Synthesis of hyacinthacine B_3 and purported hyacinthacine B_7†

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The synthesis of hyacinthacines B_3 and B_7 has confirmed the structure of the former alkaloid and shown that the structure of the latter is incorrect.

The hyacinthacine alkaloids are a recent addition to the expanding group of polyhydroxylated 3-hydroxylmethyl-pyrrolizidine natural products.[1,2] This group, along with the other related polyhydroxylated alkaloids, have glycosidase inhibitory activities and thus have potential utility as antiviral, anticancer, antidiabetic and antiobesity drugs.[1] Nineteen hyacinthacine alkaloids of general structure **1** (Fig. 1) have been isolated. The first came from the Hyacinthaceae family of plants (*Hyacinthoides nonscripta*, the common bluebell)[3a] while the others have been isolated from the bulb extracts of *Muscari armeniacum*,[3b] *Scilla campanulata*,[3a] *Scilla sibirica*[3c] and *Scilla socialis*.[3d] Related alkaloids, having extended side chains at C-5, have been isolated from *Scilla peruviana*.[3e] In general these alkaloids show relatively weak glycosidase inhibitory activities with the best only having moderate activities (IC_{50} *ca.* 5–20 μM) against α- and β-glucosidases, β-galacto-sidases and amylglucosidases.[3a–d] These alkaloids have been classified as hyacinthacines A_{1-7}, B_{1-7} and C_{1-5} based on their total number of hydroxy and hydroxymethyl groups in the ring B.[3a–d] The structures and relative configurations of these natural products have been assigned by NMR analysis with the only X-ray crystallographic study on synthetic material.[4] The synthesis of these alkaloids has confirmed many of these structures and allowed assignment of their absolute configurations. Most of these syntheses have involved starting materials from Nature's chiral pool (carbohydrates,[5a–h] amino acids[5i–l] and diethyl tartrate[5m]). Others include a lipase resolution of a *meso*-2,5-disubstituted-2,5-dihydropyrrole to prepare an A-ring precursor,[4] a [2 + 2]-cycloaddition approach using a chiral auxiliary[6] and a chemoenzymatic synthesis using an aldolase.[7] The synthesis of epimers[8] and a racemic synthesis have also been reported.[9] A recent study has revealed that the proposed structure of hyacinthacine C_3 is incorrect.[5k] Thus new methods for the synthesis of these compounds are important not only to confirm their structures but also to provide analogues for structure–activity relationship studies.

We report herein the development of a new synthetic strategy towards these alkaloids and the first synthesis of hyacinthacine B_3 **2** which confirms its structural identity and absolute configuration. The synthesis of the proposed structure of hyacinthacine B_7 (**3**), the C-5 epimer of hyacinthacine B_3, is also described which indicated that the structure proposed for the natural product was incorrect. These syntheses are noted for their conciseness (12 steps from commercially available (*S*)- or (*R*)-4-penten-2-ol) and high diastereoselectivities. This includes a Petasis reaction that allows the synthesis of an advanced intermediate containing four of the six stereogenic centres of the target molecules and a highly diastereoselective *cis*-dihydroxylation reaction to secure the remaining two stereocentres (C-1 and C-2).

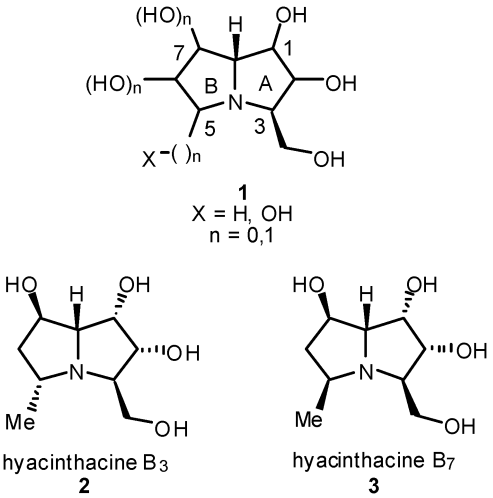

Fig. 1 General hyacinthacine alkaloid structure (**1**) and hyacinthacine B_3 (**2**) and hyacinthacine B_7 (**3**).

The synthesis of hyacinthacine B_3 **2** and hyacinthacine B_7 **3** started with commercially available (*S*)- and (*R*)-4-penten-2-ol, **4a** and **4b**, respectively, and these two separate syntheses are summarized in Scheme 1. For the synthesis of hyacinthacine B_3, (*S*)-4-penten-2-ol **4a** (ee > 98%) was protected as its PMB ether (**5a**) and then converted to the (*E*)-vinyl sulfone **5a** using a cross-metathesis reaction.[10] Using the asymmetric dihydroxyl-ation conditions of Evans and Leffray[11a] for vinyl sulfones we found that the vinyl sulfone **6a** reacted very sluggishly. Using a modified procedure and the less hindered DHQD-IND chiral ligand, however, the vinyl sulfone was converted to the corresponding α-hydroxy aldehyde **7a**, which was most likely a mixture of acetal derivatives, at rt in 24 h.[11b] This was not isolated but treated with the enantiomerically pure allylic amine **8**[12] and (*E*)-styrenyl boronic acid, under Petasis boronic acid Mannich reaction conditions,[13] to provide the *anti*-amino alcohol **9a** in 53% overall yield from **6a**. A small amount (*ca.* 6%) of another diastereomer was detected from ^{1}H NMR

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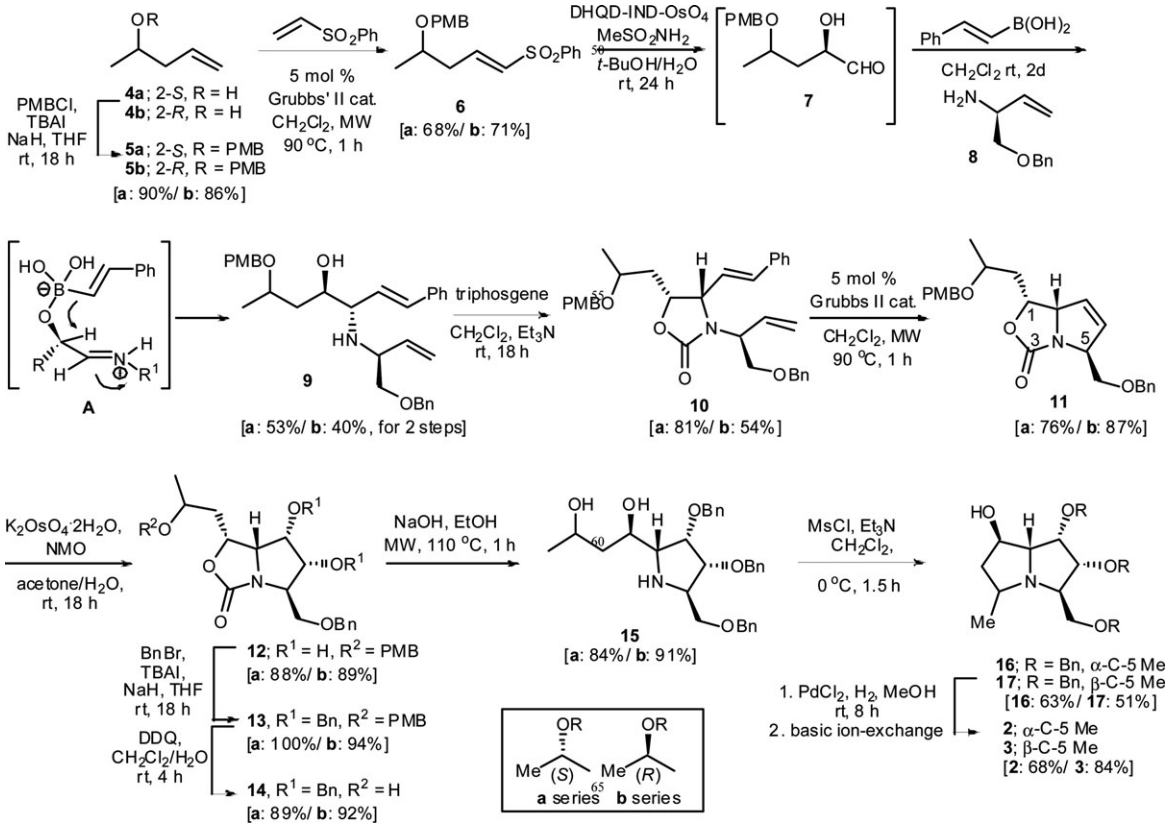
† Electronic supplementary information (ESI) available: Full experimental detail, spectroscopic data and copies of NMR spectra of **2** and **3**. See DOI: 10.1039/b918233k



Scheme 1 Synthesis of hyacinthacine B_3 and hyacinthacine B_7.

analysis of the crude reaction mixture but could not be isolated pure for further analysis. The configuration of the amino alcohol moiety in **9a** was expected based upon mechanistic considerations (see A in Scheme 1)[13] and was established by NMR analysis of its oxazolidinone derivative **10a**, which showed $J_{4,5}$ = 8.1 Hz (for **10b**, $J_{4,5}$ was 8.7 Hz). The magnitude of this vicinal coupling constant was consistent with the 4,5-*cis* relative stereochemistry of **10a**.[13c] The Petasis reaction thus provided an advanced intermediate of defined configuration at four stereogenic centres which would become C-3, C-5 (after inversion), C-7 and C-7a, in the target molecule **2**. A ring-closing metathesis reaction of the oxazolidinone **10a**, using Grubbs' second generation catalyst[14] under microwave heating, smoothly provided the pyrrolo[1,2-*c*]oxazol-3-one **11a** in good yield (76%). Based on our previous work,[14,15a] and that of Parsons,[15b–d] we expected that the *syn*-dihydroxylation (DH) of **11a** would furnish the corresponding 6β,7β-diol **12a** with the desired configuration for the synthesis of the target alkaloid. In the event, the Os(VIII)-catalysed *syn*-DH of **11a** provides the desired diol **12a** as a single diastereoisomer in 88% yield. This high level of diastereoselectivity can be explained based on stereoelectronic effects and an examination of the HOMO of **11** about the alkene moiety. The non-bonding orbital bearing the electron pair on the N-atom overlaps more effectively with the π-system of the alkene moiety on the α-(concave) face of the molecule making this face more prone to dihydroxylation.[15b–d] The β-benzyloxymethyl substituent at C-5 also contributes partially to the diastereofacial selectivity, since the DH of a similar substrate which lacked this C-5 substituent was less diastereoselective.[16] Importantly, the pyrrolo[1,2-*c*]oxazol-3-one **11a** has allowed us to secure the desired 1,2-diol configuration of the alkaloid **2**, on essentially a *trans*-2,5-disubstituted-2,5-dihydropyrrole A-ring precursor, that would otherwise be expected to be problematic. *O*-Benzylation of the diol **12a** followed by a chemoselective OPMB deprotection reaction with DDQ gave the secondary alcohol **14a**. Oxazolidinone hydrolysis of **14a** under basic conditions gave the amino diol **15a** that underwent *O*-mesylation and then S_N2 cyclization with inversion at the less hindered secondary carbinol carbon upon exposure to 1.05 equivalents of MsCl[4] under basic conditions (Et_3N) at 0 °C to give the pyrrolizidine **16** in 63% yield. A small amount of the *N*-*O*-di-mesylate of **15a** was also produced along with unreacted **15a** but these compounds could be readily separated from **16** by column chromatography. Debenzylation of **16** under hydrogenolysis conditions using $PdCl_2/H_2$[14] gave hyacinthacine B_3 **2** in 68% yield after purification and neutralization by basic ion-exchange chromatography (Scheme 1). The ^1H and ^{13}C NMR spectral data of this compound matched very closely to that reported in the literature (see ESI†).[3c] The optical rotation of this compound ($[\alpha]_D^{23}$ + 10.8 (*c* 0.33, H_2O)) was larger in magnitude but of the same sign to that reported (lit.[3c] $[\alpha]_D$ + 3.3 (*c* 0.31, H_2O)).

The proposed structure of hyacinthacine B_7 (**3**) was prepared in an analogous fashion starting with (*R*)-4-penten-2-ol **4b** (ee > 98%) (Scheme 1). The yields and diastereoselectivities were essentially the same except for the conversion of **6b** to **9b**. In this Petasis reaction the overall yield of **9b** from **6b** was only

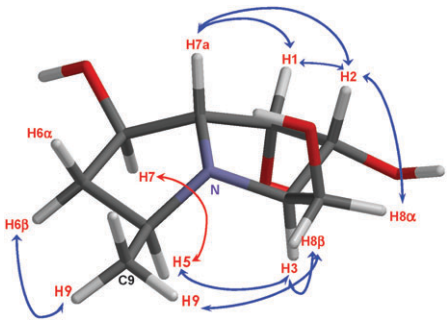


Fig. 2 HF/6-31G* optimized structure (SPARTAN) of compound **3**. Blue and red double headed arrows show NOESY correlations.

40% since a significant amount of another diastereomer of **9b** (*ca.* 20% of the crude reaction mixture from ^{1}H NMR analysis) was also formed. This diastereomer could not be characterized since it could not be isolated in pure form. We suspect that this diastereomer arises in the conversion of **6b** to **7b** due to an unmatched situation between the chiral reagent and the chiral substrate. More significantly, the ^{1}H and ^{13}C NMR spectral data of synthetic **3** did not match with that reported for hyacinthacine B_7 (see ESI†).[3d] NOESY NMR analysis of our synthetic compound clearly indicated that it had the correct relative configuration shown in structure **3** (Fig. 2). Significantly, a NOESY correlation was observed between H-5 and H-7 in **3** (Fig. 2, red arrow) but this was not reported for hyacinthacine B_7 in the original isolation paper.

The hyacinthacines are well resolved by GC-MS as their tetra-TMS derivatives.[3b] The original natural hyacinthacine B_7 was no longer available for comparison with the synthetic product reported here but GC-MS analysis of the extract of the same *S. socialis* plants used for the first report showed no hyacinthacine corresponding to the retention time of 10.71 min of **3**. The tetra-TMS derivative of **3** gave a distinctive mass spectrum with a base ion at 388 amu (100%). Four hyacinthacines in the *S. socialis* extract showed the same fragmentation pattern suggesting they were epimers of **3**. One major hyacinthacine with the 388 amu base ion had a retention time of 11.31 min by GC-MS which was the same retention time as a standard of hyacinthacine B_5. Another epimer was also observed at 10.97 min. It is not possible to conclusively identify the original natural product without an authentic standard but analysis of the original plant material strongly suggests that **3** does not occur in that plant although epimers of **3** clearly do. We thus conclude that the proposed structure of hyacinthacine B_7 is incorrect. Work is now continuing to ascertain the correct structure.

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