Base-Induced Solvolyses of [3.2.1]Bicyclic α,α′-Dichloro Ketones – 1,3-Transposition and Ring-Contraction

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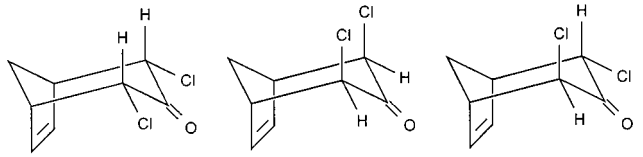
2,4-Dichlorobicyclo[3.2.1]oct-6-en-3-one (**1**) and its spirocyclopropane (**4**) and 8-oxa analogues (**15**, **16**) react with methanolic sodium methoxide to furnish bicyclic α-oxo-acetals (**3b**, **5b**, **17**, **18**) through an enolization/ionization mechanism. With trifluoroethanol/sodium trifluoroethoxide, the corresponding trifluoroethyl acetals (**3a** and **5a**) are formed. Basic hydrolysis affords 2-*endo*-hydroxynorbornene-2-*exo*-carboxylic acid (**20x**) and the 7-oxa analogues (**22x**, **23x**), presumably through benzilic acid rearrangement of the α-diketones.

Introduction

1,1,3,3-Tetrabromoacetone and 1,1,3-trichloroacetone (TCA) are well known as precursors for the generation of 1,3-dihalo oxyallyl intermediates, which undergo [4 + 3] cycloadditions with a host of 1,3-diene systems.[1] In particular, the reaction between tetrabromoacetone and furans under reductive conditions has found widespread use in organic synthesis. The standard methodology is the reduction (debromination) of the resulting 2,4-dibromo-8-oxabicyclo[3.2.1]oct-6-en-3-ones, which results in oxabicycles, unsubstituted at positions 2 and 4.[1,2] To the best of our knowledge, however, non-reductive transformations of the dihalobicycles have attracted no attention.

Some years ago it was found that TCA reacts in the presence of several bases, preferably sodium 2,2,2-trifluoroethoxide in 2,2,2-trifluoroethanol (NaTFE/TFE), through an enolization-ionization mechanism. The dichlorooxyallyl intermediate can be trapped by cycloaddition with cyclopentadiene or furan(s) to give 2,4-dichlorobicyclo[3.2.1]oct-6-en-3-one (**1**) and the 8-oxa analogues.[3] One may well ask why these bicyclic α,α′-dichloro ketones are stable under these solvolytic reaction conditions and do not undergo a further reaction.



1nn 1xx 1nx

[‡] Taken from the doctoral dissertations of A. R. and R. S., Univ. Stuttgart, **1992**.
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It is widely known that the products of the reaction of α-halogenated ketones with oxygen nucleophiles and bases depend on many factors and are difficult to predict.[4] This is in particular the case with dihalo ketones. Concerning the saturated bicyclo[3.2.1]octane skeleton, it has been reported that 2-bromobicyclo[3.2.1]octan-3-one, on treatment with methanolic sodium methoxide, forms the bicyclic methoxy ketone and methyl norbornane-2-carboxylate, the product ratio depending on base concentration.[5,6] An enolization-ionization mechanism involving oxyallyl intermediates was postulated, and the ring contraction (Favorskii rearrangement) explained by cleavage of a cyclopropanone intermediate.[6] To the best of our knowledge, no solvolysis studies of (oxa)bicyclic α,α′-dihalo ketones were available, and so we investigated the behaviour of **1** under forced conditions of its formation.

Results and Discussion

Reaction between Carbocycles and Alcohols/Sodium Alkoxides

Cyclopentadiene was made to react with TCA in NaTFE/TFE over 90 minutes at 0 °C → room temperature. The dull yellow reaction mixture, containing the cycloadducts **1nn**, **1nx**, and **1xx**,[3] was then briefly heated. After quenching with water and extraction, the ketoacetal **3a** was isolated by kugelrohr distillation in 53% yield.

Unequivocal confirmation of the acetal and ketone constitution was supplied by the carbonyl absorption at 1740 cm^{-1} (IR spectrum), and the large coupling constant of 16.4 Hz extracted from the ^1H NMR spectrum, the value of which is consistent with methylene protons in the position α to the carbonyl group. The ^{13}C NMR (DEPT technique) also indicated the new CH_2 group [δ = 44.0, C(4)], as well as the quaternary "acetal carbon atom" at δ = 101.8 [C(2)] and the carbonyl carbon atom (δ = 201.9).

In order to investigate this unexpected transposition of functional groups, *endo*,*endo*-2,4-dichlorobicyclo[3.2.1]oct-

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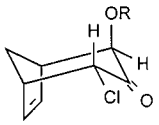
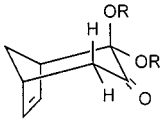
6-en-3-one (**1nn**) was isolated and allowed to react with NaTFE/TFE solution. Treatment of **1nn** with *one* equivalent of NaTFE in TFE, monitored by GLC, resulted in a new product after a few minutes. After one hour, a further four peaks were evident in the GLC. Three days later, the main component was isolated; it could be identified as the monosubstitution product **2a** by its MS, ^{1}H NMR, and ^{13}C NMR spectra, but we were unable to obtain the compound in pure form.



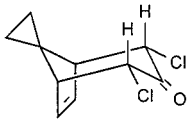


3	R
a	CH_2CF_3
b	CH_3
c	CH_2CH_2

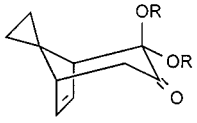
2a: R = CH_2CF_3

The presence of a trifluoroethoxy group was indicated by C−F couplings in the ^{13}C NMR spectrum. The chemical shifts of 66.4 and δ = 83.9 proved that the chloro and trifluoroethoxy substituents were not at the same position, but were bound to different carbon atoms: C(2) and C(4). The *endo* orientation of the chloro substituent was demonstrated by the magnitude of the vicinal coupling in the ^{1}H NMR (J = 3.3 Hz, δ = 4.78) (cf. the starting material **1nn**, δ = 4.67, J = 3.3 Hz). The chemical shift of δ = 3.77 (dd, J = 3.4 and 1.8 Hz) was consistent with an *endo*-proton at C(4), thus demonstrating the *exo* position of the trifluoroethoxy substituent at C(4).

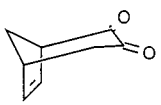
The reaction between **1** (mixture of *endo*/*exo* isomers) and two (or more) equivalents of NaTFE was complete after three days at ambient temperature, as indicated by the precipitation of the stoichiometric amount of NaCl. The ketoacetal **3a** was isolated in a 99% yield. Treatment of **1** with an excess of methanolic sodium methoxide was more rapid, reaching completion after one hour, and eventually gave the dimethoxy acetal **3b** in the same yield. The spirocyclic ethylene acetal **3c** was obtained on treatment of **1** with a solution of sodium in ethylene glycol, using diethyl ether as cosolvent (yield 72%). Treatment of *endo*,*endo*-2,4-dichlorospiro[bicyclo[3.2.1]oct-6-ene-8,1′-cyclopropan]-3-one (**4nn**)[3] with NaTFE or NaOMe gave the ketoacetals **5a** and **5b**, respectively.



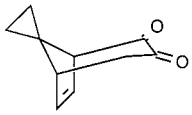
4nn



5a: R = CH_2CF_3
5b: R = CH_3



6



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Bicyclic α-Diketones

The rather high yields obtained by alcoholysis of the dichlorides **1** and **4** prompted us to prepare the α-diketones corresponding to the ketoacetals **3** and **5**. Indeed, treatment of the dimethylacetal **3b** with hydrochloric acid, after workup, chromatography, and kugelrohr distillation, gave the α-diketone **6** in 92% yield as a bright lemon-coloured, viscous liquid, which solidified at ca. 0 °C. The structure was verified by spectroscopy (see Experim. Section) and treatment with *o*-phenylenediamine to form a quinoxaline derivative. With **5b**, the same procedure resulted in the spiro diketone **7**.

Mechanism of the Alcoholyses

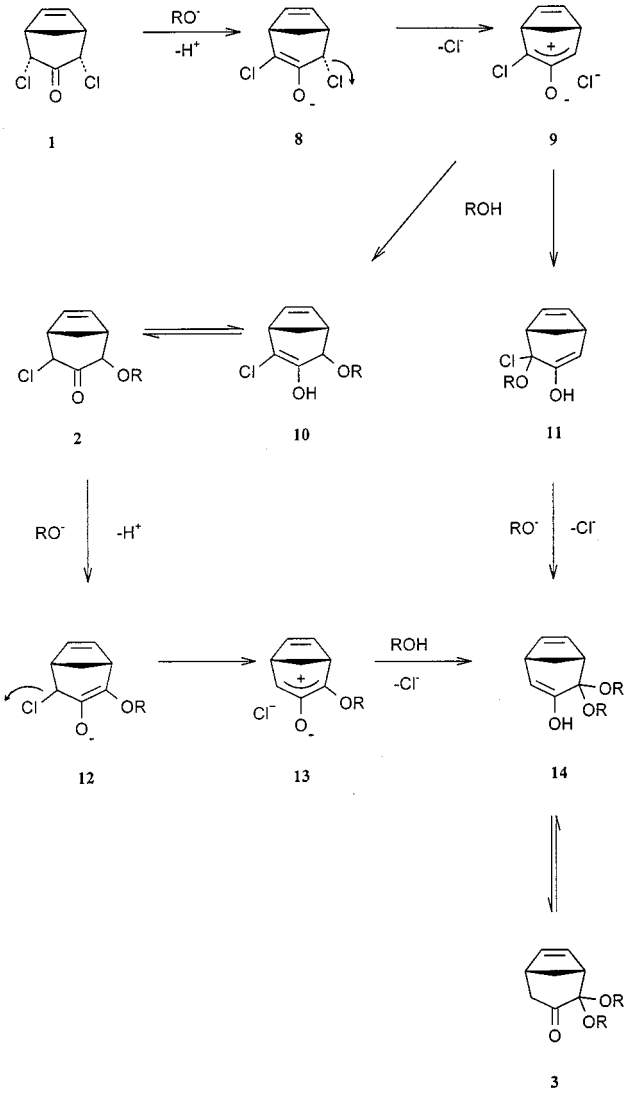
The products of the alcoholyses seem unexpected at first sight, but are in line with the enolization-ionization mechanism postulated for the parent 2-monobromobicyclo[3.2.1]octan-3-one case.[6] The difference lies in the fact that the presence of a second halo substituent results in 1,3-transposed functional groups in a highly selective transformation, and the Favorskii rearrangement is suppressed.

Deprotonation of one of the chloro-substituted α-carbon atoms of the dichloro ketone **1** initiates the reaction cascade (Scheme 1). The resulting enolate **8** can dissociate to form the ion-pair **9**. Association of an alcohol or alkoxide molecule is possible at both termini of the allyl cation, through which the two alkoxychloroenols **10** and **11** should result.[7] The ketone **2**, isolated on trifluoroethanolysis of the carbocycle **1**, is consistent with this interpretation, and the *exo* configuration at the alkoxy-substituted α-carbon atom [C(4)] is not unexpected.[6] Obviously, in the ion pair **9** the *exo* face is more accessible than the concave *endo* face and allows association with alcohol(ate) molecules.

At longer reaction times, or on heating, the alkoxychloro ketones **2** gave the geminal dialkoxy ketones **3** with 1,3-transposed functional groups. In view of the fact that we observed no α,α′-dialkoxy ketones, it may be concluded that the enolization-ionization mechanism again operates: enolization in the direction of the alkoxy-substituted carbon atom again gives an allylic structure (**12**), which may form a second ion-pair (**13**). Obviously, association of the alcohol at the substituted allylium terminus is preferred, finally giving the acetals.[7] However, it cannot be ruled out that the α,α-dialkoxy ketones may result from nucleophilic substitution of the geminal disubstituted enols **11**.

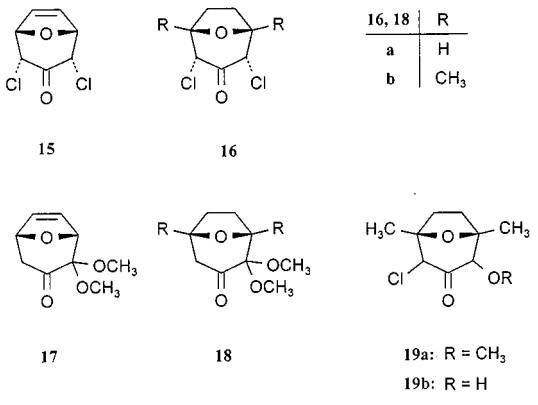
Alcoholyses of Oxabicycles

Treatment of dichloro ketone **15**, the 8-oxa analogue of **1**, with sodium methoxide in methanol at 0 °C → room temperature (3 days), followed by extraction and chromatography, gave the ketoacetal **17**. However, the product proved to be temperature-sensitive, and the yield was mediocre (38%). Less labile products were isolated on long-term reaction (ca. 1 week) of the *saturated* oxabicycles **16a** and **16b**,[8] which gave the ketoacetals **18a** and **18b** (21%, 67%). In analogy to **2**, exposure of **16b** to sodium methoxide solution



Scheme 1. Proposed alcoholysis mechanism with the dichloro ketone **1**

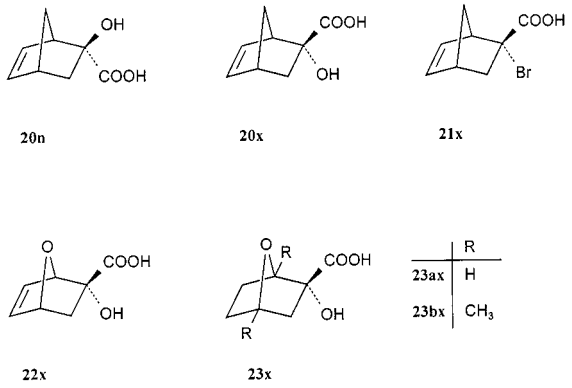
for a more usual, shorter reaction time (100 min) resulted in the exchange of only *one* chloro atom, producing the chloro-substituted monomethoxy ketone **19a** in 55% yield.



Solvolysis in Water/THF: Ring Contraction

α,α′-Dibromocyclohexanones have long been known to undergo rearrangement on treatment with potash lye, with formation of 1-hydroxycyclopentanecarboxylic acids.[9] This ring contraction starts from intermediate 2-hydroxycyclohex-2-enones[10] (or rather their 1,2-dioxo tautomers, α-diketones), which undergo benzilic acid rearrangement,[11] initiated by the attack of hydroxide anion on the carbonyl groups. Utaka, Matsushita, and Takeda reported that cyclohexane-1,2-diones could be obtained in high yield when THF was used as a cosolvent and the reaction was conducted with aqueous sodium hydroxide at 0 °C.[12]

With the goal of obtaining these α-diketones directly, we subjected the bicyclic dichloro ketones **1**, **15**, **16a**, and **16b** to the Utaka conditions. The resulting products were nonvolatile, giving no GLC signals. On acidification with hydrochloric acid, no (tautomeric) α-diketones were isolated, but (hydroxy)carboxylic acids were found. In other words, ring contraction had occurred even under these mild conditions. In the case of **1**, both the *endo* and the *exo* isomers (**1nn** and **1xx**) were found to give practically the same result. Examination of the spectra (see Experim. Section) indicated that one of the diastereomeric 2-hydroxynorbornene-2-carboxylic acids (**20**), with a m.p. of 108−109 °C, must have been formed from **1**.



Alder, Hartmann, and Roth reported that the *exo*-carboxylic acid (**20x**) was formed on heating 2*endo*-bromonorbornene-2*exo*-carboxylic acid (**21x**) with 10 % aqueous sodium carbonate, in addition to small amounts of a hydroxynortricyclenecarboxylic acid.[13] However, these authors reported a melting point of 145 °C for **20x**. Spectra were not mentioned; NMR, of course, was not available in those days. To the best of our knowledge, the *endo*-carboxylic acid (**20n**) was not known in the literature. The different melting points − 108 °C versus 145 °C − led us for the moment to the conclusion that **20n** was the formula of the compound formed from **1**: namely the *endo*-carboxylic acid. We therefore expected that the compound would undergo iodolactonization.[14] However, to our surprise, we could not succeed in obtaining an iodolactone on treatment of our acid **20** in aqueous sodium carbonate solution with the iodine/potassium iodide reagent.[15]

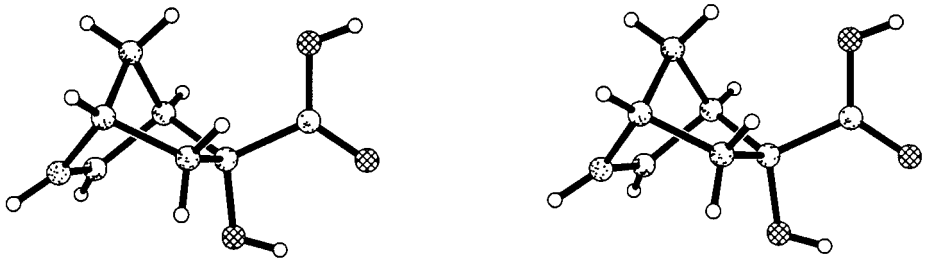


Figure 1. X-ray structure of the 2-hydroxynorbornene-2-carboxylic acid with m.p. 108−109 °C (**20x**): stereoscopic projection of the single molecule; see also refs.[16,17]

In order to identify the acids by spectral comparison, we tried to prepare **20x** or **20n** by the procedure given by Alder et al.[14] However, we were unable to confirm Alder's results.[16] Finally, the structure was determined by X-ray analysis, which showed the *exo* position of the COOH group and the *endo* position of the hydroxy group (Figure 1).[17]

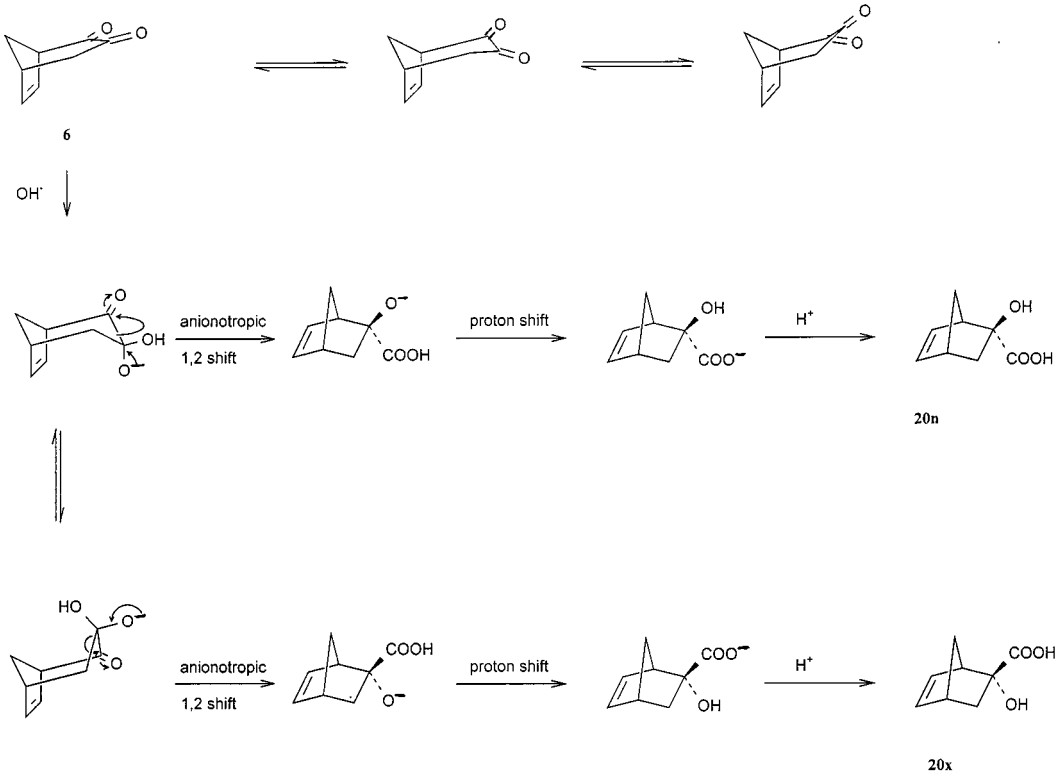
The 8-oxa analogue **15**, on treatment with aqueous NaOH/THF, gave an unsaturated oxanorbornenecarboxylic acid (**22**) in a disappointing 19% yield: again, only one of the possible stereoisomers. Since we were once more unable to obtain an iodolactone, formula **22x** seems likely. From the 1,5-dimethyl analogue, *endo*,*endo*-2,4-dichloro-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one,[3] no acidic product could be extracted from the reaction mixture.

Better results were obtained with the *saturated* oxabicycles **16a** and **16b**. The oxanorbornanecarboxylic acids **23ax** and **23bx** were isolated in 37% and 60% yields, respectively. In order to demonstrate that the acids **22x** and **23ax** had the same configuration at C(2), the unsaturated acid was hydrogenated over palladium-charcoal catalyst. The products were found to be identical according to their ^{1}H NMR spectra.

When **16b** was allowed to hydrolyse at 0 °C (ice bath) for 4 hours, the monochloro hydroxy ketone **19b** − an analogue of the oxabicycle **19a** (OH instead of OCH_3) − could be isolated in 37% yield. This demonstrates that at least the first step of the hydrolysis and the aforementioned alcoholysis reactions was the same.

Mechanism

The different behaviour of the dichloro ketones **1**, **15**, and **16** on basic hydrolysis and alcoholysis is striking at first sight. Whereas in the latter case the carbon skeleton is retained, ring contraction occurs in the aqueous solvent. The discrepancy was resolved by our finding that the diketone **6** rearranged to **20x** in alkaline aqueous media.



Scheme 2. Benzilic acid rearrangement of diketone **6**

The outcome is explained by attack of hydroxide anion at C(3) (Scheme 2). However, *exo*-attack of hydroxide would be expected to produce an intermediate with a *chair* conformation; assuming the anionotropic 1,2-shift to be concerted, one would anticipate formation of the *endo*-carboxylic acid **20n**. The formation of **20x** may be explained by a *boat* conformer intermediate arising from ring-inversion or *endo*-attack of hydroxide.[18]

It is therefore probable that on basic hydrolysis the dichloro ketones **1**, **15**, and **16** at first give the diketones such as **6**, following the mechanism shown in Scheme 1 (with H_2O instead of ROH) and in analogy with the monocyclic system: α,α′-dibromocyclohexanone. The difference may be that cyclohexane-1,2-dione would be stabilized as the monoanion by rapid enolization in alkaline water; enolization of the bicyclic diketones may be impeded by ring strain, opening a channel for nucleophilic attack on the carbonyl groups by hydroxide ion.[19] As a matter of course, a Favorskii rearrangement of the dichloro ketones **1**, **15**, and **16** by way of the cyclopropanone mechanism[6] cannot be rigorously ruled out. A further possibility, the *semi*benzilic acid pathway, is not very probable since **1** – according to Scheme 1 – reacts rapidly through the enolate, and the semibenzilic mechanism is known to be followed in cases in which the α-halo ketone lacks enolizable α′-carbon atoms.[20,21] Moreover, in this case, it would be anticipated that 2-chloronorbornene-1-carboxylic acid would be formed from **1**, followed by hydrolysis to 2-hydroxynorbornene-1-carboxylic acid and/or a hydroxynortricyclenecarboxylic acid,[13,16] rather than **20x**.

Conclusion

Apart from providing a deeper mechanistic insight into the behaviour of (bi)cyclic α,α′-dihalo ketones under solvolytic conditions, the ketoacetals and α-diketones are anticipated to be useful as building blocks in organic synthesis, and so should stimulate further research.[22] Presumably, optimization of the conditions of alcoholysis and workup for the oxabicycles **16**–**18** would give better yields. It may also be anticipated that the corresponding α,α′-dibromo ketones, available by cyclocondensation with tetrabromoacetone under reductive conditions (see, for example, ref.[2]), would give the same results. The ring contraction to the norbornene system should be exploitable too, especially with the spiro compound(s).[23]

Experimental Section

General Remarks: IR: Perkin–Elmer 457. – NMR: Bruker AC 250 for 62.9 MHz ^{13}C NMR and 250 MHz ^{1}H NMR spectra, Bruker CXP 300 for 300 MHz ^{1}H NMR and 75.47 MHz ^{13}C NMR spectra. $CDCl_3$ or [D_6]DMSO as solvent, TMS as internal standard. Assignment of the ^{13}C NMR signals of the cycloadducts and their transformation products was made with off-resonance or DEPT spectra. – EIMS: Varian MAT 711 with data system SS 100. – Analytical TLC: precoated sheets, Polygram Sil G/UV_{254} (silica), or Polygram N/UV_{254} (alumina), distributed by Macherey–Nagel & Co, Düren, Germany; detection by UV extinction, exposure to iodine vapour, or by spraying with vanillin/H_2SO_4 solution, followed by warming. – Preparative column chromatography: silica gel 60 (63–200 μm), distributed by Macherey–Nagel & Co, Düren, Germany. Alumina B was supplied by ICN Biomedicals, Eschwege, Germany. – Dry petroleum ether (PE) was distilled (b.p. 40–65 °C). Ethyl acetate (EA) was dried over calcium chloride, distilled, and kept dry over 4-Å molecular sieves. – Melting points were determined with a Büchi 510 apparatus (Büchi Laboratoriumstechnik AG, Flawil/Switzerland) and are not corrected. – Elemental analyses were performed by the service of the Institut für Organische Chemie, University of Stuttgart. – Dichloromethane was dried by refluxing over powdered calcium hydride and distilled. For sodium trifluoroethoxide/trifluoroethanol (NaTFE/TFE) reagent see ref.[8] Palladium on activated charcoal (10%) hydrogenation catalyst was supplied by Janssen, Beerse, Belgium. 1,1,3-Trichloroacetone (TCA, 1,1,3-trichloropropan-2-one) was obtained from Wacker Chemie, Munich, Germany in "technical" grade. It was distilled prior to use over a 25 cm Vigreux column in vacuo (b.p. 89–92/75 Torr).

Treatment of Dichlorobicyclo[3.2.1]oct-6-en-3-one (1nn) with NaTFE (1 equivalent). – 2-*endo*-Chloro-4-*exo*-(2,2,2-trifluoroethoxy)bicyclo[3.2.1]oct-6-en-3-one (2a): A solution of NaTFE in TFE (c = 2.0 mol/L, 5 mL) was added dropwise with magnetic stirring to a solution of **1nn**[3] (1.91 g, 10.0 mmol) in TFE (10 mL). The mixture was stirred for 3 days at room temperature. Water (30 mL) was added, and the mixture was extracted with dichloromethane (6 × 10 mL). The combined extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. The yellow, oily residue (2.83 g) was distilled in a kugelrohr apparatus at 70–80 °C/0.005 Torr. The colourless liquid (2.15 g) consisted mainly of **2a**, together with **3a** and further unidentified components (ca. 10% by GLC). The yield of **2a** was ca. 76%. The following data for **2a** were extracted from the spectra of the mixture: ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 38.35, 44.2, 47.7, 66.4, 67.4 (q, J = 35.0 Hz), 83.9, 123.35 (q, J = 278 Hz), 133.3, 137.9, 198.7. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.11 (mc, 1 H), 2.46 (d, J = 12.1 Hz, 1 H), 3.11 (mc, 1 H), 3.17 (mc, 1 H), 3.77 (dd, J = 3.4, J = 1.8, 1 H), 3.91 (m, 2 H), 4.78 (d, J = 3.3 Hz, 1 H), 6.06 (dd, J = 5.8, J = 2.9, 1 H), 6.35 (dd, J = 5.8, J = 2.1, 1 H). – IR (film): $\tilde{\nu}$ = 1735 cm^{-1} (C=O). – EIMS (70 eV): m/z (%) = 318 (5) [M^+ from $C_{12}H_{12}F_6O_3$ (**3a**)], 256 (6) [M^+ from $C_{10}H_{10}{}^{37}ClF_3O_2$], 254 (19) [$M^+$ from $C_{10}H_{10}{}^{35}ClF_3O_2$], 66 (100) [$C_5H_6{}^+$]. – HRMS: calcd. for $C_{10}H_{10}{}^{35}ClF_3O_2$ 254.0321; found 254.0323.

2,2-Bis(2,2,2-trifluoroethoxy)bicyclo[3.2.1]oct-6-en-3-one (3a): a) Cyclopentadiene (1.32 g, 20.0 mmol), freshly prepared by cracking distillation of dicyclopentadiene, was mixed with 1,1,3-trichloropropan-2-one (TCA) (1.61 g, 10 mmol) and cooled in an ice bath. A solution of NaTFE in TFE (c = 2.0 mol/L, 20 mL) was added dropwise at 0 °C with magnetic stirring. A white precipitate (NaCl) appeared. The mixture was stirred at room temperature for one hour. The dull yellow mixture was then refluxed for 5–10 minutes, whereupon the colour turned brown. When the mixture had cooled to room temperature, water (50 mL) was added and the mixture was extracted with dichloromethane (5 × 25 mL). The combined organic layers were dried with magnesium sulfate and concentrated in a rotary evaporator. The dark, oily residue was distilled in a kugelrohr apparatus at 90–100 °C/0.03 Torr, giving 1.67 g of a pale yellow oil; yield 53%.

b) A solution of NaTFE in TFE (c = 2.0 mol/L, 6 mL) was added to a solution of **1** [mixture of isomers, 0.96 g, 5 mmol)] in TFE

(10 mL), and the mixture was stirred at room temperature for 3 days. Water (30 mL) was added, and the mixture was extracted with dichloromethane (6 × 10 mL). The combined extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. Kugelrohr distillation of the remaining yellow oil (1.81 g) at 70−80 °C/0.001 Torr gave 1.58 g (99%) of **3a**, as a yellow oil. − IR (film): $\tilde{\nu}$ = 1740 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 2.15 (mc, 2 H), 2.40 (mc, 1 H), 2.64 (dd, *J* = 16.4, *J* = 3.2, 1 H), 2.91 (mc, 1 H), 2.91 (mc, 1 H), 3.07 (mc, 1 H), 3.92 (m, 2 H), 4.31 (dq, *J* = 12.1, *J* = 8.6, 2 H), 5.90 (dd, *J* = 5.7, *J* = 3.0, 1 H), 6.24 (dd, *J* = 5.7, *J* = 2.8, 1 H). − ^{13}C NMR/DEPT (62.8 MHz, $CDCl_3$): δ = 38.3, 44.0, 45.9, 60.1 (q, *J* = 35.0 Hz), 61.1 (q, *J* = 35.0 Hz), 101.75, 123.5, 123.7 (q, *J* = 277 Hz), 130.1, 140.2, 201.9. − $C_{12}H_{12}F_6O_3$ (318.2) calcd. C 45.30, H 3.80; found C 45.26, H 3.73.

2,2-Dimethoxybicyclo[3.2.1]oct-6-en-3-one (3b): A solution of sodium methoxide in methanol (*c* = 2.0 mol/L, 24 mL) was added with stirring over 5 min to a cooled solution (−14 °C) of **1** (mixture of isomers, 1.91 g, 10.0 mmol) in dry methanol (50 mL). The cooling bath was removed, and the mixture was stirred for 1 hour. On warming to room temperature, a white precipitate (NaCl) formed. Water was added, and the mixture was extracted with diethyl ether (5 × 50 mL). The combined ether extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. Kugelrohr distillation of the remaining yellow oil (1.93 g) at 80−90 °C/0.005 Torr gave 1.80 g (99%) of **3b** as a colourless oil. − IR (film): $\tilde{\nu}$ = 1730 cm^{-1} (C=O). − ^1H NMR (300 MHz, $CDCl_3$): δ = 2.08 (mc, 1 H), 2.22 (d, *J* = 11.2 Hz, 1 H), 2.34 (dt, *J* = 16.0, *J* = 3.0, 1 H), 2.56 (dd, *J* = 16.0, *J* = 3.1, 1 H), 2.84 (mc, 1 H), 3.16 (dd, *J* = 5.2, *J* = 2.9, 1 H), 3.33 (s, 3 H), 3.38 (s, 3 H), 5.89 (mc, 1 H), 6.17 (mc, 1 H). − ^{13}C NMR/off-resonance (75.5 MHz, $CDCl_3$): δ = 38.5 (d), 38.75 (t), 44.0 (t), 45.2 (d), 48.8 (q), 50.15 (q), 101.9 (s), 139.0 (d), 203.1 (s). − $C_{10}H_{14}O_3$ (182.2) calcd. C 65.92, H 7.74; found C 65.96, H 7.62.

2,2-Ethylenedioxybicyclo[3.2.1]oct-6-en-3-one (3c): A solution of **1** (mixture of isomers, 1.91 g, 10.0 mmol) in diethyl ether (10 mL) was cooled to 0 °C under nitrogen. A solution of sodium ethane-1,2-diolate in ethane-1,2-diol (*c* = 2.0 mol/L, 20 mL) was added over 15 min, with continuous stirring and cooling. The mixture was stirred overnight at room temperature, whereupon the colour changed to brown. Brine (20 mL) was added, and the mixture was extracted with dichloromethane (5 × 20 mL). The combined organic layers were dried with magnesium sulfate. Evaporation of the solvent and kugelrohr distillation of the remaining brown liquid (2.86 g) at 70−90 °C/0.005 Torr gave 1.29 g (72%) of a yellow oil (**3c**). − IR (CCl_4): $\tilde{\nu}$ = 1730 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 2.16 (mc, 1 H), 2.24 (mc, 1 H), 2.30 (dt, *J* = 16.8, *J* = 2.9, 1 H), 2.61 (dd, *J* = 16.6, *J* = 3.3, 1 H), 2.79 (mc, 1 H), 2.86 (mc, 1 H), 3.80−4.40 (m, 4 H), 5.97 (dd, *J* = 5.7, *J* = 2.9, 1 H), 6.21 (dd, *J* = 5.7, *J* = 2.7, 1 H). − ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 38.2, 39.6, 43.7, 48.3, 64.7, 67.1, 108.1, 131.1, 139.7, 206.6. − $C_{10}H_{12}O_3$ (180.2) calcd. C 66.65, H 6.71; found C 66.94, H 6.83.

2,2-Bis(2,2,2-trifluoroethoxy)spiro[bicyclo[3.2.1]oct-6-ene-8,1′-cyclopropan]-3-one (5a): A solution of NaTFE in TFE (*c* = 2.0 mol/L, 6 mL) was added dropwise to a solution of **4nn**[3] (2.17 g, 10.0 mmol) in TFE (10 mL), and the mixture was stirred at room temperature for 3 days. Brine (20 mL) was added, and the precipitate was dissolved by adding water. The mixture was extracted with dichloromethane (5 × 25 mL). The combined extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. Kugelrohr distillation of the remaining yellow oil (3.40 g) at 70−90 °C/0.001 Torr gave 2.89 g (84%) of **5a**, as a yellow viscous oil that solidified on storage in the refrigerator. − ^1H NMR (250 MHz, $CDCl_3$): δ = 0.52−0.79 (m, 2 H), 1.07−1.15 (m, 2 H), 2.12 (dd, *J* = 5.8, *J* = 2.9, 1 H), 2.46 (d, *J* = 3.0 Hz, 1 H), 2.50 (dd, *J* = 16.0, *J* = 3.8, 1 H), 2.68 (dd, *J* = 16.9, *J* = 3.5, 1 H), 3.70−4.04 (m, 4 H), 6.02 (dd, *J* = 5.9, *J* = 2.9, 1 H), 6.31 (dd, *J* = 5.9, *J* = 2.8, 1 H). − ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 7.7, 11.4, 32.7, 43.5, 45.3, 51.3, 59.6, (q, *J* = 36.0 Hz), 61.0 (q, *J* = 35.0 Hz), 100.6, 123.6 (q, *J* = 276 Hz), 130.55, 140.85, 201.3. A satisfactory combustion analysis could not be obtained.

2,2-Dimethoxyspiro[bicyclo[3.2.1]oct-6-ene-8,1′-cyclopropan]-3-one (5b) A solution of sodium methoxide in methanol (*c* = 2.0 mol/L, 25 mL) was added with stirring over 15 min to a solution of **4nn** (2.17 g, 10.0 mmol) in dry methanol (50 mL), cooled in an ice bath. The cooling bath was removed, and the mixture was stirred for 1 hour. Water was added, and the mixture was extracted with diethyl ether (5 × 50 mL). The combined ether extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. Kugelrohr distillation of the residue at 75−85 °C/0.001 Torr gave 1.85 g (89%) of **5b**, as a pale yellow viscous oil. − IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (C=O). − ^1H NMR (250 MHz, $CDCl_3$): δ = 0.67−0.75 (m, 2 H), 1.08−1.18 (m, 2 H), 2.07 (mc, 1 H), 2.41 (dd, *J* = 16.1, *J* = 2.9, 1 H), 2.50 (mc, 1 H), 2.64 (dd, *J* = 16.0, *J* = 3.2, 1 H), 3.17 (s, 3 H), 3.31 (s, 3 H), 6.03 (dd, *J* = 5.9, *J* = 2.9, 1 H), 6.28 (dd, *J* = 5.9, *J* = 2.8, 1 H). − ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 8.3, 11.4, 33.0, 43.6, 45.8, 48.2, 50.8, 50.9, 101.5, 132.1, 139.3, 203.8. − $C_{12}H_{16}O_3$ (208.3): calcd. C 69.21, H 7.74; found C 69.04, H 7.84.

Bicyclo[3.2.1]oct-6-ene-2,3-dione (6): A mixture of **3b** (1.82 g, 10.0 mmol), water (10 mL), and conc. hydrochloric acid (10 mL) was stirred overnight at room temperature. The mixture was extracted with dichloromethane (6 × 50 mL). The combined extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. The remaining yellow oil (1.60 g) was purified by filtration over silica (80 g) with PE/EA (1:1, 250 mL). The filtrate was concentrated, and the viscous residue (1.43 g) was distilled in a kugelrohr apparatus at 100 °C/0.001 Torr. Yield 1.25 g (92%) **6**. The lemon-coloured, viscous oil solidified at ca. 0 °C. − IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (broad absorption band). − ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (d, *J* = 12.1 Hz, 1 H), 2.55−2.75 (m, 3 H), 3.13 (mc, 1 H), 3.58 (dd, *J* = 4.6, *J* = 3.1, 1 H), 5.88 (dd, *J* = 5.4, *J* = 2.9, 1 H), 6.56 (dd, *J* = 5.5, *J* = 2.8, 1 H). − ^{13}C NMR/off-resonance (75.47 MHz, $CDCl_3$,): δ = 37.7 (d), 39.2 (t), 45.6 (t), 54.7 (d), 127.6 (d), 142.9 (d), 189.5, 197.1. − EIMS (70 eV): *m/z* (%) = 136 (12) [M^+ from $C_8H_8O_2$], 108 (16) [M^+ − CO], 79 (15), 66 (100), 39 (11). − $C_8H_8O_2$ (136.15): calcd. C 70.58, H 5.92; found C 68.54, H 6.10; a satisfactory combustion analysis could not be obtained. − Quinoxaline derivative:[16,24] $C_{14}H_{12}N_2$ (208.3): calcd. C 80.74, H 5.81, N 13.45; found C 80.50, H 5.85, N 13.45.

Spiro[bicyclo[3.2.1]oct-6-ene-8,1′-cyclopropane]-2,3-dione (7): Compound **5b** (1.46 g, 7 mmol) was stirred with water (10 mL) and conc. hydrochloric acid (10 mL) as described for **6**. After 2 days, the mixture was diluted with water (10 mL) and extracted with dichloromethane (5 × 50 mL). The combined extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. The residue (1.30 g) was purified by filtration over silica (80 g) with PE/EA (4:1). The filtrate was concentrated, and the remaining yellow solid (1.15 g) was sublimed at 50−60 °C/0.001 Torr. The yellow sublimate (1.12 g, yield 99%) **7** had m.p. 82−84 °C. − IR ($CDCl_3$): $\tilde{\nu}$ = 1740, 1720 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 0.75 (mc, 4 H), 2.44 (mc, 1 H), 2.64 (dd, *J* = 18.3, *J* = 2.0, 1 H), 2.75 (dd, *J* = 18.3, *J* = 4.1, 1 H), 2.97 (d, *J* = 3.0 Hz, 1 H), 6.00 (dd, *J* = 5.7, *J* = 3.0, 1 H), 6.62 (dd, *J* = 5.7, *J* = 2.9, 1 H). − ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 5.4, 11.5, 34.0, 44.65, 45.4,

61.8, 127.9, 142.9, 188.4, 198.3. − EIMS (70 eV); (*m*/*z*): 162 (6) [M+ from $C_{10}H_{10}O_2$], 134 (5) [M − CO], 106 (4) [M − 2 CO], 93 (8), 92 (100) [M − $C_3H_2O_2$]. − $C_{10}H_{10}O_2$ (161.2): calcd. C 74.06, H 6.21; found C 73.25, H 6.22. A satisfactory combustion analysis could not be obtained. − HRMS: calcd. for $C_{10}H_{10}O_2$ 162.0681; found 162.0682.

2,2-Dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (17): A solution of **15** (1.93 g, 10.0 mmol) in dry methanol (50 mL) was added dropwise over 15 minutes to a solution of sodium methoxide in dry methanol (*c* = 1 mol/L, 50 mL), cooled in an ice bath. The ice bath was removed, and the mixture was stirred for 3 days at room temperature. After addition of water (60 mL), the mixture was concentrated by half in a rotary evaporator and extracted with ethyl acetate (7 × 20 mL). The combined extracts were dried with magnesium sulfate, and the solvent was removed by rotary evaporation. The residue (1.31 g), a brown oil, was purified by chromatography on alumina (activity 3, 200 g) with PE/EA (5:1). The eluted product with R_f = 0.21 was dried in vacuo (oil pump). The substance, a pale yellow oil (0.70 g **17**, 38%) proved to be very temperature-sensitive and so was not subjected to kugelrohr distillation. − IR (film): $\tilde{\nu}$ = 1735 cm^{-1}. − ^1H NMR (80 MHz, $CDCl_3$): δ = 2.31 (dd, *J* = 15.0, *J* = 1.0, 1 H, 4n-H), 2.95 (dd, *J* = 15.0, *J* = 4.5, 1 H, 4x-H), 3.36 (s, 3 H, CH_3O-), 3.50 (s, 3 H, CH_3O-), 4.98−5.04 (m, 2 H, 1-H and 5-H), AB sub-spectrum centred at δ = 6.30, with δ_A = 6.37 and δ_B = 6.22, *J* = 6.0 Hz; the lines of the A- and B-parts are split into doublets with *J* = 1.5 Hz, 6-H and 7-H). − ^{13}C NMR/off-resonance (75.47 MHz, $CDCl_3$): δ = 44.8 (t, C-4), 50.1 (q, CH_3O), 50.9 (q, CH_3O), 78.3 (d, C-5), 80.2 (d, C-1), 100.6 (s, C-2), 129.8 (d, C-6 or C-7), 136.0 (d, C-6 or C-7), 200.8 (s, C-3). − $C_9H_{12}O_4$ (184.2): calcd. C 58.69, H 6.57; found C 58.55, H 6.49.

2,2-Dimethoxy-8-oxabicyclo[3.2.1]octan-3-one (18a): This compound was prepared from **16a** (1.95 g, 10.0 mmol) as described for **17** (see above). Treatment was at 0 °C for 1 h, then 7 days stirring at room temperature. The same workup and chromatography provided a colourless oil (R_f = 0.28) that crystallized in the refrigerator. Yield 0.39 g (21%) with m.p. 42−43 °C. − IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62−2.08 (m, 4 H, 6-H and 7-H), 2.30 (finely split d, *J* = 14.6 Hz, 1 H, 4n-H), 2.93 (dd, the low-field part of the doublets is finely split, *J* = 14.6, *J* = 4.9, 1 H, 4x-H), 3.26 (s, 3 H, CH_3O), 3.38 (s, 3 H, CH_3O), 4.60−4.62 (m, 1 H, 1-H or 5-H), 4.68−4.71 (m, 1 H, 1-H or 5-H). − ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 23.5 (C-7), 28.6 (C-6), 48.2 (C-4), 49.5 and 50.3 (CH_3O), 75.8 (C-5), 77.9 (C-1), 100.3 (C-2), 202.9 (C-3). − $C_9H_{14}O_4$ (186.2): calcd. C 58.05, H 7.58; found C 58.20, H 7.57.

2,2-Dimethoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (18b): A solution of **16b** (2.23 g, 10.0 mmol) in dry methanol (80 mL) was added dropwise over 20 minutes to a solution of sodium methoxide in dry methanol (*c* = 1 mol/L, 45 mL), cooled in an ice bath. The mixture was stirred for 1 h in the ice bath and then for 5 days at room temperature. After addition of water (30 mL), the mixture was concentrated by half in a rotary evaporator, and extracted with dichloromethane (5 × 25 mL). The combined extracts were dried with magnesium sulfate, and the solvent was removed by rotary evaporation. The residue was distilled in a kugelrohr apparatus at 150 °C/0.01 Torr, to give 1.44 g (67%) of **18b**, as a colourless oil. For analysis, a sample was purified by chromatography on alumina (activity 3) with PE/EA (10:1). The eluted product with R_f = 0.25 was dried in vacuo (oil pump). − IR (KBr): $\tilde{\nu}$ = 1735 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.61−1.83 (m, 3 H, 6-H and 7-H), 2.00−2.11 (m, 1 H, 6-H or 7x-H), 2.38 (d, *J* = 14.3 Hz, 1 H, 4n-H), 2.70 (d, *J* = 14.3 Hz, the lines are split into doublets with *J* = 1.4 Hz, 1 H, 4x-H), 3.31 (s, 3 H, CH_3O), 3.47 (s, 3 H, CH_3O). − ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.65, 25.8, 33.1, 36.4, 51.6 (CH_3O), 52.3 (CH_3O), 54.0, 82.05, 86.45, 101.04, 204.2. − $C_{11}H_{18}O_4$ (214.3): calcd. 61.66, H 8.47; found C 61.45, H 8.31.

2-Chloro-4-methoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (19a): This compound was prepared from **18b** (2.23 g, 10.0 mmol) in methanol (60 mL) and sodium methoxide solution (50 mL, *c* = 1 mol/L) at 0 °C (80 min). After stirring at room temperature for 20 min and workup as usual, the residue was distilled in a kugelrohr apparatus at 120 °C/0.01 Torr, giving 1.73 g of a yellow oil. It was purified by filtration over alumina (activity 3) with PE/EA (10:1). The eluate, a colourless oil, was concentrated and distilled in a kugelrohr apparatus at 130 °C/0.02 Torr. Yield 1.20 g (55%), as a colourless oil. − IR (film): $\tilde{\nu}$ = 1735 with shoulder at 1725 cm^{-1}. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37−2.08 (m, 10 H, surmounted by two singlets at δ = 1.46 and 1.57 (CH_3), 3.32 (s, 1 H, 4-H), 3.39 (s, 3 H, CH_3O), 4.67 (d, *J* = 1.4 Hz, 1 H, 2x-H). − ^{13}C NMR/off-resonance (62.8 MHz, $CDCl_3$): δ = 20.8 (q), 24.15 (q), 31.0 (t), 33.4 (t), 58.4 (q, CH_3O), 68.8 (d), 83.6 (s), 86.95 (s), 89.7 (d), 199.0 (s, C-3). − EIMS (20 eV): *m*/*z* (%) = 218 (5) [M^+], 184 (10), 183 (98), 155 (11), 154 (76), 151 (16), 142 (14), 139 (17), 122 (12), 118 (18), 109 (48), 99 (11), 98 (16), 97 (100), 96 (23), 72 (61), 43 (50). − HRMS. calcd. for $C_{10}H_{15}ClO_3$ 218.0710; found 218.0708.

2-*endo*-Hydroxybicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic Acid (20x): a) Compound **1nn** (0.96 g, 5.00 mmol) was dissolved in a stirred mixture of THF (5 mL) and water (10 mL). A solution of sodium hydroxide (3.00 g, 75.0 mmol) in water (15 mL) was added dropwise under nitrogen over 30 min and with cooling in an ice bath. The colour of the mixture turned pale yellow. Stirring was continued for 1 h at 0 °C and 3 h at room temperature. The mixture was acidified by addition of a mixture of conc. hydrochloric acid (10 mL) and water (25 mL) and stirred overnight. It was extracted with ethyl acetate (10 × 20 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was removed in a rotary evaporator. The resinous residue (0.97 g) was dissolved in dichloromethane (100 mL). Slow evaporation at room temperature in a flask, covered with a watch glass, gave (after 4 weeks) 0.67 g of colourless crystals with m.p. 108−109 °C (87% yield). From the first, square-shaped crystals (appearing after one week) one (with a length of ca. 2 mm) was selected and cut into two halves with a razor blade. One half was taken for the X-ray crystal structure analysis.[17]

b) The same procedure was performed with 0.96 g of **1xx**. Yield 0.64 g (83%) of colourless crystals with m.p. 108 °C. The spectra were identical with those from the substance obtained by procedure a).

c) A solution of potassium hydroxide (2.00 g) in water (10 mL) was added to diketone **6** (1.36 g, 10.0 mmol) . The yellow mixture discoloured and finally took on a brownish colour. The mixture was acidified with 10% hydrochloric acid (10 mL), stirred overnight, and worked up as described above; the resinous residue (1.51 g) was dissolved in ethyl acetate (10 mL). Petroleum ether (20 mL) was added dropwise, and the mixture was stored in the refrigerator. Colourless crystals with m.p. 108 °C were deposited (1.03 g, 67% yield). The NMR spectra were in agreement with those of the substances described above. − IR (KBr): $\tilde{\nu}$ = 3440 (OH), broad absorption band at ca. 3000 with peaks at 3070 (=CH), 2990, 2940; 1700 cm^{-1} (broad, COOH). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (dd, *J* = 12.5, *J* = 3.7, 1 H), 1.56 (dt, *J* = 9.1, *J* = 1.8, 1 H),

2.06 (d, J = 9.1 Hz, 1 H), 2.50 (dd, J = 12.5, J = 3.7, 1 H), 3.02 (br. s, 1 H), 3.09 (br. s, 1 H), 6.21 (dd, J = 5.6, J = 3.0, 1 H), 6.55 (dd, J = 5.6 Hz, J = 3.1 Hz). − ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 1.00 (dd, J = 11.0, J = 3.4, 1 H), 1.32 (m, 1 H), 1.60 (d, J = 8.6 Hz, 1 H), 2.25 (dd, J = 12.0, J = 3.8, 1 H). 2.80 (br. s, 1 H), 2.93 (br. s, 1 H), 6.03 (dd, J = 5.7 Hz, 1 H), 6.30 (dd, J = 5.7, J = 3.0, 1 H). − ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 42.8, 42.9, 49.35, 53.1, 81.6, 132.8, 142.0, 178.1. − ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 40.1, 41.7, 47.8, 51.1, 80.2, 133.9 138.0, 177.5. − EIMS (70 eV): *m/z* (%) = 154 (2) [M$^+$ from $C_8H_{10}O_3$], 109 (2) [M$^+$ − CO_2H], 67 (7), 66 (100). − HRMS: calcd. for $C_8H_{10}O_3$ 154.0630; found 154.0632.

2-Hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (22x): A solution of sodium hydroxide (6.04 g, 151 mmol) in water (51 mL) was added dropwise over 15 min to a solution of **4nn** (1.93 g, 10.0 mmol) in THF (8 mL) under nitrogen, with cooling in an ice bath. The mixture, which turned dark red, was stirred for 3.5 h at 0 °C. The ice bath was removed, and stirring was continued for a further 1.5 h at room temperature. The mixture was extracted with ethyl acetate (4 × 20 mL). The aqueous layer was carefully acidified to pH 1 (indicator paper) in the ice bath with conc. hydrochloric acid. The acidic solution was extracted with ethyl acetate (8 × 20 mL). After drying with sodium sulfate, the organic extracts were concentrated in a rotary evaporator to give 1.39 g of a brown oil. The aqueous layer was further extracted by liquid-liquid continuous extraction with ethyl acetate for 12 h. This operation gave a further 400 mg of a brown oil. Both oily residues were combined and dissolved in boiling diethyl ether (50 mL). On cooling, 0.30 g of a pale yellow solid with m.p. 105−106 °C (dec.) crystallized. Yield 19% **22x**. − IR (KBr): $\tilde{\nu}$ = 3420 (sharp, OH), 2960 (broad absorption, COOH), 1705 cm^{-1} (broad, COOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.14 (d, J = 11.6 Hz, 1 H, 3n-H), 2.38 (dd, J = 11.6, J = 4.9, 1 H, 3x-H), 4.82 (d, J = 1.2 Hz, the highfield part is split with J = 0.7 Hz, 1 H, 1-H), 4.91 (d, J = 4.4 Hz, the lowfield part is split into doublets with J = 0.5 Hz, 1 H, 4-H), AB sub-spectrum centred at δ = 6.45 with δ_A = 6.56 and δ_B = 6.34, J_{AB} = 5.7 Hz; the lines of the A and B parts are split into doublets with J = 1.7 Hz, 5-H and 6-H). − ^{13}C NMR/off-resonance (75.47 MHz, [D$_6$]DMSO): δ = 175.6 (s), 137.6 (d), 133.6 (d), 81.7 (d), 78.5 (d), 77.9 (s), 38.9 (t). − $C_7H_8O_4$ (156.1): calcd. C 53.85, H 5.16; found C 53.78, H 5.17.

2-Hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxylic Acid (23ax): This compound was prepared from **16a** (1.95 g, 10.0 mmol) in THF (8 mL) and NaOH (6.04 g, 151 mmol) in water (51 mL). After evaporation of the solvent, the viscous residue was dissolved in the minimum amount possible of boiling PE/EA (5:1). On standing, pale yellow crystals (0.59 g, 37%) with m.p. 100−101 °C were collected. A sample for analysis was sublimed at 100 °C/0.03 Torr. Colourless solid with m.p. 102−103 °C. − IR (KBr): $\tilde{\nu}$ = 3400, 3200 (broad absorption, OH), 1725 cm^{-1} (COOH). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.26 (d, J = 12.4 Hz, 1 H, 3n-H), 1.36−1.60 (m, 3 H, 3x-H, 5-H, 6n-H), 2.12−2.20 (m, 1 H, 5-H or 6x-H), 2.29−2.35 (m, 1 H, 5-H or 6x-H), 4.42−4.45 (m, 2 H, 1-H, 4-H), 5.72 (broad s, 1 H, HO-), 12.42 (broad s, 1 H, COOH). − ^{13}C NMR/off-resonance (75.47 MHz, [D$_6$]DMSO): δ = 22.6 (t), 29.15 (t), 42.3 (t, C-3), 76.5 (d), 79.6 (s, C-2), 80.6 (d), 175.5 (s, COOH). − $C_7H_{10}O_4$ (158.2): calcd. C 53.16, H 6.37; found C 53.01, H 6.37.

2-Hydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxylic Acid (23ax) by Hydrogenation of 22x: Palladium on charcoal (10%) hydrogenation catalyst (40 mg) was added to a solution of **22x** (0.20 g, 1.30 mmol) in ethyl acetate (25 mL). The mixture was shaken in an atmosphere of hydrogen gas until the uptake of hydrogen stopped (50 min). The mixture was filtered, and the catalyst was washed with ethyl acetate. The filtrates were concentrated in a rotary evaporator, and the residue was crystallised from 12 mL of PE/EA (5:1). A colourless solid (0.20 g, 97%) with m.p. 103−104 °C was obtained. The ^{1}H NMR spectrum was in agreement with the one obtained from **16a** described above.

2-Hydroxy-1,4-dimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic Acid (23bx): This compound was prepared from **16b** (2.23 g, 10.0 mmol) in THF (10 mL) and NaOH (6.04 g, 151 mmol) in water (53.5 mL). After removal of the solvent, the pale yellow residue was sublimed at 100 °C/0.05 Torr to give 1.11 g (60%) of colourless **23bx**, as a solid with m.p. 122−123 °C. − IR (KBr): $\tilde{\nu}$ = 3300 (broad, OH), 1720 cm^{-1} (COOH). − ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.39 (s, 3 H, 4-CH_3), 1.50 (s, 3 H, 1-CH_3), 1.58−2.80 (m, 6 H, 3-H, 5-H and 6-H), 6.24−7.61 (broad, flat signal, COOH). − ^{13}C NMR/off-resonance (75.47 MHz, [D$_6$]DMSO): δ = 16.95 (q, 1-CH_3), 21.3 (q, 4-CH_3), 32.4 (t), 36.8 (t), 49.5 (t), 82.45 (s), 82.7 (s), 87.5 (s), 176.1 (s, COOH). − EIMS (20 eV): *m/z* (%) = 186 (19) [M$^+$], 168 (73) [M$^+$ − H_2O], 141 (65), 140 (54), 128 (70), 125 (13), 124 (32), 123 (13), 112 (54), 111 (66), 109 (56), 98 (100). − $C_9H_{14}O_4$ (186.2): calcd. C 58.05, H 7.58; found C 57.83, H 7.50.

2-Chloro-4-hydroxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (19b): A solution of NaOH (4.06 g, 102 mmol) in water (34 mL) was rapidly added dropwise, under a nitrogen atmosphere, to a solution of **16b** (1.50 g, 6.72 mmol) in THF (7 mL), cooled in an ice bath. After 4 h stirring with ice cooling, the mixture was neutralised with conc. hydrochloric acid (to pH 7). The mixture was extracted with ethyl acetate (5 × 30 mL), and the combined extracts were dried with magnesium sulfate. After concentration in a rotary evaporator, the residue was distilled in a kugelrohr apparatus at 140 °C/0.005 Torr. The distillate, a pale yellow oil (0.97 g), was dissolved in 40 mL of boiling PE (40−65 °C). After cooling, a colourless solid (0.51 g, 37%) with m.p. 103−106 °C was obtained. − IR (KBr): $\tilde{\nu}$ = 3400 (broad, OH), 1730 cm^{-1} (COOH). − ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.38−2.15 (m, 10 H, surmounted by 2 singlets at 1.46 and 1.58, 6-H, 7-H, 5-CH_3 and 1-CH_3), 3.45−3.75 (m, 1 H, OH), 3.83 (s, 1 H, 4-H), 4.79 (d, J = 2.0 Hz, 1 H, 2-H). − ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.7, 24.1, 30.9, 33.1, 67.9, 81.0, 84.1, 87.3, 199.0 (C-3). − $C_9H_{13}ClO_3$ (204.7): calcd. C 52.82, H 6.40, Cl 17.32; found C 52.79, H 6.41 Cl 17.49.

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