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Asymmetric syntheses of (−)-lentiginosine and an original pyrrolizidinic analogue thereof from a versatile epoxyamine intermediate

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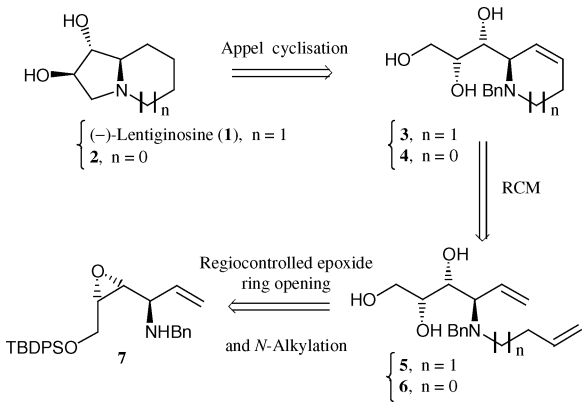
Ready access to natural (−)-lentiginosine and its pyrrolizidinic analogue from a chiral vinylic epoxyamine in a straightforward five-step sequence is presented. Careful use of the RCM reaction on aminotriols **5** and **6** constitutes the key feature of the synthetic pathway. The α-amyloglucosidase inhibitory activities of the target compounds were evaluated and showed that the more easily accessible pyrrolizidinic analogue possesses an inhibitory activity quite similar to that of (−)-lentiginosine.

Introduction

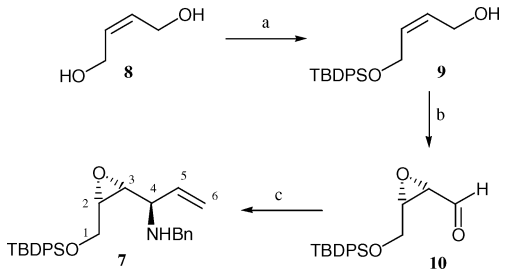
Naturally occurring and synthetic polyhydroxylated alkaloids with glycosidase inhibitory properties have been the subject of an intense research effort during the past two decades.[1] Such inhibitors are not only useful as potential drugs[2] for the treatment of viral infections, cancer, autoimmune pathologies, diabetes and other metabolic disorders but can also provide new insight into the widespread and important glycoside cleavage/formation process. Iminosugars such as polyhydroxylated pyrrolidines, piperidines, and their bicyclic congeners, indolizidines and pyrrolizidines represent by far, the broadest and most studied class of glycosidase inhibitors.[3] Their pronounced biological activity has been ascribed to their ability to mimic the transition state involved in enzymatic glycoside hydrolysis.[4]

As part of a continuing program directed towards the total synthesis of iminosugars, we have recently reported a flexible approach for the construction of five-membered ring iminosugars based on the use of a chiral *cis* α,β-epoxyamine and demonstrated its effectiveness through the preparation of 1,4-dideoxy-1,4-imino-D-glucitol, 1,4-dideoxy-1,4-imino-D-arabinitol, 1,4-dideoxy-1,4-imino-L-galactitol and novel 2-deoxy-2-fluoro analogues.[5] We now wish to report a detailed account of the extension of our approach to polyhydroxylated indolizidines and pyrrolizidines.[6]

Our general retrosynthetic analysis for the synthesis of these classes of alkaloids is outlined in Scheme 1. We envisioned a highly convergent route in which the last annulation process should be an Appel cyclisation reaction.[7] The six- or five-membered ring of the indolizidine and pyrrolizidine cores respectively, would be constructed from dienic derivatives **5, 6** by a ring closing metathesis reaction (RCM).[8] In turn, these dienes would arise from the key intermediate **7** by regioselective epoxide ring-opening followed by *N*-alkylation with the appropriate alkenyl moiety. On the basis of the above simple retrosynthetic analysis, (−)-lentiginosine (**1**)[9] as well as its original pyrrolizidinic analogue **2** were chosen as our first targets.



Scheme 1 Retrosynthetic scheme for synthesis of (−)-lentiginosine (**1**) and its pyrrolozidinic analogue **2**.



Scheme 2 *Reagents and conditions*: a) *n*-BuLi, TBDPSCl, THF, −78 °C, then reflux, 91%; b) i) Ti(O*i*-Pr$_4$), (−)-DET, *t*-BuOOH, CH_2Cl_2, 4 Å MS, −23 °C, 93%; ii) IBX, DMSO, 92%; c) $BnNH_2$, 4 Å MS, Et_2O, rt, then Et_2OBF_3, $CH_2CHMgBr$, −78 °C, 67%.

Results and discussion

Chemistry

According to our previous work,[10] the required *cis* α,β-epoxyamine **7** was conveniently prepared from commercially available *cis*-2-butene-1,4-diol through a reaction sequence based on the stereocontrolled addition of vinylmagnesium bromide to an imine derived from the readily accessible aldehyde **10** (Scheme 2).

With this efficient route to **7**, highly regio- and stereoselective conversion of the 2,3-epoxy alcohol moiety into amino triol **11** possessing the three stereogenic centers related to our target molecules was readily achieved using aqueous acidic conditions. Thus, treatment of epoxyamine **7** with 3 M H_2SO_4 in refluxing *p*-dioxane gave exclusively the desired (2*R*,3*R*,4*R*)-amino triol as a result of the electron withdrawing ammonium group-directed C-2 hydrolysis.[11] As expected, under such conditions, concomitant cleavage of the silyl ether protecting-group occurred. Unambiguous assignment of the configuration of **7** was first confirmed

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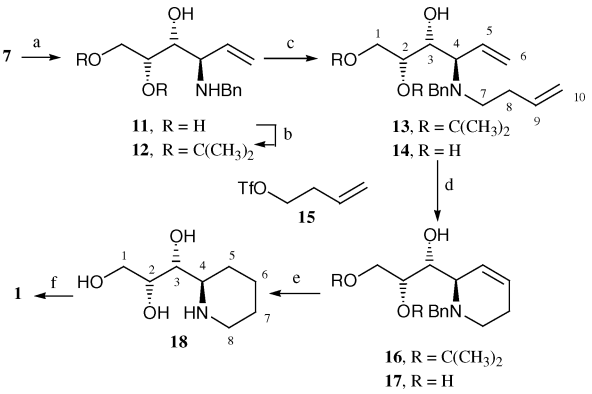
by the total synthesis of the known 1,4-dideoxy-1,4-imino-D-arabinitol[5c] and by its transformation into the targeted (−)-lentiginosine (**1**) (*vide infra*).

With the advanced intermediate **11** in hand, we embarked on the synthesis of (−)-lentiginosine according the sequence depicted in Scheme 3. In order to secure our plan, preliminary studies were first conducted on the partially protected derivative **12**. Thus, exposure of **11** to 2,2-dimethoxypropane in the presence of a catalytic amount of camphorsulfonic acid (CSA), cleanly proceeded to give the corresponding (1,2)-acetonide in 80% isolated yield. At this stage, introduction of the butenyl moiety as the second olefinic partner necessary for tetrahydropyridine ring construction, *via* the key RCM step, turned out to be particularly reluctant. Indeed, initial attempts to alkylate the secondary amine **12** with 1-bromobutene under standard reaction conditions (Et_3N, NaI, THF, reflux or K_2CO_3, NaI, DMF, 100 °C) were unsuccessful and led at the best, to the recovery of the starting material. Similar results were obtained when the reaction was conducted with the tosylate derivative instead of the bromide. In view of these unsuccessful results, we turned our attention to the use of the much more reactive but-3-en-1-yl trifluoromethanesulfonate (**15**) as a potential electrophilic reagent. Although preparation of **15** from the corresponding alcohol had been mentioned to proceed well,[12] in our hands the use of such standard conditions (*i*-Pr_2EtN, triflic anhydride, CH_2Cl_2) invariably resulted in low yield (*ca.* 20%). We reasoned that the presence of salts in the raw material might be detrimental to the distillation. Filtering the crude product on heat-activated silica prior to distillation, thus affording **15** in 70% yield, indeed solved the problem. Then we were very pleased to find that exposure of compound **12** to 1.2 eq. of but-3-en-1-yl trifluoromethanesulfonate (**15**) in presence of 1.2 eq. of the hindered 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 proceeded smoothly (over 24 h) to afford the expected diene **13**, albeit in a low yield (25%), along with 70% yield of the recovered starting material. Somewhat surprising was that completion of the reaction could not be achieved, even under forced conditions. In each attempt, and despite a relatively clean transformation as judged by TLC monitoring, compound **13** was isolated in typically low yield 25–30% with only 30–50% of conversion.



Scheme 3 *Reagents and conditions*: a) 3 M H_2SO_4, *p*-dioxane, reflux, 70%; b) dimethoxypropane, CSA, rt, 80%; c) but-3-en-1-yl trifluoromethanesulfonate (**15**), proton-sponge®, CH_2Cl_2, rt, 67%; d) Grubbs II catalyst, toluene, 70 °C, 66%; e) 12 bars H_2, 10% Pd/C, MeOH, 12 M HCl (cat.), 90%; f) PPh_3, CCl_4, Et_3N, DMF, rt, 68%.

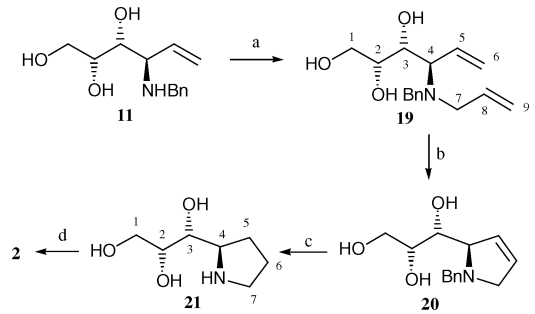
These observations led us to assume that aminoalcohols **12** and/or **13** could be converted into non-nucleophilic ammonium salts through competitive quenching of the trifluoromethane sulfonic acid generated in the course of the reaction, thus preventing its completion. We therefore thought that the use of a strongly sequestering base would lead to a more favourable issue. The proton-sponge® (1,8-bis(dimethylamino)naphthalene) turned out to be an excellent base for this purpose, yielding diene **13** in 72% isolated yield.

Our next objective was to construct the required tetrahydropyridine **16** by ruthenium-catalysed RCM. Unfortunately, treatment of **13** with 5–10% mol of either Grubbs I or Grubbs II catalyst in refluxing CH_2Cl_2 completely failed to provide the cyclised product.[13] Pleasingly, when the second generation catalyst was used in toluene at 70 °C, instead of refluxing CH_2Cl_2, tetrahydropyridine **16** was rapidly (over *ca.* 50 min) obtained in 72% yield after purification.

With the above pilot experiment completed, we concentrated our efforts to its application to the free triol **11**, according to our synthetic plan. Thus, treatment of *N*-benzyl derivative **11** with 1.2 eq. of but-3-en-1-yl trifluoromethanesulfonate (**15**) in the presence of proton sponge® gave the diolefin **14**, which was then cyclised under the RCM conditions described above to provide **17** in 67% yield after purification. It should be noted that, to the best of our knowledge, although ruthenium-based RCM catalysts are known to be tolerant to a wide variety of functionalities, no previous reports have dealt with a dienic substrate bearing three non-protected hydroxyl groups such as **14**. Compound **17** represents an attractive platform for further oxidative functionalisation on the remaining olefin, thereby offering a potential access to a variety of polyhydroxylated indolizidines.[14]

Completion of the synthesis required three further transformations. One-pot *N*-debenzylation and reduction of the olefin by catalytic hydrogenation provided after simple filtration on Celite® the corresponding piperidine **18**, in nearly quantitative yield. The latter was then directly submitted to Appel cyclisation conditions, which smoothly delivered (−)-lentiginosine (**1**) in 67% isolated yield through a remarkably selective activation of the primary hydroxyl group. The ^1H NMR, ^{13}C NMR and mass spectra of our synthetic sample were in agreement with those reported in the literature.[9]

With the preparation of (−)-lentiginosine successfully accomplished, attention was then focused on the synthesis of the original target compound **2** (Scheme 4) *via* a parallel synthetic route. Allylation of amino triol **11** under standard conditions proceeded cleanly to afford, in 85% yield, the dienic precursor **19** required for the RCM. However, unsatisfactory results were obtained under the conditions previously used for the preparation of (−)-lentiginosine precursor **17**. In fact, although a fast reaction ensued, the expected dihydropyrrole **20** was isolated in moderate yield (50%) accompanied by oligomeric products. Extended reaction times resulted in decomposition of both starting material and product.



Scheme 4 *Reagents and conditions*: a) allyl bromide, $NaHCO_3$, THF–H_2O, rt 85%; b) Grubbs I catalyst, CH_2Cl_2, reflux, 70%; c) 12 bars H_2, 10% Pd/C, MeOH, 12 M HCl (cat.), 90%; d) PPh_3, CCl_4, Et_3N, DMF, rt, 68%.

It was clear that in this case, the greater reactivity of the second-generation Grubbs' catalyst was detrimental to the success of the reaction. Much to our delight, the dihydropyrrole derivative **20** was obtained in a 70% yield when the reaction was carried out using the less reactive Grubbs I catalyst in refluxing CH_2Cl_2. Finally, sequential catalytic hydrogenation–Appel cyclisation was again used to convert **20** into dihydroxypyrrolizidine **2** *via* pyrrolidine intermediate **21** (61% overall yield).

Biological evaluation

This synthetic work was complemented by enzymatic inhibition experiments with respect to the amyloglucosidase from *Aspergillus niger*. The enzymatic assay was performed in the presence of 0.01 to 0.5 u ml^{-1} of 1,4-α-D-glucanglucohydrolase from *Aspergillus niger*. After preincubation with the inhibitor, 5 mM of an aqueous solution of *p*-nitrophenyl glucoside used as substrate was added and the mixture was allowed to react at 45 °C for 20 min. After quenching, the inhibitory activity was determined spectrophotometrically ($\lambda = 410$ nm) by measuring the quantity of *p*-nitrophenate released. An IC_{50} of 25.5 μg mL^{-1} was measured for our sample of (−)-lentiginosine (**1**). This is in agreement with the IC_{50} value (17 μg mL^{-1}) that Brandi *et al.* found for the laevorotatory isomer, proposed to be the unnatural enantiomer of lentiginosine.[15] The novel dihydroxylated pyrrolizidine **2** was found to display an IC_{50} of 27.3 μg mL^{-1}, comparable with that of (−)-lentiginosine, and to behave as a competitive inhibitor ($K_i = 121$ μM).

Conclusion

In conclusion, we achieved the total synthesis of (−)-lentiginosine (**1**) and of its pyrrolizidinic analogue **2** through a common straightforward five-step sequence in 19 and 26% overall yield respectively, from the versatile chiral *cis* α,β-epoxyamine **7**. Interestingly, the activity of the more easily accessible pyrrolizidinic analogue **2** is quite similar to that of (−)-lentiginosine.

A key feature of these syntheses is the RCM of highly functionalised aminotriols **14** and **19**. Tetrahydropyridine **17** and dihydropyrrole **20** thus prepared constitute valuable intermediates for further late transformations, *via* oxidation of the olefin. In addition, the starting epoxyamine being equally available in both optical series and *cis* or *trans* isomeric structures, the chemistry disclosed here opens an expeditious route to the synthesis of a large number of indolizidines and pyrrolizidines iminosugars of biological interest. Efforts toward this aim are currently in progress in our laboratory and will be reported in due course.

Experimental

General methods

Reactions were performed in flame-dried glass, sealed with a rubber septum, and stirred with a magnetic stirring bar, under argon or nitrogen when required. Materials were obtained from commercial suppliers and were used without purification, unless otherwise stated. The following solvents were dried prior to use: CH_2Cl_2 (freshly distilled from calcium hydride), DMF (from calcium hydride, stored over 4-Å molecular sieves), Et_2O and THF (distilled from sodium–benzophenone), toluene (distilled from calcium hydride). Thin layer chromatography (TLC) reaction monitoring was carried out with Macherey-Nagel ALUGRAM® SIL G/UV_{254} (0.2 mm) plates visualised with 10% phosphomolybdic acid in ethanol or Dragendorff reagent as dipping solutions. Standard column chromatography was performed with SDS 70–200 μm silica gel. Flash column chromatography was carried out with SDS 35–70 μm silica gel. Medium-pressure liquid chromatography was performed with a Jobin-Yvon apparatus using Merck 15–40 μm silica gel. Deactivated silica gel was obtained by treatment with 2.5% v/v Et_3N. NMR spectroscopic data were obtained with Bruker AC200, AC250, and AC400 instruments operating for ^1H spectra at 200, 250, and 400 MHz, and ^{13}C spectra at 50, 63, and 100 MHz, respectively. Chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane and coupling constants are in Hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrometer. High-resolution mass spectra (HRMS) were performed on a ThermoFinnigan MAT 95 XL spectrometer (DCI). Optical rotations were measured on a Perkin-Elmer model 141 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}.

(1*R*,2*R*)-2-(Benzylamino)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-1-ol (12)

To aminotriol **11** (200 mg, 0.84 mmol) dissolved in 10 mL of freshly distilled 2,2-dimethoxypropane, camphorsulfonic acid (46 mg, 0.93 mmol) was added. After stirring for 48 h in an inert atmosphere at room temperature, the reaction mixture was neutralised by addition of saturated aq. $NaHCO_3$ (5 mL). The 2,2-dimethoxypropane was then evaporated under reduced pressure and the resulting aqueous solution extracted with Et_2O (3 × 50 mL). The combined organic layers were successively washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with petroleum ether–EtOAc (70 : 30) to afford acetonide **12** (186 mg, 0.82 mmol, 80% yield). $R_f = 0.25$ (petroleum ether–EtOAc, 70 : 30). $[\alpha]_D^{25}$ −3.0 (*c* 1.30 in $CHCl_3$). ν_{max} (film)/cm^{-1}: 3256 (O–H), 1499 (C=C); δ_H (250 MHz, $CDCl_3$) 1.32 (s, 6H, 2 × Me), 3.02 (pseudot, $^3J_{H4H5} = {}^3J_{H4H3} = 7.8$ Hz, 1H, H-4), 3.20–3.47 (m, 1H, O-*H*), 3.50–3.60 (m, 3H, H-1′, H-3 and 1 × NCH_2Ph), 3.70–3.90 (m, 3H, H-1, H-2 and 1 × NCH_2Ph), 5.19 (dd, $^2J_{gem} = 1.1$ Hz and $^3J_{H6'H5} = 17.2$ Hz, 1H, H-6′), 5.33 (dd, $^2J_{gem} = 1.1$ Hz and $^3J_{H6H5} = 10.2$ Hz, 1H, H-6), 5.62–5.77 (m, 1H, H-5), 7.20–7.28 (m, 5H, H-Ph); δ_C (63 MHz, $CDCl_3$) 26.9, 26.8 (2 × Me), 50.8 (NCH_2Ph), 62.3 (C-4), 62.8 (C-1), 80.5 (C-2), 82.3 (C-3), 108.7 (Cquat. acetonide), 118.5 (C-6), 127.4, 128.6 (CH arom.), 136.2 (C-5), 138.8 (Cquat. arom.); HRMS (DCI/NH_3) *m*/*z*: Calc. for $C_{16}H_{24}NO_3$ 278.1756, found 278.1752.

But-3-en-1-yl trifluoromethanesulfonate (15)

To a solution of but-3-en-1-ol (586 mg, 8.10 mmol) and diisopropylethylamine (1.15 g, 8.90 mmol) dissolved in 35 mL of freshly distilled CH_2Cl_2, triflic anhydride (1.50 mL, 8.90 mmol) was added dropwise, at 0 °C in an inert atmosphere. After stirring for 2 h at this temperature, the reaction mixture was allowed to warm to room temperature for 30 min before being rapidly filtered through a plug of activated silica (70–200 μm, heated overnight at 110 °C in an oven), and rinsed with freshly distilled CH_2Cl_2 (20 mL) to remove the salt. The solvent was then evaporated *in vacuo* and the crude product was purified by distillation under reduced pressure (65 °C/10 mbar) to afford pure **15** as an colorless liquid which can be stored for a few weeks at −20 °C (1.55 mg, 70% yield). ν_{max} (film)/cm^{-1}: 1425, 1355, 1220, 1150, 960; δ_H (250 MHz, $CDCl_3$) 2.59 (pseudoq, 2H, $^3J_{H2H1} = {}^3J_{H2H3} = 6.6$ Hz, H-2), 4.56 (t, 2H, $^3J_{H1H2} = 6.6$ Hz, H-1), 5.18–5.30 (m, 2H, 2 × H-4), 5.67–5.82 (m, 1H, H-3); δ_C (63 MHz, $CDCl_3$) 33.5 (C-2), 76.1 (C-1), 119.5 (C-4), 131.1 (C-3).

(1*R*,2*R*)-2-[Benzyl(but-3-en-1-yl)amino]-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-1-ol (13)

In an inert atmosphere at room temperature, 1,8-bis(dimethylamino)naphthalene (289 mg, 1.35 mmol) and but-3-en-1-yl trifluoromethanesulfonate (**15**) (110 mg, 0.54 mmol) were successively added to a solution of acetonide **12** (250 mg, 0.90 mmol) dissolved in 10 mL of anhydrous CH_2Cl_2. After stirring for 6 h at this temperature, but-3-en-1-yl trifluoromethanesulfonate (**15**) (110 mg, 0.54 mmol) was again added. The reaction mixture was then stirred overnight before being neutralised by addition of saturated aq. $NaHCO_3$ (10 mL). The resulting aqueous solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were successively washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel eluting with petroleum ether–EtOAc (gradient 85 : 15 to 75 : 25) afforded pure **13** (214 mg, 0.64 mmol, 72% yield).

$R_f = 0.30$ (solvent petroleum ether–AcOEt, 75 : 25). $[\alpha]_D^{25}$ −23.2 (*c* 1.70 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3256 (O–H), 1499 (C=C); δ_H (250 MHz, $CDCl_3$) 1.26 (s, 3H, Me), 1.36 (s, 3H, Me), 2.27–2.34 (m, 2H, 2 × H-8), 2.36–2.47 (m, 1H, H-7′), 2.69–2.81 (m, 1H, H-7), 3.07 (pseudot, 1H, $^3J_{H4H3} = {}^3J_{H4H5} = 8.8$ Hz, H-4), 3.63 (AB_q, 2H, $^2J_{gem} = 13.3$ Hz, NCH_2Ph) $\Delta\delta a - \delta b = 140.2$ Hz, 3.55–3.62 (m, 1H, H-2), 3.72 (AB of an ABX, 2H, $^3J_{H1'H2} = 3.8$ Hz, $^3J_{H1H2} = 6.1$ Hz and $^2J_{gem} = 10.7$ Hz, 2 × H-1), $\Delta\delta a - \delta b = 28.0$ Hz, 3.95 (pseudot, 1H, $^3J_{H3H2} = {}^3J_{H3H4} = 7.9$ Hz, H-3), 4.99–5.10 (m, 2H, 2 × H-10), 5.19 (dd, 1H, $^2J_{gem} = 1.8$ Hz and $^3J_{H6'H5} = 17.2$ Hz, H-6′), 5.46 (dd, 1H, $^2J_{gem} = 1.8$ Hz and $^3J_{H6H5} = 10.2$ Hz, H-6), 5.68–5.95 (m, 2H, H-5 and H-9), 7.20–7.40 (m, 5H, H–Ph); δ_C (63 MHz, $CDCl_3$) 26.8, 26.9 (2 × Me), 32.6 (C-8), 50.1 (C-7), 55.6 (NCH_2Ph), 62.7 (C-1), 64.9 (C-4), 79.2 (C-3), 81.1 (C-2), 108.8 (Cquat. acetonide), 116.1 (C-10), 121.2 (C-6), 127.4, 128.5, 129.4 (CH arom.), 131.8 (C-9), 136.1 (C-5), 138.1 (Cquat. arom.); HRMS (DCI/NH_3) *m*/*z*: Calc. for $C_{20}H_{30}NO_3$ 332.2226, found 332.2226.

(2*R*,3*R*,4*R*)-4-[Benzyl(but-3-en-1-yl)amino]hex-5-ene-1,2,3-triol (14)

By applying to aminotriol **11** (200 mg, 0.84 mmol) the alkylation procedure described above for compound **13**, pure diene **14** (163 mg, 0.56 mmol, 67% yield) was obtained after purification by flash column chromatography on deactivated silica gel eluting with AcOEt–THF–MeOH (gradient from 83 : 17 : 0 to 78 : 17 : 5). $R_f = 0.31$ (solvent AcOEt–THF–MeOH, 80 : 17 : 3 in a saturated atmosphere of NH_3). $[\alpha]_D^{25}$ −15.8 (*c* 0.90 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3490, 1495; δ_H (250 MHz, $CDCl_3$) 2.18–2.31 (m, 2H, 2 × H-8), 2.38–2.53 (m, 1H, H-7′), 2.59–2.74 (m, 1H, H-7), 3.10–3.30 (m, 4H, H-4 and 3 × O-*H*), 3.48–3.62 (m, 2H, 2 × H-1), 3.59 (AB_q, 2H, $^2J_{gem} = 13.5$ Hz, NCH_2Ph), $\Delta\delta a - \delta b = 118$ Hz, 3.72 (dd, 1H, $^3J_{H3H2} = 2.7$ Hz and $^3J_{H3H4} = 8.9$ Hz, H-3), 3.94–4.03 (m, 1H, H-2), 4.96–5.11 (m, 2H, 2 × H-10), 5.24 (dd, 1H, $^2J_{gem} = 1.7$ Hz and $^3J_{H6'H5} = 17.0$ Hz, H-6′), 5.45 (dd, 1H, $^2J_{gem} = 1.7$ Hz and $^3J_{H6H5} = 10.2$ Hz, H-6), 5.68–5.87 (m, 2H, H-5 and H-9), 7.20–7.37 (m, 5H, H–Ph); δ_C (63 MHz, $CDCl_3$) 32.6 (C-8), 50.1 (C-7), 55.2 (NCH_2Ph), 64.5 (C-4), 64.4 (C-1), 70.9 (C-2), 71.2 (C-3), 116.2 (C-10), 121.7 (C-6), 127.3, 128.5, 128.6, 129.1 (CH arom.), 132.6 (C-9), 136.6 (C-5), 139.2 (Cquat. arom.); HRMS (DCI/NH_3) *m*/*z*: Calc. for $C_{17}H_{26}NO_3$ 292.1913, found 292.1911.

(*R*)-[(2*R*)-1-Benzyl-1,2,5,6-tetrahydropyridin-2-yl][(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (16)

The RCM precursor **13** (100 mg, 0,34 mmol) was dissolved in 10 mL of dry toluene and the solution degassed by bubbling with argon over 30 min. Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (GrubbsII catalyst) (23 mg, 8% mol) was then added and the mixture was stirred at 70 °C in an inert atmosphere until TLC analysis showed no remaining starting material (*ca.* 50 min). The reaction mixture was then allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash column chromatography on deactivated silica gel eluting with petroleum ether–EtOAc (gradient from 85 : 15 to 70 : 30) to afford **16** (79 mg, 0.26 mmol, 77% yield). $R_f = 0.24$ (solvent petroleum ether–AcOEt, 75 : 25 in a saturated atmosphere of NH_3). $[\alpha]_D^{25}$ +25.6 (*c* 0.40 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3352 (O–H), 1625 (C=C); δ_H (400 MHz, $CDCl_3$) 1.83 (dpseudot, 1H, $^3J_{H7'H8} = {}^3J_{H7'H8'} = 4.8$ Hz and $^2J_{gem} = 18.3$ Hz, H-7′), 2.32–2.42 (m, 1H, H-7), 2.88 (AB of an ABX, 2H, $^3J_{H8'H7} = 4.7$ Hz, $^3J_{H8H7'} = 5.0$ Hz and $^2J_{gem} = 14.2$ Hz, 2 × H-8) $\Delta\delta a - \delta b = 55.0$ Hz, 2.90 (dd, 1H, $^3J_{H4H3} = 4.7$ Hz and $^2J_{H4H5} = 14.0$ Hz, H-4), 3.54–3.59 (m, 1H, H-2), 3.70 (AB of an ABX, 2H, $^3J_{H1H2} = 3.2$ Hz, $^3J_{H1'H2} = 9.1$ Hz and $^2J_{gem} = 9.7$ Hz, 2 × H-1) $\Delta\delta a - \delta b = 150.0$ Hz, 3.74–3.80 (m, 3H, H-3 and NCH_2Ph), 5.87–5.92 (m, 2H, H-5), 6.02–6.06 (m, 2H, H-6), 7.28–7.38 (m, 5H, H–Ph); δ_C (100 MHz, $CDCl_3$) 18.9 (C-7), 26.9, 27.0 (2 × Me), 42.9 (C-8), 57.7 (NCH_2Ph), 59.2 (C-4), 63.5 (C-1), 81.0 (C-2), 83.7 (C-3), 108.9 (Cquat. acetonide), 125.9 (C-5), 126.5 (C-6), 128.0, 128.7, 130.2 (CH arom.), 136.9 (Cquat. arom.); HRMS (DCI/NH_3) *m*/*z*: Calc. for $C_{18}H_{26}NO_3$ 304.1913, found 304.1912.

(1*R*,2*R*)-1-[(2*R*)-1-Benzyl-1,2,5,6-tetrahydropyridin-2-yl]propane-1,2,3-triol (17)

Following the procedure described above for the preparation of **16**, starting aminotriol **14** (100 mg, 0.34 mmol) gave after reaction and purification by flash preparative chromatography (silica gel, eluent AcOEt–THF–MeOH (80 : 10 : 10 in a saturated atmosphere of NH_3), the tetrahydropyridine **17** (60 mg, 0.22 mmol, 66% yield). $R_f = 0.20$ (solvent AcOEt–THF–MeOH, 90 : 10 : 10 in a saturated atmosphere of NH_3). $[\alpha]_D^{25}$ +35.0 (*c* 3.00 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3365 (O–H); δ_H (250 MHz, $CDCl_3$–D_2O) 2.00–2.10 (m, 2H, 2 × H-7), 2.34–2.45 (m, 1H, H-8′), 2.94 (dpseudot, 1H, $^3J_{H8H7'} = {}^3J_{H8H7} = 5.2$ Hz and $^2J_{gem} = 12.1$ Hz, H-8), 3.35–3.40 (m, 1H, H-4), 3.72 (AB of an ABX, 2H, $^3J_{H1'H2} = 3.9$ Hz, $^3J_{H1H2} = 4.2$ Hz and $^2J_{gem} = 11.6$ Hz, 2 × H-1) $\Delta\delta a - \delta b = 27.3$ Hz, 3.92 (AB_q, 2H, $^2J_{gem} = 13.0$ Hz, NCH_2Ph) $\Delta\delta a - \delta b = 238$ Hz, 3.85–3.93 (m, 2H, H-2 and H-3), 5.61–5.66 (m, 1H, H-5), 5.99–6.04 (m, 1H, H-6), 7.26–7.35 (m, 5H, H–Ph); δ_C (63 MHz, $CDCl_3$–D_2O) 23.1 (C-7), 46.6 (C-8), 60.3 (NCH_2Ph), 62.2 (C-4), 65.1 (C-1), 71.0 (C-2), 74.5 (C-3), 125.8 (C-5), 127.4 (C-6), 128.4, 128.5, 129.3 (CH arom.), 138.2 (Cquat. arom.); HRMS (DCI/NH_3) *m*/*z*: Calc. for $C_{15}H_{22}NO_3$ 264.1600, found 264.1599.

(1*R*,2*R*)-1-[(2*R*)-Piperidin-2-yl]propane-1,2,3-triol (18)

To a solution of **17** (60 mg, 0.23 mmol) in MeOH (4 mL) containing 12 M HCl (3 drops) was added 10% Pd/C (12 mg) and the resulting suspension was stirred under 12 bars of H_2. After 4 days, the reaction mixture was filtered through Celite® and concentrated to dryness under reduced pressure. The crude product was then dissolved in H_2O–MeOH (66 : 33) 10 mL, acidic resin (Dowex 50 WX8, 100–200 mesh, 5 g) was added and the suspension was stirred slowly for 1 h before being filtered. The resin was successively rinsed with water (150 mL) and MeOH (50 mL), taken up in 2.5 M aqueous NH_4OH (20 ml) and the mixture stirred slowly for 1 h. The suspension was then filtered and the resin rinsed with 2.5 M aqueous NH_4OH (200 mL). The resulting solution was lyophilised to give piperidine **18** (37 mg, 0.21 mmol, 92% yield). $R_f = 0.30$ (solvent AcOEt–petroleum ether: 25 : 75). $[\alpha]_D^{25}$ −6.8 (*c* 3.00 in MeOH); ν_{max} (film)/cm^{-1}: 3335 (O–H); δ_H (400 MHz, CD_3OD–D_2O) 1.28–1.55 (m, 3H, H-5′, H-6′ and H-7′), 1.65–1.72 (m, 1H, H-7), 1.88–1.92 (m, 2H, H-5 and H-6), 2.68 (dpseudot, 1H, $^3J_{H8'H7} = {}^3J_{H8'H7'} = 2.6$ Hz and $^2J_{gem} = 12.3$ Hz, H-8′), 2.82–2.88 (m, 1H, H-4), 3.15 (d, 1H, $^2J_{gem} = 12.3$ Hz, H-8), 3.53 (dd, 1H, $^3J_{H3H2} = 3.2$ Hz and $^3J_{H3H4} = 5.5$ Hz, H-3), 3.59–3.67 (m, 2H, 2 × H-1), 3.71–3.75 (m, 1H, H-2); δ_C (100 MHz, CD_3OD–D_2O) 23.8 (C-6), 25.2 (C-7), 27.1 (C-5), 46.2 (C-8), 59.2 (C-4), 63.3 (C-1), 71.8 (C-2), 72.9 (C-3); MS (DCI/NH_3) *m*/*z*: 176 (MH^+, 100%).

(−)-Lentiginosine (1)

To a solution of amino triol **18** (36.4 mg, 0.21 mmol) in anhydrous DMF (4 mL) were successively added Ph_3P (113 mg, 0.42 mmol), CCl_4 (56 μL, 0.42 mmol) and Et_3N (58.5 μL, 0.42 mmol). After stirring overnight at room temperature in an inert atmosphere, MeOH (0.5 mL) was added. The reaction mixture was then stirred for an additional 45 min before being concentrated to dryness under reduce pressure. The crude product was dissolved in H_2O–MeOH (66 : 33) 10 mL, acidic resin (Dowex 50 WX8, 100–200 mesh, 5 g) was added and the suspension was stirred slowly for 1 h before being filtered. The resin was successively rinsed with water (150 mL) and MeOH

(50 mL), taken up in 2.5 M aqueous NH_4OH (20 ml) and the mixture stirred slowly for 1 h. The suspension was then filtered and the resin rinsed with 2.5 M aqueous NH_4OH (200 mL). The resulting solution was lyophilised and the residue obtained was purified by flash column chromatography on deactivated silica gel eluting with CH_2Cl_2–MeOH–NH_4OH (gradient from 95 : 4 : 1 to 89 : 10 : 1) to give (−)-lentiginosine (**1**) (22 mg, 0.14 mmol, 67% yield). $R_f = 0.33$ (solvent CH_2Cl_2–MeOH–NH_4OH, 90 : 9 : 1). $[\alpha]_D^{25}$ −2.0 (c 1.01 in MeOH); ν_{max} (film)/cm^{-1}: 3285 (O–H); δ_H (400 MHz, CD_3OD) 1.19–1.35 (m, 4H, H-6′, H-7′ and 2 × O-H), 1.48–1.70 (m, 2H, H-5′ and H-8′), 1.79–1.88 (m, 2H, H-7 and H-8), 1.95–2.09 (m, 2H, H-5 and H-6), 2.70 (AB of an ABX, 2H, $^3J_{H1H2} = 1.4$ Hz, $^3J_{H1'H2} = 7.2$ Hz and $^2J_{gem} = 10.8$ Hz, 2 × H-1) $\Delta\delta a - \delta b = 130.0$ Hz, 2.96–3.02 (m, 1H, H-4), 3.63 (dd, 1H, $^3J_{H3H2} = 3.4$ Hz and $^3J_{H3H4} = 8.4$ Hz, H-3), 3.96 (ddd, 1H, $^3J_{H2H1} = 1.5$ Hz, $^3J_{H2H3} = 3.4$ Hz and $^3J_{H2H1'} = 7.2$ Hz and H-2); δ_C (100 MHz, CD_3OD) 25.8 (C-6), 26.6 (C-7), 30.3 (C-5), 55.4 (C-8), 63.8 (C-1), 72.0 (C-4), 78.5 (C-2), 86.0 (C-3); HRMS (EI) *m/z*: Calc. for $C_8H_{15}NO_2$ 157.1102, found 157.1101.

(2*R*,3*R*,4*R*)-4-[Allyl(benzyl)amino]hex-5-ene-1,2,3-triol (19)

To a solution of **11** (200 mg, 0,84 mmol) in THF–H_2O (4 : 2) were successively added allyl bromide (0.291 μL, 3.36 mmol) and potassium carbonate (697 mg, 5,04 mmol). After stirring for 48 h at room temperature, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 ml) and then with EtOAc (2 × 15 mL). The combined organic layers were successively washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on deactivated silica gel eluting with petroleum ether–Et_2O–AcOEt (gradient from 60 : 10 : 30 to 30 : 10 : 60) to give **19** (197 mg, 0.71 mmol, 85% yield). $R_f = 0,22$ (solvent petroleum ether–Et_2O–AcOEt, 30 : 10 : 60). $[\alpha]_D^{25}$ −2.8 (*c* 1.00 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3465 (O–H), 1489 (C=C); δ_H (250 MHz, $CDCl_3$) 2.91 (dd, 1H, $^3J_{H7'H8} = 8.2$ Hz and $^2J_{gem} = 14.0$ Hz, m, H-7′), 3.20–3.36 (m, 2H, H-4 and H-7), 3.48–3.60 (m, 2H, 2 × H-1), 3.58 (AB_q, 2H, $^2J_{gem} = 13.4$ Hz, NCH_2Ph) $\Delta\delta a - \delta b = 137.5$ Hz, 3.79 (dd, 1H, $^3J_{H3H2} = 3.0$ Hz and $^2J_{H3H4} = 9.1$ Hz, H-3), 4.03–3.98 (m, 1H, H-2), 4.71–4.85 (m, 3H, O–*H*), 5.17–5.32 (m, 3H, H-6′ and 2 × H-9), 5.51 (dd, 1H, $^2J_{gem} = 2.0$ Hz and $^3J_{H6H5} = 10.2$ Hz, H-6), 5.77–5.93 (m, 2H, H-5 and H-8), 7.20–7.37 (m, 5H, H-Ph); δ_C (63 MHz, $CDCl_3$) 53.6 (C-7), 55.6 (NCH_2Ph), 63.9 (C-4), 64.3 (C-1), 71.1 (C-2), 71.5 (C-3), 118.1, 121.6 (C-6 and C-9), 127.3, 128.5, 129.1 (CH arom.), 132.7 (C-8), 136.0 (C-5), 139.0 (Cquat. arom.); HRMS (DCI/NH_3) *m/z*: Calc. for $C_{16}H_{24}NO_3$ 278.1756, found 278.1756.

(1*R*,2*R*)-1-[(2*R*)-1-Benzyl-2,5-dihydro-1*H*-pyrrol-2-yl]propane-1,2,3-triol (20)

To a solution of diene **19** (100 mg, 0,36 mmol) in freshly distilled CH_2Cl_2 (10 mL) was added benzylidene-bis (tricyclohexylphosphine)dichlororuthenium (Grubbs I catalyst) (25 mg, 8% mol) at room temperature. The resulting mixture was refluxed in an inert atmosphere until no remaining starting material could be detected by TLC (*ca.* 5 h). The reaction mixture was then allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash column chromatography on deactivated silica gel eluting with AcOEt–petroleum ether–MeOH (gradient from 60 : 30 : 10 to 80 : 10 : 10) to give **20** (63 mg, 0.25 mmol, 70% yield). $R_f = 0,23$ (solvent AcOEt–petroleum ether–MeOH, 80 : 10 : 10). $[\alpha]_D^{25}$ +60.2 (*c* 2.80 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 3465 (O–H), 1489 (C=C); δ_H (250 MHz, CD_3OD) 3.20–3.31 (m, 1H, H-7′), 3.54–3.69 (m, 3H, 2 × H-1, H-7), 3.71 (dd, 1H, $^3J_{H3H2} = 2.0$ Hz, $^3J_{H3H4} = 4.0$ Hz, H-3), 3.84 (td, 1H, $^3J_{H2H3} = 2.0$ Hz, $^3J_{H2H1} = 6.0$ Hz, H-2), 3.98 (AB_q, 2H, $^2J_{gem} = 13.0$ Hz, NCH_2Ph), $\Delta\delta a - \delta b = 203.0$ Hz, 4.05–4.13 (m, 1H, H-4), 5.75–5.87 (m, 2H, H-5 and H-6), 7.24–7.39 (m, 5H, H–Ph); δ_C (63 MHz, CD_3OD) 60.6 (C-7), 61.2 (NCH_2Ph), 65.7 (C-1), 71.2 (C-2), 72.9 (C-3), 75.4 (C-4), 127.4, 127.5 (C-6 and C-5), 128.8, 128.9, 129.0 (CH arom.), 138.8 (Cquat. arom.); HRMS (DCI/NH_3) *m/z*: Calc. for $C_{14}H_{20}NO_3$ 250.1443, found 250.1447.

(1*R*,2*R*)-1-[(2*R*)-Pyrrolidin-2-yl]propane-1,2,3-triol (21)

Following the catalytic hydrogenation procedure described above for **18**, dihydropyrrole **20** (60 mg, 0.24 mmol) gave after purification pyrrolidine **21** (35 mg, 0.22 mmol, 92% yield). $R_f = 0.18$ (EtOAc–Et_2O–MeOH, 80 : 10 : 10 in a saturated atmosphere of NH_3). $[\alpha]_D^{25}$ +7.8 (*c* 1.80 in MeOH); ν_{max} (film)/cm^{-1}: 3378 (O–H and N–H); δ_C (63 MHz, CD_3OD) 26.3, 28.3 (C-5 and C-6), 47.1 (C-7), 62.3 (C-4), 64.6 (C-1), 73.2, 73.8 (C-3 and C-2); MS (DCI/NH_3) *m/z*: 162 (MH^+, 100%).

(1*R*,2*R*,7a*R*)-Hexahydro-1*H*-pyrrolizine-1,2-diol (2)

Using the Appel cyclisation procedure described above for the preparation of the compound **1**, pyrrolizidine **2** was obtained (18 mg, 0.90 mmol, 68% yield) from **21** after purification by flash column chromatography on deactivated silica gel eluting with CH_2Cl_2–MeOH–EtOH–NH_4OH (gradient from 60 : 10 : 20 : 10 to 50 : 20 : 20 : 10). $R_f = 0.27$ (solvent CH_2Cl_2–MeOH–EtOH–NH_4OH, 50 : 20 : 20 : 10). $[\alpha]_D^{25}$ +7.6 (*c* 1.28 in MeOH); ν_{max} (film)/cm^{-1}: 3465 (O–H); δ_H (400 MHz, CD_3OD) 1.78–1.87 (m, 1H, H-6′), 1.93–2.09 (m, 2H, H-5′ and H-6), 2.10–2.20 (m, 1H, H-5), 2.90–3.23 (m, 1H, H-7′), 3.25–3.28 (m, 1H, H-7), 3.19 (AB of an ABX, 2H, $^3J_{H1'H2} = 4.4$ Hz, $^3J_{H1H2} = 5.2$ and $^2J_{gem} = 11.60$ Hz, 2 × H-1) $\Delta\delta a - \delta b = 230.0$ Hz, 3.55–3.63 (m, 1H, H-4), 3.88–3.95 (m, 1H, H-3), 4.13–4.23 (m, 1H, H-2); δ_C (100 MHz, CD_3OD) 28.0 (C-6), 32.1 (C-5), 58.9 (C-7), 61.0 (C-1), 75.0 (C-4), 80.0 (C-2), 82.8 (C-3); HRMS (EI) *m/z*: Calc. for $C_7H_{13}NO_2$ 143.0946, found 143.0950.

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