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Concise asymmetric syntheses of (−)-lentiginosine and of its pyrrolizidinic analogue

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(−)-Lentiginosine and its pyrrolizidinic analogue have been prepared in a straightforward five-step sequence from a versatile chiral *cis*-α,β-epoxyamine.

We recently demonstrated that *cis*-α,β-epoxyamine **1**, readily prepared from the corresponding chiral epoxyaldehyde, is a valuable precursor of five-membered ring azasugars (Fig. 1).[1] We wish to describe here the extension of this methodology to the asymmetric synthesis of polyhydroxylated indolizidines and pyrrolizidines.

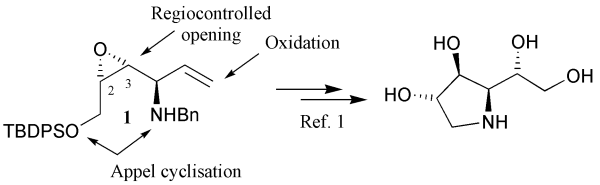


Fig. 1

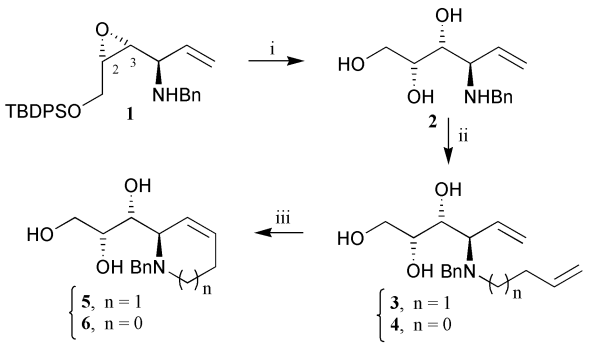
In our previous work, the epoxyamine precursor **1** was efficiently transformed into a polyhydroxylated pyrrolidine *via* the regiocontrolled C-3 opening of the epoxide, followed by the Appel cyclisation of the activated primary alcohol, and olefin dihydroxylation (Fig. 1). We envisioned that the vinyl moiety, instead of being directly oxidised, could be first engaged in a ring closing metathesis (RCM), allowing access to bicyclic analogues of five-membered ring azasugars (Fig. 2).[2] At some stage this would require the attachment onto the amine of a second olefinic partner, namely a butenyl residue for indolizidine syntheses and an allyl moiety for the preparation of pyrrolizidines.

Lentiginosine was targeted to validate our synthetic plan. Indeed this dihydroxylated indolizidine possesses some unique features, being the least hydroxylated biologically active bicyclic azasugar, and the most potent inhibitor of amyloglucosidase.[3] It has therefore inspired a lot of synthetic work, mostly based on chiral pool starting material, relying much more rarely on asymmetric synthesis.[4] We also wished to demonstrate the flexibility of our approach in preparing a novel pyrrolizidinic analogue of lentiginosine.

The amino triol **2**, possessing the relative configuration related to lentiginosine, was prepared in 70% yield by acidic hydrolysis of (2*S*, 3*R*, 4*R*)-α,β-epoxyamine **1** (Scheme 1). Ring opening, occurring exclusively at C-2, was accompanied by the desilylation of the primary alcohol. Direct introduction of the butenyl moiety *via* the alkylation of the unreactive secondary amine **2** then required considerable experimentation. It was however preferred to the alternative amine acylation which implicates an additional carbonyl reduction step.[5] Although most of the conditions tested proved unsuccessful, treatment of **2** with butenyl triflate gratifyingly afforded the desired tertiary amine **3** in 67% yield. Use of proton-sponge® as base proved to be determining for completion of the reaction. The allylation of the secondary amine **2** was achieved in 85% yield under standard conditions to afford **4**.

With the dienic precursors **3** and **4** in hand, we were in a position to test the key RCM step. Preliminary studies were conducted on the partially protected (1,2)-acetonide derivative of **3** (not shown). They indicated that the second generation 1,3-bis(mesityl)-2-imidazolidinylidene-substituted ruthenium Grubbs catalyst (Grubbs II) was superior to the classical benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (Grubbs I) in forming the tetrahydropyridine ring. To our satisfaction, treatment of the fully unprotected precursor **3** with the Grubbs II ruthenium complex in toluene at 70 °C for less than an hour led to the desired cyclised compound **5** in 66% yield (Scheme 1). Formation of the dihydropyrrole ring from the *N*-allylated free triol **4** was best accomplished with the Grubbs I catalyst, giving **6** in 70% yield. Both derivatives **5** and **6** possess an intracyclic olefin well positioned for further oxidative functionalisation. They therefore represent valuable intermediates for the synthesis of various polyhydroxylated bicyclic alkaloids.

Completion of the synthesis required formation of the dihydroxylated five-membered ring of the lentiginosine framework. Catalytic hydrogenation first ensured *N*-debenzylation with concomitant olefin saturation, yielding piperidine **7** and pyrrolidine **8** (Scheme 2). Appel cyclisation of **7** then delivered, in 67% yield, the all-*R*-lentiginosine (**9**). This compound ($[\alpha]^{25}_{D}$ −2.0° (*c* 1.0, MeOH); lit.[3b,4b,4f,4j] −1.6, −2.6, −3.05, −4.5) had spectral data in agreement with that reported in the literature.[4] Dihydroxypyrrolizidine **10** was prepared from **8** in the same manner and in comparable yield.† The starting epoxyamine **1** being equally available in both optical series, this



Scheme 1 *Reagents and conditions*: i, 3 M H_2SO_4 (8 eq.), dioxane, reflux, 70%; ii, for n = 0: allylbromide (4 eq.), $NaHCO_3$ (6 eq.), THF/H_2O, rt, 85%; for n = 1: 4-butenyltrifluoromethanesulfonate (1.2 eq.), proton-sponge® (1.5 eq.), CH_2Cl_2, rt, 67%; iii, for n = 0: Grubbs I cat. (8 mol%), CH_2Cl_2, reflux, 70%; for n = 1: Grubbs II cat. (8 mol%), toluene, 70 °C, 66%. Grubbs I cat.: benzylidene-bis(tricyclohexylphosphine)dichlororuthenium; Grubbs II cat.: benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium.

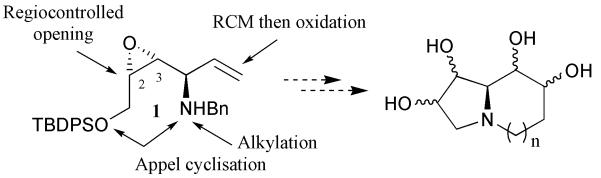


Fig. 2

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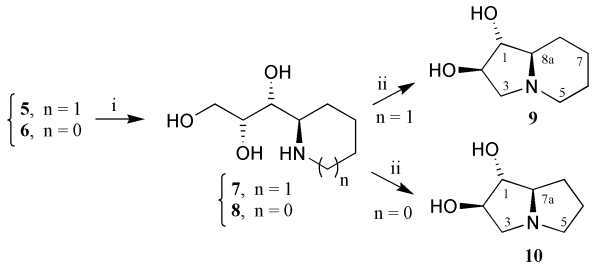

Scheme 2 *Reagents and conditions*: i, 12 bar H_2, 10% Pd/C (10% w/w), MeOH, 12 M HCl (cat.), for $n = 0$, 1: 90%; ii, PPh_3 (2 eq.), CCl_4 (2 eq.), Et_3N (2 eq.), DMF, rt, for $n = 0$, 1: 68%.

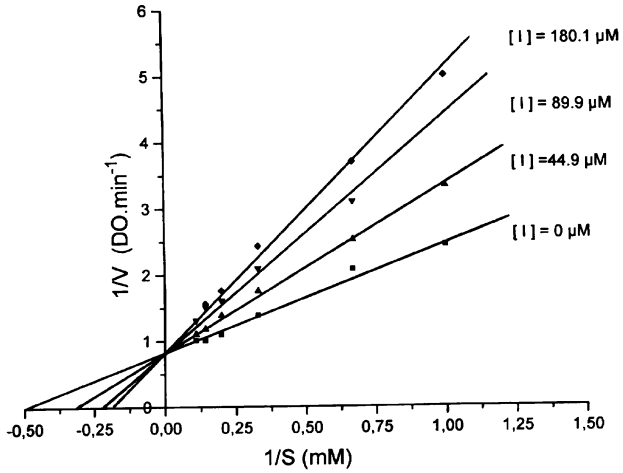

Fig. 3 Effect of substrate (*p*-nitrophenyl-α-D-glucopyranoside) concentration on amyloglucosidase (*Aspegillus niger*) inhibition by various concentrations of **10**.

new route also offers a direct access to the other enantiomer of these bicyclic azasugars.

This synthetic work was complemented by enzymatic inhibition experiments with respect to the amyloglucosidase from *Aspergillus niger*.‡ An IC_{50} of 25.5 µg mL^{-1} was measured for our sample of (−)-lentiginosine. This value is in agreement with the IC_{50} (17 µg mL^{-1}) that Brandi *et al* found for the laevorotatory isomer, proposed to be the unnatural enantiomer of lentiginosine.[3b] The novel dihydroxylated pyrrolizidine **10** 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), as indicated by the Lineweaver–Burk plot shown in Fig. 3.

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Notes and references

† *Characteristic data* for compound **10**: $[\alpha]^{25}_D$ +7.6° (*c* 1.3, MeOH); δ_H (400 MHz, CD_3OD): 4.23–4.13 (1H, m, H-2), 3.90 (1H, br s, H-1), 3.63–3.55 (1H, m, H-7a), 3.19 (2H, AB of ABX, J_{ab} = 11.6 Hz, J_{ax} = 5.2 Hz, J_{bx} = 4.4 Hz ($\delta_a - \delta_b$ = 230 Hz), H-3 and H-3′), 3.28–3.25 (1H, m, H-5), 3.23–2.90 (1H, m, H-5′), 2.26–2.10 (1H, m, H-7), 2.09–1.93 (2H, m, H-7′ and H-6), 1.83–1.78 (1H, m, H-6′); δ_C (100 MHz, CD_3OD): 82.8 (C-1), 80.0 (C-2), 75.0 (C-7a), 61.0 (C-3), 58.9 (C-5), 32.1 (C-7), 28.0 (C-6); mass spectrum (DCI): *m*/*z* 144 (MH^+, 100); HRMS: *m*/*z* (M^+) calc. for $C_7H_{13}NO_2$ 143.0946, found 143.0951.

‡ Conditions were essentially identical to those used in ref. 3*b*.

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5 This stepwise formation of tetrahydropyridine ring has been used in several syntheses of polyhydroxylated indolizidines. For lentiginosine, see: refs. 4*j* and 4*m*. For related alkaloids, see: C. Paolucci and L. Mattioli, *J. Org. Chem.*, 2001, **66**, 4787.