Synthesis of hyacinthacine B-3 and purported hyacinthacine B-7

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Abstract
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Synthesis of hyacinthacine B₃ and purported hyacinthacine B₇†

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The synthesis of hyacinthacines B₃ and B₇ 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-hydroxymethylpyrrolizidine 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, anti-diabetic and anti-obesity drugs.1 Nineteen hyacinthacine alkaloids of general structure I (Fig. 1) have been isolated. The first came from the Hyacinthaceae family of plants (Hyacinthoides non-scripta, the common bluebell)3a while the others have been isolated from the bulb extracts of Muscari armeniacum,3b Scilla campanulata,3c Scilla sibirica3d and Scilla socialis.3e Related alkaloids, having extended side chains at C-5, have been isolated from Scilla peruviana.3f In general these alkaloids show relatively weak glycosidase inhibitory activities with the best only having moderate activities (IC₅₀ ca. 5–20 μM) against α- and β-glucosidases, β-galactosidases and amyglucosidases.3a–d These alkaloids have been classified as hyacinthacines A₁,7, B₁,7 and C₁,5 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 the structures and allowed assignment of their absolute configurations. Most of these syntheses have involved starting materials from Nature's chiral pool (carbohydrates,5a–b amino acids5c–d and diethyl tartrate5e). Others include a lipase resolution of a meso-2,5-disubstituted-2,5-dihydropyrrole to prepare an A-ring precursor,5a a [2 + 2]-cycloaddition approach using a chiral auxiliary5b and a chemoenzymatic synthesis using an aldolase.5c The synthesis of epimers5a and a racemic synthesis have also been reported.5a A recent study has revealed that the proposed structure of hyacinthacine C₃ is incorrect.5f 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 B₇ 2 which confirms its structural identity and absolute configuration. The synthesis of the proposed structure of hyacinthacine B₇ (3), the C-5 epimer of hyacinthacine B₃, is also described which indicated that the structure proposed for the natural product was incorrect. These syntheses are not 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).

The synthesis of hyacinthacine B₇ 2 and hyacinthacine B₃ 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 B₇ 2, (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.6 Using the asymmetric dihydroxylation conditions of Evans and Leffray11a 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 812 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 1H NMR

Fig. 1 General hyacinthacine alkaloid structure (1) and hyacinthacine B₃ (2) and hyacinthacine B₇ (3).

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

Scheme 1  Synthesis of hyacinthacine B$_3$ and hyacinthacine B$_7$.

which lacked this C-5 substituent was less diastereoselective. Importantly, the pyrrolo1,2-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 chemo-selective 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$_N$2 cyclization with inversion at the less hindered secondary carbinol carbon upon exposure to 1.05 equivalents of MsCl$_2$ under basic conditions (Et$_3$N) 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$_2$ gave hyacinthacine B$_3$ in 68% yield after purification and neutralization by basic ion-exchange chromatography (Scheme 1). The $^{1}$H and $^{13}$C NMR spectral data of this compound matched very closely to that reported in the literature (see ESI$^+$). The optical rotation of this compound ([a]$_{D}^{23}$ = 10.8 (c 0.33, H$_2$O)) was larger in magnitude but of the same sign to that reported (lit. $^{3}$ [a]$_{D}^{23}$ = 3.3 (c 0.31, H$_2$O)).

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...
40% since a significant amount of another diastereomer of 9b (ca. 20% of the crude reaction mixture from 1H 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 1H and 13C NMR spectral data of synthetic 3 did not match with that reported for hyacinthacine B7 (see ESI).\(^5\)\(^{\text{27}}\) 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 B7 in the original isolation paper.

The hyacinthacines are well resolved by GC-MS as their tetra-TMS derivatives.\(^5\)\(^{\text{27}}\) The original natural hyacinthacine B7 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 with the 388 amu base ion had a retention time 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 B5. Another epimer was also observed at 10.97 min. It is not possible to conclusively identify the original natural product without an authentic sample.

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Notes and references


11. (a) P. Evans and M. Leffray, Tetrahedron, 2003, 59, 7973; (b) No aldehyde signal could be observed in the 1H NMR spectrum of the crude product.


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