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# *exo*-Adduct Predominance in the Diels-Alder Reaction of Novel 1,3-Bis-(trimethylsiloxy)cyclohexa-1,3-dienes with Acrylonitrile[1)]

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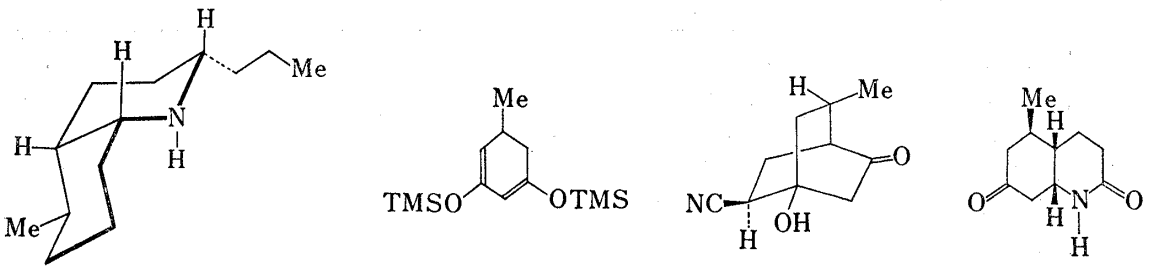
The Diels-Alder reaction of the novel 1,3-bis(trimethylsiloxy)cyclohexa-1,3-dienes (**3a**—**3c**) with acrylonitrile followed by hydrolysis afforded the *exo*-2-cyano-1-hydroxybicyclo[2.2.2]octanes (**4a**—**4c**) and the *endo*-2-cyano-1-hydroxybicyclo[2.2.2]octanes (**5a**—**5c**) as the major and the minor adducts, respectively. The configuration of the cyano group of the adducts were inferred from the nuclear magnetic resonance spectral inspections of the appropriate derivatives obtained from the adducts and these assignments of the adducts (**4a**, **4b**, **5a**, and **5b**) were supported by chemical evidence.

**Keywords**——1,3-bis(trimethylsiloxy)cyclohexa-1,3-dienes; Diels-Alder reaction; Alder-rule exception; bicyclo[2,2,2]octane; iodolactonization

Pumiliotoxin C (**1**) is one of a group of toxic alkaloids isolated from the skin extract of Central American arrow poison frogs, *Dendrobates pumilio* and *D. auratus*.[3)] Extensive synthetic efforts have been made on the toxin, culminating in seven independent total syntheses.[1,4)] One of our synthetic strategies for the stereoselective synthesis of pumiliotoxin C (**1**) was based on the synthesis of the keto-lactam (**2**) with three of the four chiral centers of the toxin *via* the Diels-Alder cycloadduct such as 1-hydroxybicyclo[2.2.2]octane derivative (**4b**). The 1,3-bis(trimethylsiloxy)cyclohexa-1,3-dienes would be suitable as a diene component in the Diels-Alder reaction for the preparation of the 1-hydroxybicyclo[2.2.2]octane derivatives, since facile removal of trimethylsilyl group from the resulting cycloadducts could be expected.

In the previous paper,[1)] the authors reported that the Diels-Alder reaction of acrylonitrile with novel 1,3-bis(trimethylsiloxy)-5-methylcyclohexa-1,3-diene (**3b**) was effectively employed for the stereoselective synthesis of pumiliotoxin C (**1**) and the *exo*-adduct predo-



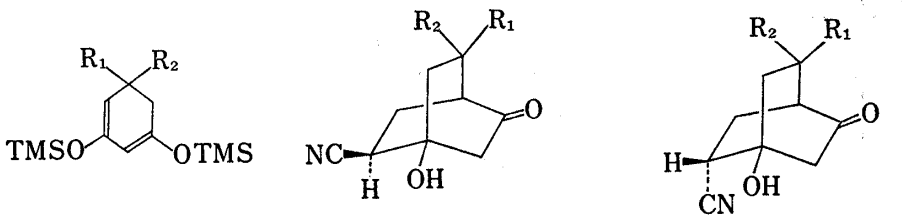

**1** **3b** **4b** **2**

Chart 1

1) A preliminary communication of a part of this work appeared in *Tetrahedron Lett.*, **1976**, 3169.
2) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*
3) *a*) J.W. Daly, T. Tokuyama, G. Habermehl, I.L. Karle, and B. Witkop, *Ann. Chem.*, **729**, 198 (1969); *b*) D. Mebs, *Experientia*, **29**, 1328 (1973).
4) *a*) T. Ibuka, N. Masaki, I. Saji, K. Tanaka, and Y. Inubushi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2779 (1975); *b*) W. Oppolzer, W. Fröstl, and H.P. Weber, *Helv. Chim. Acta*, **58**, 593 (1975); *c*) G. Habermehl, H. Andres, K. Miyahara, B. Witkop, and J.W. Daly, *Ann. Chem.*, **1976**, 1577; *d*) W. Oppolzer, C. Fehr, and J. Warneke, *Helv. Chim. Acta*, **60**, 48 (1977); *e*) W. Oppolzer and E. Flaskamp, *Helv. Chim. Acta*, **60**, 204 (1977); *f*) L.E. Overman and P.J. Jessup, *Tetrahedron Lett.*, **1977**, 1253.

minance in this reaction was suggested. We report here further details of the *exo*-adduct predominance in the Diels-Alder reaction of acrylonitrile not only with the diene (**3b**) but with two novel dienes (**3a**) and (**3c**).

Treatment of cyclohexane-1,3-dione, 5-methylcyclohexane-1,3-dione, and dimedone with trimethylchlorosilane in the presence of $Et_3N$–$ZnCl_2$[5] in ether afforded the dienes, (**3a**), (**3b**), and (**3c**), respectively, in a high yield. The Diels-Alder reaction of these dienes (**3a**—**3c**) with acrylonitrile gave a mixture of cycloadducts. Because of its highly moisture-sensitive property, the mixture, without separation, was treated with a dilute acid to yield a separable pair of cycloadducts (see Table I).




**3a**: $R_1=R_2=H$ **4a**: $R_1=R_2=H$ **5a**: $R_1=R_2=H$
**3b**: $R_1=Me$, $R_2=H$ **4b**: $R_1=Me$, $R_2=H$ **5b**: $R_1=Me$, $R_2=H$
**3c**: $R_1=R_2=Me$ **4c**: $R_1=R_2=Me$ **5c**: $R_1=R_2=Me$

Chart 2

Table I. Product Ratios for the Diels-Alder Reaction of the Dienes (**3a**—**3c**) with Acrylonitrile in Xylene

| Diene | Reaction Temp. and time | Ratio of products[a] *exo*-CN | | *endo*-CN | | Yield |
|---|---|---|---|---|---|---|
| **3a** | 170° (48 hr) | **4a** | 82% | **5a** | 18% | 31% |
| **3b** | 170° (96 hr) | **4b** | 75.7% | **5b** | 24.3% | 67%[b] |
| **3c** | 140° (72 hr) | **4c** | 78.5% | **5c** | 21.5% | 81% |

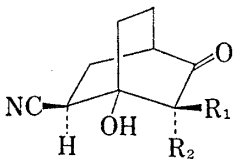
*a*) The ratio of the *exo*-CN to the *endo*-CN was determined by GC analysis.
*b*) Though not isolated, other two stereoisomers with respect to the $C_8$ methyl group were detected in *ca.* 9% yield judging from NMR and GC analyses.

The *endo*-addition rule of Alder[6] and the orbital symmetry rule of Woodward and Hoffmann[7] state that during the Diels-Alder reaction the diene and the dienophile orientate themselves preferentially into an *endo* position, and this results in complete or preferential formation of the *endo*-adduct. However, there have been reported a few exceptions to this rule.[8] Therefore, the configuration of the cyano group of the adduct from the novel dienes (**3a**—**3c**) should be unambiguously established. Since the routine techniques such as nuclear magnetic resonance (NMR) and infrared (IR) spectral methods were not accessible for the

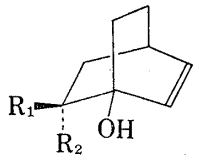
5) *a*) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974); *b*) *Idem*, *J. Org. Chem.*, **40**, 538 (1975).
6) *a*) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937); *b*) A.S. Onishchenko, "Diene Synthesis," Israel Program of Scientific Translations, Daniel Davy and Co., New York, N.Y., 1964, pp. 37—59; *c*) A. Wassermann, "Diels-Alder Reactions," Elsevier, Amsterdam, 1964, pp. 26—31, 74—83.
7) R. Hoffmann and R.B. Woodward, *J. Am. Chem. Soc.*, **87**, 4388 (1965).
8) *a*) R.B. Woodward and H. Bear, *J. Am. Chem. Soc.*, **70**, 1161 (1948); *b*) F.A.L. Anet, *Tetrahedron Lett.*, **1962**, 1219; *c*) M. Schwarz and M. Maienthal, *J. Org. Chem.*, **25**, 449 (1960); *d*) A.J. Birch, P.L. Macdonald, and V.H. Powell, *J. Chem. Soc.* (*C*). **1970**, 1469; *e*) F. Kienzle, *Helv. Chim. Acta*, **58**, 1180 (1975); *f*) K. Alder, H. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958); *g*) I. Alfaro, W. Ashton, L.D. McManus, R.C. Newstead, K.L. Rabone, N.A. Rogers, and W. Kernick, *Tetrahedron*, **26**, 201 (1970).

determination of the stereochemistry of the cycloadducts (**4a**—**4c**) and (**5a**—**5c**) themselves, the adducts were transformed into suitable derivatives for the structural analysis.

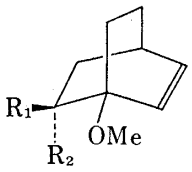
Configurations of the cyano group of the adducts (**4a**) and (**5a**) were determined through the following transformation. Bromination of the keto-nitrile (**4a**) with pyridinium hydrobromide perbromide ($C_5H_5NHBr_3$)[9] afforded a mixture of two kinds of the monobromo-ketones, (**6**) and (**7**), and the dibromo-ketone (**8**) in 91% and 8% yields, respectively. Reduction of the mixture of the monobromo-ketones with $NaBH_4$ gave a mixture of bromohydrins which was allowed to react with Zn-AcOH to give the hydroxynitrile (**9**) in 95% overall yield. The hydroxy-nitrile (**9**) was also obtained from the dibromo-ketone (**8**) by the same treatments in 95% overall yield. Methylation of the compound (**9**) with NaH–$CH_3I$ gave the methoxy-nitrile (**11**) in 74% yield.



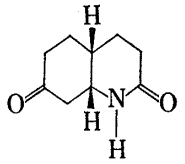
**6**: $R_1$=H, $R_2$=Br
**7**: $R_1$=Br, $R_2$=H
**8**: $R_1$=$R_2$=Br



**9**: $R_1$=CN, $R_2$=H
**10**: $R_1$=H, $R_2$=CN



**11**: $R_1$=CN, $R_2$=H
**12**: $R_1$=H, $R_2$=CN

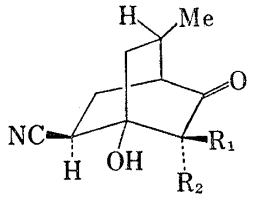


**13**

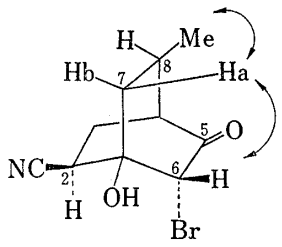
Chart 3

On the other hand, the keto-nitrile (**5a**) of the minor adduct was converted to the methoxy-nitrile (**12**) *via* the hydroxy-nitrile (**10**) in the same way as with **4a**. The methoxy-nitriles (**11**) and (**12**) were identified, respectively, with the samples of established stereostructures prepared from the Diels-Alder reaction of 1-methoxycyclohexa-1,4-diene with acrylonitrile.[8d] From these results, the configuration of the cyano group of the major Diels-Alder cycloadduct (**4a**) was determined to be *exo* and consequently, that of the cyano group of the minor adduct (**5a**) was assigned to be *endo*. It should be emphasized that treatment of both the bicyclo[2.2.2]-octane derivatives (**9**) and (**10**) with $HClO_4$–AcOH gave *cis*-decahydroquinol-2,7-dione (**13**) through the retroaldol type bond cleavage and the subsequent intramolecular Michael type addition.

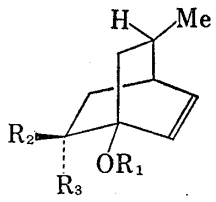
The stereochemistries of the cycloadducts (**4b**) and (**5b**) were elucidated in the following way. Bromination of the adduct (**4b**) with $C_5H_5NHBr_3$ gave the monobromo-ketone (**14**) and the dibromo-ketone (**15**) in 68% and 2% yields, respectively. The configurations of $C_6$–Br and $C_8$–$CH_3$ of the monobromo-ketone (**14**) were determined by the nuclear Overhauser effect (NOE) measurements. a) Irradiation of the doublet at $\delta$ 0.97 assignable to the $C_8$–$CH_3$ group led to



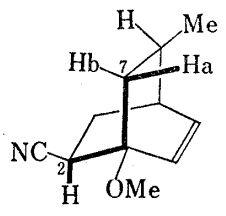
**14**: $R_1$=H, $R_2$=Br
**15**: $R_1$=$R_2$=Br



**16**



**17**: $R_1$=H, $R_2$=CN, $R_3$=H
**18**: $R_1$=Me, $R_2$=CN, $R_3$=H
**19**: $R_1$=Me, $R_2$=H, $R_3$=CN



**20**

Chart 4

9) C. Djerassi and C.R. Scholz, *J. Am. Chem. Soc.*, **70**, 417 (1948).

8% enhancement of the integrated intensity of the $C_7$–Ha signal at $\delta$ 1.45 (oct., $J$=14.0, 6.0, and 3.0 Hz). b) *ca.* 5% NOE enhancement of the singlet signal at $\delta$ 4.44 due to the $C_6$-proton geminal to the bromine was observed when irradiated the $C_7$-Ha signal at $\delta$ 1.45 [see formula (**16**)]. From these observations, the configuration of $C_6$–Br of **14** is *endo* and that of $C_8$–$CH_3$ *syn* to the carbonyl group, and it follows that the $C_8$–$CH_3$ group of **4b** is *syn* to the carbonyl group at $C_5$.

Both the bromo-ketones (**14**) and (**15**) were converted to the hydroxy-nitrile (**17**) by successive treatments with $NaBH_4$ and Zn–AcOH. Methylation of the hydroxy-nitrile (**17**) with NaH–$CH_3I$ or $Ag_2O$–$CH_3I$[10] gave the methoxy-nitrile (**18**) which was equilibrated by treatment with lithium diisopropylamide in tetrahydrofuran (THF) to afford a mixture of the compound (**19**) and the unchanged compound (**18**). The keto-nitrile (**5b**) was treated successively with $C_5H_5NHBr_3$, $NaBH_4$, Zn–AcOH, and NaH–$CH_3I$ to yield the methoxy-nitrile (**19**).

Configurations at $C_2$ in **18** and **19** were determined by inspection of their NMR spectra as follows. Thus, the NMR spectrum of the methoxy-nitrile (**18**) showed a signal due to the $C_2$-proton at $\delta$ 2.65 as an octet ($J$=9.0, 7.0, and 2.5 Hz). Judging from the long-range coupling (2.5 Hz) between the $C_2$-proton and the $C_7$–Ha proton, the $C_2$-proton is *endo* and consequently, the $C_2$–CN group is *exo* [W letter rule, see formula (**20**)].[8d,11] This conclusion also agrees with the fact that the signal for $C_2$–H of **18** at $\delta$ 2.65 appears at higher field owing to the shielding effect of the double bond than that for $C_2$–H of **19** at $\delta$ 2.83.[8d] From these results, it is apparent that the configuration of $C_2$–CN of the methoxynitrile (**19**) is *endo*.

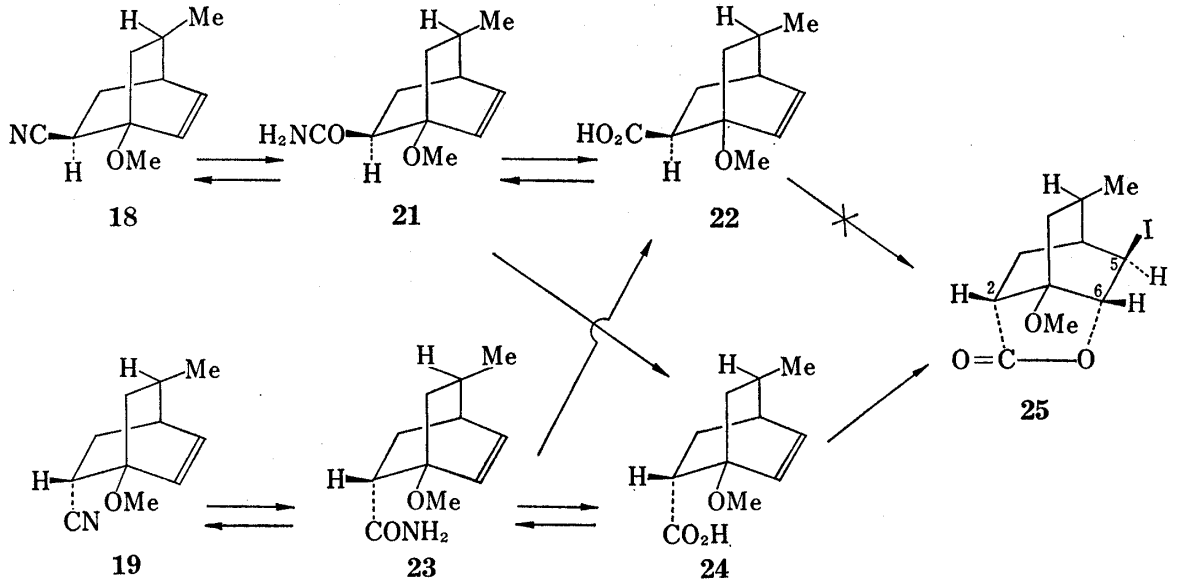
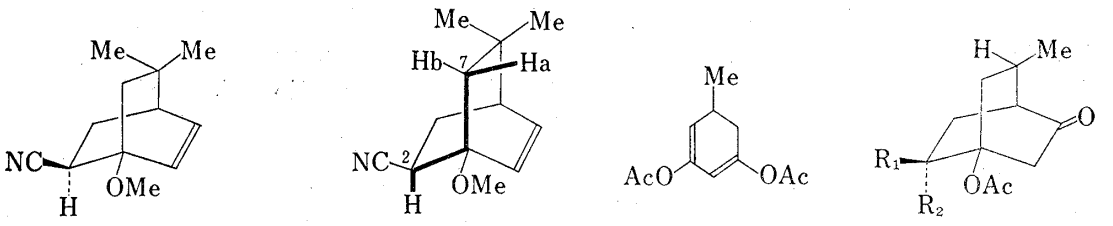



Chart 5

These configurational assignments of $C_2$–CN of **18** and **19** were also chemically ascertained by the following evidence. Treatment of the *exo*-nitrile (**18**) with aq. NaOH–$H_2O_2$ gave the *exo*-amide (**21**: 83% yield) which was then hydrolyzed with aq. KOH to afford the *exo*-acid (**22**) and the *endo*-acid (**24**) in a *ca.* 1: 4 ratio. By the same treatments, the *endo*-nitrile (**19**) was converted to a 1: 4 mixture of the *exo*-acid (**22**) and the *endo*-acid (**24**). The *exo*-acid (**22**) was converted to the *exo*-amide (**21**) by successive treatments with $SOCl_2$ and $NH_3$, and dehydration of the amide (**21**) with trifluoroacetic anhydride-pyridine[12] furnished the

10) R. Buchecker, P. Hamm, and G.H. Eugster, *Helv. Chim. Acta*, **57**, 631 (1974).
11) *a*) R.R. Fraser, *Can. J. Chem.*, **40**, 78 (1962); *b*) J.M. Mellor and C.F. Webb, *J. Chem. Soc. Perkin II*, **1974**, 26; *c*) B.C.C. Cantello, J.M. Mellor, and C.F. Webb, *ibid.*, **1974**, 22.
12) L.A. Carpino, *J. Am. Chem. Soc.*, **82**, 2725 (1960).

methoxy-nitrile which was identical with the *exo*-nitrile (**18**). In the same manner as with **22**, the *endo*-acid (**24**) was converted to the *endo*-nitrile (**19**) *via* the *endo*-amide (**23**). Because conversion of the acid (**22**) to the nitrile (**18**) proceeded without isomerization about the $C_2$-substituent, the configuration of the carboxyl group of the acid (**22**) is *exo*, and that of the carboxyl group of the acid (**24**) *endo*. When treated with $I_2$–KI in 0.5 N $NaHCO_3$, the *endo*-acid (**24**) gave the iodolactone (**25**)[13] in 26% yield, whereas the *exo*-acid (**22**) recovered unchanged by the same treatment. On the basis of the results stated above, the configurations of the cyano group of the methoxy-nitrile (**18**) and (**19**), hence those of the major adduct (**4b**) and the minor adduct (**5b**) were completely established to be *exo* and *endo*, respectively.




**26** **27** **28** **29**: $R_1$=CN, $R_2$=H; **30**: $R_1$=H, $R_2$=CN

Chart 6

Finally, the configurations of the cyano group of **4c** and **5c** were assigned as follows. Successive treatments of the major adduct (**4c**) with $C_5H_5NHBr_3$, $NaBH_4$, Zn–AcOH, and NaH–$CH_3I$ furnished the methoxy-nitrile (**26**). The NMR spectrum of **26** revealed a signal assignable to the $C_2$-proton at $\delta$ 2.67 as an octet ($J$=12.0, 5.0, and 2.5 Hz). Judging from the long-range coupling (2.5 Hz) between the $C_2$-proton and the $C_7$–Ha proton, the $C_2$-proton of **26** is *endo* and hence the $C_2$–CN group *exo* [W letter rule, see formula (**27**)]. From the result stated above, it is concluded that the configuration of the $C_2$–CN group of the major adduct (**4c**) is *exo*. Consequently, the configuration of the $C_2$–CN group of the minor adduct (**5c**) is *endo*.

Summarizing the above results, the Diels-Alder reaction of the cyclic 1,3-bis(trimethylsiloxy)-1,3-dienes (**3a**—**3c**) with acrylonitrile afforded predominantly the *exo*-adducts (**4a**—**4c**) and the present cases are additional exceptions to the *endo*-addition rule.[6,7]

We wish to point out some remarkable features on the novel cyclic dienes (**3a**—**3c**). a) The ease of preparation and the high stability of the dienes in an inert gas atmosphere at 0°. b) The high regioselectivity and the acceptable yield in the Diels-Alder reaction. The Diels-Alder reaction of acrylonitrile with the diacetoxy-1,3-diene (**28**), generated *in situ* from 5-methylcyclohexane-1,3-dione and isopropenyl acetate,[14] followed by hydrolysis gave the *exo*-adduct (**29**) and the *endo*-adduct (**30**) only in 3.4% and 2.4% yields, respectively. c) The synthetic versatility of the adducts, *e.g.*, treatment of the hydroxy-nitriles (**9**) and (**10**), which were derived from the adducts (**4a**) and (**5a**), respectively, with aq. $HClO_4$–AcOH gave *cis*-decahydroquinol-2,7-dione (**13**).

## Experimental

All melting points were taken on a Yanagimoto melting point apparatus and uncorrected. IR spectra were recorded on a Hitachi EPI-S Spectrometer in $CHCl_3$. Unless otherwise stated, NMR spectra were measured on a Varian A-60 or HA-100D Spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard and chemical shifts were given in $\delta$ value. The abbreviations, s, d, t, q, oct, and m in the NMR spectra signify singlet, doublet, triplet, quartet, octet, and multiplet and coupling constant ($J$) is measured in Hz.

13) J.A. Berson and A. Remanick, *J. Am. Chem. Soc.*, **83**, 4947 (1961).
14) *a*) C.M. Cimarusti and J. Wolinsky, *J. Am. Chem. Soc.*, **90**, 113 (1968); *b*) J. Wolinsky and R.B. Login, *J. Org. Chem.*, **35**, 1986 (1970).

Mass spectra were recorded at 80 eV on a Hitachi RMU-6D Mass Spectrometer, and abbreviation $M^+$ signifies the molecular ion. Gas chromatography was carried out on a 1.5% SE-30 glass column (3 mm×2 m i.d., on 60—80 mesh chromosorb WAW) at 140—170° with a Hitachi Gas Chromatograph Model 063 equipped a hydrogen flame ionization detector. Helium gas was used as a carrier gas (30 ml/min). Column chromatography was performed on silica gel (Mallinckrodt silicic acid, 100 mesh). Bulb to bulb distillation was carried out using a Büchi Kugelrohr distillation apparatus (Type KR) and boiling points were shown by oven temperature. Unless otherwise specified, the extracts were dried over anhydrous magnesium sulfate.

**General Procedure for Silylation of the β-Diketones**——Anhydrous $ZnCl_2$ (3.0 g) was added to 104 ml (0.75 mol) of dry triethylamine and the mixture was stirred for 30 min at room temperature. To the above mixture were added 0.25 mol of a β-diketone and 500 ml of dry ether and 80.3 g (0.75 mol) of trimethylchlorosilane. The mixture was stirred at 0° for 12 hr and then at room temperature for 48 hr. The reaction mixture was filtered and the residue was washed with ether. The filtrate and washings were combined and concentrated under reduced pressure to give an oil. Distillation of the oil yielded a cyclic 1,3-bis(trimethylsiloxy)-1,3-diene as a colorless oil.

**1,3-Bis(trimethylsiloxy)cyclohexa-1,3-diene (3a)**——According to the general procedure, cyclohexane-1,3-dione (20 g) was converted to 35 g (77% yield) of the diene (**3a**), bp 125° (12 mmHg). IR $\nu_{max}$ $cm^{-1}$: 1641, 1598, and 855. NMR δ: 0.12 (9H, s, $SiMe_3$), 0.17 (9H, s, $SiMe_3$), 2.13 (4H, m, $-CH_2-CH_2-$), 4.50 (1H, m, olefinic proton), and 4.85 (1H, m, olefinic proton). MS *m/e*: 256 ($M^+$) and 73 (base peak).

**1,3-Bis(trimethylsiloxy)-5-methylcyclohexa-1,3-diene (3b)**——Similarly, 30 g of 5-methylcyclohexane-1,3-dione was converted to 57 g (82% yield) of the diene (**3b**), bp 92° (5 mmHg). IR $\nu_{max}$ $cm^{-1}$: 1643, 1600, 1478, 1253, and 850. NMR δ: 0.15 (9H, s, $SiMe_3$), 0.18 (9H, s, $SiMe_3$), 0.97 (3H, d, $J$=7 Hz, >CH–$CH_3$), 4.43 (1H, q, $J$=4 and 1.5 Hz, olefinic proton), and 4.85 (1H, m, olefinic proton). MS *m/e*: 270 ($M^+$) and 73 (base peak).

**1,3-Bis(trimethylsiloxy)-5,5-dimethylcyclohexa-1,3-diene (3c)**——According to the general procedure, 35 g of dimedone was converted to 50 g (72% yield) of the diene (**3c**), bp 112—113° (3 mmHg). IR $\nu_{max}$ $cm^{-1}$: 1645, 1603, and 858. NMR δ: 0.25 (18H, s, $SiMe_3$×2), 1.00 (3H, s, $CH_3$), 1.05 (3H, s, $CH_3$), 2.04 (2H, m, $-CH_2-$), 4.39 (1H, m, olefinic proton), and 4.90 (1H, m, olefinic proton). *Anal.* Calcd. for $C_{14}H_{28}O_2Si_2$: C, 59.10; H, 9.92. Found: C, 59.14; H, 10.15.

**2-Cyano-1-hydroxybicyclo[2.2.2]octan-5-ones (4a) and (5a)**——A mixture of 30 g of the diene (**3a**), 33.6 g of acrylonitrile, and 60 ml of dry xylene was heated under argon in a sealed tube at 170° for 48 hr. The reaction mixture was mixed with $CHCl_3$ and filtered through an alumina column (5×7 cm) and the filtrate was concentrated under reduced pressure to give 24 g of a colorless oil. To a solution of the oil in 45 ml of THF was added 6 ml of 10% HCl at 0° under stirring and the solution was allowed to stand at room temperature for 20 hr. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 6 g of the adducts. The adducts in $CHCl_3$ was chromatographed on a silica gel column (8×50 cm) and elution with $CHCl_3$–EtOH (98: 2) gave the *exo*-adduct (**4a**: 900 mg) as a colorless oil from the earlier eluent. GC $t_R$: 4.6 min (140°). IR $\nu_{max}$ $cm^{-1}$: 3420 (OH), 2260 (CN), and 1725 (CO). NMR δ: 2.79 (1H, m,$C_2$–H), and 3.37 (1H, s, OH, exchangeable with $D_2O$). An analytical sample was obtained by bulb to bulb distillation at 155° (oven temperature (1 mmHg). *Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.62; H, 6.83; N, 8.49. Further elution of the column with the same solvent gave the *endo*-adduct (**5a**: 350 mg) as a colorless oil. GC $t_R$: 5.6 min (140°). IR $\nu_{max}$ $cm^{-1}$: 3460 (OH), 2280 (CN), and 1724 (CO). NMR δ: 3.05 (1H, m, $C_2$–H) and 3.53 (1H, s, OH, exchangeable with $D_2O$). An analytical sample was obtained by bulb to bulb distillation at 155° (oven temperature) (1 mmHg). *Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.29; H, 6.77; N, 8.48.

**2-Cyano-1-hydroxy-*syn*-8-methylbicyclo[2.2.2]octan-5-ones (4b) and (5b)**——A mixture of 3.4 g of the diene (**3b**), 4.8 g of acrylonitrile, and 8 ml of dry xylene was heated under argon in a sealed tube at 170° for 96 hr. The reaction mixture was mixed with $CHCl_3$ and filtered through an alumina column (5×7 cm) and the filtrate was concentrated under reduced pressure to give 3.07 g of a colorless oil. To a solution of the oil in 30 ml of THF was added 5 ml of 10% HCl at 0° under stirring and the solution was allowed to stand at 0° for 12 hr. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 2.07 g of the oily adducts. Trituration of the oil with ether gave a crystalline mass which was recrystallized from ether–THF (5: 1) to give 1.08 g of the *exo*-adduct (**4b**) as colorless prisms, mp 117°. GC $t_R$: 3.4 min (160°). IR $\nu_{max}$ $cm^{-1}$: 3430 (OH), 2250 (CN), and 1725 (CO). NMR δ: 0.98 (3H, d, $J$=7 Hz, >CH–$CH_3$) and 3.55 (1H, s, OH, exchangeable with $D_2O$). *Anal.* Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.19; H, 7.33; N, 7.87. The mother liquor was concentrated and the residue in $CHCl_3$ was chromatographed on a silica gel column (4×30 cm) and the column was eluted with the same solvent. Recrystallization of the earlier eluate from ether–THF (5: 1) gave 90 mg of the *exo*-adduct (**4b**). Recrystallization of the later eluate from ether–acetone (5: 1) gave 32 mg of the *endo*-adduct (**5b**) as colorless prisms, mp 95—96°. GC $t_R$: 4.0 min (160°). IR $\nu_{max}$ $cm^{-1}$: 3450 (OH), 2260 (CN), and 1732 (CO). NMR δ: 0.97 (3H, d, $J$=6 Hz, >CH–$CH_3$) and 3.45 (1H, s, OH, exchangeable with $D_2O$). *Anal.* Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.80; H, 7.30; N, 7.76.

**2-Cyano-8,8-dimethyl-1-hydroxybicyclo[2.2.2]octan-5-ones (4c) and (5c)**——A mixture of 40 g of the diene (3c), 42 ml of acrylonitrile, and 60 ml of dry xylene was heated under argon in a sealed tube at 140° for 72 hr. The reaction mixture was mixed with $CHCl_3$ and filtered through an alumina column (8×20 cm) and the filtrate was concentrated under reduced pressure to give 40 g of a colorless oil. To a solution of the oil in 50 ml of THF was added 5 ml of 10% HCl at 0° under stirring and the solution was allowed to stand at 0° for 24 hr. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 22.1 g of the oily adducts. Trituration of the oil with ether gave a crystalline mass which was recrystallized from ether–$CHCl_3$ (5: 1) to give 14 g of the *exo*-adduct (**4c**) as colorless prisms, mp 206°. GC $t_R$: 6.0 min (140°). IR $\nu_{max}$ $cm^{-1}$: 3550, 3440 (OH), 2260 (CN), and 1732 (CO). NMR $\delta$: 0.95 (3H, s, $CH_3$), 1.22 (1H, s, $CH_3$), 3.07 (1H, oct, $J$=10.5, 5.5, and 2.5 Hz, $C_2$–H), and 4.71 (1H, s, OH, exchangeable with $D_2O$). *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.52; H, 7.97; N, 7.40. The mother liquor, from which the *exo*-adduct (**4c**) was removed as exhaustive as possible, was concentrated. The crystalline residue was recrystallized from ether–acetone (5: 1) to give 1.9 g of the *endo*-adduct (**5c**) as colorless needles, mp 153°. GC $t_R$: 7.0 min (140°). IR $\nu_{max}$ $cm^{-1}$: 3550, 3440 (OH), 2250 (CN), and 1726 (CO). NMR $\delta$: 0.95 (3H, s, $CH_3$), 1.13 (3H, s, $CH_3$), 3.13 (1H, oct, $J$=11.5, 5.5, and 2.0 Hz, $C_2$–H), and 4.71 (1H, s, OH, exchangeable with $D_2O$). *Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.24; H, 7.89; N, 7.35.

**The Bromo-ketones, (6), (7), and (8)**——To a solution of 900 mg of the keto-nitrile (**4a**) in 10 ml of AcOH was added 1.75 g of $C_5H_5NHBr_3$ and the mixture was stirred at room temperature for 2 hr. The solution was made alkaline with 28% $NH_4OH$ at 0° under stirring and extracted with AcOEt. The extract was washed with water, dried and evaporated to give 1.33 g of a colorless oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (4×50 cm) and the column was eluted with the same solvent. Recrystallization of the earlier eluate from acetone gave 150 mg of the dibromo-ketone (**8**) as colorless pillars, mp 212°. IR $\nu_{max}$ $cm^{-1}$: 3380 (OH), 2250 (CN), and 1738 (CO). NMR (acetone-$d_6$) $\delta$: 3.07 (1H, m, $C_2$–H), and 5.89 (1H, s, OH). *Anal.* Calcd. for $C_9H_9Br_2NO_2$: C, 33.46; H, 2.80; N, 4.34; Br, 49.48. Found: C, 33.44; H, 2.85; N, 4.20; Br, 49.58. Recrystallization of the later eluate from acetone gave 1.18 g of an inseparable mixture of the monobromo-ketones (**6**) and (**7**) as colorless prisms, mp 173—176°. IR $\nu_{max}$ $cm^{-1}$: 3410 (OH), 2250 (CN), and 1728 (CO). NMR (acetone-$d_6$) $\delta$: 3.33 (1H, q, $J$=10.0 and 8.0 Hz, $C_2$–H), 4.50 (1H, s, $C_6$–H), and 5.20 (1H, s, OH). *Anal.* Calcd. for $C_9H_{10}BrNO_2$: C, 44.26; H, 4.13; N, 5.74; Br, 32.73. Found: C, 44.54; H, 4.28; N, 5.80; Br, 32.53.

***exo*-2-Cyano-1-hydroxybicyclo[2.2.2]oct-5-ene (9)**——a) From the Monobromo-ketones (**6**) and (**7**): To a solution of 500 mg of a mixture of the monobromo-ketones (**6**) and (**7**) in 5 ml of EtOH was added 100 mg of $NaBH_4$ at 0° under stirring. The mixture was stirred for 2 hr at 0° and concentrated under reduced pressure. The residue was extracted with AcOEt and the extract was washed with water, dried and evaporated to leave 506 mg of a colorless oil. To a solution of the oil in 5 ml of AcOH was added 1.0 g of zinc powder and the reaction mixture was stirred for 30 min at room temperature and then filtered. The precipitate was washed with AcOEt several times. The filtrate and washings were combined and concentrated under reduced pressure. The residue was made alkaline with 5% $NH_4OH$ and extracted with ether. The extract was washed with water, dried and evaporated to give an oily residue. The residue in $CHCl_3$ was chromatographed on a silica gel column (3×50 cm) and the column was eluted with $CHCl_3$. The eluent was concentrated to give 320 mg of the hydroxy-nitrile (**9**) as a colorless oil. IR $\nu_{max}$ $cm^{-1}$: 3400 (OH) and 2240 (CN). NMR $\delta$: 3.18 (1H, s, OH, exchangeable with $D_2O$) and 6.20—6.33 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 110° (oven temperature) (1 mmHg). *Anal.* Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.19; H, 7.43; N, 9.36.

b) From the Dibromo-ketone (**8**): In the same manner as the procedure a), 260 mg of the dibromo-ketone (**8**) was converted to 126 mg of the hydroxy-nitrile (**9**), a sample of which was identical in all respects with a sample from the procedure a).

***exo*-2-Cyano-1-methoxybicyclo[2.2.2]oct-5-ene (11)**——To a stirred suspension of 38 mg of NaH (50% suspension in mineral oil, washed with dry hexane) in 1 ml of dry THF was added a solution of 115 mg of the hydroxy-nitrile (**9**) in 2 ml of dry THF at −10° under argon and the mixture was stirred for 30 min. To the reaction mixture were added a solution of 143 mg of hexamethylphosphoric triamide (HMPA) in 0.5 ml of dry THF and 1.0 ml of $CH_3I$. The mixture was stirred at −10° for 2 hr, poured into ice-water and extracted with ether. The extract was washed with water, dried and evaporated to leave 103 mg of a colorless oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (2.8×12 cm) and the column was eluted with $CHCl_3$. The eluent was concentrated to leave 37 mg of the methoxy-nitrile (**11**) as a colorless oil. IR $\nu_{max}$ $cm^{-1}$: 2260 (CN). NMR $\delta$: 2.50—2.90 (2H, m, $C_2$– and $C_4$–H), 3.43 (3H, s, $OCH_3$), and 6.28—6.41 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 95° (oven temperature) (2 mmHg). *Anal.* Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.84; H, 8.24; N, 8.44.

***endo*-2-Cyano-1-hydroxybicyclo[2.2.2]oct-5-ene (10)**——To a solution of 330 mg of the keto-nitrile (**5a**) in 10 ml of AcOH was added 640 mg of $C_5H_5NHBr_3$ and the mixture was stirred for 15 hr at room temperature. The reaction mixture was made alkaline with 28% $NH_4OH$ and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. To a solution of the residue in 5 ml of MeOH was added 100 mg

of $NaBH_4$ and the mixture was stirred for 30 min at room temperature. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 490 mg of a colorless oil. To a solution of the oil in 6 ml of AcOH was added 500 mg of zinc powder. The mixture was stirred for 5 hr at room temperature, diluted with $CHCl_3$ and filtered. The precipitates were washed with $CHCl_3$. The filtrate and washings were combined and concentrated under reduced pressure. The residue was made alkaline with 5% $NH_4OH$ and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave an oily residue. The oil in $CHCl_3$ was chromatographed on a silica gel column (2×30 cm) and the column was eluted with $CHCl_3$. The eluent was concentrated to leave 170 mg of the hydroxy-nitrile (**10**) as a colorless oil. IR $\nu_{max}$ $cm^{-1}$: 3570, 3450 (OH), and 2260 (CN). NMR $\delta$: 2.65 (1H, m, $C_4$–H), 2.85 (1H, q, $J$=10.0 and 5.0 Hz, $C_2$–H), 3.47 (1H, s, OH, exchangeable with $D_2O$), and 6.17—6.57 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 110° (oven temperature) (1 mmHg). *Anal.* Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.37. Found: C, 72.20; H, 7.57; N, 9.26.

***endo*-2-Cyano-1-methoxybicyclo[2.2.2]oct-5-ene (12)**——In the same procedure as with **11**, 40 mg of the hydroxy-nitrile (**10**) was converted to 30 mg of the methoxy-nitrile (**12**) as a colorless oil. IR $\nu_{max}$ $cm^{-1}$: 2260 (CN). NMR $\delta$: 2.63 (1H, m, $C_4$–H), 2.93 (1H, q, $J$=9.5 and 4.5 Hz, $C_2$–H), 3.42 (3H, s, $OCH_3$), and 6.33—6.48 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 85° (oven temperature) (1 mmHg). *Anal.* Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.81; H, 8.14; N, 8.54.

***cis*-Decahydroquinol-2,7-dione (13)**——a) From the Hydroxynitrile (**9**): To a solution of 150 mg of the hydroxy-nitrile (**9**) in 1.7 ml of AcOH was added 0.3 ml of 70% $HClO_4$ and the mixture was heated at 100° for 3 hr. After cooling, the reaction mixture was made alkaline with 28% $NH_4OH$ and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 137 mg of a colorless oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (1.8×10 cm) and the column was eluted with $CHCl_3$. Recrystallization of the eluate from acetone gave 120 mg of *cis*-decahydroquinol-2,7-dione (**13**) as colorless needles, mp 173—174°. IR $\nu_{max}$ $cm^{-1}$: 3400 (NH), 1719 (CO), and 1662 (lactam CO). NMR $\delta$: 3.77—4.15 (1H, m, $C_{8a}$–H) and 6.93—7.40 (1H, b, NH). *Anal.* Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.52; H, 7.70; N, 8.47.

b) From the Hydroxy-nitrile (**10**): In the same manner as the procedure a), 38 mg of the hydroxy-nitrile (**10**) was converted to 18 mg of *cis*-decahydroquinol-2,7-dione (**13**), a sample of which was identical in all respects with a sample from the procedure a).

**The Bromo-ketones (14) and (15)**——According to the same procedure as in the bromination of **4a**, 540 mg of the keto-nitrile (**4b**) was converted to 600 mg of the crude bromo-ketones. The crude bromo-ketones in $CHCl_3$ were chromatographed on a s ilica gel column (3.4×41 cm) and the column was eluted with $CHCl_3$. Recrystallization of the earlier eluate from ether gave 22 mg of the dibromo-ketone (**15**) as colorless prisms, mp 155°. IR $\nu_{max}$ $cm^{-1}$: 3550, 3320 (OH), 2260 (CN), and 1743 (CO). NMR (acetone-$d_6$) $\delta$: 1.01 (3H, d, $J$=6.0 Hz, >CH–$CH_3$), 3.47—3.85 (1H, m, $C_2$–H), and 5.87 (1H, s, OH, exchangeable with $D_2O$). *Anal.* Calcd. for $C_{10}H_{11}Br_2NO_2$: C, 35.46; H, 3.29; N, 4.15. Found: C, 35.49; H, 3.21; N, 4.16. Recrystallization of the later eluate from ether gave 526 mg of the monobromo-ketone (**14**) as colorless prisms, mp 166°. IR $\nu_{max}$ $cm^{-1}$: 3540, 3420 (OH), 2260 (CN), and 1740 (CO). NMR (acetone-$d_6$) $\delta$: 0.97 (3H, d, $J$=6.0 Hz, >CH–$CH_3$), 3.15—3.65 (1H, m, $C_2$–H), 4.43 (1H, s, $C_6$–H), and 5.13 (1H, s, OH, exchangeable with $D_2O$). *Anal.* Calcd. for $C_{10}H_{12}BrNO_2$: C, 47.26; H, 4.76; N, 5.51; Br, 29.87. Found: C, 46.98; H, 4.51; N, 5.37; Br, 29.89.

***exo*-2-Cyano-1-hydroxy-*anti*-8-methylbicyclo[2.2.2]oct-5-ene (17)**——a) From the Monobromo-ketone (**14**): In the same manner as with **9**, 145 mg of the monobromo-ketone (**14**) was converted to 65 mg of the hydroxy-nitrile (**17**) as a colorless oil. IR $\nu_{max}$ $cm^{-1}$: 3550, 3410 (OH), and 2250 (CN). NMR $\delta$: 0.83 (3H, d, $J$=6.5 Hz, >CH–$CH_3$), 3.30 (1H, b, OH, exchangeable with $D_2O$), and 6.14—6.20 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 110° (oven temperature) (1 mmHg). *Anal.* Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.65; H, 7.88; N, 8.60.

b) From the Dibromo-ketone (**15**): In the same manner as with **9**, 230 mg of the dibromo-ketone (**15**) was converted to 110 mg of the hydroxy-nitrile (**17**), a sample of which was identical in all respects with a sample from the procedure a).

***exo*-2-Cyano-1-methoxy-*anti*-8-methylbicyclo[2.2.2]oct-5-ene (18)**——In the same manner as with **11**, 1.41 g of the hydroxy-nitrile (**17**) was converted to 1.5 g of the methoxy-nitrile (**18**) as a colorless oil. IR $\nu_{max}$ $cm^{-1}$: 2250 (CN). NMR $\delta$: 0.84 (3H, d, $J$=6.0 Hz, >CH–$CH_3$), 2.63 (1H, oct, $J$=9.0, 7.0, and 2.5 Hz, $C_2$–H), 3.41 (3H, s, $OCH_3$), and 6.00—6.50 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 90° (oven temperature) (1 mmHg). *Anal.* Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.28; H, 8.26; N, 8.16.

**The Equilibrium Experiment of the Methoxy-nitrile (18) with Lithium Diisopropylamide**——To a stirred solution of lithium diisopropylamide prepared from 2 ml of 1.8 M *n*-butyllithium in hexane and 1.1 ml of diisopropylamine in 2 ml of THF was added a solution of 600 mg of the methoxy-nitrile (**18**) in 2 ml of THF at −78° under argon and the mixture was stirred for 2 hr at the same temperature. The reaction mixture was quenched by addition of 2 ml of water and extracted with ether. The extract was washed with 5%

HCl, 5% $NaHCO_3$, water, dried and evaporated to leave 600 mg of a colorless oil. The oil in $CHCl_3$–hexane (1: 1) was chromatographed on a silica gel column (3.0×41 cm) and the column was eluted with $CHCl_3$–hexane (1: 1). Concentration of the earlier eluent gave 232 mg of the unchanged methoxy-nitrile (**18**). GC $t_R$: 4.6 min (140°). Concentration of the later eluent gave 192 mg of the methoxy-nitrile (**19**) as a colorless oil. GC $t_R$: 5.8 min (140°). IR $\nu_{max}$ $cm^{-1}$: 2250 (CN). NMR $\delta$: 0.83 (3H, d, $J$=6.5 Hz, >CH–$CH_3$), 2.83 (1H, q, $J$=10.0 and 5.0 Hz, $C_2$–H), 3.40 (3H, s, $OCH_3$), and 6.27—6.40 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 150° (oven temperature) (20 mmHg). *Anal.* Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.24; H, 8.76; N, 8.06.

***endo*-2-Cyano-1-methoxy-*anti*-8-methylbicyclo[2.2.2]oct-5-ene (19)**——In the same manner as with **10**, 145 mg of the keto-nitrile (**5b**) was converted to 43 mg of the hydroxy-nitrile as colorless prisms, mp 36—37° [ether–hexane (1: 5)]. IR $\nu_{max}$ $cm^{-1}$: 3550, 3430 (OH), and 2260 (CN). NMR $\delta$: 0.82 (3H, d, $J$=6.0 Hz, >CH–$CH_3$), 2.78 (1H, q, $J$=9.0 and 5.0 Hz, $C_2$–H), 3.62 (1H, s, OH, exchangeable with $D_2O$), and 6.17—6.37 (2H, m, olefinic proton). *Anal.* Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.29; H, 7.96; N, 8.50. In the same manner as with **11**, 30 mg of the hydroxy-nitrile was converted to 25 mg of the methoxy-nitrile (**19**). The methoxy-nitrile (**19**) was identical in all respects with a sample of **19** obtained by the equilibrium experiment of the methoxy-nitrile (**18**) with lithium diisopropylamide.

**The *exo*-Amide (21)**——To a solution of 200 mg of the *exo*-nitrile (**18**) in 2 ml of MeOH were added 1.0 ml of 5 M NaOH and 2.5 ml of 30% $H_2O_2$ and the mixture was stirred overnight at 0°. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated. The oily residue in $CHCl_3$ was chromatographed on a silica gel column (1.8×14 cm) and the column was eluted with $CHCl_3$. Recrystallization of the eluate from ether gave 188 mg of the *exo*-amide (**21**) as colorless prisms, mp 103—105°. IR $\nu_{max}$ $cm^{-1}$: 3500, 3380 ($NH_2$), and 1675 ($CONH_2$). NMR $\delta$: 0.80 (3H, d, $J$=6.5 Hz, >CH–$CH_3$), 3.38 (3H, s, $OCH_3$), 6.18—6.35 (2H, m, olefinic proton), and 5.80—6.90 (2H, b, $NH_2$). *Anal.* Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.44; H, 8.62; N, 7.09.

**The *endo*-Amide (23)**——In the same way as with **21**, 80 mg of the *endo*-nitrile (**19**) was converted to 70 mg of the *endo*-amide (**23**) as colorless prisms, mp 62—64°. IR $\nu_{max}$ $cm^{-1}$: 3500, 3370 ($NH_2$), and 1670 ($CONH_2$). NMR $\delta$: 0.82 (3H, d, $J$=6.5 Hz, >CH–$CH_3$), 2.64 (1H, q, $J$=8.0 and 6.0 Hz, $C_2$–H), 3.38 (3H, s, $OCH_3$), 6.16—6.31 (2H, m, olefinic proton), and 5.50—6.90 (2H, b, $NH_2$). *Anal.* Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78, N, 7.17. Found: C, 67.39; H, 8.56; N, 7.05.

**The *exo*-Acid (22) and the *endo*-Acid (24)**——a) From the *endo*-Amide (**23**): A mixture of 750 mg of the *endo*-amide (**23**), 6.0 g of ethylene glycol, 2.5 g of KOH, 1.5 ml of water, and two drops of hydrazine hydrate was refluxed for 3 hr under argon. After cooling, the reaction mixture was made acidic with 5% HCl and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 580 mg of an oily residue. The residue in $CHCl_3$ was chromatographed on a silica gel column (3.0×25 cm) and the column was eluted with $CHCl_3$. Recrystallization of the earlier eluate from hexane gave 95 mg of the *exo*-acid (**22**) as colorless prisms, mp 115—117°. GC $t_R$: 3.0 min (170°). IR $\nu_{max}$ $cm^{-1}$: 3550—2440 (OH), 1745, and 1702 (CO). NMR $\delta$: 0.81 (3H, d, $J$=6.0 Hz, >CH–$CH_3$), 2.65 (1H, oct, $J$=11.0, 5.0, and 2.0 Hz, $C_2$–H), 3.46 (3H, s, $OCH_3$), 5.98—6.50 (2H, m, olefinic proton), and 10.56 (1H, s, OH). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.46; H, 8.31. Recrystallization of the later eluate from hexane gave 357 mg of the *endo*-acid (**24**) as colorless pillars, mp 68°. GC $t_R$: 3.6 min (170°). IR $\nu_{max}$ $cm^{-1}$: 3550—2400 (OH), 1745, and 1705 (CO). NMR $\delta$: 0.84 (3H, d, $J$=6.5 Hz, >CH–$CH_3$), 2.74 (1H, q, $J$=8.0 and 7.0 Hz, $C_2$–H), 3.47 (3H, s, $OCH_3$), 6.18—6.31 (2H, m, olefinic proton), and 8.75—9.50 (1H, b, OH). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.39; H, 8.29.

b) From the *exo*-Amide (**21**): In the same manner as the procedure a), 50 mg of the *exo*-amide (**21**) was converted to 4 mg of the *exo*-acid (**22**) and 18 mg of the *endo*-acid (**24**). The *exo*-acid (**22**) and the *endo*-acid (**24**) were identified, respectively, in all respects with the samples from the procedure a).

**The Conversion of the *exo*-Acid (22) to the *exo*-Nitrile (18) *via* the *exo*-Amide (21)**——To a solution of 50 mg of the *exo*-acid (**22**) in 5 ml of dry benzene was added 1 ml of $SOCl_2$ under ice cooling and the mixture was allowed to stand overnight at room temperature. The solvent and excess $SOCl_2$ were removed under reduced pressure. To a solution of the residue in 5 ml of dry benzene was bubbled ammonia. After evaporation of the solvent under reduced pressure, the residue was extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$, water, dried and evaporated. Recrystallization of the residue from ether–hexane (1: 2) gave 21 mg of the *exo*-amide (**21**). The *exo*-amide (**21**) was identical in all respects with a sample of the *exo*-amide (**21**) prepared from the *exo*-nitrile (**18**). To a solution of 48 mg of the *exo*-amide (**21**) in 1.0 ml of dry pyridine was added 0.8 ml of trifluoroacetic anhydride at 0° under stirring and the mixture was stirred at 0° for 30 min. Excess trifluoroacetic anhydride was evaporated under reduced pressure and the residue was extracted with ether. The extract was washed with 5% HCl, 5% $NaHCO_3$, water, dried and evaporated to leave 40 mg of a colorless oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (1.8×12 cm) and the column was eluted with $CHCl_3$. Concentration of the eluent gave 35 mg of the *exo*-nitrile (**18**), a sample of which was identical in all respects with a sample of **18** prepared from **17**.

**The Conversion of the *endo*-Acid (24) to the *endo*-Nitrile (19) *via* the *endo*-Amide (23)**——In the same procedure as the conversion of the *exo*-acid (**22**) to the *exo*-nitrile (**18**), 70 mg of the *endo*-acid (**24**) was converted

to 41 mg of the *endo*-amide (**23**), which was identical in all respects with the *endo*-amide (**23**) prepared from the *endo*-nitrile (**19**). The *endo*-amide (**23**; 40 mg) was converted to 28 mg of the *endo*-nitrile (**19**) which was identical in all respects with the *endo*-nitrile (**19**) prepared from the keto-nitrile (**5b**).

**The Iodolactone (25)**——To a solution of 90 mg of the *endo*-acid (**24**) in 5.0 ml of 0.5 N $NaHCO_3$ was added a solution of 160 mg of $I_2$ and 600 mg of KI in 2.0 ml of water and the mixture was allowed to stand overnight at room temperature in the dark. The reaction mixture was made acidic with 5% HCl and extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$, water, dried and evaporated to leave 40 mg of a colorless oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (1.3×12 cm) and the column was eluted with $CHCl_3$. Sublimation of the eluate at 87° (1 mmHg) gave 33 mg of the iodolactone (**25**) as a crystalline mass, mp 117°. IR $\nu_{max}$ $cm^{-1}$: 1785 (CO). NMR $\delta$: 1.45 (3H, m, >CH–$CH_3$), 2.60 (1H, m. $C_2$–H), 3.25 (3H, s, $OCH_3$), 4.35 (1H, m, $C_5$–H), and 5.02 (1H, d, $J$=1.5 Hz, $C_6$–H). *Anal.* Calcd. for $C_{11}H_{15}IO_3$: C, 41.01; H, 4.69. Found: C, 40.87; H, 4.60.

***exo*-2-Cyano-1-methoxy-8,8-dimethylbicyclo[2.2.2]oct-5-ene (26)**——In the same manner as with **10**, 300 mg of the keto-nitrile (**4c**) was converted to 76 mg of the hydroxy-nitrile as colorless prisms, mp 77—79°. IR $\nu_{max}$ $cm^{-1}$: 3550, 3425 (OH), and 2250 (CN). NMR $\delta$: 0.91 (3H, s, $CH_3$), 1.20 (3H, s, $CH_3$), 2.58 (1H, oct, $J$=12.0, 5.0, and 2.5 Hz, $C_2$–H), 2.68 (1H, s, OH, exchangeable with $D_2O$), and 5.98—6.48 (2H, m, olefinic proton). *Anal.* Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.50; H, 8.79; N, 8.09. In the same manner as with **11**, 70 mg of the hydroxy-nitrile was converted to 46 mg of the methoxy-nitrile (**26**) as a colorless oil. IR $\nu_{max}$ $cm^{-1}$: 2250 (CN). NMR $\delta$: 0.92 (3H, s, $CH_3$), 1.22 (3H, s, $CH_3$), 2.67 (1H, oct, $J$=12.0, 5.0, and 2.5 Hz, $C_2$–H), 3.38 (3H, s, $OCH_3$), and 6.10—6.58 (2H, m, olefinic proton). An analytical sample was obtained by bulb to bulb distillation, bp 90° (oven temperature) (1 mmHg). *Anal.* Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.38; H, 9.02; N, 7.26.

**The Acetoxy-nitriles (29) and (30)**——A mixture of 15 g of 5-methylcyclohexane-1,3-dione, 70 ml of acrylonitrile, 100 ml of isopropenyl acetate, and 0.5 g of *p*-toluenesulfonic acid was refluxed for 50 hr under argon. After cooling, excess acrylonitrile and isopropenyl acetate were removed under reduced pressure. To a solution of the residue in 50 ml of acetone was added 25 ml of 10% HCl and the mixture was refluxed for 3 hr. After cooling, the solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to leave 1.7 g of a crystalline mass. Recrystallization of the mass from ether gave 624 mg of the *endo*-adduct (**30**) as colorless needles, mp 127—128°. GC $t_R$: 6.4 min (150°). IR $\nu_{max}$ $cm^{-1}$: 2260 (CN) and 1735 (CO). NMR $\delta$: 1.00 (3H, d, $J$=6.5 Hz, >CH–$CH_3$), 2.01 (3H, s, $COCH_3$), 2.95 (2H, s, $C_6$–H), and 3.87 (1H, m, $C_2$–H). *Anal.* Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.14; H, 6.86; N, 6.49. Treatment of the *endo*-adduct (**30**: 70 mg) in MeOH (2 ml) with 10% aq. NaOH (0.5 ml) gave the keto-nitrile (52 mg) which was identical in all respects with a sample of the keto-nitrile (**5b**). The mother liquor, from which the *endo*-adduct (**30**) was removed as exhaustive as possible, was concentrated. Trituration of the residue with ether gave crystals which were recrystallized from ether gave 872 mg of the *exo*-adduct (**29**) as colorless plates, mp 84—85°. GC $t_R$: 5.6 min (150°). IR $\nu_{max}$ $cm^{-1}$: 2260 (CN) and 1735 (CO). NMR $\delta$: 1.01 (3H, d, $J$=6.5 Hz, >CH–$CH_3$), 2.09 (3H, s, $COCH_3$), 2.67 (1H, d, $J$=19 Hz, $C_{6\beta}$–H), 3.13 (1H, q, $J$=19 and 3 Hz, $C_{6\alpha}$–H), and 3.75 (1H, m, $C_2$–H). *Anal.* Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.00; H, 6.81; N, 6.43. A sample of the *exo*-adduct (**29**) was identical in all respects with a sample of the *exo*-adduct prepared from the keto-nitrile (**4b**) by treatment with $Ac_2O$-pyridine.