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Total synthesis of the proposed structures of hyacinthacines C₂, C₃, and their C5-epimers

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ABSTRACT

Synthesis and structural confirmation of highly oxygenated pyrrolizidine alkaloids, hyacinthacines C_2 [(1*S*,2*R*,3*R*,5*S*,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. © 2009 Elsevier Ltd. All rights reserved.

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 C2, C3, 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

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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 OsO₄ and NaIO₄ 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 NH₄Cl 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 TBSCI, dihydroxylation





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Scheme 1. Reagents and conditions: (a) (i) vinylmagnesium bromide, THF, -78 °C, 83%; (ii) NaBH₄, CeCl₃, MeOH, -20 °C, 67%; (iii) MsCl, Et₃N, 0 °C, 90%; (b) (i) TBAF, THF, 0 °C, then NaH, rt, 98%; (ii) CbzCl, NaHCO₃, MeOH, 97%; (iii) TBDPSCl, imidazole, DMF, 97%; (c) (i) OsO₄, aq NMO, acetone/*t*-BuOH, 97%; (ii) NalO₄, THF/H₂O = 2/1, 99%; (d) Zn, 3-bromopropene, THF/satd NH₄Cl aq = 1/5, rt, 73% (**9a**), 19% (**9b**).



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

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% threestep 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 TBDPSCI, and protection of the remaining 1,3-diols as acetonides (TBAF, THF; TBDPSCI, DMAP, Et₃N, CH₂Cl₂;



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



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



Scheme 2. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, 99%; (ii) OsO4, aq NMO, acetone/t-BuOH, 98%; (iii) TBSCl, Et₃N, CH₂Cl₂, 46% (3a), 49% (3b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 74% (from 3a), 71% (from 3b); (ii) H₂, 5% Pd/C, EtOH, 89% (12a), 70% (12b); (c) (i) TBAF, THF; (ii) TFA/H₂O = 1/2, 73% (1a), 84% (1b) (two steps).

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Scheme 3. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, 97%; (ii) OsO4, aq NMO, acetone/t-BuOH, 98%; (iii) TBSCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4a), 46% (4b); (b) (i) MsCl, Et₃N, CH₂Cl₂, 48% (4b); (b) (i) MsCl, Et₃N, CH₂, 48% (4b); (b) (i) MsCl, Et₃N, CH₂, 48% (4b); (b) (i) MsCl, Et₃ CH₂Cl₂, 82% (from 4a), 75% (from 4b); (ii) H₂, 5% Pd/C, EtOH, 91% (14a), 90% (14b); (c) (i) TBAF, THF; (ii) TFA/H₂O = 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 ¹³C 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 mesvlate 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, H₂O, *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 ¹³C 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 C₂ and C₃ has been achieved along with the derivation of the two C5epimers, 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 C₃ 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 C5epimers.

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- Rychnovsky, S. D.; Skalitzky, D. J. Tetrahedron Lett. **1990**, 31, 945. Synthetic hyacinthacine C₂ **1a**: $[\alpha]_D^{25}$ +12.8 (c 0.2, H₂O) {lit. $[\alpha]_D$ +12.9 (c 0.22, H₂O)}; IR (NaCl) 3312 (O–H), 2926 (C–H), 1043 (C–O) cm⁻¹; ¹H NMR (D₂O) δ 8 4.40 (m, 1H, CH), 4.17 (t, J = 4.3 Hz, 1H, CH), 3.85 (dd, J = 7.8, 4.3 Hz, 1H, CH), 3.85 (dd, J = 11.7, 6.9 Hz, 1H, CH₂), 3.66 (dd, J = 11.7, 4.8 Hz, 1H, CH₂), 3.58 (dd, $I = 12.0, 5.1, Hz, 1H, CH_2$, 3.54 (dd, $I = 12.0, 5.7 Hz, 1H, CH_2$), 3.42 (I = 6.9, 4.5 Hz, 1H, CH), 3.35 (m, 1H, CH), 3.25 (m, 1H, CH), 2.04 (m, 1H, CH₂), 1.78 (m, 1H, CH₂); ¹³C NMR (D₂O) δ 78.2 (CH), 75.4 (CH), 75.1 (CH), 70.7 (CH), 66.3 (CH₂), 66.2 (CH), 64.3 (CH₂), 64.2 (CH), 40.8 (CH₂). Anal. Calcd for C₉H₁₇NO₅: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.12; H, 7.88; N, 6.64.
- Synthetic 5-epi-hyacinthacine (2 + 10, 12) + 13.7 (c 0.2, H₂O); IR (NaCl) 3312 (O-H), 2924 (C-H), 1030 (C-O) cm⁻¹; ¹H NMR (D₂O) δ 4.53 (m, 1H, CH), 4.36 (t, J = 5.1 Hz, 1H, CH), 3.91 (dd, J = 7.4, 5.1 Hz, 1H, CH), 3.72 (dd, J = 11.4, 4.4 Hz, 11.4 Hz, 11 1H, CH₂), 3.59 (dd, J = 12.2, 6.4 Hz, 1H, CH₂), 3.56–3.53 (m, 2H, CH₂ and CH), 3.52 (dd, J = 11.4, 5.3 Hz, 1H, CH₂), 3.39 (m, 1H, CH), 3.10 (m, 1H, CH), 2.15 (m, 1H, CH₂), 1.76 (m, 1H, CH₂); ¹³C NMR (D₂O) δ 74.9 (CH), 73.2 (CH), 72.9 (CH), 72.7 (CH), 69.8 (CH), 68.2 (CH), 66.0 (CH₂), 63.7 (CH₂), 39.1 (CH₂). Anal. Calcd for
- $^{12.7}$ (c11), 05.3 (c11), 05.2 (c11), 05.0 (c12), 05.1 (c12), 10. $J = 11.2, 5.8 \text{ Hz}, 1\text{ H}, CH_2), 3.49 \text{ (m, 1H, CH)}, 3.38 \text{ (t, } J = 4.2 \text{ Hz}, 1\text{ H}, CH), 3.20 \text{ (dt, } J = 7.8, 5.1 \text{ Hz}, 1\text{ H}, CH), 2.13 \text{ (m, 1H, CH_2)}, 1.92 \text{ (m, 1H, CH_2)}; 1^3\text{C NMR (D}_2\text{O}) \delta$ 75.5 (CH), 75.0 (CH), 70.9 (CH), 69.2 (CH), 63.0 (CH₂), 62.5 (CH), 62.5 (CH), 61.4 (CH₂), 38.3 (CH₂). Anal. Calcd for C₉H₁₇NO₅: 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 (D₂O) δ 4.56 (ddd, *J* = 4.4, 2.5, 2.5 Hz, 1H, CH), 4.32 (t, *J* = 4.4 Hz, 1H, CH), 4.04 (dd, *J* = 9.5, 4.4 Hz, 1H, CH), 3.85 (dd, *J* = 12.6, 3.2 Hz, 1H, CH₂), 3.85 (overlapped, 1H, CH), 3.84 (overlapped, 2H, CH₂, CH), 3.79 (dd, J = 12.0, 6.2 Hz, 1H, CH₂), 3.69 (dd,

 $J = 12.6, 3.2 \text{ Hz}, 1\text{H}, CH_2), 3.50 \text{ (m}, 1\text{H}, CH), 2.07 \text{ (m}, 1\text{H}, CH_2), 1.93 \text{ (m}, 1\text{H}, CH_2);$ $^{13}C \text{ NMR} (D_2O) \delta 79.9 (CH), 75.4 (CH), 72.2 (CH), 71.7 (CH), 67.5 (CH), 65.5 (CH), 61.8 (CH_2), 61.7 (CH_2), 39.4 (CH_2).$ Sumthatics and business and a constraint of the second secon

61.8 (CH₂), 61.7 (CH₂), 39.4 (CH₂). 11. Synthetic 5-epi-hyacinthacine C₃ **2b**: $[\alpha]_{2}^{22}$ +14.8 (c 0.3, H₂O); IR (NaCl) 3312 (O–H), 2928 (C–H), 1038 (C–O) cm⁻¹; ¹H NMR (D₂O) 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, CH₂), 3.52 (dd, *J* = 11.2, 6.4 Hz, 1H, CH₂), 3.49 (dd, *J* = 11.6, 6.2 Hz, 1H, CH₂), 3.40 (dd, *J* = 11.2, 5.3 Hz, 1H, CH₂), 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, CH₂), 1.50 (m, 1H, CH₂); ¹³C NMR (D₂O) δ 75.8 (CH), 74.4 (CH), 71.7 (CH), 70.4 (CH), 70.2 (CH), 69.0 (CH), 65.9 (CH₂), 63.9 (CH₂), 3.9.0 (CH₂), Anal. Calcd for C₉H₁₇NO₅: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.49; H, 7.94; N, 6.46.