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Stereoselective Synthesis of the Glycosidase Inhibitor Australine through a One-Pot, Double-Cyclization Strategy†

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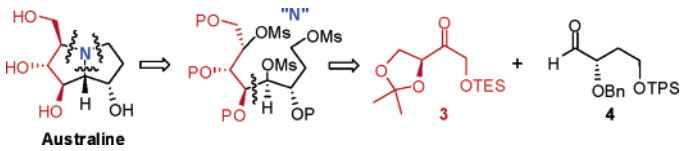
ABSTRACT



A stereocontrolled, convergent synthesis of the alkaloid australine, a glycosidase inhibitor of the pyrrolizidine class, is described. The chiral starting materials were ketone 3, derived from L-erythrulose, and α-alkoxy aldehyde 4, prepared from L-malic acid. A key step of the synthesis was the highly stereoselective aldol reaction between 4 and a *Z* boron enolate derived from 3. Another key step was the one-pot construction of the bicyclic pyrrolizidine system by means of a three-step sequence of S_N2 displacements induced by benzylamine on a trimesylate precursor.

Pyrrolizidine alkaloids have been isolated from species of several plant families.[1] Polyhydroxylated representatives have been found in some genera belonging to the Leguminosae and a few other families. For instance, australine **1** and alexine **2** (Figure 1), its epimer at C-7a, were isolated from

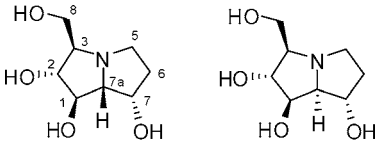


Figure 1. Structures of australine **1** and alexine **2**.

Castanospermum australe[2] and *Alexa leiopetala*,[3] respectively. Australine is an inhibitor of fungal amyloglucosidase and of some glycoprotein-processing enzymes.[4] Furthermore, it displays anti-HIV activity.[5] The diverse array of potentially useful biological activities[6] and the high degree of functionality embedded in these alkaloids make them attractive targets for total synthesis.[7,8]

There has been formerly some confusion in the literature about the true structure of australine. While that originally

† Dedicated to the memory of Dr. Jasmin Jakupovic (deceased September 6, 2005).

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(1) For general reviews on pyrrolizidine alkaloids, see: Liddell, J. R. *Nat. Prod. Rep*. **2002**, *19*, 773−781 and the previous papers in this series.

(2) (a) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198−1206. (b) An X-ray diffraction analysis of australine tetraacetate has been reported: Gainsford, G. J.; Furneaux, R. H.; Mason, J. M.; Tyler, P. C. *Acta Crystallogr. Sect. C* **2000**, *C56*, E477−E478.

(3) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487−2490.

(4) (a) Tropea, J. E.; Molyneux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027−2034. (b) Zeng, Y. C.; Elbein, A. D. *Arch. Biochem. Biophys.* **1998**, *355*, 26−34.

(5) Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97−109. See also: Taylor, D. L.; Nash, R. J.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273−277.

(6) For further recent reviews on the chemistry and biology of pyrrolizidine alkaloids, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680. (b) Mroczek, T.; Gbwniak, K. *Proc. Phytochem. Soc. Eur.* **2002**, *47*, 1−46. (c) Fu, P. P.; Xia, Q.; Lin, G.; Chou, M. W. *Drug Metabol. Rev.* **2004**, *36*, 1−55. (d) Pyne, S. G.; Tang, M. *Curr. Org. Chem.* **2005**, *9*, 1393−1418.

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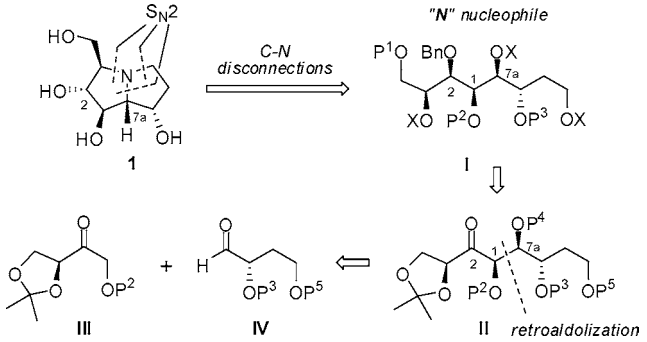
published for the natural compound relied on an X-ray diffraction analysis[2] and was thus unambiguous, the reported NMR data[2a] were actually those of the epimer at C-1. These inconsistencies were resolved in later publications as a consequence of accurate NMR studies[9] and stereoselective syntheses.[7]

The published synthetic strategies for pyrrolizidine derivatives vary widely.[10] Considering only the *total* synthesis of australine, five different approaches have been reported. Denmark's synthesis was based on an asymmetric tandem [4 + 2]/[3 + 2] cycloaddition methodology,[7b] whereas Pearson's synthesis started from a sugar precursor[7c] and Wong and Romero made use of a chemoenzymatic strategy.[7d] In all three cases, one C−N bond was created first and the other two in a subsequent, one-pot process. In contrast with these methodologies, White's and Madsen's syntheses of australine relied upon the ruthenium-catalyzed ring-closing metathesis (RCM).[7e,f] This reaction was used to generate hexahydroazocine epoxides, which underwent transannular cyclizations to the desired pyrrolizidine system. RCM played also an important role in Pyne's attempted synthesis,[11] in which it was employed to create one of the two five-membered rings. The strategy, however, proved suitable for the preparation of 1-epiaustraline but failed in the case of australine itself.

Our own retrosynthetic concept is depicted in Scheme 1. As compared with the aforementioned syntheses, a distinctive feature is the simultaneous disconnection of all C−N bonds by means of three consecutive S_N2 reactions with a nitrogen nucleophile in a single precursor. This unveils the polyhydroxylated chain of **I** (OX = leaving group), in which the stereogenic centers of C-2 and C-7a carbons show a configuration opposite to the corresponding carbons in australine. Intermediate **I** could be derived from ketone **II** which in turn can be disconnected, via retroaldol cleavage of the C1−C7a bond, to ketone **III** and chiral aldehyde **IV**. This represents a very convergent strategy in which the eight carbon atoms of the target molecule are joined from two four-carbon precursors.

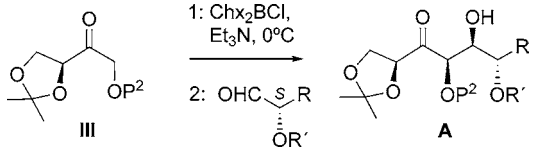
We have recently demonstrated that *Z* boron enolates derived from L-erythrulose derivatives such as **III** add

Scheme 1. Retrosynthetic Analysis of Australine **1**



stereoselectively to (*S*)-α-alkoxyaldehydes to yield adducts of general structure **A** (Scheme 2).[12] The retrosynthetic

Scheme 2. Aldol Reaction of Ketones **III** with α-Alkoxyaldehydes



scheme proposed for australine relied upon this finding. Thus, after a careful choice of appropriate protecting groups, **III** and **IV** (Scheme 1) became **3** (**III**, P^2 = TES) and **4** (**IV**, P^3 = Bn, P^5 = TPS), respectively (Scheme 3).

The aldol addition of ketone **3**[13] to aldehyde **4**[14] was accomplished under the described conditions.[12] After oxidative workup, the polyoxygenated ketone **5** was obtained as a single stereoisomer in 72% yield (Scheme 3). In order to achieve a stereoselective reduction of the ketone carbonyl

(7) Previous syntheses of australine: (a) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M., Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131−2160. (b) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046−3056. (c) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785−5793. (d) Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264−8268.(e) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129−9142. (f) Lauritsen, A.; Madsen, R. *Org. Biomol. Chem.* **2006**, *4*, 2898−2905.

(8) For recent reviews on syntheses of this compound class, see: (a) Yoda, H. *Curr. Org. Chem.* **2002**, *6*, 223−243. (b) Ayad, T.; Genisson, Y.; Baltas, M. *Curr. Org. Chem.* **2004**, *8*, 1211−1233.

(9) (a) Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549−2558. (b) Kato, A.; Kano, E.; Adachi, I.; Molyneux, R. J.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Wormald, M. R.; Kizu, H.; Ikeda, K.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 325−331.

(10) (a) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299−305. (b) Oppolzer, W. *Gazz. Chim. Ital.* **1995**, *125*, 207−213. (c) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905−917. (d) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959−968. (e) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. I* **2002**, 2747−2762. (f) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670−2680.

(11) Tang, M.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 5759−5767.

(12) Marco, J. A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Röper, H. *J. Org. Chem.* **2003**, *68*, 8577−8582.

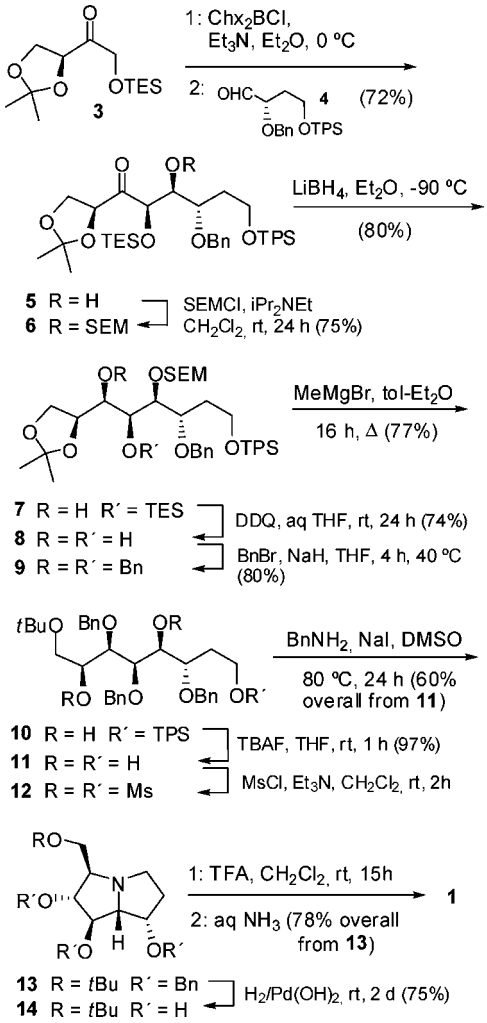
(13) For the preparation of variously protected D- and L-erythrulose derivatives using chiral precursors other than erythrulose itself, see: Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996**, 1801−1810. For an improved preparation of silylated L-erythrulose acetonides III (P^2 = TES, TBS, TPS) from L-erythrulose hydrate, see: Carda, M.; Rodríguez, S.; Murga, J.; Falomir, E.; Marco, J. A.; Röper, H. *Synth. Commun.* **1999**, *29*, 2601−2610.

(14) Aldehyde **4** was prepared through modification of a previously published method for the synthesis of a closely related product (TES instead of Bn: Hayashi, Y.; Yamaguchi, J.; Shoji, M. *Tetrahedron* **2002**, *58*, 9839−9846). See details of the preparation in the Supporting Information.

(15) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; pp 45−48.

(16) The SEM group was selected for its ability to allow control of the carbonyl reduction of **6** by means of a chelation mechanism. When other protecting groups with the same property, such as MOM or a MEM, were assayed, cyclic methylenedioxy derivatives (formaldehyde acetals) were formed in the reduction process with $LiBH_4$. Precedents of such side reactions are known: (a) Herbert, J. M.; Knight, J. G.; Sexton, B. *Tetrahedron* **1996**, *52*, 15257−15266. (b) Kiyooka, S.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967−7978. (c) Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2004**, *69*, 6294−6304. In some cases, however, formation of formaldehyde acetals may be the desired reaction: Durham, T. B.; Blanchard, N.; Savall, B. M.; Powell, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2004**, *126*, 9307−9317.

Scheme 3. Stereoselective Synthesis of Australine **1**[a]



[a] Acronyms and abbreviations: Chx, cyclohexyl; TES, triethylsilyl; TPS, *tert*-butyldiphenylsilyl; SEM 2-(trimethylsilyl)ethoxymethyl; TBAF, tetra-*n*-butylammonium fluoride hydrate; TFA, trifluoroacetic acid.

group, aldol **5** was treated with SEMCl[15,16] to yield the fully protected ketone **6**. Reduction of **6** with $LiBH_4$ at −90 °C stereoselectively furnished alcohol **7** (dr > 95:5) in 80% chemical yield. The TES group was then selectively removed with the aid of catalytic amounts of DDQ in aqueous THF.[17] This gave diol **8**, which was then converted into the perbenzylated derivative **9**. In order to set the polyhydroxylated chain in a situation suitable for the foreseen S_N2 displacements, the TPS, SEM, and acetonide groups had to be removed with parallel protection of the primary alcohol group liberated after acetonide hydrolysis. A number of methods were assayed to accomplish this goal, but all attempts at selective cleavage of the acetonide moiety were plagued with formation of side products and low yields. Eventually, treatment of compound **9** with an excess of MeMgBr in a refluxing toluene−ether mixture not only caused an alkylative opening of the acetonide ring[18] but also cleaved the SEM group to yield diol **10**. This admittedly unanticipated but felicitous finding increased the efficiency of our synthetic strategy. Removal of the TPS group with TBAF was followed by conversion of the corresponding triol **11** into trimesylate **12**. Attempts at one-pot cyclization of **12** to a pyrrolizidine derivative through reaction with ammonia[19] were unsuccessful. While no reaction took place at room temperature, decomposition was observed under forcing conditions. Interestingly, when a solution of **12** in DMSO was heated at 80 °C with benzylamine and catalytic amounts of NaI, the fully protected australine derivative **13** was obtained rather than the anticipated quaternary *N*-benzylammonium salt. The reaction requires an excess of benzylamine, as it is otherwise very slow, and the presence of catalytic amounts of iodide ion, the yield being much lower in its absence. It is likely that I^-, as a better both nucleophile and leaving group, displaces first the primary mesylate group in **12** and becomes then displaced by the amine nucleophile. The second and third nucleophilic substitutions by the nitrogen atom are intramolecular. After formation of the third C−N bond, iodide ion attacks on the benzylic position of quaternary ammonium salt **i** to yield **13** and benzyl iodide. The latter will then react with excess benzylamine to give dibenzylamine (see proposed catalytic cycle in Scheme 4).[20] A key aspect for the success may be the fact that one mesylate is primary while the other two are secondary and relatively hindered. Thus, *the first and intermolecular S_N2 step takes place only on the primary mesylate*. Indeed, when we studied the reaction on a simplified model compound (the trimesylate of heptane-1,4,7-triol), double S_N2 substitution at both primary ends was observed and no detectable amounts of pyrrolizidine were recovered.

Compound **13** was then hydrogenolytically debenzylated to **14**. Finally, acid-catalyzed cleavage of the *tert*-butyl residue of **14** followed by alcalinization provided synthetic australine, with physical and spectral properties identical to those reported for the natural compound.[1,7,9] The overall yield of the 11-step sequence was 10% based on ketone **3**.

In summary, the pyrrolizidine alkaloid australine has been synthesized using our recently reported double asymmetric aldol addition as one key step. This allowed us to build up the C1−C7a bond in one step with the desired configuration at these two stereocenters. As a second key feature, the pyrrolizidine ring system was constructed in a one-pot procedure by means of three consecutive inter/intramolecular

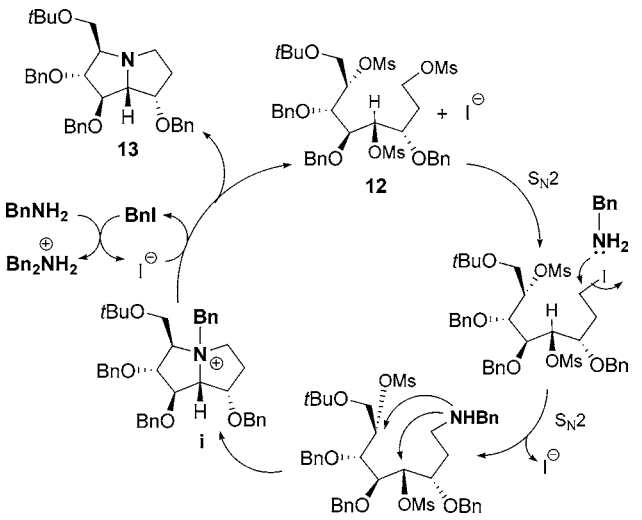
(17) Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997−2998. These unconventional conditions were found to be the only suitable means for the selective removal of the TES group without cleaving the acetonide moiety and the TPS group.

(18) Cheng, W.-L.; Yeh, S.-M.; Luh, T.-Y. *J. Org. Chem.* **1993**, *58*, 5576−5677.

(19) (a) We have found only one example in the recent literature of this method of creation of pyrrolizidine systems: Dong, H. Q.; Shi, Z. C.; Lin, G. Q. *Chin. Chem. Lett.* **1997**, *8*, 773−776. (b) An old publication reported the nonstereoselective formation of racemic 3-methylpyrrolizidine in the reaction of 1,4,7-tribromo-3-methylheptane with ammonia under harsh conditions (130 °C): Seiwerth, R.; Orescanin-Majhofer, B. *Monatsh. Chem.* **1952**, *83*, 1298−1300.

(20) The yield of **13** (60% overall from triol **11**) is excellent, taking into account that it is the result of seven consecutive steps (three mesylations, three nucleophilic substitutions, and the N-debenzylation step).

Scheme 4. Mechanistic Proposal for the Formation of **13** from **12**



S_N2 displacements on a trimesylate mediated by benzylamine. The formation of the bicyclic ring system took place with concomitant *N*-debenzylation of the presumed quaternary ammonium salt intermediate. Future studies will focus on the application of our methodology to the synthesis of other members of the australine/alexin family.

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Supporting Information Available: Experimental procedures for the preparation and tabulated spectral data of all new compounds. Graphical NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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