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Synthetic study of hetisine-type aconite alkaloids. Part 3: Total synthesis of (±)-nominine

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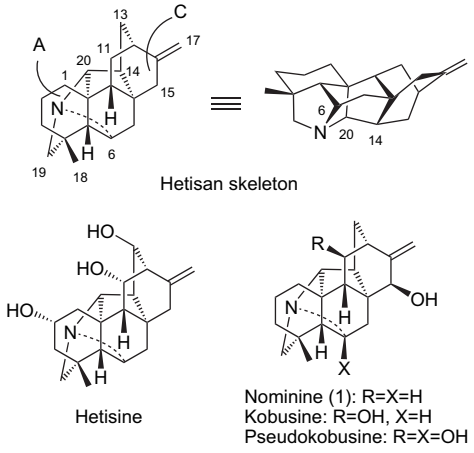
Abstract—Completion of the total synthesis of (±)-nominine (**1**) is described in detail. Based on the results of the preceding two papers, total synthesis of (±)-nominine was accomplished diverging from the intermediate **7**. Thus, following pyrrolidine ring formation through transformation from **7** to **8**, the C-ring was constructed by radical cyclization to form **10** from the enyne precursor **9**. Subsequent elaboration of the C-ring, followed by formation of the azabicyclic ring system, completed a total synthesis of (±)-**1**. Single-crystal X-ray analysis of (±)-**1** unambiguously confirmed its molecular structure and racemic crystal structure.

1. Introduction

1.1. The hetisine-type aconite alkaloid nominine

The term aconite alkaloid is applied to the diterpene alkaloids isolated from *Aconitum*, *Delphinium*, *Consolida*, *Thalictrum*, and *Spiraea*. These alkaloids are generally classified into five skeletons, atidane, veatchane, cycloveatchane, aconitane, and hetisan (the name of which is derived from hetisine) based on their fundamental frameworks.[1,2] Extensive synthetic efforts over the last 40 years have resulted in total syntheses of several alkaloids belonging to the first four of the above five groups. However, the synthesis of even the basic skeleton of the hetisine-type alkaloids, which include hetisine, nominine, kobusine, etc. had remained elusive until we recently reported a total synthesis of (±)-nominine (**1**) (Scheme 1).[3]



Scheme 1. Hetisan skeleton and representative hetisine-type aconite alkaloids.

Nominine (**1**) is structurally the simplest hetisine-type aconite alkaloid. Ochiai et al. first isolated **1** as 'Nomi-base I' from *Aconitum sanyoense* Nakai, collected at Nomi, Sakyo-ku, Kyoto prefecture, Japan in 1956.[4] Sakai et al. gave it the name nominine in 1982 and determined the absolute structure by chemical correlation with kobusine, whose structure was established unequivocally by single crystal X-ray analysis.[5] The name nominine was redundantly given to an insecticidal indole diterpene in 1989.[6]

1.2. Synthetic background

Discovery of the palladium-catalyzed intramolecular α-arylation reaction of aliphatic ketone, formyl, and nitro groups[7] triggered our synthetic studies leading toward the total synthesis of aconite alkaloids with the hetisan skeleton.[8] Our synthetic efforts culminated in a total synthesis of **1**, which was reported in a preliminary communication.[3] In the preceding two papers,[9,10] we have presented full details of the preparation of compound **2** lacking the C-ring of the hetisan framework, starting from **3** by way of the intermediates **4**–**7**. We employed the acetal ene-reaction to form **6**, stereoselective hydrocyanation to form **7**, and azabicyclic ring formation to form **2**, as well as the above Pd-catalyzed cyclization reaction (**4**→**5**), as the key reactions (Scheme 2). Here, we present full details of the synthesis of **1**, diverging from the above-mentioned intermediate **7**.

Keywords: Aconite; Alkaloid; (±)-Nominine; Hetisan; Radical cyclization; X-ray analysis.
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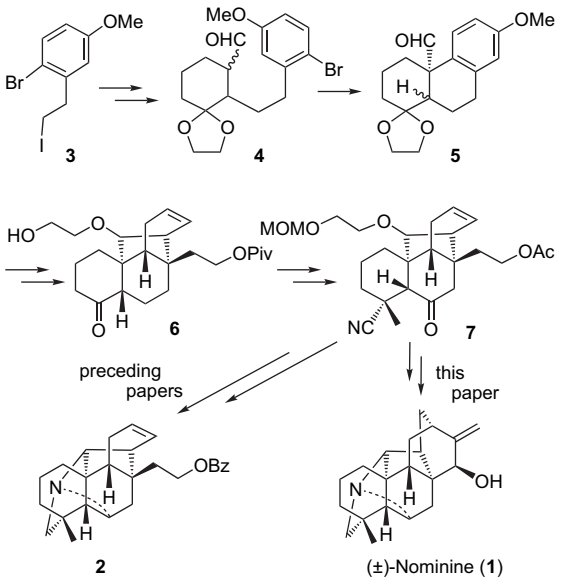
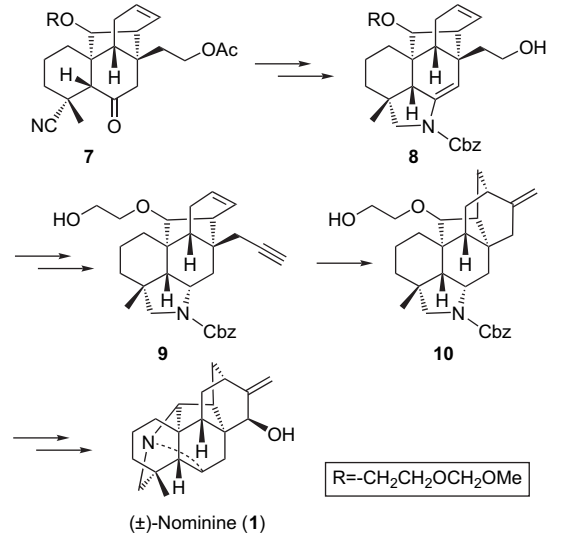


Scheme 2. Outline of the synthetic pathways in the three papers.

We had initially considered synthesizing **1** from **2** through C-ring construction followed by functionalization at C15 with a β-hydroxy substituent. However, taking into consideration that the strong basicity of **2** seriously restricts its versatility as a synthetic intermediate, we decided to construct the bicyclo[2.2.2]octane ring (C-ring) from the intermediate **7**, keeping the nitrogen protected as a carbamate, prior to the creation of the azabicyclic ring system for completion of the total synthesis of **1**.

2. Results and discussion

An outline of the reaction sequence described in this paper is shown in Scheme 3. Compound **7** was transformed to a pentacyclic intermediate **8** according to the method reported in the preceding paper.[10] Compound **8** was led to an enyne derivative **9**, which was then subjected to radical cyclization reaction to secure the hexacyclic intermediate **10**. C-ring elaboration followed by *O*- and *N*-deprotections and azabicyclic ring formation completed the total synthesis of (±)-nominine (**1**). These results constitute the first total synthesis of a hetisine-type aconite alkaloid. We present below full details of not only the reactions along Scheme 3, but also reaction procedures that were ultimately not employed for the total synthesis.

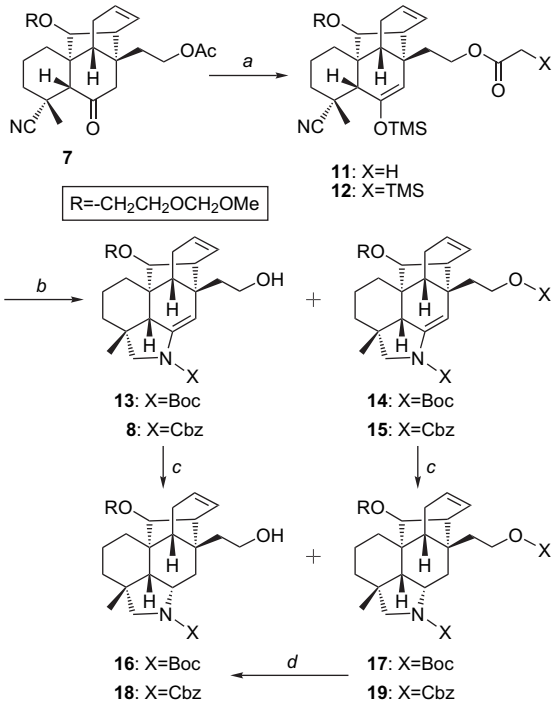


Scheme 3. Outline of the synthesis of **1** from **7**.

2.1. Preparation of pentacyclic intermediates 16 and 18 from 7 by way of 13 and 8

In the preceding paper,[10] we formed the pyrrolidine ring after deprotection of the C20 hydroxy group. In this paper, this protecting group was retained until the final stage of the synthesis with a change of the functional group at the primary hydroxy part of the 2-hydroxyethyl protecting group. The protecting group played a pivotal role in this total synthesis in that it prevented a possible retro-ene reaction with the bond fission of C14 and C20, and it was extremely stable under a wide variety of reaction conditions encountered in the synthetic procedures.

Kinetic enolate formation from **7** with lithium diisopropylamide (LDA) and simultaneous trapping with chlorotrimethylsilane (TMSCl) afforded two products, **11** and **12** (Scheme 4). The latter was a trimethylsilylated compound at the methyl carbon of the acetyl group. Compound **11** was the product derived from the corresponding O-silylated intermediate, which was hydrolyzed during extractive isolation. Of the two products, **11** was subjected, as before,[10] to



Scheme 4. Preparation of **16** and **18** from **7** by way of **13** and **8**: (a) TMSCl, LDA, THF, **11** (79%), **12** (12%); (b) $LiAlH_4$, THF, then Boc_2O or ClCbz, Et_3N, CH_2Cl_2, **13** (62%) from **11**, **14** (16%) from **11**, **13** (55%) overall from **7**, **14** (10%) overall from **7**, **8** (63%) overall from **7**, **15** (4%) overall from **7**; (c) $NaBH_3CN$, 2.5% HCl–H_2O, MeOH, **16** (91%) from **13**, **17** (93%) from **14**, **18** (90%) from **8**, **19** (91%) from **15** and (d) K_2CO_3, MeOH, **16** (quant.) from **17**, **18** (quant.) from **19**.