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Heterocage Compound. V.[1] Synthesis of Oxacage Tricyclic Systems: Oxaisotwistane and Oxatwistane Skeleton with an Amino Function

SHUN INOKUMA, AKIHIKO SUGIE, KOICHI MORIGUCHI, HIROMI SHIMOMURA, SHIGENARI KATAYAMA, KIKUO ISHIZUMI, and JUNKI KATSUBE*

Pharmaceuticals Research Laboratory, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Takatsukasa, Takarazuka 665, Japan

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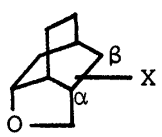
Oxaisotwistane and oxatwistane systems with various versatile functions including an amino moiety were synthesized in order to examine their chemical, physicochemical and biological properties. The synthesis involved bicyclo[2.2.2]octenes, easily accessible Diels–Alder reaction adducts, as key intermediates (bicyclic units) for constructing the target oxacage tricyclic skeletons.

Keywords——oxacage compound; cyclization; isotwistane; twistane

The chemistry of cage polycycles and related heterocage polycycles has received a great deal of attention in recent years.[2] In addition to many challenging synthetic problems involved in cage polycycles, a number of compounds with such ring systems are known to exhibit interesting chemical, physicochemical and biological properties. However, few systematic studies on heterocage polycycles have been reported, and in particular, syntheses of heterocage tricyclic systems have not been extensively studied.[3]

Thus, our research interest has been focused on such heterocage polycycles, and attempts have been made to synthesize a series of oxacage tricycles. In this paper, we wish to report the synthesis and structural elucidation of oxaisotwistane (**1**) and oxatwistane (**2**) skeletons with various versatile functions at the α- or β- (*exo* or *endo*) position.[4] Synthesis and biological evaluation of heterocage tricyclic systems with an amino function were of particular interest, since some cage carbotricycles with an amino function such as amantadine (**3a**),[5] rimantadine (**3b**),[6] amino-homoisotwistane (**4**)[7] and so on have been reported to have antiviral activity or central nervous system effects.

The basic principle of our synthesis is outlined in Chart 1.[8] In this synthesis, the bicyclic system with an *endo*-hydroxymethyl group (**9**) was cyclized with the aid of *N*-bromosuccinimide (NBS), mercuric acetate, a proton catalyst or photoelectrons to give the target tricyclic systems. Alternatively, the bicyclic system with a carboxygroup (**6**) was halo-



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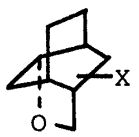

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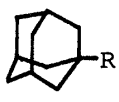

R: $-NH_2$ 3a

$-\overset{CH_3}{\underset{}{CH}}-NH_2$ 3b

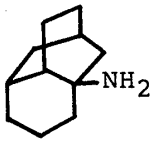

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Fig. 1

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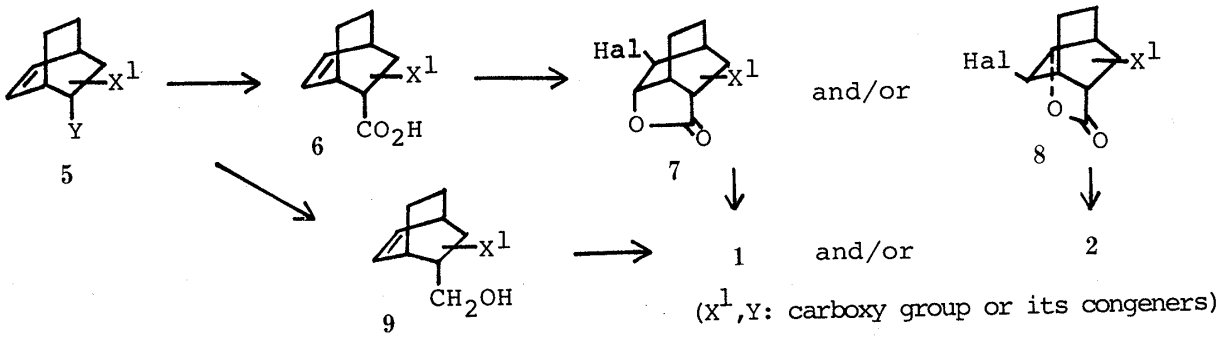

Chart 1

lactonized, and the resulting lactone linkage was transformed into the ether linkage of the target system. Introduction of the amino function from X^1 (carboxy group) was conducted by applying the Curtius or the Hofmann rearrangement before or after the formation of the tricyclic system.

During this study, our attention had to be directed toward the following points; (1) how to distinguish the two substituents (X^1 and Y), (2) whether the direction of the cyclization *via* etherification or lactonization would be "frontwise" to yield **1** or **7** or "crosswise" to yield **2** or **8**, and (3) whether cationic rearrangement would accompany the cyclization or not. The direction of the cyclization in bicyclo[2.2.2]octene systems remains a subject of debate, since apparently conflicting results have been reported.[9] Furthermore, in such polycyclic systems, there is considerable difficulty in structure elucidation and also a pronounced tendency for cationic rearrangement to occur,[10] which can lead to misassignments.

Results and Discussion

Synthesis of α-Amino-oxaisotwistane (10)

The synthesis of amino-oxaisotwistane (**10**) is summarized in Chart 2. The Diels–Alder reaction of 1,3-cyclohexadiene and methyl α-cyanoacrylate proceeded nearly quantitatively to give the *exo*-cyano (**11**) and the *endo*-cyano components in a 93.2:6.8 ratio. Subsequent reactions through the iodo-lactone (**13**) proceeded normally. Dehalogenation of **13** was carried out by treatment wih Bu_3SnH in a good yield. Conversion of the lactone (**14**) into the ether with the target oxaisotwistane system (**16**) was achieved as follows: reduction of **14** with $Ca(BH_4)_2$ in ethanol gave the diol (**15**, 98%), and dehydration of the diol with *p*-TsCl and pyridine gave the tricyclic ether **16** in 34% yield. The frontwise regioselectivity of the lactonization was assumed on the basis of the carbonyl infrared (IR) stretching frequency of **13** of 1795 cm^{-1} in $CHCl_3$ (the γ-lactone). Furthermore, in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, vicinal coupling constants of **13** are in agreement with those of the literature[11] for couplings of *exo* H-6 to bridgehead H-7 (5.6 Hz) and to iodo-methine H-10 (0 Hz). The cyano-oxaisotwistane (**16**) could also be synthesized by the haloetherfication route. Reduction of **11** with $Ca(BH_4)_2$ gave the corresponding cyano-methanol (**18**) in 89% yield. Treatment of the alcohol (**18**) with NBS gave the bromoether (**19**) in good yield (90%). This reaction was found to proceed only in a frontwise direction. The structure (**19**) was supported by both ^{1}H-NMR and carbon-13 nuclear magnetic resonance (^{13}C-NMR). Proton–proton decoupling experiments permitted the assignment of the isotwistane structure. Thus, irradiation of the bridgehead methine (H-7) at 2.42 ppm changed the 4.42 ppm doublet due to H-6 to a singlet. Irradiation of H-6 changed the H-7 multiplet to a doublet. Final proof of the isotwistane structure for **19** was obtained by X-ray analysis.[12] Catalytic hydrogenation (Pd/C) of **19** in the presence of sodium hydroxide afforded **16** in 85% yield; it was identical

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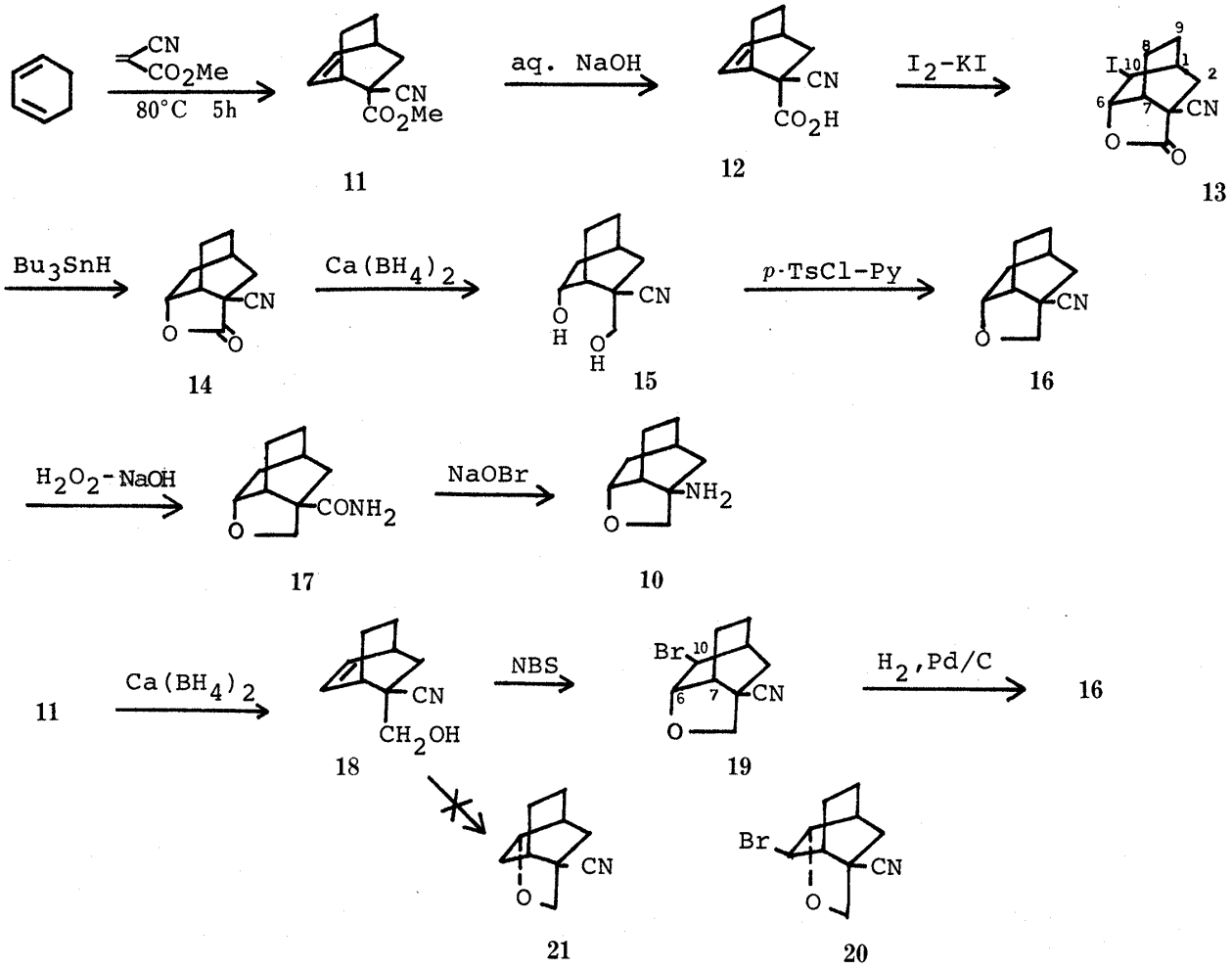

Chart 2

with the product obtained by the halolactonization route. The nitrile was then partially hydrolyzed with H_2O_2–NaOH to give the amide (**17**) in moderate yield. The Hofmann rearrangement of **17** with aqueous sodium hypobromite gave the desired α-amino-oxa-isotwistane (**10**) in moderate yield.

Synthesis of α-Amino-oxatwistane (42)

In the haloetherification of **18**, the "crosswise" cyclized product (**20**) could not be detected. In order to obtain the twistedly cyclized product (**21**), the photocyclization method was applied to the methanol (**18**) according to Kropp's procedure,[13] but the attempt failed in this case.[14] Moreover, we investigated the reaction of methyl bicyclooctenecarboxylate (**11**) with halogens according to a procedure reported to yield both γ- and δ-lactones in the case of dimethyl bicyclooctenedicarboxylate (**22**).[9h] The lactone obtained by this procedure, however, was principally the γ-lactone (**23**) with iodine, bromine and chlorine, and no appreciable amount of the δ-lactone (**23'**) was found in the reaction products.

The δ-lactone was finally synthesized by an alternative route as shown in Chart 3 and an attempt to prepare the target system **21** from **28** was made.

The Diels–Alder reaction of trimethylsilyloxy-cyclohexadiene (**24**)[15] with methyl α-cyanoacrylate was carried out by refluxing in benzene, and the product was hydrolyzed with methanol followed by chromatographic separation to give the bicyclooctan-5-one (**25**) in 53.6% yield. Reduction of **25** with $NaBH_4$ in methanol at −5 °C gave an isomeric mixture of

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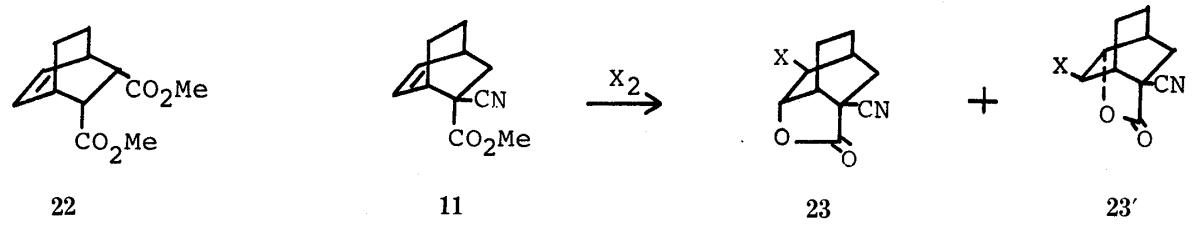
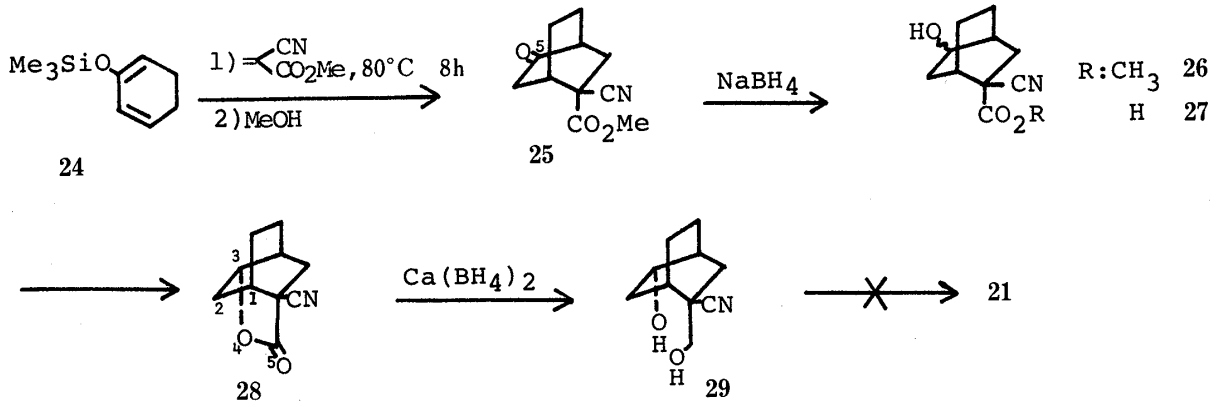


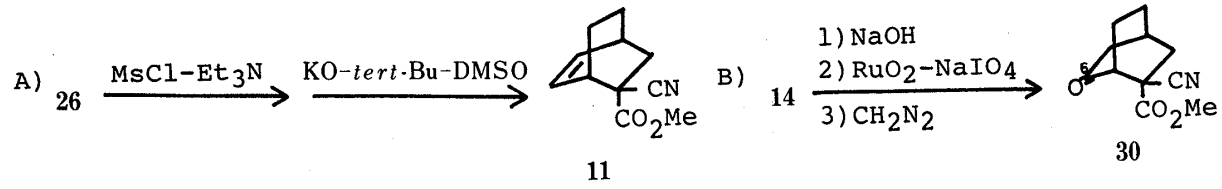
22 11 23 23′

Fig. 2



24 25 28 29

Chart 3



11 30

Chart 4

the alcohol (**26**), which was saponified with aqueous NaOH to give the hydroxy acid (**27**), followed by treatment with triphenylphosphine-2,2′-dipyridyl disulfide[16] in benzene to give the δ-lactone (**28**) in 37% yield from **26**. Evidence supporting the structure (**25**) was obtained as follows (Chart 4).

(A) The *endo*-methoxycarbonyl configuration of **25** was confirmed by dehydrating **26** with MsCl in triethylamine, followed by treatment with potassium *tert*-butoxide in DMSO to give the *endo*-ester (**11**). (B) The 5-oxostructure was confirmed by comparing the ^{1}H-NMR spectrum with that of an isomeric bicyclooctan-6-one (**30**), which was obtained from **14** as follows: treatment of the lactone (**14**) with ruthenium tetroxide under neutral conditions at room temperature, followed by esterification with diazomethane yielded **30**. The structure of the δ-lactone (**28**) was confirmed by the following data. In the IR spectrum, the carbonyl stretching frequency in $CHCl_3$ was 1765 cm^{-1}, indicative of the δ-lactone. In the ^{1}H-NMR, the chemical shift of the oxygen–methine proton was 4.84 ppm (broad triplet) while that of the corresponding γ-lactone (**14**) was 4.77 ppm (triplet). Reduction of **28** with $Ca(BH_4)_2$ gave the diol (**29**) in 65% yield. The diol (**29**) was subjected to intramolecular dehydration by heating with *p*-TsCl and pyridine, but no cyclized product (**21**) could be obtained in this case. Another attempt to reduce **28** to **21** with trichlorosilane under photo-irradiation[17] also failed.

Next, the same type of reactions as described for **18** were applied to a bicyclooctene bearing a methyl group at the 5-position, since it was expected that a favorable carbonium

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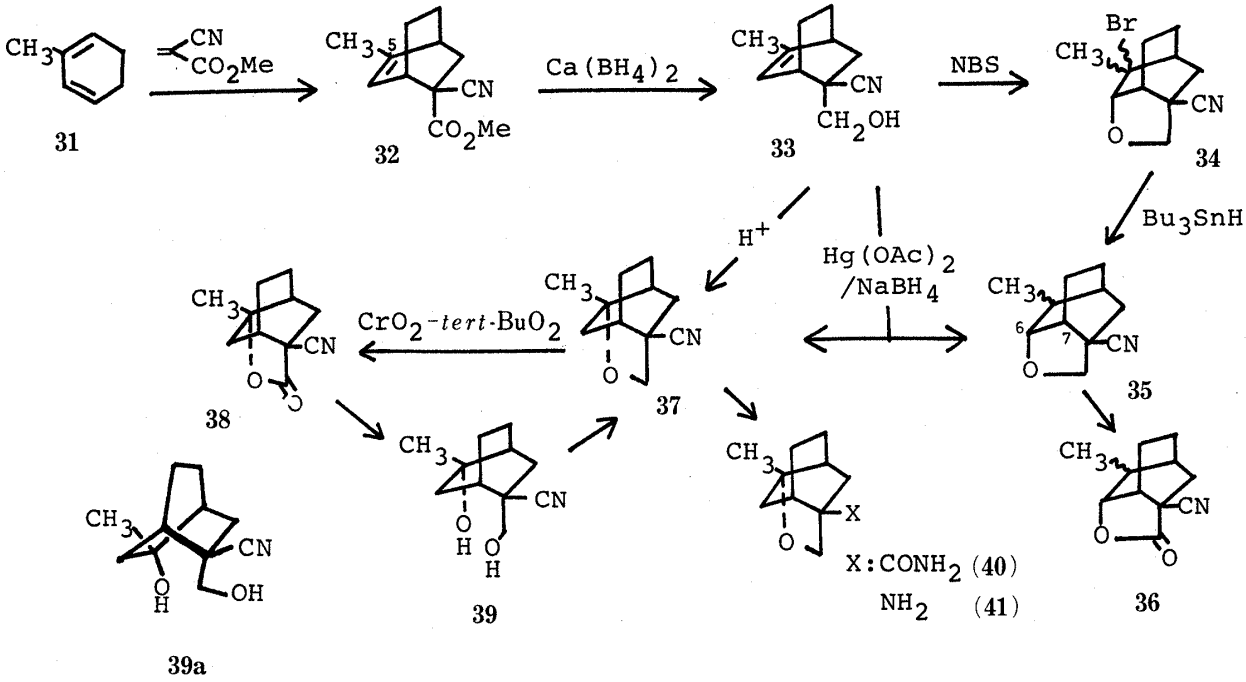

Chart 5

cation of **33** would be induced at the 5-position due to the methyl group (Chart 5).

Thus, the Diels–Alder reaction of 2-methylcyclohexadiene[18] with methyl α-cyanoacrylate yielded the bicyclooctene (**32**). Reduction of **32** with $Ca(BH_4)_2$ gave the methanol (**33**), which was subjected to cyclization induced by an electrophile such as NBS or $Hg(OAc)_2$. The reaction of **33** with NBS, however, yielded the frontwise cyclized product (**34**), the structure of which was assigned after debromination of **34** to **35** with Bu_3SnH. The structure of **35** was confirmed by ^{1}H-NMR and ^{13}C-NMR, especially as regards the oxygen–methine proton signal. In ^{13}C-NMR (C_6D_6), two low field methine carbon peaks were observed at 81.4 and 78.5 ppm, two methylene carbon peaks were observed at 77.5 and 77.3 ppm, and only on quaternary carbon peak was observed at 36.2 ppm. In the ^{1}H-NMR, proton–proton decoupling experiments permitted the assignment of the isotwistane structure: in CD_2Cl_2, irradiation of the bridgehead methine (H-7) at 2.35 ppm changed the 3.40 ppm doublet peak (H-6) to a singlet and the 3.72 ppm triplet to a doublet. In C_6D_6, the *endo*-methyl protons (*cis* to the oxygen function) appeared to 0.13 ppm lower field (0.76) than the *exo*-methyl protons (0.63), and from the height of each methyl peak, the *endo*/*exo* ratio of the mixture was assumed to be 67 : 33. Moreover, oxidation of **35** with RuO_4 at room temperature gave the γ-lactone (**36**) showing a carbonyl IR stretching frequency in $CHCl_3$ at 1785 cm^{-1} (similar to **14**; 1785 cm^{-1}). Oxymercuration–demercuration with $Hg(OAc)_2$ was next applied to the cyclization of **33**. In this case, the product was found to consist of a mixture of **35** and **37** from ^{13}C-NMR spectra.

The target ether **37** could be obtained in a pure form as follows. Treatment of **33** with conc. HCl–EtOH (1 : 1) at 80 °C was found to give **37** in 30% yield. The structure of **37** was elucidated by ^{1}H-NMR and ^{13}C-NMR spectroscopy and the synthesis of **38**. The ^{13}C-NMR spectrum showed an oxygen–quaternary carbon peak at 74.2 ppm and in the ^{1}H-NMR, there were oxygen–methylene peaks at 4.10 (dd) and 3.78 (d) ppm. Moreover, oxidation of **37** with CrO_2 (*tert*-BuO)$_2$ in CCl_4–AcOH–Ac_2O under reflux for 2 h gave the δ-lactone (**38**) showing a carbonyl stretching frequency in $CHCl_3$ of 1760 cm^{-1}. The frequency is similar to that of **28** (1765 cm^{-1}). Reduction of **38** with $Ca(BH_4)_2$ gave the diol (**39**) in 72% yield. In contrast the case of **29**, crosswise intramolecular dehydration of **39** was found to occur under reflux with

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TsCl/pyridine to regenerate the target ether (**37**) in 35% yield.

Examination of Dreiding models indicates that there would be some significant differences in conformation between **29** and **39**: the most favorable conformer for **39** would be **39a** owing to repulsion of the methyl group and the neighboring methylene groups, and thus the two hydroxy groups of **39a** would be closely located due to their *quasi*-axial conformations. The two hydroxyl groups of **29**, on the other hand, would be comparatively far apart due to their *quasi*-equatorial conformation in the most favorable conformer for **29**. In the course of crosswise etherification of **33** to **37**, there would be a similar steric effect of the methyl group in addition to its electronic effect.[19] Thus, the results obtained here suggest that the crosswise ring closures in bicyclo[2.2.2]octene or octane systems are disfavored mainly due to the insufficient proximity between the two reaction sites.[20]

The nitrile (**37**) was then partially hydrolyzed with H_2O_2–NaOH to give the amide (**40**) in 37% yield. The Hofmann rearrangement of **40** with aqueous sodium hypobromite gave the desired α-amino-oxatwistane (**41**).

Synthesis of β-Amino-oxaisotwistanes (*exo*: 42, *endo*: 43)

The syntheses of the β-amino-oxaisotwistanes (**42**) and (**43**) are summarized in Chart 6.

***exo*-Amino Series**——The Diels–Alder reaction of 1,3-cyclohexadiene and fumaryl chloride yielded the bicyclooctene dicarboxylic acid, which was then treated with I_2–KI to give the iodo-lactone (**44**)[21b] in good yield.

Conversion of **44** into the ether with a target oxaisotwistane system (**48**) was achieved as follows: the Curtius rearrangement of **44** with ethyl chloroformate–NaN_3–ethanol gave the ethoxycarbonylamino derivative (**45**, 55%); reduction of **45** with Bu_3SnH gave the lactone (**46**, 47%), reduction of **46** gave the diol (**47**, 80%) and dehydration of the diol with *p*-TsCl/pyridine gave the tricyclic ether (**48**) in 42% yield. Hydrolysis of **48** with KOH in ethylene glycol gave the amino compound (**42**) in 55% yield. The γ-lactone structure (**45**) was assigned on the basis of the carbonyl IR stretching frequency of 1780 cm^{-1}, and in the ^{1}H-NMR spectra, the vicinal coupling constants of **45** are in excellent agreement with those of **13** for the couplings of *exo* H-6 to bridgehead H-7 (5.3 Hz) and to iodo-methine H-10 (0 Hz). The amino moiety was assumed to take the *exo*-position because the Curtius rearrangement is thought to proceed with retention, of configuration. Final confirmation was obtained by comparison of

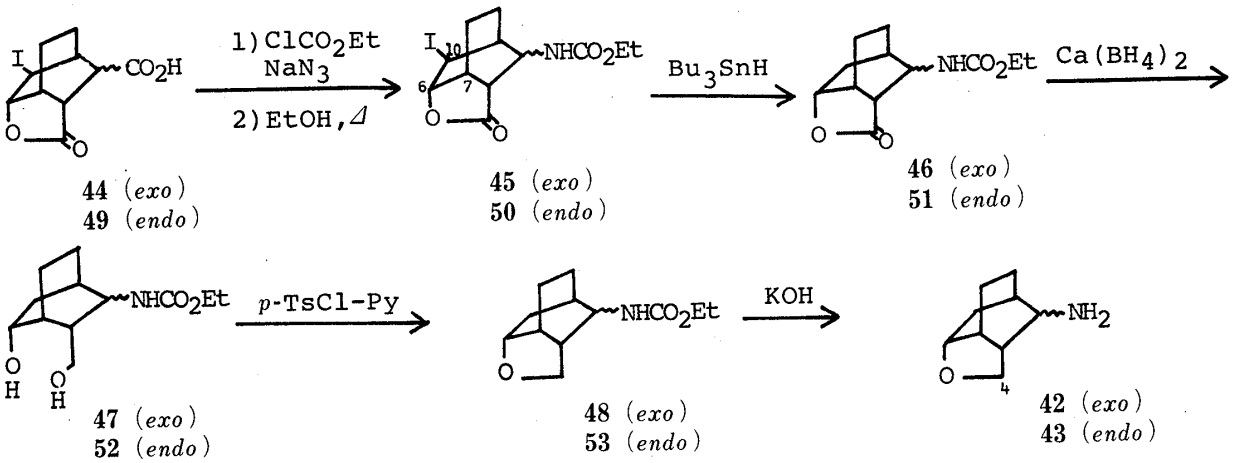

Chart 6

the ^{13}C-NMR with that of the *endo*-amino isotwistane (**43**).

***endo*-Amino Series**——The synthesis of the *endo*-amino series was carried out by using

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the iodo-lactone (**49**)[21a] as a starting material.

Conversion of **49** into **43** was achieved in a manner similar to that described above for the *exo*-series (**42**). The yields for each step were as follows: the ethoxycarbonylamino derivative (**50**) 59%, the lactone (**51**) 52%, the diol (**52**) 88%, the tricyclic ether (**53**) 30% and the amine (**43**) 54%. The structure of the γ-lactone (**49**) was assigned from the IR carbonyl stretching frequency of **50** at 1790 cm^{-1}; in the ^{1}H-NMR spectrum, H-6 appeared at 5.10 ppm as a doublet and the vicinal coupling constant of H-6 to bridgehead H-7 was 5.0 Hz.

The ^{13}C-NMR parameters of (**42**) and (**43**) provide further support to the *exo–endo* amino configurational assignments. Thus, C-4 in (**43**) resonates at higher field than C-4 in (**42**): 66.0 ppm *vs.* 73.9 ppm. This might be due to the more pronounced interaction between the oxygen–methylene carbon (C-4) and the amino moiety in the *endo*-amino structure (**43**) compared to the case of the *exo*-amino structure (**42**).

Properties of the Substituted Oxacage Tricyclic Systems

The substituted oxacage tricyclic compounds obtained in this study were found to be fairly stable; they did not decompose under ordinary storage conditions, or even in aqueous or non aqueous basic, or aqueous acidic media. The amines obtained in this study (free bases) were all volatile oily substances and their hydrochloride salts were all powdery substances which tended to sublime at high temperature. Further investigations of their chemical and physicochemical properties are under way. These oxatricyclic amines were found to show anti-viral (influenza A, PR8) activity comparable to that of amantadine, but interestingly, they showed weaker central nervous system (CNS) effects.

Experimental

Melting points are uncorrected. IR absorption spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were recorded on Varian XL-200, and JEOL FX-90Q and FX-100 spectrometers, and ^{13}C-NMR spectra were recorded on the same machines (solvent $CDCl_3$ unless otherwise stated, Me_4Si as internal standard). All chemical shifts are expressed in parts per million from TMS (^{1}H in δ-scale). Mass spectra were measured on a Shimadzu LKB-9000 instrument. High-resolution mass spectra (Exact-MS) and field-desorption mass spectra (FD-MS) were measured on a Hitachi M-80 instrument.

2-Cyano-2-methoxycarbonylbicyclo[2.2.2]oct-5-ene (11)——1,3-Cyclohexadiene (1.6 g, 20 mmol) and methyl α-cyanoacrylate (2.22 g, 20 mmol) was gently refluxed in benzene (20 ml) for 5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (elution with benzene). The eluate was evaporated to give a **11** as a colorless oil (3.7 g, almost quantitative yield). IR (neat): 2950, 2240, 1750, 1255, 1220 cm^{-1}; ^{1}H-NMR: 1.29—1.40 (m, 2H), 1.42—1.89 (m, 2H), 2.00 (d, 1H), 2.11—2.17 (m, 1H), 2.71 (m, 1H), 3.20 (m, 1H), 3.77 (*endo*) and 3.85 (*exo*) (s, 3H), 6.07 (t, 1H), 6.30 (t, 1H); MS *m/e* 191 (M^+), 160, 104. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.20; H, 6.95; N, 7.30. The ratio of *endo*-methoxycarbonyl and *exo*-methoxycarbonyl-bicyclooctene was determined from the ^{1}H-NMR methyl peak integrals (93.2 : 6.8).

2-Cyano-2-carboxybicyclo[2.2.2]oct-5-ene (12)——A solution of **11** (4.3 g, 20 mmol) in THF (20 ml), MeOH (20 ml) and 10% aq. NaOH (20 ml) was stirred for 2 h at 25 °C. After removal of the solvent, the aq. layer was acidified with conc. HCl, and extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 3.55 g of **12** (quantitative yield) as a crystalline solid; mp 129—130 °C (from ether); IR (Nujol): 3460, 2950, 2600, 2240, 1750, 1210, 700 cm^{-1}; ^{1}H-NMR: 1.25—2.60 (m, 6H), 2.75 (m, 1H), 3.20 (d, 1H), 6.15 (m, 1H), 6.40 (m, 1H); FD-MS: *m/e* 177 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.61; H, 6.35; N, 8.12.

3-Cyano-4-oxo-5-oxa-*exo*-10-iodotricyclo[4.3.1.0^{3,7}]decane (13)——An aq. solution (50 ml) of I_2 (5.1 g, 20 mmol) and KI (10.2 g) was added to a solution of **12** (3.55 g, 20 mmol) in 5% aq. $NaHCO_3$ (60 ml) at 25 °C. The mixture was stirred for 2 h, then excess iodine was decomposed with 10% aq. $Na_2S_2O_3$, and the solution was extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 5.76 g of **13** (90% yield) as a crystalline solid; mp 178—179 °C (from benzene); IR ($CHCl_3$): 2260, 1795, 1140, 1080 cm^{-1}; ^{1}H-NMR: 1.60—2.32 (m, 5H), 2.39 (d, 2H), 2.86 (d, 1H), 4.29 (d, 1H), 5.09 (d, J = 5.4 Hz, 1H); MS *m/e* 303 (M^+), 176. *Anal.* Calcd for $C_{10}H_{10}INO_2$: C, 39.62; H, 3.32; I, 41.86; N, 4.62. Found: C, 39.82; H, 3.40; I, 41.53; N, 4.76.

3-Cyano-4-oxo-5-oxatricyclo[4.3.1.0^{3,7}]decane (14)——Bu_3SnH (5.79 g, 20 mmol) and azobisisobutyronitrile (200 mg) were added to a solution of **13** (3.03 g, 10 mmol) in THF (100 ml) with stirring at 25 °C. The mixture was

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stirred for 12 h, and evaporated under reduced pressure to give an oily residue. The residual oil was purified by silica gel column chromatography (elution with benzene) to give 1.50 g (85%) of **14** as white crystals; mp 203—205 °C; IR ($CHCl_3$): 2945, 2870, 2250, 1785 cm^{-1}; ^{1}H-NMR: 1.60—2.30 (m, 9H), 2.86 (dq, 1H), 4.77 (t, 1H); ^{13}C-NMR: 172.7 (CO), 117.9 (CN), 77.7 (d, CH–O), 40.1 (s, –C–); MS *m/e* 178 ($M^+ + 1$), 167, 133. *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.68; H, 6.49; N, 7.70.

2-Cyano-2-hydroxymethyl-6-hydroxybicyclo[2.2.2]octane (15)——$NaBH_4$ (661 mg, 17.4 mmol) was added to a solution of **14** (770 mg, 4.3 mmol) and $CaCl_2$ (965 mg, 8.7 mmol) in EtOH (30 ml) at 0 °C. The mixture was stirred for 12 h, then excess reagent was decomposed with conc. HCl and the solution was concentrated. The residue was extracted with $CHCl_3$, and the extract was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 763 mg (98%) of **15** as an oily product; IR (neat): 3300—3400, 2950, 2230, 1450, 1100 cm^{-1}; MS *m/e* 180 ($M^+ - 1$), 163 ($M^+ - H_2O$).

3-Cyano-5-oxatricyclo[4.3.1.0^{3,7}]decane (16)——A solution of **15** (1.81 g, 10 mmol) in pyridine (5 ml) and benzene (20 ml) was treated with *p*-TsCl (1.90 g, 10 mmol) at 0 °C. The reaction mixture was allowed to stand for 2 h at 0 °C and then for 18 h at 25 °C, and poured into 5% aq. $NaHCO_3$. The org. layer was washed with sat. NaCl, and dried over $MgSO_4$, then evaporated to give an oil which was chromatographed on silica gel (elution with *n*-hexane : EtOAc = 4 : 1) to give **16** as a crystalline solid (550 mg, 34% yield); mp 105 °C; IR (neat): 2930, 2240, 1470, 1030, 1010, 880 cm^{-1}; ^{1}H-NMR: 1.40—2.10 (m, 9H), 2.31 (m, 1H), 3.84 (q, J = 7.5 Hz, 2H), 4.29 (dd, J = 5.4 Hz, 1H); MS *m/e* 164 ($M^+ + 1$), 163 (M^+), 133. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.41; H, 8.05; H, 8.52.

3-Carbamoyl-5-oxatricyclo[4.3.1.0^{3,7}]decane (17)——A solution of **16** (1.3 g, 8 mmol) in EtOH (7.1 ml) was added to a solution of 6 N aq. NaOH (1.2 ml) in 10% aq. H_2O_2 (21.7 ml) at 23 °C. The mixture was stirred for 2 h, then the excess reagent was decomposed with 10% aq. $Na_2S_2O_3$ and the solution was extracted with EtOAc. The extract was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 900 mg of **17** (62.5% yield); mp 166.5—167.5 °C (from isopropyl ether); IR (Nujol): 3380, 3160, 2930, 2850, 1680, 1470, 1010 cm^{-1}; ^{1}H-NMR: 1.40—2.00 (m, 8H), 2.05—2.15 (m, 1H), 2.25—2.35 (m, 1H), 3.85 (q, 2H), 3.36 (t, 1H), 5.8—6.6 (m, 2H); MS *m/e* 181 (M^+), 164, 163, 152. *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.72. Found: C, 65.99; H, 8.45; N, 7.55.

3-Amino-5-oxatricyclo[4.3.1.0^{3,7}]decane (10)——A solution of NaOH (1.1 g) in H_2O (9.4 ml) was treated with Br_2 (900 mg, 5.6 mmol) at 0 °C, then **17** (850 mg, 4.7 mmol) was added to the resulting solution at once with vigorous stirring. After being stirred for 1 h at 0 °C, the reaction mixture was allowed to stand for 30 min at 80 °C, and then extracted with ether. The extract was washed with water and brine, then dried over $MgSO_4$, and evaporated under reduced pressure to give an oily residue **10**, (400 mg, 55% yield); mp 240—250 °C (dec.) (as a HCl salt); IR (neat): 3350, 3290, 2930, 1030, 755 cm^{-1}; ^{1}H-NMR: 1.25—1.80 (m, 12H), 3.30 (d, 2H), 4.21 (t, 1H); MS *m/e* 153 (M^+), 123, 94. *Anal.* Calcd for $C_9H_{16}ClNO$: C, 56.98; H, 8.50; Cl, 18.69; N, 7.38. Found: C, 57.02; H, 8.32; Cl, 19.03; N, 7.50.

2-Cyano-2-hydroxymethylbicyclo[2.2.2]oct-5-ene (18)——A solution of **11** (2.8 g, 15.8 mmol) and $CaCl_2$ (5.3 g, 47.4 mmol) in EtOH (45 ml) was treated with $NaBH_4$ (2.4 g, 63.2 mmol) at 0 °C. The mixture was stirred for 4 h, then the excess reagent was decomposed with conc. HCl and the solution was concentrated. The residue was extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$, and evaporated to give an oily residue. The residual oil was purified by silica gel column chromatography (elution with benzene) to give 2.1 g of **18** as an oily substance (89% yield); IR (neat): 3400, 2950, 2870, 2240, 1460, 1050 cm^{-1}; ^{1}H-NMR: 1.0—2.4 (m, 6H), 2.62 (m, 1H), 2.90 (m, 1H), 3.40 (s, 2H), 3.90 (m, 1H), 6.10—6.50 (m, 2H); MS *m/e* 163 (M^+), 164 ($M^+ + 1$), 133. *Anal.* Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.81; H, 8.15; N, 8.42.

3-Cyano-5-oxa-*exo*-10-bromotricyclo[4.3.1.0^{3,7}]decane (19)——*N*-Bromosuccinimide (600 mg, 3.37 mmol) was added to a solution of **18** (500 mg, 3.07 mmol) in $CHCl_3$ (10 ml) at 25 °C with stirring. The reaction mixture was stirred for 1 h, then poured into 10% aq. $Na_2S_2O_3$ (10 ml), and extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$, and evaporated under reduced pressure to give an oily mixture. This residual oil was purified by silica gel column chromatography (elution with benzene) to give 668 mg of **19** (90% yield): mp 108.5—109 °C; IR: 2930, 2240, 1470, 1020 cm^{-1}; ^{1}H-NMR: 1.60 (m, 1H), 1.82—2.20 (m, 5H), 2.42 (dd, J = 11.1, 2.4 Hz, 2H), 3.72 (d, J = 7.6 Hz, 1H), 3.88 (d, J = 7.6 Hz, 1H), 3.90 (d, J = 2.5 Hz, 1H), 4.42 (d, J = 5.8 Hz, 1H); MS *m/e* 243, 241 (M^+), 213, 211, 162. *Anal.* Calcd for $C_{10}H_{12}BrNO$: C, 49.60; H, 4.99; Br, 33.00; N, 5.78. Found: C, 49.51; H, 5.10; Br, 32.76; N, 5.89.

Preparation of 16——A mixture of **19** (2.42 g, 10 mmol), KOH (1.12 g, 20 mmol) and 10% Pd/C (0.5 g) in MeOH (80 ml) was stirred under a hydrogen atmosphere for 3 h at 25 °C. The reaction mixture was filtered through Celite. The filtrate was concentrated and extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$, and evaporated *in vacuo* to give an oily residue. The residual oil was purified by silica gel column chromatography (elution with benzene) to give 1.40 g of **16** as white crystals (85% yield). The IR and ^{1}H-NMR spectra of this substance were identical with the corresponding spectra of compound (**16**) prepared by the iodolactonization method.

Attempts to Cyclize 11 into the δ-Lactone (23′) with Halogens——A solution containing 1 molar eq of halogen predissolved in CH_2Cl_2 (50 ml) was added dropwise to a solution of **11** (5.73 g, 30 mmol) in CH_2Cl_2 (150 ml). Upon completion of the reaction, the solvent was removed by evaporation. Products obtained were dehalogenated by treatment with Bu_3SnH and compared with **14**.

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Halogen	Product	
	γ-Lactone	δ-Lactone
Cl_2	43%	—
Br_2	45%	—
I_2	5.4% (**13**)	—

Compound (**23**: X=Cl): mp 181—184 °C; IR ($CHCl_3$): 2260, 1805, 1335, 1080, 990 cm^{-1}; ^{1}H-NMR: 2.00—2.40 (m, 7H), 2.93 (dq, 1H), 4.12 (br s, 1H), 4.69 (d, J=5.4 Hz, 1H); MS *m/e* 167, 169 ($M^+ - CO_2$), 139, 91. *Anal.* Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; Cl, 16.75; N, 6.62. Found: C, 56.61; H, 4.81; Cl, 16.64; N, 6.43.

Compound (**23**: X=Br): mp 175—177 °C; IR ($CHCl_3$): 2250, 1800, 1330, 1080, 980 cm^{-1}; ^{1}H-NMR: 2.0—2.40 (m, 7H), 2.93 (dq, 1H), 4.18 (br s, 1H), 4.88 (d, J=5.3 Hz, 1H); MS *m/e* 258, 256 ($M^+ + 1$), 176, 178. *Anal.* Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; Br, 31.20; N, 5.47. Found: C, 46.57; H, 3.88; Br, 31.53; N, 5.31.

2-Cyano-2-methoxycarbonylbicyclo[2.2.2]octan-5-one (25)——2-Trimethylsilyloxy-1,3-cyclohexadiene[15] (12.3 g, 73 mmol) and methyl α-cyanoacrylate (8.2 g, 73 mmol) was gently refluxed in benzene (300 ml) for 8 h. The solvent was removed under reduced pressure and the residue was hydrolyzed in 80% aq. MeOH (300 ml) for 3 h at 60 °C. The hydrolysate was concentrated, and the residue was extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$ and evaporated under reduced pressure to give an oily residue. This was purified by silica gel column chromatography (elution with benzene) to give 8.1 g of **25** (53.6% yield), mp 101—102 °C; IR (KBr): 2970, 2250, 1740, 1720, 1230, 1070, 1060 cm^{-1}; ^{1}H-NMR: 1.60—2.10 (m, 4H), 2.28—2.50 (m, 4H), 2.75 (m, 2H), 3.86 (s, 3H); MS *m/e* 207 (M^+), 179, 152. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.76; H, 6.44; N, 6.71.

2-Cyano-2-methoxycarbonylbicyclo[2.2.2]octan-5-ol (26)——$NaBH_4$ (190 mg, 5 mmol) was added to a solution of **25** (1.05 g, 5 mmol) in MeOH (50 ml) at −5 °C over 1.5 h with stirring. The reaction mixture was then acidified with 10% aq. HCl and evaporated under reduced pressure. The residue was extracted with CH_2Cl_2, and the extract was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 0.9 g (85% yield) of **26** as a crystalline solid; mp 90—91 °C; IR (KBr): 3400, 2950, 2250, 1750, 1450, 1230 cm^{-1}; ^{1}H-NMR: 3.86 (s, 3H); MS *m/e* 210 ($M^+ + 1$), 180, 135.

4-Oxa-5-oxo-6-cyanotricyclo[4.4.0.0^{3,8}]decane (28)——A mixture of **26** (3.85 g, 18 mmol) in THF (10 ml), MeOH (10 ml) and 10% aq. NaOH (10 ml) was stirred for 12 h at 25 °C. After removal of the organic solvents, the aq. layer was acidified with conc. HCl, and extracted with CH_2Cl_2. The extract was washed with water and brine, then dried over $MgSO_4$ and evaporated to give 1.7 g of crude **27**. A mixture of **27** (1.7 g, 8.7 mmol), 2.2′-dipyridyl disulfide (2.876 g, 13 mmol) and triphenylphosphine (3.42 g, 13 mmol) in benzene (200 ml) was stirred for 2 d at 25 °C and heated for 8 h at 80 °C. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (elution with benzene: EtOAc=10:1). The eluate was evaporated to give a crystalline solid **28** (1.2 g, 37% yield from **26**); mp 198—199.5 °C; IR ($CHCl_3$): 2970, 2250, 1765, 1470, 1360 cm^{-1}; ^{1}H-NMR: 1.60—2.20 (m, 7H), 2.48 (t, 2H), 4.84 (br t, 1H); ^{13}C-NMR: 169.9 (CO), 117.6 (CN), 77.2 (d, CH–O), 42.9 (s, –C–); MS *m/e* 178 ($M^+ + 1$), 133, 105. *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.87; H, 6.29; N, 7.81.

2-Cyano-2-hydroxymethyl-5-hydroxybicyclo[2.2.2]octane (29)——$NaBH_4$ (990 mg, 26.1 mmol) was added to a solution of **28** (1.2 g, 6.7 mmol) and $CaCl_2$ (1.45 g, 13 mmol) in EtOH (50 ml) at 0 °C. The mixture was stirred for 12 h, then the excess reagent was decomposed with conc. HCl and the solution was concentrated. The residue was extracted with $CHCl_3$, and the extract was washed with water and brine, then dried over $MgSO_4$, and evaporated to give an oil 788 mg (65% yield); IR (neat): 3400, 2950, 2240, 1450 cm^{-1}; FD-MS *m/e* 182 ($M^+ + 1$).

Attempts to Cyclize the Diol (29)——No cyclized compound (**21**) was obtained refluxing the diol (**29**) with *p*-TsCl in pyridine.

Conversion of 26 into 11——Methanesulfonyl chloride (1.02 g, 8.9 mmol) was added to a solution of **26** (1.7 g, 8.1 mmol) and triethylamine (1.22 g, 12 mmol) in CH_2Cl_2 (50 ml) at 0 °C. The reaction mixture was stirred for 2 h then allowed to stand for 10 h at 25 °C, poured into 5% aq. HCl, and extracted with CH_2Cl_2. The extract was washed with sat. $NaHCO_3$ and sat. NaCl, then dried over $MgSO_4$, and evaporated to give a residue (2.1 g). A mixture of this residue (2.1 g) and potassium *tert*-butoxide (7.34 g, 65.6 mmol) in dry DMSO (20 ml) was stirred for 3 h at 25 °C. The reaction mixture was poured into water, and extracted with ether (50 ml × 3). The extract was washed with water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (elution with benzene) to give **11** (0.315 g, 20% yield). The IR and ^{1}H-NMR spectra of this substance were identical with those spectra of **11**.

2-Cyano-2-methoxycarbonylbicyclo[2.2.2]octan-6-one (30)——A solution of **14** (1.1 g, 6.2 mmol) in 0.5 N

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aq. NaOH (20 ml) was stirred for 30 min at 80 °C. The reaction mixture was cooled and then excess based was neutralized with 0.6 N HCl. RuO_2 (30 mg) was added to a neutral solution of the sodium salt of the hydroxy-acid. The solution was cooled at 20 °C and vigorously stirred while 20 ml of a solution of $NaIO_4$ (1.0 g, 4.6 mmol) was added dropwise. After addition of isopropanol, the mixture was acidified with aq. HCl and thoroughly extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$. The mixture was concentrated *in vacuo* and reacted with excess diazomethane in ether (20 ml). After removal of the solvent, the residue was chromatographed on silica gel with benzene–EtOAc (10 : 1). The eluate was evaporated to give 250 mg of **30** (19% yield); mp 104—106 °C; IR (KBr): 2950, 2250, 1750, 1440, 1270 cm^{-1}; ^{1}H-NMR: 1.70—1.95 (m, 3H), 2.20—2.58 (m, 6H), 2.65 (t, 1H), 3.82 (s, 3H); MS *m/e* 207 (M^+), 208 ($M^+ + 1$), 179, 147.

2-Cyano-2-methoxycarbonyl-5-methylbicyclo[2.2.2]oct-5-ene (32)——By the same procedure as used for the preparation of **11**, the Diels–Alder adduct **32** was obtained in 75% crude yield. The regioselectivity of the methyl group in this Diels–Alder reaction was assumed based on the work of Titov.[22] The spectral features of **32** were as follows. IR (neat): 2930, 2220, 1740, 1430, 1240, 1210 cm^{-1}; ^{1}H-NMR: 1.80 (s, 3H), 3.15 (m, 1H), 3.80 (s, 3H), 5.70 (d, 1H); Exact-MS: Calcd for $C_{15}H_{15}NO_2$: 205.1103, Found *m/e* 205.1119 (M^+).

2-Cyano-2-hydroxymethyl-5-methylbicyclo[2.2.2]oct-5-ene (33)——By the same procedure as used for the preparation of **12**, the alcohol **33** was obtained in 63% yield after column chromatography on silica gel (elution with $CHCl_3$); IR (neat): 3400, 2950, 2230, 1450, 1050 cm^{-1}; ^{1}H-NMR: 1.10—1.60 (m, 5H), 1.79 and 1.77 (s, 3H), 1.98 (d, 1H), 2.39 (m, 1H), 2.80 (d, 1H), 3.38 and 3.39 (s, 3H), 5.72 (d, 1H); Exact-MS: Calcd for $C_{11}H_{15}NO$: 177.1161, Found *m/e* 177.1157 (M^+).

3-Cyano-5-oxa-10-bromo-10-methyltricyclo[4.3.1.0^{3,7}]decane (34)——By the same procedure as used for the preparation of **19**, the bromide **34** was obtained in 95% yield after column chromatography on silica gel (elution with benzene); IR (neat): 2930, 2230, 1440, 1370, 1280 cm^{-1}; ^{1}H-NMR: 1.30—2.30 (m, 10H), 2.45 (m, 1H), 3.80 (dd, 2H), 4.55 (d, 1H); ^{13}C-NMR (C_6D_6): 77.2 and 67.8 (t, CH_2–O); MS *m/e* 225, 257 (M^+), 176, 146. *Anal.* Calcd for $C_{11}H_{14}BrNO$: C, 51.58; H, 5.51; Br, 31.20; N, 5.47. Found: C, 51.70; H, 5.50; Br, 30.67; N, 5.42. The product thus obtained was found to be an isomeric mixture (*exo–endo*).

3-Cyano-5-oxa-10-methyltricyclo[4.3.1.0^{3,7}]decane (35)——A solution of **34** (2.57 g, 10 mmol), azobisisobutyronitrile (100 mg) and Bu_3SnH (5.81 g, 20 mmol) in THF (100 ml) was stirred for 3 h at 50 °C. The solution was then cooled, and concentrated *in vacuo*. Chromatography of the residue on silica gel (elution with benzene) afforded 1.11 g (63%) of **35** as an oil, which was found to be an isomeric mixture (*exo* and *endo*); IR (neat): 2930, 2860, 2230, 1450, 1370, 1030 cm^{-1}; ^{1}H-NMR (C_6D_6): 0.76, 0.63 (d, 3H), 3.25 (d, 1H), 3.65 (d, 1H), 3.40 (d) and 3.72 (t) (1H); ^{13}C-NMR (C_6D_6): 121.5, 121.3 (–CN), 81.4, 78.5 (d, CH–O–), 77.3, 77.5 (t, CH_2–O–), 36.2 (s, –O–); MS *m/e* 177 (M^+), 147, 105. *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.42; H, 8.58; N, 7.61.

3-Cyano-4-oxo-5-oxa-10-methyltricyclo[4.4.1.0^{3,7}]decane (36)——By the same procedure as used for the preparation of **30**, the lactone **36** was obtained in 14% yield (*exo–endo* mixture from ^{13}C-NMR spectra); FD-MS *m/e* 192 ($M^+ + 1$); Exact-MS: Calcd for $C_{10}H_{13}N$: 147.1047; *m/e* 147.1095 ($M^+ - CO_2$); IR ($CHCl_3$): 2250, 1785, 1130, 1080, 980 cm^{-1}; ^{1}H-NMR: 2.90 (m, 1H), 4.76 (t, 1H).

3-Methyl-4-oxa-6-cyanotricyclo[4.4.0.0^{3,8}]decane (37)——A solution of **33** (1.77 g, 10 mmol) in conc. HCl (30 ml) and EtOH (30 ml) was refluxed for 4 h. The mixture was cooled, diluted with water (100 ml), and extracted with $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue on silica gel (elution with benzene) afforded 530 mg (30%) of **37**; mp 81—83 °C; IR (KBr): 2950, 2230, 1370, 1030 cm^{-1}; ^{1}H-NMR: 1.13 (s, 3H), 1.29 (d, 1H), 1.40—2.15 (m, 8H), 2.30 (m, 1H), 3.75 (d, 1H), 4.12 (dd, 1H); ^{13}C-NMR: 121.7 (–CN), 73.7 (–C–O–), 68.4 (CH_2–O–); MS *m/e* 177 (M^+), 162, 150. *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.88; H, 8.57; N, 7.90.

Attempts to Cyclize 33 with $Hg(OAc)_2$——A mixture of **33** (1.77 g, 10 mmol), $Hg(OAc)_2$ (3.18 g, 10 mmol) in THF (20 ml) and water (20 ml) was stirred for 24 h at 25 °C. Then $NaBH_4$ (0.76 g, 20 mmol) and NaOH (1.2 g, 30 mmol) in water (10 ml) were added at 25 °C. The reaction mixture was stirred for 2 h, then filtered, and the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, and the extract was washed with water and brine, then dried over $MgSO_4$ and evaporated to give a residue. The residue was purified by silica gel column chromatography (elution with $CHCl_3$) to give a mixture of **35** and **37** (560 mg, 32% yield) and the starting material **33** (620 mg, 35% recovery). The identity of the product was confirmed by ^{13}C-NMR spectroscopy.

3-Methyl-4-oxa-5-oxo-6-cyanotricyclo[4.4.0.0^{3,8}]decane (38)——A solution of **37** (0.885 g, 5 mmol) in CCl_4 (20 ml), AcOH (3.2 ml) and Ac_2O (1.8 ml) was added to a solution of CrO_2(*tert*-BuO)$_2$ (9.2 g, 40 mmol) in CCl_4 (21 ml) and the mixture was refluxed for 2 h, then cooled, poured into 5% aq. $(CO_2H)_2$ (100 ml) and extracted with $CHCl_3$. The extract was washed with 10% aq. $NaHCO_3$ and brine, then dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography of the residue on silica gel (elution with benzene) afforded 0.53 g (55%) of **38**; mp 163—166 °C; IR ($CHCl_3$): 2950, 2250, 1760, 1390, 1340, 1080 cm^{-1}; ^{1}H-NMR: 1.46 (s, 3H), 1.67—1.79 (m, 5H), 2.09—2.14 (m, 4H), 2.47 (s, 1H); MS *m/e* 191 (M^+), 192 ($M^+ + 1$), 147, 106. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.14; H, 6.91; N, 7.20.

***exo*-2-Cyano-*endo*-2-hydroxymethyl-*endo*-5-hydroxy-*exo*-5-methylcyclo[2.2.2]octane (39)**——By the same procedure as used for the preparation of **15**, the diol **39** was obtained in 72% yield; mp 103—105 °C; IR (neat): 3350,

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2950, 2240, 1450, 1120 cm^{-1}; ^{1}H-NMR: 1.30 (s, 3H); FD/MS: *m/e* 195 (M^+).

Crosswise Cyclization of 39 into 37——A mixture of **39** (200 mg, 1.02 mmol) and *p*-TsCl (200 mg, 1.05 mmol) in pyridine (10 ml) was stirred for 12 h at 0 °C then refluxed for 24 h. Work-up as described for the preparation of **16** gave the desired oxatwistane **37** in 35% yield.

3-Methyl-4-oxa-6-carbamoyltricyclo[4.4.0.0^{3,8}]decane (40)——By the same procedure as used for the preparation of **17**, the amide **40** was obtained in 37% yield; mp 110—112 °C; IR (Nujol): 3350, 3150, 1660, 1170, 1120, 1000 cm^{-1}; ^{1}H-NMR: 1.16 (s, 3H), 1.40—2.10 (m, 9H), 2.35 (br s, 1H), 3.60 (d, 1H), 4.06 (dd, 1H), 5.80 (m, 1H), 6.50 (m, 1H); MS *m/e* 195 (M^+), 178, 150, 138. *Anal.* Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.45; H, 8.51; N, 6.57.

3-Methyl-4-oxa-6-aminotricyclo[4.4.0.0^{3,8}]decane (41)——By the same procedure as used for the preparation of **10**, the amine **41** was obtained in 78% yield; mp 235—236 °C (as the HCl salt); IR (film): 3360, 3300, 2950, 1380, 1030, 860 cm^{-1}; ^{1}H-NMR: 1.11 (s, 3H), 1.13 (s, 2H), 1.20—2.00 (m, 10H), 3.25 (d, 1H), 3.80 (dd, 1H); MS *m/e* 167 (M^+), 137, 95. *Anal.* Calcd for $C_{10}H_{17}NO \cdot HCl$: C, 58.96; H, 8.91; Cl, 17.40; N, 6.88. Found: C, 59.00; H, 9.21; Cl, 17.03; N, 6.82.

***exo*-2-Carboxy-4-oxo-5-oxa-*exo*-10-iodotricyclo[4.3.1.0^{3,7}]decane (44)**——The procedure of Varech and Jacques[21b] provided **44**. mp 182—185 °C (lit. 180 °C), in 94% yield.

***exo*-2-Ethoxycarbonylamino-4-oxo-5-oxa-*exo*-10-iodotricyclo[4.3.1.0^{3,7}]decane (45)**——Ethyl chloroformate (3.6 g, 33.1 mmol) in acetone (20 ml) was added to a solution of **44** (8.9 g, 27.6 mmol) and triethylamine (2.8 g, 27.6 mmol) in acetone (118 ml) at −20 °C. After 2 h, the solution was cooled to −30 °C, and NaN_3 (2.3 g, 35.9 mmol) in water (15 ml) was added over a period of 30 min. After an additional 1 h at 20 °C, the reaction mixture was quenched by the addition of water (100 ml). The aqueous layer was extracted with three 100 ml portions of benzene. The extract was washed with water and brine, then drid over $MgSO_4$ and concentrated to half the initial volume *in vacuo*. The resulting solution was diluted with EtOH (200 ml) and warmed at 80 °C for 3 h. After removal of the solvent, chromatography of the residue on silica gel (elution with benzene) afforded 5.5 g (55%) of **45**; mp 90—91 °C; IR ($CHCl_3$): 3450, 2940, 1780, 1720 cm^{-1}; ^{1}H-NMR: 1.26 (t, 3H), 1.73 (s, 1H), 1.85—2.10 (m, 3H), 2.33 (m, 1H), 2.50 (m, 1H), 4.04 (m, 1H), 4.14 (q, 2H), 4.31 (d, J=3.8 Hz, 1H), 4.98 (d, J=5.3 Hz, 1H), 5.10 (m, 1H); MS *m/e* 365 (M^+), 320, 277, 238. *Anal.* Calcd for $C_{12}H_{16}INO_4$: C, 39.47; H, 4.42; I, 34.75; N, 3.84. Found: C, 39.05; H, 4.65; I, 34.35; N, 3.71.

***exo*-2-Ethoxycarbonylamino-4-oxo-5-oxatricyclo[4.3.1.0^{3,7}]decane (46)**——By the same procedure as used for the preparation of **14**, the lactone **46** was obtained in 47% yield after column chromatography on silica gel (elution with benzene/EtOAc); mp 156—159 °C; IR (KBr): 3300, 1950, 1770, 1680, 1530, 1270, 970 cm^{-1}; ^{1}H-NMR: 1.25 (t, 3H), 1.63—1.90 (m, 6H), 2.20 (m, 1H), 2.37 (d, 1H), 2.60 (m, 1H), 4.00 (m, 2H), 4.64 (d, 2H), 5.30 (m, 1H); MS *m/e* 239 (M^+), 193, 180, 128. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.51. Found: C, 59.75; H, 7.03; N, 5.51.

***exo*-2-Ethoxycarbonylamino-*endo*-3-hydroxymethyl-*endo*-5-hydroxybicyclo[2.2.2]octane (47)**——By the same procedure as used for the preparation of **15**, the diol **47** was obtained in 80% crude yield. The lactone carbonyl signal was no longer detectable.
IR (neat): 3300, 2930, 1700, 1530, 1040, 760 cm^{-1}.

***exo*-2-Ethoxycarbonylamino-5-oxatricyclo[4.3.1.0^{3,7}]decane (48)**——By the same procedure as used for the preparation of **16**, the cyclized ether **48** was obtained in 42% yield after column chromatography on silica gel (elution with benzene); mp 133—135 °C; IR (KBr): 3290, 2940, 1710, 1530, 1240, 1060 cm^{-1}; ^{1}H-NMR: 1.35 (t, 3H), 1.50—2.05 (m, 10H), 3.55 (m, 1H), 3.70 (d, 2H), 4.15 (m, 1H), 4.15 (q, 2H), 5.15 (m, 1H); MS *m/e* 225 (M^+), 207, 181, 144. *Anal.* Calcd for $C_{12}H_{19}NO_3$; C, 63.97; H, 8.50; N, 6.22. Found: C, 63.60; H, 8.55; N, 6.16.

***exo*-2-Amino-5-oxatricyclo[4.3.1.0^{3,7}]decane (42)**——A mixture of **48** (4.0 g, 17.8 mmol) and KOH (4.7 g, 71 mmol) in ethylene glycol (16.7 ml) was refluxed with stirring under an atmosphere of nitrogen for 30 min. The mixture was cooled, poured into water (100 ml) and extracted with three 100 ml portions of $CHCl_3$. The extract was washed with water and brine, then dried over $MgSO_4$ and concentrated to give 1.49 g (55%) of **42** as an oil; mp 265—275 °C (as a HCl salt); IR (neat): 3350, 3290, 2930, 1600, 1100, 1050, 1020, 750 cm^{-1}; ^{1}H-NMR: 1.09 (m, 1H), 1.45 (s, 2H), 1.46—2.00 (m, 8H), 2.82 (br s, 1H), 3.52 (s, 1H), 3.71 (dd, 1H), 4.07 (t, 1H); ^{13}C-NMR: 74.4 (d, CH–O–), 73.9 (t, CH_2–O–); MS *m/e* 153 (M^+), 136, 118, 107. *Anal.* Calcd for $C_9H_{16}ClNO$; C, 56.99; H, 8.51; Cl, 18.66; N, 7.39. Found: C, 56.86; H, 8.55; Cl, 18.42; N, 7.53.

***endo*-2-Carboxy-4-oxo-5-oxa-*exo*-10-iodotricyclo[4.3.1.0^{3,7}]decane (49)**——The iodolactone (**49**) was prepared following the procedure of Alberts *et al.*,[21a] mp 191—193 °C (dec., recrystallized from water) (lit. 161—165 °C), in 77% yield. Alberts' spectral data are consistent with ours; ^{1}H-NMR (C_5D_5N); 5.40 (d, 1H), 5.05 (d, 1H), 3.36 (d, 1H), 3.04 (dd, 1H), 2.44 (m, 2H), 2.13 (br d, 1H), 1.65 (3H). Irradiation at 2.45 ppm changed both the 5.40 and 5.05 ppm doublets to singlets.

***endo*-2-Ethoxycarbonylamino-4-oxo-5-oxa-*exo*-10-iodotricyclo[4.3.1.0^{3,7}]decane (50)**——By the same procedure as used for the preparation of **45**, the urethane **50** was obtained in 59% yield after column chromatography on silica gel (elution with *n*-hexane/EtOAc); mp 158—159 °C; IR ($CHCl_3$): 3420, 2940, 1790, 1720, 1500, 970 cm^{-1}; ^{1}H-NMR: 1.25 (t, 3H), 1.69—1.91 (m, 4H), 2.27 (s, 1H), 2.63 (s, 1H), 2.95 (dd, 1H), 4.20 (t, 1H), 4.12 (q, 2H), 4.43 (d, 1H), 4.99 (d, 1H), 5.10 (m, 1H); MS *m/e* 365 (M^+), 320, 302, 238. *Anal.* Calcd for $C_{12}H_{16}INO_4$: C, 39.47; H, 4.41; I,

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34.75; N, 3.83. Found: C, 39.45; H, 4.52; I, 34.50; N, 3.91.

***endo*-2-Ethoxycarbonylamino-4-oxo-5-oxatricyclo[4.3.1.0^{3,7}]decane (51)**——By the same procedure as used for the preparation of **14**, the lactone **51** was obtained in 52% yield after column chromatography on silica gel (elution with benzene); mp 157—159 °C; IR (neat): 3300, 2950, 1780, 1700, 1540, 1260, 1050 cm^{-1}; ^{1}H-NMR 1.24 (t, 3H), 1.58—1.92 (m, 7H), 2.66 (m, 1H), 2.85 (dd, 1H), 2.96 (t, 1H), 4.12 (q, 2H), 4.64 (t, 1H), 5.08 (m, 1H); MS *m/e* 239 (M^+), 193, 180, 150. *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.15; H, 7.15; N, 5.73.

***endo*-2-Ethoxycarbonylamino-*endo*-3-hydroxymethyl-*endo*-5-hydroxybicyclo[2.2.2]octane (52)**——By the same procedure as used for the preparation of **15**, the diol **52** was obtained in 88% crude yield. The lactone carbonyl signal was no longer detectable. IR (neat): 3360, 2950, 1700, 1520, 1240 cm^{-1}.

***endo*-2-Ethoxycarbonylamino-5-oxatricyclo[4.3.1.0^{3,7}]decane (53)**——By the same procedure as used for the preparation of **16**, the cyclized ether **53** was obtained in 30.8% yield after column chromatography on silica gel (elution with $CHCl_3$); mp 83—84 °C; IR (Nujol): 3300, 2930, 1720, 1520, 1250, 1040 cm^{-1}; ^{1}H-NMR: 1.21 (t, 3H), 1.50—1.65 (m, 7H), 2.09 (t, 1H), 2.55 (dd, 1H), 3.75 (dd, 2H), 4.05—4.20 (m, 4H), 5.05 (m, 1H); MS *m/e* 225 (M^+), 207, 180, 144. *Anal.* Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.62; H, 8.48; N, 6.00.

***endo*-2-Amino-5-oxatricyclo[4.3.1.0^{3,7}]decane (43)**——By the same procedure as used for the preparation of **42**, the amine **43** was obtained in 54% yield; mp 248—256 °C (dec.) (as a HCl salt); IR (neat): 3350, 3270, 2950, 1460, 1050, 990, 750 cm^{-1}; ^{1}H-NMR: 1.50—1.75 (m, 9H), 2.10 (m, 1H), 2.40 (dd, 1H), 3.15 (d, 1H), 3.57 (dd, 1H), 4.10 (m, 2H); ^{13}C-NMR: 75.0 (d, CH–O), 66.0 (t, CH_2–O); MS *m/e* 153 (M^+), 136, 118, 108. *Anal.* Calcd for $C_9H_{16}ClNO$: C, 56.99; H, 8.50; Cl, 18.69; N, 7.38. Found C, 57.15; H, 8.72; Cl, 18.67; N, 7.76.

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References and Notes

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2) Interest is based on their characteristic features arising from the conformationally rigid structure, and they are useful in studies pertaining to stereochemistry and intramolecular interactions. For reviews, see *a*) L. N. Ferguson and J. C. Nadi, *J. Chem. Educ.*, **42**, 529 (1965); *b*) I. Tabuse, *Yuki Gosei Kagaku Kyokai Shi*, **27**, 403 (1969); *c*) C. F. Raymond, Jr., "Adamantane," Marcel Dekker, 1976, and for a description of heterocage compounds, p. 267; *d*) T. Sasaki, *Kagaku No Ryoiki*, **25**, 835 (1971) and *ibid.*, **33**, 147 (1979) and *Heterocycles*, **13**, 531 (1979).
3) Syntheses of the following oxaisotwistane or oxatwistane systems have been recorded in the literature: *a*) Oxaisotwistane (without data): M. Nakazaki and K. Naemura, *Yuki Gosei Kagaku Kyokai Shi*, **35**, 839 (1977); *b*) Oxatwistane (an isomeric system): N. V. Averina, G. Gleigniene, N. S. Zefirov, P. Kadjiauskas, and N. K. Sadovaya, *Zh. Org. Chem.*, **10**, 1125 (1974) [*Chem. Abstr.*, **81**, 63469*c* (1974)].
4) In this paper, semi-trivial names and the designation "α- or β-" are adopted for ease of understanding instead of the names and position numbering following the IUPAC organic nomenclature rules. The relation between them is shown below.
Oxaisotwistane——5-oxatricyclo[4.3.1.0^{3,7}]decane α: −3 β: −2.
Oxatwistane——4-oxatricyclo[4.4.0.0^{3,8}]decane α: −6.
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20) Strictly speaking, the proximity between the two reaction sites in the transition state is important. Thus, the difference between the cases of NBS and $Hg(OAc)_2/NaBH_4$ in the cyclization of **33** might be explained by assuming a difference in the type of intermediate in the transition state. Thus, in the course of the cyclization with NBS, a fairly stable bridged bromonium ion seems a probable intermediate (**54**), the rigidity of which would not allow crosswise cyclization. On the other hand, in the case of $Hg(OAc)_2$, the intermediate may be a more loosely bridged ion (or a classical carbonium ion), which might permit both cyclizations, leading to both frontwise and crosswise cyclized products.

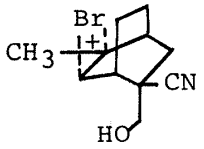

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Fig. 3

21) *a*) V. Alberts, F. J. Brecknell, R. M. Carman, and S. S. Smith, *Aust. J. Chem.*, **34**, 1722 (1981); *b*) D. Varech and J. Jacques, *Tetrahedron*, **28**, 5672 (1972).
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