Intramolecular ring closure *via* ether bond in reaction of α,α′-halogeno bicyclo[3.3.1]nonanediones under basic conditions

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Received (in Cambridge) 1st March 1999, Accepted 15th April 1999

The stereoselectivity of halogenation of bicyclo[3.3.1]nonan-2-one **1** and bicyclo[3.3.1]nonane-2,6-dione **2** with molecular bromine and chlorine was studied. The transformation of α-bromo- and chloro-bicyclo[3.3.1]nonanones **3**–**5** under Favorskii reaction conditions was studied. The reaction of α,α′-dihalogeno diones in the presence of sodium methoxide, ethoxide, propoxide and potassium cyanide led to the intramolecular ring closure *via* C–O bond formation giving the highly functionalized chiral 2-oxatricyclo[4.3.1.$0^{3,8}$]decane (2-oxaprotoadamantane) structure. Enantiomers of this cage structure were resolved by chiral GLC. The intramolecular ring closure pathway involving the intermediate alkoxybicyclo[3.3.1]nonanolate structure was proposed.

The Favorskii rearrangement, due to its versatility, has become an increasingly employed method in organic synthesis.[1] A number of successful syntheses of complex molecules including cage structures[2] and natural products[3] have been accomplished using this reaction. However, we are still far from a detailed understanding of the reaction mechanism,[4] and one is left confused as to how to predict the synthetic utility of a certain example for a synthesis of a product of desirable structure. In the course of our research programme[5] we needed chiral, bridged functionalized structures with chromophores at appropriate positions, and the Favorskii rearrangement reaction of halogeno ketones of the bicyclo[3.3.1]nonane skeleton was chosen for the synthesis. Bridged bicyclic compounds, namely bicyclo[3.3.1]nonanes, containing various reactive functional groups are valuable models for elucidation of reaction mechanisms[6] and stereochemistry.[7] The use of substituted compounds of this framework as synthetic intermediates was also intensively explored since the inherent features of this ring system have been exploited for the construction of complex natural products,[8] and of various ring sized bridged polycyclic structures and lattice inclusion hosts.[9] A few examples of the Favorskii rearrangement reaction of α-halogenobicyclo[3.3.1]nonane ketones for the synthesis of ring-contracted cyclic structures of related series have been reported.[10] However, preliminary results on the reaction of halogeno derivatives of bicyclo[3.3.1]nonanones **1** and **2** in the presence of sodium methoxide under the Favorskii reaction conditions revealed a different reaction course.[11] To extend the scope of these investigations we now report our investigation of the reaction of chloro- and bromo-bicyclo[3.3.1]nonanone derivatives **3**–**5** with several bases under the Favorskii rearrangement reaction conditions directed toward elucidating the factors that effect intramolecular cyclization. The tricyclic ketones obtained in this reaction could be promising synthons of natural product tetrodotoxin carbocyclic analogues and other related structures.[12]

Results and discussion

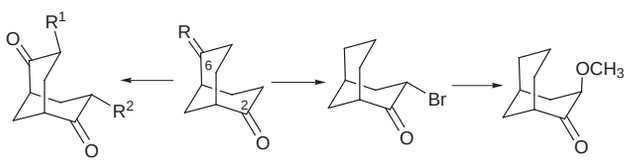
Halogenation of bicyclo[3.3.1]nonanones

Bromo ketone **3** was prepared by reaction of ketone **1** with an equimolar ratio of molecular bromine in acetic acid and all the data confirmed the formation of *exo*-3-bromobicyclo[3.3.1]-nonan-2-one **3** (Scheme 1). The *exo*-orientation of bromine was confirmed from the H-3 signal in the ^{1}H NMR spectrum and is in agreement with the literature data.[13] Bromination of the dione **2** in this work was performed using several reagents from which a direct bromination with bromine in acetic acid and pyridinium bromide-perbromide proceeded instantaneously at room temperature. Although the synthesis of dibromo dione **4** by a direct bromination of dione **2** has been reported in the literature,[14] the configuration of the bromine atoms was not unequivocally established. Recently the bromination of dione **2** with copper(II) bromide has been studied.[15] A mixture of *exo*,*exo*- and *exo*,*endo*-dibromo ketones in the ratio 3:7 was found to be formed in this reaction and the preferred chair-boat conformation for the latter structure was proposed due to the repulsion between 3-Br and 7-H. The difference in protocol was that the reactions performed here were very short (until the intense color of bromine disappeared: *ca*. 10 min with bromine and 30 min with pyridinium perbromide) whereas previously the reaction was carried out for 3 h. The chemical shifts in the ^{1}H NMR spectrum of dibromo derivative **4** at δ 4.61 and 4.95 refer to the protons of CHBr groups in the chair and the boat conformation, respectively. The boat conformation is supported by consideration of H-7 coupling constants to H-8 protons ($J_{7endo,8endo}$ = 10.5 Hz and $J_{7endo,8exo}$ = 9.3 Hz). The coupling constants of the CHBr group in the chair conformation ($J_{3endo,4endo}$ = 7.5 Hz and $J_{3endo,4exo}$ = 7.3 Hz) suggest a flattening of the ring. It was shown in an early work by Corey and confirmed later that the most stable conformation of substituted α-halogeno cyclohexanones is the chair form in which the halogen atom is equatorial.[16] The chair-chair form of the *exo*,*exo*-3,7-dibromo isomer was calculated by us (MM2 method) to be the most stable by 2.8 kcal mol^{-1}† compared to any other conformation. The kinetically controlled bromination product should be the symmetrically substituted α,α′-*exo*,*exo*-dibromo dione **4**; however, bromination is a reversible reaction and epimerization of bromo ketones takes place readily during the reaction.[13] Therefore the *exo*,*endo*-isomer was also formed in this reaction. This was further supported by the observed changes in the ^{1}H NMR spectrum of **4** in which the initial doublet of doublets of 3- and 7-H at δ ~4.6 were transformed into a multiplet during the short period when the bromination was performed directly in the NMR tube. It is interesting to note that, according to molecular mechanics calculations, we found that the conformational energies of the *exo*,*endo*-diastereomer practically do not differ irrespective of which conformation, *i.e*. chair-chair or chair-boat, is considered (7.76

† 1 cal = 4.184 J.

kcal mol^{-1}). The predominance of the lowest energy *exo*,*exo*-diastereomer **4** (4.9 kcal mol^{-1}) was established from spectral data; however, it was obtained in diastereomerically pure enough form (>90%) only after several recrystallizations from ethyl acetate. Thus the bromination of dione **2** with bromine and pyridinium perbromide proceeded unselectively and the ratio of diastereoisomers depended strongly on the reaction conditions and could not be controlled properly.

Dichloro dione **5** was obtained in a diastereomerically pure form by direct chlorination of dione **2** with molecular chlorine in dichloromethane (Scheme 1). An 11.0 Hz coupling from



4 $R^1 = R^2 = Br$ **1** $R = H_2$ **3** **6**

5 $R^1 = R^2 = Cl$ **2** R O

Scheme 1

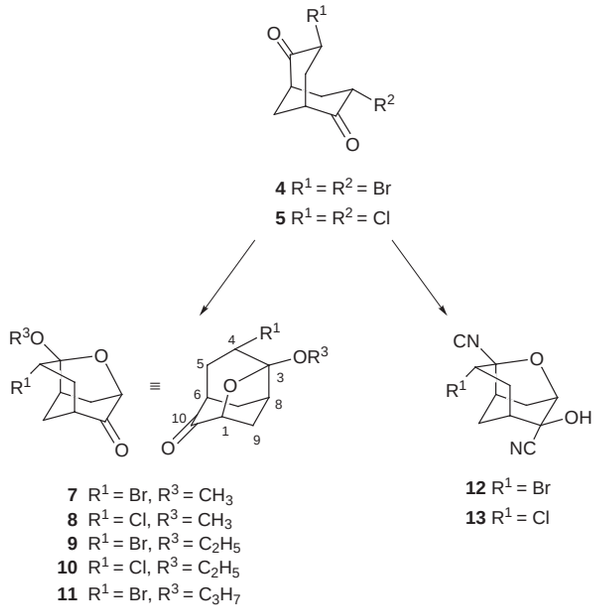
H-4(8)$_{exo}$ to H-3(7) and an 8.0 Hz coupling from H-4(8)$_{endo}$ to H-3(7) in the ^{1}H NMR spectrum are consistent with an *endo* orientation of H-3(7) and, hence, *exo* orientation of the C-3 and C-7 chlorine atoms. The ^{13}C NMR spectrum shows only five different carbon signals, in agreement with the C_2 molecular symmetry of **5**.

Reaction of halogeno bicyclo[3.3.1]nonanones under Favorskii reaction conditions

Addition of a solution of sodium methoxide to bromo ketone **3** led to the isolation of a single product. The identity of *endo*-3-methoxybicyclo[3.3.1]nonan-2-one **6** was established from the analytical data. The C=O absorption band at 1720 cm^{-1} and the absence of ester or acid C=O as well as of OH and C–Br bands in the IR spectrum confirmed the presence of the carbonyl group in the reaction product. The sharp singlet of OCH_3 signal at δ 3.35 in the ^{1}H NMR spectrum together with the GLC data confirmed that a single isomer was formed. Thus the result of this reaction was a halide displacement by methoxide ion; analogous examples in bicyclo[3.2.1]octane and related structures have been reported.[17] This could be rationalized in terms of instability of the intermediate cyclopropanone ring, which should be a key intermediate in the Favorskii rearrangement.

The reaction of dihalogeno diones **4** and **5** with sodium methoxide was studied in order to get evidence for the course of the reaction under analogous conditions. A single product was isolated in both reactions using typical base-promoted Favorskii reaction conditions. The molecular weight (GC-MS) of the products and the spectral data of the bromo- and chloro-containing derivatives **7** and **8** led us to the conclusion that the oxatricyclo[4.3.1.0^{3,8}]decane (oxaprotoadamantane[18]) structure was formed (Scheme 2).

Instead of the structural changes expected for the Favorskii rearrangement, the IR spectra of the compounds showed no vibrations characteristic of ester or acid groups. A band at ~1730 cm^{-1} is diagnostic of the carbonyl group with no halogen atom near it. The doublets of signals in ^{1}H NMR spectra at δ 4.65 and 4.36 in **7**, and δ 4.61 and 4.36 in **8** correspond to the protons at C-4 atoms bearing halogens and at C-1 atoms between the cyclic oxygen atom and carbonyl group in the tricyclic skeleton, respectively.[19] The coupling constants for these protons appear as doublets with J = 7.5 Hz and 6.0 Hz, respectively, although a doublet of doublets should be expected in each case. The coupling constants are consistent with the geometry of molecules **7** and **8**. The dihedral angle of proton H-4 to one



Scheme 2

of the C-5 protons in a six-membered ring in the boat conformation is close to 90° in both structures as we calculated for minimized geometries by the MM2 method. Consequently the splitting due to this coupling is negligible and not detectable in the spectrum. The dihedral angles of the proton at C-1 with C-9 protons are practically equal. The ^{13}C NMR spectra are characteristic of an oxatricyclodecane skeleton and off-resonance spectra correspond to the appropriately substituted carbon atoms in the tricyclic structure. The chemical shift of C-3 at δ ~109 in the ^{13}C NMR spectrum is very characteristic and is in good agreement with the calculated value for the quaternary carbon atom between two oxygen atoms and a C-Hal group nearby in the tricyclodecane structure.[20]

The scope of the intramolecular cyclization of dihalogeno diones **4**, **5** was studied in the presence of other nucleophiles. Performing the reaction of halogeno diones **4**, **5** with sodium ethoxide, sodium propoxide and potassium cyanide under analogous reaction conditions, with the only exception being the solvents, the tricyclic reaction products were isolated from the complex mixture of products. The base–solvent combinations for the reaction of **4** and **5** with other reagents were used due to an insufficient solubility of these compounds. The analytical and spectral data confirmed a tricyclic structure for compounds **9**–**13**. The structural proof of these compounds was gained by spectroscopic methods and all the spectra for ethoxy derivatives **9**, **10** were very similar to those of the methoxy derivatives **7**, **8**. The yield of the cyclization product using ethoxide and propoxide nucleophiles was low, and the product **11** was rather unstable, and was identified only by GC-MS. Dehydrobromination reaction took place during this process, therefore the reaction has to be followed carefully and stopped after 15–20 min to avoid predomination of the elimination products.

The reaction with potassium cyanide resulted in a formation of a tricyclic skeleton as well. Following the intramolecular ring closure, the second carbonyl group of the dihalogeno dione was involved in the reaction and a cyanohydrin at position 10 was formed. The dicarbonitriles of tricyclic structure **12** and **13** were the main products, with high yields, of this reaction and the results confirmed that the basicity of the nucleophile strongly governs the course of the reaction. The ^{13}C NMR shift values of both dicarbonitriles **12** and **13** are very similar except for the signals of carbon atoms of the C-Hal function, as are the fragment ions in mass spectra after the elimination of HCN and HHal from the molecular ion. The fragmentation of **12** and

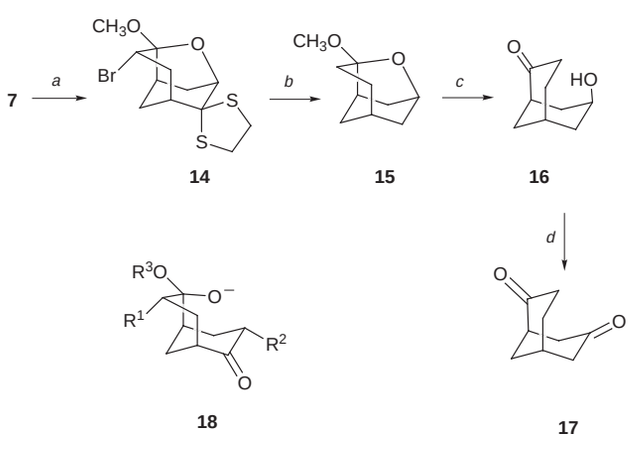
13 under electron impact occurs readily and the molecular ion is detectable only in FAB mode.

The reaction of sodium isopropoxide and *tert*-butoxide on dihalogeno dione **4** gave complex mixtures of dehydrobromination products identified by GLC, ^{1}H NMR and mass spectroscopic data (*cf.* ref. 15).

A chemical correlation between the oxatricyclodecane and bicyclononane structures

Chemical evidence for the tricyclic ring formation was gained by converting **7** and **8** to bicyclo[3.3.1]nonane-2,7-dione **17** (Scheme 3). Protection of the carbonyl group in **7** and **8** was achieved by dithioketalization with ethane-1,2-dithiol. Subsequent catalytic reduction of **14** afforded tricyclic methoxy derivative **15**. Hydrolysis of the latter structure in acidified water–methanol solution led to ring opening with the formation of *endo*-7-hydroxybicyclo[3.3.1]nonane structure **16**. The *endo*-configuration of the hydroxy group at C-7 was deduced from the shape and half-width of the corresponding signal in the ^{1}H NMR spectrum.[21] The corresponding dione **17** was obtained by oxidation of **16** with Jones' reagent. The ^{13}C NMR spectra of 2,7-dione **17** in comparison with those of the 2,6- and 3,7-diones and appropriate monoketones[22] of this skeleton permitted us to assign all carbon resonances of the bicyclic framework.

Additional evidence that carbonyl shift in bicyclononane skeletons took place during the transformation of **7** to **17** was obtained by GLC analysis of diones **17** and **2**, showing a good separation of both stereoisomeric diones.



Scheme 3 *Reagents*: *a*, $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$; *b*, Raney Ni; *c*, HCl; *d*, CrO_3, H^+.

The chromatographic enantiomer separation of oxaprotoadamantanes **7**, **8**, **12**, and **13** was achieved by chiral GLC using a permethylated β-cyclodextrin stationary phase. A gas chromatogram is shown in Fig. 1. The base-line separation of the enantiomers confirmed the diastereomeric purity of the synthesized chiral structures. Retention times were governed by the molecular weight of the compounds, *i.e.* the bromo derivatives had longer elution times.

Mechanistic considerations

The process leading to the intramolecular ring closure can be explained by a pathway implying intermediate alkoxy bicyclo[3.3.1]nonanolate species **18** (Scheme 3). The anion **18** is the key intermediate in the process and halogen is released during an intramolecular process at C-7 and not at C-3 as in a usual Favorskii process. The ring with the charged oxygen atom at C-2 should adopt the twist-boat conformation to undergo transannular ring closure, and this is also a favorable conformation for the intramolecular nucleophilic bromine substitution at C-7. Evidently the cyclopropanone mechanism of the

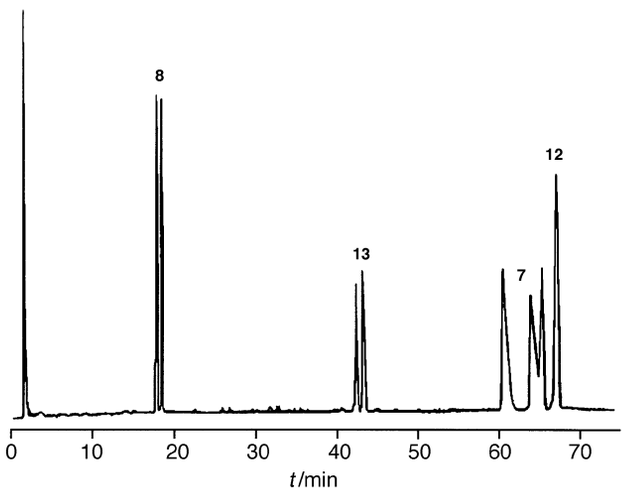


Fig. 1 Gas chromatogram of enantiomer separation of oxaprotoadamantanes **7**, **8**, **12**, and **13** on a permethylated β-cyclodextrin column (30 m × 0.25 μm) at 120 °C in isothermal elution, inlet pressure 6 bar (6×10^5 Pa) of helium.

Favorskii rearrangement involving a highly strained symmetrical intermediate makes this path much less favorable even though an α-hydrogen is present in the initial halogeno ketones. Moreover, this pathway is prevented at an earlier stage than the cyclopropanone formation due to the impediment of deprotonation at the bridgehead C–H group in agreement with Bredt's rule.[23] Therefore the semibenzylic mechanism at the initial stage is operative in this structure and it is viable stereoelectronically in this system. The subsequent intramolecular nucleophilic attack of the bromine atom by the anionic oxygen leads to the cyclic ether formation. This process is competing with the nucleophilic displacement of bromide and elimination of hydrohalogenide depending on the basicity of the alkoxide, its bulkiness and polarity of the media. The latter reaction course is predominant with the use of isopropoxide and *tert*-butoxide in the corresponding alcohols.

There are a few examples where some bicyclic α-halogeno ketones undergo base-promoted intramolecular cyclization reaction or Haller–Bauer-type reaction instead of a normal Favorskii-type ring contraction.[4c,24,25]

In conclusion, we have accomplished the synthesis of a highly functionalized chiral oxatricyclo[4.3.1.0^{3,8}]decanone structure from α,α′-dihalogeno bicyclo[3.3.1]nonanediones under basic conditions using various nucleophiles. The result obtained in this work is a rather interesting example of intramolecular ring closure under Favorskii reaction conditions and to our knowledge is the first synthetic entry into functionalized oxaprotoadamantane systems.

Experimental

Mps and bps are uncorrected. IR spectra were recorded in KBr pellets (unless stated otherwise) on Specord M80 or UR 20 spectrometers. ^{1}H NMR spectra were recorded on Varian (300 MHz) or Bruker (200 MHz) and Tesla BS-587A (80 MHz) instruments for samples in deuteriochloroform (unless stated otherwise) and are reported as chemical shifts (δ) in ppm relative to $(CH_3)_4Si$. Mass spectra were run by GLC-MS on a Hewlett-Packard 6980 instrument with mass-selective detector HP 5973 using Supelcowax capillary column (30 m × 0.25 mm) or on an AEI MS 902S mass spectrometer (FAB in the positive mode). GLC analysis was carried out on a Varian 3700 instrument (FID) by using a 30 m long column (9% silicon on Chromosorb W-AW). A Perkin-Elmer Autosystem GC, equipped with split/splitless injector and flame ionization detector, was used for enantioseparation on BetaDex 120 fused silica capillary column. TLC was carried out on Silufol

aluminium sheets coated with silica gel and column chromatography on silica gel L 100/160 (Lachema, Czech Republic). Molecular mechanics calculations were performed using the SPARTAN Plus program package.[26] Bicyclo[3.3.1]nonan-2-one **1** and bicyclo[3.3.1]nonane-2,6-dione **2** were synthesized according to the literature methods.[27,28] Organic extracts were dried over Na_2SO_4 unless stated otherwise. 'Ether' refers to diethyl ether.

exo-3-Bromobicyclo[3.3.1]nonan-2-one 3

To a solution of ketone **1** (1.38 g, 10 mmol) in 20 ml of glacial acetic acid was added a solution of bromine (0.51 g, 10 mmol) in 5 ml of glacial acetic acid. The reaction mixture was allowed to stir at room temperature for 30 min and then was poured into ice cold water. A white precipitate was collected by filtration, washed with water and dried to yield 2.05 g (94.5%) of the bromo ketone **3**, mp 74–75 °C and was identified by comparison of its mp and ^{1}H NMR spectra with literature values.[13]

Bromination of bicyclo[3.3.1]nonane-2,6-dione 2

(a) With bromine in chloroform. To a solution of dione **2** (3.04 g, 20 mmol) in 125 ml of chloroform was added a solution of bromine (2.13 g, 41 mmol) in 25 ml of chloroform. The reaction mixture was kept at room temperature until the color of bromine disappeared (5–10 min). Work-up involved washing the solution successively with water, 5% aqueous Na_2CO_3, and water. The organic layer was dried, evaporated and the residue was recrystallized from glacial acetic acid to yield 6.1 g (97%) of dibromo diketone.

(b) With pyridinium tribromide. To a solution of dione **2** (5.0 g, 0.032 mol) in glacial acetic acid (30 ml) was added pyridinium tribromide (26.3 g, 0.082 mol) at 40 °C. The reaction was thoroughly mixed and cooled to 5 °C. The crystallization started in 20 min and the intense red color of the solution became less intense and the reaction finished in 2 h. The crystals were filtered, washed with acetic acid (10 ml) and recrystallized from ethyl acetate to give *exo*,*exo*- and *exo*,*endo*-3,7-dibromobicyclo[3.3.1]nonane-2,6-dione **4** (7.4 g, 73%) as white crystals, mp 170–172 °C (Found: C, 34.95; H, 3.38; Br, 51.10. Calc. for $C_9H_{10}Br_2O_2$: C, 34.87; H, 3.25, Br, 51.55%); ν_{max}/cm^{-1} 1750, 730; δ_H(200 MHz) 1.72–3.25 (8 H, m), 4.61 (2 H, dd, J = 10.0 Hz, 3-H), 4.95 (2 H, dd, J = 10.5 Hz); δ_C 203.9 (C=O), 201.7 (C=O), 200.8 (C=O), 77.5 (C-3), 77.1 (C-7), 76.8 (C-3), 76.6 (C-7), 49.9, 48.9, 48.0, 44.6, 44.5, 44.2, 41.6, 38.0, 33.7, 30.9, 29.6, 29.4 (all skeletal C).

exo,*exo*-3,7-Dichlorobicyclo[3.3.1]nonane-2,6-dione 5

A solution of dione **2** (1.52 g, 10 mmol) in 65 ml of CH_2Cl_2 was cooled to 0 °C and treated during 1 h with a solution of chlorine (1.42 g, 10 mmol) in 35 ml of CH_2Cl_2. After washing successively with water, 5% aqueous Na_2CO_3, and water, the organic phase was separated, dried, and evaporated. The residue was recrystallized from chloroform to yield 2.0 g (90%) of **5**, mp 183–185 °C (Found: C, 48.56; H, 4.60; Cl, 32.42. Calc. for $C_9H_{10}Cl_2O_2$: C, 48.90; H, 4.56; Cl, 32.07%); ν_{max}/cm^{-1} 1755, 710; δ_H[200 MHz, $(CD_3)_2CO$] 5.12 (2 H, dd, J = 11.0 and 9.5 Hz, 3- and 7-H), 3.03 (2 H, m, 1- and 5-H), 2.73–2.02 (6 H, m); δ_C 201.7 (CO), 58.2 (C–Cl), 44.7 (C-1, C-5), 37.7 (C-4, C-8), 31.6 (C-9).

endo-3-Methoxybicyclo[3.3.1]nonan-2-one 6

A solution of bromo ketone **3** (1.2 g, 5.5 mmol) in 15 ml of CH_3OH was treated with sodium methoxide (0.6 g, 11 mmol) for 20 min at 40 °C. After being cooled to room temperature, the reaction was quenched and neutralized with 2 M HCl, and evaporated. The residue was dissolved in benzene, filtered and purified by silica gel chromatography (elution with benzene) to give **6** (0.6 g, 65%) as a colorless oil, bp 105–107 °C/17 mmHg; n_D^{25} 1.4955 (Found: C, 71.05; H, 9.21. Calc. for $C_{10}H_{16}O_2$: C, 71.39; H 9.60%); ν_{max}(liquid film)/cm^{-1} 1720 (C=O), 1130 (C–O); δ_H(80 MHz) 3.62 (1 H, dd, J = 4.5 and 6.0 Hz, 3-H), 3.35 (3 H, s, OCH_3), 1.26–2.55 (12 H, m).

General procedure for the reaction of halogeno ketones with sodium methoxide

To a solution of halogeno ketone (5 mmol) in 50 ml of methanol was added a 2 equiv. solution of sodium methoxide in 15 ml of methanol. The reaction mixture was stirred at room temperature for 1 h, quenched with 2 M HCl and diluted with a two-fold volume of water. The product was extracted into $CHCl_3$ (3 × 40 ml) and the combined organic phases were dried and concentrated. The residue was purified by silica gel chromatography (elution with $CHCl_3$).

(±)-(1*R,3*S**,4*S**,6*R**,8*R**)-4-Bromo-3-methoxy-2-oxatricyclo[4.3.1.0^{3,8}]decan-10-one 7.** Yield 57.5% (R_f 0.56), mp 94–95 °C (Found: C, 46.32; H, 4.84; Br, 30.34. Calc. for $C_{10}H_{13}BrO_3$: C, 46.01; H, 5.02, Br, 30.60%); ν_{max}/cm^{-1} 1735, 730; δ_H(300 MHz) 4.65 (1 H, d, J = 7.5 Hz, 4-H), 4.36 (1 H, d, J = 6.0 Hz, 1-H), 3.38 (3 H, s, OCH_3), 2.80–2.89 (2 H, m), 2.48–2.76 (4 H, m), 1.88 (1 H, d, J = 13.5 Hz), 1.71 (1 H, dd, J = 4.5 and 13.5 Hz); δ_C 209.2 (C=O), 109.1 (C-3), 83.8 (C-1), 49.1 (OCH_3), 43.9 (C-4), 44.5, 39.9, 38.9, 35.1, 29.3 (all skeletal C).

(±)-(1*R,3*S**,4*S**,6*R**,8*R**)-4-Chloro-3-methoxy-2-oxatricyclo[4.3.1.0^{3,8}]decan-10-one 8.** Yield 65% (R_f 0.47), mp 81–82 °C (Found: C, 55.29; H, 6.03; Cl, 16.74. Calc. for $C_{10}H_{13}ClO_3$: C, 55.44; H, 6.05; Cl, 16.36); ν_{max}/cm^{-1} 1730, 720; δ_H(300 MHz) 4.61 (1 H, d, J = 7.5 Hz, 4-H), 4.36 (1 H, d, J = 6.0 Hz, 1-H), 3.38 (3 H, s, OCH_3), 2.77–2.65 (3 H, m), 2.60–2.48 (2 H, m), 2.34 (1 H, dd, J = 7.5 and 9.0 Hz, 5-H), 1.86 (1 H, d, J = 12.0 Hz), 1.75–1.66 (1 H, m); δ_C 209.0 (C=O), 109.2 (C-3), 83.9 (C-1), 53.1 (C-4), 49.3 (OCH_3), 44.3, 39.6, 38.8, 35.1, 29.8 (all skeletal C).

General procedure for the reaction of halogeno ketones with sodium ethoxide

To a cooled solution of halogeno dione (2.3 mmol) in a mixture of 60 ml of ethanol and 20 ml of acetone was added a 2 equiv. solution of sodium ethoxide in 20 ml of ethanol. The reaction mixture was stirred at room temperature for 20–30 min, quenched with 2 M HCl and diluted with a two-fold volume of water. The product was extracted into $CHCl_3$ (3 × 20 ml) and the combined organic phases were dried and concentrated. The residue was purified by silica gel column chromatography (elution with $CHCl_3$).

(±)-(1*R,3*S**,4*S**,6*R**,8*R**)-4-Bromo-3-ethoxy-2-oxatricyclo[4.3.1.0^{3,8}]decan-10-one 9.** Yield 16.0% (R_f 0.45), mp 66–68 °C (Found: C, 47.57; H, 5.43; Br, 26.98. Calc. for $C_{11}H_{15}BrO_3$: C, 48.02; H, 5.49; Br, 29.04%); ν_{max}/cm^{-1} 1726, 694; δ_H(200 MHz) 4.67 (1 H, d, J = 4.0 Hz, 4-H), 4.35 (1 H, d, J = 5.5 Hz, 1-H), 3.65 (2 H, q, CH_2), 2.83–2.3 (6 H, m), 1.85–1.60 (2 H, m), 1.23 (3 H, t, CH_3); δ_C 210.4 (C=O), 109.7 (C-3), 84.5 (C-1), 57.8 (OCH_2), 45.4 (C-4), 41.0, 39.7, 35.9, 30.0 (all skeletal C), 16.1 (CH_3); *m*/*z* (>10%) 274/276 (M^+), 246/248 (10/10%), 195 (44), 168 (64), 167 (100), 140 (17), 122 (23), 121 (40), 109 (14), 95 (61), 81 (11), 79 (12), 67 (17), 55 (53).

(±)-(1*R,3*S**,4*S**,6*R**,8*R**)-4-Chloro-3-ethoxy-2-oxatricyclo[4.3.1.0^{3,8}]decan-10-one 10.** Yield 9.6% (R_f 0.5), mp 58–59 °C (Found: C, 58.58; H, 6.42; Cl, 15.01. Calc. for $C_{11}H_{15}ClO_3$: C, 57.27; H, 6.51; Cl 15.40%); ν_{max}/cm^{-1} 1726, 694; δ_H(200 MHz) 4.62 (1 H, d, J = 7.2 Hz, 4-H), 4.34 (1 H, d, J = 5.6 Hz, 1-H), 3.62 (2 H, q, J = 7.2 Hz, CH_2), 2.83–1.50 (8 H, m), 1.22 (3 H, t, J = 7.2 Hz, CH_3); δ_C 210.1 (C=O), 108.8 (C3),

83.6 (C-1), 57.1 (OCH_2), 53.7 (C-4), 44.4, 39.9, 38.8, 35.2, 29.8 (all skeletal C), 15.4 (CH_3); *m/z* (>10%) 231/233 ($[M + 1]^+$, 54/17%), 202/204 (37/11), 194 (56), 185 (11), 168 (69), 156 (29), 140 (48), 122 (50), 121 (44), 109 (56), 94 (45), 81 (61), 67 (29), 55 (63), 39 (71), 27 (100).

General procedure for the reaction of halogeno ketones with potassium cyanide

To a solution of dihalogeno dione **4** or **5** (1.8 mmol) in 20 ml of pyridine was added a solution of potassium cyanide (4.3 mmol, 70% purity) in 10 ml of water. The resulting mixture was allowed to stir at room temperature for 24 h and then poured into 240 ml of aqueous HCl (5%). Extractive work-up (ethyl acetate) followed crystallization or column chromatography on silica gel ($CHCl_3$–ether 3 : 1) yielded the tricyclic compounds.

(±)-(1*R,3*R**,4*S**,6*R**,8*R**,10*R**)-4-Bromo-10-hydroxy-2-oxatricyclo[4.3.1.0^{3,8}]decane-3,10-dicarbonitrile 12.** Yield 92% (R_f 0.47), mp 161 °C (Found: C, 46.46; H, 4.05; Br, 26.86; N, 9.93. Calc. for $C_{11}H_{11}BrN_2O_2$: C, 46.67; H, 3.92; Br, 28.22; N, 9.89%); ν_{max}/cm^{-1} 3398, 3316, 2256, 1464, 1088, 1030; δ_H[200 MHz, $(CD_3)_2CO$] 4.82 (1 H, d, J = 8 Hz, 4-H), 4.65 (1 H, d, J = 5.2 Hz, 1-H), 2.95–2.75 (2 H, m), 2.5–2.1 (7 H, m); δ_C 121.3 (CN), 119.8 (CN), 83.5 (C-3), 81.0 (C-1), 74.5 (C-10), 45.2 (C-4), 40.6, 38.3, 34.7, 33.5, 24.1 (all skeletal C); *m/z* (>5%) 283/285 ($[M + 1]^+$, 1.5/1.5%), 255/57 (6/6), 227/29 (7/7), 148 (8), 130 (3), 120 (10), 104 (100), 91 (8), 77 (10).

(±)-(1*R,3*R**,4*S**,6*R**,8*R**,10*R**)-4-Chloro-10-hydroxy-2-oxatricyclo[4.3.1.0^{3,8}]decane-3,10-dicarbonitrile 13.** Yield 67% (R_f 0.52), mp 150–153 °C (Found: C, 55.52; H, 4.38; Cl, 13.10; N, 11.70. Calc. for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; Cl, 14.85; N, 11.74%); ν_{max}/cm^{-1} 3400, 3310, 2260, 1466, 1088, 1032; δ_H[200 MHz, $(CD_3)_2CO$] 4.79 (1 H, d, J = 8 Hz), 4.63 (1 H, d, J = 5.2 Hz), 2.95 (2 H, m), 2.81–2.14 (7 H, m); δ_C 121.3 (CN), 119.7 (CN), 83.4 (C-3), 80.8 (C-1), 74.3 (C-10), 55.3 (C-4), 40.2, 38.1, 34.7, 33.7, 24.5 (all skeletal C); *m/z* (>10%) 239/241 ($[M + 1]^+$, 10/15%), 212/14 (38/14), 203 (6), 176 (12), 130 (29), 115 (27), 104 (73), 91 (53), 77 (71), 65 (46), 55 (100).

(±)-(1*R**,3*S**,4*S**,6*R**,8*R**)-4-Bromo-10-ethylenedithio-3-methoxy-2-oxatricyclo[4.3.1.0^{3,8}]decane 14

A solution of **7** (1.2 g, 4.6 mmol) in 7 ml of glacial acetic acid was mixed with freshly distilled boron trifluoride–ether (0.7 ml) and ethane-1,2-dithiol (0.4 ml, 4.7 mmol). The reaction mixture was allowed to stir for 18 h at room temperature, quenched with ice (20 g), and neutralized with 10% NaOH solution. The product was extracted into ether (3 × 10 ml), washed successively with 10% K_2CO_3 solution, and saturated NaCl solution, dried and evaporated. The residue was subjected to column chromatography on silica gel (R_f 0.63, $CHCl_3$) to give **14** (1.1 g, 71%), mp 115–116 °C (Found: C, 42.97; H, 5.38. Calc. for $C_{12}H_{17}BrO_2S_2$: C, 42.73; H, 5.08%); δ_H(80 MHz) 4.5 (1 H, d, J = 8 Hz, 4-H), 4.2 (1 H, d, J = 5 Hz, 1-H), 3.2 (3 H, s, CH_3), 3.1 (4 H, m, SCH_2CH_2S), 2.9–1.6 (8H, m); δ_C 108.5 (C-3), 87.1 (C-1), 76.2 (C-10), 49.5 (C-4), 45.7, 44.4, 40.0, 39.3, 39.1, 37.9, 29.9.

(±)-(1*R**,3*S**,6*R**,8*S**)-3-Methoxy-2-oxatricyclo[4.3.1.0^{3,8}]-decane 15

A solution of **14** (1.0 g, 3 mmol) in 30 ml of ethanol was refluxed and stirred for 10 h with 3.0 g of freshly prepared Raney nickel. Reaction progress was monitored by TLC, and a complete reduction was achieved after additional treatment with hydrogen and the addition of 1 g of Raney nickel at room temperature. The reaction mixture was filtered, evaporated and distilled *in vacuo* to yield **15** (0.42 g, 79%), bp 120–124 °C/6 mmHg, n_D^{23} 1.4940 (Found: C, 71.59; H, 9.40. Calc. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52%); δ_H (80 MHz) 4.2 (1 H, d, J = 5 Hz, 1-H), 3.1 (3 H, s, CH_3), 2.3–1.55 (11 H, m); δ_C 108.4 (C-3), 76.8 (C-1), 57.0, 49.3, 41.5, 40.7, 38.6, 32.2, 28.6, 27.7.

(±)-*endo*-7-Hydroxybicyclo[3.3.1]nonan-2-one 16

A mixture of **15** (0.42 g, 2.5 mmol), 5 ml of methanol and 10 ml of water with 2 ml of HCl was refluxed for 2 h. The reaction mixture was quenched with ice (10 g), extracted with $CHCl_3$ (3 × 20 ml), and the product dried, and purified by silica gel chromatography (R_f 0.36, elution with 10% acetone in $CHCl_3$) to give **16** (0.31 g, 80.5%), mp 190–193 °C (Found: C, 69.86; H, 9.13. Calc. for $C_9H_{14}O_2$: C, 70.10; H, 9.15%); ν_{max}/cm^{-1} 3350br, 1685; δ_H(80 MHz) 4.2 (1 H, m, $w_{1/2}$ 15 Hz, 7-H), 3.7 (1 H, s, OH), 2.3–1.25 (12 H, m); δ_C 209.0 (C=O), 76.8 (C-7), 49.4, 42.8, 40.6, 38.6, 32.1, 30.8, 28.6.

(±)-Bicyclo[3.3.1]nonane-2,7-dione 17

To a solution of hydroxy ketone **16** (0.23 g, 1.5 mmol) in 5 ml of acetone was added 0.3 ml of Jones' reagent and the resulting mixture was stirred for 15 min. The reaction mixture was neutralized with sodium hydrogen carbonate, filtered and evaporated. An analytical sample of **17** (0.21 g, 92.5%) was obtained by silica gel column chromatography (elution with $CHCl_3$, R_f 0.47), mp 166–168 °C (Found: C, 70.79; H, 7.81. Calc. for $C_9H_{12}O_2$: C, 71.03; H, 7.95%); ν_{max}/cm^{-1} 1710, 1690; δ_H(200 MHz) 2.4–1.20 (12 H, m); δ_C 214.2 (s, C=O), 210.2 (s, C=O), 48.0 (d, C-1), 46.8 (t, C-8), 44.5 (t, C-6), 36.0 (t, C-3), 33.5 (t, C-9), 32.5 (t, C-4), 29.7 (d, C-5).

Acknowledgements

We thank Dr U. Berg and Mr Š. Zigmantas for ^{1}H NMR spectra, and Dr D. Myers for linguistic advise. Dr G. Laus (FAB mode, Brussels Vrije university) and Mr J. Stukas are acknowledged for mass spectra. We thank the Lithuanian Science and Studies Foundation for partial financial support. The IUPAC names of the new tricyclodecane derivatives were checked using the ACD/Lab Web free service version 2.6 at http://www/acdlabs.com/ilab/.

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