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Flexibility in the Partial Reduction of 2,5-Disubstituted Pyrroles: Application to the Synthesis of DMDP

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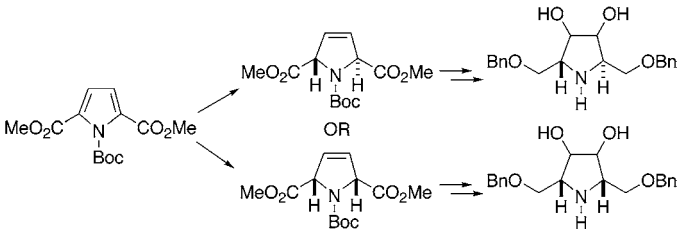
ABSTRACT



The partial reduction of electron-deficient 2,5-disubstituted pyrroles has been developed into a flexible procedure that gives control of relative stereochemistry by variation of the reduction conditions. After the reaction, the pyrroline products were dihydroxylated at C-3,4 to give either the cis or trans isomers; this flexibility means that a variety of polyhydroxylated pyrrolidines can be prepared in a short sequence. Finally, this method was applied to a synthesis of the naturally occurring glycosidase inhibitor DMDP.

Polyhydroxylated pyrrolizidines and pyrrolidines are a series of natural products with intriguing structures and potent biological activity, which centers around their ability to inhibit a variety of glycosidases, Figure 1.[1]

In particular, there are two stereochemical motifs that are common to several of these natural products: most have either cis or trans hydroxymethyl substituents at C-2 and C-5, combined with either a cis or trans array of hydroxyl groups at C-3 and C-4.

Our approach to this polyhydroxylated skeleton derives from the partial reduction of substituted pyrroles[2] and, in

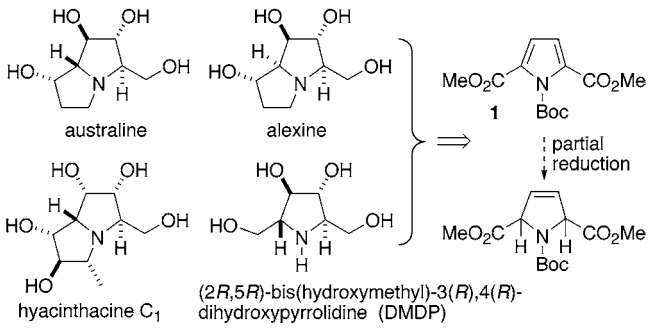


Figure 1.

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(1) See: (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129. (b) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1.

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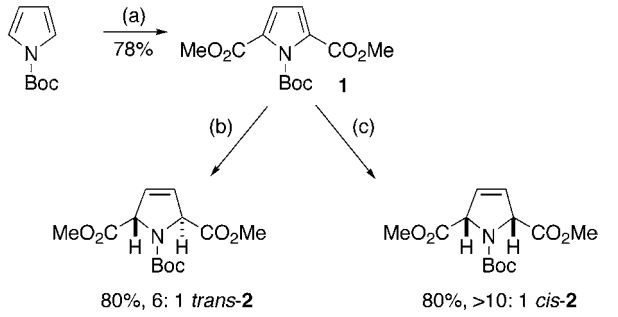
particular, our ability to partially reduce compound **1** (Figure 1).[3] We sought a method of varying the stereochemistry obtained after reduction and, in addition, the means to produce either *cis*- or *trans*-diols at the C-3,4 positions. We view this flexible approach to the simple pyrrolidine skeleton (see DMDP[4]) as an introduction to the synthesis of the more complex pyrrolizidine analogues such as australine, alexine and hyacinthacine C_1.[1]

This program of research relies on an efficient synthesis of the diester starting material **1**. After some experimentation, we found that commercially available *N*-Boc pyrrole could be doubly lithiated with lithium 2,2,6,6-tetramethylpiperidide (LiTMP), followed by a quench with methyl chloroformate, Scheme 1.[5] With a multigram, one-step synthesis of **1** in

Scheme 1[a]



[a] Reagents and conditions: (a) LiTMP, MeOCOCl; (b) Li, NH_3, THF, then NH_4Cl; (c) Li, cat. DBB, THF, then 2,6-di-*tert*-butylphenol.

hand, we then examined the partial reduction of this compound, searching for conditions that would influence the stereochemistry of this process.

By variation of the reaction conditions, we discovered that pyrrole **1** could be reduced to give the trans isomer of **2** with good diastereoselectivity, using lithium in ammonia and quenching with ammonium chloride, Scheme 1.[3] Remarkably, reduction under "ammonia-free" conditions (Li, catalytic DBB, THF)[6] followed by protonation with 2,6-di-*tert*-butylphenol gave *cis*-**2** exclusively.[7] Control experiments showed that each isomer was formed under kinetic control and that *cis*-**2** did not equilibrate under ammonia conditions. This chemistry effectively achieves our first goal and allows us to set the stereochemistry at C-5,6 at will.

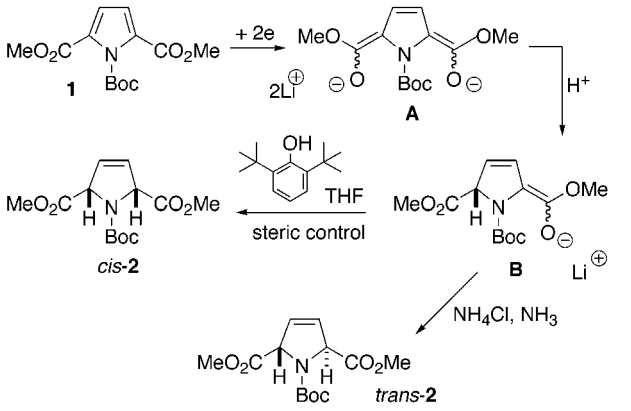


Figure 2.

The mechanism of reduction can be explained by formation of a relatively stable dianion **A** after addition of two electrons to the starting material **1** (Figure 2). We suggest that reaction with a bulky acid such as 2,6-di-*tert*-butylphenol means that, after a single protonation, the resulting monoenolate **B** reacts from the least hindered face to produce *cis*-**2**. The reason for the trans selectivity during (kinetic) protonation in ammonia is more obscure. At this juncture, we wish only to point out the differences between reduction/protonation in ammonia versus that in THF: (1) the aggregation state of the enolate intermediate **B** is likely to be very different in ammonia versus THF;[8] (2) the geometry of enolate **B** is not known and may differ depending on the amount of chelation between the enolate OLi and the Boc group; and (3) ammonia solvent has the ability to act as an acid whereby the proton that becomes attached to the enolate carbon may not be the same one as that added to the reaction mixture as ammonium chloride.[9]

With the synthesis of *cis*- and *trans*-**2** in hand, we attempted to prepare the substitution pattern of the pyrrolidine natural products. Ideally, we want to be able to set the stereochemistry of the C-3,4 hydroxyl groups as either cis or trans, starting from both *cis*- and *trans*-**2**.

Initially, the protected diols **3** and **6** were prepared via a two-step sequence from the corresponding esters, Scheme 2. X-ray structural analysis confirmed the stereochemistry of *trans*-**2**.

The corresponding C-3,4 *cis*-diol motif was easily prepared by dihydroxylation with catalytic osmium tetroxide. The facial selectivity of oxidation is not an issue during formation of **4** because compound **3** can only form a single cis diastereoisomer. However, the oxidation of **6** was diastereoselective upon dihydroxylation; the product **7** was shown to be the C-2,3 anti compound by X-ray crystallography on the *N*-Boc tetrol **9** derived from deprotection of **7**. In both

(2) (a) Donohoe, T. J.; Guyo, P. M. *J. Org. Chem.* **1996**, *61*, 7664. (b) Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 667.

(3) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1327.

(4) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.

(5) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.

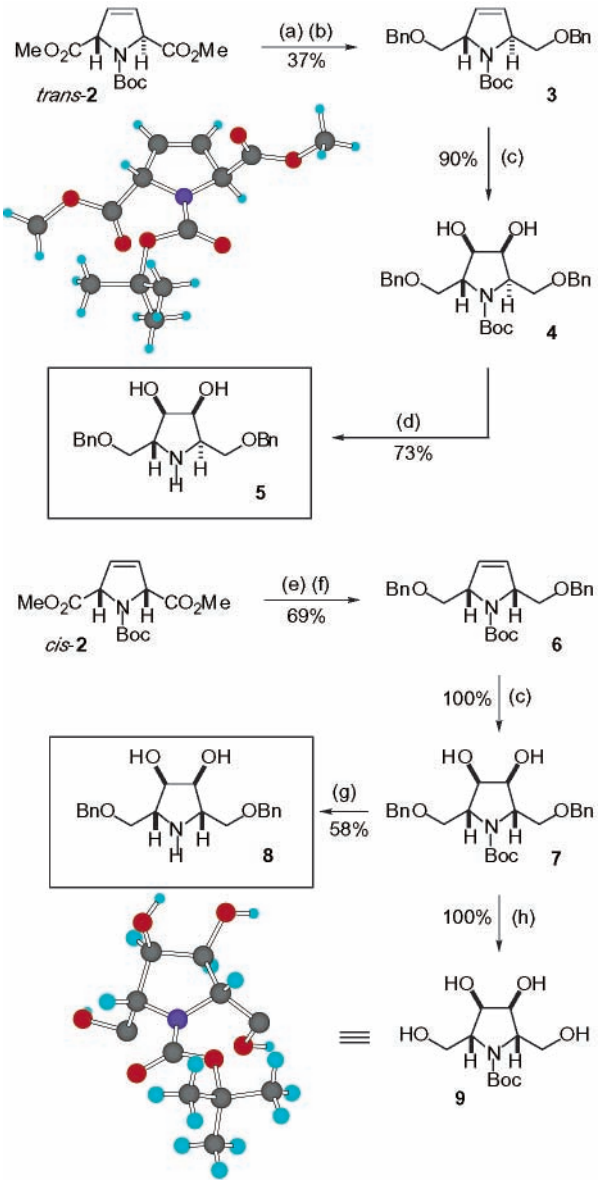
(6) (a) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1331. (b) Donohoe, T. J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015.

(7) The diethyl ester analogue of **1** has previously been reduced and reductively alkylated in ammonia.[3] While reductive alkylation proceeds to give the trans isomers exclusively, protonation in ammonia had been reported to give a (7:3) mixture of cis and trans isomers. This ratio is our error, and further study confirms that reduction (followed by protonation) in ammonia definitely proceeds to give the trans isomer as the major compound (6:1).

(8) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

(9) See: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. This is reminiscent of the Grotthus mechanism for proton transfer in water; see: Pilling, M. J.; Seakins, P. W. *Reaction Kinetics*; Oxford University Press: New York, 1995.

Scheme 2[a]



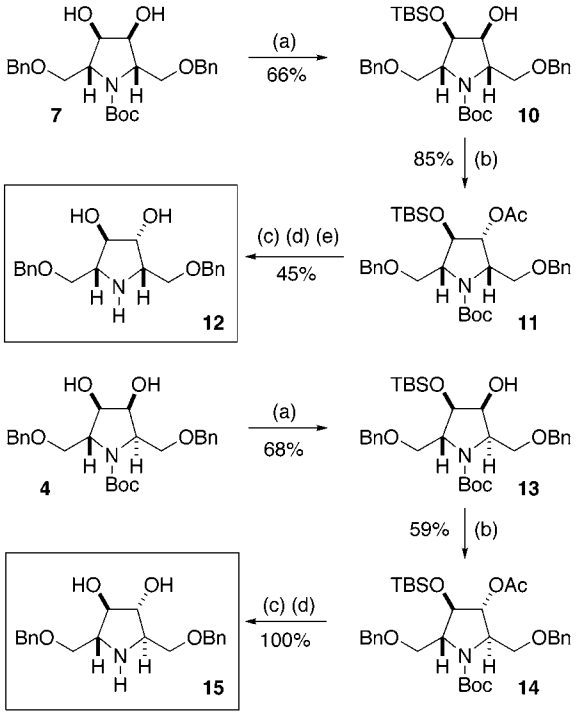
[a] Reagents and conditions: (a) $LiEt_3BH$, THF; (b) Ag_2O, BnBr; (c) OsO_4 (cat.), NMO, acetone, H_2O; (d) HCI, MeOH; (e) $LiBH_4$, THF; (f) NaH, BnBr, TBAI; (g) TFA, CH_2Cl_2; (h) H_2, Pd/C, MeOH.

series, the Boc group was deprotected to reveal the free pyrrolidines **5** and **8** in good yield.[10]

Formation of the *trans*-diol isomers at C-3,4 proved to be much more troublesome than their cis counterparts. While we were able to form the epoxides derived from **3** and **6**, opening to the *trans*-diol under either acidic or basic conditions was not successful and, if forced, gave re-aromatized products. Other methods of directly forming the *trans*-diol array such as the Woodward−Prevost conditions (I_2, AgOAc, H_2O) were also not viable.

Therefore, we set about inverting one of the hydroxyl groups from the cis compounds **4** and **7**, Scheme 3. In each case, monoprotection was accomplished with TBSOTf at low temperatures. The symmetrical nature of **7** means that mono-

Scheme 3[a]

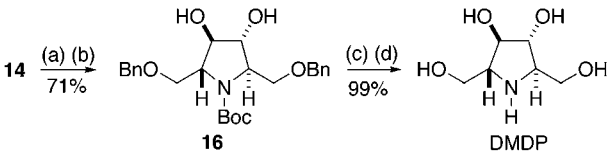


[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C (b) Tf_2O, pyr, CH_2Cl_2, then KOAc, DMF; (c) NaOMe, MeOH; (d) HCI, MeOH; (e) TFA, CH_2CI_2.

protection is free from complications arising from regiochemistry. However, the monosilylation (**4**→**13**) is rationalized by reaction of the least hindered hydroxyl group at −78 °C. Mitsunobu inversion of the free hydroxyl group within either **10** or **13** was unsuccessful, so we formed the reactive triflates from these two monoalcohols. Neither of these triflates were isolated but instead reacted immediately with potassium acetate in DMF to furnish the inverted derivatives **11** and **14** in good yield (Scheme 3). In each case, the Boc protecting group was removed so that the symmetry of compounds **12** and **15** was apparent from the NMR spectra.[11]

Finally, compound **14** could be converted into the (racemic) natural product DMDP by simple deprotection; the spectroscopic data for this compound was an exact match with that in the literature[12] (Scheme 4).

Scheme 4[a]



[a] Reagents and conditions: (a) NaOMe, MeOH; (b) HCI, MeOH; (c) H_2, Pd/C, MeOH; (d) HCI, MeOH, ion-exchange chromatography.

To conclude, we report here that disubstituted pyrroles can serve as versatile precursors for the synthesis of polyhydroxylated pyrrolidine natural products. Variation of the reduction procedure is sufficient to influence the stereochemistry at C-5,6, while that at C-3,4 can be set by *cis*-dihydroxylation (followed by inversion). The flexibility that this sequence holds for the synthesis of diastereoisomeric pyrrolidines has been exemplified, and the stage is now set for application of this method to more complex systems.

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Supporting Information Available: Copies of ^{1}H NMR spectra and detailed spectroscopic data for all new compounds and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Compound **5**: ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 60.0 (−), 62.1 (−), 68.4 (+), 68.9 (+), 71.9 (−), 73.4 (−), 73.5 (+), 73.6 (+), 127.9 (−), 128.0 (−), 128.5 (−), 137.3 (+), 137.4 (+). Compound **8**: ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 63.0 (+), 69.3 (−), 72.7 (+), 73.3 (−), 127.7 (+), 127.8 (+), 128.5 (+), 137.6 (−).

(11) Compound **12**: ^{13}C NMR (100 MHz, $CDCl_3$, APT) δ 58.9 (−), 63.9 (−), 69.3 (+), 70.7 (+), 73.5 (+), 73.6 (+), 78.8 (−), 80.6 (−), 127.8 (−), 127.9 (−), 128.5 (−), 137.4 (+) 137.7 (+). Compound **15**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.3, 72.1, 74.0, 81.0, 128.3, 128.4, 129.0, 137.9.

(12) For a copy of the ^{1}H NMR spectrum of (+)-DMDP, see: Fechter, M. H.; Gradnig, G.; Berger, A.; Mirtl, C.; Schmid, W.; Stütz, A. E. *Carbohydr. Res.* **1998**, *309*, 367. For general references to the isolation and previous syntheses of DMDP, see: Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1503.