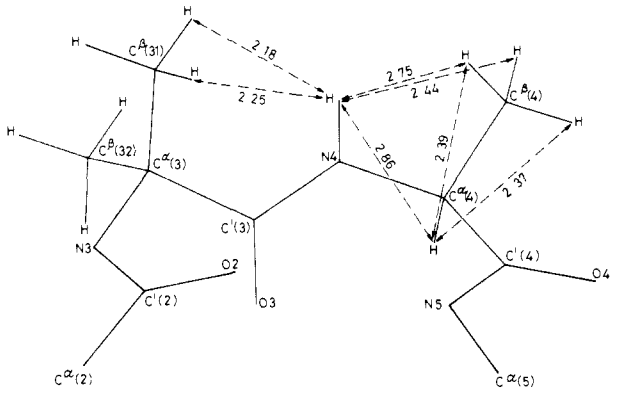

Figure 4. Schematic representation of the Aib-Ala type II' β-turn segment with interproton distances as found in the crystal. Double-edged arrows indicate diagnostically useful NOEs. In solution the methyl groups may be rotating.

deg cm^2 dmol^{-1}) are as follows: $CHCl_3$, 270 (-6550); $(CH_3)_2CO$, 273 (-2750); dioxane, 268 (-6250); dioxane-hexane (1:1), 260 (-7750); methanol, 270 (-4000); methanol-water (1:1), 270 (-3000); trifluoroethanol, 272 (-2530); trimethyl phosphate, 272 (-2950). The relatively high ellipticity values in apolar solvents are characteristic of a conformationally rigid disulfide chromophore.[24] The observed negative sign of the CD band is consistent with a right-handed chirality having $\chi_{SS} \sim 110 \pm 10°$, as suggested for a 2,7-cystine-gramicidin S analogue.[25] This is an excellent agreement with the χ_{SS} value of 101° in the crystal structure. In more polar solvents, the diminished ellipticity values suggest enhanced flexibility about the S-S linkage.

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Registry No. 1, 112159-35-0.

Supplementary Material Available: Tables of anisotropic thermal parameters of non-hydrogen atoms and atomic coordinates of hydrogen atoms (2 pages); observed and calculated structure factors (7 pages). Ordering information is given on any current masthead page.

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Communications to the Editor

Stereoselective Total Synthesis of (±)-Atisine via Intramolecular Double Michael Reaction

Masataka Ihara,† Makoto Suzuki,† Keiichiro Fukumoto,*† Tetsuji Kametani,‡ and Chizuko Kabuto§

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
Institute of Medicinal Chemistry, Hoshi University Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan
Instrumental Analysis Center for Chemistry Faculty of Science, Tohoku University Aobayama, Sendai 980, Japan

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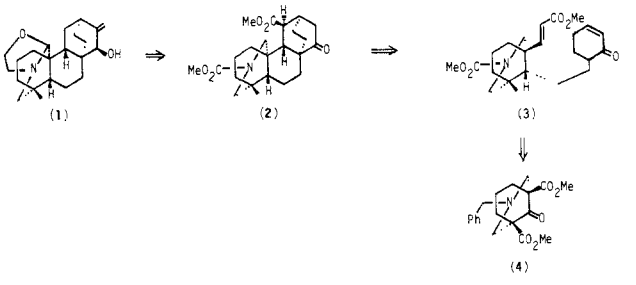
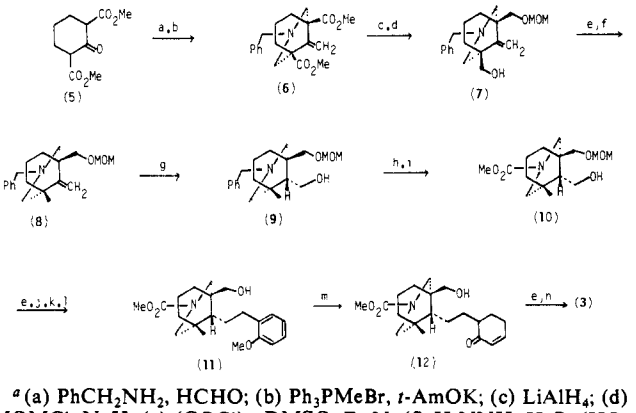
Atisine, the predominant alkaloid of *Aconitum heterophyllum*, possesses a unique hexacyclic structure **1** including azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane rings[1] and has attracted the attention of synthetic organic chemists as a target molecule due to its architectural features. Three different routes[2] have been successful in reaching Pelletier's synthetic intermediates[3,4] for atisine. Recently a new methodology for construction of bicyclo[2.2.2]octane skeleton employing an intramolecular double Michael reaction was developed by us.[5] We envisioned assembly of a synthetic intermediate **2** of the aconitium alkaloid by its exploitation and preparation of the substrate **3** of the key reaction starting from a symmetrical azabicyclo[3.3.1]nonane derivative **4**. Here we wish to communicate a stereocontrolled formal total

Scheme I



Scheme II[a]



[a] (a) $PhCH_2NH_2$, HCHO; (b) Ph_3PMeBr, *t*-AmOK; (c) $LiAlH_4$; (d) MOMCl, NaH; (e) $(COCl)_2$, DMSO; Et_3N; (f) $H_2NNH_2 \cdot H_2O$, $(HOCH_2CH_2OCH_2)_2$, NaOH, 150 → 180 °C; (g) $NaBH_4$, $BF_3 \cdot Et_2O$, $(MeOCH_2CH_2)_2O$; $Me_3N \rightarrow O$; (h) 10% Pd-C, HCO_2NH_4; (i) $ClCO_2Me$, K_2CO_3; (j) *o*-methoxybenzyltriphenylphosphonium bromide, *n*-BuLi; (k) H_2, 10% Pd-C; (l) concentrated HCl; (m) Na, liquid NH_3, EtOH, diluted HCl; (n) $Ph_3P{=}CHCO_2Me$.

† Pharmaceutical Institute, Tohoku University.
‡ Hoshi University.
§ Instrumental Analysis Center for Chemistry, Tohoku University.

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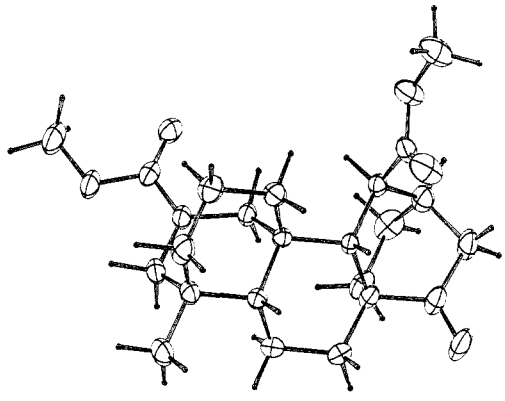


Figure 1. Molecular structure of 2.

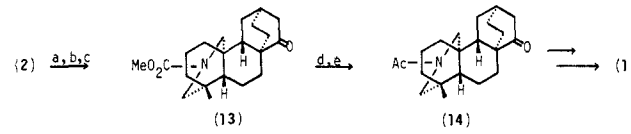
synthesis of (±)-atisine (1) according to this strategy as shown in Scheme I.

The azabicyclononane 4 corresponding to the AE part was synthesized in 97% yield by double Mannich reaction from diester 5[6a] using benzylamine and formaldehyde.[6b] The ketone 4, mp 121-122 °C, was treated with $Ph_3P{=}CH_2$ to afford methylene 6 in 78% yield. Conversion of 6 into asymmetrical 7 was carried out by two steps: reduction of 6 with $LiAlH_4$ (93%) and monoprotection of the resulting diol with methoxymethyl (MOM) group[7] (see Scheme II). The accompanied di-MOM ether was quantitatively hydrolyzed to the diol, which was recycled to monoether 7. Thus the diol was transformed into 7 in 61% yield. Conversion of 7 into ether 8 was performed by Swern oxidation (98%) followed by Wolff-Kishner reduction (80%). Stereoselective anti-Markovnikov hydration was achieved by reaction of 8 with $NaBH_4$ in the presence of $BF_3{\cdot}Et_2O$[8] and subsequent oxidation with $Me_3N \rightarrow O$[9] to give primary alcohol 9 in 72% yield along with a stereoisomer (5%). When hydroboration was carried out by using ordinary boranes, two isomers of nearly equal amount formed. Coordination of the amino group with BF_3 hindering the approach of borane would bring about the desired stereoselectivity. The stereochemistry of 9 was ascertained by ^1H NMR NOE experiments. Positive NOE effects were observed between the carbinol CH_2 and $-N(CH_2)_2$ of 9, while the isomer showed no NOE between those. Since oxidation of 9 to corresponding aldehyde failed because of the amino group existing near the hydroxyl group, 9 was transformed into urethane 10 in 86% overall yield after removal of the *N*-benzyl group.[10] Swern oxidation of 10 (96%), followed by Wittig reaction (98%), hydrogenation of the olefin, and deblocking of the MOM group (82% for two steps) gave the alcohol 11. Transformation of 11 into the key substrate 3 was accomplished by the following sequence: (1) Birch reduction followed by acidic treatment (65%), (2) Swern oxidation of enone 12 (69%), and (3) Wittig reaction (97%).

Intramolecular double Michael reaction[5] of 3 was conducted by using $LiN(SiMe_3)_2$ in Et_2O-hexane (1:6) at -78 ~ 0 °C to furnish the objective pentacyclic ketone 2 in 43% yield together with one stereoisomer[11] (8%). The structure of 2, mp 172-173 °C, was indicated from spectral data and verified by an X-ray analysis.[12] The molecular structure of 2 is shown in Figure 1.

After hydrolysis of 2 (88%), the decarboxylation was performed in 48% overall yield according to the established method.[13]

Scheme III[a]



(13) (14)

[a] (a) KOH; (b) $(COCl)_2$, DMF; (2) 2-mercaptopyridine-*N*-oxide Na, DMAP, toluene, reflux; *n*-Bu_3SnH, AIBN, reflux; (d) Me_3SiI; (e) AcCl, aqueous $NaHCO_3$.

Urethane 13 was transformed into acetamide 14 in 63% overall yield by exposure to Me_3SiI[14] followed by acetylation (see Scheme III). IR data of 14, mp 191-193 °C, were identical with reported ones,[3b] and the 500 MHz ^1H NMR data well supported structure 14, although the spectrum was complicated due to rotational isomers. Since 2 has been correlated with atisine by Pelletier and co-workers,[3] the present work represents a stereoselective formal total synthesis of (±)-atisine.

Noteworthy features of the present work form the viewpoint of synthetic methodology include the following: (1) the use of the azabicyclononane 4 readily available by a double Mannich reaction, (2) the stereoselective hydroboration in the presence of $BF_3{\cdot}Et_2O$, and (3) the stereoselective construction of the bicyclo[2.2.2]octane ring by an intramolecular double Michael reaction.

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(11) Removal of the methoxycarbonyl group of the minor product gave a ketone different from 13, and the stereochemistry remained obscure.
(12) Monoclinic, space group $P2_1/c$ with a = 18.991 (1) Å, b = 7.651 (1) Å, c = 14.707 (1) Å, β = 93.73° (1), V = 2132.4 (3) Å^3, Z = 4. Final R value was 0.059 (R_w = 0.051) for 3370 reflections with $|F_o| > 3\sigma(|F_o|)$.
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Negative Hyperconjugation. The Rotation-Inversion Barrier in α-Fluoramines

M. Moklesur Rahman and David M. Lemal*

Department of Chemistry, Dartmouth College Hanover, New Hampshire 03755

W. P. Dailey

Department of Chemistry, University of Pennsylvania Philadelphia, Pennsylvania 19104

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Despite a controversial history,[1] negative hyperconjugation (or the generalized anomeric effect) now rests on a solid foundation, both experimental and theoretical.[2,3] It manifests itself in many ways, among them the anomeric effect per se:[4] the mutual strengthening and shortening of bonds from a carbon to more than one fluorine[5] and the stabilization of anions having β-fluoro substituents.[6] Particularly dramatic recent evidence for negative hyperconjugation is provided by the trifluoromethoxide ion, whose crystal structure reveals an unusually short C-O bond and stretched C-F bonds.[7]

Among neutral species, negative hyperconjugation should be especially important when the excellent lone-pair donor di-

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