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Synthesis of a compound having the essential structural unit for the hetisine-type of aconite alkaloids

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Abstract—A hexacyclic compound **1**, which carries an almost full structure of the hetisine skeleton lacking only the six-membered ring with an *exo* methylene group, was synthesized by applying an acetal-ene reaction on **5** for the bond formation of C-14 and C-20 as well as stereoselective hydrocyanation reaction on **7** for construction of the azabicyclo ring system.

More than four hundred aconite alkaloids have so far been isolated from genera *Aconitum*, *Delphinium*, *Consolida* and *Spiraea*. Their chemical structures are generally classified into five types, which possess the frameworks of atidane, veatchane, cycloveatchane, aconitane, and hetisan (Fig. 1).[1,2] Hetisine[3] is a representative of nearly a hundred hetisan alkaloids, and its heptacyclic structure is characteristic of the chemical bonds between N and C-6, and also C-14 and C-20 in addition to the atidane structure.

We commenced synthetic work aiming at the hetisine-type of aconite alkaloids, whose total synthesis has not been accomplished for 40 years since the first clarification of the hetisine structure. Nominine, kobusine, and pseudokobusine are particularly our synthetic targets. On the way to these objectives, we report here a synthesis of the hexacyclic compound **1**, which carries the above essential structural unit for the hetisine structure. Okamoto and co-worker once synthesized a pentacyclic compound **2**.[4,5]

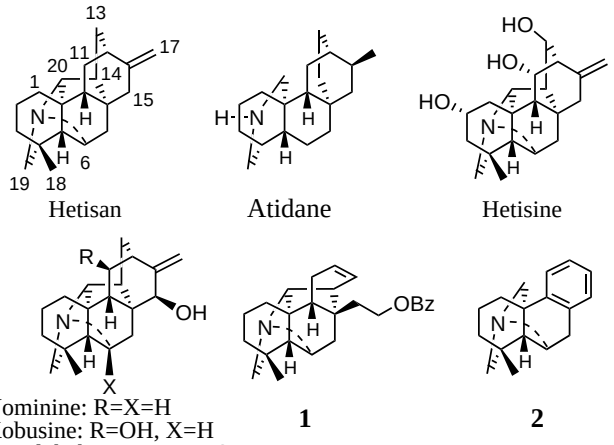

Figure 1.

The synthetic plan of **1** is based on (i) our previous finding of a palladium-catalyzed intramolecular arylation reaction of aldehyde compounds,[6] i.e. **3**→**4** (Fig. 2), (ii) application of the Lewis acid-catalyzed ene reaction[7] to an acetal **5** for the formation of the bond

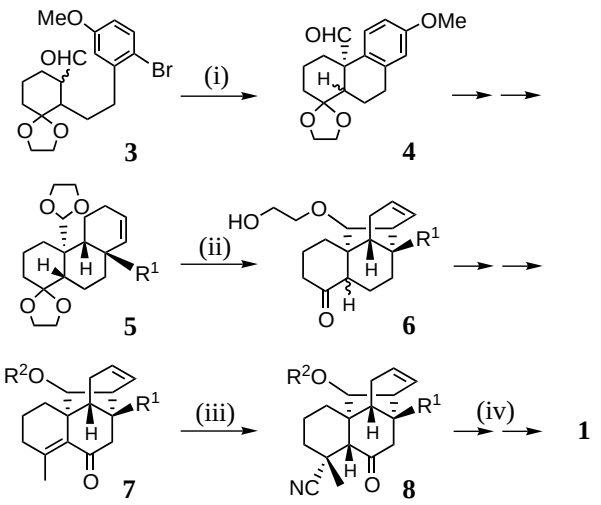

Figure 2.

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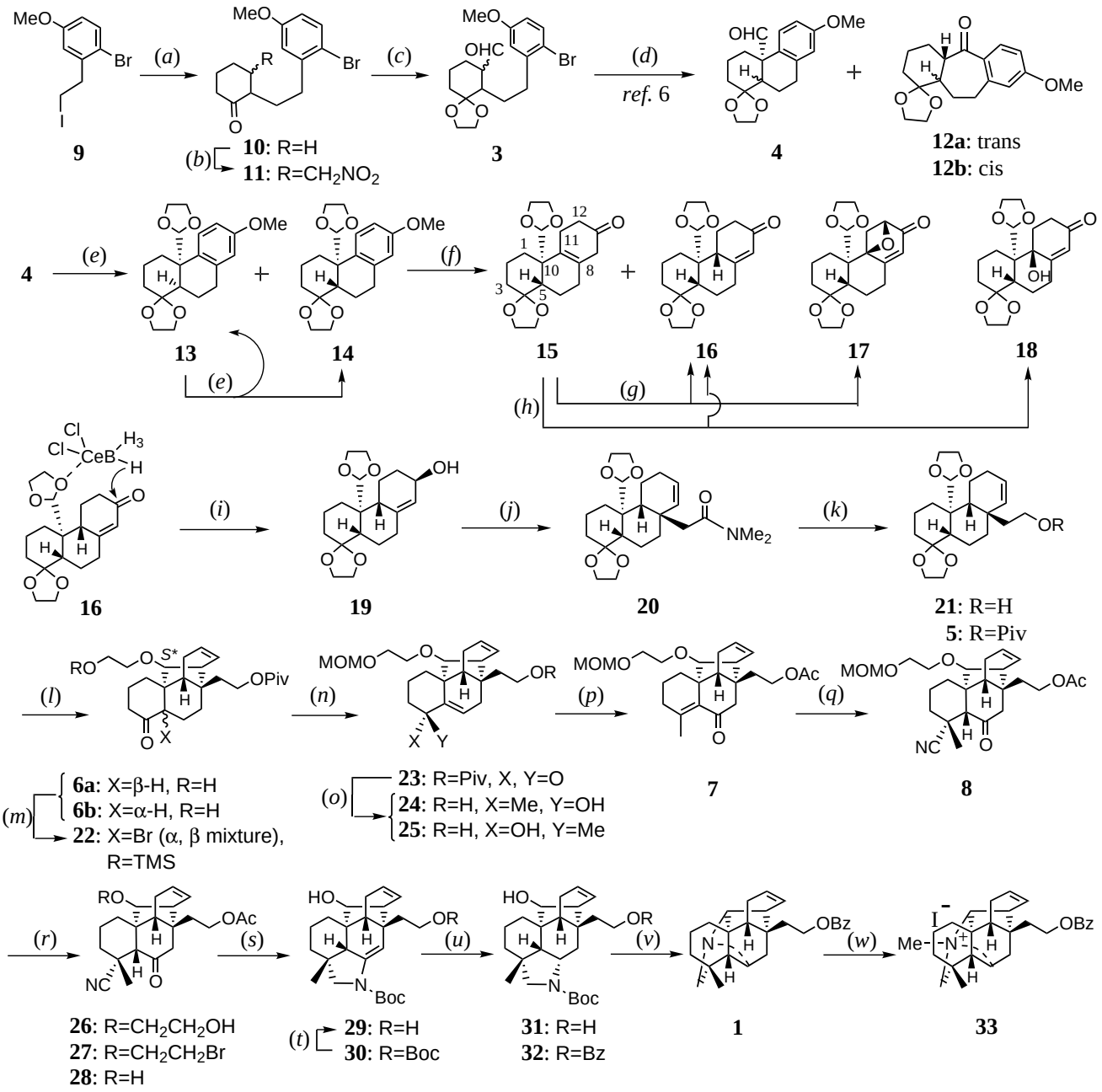


Scheme 1. *Reagents and yields*: (a) *N*-cyclohexylidenecyclohexylamine, LDA, THF, −18°C, then oxalic acid, THF/H_2O (4:1), rt, **10** 95%. (b) TMSCl, NaI, $(TMS)_2NH$, CH_3CN, rt, then NBS, THF, −18°C to rt, 80%; Li_2CO_3, LiBr, DMF, 120°C, 73%; CH_3NO_2, KF, 18-crown-6, CH_3CN, reflux, **11** 96%. (c) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux 97%; KOH, MeOH, 0°C, then $KMnO_4$, $MgSO_4$, MeOH/H_2O (7:1), 0°C–rt, **3** 75%. (d) $PdCl_2(Ph_3P)_2$, Cs_2CO_3, THF, reflux, **4** 65% (*cis*/*trans* = 4.2), **12a** 11%, **12b** 6%. (e) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux, **13** 61%, **14** 34% from **4**; **13** 61%, **14** 35% from **13**. (f) Li, EtOH, liq. NH_3/THF, −78 to −60°C, 92%; 0.5% HCl in THF/H_2O (4:1), 0°C, **15** 88%, **16** 7%. (g) NaOMe, MeOH, rt, **16** 55%, **17** 10%, recovery of **15** 10%. (h) NaOMe, Me_2S, MeOH, rt, **16** 58%, **18** 14%, recovery of **15** 13%. (i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, **19** 94%. (j) *N*,*N*-Dimethylacetamide dimethyl acetal, toluene, 165–170°C (sealed tube), **20** 68%. (k) $BH_3{\cdot}NH_3$, BuLi, THF, 0°C–rt, **21** 94%; Piv_2O, Et_3N, 4-DMAP, CH_2Cl_2, −18°C to rt, **5** 98%. (l) $BF_3{\cdot}OEt_2$, toluene, −18°C; *p*-TsOH, acetone, rt, **6a** 66%, **6b** 3%. (m) TMSCl, NaI, $(TMS)_2NH$, CH_3CN, reflux; NBS, THF, 0°C–rt. (n) 0.2% HCl, THF/H_2O (12:1), 0°C; MOMCl, *i*-Pr_2NEt, CH_2Cl_2, −20°C to rt; DBU, benzene, reflux, **23** 52% overall from **6a**, 45% overall from **6b**. (o) MeLi, THF, −78°C, **24** 59%, **25** 11%. (p) Ac_2O, pyridine, CH_2Cl_2, rt; 20 wt.% PCC/Al_2O_3, benzene, 5°C–rt, **7** 93% and 63% for each step from **24**, **7** 90% and 65% for each step from **25**. (q) Et_2AlCN, toluene, 0°C–rt, **8** 94%. (r) TMSCl, NaI, CH_3CN, 0°C, **26** 92%; CBr_4, Ph_3P, CH_2Cl_2, rt, **27** 93%; Zn, NH_4Cl, 2-propanol/H_2O (14:1), reflux, **28** 95%. (s) TMSCl, LDA, THF, −78 to −67°C; $LiAlH_4$, THF, reflux; Boc_2O, Et_3N, CH_2Cl_2, rt, **29** 31%, **30** 25%. (t) K_2CO_3, MeOH, reflux, **29** 89%. (u) $NaBH_3CN$, 1% HCl, MeOH/H_2O (8:1), 0°C–rt, **31** 85%; BzCl, pyridine, CH_2Cl_2, rt, **32** 95%. (v) CF_3COOH, CH_2Cl_2, 0°C; $SOCl_2$, pyridine, CH_2Cl_2, rt, **1** 78%. (w) MeI, MeOH, rt, **33** 73%.

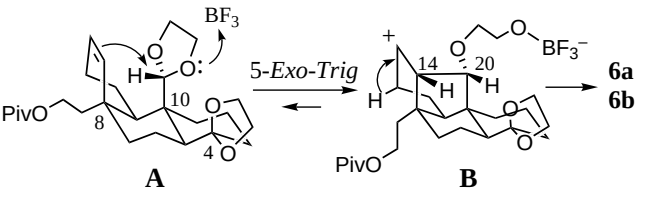
between C-14 and C-20 to give **6**, (iii) stereoselective Michael addition of a cyano group into the enone function of **7**, and (iv) construction of the azabicyclo ring system by utilizing primary amine derived from the cyano group in **8**. Preparation of **3** was started by condensation of 2-bromo-5-methoxyphenethyl iodide[8] (**9**) with an anion derived from *N*-cyclohexylidenecyclohexylamine and LDA (Scheme 1).[9] The resulting **10** was converted to a thermodynamically stable enol silyl ether,[10] which was brominated[11] to afford 2-bromo-2-phenethylcyclohexanone. Regioselective dehydrobromination of the latter gave a cyclohexenone derivative, and conjugate addition of nitromethane[12] afforded **11**. The ketone group was protected and the nitromethyl group was transformed into the aldehyde function[13] providing **3** as a mixture of two stereoisomers.

As reported previously,[6] the palladium-catalyzed reaction of aldehyde **3** afforded an inseparable mixture of *cis* and *trans* isomers **4** (ca. 4:1) in 65% yield together with by-products **12a** and **12b**. When this mixture **4** was treated under the usual conditions of acetal formation, we observed that an acid-catalyzed equilibration took place at the C-5 position adjacent to the original acetal group, and the ratio of the resulting products **13** and **14** was changed to ca. 2:1. This knowledge was useful for enrichment of the *trans* isomer, and the *cis* isomer **13** once isolated in 61% yield in addition to **14** in 34% yield was submitted again to the same acetalization conditions to give **13** and **14** in 61 and 35% yields. Thus this recycling process of **13** made it possible to accumulate the important *trans* compound **14** for further use.

Birch reduction of **14** with Li metal afforded β,γ-enone **15** in 88% yield after quenching with dilute aq. HCl, accompanied by α,β-enone **16** in 7% yield. As conversion of **15** into **16** had to be carried out under the basic conditions in order to avoid hydrolysis of the acetal group, **15** was treated with NaOMe in MeOH. The required **16** was obtained in 55% yield in addition to the recovery of **15** in 10% yield, accompanied by the formation of oxetane **17** in 10% yield. Probably autoxidation took place partially at the C-9 position of **16**, and the resulting hydroperoxide group would react to the enolate anion at C-12 to afford **17**. This assumption was supported by the fact that γ-hydroxy-α,β-enone **18** was obtained in 14% yield in addition to **16** and **15** in respective yields of 58 and 13%, when Me_2S was added to the treatment of **15** with NaOMe in MeOH.[14]

α,β-Enone **16** was exclusively reduced to **19** in 94% yield with $NaBH_4$ in the presence of $CeCl_3$.[15] Introduction of a two-carbon unit at the C-8 position was achieved by Claisen rearrangement on **19** with $MeC(OMe)_2NMe_2$[16] to afford **20** in 68% yield. Subsequent reduction of **20** with LiH_2NBH_3[17] produced **21** in 94% yield, and the hydroxy function of **21** was protected by the pivaloyl group to give **5** in 98% yield. When **5** was treated with $BF_3{\cdot}OEt_2$ in toluene, acetalene reaction[7] took place to afford **6a** and **6b** in 66 and 3% yields, respectively. In these compounds **6a** and **6b**, stereochemical relationship between 14-H and 20-H was shown to be *cis* ($J_{14,20}=6$ Hz). This meant that the ene reaction occurred by interaction of BF_3 with the acetal oxygen as shown in **A** (Scheme 2), where the angular acetal group possessed the conformation of restricted rotation so as to avoid the steric environment of the C-4 acetal group to result in the 20*S** configuration in **6a** and **6b** via **B**. Realization of the bond between C-14 and C-20 implied that the C-14 of **5** was situated in the same face as the angular acetal at the α side, and further, the origin of this stereochemical situation could be traced back to the configuration of the hydroxy group of **19**, which regulated stereochemistry of the dimethylacetamide function of **20**. Eventually, reduction of **16** took place coveniently to give stereoselectively **19** with the β-hydroxy group, probably due to complex formation of the borohydride with the angular acetal oxygen in aid of the ceric species to deliver hydride from the α-side.[18] The ene reaction products **6a** and **6b** were separately converted to enone **23** in 52 and 45% yields, respectively, by successive operations of the enol silyl ether formation between C-4 and C-5, bromination with NBS to afford **22**, hydrolysis of TMS–O bond with diluted acid, protection of the primary OH with MOM group, and dehydrobromination with DBU.

The next task was to construct the two substituents at the C-4 position, i.e. α-cyano and β-methyl groups as shown by **8**. The methyl group was first introduced by reaction of **23** with MeLi to afford **24** and **25** in 59 and 11% yields, respectively. In the ^{1}H NMR spectrum of the major product **24**, NOESY data exhibiting a correlation between CH_3 and H-20 revealed that the methyl group was situated at the α-side, and the attack of MeLi mostly occurred from the side of C-14 and C-20 bridge. Both products **24** and **25** were separately converted to their acetates in 93 and 90% yields and further oxidized with PCC/Al_2O_3[19] to provide **7** in 63 and 65% yields, respectively. The cyano group was introduced to **7** by reaction with Et_2AlCN[20] to obtain stereoselectively in 94% yield the desired **8**, whose stereochemical proof was secured by NOE data (6.5% from H-5 to H-9 as well as 1.2% from CH_3 to H-5 and vice versa) in the ^{1}H NMR spectrum of **26** produced by removal of the MOM group from **8** with TMSI[21] in 92% yield. Again, approach of the cyano group to the C-4 position of enone **7** was observed exclusively to take place from the side of C-14 and C-20 bridge, giving the required stereochemistry in **8**. Here the ethanol function, which served as a protecting group of the C-20 hydroxy group, was removed by treatment of **26** with CBr_4/Ph_3P to afford **27** in 93% yield, followed by reductive cleavage with Zn in the presence of NH_4Cl to produce **28** in 95% yield.



Scheme 2.

Having arrived at the final stage of the synthesis, the formation of a primary amine from the cyano group was to be attempted. For that purpose, prior protection of the ketone group in **28** was carried out by converting it to enol silyl ether by treatment with LDA and TMSCl. This product was reduced with $LiAlH_4$ in refluxing THF, and after quenching of the reaction with H_2O, the crude reaction product was treated with Boc_2O and Et_3N to isolate **29** (31% yield) and **30** (25% yield), and the latter was easily converted to **29** in 89% yield with K_2CO_3 in refluxing MeOH. Structure of **29** was supported by the ^1H NMR signal of the vinyl proton involved in the ene carbamate system at 5.39 ppm (br s). Compound **29** was reduced with $NaBH_3CN$ in 85% yield, and the product **31** was benzoylated to **32** in 95% yield.[22] The final compound **1** was readily obtained in 78% yield by two reactions, i.e. removal of the Boc group from **32** and dehydration of the resulting amine with $SOCl_2$ in the presence of pyridine. The tertiary amine nature of **1** was supported by the formation of its quaternary salt **33**. ^1H NMR spectral study confirmed the structure of **1**, and the existence of both long-range coupling (0.8 Hz) between H-6 and H-20 (Fig. 3), and NOE enhancement of the H_b-19 signal on irradiation of the H-20 signal ascertained the N–C-20 bond connection during the $SOCl_2$ treatment. In the ^1H NMR spectra of nominine and kobusine, spin–spin coupling between H-6 and H-20 was also observed as shown in Fig. 3.[23]

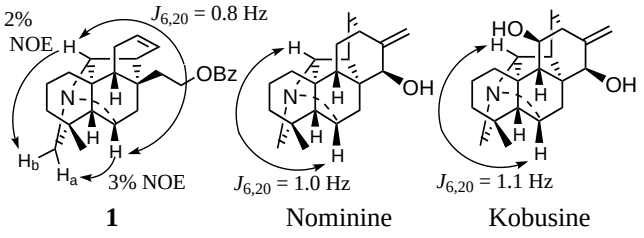


Figure 3.

Here we have succeeded for the first time in the synthesis of a hexacyclic compound **1**, which has an almost full structure of hetisan lacking only the six-membered ring with the *exo* methylene group. Applying this work, synthetic studies of nominine, kobusine, and pseudokobusine are now in progress.

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