

Synthesis of (+)-DGDP and (–)-7-epialexine†

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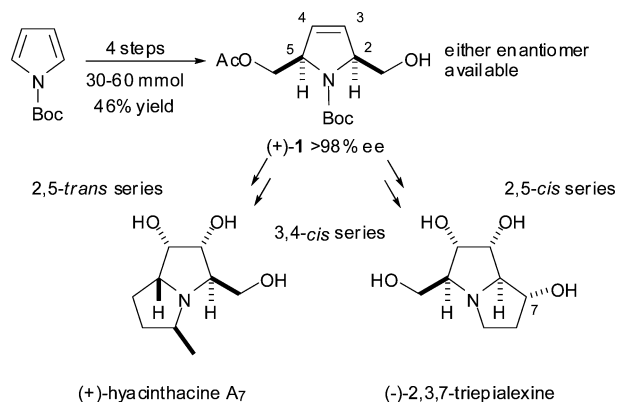
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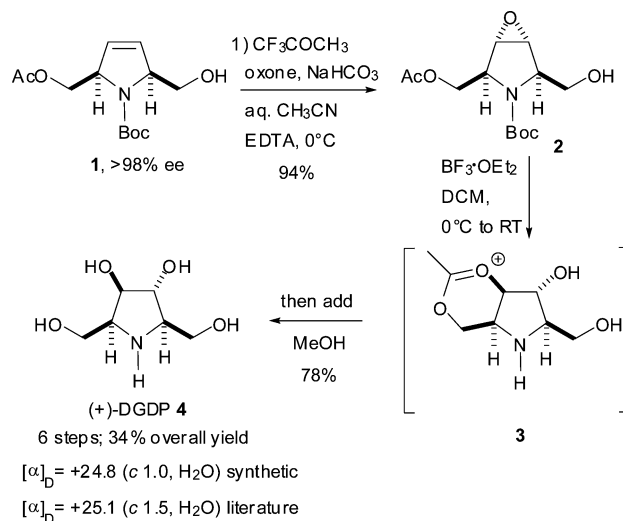
The partial reduction of electron deficient pyrroles is an extremely versatile method that allows us to prepare substituted pyrrolidines and pyrrolizidines with *trans*-diol stereochemistry on the five membered ring.

As part of a programme designed to explore and exploit the partial reduction of heterocycles, we have developed a short, four step sequence to prepare enantiopure mono-acetate **1**, Scheme 1, starting from commercially available *N*-Boc pyrrole.¹ The key steps in this route are a diastereoselective partial reduction reaction and a subsequent enzymatic desymmetrisation. Compound **1** has proven to be very useful in the synthesis of a wide array of natural products and compounds with important biological activity,² notably the pyrrolizidine alkaloids, Scheme 1. One of the limitations of an otherwise extremely flexible route was the requirement to incorporate *cis*-C3,4-diol stereochemistry, which was installed by diastereoselective dihydroxylation of alkene **1**. We now report a solution to the problem of introducing *trans*-C3,4-diol stereochemistry from a cyclic pyrroline, thus allowing access to a widely occurring stereochemical motif.³



Scheme 1 Synthesis of polyhydroxylated pyrrolizidines from **1**.

The essence of our approach can be highlighted in the short (6 step) synthesis of the glycosidase inhibitor (+)-2,5-dideoxy-2,5-imino-D-glucitol (DGDP **4**) Scheme 2.⁴ Thus, compound **1** was epoxidised with high *anti*-stereoselectivity (rationalised on steric



Scheme 2 Synthesis of DGDP **4**.

grounds and confirmed by NOE analysis of **2**) using a dioxirane generated *in situ*.⁵ The acetate group of **2** was then allowed to participate in a highly regio- and stereoselective ring opening reaction at C4 following epoxide activation with $\text{BF}_3 \cdot \text{OEt}_2$.⁶ Under these conditions, the *N*-Boc group was also cleaved and the (putative) intermediate **3** formed; however, the addition of methanol to the reaction mixture had the desired effect of cleaving the acetate-derived protecting groups *in situ* and formed DGDP **4** directly.⁷ The result of this approach is an exceptionally short route to the target compound (6 steps and 34% overall yield). The spectroscopic data exhibited by our synthetic sample matched exactly those in the literature;⁸ furthermore, we confirmed the structure of our material by X-ray crystallographic analysis.⁹

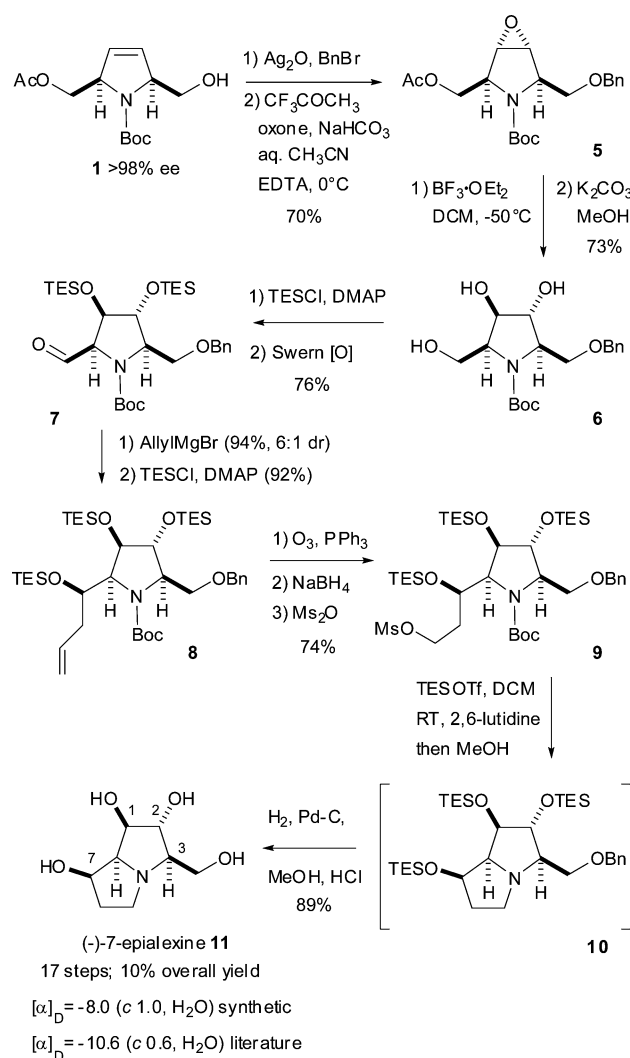
Next we attempted to prepare one of the more complex pyrrolizidine alkaloids that have the same *trans*-C3,4-diol substitution pattern around the pyrrolidine ring. The synthetic challenges to be addressed are as follows: the protection of the free alcohol of **1** without cleavage of the labile OAc group, acetate mediated epoxide opening without cleavage of the *N*-Boc group and finally an appropriate protecting group strategy to allow for subsequent chain extension and formation of the second ring.

Therefore, we embarked upon a route that was related to that described above. Following benzyl protection of **1**,¹⁰ to allow for discrimination between hydroxyl groups later on, the product was reacted under the previously described epoxidation conditions to give epoxide **5** as a single diastereoisomer and in excellent yield over two steps, Scheme 3. The ring opening reaction of epoxide **5** was performed at -50°C so as to prevent *N*-Boc removal under the reaction conditions. The resulting mixture of mono-acetate regioisomers was deprotected by the addition of basic

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Scheme 3 Synthesis of (-)-7-epialexine 11.

methanol, which formed triol **6**.¹¹ Protection of **6** as a tris-OTES ether was followed by the direct and selective oxidation of the primary OTES group by reaction under Swern conditions and gave aldehyde **7**.¹² The addition of allylmagnesium bromide to aldehyde **7** gave a secondary alcohol as a 6 : 1 mixture of (partially separable) diastereoisomers. The major product had arisen from chelation control (to the *N*-Boc) and our attempts to reverse this stereoselectivity and produce the Felkin–Anh isomer were unsuccessful.¹³

Following protection of the alcohol as TES-ether **8** the alkene was cleaved with ozone and then reduced with NaBH_4 . This step could not be performed as a one-pot procedure following ozonolysis because of TES group migration to the primary alcohol during purification. The resulting primary hydroxyl group was activated (Ms_2O) to furnish **9** and TESOTf was then employed to deprotect the *N*-Boc group in order to prevent facile TES-ether deprotection under Lewis acidic conditions. Subsequent addition of methanol to the reaction mixture resulted in cyclisation to give pyrrolizidine **10**. Finally, global deprotection of the crude benzyl ether **10** was carried out under acidic hydrogenolysis conditions to provide (-)-7-epialexine **11** as a colourless oil. The spectroscopic

data for our sample matched that previously reported in the literature.¹⁴

To conclude, this paper reports an epoxidation–intramolecular ring opening approach to enable the *trans*-dihydroxylation of pyrrolidine **1**. The result is an extremely efficient route to *trans*-C3,4-diol configured pyrrolidines. The monocyclic target DGDP **4** was synthesised in only six steps (34% overall yield). More complex targets with *trans*-C3,4-diol stereochemistry, such as the bicyclic 7-epialexine **11**, can also be made *via* this chemistry (17 steps and 10% overall yield). As such, this work complements our earlier studies on routes to pyrrolizidine alkaloids with *cis*-C2,5- and *trans*-C2,5-stereochemistry, which were restricted to the *cis*-C3,4-diol array. Consequently, we now have access to almost every possible stereochemical arrangement within the pyrrolidine ring and this leads to exciting possibilities for the flexible syntheses of pyrrolizidines with important biological activity.

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