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Total synthesis of hyacinthacines B3, B4, and B 5 and purported hyacinthacine B7, 7-epi-hyacinthacine B7, and 7a-epi-hyacinthacine B3 from a common precursor

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Abstract

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Total Synthesis of Hyacinthacines B_3, B_4, and B_5, Purported Hyacinthacine B_7, 7-*epi*-Hyacinthacine B_7, and 7a-*epi*- Hyacinthacine B_3 from a Common Precursor

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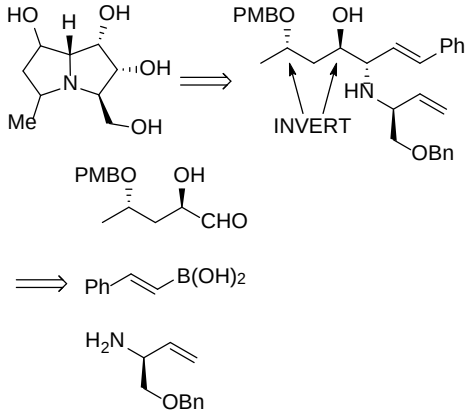


ABSTRACT: The total synthesis of hyacinthacines B_3, B_4, and B_5, purported hyacinthacine B_7, 7-*epi*- hyacinthacine B_7, and 7a-*epi*- hyacinthacine B_3 from a common *anti*-1,2-amino alcohol precursor is described. These syntheses confirmed that the proposed structures and absolute configurations of hyacinthacines B_3, B_4, and B_5 were correct and disclosed that the proposed structure of hyacinthacine B_7 was incorrect. Our synthetic and spectroscopic studies suggest that the natural hyacinthacines B_5 and B_7 are the same compounds; however without access to authentic samples this cannot be unequivocally proven.

INTRODUCTION

The hyacinthacine alkaloids are a relatively recent addition to the group of polyhydroxylated 3-hydroxymethylpyrrolizidine natural products.[1,2] These alkaloids, along with the other related polyhydroxylated pyrrolidine, piperidine, indolizidine and nortropane alkaloids, often have specific glycosidase inhibitory activities. Some of these, and their more drug like derivatives, have been identified as potential 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] *S. sibirica*,[3c] and *S. sociali*.[3d] Related alkaloids, having extended side chains at C-5, have been isolated from *S. 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-galactosidases, 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 based solely on NMR and MS spectroscopic analysis with the only X-ray crystalographic study made 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−o] amino acids,[5p−r] and diethyl tartrate[5s-u]). Others include an enzymatic resolution step followed by diastereoselective

synthesis,[4,6] a [2+2]-cycloaddition approach using a chiral auxiliary[7] and a chemoenzymatic synthesis using an aldolase.[8] The synthesis of epimers[9] and a racemic synthesis have also been reported.[10] Synthetic studies have revealed that the proposed structures of hyacinthacines B_7,[11] C_3,[5q] and C_5[9f] are incorrect. Thus new methods for the synthesis of these compounds is important not only to confirm their structures but also to provide analogues for structure-activity relationship studies. In an earlier communication we reported the development of a new synthetic strategy towards these alkaloids and the first synthesis of hyacinthacine B_3 **2** from (2*S*)-4-penten-2-ol.[11] This synthesis confirmed the structural identity and the absolute configuration of this alkaloid. The synthesis of the proposed structure of hyacinthacine B_7 **3**, the C-5 epimer of hyacinthacine B_3, was also described starting from (2*R*)-4-penten-2-ol, which indicated that the structure proposed for the natural product was incorrect.[11] We report here the full details of the synthesis of these compounds and the synthesis of hyacinthacine B_5 **5** and the analogue 7-*epi*-hyacinthacine B_7 **6**, a possible correct structure for natural hyacinthacine B_7, from (2*S*)-4-penten-2-ol as a common chiral synthetic precursor. Two side products from the synthesis of **5** were hyacinthacine B_4 **4** and 7a-*epi*- hyacinthacine B_3. These syntheses confirmed the structures and absolute configurations of natural hyancinthacines B_3, B_4, and B_5. From further analysis of their NMR spectroscopic data, and those of the other epimeric compounds that we have prepared, we propose that the structure of naturally occuring hyacinthacine B_7 has been missassigned and is actually hyacinthacine B_5. Unfortunately, the unavailabilty of these natural products does not allow us to be unequivocal about this structural reassignment.

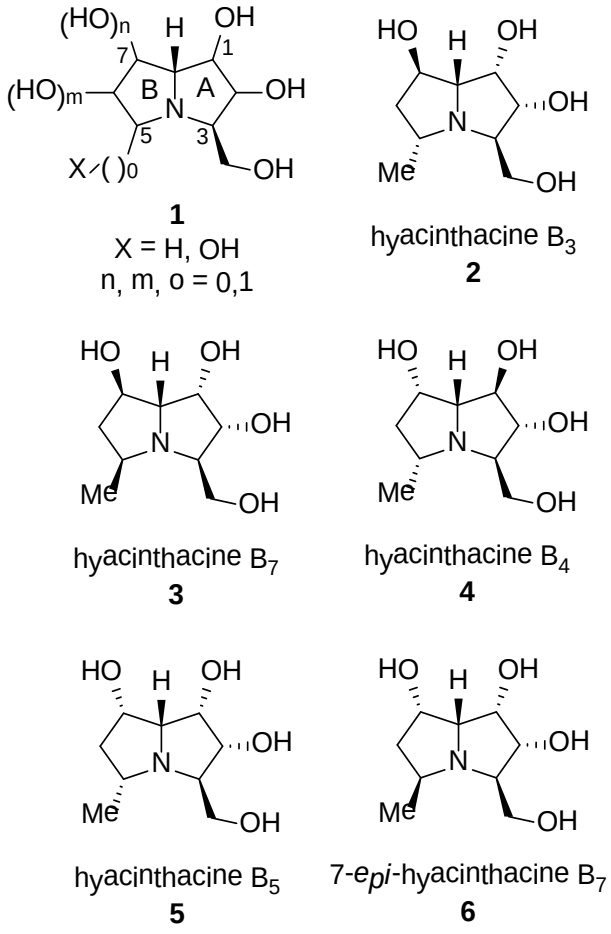


Figure 1. General structure of the hyacinthacine alkaloids and target molecules

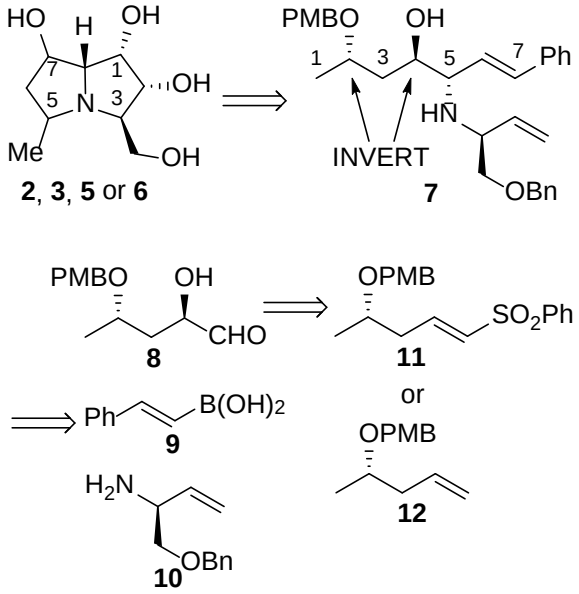
RESULTS AND DISCUSSION

Synthesis of hyacinthacine B_3

Our retrosynthetic analysis of hyacinthacines B_3, B_5, B_7, and 7-*epi*-hyacinthacine B_7 suggested that the 1,2-*anti*-amino alcohol **7**, which we used earlier as a precursor for the total synthesis of hyacinthacine B_3 **2**,[11] could serve as a useful common intermediate to the total synthesis of all four target compounds (Scheme 1). We anticipated that the configurations at C-2 and/or C-4 in **7** could be sequentially inverted to allow ready access

to each of these related synthetic targets. In our earlier synthesis of hyacinthacine B_3 **2** the α-hydroxy aldehyde **8**, or its cyclic acetal derivative, was prepared by an asymmetric dihydroxylation (ADH) reaction of the vinyl sulfone **11** (Scheme 1).[11,12] This aldehyde was not isolated but treated with a mixture of β-styrenyl boronic acid **9** and the chiral allylic amine **10**[13] under boronic acid Mannich reaction conditions[14] to give the 1,2-*anti*-amino alcohol **7**.[11] However we found that this method was not readily amenable to the scale up synthesis of **7** that was required here and the best overall yield of **7** that we could obtain on a several hundred milligram scale was 37% for the two steps. We thus devised an alternative synthesis of the aldehyde **8** from the alkene **12**.

Scheme 1. Retrosynthetic analysis of targets **2**, **3**, **5**, and **6**.

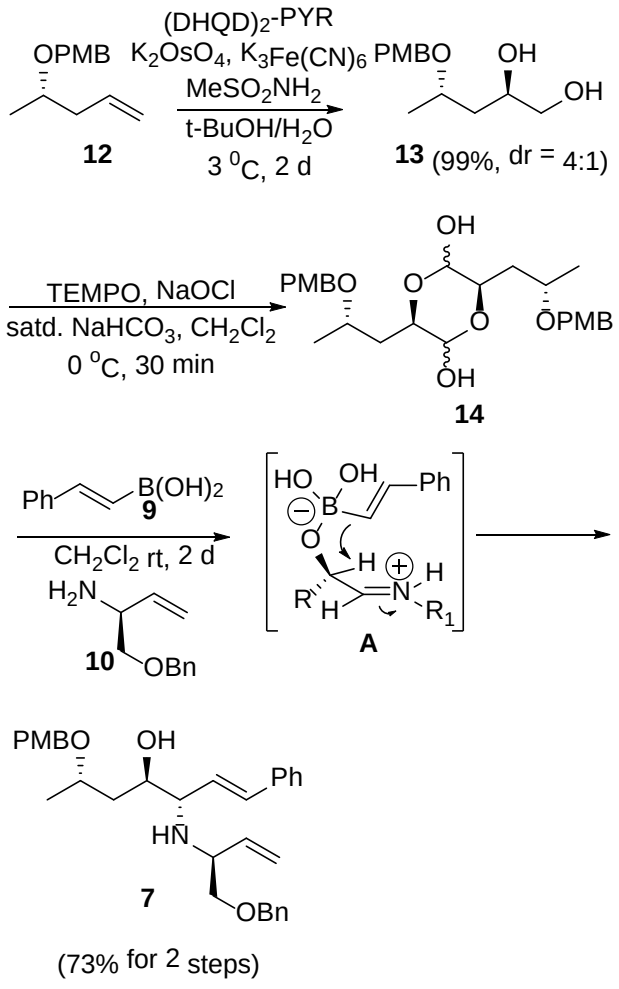


The ADH reactions of the alkene **12** using AD-mix-β ((1 mol % $(DHQD)_2PHAL$, *t*-BuOH/H_2O (1:1), methanesulfonamide (1 mol equiv) at rt or at 3 ^oC over 3 d gave the desired diol **13**, however in poor yields (15% and 24%, respectively) with no diastereoselectivity (dr = 1:1) (Scheme 2). The dr of **13** was conveniently determined by

^{1}H NMR analysis, the desired 2*R* diastereomer showed a resolved doublet resonance at δ 4.54 (*J* 11.5 Hz, OC*H*HPMP) while the undesired 2*S* diastereomer had a resolved doublet resonance at δ 4.57 (*J* 11.5 Hz, OC*H*HPMP). The yields and diastereoselectivities were enhanced significantly when DHQD-IND or $(DHQD)_2PYR$ were used instead of $(DHQD)_2PHAL$ as the chiral ligand at 3 ^oC over 3 d (65% yield, dr = 3:1 and 61% yield and dr = 4:1, respectively).[15] However, the yield of the diol **13** was nearly quantitative (99%) when the latter reaction was run at 3 ^oC for 3 d in *t*-BuOH/H_2O (1:2) without compromising the diastereoselectivity (dr = 4:1). While these diastereomeric diols could be separated by careful column chromatography it proved more convenient to take the diastereomeric mixture through to the 1,2-*anti*-amino alcohol **7** and purify the reaction product mixture at this stage. Thus the diol **13** (dr = 4:1) was oxidized with TEMPO and sodium hypochlorite in a two phase system (sat. aqueous $NaHCO_3/CH_2Cl_2$) at 0 ^oC for 30 min[16] to give a product mixture which we assumed was a mixture of hemiacetals **14** since NMR analysis showed no aldehyde signals (Scheme 2). The unpurified material was then immediately treated with β-styrenyl boronic acid **9** and the chiral allylic amine **10** in CH_2Cl_2 solution at rt for 2 d.[14] The crude reaction mixture was purified by column chromatography to give the 1,2-*anti*-amino alcohol **7** in 73% overall yield for the two steps as essentially a single diastereomer (dr = 95:5, Scheme 2). The minor diastereomer of **7**, that could possibly arise from the reaction of 2*S*-**13** with **9** and **10**, could not be isolated from the above mentioned column chromatography. The ^{1}H and ^{13}C NMR spectra of **7** matched closely with those of compound **7** that we prepared earlier starting from the vinyl sulfone **11**.[11]

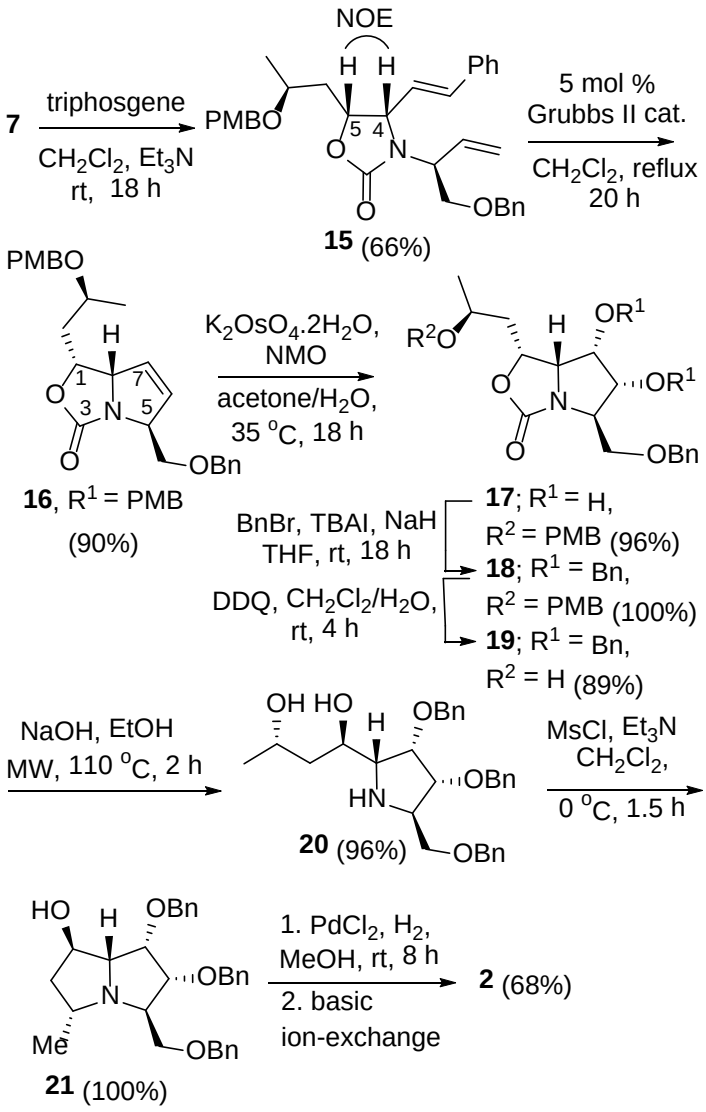
In order to prepare the A-ring of hyacinthacine B_3 **2**, via a ring closing metathesis (RCM) reaction of the diene **7**, the 1,2-amino alcohol moiety of **7**, which may deactivate the ruthenium catalyst by coordination, was protected first as its oxazolidinone derivative **15** (66% yield) by treatment with triphosgene/Et_3N (Scheme 3). ^1H NMR analysis of **15**, showed $J_{4,5}$ = 8.1 Hz, the magnitude of this vicinal coupling constant was consistent with the 4,5-*cis* relative stereochemistry of **15**,[14c] this assignment was further established from the NOESY correlation between H4 and H5 (Scheme 3). These results also confirmed the *anti*-configuration assigned to the 1,2-amino alcohol moiety in **7** which was expected

Scheme 2. Synthesis of the *anti*-1,2-amino alcohol **7**.



based upon mechanistic considerations and literature precedent (see intermediate **A** in Scheme 2)[14]

Scheme 3. Synthesis of hyacinthacine B_3 **2**.



A ruthenium catalyzed RCM reaction of **15**, using 5 mol% Grubbs' second generation catalyst, gave the pyrrolo[1,2-*c*]oxazol-3-one **16** in 90% yield. Based on our previous work,[17,18a] and that of Parsons,[18b,c] we expected that the *syn*-dihydroxylation (DH) of **16** would furnished the corresponding 6α,7α-diol **17** with the desired configuration for the

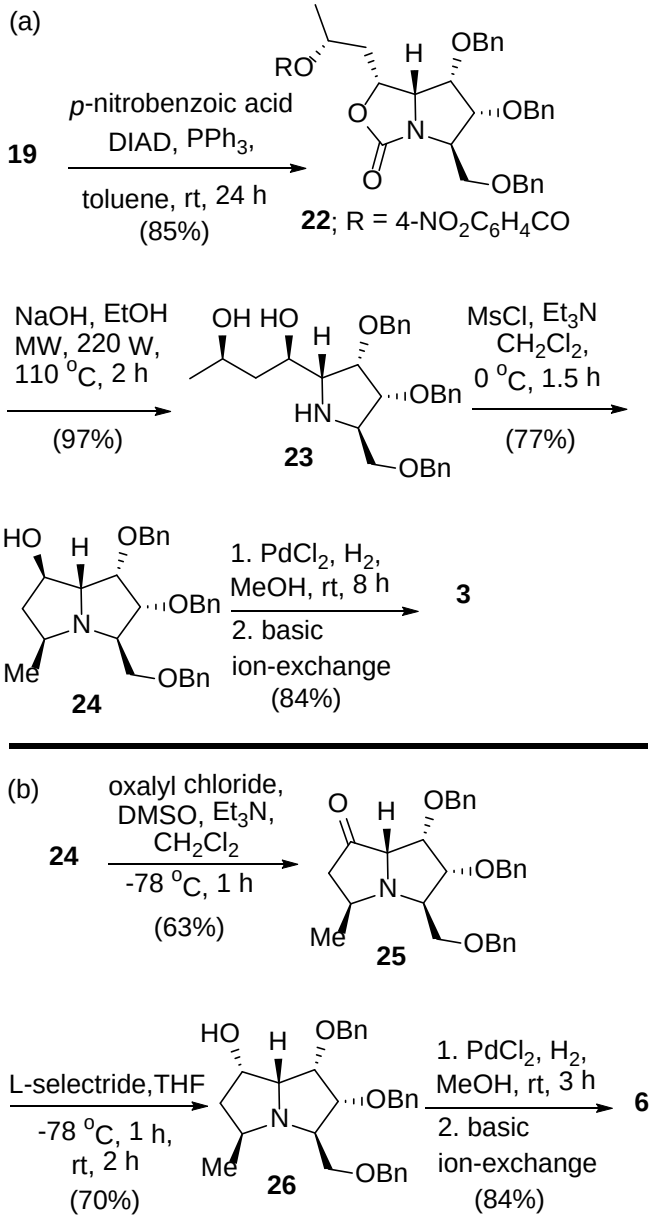
synthesis of the target alkaloid. In the event, the Os(VIII)-catalysed *syn*-DH of **16** provided the desired diol **17** as a single diastereoisomer in 96% yield. Earlier we explained this high level of diastereoselectivity based on stereoelectronic effects and an examination of the HOMO of **16** about the alkene moiety.[11] 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 concave face (α-face) of the molecule making this more hindered face more prone to dihydroxylation.[18b,c] 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.[19] Importantly, the pyrrolo[1,2-*c*]oxazol-3-one **16** has allowed us to secure the desired 2,3-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. Compound **17** was readily converted to the amino diol **20** (Scheme 3) by three efficient consecutive reactions: (i) a bis-*O*-benzylation reaction to give **18** (100% yield); (ii) *O*-PMB deprotection of **18** with DDQ under aqueous conditions[11] to give **19** (89% yield); and (iii) base hydrolysis of **19** under microwave heating (96% yield of **20**). Treatment of **20** with 1.05 equivalents of MsCl[4] under basic conditions (Et_3N) at 0 ^oC gave the pyrrolizidine **21** in 100% yield. Debenzylation of **21** under hydrogenolysis conditions using $PdCl_2/H_2$[17] gave hyacinthacine B_3 **2** in 68% yield after purification and neutralization by basic ion-exchange chromatography (Scheme 3). The overall yield of **2** from **12** was 24%. The ^1H and ^{13}C NMR spectral data of this compound matched very closely to those reported in the literature (see SI).[3b] The configuration assigned to this compound was confirmed by NOESY NMR studies (see SI). 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.[3b] $[\alpha]_D$ +3.3 (*c* 0.31, H_2O)). Thus this synthesis confirms the proposed structure and absolute configuration of hyacinthacine B_3 **2**.

Synthesis of the purported structure of hyacinthacine B_7 and 7-epi-hyacinthacine B_7

The proposed structure of hyacinthacine B_7 (**3**) was prepared from **19** according to Scheme 4 (a). The unprotected secondary alcohol of **19** was converted to the 4-nitrobenzoate derivative **22**, with inversion of configuration, under Mitsunobu reaction conditions.[20] Base hydrolysis of both the ester and oxazolidinone moieties of **22** was achieved under microwave heating conditions which furnished the amino diol **23** in 97% yield. This compound was identical to the compound we prepared in our earlier synthesis of **23** starting from (2*R*)-4-penten-2-ol.[11] Treatment of **23** with 1.05 equivalents of MsCl under basic conditions (Et_3N) at 0 ^oC gave the pyrrolizidine **24** in 77% yield after purification by column chromatography. Debenzylation of **24** under hydrogenolysis conditions using $PdCl_2/H_2$[14] gave the purported structure of hyacinthacine B_7 (**3**) in 68% yield after purification and neutralization by basic ion-exchange chromatography (Scheme 4 (a)). Of significant concern was that the ^1H and ^{13}C NMR spectral data of synthetic **3** did not match with those reported for hyacinthacine B_7 (see SI).[3d] Further its specific rotation $[\alpha]_D^{24}$ + 31.2 (*c* 0.20, H_2O) was significantly different and of the opposite sign to that of the natural product ($[\alpha]_D$ − 4.4 (*c* 0.20, H_2O).[3d] NOESY NMR analysis of our synthetic compound clearly indicated that it had the correct relative configuration, significantly, a NOESY correlation was observed between H-5 and H-7 in **3** (See ref 11 for details) but this was not reported for hyacinthacine B_7 in the original isolation paper.

Scheme 4. (a) Synthesis of the purported structure of hyacinthacine B_7 (**3**) and (b) 7-*epi*-hyacinthacine B_7 (**4**)



Unfortunately a sample of natural hyacinthacine B_7 was no longer available from the authors for comparison with our synthetic product.[11] However, as communicate earlier, a GC-MS analysis of the crude extract of the same *Scilla socialis* plants used in the original

isolation paper showed no hyacinthacine corresponding to the retention time of 10.71 min for the tetra-TMS derivative of **3** (base ion at 388 amu (100%)) while four hyacinthacines in the *S. socialis* extract showed the same fragmentation pattern suggesting they were epimers of **3**.[11] This analysis strongly suggested that **3** does not occur in that plant although epimers of **3** clearly do.

This information, and the differences in NOESY correlations between H-5 and H-7 in synthetic **3** and natural hyacinthacine B_7, suggested to us that the natural product might be 7-*epi*-hyacinthacine B_7 (**6**), since the other possible A-ring epimer, hyacinthacine B_5 (**5**), had already been reported as a natural product.[3c] To examine this possibility compound **6** was prepared from the pyrrolizidine **24** according to Scheme 4 (b). Thus the unprotected secondary alcohol in pyrrolizidine **24** was oxidized under Swern oxidation conditions[21] to give the ketone **25** in 63% yield. A diastereoselective reduction of this ketone with L-selectride from the less hindered convex face (β-face) of the pyrrolizidine structure gave the alcohol **26**, which was epimeric at C-7 with its precursor **24**. Debenzylation of **26** over $PdCl_2/H_2$[17] gave 7-*epi*-hyacinthacine B_7 (**6**) in 84% yield after purification and neutralization by basic ion-exchange chromatography (Scheme 4 (b)). While the ^1H and ^{13}C NMR spectroscopic data for this compound were a closer match to those of hyacinthacine B_7 than to those of synthetic **3**, they were nonetheless not identical (see SI).

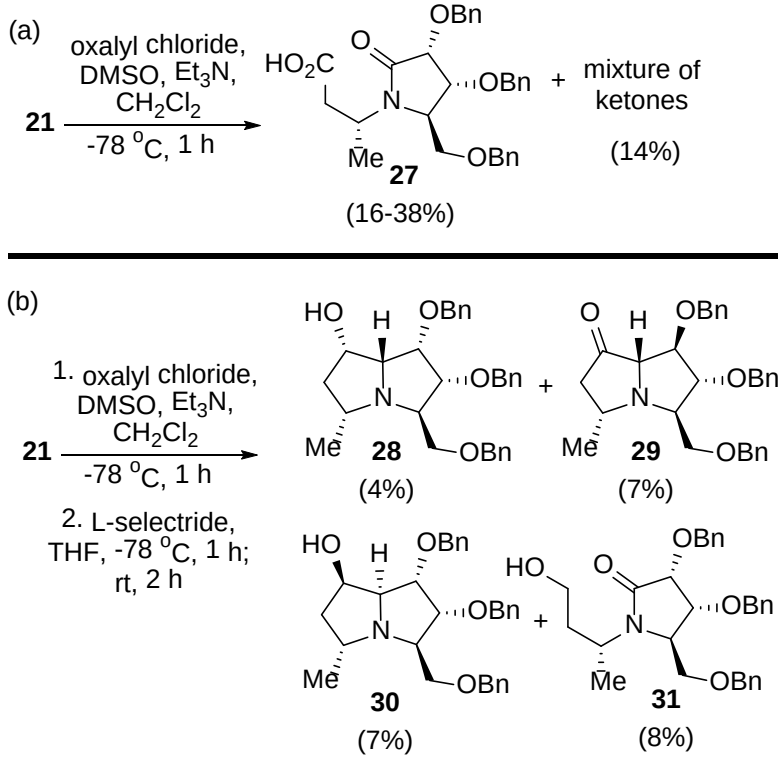
Synthesis of hyacinthacines B_4 and B_5 and 7a-epi-hyacinthacine B_3

While the above synthetic strategies readily provided the three desired target molecules, our synthesis of hyacinthacine B_5 (**5**) did not proceeded as efficiently as planned. Our

plan was to oxidize the secondary alcohol of **21** to the corresponding C-7 ketone and then convert this to the C-7 α-carbinol **28** by a diastereoselective reduction with L-selectride using the conditions we had successfully employed in Scheme 4 (b). Compound **28** would then be de-*O*-benzylated to give hyacinthacine B_5 (**5**). Surprizingly, the Swern oxidation of alcohol **21** gave the unexpected lactam-carboxylic acid **27** as the major oxidation product along with an inseparable mixture that comprised three other products from ^{1}H NMR analysis (Scheme 5 (a)). MS analysis of this mixture indicated that one of the components of this mixture might have been the desired ketone. The yield of **27** was 16% when the reaction mixture was held at −78 ^{o}C for 1 h and 38% when the oxidation mixture was treated with Et_3N at −78 ^{o}C and then warmed to rt for 1 h. When the crude oxidation product mixture from the former oxidation reaction conditions (−78 ^{o}C for 1 h) was treated with L-selectride, and then separated by column chromatography, four new compounds could be isolated, all in low yields, and identified. One product was the lactam-alcohol **31** (8% yield), while the diastereomeric alcohols **28** (7%), and **30** (4%) and the ketone **29** (7%) comprised the other three products (Scheme 5 (b)). The configurations of the products **28**, **29** and **30** were determined from NOESY NMR experiments and their structures were further supported by their conversions to, hyacinthacine B_5 (**5**) via hydrogenolysis, hyacinthacine B_4 (**4**) via a diastereoselective L-selectride reduction to alcohol **32** and then hydrogenolysis, and 7a-*epi*-hyacinthacine B_3 **33** via hydrogenolysis, respectively (Scheme 5 (c)). The ^{1}H and ^{13}C NMR spectroscopic data of synthetic compounds **4** and **5** matched very closely to those reported for these individual natural products, respectively (see SI).[3c] The configurations assigned to these synthetic compounds were confirmed by NOESY NMR studies (see SI). The optical

rotation of **5** ($[\alpha]_D^{25}$ - 21.6 ^{o}, *c* 0.08, H_2O) matched well with that of natural hyacinthacine B_5 ($[\alpha]_D$ - 25.4 ^{o}, *c* 0.26, H_2O)[3c] as did that of **4** ($[\alpha]_D^{25}$ - 7.7 ^{o}, *c* 0.18, H_2O) and natural hyacinthacine B_4 ($[\alpha]_D$ - 6.7 ^{o}, *c* 1.19, H_2O).[3c] Thus these syntheses confirm the proposed structures and absolute configurations of hyacinthacines B_4 and B_5.

Scheme 5. Synthesis of hyacinthacine B_4 **4,** hyacinthacine B_5 **5**, and 7a-*epi*-hyancinthacine B_3 **33**

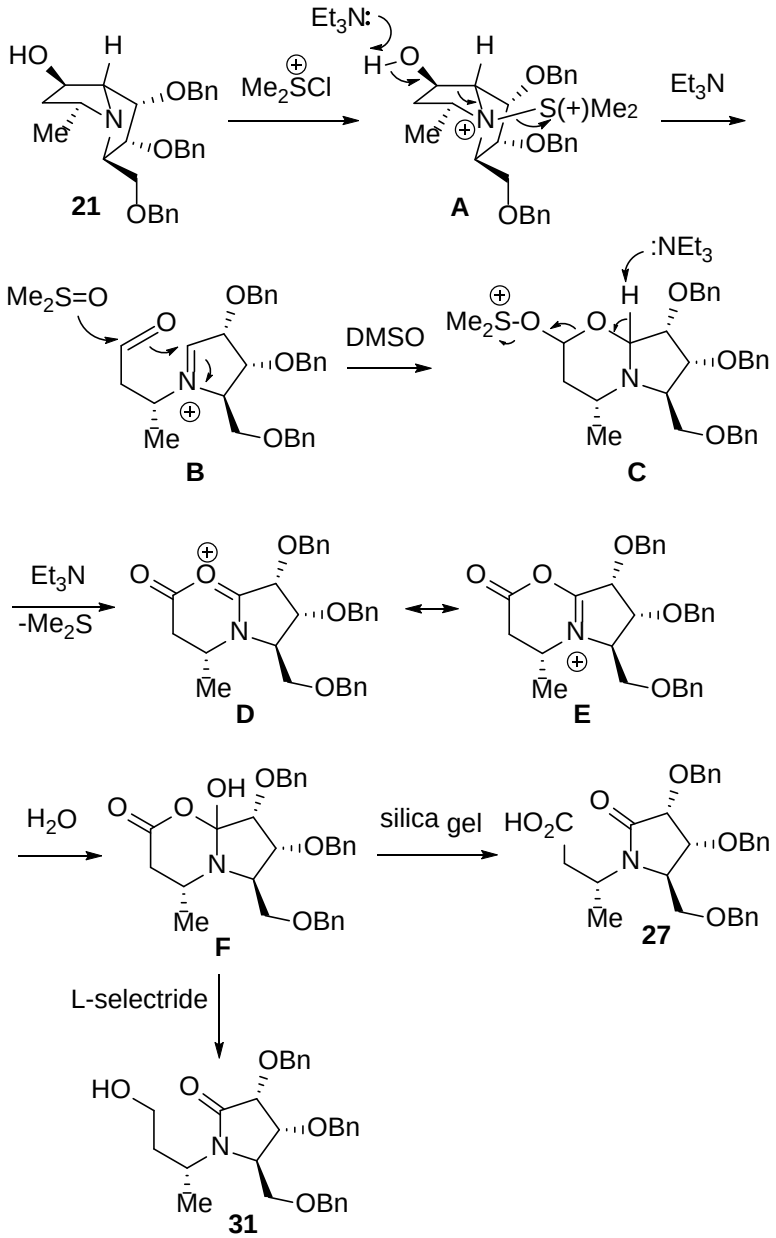


A possible mechanistic scheme for the formation of the B-ring fragmented products **27** and **31** is outlined in Scheme 6. This mechanism is also consistent with the finding that **27** was inert to reduction when treated with an excess amount of L-selectride under the reaction conditions indicated in Scheme 5 (b). Reaction of **21**, via its tertiary nitrogen atom, with the dimethylchlorosulfonium species (Me_2SCl^+)[21] would lead to the N-sulfonium intermediate **A** which upon base assisted fragmentation could give rise to the iminum ion **B** (Scheme 6). DMSO assisted cyclization of **B** could lead to the bicyclic intermediate **C** which upon base promoted elimination-fragmentation would give the resonance stabilized cation intermediate **D**. Quenching of the reaction mixture with water could give rise to the aminal **F** which could give the lactam **27** upon chromatography on silica gel. Reduction of **F** with an excess amount of L-selectride could give alcohol **31** (Scheme 6).

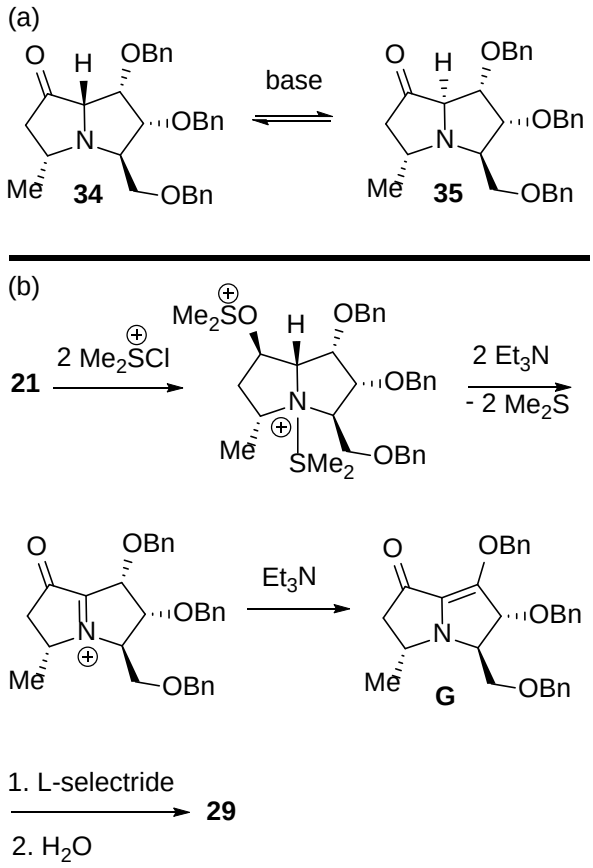
The alcohol **28**, however, clearly arises from reduction of the expected and desired C-7 ketone **34**, that could not be isolated in pure form, while alcohol **30** seems to have formed from reduction of ketone **35**, the C-7a epimer of ketone **34** (Scheme 7 (a)). Such an epimerization process would seem likely as it would relieve unfavorable steric interactions between the substituents at C-1, C-2 and C-5 on the more crowded concave face of **34** (Scheme 7 (a)). In the C-7a epimeric ketone **35** these substituents are now on the less crowded convex face of the molecule. The isolation of ketone **29** in Scheme 5 (b), suggests that this compound was protected from reduction with L-selectride by formation of its corresponding enolate anion. A tentative mechanism to support such an enolate intermediate, which also accounts for the inversion of configuration at C-1, is shown in Scheme 7 (b). This mechanism involves formation of the enone **G** which upon 1,4-

reduction by L-selectride, with addition of hydride at C-1 from the stereoelectronically favored pseudo-axial direction, would give an enolate anion which upon quenching with water and protonation at C-7a, from the stereoelectronically favored pseudo-axial direction, would give **29** (Scheme 7 (b)).

Scheme 6. Proposed mechanism for the formation of ring-fragmented products **27** and **31**.

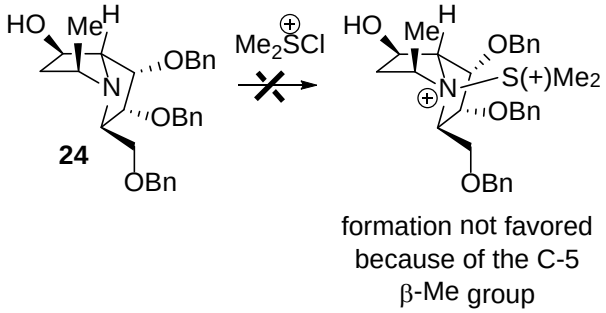


Scheme 7. Proposed intermediates and mechanisms.



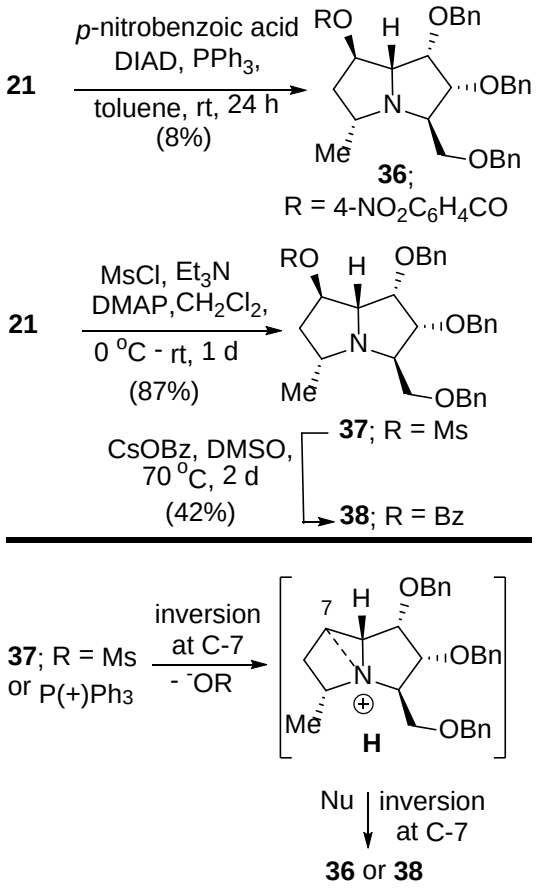
The relatively more straight forward oxidation of alcohol **24** to its desired ketone **25** (Scheme 4 (b)) is likely a consequence of the C-5 β-methyl substituent which would sterically hinder the formation of an intermediate analogous to **A** in Scheme 6 (Scheme 8).

Scheme 8.



Attempts to prepare the C-7 inverted alcohol **28** more efficiently by S_N2 inversion reactions of the alcohol **21** were also unsuccessful (Scheme 9). The Mitsunobu reaction of **21** gave the *p*-nitrobenzoate **36** in very poor yield (8%) and with retention of configuration at C-7. The *O*-mesylate derivative **37** of **21** gave a more respectable yield of the benzoate **38**, upon treatment with CsOBz[22] however again with retention of configuration at C-7. The configuration of esters **36** and **38** were confirmed from there base hydrolysis back to the alcohol **21**. While the Mitsunobu reaction of hindered alcohols can proceed with retention of configuration by direct *O*-acylation of the alcohol by $[ArCO_2PPh_3]^+$,[23] we suspect that the aziridinium ion intermediate **H**[24] is formed in these reactions leading to C-7 esters with overall retention of configuration (Scheme 9).

Scheme 9. Attempts to invert the configuration at C-7 of alcohol **21**.



A comparison of the ^{13}C NMR chemical shifts (rounded up to the nearest whole integer) of synthetic compounds **2**, **3**, **5** and **6** (all with the same configurations at C-1 – C-3 and C-7a) and those of natural hyacinthacine B_7 is shown in Figure 3. Compounds **2** and **5**, with an α-methyl group at C-5, have nearly the same ^{13}C NMR chemical shifts for C-3, C-5, C-8 and C-9. This is also true for compounds **3** and **6**, having a β-methyl group at C-5. However, these particular chemical shifts observed for compounds **3** and **6** are significantly downfield of those of their corresponding carbons seen in the ^{13}C NMR spectra of compounds **2** and **5**, except for the chemical shift of C-8 which is insensitive to the configuration at C-5. Interestingly, the ^{13}C NMR chemical shifts for C-3, C-5, C-8 and C-9 of hyacinthacine B_4 **4**, the C-1 epimer of **5**, and **5** are also nearly the same.

Compounds **2** and **3**, with a β-hydroxy group at C-7, have nearly the same ^{13}C NMR chemical shifts for C-1, C-7 and C-7a. This is also observed for compounds **5** and **6**, having an α-hydroxy group at C-7. In compounds **2** and **3**, C-7a resonates at δ 75-76, downfield of the signals for C-1 and C-7 (δ 71−74), while in the ^{13}C NMR spectra of compounds **5** and **6**, the reverse trend is observed (C-7a, δ 70-71 and C-1 and C-7 (δ 75−76).

In light of this analysis, an examination of the ^{13}C NMR chemical shifts for C-3, C-5, C-8 and C-9 of natural hyacinthacine B_7 (Figure 2), would indicate the α-configuration of the C-5 methyl group rather than the assigned β-configuration. Further, if one assumes that the chemical shifts of C-1 (reported as δ 77.9) and C-2 (reported as δ 74.9) have been missassigned in natural hyacinthacine B_7 [these chemical shifts are not consistent with those of the other hyacinthacine alkaloids (in compounds **2**−**6**, the ^{13}C NMR chemical shift of C-2 is always downfield of that of C-1, see SI)] then this compound should have the α-configuration at C-1 and not the initially assigned β-configuration. This analysis suggests that natural hyacinthacine B_7 is actually hyacinthacine B_5 **5**. Further, analysis of Table 1 indicates a close match between their ^{13}C NMR chemical shifts. A comparison of the ^{1}H NMR chemical shifts and coupling constants for these two alkaloids shows close agreement for the protons H-1, H-2, H-6β, H-7, H-8 and H-9 (Table 2) and a consistent difference of *ca* 0.2 ppm for the protons H-3, H-5, H-6α, H-7a and H-8'. Considering that the chemical shifts of these types of compounds are sensitive to pH and concentration effects[4] these NMR data would seem to be a good match, and support our proposal that they are the same compound (hyacinthacine B_5). Their specific rotations however, are of the same sign but differ significantly in magnitude (hyacinthacine B_5: $[\alpha]_D$ −25.4 (*c* 0.26,

H_2O)[3c]; natural hyacinthacine B_7: $[\alpha]_D$ −4.4 (*c* 0.20, H_2O)[3b]). However, without having authentic samples of these two natural products in hand it is impossible to either verify or disprove our proposal and thus unequivocally demonstrate the correct structure of natural hyacinthacine B_7.

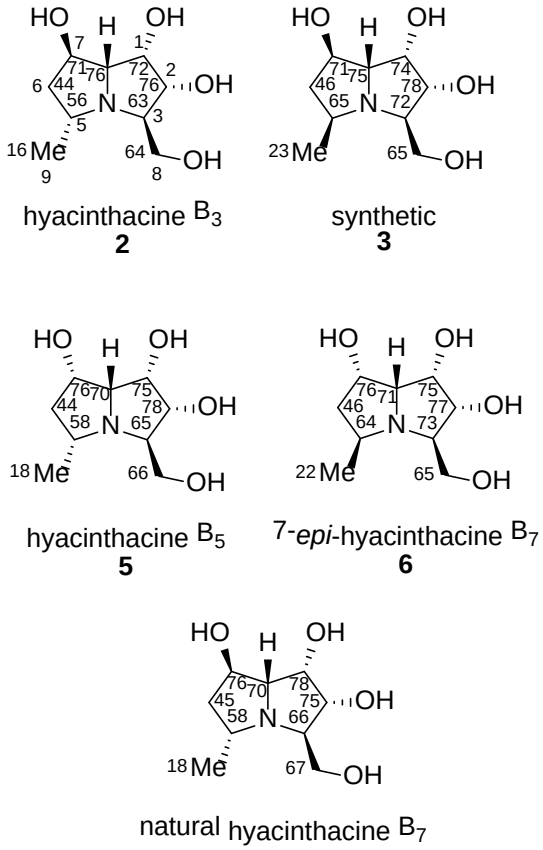


Figure 2. ^{13}C NMR chemical shifts (rounded to the nearest whole integer) of compounds **2**, **3**, **4**, **5**, **6** and natural hyacinthacine B_7.

Table 1. Comparison of literature ^{13}C NMR chemical shifts (125 MHz, D_2O) of natural hyacinthacine B_7[3d] and natural hyacinthacine B_5[3c]

carbon	natural hyacinthacine B_7[3d] δ_C (ppm)	natural hyacinthacine B_5[3c] δ_C (ppm)
1	77.9	74.8
2	74.9	76.9
3	66.2	65.5
5	57.7	58.5
6	45.2	43.9
7	76.5	75.0
7a	69.9	70.1
8	66.8	64.7
9	18.4	17.9

Table 2. Comparison of literature ^{1}H NMR chemical shifts (500 MHz, D_2O) of natural hyacinthacine B_7[3d] and natural hyacinthacine B_5[3c]

proton	natural hyacinthacine B_7[3d]		natural hyacinthacine B_5[3c]	
	δ_H (ppm)	Mult., *J* (Hz)	δ_H (ppm)	Mult., *J* (Hz)
1	4.35	t (4.4)	4.37	dd (4.4, 4.2)
2	3.97	dd (7.6, 4.4)	4.08	dd (8.0, 4.2)
3	3.29	ddd (7.6, 5.5, 3.5)	3.48	ddd (5.1, 4.6, 4.2)
5	3.22	m	3.44	m
6α	1.68	m	1.86	ddd (12.5, 10.0, 8.0)
6β	2.16	m	2.22	ddd (12.5, 6.4, 6.0)
7	4.50	m	4.55	ddd (8.0, 7.6, 6.4)
7a	3.45	dd (7.6, 4.4)	3.66	dd (7.6, 4.4)
8	3.57	dd (11.5, 3.5)	3.70	dd (12.0, 5.1)
8′	3.63	dd (11.5,5.5)	3.73	dd (12.0, 4.6)
9	1.25	d (7.0)	1.32	d (7.0)

CONCLUSIONS

In conclusion, the total synthesis of hyacinthacines B_3, B_4, and B_5, purported hyacinthacine B_7, 7-*epi*- hyacinthacine B_7, and 7a-*epi*- hyacinthacine B_3, from a common *anti*-1,2-amino alcohol precursor (**7**), has been achieved. These syntheses have confirmed that the proposed structures and absolute configurations of hyacinthacines B_3, B_4, and B_5 are correct and disclosed that the proposed structure of natural hyacinthacine B_7 was incorrect. Our synthetic and spectroscopic studies suggest that the natural hyacinthacines B_5 and B_7 are the same compound; however without access to authentic samples this cannot be unequivocally proven.

EXPERIMENTAL SECTION

General Methods. Flash column chromatography packed with Merck Kieselgel 60 PF_{254} was used for purification. A single quadrupole mass spectrometer was used for obtaining the LRESIMS. Quadrupole time-of-flight mass spectrometers were used for acquiring HRESIMS and HRASAPMS. IR spectra were run on neat samples. ^1H (500 or 300 MHz) and ^{13}C NMR (125 or 75 MHz) NMR spectra were recorded in deuterochloroform ($CDCl_3$), deuterium oxide (D_2O) or deuterated methanol-d_4 (CD_3OD) solution. All signals which were recorded in $CDCl_3$ were relative to the tetramethylsilane (TMS) signal and the $CDCl_3$ signal, referenced at 0.00 ppm (for ^1H NMR) and 77.16 ppm, (for ^{13}C NMR), respectively. All signals which were recorded in CD_3OD were relative to the CD_2HOD signal for ^1H NMR and the CD_3OD for ^{13}C NMR, referenced at 3.31 ppm and 49.00 ppm, respectively. All signals which were recorded in D_2O were relative to the D_2O signal for ^1H NMR, referenced at 4.49 ppm. For ^{13}C NMR spectra in D_2O the referencing of peaks is relative to internal MeOH (49.50 ppm). In some cases the ^{13}C

NMR spectral data were referenced to sodium 3-(trimethylsilyl)propionate (TSP) at δ -2.19 in D_2O. In order to compare our ^{13}C NMR data recorded in D_2O (and referenced to internal MeOH) with those of the literature which were run in D_2O and referenced to TSP at δ 0.00 we have added 2.19 ppm to our observed ^{13}C NMR chemical shifts in the ^{13}C NMR comparison tables (SI). NMR assignments were based upon gCOSY, APT, gHSQC, gHMBC and NOESY experiments. In some cases, ^{13}C NMR signals that were absent in the standard ^{13}C NMR spectrum were identified using gHSQC and gHMBC experiments. Petrol refers to the hydrocarbon fraction of bp. 40-60 °C. are named using systematic nomenclature. The NMR assignments made to pyrrolizidine compounds are based on the numbering system of the hyacinthacine alkaloids and not the systematic name.

Synthesis of hyacinthacine B_3 (2).

*(2R,4S)-4-(4-Methoxybenzyloxy)pentane-1,2-diol (**13**)* A solution of **12** (2.58 g, 12.49 mmol) in *tert*-butanol (20 mL) was slowly added dropwise into a solution of potassium ferric cyanide (12.34 g, 37.48 mmol), potassium carbonate (5.18 g, 37.48 mmol), methanesulfonamide (1.19 g, 12.49 mmol), potassium osmate dihydrate (55 mg, 0.150 mmol) and $(DHQD)_2PYR$ (0.110 g, 0.125 mmol) in H_2O (40 mL) which was cooled in an ice bath. The reaction mixture was stirred at 3 - 5 ^oC (in a cold room) for 2 d. The reaction was quenched with sodium sulfite (9.44 g, 74.94 mmol) and then allowed to warm to rt (21 ^oC), stirred for 30 min and then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by flash column chromatography (increasing polarity from 0:100 to 4:96 of $MeOH/CH_2Cl_2$) gave the title compound as a colorless oil (2.736 g, 99 %, dr = 4:1). R_f 0.50 (10:90 $MeOH/CH_2Cl_2$). $[\alpha]_D^{25}$ - 46.5 (*c* 1.64, $CHCl_3$). IR υ_{max} (cm^{-1}): 3396, 2925, 1614, 1512,

1244, 1031, 818. δ_H (500 MHz, $CDCl_3$): (major diastereomer) 7.25 (2H, d, *J* = 8.8 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 4.54 (1H, d, *J* = 11.2 Hz), 4.36 (1H, d, *J* = 11.2 Hz), 3.96 (1H, s (br), H2), 3.87 - 3.82 (1H, m, H4), 3.78 (3H, s), 3.56 (1H, dd, *J* = 10.8, 9.8 Hz, $H1_A$), 3.43 (1H, dd, *J* = 9.8, 7.3 Hz, $H1_B$), 1.74 - 1.65 (1H, m, $H3_A$), 1.55 (1H, ddd, *J* = 10.7, 7.8, 2.9 Hz, $H3_B$), 1.24 (3H, d, *J* = 6.3 Hz, H5). (minor diastereomer, in part) 4.59 (1H, d, *J* = 11.2 Hz), 4.34 (1H, d, *J* = 11.2 Hz). δ_C (125 MHz, $CDCl_3$): (major diastereomer) 159.3 (ArC), 130.4 (ArC), 129.5 (2 x Ar*C*H), 114.0 (2 x Ar*C*H), 72.2 (C4), 70.3 (O*C*H_2PMP), 69.3 (C2), 66.9 (C1), 55.3 (O*C*H_3), 39.3 (C3), 19.5 (C5). (minor diastereomer, in part) 132.1 (ArC), 131.9 (ArC), 114.4 (Ar*C*H), 71.9 (C4), 70.1 (O*C*H_2PMP), 66.7 (C1), 33.9 (C3), 19.7 (C5). ESIMS *m/z* 263 (100%) $[M+Na]^+$. HRESIMS found 263.1258, calcd for $C_{13}H_{20}O_4Na$, 263.1259 $[M+Na]^+$.

*Oxidation of diol **13.*** A mixture of **13** (208 mg, 0.87 mmol), 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (3 mg, 0.02 mmol), potassium bromide (113 mg, 0.95 mmol), anhydrous CH_2Cl_2 (9.5 mL) and saturated aq $NaHCO_3$ solution (3.8 mL) was cool to 0 ^oC. Commercial sodium hypochlorite solution (0.4 M, 3.0 mL, 1.21 mmol) was added slowly dropwise and stirred at 0 ^oC for 30 min. Saturated aq sodium thiosulfate solution (8.6 mL) was added at 0 ^oC. The reaction mixture was extracted with EtOAc (3 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a white solid which was used in the subsequent Petasis reaction without further puricication.

*(3S,4R,6S,E)-3-((S)-1-(Benzyloxy)but-3-en-2-ylamino)-6-(4-methoxybenzyloxy)-4-methoxy-1-phenylhept-1-en-4-ol (**7**).* A solution of **10** (183 mg, 1.03 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added to a solution of the above crude oxidation product and (*E*)-2-phenylvinylboronic acid (153 mg, 1.03 mmol) in 1,1,1,3,3,3-

hexafluoroisopropanol/CH_2Cl_2 (1:9, 3.5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at rt (32 ^oC) for 2 d, diluted with EtOAc (25 mL) and washed with 0.5 M NaOH solution (3 x 25 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a dark brown oil. Purification by flash column chromatography (0:100 to 40:60 EtOAc/CH_2Cl_2 as eluent) gave the title compound (314 mg, 73 %, 2 steps) as a brown oil. R_f 0.45 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 11.9 (*c* 0.56, $CHCl_3$). IR υ_{max} (cm^{-1}): 3438, 3066, 3027, 2905, 2860, 1648, 1611, 1511, 1452, 1245, 1076, 1035, 975, 925, 818, 746, 696. δ_H (500 MHz, $CDCl_3$): 7.36 - 7.19 (12H, m), 6.8 (2H, d, *J* = 8.3, Hz), 6.43 (1H, d, *J* = 16.1 Hz, H1), 6.08 (1H, dd, *J* = 16.1, 8.3 Hz, H2), 5.63 - 5.56 (1H, m, H2′), 5.21 (1H, d, *J* = 17.1 Hz, H3′*trans*), 5.17 (1H, d, *J* = 10.2 Hz, H3′*cis*), 4.51 (1H, d, , *J* = 11.2 Hz), 4.49 (2H, s), 4.37 (1H, d, *J* = 11.2 Hz), 4.02 (1H, s (br), H4), 3.84 - 3.81 (1H, m, H6), 3.75 (3H, s), 3.49 - 3.42 (3H, m), 3.24 (1H, dd, *J* = 8.3, 3.4 Hz, H3), 1.58 (2H, dd, *J* = 6.4, 5.4 Hz, H5), 1.21 (3H, d, *J* = 6.4 Hz, H7). δ_C (125 MHz, $CDCl_3$): 159.1 (ArC), 138.2 (ArC), 138.0 (CH=), 136.9 (ArC), 132.8 (C1), 130.9 (ArC), 129.3 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 128.1 (C2), 127.7 (2 x Ar*C*H), 127.5 (2 x Ar*C*H), 126.4 (2 x Ar*C*H), 117.9 (=CH_2), 113.8 (2 x Ar*C*H), 73.4 (CH_2), 73.0 (O*C*H_2Ph), 72.2 (C6), 70.4 (O*C*H_2PMP), 70.4 (C4), 62.3 (C3), 58.0 (CH), 55.3 (OCH_3), 40.2 (C5), 19.8 (C7). ESIMS *m/z* 502 (100%) $[M+H]^+$, HRESIMS found 502.2954, calc for $C_{32}H_{40}NO_4$, 502.2957 $[M+H]^+$.

*(4S,5R)-3-((S)-1-(Benzyloxy)but-3-en-2-yl)-5-((S)-2-(4-methoxybenzyloxy)propyl)-4-styryloxazolidin-2-one (**15**). Small scale reaction*: Triphosgene (6 mg, 0.020 mmol) was slowly added to the solution of the 1,2-amino alcohol **7** (20 mg, 0.040 mmol) and triethylamine (11 μL, 0.080 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 ^oC under a nitrogen

atmosphere. After stirring for 15 min the reaction mixture was allowed to warm to rt, stirred for 18 h and then concentrated *in vacuo* to give a yellow solid. Purification by flash column chromatography (increasing polarity from 0:100 to 1:99 of MeOH/CH_2Cl_2 as eluent) gave the title compound (17 mg, 81%) as a colorless oil. *Larger scale reaction*: Using triphosgene (0.186 g, 0.625 mmol), **7** (625 mg, 1.25 mmol) and triethylamine (697 μL, 4.99 mmol) the title compound (0.435 g, 66%) was obtained as a colorless oil. R_f 0.66 (2:98 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 20.9 (*c* 0.05, $CHCl_3$). IR υ_{max} (cm^{-1}): 3028, 2966, 2929, 2865, 1743, 1612, 1512, 1453, 1402, 1246, 1072, 1033, 977, 932, 820, 753, 695, 608. δ_H (500 MHz, $CDCl_3$): 7.33 - 7.23 (12H, m), 6.86 (2H, d, *J* = 8.3 Hz), 6.30 (1H, d, *J* = 15.9 Hz), 6.00 (1H, dd, *J* = 15.9, 9.8 Hz), 5.86 - 5.78 (1H, m), 5.25 (1H, d, *J* = 16.1 Hz), 5.18 (1H, d, *J* = 10.2 Hz), 4.86 (1H, ddd, *J* = 10.3, 8.8, 1.5 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.52 (1H, d, *J* = 10.7 Hz), 4.47 (1H, d, *J* = 11.7 Hz), 4.37 - 4.40 (2H, m), 4.34 (1H, d, *J* = 10.7 Hz), 3.89 (1H, dd, *J* = 10.0, 9.3 Hz), 3.83 - 3.81 (1H, m), 3.79 (3H, s), 3.61 (1H, dd, *J* = 10.0, 4.9 Hz), 1.70 (1H, td, *J* = 11.9, 2.0 Hz), 1.60 (1H, dd, *J* = 11.9, 11.2 Hz), 1.19 (3H, d, *J* = 6.3 Hz). δ_C (75 MHz, $CDCl_3$): 159.3 (ArC), 157.5 (CO), 138.0 (ArC), 135.8 (ArC), 135.2 (=CHPh), 133.9 (CH=), 130.8 (ArC), 129.6 (2 x Ar*C*H), 128.8 (Ar*C*H), 128.6 (2 x Ar*C*H), 128.5 (Ar*C*H), 128.1 (2 x Ar*C*H), 128.0 (2 x Ar*C*H), 126.8 (2 x Ar*C*H), 125.1 (CH=), 118.6 (=CH_2), 114.0 (2 x Ar*C*H), 74.9 (C5), 73.2 (CH_2), 71.5 (CH), 71.1 (CH_2), 69.1 (CH_2), 61.4 (C4), 56.4 (CH), 55.4 (O*C*H_3), 38.8 (CH_2), 20.3 (Me). ESIMS *m/z* 550 (80%) $[M+Na]^+$, 528 (18%) $[M+H]^+$, HRESIMS found 528.2737, calcd for $C_{33}H_{38}NO_5$, 528.2750 $[M+H]^+$.

*(1R,5S,7aS)-5-(Benzyloxymethyl)-1-((S)-2-(4-methoxybenzyloxy)propyl)-1,7a-dihydropyrrolo[1,2-c]oxazol-3(5H)-one (**16**).* A solution of the oxazolidinone **15** (239 mg,

0.45 mmol) and Grubbs' II ruthenium catalyst (19 mg, 0.02 mmol) in anhydrous CH_2Cl_2 (8 mL) under a nitrogen atmosphere was heated at reflux for 18 h. The reaction mixture was cooled to rt and was then concentrated *in vacuo* to give a black semi-solid. Purification by flash column chromatography with increasing polarity from 0:100 to 30:70 of EtOAc/petrol as eluent gave the title compound (172 mg, 90%) as a yellow oil. R_f 0.24 (30:70 EtOAc/petrol). $[\alpha]_D^{25}$ - 22.5 (*c* 0.12, $CHCl_3$). IR υ_{max} (cm^{-1}): 2967, 2864, 1745, 1610, 1513, 1454, 1375, 1246, 1213, 1072, 820, 746, 697, 608. δ_H (500 MHz, $CDCl_3$): 7.34 - 7.23 (7H, m), 6.86 (2H, d, *J* = 8.3 Hz), 5.99 (1H, d, *J* = 5.9 Hz), 5.89 (1H, d, *J* = 5.9 Hz), 4.98 (1H, td, *J* = 9.3, 3.4 Hz), 4.80 - 4.76 (2H, m), 4.55 (1H, d, *J* = 11.2 Hz), 4.54 (2H, s), 4.33 (1H, d, *J* = 11.2 Hz), 3.79 - 3.75 (1H, m), 3.78 (3H, s), 3.52 (2H, d, *J* = 4.5 Hz), 1.72 (1H, ddd, *J* = 12.4, 10.7, 3.4 Hz), 1.62 (1H, ddd, *J* = 10.7, 9.3, 2.9 Hz), 1.21 (3H, d, *J* = 5.8 Hz). δ_C (125 MHz, $CDCl_3$): 162.4 (C3), 159.3 (ArC), 138.0 (ArC), 132.9 (C7), 130.6 (ArC), 129.5 (2 x Ar*C*H), 128.5 (C6), 128.4 (2 x Ar*C*H), 127.7 (Ar*C*H), 127.6 (2 x Ar*C*H), 113.9 (2 x Ar*C*H), 76.4 (C1), 73.3 (O*C*H_2Ph), 71.4 (CH_2), 71.2 (CH), 70.9 (CH_2), 68.2 (C5), 67.0 (C7a), 55.3 (O*C*H_3), 40.1 (CH_2), 20.0 (Me). ESIMS *m/z* 446 (100%) $[M+Na]^+$, HRESIMS found 446.1956, calcd for $C_{25}H_{29}NO_5Na$, 446.1943 $[M+Na]^+$.

(1R,5R,6R,7S,7aS)-5-(Benzyloxymethyl)-6,7-dihydroxy-1-((S)-2-(4-methoxybenzyloxy)propyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (***17***). *N*-methylmorpholine-*N*-oxide (335 mg, 2.86 mmol) and potassium osmate dihydrate (26 mg, 0.07 mmol) were added to a solution of **16** (605 mg, 1.43 mmol) in 3:1 acetone/water (18 mL). The reaction mixture was stirred at 35 ^oC for 18 h, concentrated *in vacuo*, diluted with H_2O and extracted with EtOAc (3 x 30 mL). The combined organic layers were

dried ($MgSO_4$) and concentrated *in vacuo* to afford a black oil. Purification by flash column chromatography (0:100 to 3:97 MeOH/CH_2Cl_2 as eluent) gave the title compound (629 mg, 96%) as a yellow oil. R_f 0.18 (60:40 EtOAc/petrol). $[\alpha]_D^{25}$ + 6.2 (*c* 0.14, $CHCl_3$). IR υ_{max} (cm^{-1}): 3402, 2931, 2863, 1723, 1612, 1513, 1455, 1370, 1303, 1245, 1176, 1121, 1061, 1031, 950, 821, 741, 698. δ_H (500 MHz, $CDCl_3$): 7.31 - 7.20 (5H, m), 6.85 - 6.84 (2H, m), 4.86 - 4.83 (1H, m), 4.60 - 4.51 (3H, m), 4.30 (1H, d, *J* = 10.7 Hz) 4.24 (1H, s (br)), 3.91 (1H, s (br)), 3.78 (3H, s), 3.76 - 3.74 (1H, m), 3.69 - 3.67 (1H, m), 3.65 - 3.63 (3H, m), 2.35 (1H, ddd, *J* = 10.5, 8.8, 3.4 Hz), 1.92 (1H, td, *J* = 10.5, 4.4 Hz), 1.22 (3H, d, *J* = 4.9 Hz). δ_C (125 MHz, $CDCl_3$): 163.0 (C3), 159.3 (ArC), 138.0 (ArC), 130.6 (ArC), 129.6 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 127.8 (Ar*C*H), 127.7 (2 x Ar*C*H), 113.9 (2 x Ar*C*H), 76.0 (C7), 74.0 (C1), 73.5 (CH_2), 72.3 (C6), 72.2 (CH), 70.7 (CH_2), 70.3 (CH_2), 65.2 (C7a), 62.5 (C5), 55.4 (O*C*H_3), 37.5 (CH_2), 20.0 (Me). ESIMS *m/z* 480 (100%) $[M+Na]^+$, 458 (10%) $[M+H]^+$, HRESIMS found 458.2187, calcd for $C_{25}H_{32}NO_7$, 458.2179 $[M+H]^+$.

*(1R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-1-((S)-2-(4-methoxybenzyloxy)propyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (**18**):* A solution of the diol **17** (18 mg, 0.039 mmol) and tetrabutylammonium iodide (TBAI) (1 mg, 0.004 mmol) in anhydrous THF (5 mL) was stirred at rt (18 ^oC) for 15 min under a nitrogen atmosphere. Benzyl bromide (20 μL, 0.157 mmol) was added and then the solution was cooled to 0 ^oC. Sodium hydride (50% dispersion in mineral oil, 6 mg, 0.117 mmol) was slowly added and the reaction mixture was allowed to warm to rt and was stirred for 18 h. Quenching with H_2O (50 mL) gave a cloudy mixture, which was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in*

vacuo to give a light yellow solid. Purification by flash column chromatography (0:100 to 30:70 EtOAc/petrol as eluent) gave the title compound (25 mg, 100%) as a colorless oil. R_f 0.70 (60:40 EtOAc/petrol). $[\alpha]_D^{25}$ + 29.1 (*c* 0.14, $CHCl_3$). IR υ_{max} (cm^{-1}): 3031, 2929, 2862, 1750, 1611, 1513, 1455, 1390, 1359, 1303, 1246, 1228, 1065, 1031, 821, 736, 698. δ_H (500 MHz, $CDCl_3$): 7.32 - 7.18 (17H, m), 6.84 (2H, d, *J* = 7.3 Hz), 4.99 (1H, d, *J* = 11.2 Hz), 4.77 (1H, dt, *J* = 7.8, 6.6 Hz), 4.58 - 4.48 (4H, m), 4.40 (1H, d, *J* = 12.2 Hz), 4.37 (1H, d, *J* = 12.2 Hz), 4.22 (1H, d, *J* = 10.7 Hz), 4.15 (1H, dd, *J* = 7.8, 1.5 Hz), 3.97 (1H, dd, *J* = 7.8, 2.4 Hz), 3.93 (1H, s (br)), 3.77 - 3.75 (1H, m), 3.73 (3H, s), 3.66 - 3.61 (2H, m), 3.56 (1H, dd, *J* = 10.2, 2.0 Hz), 2.09 (1H, dd, *J* = 14.2, 7.1 Hz), 1.79 - 1.75 (1H, m), 1.07 (3H, d, *J* = 5.9 Hz). δ_C (125 MHz, $CDCl_3$): 162.1 (C3), 159.4 (ArC), 138.3 (ArC), 138.1 (ArC), 137.7 (ArC), 130.7 (ArC), 129.6 (2 x Ar*C*H), 128.6 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 128.1 (Ar*C*H), 127.8 (5 x Ar*C*H), 127.5 (Ar*C*H), 127.3 (2 x Ar*C*H), 114.0 (2 x Ar*C*H), 83.3 (C6), 77.2 (C7), 73.9 (C1), 73.4 (CH_2), 73.3 (CH_2), 73.0 (CH_2), 72.3 (CH), 70.8 (CH_2), 69.3 (CH_2), 64.4 (C7a), 61.1 (C5), 55.4 (O*C*H_3), 37.4 (CH_2), 19.9 (Me). ESIMS *m/z* 660 (70%) $[M+Na]^+$, 638 (3%) $[M+H]^+$, HRESIMS found 638.3093, calcd for $C_{39}H_{44}NO_7$, 638.3118 $[M+H]^+$.

(1R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-1-((S)-2-hydroxypropyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one ***(19)***. Dichloro-5,6-dicyanobenzoquinone (103 g, 0.45 mmol) was added to a solution of **18** (131 mg, 0.21 mmol) in CH_2Cl_2/H_2O (8:1, 9 mL). The reaction mixture was stirred at rt (26 ^oC) until TLC analysis (50:50 EtOAc/petrol) showed complete consumption of **18** (4 h). Purification by flash column chromatography (increasing polarity from 50:50 to 80:20 of EtOAc/petrol as eluent) gave the title compound (94 mg, 89%) as a yellow oil. R_f 0.23

(50:50 EtOAc/petrol). $[\alpha]_D^{25}$ + 19.7 (*c* 0.08, $CHCl_3$). IR υ_{max} (cm^{-1}): 3452, 2972, 2864, 1742, 1511, 1397, 1361, 1231, 1206, 1127, 1071, 739, 699. δ_H (500 MHz, $CDCl_3$): 7.33 - 7.23 (15H, m), 5.04 (1H, d, *J* = 11.7 Hz), 4.79 (1H, ddd, *J* = 12.7, 8.3, 2.9 Hz), 4.65 (1H, d, *J* = 11.7 Hz), 4.57 - 4.50 (3H, m), 4.40 (1H, d, *J* = 12.2 Hz), 4.28 (1H, d, *J* = 7.8 Hz), 4.03 (1H, s), 3.99 - 3.98 (1H, m), 3.92 - 3.88 (1H, m), 3.76 (1H, dd, *J* = 10.2, 2.4 Hz), 3.73 (1H, d, *J* = 7.8 Hz), 3.60 (1H, dd, *J* = 10.2, 2.4 Hz), 2.09 (1H, ddd, *J* = 14.4, 8.3, 2.4 Hz), 1.64 (1H, ddd, *J* = 14.4, 9.8, 4.4 Hz), 1.07 (3H, d, *J* = 6.4 Hz). δ_C (125 MHz, $CDCl_3$): 162.2 (C3), 138.2 (ArC), 138.1 (ArC), 137.7 (ArC), 128.6 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 128.1 (Ar*C*H), 127.8 (5 x Ar*C*H), 127.6 (Ar*C*H), 127.4 (2 x Ar*C*H), 83.4 (C6), 76.9 (C7), 74.0 (C1), 73.4 (2 x CH_2), 73.0 (CH_2), 69.4 (CH_2), 65.2 (CH), 64.4 (C7a), 61.1 (C5), 38.3 (CH_2), 24.5 (Me). ESIMS *m/z* 540 (100%) $[M+Na]^+$, 518 (48%) $[M+H]^+$, HRESIMS found 518.2523, calcd for $C_{31}H_{36}NO_6$, 518.2543 $[M+H]^+$.

General method for hydrolysis of oxazolidinones

*(1R,3S)-1-((2R,3S,4R,5R)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)butane-1,3-diol (**20**):* Sodium hydroxide (38 mg, 1.66 mmol) and 3 drops of H_2O were added to a solution of **19** (171 mg, 0.33 mmol) in ethanol (3 mL). The reaction mixture was stirred and irradiated in a CEM microwave reactor (the temperature control was set at 110 ^oC and the maximum applied power at 200 W) for 1 h. After the reaction mixture had cooled to rt it was concentrated *in vacuo* to give a yellow semi-solid. Purification by flash column chromatography (increasing polarity from 0:100 to 8:92 of MeOH/CH_2Cl_2 as eluent) gave the title compound (156 mg, 96%) as a colorless oil. R_f 0.32 (7.5:92.5 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 31.3 (*c* 0.06, $CHCl_3$). IR υ_{max} (cm^{-1}): 3355, 3029, 2894, 2858, 1494, 1451, 1405, 1344, 1208, 1145, 1084, 1051, 731, 694, 656. δ_H (500 MHz, $CDCl_3$):

7.35 - 7.24 (15H), 4.85 (1H, d, *J* = 11.2 Hz), 4.60 (1H, d, *J* = 12.2 Hz), 4.55 (1H, d, *J* = 12.2 Hz), 4.53 (1H, d, *J* = 11.2 Hz), 4.49 (1H, d, *J* = 11.7 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.15 - 4.12 (2H, m, *J* = 5.0 Hz), 3.99 - 3.96 (1H, m), 3.90 (1H, dd, *J* = 5.4, 5.0 Hz), 3.53 - 3.47 (2H, m), 3.46 - 3.44 (1H, m), 3.10 (1H, dd, *J* = 8.3, 5.4 Hz), 1.71 (1H, ddd, *J* = 14.4, 5.4, 2.4 Hz), 1.65 (1H, ddd, *J* = 14.4, 8.8, 5.8 Hz), 1.18 (3H, d, *J* = 6.4 Hz). δ_C (75 MHz, $CDCl_3$): 138.0 (ArC), 137.9 (ArC), 137.8 (ArC), 128.6 (2 x Ar*C*H), 128.5 (4 x Ar*C*H), 128.2 (3 x Ar*C*H), 128.1 (3 x Ar*C*H), 128.0 (Ar*C*H), 127.9 (2 x Ar*C*H), 80.6 (C4), 79.8 (C3), 73.4 (CH_2), 73.3 (CH_2), 72.6 (CH_2), 70.4 (CH), 69.8 (CH_2), 65.3 (CH), 63.1 (C2), 60.7 (C5), 44.6 (CH_2), 23.9 (Me). ESIMS *m/z* 492 (100%) $[M+H]^+$, HRESIMS found 492.2758, calcd for $C_{30}H_{38}NO_5$, 492.2750 $[M+H]^+$.

General method for mesylation-cyclization

*(1R,3R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-ol (**21**).* Triethylamine (40 μL, 0.25 mmol) was slowly added to a solution of **20** (140 mg, 0.25 mmol) in CH_2Cl_2 (12.8 mL) at 0 ^oC under a nitrogen atmosphere followed by a 0.13 M solution of methanesulfonyl chloride in anhydrous CH_2Cl_2 (2.2 mL, 0.28 mmol $MeSO_2Cl$). The reaction mixture was stirred at 0 ^oC for 1.5 h and quenched with sat. aqueous $NaHCO_3$ solution (3.5 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (increasing polarity from 2:98 to 10:90 of MeOH/CH_2Cl_2 as eluent) gave compound **21** (134 mg, 100%) as a colorless oil. R_f 0.22 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 16.5 (*c* 0.26, $CHCl_3$). IR υ_{max} (cm^{-1}): 3354, 2913, 2865, 1453, 1360, 1207, 1139, 1090, 1026, 732, 696. δ_H (500 MHz, $CDCl_3$): 7.33 - 7.27 (15H, m), 4.71 (1H, d, *J* = 12.2 Hz), 4.66 (1H, dd, *J* = 8.8, 4.4 Hz), 4.58 - 4.50 (5H,

m), 4.14 (1H, dd, *J* = 5.4, 4.9 Hz), 3.90 (1H, dd, *J* = 5.0, 4.4 Hz), 3.70 - 3.67 (1H, m), 3.58 (1H, dd, *J* = 4.9, 4.4 Hz), 3.45 - 3.43 (1H, m), 3.39 - 3.36 (2H, m), 1.85 (2H, dd, *J* = 7.3, 5.4 Hz), 1.17 (3H, d, *J* = 6.8 Hz). δ_C (125 MHz, $CDCl_3$): 138.4 (ArC), 138.3 (ArC) 138.2 (ArC), 128.5 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 127.9 (5 x Ar*C*H), 127.8 (3 x Ar*C*H), 127.7 (Ar*C*H), 81.2 (C2), 76.6 (C1), 75.8 (C7a), 73.5 (CH_2), 73.1 (CH_2), 72.2 (CH_2), 71.8 (C8), 71.3 (C7), 60.2 (C3), 56.9 (C5), 42.4 (C6), 16.2 (C9). ESIMS *m/z* 474 (100%) $[M+H]^+$, HRESIMS found 474.2624, calcd for $C_{30}H_{36}NO_4$, 474.2644 $[M+H]^+$.

General method for hydrogenolysis of benzyl ethers

*(1S,2R,3R,5R,7R,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,7-triol (hyacinthacine B$_3$) (**2**).* $PdCl_2$ (7 mg, 0.04 mmol) was added to a N_2 flushed solution of **21** (17 mg, 0.036 mmol) in MeOH (4 mL). The reaction mixture was then stirred at rt under a H_2 atmosphere (balloon) for 8 h and then filtered through a pad of celite and washed with MeOH (10 mL). The combined filtrates were concentrated *in vacuo* to give a colorless film which was dissolved in water (2 mL) and held for 15 min in a column containing Amberlyst A-26 (OH^-) ion-exchange resin (1 g). Elution with water (3 x 5 mL) followed by evaporation *in vacuo* gave the title compound (5 mg, 68%) as a colorless film. $[\alpha]_D^{23}$ + 10.8 (*c* 0.33, H_2O). [Lit.[3b] $[\alpha]_D$ + 3.1 (*c* 0.33, H_2O), temperature not reported]. IR υ_{max} (cm^{-1}): 3317, 2960, 2929, 2878, 1652, 1338, 1133. δ_H (500 MHz, CD_3OD): 4.52 (1H, m, H7), 4.04 (1H, t, *J* = 4.4 Hz, H1), 3.91 (1H, dd, *J* = 4.2, 7.3 Hz, H2), 3.57 (1H, dd, *J* = 4.9, 11.0 Hz, $H8_A$), 3.53 (1H, dd, *J* = 4.5, 11.1 Hz, $H8_B$), 3.50 (1H, m, H5), 3.30 (1H, t, *J* = 4.6 Hz, H7a), 3.10 (1H, ddd, *J* = 4.7, 4.9 7.3 Hz, H3), 1.86-1.82 (2H, m, $H6_\alpha$ and $H6_\beta$), 1.19 (3H, d, *J* = 6.9 Hz, H9). δ_H (75 MHz, CD_3OD): 76.5 (C2), 76.2 (C7a),

71.4 (C1), 70.6 (C7), 64.2 (C8), 63.0 (C3), 56.4 (C5), 43.5 (C6), 16.7 (C9). ESIMS *m/z* 204 (100%) $[M+H]^+$. HRMS found 204.1232, calcd for $C_9H_{18}NO_4$, 204.1236 $[M+H]^+$.

Synthesis of hyacinthacine B_7 (3) and 7-*epi*-hyacinthacine B_7 (6)

General method for the Mitsunobu reaction

(*R*)-1-((1*R*,5*R*,6*R*,7*S*,7a*R*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-oxohexahydropyrrolo[1,2-*c*]oxazol-1-yl)propan-2-yl 4-nitrobenzoate (**22**). A solution of **19** (455 mg, 0.88 mmol), triphenylphosphine (1038 mg, 3.96 mmol) and *p*-nitrobenzoic acid (662 mg, 3.959 mmol) in toluene (9 mL) was cool to 0 ^oC and diisopropyl azodicarboxylate (0.78 mL, 3.96 mmol) was added. The reaction mixture was allowed to warm to rt (27 ^oC) and stirred for 24 h. The volatiles were removed *in vacuo*, extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a dark brown oil. Purification by flash column chromatography (increasing polarity from 0:100 to 10:90 of MeOH/CH_2Cl_2 as eluent) gave the title compound (498 mg, 85%) as a yellow oil. R_f 0.30 (30:70 EtOAc/petrol). $[\alpha]_D^{25}$ - 26.6 (*c* 0.64, $CHCl_3$). IR υ_{max} (cm^{-1}): 2934, 2864, 1752, 1719, 1525, 1346, 1274, 1100, 737. δ_H (500 MHz, $CDCl_3$): 8.24 (2H, d, *J* = 8.8 Hz), 8.13 (2H, d, *J* = 8.8 Hz), 7.35 - 7.20 (15H, m), 5.27 - 5.21 (1H, m), 5.10 (1H, d, *J* = 11.7 Hz), 4.72 (1H, dt, *J* = 7.3, 6.6 Hz), 4.66 (1H, d, *J* = 11.7 Hz), 4.57 (1H, d, *J* = 11.7 Hz), 4.52 (1H, d, *J* = 11.7 Hz), 4.51 (1H, d, *J* = 11.7 Hz), 4.38 (1H, d, *J* = 11.7 Hz), 4.32 (1H, dd, *J* = 7.8, 2.0 Hz), 4.07 (1H, s, H7), 4.00 (1H, dt, *J* = 7.8, 2.9 Hz), 3.76 (2H, d, *J* = 8.3 Hz), 3.59 (1H, *J* = 10.3, 2.4 Hz), 2.42 (1H, dt, *J* = 14.6, 7.8 Hz), 2.07 (1H, dt, *J* = 14.6, 4.4 Hz), 1.31 (3H, d, *J* = 6.4 Hz). δ_C (125 MHz, $CDCl_3$): 164.2 (CO), 161.8 (C3), 150.6 (ArC), 138.1 (ArC), 137.8 (ArC), 137.4 (ArC), 135.7 (ArC), 130.8 (2 x Ar*C*H), 128.6 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 128.2 (Ar*C*H), 127.8 (6 x Ar*C*H), 127.7

(2 x Ar*C*H), 127.4 (2 x Ar*C*H), 123.6 (2 x Ar*C*H), 83.3 (C6), 76.7 (C7), 73.4 (2 x CH_2), 73.0 (CH_2), 72.8 (C1), 70.3 (CH), 69.2 (CH_2), 63.9 (C7a), 61.1 (C5), 35.5 (CH_2), 22.1 (Me). ESIMS *m/z* 667 (100%) $[M+H]^+$. HRASAPMS found 667.2671, calcd for $C_{38}H_{39}N_2O_9$, 667.2656 $[M+H]^+$

(1R,3R)-1-((2R,3S,4R,5R)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)butane-1,3-diol ***(23)****.* Following the general method for hydrolysis of an oxazolidinone, compound **22** (167 mg, 0.25 mmol) was treated with sodium hydroxide (58 mg, 2.51 mmol) in ethanol (3 mL) and 3 drops of H_2O at 110 ^oC in a CEM microwave reactor. Purification by flash column chromatography (0:100 to 5:95 MeOH/CH_2Cl_2 as eluent) gave the title compound (120 mg, 97%) as a colorless oil. R_f 0.30 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 18.7 (*c* 0.83, $CHCl_3$). IR υ_{max} (cm^{-1}): 3323, 3030, 2864, 1496, 1453, 1360, 1208, 1075, 915, 835, 736, 640. δ_H (500 MHz, $CDCl_3$): 7.33 - 7.27 (15H), 4.88 (1H, d, *J* = 11.7 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.56 (1H, d, *J* = 11.7 Hz), 4.53 (1H, d, *J* = 11.7 Hz), 4.50 (1H, d, *J* = 12.2 Hz), 4.44 (1H, d, *J* = 12.2 Hz,), 4.17 (1H, t, *J* = 4.4 Hz), 4.08-4.05 (1H, m), 4.03 - 4.01 (1H, m), 3.89 (1H, dd, *J* = 5.8, 4.4 Hz), 3.54 (1H, dd, *J* = 11.2, 5.4 Hz), 3.48 - 3.46 (2H, m), 3.02 (1H, dd, *J* = 7.3, 4.4 Hz), 1.72 (1H, d, *J* = 14.2 Hz), 1.44 (1H, dt, *J* = 14.2, 9.8 Hz), 1.16 (3H, d, *J* = 5.8 Hz). δ_C (125 MHz, $CDCl_3$): 138.1 (ArC), 138.0 (ArC), 137.9 (ArC), 128.7 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.2 (2 x Ar*C*H), 128.1 (3 x Ar*C*H), 128.0 (3 x Ar*C*H), 127.8 (3 x Ar*C*H), 81.3 (C4), 79.2 (CH), 73.5 (CH_2), 73.3 (CH_2), 72.9 (C3), 72.8 (CH_2), 70.2 (CH_2), 68.3 (CH), 63.1 (C2), 60.4 (C5), 42.6 (CH_2), 23.8 (Me). ESIMS *m/z* 492 (100%) $[M+H]^+$, HRESIMS found 492.2765, calcd for $C_{30}H_{38}NO_5$, 492.2750 $[M+H]^+$.

*(1R,3S,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-ol (**24**).* Following the general method for mesylation-cyclization, compound **23** (259 mg, 0.53 mmol) was treated with triethylamine (73 μL, 0.53 mmol), 0.13 M solution of methanesulfonyl chloride in anhydrous CH_2Cl_2 (4.04 mL, 0.53 mmol $MeSO_2Cl$) in CH_2Cl_2 (28 mL) at 0 ^oC for 1.5 h. Purification by flash column chromatography (0:100 to 10:90 MeOH/CH_2Cl_2 as eluent) gave the title compound (198 mg, 77%) as a colorless oil. R_f 0.30 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 21.7 (*c* 1.03, $CHCl_3$). IR υ_{max} (cm^{-1}): 3360, 3030, 2922, 2862, 1469, 1452, 1359, 1310, 1208, 1094, 1048, 1027, 914, 735, 696. δ_H (500 MHz, $CDCl_3$): 7.32 - 7.27 (15H, m), 4.74 (1H, *J* = 11.7 Hz), 4.67 (1H, td, 7.8, 6.6), 4.55 - 4.48 (5H, m), 4.06 (1H, t, *J* = 4.6 Hz), 3.92 (1H, dd, *J* = 5.6, 4.4 Hz), 3.45 - 3.41 (3H, m), 3.09 (1H, dd, *J* = 10.1, 5.6 Hz), 3.06 - 3.02 (1H, m), 2.27 (1H, dt, *J* = 11.9, 6.1 Hz), 1.59 (1H, td, *J* = 11.9, 9.8 Hz), 1.14 (3H, d, *J* = 6.1 Hz). δ_C (75 MHz, $CDCl_3$): 138.7 (ArC), 138.5 (ArC) 138.2 (ArC), 128.5 (4 x Ar*C*H), 128.4 (2 x Ar*C*H), 127.9 (4 x Ar*C*H), 127.8 (2 x Ar*C*H), 127.7 (3 x Ar*C*H), 82.0 (C2), 77.6 (C1), 73.4 (CH_2), 73.3 (C7a), 73.2 (CH_2), 72.4 (CH_2), 71.7 (C8), 71.0 (C7), 68.2 (C3), 62.4 (C5), 44.0 (C6), 22.0 (C9). ESIMS *m/z* 474 (100%) $[M+H]^+$, HRESIMS found 474.2665, calcd for $C_{30}H_{36}NO_4$, 474.2644 $[M+H]^+$.

*(1S,2R,3S,5R,7R,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,7-triol (putative hyacinthacine B_7) (**3**).* Following the general method for hydrogenolysis of benzyl ethers, the alcohol **24** (27 mg, 0.059 mmol) was treated with $PdCl_2$ (16 mg, 0.09 mmol) and MeOH (2 mL) at rt for 3 h. The title compound (10 mg, 84 %) was obtained as a colorless film. $[\alpha]_D^{24}$ + 31.2 (*c* 0.20, $CHCl_3$). δ_H (500 MHz, D_2O): 4.60 (1H, ddd, *J* = 5.8, 7.0, 9.2 Hz), 4.13 (1H, app. t, *J* = 4.0 Hz), 4.03 (1H, dd, *J* = 4.0, 9.1 Hz), 3.74 (1H,

dd, *J* = 4.9, 11.7 Hz), 3.70 (1H, dd, *J* = 4.9, 11.7 Hz), 3.32 (1H, dd, *J* = 4.0, 5.8 Hz), 3.06 - 2.97 (1H, m), 2.81 (1H, app. dd, *J* = 4.9, 9.1 Hz), 2.38 (1H, ddd, *J* = 5.0, 7.0, 12.2 Hz), 1.60 (1H, ddd, *J* = 9.3, 11.0, 12.2 Hz), 1.17 (1H, d, *J* = 6.3 Hz). δ_C (125 MHz, D_2O): 80.3 (C2), 75.8 (C1), 74.0 (C3), 73.5 (C7), 77.6 (C7a), 67.8 (C8), 67.4 (C5), 48.4 (C6), 24.7 (C9). ESIMS *m/z* 204 (100%) $[M+H]^+$.

General method for Swern oxidation

*(3S,5R,6R,7S,7aS)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-one (**25**).* Oxalyl chloride (79 μL, 0.92 mmol) was dropwise *via* syringe in to a stirred solution of DMSO (130 μL, 1.84 mmol) in CH_2Cl_2 (5 mL) at -78 ^oC. The solution was stirred at -78 ^oC for 5 min and then a solution of **24** (43 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) cooled to -78 ^oC was added dropwise *via* syringe, followed by Et_3N (513 μL, 3.68 mmol). The reaction mixture was stirred at -78 ^oC for 1 h and then poured into H_2O (40 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (increasing polarity from 0:100 to 10:90 of MeOH/CH_2Cl_2 as eluent) gave the title compound **25** (27 mg, 63%) as a colorless oil, and recovered **24** (13.2 mg, 30%). R_f 0.61 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 28.2 (*c* 0.32, $CHCl_3$). IR υ_{max} (cm^{-1}): 3030, 2864, 1750, 1698, 1452, 1361, 1270, 1207, 1098, 736, 661. δ_H (500 MHz, $CDCl_3$): 7.32 - 7.23 (15H, m), 4.65 (1H, d, *J* = 11.7 Hz), 4.60 (1H, d, *J* = 12.2 Hz), 4.59 (1H, d, *J* = 11.7 Hz), 4.51 (1H, d, *J* = 12.2 Hz), 4.50 (1H, d, *J* = 11.7 Hz), 4.36 (1H, d, *J* = 11.7 Hz), 4.18 (1H, t, *J* = 3.4 Hz), 3.91 (1H, dd, *J* = 8.8, 3.4 Hz), 3.69 (1H, d, *J* = 3.4 Hz), 3.63 (1H, dd, *J* = 9.8, 3.4 Hz), 3.56 (1H, dd, *J* = 9.8, 4.9 Hz), 3.50 - 3.46 (1H, m), 3.35 (1H, dt, *J* = 8.8, 4.4 Hz), 2.61 (1H, dd, *J* = 17.6, 6.8 Hz), 2.10 (1H, dd,

J = 17.6, 8.3 Hz), 1.21 (3H, d, J = 5.9 Hz). δ_C (125 MHz, $CDCl_3$): 214.7 (C7), 138.5 (ArC), 138.4 (ArC), 137.9 (ArC), 128.5 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 128.0 (3 x Ar*C*H), 127.9 (4 x Ar*C*H), 127.8 (2 x Ar*C*H), 83.4 (C2), 78.8 (C1), 73.8 (CH_2), 73.5 (CH_2), 73.1 (CH_2), 72.0 (C8), 71.8 (C7a), 69.1 (C3), 60.7 (C5), 46.6 (C6), 22.5 (C9). ESIMS *m/z* 472 (100%) $[M+H]^+$. HRASAPMS found 472.2494, calcd for $C_{30}H_{34}NO_4$, 472.2488 $[M+H]^+$.

General method for the reduction of a ketone to a secondary alcohol with L-selectride®

*(1S,3S,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-ol (**26**).* A solution of the cyclic ketone **25** (63 mg, 0.13 mmol) in THF (5 mL) was cooled to -78 ^oC and then L-selectride® (1.0 M solution in THF, 536 μL, 0.54 mmol) was slowly added dropwise. The reaction mixture was stirred at -78 ^oC for 1 h, warm to rt (22 ^oC) and stirred for 2 h. Ammonia solution (1.0 M, 24 mL) was added and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts was washed with brine, dried (K_2CO_3) and concentrated *in vacuo* to give a light brown film. Purification by flash column chromatography (increasing polarity from 0:100 to 10:90 of MeOH/CH_2Cl_2 as eluent) gave the title compound (44 mg, 70%) as a colorless oil. R_f 0.34 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 36.2 (*c* 1.26, $CHCl_3$). IR υ_{max} (cm^{-1}): 3415, 3030, 2864, 1696, 1452, 1363, 1204, 1098, 1024, 736, 697. δ_H (500 MHz, $CDCl_3$): 7.33 - 7.28 (15H, m), 4.74 (1H, d, J = 11.6 Hz), 4.59 (2H, s), 4.53 (2H, s), 4.48 (1H, d, J = 11.6 Hz), 4.37 - 4.33 (2H, m), 4.02 (1H, dd, J = 5.4, 4.9 Hz), 3.80 (1H, s (br)), 3.53 (1H, s (br)), 3.47 - 3.41 (2H, m), 3.33 (1H, s (br)), 2.08 (1H, dd, J = 12.7, 5.4 Hz), 1.60-1.56 (1H, m), 1.20 (3H, d, J = 4.4 Hz). δ_C (125 MHz, $CDCl_3$): 138.2 (ArC), 137.6 (ArC), 137.5 (ArC), 128.8 (2 x Ar*C*H), 128.7 (2 x Ar*C*H), 128.6 (2 x Ar*C*H), 128.3 (2 x Ar*C*H),

128.1 (4 x Ar*C*H), 128.0 (Ar*C*H), 127.8 (2 x Ar*C*H), 80.6 (C2), 78.6 (C1, br), 73.6 (CH_2), 73.5 (CH_2), 73.2 (C7), 72.9 (CH_2), 71.2 (C8, br), 70.1 (C7a), 69.3 (C3), 62.3 (C5, br), 45.0 (C6), 21.4 (C9, br). ESIMS *m/z* 474 $[M+H]^+$. HRASAPMS found 474.2642, calcd for $C_{30}H_{36}NO_4$, 474.2644 $[M+H]^+$.

*(1S,2R,3R,5S,7S,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,7-triol (7-epi-hyacinthacine B$_7$) (**6**).* Following the general method for hydrogenolysis of benzyl ethers, the alcohol **26** (38 mg, 0.08 mmol) was treated with $PdCl_2$ (22 mg, 0.12 mmol) and MeOH (6 mL) at rt for 3 h. The title compound (14 mg, 84%) was obtained as a colorless film. $[\alpha]_D^{25}$ + 18.5 (*c* 0.14, H_2O). IR υ_{max} (cm^{-1}): 3287, 2929, 1589, 1381, 1344, 1199, 1127, 1081. δ_H (500 MHz, D_2O): 4.59 (1H, t, *J* = 4.9 Hz, H7), 4.41 (1H, dd, *J* = 5.4, 4.9 Hz, H1), 3.99 (1H, dd, *J* = 7.3, 4.9 Hz, H2), 3.71 (1H, dd, *J* = 11.7, 5.4 Hz, $H8_A$), 3.67 (1H, dd, *J* = 11.7, 5.8 Hz, $H8_B$), 3.58 (1H, t, *J* = 5.4 Hz, H7a), 3.40 - 3.32 (1H, m, H5), 3.04 (1H, app. dt, *J* = 6.3, 5.4 Hz, H3), 2.11 (1H, dd, *J* = 13.7, 5.8 Hz, H6$_\beta$), 1.71 (1H, ddd, *J* = 13.7, 10.2, 4.9 Hz, H6$_\alpha$), 1.18 (3H, d, *J* = 5.9 Hz, H9). δ_H (125 MHz, D_2O): 77.8 (C2), 75.7 (C7), 75.3 (C1), 73.3 (C3), 70.6 (C7a), 65.5 (C8), 64.2 (C5), 46.5 (C6), 22.8 (C9). ESIMS *m/z* 204 $[M+H]^+$. HRASAPMS found 204.1239, calcd for $[C_9H_{18}NO_4]^+$, 204.1236 $[M+H]^+$.

Synthesis of hyacinthacine B$_4$ (4), hyacinthacine B$_5$ (5), and 7a-*epi*-hyacinthacine B$_3$ (33)

Swern oxidation of 18

*(R)-3-((2R,3R,4R)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-oxopyrrolidin-1-yl)butanoic acid (**27**).* The title compound was prepared following the general method for the Swern oxidation using **21** (107 mg, 0.23 mmol), oxalyl chloride (195 μL, 2.27 mmol), DMSO

(322 μL, 4.54 mmol) and Et_3N (1.26 mL, 9.08 mmol) in CH_2Cl_2 (17 mL). Purification by flash column chromatography (0:100 to 15:85 MeOH/CH_2Cl_2 as eluent) gave the title compound **27** (17 mg, 16%), a mixture of 3 unknown ketones (16 mg, 15%) and recovered **21** (41.4 mg, 39%), all as colorless oils. R_f 0.50 (10:90 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 33.3 (*c* 0.33, $CHCl_3$). IR υ_{max} (cm^{-1}): 3062, 3030, 2931, 2867, 1696, 1495, 1452, 1354, 1307, 1102, 1026, 774, 657. δ_H (500 MHz, $CDCl_3$): 7.36 - 7.26 (13H, m), 7.16 (2H, d, *J* = 7.5 Hz), 4.87 (1H, d, *J* = 12.2 Hz), 4.71 (1H, d, *J* = 12.2 Hz), 4.63 (1H, d, *J* = 12.2 Hz), 4.54 (1H, d, *J* = 12.2 Hz), 4.43 (1H, d, *J* = 11.7 Hz), 4.39 (1H, d, *J* = 11.7 Hz), 4.22 (1H, d, *J* = 5.4 Hz), 4.05 - 3.98 (1H, m), 3.94 (1H, d, *J* = 5.4 Hz), 3.63 (1H, s (br)), 3.48 (1H, dd, *J* = 10.2, 4.4 Hz), 3.47 (1H, dd, *J* = 10.2, 3.4 Hz), 2.96 (1H, dd, *J* = 16.1, 7.3 Hz), 2.76 (1H, dd, *J* = 16.1, 6.8 Hz), 1.31 (3H, d, *J* = 2.9 Hz). δ_C (75 MHz, $CDCl_3$): 174.9 (CO), 172.6 (CO), 137.8 (2 x ArC), 137.5 (ArC), 128.6 (2 x Ar*C*H), 128.5 (4 x Ar*C*H), 128.3 (2 x Ar*C*H), 128.1 (2 x Ar*C*H), 128.0 (2 x Ar*C*H), 127.9 (Ar*C*H), 127.7 (2 x Ar*C*H), 75.9 (CH), 75.7 (CH), 73.4 (CH_2), 72.7 (CH_2), 71.9 (CH_2), 68.5 (CH_2), 62.1 (CH), 47.4 (CH), 38.3 (CH_2), 18.2 (Me). ESIMS *m/z* 526 (100%) $[M+Na]^+$. HRASAPMS found 504.2407, calcd for $C_{30}H_{34}NO_6$, 504.2386 $[M+H]^+$.

Swern oxidation of 21 followed by reduction of ketone to secondary alcohols with L-selectride®

*(1S,3R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-ol (**28**), (3R,5R,6R,7R,7aS)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-one (**29**), (1R,3R,5R,6R,7S,7aS)-6,7-Bis(benzyloxy)-5-*

*(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-ol (**30**), and (3R,4R,5R)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)-1-((R)-4-hydroxybutan-2-yl)pyrrolidin-2-one (**31**).*

Step 1: Following the general method for the Swern oxidation using DMSO (778 μL, 10.96 mmol), oxalyl chloride (470 μL, 5.48 mmol), alcohol **18** (259 mg, 0.55 mmol), anhydrous CH_2Cl_2 (30 mL) and Et_3N (3.04 mL, 21.92 mmol) at -78 ^oC a yellow oil was obtained which was used without further purification in the next reaction with L-Selectride®.

Step 2: Following the general method for reduction of a ketone to a secondary alcohol with L-selectride® the above Swern oxidation crude product in THF (20 mL) was treated with L-selectride® (1.0 M solution in THF, 2.19 mL, 2.19 mmol). Purification by flash column chromatography (2:98 to 15:85 MeOH/CH_2Cl_2 as eluent) gave compounds **28** (11.7 mg, 4%), **29** (18.0 mg, 7%), **30** (20.5 mg, 7%) and **31** (17.8 mg, 8%) and recovered **21** (18.1 mg, 7%).

28: R_f 0.44 (10:90 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 11.5 (*c* 0.33, $CHCl_3$). IR υ_{max} (cm^{-1}): 3350, 3030, 2919, 2868, 1690, 1452, 1363, 1097, 1026, 735, 644. δ_H (500 MHz, $CDCl_3$): 7.34 - 7.26 (15H, m), 4.81 (1H, d, *J* = 11.7 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.59 (1H, d, *J* = 11.7 Hz), 4.55 (1H, d, *J* = 11.7 Hz), 4.54 (2H, s), 4.44 - 4.39 (1H, m), 4.34 (1H, dd, *J* = 5.4, 4.9 Hz), 4.04 (1H, dd, *J* = 5.8, 4.4 Hz), 3.83 (1H, s (br)), 3.68 - 3.66 (1H, m), 3.60 - 3.55 (2H, m), 3.46 - 3.43 (1H, m), 2.17 (1H, dt, *J* = 12.2, 6.3 Hz), 1.69 - 1.78 (1H, m), 1.28 (3H, d, *J* = 6.8 Hz). δ_C (75 MHz, $CDCl_3$): 138.1 (ArC), 137.5 (ArC), 137.3 (ArC), 128.8 (4 x Ar*C*H), 128.6 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 128.3 (2 x Ar*C*H), 128.2 (2 x Ar*C*H), 128.1 (2 x Ar*C*H), 128.0 (Ar*C*H), 81.4 (C2), 78.3 (C1), 73.6 (2 x CH_2), 73.0 (CH_2), 71.4 (C7, absent), 70.8 (C8, observed in HSQC), 68.3 (C7a), 61.2 (C3), 56.6 (C5, observed in

HSQC), 43.0 (C6), 16.8 (C9). ESIMS *m/z* 474 (100%) $[M+H]^+$. HRASAPMS found 474.2649, calcd for $C_{30}H_{36}NO_4$, 474.2644 $[M+H]^+$.

29: R_f 0.32 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ - 62.5 (*c* 0.81, $CHCl_3$). IR υ_{max} (cm^{-1}): 3031, 2926, 2870, 1717, 1452, 1361, 1267, 1097, 737, 697. δ_H (500 MHz, $CDCl_3$): 7.32 - 7.24 (13H, m), 7.20 (2H, d, *J* = 7.0 Hz), 4.55 (2H, d, *J* = 12.0 Hz), 4.45 (1H, *J* = 12.0 Hz), 4.43 (2H, d, *J* = 12.0 Hz), 4.34 (1H, *J* = 12.0 Hz), 4.15 (1H, s), 3.99 (1H, s), 3.71 - 3.67 (2H, m), 3.54 - 3.48 (3H, m), 2.25 - 2.13 (2H, m), 1.36 (3H, d, *J* = 6 .7 Hz). δ_C (125 MHz, $CDCl_3$): 218.0 (C7), 138.4 (ArC), 137.6 (2 x ArC), 128.7 (2 x Ar*C*H), 128.6 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.0 (2 x Ar*C*H), 127.8 (4 x Ar*C*H), 127.6 (3 x Ar*C*H), 84.0 (C1), 83.0 (C2), 76.4 (C7a), 73.3 (CH_2), 73.0 (C8), 71.6 (CH_2), 70.9 (CH_2), 62.7 (C3), 54.5 (C5), 43.1 (C6), 17.2 (C9). ESIMS *m/z* 472 (100%) $[M+H]^+$. HRASAPMS found 472.2469, calcd for $C_{30}H_{34}NO_4$, 472.2488 $[M+H]^+$.

30: R_f 0.69 (20:80 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 30.3 (*c* 0.12, $CHCl_3$). IR υ_{max} (cm^{-1}): 3271, 3030, 2919, 2861, 1454, 1364, 1206, 1102, 1035, 665, 645. δ_H (500 MHz, $CDCl_3$): 7.35 - 7.18 (15H, m), 4.71 (1H, d, *J* = 12.7 Hz), 4.68 (1H, d, *J* = 12.7 Hz), 4.56 (2H, s), 4.45 (1H, d, *J* = 11.7 Hz), 4.39(1H, d, *J* = 11.7 Hz), 4.20 (1H, dd, *J* = 7.3, 4.9 Hz), 4.07 - 4.04 (2H, m), 3.85 (1H, s (br)), 3.71 (1H, dd, *J* = 10.5, 2.9 Hz), 3.48 (1H, s (br)), 3.33 (1H, dd, *J* = 10.5, 2.0 Hz), 3.24 - 3.20 (1H, m), 2.05 (1H, dd, *J* = 12.7, 5.4 Hz), 1.72 (1H, td, *J* = 12.7, 3.4 Hz), 1.30 (3H, d, *J* = 5.8 Hz). δ_C (125 MHz, $CDCl_3$): 138.8 (ArC), 136.9 (2 x ArC), 128.7 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.3 (2 x Ar*C*H), 128.1 (2 x Ar*C*H), 127.9 (2 x Ar*C*H), 127.7 (2 x Ar*C*H), 84.1 (C7, observed in HMBC), 75.6 (C1, br), 73.7 (CH_2), 73.3 (C2, br), 72.2 (CH_2), 71.8 (CH_2), 71.6 (C7a, br), 68.0 (C8, observed in HMBC), 62.0

(C3), 50.2 (C5, observed in HMBC), 46.6 (C6, br), 29.8 (C9). ESIMS *m/z* 474 (100%) $[M+H]^+$. HRASAPMS found 474.2635, calcd for $C_{30}H_{36}NO_4$, 474.2644 $[M+H]^+$.

31: R_f 0.54 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ + 77.2 (*c* 0.95, $CHCl_3$). IR υ_{max} (cm^{-1}): 3400, 2929, 2866, 1645, 1452, 1359, 1259, 1101, 1025, 697. δ_H (500 MHz, $CDCl_3$): 7.38 - 7.16 (15H, m), 4.93 (1H, d, *J* = 12.2 Hz), 4.76 (1H, d, *J* = 12.2 Hz), 4.70 (1H, d, *J* = 12.2 Hz), 4.53 (1H, d, *J* = 12.2 Hz), 4.42 (2H, s), 4.36 (1H, d, *J* = 4.9 Hz), 4.33 - 4.26 (1H, m), 4.01 (1H, d, *J* = 4.9 Hz), 3.57 (2H, s (br)), 3.52 (1H, s (br)), 3.48 (1H, dd, *J* = 10.2, 2.9 Hz), 3.44 (1H, dd, *J* = 10.2, 4.9 Hz), 1.74 - 1.70 (2H, m), 1.17 (1H, d, *J* = 7.3 Hz). δ_C (125 MHz, $CDCl_3$): 173.8 (CO), 137.9 (2 x ArC), 137.3 (ArC), 128.7 (2 x Ar*C*H), 128.5 (2 x Ar*C*H), 128.4 (2 x Ar*C*H), 128.2 (2 x Ar*C*H), 128.1 (Ar*C*H), 128.0 (2 x Ar*C*H), 127.9 (Ar*C*H), 127.8 (3 x Ar*C*H), 76.9 (CH), 76.2 (CH), 73.6 (CH_2), 72.7 (CH_2), 72.3 (CH_2), 69.1 (CH_2), 59.9 (CH), 58.6 (CH_2), 45.1 (CH), 36.1 (CH_2), 19.8 (Me). ESIMS *m/z* 512 (100%) $[M+Na]^+$. HRESIMS found 512.2413, calcd for $C_{30}H_{35}NO_5Na$, 512.2413 $[M+Na]^+$.

*(1S,3R,5R,6R,7R,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-ol (**32**):* Following the general method for the reduction of a ketone to a secondary alcohol with L-selectride®, the ketone **29** (16 mg, 0.034 mmol) in THF (6 mL) was treated with L-selectride® (1.0 M solution in THF, 136 μL, 0.14 mmol). Purification by flash column chromatography (2:98 to 10:90 MeOH/CH_2Cl_2 as eluent) gave the title compound (9 mg, 58%) as a colorless oil. R_f 0.54 (10:90 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ - 16.5 (*c* 0.47, $CHCl_3$). IR υ_{max} (cm^{-1}): 3369, 3063, 3032, 2927, 2865, 1690, 1454, 1365, 1207, 1099, 1028, 740, 670. δ_H (500 MHz, $CDCl_3$): 7.31 - 7.24 (15H, m), 4.61 (1H, d, *J* = 11.6

Hz), 4.56 (1H, d, *J* = 11.7 Hz), 4.55 (1H, d, *J* = 11.7 Hz), 4.50 (1H, d, *J* = 12.0 Hz), 4.46 (1H, d, *J* = 11.6 Hz), 4.44 (1H, d, *J* = 12.0 Hz), 4.28 (1H, s (br)), 4.18 (1H, s), 4.09 (1H, s), 3.70 (1H, br), 3.50 (1H, s (br)), 3.45 (1H, dd, *J* = 9.1, 8.8 Hz), 3.38 (1H, s (br)), 3.20 (1H, s (br)), 2.24 (1H, dt, *J* = 12.5, 5.9 Hz), 1.37 (1H, dd, *J* =12.5, 10.5 Hz), 1.24 (3H, d, *J* = 6.6 Hz). δ_C (125 MHz, $CDCl_3$): 138.4 (ArC), 138.2 (ArC), 137.2 (ArC), 128.8 (2 x Ar*C*H), 128.6 (4 x Ar*C*H), 128.3 (3 x Ar*C*H), 128.0 (2 x Ar*C*H), 127.9 (3 x Ar*C*H), 127.8 (Ar*C*H), 85.6 (C2), 82.6 (C1, br), 73.7 (C7), 73.5 (C7a, observed in the HSQC), 73.4 (CH_2), 72.8 (C8, observed in the HSBC), 71.8 (2 x CH_2), 62.5 (C3, br), 54.6 (C5, br), 42.9 (C6, br), 17.0 (C9, br). ESIMS *m/z* 474 (100%) $[M+H]^+$. HRASAPMS found 474.2652, calcd for $C_{30}H_{36}NO_4$, 474.2644 $[M+H]^+$.

*(1S,2R,3R,5R,7S,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,7-triol (hyacinthacine B$_5$) (**5**).* Following the general method for hydrogenolysis of benzyl ethers, the alcohol **28** (11.7 mg, 0.03 mmol) was treated with $PdCl_2$ (6.6 mg, 0.04 mmol) and MeOH (2 mL) at rt (19 ^oC) for 3 h. The title compound (1.5 mg, 21%) was obtained as a colorless film. $[\alpha]_D^{25}$ - 21.6 (*c* 0.08, H_2O). [Lit.[3c] $[\alpha]_D$ - 25.4 (*c* 0.26, H_2O), temperature not reported]. IR υ_{max} (cm^{-1}): 3299, 2953, 1587, 1555, 1399, 1044, 839, 760, 692. δ_H (500 MHz, D_2O): 4.55 (1H, td, *J* = 7.1, 6.8 Hz, H7), 4.34 (1H, dd, *J* = 4.4, 3.9 Hz, H1), 4.04 (1H, dd, *J* = 7.3, 4.4 Hz, H2), 3.69 (1H, dd, *J* = 11.2, 4.4 Hz, $H8_A$), 3.65 (1H, dd, *J* = 11.2, 5.4 Hz, $H8_B$), 3.52 (1H, dd, *J* = 6.9, 4.4 Hz, H7a), 3.39 (1H, td, *J* = 6.1, 5.3 Hz, H3), 3.34 - 3.30 (1H, m, H5), 2.19 (1H, dt, *J* = 12.7, 6.3 Hz, $H6_\beta$), 1.79 (1H, dt, *J* = 12.7, 8.3 Hz, $H6_\alpha$), 1.29 (3H, d, *J* = 6.8 Hz, H9). δ_C (75 MHz, D_2O): 77.6 (C2), 75.6 (C7), 75.1 (C1), 69.7 (C7a), 66.0 (C8), 65.3 (C3), 57.7 (C5), 44.3 (C6), 18.1 (C9). ESIMS *m/z* 204 (100%) $[M+H]^+$. HRASAPMS found 204.1249, calcd for $C_9H_{18}NO_4$, 204.1236 $[M+H]^+$.

*(1R,2R,3R,5R,7S,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,7-triol (hyacinthacine B_4) (**4**).* Following the general method for hydrogenolysis of benzyl ethers, the alcohol **32** (8.4 mg, 0.018 mmol) was treated with $PdCl_2$ (4.8 mg, 0.027 mmol) and MeOH (1.4 mL) at rt (22 ^oC) for 3 h. The title compound (3.6 mg, 100%) was obtained as a colorless film. $[\alpha]_D^{25}$ - 7.7 (*c* 0.18, H_2O). [Lit.[3c] $[\alpha]_D$ - 6.7 (*c* 1.19, H_2O), temperature not reported]. IR υ_{max} (cm^{-1}): 3291, 2930, 2882, 1637, 1592, 1384, 1343, 1137, 1064, 612. δ_H (500 MHz, D_2O): 4.44 (1H, td, *J* = 6.4, 5.7 Hz, H7), 4.16 (1H, dd, *J* = 7.8, 7.3 Hz, H1), 3.97 (1H, dd, *J* = 7.8, 7.0 Hz, H2), 3.69 (2H, d, *J* = 5.4 Hz, H8), 3.30 (1H, dd, *J* = 7.3, 6.8 Hz, H7a), 3.28 - 3.24 (1H, m, H5), 3.14 (1H, dt, *J* = 7.8, 5.4 Hz, H3), 2.14 (1H, dt, *J* = 13.2, 5.7 Hz, $H6_\beta$), 1.71 (1H, ddd, *J* = 13.2, 7.3, 6.4 Hz, $H6_\alpha$), 1.26 (3H, d, *J* = 7.3 Hz, H9). δ_C (125 MHz, D_2O): 82.0 (C2), 77.1 (C1), 73.1 (C7), 72.9 (C7a), 66.0 (C8), 64.5 (C3), 57.0 (C5), 42.7 (C6), 19.0 (C9). ESIMS *m/z* 204 (100%) $[M+H]^+$. HRASAPMS found 204.1246, calcd for $C_9H_{18}NO_4$, 204.1236 $[M+H]^+$.

*(1S,2R,3R,5R,7R,7aS)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,7-triol (7a-epi-hyacinthacine B_3) (**33**).* Following the general method for hydrogenolysis of benzyl ethers, the alcohol **30** (2.3 mg, 0.005 mmol) was treated with $PdCl_2$ (1.3 mg, 0.008 mmol), and MeOH (0.5 mL) at rt (24 ^oC). The title compound (1.0 mg, 100%) was obtained as a colorless film. $[\alpha]_D^{25}$ - 5.3 (*c* 0.11, H_2O). IR υ_{max} (cm^{-1}): 3294, 2967, 1649, 1552, 1405, 1083, 1044. δ_H (500 MHz, D_2O): 4.38 (1H, t, *J* = 3.9 Hz, H7), 4.26 (1H, dd, *J* = 4.4, 3.9 Hz, H1), 4.08 (1H, dd, *J* = 7.3, 4.9 Hz, H2), 3.97 (1H, dd, *J* = 12.7, 6.8 Hz, $H8_A$), 3.89 (1H, dd, *J* = 12.7, 3.9 Hz, $H8_B$), 3.59 (1H, dd, *J* = 4.4, 3.9 Hz, H7a), 3.51, (1H, ddd, *J* = 5.9, 4.4, 3.9 Hz, H5), 3.23 (1H, ddd, *J* = 6.8, 4.9, 3.9 Hz, H3), 2.05 (1H, ddd, *J* =

13.2, 4.4, 3.9 Hz, H6$_\beta$), 1.71 (1H, ddd, *J* = 13.2, 11.2, 4.4 Hz, H6$_\alpha$), 1.22 (3H, d, *J* = 5.9 Hz, H9). δ_C (125 MHz, D_2O): 77.5 (C7a), 76.4 (C2), 72.1 (C7), 72.0 (C1), 66.8 (C3), 61.4 (C8), 55.2 (C5), 46.3 (C6), 22.0 (C9). ESIMS *m/z* 204 (100%) $[M+H]^+$. HRASAPMS found 204.1234, calcd for $C_9H_{18}NO_4$, 204.1236 $[M+H]^+$.

*(1R,3R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-yl 4-nitrobenzoate (**36**).* Following the general method for the Mitsunobu reaction, the alcohol **21** (144 μg, 0.30 mmol) was treated with triphenylphosphine (354 mg, 1.35 mmol), *p*-nitrobenzoic acid (226 mg, 1.35 mmol) and diisopropyl azodicarboxylate (266 μL, 3.96 mmol) in toluene (3 mL) at 80 ^oC for 2 d. Purification by flash column chromatography (20:70 to 50:50 EtOAc/petrol as eluent) gave the title compound (*ca* 70% pure) (40 mg) as a yellow film and recovered **21** (45.5 mg, 32%) was also isolated. R_f 0.60 (5:95 MeOH/CH_2Cl_2). IR υ_{max} (cm^{-1}): 2921, 2854, 1722, 1527, 1347, 1273, 1103, 1027, 736, 697. δ_H (500 MHz, $CDCl_3$): 8.28 (2H, d, *J* = 8.8 Hz), 8.16 (2H, d, *J* = 8.8 Hz), 7.37 - 7.22 (15H, m), 5.77 (1H, dt, *J* = 7.3, 4.1 Hz), 4.75 (1H, d, *J* = 11.7 Hz), 4.64 - 4.47 (5H, m), 4.19 (1H, dd, *J* = 5.3, 4.1 Hz), 3.93 (1H, s (br)), 3.78 (1H, dd, *J* = 5.3, 3.2 Hz), 3.68 - 3.60 (1H, m), 3.42 (3H, s (br)), 2.01 (2H, m), 1.27 (3H, d, *J* = 6.2 Hz). δ_C (125 MHz): 164.4 (CO), 150.6 (ArC), 138.3 (2 x ArC), 138.2 (ArC), 135.7 (ArC), 130.8 (2 x Ar*C*H), 128.7 (2 x Ar*C*H), 128.5 (4 x Ar*C*H), 127.9 (3 x Ar*C*H), 127.8 (5 x Ar*C*H), 127.7 (2 x Ar*C*H), 123.6 (Ar*C*H), 81.4 (C2), 76.9 (C1), 76.1 (C7, br), 73.5 (CH_2), 73.4 (CH_2), 72.6 (CH_2), 72.4 (C8), 60.1 (C3), 56.7 (C5), 39.8 (C6), 22.1 (C1). ESIMS *m/z* 623 (100%) $[M+H]^+$. HRESIMS found 623.2737, calcd for $C_{37}H_{39}N_2O_7$, 623.2757 $[M+H]^+$.

*(1R,3R,5R,6R,7S,7aS)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-yl methanesulfonate (**37**).* Following the general method for mesylation-cyclization, the alcohol **21** (16.8 mg, 0.034 mmol) was treated with triethylamine (81 μL, 0.58 mmol), methanesulfonyl chloride (184 μL, 2.38 mmol) and CH_2Cl_2 (1.5 mL) at rt for 24 h. Purification by flash column chromatography (0:100 to 5:95 MeOH/CH_2Cl_2 as eluent) gave the title compound (16.5 mg, 87%) as a colorless oil. R_f 0.67 (5:95 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ - 10.5 (*c* 0.16, $CHCl_3$). IR υ_{max} (cm^{-1}): 3063, 3030, 2929, 2866, 1453, 1351, 1174, 1116, 1026, 935, 895, 697. δ_H (500 MHz, $CDCl_3$): 7.35 - 7.25 (15H, m), 5.50 - 5.49 (1H, m), 4.59 - 4.44 (6H, m), 4.22 (1H, dd, *J* = 5.9, 4.9 Hz), 3.89 (1H, s (br)), 3.66 - 3.64 (1H, m), 3.56 - 3.49 (1H, m), 3.33 (1H, dd, *J* = 8.5, 4.4 Hz), 3.28 - 3.25 (1H, m), 3.20 (1H, dd, *J* = 8.5, 7.8 Hz), 2.81 (3H, s), 2.06 (1H, dd, *J* = 13.7, 4.9 Hz), 1.93 - 1.86 (1H, m), 1.19 (3H, d, *J* = 6.8 Hz). δ_C (75 MHz, $CDCl_3$): 138.3 (ArC), 137.9 (2 x ArC), 132.2 (2 x Ar*C*H), 128.5 (Ar*C*H), 128.2 (4 x Ar*C*H), 128.0 (2 x Ar*C*H), 127.9 (4 x Ar*C*H), 127.8 (2 x Ar*C*H), 83.3 (C7), 79.2 (C2), 77.2 (C1), 73.6 (CH_2), 73.4 (C7a), 72.9 (CH_2), 72.4 (C8), 71.6 (CH_2), 60.6 (C3), 56.8 (C5), 39.9 (C6), 37.7 (Me), 15.5 (C9). ESIMS *m/z* 552 (100%) $[M+H]^+$. HRESIMS found 552.2418, calcd for $C_{31}H_{38}NO_6S$, 552.2420 $[M+H]^+$.

*(1R,3R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-yl benzoate (**38**).* A solution of the mesylate **36** (31 mg, 0.06 mmol) in DMSO (6 mL) was stirred at rt for 5 min and then cesium benzoate (26 mg, 0.11 mmol) was added. The reaction mixture was stirred at 70 ^oC for 2 d. After the reaction mixture had cooled to rt, a satd aqu solution of Na_2CO_3 (5 mL) was added and then extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a light brown film.

Purification by flash column chromatography (increasing polarity from 5:95 to 20:80 of EtOAc/CH_2Cl_2 as eluent) gave the title compound (14 mg, 42%) as a colorless film. R_f 0.20 (2:98 MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ - 18.7 (*c* 0.28, $CHCl_3$). IR υ_{max} (cm^{-1}): 3063, 3031, 2924, 2862, 1715, 1452, 1358, 1273, 1111, 1025, 736, 696. δ_H (500 MHz, $CDCl_3$): 8.01 (2H, d, *J* = 7.8 Hz), 7.52 (1H, t, *J* = 7.3 Hz), 7.42 (2H, dd, *J* = 7.8, 7.3 Hz), 7.33 - 7.22 (15H, m), 5.75 - 5.72 (1H, m), 4.74 (1H, d, *J* = 11.7 Hz), 4.67 (1H, d, *J* = 11.7 Hz), 4.62 (1H, d, *J* = 11.7 Hz), 4.56 (1H, d, *J* = 12.2 Hz), 4.51 (1H, d, *J* = 11.7 Hz), 4.49 (1H, d, *J* = 12.2 Hz), 4.18 (1H, dd, *J* = 4.9, 3.9 Hz), 3.92 (1H, t, *J* = 3.9 Hz), 3.78 (1H, s (br)), 3.66 - 3.62 (1H, m), 3.43 (3H, s (br)), 2.02 - 2.00 (2H, m), 1.22 (3H, d, *J* = 6.8 Hz). δ_C (125 MHz, $CDCl_3$): 166.4 (CO), 138.6 (2 x ArC), 138.4 (ArC), 133.0 (2 x Ar*C*H), 130.7 (ArC), 129.7 (2 x Ar*C*H), 128.4 (4 x Ar*C*H), 127.9 (2 x Ar*C*H), 127.8 (4 x Ar*C*H), 127.7 (2 x Ar*C*H), 127.6 (2 x Ar*C*H), 81.7 (C2), 76.9 (C1), 75.6 (C7), 73.5 (CH_2), 73.3 (CH_2), 72.5 (C7a and CH_2), 72.2 (C8), 59.9 (C3), 56.4 (C5), 39.9 (C6), 16.2 (C9). ESIMS *m/z* 578 $[M+H]^+$. HRESIMS found 578.2902, calcd for $C_{37}H_{40}NO_5$, 578.2906 $[M+H]^+$.

ASSOCIATED CONTENT

Supporting Information

Comparative tables of the ^1H and ^{13}C NMR spectroscopic data of synthetic and natural samples of compounds **2**-**6**, copies of the ^1H and ^{13}C NMR spectra of all new compounds, and NOESY spectra of compounds **2**-**6** and **33**. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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