

Exploiting the borono-Mannich reaction in bioactive alkaloid synthesis*

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Abstract: We have demonstrated that the borono-Mannich reaction is a versatile and efficient reaction for the diastereoselective preparation of chiral 1,2-amino alcohols. These Mannich products are valuable starting materials as shown in this report by the synthesis of bioactive polyhydroxylated pyrrolizidine and indolizidine alkaloids. Initial studies, directed at the more complex *Stemona* alkaloids and using the borono-Mannich reaction on cyclic *N*-acyliminium ions, are encouraging, as demonstrated by the synthesis of the pyrido[1,2-*a*]azepine core structure of stemocurtisinol.

Keywords: Mannich reaction; alkaloids; *Stemona*; boronic acids; amino alcohols.

INTRODUCTION

This paper describes our work on the synthesis of two different alkaloid family types, and these are discussed under different subheadings: (i) polyhydroxylated pyrrolidine, pyrrolizidine, and indolizidine alkaloids and (ii) *Stemona* alkaloids.

Polyhydroxylated pyrrolidine, pyrrolizidine, and indolizidine alkaloids

Polyhydroxylated pyrrolidine, pyrrolizidine, and indolizidine alkaloids are well-known potent glycosidase enzyme inhibitors. For example, the pyrrolizidine alkaloids australine **1** [1] and casuarine **2** [2], and related alkaloids [3,4], are powerful inhibitors of glycosidase enzymes and thus exhibit antiviral and anti-HIV activity by effectively inhibiting the enzymatic processing of glycoproteins [5]. More recently, the structurally related polyhydroxylated pyrrolizidine alkaloids, for example, hyacinthacines A₁ (**3**) and A₂ (**4**) were isolated from the bulbs of Hyacinthaceae [6]. Compound **3** was found to be an inhibitor of rat intestinal lactase (IC₅₀ = 4.4 μM) while **4**, the C-1 epimer of **3**, was a selective inhibitor of amyloglucosidase [6]. Related pyrrolizidine alkaloids (e.g., **5**) have been isolated from the bulbs of *Scilla peruviana* along with the pyrrolidine alkaloid **6** [X = OH, R = (CH₂)₃CH(OH)CH₂CH(OH)(CH₂)₄CH(OH)CH₂(OH)] which was found to be a potent β-glucosidase inhibitor (IC₅₀ = 0.08 μM) [7].

Similar biological activities are found in the polyhydroxylated indolizidine alkaloids, for example, castanospermine **7** [8,9] and the more recently discovered and structurally related alkaloid, uniflorine A **8** [10]. These alkaloids are powerful inhibitors of both α- and β-glucosidases and α-glucosidase, respectively. The latter alkaloid was isolated from the leaves of *Eugenia uniflora* in Paraguay in

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2000 [10], and the leaf extracts are used in traditional medicine as natural antidiabetics. Uniflorine A was found to be an inhibitor of the α -glucosidases, rat intestinal maltase and sucrase, with IC_{50} values of 12 and 3.1 μ M, respectively.

Stemona alkaloids

The *Stemona* group of alkaloids includes more than 80 different natural products that have been structurally classified into five different groups [11]. The pyrrolo[1,2-*a*]azepine (5,7-bicyclic A,B-ring system) nucleus is common to all compounds in these groups (e.g., croomine **10**). In 2003, we [12] and then Greger [13] reported the structures of *Stemona* alkaloids with a pyrido[1,2-*a*]azepine A,B-ring system (that is, a 6,7-bicyclic A,B-ring system), including stemocurtisine **11** and oxystemokerrin **12**, and in 2004 we disclosed the structure of another pyrido[1,2-*a*]azepine *Stemona* alkaloid, stemocurtisinol **13** [14]. These alkaloids comprise a new and sixth structural group. We [12] and Greger [13] also published the isolation of **14** a new pyrrolo[1,2-*a*]azepine alkaloid.

The extracts of *Stemona* roots have been used in traditional medicine to treat the symptoms of bronchitis, pertussis, and tuberculosis and have been used as antiparasitics on humans and animals [11]. Some of the pure alkaloids derived from the extracts of the leaves and roots of *Stemona* species have been shown to have significant antitussive activity in guinea pigs after cough induction [15] as well as insect toxicity, antifeedant, and repellent activities [13,16]. We found that compounds **11**, **12**, and **14** had significant larvicidal activity on malaria-carrying mosquito larvae (*Anopheles minimus* HO) [14].

DISCUSSION

The alkaloids shown in Figs. 1 and 2 have in common a 1,2-amino alcohol structural moiety (Fig. 3), and we have therefore been developing synthetic methods toward a general synthesis of chiral 1,2-amino alcohols.

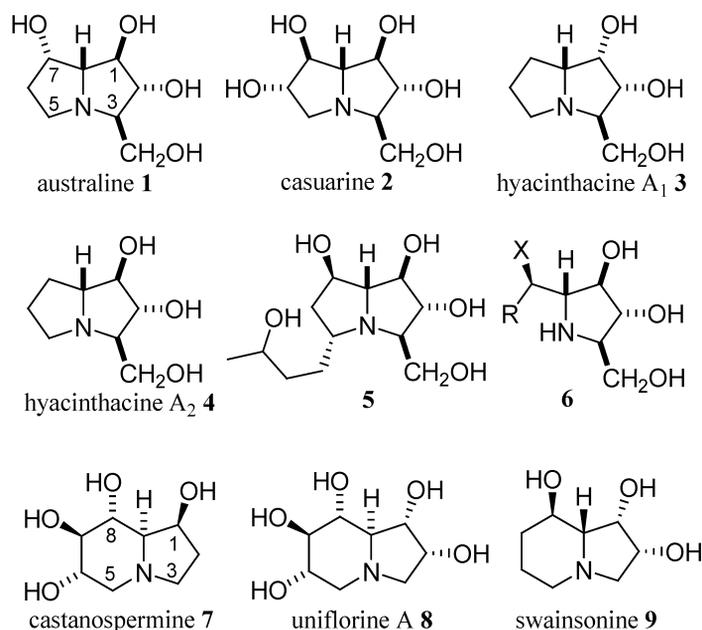


Fig. 1 Representative examples of polyhydroxylated pyrrolidine, pyrrolizidine, and indolizidine alkaloids.

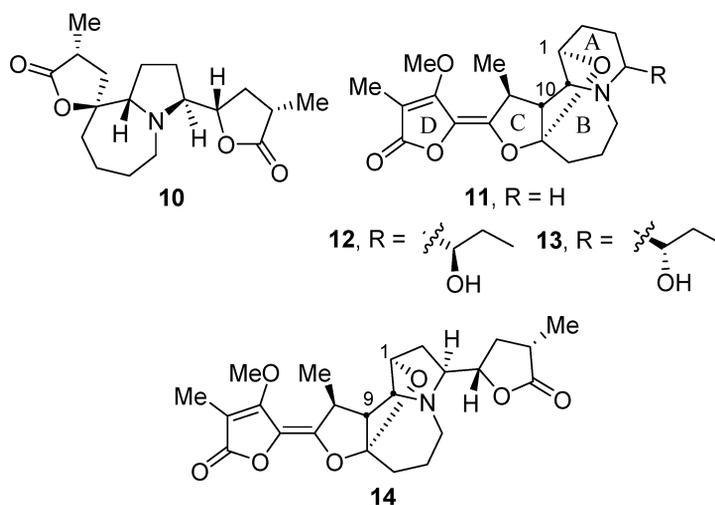


Fig. 2 Representative examples of *Stemona* alkaloids.

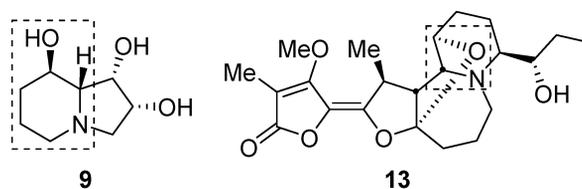
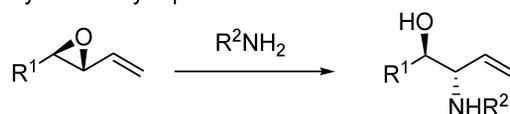


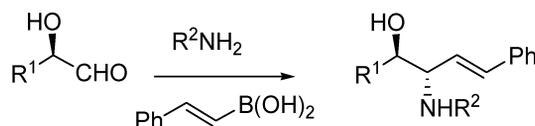
Fig. 3 Structures of swainsonine **9** and stemocurtisinol **13** with their common 1,2-amino alcohol structural feature highlighted.

The three synthetic methods that we have employed to prepare chiral 1,2-amino alcohols are shown in Scheme 1. These include the aminolysis of chiral vinyl epoxides, the borono-Mannich reaction (Petasis reaction), and the borono-Mannich reaction via cyclic *N*-acyliminium ions.

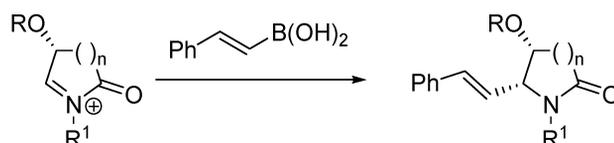
1. Aminolysis of Vinyl Epoxides



2. Borono-Mannich Reaction (Petasis Reaction)



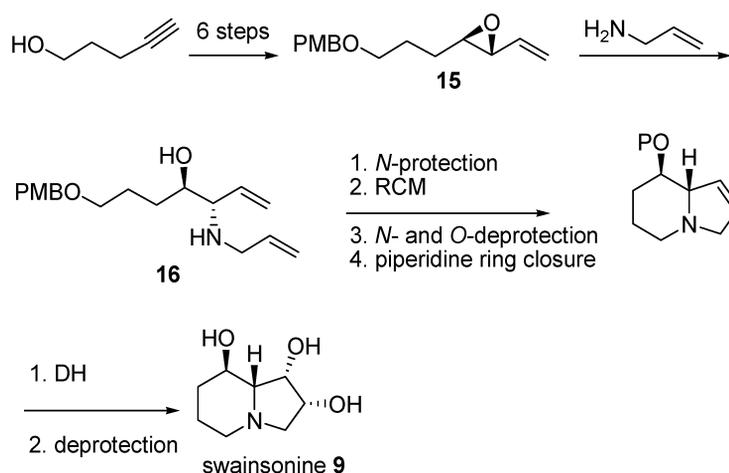
3. Borono-Mannich Reaction via cyclic *N*-acyliminium ions



Scheme 1 Methods of preparing chiral 1,2-amino alcohols.

Synthesis of polyhydroxylated alkaloids via the aminolysis of chiral vinyl epoxides

We have employed 1,2-amino alcohols that were prepared from the aminolysis of chiral vinyl epoxides, to the synthesis of (–)-swainsonine **9** and its epimers [17,18] and 1,7-di-*epi*-australine and 7-*epi*-australine [19,20]. Our first synthesis of swainsonine is outlined in Scheme 2 [17]. The synthesis of the desired chiral vinyl epoxide **15** (ee = 92 %) took six synthetic steps from commercially available 1-pentyn-5-ol. Aminolysis of this epoxide with allyl amine gave the key 1,2-amino alcohol **16** in a total of seven synthetic steps from the commercially available starting material. The epoxide **16** was then converted to swainsonine **9** in a further six steps that involved a ring-closing metathesis (RCM) reaction to secure the pyrrolidine ring, an N-alkylation reaction to provide the piperidine ring, and a *syn*-di-hydroxylation reaction to introduce the 1,2-diol functionality of **9**. While this synthesis was efficient and diastereoselective, we required a more direct method of preparing the key 1,2-amino alcohols.

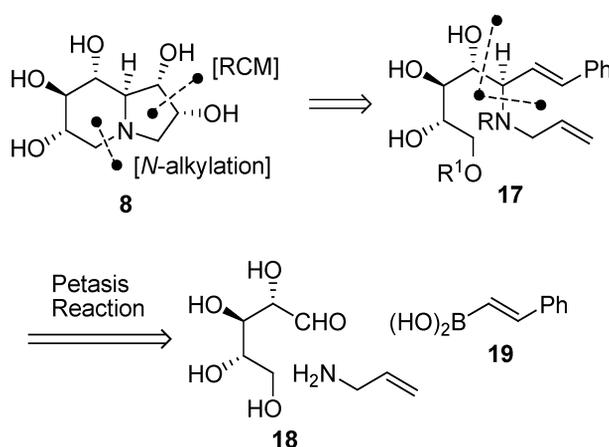


Scheme 2 Synthesis of swainsonine **9**.

Synthesis of polyhydroxylated alkaloids via the borono-Mannich reaction

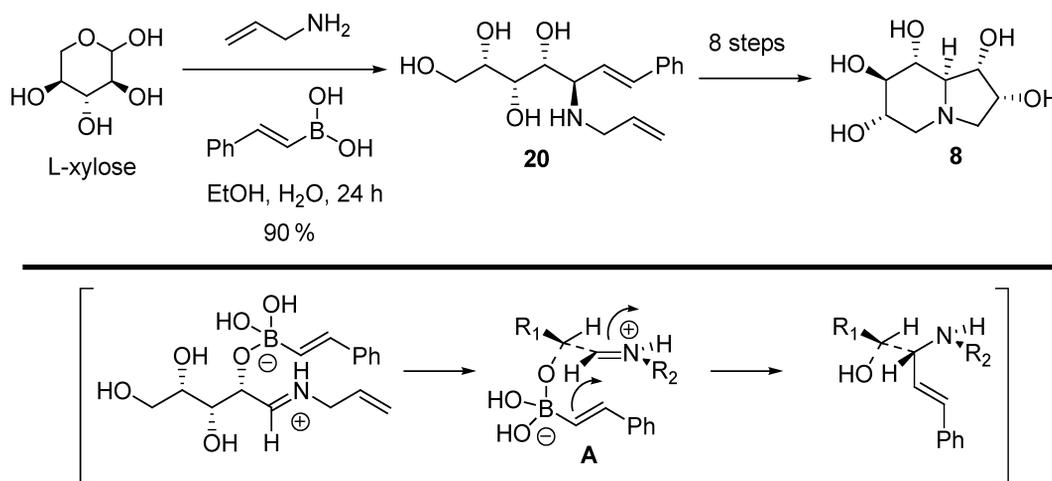
In 1998, Petasis reported the synthesis of *anti*-1,2-amino alcohols from a borono-Mannich reaction of aryl or vinyl boronic acids, with primary or secondary amines and chiral α -hydroxy-aldehydes [21]. To demonstrate the feasibility of this reaction to alkaloid synthesis, we chose uniflorine A as our synthetic target. The structure of uniflorine A was deduced from NMR analysis to be that shown as structure **8** [10], and this proposed structure is similar to that of castanospermine **7**, except for the stereochemistry at C-1 and the extra hydroxyl substitution at C-2 (Fig. 1).

Our retrosynthetic analysis suggested that the target compound **8** (Scheme 3) could be acquired from the precursor **17** using a RCM reaction and N-alkylation to prepare the five- and six-membered rings of **8**, respectively. The 1,2-*anti* amino alcohol **17** was expected to be readily obtained from the borono-Mannich reaction (Petasis reaction) [21] of L-xylose **18**, allylamine, and (*E*)-styrene boronic acid **19**, followed by chemo- and regioselective *N*- and *O*-protection reactions (Scheme 3).



Scheme 3 Retrosynthetic analysis of uniflorine A **8**.

In the event, the requisite Petasis reaction gave the desired amino-tetraol **20** in 90 % yield as a single diastereomer after purification by ion-exchange chromatography (Scheme 4) [22]. The stereochemical outcome of this reaction can be rationalized as arising from the boronate intermediate **A**, in which the reactive conformation is one that minimized 1,3-allylic strain as shown in Scheme 4. The amino-tetraol **20** was converted to **8** in eight synthetic steps [22]. The structure of our synthetic **8** was unequivocally established by single-crystal X-ray structural analysis of its pentaacetate derivative. The ^1H and ^{13}C NMR data for synthetic **8**, however, did not match with those reported for uniflorine A; the latter showed many more downfield peaks in the ^1H NMR, perhaps consistent with the amine salt. The ^1H NMR of the hydrochloride salt of synthetic **8** however, did not match the literature spectral data either. We therefore concluded that the structure assigned to uniflorine A was not correct and if it was an indolizidine alkaloid, it had the same H-1 stereochemistry as castanospermine **7** based on the reported coupling constant for $J_{1,2}$ in the natural product [22].



Scheme 4

In 2006, Dhavale [23] also reported the synthesis of compound **8**, their sample had NMR data identical to ours. This paper also reported the synthesis of 1,2,8a-tri-*epi*-**8** and 8a-*epi*-**8**, these also had

NMR data significantly different to that of uniflorine A. In 2005, Mariano [24] reported the synthesis of 1-*epi*-**8**, while 1,2-di-*epi*-**8** was reported by Fleet [25] in 1996 (Fig. 4), before uniflorine was even isolated, and later by Mariano [25] in 2005. These indolizidine molecules also had NMR data different to that of uniflorine A. Thus, if uniflorine A was epimeric at C-1 and/or C-2 with compound **8** then the only remaining possible structure for the natural product was 2-*epi*-**8**. We have recently synthesized 2-*epi*-**8**, starting with the borono-Mannich product **20** (Scheme 5), and found that it is differently spectroscopically from the natural product [26]. A more careful inspection of the published NMR data of the natural product suggests to us that uniflorine A has a 1,2,6,7-tetrahydroxy-3-hydroxy-methylpyrrolizidine structure similar to casuarine **2** (Fig. 1), that is, uniflorine A is an epimer of casuarine [26]. We are currently preparing such compounds with the aim of determining the structure of the natural product.

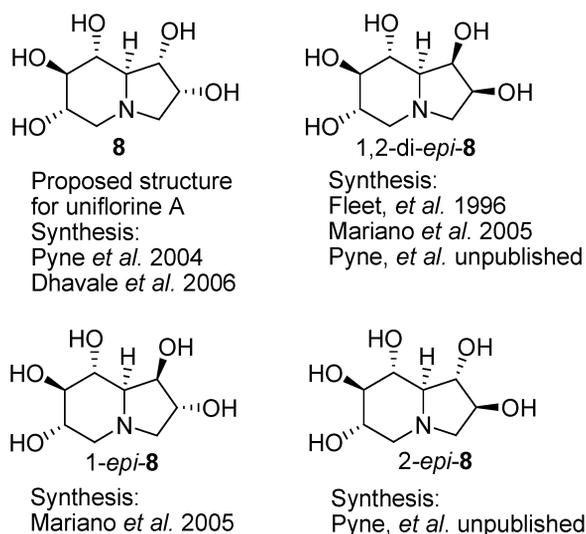
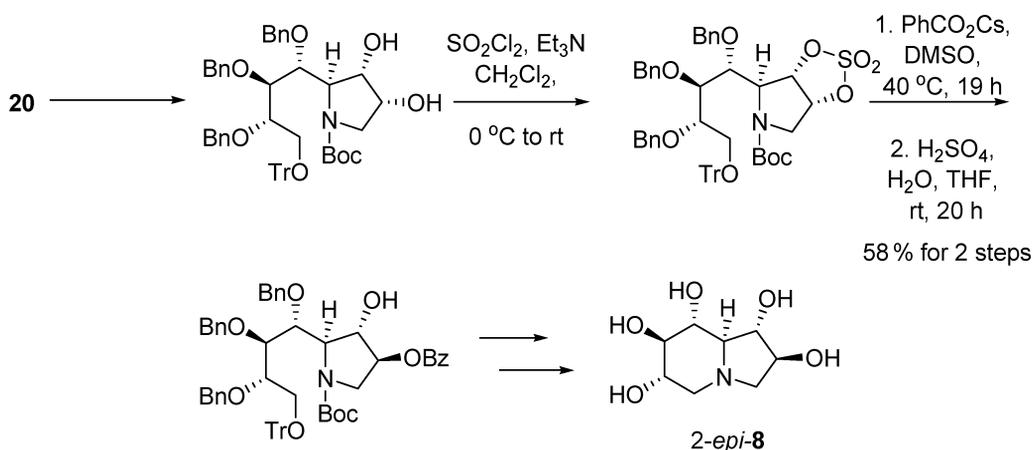
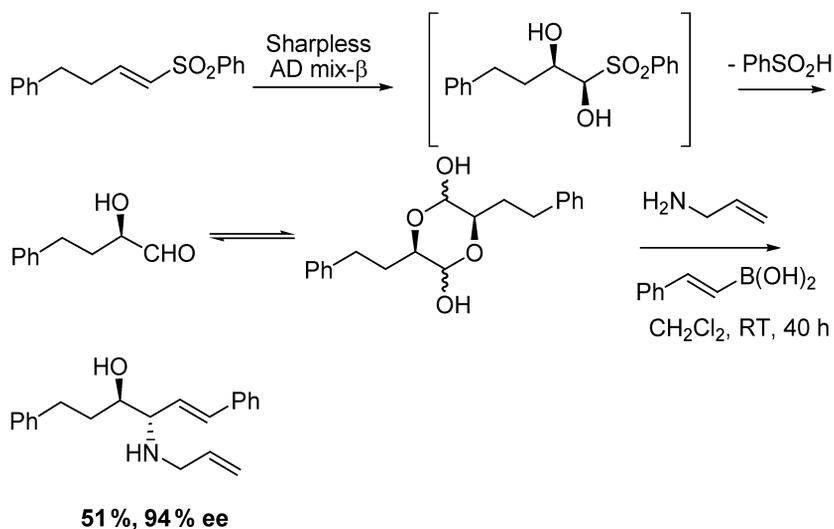


Fig. 4 Synthesized epimers of uniflorine A.



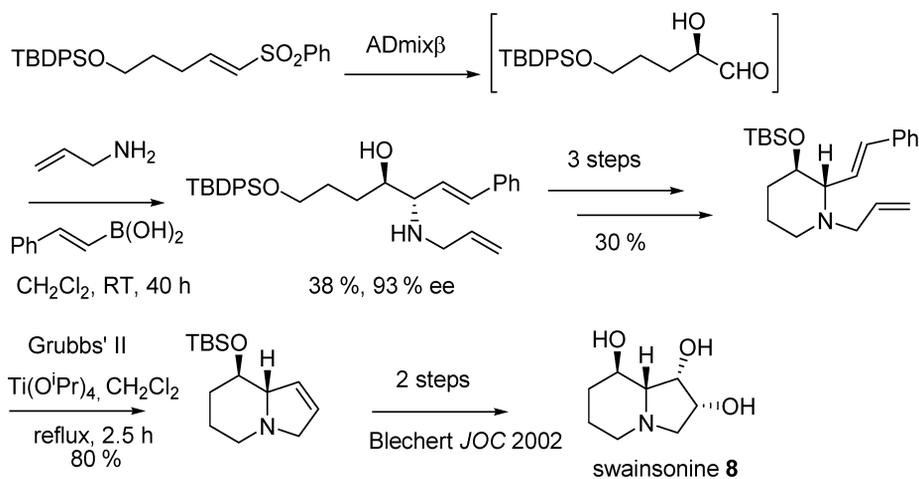
Scheme 5

While we had developed an efficient nine-step synthesis of purported uniflorine A from L-xylose using the borono-Mannich reaction, the development of this reaction into a general synthetic method was problematic since enantiomerically enriched chiral α -hydroxy-aldehydes were not generally available. A more recent paper by Evans, however, showed that these valuable substrates could be prepared in situ from the Sharpless asymmetric dihydroxylation (ADH) reaction of vinyl sulfones [27]. We found that chiral α -hydroxy-aldehydes generated in situ by this method undergo the borono-Mannich reaction with β -styrenyl boronic acid and primary amines to give *anti*-1,2-amino alcohols in high enantiomeric purities (89–94 % ee) (Scheme 6) [28].



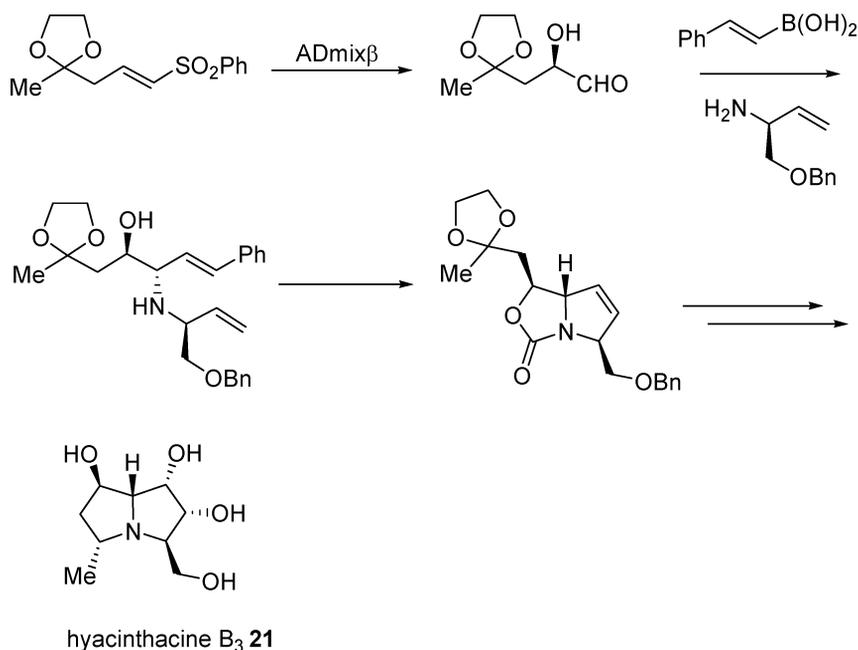
Scheme 6

This new method allowed a much more rapid access to these valuable chiral building blocks. More specifically, the derived *anti*-1,2-amino alcohol diene products, obtained using allylamine, are valuable precursors for alkaloid synthesis, as we demonstrated by a short, formal synthesis of the important natural product (–)-swainsonine **8** (Scheme 7) [28].



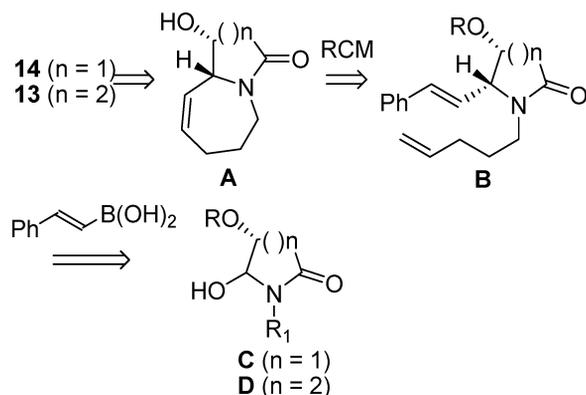
Scheme 7

We are currently extending this synthetic strategy to the synthesis of the pyrrolizidine alkaloid hyacinthacine B₃ **21** (Scheme 8).



Scheme 8

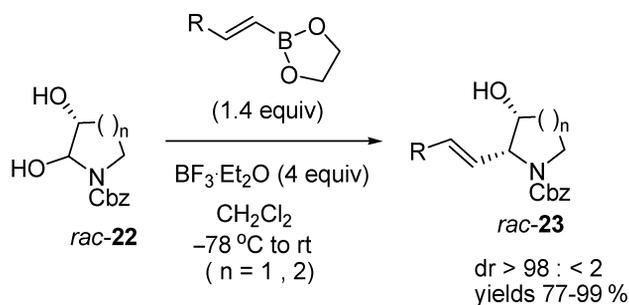
As part of a research program aimed at the synthesis of the *Stemona* alkaloids, oxyprotostemonine **14** and stemocurtisinol **13**, we are examining methods of preparing the key pyrrolo[1,2-*a*]azepine and pyrido[1,2-*a*]azepine core structures of these alkaloids, respectively. Our retrosynthetic analysis of these *Stemona* alkaloids is shown in Scheme 9. A key step in securing the correct C-1, C-9a or C-1, C-10a stereochemistry of these molecules, respectively, relies on *cis*-diastereoselective borono-Mannich reactions of five- and six-membered ring *N*-acyliminium ions, generated in situ from the 5-hydroxy-2-pyrrolidinone and 6-hydroxy-2-piperidone derivatives **C** and **D**, respectively, with (*E*)-2-styrene boronic acid. While the synthesis of *cis* 4,5- and 5,6-substituted compounds related to **B** can be achieved from the addition of tin- or silicon-based nucleophiles to five- and six-membered ring *N*-acyl-



Scheme 9

iminium ions, these reactions are poorly diastereoselective. A general diastereoselective synthesis of the required *cis* compounds is not available [29].

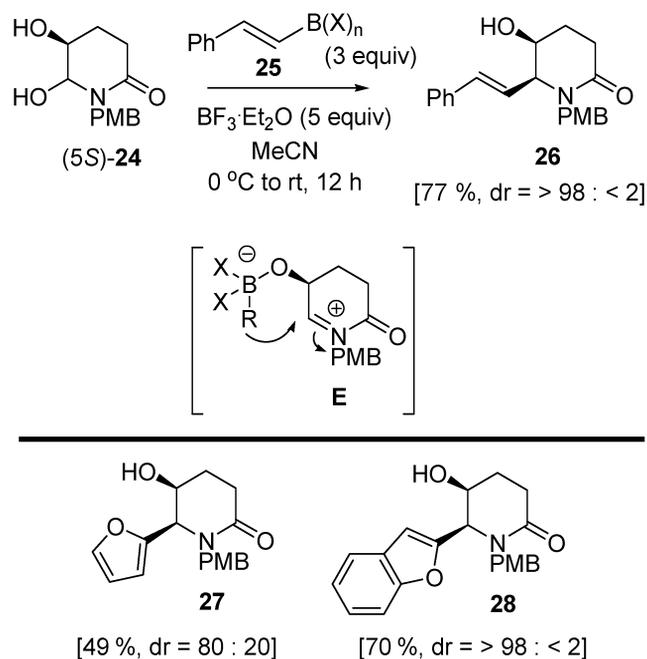
Batey has shown, however, that racemic hemi-aminal derivatives *rac*-**22** ($n = 1$ or 2), having an *exo*-cyclic *N*-acyl group, that such diastereoselective reactions are feasible and are highly *cis*-selective with 2-substituted vinyl and aryl boronate ethylene glycol esters (Scheme 10) [30]. For the synthesis of **13** and **14**, we have examined the borono-Mannich reactions on the cyclic *N*-acyliminium ions generated from the enantiomerically enriched cyclic hemi-aminals **C** and **D** having an *endo*-cyclic *N*-acyl group.



Scheme 10

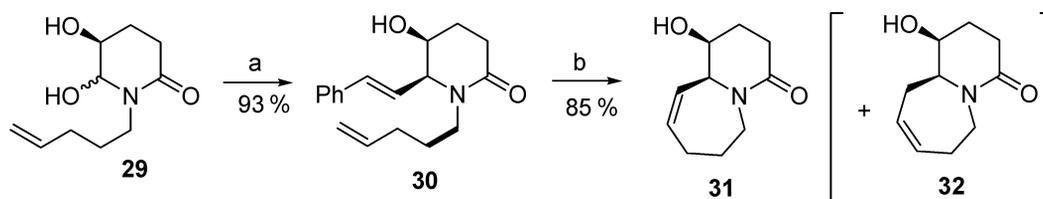
The six-membered ring hemi-aminal (*5S*)-**24** was prepared from the known *N*-PMB-(*3S*)-hydroxyglutarimide [31] (the less expensive enantiomer to that required for the synthesis of **13**) by NaBH_4 reduction. The diol (*5S*)-**24** was then treated with (*E*)-2-styrylboronic acid **25** ($X = \text{OH}$, $n = 2$) in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ under similar conditions to that described by Batey, except that MeCN was used as solvent since **24** was poorly soluble in CH_2Cl_2 . This reaction gave rise to the desired *cis*-adduct **26** in a yield of 77 % and with high diastereoselectivity (>98:<2) from ^1H NMR analysis at 500 MHz (Scheme 11) [32]. The corresponding potassium trifluoroborate **25** ($X = \text{F}$, $n = 3$) also provided the *cis*-adduct **26**, however, in a reduced yield (72 %) and in lower, but good diastereoselectivity (d.r. = 92:8). We have examined the reactions of (*5S*)-**24** with other aromatic boronic acids and boronates. Only 2-furylboronic acid and 2-benzofuranylboronic acid gave the desired adducts, **27** and **28**, respectively (Scheme 11).

The stereochemical outcomes of the major products in Scheme 11 are consistent with the formation of an initial boronate complex **E** with the 5-hydroxy group of (*5S*)-**24** followed by intramolecular delivery of the sp^2 -hybridized boron ligand to the same face of the iminium ion intermediate. The analogous borono-Mannich reactions of the five-membered ring analog of **24** proceeded in much poorer yields [32].



Scheme 11

To examine the potential of the borono-Mannich reaction of six-membered ring *N*-acyliminium ions to prepare the key pyrido[1,2-*a*]azepine core structure of stemocurtisinol **13**, we treated the hemiaminal **29** with potassium (*E*)-2-styryltrifluoroborate in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. This reaction gave the desired *cis*-product **30** in high yield (93 %) and diastereoselectivity (d.r. = 98:2, Scheme 12). The successful RCM of **30** to the azepine **31** required the use of the more reactive Grubbs' second-generation catalyst. However, under standard conditions (10 % catalyst, 2.7 mM CH_2Cl_2 with heating at reflux for 12 h), a 1:1 mixture of **31** and its double-bond isomer **32** was obtained. However, when *p*-benzoquinone (0.88 molar equiv) [33] was added at the beginning of the reaction and the reaction was performed at room temperature (rt), then the desired alkene **31** was isolated in 85 % yield contaminated with ca. 3 % of the isomeric alkene **32**.



Scheme 12

Reagents and conditions: (a) *E*- $\text{PhCH=CHBF}_3\text{K}$ (3 equiv), $\text{BF}_3 \cdot \text{OEt}_2$ (5 equiv), MeCN, 0 °C to rt, 18 h. Then reflux for 30 min. (b) Grubbs' second-generation catalyst (13 mol %), *p*-benzoquinone (0.88 equiv), CH_2Cl_2 (2.67 mM), rt, 1.5 h.

CONCLUSIONS

We have demonstrated that the borono-Mannich reaction is a versatile and efficient reaction for the diastereoselective preparation of chiral 1,2-amino alcohols. We have also shown that these Mannich products are valuable starting materials for the synthesis of bioactive polyhydroxylated pyrrolizidine and indolizidine alkaloids. Future studies are directed at the more complex *Stemona* alkaloids. Preliminary results look encouraging as demonstrated by the synthesis of pyrido[1,2-*a*]azepine core structure of stemocurtisinol.

ACKNOWLEDGMENTS

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