 94%; (e) $LiAlH_4$, THF, reflux, 8 h, 92%.

Mitsunobu reaction to give **119**. Further functional group transformations and cyclisation led to racemic lentiginosine.

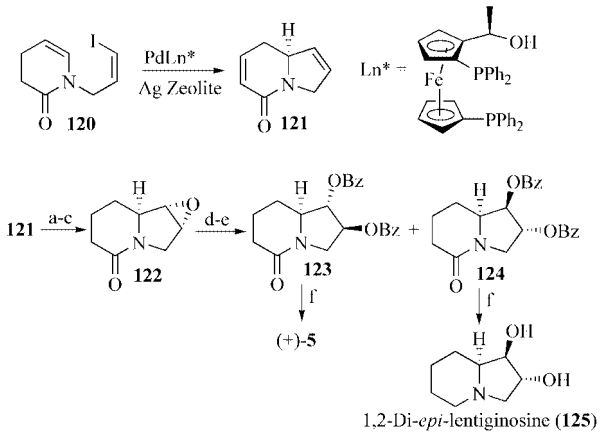


Scheme 27. Reagents and conditions: (a) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 90%; (b) TBSCl, Imidazole, DMF, room temp., 95%; (c) O_3, CH_2Cl_2, –78 °C then Me_2S, 92%; (d) $LiBH_4$, Et_2O, 91%; (e) p-$NO_2C_6H_4COOH$, DIAD, PPH_3, THF, then NaOH, MeOH, 55%; (f) TsCl, pyridine, CH_2Cl_2, 60%; (g) $BF_3{\cdot}Et_2O$; (h) KOH, MeOH.

Enantioselective Syntheses

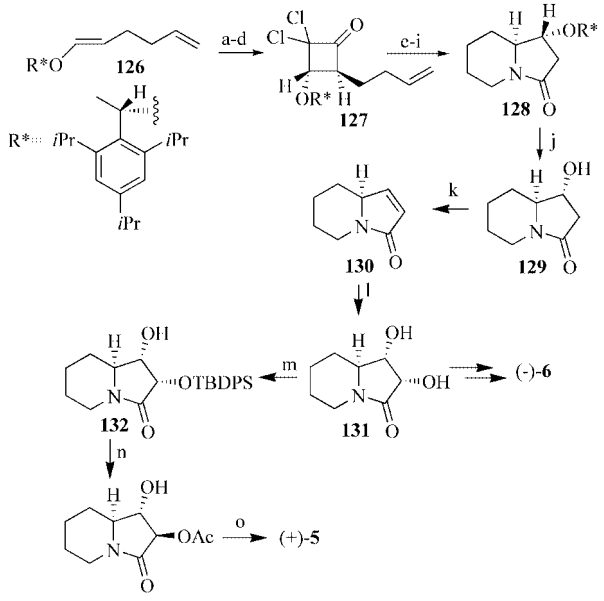
Only a few syntheses of lentiginosine have been reported that rely on enantioselective procedures. Some of them are especially valuable because they are very concise and afford good yields of the chiral products with high enantiomeric excess.

In 1995, Shibasaki and coworkers reported the first example of an enantioselective synthesis which afforded enantioenriched (+)-**5** (and its enantiomer).[67] The key optically active intermediate, 3,5,8,8a-tetrahydro-5-oxoindolizine **121**, was obtained with 86% *ee* through the catalytic, asymmetric Heck-type cyclisation of **120**[68] by using the Kumada catalyst (Scheme 28).[69] The 6,7-double bond in **121** was chemoselectively reduced by K-Selectride, followed by a two-step epoxidation of the 1,2-double bond. Epoxide **122**, obtained in three steps and 43% overall yield from **121**, was then underwent ring opening at the less hindered C-2 position with about 2:1 regioselectivity using 1% aq H_2SO_4/acetone (1:1), and the resulting diols were isolated as dibenzoates **123** and **124**. Finally, major compound **123** was reduced with lithium aluminium hydride to afford (+)-**5**, which showed $[\alpha]_d$ = +0.55 (*c* 0.16, MeOH). The low value of the optical rotation only in part accounted for the enantiomeric excess of 86%. Similar treatment of **124** afforded 1,2-diepilentiginosine (**125**), a novel nonnatural analogue of (+)-**5** (Scheme 28).



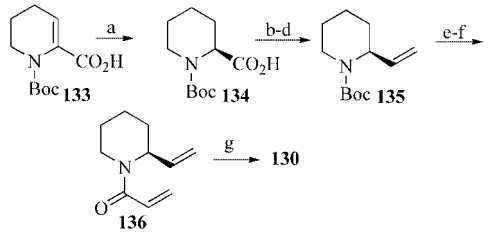
Scheme 28. Reagents and conditions: (a) K-Selectride, Et_2O, –78 °C to 0 °C; (b) NBS, THF/Et_2O/H_2O; (c) K_2CO_3, MeOH, 43% (3 steps); (d) acetone/1% H_2SO_4 (1:1), 45 °C; (e) BzCl, Py, cat. DMAP, CH_2Cl_2, 59% (2 steps) for **123**, 29% (2 steps) for **124**; (f) $LiAlH_4$, Et_2O, 98% for (+)-**5**, 100% for **125**.

A few years later, Greene and coworkers accomplished an enantioselective synthesis of (+)-**5** and of its C-2 epimer (–)-**6**, the minor metabolite of the fungus *Rhizoctonia leguminicola* through the use of a chiral auxiliary (Scheme 29).[22] The synthesis was based on a regio- and diastereoselective cycloaddition of dichloroketene with the enantiopure dienol ether **126**,[70] which afforded cyclobutanone **127** with the correct stereochemistry at C-8a of the target molecule. By way of a Beckmann ring expansion, dechlorination, hydroboration/oxidation and cyclisation, indolizidinone **128** was obtained. After removal of the chiral auxiliary with neat trifluoroacetic acid, α-hydroxylation of **129** was accomplished by a two-step dehydroxylation-dihydroxylation procedure (using Martin sulfurane reagent followed by OsO_4) stereochemically governed by the C-8a stereogenic center, which allowed reintroduction of the C-1 hydroxy group from the same face. Diol **131** was then readily transformed into target compound **6** (Scheme 29). For the synthesis of (+)-**5**, the necessary inversion of configuration at C-2 was readily accomplished by selective conversion into silyl derivative **132** followed by nucleophilic displacement with tetrabutylammonium acetate (TBAA) in toluene. Final treatment with lithium aluminium hydride afforded (+)-**5**, which showed $[\alpha]_D^{24}$ = +3.1 (*c* 0.31, MeOH). With Greene's approach, natural occurring indolizidines (–)-**6** and (+)-**5** were each obtained enantioselectively (≥ 99:1) in ca. 8.5% overall yield.



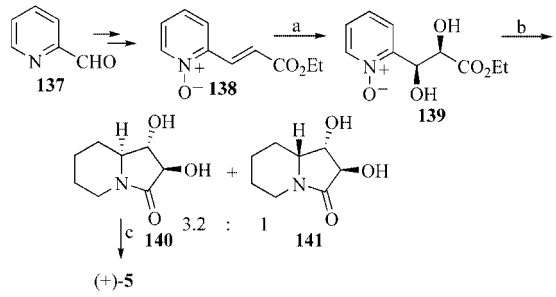
Scheme 29. Reagents and conditions: (a) KH, $Cl_2C{=}CHCl$; (b) BuLi, 3-butenyl triflate; (c) $LiAlH_4$, 60% (3 steps); (d) Cl_3CCOCl, Zn–Cu; (e) *O*-mesitylenesulfonylhydroxylamine, Al_2O_3; (f) Zn–Cu, NH_4Cl, 82% (3 steps); (g) Sia_2BH, H_2O_2, NaOH, 84%; (h) MsCl, TEA; (i) NaH, 88% (70% after recrystallisation, 2 steps); (j) CF_3COOH (98%); (k) Martin sulfurane; (l) OsO_4, TMAO, 57% (2 steps); (m) TBDPSCl, TEA, 91%; (n) TBAA, 70%; (o) $LiAlH_4$, 75%.

A formal synthesis of (+)-**5** and (–)-**6** was accomplished shortly after by Beak and coworkers,[71] who prepared same intermediate **130** based on an enantioselective catalytic reduction for the installation of the correct stereochemistry at C-8a, followed by ring closing metathesis. By using the Noyori catalyst (*S*)-BINAP-$RuCl_2$, 2-carboxy-*N*-Boc-1,4,5,6-tetrahydropyridine (**133**) was reduced to (*S*)-pipecolic acid **134**, from which **135** could be prepared by acid reduction with BH_3·THF, Swern oxidation to the corresponding aldehyde and Wittig reaction for the introduction of the vinyl moiety (Scheme 30). After conversion of **135** into **136**, ring closing metathesis readily afforded lactam **130**, the same intermediate previously converted into (+)-**5** and (–)-**6** by Greene.[70]



Scheme 30. Reagents and conditions: (a) (*S*)-BINAP-$RuCl_2$, H_2, 1000 psi; (b) BH_3·THF, 97%; (c) Swern; (d) Wittig, 92% (2 steps); (e) CF_3COOH; (f) $ClCOCH{=}CH_2$, TEA, 67%; (g) 2nd generation Grubbs catalyst, 82%.

A very concise enantioselective total synthesis of (+)-lentiginosine was achieved by Zhou and coworkers[72] and based on ethyl 3-(pyridine-2-yl)acrylate *N*-oxide (**138**), derived from picolinaldehyde (**137**), as the starting material, and on an improved Sharpless asymmetric dihydroxylation as the key step (Scheme 31). Asymmetric dihydroxylation, performed with a higher excess of $(DHQ)_2PHAL$ and K_2CO_3 compared to the usual AD system, gave diol **139** with >99.9% *ee*. Hydrogenation under 10 atm H_2 over 10% Pd–C in MeOH afforded a 3.2:1 mixture of lactams **140** and **141**. After removal of the minor isomer by recrystallisation from ethyl acetate, reduction of **140** with BH_3·SMe_2 in THF furnished (+)-**5** with $[\alpha]_d$ = +1.7 (*c* 0.37, MeOH).



Scheme 31. Reagents and conditions: (a) 0.4 mol-% $K_2[OsO_2(OH)_4]$, 3 mol-% $(DHQ)_2PHAL$, 3 equiv. of $K_3[Fe(CN)_6]$, 5 equiv. of K_2CO_3, 1 equiv. of $MeSO_2NH_2$, H_2O/*t*BuOH (1:1), 24 h, 62% with 20% recovery of the starting material; (b) 10% Pd-C, 10 atm H_2, MeOH, 24 h, 43% of **140**; (c) BH_3·THF, THF, 75%.

A Molecular Dynamic (MD) Simulation: The Lentiginosine–Glucoamylase Complex

The high and selective inhibitory activity of (+)-lentiginosine towards amyloglucosidases (α-D-1,4-glucan glucohydrolase EC 3.2.1.3) was immediately apparent during isolation from natural sources[16] and was later confirmed by our studies after total synthesis.[17] Amyloglucosidases are able to catalyse the release of β-D-glucose from the nonreducing end of starch and other related oligo- and polysaccharides, and for this reason they are widely employed in industry for the conversion of starch into glucose.[73] Common inhibitors of amyloglucosidases are sugar analogues with a structure generally resembling that of amylose, the natural substrate, and possessing a basic nitrogen which replaces the endocyclic oxygen atom of the sugar. However, whereas in the case of 1-deoxynojirimycin (**2**) and castanospermine (**4**), both good inhibitors of amyloglucosidases, the analogy with amylose is apparent (both molecules have the same absolute configuration of glucose at all the stereogenic carbon atoms), (+)-lentiginosine does not have a strict structural analogy with the sugar because it bears only two hydroxy groups which are located, moreover, on the five-membered ring and not on the piperidine portion. On the basis of the simple observation of the structures of molecules such as **5** and similar compounds inhibiting amyloglucosidase, we proposed a tentative model according to which the absolute requirements for biological activity are the basic nitrogen atom, the *trans*-dihydroxypyrrolidine unit and, in addition, also the (*S*,*S*) absolute configuration of the carbon atoms bearing the hydroxy groups.[37] In order to validate this hypothesis on a solid structural basis and to build

a model for the complex (+)-lentiginosine-amyloglucosidase in solution, we performed a computational study by molecular dynamic (MD) techniques.[74] The study started with the complex 1-deoxynojirimycin (**2**)-glucoamylase, for which the X-ray structure was available. A 105 ps MD calculation of the complex was carried out over a 15 Å sphere centred on the inhibitor after explicit introduction of water molecules (in addition to the crystallographic water molecules) in order to imitate the role of the solvent. Two molecules of 1-deoxynojirimycin were present in the active cavity in close proximity to each other (Figure 1 a).

The strongest hydrogen bonds in the X-ray structure for deoxynojirimycin (**2**) at its primary binding site are between O6, O3 and O4 of **2** and Asp55, Arg54 and Leu177. It is worth noting that Asp55 and Arg54 are supposed to be the key residues for the enzyme because mutation experiments led to a complete loss of enzymatic activity.[75] Moreover, a crystallographic water molecule (WAT3, Figure 1 a) is directly oriented towards the C1 anomeric carbon atom of the inhibitor. Finally, the endocyclic nitrogen atom is strongly anchored in its position by a square hydrogen bonding network involving Glu400, WAT3 and Tyr48. This is consistent with the fact that the endocyclic nitrogen atom of the inhibitor is protonated at physiological pH. Along all of the MD simulation, 1-deoxynojirimycin in its primary binding site experienced small fluctuations into the enzyme cavity; the extensive H-bond network involving the nitrogen atom of **2** remained unaltered, and the position of WAT3 remained the same, which confirms the role of WAT3 as the nucleophile of a general base-catalysed mechanism in which Glu400 is the catalytic base, as well as the essential role for inhibition played by the amino moiety of **2**. However, deoxynojirimycin in the secondary binding site was subjected to a shift during the dynamic run, which suggests that what was reported in the X-ray structure might not reflect the true binding of the substrate at the second subsite.

The lentiginosine (**5**)-glucoamylase complex in solution was obtained by performing an analog MD simulation. The starting point consisted of the introduction of (+)-lentiginosine (**5**) into the enzyme cavity according to an initial tentative model which almost superimposed the endocyclic nitrogen atom of both inhibitors and O1 and O2 of **5** with O2 and O3 of **2** (Figure 1 b). However, it was immediately apparent that in this initial position lentiginosine suffered repulsive van der Waals interactions with the nearest residues. In analogy to the deoxynojirimycin–glucoamylase complex structure determined by X-ray diffraction studies, two molecules of (+)-lentiginosine were initially docked into the enzyme cavity.

We then performed the 105 ps dynamic simulation in analogy with the previous experiment. After approximately 30–40 ps, (+)-lentiginosine in its primary binding site experienced a large rotation, which moved O1 and O2 into close contact with Arg54 and Asp55, the key residues for bioactivity. Moreover, despite the extensive shifts experienced by the molecule in the dynamic run, the bridgehead nitrogen atom of **5** remained anchored to the nucleophile WAT3 be-

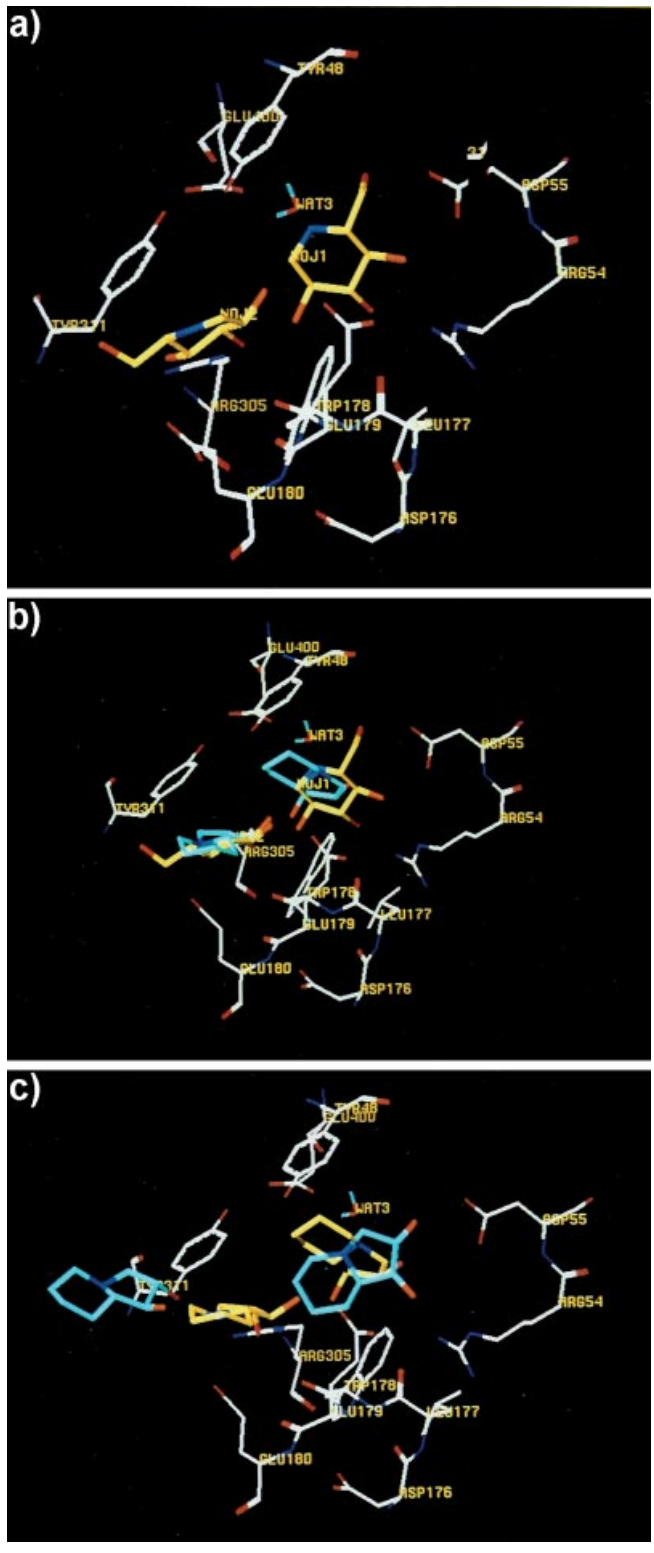


Figure 1. a) Molecular dynamics resulting structure of the deoxynojirimycin–glucoamylase complex (NOJ1 and NOJ2 are the molecules of 1-deoxynojirimycin in the primary and secondary binding sites, respectively); b) Starting point for the molecular dynamics calculation of the lentiginosine–glucoamylase complex (lentiginosine represented in blue, 1-deoxynojirimycin in yellow); c) Molecular dynamics resulting structure of the lentiginosine–glucoamylase complex (lentiginosine in blue) compared to the starting working hypothesis (lentiginosine in yellow).

cause of the strong H-bond interaction. During the dynamic run, the molecule of lentiginosine in the secondary binding site ran away from the cavity towards the solvent, which suggests that a second molecule is not relevant for inhibition. In Figure 1 c the comparison between the (+)-lentiginosine–glucoamylase complex initially built (yellow) and the (+)-lentiginosine–glucoamylase complex MD average structure[76] (blue) is shown.

The importance of our pioneering molecular dynamics simulation on 1-deoxynojirimycin and lentiginosine is evidenced by some more recent reports, which show that this matter is of great interest.[77] These studies also furnished similar conclusions, albeit by using more updated or different calculation techniques.

In conclusion, our molecular dynamic simulations definitely proved the crucial requirement of the basic amino moiety in glucoamylase inhibitors. It was also able to rationalise the high and selective inhibition of (+)-lentiginosine towards amyloglucosidase as a result of the selective interaction of lentiginosine hydroxy groups towards the enzyme key residues for bioactivity, Arg54 and Asp55. In this context, it is evident that only (+)-lentiginosine with the (1*S*,2*S*) absolute configuration, and not its enantiomer, can form these strong H-bonds. This fact, together with the biological activity found for natural lentiginosine which is much similar in value to that found for our synthetic (1*S*,2*S*,8a*S*)-lentiginosine (IC_{50} = 0.43 μg/mL and K_i = 2 μM for amyloglucosidase from *Aspergillus niger*) than to its (1*R*,2*R*,8a*R*) enantiomer (IC_{50} = 17 μg/mL and K_i = 70 μM for amyloglucosidase from *Aspergillus niger*),[17] should not raise any further doubt about the absolute configuration of natural lentiginosine.[78]

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