Natural Products Synthesis

Total Synthesis of (±)-Nominine, a Heptacyclic Hetisine-Type Aconite Alkaloid**

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Nominine (**1**) is structurally the simplest hetisine-type aconite alkaloid (Scheme 1). It was first isolated as "Nomi-base I" from *Aconitum sanyoense* Nakai, collected at Nomi, Sakyo-ku, Kyoto prefecture in Japan by Ochiai et al. in 1956.[1] Sakai et al.[2] later gave it the name nominine[3] and determined the structure, including the absolute configuration, by chemical correlation with kobusine, whose structure was established

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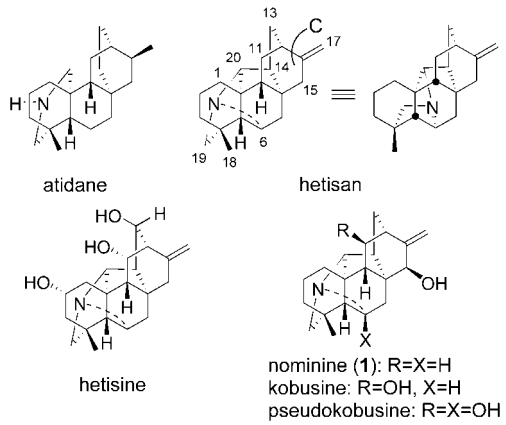
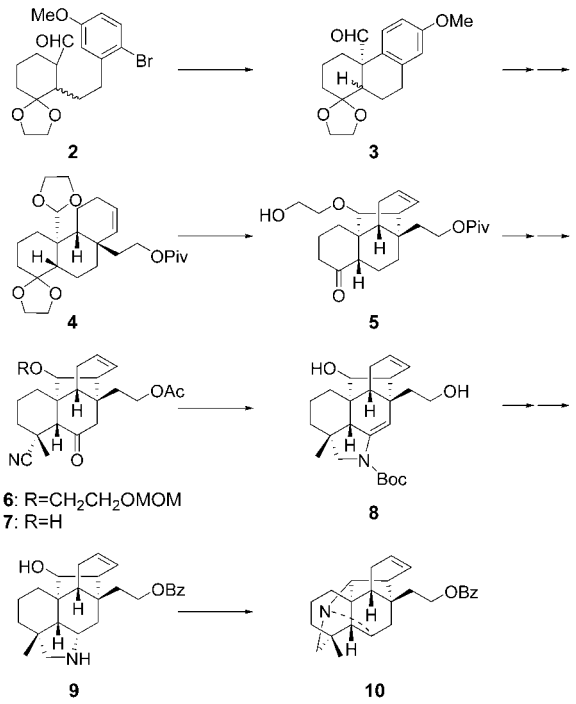


Scheme 1. Atidane and hetisan skeletons, and hetisine-type aconite alkaloids.

unambiguously by X-ray crystal-structure analysis.[4] Our extensive synthetic efforts towards the heptacyclic hetisine-type alkaloids, of which nearly 100 are now known, have culminated in the total synthesis of (±)-nominine (**1**).[5] This constitutes the first total synthesis of a hetisine-type aconite alkaloid.

More than 400 aconite alkaloids have been isolated from plants of the species *Aconitum*, *Delphinium*, *Spiraea*, *Consolida*, and *Thalictrum*. They are generally classified based on their fundamental framework as atidane, veatchane, cycloveatchane, aconitane, or hetisan (the name of which is derived from hetisine) alkaloids.[6,7] Synthetic studies on these pharmacologically important alkaloids during the last approximately 40 years have led to the total synthesis of several alkaloids of the first four of the above skeletal types. [6,7] However, attempts to construct even a simple framework corresponding to the hetisine-type alkaloids, not to mention the total synthesis of one of these alkaloids, have remained unsuccessful until now (Scheme 1). Distinctive structural characteristics of the hetisan framework are the atidane skeleton and the presence of the N–C6 and C14–C20 bonds, which contribute to the difficulty of synthesizing the hetisine-type alkaloids. Shibanuma and Okamoto prepared a pentacyclic compound that contains the N–C6 bond.[8] Two other reports that describe synthetic studies of hetisine-type alkaloids have also appeared.[9]

Previously we reported a palladium-catalyzed intramolecular α arylation reaction of aliphatic ketone, aldehyde (e.g. **2**→**3**), and nitro groups (Scheme 2).[10] As an application of this reaction, we embarked on a project to synthesize hetisine-type alkaloids. Our fundamental synthetic plan was to form the N–C6 and C14–C20 bonds at an early stage of the synthesis, since they greatly restrict the molecular conformation and would become more difficult to form at a later stage. Accordingly, we reported the preparation of a hexacyclic compound **10**, which lacks the C ring of the hetisan framework.[5] Following the transformation of compound **3** into **4**, the C14–C20 bond was created by an intramolecular acetalene reaction to form tetracyclic **5**. The connection between the N atom and C6 was established by utilizing the β-cyanoketone **7**, which was prepared from **5** via **6** and



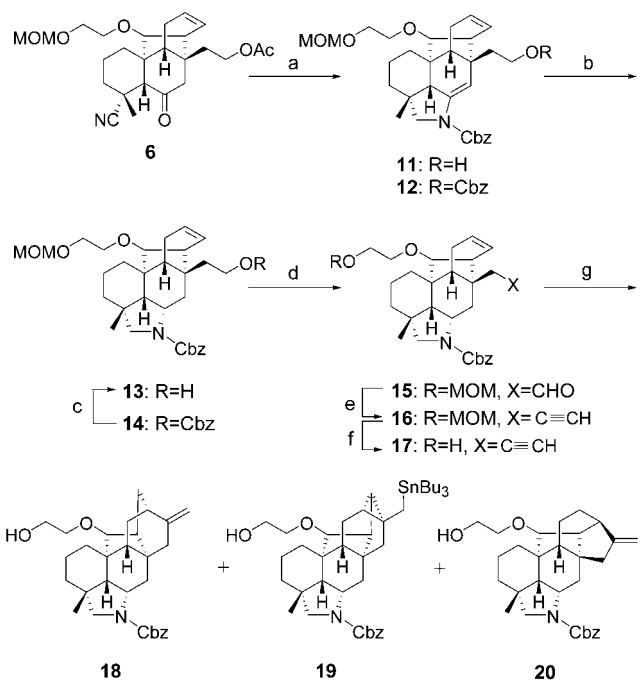
Scheme 2. Previously reported preparation of the hexacyclic compound **10**. Bz = benzoyl, MOM = methoxymethyl, Piv = pivaloyl.

converted into the pentacyclic alkenyl carbamate **8**. The construction of the azabicyclic ring system was completed with the formation of the N–C20 bond upon the treatment of **9** with $SOCl_2$ and pyridine to afford **10**.

At first glance, C-ring formation from compound **10**, followed by functionalization at C15 with a hydroxy substituent in the β orientation, should lead readily to the target nominine (**1**). However, the strong basicity of **10** seriously restricts its versatility as an intermediate. Therefore, we decided to generate the bicyclo[2.2.2]octane ring from the intermediate **6** prior to the creation of the azabicyclic ring system.

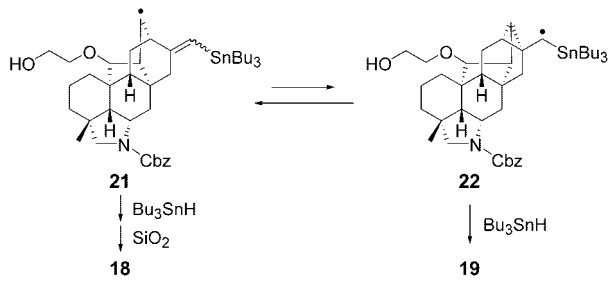
The ketone group of **6** was protected as an enol silyl ether, and then the cyano group of the resulting product was reduced with $LiAlH_4$ in THF at reflux (Scheme 3). The careful decomposition of excess $LiAlH_4$ followed by protection of the nitrogen atom with a Cbz group provided the alkenyl carbamate **11** and a small amount of **12**. The Cbz group was employed this time in place of the *tert*-butoxycarbonyl (Boc) group, because we were unable to find suitable reaction conditions to remove the Boc group after the formation of the methylenebicyclo[2.2.2]octane ring system. The alkene bond adjacent to the nitrogen atom of the carbamate group in **11** and **12** was reduced with $NaBH_3CN$ to give **13** and **14**, respectively, and the latter was converted into **13** by methanolysis of the carbonate group. Compound **13** was transformed into the enyne–alcohol **17** via the aldehyde **15** and enyne **16**.[11]

The enyne **17** was the precursor of choice for formation of the C ring through a radical cyclization reaction. A solution of Bu_3SnH (70 mM) in toluene was added slowly (over 1.5 h) to a solution of **17** (5.5 mM) and a catalytic amount of AIBN in



Scheme 3. Preparation of the intermediate **18** from **6** for the synthesis of (±)-nominine: a) TMSCl, LDA, THF, −78 °C; $LiAlH_4$, THF, reflux; CbzCl, Et_3N, CH_2Cl_2, −18 °C→RT, **11**: 63 %, **12**: 4 %; b) $NaBH_3CN$, aqueous HCl (2.5 %), MeOH, 0 °C→RT, **13**: 90 % from **11**, **14**: 91 % from **12**; c) K_2CO_3 (1 %), MeOH, room temperature, quantitative; d) PCC (20 wt.%)/Al_2O_3, CH_2Cl_2, 0 °C→RT, 84 %; e) dimethyl (1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, 0 °C→RT, 98 %; f) HCl (5 %), DME/H_2O (3:1), 0 °C→RT, 96 %; g) Bu_3SnH, AIBN, toluene, reflux; SiO_2, CH_2Cl_2, room temperature, **18**: 57 %, **19**: 31 %, **20**: 8 %. AIBN = azobisisobutyronitrile, Cbz = benzyloxycarbonyl, DME = dimethoxyethane, LDA = diisopropylamide, PCC = pyridinium chlorochromate, TMS = trimethylsilyl.

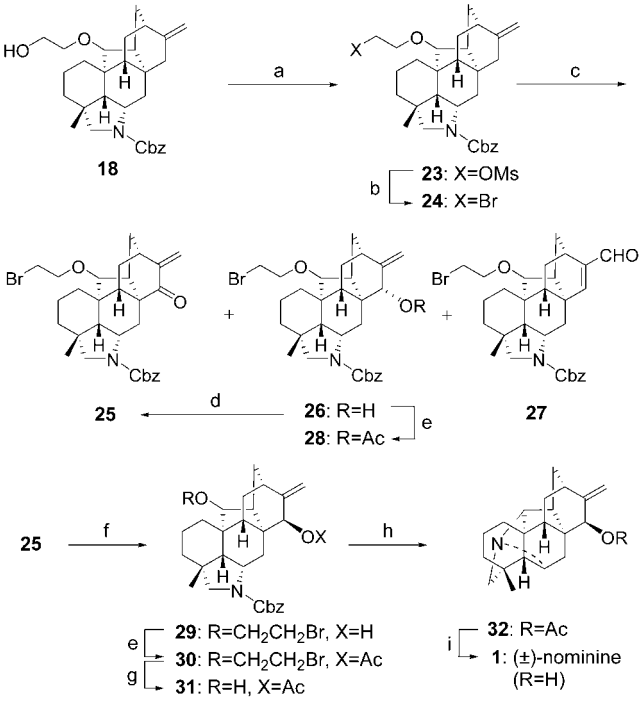
toluene at reflux to secure the desired methylenebicyclo[2.2.2]octane derivative **18** (57 %), the stannyl cyclopropane derivative **19** (31 %), and the methylenebicyclo[3.2.1]octane derivative **20** (8 %) after destannylation of the vinyl stannane products with silica gel.[12] Simple heating of a mixture of **17**, Bu_3SnH, and AIBN in toluene afforded **19** as the major product. Thus, there appears to be an equilibrium between the radical intermediates **21** and **22**, with the former favored thermodynamically (Scheme 4). Similar radical cyclization reactions reported by Toyota et al. afforded mainly bicyclo[2.2.2]octanes or bicyclo[3.2.1]octanes, depending on the substituents of the substrates; no stannyl cyclopropane



Scheme 4. Equilibration between radical intermediates.

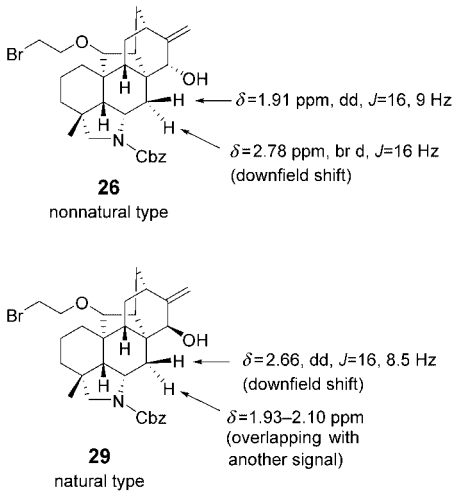
derivatives were formed.[13] However, in our case the desired compound **18** and the stannyl cyclopropane **19** were formed as the main products, and the bicyclo[3.2.1]octane derivative **20** was a minor product, probably as a result of the distorted nature of the molecule. The structure of **20** was confirmed by generation of the corresponding cyclopentanone derivative (IR: $\tilde{\nu} = 1730\ cm^{-1}$) by the Lemieux oxidation.

Next, **18** was transformed into the bromide **24** via the mesylate **23** (Scheme 5). Compound **24** underwent allylic



Scheme 5. Synthesis of (±)-nominine (**1**) from **18**: a) MsCl, Et_3N, CH_2Cl_2, −20 °C, 97 %; b) LiBr, acetone, reflux, 90 %; c) *tert*-BuOOH, SeO_2, CH_2Cl_2, 0 °C→RT, **25**: 77 %, **26**: 14 %, **27**: trace; d) MnO_2, CH_2Cl_2, 0 °C→RT, quantitative; e) Ac_2O, pyridine, CH_2Cl_2, room temperature, 93 %; f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, quantitative; g) Zn, NH_4Cl, *i*PrOH/H_2O (14:1), reflux, 97 %; h) Et_3SiH, cat. $Pd(OAc)_2$, cat. Et_3N, CH_2Cl_2, room temperature; $SOCl_2$, pyridine, CH_2Cl_2, 0 °C→RT, 80 %; i) K_2CO_3, MeOH, reflux, 95 %. Ms = methanesulfonyl.

oxidation with aqueous *tert*-BuOOH and SeO_2[14] in CH_2Cl_2 at ambient temperature to afford the enone **25** (77 %), the alcohol 15α-**26** (14 %), and a trace amount of the enal **27**. The 15α-hydroxy product **26**, with the opposite configuration at C15 to the natural product, was oxidized quantitatively to **25** with MnO_2. The enone **25** was reduced with $NaBH_4$ in the presence of $CeCl_3$ to afford the desired 15β-hydroxy compound **29** exclusively. The structures of **26** and **29** were confirmed on the basis of the rule reported by Kawazoe et al. (Scheme 6).[15] Thus, in their ^1H NMR spectra, the signals for 7α-H of **26** and 7β-H of **29** were shifted downfield owing to the influence of the *syn* 15-hydroxy group. Furthermore, upon acetylation of the hydroxy group, the signal for the corresponding hydrogen atom in the resulting compounds **28** and **30** was shifted upfield in accordance with the rule ($\delta = 2.38$–



Scheme 6. Structural assignment of **26** and **29**.

2.58 ppm for 7α-H of **28** and $\delta \approx 2.0$–2.2 ppm for 7β-H of **30** (overlapping with signals for other hydrogen atoms)). The bromoethyl residue of **30** was removed with zinc and NH_4Cl in 2-propanol/H_2O (14:1) at reflux to give the precursor **31**.

Now the synthesis was in its final stage. The Cbz group was removed with Et_3SiH in the presence of palladium acetate and Et_3N.[16] The resulting amino alcohol was then treated with $SOCl_2$ and pyridine to furnish *O*-acetylnominine (**32**) in good yield. Cleavage of the protecting group completed the total synthesis of (±)-nominine (**1**), which was identical to an authentic specimen (MS, IR, ^1H NMR, ^{13}C NMR).

In summary, we have completed the first total synthesis of (±)-nominine (**1**) in 40 steps and 0.15% overall yield (ca. 85% per step) from 2-bromo-5-methoxyphenethyl iodide.[5] On the basis of the results obtained, further investigations directed towards the total synthesis of other hetisine-type aconite alkaloids, such as kobusine and pseudokobusine, are in progress.

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