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5-Cyano-1-azabicyclo[3.3.0]octane (**1**) was prepared in one step from 1,7-dichloro-4-heptanone (**4**) under mild conditions. The application of this method for the preparation of 5-cyano-4,6-dimethyl-1-azabicyclo[3.3.0]octane (**11**) gave two diastereomers in equilibrium. The NMR measurements of **11** and its reduced compound **15** showed that the major isomer is the *cis-exo* form, and the minor isomer is the *trans* form. Molecular orbital calculations indicated that the *cis-exo* form is more stable than the *trans* form, in agreement with the experimental results. Furthermore, 6-cyano-1-azabicyclo[4.3.0]nonane (**17**) and 1-azabicyclo[4.4.0]decane (**19**), both including a six-membered ring, were prepared from appropriate haloketones by using this double cyclization method.

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## Introduction.

1-Aazabicyclo[3.3.0]octane is a useful amine moiety for producing biologically active substances, for example, antiarrhythmic agents, cerebral function activators, and muscarinic $M_1$ receptor agonists (Figure 1) [1]. 5-Cyano-1-azabicyclo[3.3.0]octane (**1**) is a useful intermediate for introducing a 1-azabicyclo[3.3.0]octane ring through a conversion of a cyano group to various functional groups [2]. However, the known preparation methods for **1** require many steps, as well as the handling of an unstable intermediate [3,4]. In this paper, we describe a novel preparation method for **1** that avoids these disadvantages [5]. We discuss the stereochemistry involved in the formation of this ring with methyl groups. We also describe the formation of 1-azabicyclic compounds containing a six-membered ring.

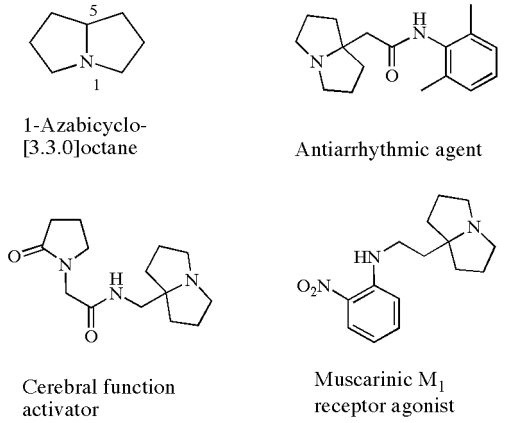
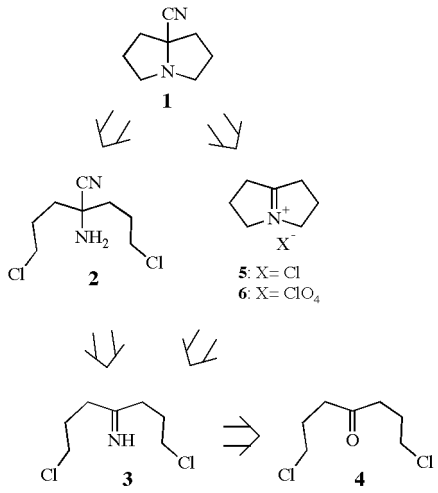



Figure 1. Biologically active substances with 1-azabicylco[3.3.0]octane.

## Results and Discussion.

The retrosynthesis of **1** is shown in Scheme 1. Compound **1** might be synthesized by double cyclization of 2-amino-5-chloro-2-(3-chloropropyl)pentanenitrile (**2**),

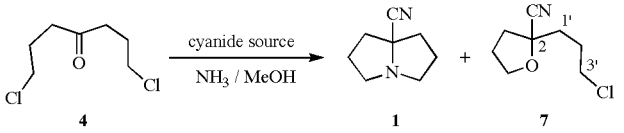
Scheme 1




which is an intermediate of the Strecker reaction [6] of 1,7-dichloro-4-heptanone (**4**) [7] *via* imine **3**. Alternatively, double cyclization of **3** can lead to 1-azoniabicyclo-[3.3.0]oct-1(5)-ene chloride (**5**); the known perchlorate **6** [3a] can be transformed to **1** *via* addition of cyanide ion. When we first stirred **4** in MeOH with acetone cyanohydrine (**8**) and ammonia, we obtained a mixture of **1** and 2-(3-chloropropyl)tetrahydrofuran-2-carbonitrile (**7**) (Table 1, entry 1). Compound **7** was formed by transcyanation of **4** prior to imine formation, and subsequent cyclization. When we replaced **8** by the more stable 2-amino-2-methylpropanenitrile (**9**) [8] as a cyanide source, we obtained **1** in 83% yield without the formation of **7** (Table 1, entry 2).

The reaction of **10** [9] with **9** and ammonia in a sealed tube at 50° gave **11** as a mixture of two diasteroisomers in 40% yield. The $^1$H NMR spectrum analysis indicated that the major (*cis*) isomer had only one signal peak for the methyl hydrogens at δ 1.25 ppm, and the minor (*trans*) isomer had two signal peaks for the methyl hydrogens at δ

Table 1



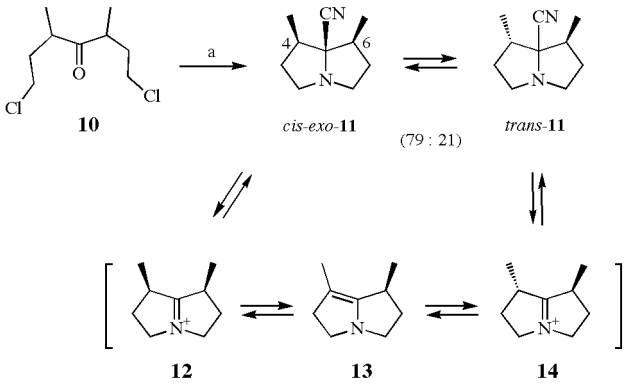

**4** **1** **7**

Double Cyclization of **4** to **1**

| entry | cyanide source | conditions | products (%) |
|---|---|---|---|
| 1 | $(CH_3)_2C(OH)CN$ (**8**) (10 eq.) | 20°, 24 hours | **1** (60), **7** (8.2) |
| 2 | $(CH_3)_2C(NH_2)CN$ (**9**) (3 eq.) | 20°, 24 hours | **1** (83) |

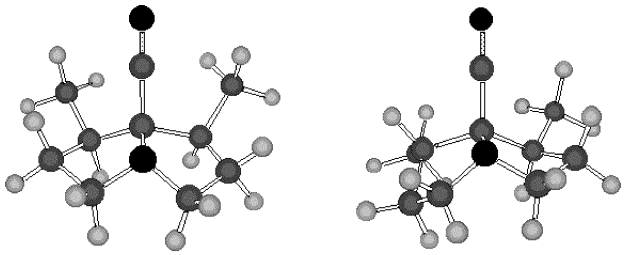
1.14 ppm and δ 1.23 ppm. The observed *cis*/*trans* ratio was 79:21 (Scheme 2). Furthermore, the fact that the methine protons at the 4- and 6-positions of **11** were replaced with deuterium at room temperature in deuterated methanol indicated that *cis*-**11** and *trans*-**11** are in a thermodynamic equilibrium *via* **12**, **13**, and **14** (Scheme 2). The *ab initio* MO calculations at MP2/6-31G* showed that *cis-exo*-**11** is 1.8 kcal $mol^{-1}$ more stable than *trans*-**11**, a finding in accord with the experimental results (Figure 2). Meanwhile, *cis-endo*-**11** could not be formed because of the instability caused by the steric repulsion between the methyl groups; the relative energy difference between *cis-exo*-**11** and the hypothetical *cis-endo*-**11** was calculated as 6.7 kcal $mol^{-1}$.

Scheme 2




Reagents and Conditions: (a) $NH_3$ (excess), **9** (3 eq.), MeOH in sealed tube, 50°, overnight (40%).

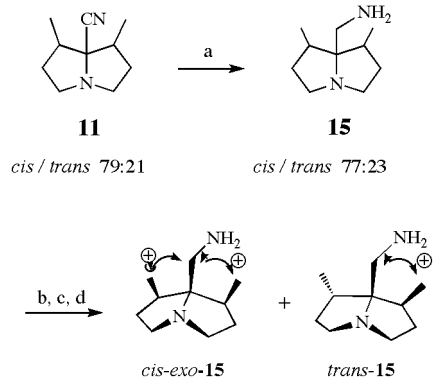
Compound **11** was reduced to generate **15** using $LiAlH_4$ without changing the ratio of the diastereoisomers. The mixture of diastereoisomers was converted to benzyl carbamates, separated by chromatography on alumina, and hydrogenated with 5% Pd-C to give each isomer of **15** (Scheme 3). The $^1H$ NMR spectrum showed that the major isomer had one signal peak (δ 1.03 ppm) for the methyl hydrogens, and the protons of the $CH_2$-$NH_2$ methylene group are magnetically equivalent. The minor isomer



*cis-exo*-**11**: -498.512278 (0.0) *trans*-**11**: -498.509445 (1.8)

Figure 2. Optimized structures and energies (Hartree) of *cis-exo*-**11** and *trans*-**11** at the MP2/6-31G* level. Numbers in parentheses are relative energies in kcal $mol^{-1}$.

Scheme 3



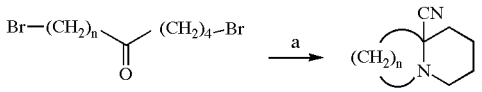

Reagents and Conditions: (a) $LiAlH_4$, $Et_2O$, reflux, 3 hours (78%); (b) CbzCl, NaOH, dioxane/$H_2O$, room temperature, overnight; (c) chromatography on $Al_2O_3$; (d) $H_2$, 5% Pd/C, EtOH, room temperature, overnight (*cis-exo*-**15**, 49%; *trans*-**15**, 8.9%); (+) NOE correlations observed from NOESY spectra.

showed two signal peaks (δ 0.97 ppm and δ 1.04 ppm) for the methyl hydrogens, and the methylene protons of the $CH_2$-$NH_2$ group are in this case nonequivalent. These results indicate that the major isomer is in the symmetric *cis* form, while the minor isomer is in the *trans* form. Furthermore, a NOE correlation from the NOESY spectrum of the *cis* isomer was observed between the signals at δ 2.52 ppm, corresponding to the $CH_2$-$NH_2$ methylene group, and at δ 1.03 ppm, corresponding to the methyl groups; this result indicated the *cis-exo* configuration. In the *trans* isomer, a NOE correlation was observed between the signals (δ 2.50 ppm and δ 2.56 ppm) corresponding to the $CH_2$-$NH_2$ methylene group and the signal at δ 0.97 ppm, corresponding to the *exo*-methyl group.

The reaction of **16** [10] at 20° for 24 hours with ammonia and **9** gave 6-cyano-1-azabicyclo[4.3.0]nonane (**17**) [11] in 57% yield (Scheme 4); the reaction of **18** [10] gave 6-cyano-1-azabicyclo[4.4.0]decane (**19**) [11] in 21% yield.

In conclusion, we have developed a novel method for preparing **1** by double cyclization of **4**. The application of this method to the preparation of **11** gave two diastereoisomers

Scheme 4




**16** (n = 3) **17** (n = 3)
**18** (n = 4) **19** (n = 4)

Reagents and Conditions: (a) $NH_3$ (excess), **9** (3 eq.), MeOH, room temperature, 24 hours (**17**, 57%; **19**, 21%).

reflecting possible configurations of the methyl groups. The observed ratio of the isomers as determined by NMR measurements is consistent with the relative energies estimated by *ab initio* MO calculations. Furthermore, this reaction was applied to prepare six-five and six-six fused-ring systems in the case of compounds **17** and **19**. The conversion of the nitrile group to various functional groups allows the transformation of bicyclic amine moieties into various biologically active substances. The introduction of a cyanomethyl group [12], an ethoxycarbonylmethyl group [12], and a nitromethyl group [1b] to this ring has been reported by modifications of the presented method. Further applications of this method are expected.

## EXPERIMENTAL

Infrared (IR) spectra were obtained on a JASCO FT/IR-8000 or a PERKIN ELMER FTIR 1600, and NMR spectra were obtained using a JEOL JNM-GSX270 spectrometer (270 MHz for $^1H$ and 68 MHz for $^{13}C$) or a JEOL JNM-ECP400 (400 MHz for $^1H$ and 100 MHz for $^{13}C$) using tetramethylsilane (TMS) as an internal standard. The mass spectra were obtained on a JEOL JMS-DX 300 spectrometer.

Computational Methods.

All of the *ab initio* MO calculations were carried out using the Gaussian98 software package [13]. Geometries were fully optimized at the MP2/6-31G* level.

5-Cyano-1-azabicyclo[3.3.0]octane (**1**).

To a solution of $NH_3$ (27 g, 1.6 mol) in MeOH (150 g), **4** (30 g, 0.16 mol) and **9** (41 g, 0.49 mol) were added at 5°. The mixture was stirred at 20° for 24 hours, and concentrated. The residue was dissolved in 5 *N* NaOH aqueous solution, and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$, concentrated, and distilled to give **1** (18 g, 81%) as a colorless oil, bp 91-94° (4.4 mmHg) [Lit. [3a] 93-94° (5 mmHg)]; $^1H$ NMR ($CDCl_3$): δ 1.76-2.10 (m, 6H, H3, H7, two protons of H4 and H6), 2.27-2.38 (m, 2H, two protons of H4 and H6), 2.53-2.63 and 3.07-3.25 (m, 4H, H2, H8); $^{13}C$ NMR ($CDCl_3$): δ 26.40 (C3, C7), 38.45 (C4, C6), 55.33 (C2, C8), 67.09 (C5), 124.56 (CN); IR (neat): 2969, 2870 (C-H), 2232 (CN) $cm^{-1}$; HRMS (EI): calcd for $C_8H_{12}N_2$ ($M^+$) 136.1000, found 136.0982.

2-(3-Chloropropyl)tetrahydrofuran-2-carbonitrile (**7**).

To a solution of $NH_3$ (0.60 g, 35 mmol) in MeOH (5 mL), **4** (0.50 g, 2.7 mmol) and **8** (2.3 g, 27 mmol) were added at 5°. The mixture was stirred at 20° for 24 hours, and concentrated. The residue was dissolved in 1 *N* aqueous solution, and extracted with $CH_2Cl_2$. The organic layers were combined, dried over $Na_2SO_4$, concentrated, and purified by chromatography on silica (n-hexane/EtOAc) to give **7** (39 mg, 8.2%) as a colorless oil, $^1H$ NMR ($CDCl_3$): δ 1.86-2.46 (m, 8H, H3, H4, H2', H1'), 3.58-3.65 (m, 2H, H3'), 4.01 (t, *J* = 6.8 Hz, 2H, H5); $^{13}C$ NMR ($CDCl_3$): δ 24.78 and 27.88 (C4, C2'), 35.88 and 37.52 (C3, C1'), 44.22 (C3'), 68.83 (C5), 78.92 (C2), 120.46 (CN); IR (neat): 2963, 2882 (C-H), 2232 (CN) $cm^{-1}$; HRMS (EI): calcd for $C_8H_{12}ClNO$ ($M^+$, $^{35}Cl$) 173.0607, found 173.0596.

5-Cyano-4,6-dimethyl-1-azabicyclo[3.3.0]octane (**11**).

To a solution of **10** (1.0 g, 4.7 mmol) and **9** (1.2 g, 14 mmol) in MeOH (1 mL), $NH_3$ (1.8 g, 0.11 mol) was introduced at -50°. The mixture was stirred in a sealed tube at 50-60° overnight. After cooling, the resulting mixture was poured into $Et_2O$, and a precipitate was filtered off. The filtrate was concentrated, and purified by chromatography on alumina (*n*-hexane/EtOAc 50:1) to give **11** (0.31 g, 40%, the ratio of the isomers was 79:21) as a colorless oil, $^1H$ NMR ($CDCl_3$): major isomer δ 1.25 (d, *J* = 6.4 Hz, 6H, $CH_3$x2), 1.84-2.13 (m, 6H, H3, H4, H6, H7), 2.47-2.56 and 3.21-3.28 (m, 4H, H2, H8); minor isomer δ 1.14 (d, *J* = 7.3 Hz, 3H, $CH_3$), 1.23 (d, *J* = 5.9 Hz, 3H, $CH_3$), 1.46-1.60 and 1.88-2.10 (m, 5H, H3, H7, one proton of H4 and H6), 2.41-2.69 (m, 3H, one proton of H4 and H6, two protons of H2 and H8), 3.04-3.15 (m, 2H, two protons of H2 and H8); $^{13}C$ NMR ($CDCl_3$): major isomer δ 15.89 ($CH_3$), 36.53 (C3, C7), 43.50 (C4, C6), 54.53 (C2, C8), 77.79 (C5), 119.93 (CN); minor isomer δ 13.89, 15.75, 32.36, 35.22, 37.62, 43.06, 53.83, 55.33, 74.23, 122.53; IR (neat): 2964, 2926 (C-H), 2219 (CN) $cm^{-1}$; HRMS (EI): calcd for $C_{10}H_{16}N_2$ ($M^+$) 164.1313, found 164.1289.

5-Aminomethyl-4,6-dimethyl-1-azabicyclo[3.3.0]octane (**15**).

A solution of **11** (0.38 g, 2.3 mmol) in ether (3 mL) was added dropwise to a suspension of $LiAlH_4$ (0.26 g, 6.8 mmol) in ether (7 mL) under reflux. The mixture was refluxed for 3 hours, quenched with water (0.26 mL), 15% NaOH (0.26 mL) and water (0.79 mL). The white precipitate was filtered off, and the filtrate was concentrated to give a mixture of two diastereoisomers of **15** (0.30 g, the ratio of the isomers was 77:23) as a colorless oil. To a solution of **15** (0.30 g, 1.8 mmol) in dioxane (0.5 mL) and 5 *N* NaOH (0.54 mL, 2.7 mmol), CbzCl (0.40 g, 2.3 mmol) was added at 4°. The solution was stirred overnight at room temperature, and extracted with EtOAc. The organic layer was dried over $Na_2SO_4$ and concentrated. The resulting mixture was separated into a major isomer (0.28 g) and a minor isomer (0.053 g) by chromatography on alumina (*n*-hexane/EtOAc). Each solution of the isomers in EtOH was stirred under $H_2$ with 5% Pd-C (20 wt%) overnight at room temperature, and filtered. The filtrates were concentrated to give *cis-exo*-**15** (0.15 g, 49%) and *trans*-**15** (0.027 g, 8.9%) as colorless oils, respectively. *cis-exo*-**15**: $^1H$ NMR ($CDCl_3$): δ 1.03 (d, *J* = 7.0 Hz, 6H, $CH_3$x2), 1.73-2.03 (m, 6H, H3, H4, H6, H7), 2.52 (s, 2H, C$H_2$NH$_2$), 2.49-2.55 and 3.14-3.18 (m, 4H, H2, H8); $^{13}C$ NMR ($CDCl_3$): δ 14.40 ($CH_3$), 37.51 (C3, C7), 43.63 ($CH_2NH_2$), 45.13 (C4, C6), 55.27 (C2, C8), 75.14 (C5); IR (neat): 3329 (N-H), 2953, 2876 (C-H) $cm^{-1}$; HRMS (EI): calcd for $C_9H_{16}N$ (M-$CH_2NH_2$)$^+$ 138.1283, found 138.1278. *trans*-**15**: $^1H$ NMR ($CDCl_3$): δ 0.97 (d, *J* = 7.0 Hz, 3H, *exo*-$CH_3$), 1.04 (d, *J* = 7.0 Hz, 3H, *endo*-$CH_3$), 1.46-1.96 (m, 4H, H3, H7), 1.80-1.96 (m, 1H, *endo*-CH), 2.14-2.24 (m, 1H, *exo*-CH), 2.50 and 2.56 (d, *J* = 12.5 Hz, 2H, C$H_2$NH$_2$), 2.37-2.43,

2.56-2.60, 2.75-2.82 and 3.11-3.15 (m, 4H, H2, H8); $^{13}$C NMR ($CDCl_3$): δ 13.68 (s, 3H, *exo*-$CH_3$), 14.05 (s, 3H, *endo*-$CH_3$), 32.04 and 34.19 (C3, C7), 37.39 and 37.82 (C4, C6), 44.75 ($CH_2NH_2$), 54.63 and 55.34 (C2, C8), 74.55 (C5); IR (neat): 3364 (N-H), 2957, 2875 (C-H) cm$^{-1}$; HRMS (EI): calcd for $C_9H_{16}N$ (M-$CH_2NH_2$)$^+$ 138.1283, found 138.1294.

6-Cyano-1-azabicyclo[4.3.0]nonane (**17**).

By using a similar procedure as that described for **1**, **17** was prepared from **16** (0.50 g, 1.7 mmol) and isolated after chromatography on alumina (*n*-hexane/EtOAc) as a colorless oil (0.15 g, 57%), $^1$H NMR ($CDCl_3$): δ 1.38-1.90 and 2.34-2.53 (m, 10H, H3, H4, H5, H7, H8), 2.08-2.27 and 2.92-3.01 (m, 4H, H2, H9); $^{13}$C NMR ($CDCl_3$): δ 19.28 (C8), 21.55 (C4), 24.51 (C3), 34.07 and 36.78 (C5 and C7), 48.01 and 51.11 (C2 and C9), 63.86 (C6), 118.71 (CN); IR (neat): 2938 (C-H), 2214 (CN) cm$^{-1}$; HRMS (EI): calcd for $C_{10}H_{16}N_2$ ($M^+$) 150.1157, found 150.1148.

6-Cyano-1-azabicyclo[4.4.0]decane (**19**).

By using the same procedure as described for **17**, **19** (34 mg, 21%) was prepared from **18** (300 mg, 1.0 mmol) as a colorless oil, $^1$H NMR ($CDCl_3$): δ 1.48-1.87 (m, 12H, H3, H4, H5, H7, H8, H9), 2.33-2.40 and 2.65-2.69 (m, 4H, H2, H10); $^{13}$C NMR ($CDCl_3$): δ 21.42 (C4, C8), 25.01 (C3, C9), 36.89 (C5, C7), 52.43 (C2, C10), 64.34 (C6), 118.04 (CN); IR (neat): 2939 (C-H), 2215 (CN) cm$^{-1}$; HRMS (EI): calcd for $C_{10}H_{16}N_2$ ($M^+$) 164.1313, found 164.1312.

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