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

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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-bromo-succinimide (NBS), mercuric acetate, a proton catalyst or photoelectrons to give the target tricyclic systems. Alternatively, the bicyclic system with a carboxygroup (6) was halo-
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. Furthermore, in such polycyclic systems, there is considerable difficulty in structure elucidation and also a pronounced tendency for cationic rearrangement to occur, which can lead to misassignments.

**Results and Discussion**

**Synthesis of \( \alpha \)-Amino-oxaisotwistane (10)**

The synthesis of amino-oxaisotwistane (10) is summarized in Chart 2. The Diels–Alder reaction of 1,3-cyclohexadiene and methyl \( \alpha \)-cyanocrylate proceeded nearly quantitatively to give the \( \alpha \)-cyano (11) and the \( \alpha \)-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 with Bu₄SnH 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(BH₄)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 CHCl₃ (the \( \gamma \)-lactone). Furthermore, in the proton nuclear magnetic resonance (¹H-NMR) spectrum, vicinal coupling constants of 13 are in agreement with those of the literature for couplings of \( \alpha \)-exo H-6 to bridgehead H-7 (5.6 Hz) and to iodo-methylene H-10 (0 Hz). The cyan-oxaisotwistane (16) could also be synthesized by the haloetherification route. Reduction of 11 with Ca(BH₄)₂ gave the corresponding cyanomethanol (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 ¹H-NMR and carbon-13 nuclear magnetic resonance (¹³C-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. Catalytic hydrogenation (Pd/C) of 19 in the presence of sodium hydroxide afforded 16 in 85% yield; it was identical.
with the product obtained by the halolactonization route. The nitrile was then partially hydrolyzed with $\text{H}_2\text{O}_2$-$\text{NaOH}$ to give the amide (17) in moderate yield. The Hofmann rearrangement of 17 with aqueous sodium hypobromite gave the desired $\alpha$-amino-oxa-isotwistane (10) in moderate yield.

**Synthesis of $\alpha$-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, but the attempt failed in this case. Moreover, we investigated the reaction of methyl bicyclooctene carboxylate (11) with halogens according to a procedure reported to yield both $\gamma$- and $\delta$-lactones in the case of dimethyl bicyclooctenedicarboxylate (22). The lactone obtained by this procedure, however, was principally the $\gamma$-lactone (23) with iodine, bromine and chlorine, and no appreciable amount of the $\delta$-lactone (23') was found in the reaction products.

The $\delta$-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) with methyl $\alpha$-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 $\text{NaBH}_4$ in methanol at $-5^\circ\text{C}$ gave an isomeric mixture of
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 \(\delta\)-lactone (28) in 37\% yield from 26. Evidence supporting the structure (25) was obtained as follows (Chart 4).

(A) The \textit{endo}-methoxycarbonyl configuration of 25 was confirmed by dehydrating 26 with MsCl in triethylamine, followed by treatment with potassium \textit{tert}-butoxide in DMSO to give the \textit{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 \(\delta\)-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 \(\delta\)-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 \(\gamma\)-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 bicyclooctane bearing a methyl group at the 5-position, since it was expected that a favorable carbonium
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 with methyl α-cyanoacrylate yielded the bicyclooctene (32). Reduction of 32 with Ca(BH₄)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 Bu₃SnH. The structure of 35 was confirmed by ¹H-NMR and ¹³C-NMR, especially as regards the oxygen–methylene proton signal. In ¹³C-NMR (C₆D₆), 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 ¹H-NMR, proton–proton decoupling experiments permitted the assignment of the isosistane structure: in CD₂Cl₂, 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 C₆D₆, 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 RuO₄ at room temperature gave the γ-lactone (36) showing a carbonyl IR stretching frequency in CHCl₃ 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 ¹³C-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 ¹H-NMR and ¹³C-NMR spectroscopy and the synthesis of 38. The ¹³C-NMR spectrum showed an oxygen–quaternary carbon peak at 74.2 ppm and in the ¹H-NMR, there were oxygen–methylene peaks at 4.10 (dd) and 3.78 (d) ppm. Moreover, oxidation of 37 with CrO₂(tert-BuO)₂ in CCl₄–AcOH–Ac₂O under reflux for 2 h gave the δ-lactone (38) showing a carbonyl stretching frequency in CHCl₃ of 1760 cm⁻¹. The frequency is similar to that of 28 (1765 cm⁻¹). Reduction of 38 with Ca(BH₄)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
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. 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.

The nitrile (37) was then partially hydrolyzed with H₂O₂-NaOH to give the amide (40) in 37% yield. The Hofmann rearrangement of 40 with aqueous sodium hypobromite gave the desired α-amino-oxtwistane (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 bicyclooctane dicarboxylic acid, which was then treated with I₂-KI to give the iodo-lactone (44) 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-Na₂S₃-ethanol gave the ethoxycarbonylamino derivative (45, 55%); reduction of 45 with Bu₃SnH 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 ¹H-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 the ¹³C-NMR with that of the endo-amino isotwistane (43).

- **endo-Amino Series**—The synthesis of the endo-amino series was carried out by using
the iodo-lactone (49)\(^{21}\) 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 \(\gamma\)-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 oxacrylic 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\(_4\)Si as internal standard). All chemical shifts are expressed in parts per million from TMS (\(^1\)H in \(\delta\)-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-methoxyxycarbonyl bicyclo[2.2.2] oct-5-ene (11) — 1,3-Cyclohexadiene (1.6 g, 20 mmol) and methyl acrylate (2.2 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 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-methoxyxycarbonyl and exo-methoxyxycarbonyl-bicyclooctene was determined from the \(^1\)H-NMR methyl peak integrals (93.2: 6.8).

2-Cyano-2-carboxyliclo[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, theaq. 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), 6.14 (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\(^2,7\)] 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\(_2\)S\(_2\)O\(_3\), 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\(_{14}\)I\(_2\)O\(_2\): 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\(^2,7\)] decane (14) — Bu\(_3\)SnH (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
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 (CHCl₃): 2945, 2870, 2250, 1785 cm⁻¹, 1H-NMR: 1.60–2.30 (m, 9H), 2.86 (dq, 1H), 4.77 (t, 1H); 13C-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 C₁₀H₁₁NO₂: 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) — NaBH₄ (366 mg, 17.4 mmol) was added to a solution of 14 (770 mg, 4.3 mmol) and CaCl₂ (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 CHCl₃, and the extract was washed with water and brine, then dried over MgSO₄, 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⁺ – H₂O).

3-Cyano-5-oxatricyclo[4.3.1.0³⁷]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. NaHC₂O₃. The org. layer was washed with sat. NaCl, and dried over MgSO₄, 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; 1H-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⁺). Anal. Calcd for C₁₃H₁₂NO: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.41; H, 8.05; H, 8.52.

3-Carbamoyl-5-oxatricyclo[4.3.1.0³⁷]decane (17) — A solution of 16 (1.3 g, 8 mmol) in EtOH (7.1 ml) was added to a solution of 6N aq. NaOH (1.2 ml) in 10% aq. H₂O₂ (21.7 ml) at 23°C. The mixture was stirred for 2 h, then the excess reagent was decomposed with 10% aq. Na₂S₂O₄ and the solution was extracted with EtOAc. The extract was washed with water and brine, then dried over MgSO₄, and evaporated to give 700 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; 1H-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 C₁₄H₁₄NO₂: C, 66.27; H, 8.34; N, 7.72. Found: C, 65.99; H, 8.45; N, 7.55.

3-Amino-5-oxatricyclo[4.3.1.0³⁷]decane (18) — A solution of NaOH (1.1 g) in H₂O (9.4 ml) was treated with Br₂ (900 mg, 5.6 mmol) and 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 0°C, and then extracted with ether. The extract was washed with water and brine, then dried over MgSO₄, and evaporated under reduced pressure to give an oily residue 18 (400 mg, 55% yield); mp 240–250°C (dec.) (as a HCl salt); IR (neat): 3350, 3290, 2930, 1030, 755 cm⁻¹; 1H-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 C₁₃H₁₂ClNO: 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-hydroxyethylbicyclo[2.2.2]oct-5-ene (19) — A solution of 11 (2.8 g, 15.8 mmol) and CaCl₂ (5.3 g, 47.4 mmol) in EtOH (45 ml) was treated with NaBH₄ (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 CHCl₃. The extract was washed with water and brine, then dried over MgSO₄, and evaporated to give an oily residue. The residual oil was purified by silica gel column chromatography (elution with benzene) to give 3.7 g of 19 (19% yield); mp 108.5–109°C; IR: 2930, 2240, 1470, 1020 cm⁻¹; 1H-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 C₁₀H₁₂BrNO: 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 solution 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 CHCl₃. The extract was washed with water and brine, then dried over MgSO₄, 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 1H-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 CH₂Cl₂ (30 ml) was added dropwise to a solution of 11 (5.73 g, 30 mmol) in CH₂Cl₂ (150 ml). Upon completion of the reaction, the solvent was removed by evaporation. Products obtained were dehalogenated by treatment with Bu₃SnH and compared with 14.
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<thead>
<tr>
<th>Halogen</th>
<th>Product</th>
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<tr>
<td>Cl₂</td>
<td>γ-Lactone: 43%</td>
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<tr>
<td>Br₂</td>
<td>γ-Lactone: 45%</td>
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<tr>
<td>I₂</td>
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2-Cyano-2-methoxy benzylidene[2.2.2]octan-5-one (25) —— 2-Trimethylsilyloxy-1,3-cyclohexadiene (12.3 g, 73 mmol) and methyl α-cyanoacrylate (8.2 g, 73 mmol) was gently refluxed in benzene (300 ml) for 6 h. The solvent was removed under reduced pressure and the residue was hydrolyzed in 80% eq. MeOH (300 ml) for 3 h at 60°C. The hydrolysate was concentrated, and the residue was extracted with CHCl₃. The extract was washed with water and brine, then dried over MgSO₄ 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—103°C; IR (KBr): 2970, 2250, 1740, 1720, 1230, 1070, 1060 cm⁻¹; ¹H-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 C₁₀H₁₃NO₃: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.76; H, 6.44; N, 6.71. |

2-Cyano-2-methoxy carbonyl[bicyclo[2.2.2]octan-5-ol (26) —— NaBH₄ (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% eq. HCl and evaporated under reduced pressure. The residue was extracted with CH₂Cl₂, and the extract was washed with water and brine, then dried over MgSO₄, 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; ¹H-NMR: 3.86 (s, 3H); MS m/e 210 (M⁺ + 1), 180, 135. |

4-Oxa-5-oxo-6-cyanotricycl[4.4.0][3-8]decane (28) —— A mixture of 26 (3.85 g, 18 mmol) in THF (10 ml), MeOH (10 ml) and 10% eq. NaOH (10 ml) was stirred for 12 h at 25°C. After removal of the organic solvents, the aqueous layer was acidified with conc. HCl, and extracted with CH₂Cl₂. The extract was washed with water and brine, then dried over MgSO₄ and evaporated to give 1.7 g of crude 27. A mixture of 27 (1.7 g, 8.7 mmol), 2,2'-dipropyridyl 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, 57% yield from 26); mp 198—199.5°C; IR (CHCl₃): 2970, 2250, 1765, 1470, 1360 cm⁻¹; ¹H-NMR: 1.60—2.20 (m, 7H), 2.48 (t, 2H), 4.84 (br t, 1H); ¹³C-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 C₁₀H₁₃NO₂: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.87; H, 6.29; N, 7.81. |

2-Cyano-2-hydroxymethyl-5-hydroxycarbonyl[bicyclo[2.2.2]octan (29) —— NaBH₄ (990 mg, 26.1 mmol) was added to a solution of 28 (1.2 g, 6.7 mmol) and CaCl₂ (1.45 g, 13 mmol) in EtOH (50 ml) at 0°C. The mixture was stirred for 12h, then the excess reagent was decomposed with conc. HCl and the solution was concentrated. The residue was extracted with CHCl₃, and the extract was washed with water and brine, then dried over MgSO₄, 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 product (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 CH₂Cl₂ (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% eq. HCl, and extracted with CH₂Cl₂. The extract was washed with sat. NaHCO₃ and sat. NaCl, then dried over MgSO₄, 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 MgSO₄ 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 ¹H-NMR spectra of this substance were identical with those spectra of 11. 2-Cyano-2-methoxy carbonylbicyclo[2.2.2]octan-6-one (30) —— A solution of 14 (1.1 g, 6.2 mmol) in 0.5N...
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. RuO₄ (30 mg) was added to a neutral solution of the sodium salt of the hydroxyl-acid. The solution was cooled at 20°C and vigorously stirred while 20 ml of a solution of NaIO₄ (1.0 g, 4.6 mmol) was added dropwise. After addition of isopropanol, the mixture was acidified with aq HCl and thoroughly extracted with CHCl₃. The extract was washed with water and brine, then dried over MgSO₄. 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 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; ¹H-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-methoxy carbonyl-5-methylbenzyl[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; ¹H-NMR: 1.80 (s, 3H), 3.15 (m, 1H), 3.80 (s, 3H), 5.70 (d, 1H), 3.30 (m, 2H); Exact-MS: Calculated for C₁₅H₂₃NO₃: 244.1593, Found m/e 244.1589 (M⁺).

2-Cyano-2-hydroxymethyl-5-methylbenzyl[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 benzene); IR (neat): 3400, 2950, 2230, 1450, 1050 cm⁻¹; ¹H-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: Calculated for C₁₅H₂₁BrNO: 277.1161, Found m/e 277.1157 (M⁺).

3-Cyano-5-oxa-10-bromo-10-methyltricyclo[4.3.1.0³,7]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; ¹H-NMR: 1.30—2.30 (m, 10H), 2.45 (m, 1H), 3.80 (dd, 2H), 4.55 (d, 1H); ¹C-NMR (CDCl₃): 77.2 and 67.8 (t, CH₃); MS m/e 225, 257 (M⁺), 176, 146. Anal. Calculated for C₁₅H₂₃BrNO: 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[4.3.1.0³,7]decane (35)—A solution of 34 (2.57 g, 10 mmol), azobisisobutyronitrile (100 mg) and Bu₃SnH (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; ¹H-NMR (CDCl₃): 0.76, 0.63 (d, 3H), 3.25 (d, 1H), 3.65 (d, 1H), 3.40 (d) and 3.72 (t) (1H); ¹C-NMR (CDCl₃): 121.5, 121.3 (2C), 81.4, 78.5 (d, CH₂—), 77.3, 77.5 (t, CH₃—O—), 36.2 (s, —O); MS m/e 177 (M⁺), 147, 105. Anal. Calculated for C₁₅H₂₃NO: 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[4.3.1.0³,7]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 13C-NMR spectra); FD-MS m/e 192 (M⁺ + 1); Exact-MS: Calculated for C₁₅H₂₃N: 147.1047; m/e 147.1095 (M⁺—CO₂); IR (CHCl₃): 2250, 1785, 1130, 1080, 980 cm⁻¹; ¹H-NMR: 2.90 (m, 1H), 4.76 (t, 1H).

Methyl-4-oxa-5-oxo-6-cyanotricyclo[4.4.0.0³,⁷]decanes (37)—A solution 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 Na₂H₂O₂ (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 CHCl₃, and the extract was washed with water and brine, then dried over MgSO₄ and evaporated to give a residue. The residue was purified by silica gel column chromatography (elution with CHCl₃) 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 ¹³C-NMR Spectroscopy.

Methyl-4-oxa-5-oxo-6-cyanotricyclo[4.4.0.0³,⁷]decanes (38)—A solution of 37 (0.885 g, 5 mmol) in CCl₄ (20 ml), AcOH (3.2 ml) and Ac₂O (1.8 ml) was added to a solution of Cr₂O₃ (tert-ButO₂) (9.2 g, 40 mmol) in CCl₄ (21 ml) and the mixture was refluxed for 2 h, then cooled, poured into 5% aq (CO₂H₂, (100 ml) and extracted with CHCl₃. The extract was washed with 10% aq NaHCO₃ and brine, then dried over MgSO₄, and concentrated in vacuo. Chromatography of the residue on gel column chromatography (elution with benzene) afforded 0.53 g (55% of 38); mp 163—166°C; IR (CHCl₃): 2950, 2250, 1760, 1390, 1340, 1080 cm⁻¹; ¹H-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. Calculated for C₁₅H₂₃NO₂: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.14; H, 6.91; N, 7.20.

exo-2-Cyano-endo-endo-5-hydroxy-endo-5-methylcylobenzene[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,
2950, 2240, 1450, 1120 cm⁻¹; ¹H-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 oxatristane 37 in 35% yield.

3-Methyl-4-oxa-6-carbamoyltrycloc[4.4.0.0³⁹]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; ¹H-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. Calc'd for C₁₅H₂₇N₂O₅: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.45; H, 8.51; N, 6.57.

3-Methyl-4-oxa-6-aminotricloc[4.4.0.0³⁹]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; ¹H-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. Calc'd for C₁₀H₁₅NO·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-oxo-exo-10-idotricloc[4.3.1.0⁵]decane (44)—The preparation of Varech and Jacques²¹ provided 44. mp 182–185°C (lit. 180°C), in 94% yield.

exo-2-Ethoxycarbonylamino-4-oxo-5-oxo-exo-10-idotricloc[4.3.1.0⁵]decane (45)—Ethyl chloroformate (3.6 g, 33.1 mmol) in acetonitrile (20 ml) was added to a solution of 44 (8.9 g, 27.6 mmol) and triethylamine (2.8 g, 27.6 mmol) in acetonitrile (118 ml) at 0°C. After 2 h, the solution was cooled to −30°C, and NaN₃ (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 dried over MgSO₄ 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/EtOAc) mp 156–159°C; IR (KBr): 3300, 1950, 1770, 1680, 1530, 1270, 970 cm⁻¹; ¹H-NMR: 1.25 (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. Calc'd for C₁₂H₁₈NO₄: 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-oxatricloc[4.3.1.0⁵]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 benzene/EtOAc): mp 156–159°C; IR (KBr): 3300, 1950, 1770, 1680, 1530, 1270, 970 cm⁻¹; ¹H-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. Calc'd for C₁₂H₁₆NO₃: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.60; H, 8.55; N, 6.16.

exo-2-Amino-5-oxatricloc[4.3.1.0⁵]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 CHCl₃. The extract was washed with water and brine, then dried over MgSO₄ and concentrated to give 1.49 g (55%) of 42 as an oil; mp 256–275°C (as a HCl salt); IR (neat): 3350, 3290, 2930, 1600, 1100, 1050, 1020, 750 cm⁻¹; ¹H-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); ¹C-NMR: 74.4 (d, CH-O-), 73.9 (t, CH₂-O-); MS m/e 153 (M⁺), 136, 118, 107. Anal. Calc'd for C₂₅H₃₅ClNO: 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-oxo-exo-10-idotricloc[4.3.1.0⁵]decane (49)—The iodolactone (49) was prepared following the procedure of Alberts et al.,²⁰ mp 191–193°C (dec., recrystallized from water) (lit. 161–165°C), in 77% yield. Alberts' spectral data is consistent with ours; ¹H-NMR (CD₂Cl₂): 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-oxo-exo-10-idotricloc[4.3.1.0⁵]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 (CHCl₃): 3420, 2940, 1790, 1720, 1500, 970 cm⁻¹; ¹H-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. Calc'd for C₁₂H₁₆NO₄: C, 39.47; H, 4.41; I,
34.75; N, 3.83. Found: C, 39.45; H, 4.52; I, 34.50; N, 3.91.

**endo-2-Ethoxycarbonylamino-4-oxo-5-oxatricycl[4.3.1.0^2,7]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; ¹H-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 C₁₃H₁₇NO₄: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.15; H, 7.15; N, 5.73.

**endo-2-Ethoxycarbonyl-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-oxatricycl[4.3.1.0^2,7]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 CHCl₃); mp 83—84 °C; IR (Nujol): 3300, 2930, 1720, 1520, 1250, 1040 cm⁻¹; ¹H-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 C₁₃H₁₇NO₄: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.62; H, 8.48; N, 6.01.

**endo-2-Amino-5-oxatricycl[4.3.1.0^2,7]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; ¹H-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); ¹³C-NMR: 75.0 (d, CH—O), 66.0 (t, CH₂—O); MS m/e 153 (M⁺), 136, 118, 108. Anal. Calcd for C₉H₁₅CINO₂: 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**


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.


10) Some typical examples from the literatures are: a) D. I. Davies, M. D. Dowle, and R. F. Kenyon, *Synthesis,*
12) X-Ray crystallography analysis was performed by Mr. M. Minobe of the Central Research Institute of Sumitomo Chem. Co., Ltd.
14) A solution of the methanol (18) in benzene was irradiated with a mercury lamp for 100 h. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica gel. The methanol (18) was recovered quantitatively.
19) A similar steric effect was noted in reference 9i).
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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\begin{align*}
\text{CH}_3 & \quad \text{CN} \\
\text{Br} & \quad \text{HO} \\
\text{54} & \\
\text{Fig. 3}
\end{align*}
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