JOC The Journal of Organic Chemistry

Article

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Alkoxyallene-Based Stereodivergent Syntheses of (−)-Hyacinthacine B_4 and of Putative Hyacinthacine C_5 Epimers: Proposal of Hyacinthacine C_5 Structure

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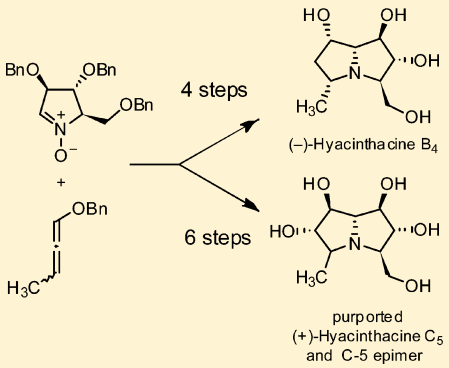
Supporting Information

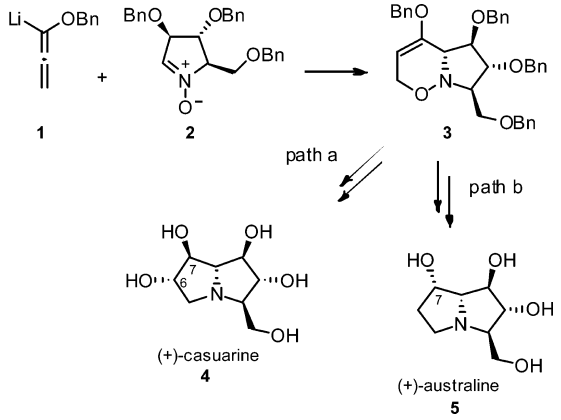
ABSTRACT: Hyacinthacines are members of the class of polyhydroxylated pyrrolizidines exhibiting outstanding biological activity as glycosidases inhibitors. Their structural complexity is embodied in the densely functionalized core, possessing a series of contiguous stereogenic centers. In this synthetic study we report a route to the more complex congeners of this class of alkaloids exploiting the diastereoselective addition of an axially chiral lithiated alkoxyallene to an enantiopure cyclic nitrone. Our stereodivergent approach enabled the installation of the targeted configuration at the ring A by minimal synthetic manipulations and at ring B by using stage dependent selective functionalizations. The versatility and robustness of this methodology were demonstrated by the syntheses of (−)-hyacinthacine B_4 and of two epimers of (+)-hyacinthacine C_5, allowing a suggestion of the likely structure of the isolated natural product.



INTRODUCTION

Our research groups have been strongly involved for many years in the synthesis of iminosugars,[1] both of natural and synthetic origin (Firenze),[2] and in the application of lithiated alkoxyallenes in the syntheses of heterocycles, natural products, and their analogs, e.g. carbohydrate mimetics (Berlin).[3] Recently, we have combined our efforts to achieve a very straightforward and convenient access to the class of polyhydroxylated pyrrolizidines by exploiting the stereoselective domino addition−cyclization of lithiated benzyloxyallene **1** to D-arabinose derived nitrone **2**[4] which furnished the key intermediate 1,2-oxazine **3** exclusively (Scheme 1).[5] Advantages of this approach are (i) perfect stereoselectivity of the key addition step; (ii) high reaction yields; (iii) direct installation of a protected hydroxyl group at C-7 of the final pyrrolizidine skeleton; and (iv) versatility of the intermediate 1,2-oxazine **3** in subsequent synthetic elaborations. The latter point was nicely demonstrated by selective addition reactions carried out alternatively at the opposite faces of the endocyclic double bond, depending on the stage at which the addition itself was performed.[5] Hydroboration of 1,2-oxazine **3** occurred from the bottom face (Scheme 1, path a), while hydrogenation of the double bond after a ring contraction to a pyrrolizidine derivative occurred from the top face (Scheme 1, path b), thus affording opposite configurations of the new stereogenic center at C-7, as illustrated by the syntheses of (+)-casuarine **4** and (+)-australine **5**, respectively, in a few steps. In order to extend the scope of this efficient synthetic strategy, different nitrones and alkoxyallenes might be employed.

Scheme 1. Stereoselective Syntheses of (+)-Casuarine (4) and (+)-Australine (5)



Recently, a large group of novel polyhydroxylated pyrrolizidines, with interesting inhibition properties toward glycosidases, has been isolated from natural sources mainly from plants of the *Hyacinthaceae* family and named hyacinthacines.[6] Their structures have been proposed on the basis of extensive NOESY analyses, showing a common substitution pattern at ring A. The terms A, B, or C have been given according to the number (0, 1, or 2, respectively) of

Received: March 21, 2017
Published: May 8, 2017

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

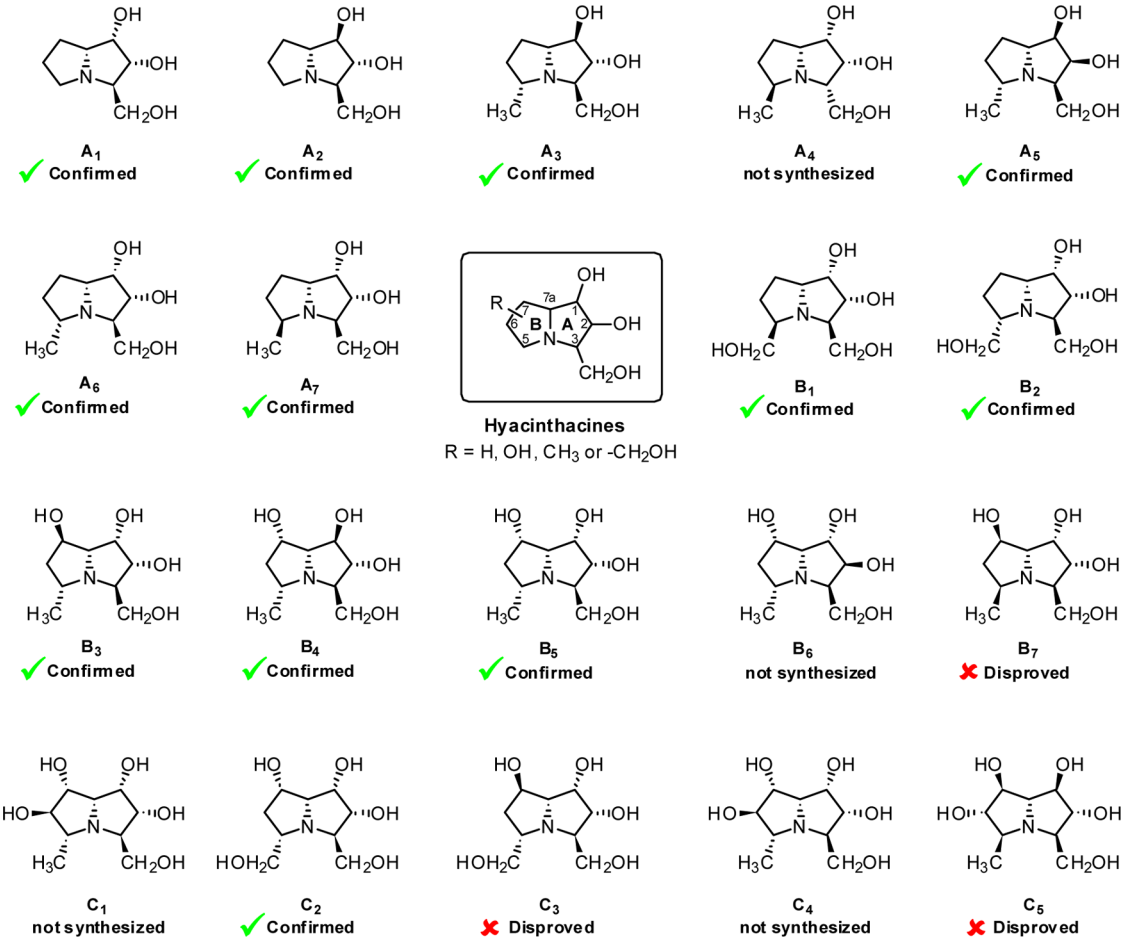


Figure 1. Reported structures of isolated alkaloids of the *Hyacinthaceae* family.

hydroxyl groups at the ring B (Figure 1).[6,7] However, the constitutional complexity and variety of these alkaloids makes, in certain cases, their structural assignment ambiguous: a structure was attributed for a compound named hyacinthacine C_4 that was identical to the previously isolated C_1 analogue, although spectroscopic and analytic data were different,[7a,c] thus emphasizing the need for further validation. So far, the configurations of the A_{1-3} and A_{5-7} alkaloids were proved by synthesis, while the A_4 has not been the subject of studies.[8] The preparation of hyacinthacines B_{1-5} and C_2 confirmed the purported structures, whereas synthesis of the B_7, C_3, and C_5 congeners disproved the initial proposal.[9−11] In particular, the latter alkaloid has recently been the object of considerable attention: synthesis of purported (−)-hyacinthacine C_5 was achieved in 2011 by the group of Yu[10] followed in the same year by Tamayo and co-workers[11] with the synthesis of the opposite enantiomer (the putative natural compound). In Yu's synthesis the pyrrolizidine core was assembled using a Cope−House cyclization between a lithiated dithiane and an enantiopure nitrone prepared from D-xylose. Tamayo and co-workers employed a chiral pyrrolidine as a synthetic equivalent for ring A, while the second ring was constructed by olefination followed by oxidation and final cyclization to give the pyrrolizidine core. The same groups also performed the synthesis of the 6-*epi*, 7-*epi*, and 6,7-di-*epi*-hyacinthacine C_5, in an effort to reassign the original structure, achieving both configurations at C-7 and C-6.[10,11] However, access to the C-5 epimer of the postulated hyacinthacine C_5 has not yet been reported and might prove pivotal in the elucidation of its correct structure.

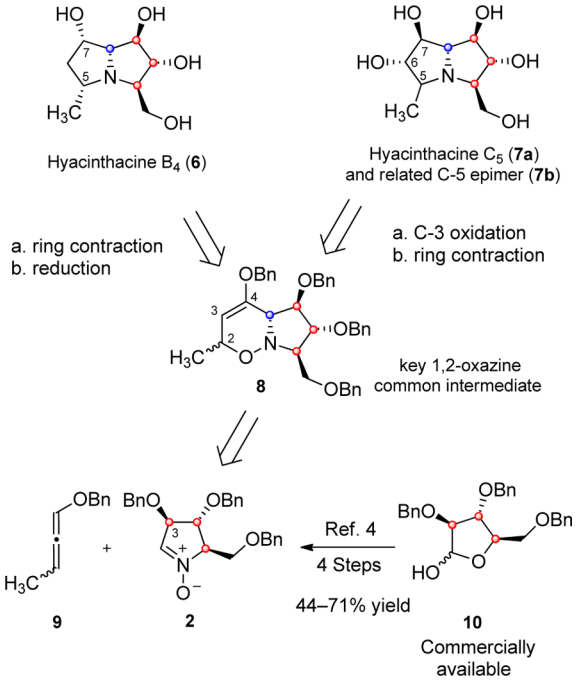
We envisaged that this type of compounds might be accessed by our strategy employing 3-methyl-substituted alkoxyallenes and aimed to test this option to broaden the scope of this approach. In this report, the results of this seemingly trivial extension of our strategy are presented, which finally led to the total synthesis of (−)-hyacinthacine B_4 (**6**), as well as that of the purported (+)-hyacinthacine C_5 (**7a**) and of (+)-5-*epi*-hyacinthacine C_5 (**7b**) (Scheme 2).

RESULTS AND DISCUSSION

Addition of lithiated benzyloxyallene to enantiomerically pure D-arabinose derived nitrone **2** has been proven to be efficiently controlled by steric and stereoelectronic effects.[5,12] The exclusive *trans* stereoselectivity, with respect to the vicinal benzyloxy group at C-3 of the nitrone, generates the configuration required at the bridgehead carbon of the natural alkaloids. On the basis of our preliminary investigations, hyacinthacines B_4 (**6**) and C_5 (**7a**), possessing the desired structural motif at the A ring, were targeted as primary goals of our studies (Scheme 2). Following the retrosynthetic analysis, we planned to start from axially chiral benzyloxyallene **9** in order to obtain the 2-methyl-substituted 1,2-oxazines **8**. Then, our route would diverge in order to install the configuration and the oxidation level required at C-7 and C-6 of the final alkaloids (Scheme 2).

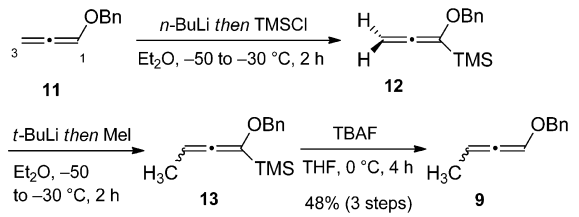
DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

Scheme 2. Targeted Alkaloids and Retrosynthetic Analysis



The synthetic route toward the hyacinthacines **6**, **7a**, and **7b** began with the preparation of racemic 3-methyl-substituted benzyloxyallene **9**. Attempts to carry out a one-step alkyne to allene isomerization using alkoxides or stronger bases such as *n*-butyllithium from 1-benzyloxy-2-butyne led to isolation of **9** in only very low yields.[13] On the other hand, application of a three-step procedure, previously developed in the Reissig group,[14] gave the desired allene derivative **9** in 48% overall yield (Scheme 3). For this purpose, the more acidic C-1 proton of **11**

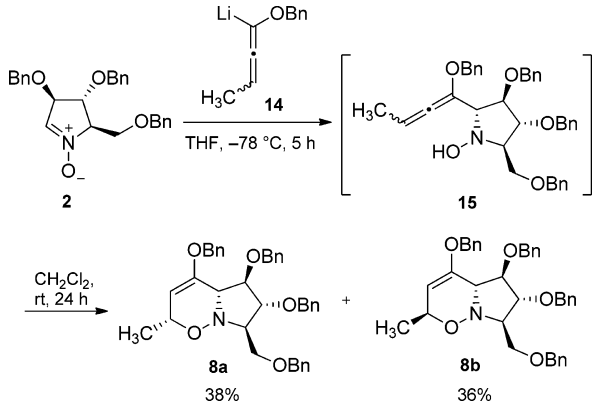
Scheme 3. Preparation of Racemic 3-Methyl-Substituted Benzyloxyallene 9



was exchanged by a trimethylsilyl group, then the reaction of intermediate **12** with *tert*-butyllithium allowed the clean deprotonation at the C-3 position giving after treatment with iodomethane the 3-methyl-substituted allene derivative **13**. Its deprotection with fluoride afforded racemic target compound **9**.

Enantiopure nitrone **2** was prepared starting from commercially available **10** following a known protocol[4,2a] which permitted setting the stereogenic centers of ring A from the chiral pool, thus avoiding C−C bond forming reactions in this part of the target compounds. Assembly of the final carbon network was performed in one step by diastereoselective addition of lithiated benzyloxyallene **14** (generated by treatment of **9** with *n*-butyllithium at −45 °C in THF) to nitrone **2**. During standing at room temperature for 24 h the intermediate addition products **15** completely cyclized and the two expected[15] epimeric 1,2-oxazines **8a** and **8b** were formed in a 1:1 ratio as evidenced by analysis of the proton NMR spectrum of the crude product (Scheme 4). Despite the use of an excess

Scheme 4. Stereodivergent Preparation of the Key 1,2-Oxazine Intermediates 8a and 8b



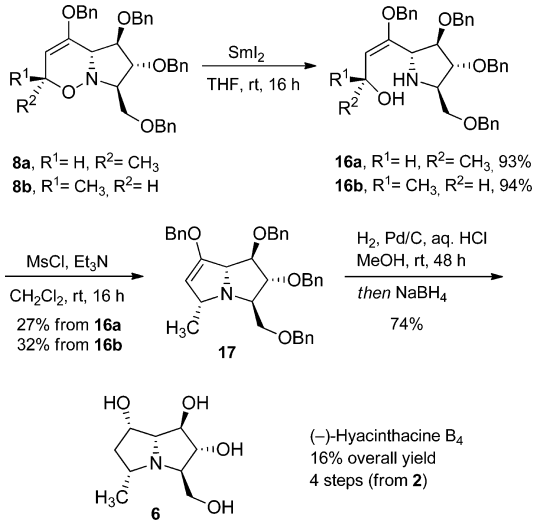
of racemic **14** (3.5 equiv) the obtained 1:1 ratio of the two epimers **8a** and **8b** revealed that no kinetic discrimination of the two enantiomers of **14** occurred during its addition to enantiopure nitrone **2**. The methyl group of **14** is apparently too far from the C−C bond forming event, and therefore its orientation has no influence on rate and diastereoselectivity. Column chromatography allowed separation and isolation of **8a** and **8b** in a combined 74% yield.

(−)-Hyacinthacine B_4. In order to forge the final C−N bond we planned to directly submit 1,2-oxazines **8a** and **8b** to ring contraction. Subsequent reduction of the endocyclic double bond would occur from the less sterically congested convex face installing the desired configuration at C-7. Therefore, the unsaturated ring was chemoselectively cleaved employing a samarium diiodide mediated reductive N−O cleavage. The two diastereomeric amino alcohols **16a** and **16b** were obtained in 93% and 94% yield, respectively. Treatment of intermediate **16b** with MsCl and Et_3N gave the expected pyrrolizidine **17** in 32% yield. This compound possesses the targeted pseudoequatorial conformation for the methyl group at C-5 (Scheme 5 and Figure 2). Interestingly, diastereomer **16a** provided the same pyrrolizidine **17** in a slightly reduced yield.

The fact that **16a** and **16b** provided the identical cyclization product **17** indicates an S_N1 mechanism, involving a well stabilized transient allylic carbenium ion intercepted by a more favorable top attack of the nitrogen atom. Likely, steric effects control attack from the top, allowing the two bulkiest groups (methyl and hydroxymethyl) to be positioned in the less crowded *trans* relative configuration. The low product yields obtained in this step are also suggestive of formation of a carbenium ion intermediate which may evolve in a number of ways, leading to several byproducts. Application of milder Mitsunobu conditions for the ring closure of **16a** did not lead to cyclization, preventing access to the C-5 epimer. Finally, hydrogenolysis of **17** and subsequent sodium borohydride treatment of the resulting 2:1 mixture (7-oxo/7-hydroxy) delivered the saturated pyrrolizidine **6**. After purification on a Dowex 50WX8 ion-exchange resin, (−)-hyacinthacine B_4 (**6**) was collected as the free base. The structure was carefully proven by a series of 1D NOESY analyses (Figure 2). In particular, saturation of the methyl protons gave rise to NOE

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

Scheme 5. Stereoconvergent Synthesis of (−)-Hyacinthacine B_4 (6)



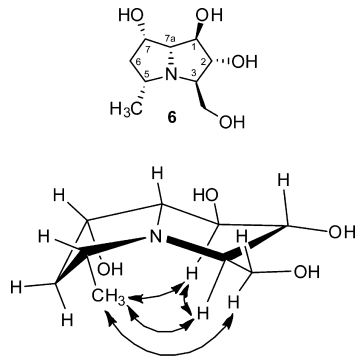


Figure 2. Key 1D NOESY correlations for synthetic (−)-hyacinthacine B_4 (**6**).

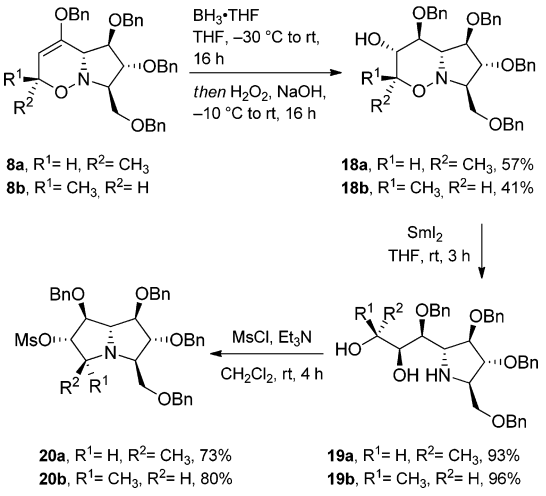
enhancement of the H-1 and H-3 multiplets, supporting our rationale for the formation of unsaturated pyrrolizidine **17**.

The synthetic alkaloid **6** was obtained in four steps in a satisfying 16% overall yield starting from nitrone **2**, as the result of the stereoconvergent ring closure of the epimers **16a/b** to the common pyrrolizidine **17**. Spectroscopic and physical data for pyrrolizidine **6** were in full accordance with those reported in the literature for the extracted natural product, confirming complete consistence with the findings of Pyne[9a] and the structure proposed by Asano and co-workers.[7b]

Approach to Purported (+)-Hyacinthacine C_5 and Its C-5 Epimer. Hyacinthacine C_5 is distinguished from pyrrolizidine **6** by a higher oxidation state at C-6. In analogy to our previous studies,[5] we decided to install the required hydroxyl moiety prior to the final ring contraction. At this stage, the double bond would be selectively functionalized generating the desired configuration at C-7 and C-6 of the final pyrrolizidine.

The epimeric 1,2-oxazines **8a** and **8b** were subjected to the reliable one-pot hydroboration/oxidation sequence. We propose that coordination of the electrophilic boron to the lone pair of the bridgehead nitrogen atom led to a selective bottom attack of the borane reagent. Subsequent in situ oxidation afforded the alcohols **18a** and **18b** in moderate yields (Scheme 6).

Scheme 6. Hydroboration/Oxidation of 1,2-Oxazines 8a and 8b and Subsequent Conversion into Pyrrolizidines 20a and 20b



The structure of alcohols **18a** and **18b** was confirmed after conversion to the corresponding pyrrolizidines **20a** and **20b**, also providing the configuration at C-5. Treatment of 1,2-oxazines **18a** and **18b** with samarium diiodide caused reductive cleavage of the N−O bonds. The diols **19a** and **19b** were converted into the corresponding bis(mesylates) that underwent a spontaneous S_N2-type ring closure with inversion of configuration at the farther secondary carbon atom, smoothly furnishing the protected pyrrolizidine derivatives **20a** and **20b** (Scheme 6). At this stage, the relative configuration was determined by 1D NOESY analyses of the bicyclic amines (Figure 3). The structure of **20a** was unambiguously assigned

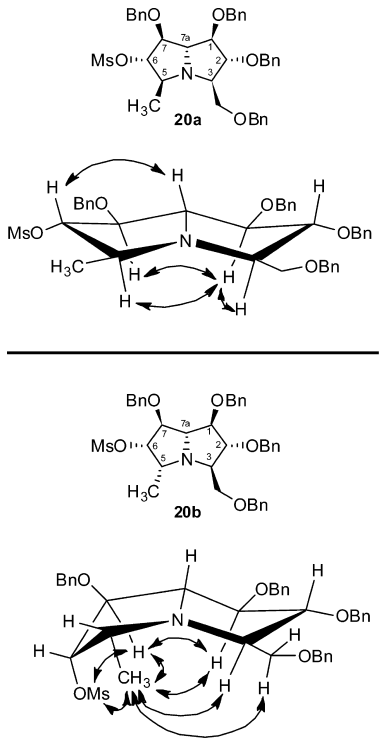


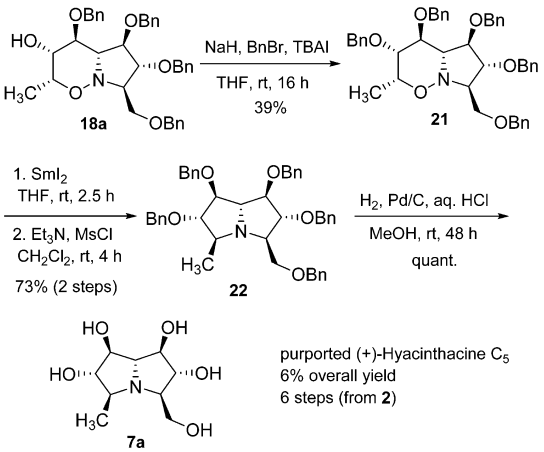
Figure 3. Key 1D NOESY correlations for the pyrrolizidines **20a** and **20b**.

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

on the basis of positive NOE correlations between spatially close H-1, H-3, H-5, and H-7. Irradiation of H-6 generated enhancement of the H-7a multiplet intensity, confirming the assignment and retention of configuration at C-6 under the applied cyclization conditions. On the other hand, through space interactions between H-1, H-3, H-7 and the methyl groups clearly indicated the relative configuration of **20b**.

Completion of the synthesis of purported (+)-hyacinthacine C_5 is illustrated in Scheme 7. To avoid bismesylation the

Scheme 7. Synthesis of Purported (+)-Hyacinthacine C_5 (7a)

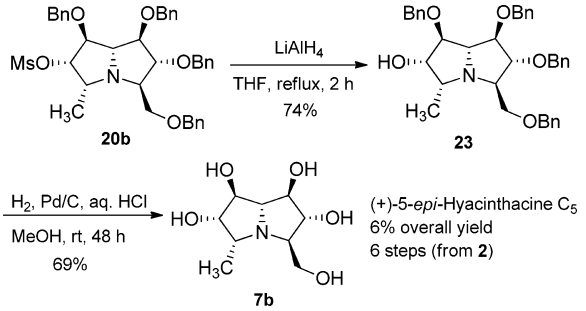


hydroxyl group of **18a** was benzylated under basic conditions using sodium hydride and benzyl bromide (not optimized). Finally, ring contraction of the benzyl ether **21** under standard conditions (SmI_2, then $MsCl/NEt_3$), followed by hydrogenolysis, afforded deprotected pyrrolizidine **7a**, obtained in six steps from enantiopure **2** with 6% overall yield. The spectroscopic data of synthetic **7a** were in agreement with those reported independently by Tamayo and Yu et al.,[10,11] confirming that the synthesized material differs in configuration from the isolated natural alkaloid.[7a] A predominant inconsistency was found for the C-5 (+9.5 ppm) and minor deviations for the C-2 (−2.6 ppm) and C-8 (−4.0 ppm) chemical shifts on comparing the ^{13}C NMR data of synthetic **7a** with those of the extracted hyacinthacine C_5 (for details, see the Supporting Information).

We then focused our efforts on the preparation and spectroscopic analysis of the C-5 epimer of **7a**. The hyacinthacine derivative **7b** was obtained from the intermediate mesylate **20b**. Removal of the sulfonyl group was achieved in good yield using lithium aluminum hydride as a reducing agent. Analogous selective cleavage of the S−O bond was already observed during our studies for the synthesis of casuarine.[5] Final deprotection and purification afforded 5-*epi*-hyacinthacine C_5 **7b** in six steps from nitrone **2** again with 6% overall yield (Scheme 8).

The spectroscopic properties of **7b** were also compared with those reported for the natural hyacinthacine C_5.[7a] As described above for **7a**, the examined proton and carbon NMR spectra showed no accordance. Significant deviations in the latter one were found for the chemical shifts of C-8 (−6.6 ppm), C-7a (+4.9 ppm), and C-2 (−5.7 ppm) (see the Supporting Information). Notably, in contrast to synthetic **7a** the chemical shift for the nitrogen bound C-5 in **7b** closely matches the one reported in the isolated hyacinthacine C_5 suggesting a plausible pseudoequatorial conformation for the exocyclic carbon.

Scheme 8. Synthesis of 5-*epi*-Hyacinthacine C_5 (7b)



Having in hand both C-5 epimers we decided to compare the NOESY correlations previously shown for pyrrolizidines **20a** and **20b** with the ones described for the natural occurring hyacinthacine C_5.[7a] In particular, Asano and co-workers observed a correlation between the CH_3 and CH_2OH groups that we also found in both **20b** and synthetic **6**, while in pyrrolizidine **20a** such interaction was not detected. By careful analysis of each NOE enhancement reported for the isolated hyacinthacine C_5 we can also propose a different structure to the one published, namely that of 1-*epi*-hyacinthacine C_4 **24** (Figure 4).

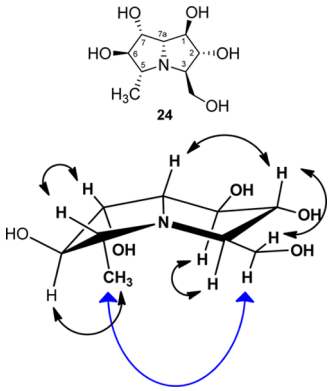


Figure 4. Proposed structure for natural hyacinthacine C_5 with reported NOE interactions.[7a]

This structure would also be consistent with the large coupling constant reported for H-7a (3.24 ppm, t, J = 7.6 Hz) attributed to the dihedral angle between H-7a and H-7, as observed in the case of our synthetic hyacinthacine B_4 (**6**) (3.41 ppm, t, J = 7.3 Hz). All signals in the ^1H NMR spectrum of **6** resemble those of natural hyacinthacine C_5, with the obvious exceptions of protons at C-6 and, to a minor extent, those at C-5 and C-7, due to the lack of the hydroxyl group at C-6 in compound **6**. Moreover, the light shielding effect (about 0.5 ppm) observed for protons at C-5 and C-7 in natural hyacinthacine C_5 with respect to **6** is also consistent with the presence of a *cis* OH at C-6. Analogous resemblance can be observed in the ^{13}C NMR spectra of the two compounds (see the Supporting Information for a detailed comparison of ^1H NMR and ^{13}C NMR spectra).

These similarities are also a strong indication that natural hyacinthacine C_5 might be a C-1-epimer of hyacinthacine C_4. However, the 1-*epi*-hyacinthacine C_4 has not been synthesized yet and its preparation will finally answer the question.

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

CONCLUSION

In summary, as an extension of our successful strategy for the synthesis of hydroxylated pyrrolizidine alkaloids, we have accomplished a reliable entry to 5-methyl-substituted hyacinthacine derivatives. Stereoselective addition of racemic lithiated 3-methyl-substituted benzyloxyallene **14** to nitrone **2** occurred smoothly leading after cyclization to 1,2-oxazines **8a** and **8b** in good yields. The versatility of this approach was confirmed in the subsequent elaborations of the common intermediates. The use of two stereodivergent routes allowed selective installation of the required stereogenic centers at C-7 and C-6 of the targeted pyrrolizidines starting from the key 1,2-oxazines. The advantages of our approach were finally demonstrated by the synthesis of (−)-hyacinthacine B_4 and of the purported (+)-hyacinthacine C_5 accessing as well its challenging C-5 epimer. Careful comparison of our spectroscopic data with those reported for the isolated hyacinthacine C_5 allowed the suggestion of its revised structure.

EXPERIMENTAL SECTION

Commercial reagents and solvents were used as received unless otherwise stated. Anhydrous solvents were purified with a solvent purification system. All reactions have been carried out under magnetic stirring and were monitored by TLC analysis on 0.25 mm silica gel plates. SmI_2 has been prepared from Sm and I_2 following known protocols.[16] Column chromatography has been carried out on silica gel (32−63 μm or 230−400 mesh) or Al_2O_3 (neutral, 6% water, activity grade III). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra have been recorded on 200, 250, 300, 400, 500, and 700 MHz instruments. Chemical shifts are reported relative to TMS (^{1}H: δ = 0.00 ppm) and $CDCl_3$ (^{13}C: δ = 77.0 ppm). ^{13}C chemical shifts of aryl groups are frequently given as a range when their peaks strongly overlap. For detailed peak assignments 2D spectra have been measured (COSY, DEPT, HSQC, HMQC, HMBC, and NOESY as necessary). IR spectra have been recorded with an FT-IR spectrometer. Mass spectra have been recorded on a quadrupole mass spectrometer by direct inlet. HRMS analyses have been performed with an FTICR mass spectrometer (ESI-TOF, 4 μL/min, 1.0 bar, 4 kV). Elemental analyses were performed using a CHN mode analyzer. Optical rotation measurements have been performed using a 1 dm optical-path length cell with the frequency of the Na_D line measured at the indicated temperature and concentration reported in g/100 mL.

[(Buta-1,2-dien-1-yloxy)methyl]benzene (9). Lithiated benzyloxyallene was generated under an argon atmosphere by treating a solution of benzyloxyallene **11** (5.00 g, 34.2 mmol) in anhydr. Et_2O (25 mL) with *n*-BuLi (2.5 M in hexanes; 13.7 mL, 34.2 mmol) at −50 °C. After 10 min, a solution of TMSCl (4.35 mL, 34.2 mmol) in anhydr. Et_2O (5 mL) was slowly added at −50 °C. The mixture was warmed to −30 °C within 2 h and then quenched by addition of sat. aq. $NaHCO_3$ solution (15 mL). The mixture was warmed to room temperature and then extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried with Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product **12** (7.46 g) was isolated and used in the next step without further purification.

An aliquot of crude **12** (2.18 g, max. 10.0 mmol) was dissolved in anhydr. THF (40 mL) under an argon atmosphere and then cooled to −50 °C, and *t*-BuLi (1.5 M in pentane; 6.7 mL, 10.0 mmol) was slowly added. After 20 min, methyl iodide (0.62 mL, 10.0 mmol) was added at −50 °C. The mixture was warmed to −30 °C within 2 h and then carefully quenched by addition of sat. aq. $NaHCO_3$ solution (20 mL). The mixture was warmed to room temperature and then extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried with Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the crude product **13** (2.27 g, 9.78 mmol) was isolated and used without further purification.

To a cooled (0 °C) solution of crude **13** (2.27 g, 9.78 mmol) in anhydr. THF (37 mL), TBAF solution (1 M in THF; 11.7 mL, 11.7 mmol) was added dropwise under an argon atmosphere and stirred for 4 h. Afterward, the mixture was quenched by addition of sat. aq. $NaHCO_3$ solution (20 mL). The mixture was warmed to room temperature and then extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (FCC) on alumina (neutral, activity III; pentane) afforded pure **9** (762 mg, 4.76 mmol, overall 48%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39−7.25 (m, 5H), 6.74−6.72 (m, 1H), 5.83 (qd, $^3J_{H-H}$ = 6.4 Hz, $^4J_{H-H}$ = 5.6 Hz, 1H), 4.65, 4.58 (AB system, J_{AB} = 11.6 Hz, 1H each), 1.75 (dd, $^3J_{H-H}$ = 6.8 Hz, $^5J_{H-H}$ = 2.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.5, 137.7, 128.6−127.8, 120.4, 102.3, 70.4, 17.6. IR ($CDCl_3$): $\tilde{\nu}$ 3035, 2920, 2855, 1970, 1945, 1500, 1455, 1410, 1375, 1215, 1180, 1085, 1060, 870 cm^{-1}.

Synthesis of 1,2-Oxazines 8a and 8b. To generate **14**, a solution of *n*-BuLi (2.5 M in hexanes; 2.01 mL, 5.03 mmol) was added dropwise at −45 °C to a stirred solution of 3-methyl-substituted allene **9** (1.13 g, 7.04 mmol) in anhydr. THF (7 mL) under an argon atmophere. After 15 min, a solution of nitrone **2** (0.84 g, 2.01 mmol) in anhydr. THF (4.5 mL) was added slowly at −78 °C. The mixture was stirred at −78 °C for 5 h. TLC control (hexanes/AcOEt 1:1) showed the disappearance of the starting material (R_f 0.11) and the appearance of new products (R_f 0.89). Then the mixture was quenched by the addition of water (10 mL), warmed to room temperature, and then extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried with Na_2SO_4, filtered, and stirred at room temperature for 24 h. Evaporation under reduced pressure and purification of the residue by FCC on silica gel (hexanes/AcOEt 20:1) afforded pure **8b** (416 mg, 36%) as a colorless solid and pure **8a** (445 mg, 38%) as a pale orange oil.

(2*S*,4a*S*,5*R*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-2-methyl-4a,5,6,7-tetrahydro-2*H*-pyrrolo[1,2-*b*][1,2]-oxazine (8b). Mp 82−83 °C. R_f 0.44 (hexanes/AcOEt 4:1). $[\alpha]_D^{21}$ −68.4 (*c* 0.66 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.40−7.20 (m, 20H), 4.87−4.78 (m, 2H), 4.82 (s, 1H), 4.68−4.41 (m, 4H), 4.56 (qt, $^3J_{H-H}$ = 7.0 Hz, $^3J_{H-H} \approx {}^5J_{H-H} \approx$ 1.4 Hz, 1H), 4.54−4.49 (m, 2H), 4.17 (t, $^3J_{H-H}$ = 3.5 Hz, 1H), 4.06 (br t, $^3J_{H-H} \approx {}^5J_{H-H} \approx$ 2.1 Hz, 1H), 4.04 (dd, $^3J_{H-H}$ = 7.0, 4.2 Hz, 1H), 3.77−3.71 (m, 2H), 3.59 (dt, $^3J_{H-H}$ = 7.0, 4.2 Hz, 1H), 1.30 (d, $^3J_{H-H}$ = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 175 MHz): δ 150.1, 138.6, 138.1, 138.1, 136.6, 128.6−127.5, 97.7, 84.3, 83.6, 73.4, 72.2, 71.6, 69.2, 69.1, 64.2, 64.1, 63.8, 20.4. IR ($CDCl_3$): $\tilde{\nu}$ 3030, 2925, 1670, 1495, 1455, 1360, 1215, 1200, 1100, 1030 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{37}H_{39}NO_5$ + H^+, 578.2906 [M + H]$^+$; found, 578.2924.

(2*R*,4a*S*,5*R*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-2-methyl-4a,5,6,7-tetrahydro-2*H*-pyrrolo[1,2-*b*][1,2]-oxazine (8a). R_f 0.37 (hexanes/AcOEt 4:1). $[\alpha]_D^{21}$ +1.3 (*c* 1.3 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.14 (m, 20H), 4.86−4.79 (m, 2H), 4.78 (br s, 1H), 4.64−4.48 (m, 8H), 4.14 (dd, $^3J_{H-H}$ = 4.8, 3.6 Hz, 1H), 3.67 (td, $^3J_{H-H}$ = 6.4, 3.2 Hz, 1H), 3.62−3.56 (m, 2H), 3.45 (dd, $^2J_{H-H}$ = 9.8 Hz, $^3J_{H-H}$ = 6.8 Hz, 1H), 1.22 (d, $^3J_{H-H}$ = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.1, 138.6, 138.3, 136.9, 128.7−127.7, 99.0, 90.8, 88.2, 73.5, 72.9, 72.0, 72.0, 71.6, 70.2, 69.5, 66.6, 21.0. IR ($CDCl_3$): $\tilde{\nu}$ 3030, 2865, 1670, 1500, 1455, 1365, 1215, 1195, 1100, 1025 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{37}H_{39}NO_5$ + H^+, 578.2906 [M + H]$^+$; found, 578.2924.

(*E*,*R*)-1′-(Benzyloxy)-1′-[(2*S*,3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]but-1′-en-3′-ol (16a). To a stirred solution of **8a** (200 mg, 0.35 mmol) in anhydr. and degassed THF (1.5 mL) a solution of SmI_2 (0.07 M in THF; 19.8 mL, 1.38 mmol) was added under an argon atmosphere. The mixture was stirred for 16 h at room temperature. TLC control (hexanes/AcOEt 1:1) showed the disappearance of the starting material (R_f 0.90) and the appearance of a new compound (R_f 0.12), then a saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried with Na_2SO_4. Filtration and evaporation under reduced

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

pressure afforded spectroscopically pure **16a** (187 mg, 93%), used without further purification, as a yellow pale oil. An analytically pure sample was obtained by purification of the residue by FCC on silica gel (AcOEt/hexanes 2:1).

R_f 0.12 (hexanes/AcOEt 1:1). $[\alpha]_D^{21}$ +22.6 (*c* 0.71 in $CHCl_3$). ^1H NMR ($CDCl_3$, 700 MHz): δ 7.37−7.26 (m, 20H), 4.88 (d, $^3J_{H-H}$ = 8.4 Hz, 1H), 4.76 (AB system, $^2J_{AB}$ = 11.9 Hz, 2H), 4.68 (dq, $^3J_{H-H}$ = 8.4, 6.3 Hz, 1H), 4.56−4.54 (m, 6H), 4.37 (dd, $^3J_{H-H}$ = 7.0, 4.2 Hz, 1H), 4.18 (d, $^3J_{H-H}$ = 7.0 Hz, 1H), 4.05 (t, $^3J_{H-H}$ = 4.2 Hz, 1H), 3.56 (d, $^3J_{H-H}$ = 5.6 Hz, 2H), 3.44 (dt, $^3J_{H-H}$ = 5.6, 5.0 Hz, 1H), 2.95 (br s, 2H), 1.31 (d, $^3J_{H-H}$ = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 175 MHz): δ 154.7, 138.2, 138.2, 138.1, 136.6, 128.5−127.5, 107.8, 86.7, 86.5, 73.3, 72.3, 72.0, 70.8, 69.2, 63.4, 61.7, 61.0, 24.0. IR ($CDCl_3$): $\tilde{\nu}$ 3335, 3030, 2925, 2855, 1660, 1495, 1455, 1365, 1215, 1190, 1090, 1075, 1030 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{37}H_{41}NO_5$ + H^+, 580.3063 $[M + H]^+$; found, 580.3025.

(*E*,*S*)-1′-(Benzyloxy)-1′-[(2*S*,3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]but-1′-en-3′-ol (16b). Analogously to the preparation of **16a**, **8b** (294 mg, 0.51 mmol) in THF (2 mL) and SmI_2 (0.07 M in THF; 29.1 mL, 2.04 mmol) afforded spectroscopically pure **16b** (276 mg, 94%) as a yellow pale oil used without further purification. An analytically pure sample was obtained by purification by FCC on silica gel (hexanes/AcOEt 3:1).

R_f 0.45 (hexanes/AcOEt 1:1). $[\alpha]_D^{21}$ +6.2 (*c* 1.17 in $CHCl_3$). ^1H NMR ($CDCl_3$, 700 MHz): δ = 7.39−7.28 (m, 20H), 4.91 (d, $^3J_{H-H}$ = 7.7 Hz, 1H), 4.74−4.70 (m, 2H), 4.67−4.66 (m, 1H), 4.63−4.60 (m, 4H), 4.55 (dd, $^3J_{H-H}$ = 8.4, 6.3 Hz, 1H), 4.53−4.51 (m, 1H), 4.14−4.10 (m, 3H), 3.59−3.54 (m, 2H), 3.49 (td, $^3J_{H-H}$ = 6.3, 4.2 Hz, 1H), 2.71 (br s, 2H), 1.31 (d, $^3J_{H-H}$ = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 175 MHz): δ 154.7, 138.2, 138.1, 137.3, 136.5, 128.5−127.7, 107.7, 87.4, 86.9, 73.4, 72.6, 72.0, 71.8, 69.3, 62.7, 61.6, 60.2, 23.4. IR ($CDCl_3$): $\tilde{\nu}$ 3390, 3030, 2925, 2865, 1655, 1495, 1455, 1365, 1210, 1190, 1085, 1075, 1030 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{37}H_{41}NO_5$ + H^+, 580.3063 $[M + H]^+$; found, 580.3045.

(1*R*,2*R*,3*R*,5*R*,7a*S*)-1,2,7-Tris(benzyloxy)-3-(benzyloxymethyl)-5-methyl-2,3,5,7a-tetrahydro-1*H*-pyrrolizine (17). To a stirred solution of **16b** (136 mg, 0.24 mmol) in anhydr. CH_2Cl_2 (10 mL), triethylamine (162 μL, 1.20 mmol) and MsCl (27 μL, 0.35 mmol) were added at room temperature under an argon atmosphere. The solution was stirred for 16 h at room temperature. TLC control (hexanes/AcOEt 1:1) showed the disappearance of the starting material (R_f 0.45) and the appearance of a new product (R_f 0.85). Water (4 mL) was added, then the mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by FCC on silica gel (hexanes/AcOEt 4:1) afforded pure **17** (43 mg, 32%) as a pale yellow oil.

R_f 0.21 (hexanes/AcOEt 4:1). $[\alpha]_D^{21}$ −17.9 (*c* 0.88 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.22 (m, 20H), 4.85−4.50 (m, 9H), 4.28−4.20 (m, 2H), 4.11 (t, $^3J_{H-H}$ = 5.0 Hz, 1H), 4.02 (t, $^3J_{H-H}$ = 5.5 Hz, 1H), 3.55−3.47 (m, 3H), 1.25 (d, $^3J_{H-H}$ = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.1, 138.6, 138.5, 138.4, 136.6, 128.4−127.4, 99.6, 87.2, 87.0, 73.3, 73.3, 72.5, 72.1, 72.0, 71.9, 60.7, 19.7. IR ($CDCl_3$): $\tilde{\nu}$ 3030, 2925, 2860, 1660, 1495, 1455, 1365, 1230, 1215, 1100, 1030 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{37}H_{39}NO_4$ + H^+, 562.2957 $[M + H]^+$; found, 562.2960.

(−)-Hyacinthacine B$_4$ (6). To a stirred solution of **17** (76 mg, 0.135 mmol) in CH_3OH (8 mL), 10% Pd/C (57 mg) and conc. HCl (4 drops) were added at room temperature under an argon atmosphere. The mixture was stirred at room temperature under a hydrogen atmosphere for 48 h. ^1H NMR spectroscopic control showed the disappearance of the signals of the benzyl groups and the formation of a ketone/alcohol mixture (2:1) at the C-7. After filtration through Celite and concentration under reduced pressure, the crude product obtained was dissolved in anhydr. CH_3OH (8 mL) and $NaBH_4$ (26 mg, 0.68 mmol) was added. The suspension was stirred at room temperature for 16 h. Four drops of conc. HCl were added, and then the mixture was filtered through Celite and concentrated under reduced pressure. The free amine was obtained by passing the hydrochloride salt through a Dowex 50WX8 ion-exchange resin. Washing with MeOH (20 mL) and H_2O (20 mL) to remove products without an amino group and finally elution with an ammonia solution (2 N in MeOH; 40 mL) released free base **6**. Evaporation of the solvent under reduced pressure afforded pure **6** (20 mg, 74% yield over two steps, dr > 20:1) as a yellowish vitreous oil.

$[\alpha]_D^{21}$ −8.6 (*c* 0.43 in H_2O); $[\alpha]_D$ −6.7 (*c* 1.19 in H_2O) [ref 7b]; ^1H NMR (D_2O, 500 MHz): δ 4.45 (dt, $^3J_{H-H}$ = 6.0, 5.0 Hz, 1H), 4.17 (m, 1H), 3.97 (t, $^3J_{H-H}$ = 8.0 Hz, 1H), 3.70 (d, $^3J_{H-H}$ = 4.5 Hz, 2H), 3.41 (t, $^3J_{H-H}$ = 7.3 Hz, 1H), 3.36 (q, $^3J_{H-H}$ = 7.0 Hz, 1H), 3.20 (dt, $^3J_{H-H}$ = 8.0, 4.5 Hz, 1H), 2.16 (dt, $^2J_{H-H}$ = 13.5 Hz, $^3J_{H-H}$ = 5.5 Hz, 1H), 1.73 (dt, $^2J_{H-H}$ = 13.5 Hz, $^3J_{H-H}$ = 6.5 Hz, 1H), 1.26 (d, $^3J_{H-H}$ = 7.0 Hz, 3H). ^{13}C NMR (D_2O, 125 MHz): δ 78.3, 74.0, 70.5, 69.9, 62.3, 61.9, 55.5, 39.6, 16.0. HRMS (ESI-TOF): *m*/*z* calcd for $C_9H_{17}NO_4$ + H^+, 204.1236 $[M + H]^+$; found, 204.1237.

(2*R*,3*R*,4*S*,4a*R*,5*R*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-2-methylhexahydro-2*H*-pyrrolo[1,2-*b*][1,2]oxazin-3-ol (18a). To a solution of **8a** (210 mg, 0.36 mmol) in anhydr. THF (7 mL) a solution of BH_3·THF (1 M in THF; 1.82 mL, 1.82 mmol) was added at −30 °C under an argon atmosphere. The solution was warmed to room temperature and stirred for 16 h. TLC control (hexanes/AcOEt 4:1) showed the appearance of a new product (R_f 0.55), then the solution was cooled to −10 °C, and aqueous NaOH solution (2 N; 3 mL) and H_2O_2 (30% v/v; 1.11 mL) were added. The mixture was stirred for 16 h at room temperature. A TLC control (hexanes/AcOEt 4:1) showed the disappearance of the intermediate product (R_f 0.55) and the appearance of a new product (R_f 0.22). A sat. aq. $Na_2S_2O_3$ solution (6 mL) was added carefully, and the mixture was stirred for 10 min and then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by FCC on silica gel (hexanes/AcOEt 4:1) afforded pure **18a** (124 mg, 0.21 mmol, 57%) as a colorless solid.

Mp 100−102 °C. R_f 0.22 (hexanes/AcOEt 4:1). $[\alpha]_D^{21}$ −32.1 (*c* 0.56 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.21 (m, 20H), 4.71 (dd, $^3J_{H-H}$ = 10.5, 3.0 Hz, 1H), 4.70−4.49 (m, 8H), 4.32 (qd, $^3J_{H-H}$ = 6.5, 1.4 Hz, 1H), 4.11 (dd, $^3J_{H-H}$ = 3.5, 2.8 Hz, 1H), 3.79 (br t, $^3J_{H-H}$ ≈ 2.0 Hz, 1H), 3.74−3.71 (m, 1H), 3.67 (dd, $^2J_{H-H}$ = 9.5 Hz, $^3J_{H-H}$ = 5.5 Hz, 1H), 3.52 (br t, $^3J_{H-H}$ ≈ 1.5 Hz, 1H), 3.47 (dd, $^2J_{H-H}$ = 9.5 Hz, $^3J_{H-H}$ = 8.4 Hz, 1H), 3.35 (br d, $^3J_{H-H}$ = 10.5 Hz, 1H), 2.23 (br s, 1H), 1.23 (d, $^3J_{H-H}$ = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.5, 138.3, 138.2, 138.2, 128.6−127.7, 87.1, 86.2, 73.8, 73.5, 73.3, 72.8, 72.5, 71.8, 71.5, 70.1, 68.7, 67.3, 15.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{37}H_{41}NO_6$ + H^+, 596.3012 $[M + H]^+$; found, 596.3015.

(2*S*,3*R*,4*S*,4a*R*,5*R*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-[(benzyloxy)methyl]-2-methylhexahydro-2*H*-pyrrolo[1,2-*b*][1,2]oxazin-3-ol (18b). Analogously to the preparation of **18a**, **8b** (100 mg, 0.17 mmol) in THF (3.5 mL) and BH_3·THF (1 M in THF; 0.69 mL, 0.69 mmol) afforded after purification by FCC on silica gel (hexanes/AcOEt 4:1) pure **18b** (42 mg, 41%) as a colorless solid.

Mp 77−79 °C. R_f 0.17 (hexanes/AcOEt 4:1). $[\alpha]_D^{21}$ −20.1 (*c* 0.73 in $CHCl_3$); ^1H NMR ($CDCl_3$, 700 MHz): δ 7.38−7.24 (m, 20H), 4.77−4.75 (m, 1H), 4.65−4.57 (m, 4H), 4.52−4.50 (m, 1H), 4.47−4.42 (m, 2H), 4.04 (t, $^3J_{H-H}$ = 2.1 Hz, 1H), 3.96 (dd, $^3J_{H-H}$ = 4.9, 2.1 Hz, 1H), 3.86 (dd, $^2J_{H-H}$ = 9.1 Hz, $^3J_{H-H}$ = 3.5 Hz, 1H), 3.82 (dq, $^3J_{H-H}$ = 9.2, 6.2 Hz, 1H), 3.74 (ddd, $^3J_{H-H}$ = 8.4, 3.5, 1.6 Hz, 1H), 3.63 (dd, $^2J_{H-H}$ = 9.1 Hz, $^3J_{H-H}$ = 8.4 Hz, 1H), 3.53 (dd, $^3J_{H-H}$ = 9.1, 8.4 Hz, 1H), 3.36 (dd, $^3J_{H-H}$ = 8.4, 4.9 Hz, 1H), 3.29 (t, $^3J_{H-H}$ = 9.1 Hz, 1H), 2.08 (br s, 1H), 1.26 (d, $^3J_{H-H}$ = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 175 MHz): δ 138.3, 138.3, 137.8, 137.7, 128.6−127.6, 84.2, 84.1, 81.2, 76.6, 74.1, 73.8, 73.5, 71.6, 71.2, 68.1, 67.6, 65.0, 16.3. IR ($CDCl_3$): $\tilde{\nu}$ 3435, 3060, 3030, 2930, 2865, 1495, 1360, 1205, 1095, 1075, 1030 cm^{-1}. HRMS (ESI-TOF): *m*/*z* calcd for $C_{37}H_{41}NO_6$ + H^+, 596.3012 $[M + H]^+$; found, 596.2994.

(1′*S*,2′*S*,3′*R*)-1′-(Benzyloxy)-1′-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]butane-2′,3′-diol (19a). To a stirred solution of **18a** (634 mg, 1.06 mmol) in anhydr. and degassed THF (4 mL) a solution of SmI_2 (0.08 M in THF; 53.2 mL, 4.26 mmol) was added under an argon atmosphere. The mixture was stirred 3 h at room temperature. TLC control

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

(hexanes/AcOEt 1:1) showed the disappearance of the starting material (R_f 0.78) and the appearance of a new compound (R_f 0.41), then sat. aq. $NaHCO_3$ (20 mL) was added, and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by FCC on silica gel (hexanes/AcOEt 1:1) afforded pure **19a** (592 mg, 93%) as a yellowish pale oil.

R_f 0.41 (hexanes/AcOEt 1:1). $[\alpha]_D^{27}$ +3.7 (*c* 0.69 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.21 (m, 20H), 4.59−4.42 (m, 8H), 4.01 (t, $^3J_{H-H}$ = 3.4 Hz, 1H), 3.97−3.92 (m, 2H), 3.65 (dd, $^3J_{H-H}$ = 8.0, 3.6 Hz, 1H), 3.61−3.57 (m, 2H), 3.52 (d, $^3J_{H-H}$ = 4.8 Hz, 2H), 3.33 (dt, $^3J_{H-H}$ = 5.6, 4.8 Hz, 1H), 1.13 (d, $^3J_{H-H}$ = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.2−138.0, 128.5−127.8, 86.3, 85.7, 76.9, 75.5, 73.2, 72.5, 72.1, 71.6, 68.9, 67.0, 63.7, 61.9, 19.9. IR ($CDCl_3$): $\tilde{\nu}$ 3675, 3005, 2865, 1600, 1495, 1455, 1360, 1260 cm^{-1}. MS (ESI): *m/z*: 598.33 (100) $[M + H]^+$. Anal. calcd for $C_{37}H_{43}NO_6$: C, 74.35; H, 7.25; N, 2.34. Found: C, 74.27; H, 7.30; N, 2.58.

(1′*S*,2′*S*,3′*S*)-1′-(Benzyloxy)-1′-[(2*R*,3*R*,4*R*,5*R*)-3,4-bis-(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)butane-2′,3′-diol (19b). Analogously to the preparation of **19a**, **18b** (345 mg, 0.58 mmol) in THF (3 mL) and SmI_2 (0.07 M in THF; 33.3 mL, 2.33 mmol) afforded after purification by FCC on silica gel (hexanes/AcOEt 1:1) pure **19b** (335 mg, 96%) as a yellow pale oil.

R_f 0.22 (hexanes/AcOEt 1:1); $[\alpha]_D^{27}$ +1.9 (*c* 0.90 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35−7.22 (m, 20H), 4.71−4.68 (m, 1H), 4.54−4.41 (m, 7H), 4.00 (t, $^3J_{H-H}$ = 2.8 Hz, 1H), 3.96 (dd, $^3J_{H-H}$ = 5.2, 2.8 Hz, 1H), 3.93 (dq, $^3J_{H-H}$ = 8.4, 6.0 Hz, 1H), 3.80 (dd, $^3J_{H-H}$ = 9.2, 3.2 Hz, 1H), 3.66 (dd, $^3J_{H-H}$ = 9.2, 2.8 Hz, 1H), 3.61 (dd, $^3J_{H-H}$ = 8.4, 3.2 Hz, 1H), 3.53 (d, $^3J_{H-H}$ = 4.8 Hz, 2H), 3.34 (dt, $^3J_{H-H}$ = 5.6, 4.4 Hz, 1H), 1.30 (d, $^3J_{H-H}$ = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 138.0−137.2, 128.6−127.7, 86.5, 85.7, 76.7, 74.5, 73.2, 73.0, 72.1, 71.5, 69.0, 68.7, 63.9, 62.2, 20.5. IR ($CDCl_3$): $\tilde{\nu}$ 3480, 3010, 2865, 1605, 1495, 1455, 1365, 1225, 1090, 1070, 1030 cm^{-1}; MS (ESI): *m/z*: 620.42 (30) $[M + Na]^+$, 598.42 (100) $[M + H]^+$; Anal. calcd for $C_{37}H_{43}NO_6$: C, 74.35; H, 7.25; N, 2.34. Found: C, 74.66; H, 7.44; N, 2.39.

(1*S*,2*S*,3*S*,5*R*,6*R*,7*R*,7a*S*)-1,6,7-Tris(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1*H*-pyrrolizin-2-yl methanesulfonate (20a). To a stirred solution of **19a** (320 mg, 0.54 mmol) in anhydr. CH_2Cl_2 (18 mL), triethylamine (371 μL, 2.68 mmol) and MsCl (100 μL, 1.28 mmol) were added at room temperature under argon atmosphere. The solution was stirred 4 h at room temperature. TLC control (petrol ether/AcOEt 1:1) showed the disappearance of the starting material (R_f 0.41) and the appearance of a new product (R_f 0.91). Water (10 mL) was added, then the mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by FCC on silica gel (petrol ether/AcOEt 2:1) afforded pure **20a** (257 mg, 73%) as a colorless solid.

Mp 93−94 °C; R_f 0.68 (petrol ether/AcOEt 2:1); $[\alpha]_D^{26}$ +11.2 (*c* 0.81 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35−7.23 (m, 20H), 4.71 (t, $^3J_{H-H}$ = 6.0 Hz, 1H), 4.56−4.43 (m, 8H), 4.12 (t, $^3J_{H-H}$ = 5.8 Hz, 1H), 4.07 (t, $^3J_{H-H}$ = 3.4 Hz, 1H), 3.99 (dd, $^3J_{H-H}$ = 4.0, 3.6 Hz, 1H), 3.52 (m, 1H), 3.45 (d, $^3J_{H-H}$ = 6.8 Hz, 2H), 3.35−3.26 (m, 2H), 2.94 (s, 3H), 1.23 (d, $^3J_{H-H}$ = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.3, 138.0, 137.8, 137.4, 128.5−127.6, 89.3, 87.2, 86.1, 84.7, 73.3, 72.1, 71.9, 71.8, 71.8, 71.5, 68.3, 63.0, 38.6, 18.7. IR ($CDCl_3$): $\tilde{\nu}$ 3030, 2865, 1495, 1455, 1360, 1180, 1095, 970, 925, 920 cm^{-1}; MS (ESI): *m/z* 680.00 (100) $[M + Na]^+$, 658.25 (23) $[M + H]^+$. Anal. calcd for $C_{38}H_{43}NO_7S$: C, 69.38; H, 6.59; N, 2.13. Found: C, 69.09; H, 6.56; N, 2.34.

(1*S*,2*S*,3*R*,5*R*,6*R*,7*R*,7a*S*)-1,6,7-Tris(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1*H*-pyrrolizin-2-yl methanesulfonate (20b). Analogously to the preparation of **20a**, **19b** (325 mg, 0.54 mmol) in CH_2Cl_2 (18 mL), triethylamine (374 μL, 2.70 mmol), and MsCl (101 μL, 1.30 mmol) afforded after purification by FCC on silica gel (petrol ether/AcOEt 2:1) pure **20b** (284 mg, 80%) as a yellowish oil.

R_f 0.46 (petrol ether/AcOEt 2:1). $[\alpha]_D^{23}$ −3.53 (*c* 1.89 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.15 (m, 20H), 5.00 (dd, $^3J_{H-H}$ = 4.4, 1.2 Hz, 1H), 4.63−4.38 (m, 8H), 4.21 (dd, $^3J_{H-H}$ = 5.2, 1.2 Hz, 1H), 4.04 (t, $^3J_{H-H}$ = 2.6 Hz, 1H), 3.92 (t, $^3J_{H-H}$ = 2.8 Hz, 1H), 3.72−3.65 (m, 1H), 3.56−3.53 (m, 1H), 3.52−3.44 (m, 2H), 3.39−3.35 (m, 1H), 2.64 (s, 3H), 1.33 (d, $^3J_{H-H}$ = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.3, 138.1, 137.9, 137.6, 128.5−127.7, 88.0, 86.5, 85.5, 84.3, 74.8, 73.3, 72.6, 71.7, 71.5, 71.3, 62.5, 59.3, 38.2, 12.0. IR ($CDCl_3$): $\tilde{\nu}$ = 3065, 3025, 2910, 2865, 1725, 1490, 1450, 1360, 1335, 1245, 1170, 1090, 1020 cm^{-1}. MS (ESI): *m/z* 679.83 (88) $[M + Na]^+$, 658.00 (100) $[M + H]^+$. Anal. calcd for $C_{38}H_{43}NO_7S$: C, 69.38; H, 6.59; N, 2.13. Found: C, 69.34; H, 6.40; N, 1.88.

(2*R*,3*R*,4*S*,4a*S*,5*R*,6*R*,7*R*)-3,4,5,6-Tetrakis(benzyloxy)-7-(benzyloxymethyl)-2-methylhexahydro-2*H*-pyrrolo[1,2-*b*][1,2]-oxazine (21). A stirred solution of **18a** (40 mg, 0.07 mmol) in anhydr. THF (2 mL) was treated with NaH (60% in mineral oil; 2.70 mg, 0.07 mmol) at 0 °C under an argon atmosphere. After 15 min of stirring, tetra-*n*-butylammonium iodide (0.3 mg, 1 mol %) and benzyl bromide (11.5 mg, 0.07 mmol) were added. The mixture was warmed to room temperature and stirred for 16 h. A TLC control (hexanes/AcOEt 4:1) showed the appearance of a new product (R_f 0.30). Then water (2 mL) was added, and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by FCC on silica gel (hexanes/AcOEt 4:1) afforded pure **21** (18 mg, 39%) as a colorless oil.

R_f 0.30 (hexanes/AcOEt 4:1); $[\alpha]_D^{21}$ −23.6 (*c* 0.80 in $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.10 (m, 25H), 4.84 (dd, $^3J_{H-H}$ = 10.5, 5.0 Hz, 1H), 4.65−4.45 (m, 7H), 4.38−4.35 (m, 2H), 4.28−4.25 (m, 1H), 4.18 (qd, $^3J_{H-H}$ = 6.5, 1.5 Hz, 1H), 4.04 (dd, $^3J_{H-H}$ = 5.0, 3.0 Hz, 1H), 3.79 (t, $^3J_{H-H}$ = 2.0 Hz, 1H), 3.63−3.59 (m, 2H), 3.43 (dd, $^2J_{H-H}$ = 11.0 Hz, $^3J_{H-H}$ = 9.5 Hz, 1H), 3.27 (br d, $^3J_{H-H}$ = 10.5 Hz, 1H), 3.13 (br t, $^3J_{H-H}$ ≈ 2.5 Hz, 1H), 1.18 (d, $^3J_{H-H}$ = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.7, 138.5, 138.2, 138.1, 138.0, 128.5−127.5, 86.9, 85.3, 74.4, 73.4, 73.1, 72.7, 72.4, 72.2, 71.5, 71.3, 70.4, 69.8, 66.5, 15.8. IR ($CDCl_3$): $\tilde{\nu}$ 3030, 2930, 2865, 1740, 1495, 1455, 1365, 1230, 1215, 1095, 1075, 1030 cm^{-1}. HRMS (ESI-TOF): *m/z* calcd for $C_{44}H_{47}NO_6 + H^+$, 686.3482 $[M + H]^+$; found, 686.3504.

(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*R*)-1,2,6,7-Tetrakis(benzyloxy)-3-(benzyloxymethyl)-5-methylhexahydro-1*H*-pyrrolizine (22). To a stirred solution of **21** (80 mg, 0.12 mmol) in anhydr. and degassed THF (1 mL) a solution of SmI_2 (0.07 M in THF; 6.7 mL, 0.47 mmol) was added under an argon atmosphere. The mixture was stirred 2.5 h at room temperature. Then a sat. aq. $NaHCO_3$ (3 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Then, anhydr. CH_2Cl_2 (3 mL) was added to the residue (70 mg) and the stirred solution was treated with triethylamine (49 μL, 0.36 mmol) and MsCl (9 μL, 0.11 mmol) at room temperature under an argon atmosphere. The solution was stirred for 4 h at room temperature. A TLC control (petrol ether/AcOEt 1:1) showed the disappearance of the intermediate product (R_f 0.47) and the appearance of a new compound (R_f 0.90). Then water (2 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by FCC on silica gel (petrol ether/AcOEt 6:1) afforded pure **22** (57 mg, 73% over two steps) as a colorless solid.

Mp 66−67 °C. R_f 0.66 (petrol ether/AcOEt 6:1); $[\alpha]_D^{26}$ +1.2 (*c* 0.83 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.26 (m, 25H), 4.65−4.45 (m, 10H), 4.09−4.04 (m, 2H), 4.02 (t, $^3J_{H-H}$ = 5.2 Hz, 1H), 3.74 (t, $^3J_{H-H}$ = 6.4 Hz, 1H), 3.52−3.44 (m, 3H), 3.29−3.25 (m, 1H), 3.17 (m, 1H), 1.17 (d, $^3J_{H-H}$ = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.4−138.3, 128.3−127.5, 89.8, 87.5, 86.7, 86.5, 73.3, 72.4, 72.3, 72.2, 71.8, 71.6, 71.4, 68.1, 64.1, 19.6. IR ($CDCl_3$): $\tilde{\nu}$ 3025, 2925, 2870, 1490, 1455, 1365, 1265, 1200, 1095, 1065, 1025 cm^{-1}. MS (ESI): *m/z* 692.25 (16) $[M + Na]^+$, 670.42 (100) $[M + H]^+$. Anal. calcd for $C_{44}H_{47}NO_5$: C, 78.89; H, 7.07; N, 2.09. Found: C, 78.58; H, 7.07; N, 1.98.

(1*R*,2*R*,3*R*,5*S*,6*S*,7*S*,7a*R*)-1,2,6,7-Tetrahydroxy-3-hydroxymethyl-5-methylpyrrolizidine [Purported (+)-Hyacinthacine C$_5$] (7a). To a stirred solution of **22** (50 mg, 0.075 mmol) in

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

CH_3OH (4 mL), 10% Pd/C (36 mg) and aq. conc. HCl (2 drops) were added at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature under a hydrogen atmosphere for 48 h. Then the mixture was filtered through Celite and concentrated under reduced pressure. The free amine was obtained by passing the hydrochloride salt through a Dowex 50WX8 ion-exchange resin. Washing with MeOH (20 mL) and H_2O (20 mL) to remove products without an amino group and then elution with ammonia solution (2 N in MeOH; 40 mL) released the free base **7a**. Evaporation of the solvent under reduced pressure afforded pure **7a** (17 mg, quant.) as a colorless vitreous oil.

$[\alpha]_D^{23}$ +10.0 (*c* 0.60 in H_2O); natural hyacinthacine C_5 $[\alpha]_D$ +1.5 (*c* 0.22 in H_2O) [ref 7a]; $[\alpha]_D^{28}$ +8 (*c* 1 in H_2O) [ref 11]; ^1H NMR (D_2O, 400 MHz): δ 4.03 (t, $^3J_{H-H}$ = 6.4 Hz, 1H), 3.99 (t, $^3J_{H-H}$ = 7.2 Hz, 1H), 3.83 (t, $^3J_{H-H}$ = 6.8 Hz, 1H), 3.59−3.51 (m, 3H), 3.01−2.96 (m, 1H), 2.90−2.81 (m, 2H), 1.09 (d, $^3J_{H-H}$ = 5.6 Hz, 3H). ^{13}C NMR (D_2O, 100 MHz): δ 81.9, 79.3, 78.7, 78.4, 70.9, 70.8, 65.9, 61.7, 16.8. MS (ESI): *m*/*z* 242.08 (100) $[M + Na]^+$, 220.00 (63) $[M + H]^+$. Anal. calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.01; H, 7.85; N, 6.41.

(1*S*,2*S*,3*R*,5*R*,6*R*,7*R*,7a*R*)-1,6,7-Tris(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1*H*-pyrrolizin-2-ol (23). To a stirred solution of **20b** (108 mg, 0.16 mmol) in anhydr. THF (4 mL) $LiAlH_4$ (1 M in THF; 0.66 mL, 0.66 mmol) was added at 0 °C under a nitrogen atmosphere. The solution was stirred under reflux for 2 h. TLC control (petrol ether/AcOEt 1:1) showed the disappearance of the starting material (R_f 0.85) and the appearance of a new product (R_f 0.37). Then the mixture was cooled to room temperature, sat. aq. Na_2SO_4 (1 mL) was added, the mixture was filtered through Celite, and the solvent was removed under reduced pressure. Purification of the residue by FCC on silica gel (petrol ether/AcOEt 1:1) afforded pure **23** (70 mg, 74%) as a colorless oil.

R_f 0.37 (petrol ether/AcOEt 1:1). $[\alpha]_D^{21}$ −16.7 (*c* 0.70 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35−7.19 (m, 20H), 4.60−4.40 (m, 8H), 4.11−4.09 (m, 1H), 4.01−4.00 (m, 1H), 3.88 (d, $^3J_{H-H}$ = 3.2 Hz, 1H), 3.80 (d, $^3J_{H-H}$ = 3.2 Hz, 1H), 3.76 (t, $^3J_{H-H}$ = 7.8 Hz, 1H), 3.65−3.62 (m, 1H), 3.50 (qd, $^3J_{H-H}$ = 7.2, 3.6 Hz, 1H), 3.41 (d, $^3J_{H-H}$ = 8.0 Hz, 2H), 1.31 (d, $^3J_{H-H}$ = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 138.1, 137.8, 136.6, 128.6−127.5, 89.4, 85.7, 85.2, 79.3, 75.8, 73.1, 72.8, 71.8, 71.5, 71.2, 63.1, 60.7, 11.5. IR ($CDCl_3$): $\tilde{\nu}$ 3410, 3055, 3030, 2925, 2855, 1725, 1495, 1450, 1360, 1250, 1110, 1075, 1025 cm^{-1}. MS (ESI): *m*/*z* 580.33 (100) $[M + H]^+$. Anal. calcd for $C_{37}H_{41}NO_5$: C, 76.66; H, 7.13; N, 2.42. Found: C, 76.74; H, 7.46; N, 2.44.

(1*R*,2*R*,3*R*,5*R*,6*S*,7*S*,7a*R*)-1,2,6,7-Tetrahydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(+)-5-*epi*-Hyacinthacine C_5] (7b). To a stirred solution of **23** (54 mg, 0.093 mmol) in CH_3OH (4 mL), 10% Pd/C (33 mg) and conc. HCl (3 drops) were added at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature under a hydrogen atmosphere for 48 h. Then the mixture was filtered through Celite and concentrated under reduced pressure. The free amine was obtained by passing the hydrochloride salt through a Dowex 50WX8 ion-exchange resin. Washing with MeOH (20 mL) and H_2O (20 mL) to remove products without an amino group and then elution with an ammonia solution (2 N in MeOH; 40 mL) released the free base **7b**. Evaporation of the solvent under reduced pressure afforded pure **7b** (14 mg, 69%) as a colorless vitreous oil.

$[\alpha]_D^{21}$ +0.75 (*c* 0.48 in H_2O). ^1H NMR (D_2O, 400 MHz): δ 4.15 (t, $^3J_{H-H}$ = 2.4 Hz, 1H), 3.99 (t, $^3J_{H-H}$ = 8.6 Hz, 1H), 3.95 (t, $^3J_{H-H}$ = 3.0 Hz, 1H), 3.80 (dd, $^3J_{H-H}$ = 9.6, 8.4 Hz, 1H), 3.64−3.56 (m, 3H), 3.41 (dt, $^3J_{H-H}$ = 9.2, 3.6 Hz, 1H), 3.28 (dd, $^3J_{H-H}$ = 8.4, 1.0 Hz, 1H), 1.21 (d, $^3J_{H-H}$ = 6.8 Hz, 3H). ^{13}C NMR (D_2O, 100 MHz): δ 79.1, 76.8, 76.7, 75.3, 74.1, 63.4, 60.8, 59.1, 9.5. MS (ESI): *m*/*z* 242.00 (67) $[M + Na]^+$, 220.08 (100) $[M + H]^+$. Anal. calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.03; H, 7.59; N, 6.60.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00667.

Copies of ^1H and ^{13}C NMR spectra of all new and final compounds; 1D NOESY spectra for compounds **6**, **20a**, and **20b**; Comparison of spectroscopic data of synthetic **7a** and **7b** and **6** with data of isolated hyacinthacine C_5 (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Luise Schefzig (Berlin) for her help to prepare starting materials. The European ERASMUS program is gratefully acknowledged for providing a mobility grant to T.P. The work in Berlin was supported by the Deutsche Forschungsgemeinschaft and by Bayer HealthCare. The work in Firenze has been supported by MIUR Italy (PRIN 2010−2011, 2010L9SH3K 006).

■ REFERENCES

(1) Compain, P.; Martin, O. R. *Iminosugars: from Synthesis to Therapeutic Applications*; Wiley VCH: New York, 2007.

(2) (a) Martella, D.; D'Adamio, G.; Parmeggiani, C.; Cardona, F.; Moreno-Clavijo, E.; Robina, I.; Goti, A. *Eur. J. Org. Chem.* **2016**, 1588−1598. (b) Matassini, C.; Mirabella, S.; Ferhati, X.; Faggi, C.; Robina, I.; Goti, A.; Moreno-Clavijo, E.; Moreno-Vargas, A. J.; Cardona, F. *Eur. J. Org. Chem.* **2014**, 5419−5432. (c) Martella, D.; Cardona, F.; Parmeggiani, C.; Franco, F.; Tamayo, J. A.; Robina, I.; Moreno-Clavijo, E.; Moreno-Vargas, A. J.; Goti, A. *Eur. J. Org. Chem.* **2013**, 4047−4056. (d) D'Adamio, G.; Goti, A.; Parmeggiani, C.; Moreno-Clavijo, E.; Robina, I.; Cardona, F. *Eur. J. Org. Chem.* **2011**, 7155−7162. (e) Bonaccini, C.; Chioccioli, M.; Parmeggiani, C.; Cardona, F.; Lo Re, D.; Soldaini, G.; Vogel, P.; Bello, C.; Goti, A.; Gratteri, P. *Eur. J. Org. Chem.* **2010**, 5574−5585. (f) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. - Eur. J.* **2009**, *15*, 7808−7821 and references cited therein.

(3) Reviews: (a) Zimmer, R.; Reissig, H.-U. *Chem. Soc. Rev.* **2014**, *43*, 2888−2903. (b) Bouché, L.; Reissig, H.-U. *Pure Appl. Chem.* **2012**, *84*, 23−36. (c) Lechel, T.; Reissig, H.-U. *Pure Appl. Chem.* **2010**, *82*, 1835−1844. (d) Pfrengle, F.; Reissig, H.-U. *Chem. Soc. Rev.* **2010**, *39*, 549−557. (e) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45−56.

(4) (a) Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron* **2009**, *65*, 93−100. (b) Gurjar, M. K.; Borhade, R. G.; Puranik, V. G.; Ramana, C. V. *Tetrahedron Lett.* **2006**, *47*, 6979−6981. (c) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315−2318. (d) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485−504.

(5) Parmeggiani, C.; Cardona, F.; Giusti, L.; Reissig, H.-U.; Goti, A. *Chem. - Eur. J.* **2013**, *19*, 10595−10604.

(6) Reviews: (a) Desvergnes, V.; Landais, Y. *Stud. Nat. Prod. Chem.* **2014**, *42*, 373−419. (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265−295. (c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680.

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844

(7) (a) Kato, A.; Kato, N.; Adachi, I.; Hollinshead, J.; Fleet, G. W. J.; Kuriyama, C.; Ikeda, K.; Asano, N.; Nash, R. J. *J. Nat. Prod.* **2007**, *70*, 993−997. (b) Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 1875−1881. (c) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95−103.
(8) Reviews: (a) Ritthiwigrom, T.; Au, C. W. G.; Pyne, S. G. *Curr. Org. Synth.* **2012**, *9*, 583−612. (b) Stocker, B. L.; Dangerfield, E. D.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615−1637.
(9) (a) Hyacinthacine B_3, B_4, B_5, B_7: Savaspun, K.; Au, C. W.-G.; Pyne, S.-G. *J. Org. Chem.* **2014**, *79*, 4569−4581. (b) Hyacinthacine B_3, B_7: Au, C. W. G.; Nash, R. J.; Pyne, S. G. *Chem. Commun.* **2010**, *46*, 713−715. (c) Hyacinthacine C_2, C_3: Sengoku, T.; Satoh, Y.; Takahashi, M.; Yoda, H. *Tetrahedron Lett.* **2009**, *50*, 4937−4940. (d) Hyacinthacine B_1, B_2: Sengoku, T.; Satoh, Y.; Oshima, M.; Takahashi, M.; Yoda, H. *Tetrahedron* **2008**, *64*, 8052−8058.
(10) (−)-Hyacinthacine C_5: Zhang, W.; Sato, K.; Kato, A.; Jia, Y.-M.; Hu, X.-G.; Wilson, F. X.; van Well, R.; Horne, G.; Fleet, G. W. J.; Nash, R. J.; Yu, C.-Y. *Org. Lett.* **2011**, *13*, 4414−4417.
(11) (+)-Hyacinthacine C_5: Tamayo, J. A.; Franco, F.; Sanchez-Cantalejo, F. *Eur. J. Org. Chem.* **2011**, 7182−7188.
(12) See also: (a) Pulz, R.; Cicchi, S.; Brandi, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153−1156. (b) Delso, I.; Marca, E.; Mannucci, V.; Tejero, T.; Goti, A.; Merino, P. *Chem. - Eur. J.* **2010**, *16*, 9910−9919. (c) Delso, I.; Tejero, T.; Goti, A.; Merino, P. *J. Org. Chem.* **2011**, *76*, 4139−4143. (d) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776−782.
(13) Deagostino, A.; Prandi, C.; Toppino, A.; Venturello, P. *Tetrahedron* **2008**, *64*, 10344−10349.
(14) (a) Hausherr, A.; Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2001**, 1377−1385. (b) Hausherr, A. *Dissertation*; Freie Universität Berlin: 2001.
(15) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003−1019.
(16) Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, *16*, 501−502.

DOI: 10.1021/acs.joc.7b00667
J. Org. Chem. 2017, 82, 5835−5844