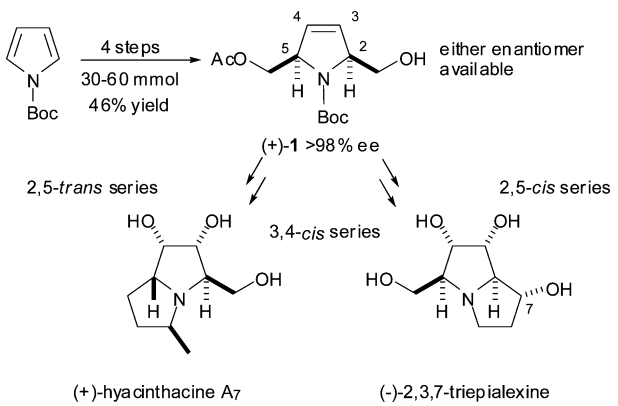
Synthesis of (+)-DGDP and (–)-7-epialexine†

Timothy J. Donohoe,* Matthew D. Cheeseman, Timothy J. C. O'Riordan and Jessica A. Kershaw‡

Received 2nd September 2008, Accepted 3rd September 2008
First published as an Advance Article on the web 19th September 2008
DOI: 10.1039/b815332a

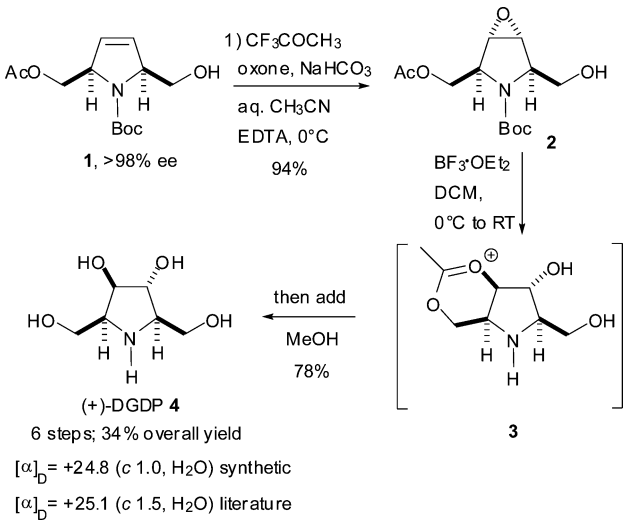
The partial reduction of electron deficient pyrroles is an extremely versatile method that allows us to prepare substituted pyrrolidines and pyrrolizidines with *trans*-diol stereochemistry on the five membered ring.

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 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 $BF_3{\cdot}OEt_2$.[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]



Scheme 2 Synthesis of DGDP **4**.

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.

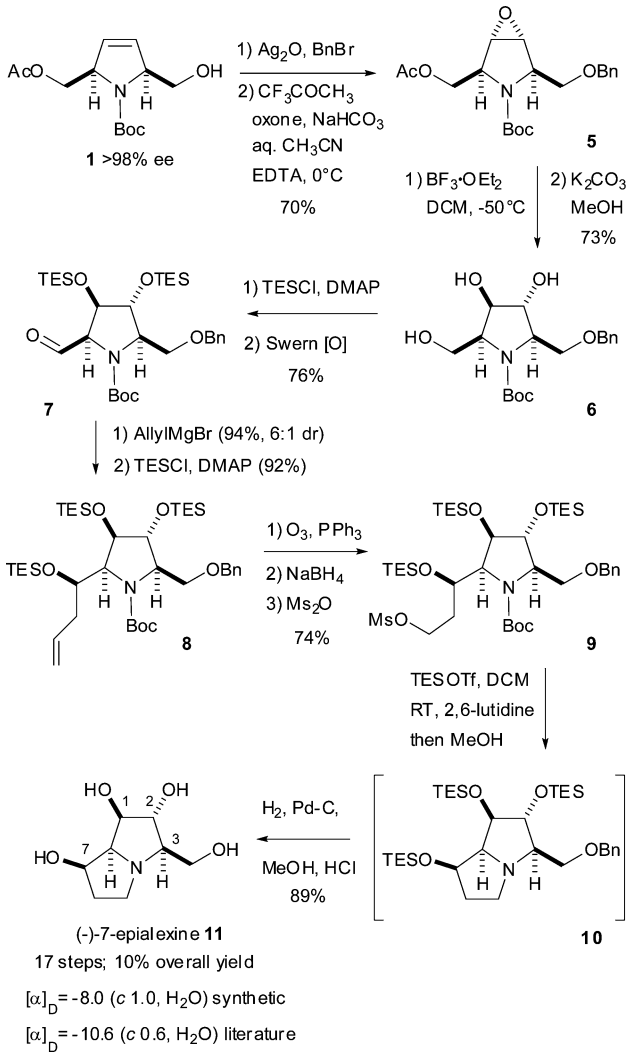
Therefore, we embarked upon a route that was related to that described above. Following benzyl protection of **1**,[10] to allow for discrimination between hydroxyl groups later on, the product was reacted under the previously described epoxidation conditions to give epoxide **5** as a single diastereoisomer 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

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: timothy.donohoe@chem.ox.ac.uk; Tel: +44 (0)1865 275649

† Electronic supplementary information (ESI) available: Details of experimental procedures, NMR data for all new compounds and X-ray crystallographic data. CCDC reference number 695945. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b815332a

‡ Author to whom correspondence regarding the X-ray crystal structure should be addressed.

 This journal is © The Royal Society of Chemistry 2008



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 pyrroline **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.

Acknowledgements

We thank the EPSRC for funding this work and Merck for unrestricted support. We would also like to thank the Oxford Chemical Crystallography Service for instrumentation.

Notes and references

1 (*a*) T. J. Donohoe, C. L. Rigby, R. E. Thomas, W. F. Nieuwenhuys, F. L. Bhatti, A. R. Cowley, G. Bhalay and I. D. Linney, *J. Org. Chem.*, 2006, **71**, 6298; (*b*) T. J. Donohoe, C. E. Headley, R. P. C. Cousins and A. Cowley, *Org. Lett.*, 2003, **5**, 999; (*c*) T. J. Donohoe, R. E. Thomas, M. D. Cheeseman, C. L. Rigby, G. Bhalay and I. Linney, *Org. Lett.*, 2008, **10**, 3615.

2 For a description of the biological activity of polyhydroxylated pyrrolizidine natural products and their epimers see: (*a*) R. J. Nash, P. I. Thomas, R. D. Waigh, G. W. J. Fleet, M. R. Wormald, P. M. Lilley and D. J. Watkin, *Tetrahedron Lett.*, 1994, **35**, 7849; (*b*) A. Kato, E. Kano, I. Adachi, R. J. Molyneux, A. A. Watson, R. J. Nash, G. W. J. Fleet, M. R. Wormald, H. Kizu, K. Ikeda and N. Asano, *Tetrahedron: Asymmetry*, 2003, **14**, 325; (*c*) T. Yamashita, K. Yasuda, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, G. W. J. Fleet and N. Asano, *J. Nat. Prod.*, 2002, **65**, 1875; (*d*) A. Kato, I. Adachi, M. Miyauchi, K. Ikeda, T. Komae, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, M. R. Wormald, G. W. J. Fleet and N. Asano, *Carbohydr. Res.*, 1999, **316**, 95; (*e*) N. Asano, H. Kuroi, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, I. Adachi, A. A. Watson, R. J. Nash and G. W. J. Fleet, *Tetrahedron: Asymmetry*, 2000, **11**, 1; (*f*) N. Asano, *Glycobiology*, 2003, **13**, 93R; (*g*) T. Cox, R. Lachmann, C. Hollak, J. Aerts, S. van Weely, M. Hrebicek, F. Platt, T. Butters, R. Dwek, C. Moyses, I. Gow, D. Elstein and A. Zimran, *Lancet*, 2000, **355**, 1481; (*h*) F. M. Platt, G. R. Neises, G. Reinkensmeier, M. J. Townsend, V. H. Perry, R. L. Proia, B. Winchester, R. A. Dwek and T. Butters, *Science*, 1997, **276**, 428.

3 For examples of the synthesis of polyhydroxylated pyrrolizidines with *trans*-C3,4-diol stereochemistry see: (*a*) M. Dressel, P. Restorp and P. Somfai, *Chem.–Eur. J.*, 2008, **14**, 3072; (*b*) H. Yoda, H. Katoh and K. Takabe, *Tetrahedron Lett.*, 2000, **41**, 7661; (*c*) J. Behr, A. Esard and G. Guillerm, *Eur. J. Org. Chem.*, 2002, 1256; (*d*) D. Koch, S. Maechling and S. Blechert, *Tetrahedron*, 2007, **63**, 7112; (*e*) D. Chikkanna, O. V. Singh, S. B. Kong and H. Han, *Tetrahedron*, 2005, **46**, 8865; (*f*) J. Calveras, J. Casas, T. Parella, J. Joglar and P. Clapes, *Adv. Synth. Catal.*, 2007, **349**, 1661; (*g*) I. Izquierdo, M. T. Plaza, R. Robles and F. Franco, *Tetrahedron: Asymmetry*, 2001, **12**, 2481.

4 For a description of the biological activity of DGDP see: (*a*) Y. Minami, C. Kuriyama, K. Ikeda, A. Kato, K. Takebayashi, I. Adachi, G. W. J. Fleet, A. Kettawan, T. Okamotoe and N. Asanoa, *Bioorg. Med. Chem.*, 2008, **16**, 2734; (*b*) I. Gautier-Lefebvre, J. Behr, G. Guillerm and M. Muzard, *Eur. J. Med. Chem.*, 2005, **40**, 1255; (*c*) C. Wong, L. Provencher, J. Porco, S. Jung, Y. Wang, L. Chen, R. Wang and D. H. Steensma, *J. Org. Chem.*, 1995, **60**, 1492; (*d*) Y. Wang, Y. Takaoka and C. Wong, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1242.

5 For an example when similar conditions have been used to epoxidise *trans*-C2,5-pyrrolines see: B. M. Trost, A. Aponick and B. N. Stanzl, *Chem.–Eur. J.*, 2007, **13**, 9547.
6 For an example where $BF_3{\cdot}OEt_2$ has been used to initiate an intramolecular epoxide ring-opening reaction see: F. E. McDonald, F. Bravo, X. Wang, X. Wei, M. Toganoh, J. R. Rodriguez, B. Do, W. A. Neiwert and K. I. Hardcastle, *J. Org. Chem.*, 2002, **67**, 2525.
7 $BF_3{\cdot}OEt_2$ has previously been shown to be an efficient reagent for *N*-Boc deprotection see: M. Bohno, K. Sugie, H. Imase, Y. B. Yusof, Y. Oishi and N. Chida, *Tetrahedron*, 2007, **63**, 6977. For an example where the combination of $BF_3{\cdot}OEt_2$ and methanol has facilitated OAc deprotection see:; X. Zhu, L. He, G. Yang, M. Lei, S. Chen and J. Yang, *Synlett*, 2006, **20**, 3510.
8 E. W. Baxter and A. B. Reitz, *J. Org. Chem.*, 1994, **59**, 3175.
9 Single crystal X-ray diffraction data for **4**: $C_6H_{13}NO_4$; $M_r = 163.17$; orthorhombic ($P2_12_12_1$); $a = 5.9247(2)$, $b = 7.2417(3)$, $c = 17.4475(9)$ Å; $\alpha = \beta = \gamma = 90°$; $V = 748.58(6)$ Å^3; $T = 150(2)$ K; $Z = 4$; $\mu = 0.121$ mm^{-1}; $D_{calc} = 1.448$ g cm^{-3}; Reflections collected = 1703; independent reflections = 1018 ($R_{int} = 0.031$); R values [$I > 2\sigma(I)$, 796 reflections]: $R_1 = 0.0382$, w$R_2 = 0.0911$. See supplementary information for details†.
10 For an example of Ag_2O mediated benzyl protection on a compound with a potentially labile OAc group see: S. Sano, T. Miwa, K. Hayashi, K. Nozaki, Y. Ozaki and Y. Nagao, *Tetrahedron Lett.*, 2001, **42**, 4029.
11 Following basic aqueous work-up of the epoxide ring-opening reaction, a 1 : 1 mixture of acetate regioisomers at the C4- and C5-hydroxyl was formed.
12 For an example of the oxidation of primary OTES-ethers under Swern conditions in the presence of secondary OTES-ethers see: W. T. Lambert, G. H. Hanson, F. Benayoud and S. D. Burke, *J. Org. Chem.*, 2005, **70**, 9382.
13 All attempts at reagent controlled asymmetric allylation resulted in either recovered starting material or decomposition possibly due to the Lewis acidic conditions required for these reactions. Our previously successful Luche-type allylation reaction (see Ref. 1*c*) on this type of aldehyde and which was selective for the Felkin–Ahn diastereomer failed to give any of the desired product.
14 (*a*) G. W. J. Fleet, M. Haraldson, R. J. Nash and L. E. Fellows, *Tetrahedron Lett.*, 1988, **29**, 5441; (*b*) W. H. Pearson and J. V. Hines, *J. Org. Chem.*, 2000, **65**, 5785; (*c*) A. Romero and C. Wong, *J. Org. Chem.*, 2000, **65**, 8264. Our synthetic sample contains a minor amount of a diastereoisomer which originates from the allyl addition to **7**.

 This journal is © The Royal Society of Chemistry 2008