1-1-2013

The boronic acid Mannich reaction in alkaloid synthesis

Stephen G. Pyne
University of Wollongong, spyne@uow.edu.au

Andrew S. Davis
University of Wollongong

Thunwadee Ritthiwigrom
University of Wollongong, tr379@uow.edu.au

Christopher W. G Au
University of Wollongong, cwga289@uow.edu.au

Kongdech Savaspun
University of Wollongong, ks375@uowmail.edu.au

See next page for additional authors

The boronic acid Mannich reaction in alkaloid synthesis

Abstract

Our work on the application of the boronic acid Mannich reaction to the synthesis of pyrrolizidine alkaloids is described.

Keywords

alkaloid, reaction, mannich, synthesis, acid, boronic, CMMB

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Pyne, S. G., Davis, A. S., Ritthiwigrom, T., Au, C. W. G., Savaspun, K. & Wotherspoon, M. (2013). The boronic acid Mannich reaction in alkaloid synthesis. Pure and Applied Chemistry, 85 (6), 1215-1225.

Authors

Stephen G. Pyne, Andrew S. Davis, Thunwadee Ritthiwigrom, Christopher W. G Au, Kongdech Savaspun, and Matthew Wotherspoon

Pure Appl. Chem., Vol. 85, No. 6, pp. 1215–1225, 2013.
http://dx.doi.org/10.1351/PAC-CON-12-07-05

The boronic acid Mannich reaction in alkaloid synthesis*

Stephen G. Pyne‡, Andrew S. Davis, Thunwadee Ritthiwigrom, Christopher W. G. Au, Kongdech Savaspun, and Matthew Wotherspoon

School of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia

Abstract: Our work on the application of the boronic acid Mannich reaction to the synthesis of pyrrolizidine alkaloids is described.

Keywords: alkaloids; alkaloid synthesis; asymmetric synthesis; boronic acid; heterocyclic chemistry; indolizidine; Mannich reaction; pyrrolizidine.

INTRODUCTION

This paper reports our progress over the past 10 years on the application of the boronic acid Mannich reaction to the synthesis of polyhydroxylated indolizidine and pyrrolizidine alkaloids. Some of our alkaloid synthetic targets are shown in Fig. 1. These groups, along with the polyhydroxylated pyrrolidine, piperidine, and nortropane alkaloids, have glycosidase inhibitory activities and thus have potential utility as antiviral, anticancer, antidiabetic, and antiobesity drugs [1]. Three structurally related synthetic compounds have been marketed as antidiabetic drugs to treat type-II diabetes based on their potent α-glucosidase inhibitory activities while others have been identified as candidates for therapeutics to treat type-1 Gaucher disease [1]. These potentially useful biological activities along with the stereochemical richness of these alkaloids (uniflorine A and casuarine have six contiguous stereogenic

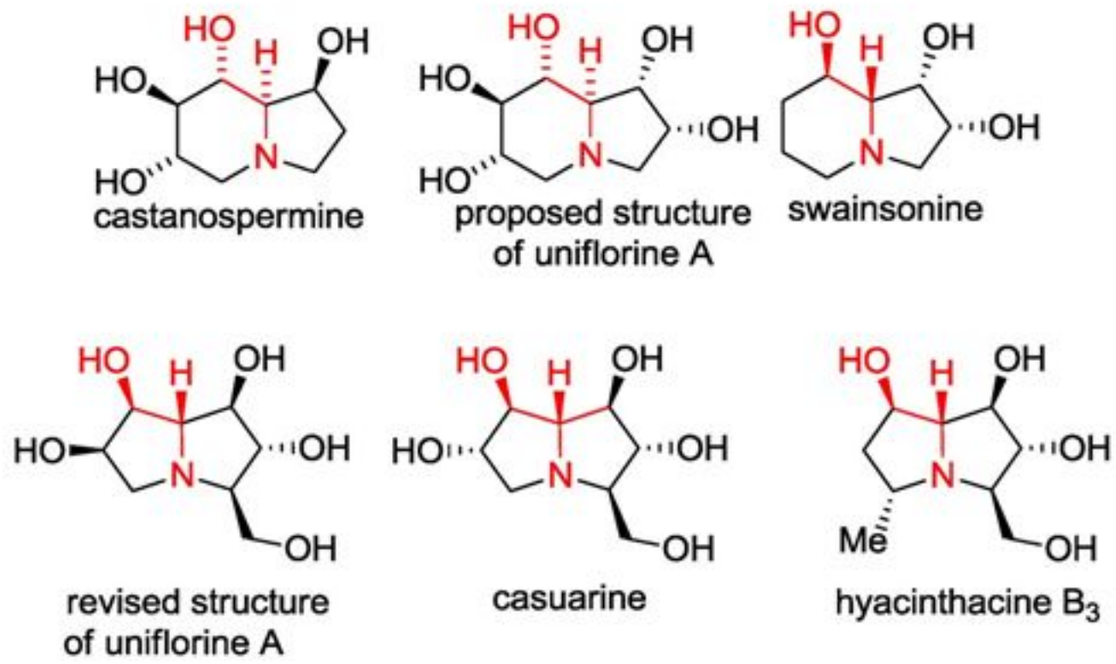


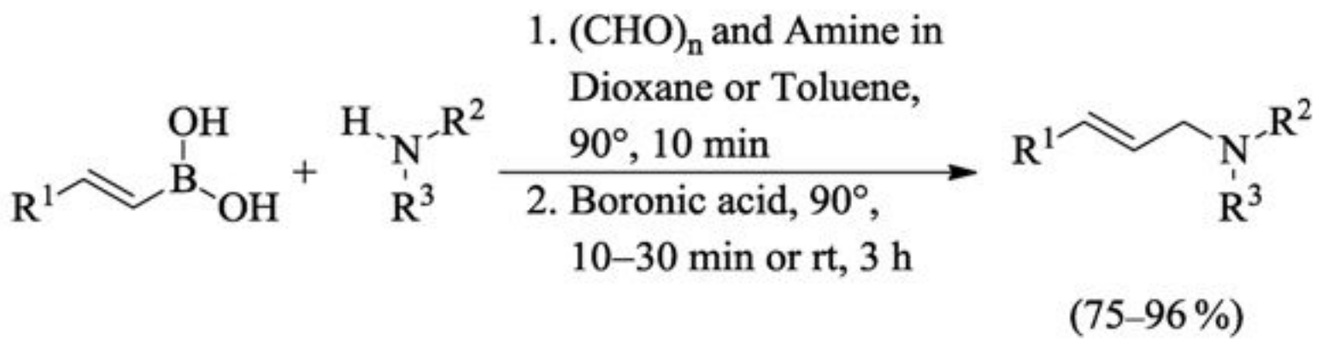
Fig. 1 Representative polyhydroxylated indolizidine and pyrrolizidine alkaloids.

*Pure Appl. Chem. **85**, 1079–1239 (2013). A collection of invited papers based on presentations at the 19th International Conference on Organic Synthesis (ICOS-19), Melbourne, Australia, 1–6 July 2012.

‡Corresponding author

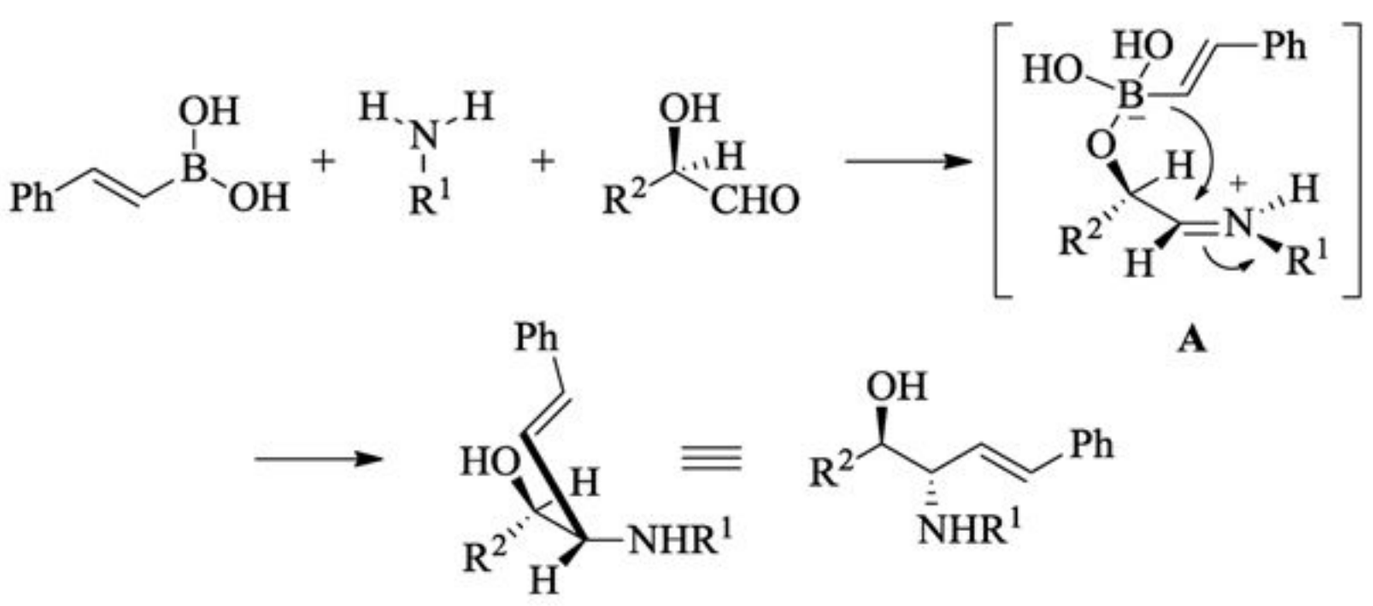
carbons) have made these compounds attractive and important synthetic targets [2]. What these alkaloids have in common is an *anti*-1,2-amino alcohol moiety which is highlighted in red in Fig. 1. Such a moiety is readily obtainable using the boronic acid Mannich reaction.

In 1993, Petasis reported the first boronic acid Mannich reaction between 1-alkenyl boronic acids, secondary amines, and paraformaldehyde. These reactions gave tertiary allylic amine products in 75–96 % yields (eq. 1) [3]. This reaction type has thus also been referred to as the Petasis reaction or the borono-Mannich reaction.



(1)

Subsequently, it was established that the boronic acid Mannich reaction could be extended to aryl, alkenyl, alkynyl, and allylboronic acids (including their esters or related potassium trifluoroborates), with ammonia, primary and secondary amines, mono-*N*-protected hydrazines, hydroxylamines, methoxyamines, and sulfinamides used as the amino component but was generally limited to certain aldehydes and ketones (usually α-hydroxy substituted ones or glyoxylic acids) [4,5]. Of relevance to our synthetic projects is that the reactions of boronic acids, α-hydroxy aldehydes, and amines give *anti*-1,2-amino alcohol reactions in a highly diastereoselective fashion (eq. 2) [4,5]. Starting with an enantio-enriched α-hydroxy aldehyde results in an enantio-enriched *anti*-1,2-amino alcohol product with little or no racemization [4,5]. For reactions involving chiral α-hydroxylaldehydes, a boronate complex intermediate **A** has been proposed (eq. 2) in which the iminium ion adopts the reactive conformation shown to minimize 1,3-allylic strain between the α-substituent and the NH of the iminium ion [4,5].



(2)

RESULTS AND DISCUSSION

Synthesis of the proposed structure of uniflorine A

The water-soluble extracts of the leaves of the tree *Eugenia uniflora* L. have been used as an antidiabetic agent in Paraguayan traditional medicine [6]. In 2000, Arisawa et al. [6] reported the isolation of uniflorine A and B from the leaves of this tree, the structures of these alkaloids were deduced from NMR analysis to be that of the pentahydroxyindolizidine structures **1** and **2**, respectively (Fig. 2). Uniflorine A and B were found to be inhibitors of the α-glucosidases, rat intestinal maltase (IC_{50} values of 12 and 4.0 μM, respectively), and sucrase (IC_{50} values of 3.1 and 1.8 μM, respectively) [6]. The biological activity of the leaf extracts may be a result of the glycosidase inhibition activities of the natural product components, including the alkaloids uniflorine A and B [1,2].

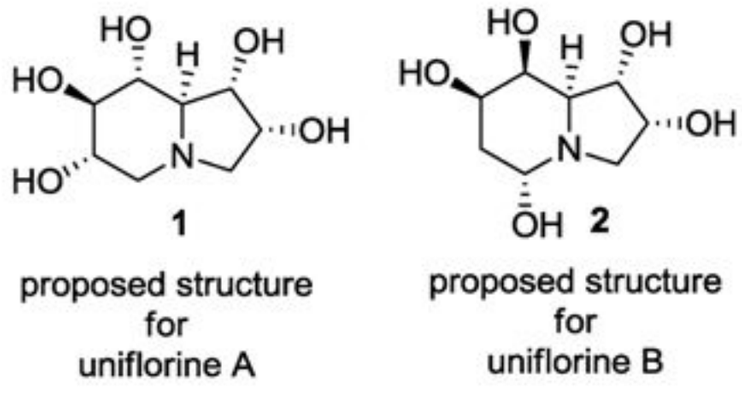
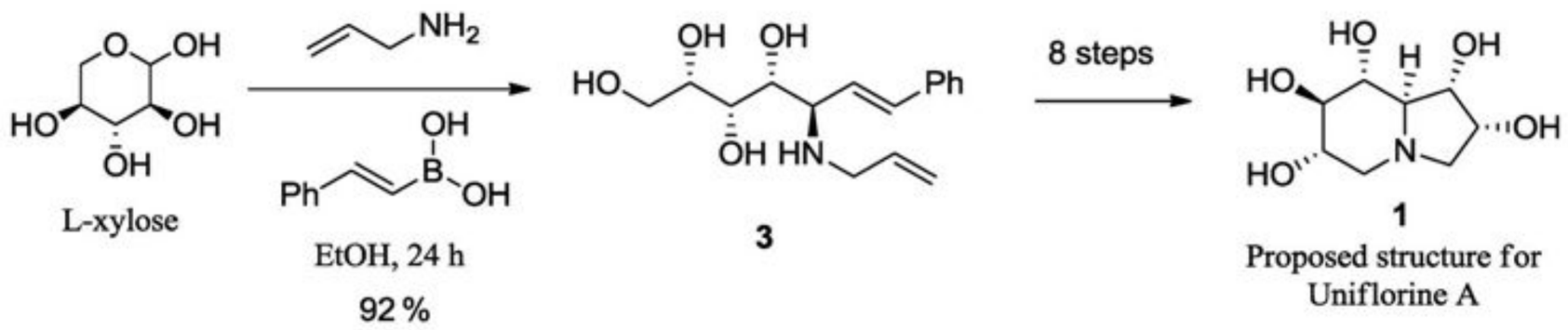


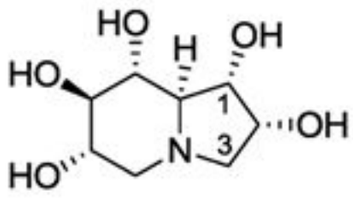
Fig. 2 Proposed structures of uniflorine A (**1**) and B (**2**).

In 2004, we synthesized the proposed structure of uniflorine A **1** using the boronic acid Mannich reaction as a key step (Scheme 1) [7]. The key 1,2-*anti*-amino alcohol **3** was obtained from the reaction (Petasis reaction) of L-xylose, allylamine, and (*E*)-styrene boronic acid in 92 % yield as a single diastereomer after purification by ion-exchange chromatography (Scheme 1). Compound **3** was then converted to the target indolizidine **1** in a further eight synthetic steps that included a ring-closing metathesis reaction to form the pyrrolidine ring of **1** and then a N-alkylation reaction to provide the bicyclic ring structure of **1**. However, the NMR spectral data for synthetic **1** did not match with those reported for uniflorine A. The structure of synthetic **1** was unequivocally established by a single-crystal X-ray crystallographic study of its pentaacetate derivative. We therefore concluded that the structure originally assigned to uniflorine A was not correct [7].



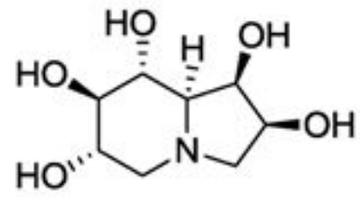
Scheme 1 Synthesis of the proposed structure of uniflorine A (**1**).

Our initial thoughts, and we assume those of several other researchers, were that uniflorine A was a diastereoisomer of structure **1**. In 2006, Dhavale et al. [8], in their paper partially titled "Attempts to find the correct structure of uniflorine A", reported the second synthesis of compound **1**, their sample had NMR spectral data identical to ours [7]. This paper also reported the synthesis of two diastereomers of **1**, 8a-*epi*-**1** and 1,2,8a-tri-*epi*-**1**. In 2005, Mariano et al. [9] reported the synthesis of 1-*epi*-**1**, while that of 1,2-di-*epi*-**1** had been reported by Fleet et al. in 1996 [10], before uniflorine A was even isolated, and later by Mariano et al. [9] and by us in 2008 [11]. In 2008, we also reported the synthesis of 2-*epi*-**1** (Fig. 3) [11]. Despite all these synthetic chemistry efforts, these 1,2,6,7,8-pentahydroxyindolizidine molecules also had NMR spectral data significantly different from that of uniflorine A.

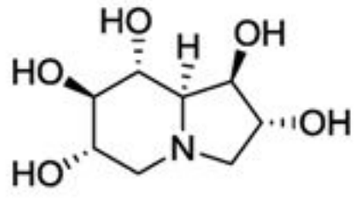


Proposed structure: Arisawa, M. *et al.* *Pharm Biol* **2000**, *38*, 302-307. Isolated from the leaf extracts of *Eugena uniflora* (Surinam cherry) Plant extracts used in South America as a traditional antidibetic agent

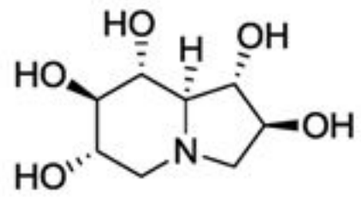
Synthesis:
Pyne, S. G. *et al.* *JOC* **2004**, *69*, 3139-3143.
Dhavale D. D. *et al.*, *JOC* **2006**, *71*, 6273-6276.



Synthesis:
Fleet, G. W. J. *et al.* *Tet. Lett.***1996**, *37*, 8561
Mariano, P. *et al.* *Tetrahedron* **2005**, *61*, 8888-8894.
Pyne, S. G. *et al.* *Tetrahedron* **2008**, *64*, 4868



Synthesis:
P. Mariano, P.*et al.* *Tetrahedron* **2005**, *61*, 8888-8894.



Synthesis:
Pyne, S. G. *et al.* *Tetrahedron* **2008**, *64*, 4868

Fig. 3 Synthetic studies around the proposed structure of uniflorine A.

From a re-examination of the original NMR data we reassigned uniflorine B as the known pyrrolizidine alkaloid casuarine **5**, while the structure of (–)-uniflorine A was suggested to be that of 6-*epi*-casuarine **4** (Fig. 4) [11].

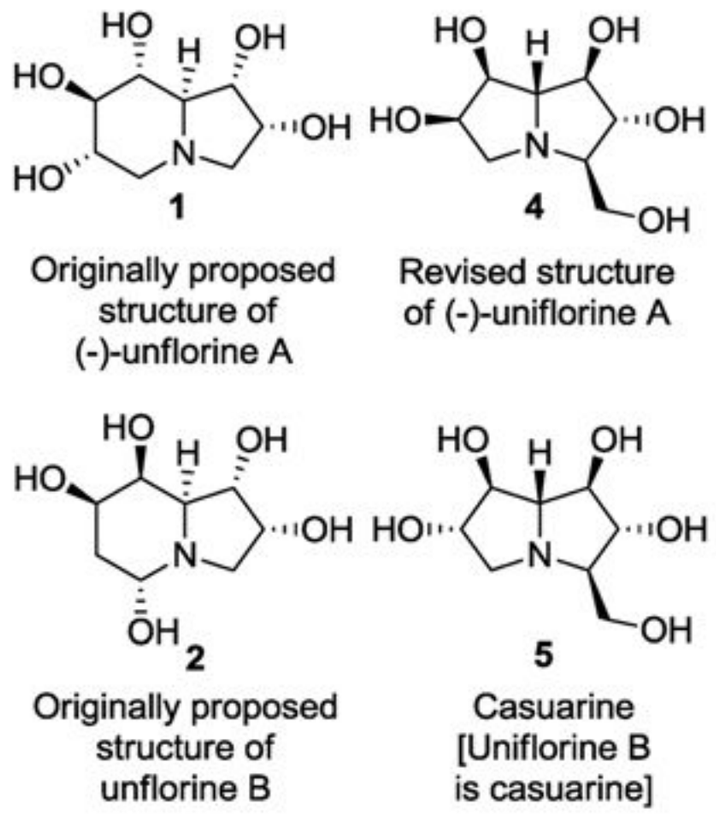
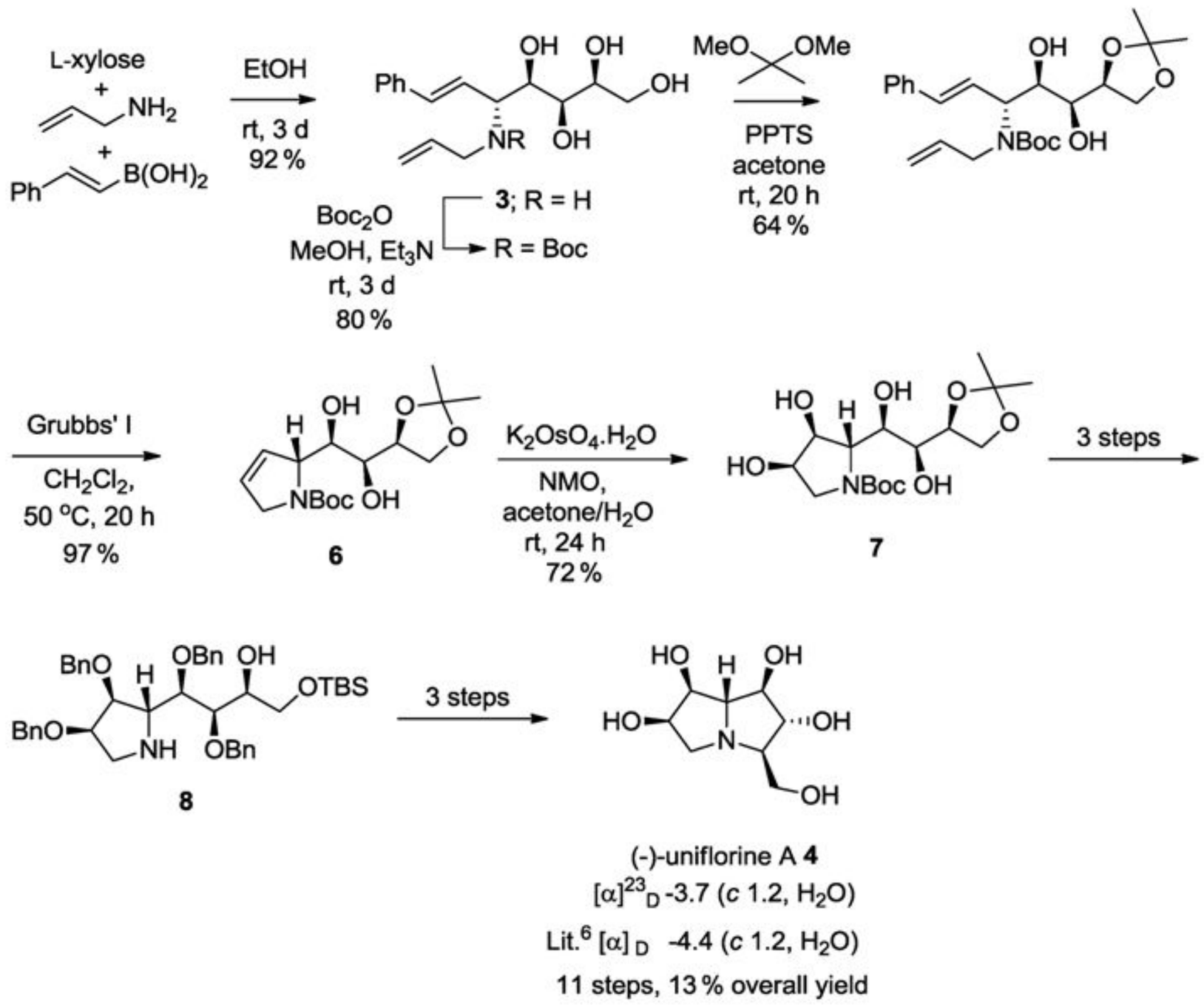


Fig. 4 Originally proposed and revised structures of uniflorine A and B.

The structural reassignment of uniflorine A to 6-*epi*-casuarine **4** was unequivocally confirmed in 2008 from our total synthesis of (+)-uniflorine A, the enantiomer of the natural product, starting from D-xylose [12]. The NMR spectral data of the synthetic compound matched almost perfectly with that of the natural product. The specific rotation of synthetic (+)-uniflorine A ($[\alpha]^{22}_D$ + 6.6 (*c* 0.35, H_2O) was essentially equal in magnitude and opposite in sign to that of the natural product (–)-uniflorine A, {$[\alpha]_D$ –4.4 (*c* 1.2, H_2O)} [6]. In 2010, we reported the synthesis of natural (–)-uniflorine A starting from L-xylose as shown in Scheme 2 [13]. (–)-Uniflorine A **4** was prepared via the chiral 2,5-dihydropyrrole **6** as shown in Scheme 2. This intermediate was readily prepared on a 4-g scale from L-xylose,



Scheme 2 Synthesis of the revised structure of (–)-uniflorine A (**4**).

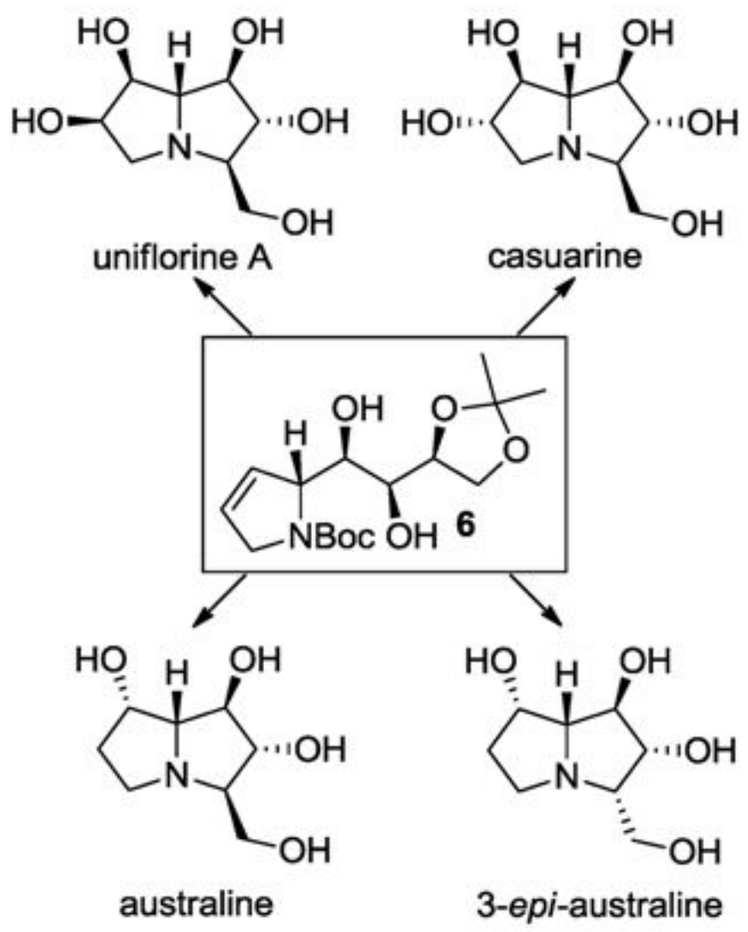
via the aforementioned amino alcohol **3**, in 4 steps and in 46 % overall yield. The 2,5-dihydropyrrole **6** underwent an osmium(VIII)-catalyzed *syn*-dihydroxylation (DH) reaction to furnish the tetrol **7** as a single diastereomer in 72 % yield (Scheme 2). The stereochemical outcome of this DH reaction was expected due to the stereodirecting effect of the C-2 pyrrolidine substituent in **6**. The tetrol **7** was readily converted to (–)-uniflorine A **4** by a Mitsunobu cyclization of the amino alcohol **8**. A deprotection step then produced (–)-uniflorine A **4** in a total of 11 synthetic steps and 13 % overall yield from L-xylose [12].

In 2009, Goti et al. [14] reported the total synthesis of (–)-uniflorine A **4** in 9 steps and 11 % overall yield. The ^{1}H NMR and ^{13}C NMR spectroscopic data were identical with those from our previous synthesis.

From this work, it is now clear that there are four natural casuarines, uniflorine A (6-*epi*-casuarine) [6,7], casuarine [15], 3-*epi*-casuarine [16], and casuarine-6-*O*-α-glucoside [17].

Synthesis of casuarine, australine, and 3-*epi*-australine

We have also employed the chiral 2,5-dihydropyrrole **6** towards the total synthesis of the pyrrolizidine alkaloids casuarine, australine, and 3-*epi*-australine through epoxidation of the double bond of the 2,5-dihydropyrrole **6** followed by diastereoselective ring-opening reactions with hydride and water (Scheme 3) [13].



Scheme 3 Synthesis of casuarine, australine, and 3-*epi*-australine from the chiral 2,5-dihydropyrrole **6**.

Synthesis of hyachinthacine B_3 and the proposed structure of hyachinthacine B_7

In the past 20 years, a large number of new polyhydroxylated pyrrolizidine alkaloids with a C-3 hydroxymethyl substituent have been isolated from plants belonging to the *Hyacinthaceae* family. These natural products have thus been named the hyacinthacine alkaloids (Fig. 5).

In 1999, the hyacinthacines B_1 and B_2 were isolated from the immature fruits and stalks of *Hyacinthoides non-scripta* (commonly known as bluebell), and hyacinthacine C_1 was isolated from the bulbs of *Scilla campanulata* (Fig. 5) [18]. In 2000, four new hyacinthacines, A_1, A_2, A_3, and B_3 (Fig. 5), were isolated from the fresh bulbs of the Hyacinthaceae plant *Muscari armeniacum* [19]. Hyacinthacine A_1, which lacks the hydroxymethyl substituent in the C-5 position, exhibited similar inhibitory activities (IC_{50} = 4.4 μM) towards β-galactosidase as hyacinthacine B_2. Hyacinthacine A_2 was found to be a weak inhibitor of the β-glucosidase and trehalase enzymes, and along with hyacinthacine A_3, showed moderate inhibition (IC_{50} = 8.6 and 17 μM, respectively) towards amyloglucosidase and weak inhibition towards β-galactosidase. Hyacinthacine B_3 was found to be a moderate inhibitor of β-galactosidase (IC_{50} = 18 μM) and was a weak amyloglucosidase inhibitor (IC_{50} = 51 μM).

In 2002, the hyacinthacines A_4, A_5, A_6, A_7, B_4, B_5, and B_6 (Fig. 5) were isolated from the bulbs of *Scilla sibirica* [20]. Of these alkaloids, only hyacinthacine A_5 (IC_{50} = 110 μM), B_4 (IC_{50} = 89 μM), and A_5 (IC_{50} = 110 μM) showed inhibitory activities towards amyloglucosidase while hyacinthacine B_4 was also found to be a moderate α-l-fucosidase inhibitor (IC_{50} = 23 μM).

In 2004, three hyacinthacines with a C-5 butyl side chain, namely, α-5-*C*-(3-hydroxybutyl)-hyacinthacine A_1, α-5-*C*-(1,3-dihydroxybutyl)-hyacinthacine A_1, and α-5-*C*-(1,3,4-trihydroxybutyl)-hyacinthacine A_1 were isolated from the bulbs of *Scilla peruviana* (Fig. 5) [21]. α-5-*C*-(1,3-Dihydroxybutyl)-hyacinthacine A_1 was found to be a good inhibitor of bacterial β-glucosidase (IC_{50} = 5.1 μM) and yeast α-glucosidase (IC_{50} = 3.6 μM). α-5-*C*-(1,3,4-trihydroxybutyl)-hyacinthacine A_1 was less potent as a bacterial β-glucosidase (IC_{50} = 11 μM) inhibitor.

More recently (2007), the hyacinthacines B_7, C_2, C_3, C_4, C_5, and another C-5 butyl side chain hyacinthacine, α-5-*C*-(3-hydroxybutyl)-hyacinthacine A_2 (Fig. 5) have been isolated from the bulbs of *Scilla socialis* [22]. It is notable that the structures of hyacinthacine C_1 are the same as that proposed for hyacinthacine C_4, even though they have different NMR data and optical rotations of opposite signs and different magnitudes. The hyacinthacines C_2, C_3, and C_5 were found to be moderate-to-weak inhibitors towards bacterial β-glucosidase, with IC_{50} values of 13, 25, and 48 μM, respectively.

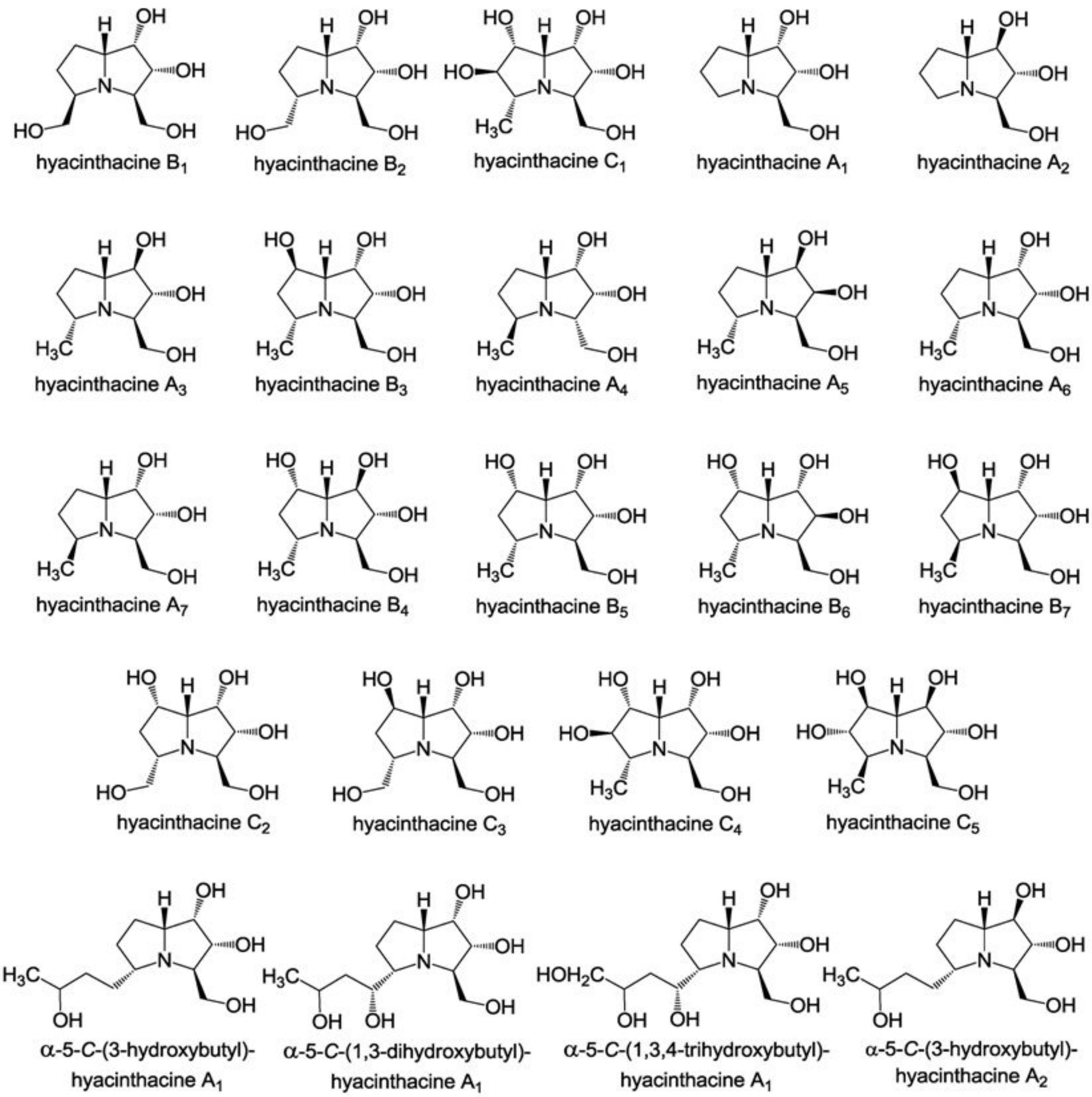
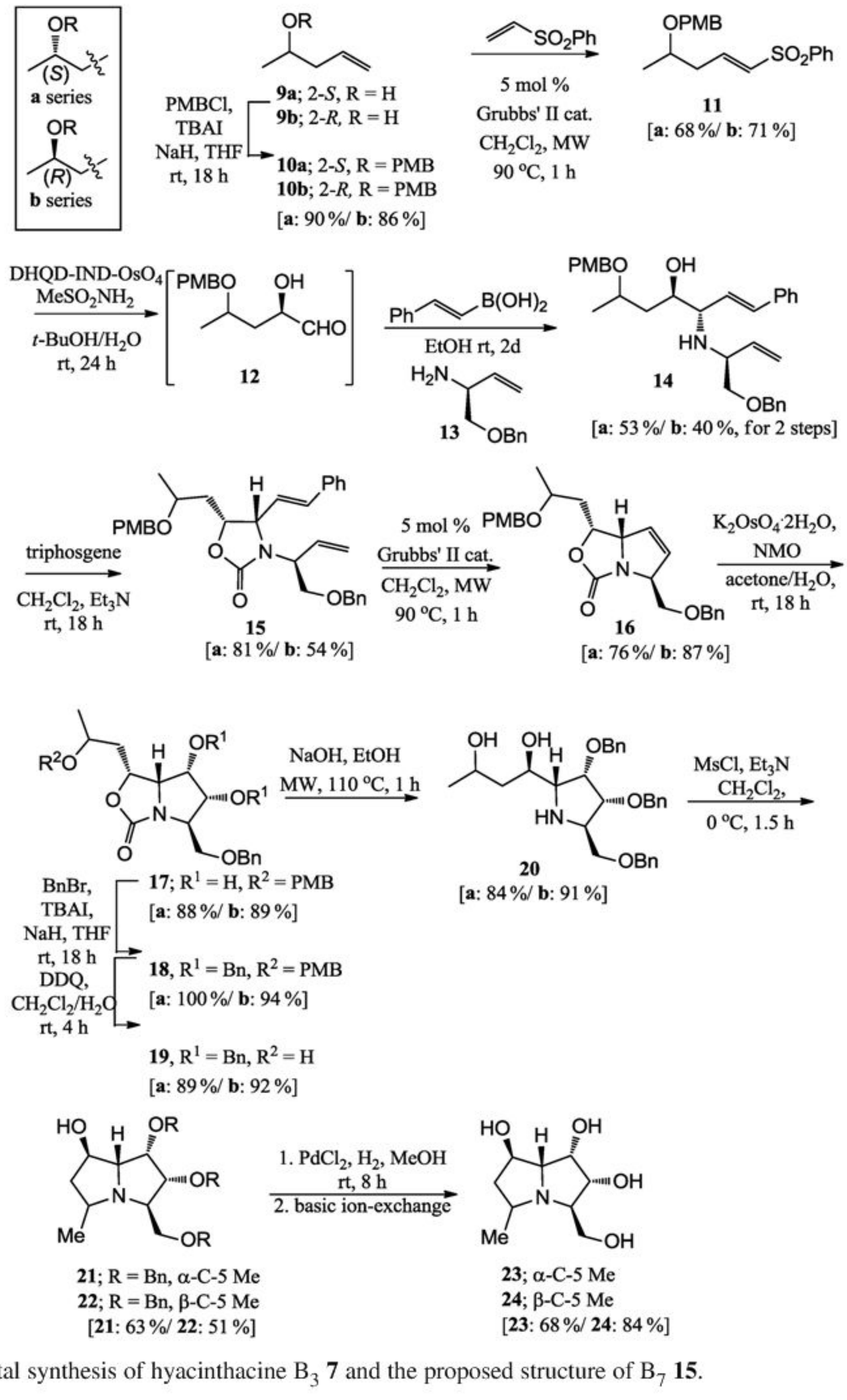


Fig. 5 Structures of the natural hyacinthacines.

Hyacinthacine C_2 also exhibited a moderate inhibition (IC_{50} = 17 μM) of the human placenta α-l-fucosidase enzyme. Hyacinthacine C_3 showed weak inhibition (IC_{50} = 52 μM) towards bovine liver β-galactosidase. α-5-*C*-(3-Hydroxybutyl)-hyacinthacine A_2, along with hyacinthacine B_7, proved to be weak inhibitors of amyloglucosidase.

In 2010, we published the synthesis of hyacinthacines B_3 and B_7 in 12 synthetic steps [23]. This syntheses started with commercially available (*S*)- and (*R*)-4-penten-2-ol, **9a** and **9b**, respectively, which are also available by enzymatic resolution. These two separate alkaloid syntheses are summarized in Scheme 4. For the synthesis of hyacinthacine B_3, (*S*)-4-penten-2-ol **9a** (ee >98 %) was protected as its *p*-methoxybenzyl (PMB) ether (**10a**) and then converted to the (*E*)-vinyl sulfone **11a** using a cross-metathesis reaction. Using the asymmetric DH reaction conditions initially reported by Evans [24] and later used by us to prepare swainsonine [25], for vinyl sulfones we found that the vinyl sulfone **11a** reacted very sluggishly. Using a modified procedure and the less-hindered DHQD-IND chiral ligand, however, the vinyl sulfone **11a** was converted to the corresponding α-hydroxy aldehyde **12a**, which was most likely a mixture of acetal derivatives, at room temperature in 24 h. This was not iso-

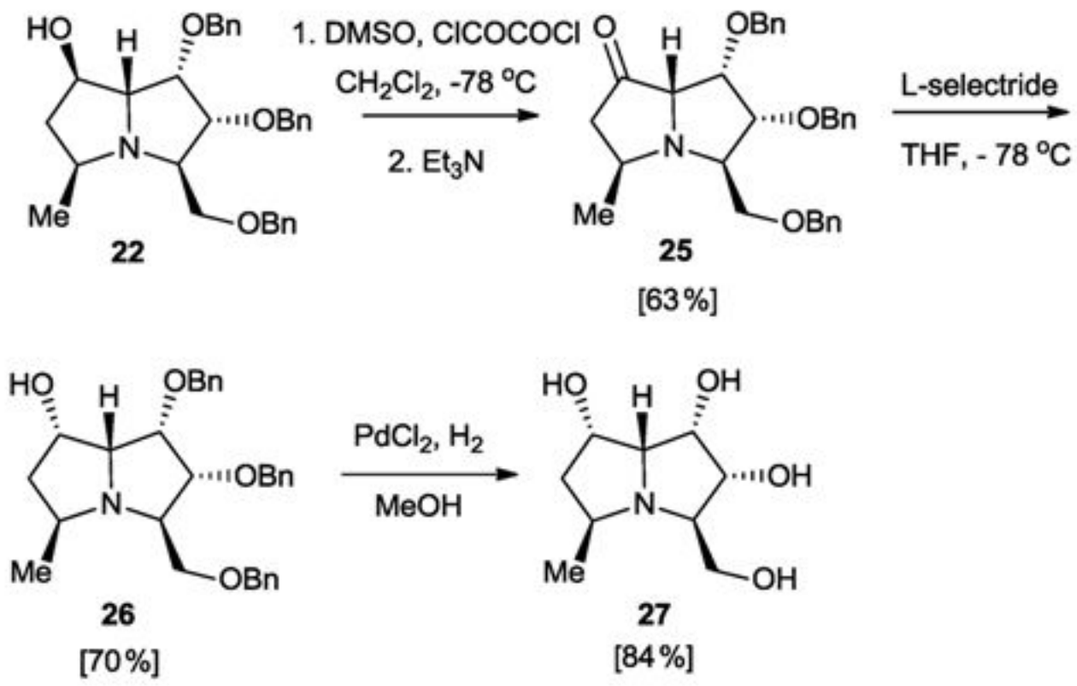


Scheme 4 Total synthesis of hyacinthacine B_3 **7** and the proposed structure of B_7 **15**.

lated but treated with the enantiomerically pure allylic amine **13** and (*E*)-styrenylboronic acid, under Petasis boronic acid Mannich reaction conditions, to provide the *anti*-amino alcohol **14a** in 53 % overall yield from **11a**. The oxazolidinone **15a** was obtained from **14a** by treatment with triphosgene and Et_3N in CH_2Cl_2 in 81 % yield. A ring-closing metathesis reaction of the oxazolidinone **15a**, using Grubbs' second-generation catalyst under microwave heating, smoothly provided the pyrrolo[1,2-

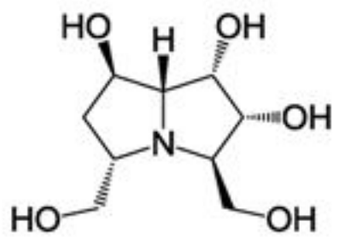
c]oxazol-3-one **16a** in good yield (76 %). The DH of **16a** furnished the corresponding 6β,7β-diol **17a** with the desired configuration for the synthesis of the target alkaloid as a single diastereoisomer in 88 % yield. *O*-Benzylation of the diol **17a** followed by a chemoselective OPMB deprotection reaction with dichlorodicyano-*p*-benzoquinone (DDQ) gave the secondary alcohol **19a**. Oxazolidinone hydrolysis of **19a** under basic conditions gave the amino diol **20a** that underwent *O*-mesylation and then S_N2 cyclization with inversion at the less-hindered secondary carbinol carbon upon exposure to 1.05 equiv of MsCl under basic conditions (Et_3N) at 0 °C to give the pyrrolizidine **21** in 63 % yield. A small amount of the *N*-*O*-di-mesylate of **20a** was also produced along with unreacted **20a**, but these compounds could be readily separated from **21** by column chromatography. Debenzylation of **21** under hydrogenolysis conditions over $PdCl_2/H_2$ gave hyacinthacine B_3 **23** in 68 % yield (12 synthetic steps, 5.6 % overall yield) after purification and neutralization by basic ion-exchange chromatography. The NMR data and the chiro-optical properties of synthetic hyacinthacine B_3 matched very well with those of the natural product, thus our synthesis confirmed the structure and absolute configuration of the natural product.

The synthesis of the proposed structure of hyacinthacine B_7 **24** was completed in 12 synthetic steps and 3.4 % overall yield from (*R*)-4-penten-2-ol, **9b** using an analogous synthetic strategy (Scheme 4). However, the NMR data did not match with those reported for the natural product. We therefore concluded that the structure assigned to hyacinthacine B_7 was incorrect. We have recently prepared 7-*epi*-hyacinthacine B_7 using the chemistry shown in Scheme 5 to invert the configuration of the alcohol **22**. Swern oxidation of **22** and then stereoselective reduction of the resulting ketone **25** gave the inverted alcohol **26**, which upon hydrogenolysis gave 7-*epi*-hyacinthacine B_7 **27** [26]. While the NMR spectral data of this compound were closer to those of hyacinthacine B_7, they were not a match. Thus, the structure of hyacinthacine B_7 still remains unsolved.



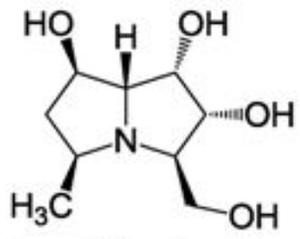
Scheme 5 Synthesis of 7-*epi*-hyacinthacine B_7 **27**.

Several other structural assignment problems made to the hyacinthacine alkaloids have recently been highlighted. It is notable that the structure of hyacinthacine C_1 is the same as that proposed for hyacinthacine C_4 (Fig. 5) even though they have different NMR data and optical rotations of opposite signs and different magnitudes (Fig. 5). The recent syntheses of hyacinthacines C_3 by Yoda [27] and C_5 by Zhang [28] have shown that these proposed structures are also incorrect (Fig. 6).



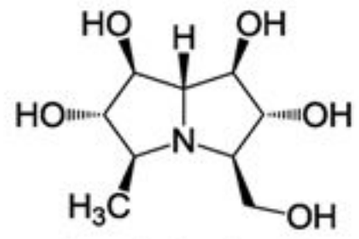
hyacinthacine C_3

Yoda, H. *et al.*
Tetrahedron Lett. **2009**, *50*, 4937-4940



hyacinthacine B_7

Pyne S. G. *et al.*
Chem. Commun. **2010**, *46*, 713-715



hyacinthacine C_5

Zhang, W. *et al.*
Org Lett. **2011**, *13*, 4414-4417

Fig. 6 Hyacinthacine alkaloids that have been assigned the incorrect structures based on their total synthesis.

In conclusion, we have demonstrated the utility of the boronic acid Mannich reaction as a key step in determining the correct structure of uniflorine A, the preparation of casuarine, australine, and 3-*epi*-australine, the synthesis of hyacinthacine B_3, and confirmation of its structure and configuration, and the preparation of the proposed structure of hyacinthacine B_7. Ongoing work in our laboratory is focused on the determination of the structure of hyacinthacine B_7 and that of α-5-*C*-(3-hydroxybutyl)-hyacinthacine A_2.

ACKNOWLEDGMENTS

We thank the Australian Research Council and the University of Wollongong for supporting this research.

REFERENCES

1. A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash. *Phytochemistry* **56**, 265 (2001).
2. N. Asano. *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*, Wiley-VCH, Weinheim (2008).
3. N. A. Petasis, I. Akritopoulou. *Tetrahedron Lett.* **34**, 583 (1993).
4. R. A. Batey. In *Boronic Acids*, D. G. Hall (Ed.), pp. 281–299, Wiley-VCH, Weinheim (2005).
5. N. R. Candeias, F. Montalbano, P. M. S. D. Cal, P. M. P. Gois. *Chem. Rev.* **110**, 6169 (2010).
6. T. Matsumura, M. Kasai, T. Hayashi, M. Arisawa, Y. Momose, I. Arai, S. Amagaya, Y. Komatsu. *Pharm. Biol.* **38**, 302 (2000).
7. A. S. Davis, S. G. Pyne, B. W. Skelton, A. H. White. *J. Org. Chem*. **69**, 3139 (2004).
8. N. S. Karanjule, S. D. Markad, D. D. Dhavale. *J. Org. Chem.* **71**, 6273 (2006).
9. Z. Zhao, L. Song, P. S. Mariano. *Tetrahedron* **61**, 8888 (2005).
10. A. W. Bell, L. Pickering, A. A. Watson, R. J. Nash, R. C. Griffiths, M. G. Jones, G. W. J. Fleet. *Tetrahedron Lett.* **37**, 8561 (1996).
11. A. D. Davis, T. Ritthiwigrom, S. G. Pyne. *Tetrahedron* **64**, 4868 (2008).
12. T. Ritthiwigrom, S. G. Pyne. *Org. Lett.* **10**, 2769 (2008).
13. T. Ritthiwigrom, A. C. Willis, S. G. Pyne. *J. Org. Chem*. **75**, 815 (2010).
14. C. Parmeggiani, D. Martella, F. Cardona, A. Goti. *J. Nat. Prod*. **72**, 2058 (2009).
15. R. J. Nash, P. I. Thomas, R. D. Waigh, G. W. J. Fleet, M. R. Wormald, P. M. de Q. Lilley, D. J. Watkin. *Tetrahedron Lett*. **35**, 7849 (1994).
16. J. Van Ameijde, G. Horne, M. R. Wormald, R. A. Dwek, R. J. Nash, P. W. Jones, E. L. Evinson, G. W. J. Fleet. *Tetrahedron: Asymmetry* **17**, 2702 (2006).

17. M. R. Wormald, R. J. Nash, A. A. Watson, B. K. Bhadoria, R. Langford, M. Sims, G. W. J. Fleet. *Carbohydr. Lett.* **2**, 169 (1996).
18. 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, N. Asano. *Carbohydr. Res.* **316**, 95 (1999).
19. N. Asano, H. Kuroi, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, I. Adachi, A. A. Watson, R. J. Nash, G. W. J. Fleet. *Tetrahedron: Asymmetry* **11**, 1 (2000).
20. T. Yamashita, K. Yasuda, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash, G. W. J. Fleet, N. Asano. *J. Nat. Prod.* **65**, 1875 (2002).
21. N. Asano, K. Ikeda, M. Kasahara, Y. Arai, H. Kizu. *J. Nat. Prod.* **67**, 846 (2004).
22. A. Kato, N. Kato, I. Adachi, J. Hollinshead, G. W. J. Fleet, C. Kuriyama, K. Ikeda, N. Asano, R. J. Nash. *J. Nat. Prod.* **70**, 993 (2007).
23. C. W. G. Au, R. J. Nash, S. G. Pyne. *Chem. Commun.* **46**, 713 (2010).
24. P. Evans, M. Leffray. *Tetrahedron* **59**, 7973 (2003).
25. C. W. G. Au, S. G. Pyne. *J. Org. Chem.* **71**, 7097 (2006).
26. K. Savaspun, S. G. Pyne. Unpublished results.
27. T. Sengoku, Y. Satoh, M. Takahashi, H. Yoda. *Tetrahedron Lett.* **50**, 4937 (2009).
28. W. Zhang, K. Sato, A. Kato, Y.-M. Jia, X.-G. Hu, F. X. Wilson, F. X. R. van Well, G. Horne, G. W. J. Fleet, R. J. Nash, C.-Y. Yu. *Org. Lett.* **13**, 4414 (2011).

