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Total synthesis of the proposed structures of hyacinthacines C_2, C_3, and their C5-epimers

Tetsuya Sengoku, Yasutaka Satoh, Masaki Takahashi, Hidemi Yoda *

Department of Materials Science, Faculty of Engineering, Shizuoka University, Johoku 3-5-1, Naka-ku, Hamamatsu 432-8561, Japan

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ABSTRACT

Synthesis and structural confirmation of highly oxygenated pyrrolizidine alkaloids, hyacinthacines C_2 [(1*S*,2*R*,3*R*,5*R*,7*S*,7*aR*)-3,5-hydroxymethyl-1,2,7-trihydroxypyrrolizidine], C_3[(1*S*,2*R*,3*R*,5*S*,7*R*,7*aR*)-3,5-hydroxymethyl-1,2,7-trihydroxypyrrolizidine], and their C5-epimers were achieved on the basis of the highly divergent method employing (*S*)-(−)-2-pyrrolidone-5-carboxylic acid as the starting material.

Hyacinthacines are a new series of polyhydroxylated pyrrolizidine alkaloids, which were originally isolated from *Hyacinthoides non-scripta* and *Scilla campanulata* as inhibitors of several glycosidases (Fig. 1).[1] Their structure and potent bioactivities have attracted a great deal of interest to synthetic chemists, and the total syntheses of hyacinthacines A and B have been achieved for this reason.[2] Recently, Asano and co-workers have isolated new hyacinthacines C_2 (**1a**) and C_3 (**2a**) from *Scilla socialis*, which inhibit bacterial β-glucosidase as well as bovine liver β-galactosidase.[3] Both compounds consist of the highly oxygenated pyrrolizidine ring, whose oxygenated patterns have never been found in the other series of hyacinthacines. Specifically, no reports have appeared previously describing synthesis of these compounds. In the present publication, we report the first total synthesis and structural confirmation of hyacinthacines C_2, C_3, and their C5-epimers, respectively, as an initial attempt to reveal the relationship between their structures and biological activities.

Our synthetic strategy is outlined in Figure 2. We envisaged that the pyrrolizidine ring system of hyacinthacines C_2 (**1a**), C_3 (**2a**), and their C5-epimers (**1b**, **2b**) could be constructed from the acyclic polyols **3** and **4** through intramolecular cyclization. On the other hand, those would be derived from aldehyde **5** via allylation followed by dihydroxylation of the terminal olefin moiety. The key intermediate **5** could be synthesized from N-protected amide **6**, which can be prepared from commercially available (*S*)-(−)-2-pyrrolidone-5-carboxylic acid according to the procedure reported in the previous publications.[2m,4]

Synthesis of homoallyl alcohols **9**, precursors of **3** and **4**, are shown in Scheme 1. A new chiral center in **7** could be diastereoselectively generated through three steps which include Grignard reaction of lactam **6**, 1,2-reduction of unsaturated ketone, and cyclization of pyrrolidine ring. In these processes, the 1,2-reduction under our developed conditions[2m] gave the corresponding desired allyl alcohol with the predominant diastereomeric ratio (83:17) in totally 81% yield,[5] which could be separated by silica gel column chromatography. In fact, spontaneous cyclization occurred efficiently by the mesylation, leading to the formation of the pyrrolidine ring due to the electrophilic nature of the allylic position. After the replacement of *N*-Boc to *N*-Cbz groups through three steps involving one-pot procedure for deprotection of TBDPS and Boc groups, oxidative cleavage of the olefin moiety of **8** with OsO_4 and $NaIO_4$ gave the aldehyde **5** without epimerization. Unfortunately, the allylation of **5** with allyl magnesium bromide resulted in inseparable mixture of allylated products **9** together with undesired bicyclic products **10** (Fig. 3). Alternatively, Reformatsky-type reaction in saturated NH_4Cl aqueous solution[2n,6] improved the yield of **9** (92%) with a moderate diastereoselectivity (**9a**:**9b** = 79:21).

As shown in Figure 3, the stereochemistry of the newly formed chiral center was determined on the basis of NOE experiments on the bicyclic derivatives **10a** and **10b** which were independently prepared from **9a** and **9b**, respectively, through treatment with NaH (NaH, THF, 92%: **10a** from **9a**, 93%: **10b** from **9b**). Thus, it has been apparent that we obtained the key intermediates **9** for the synthesis of hyacinthacines C_2 and C_3.

With two homoallyl alcohols **9a** and **9b** in hand, we next turned to the construction of pyrrolizidine ring systems (Scheme 2). After protection of the hydroxyl group on **9a** with TBSCl, dihydroxylation

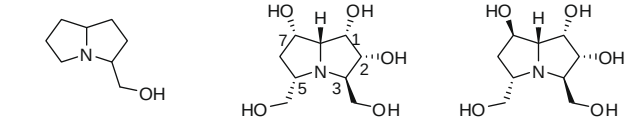

Figure 1. The structures of hyacinthacines.

* Corresponding author. Tel./fax: +81 53 478 1150.
E-mail address: tchyoda@ipc.shizuoka.ac.jp (H. Yoda).

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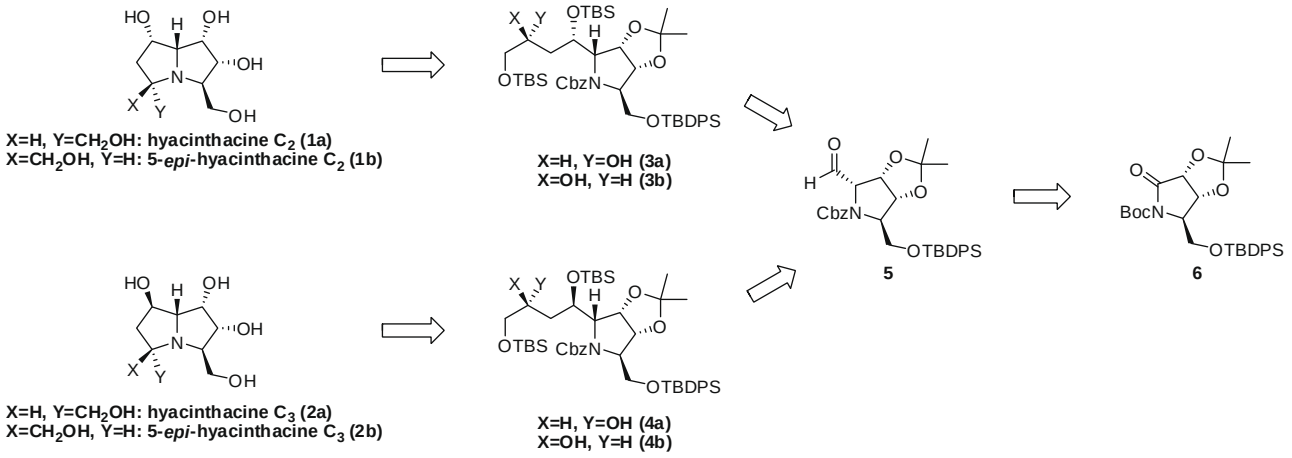
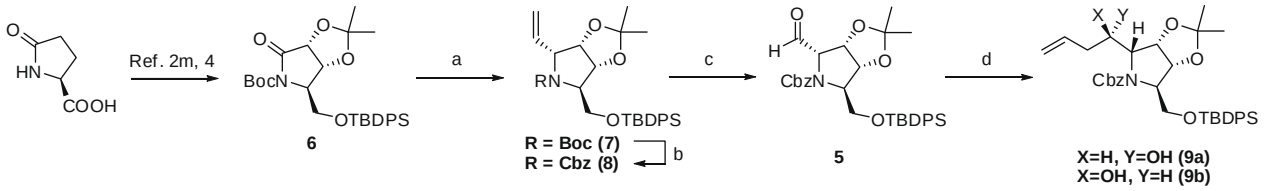


Figure 2. Retrosynthesis of hyacinthacines C_2 (**1a**) and C_3 (**2a**)



Scheme 1. Reagents and conditions: (a) (i) vinylmagnesium bromide, THF, −78 °C, 83%; (ii) $NaBH_4$, $CeCl_3$, MeOH, −20 °C, 67%; (iii) MsCl, Et_3N, 0 °C, 90%; (b) (i) TBAF, THF, 0 °C, then NaH, rt, 98%; (ii) CbzCl, $NaHCO_3$, MeOH, 97%; (iii) TBDPSCl, imidazole, DMF, 97%; (c) (i) OsO_4, aq NMO, acetone/*t*-BuOH, 97%; (ii) $NaIO_4$, THF/H_2O = 2/1, 99%; (d) Zn, 3-bromopropene, THF/satd NH_4Cl aq = 1/5, rt, 73% (**9a**), 19% (**9b**).

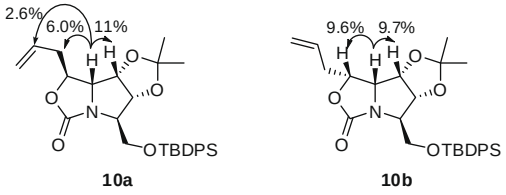


Figure 3. Observed NOE (arrow) of **10a** and **10b**.

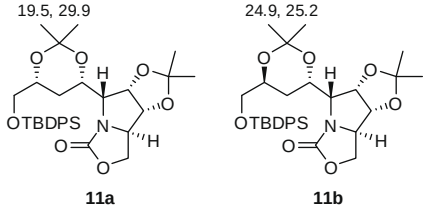


Figure 4. ^{13}C NMR chemical shifts of **11** (75 MHz, δ in ppm).

of the terminal olefin moiety and subsequent TBS protection of newly introduced primary hydroxyl group afforded separable diastereomers **3a** and **3b** in a ratio of approximately 1:1 in 92% three-step yield.

To consider the C5 stereochemistry of the products, we decided to convert these compounds into the corresponding acetonides **11** (Fig. 4) through deprotection of the silyl groups in **3a** and **3b** accompanied with simultaneous formation of 5-membered ring, selective protection of the generated primary alcohols with TBDPSCl, and protection of the remaining 1,3-diols as acetonides (TBAF, THF; TBDPSCl, DMAP, Et_3N, CH_2Cl_2;

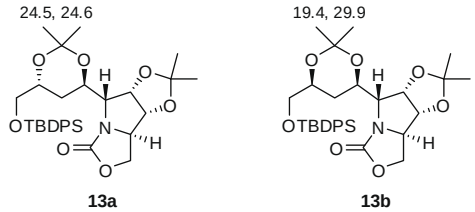
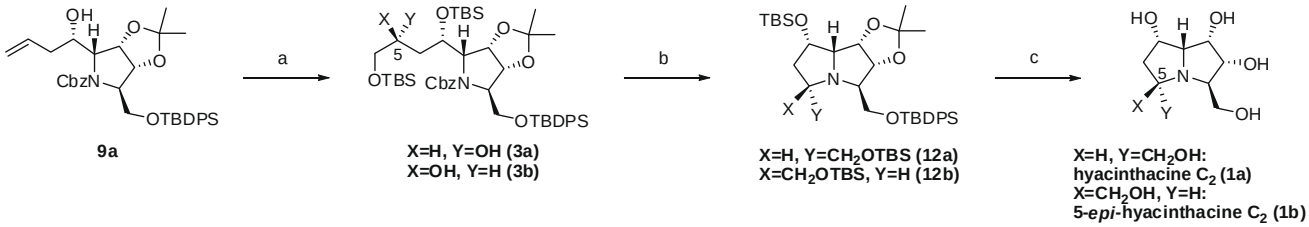
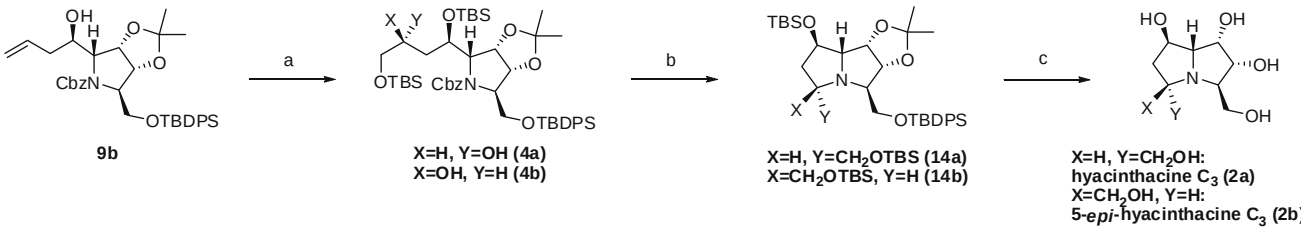


Figure 5. ^{13}C NMR chemical shifts of **13** (75 MHz, δ in ppm).



Scheme 2. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, 99%; (ii) OsO_4, aq NMO, acetone/*t*-BuOH, 98%; (iii) TBSCl, Et_3N, CH_2Cl_2, 46% (**3a**), 49% (**3b**); (b) (i) MsCl, Et_3N, CH_2Cl_2, 74% (from **3a**), 71% (from **3b**); (ii) H_2, 5% Pd/C, EtOH, 89% (**12a**), 70% (**12b**); (c) (i) TBAF, THF; (ii) TFA/H_2O = 1/2, 73% (**1a**), 84% (**1b**) (two steps).



Scheme 3. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, 97%; (ii) OsO_4, aq NMO, acetone/*t*-BuOH, 98%; (iii) TBSCl, Et_3N, CH_2Cl_2, 48% (**4a**), 46% (**4b**); (b) (i) MsCl, Et_3N, CH_2Cl_2, 82% (from **4a**), 75% (from **4b**); (ii) H_2, 5% Pd/C, EtOH, 91% (**14a**), 90% (**14b**); (c) (i) TBAF, THF; (ii) TFA/H_2O = 1/2, 72% (**2a**), 71% (**2b**) (two steps).

PPTS, 2,2-dimethoxypropane, acetone, 15%: **11a** from **3a**, 36%: **11b** from **3b**). As reported previously,[7] the two signals of **11a** at δ_c 19.5 and 29.9 ppm in the ^{13}C NMR spectrum are readily recognized as *gem*-dimethyl groups in a chair form of 6-membered ring, while those of **11b** at δ_c 24.9 and 25.4 ppm are recognized as *gem*-dimethyl groups in a twist boat conformation. Thus, the stereochemistry of 1,3-diols at the two chiral centers is assigned as *syn*-**11a** and *anti*-**11b**, respectively.

In the next step, the hydroxyl groups of **3a** and **3b** at C5 were converted to the corresponding mesylate and used for cyclization process which proceeded via deprotection of the Cbz groups, giving rise to **12a** and **12b**, respectively. Finally, desilylation of **12** with TBAF and acidic hydrolysis of the acetonide protecting group with TFA yielded hyacinthacine C_2 (**1a**)[8] and its C5-epimer (**1b**),[9] respectively, which were purified by ion-exchange column chromatography. It should be noted that the spectroscopic data of the synthetic **1a** were fully consistent with those of the natural sample.[3,8] Moreover, optical rotation of the synthetic **1a** ($[\alpha]_D^{25}$ +12.8, H_2O, *c* 0.2) also completely agreed with that of the natural sample ($[\alpha]_D$ +12.9, H_2O, *c* 0.2), confirming the absolute configuration as drawn in Figure 1.

Having elucidated the synthetic pathway to hyacinthacine C_2, our next objective was to synthesize hyacinthacine C_3 (**2a**) with a similar synthetic methodology described above (Scheme 3). Starting from **9b**, pyrrolizidine precursors **4** which serve as complementary stereoisomers of **3**, were produced in three steps with excellent yields. The stereochemical assignments of **4a** and **4b** were secured by comparable analysis of the ^{13}C NMR chemical shifts for *gem*-dimethyl carbons of their acetonide derivatives **13a** and **13b** (Fig. 5), respectively, as discussed above (39%: **13a** from **4a**, 17%: **13b** from **4b**). Each of the isomers of **4** underwent efficient cyclization to two pyrrolizidine stereoisomers **14a** and **14b** via mesylation/hydrogenolysis sequences. Complete removal of the all protecting groups in **14a** and **14b** afforded hyacinthacine C_3 (**2a**)[10] and its C5-epimer (**2b**),[11] respectively. Unfortunately, the NMR spectra of these synthetic samples do not match with those of the reported[3,10] and hence the revision in the stereochemical assignment of the natural isolate is required, which will be the subject of further work.

In summary, the total synthesis of the hyacinthacines C_2 and C_3 has been achieved along with the derivation of the two C5-epimers, employing the divergent methods for generating the well-defined stereocenters of the synthetic intermediates from (*S*)-(−)-2-pyrrolidone-5-carboxylic acid. Comparison of the characterization data for the synthetic sample of hyacinthacine C_3 with the corresponding natural product has given some indication of the inconsistency in the product stereochemistry. As far as we are aware of, this is the first report on synthetic elaboration of the hyacinthacines C_2 and C_3 as well as their C5-epimers.

Acknowledgments

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7. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
8. Synthetic hyacinthacine C_2 **1a**: $[\alpha]_D^{25}$ +12.8 (*c* 0.2, H_2O) {lit. $[\alpha]_D$ +12.9 (*c* 0.22, H_2O)}; IR (NaCl) 3312 (O–H), 2926 (C–H), 1043 (C–O) cm^{-1}; ^1H NMR (D_2O) δ 4.40 (m, 1H, C*H*), 4.17 (t, *J* = 4.3 Hz, 1H, C*H*), 3.85 (dd, *J* = 7.8, 4.3 Hz, 1H, C*H*), 3.85 (dd, *J* = 11.7, 6.9 Hz, 1H, CH_2), 3.66 (dd, *J* = 11.7, 4.8 Hz, 1H, CH_2), 3.58 (dd, *J* = 12.0, 5.1, Hz, 1H, CH_2), 3.54 (dd, *J* = 12.0, 5.7 Hz, 1H, CH_2), 3.42 (*J* = 6.9, 4.5 Hz, 1H, C*H*), 3.35 (m, 1H, C*H*), 3.25 (m, 1H, C*H*), 2.04 (m, 1H, CH_2), 1.78 (m, 1H, CH_2); ^{13}C NMR (D_2O) δ 78.2 (CH), 75.4 (CH), 75.1 (CH), 70.7 (CH), 66.3 (CH_2), 66.2 (CH), 64.3 (CH_2), 64.2 (CH), 40.8 (CH_2). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.12; H, 7.88; N, 6.64.
9. *Synthetic 5-epi-hyacinthacine* C_2 **1b**: $[\alpha]_D^{25}$ +13.7 (*c* 0.2, H_2O); IR (NaCl) 3312 (O–H), 2924 (C–H), 1030 (C–O) cm^{-1}; ^1H NMR (D_2O) δ 4.53 (m, 1H, C*H*), 4.36 (t, *J* = 5.1 Hz, 1H, C*H*), 3.91 (dd, *J* = 7.4, 5.1 Hz, 1H, C*H*), 3.72 (dd, *J* = 11.4, 4.4 Hz, 1H, CH_2), 3.59 (dd, *J* = 12.2, 6.4 Hz, 1H, CH_2), 3.56–3.53 (m, 2H, CH_2 and C*H*), 3.52 (dd, *J* = 11.4, 5.3 Hz, 1H, CH_2), 3.39 (m, 1H, C*H*), 3.10 (m, 1H, C*H*), 2.15 (m, 1H, CH_2), 1.76 (m, 1H, CH_2); ^{13}C NMR (D_2O) δ 74.9 (CH), 73.2 (CH), 72.9 (CH), 72.7 (CH), 69.8 (CH), 68.2 (CH), 66.0 (CH_2), 63.7 (CH_2), 39.1 (CH_2). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.18; H, 7.83; N, 6.68.
10. *Synthetic hyacinthacine* C_3 **2a**: $[\alpha]_D^{22}$ +8.8 (*c* 0.3, H_2O); IR (NaCl) 3312 (O–H), 2928 (C–H), 1038 (C–O) cm^{-1}; ^1H NMR (D_2O) δ 4.58 (m, 1H, C*H*), 4.16 (t, *J* = 4.2 Hz, 1H, C*H*), 3.98 (dd, *J* = 7.8, 4.2 Hz, 1H, C*H*), 3.83–3.71 (m, 3H, $3CH_2$), 3.62 (dd, *J* = 11.2, 5.8 Hz, 1H, CH_2), 3.49 (m, 1H, C*H*), 3.38 (t, *J* = 4.2 Hz, 1H, C*H*), 3.20 (dt, *J* = 7.8, 5.1 Hz, 1H, C*H*), 2.13 (m, 1H, CH_2), 1.92 (m, 1H, CH_2); ^{13}C NMR (D_2O) δ 75.5 (CH), 75.0 (CH), 70.9 (CH), 69.2 (CH), 63.0 (CH_2), 62.5 (CH), 62.5 (CH), 61.4 (CH_2), 38.3 (CH_2). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.15; H, 7.87; N, 6.35.*Natural hyacinthacine* C_3 (Ref. 3): ^1H NMR (D_2O) δ 4.56 (ddd, *J* = 4.4, 2.5, 2.5 Hz, 1H, C*H*), 4.32 (t, *J* = 4.4 Hz, 1H, C*H*), 4.04 (dd, *J* = 9.5, 4.4 Hz, 1H, C*H*), 3.85 (dd, *J* = 12.6, 3.2 Hz, 1H, CH_2), 3.85 (overlapped, 1H, C*H*), 3.84 (overlapped, 2H, CH_2, C*H*), 3.79 (dd, *J* = 12.0, 6.2 Hz, 1H, CH_2), 3.69 (dd,

J = 12.6, 3.2 Hz, 1H, CH_2), 3.50 (m, 1H, CH), 2.07 (m, 1H, CH_2), 1.93 (m, 1H, CH_2); ^{13}C NMR (D_2O) δ 79.9 (*C*H), 75.4 (*C*H), 72.2 (*C*H), 71.7 (*C*H), 67.5 (*C*H), 65.5 (*C*H), 61.8 (*C*H$_2$), 61.7 (*C*H$_2$), 39.4 (*C*H$_2$).

11. *Synthetic 5-epi-hyacinthacine C$_3$* **2b**: $[\alpha]_D^{22}$ +14.8 (*c* 0.3, H_2O); IR (NaCl) 3312 (O–H), 2928 (C–H), 1038 (C–O) cm^{-1}; ^{1}H NMR (D_2O) δ 4.46 (m, 1H, CH), 4.00 (t, J = 4.2 Hz, 1H, CH), 3.81 (dd, J = 9.0, 4.2 Hz, 1H, CH), 3.62 (dd, J = 11.6, 3.9 Hz, 1H, CH_2), 3.52 (dd, J = 11.2, 6.4 Hz, 1H, CH_2), 3.49 (dd, J = 11.6, 6.2 Hz, 1H, CH_2), 3.40 (dd, J = 11.2, 5.3 Hz, 1H, CH_2), 3.23 (t, J = 4.2 Hz, CH), 2.99 (m, 1H, CH), 2.76 (ddd, J = 9.0, 6.2, 3.9 Hz, 1H, CH), 2.25 (m, 1H, CH_2), 1.50 (m, 1H, CH_2); ^{13}C NMR (D_2O) δ 75.8 (*C*H), 74.4 (*C*H), 71.7 (*C*H), 70.4 (*C*H), 70.2 (*C*H), 69.0 (*C*H), 65.9 (*C*H$_2$), 63.9 (*C*H$_2$), 39.0 (*C*H$_2$). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.49; H, 7.94; N, 6.46.