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Synthesis of Fully Substituted Polyhydroxylated Pyrrolizidines via Cope–House Cyclization

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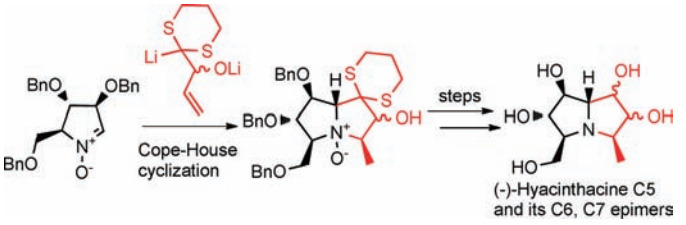
ABSTRACT



Total synthesis of the proposed structure of (−)-hyacinthacine C_5 and its epimers at C6 and C7 is described. A key step of the synthesis was the construction of the bicyclic pyrrolizidine system by means of a nucleophilic addition of a dithiane to a cyclic nitrone followed by a Cope–House cyclization.

Hyacinthacines, a series of polyhydroxylated pyrrolizidines possessing a hydroxymethyl substituent at C3, were isolated from the Hyacinthaceae family of plants (*Hyacinthoides nonscripta*,[1a] *Scilla campanulata*,[1a] *Muscari armeniacum*,[1b] *Scilla sibirica*,[1c] and *Scilla socialis*[1d]) from 1999 to 2007. Nineteen hyacinthacine alkaloids have been

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isolated to date, and they were classified into three categories A_{1-7}, B_{1-7}, and C_{1-5} according to the oxygenation pattern; their structures were initially assigned on the basis of NMR analysis.[1] They are inhibitors of α- and β-glucosidases, β-galactosidases, amyloglucosidases, and α-L-fucosidases[1] and may have chemotherapeutic potential in the treatment of diabetes II, cancer, and viral infections.[2] Consequently, many efforts for devising general strategies for accessing them and their congeners have been prompted.

The majority of these synthetic methods start with a chiral pool which have the identical stereocenters to the alkaloid.[3] Meanwhile, de novo approaches, which include chemoenzymatic procedures utilizing an adolase,[4] versatile routes reliant on the enzymatic desymmetrization of dihydropyrrole,[5] and syntheses through the use of diastereoselective dichloroketene–chiral enol ether cycloaddition,[6] making the hyacinthacines more available.

Ten hyacinthacines (A_1–A_3, A_5–A_7, B_1–B_3, C_2) have been synthesized and their absolute configurations assigned. Unambiguous syntheses of hyacinthacine B_7[3m] and C_3[3h] have shown that the initially proposed structures were incorrect; the ^1H and ^{13}C NMR spectral data of the synthetic and isolated compounds were not consistent. There are no reports of the synthesis of hyacinthacines C_1, C_4[7] and C_5 with substituents at each carbon of the pyrrolizidine nucleus so that their absolute configurations have yet to be determined; only a few analogues have been synthesized.[8] This series of pyrrolizidines has four hydroxyl groups, one hydroxymethyl group and one methyl group attached to each of the seven adjacent chiral centers (Figure 1).

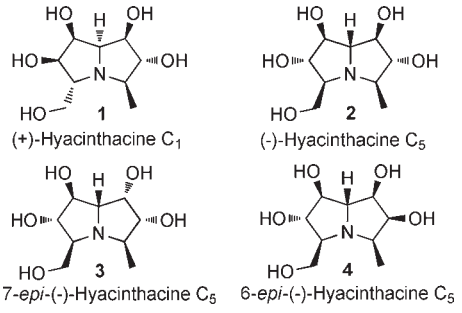
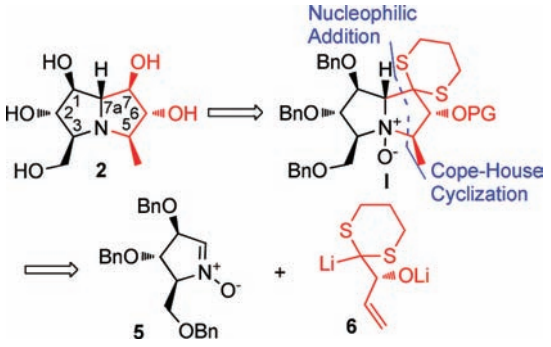


Figure 1. Examples of fully substituted pyrrolizidines.

These enticing structures pose a great challenge for their total syntheses. The development of general synthetic methods for this class of compound would allow evaluation of their potential biological activities. Our retrosynthetic strategy of hyacinthacine C_5 is depicted in Scheme 1. Starting from the cyclic nitrone **5**[9] with three chiral centers, the stereo center of C7a could be established via diastereoselective addition of lithio-dithiane **6**. The hydroxyl group at C7 could be derived from dethioketalization and diastereoselective reduction; the hydroxyl group at C6 could be initially installed at the dithiane side chain. The chiral center at C5 was commonly introduced by intramolecular S_N2 substitution[3m,h] or reductive amination[3f,i,k] or Bruylants alkylation,[6b,9g] but all these methods involved cumbersome steps. Kaliappan's method[10] employing Cope–House cyclization[11] gave excellent diastereoselectivity, and the stereochemical pattern was identical with that of (−)-hyacinthacine C_5.

Scheme 1. Retrosynthetic Analysis of (−)-Hyacinthacine C_5



Since cyclic nitrone **5** could be easily prepared on a large scale according to our improved approach,[9c] we investigated the addition of 2-lithio-1, 3-dithiane derivatives to nitrone **5**. As a classical umpolung synthon, dithiane has been widely applied in reversing the reactivity of carbonyl groups.[12] Although additions of 2-lithio-1,3-dithiane

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(7) Hyacinthacine C_4 has been determined to be the same structure as hyacinthacine C_1 (see ref 1d).

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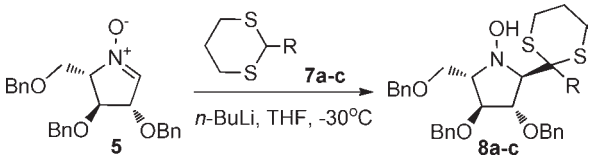
derivatives to imines are well documented,[13] the addition of 2-lithio-1,3-dithiane derivatives to nitrones has not been reported previously.

We first investigated the model reaction of dithiane **7a** and nitrone **5**. The reaction was performed at −30 °C in THF with 1.5 equivalents of dithiane. The adduct **8a** was obtained in 56% yield with excellent diastereoselectivity (>95:5) (Table 1, entry 1), together with unreacted nitrone **5**. Addition of a second equivalent of **7a** gave **8a** in good yield (80%) (Table 1, entry 2) with nitrone completely consumed. Addition of TMEDA enhanced the nucleophilicity of the dithiane anion and increased the yield to 86% (Table 1, entry 3). Treatment of **7b** and **7c** with nitrone **5** under the above conditions gave analogues of **8** in good yields with excellent diastereoselectivity (Table 1, entries 4 and 5). The relative configuration of the newly formed stereocenters was determined by analysis of the NOESY spectrum.

Table 1. Nucleophilic Addition of 2-Lithio-1,3-dithiane to Nitrone **5**

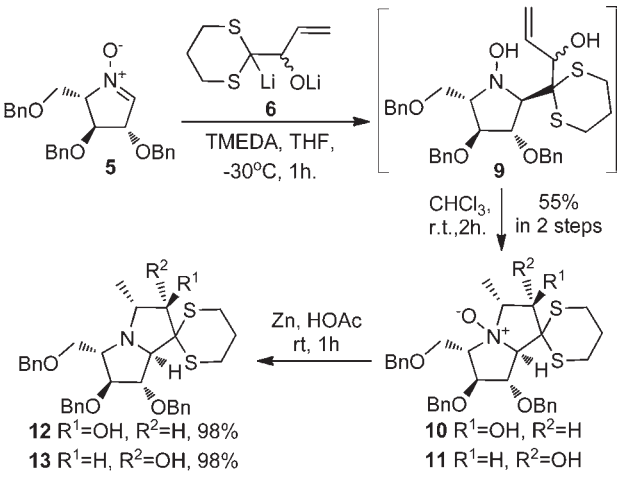


entry	dithiane	R	dithiane (equiv)	additive	yield[a] (%)	dr[b]
1	**7a**	H	1.5		56	>95:5
2	**7a**	H	3		80	>95:5
3	**7a**	H	3	TMEDA	86	>95:5
4	**7b**	phenyl	3	TMEDA	95	>95:5
5	**7c**	butyl	3	TMEDA	63	>95:5

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR analysis of a crude product.

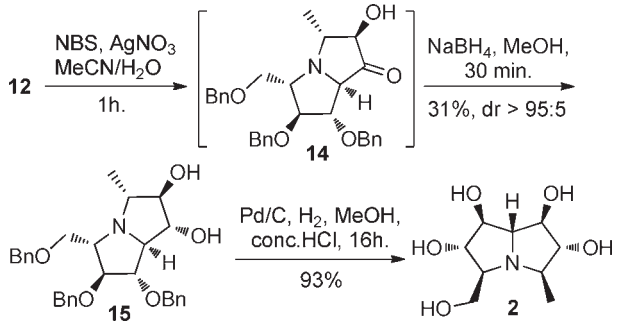
Following the successful model reactions, we turned our attention to the synthesis of hyacinthacine C_5. The addition of racemic dilithio species **6**, prepared from 1-(1,3-dithian-2-yl)propan-1-ol,[14] to nitrone **5** afforded hydroxylamine **9** which was subjected to Cope−House cyclization to give pyrrolizidine *N*-oxides **10** and **11** as the only detectable products in 55% isolated yield in a ratio of 1:1.[15] During the Cope−House cyclization, it was found that some of the unsaturated hydroxylamine **9** remained. Refluxing the reaction mixture in $CHCl_3$ did not improve the yield of products but resulted in decomposition of the hydroxylamine. Reduction of the cyclized products by a Zn−HOAc system gave the pyrrolizidines **12** and **13** in excellent yields; X-ray crystallographic analysis confirmed their relative configurations (Scheme 2 and the Supporting Information).

Scheme 2. Construction of the Pyrrolizidine Skeleton



Attempted hydrolysis of the dithioketal **12** by several methods including the Stork protocol[16] [e.g., bis(trifluoroacetoxy)iodobenzene] failed to give the ketone **14**. NBS/$AgNO_3$[17] gave a relatively good result but did not allow the purification of the ketone **14**. However, addition of $NaBH_4$ to the crude product from the NBS/$AgNO_3$ treatment formed diol **15** as a single isomer in 31% yield, the structure of which was firmly established by X-ray crystallographic analysis (Scheme 3 and the Supporting Information). Subsequent removal of the benzyl protecting groups by hydrogenolysis afforded the final product (−)-hyacinthacine C_5 **2**.

Scheme 3. Synthesis of (−)-Hyacinthacine C_5 (**2**)



Protection of the hydroxyl group in **12** with MOMCl and unmasking of the carbonyl group with NBS/$AgNO_3$ gave the ketone **17** in 61% yield. Reduction of the ketone **17** with $NaBH_4$ afforded a mixture of two diastereoisomers in a ratio of 5:1. The selectivity resulted from the favored formation of **18** by hydride attack from the less hindered side; L-Selectride, a bulky, noncoordinating alkylborohydride,

(14) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1988**, *44*, 4645.

(15) It was necessary to leave the hydroxyl group of the dithiane unprotected, since treatment of 2-(1-(benzyloxy)allyl)-1,3-dithiane with *n*-BuLi caused elimination of the benzyloxy group.

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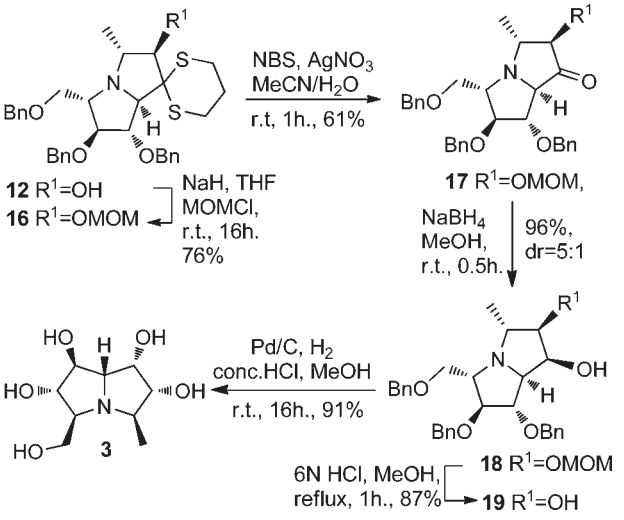
cleanly gave **18** as a single stereoisomer. Finally, after MOM deprotection, hydrogenolysis of diol **19** gave 7-*epi*-(−)-hyacinthacine C_5 **3** in 91% yield (Scheme 4); no correlation was observed between H-5 and H-7 in the NOESY NMR analysis of **3** (see the Supporting Information). The minor product from the reduction of the ketone **17** was subjected to MOM deprotection, and the diol thus yielded had an identical ^{1}H and ^{13}C NMR spectra to **15**.

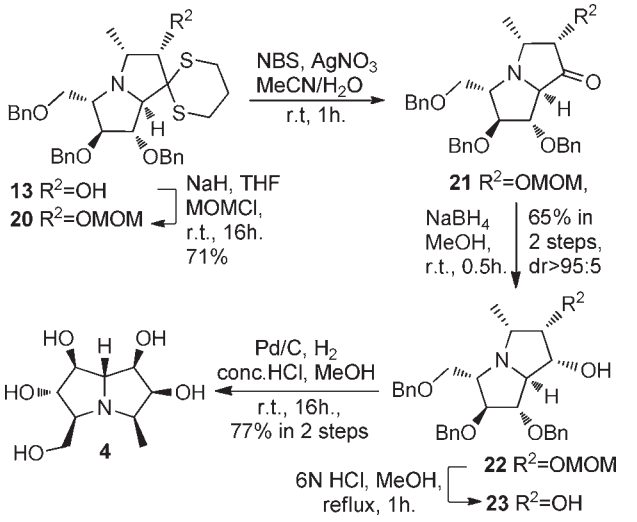
Scheme 4. Synthesis of 7-*epi*-(−)-Hyacinthacine C_5 (**3**)



6-*epi*-(-)-Hyacinthacine C_5 **4** was prepared in an analogous route from **13** (Scheme 5). The results were similar except for the reduction of ketone **21**. In this reaction, both $NaBH_4$ and L-Selectride gave diastereoselective reduction to **22** as the sole product, the structure of which was firmly established by X-ray crystallographic analysis (see the Supporting Information). Removal of the remaining *O*-MOM and *O*-benzyl protecting groups yielded 6-*epi*-(−)-hyacinthacine C_5 **4** (Scheme 4). None of the ^{1}H and ^{13}C NMR spectra of the three final products **2**−**4** matched those reported for the natural (+)-hyacinthacine C_5.[1d] Therefore, revision of the stereochemical assignment of the natural product may be required.

(−)-Hyacinthacine C_5 **2** and its C6, C7 epimers (**4** and **3**) were assayed as potential glycosidase inhibitors of a range of enzymes (see the Supporting Information). Compound **4** showed weak inhibition of α-glucosidases (IC_{50} = 58.5 μM

Scheme 5. Synthesis of 6-*epi*-(−)-Hyacinthacine C_5 (**4**)



of α-glucosidase from rat intestinal maltase; IC_{50} = 64.2 μM of α-glucosidase from rice).

In summary, the total synthesis of fully substituted pyrrolizidines with the structure originally proposed for (−)-hyacinthacine C_5 **2**, and of the C6 **4** and C7 **3** epimers, was achieved; the key step was a Cope−House cyclization of the adduct of a lithio-dithiane addition to a cyclic nitrone. The inconsistency in spectral data between synthetic compounds and the natural product proposed as **2** indicates further work is necessary to determine the actual structure of the isolated natural product. This concise synthetic strategy provides a general approach to this class of compounds and allows evaluation of their structure−activity relationship.

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Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR spectra, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.