Base-Induced Trifluoroethanolysis of Acyclic Di- and Trihalogeno Ketones: Favorskii Rearrangement and [4+3] Cycloaddition

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Reactions of five acyclic dihalogeno- and trihalogeno ketones, representing the α,α-, α,α′-, α,α,α- and α,α,α′-di- and trihalogeno substitution pattern, with sodium 2,2,2-trifluoroethoxide in 2,2,2-trifluoroethanol (NaTFE/TFE) in the presence of furan were investigated with the aim of obtaining [4+3] cycloadducts of the corresponding oxyallyl intermediates. Preference of Favorskii rearrangement over cycloaddition was observed with dichloromethyl isobutyl ketone (**1a**) and 1,3-dibromobutan-2-one (**12**) that formed mainly the trifluoroethyl esters of 3-chloro-2-isopropylpropanoic acid (**9a**), and (*Z*)-but-2-enoic acid (isocrotonic acid) (**13**), respectively. **9a** was dehydrohalogenated to form trifluoroethyl 3-isopropylacrylate (**11a**). [4+3] Cycloaddition was favored with the 1,1,3-trihalogenobutan-2-ones **24** and **25**, leading to 2,4-dihalogenated 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**26**, **27**) as a mixture of *endo*-*exo*-stereoisomers. With trichloromethyl isobutyl ketone (**30**) the isomeric 2,4-dichloro-substituted oxabicycles (**34**) were formed in lithium perchlorate/diethyl ether/furan/triethylamine, while in NaTFE/TFE solvolytic displacement of one chloro substituent occurred, providing 2-chloro-4-trifluoroethoxy-4-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**36**). By analogy, **27** reacted with sodium methoxide/methanol to form the methoxy-substituted oxabicycles **39a** and **39b**.

Introduction

Many dichlorinated and dibrominated methyl ketones react with sodium methoxide to form α,β-unsaturated carboxylic acid methyl esters, a case of Favorskii rearrangement with the oxyallyl-cyclopropanone mechanism.[1–5] In contrast to monohalogeno ketones, here the cyclopropanone intermediate bears one halogeno substituent (**7**, Scheme 1). As a rule, the strained cyclopropanone ring formed in Favorskii reactions is opened in such a way as to give the more stable carbanion.[4,5] This cleavage mode would lead to "halomethyl esters" (**9**). However, these compounds have been observed only in a few cases as minor byproducts, e.g. with dichloromethyl isobutyl ketone (1,1-dichloro-4-methylpentan-2-one, **1**, R = *i*Pr, X = Cl) and methanolic sodium methoxide.[1]

The favored reaction path is cleavage of the C-1–C-3 bond of the halogenocyclopropanone, or rather its hemiacetal anion (**8**), with dissociative expulsion of a halide ion from the C–Hal bond. The α,β-unsaturated carboxylic acid esters are formed preferentially with the *cis*-configuration (**11**).[2] The same stereoselectivity was found for "classical" Favorskii rearrangements with bases in water where, e.g., *cis*-2-butenoic acid ("isocrotonic acid") has been obtained from 1,3-dibromobutan-2-one.[6] To rationalize this selectivity, Kennedy et al. assumed that the methoxide anion associates with the carbonyl carbon of the (supposed) *cis*-bromo-alkylcyclopropanone from the "*trans*" face, followed by a concerted rearrangement-dissociation process.[2] After the Woodward–Hoffmann rules have been laid down, one is tempted to categorize this process as a disrotatory retro-electrocyclization of the Woodward–Hoffmann-DePuy type (Scheme 2).[7–9] The stereoselective formation of *cis*-2,3-dimethylcyclopropanone hemiacetals, e.g. **A**, from 2-bromo and 2-chloro-3-pentanone, which is structurally equivalent to 1,3-dibromo-2-butanone, was demonstrated years ago by our group.[10]

Chloro- and bromo-substituted oxyallyl intermediates derived from a few acyclic dihalogeno ketones having secondary or tertiary α-carbon atoms could be trapped by cycloaddition to, e.g., furan using lithium perchlorate/triethylamine in diethyl ether or fluorinated alcohols in the presence of bases, e.g. sodium 2,2,2-trifluoroethoxide in trifluoroethanol (NaTFE/TFE).[11–13] Apart from 1,1,3-trichloroacetone,[12,14] to the best of our knowledge, the behavior of other acyclic trihalogeno ketones under conditions of trifluoroethanolysis has not been investigated.

This report describes reactions of five representative acyclic α,α-, α,α′-dihalogeno ketones, α,α,α- and α,α,α′-trihalogeno ketones with NaTFE/TFE in the presence of furan, which will extend our knowledge of oxyallyl based reactions.

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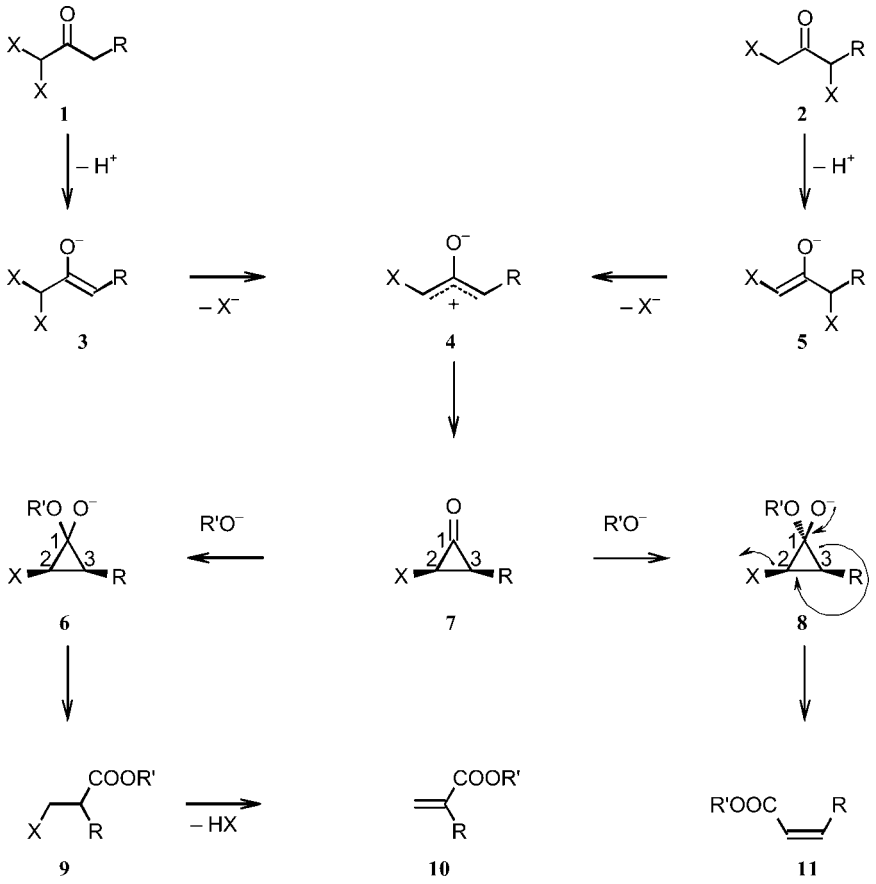
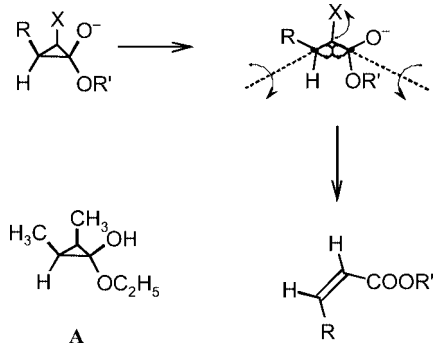


Scheme 1. Mechanism of Favorskii rearrangements of acyclic dihalogeno ketones via cyclopropanones. For the present study the following specifications hold: **1**, etc.: R = *i*Pr, X = Cl = **1a**; **2**, etc.: R = CH_3, X = Br = **12**; R′ = CF_3CH_2.



Scheme 2. Formation of *cis*-2-alkenoic acid esters by a proposed concerted cleavage of cyclopropanone hemiacetals.

Results and Discussion

Dihalogeno Ketones: Dichloromethyl Isobutyl Ketone (1a) and 1,3-Dibromobutan-2-one (12)

As a precursor for an oxyallyl intermediate, which would be interesting for incorporation of the isopropyl side chain into terpenoids,[15–17] we investigated the reaction of **1a** with TFE/NaTFE in the presence of furan. Monitoring the run by GLC, we observed a small peak in the range characteristic of [4+3] cycloadducts (t_R = 11.4 min, 5%), but we could not isolate this component. Kugelrohr distillation of the product mixture led to an impure liquid. The IR spectrum showed a band at 1760 cm^{-1}, pointing to an ester. The presence of a methylidene group was indicated by the ^{13}C NMR/DEPT spectrum ($CDCl_3$, δ = 124.1 ppm), and signals at δ = 5.67 (t, line distance 0.9 Hz), and 6.25 (s) ppm in the ^1H NMR spectrum. Further peaks at $\delta(^{13}C)$ = 145.2 and 165.5 (C=O) ppm were in accordance with an α,β-unsaturated ester of the acrylate type.[18] Analysis of the whole NMR spectrum (see Exp. Sect.) led us to the conclusion that trifluoroethyl 2-isopropylacrylate (**10a**) was formed as the main product.

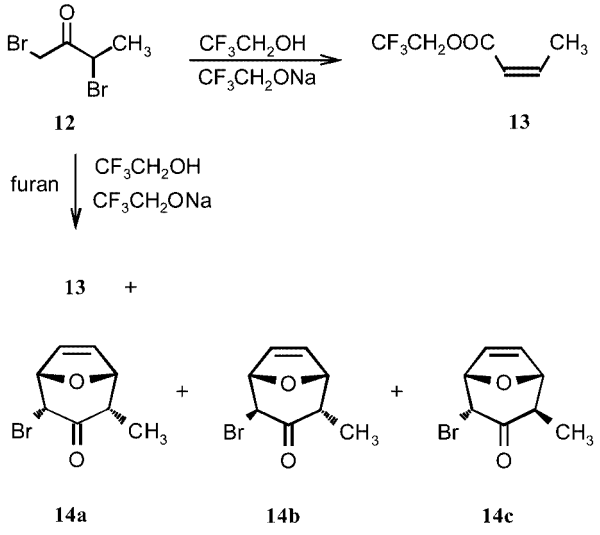
Weaker signals in the ^1H NMR spectrum, inter alia at 5.73 (dd, J = 11.5, J = 1.0 Hz), and 6.17 (dd, J = 11.5, J = 10.0 Hz) were consistent with the structure of trifluoroethyl 4-methylpent-2-enoate (trifluoroethyl 3-isopropylacrylate, **11a**) for the minor product. The value of the "olefinic" coupling constant (J = 11.5 Hz) indicates a *cis*-configuration, as can be seen by comparison with ester **13**, described below.

If the structure of the main component is as supposed, it should have been formed by a Favorskii cleavage of 2-chloro-3-isopropylcyclopropanone(s) **7a** (Scheme 1). Indeed, from a run at a lower temperature (–28 °C, 14 days), we could isolate trifluoroethyl 3-chloro-2-isopropylpropanoate (**9a**), though as an impure liquid that was contaminated by "unreacted" dichloro ketone **1a**, and fully charac-

terize the product by HRMS and the usual spectra. Obviously, this ester is the primary product of the "normal" Favorskii rearrangement, and suffers dehydrochlorination at higher temperature (0–40 °C) to form trifluoroethyl 2-isopropylacrylate. This result may indicate that the oxyallyl intermediate (**4a**), anticipated to form from the starting dichloromethyl ketone (**1a**), undergoes (disrotatory) electrocyclization more rapidly than cycloaddition with furan.

α,α′-Dihalogeno ketones (**2**) are equivalents of their α,α-isomers in connection with oxyallyl formation. An advantage is that, in particular, aliphatic α,α′-dibromo ketones can be easily prepared by treatment of alkanones with two equivalents of bromine under equilibrating conditions, though achieving a high selectivity can be a problem.[19] A simple case is 1,3-dibromobutan-2-one (**12**), which is formed by bromination of 2-butanone.[20]

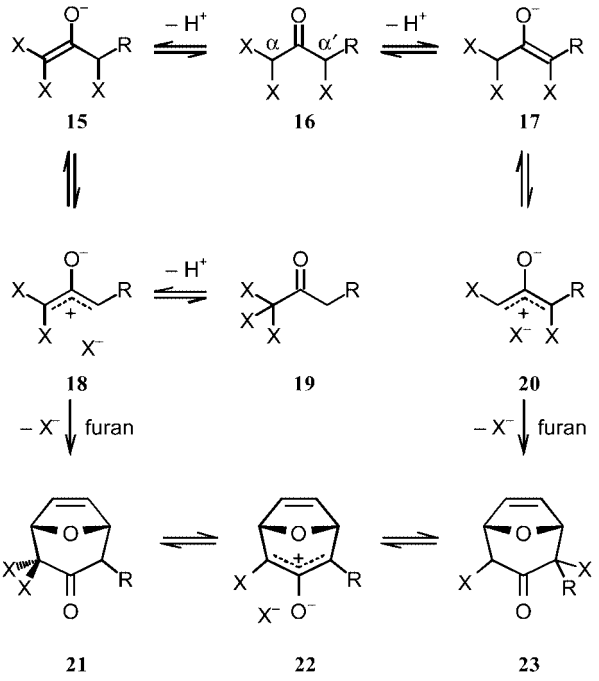
The reaction of **12** with furan in TFE/NaTFE gave a disappointing result with regards to the yield and stereoselectivity of the [4+3] cycloadducts (**14**). These were formed in a ratio of ca. 76:12:12, with a total yield of ca. 27%. We could isolate the major component, though with a great loss in yield, and identify the compound as the *endo, endo*-bicycle **14a**.[21] This configuration followed unequivocally from the coupling constants between the bridgehead protons and the protons at C-2 and C-4 (^3J = 4.8 Hz, see Table 1). Formation of trifluoroethyl (*Z*)-but-2-enoate (isocrotonic acid trifluoroethyl ester, **13**) by Favorskii rearrangement was the main reaction. The cycloadduct **14a** is a known compound that was observed by Hoffmann and Iqbal, on exploring the reaction between furan and 1,3-dibromobutan-2-one (**12**) or tribromobutan-2-ones in the presence of triethyl borate and zinc in 20–23% yield.[21]



In conclusion, Favorskii rearrangement is the preferred reaction path followed by dihalogeno ketones **1a** and **12** under basic trifluoroethanolysis conditions. This is in line with results of a recent investigation by Grainger et al. on intramolecular [4+3] cycloadditions.[22] Would introduction of a second halogeno substituent enhance the lifetime of oxallyl intermediates and thus favor cycloaddition?

Trihalogeno Ketones: 1,1,3-Tribromo- and 1,1,3-Trichlorobutan-2-one (24, 25), and Trichloromethyl Isobutyl Ketone (30)

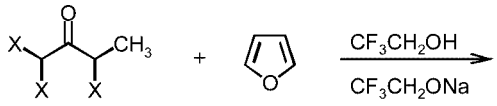
A dihalo-substituted oxyallyl intermediate generated by dehydrohalogenation needs a trihalogeno ketone as precursor. Since enolization of a trihalogenomethyl ketone at the α′ carbon atom is expected to be slower than enolization at a halogeno- or dihalogenomethyl group,[23] in the case of the butanone skeleton we preferred to investigate 1,1,3-trichloro- and -tribromobutan-2-one as oxyallyl precursors. A selective preparation has been elaborated by Barluenga et al.[24] The first step of the reaction with NaTFE/TFE is deprotonation of the trihalogeno ketone which can occur at the α- or α′-position. Enolization at the dihalogenomethyl group (C-1) is expected to be faster than at the halogenomethyl group (C-3);[23] hence, a geminal dihalogenated oxyallyl (ion pair) should be favored. In the presence of furan, 2,2-dihalogeno-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**19**, R = CH_3) is the anticipated [4+3] cycloadduct (Scheme 3).



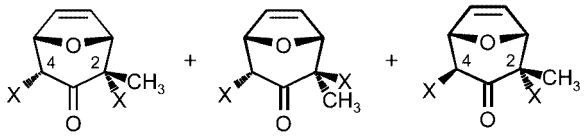
Scheme 3. Generation and [4+3] cycloaddition of oxyallyl intermediates from trihalogeno ketones. For the present study the following specifications hold: **16**, etc.: R = CH_3, X = Br = **24**; R = CH_3, X = Cl = **25**; **19**, etc.: R = *i*Pr, X = Cl.

By comparison with 1,3-dibromobutan-2-one (**12**, see above), the reaction of 1,1,3-dibromobutan-2-one with furan in TFE/NaTFE gave a higher yield of [4+3] cycloadducts (49%). However, 2,2-dibromo-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**21**, R = CH_3, X = Br) could not be detected in the product mixture: the methyl-substituent of this isomer demands a doublet in the ^{1}H NMR spectrum (cf. compound **14a**). However, singlets were found for the methyl resonances of the three 2,4-dibromo oxabicycles observed by NMR spectroscopy (Table 1), and the structures

could be assigned to *exo*-*endo* isomers (**26a**–**c**) in a ratio of 70:21:9. The configuration at C-4 can easily be derived from the value of the vicinal coupling constants $^3J_{4,5}$ which is 4.6–4.7 Hz for the main product (70%), **26a,** and for the minor component, **26b**; the 21% product shows $^3J_{4,5}$ = 0.8 Hz, which clearly indicates an *exo*-configuration at C-4 (**26c**). The configuration of the disubstituted carbon atom C-2 can be derived by comparing the ^{1}H and ^{13}C chemical shifts (Table 1 and 2) with those of related oxabicyclic compounds.[13]



24: X = Br
25: X = Cl



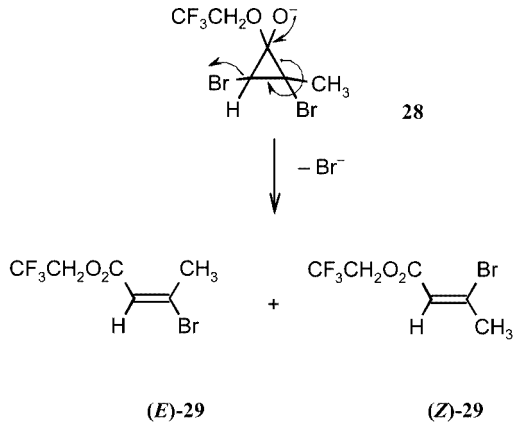
26a: X = Br
27a: X = Cl

26b: X = Br
27b: X = Cl

26c: X = Br
27c: X = Cl

We note that the methyl protons [δ(^{1}H) = 2.30, δ(^{13}C) = 31.4] of **26b** are distinctly deshielded compared with those of analogous methyl-substituted bicycles, and conclude that the methyl group neighbors the *exo*-Br at C-4, in other words, is *exo*, and consequently the bromo-atom at C-2 is *endo*. The methyl resonance of the main product (**26a**) appears at δ = 2.06, that is at lower field than **26b** (δ = 1.76 ppm). It has been observed for many 8-oxabicyclo[3.2.1]oct-6-en-3-ones that *exo*-methyl groups (and *exo*-protons) are deshielded compared with the *endo* ones.[25,13] From that one may conclude that **26a** has an *exo*-methyl, and **26c** an *endo*-methyl group.

In addition to the oxabicycles, we isolated a mixture of two bromo-substituted, unsaturated trifluoroethyl esters with a 22% yield, obviously again the result of a competing Favorskii rearrangement. Remarkably, the NMR spectra showed that trifluoroethyl 2-bromobut-2-enoates which would be expected to arise via oxyallyl **20** (Scheme 3, R = CH_3, X = Br) from a cleavage of "*geminal*" 2,2-dibromo-3-methylcyclopropanone, analogous with the path **8** → **11** (Scheme 1), were not formed. The observed doublets from the methyl group (J = 1.2 and 1.6 Hz, respectively), due to allylic coupling with an "olefinic" proton show that the methyl group has no hydrogen atom as a neighbor (cf. the spectrum of ester **13**). However, both ^{1}H and ^{13}C NMR spectra (see the Experimental Section) are in full accord with structures ***(E)*-29** and ***(Z)*-29**, i.e. trifluoroethyl 3-bromobut-2-enoates, in which bromine and methyl are geminate substituents at C-3. It can be concluded that esters **29** are formed from "*vicinal*" 2,3-dibromo-3-methylcyclopropanone(s) via hemiacetal **28**, and thus the reaction channel **16** → **17** → **20** (Scheme 3) is favored above path **15** → **18**.



(*E*)-29 (*Z*)-29

The corresponding trichloro ketone (1,1,3-trichlorobutan-2-one, **25**) reacts with furan in the presence of NaTFE/TFE to give a cycloadduct mixture (72% yield), the ^{1}H NMR spectra of which indicated stereoisomers **27a**, **27b**, and **27c** in the ratio of 73:17:10. We were unable to separate this mixture by chromatography. However, the main isomer **27a** could be obtained in a pure state by recrystallization. The NMR spectroscopic data were in line with those of the brominated oxabicycles, and thus the structures were deduced by the same arguments as for **26**.

In conclusion, introducing an additional chloro or bromo substituent at the oxyallyl and ketone, respectively, results in a higher yield of [4+3] cycloadducts. The extreme case is tetrachlorooxyallyl generated from pentachloroacetone.[26–28] This leads us to speculate that the lifetime of oxyallyl intermediates is prolonged by stabilization through several halogeno substituents, and that cycloaddition can compete more and more with electrocyclization.

As for the cycloaddition, the diastereomer **14a** is the one expected to be favored if this reaction proceeds in a concerted mode via a *compact* transition state between furan and a *(Z,Z)*-configured oxyallyl intermediate ("W-form").[25] One may conclude that the dihalogenated oxabicycles **26a** and **27a**, formed preferentially, arise also from *(Z,Z)*-configured oxyallyls, but in this case both *halogeno* substituents occupy the termini of the W. The van der Waals radii of bromine and chlorine atoms are similar to methyl groups, and hence, neglecting polar effects, the oxyallyl precursors leading to **14a**, **26a** and **27a** resemble "1,3-dimethyloxyallyl" and "1,1,3-trimethyloxyallyl" generated from 2-halogeno-pentan-3-one and 2-halogeno-2-methyl-pentan-3-one, respectively. However, in these cases a higher *endo*-selectivity (>94%) was observed.[29] A rationalization of the stereochemistry of oxyallyl formation has been given.[10]

Finally, cycloadditions between furan and the oxyallyls generated from 2,4-dichloro- and dibromo-pentan-3-one or 1,1,3,3-tetrachloroacetone take the same stereochemical course, as the *endo*-isomers are formed preferentially.[13,30] The diminished *endo*-*exo*-selectivity points to a two-step cycloaddition.

Table 1. ^{1}H NMR spectroscopic data of 2(4)-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones ($CDCl_3$, TMS as internal standard, δ-scale, coupling constants J in Hz). "4n" stands for "4*endo*", "2x" for "2*exo*" etc.

	1-H	2-H	4-H	5-H	6-H	7-H	Substituents
14a	5.15 dd, J = 4.8, 1.6	4.74 d, J = 4.8	3.04 dq, J = 7.0, 4.8	4.87 dd, J = 4.8, 1.6	6.42[a,b], J = 6.1, 1.6	6.49[a,b], J = 6.1, 1.6	1.06 d, J = 7.0 [4n-CH_3]
26a	4.90 d, J = 1.7	–	4.96[c], J = 4.7	5.1 °C, J = 4.7, 1.7	6.54[a,b], J = 6.1, 1.7	6.65[a,b], J = 6.1, 1.7	2.06 s [2x-CH_3]
26b[d]	4.92 d, J = 1.8	–	4.16 d, J = 0.8	5.02 "t", line distance 0.7–1.3 Hz	6.32[a], J = 6.0, 1.8	6.73[a], J = 6.0, 1.8	2.30 s [2x-CH_3]
26c[d]	4.94 d, J = 1.8	–	5.33 d, J = 4.6	5.15 dd, J = 4.6, 1.7	6.42[a], J = 6.0, 1.8	6.64[a], J = 6.0, 1.8	1.76 s [2n-CH_3]
27a	4.84 d, J = 1.6	–	4.81 d, J = 4.7	5.10 dd, J = 4.7, 1.6	6.50[a,b], J = 6.1, 1.7	6.59[a,b], J = 6.1, 1.7	1.90 s [2x-CH_3]
27b[d]	– [e]	–	4.06 d, J = 0.9	5.01 m	6.33[a], J = 6.1, 1.8	6.65[a], J = 6.1, 1.8	2.06 s [2x-CH_3]
27c[d]	4.88 d, J = 1.7	–	–[f]	ca. 5.12[f]	6.39[a], J = 6.1, 1.8	6.57[a], J = 6.1, 1.8	1.58 s [2n-CH_3]
***endo-endo*-34 (34α)**	5.06 d, J = 1.6	–	4.80 d, J = 4.6	5.08 dd, J = 4.6, 1.6	6.49[a,b], J = 6.1, 1.7	6.54[a,b], J = 6.1, 1.7	0.90 d, J = 6.7; 1.15 d, J = 6.7 [diastereotopic CH_3]; 2.70 sept, J = 6.7 [$CH(CH_3)_2$]
***exo-endo*-34 (34β)**	4.99 m (split s)	–	5.16 d, J = 4.5	5.07 dd, J = 4.5, 1.6	6.36 dd, J = 6.0, 1.6	6.51 m[j]	1.02 d, J = 6.8; 1.21 d, J = 6.4 [diastereotopic CH_3]; 2.15 sept, J = 6.6 [$CH(CH_3)_2$]
***endo-exo*-34 (34γ)**	5.08 d, J = 1.5	–	4.05 d, J = 1.0	5.00 m, 5 lines with distance 0.6–1.2 Hz	6.31 m[k]	6.59 m[j]	0.94 d, J = 6.7; 1.16 d, J = 6.5 [diastereotopic CH_3]; 3.12 sept, J = 6.6 [$CH(CH_3)_2$]
35	4.89 dd, J = 1.9, 0.6	–	2.25[g] J = 15.9, 0.9 [4x-H]; 2.85[g] J = 15.9, 5.6 [4n-H]	4.95 ddd J = 5.4, 1.9, 0.8	6.25[a], J = 6.1, 2.0	6.41[a], J = 6.1, 1.9	0.84 d, J = 7.0; 0.98 d, J = 7.0 [diastereotopic CH_3]; 2.17 sept, J = 7.0 [$CH(CH_3)_2$]; 3.78, 3.80 [diastereotopic OCH_2CF_3]
36	4.97 dd, J = 4.9, 1.8	4.69 d, J = 4.9	–	4.91 d, J = 1.8	6.29[a,b], J = 6.1, 1.9	6.44[a,b], J = 6.1, 1.6	0.83 d, J = 7.05; 0.98 d, J = 7.05 [diastereotopic CH_3]; 2.22 sept, J = 7.05 [$CH(CH_3)_2$]; 3.62, 3.90 [diastereotopic OCH_2CF_3]
37	4.96 dd, J = 4.4, 1.4	2.54 dd, J = 6.9. 4.4	2.17[g], J = 15.2, 1.1 [4x-H]; 2.63[g], J = 15.2, 4.9 [4n-H]	4.92 m[h]	6.16[a,b], J = 6.1, 1.4	6.19[a,b], J = 6.1, 1.4	0.82, d, J = 6.9; 0.98, d, J = 6.9 [diastereotopic CH_3]; 1.98 oct, J = 6.9 [$CH(CH_3)_2$]
26a	5.06[a], J = 4.6, 1.7	4.90[a], J = 4.6, 1.7	–	4.79 d, J = 1.8	6.33[a], J = 6.1, 1.8	6.52[a], J = 6.1, 1.6	1.21 s [4-CH_3]; 3.27 s [OCH_3]
26b	5.03[i] t, line distance 1.2 Hz	3.83 d, J = 1.1	–	4.80 d, J = 1.8	6.37[a,b], J = 6.2, 1.5	6.39[a,b], J = 6.2, 1.5	1.15 s [4-CH_3]; 3.29 s [OCH_3]

[a] AB sub-spectrum with double lines (ABXY sub-spectrum). [b] The assignments for 6-H and 7-H may be reversed. [c] AB sub-spectrum. [d] The data were picked out from the spectrum of a mixture of isomers (see Exp. Sect.). [e] Masked by signals of isomer(s) (see Exp. Sect.). [f] The signal is superimposed by the resonance of 4-H from **27c**. [g] AB part of ABX sub-spectrum with doubled lines. [h] X part of ABX sub-spectrum with split lines. [i] Multiplet center, 3 lines with 1.2 Hz distance (X-part from ABX sub-spectrum). [j] 8 lines. [k] 7 lines.

As pointed out above, the reaction path **17** → **20** → **23**, induced by deprotonation at C-3 of the 1,1,3-trihalogeno-2-butanones (**16**, R = CH_3) (Scheme 3) is preferred. As an alternative, generation of a *gem*-dihalo-substituted oxyallyl (**18**) leading to 2,2-dihalogeno oxabicycle **21**, the 1,1,1-trihalogeno-isomer **19** (R = CH_3, ethyl trihalomethyl ketone) should be investigated. Having failed to obtain the desired [4+3] cycloadduct from dichloromethyl ketone **1a** we turned instead to 1,1,1-trichloro-4-methylpentan-2-one (**30**), which was anticipated to produce a more stabilized oxyallyl intermediate and hence, the [4+3] cycloadduct (**32**) would be available (Scheme 4). Moreover, trichloro ketone **30** can be synthesized on a multigram scale from inexpensive starting materials, namely isobutene and chloral, followed by cata-

Table 2. ^{13}C NMR chemical shifts ($CDCl_3$, δ, ppm,) of 2(4)-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones.

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	Substituents
14a	82.9[a]	56.0	198.7	53.5	82.5[a]	133.0	134.5	10.6 [4n-CH_3]
26a	87.0	70.7	193.7	54.6	82.7	135.75	133.0	27.9 [2x-CH_3]
26b[b]	86.1,	_[c]	_[c]	47.0	83.1	136.7	131.75	31.4 [2x-CH_3]
26c[b]	86.3	65.0	_[c]	52.45	82.6	134.5	132.8	23.0 [2n-CH_3]
27a	86.7	75.5	194.65	63.1	82.6	135.2	132.7	26.6 [2x-CH_3]
27b[b]	85.8	74.3	196.65	57.7	83.1	136.35	131.5	29.1 [2x-CH_3]
27c[b]	86.3	_[c]	_[c]	61.0	82.32	134.5	132.95	21.8 [2n-CH_3]
34(34α)	83.5	85.3	193.5	64.5	82.9	135.2	133.3	16.4, 17.8 [CH_3][d], 32.5 [$CH(CH_3)_2$]
35	82.2	87.5	204.2	43.8	77.1	136.6	130.3	16.0, 18.4 [CH_3][d], 28.2 [$CH(CH_3)_2$], 62.6 [OCH_2], 123.7 [CF_3]
36	81.5	61.3	196.7	89.2	82.2	132.6	133.8	16.3, 18.3 [CH_3][d], 27.6 [$CH(CH_3)_2$]
37	79.5	63.8	206.2	46.1	78.0	133.6	132.3	19.9, 22.4 [CH_3][d], 24.5 [$CH(CH_3)_2$]
39a	82.2	62.8	197.1	84.3	85.35	132.85	134.3	14.2 [4-CH_3], 52.2 [OCH_3]
39b	82.6	55.9	198.0	82.8	84.9	133.3	134.0	14.4 [4-CH_3], 52.3 [OCH_3]

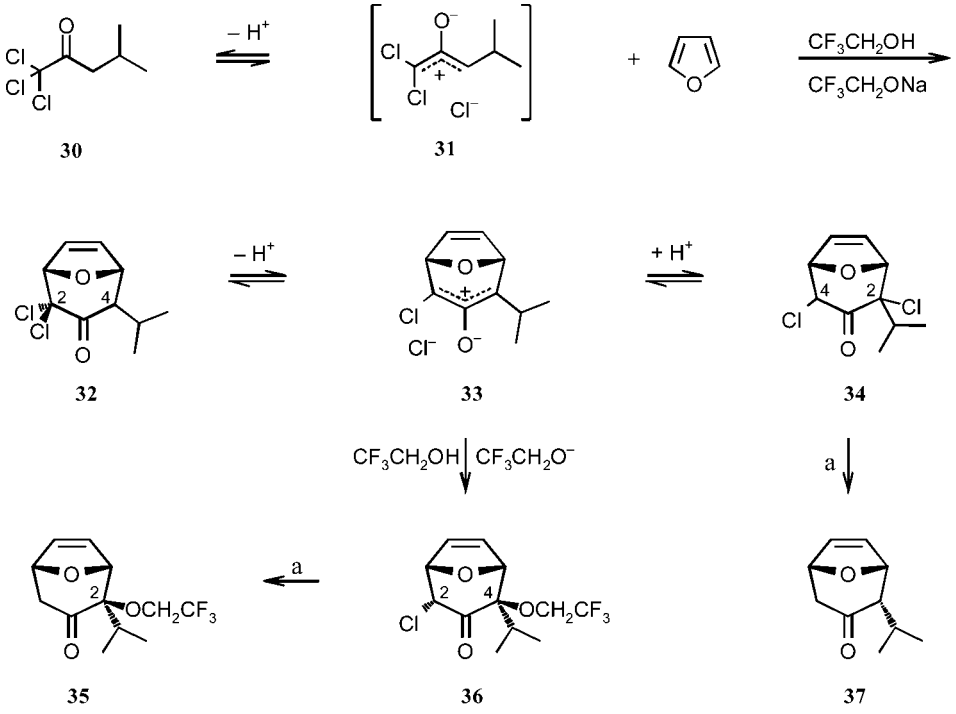
[a] The assignments may be reversed. [b] The data were picked out from the spectrum of a mixture of isomers (see Exp. Sect.). [c] The signal was too weak to be detected. [d] Diastereotopic groups.

lytic hydrogenation of the ene-reaction product and oxidation of the alcohol.[31–33]

When we investigated the reaction of **30** with furan in TFE/NaTFE, we were surprised: the α,α-dichloro bicycle **32** could not be detected. The isolated product was an oxabicyle substituted by a trifluoroethoxy group (**36**) (Scheme 4).

In the ^{13}C NMR spectrum the typical quartets of the trifluoroethoxy-group at δ = 62.5 [^2J(C,F) = 35 Hz] and 123.5 ($^1J_{C,F}$ = 277 Hz) ppm appeared. An *endo*-α-chloro ketone moiety was indicated by a doublet at δ = 4.69 ppm with the characteristic vicinal coupling constant of 4.9 Hz = $^3J_{1,2}$ or $^3J_{4,5}$, respectively (Cf. Table 1, compounds **14a**, **26a, 27a**). A septuplet for the methine proton of the isopropyl group demonstrated that no further coupling was present, i.e. the neighbor carbon atom must be quarternary. From these arguments and the assignment of the other signals of the NMR spectra (Table 1) formula **36** can be deduced. Evidently, the trifluoroethoxy ketone **36** is formed by solvolysis of a dichloro-substituted bicycle. Indeed monitoring the reaction by GLC showed a further peak at t_R = 21.7 min which vanished in the course of the reaction.

Therefore, we reacted **30** with furan in TFE/NaTFE at –40 °C and then stored the reaction mixture in a freezer at –28 °C. Workup after 14 days gave a distillate from which a dichloro-substituted oxabicycle could be isolated in 40%



Scheme 4. Formation and reactions of isopropyl-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones. a) zinc-copper couple, ammonium chloride, methanol.

yield. However, the NMR spectra (Table 1) showed that it was 2,4-dichloro-2-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**34**). Oxabicycle **36** was a byproduct (15% yield).

The result of these reactions are once more in line with an enolization-ionization mechanism (Scheme 4) leading to a 1,3-transposition of the substituents and form a parallel case to the solvolysis of other dichloro-substituted [3.2.1]-bicycles.[34] Analogous α → α′ rearrangements have been observed with α-halogenocyclobutanones and called *cine*-substitution,[35] and *cine*-rearrangement, respectively.[36]

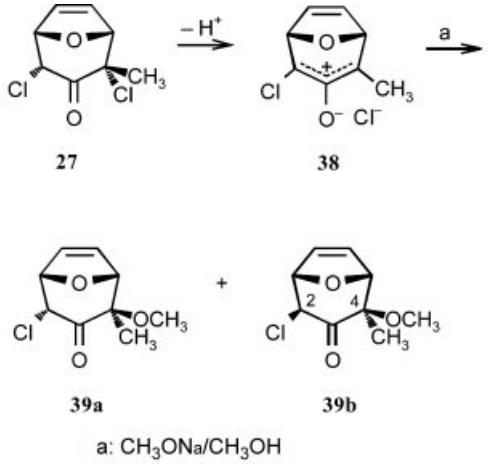
The solvolysis of the primary cycloadduct(s) cannot occur when the oxyallyl intermediate(s) are generated in lithium perchlorate/diethyl ether.[11,12] However, in this solvent the reaction between **30** and furan, in the presence of triethylamine, gave only a 23% yield of the expected dichlorooxabicycles. Three of them could be isolated by MPLC (ratio of isomers ca. 56:35:9), though in an impure state, but sufficiently characterized by ^{1}H NMR spectroscopy. For the moment, we label them as **34α**, **β**, and **γ**. According to the ^{1}H NMR spectrum, the main product proved to be identical with that obtained by NaTFE/TFE (see above). The "second product" (35%) also exhibited the characteristic doublet (J = 4.5 Hz) for the *exo*-proton at a chloro-substituted α-carbon atom, and thus indicated an *endo*-chloro-substituent at C-4, whereas the minor product (9%) showed J = 1.0 Hz, i.e. coupling with an *endo*-H atom. The low-field resonance of the methine proton of the minor product (δ = 3.12 ppm) compared with analogous isopropyl-substituted bicycles (Table 1), points to a neighbored, i.e *exo*-Cl at C-4, in other words, the isopropyl group is also *exo*, and consequently the chloro-atom at C-2 is *endo*. This would be in line with cycloadducts **26a** and **27a** (see above). Since the methine proton of **34α** (the main product) resonates at a lower field (δ = 2.71 ppm) than that of **34β** (the "second" product), we assign the latter compound to the formula of the *endo*-isopropyl isomer ***exo-endo*-34**. The down-field shift of its doublet from H-4 (δ = 5.16 ppm), obviously influenced by the 2-*exo*-Cl-substituent in a 1,3-diaxial relationship, supports this assignment. In the end the formula remains ***endo-endo*-34** for the main product, with the *isopropyl* group *exo*. This is in line with the ratio of isomers **26** and **27**.

In order to gather more data for comparison of the NMR spectra of these oxabicycles, thus securing structures, we subjected **36** and ***endo-endo*-34** to the well-known dehalogenation procedure with a zinc-copper couple,[15] which afforded oxabicycles **35** and **37**, respectively. Noyori et al. has described a 2-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (unspecified configuration) obtained from 1,1,3-tribromo-4-methylpentan-2-one and furan by reduction with nonacarbonyldiiron, followed by dehalogenation with a zinc-copper couple (35% yield over these two steps).[15] This oxabicycle was transformed into α-thujaplicin.[15] Mann et al. prepared this oxabicycle by reaction of 1,1,3,3-tetrabromo-4-methylpentan-2-one with furan "in the presence of diethylzinc (followed by reductive removal of two bromine atoms)", and stated that it was the *endo*-diastereomer (51% yield).[17] The ^{13}C NMR spectrum (Table 2) of our dechlorination product was nearly identical with the reported data.[17] However, the ^{1}H NMR spectrum (Table 1) showed smaller differences, but were fully consistent with the *endo*-position of the isopropyl group (especially $J_{1,2}$ = 4.4 Hz from the ^{1}H NMR), i.e. formula **37**.

For the solvolysis product **36** the configuration at C-4 remains to be settled. However, the proposed mechanism leads us to speculate that the trifluoroethoxy group associates with the bicyclic oxyallyl ion pair from the less hindered *exo*-face, and consequently "push" the isopropyl group to the *endo*-position. For a related carbobicycle (3,4-dibromobicyclo[3.2.1]octa-2,6-diene), methanolysis was found to occur selectively from the *exo*-face.[37] In the ^{1}H NMR spectrum of **36**, the chemical shift of the methine-proton (δ = 2.22 ppm) is not far from that of **35** (δ = 2.17 ppm) and **37** (δ = 1.98 ppm) (Table 1) and thus is consistent with an *endo*-isopropyl group.

Methanolysis of 2,4-Dichloro-2-methyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one (27)

The formation of the trifluoroethoxy-substituted bicycle **36** from dichloro ketone **34** prompted us to also examine the behavior of **27** with methanolic sodium methoxide. Not unexpectedly, the *exo*-methoxy-chloro ketone **39a** was formed on treating **27** with that reagent under "mild" conditions (0–25 °C, 2 hours), together with a minor amount of the stereoisomer **39b**. The chemical shifts of the methyl groups are nearly identical; hence it follows that the isomers have the same configuration at the quarternary carbon (C-4). As for the configuration at the chloro-substituted carbon atom (C-2), the coupling constants $J_{1,2}$ show that the methanolysis products are C-2-epimers (Table 1). Obviously, equilibration occurred in the basic medium.



Conclusions

This investigation allows us to draw a coherent picture of the reactions of representative acyclic di- and trihalogeno ketones with sodium trifluoroethoxide in trifluoroethanol

(NaTFE/TFE), which extends earlier findings and confirms earlier conclusions.[12,13] Treatment of (acyclic) dihalogeno ketones with sodium trifluoroethoxide in trifluoroethanol (NaTFE/TFE) generates oxyallyl intermediates which undergo electrocyclization to form labile (mono)halogenocyclopropanones. These intermediates are cleaved by trifluoroethoxide to form trifluoroethyl esters. The whole process represents a Favorskii rearrangement of the dihalogeno ketones. In the presence of furan, the oxyallyl intermediates can be trapped in part giving [4+3] cycloadducts in a moderate yield and stereoselectivity.

With the corresponding trihalogeno ketones [4+3] cycloaddition predominates over Favorskii rearrangement. 2,2-Dihalogeno-8-oxabicyclo[3.2.1]oct-6-en-3-ones, i.e. bicyclic compounds with geminate X-substituents, could not be detected. Presumably, these primary products undergo 1,3-transpositions with the formation of 2,4-disubstituted oxabicycles by way of enolization-ionization mechanisms.

Experimental Section

General Remarks: IR spectroscopy: Perkin–Elmer 457. NMR spectroscopy: Bruker AC 250, for 62.9 MHz ^{13}C NMR and 250 MHz ^{1}H NMR spectra, respectively. TMS was used as internal standard in $CDCl_3$ solutions. EIMS: Varian MAT 711 with data system SS 100. Reactions were monitored by gas chromatography (GLC) and/or thin layer chromatography (TLC). For GLC, a Hewlett–Packard 5710 instrument with integrator was used; analyses were made with programed oven temperatures (80–220 °C, heating rate 8 K/min) on a 2.3 m glass column packed with 5% Carbowax 20 M on Chromosorb G-AW DMCS, 60–70 mesh. A Carlo–Erba Fractovap 4200 instrument was used for GLC analyses on OV 101 (5% on Volaspher A2, 100–120 mesh, column length 2.0 m, 80–250 °C, 8 K/min). Nitrogen (30 mL/min) was used as the carrier gas. The percentage values give the relative peak areas obtained by integration of the FID signals. TLC was carried out on precoated silica sheets, Polygram Sil G/UV_{254}, distributed by Macherey–Nagel, Düren, Germany; the spots were visualized by spraying with vanilline/H_2SO_4 solution,[38] followed by warming, or by UV extinction. For preparative column chromatography and adsorptive filtrations, silica 60 (Macherey & Nagel, 63–200 μm) was used. For elution and TLC developing, predried petroleum ether (PE) was distilled (b.p. 40–65 °C). Ethyl acetate (EA) was dried over calcium chloride, distilled, and kept dry over molecular sieves 4 Å. For sodium trifluoroethoxide/trifluoroethanol (NaTFE/TFE) reagent see ref.[26] Furan (Fluka) was stored over KOH pellets and distilled from KOH prior to use. Methanol was dried by boiling with magnesium turnings, followed by distillation. Tetrahydrofuran (THF) was dried with sodium and distilled in the presence of benzophenone indicator. Kugelrohr distillations were carried out with a Büchi apparatus GKR-50, Büchi Laboratoriumstechnik AG, Flawil/Switzerland. Melting points were determined with a Büchi 510 apparatus, and are not corrected. Elemental analyses were performed by the service of the Institut für Organische Chemie, University of Stuttgart.

Reaction of 1,1-Dichloro-4-methylpentan-2-one (1a) with Sodium 2,2,2-Trifluoroethoxide in 2,2,2-Trifluoroethanol in the Presence of Furan: 2,2,2-Trifluoroethyl 3-Chloro-2-isopropylpropanoate (9a), 2,2,2-Trifluoroethyl 2-Isopropylpropenoate (2,2,2-Trifluoroethyl 2-Isopropylacrylate, 10a), 2,2,2-Trifluoroethyl 4-Methylpent-2-enoate (2,2,2-Trifluoroethyl 3-Isopropylacrylate, 11a): Procedure a): Dichloro ketone **1a**[39] (3.60 g, 20 mmol) was mixed with furan (18 mL) and chilled to –10 °C. A 2 M solution of NaTFE in TFE (20 mL) was added dropwise with magnetic stirring at this temperature. Stirring was continued at 0 °C for 3 h and for 12 h at 40 °C, monitoring the reaction by GLC (Carbowax 20 M). Apart from minor peaks at t_R = 4.2 min (<2%), 4.7 min (<2%), 6.0 min (<2%), 9.6 min (5%), and 11.4 min (5%), the most intensive FID-peak appeared at t_R = 2.2 (70%) and 2.5 min (15%).

The precipitated sodium chloride was dissolved by adding a few drops of water and the mixture was extracted with diethyl ether (3 × 10 mL). The combined extracts were washed with brine (5 mL) and dried with magnesium sulfate. The solution was concentrated by slow distillation over a 40 cm Widmer column, not allowing the boiling temperature to exceed 35 °C/130 hPa. The remaining liquid (2.1 g) was distilled in a kugelrohr at 70 °C/50 hPa (oven temperature) to give 1.7 g of a liquid, which was analyzed by the following spectra. The ^{1}H NMR spectrum indicated a mixture of trifluoroethyl esters **10a** and **11a** with a 5:1 ratio. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 [d, J = 6.6 Hz, 6 H, $(CH_3)_2CH$, **11a**], 1.11 [d, J = 6.8 Hz, 6 H, $(CH_3)_2CH$, **10a**], 2.1–2.6 (m, 1 H, H-4, **11a**), 2.82 [sept, ^{3}J = 6.8 split with 1.1 Hz, 1 H, $CH(CH_3)_2$, **10a**], 4.49 (q, $J_{H,F}$ = 8.5 Hz, 2 H, CH_2CF_3, **11a**), 4.54 (q, $^{3}J_{H,F}$ = 8.5 Hz, 2 H, CF_3CH_2, **10a**), 5.67 ("t", line distance 0.9 Hz, 1 H, **10a**), 5.73 (6 lines, M part of an AMX sub-spectrum, 1 H, J_{AM} = 11.5 Hz = $J_{2,3}$, J_{MX} = 1.0 Hz = $J_{2,4}$, H-2, **11a**), 6.17 (4 lines, A part of an AMX sub-spectrum, J_{AM} = 11.5 Hz, 1 H, H-3, **11a**), 6.25 (s, 1 H, **10a**). ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 21.6 [+, **10a**, $(CH_3)_2CH$], 22.0 [+, **11a**, $(CH_3)_2CH$], 28.0 [**11a**, $(CH_3)_2CH$], 29.4 (+, **10a**, C-3), 60.4 (**10a**, q, $J_{C,F}$ = 36.6 Hz, CH_2CF_3), 118.3 (**10a**, q, $J_{C,F}$ = 346 Hz, CH_2CF_3), 124.1 (–, **10a**, $=CH_2$), 145.6 (**10a**, C-2), 165.5 (**10a**, CO) ppm.

Procedure b): Dichloro ketone **1a** (1.70 g, 10 mmol) was mixed with furan (10 mL) and chilled to –60 °C. A 2 M solution of NaTFE in TFE (5 mL, 10 mmol) was added dropwise while stirring at this temperature. Stirring was continued for 3 h, and the mixture stored in a freezer for 14 days at –28 °C; a GLC (Carbowax 20 M) showed one peak at t_R = 2.5 min. Workup as described above gave a liquid that was distilled in a kugelrohr at 70 °C/50 hPa to give 1.0 g of impure **9a**; peaks at δ = 5.77 (s) and 2.71 (d, J = 7.0 Hz) ppm in the ^{1}H NMR spectrum ($CDCl_3$) indicated ca. 10% "unreacted" **1a**. A satisfactory combustion analysis could not be obtained. EIMS (70 eV): m/z (%) = 235 (0.2) [M^+ from $C_8H_{13}{}^{37}ClF_3O_2$], 233 (0.8) [M^+ from $C_8H_{13}{}^{35}ClF_3O_2$], 192 (12), 190 (35), 155 (100), 135 (20), 69 (23), 43 (46), 41 (28). HRMS: Calcd. for $C_8H_{13}{}^{35}ClF_3O_2$: 233.0556; found: 233.0557. IR (film): $\tilde{\nu}$ = 1760 cm^{-1} (COOR). Signals assigned to **9a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.95 (d, J = 6.8 Hz, 3 H, CH_3), 0.98 (d, J = 6.8 Hz, 3 H, CH_3), 2.01 (oct, J = 6.8 Hz, 1 H, 3-H), 2.68 (ddd, ^{3}J = $J_{2,3}$ = 6.9, ^{3}J = $J_{2,5A}$ = 4.6, ^{3}J = $J_{2,5B}$ = 9.6 Hz, 1 H, 2-H), 3.62 (dd, ^{3}J = $J_{2,5A}$ = 4.6, ^{2}J = 10.9 Hz, 1 H, 5-H_A), 3.74 (dd, ^{3}J = $J_{2,5B}$ = 9.9, ^{2}J = 10.9 Hz, 1 H, 5-H_B), 4.48 (dq, $^{3}J_{H,F}$ = 8.5 Hz ^{2}J = 12.7 Hz, 1 H, $CF_3CH_AH_B$), 4.55 (dq, $^{3}J_{H,F}$ = 8.5 Hz ^{2}J = 12.7 Hz, 1 H, $CF_3CH_AH_B$) ppm. ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 19.7 (+, CH_3), 20.0 (+, CH_3), 29.6 (+, C-3), 42.7 (–, CH_2Cl), 55.0 (+, C-2), 60.2 (–, q, $J_{C,F}$ = 36.6 Hz, CF_3CH_2), 122.8 (C_q, q, $J_{C,F}$ = 277.1 Hz, CF_3CH_2), 171.1 (C_q, C-1) ppm. Further weak peaks (not visible in the DEPT spectrum) at δ = 22.1, 24.3, 43.7, 70.0 and 197.0 ppm can be assigned to dichloro ketone **1a**.[39]

Reaction of 1,3-Dibromobutan-2-one (12) with Sodium 2,2,2-Trifluoroethoxide in 2,2,2-Trifluoroethanol in the Presence of Furan: (2*endo*,4*endo*)-, (2*exo*,4*endo*)-, (2*endo*,4*exo*)-2-Bromo-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (14a, 14b, 14c) and 2,2,2-Trifluoroethoxy-(*Z*)-but-2-enoic Acid (13): Dibromo ketone **12** (5.75 g, 25 mmol) and

furan (6.81 g, 100 mmol) were mixed and cooled in an ice bath. A 1 M solution of NaTFE in TFE (37 mL) was added dropwise with magnetic stirring over 6 h. Stirring was continued at 0 °C overnight using a cryostat. Spotting a drop of the mixture on wet pH indicator paper showed a neutral solution. Therefore, a further 13 mL of NaTFE solution was added slowly. Water (50 mL) was added to the mixture, which showed pH 14, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined dichloromethane solutions were washed with water (50 mL), brine (50 mL), and dried with sodium sulfate. The solution was filtered and concentrated at atmospheric pressure. Remaining volatile components (inter alia **13**) were condensed in a trap cooled by liquid nitrogen, using oil-pump vacuum. The residue was purified by filtration through silica (20 g), eluting with 400 mL of PE/EA (5:1). The solvent was evaporated, and the remaining pale-yellow oil (1.44 g) examined by GLC (OV 101) and ^{1}H NMR spectroscopy. Two peaks with t_R = 10.9 and 11.2 min appeared on the GLC trace with a 27:73 ratio. The ^{1}H NMR spectrum (250 MHz, $CDCl_3$) showed, in addition to the resonances from the main product **14a** (Table 1 and 2), signals at δ = 1.02 (d, J = 7.1 Hz, **14b**), 1.39 (d, J = 7.4 Hz, **14c**), 2.69 (q, J = 7.4 Hz, **14c**), 3.38 (dq, J = 7.1, J = 4.8 Hz, **14b**), 3.94 (d, J = 0.7 Hz, **14b**) ppm, and peaks between 4.6–5.2 and 6.3–6.5 ppm partly overlapping those of **14a**. These resonances can be assigned to isomers **14b** and **14c**, by comparison with chemical shift ranges and coupling constants for related oxabicycles.[13] From the integrals of the resonances at 2.69, 3.04 and 3.38 ppm, the ratio of the three isomers **14c**, **14a**, **14b** was determined as 12:76:12. The yield of the mixture of isomers (1.44 g) was 27%. Chromatography on silica (150 g, 34 cm-gravity column, diameter 3.5 cm), eluting with PE/EA (10:1) gave no separation: the eluent showed two GLC peaks with t_R = 10.9 and 11.2 min (13:87). After evaporation of the solvent, the remaining oil (0.76 g) was dissolved in a little *n*-hexane and stored in a freezer. The colorless crystals that formed (0.25 g) proved to be **14a**; m.p. 55 °C (ref.[21] m.p. 55–56 °C), yield: 5%. TLC (PE/EA, 4:1, spraying with vanilline/H_2SO_4 solution): red spot with R_f = 0.43.

(2*endo*,4*endo*)-2-Bromo-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (14a): IR (KBr): $\tilde{\nu}$ = 3075 (=C–H), 2975, 2950, 2925, 2885, 2860 (C–H), 1715 (C=O), 1585 (C=C) cm^{-1}. Data from a 100 MHz ^{1}H NMR spectrum in CCl_4 were reported by Hoffmann and Iqbal.[21] The chemical shifts and coupling constants determined from a 250 MHz ^{1}H NMR spectrum in $CDCl_3$ (Table 1) were slightly different, but consistent. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2.

The liquid that condensed in the cold trap was distilled in a kugelrohr at 80 °C. According to the ^{1}H NMR spectrum, the distillate, a colorless liquid (0.5 g) consisted of trifluoroethanol and **13** (see the following preparation) in ca. 2:3 ratio.

2,2,2-Trifluoroethyl (*Z*)-But-2-enoate (13) by Favorskii Rearrangement of 1,3-Dibromo-2-butanone (12): 1,3-Dibromobutan-2-one (**12**) (4.60 g, 20 mmol) was cooled in an ice bath. A 1 M NaTFE solution (40 mL) was added dropwise with magnetic stirring over 70 min. The ice bath was removed and stirring was continued for 1 h at 0 °C, and then for two days at room temperature. Water (20 mL) was added and the layers separated. The aqueous layer was extracted with pentane (5 × 15 mL). The combined organic layers were dried with sodium sulfate, filtered, and concentrated with a rotary evaporator. The residue was distilled in a kugelrohr at 80 °C to give 0.51 g (15%) of colorless, very volatile liquid **13**. $C_6H_7F_3O_2$ (168.1): calcd. C 42.87, H 4.20; found: C 42.84, H 4.05. IR ($CDCl_3$): $\tilde{\nu}$ = 3020 (=C–H), 2995 (C–H), 1730 (C=O), 1640 (C=C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.17 (dd, $^3J_{3,4}$ = 7.3, $^4J_{2,4}$ = 1.8 Hz, 3 H, 4-H), 4.50 (q, $^3J_{H,F}$ = 8.5 Hz, 2 H, CH_2CF_3), 5.88 (dq, $^3J_{2,3}$ = 11.4, $^4J_{2,4}$ = 1.8 Hz, 1 H, 2-H), 6.50 (dq, $^3J_{2,3}$ = 11.4, $^3J_{3,4}$ = 7.3 Hz, 1 H, 3-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.6 (C-4), 59.8 (q, $^3J_{C,F}$ = 36.4 Hz, CH_2CF_3), 118.8 (C-2), 123.15 (q, $^1J_{C,F}$ = 277.2 Hz, CH_2CF_3), 148.3 (C-3), 164.35 (C-1) ppm.

2,2,2-Trifluoroethyl (*E*)-But-2-enoate: (*E*)-But-2-enoic acid chloride (crotonic acid chloride)[40] (4.18 g, 40 mmol) was added via syringe with stirring to ice-chilled TFE (4.00 g, 40 mmol) over 15 min. Stirring was continued for 1 h at 0 °C, and then at room temperature (225 min). Pentane (120 mL) was added, and the mixture washed with water and saturated $NaHCO_3$ solution (60 mL each). The pentane solution was dried with sodium sulfate and concentrated with a rotary evaporator. The remaining liquid was distilled in a 15 cm-Vigreux column to a give a colorless, volatile liquid (3.38 g, 50%) with b.p. 123–124 °C. $C_6H_7F_3O_2$ (168.1): calcd. C 42.87, H 4.20; found C 42.89, H 4.27. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.93 (dd, $^3J_{3,4}$ = 6.9, $^4J_{2,4}$ = 1.7 Hz, 3 H, 4-H), 4.51 (q, $^3J_{H,F}$ = 8.5 Hz, 2 H, CH_2CF_3), 5.92 (dq, $^3J_{2,3}$ = 15.5, $^4J_{2,4}$ = 1.7 Hz, 1 H, 2-H), 7.12 (dq, $^3J_{2,3}$ = 15.5, $^3J_{3,4}$ = 6.9 Hz, 1 H, 3-H) ppm. Weak signals of the (*Z*)-isomer (**13**) were also present. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.2 (C-4), 60.2 (q, $^3J_{C,F}$ = 36.5 Hz, CH_2CF_3), 120.9 (C-2), 123.2 (q, $^1J_{C,F}$ = 277.0 Hz, CH_2CF_3), 147.7 (C-3), 164.6 (C-1) ppm.

Reaction of 1,1,3-Tribromo-butan-2-one (24) with Sodium 2,2,2-Trifluoroethoxide in 2,2,2-Trifluoroethanol in the Presence of Furan. (2*endo*,4*endo*)-2,4-Dibromo-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (26a), (2*exo*,4*endo*)-2,4-Dibromo-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (26b), (2*endo*,4*exo*)-2,4-Dibromo-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (26c), 2,2,2-Trifluoroethoxy 3-Bromobut-2-enoate [(*E*)-29, (*Z*)-29)]: 1,1,3-Dibromo-2-butanone **(24)**[24] (2.60 g, 8.4 mmol) and furan (2.30 g, 34 mmol) were mixed and cooled in an ice bath. A 1 M solution of NaTFE in TFE (8.5 mL) was added dropwise with magnetic stirring over 3 h. Stirring was continued at 0 °C for 40 min. Since the mixture showed neutrality after that time, a little more NaTFE solution was added (0.5 mL), and the mixture stirred for a further 70 min. Now, spotting on wet pH paper showed an alkaline reaction (pH 14). Water (20 mL) was added while stirring, and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined dichloromethane solutions were washed with saturated brine (20 mL), and dried with sodium sulfate. The solution was filtered and concentrated with a rotary evaporator. The remaining brown oil was analyzed by GLC (OV 101), which showed three peaks at t_R = 4.1, 4.7 and 14.2 min with relative FID-peak areas of 13:19:68. The volatile components were condensed in a trap cooled by liquid nitrogen, using oil pump vacuum. The residue was purified by filtration through silica (20 g), eluting with 300 mL of PE/EA (5:1). A colorless solid (1.22 g, 49% yield) was obtained which was examined by ^{1}H NMR spectroscopy. From the integrals of characteristic signals (Table 1), a ratio of 70:21:9 of isomers **26a**, **26b** and **26b** was calculated. We were unable to separate these isomers by chromatography or crystallization. A very small amount of the main product **26a** was isolated from a fraction of the eluent, which was analytically pure and showed m.p. 94 °C. $C_8H_8Br_2O_2$ (295.96): calcd. C 32.47, H 2.72, Br 54.00; found C 32.66, H 2.76, Br 54.00. IR (KBr): $\tilde{\nu}$ = 3065 (=CH), 2965, 2940, 2900 (C–H), 1730, 1700 (C=O), 1585 (C=C) cm^{-1}. ^{1}H NMR and ^{13}C NMR spectroscopic data: Table 1 and Table 2. The liquid condensed in the cold trap was distilled in a kugelrohr at 100 °C (oven temperature). The colorless distillate (0.45 g, 22% yield) was analyzed by NMR and GC-EIMS, thus proving that structures *(E)*-**29** and *(Z)*-**29** are in a ratio of 39:61. A GC-EIMS (70 eV) showed two main peaks at t_R = 9.2 and 10.0 min; both gave rise to a parent ion with m/z = 248/246, thus indicating $C_6H_6BrF_3O_2$ isomers [**(*E*)-29**

and **(*Z*)-29)]**: EIMS of the major component with t_R = 9.2 min [**(*Z*)-29**]: *m/z* (%) = 248 (44) [M^+ from $C_6H_6{}^{81}BrF_3O_2$], 246 (45) [M^+ from $C_6H_6{}^{79}BrF_3O_2$], 167 (100) [M^+ – Br], 149 (86) [M^+ – OCH_2CF_3 from $C_6H_6{}^{81}BrF_3O_2$], 147 (88) [M^+ – OCH_2CF_3 from $C_6H_6{}^{79}BrF_3O_2$], 121 (45) [M^+ – $CO_2CH_2CF_3$ from $C_6H_6{}^{81}BrF_3O_2$], 119 (50) [M^+ – $CO_2CH_2CF_3$ from $C_6H_6{}^{79}BrF_3O_2$], 83 (93) [$CH_2CF_3{}^+$], 69 (37) [$CF_3{}^+$], 56 (23), 53 (15). EIMS of the minor component with t_R = 10.0 min [**(*E*)-29**]: *m/z* = 248 (6) [M^+ from $C_6H_6{}^{81}BrF_3O_2$], 246 (6) [M^+ from $C_6H_6{}^{79}BrF_3O_2$], 167 (100) [M^+ – Br], 149 (38) [M^+ – OCH_2CF_3 from $C_6H_6{}^{81}BrF_3O_2$], 147 (39) [M^+ – $CO_2CH_2CF_3$ from $C_6H_6{}^{79}BrF_3O_2$], 121 (19) [M^+ – $CO_2CH_2CF_3$ from $C_6H_6{}^{81}BrF_3O_2$], 119 (19) [M^+ – $CO_2CH_2CF_3$ from $C_6H_6{}^{79}BrF_3O_2$], 83 (66) [$CH_2CF_3{}^+$], 69 (11) [$CF_3{}^+$], 67 (16). IR ($CDCl_3$): $\tilde{\nu}$ = 2950 (C–H), 1740 (C=O), 1630 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.04 [d, *J* = 1.6 Hz, 3 H, H-4, **(*E*)-29**], 2.52 [d, *J* = 1.2 Hz, 3 H, H-4 **(*Z*)-29**], 4.52 [q, *J* = 8.5 Hz, 2 H, **(*Z*)-29**], 4.58 [q, *J* = 8.4 Hz, 2 H, **(*E*)-29**], 6.39 [q, *J* = 1.2 Hz, 1 H, H-2 **(*Z*)-29**], 6.75 [q, *J* = 1.6 Hz, 1 H, H-2 **(*E*)-29**] ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.5 [**(*E*)-29**], 31.4 [**(*Z*)-29**], 60.2 [q, *J* = 36.7 Hz, **(*Z*)-29**], 60.6 [q, **(*E*)-29**], 114.05 [**(*E*)-29**], 118.2 [**(*Z*)-29**], 123.05 (q, *J* = 277.0 Hz), 131.8 [**(*E*)-29**], 140.75 [**(*Z*)-29**], 162.2 [**(*Z*)-29**], 164.3 [**(*E*)-29**] ppm.

Reaction of 1,1,3-Trichlorobutan-2-one (25) with Sodium 2,2,2-Trifluoroethoxide in 2,2,2-Trifluoroethanol in the Presence of Furan: (2*endo*,4*endo*)-2,4-Dichloro-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (27a), (2*exo*,4*endo*)-2,4-Dichloro-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (27b) and (2*endo*,4*exo*)-2,4-Dichloro-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (27c): 1,1,3-Dichloro-2-butanone **(25)**[24] (1.75 g, 10 mmol) and furan (2.72 g, 40 mmol) were mixed and cooled in an ice bath. A 1 M solution of NaTFE in TFE (11 mL) was added dropwise with magnetic stirring over 1 h. Stirring was continued at room temperature for 3 h. Water (10 mL) was added with stirring, and the layers separated. The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined dichloromethane solutions were washed with saturated brine (10 mL) and dried with sodium sulfate. The solution was filtered and concentrated with a rotary evaporator. The residue was dissolved in a little dichloromethane, adsorbed on silica (5 g), and placed on a chromatography column (34 cm effective length, diameter 3.5 cm) charged with 175 g of silica. For elution by gravity, PE/EA (10:1) was used. After a fore-run (400 mL) that was discarded, 20 mL-fractions were taken, and the separation checked by TLC. Fractions 24–48 contained 1.49 g of a pale yellow solid, which was examined by ^1H NMR spectroscopy (Table 1). From the integrals it was calculated that isomers **27a**, **27b** and **27c** had been formed in a ratio of 73:17:10 with a 72% yield. The solid was boiled with diethylether (ca. 4 mL) and the solution allowed to cool in a refrigerator. Nearly colorless crystals were formed (0.86 g, 42%) with m.p. 72–73 °C. They were recrystallized from ca. 4 mL of diethyl ether/hexane (1:1 v/v) whereupon the m.p. rose to 75–76 °C.

(2*endo*,4*endo*)-2,4-Dichloro-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (27a): $C_8H_8Cl_2O_2$ (207.1): calcd. C 46.41, H 3.89, Cl 34.25; found C 46.55, H 3.93, Cl 34.25. IR (KBr): $\tilde{\nu}$ = 3080 (=C–H), 2980, 2970, 2920, 2900, 2850 (C–H), 1740, 1700 (C=O), 1590 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): Table 1. **(2*exo*,4*endo*)-2,4-Dichloro-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (27b):** ^1H NMR (250 MHz, $CDCl_3$): Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2. **(2*endo*,4*exo*)-2,4-Dichloro-2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (27c):** ^1H NMR (250 MHz, $CDCl_3$): Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2.

Reaction of 1,1,1-Trichloro-4-methylpentan-2-one (30) with Sodium 2,2,2-Trifluoroethoxide in 2,2,2-Trifluoroethanol in the Presence of Furan: 2-Chloro-4-isopropyl-4-(2,2,2-trifluoroethoxy)-8-oxabicyclo[3.2.1]-oct-6-en-3-one (36): Procedure a): A solution of trichloro ketone **30** (2.05 g, 10 mmol) in furan (10 mL) was cooled to –10 °C. A 2 M solution of NaTFE in TFE (10 mL) was added dropwise with magnetic stirring over 1 h. After 4 h stirring at 0 °C, the progress of the reaction was checked by GLC (Carbowax 20 M) which showed peaks at t_R = 6.5 min (**30**), 7.7 min (26%), 12.9 (33%), 18.3 (35%) (**36**) and 21.7 min (6%) (**34**). Since, according to the GLC, **30** was still present, and spotting of a sample on wet pH paper showed an alkaline reaction, the mixture was allowed to stir at room temperature for a further 16 h. However, the GLC differed only negligibly from the first one. Therefore the reaction was quenched by adding 10 mL of brine. The mixture was extracted with dichloromethane (5 × 5 mL); the combined organic layers were washed with brine (10 mL) and dried with magnesium sulfate. The solvent was evaporated, and the remaining oil (3.25 g) distilled in a 20 cm Vigreux column using oil-pump vacuum. After a fore-run, we obtained an oily fraction (0.8 g, 27% yield of **36**) with b.p. 73 °C/0.1 Pa that became solid on storing. $C_{12}H_{14}ClF_3O_3$ (298.7): calcd. C 48.25, H 4.72, Cl 11.87; found C 48.25, H 4.75, Cl 11.80. IR (KBr): $\tilde{\nu}$ = 1740 cm^{-1} (C=O). ^1H NMR (250 MHz, $CDCl_3$): Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2.

Procedure b): A solution of trichloro ketone **30** (2.05 g, 10 mmol) in furan (10 mL) was cooled to –40 °C. A 2 M solution of NaTFE in TFE (5 mL) was added dropwise with magnetic stirring. The mixture was stirred at this temperature for 3 h, and then stored in a freezer at –28 °C. After 14 days, progress of the reaction was checked by GLC (Carbowax 20 M) which showed peaks at t_R = 6.5 min (**30**), 7.5 min, 12.8 min (unknown components, relative peak area <10%), 18.3 min (20%) (**36**), 21.5 min (55%) (**34**). Spotting a sample on wet pH indicator paper showed neutrality of the reaction mixture. Precipitated sodium chloride was dissolved by adding brine (10 mL) and a few mL of water. The organic layer was separated, and the aqueous layer extracted with diethyl ether (3 × 10 mL). The combined organic solutions were washed with brine (5 mL) and dried with magnesium sulfate. The solvent was evaporated at atmospheric pressure, using a 20 cm Vigreux column. When the ether and furan had been distilled (b.p. 34 °C), trifluoroethanol was removed at reduced pressure (30 °C/100 hPa). The remaining liquid was transferred to a kugelrohr and distilled with an oil-pump vacuum (0.1 Pa). Unreacted trichloro ketone **30** distilled at 40 °C, together with an unknown byproduct. The fraction with b.p. 90–120 °C (1.3 g) consisted of oxabicycles **36** and **34**, according to an ^1H NMR spectrum. The substance was taken up in ca. 5 mL of boiling diethyl ether and cooled in a refrigerator. Hexagonal platelets of **34** (1.0 g, 42%) crystallized which were analytically pure. The mother liquor contained compound **36**, in addition to **34**. $C_{10}H_{12}Cl_2O_2$ (235.1): calcd. C 51.09; H 5.14; Cl 30.16; found C 51.03; H 4.96; Cl 30.02. IR (KBr): $\tilde{\nu}$ = 1740 cm^{-1} (CO). ^1H NMR (250 MHz, $CDCl_3$): Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2.

Reaction of 1,1,1-Trichloro-4-methylpentan-2-one (30) with Furan in Lithium Perchlorate/Diethylether: 2,4-Dichloro-2-isopropyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one (Isomers *endo-endo*-34, *exo-endo*-34, *endo-exo*-34)[41]: Dry lithium perchlorate (1.00 g, 9.6 mmol) was dissolved in dry diethyl ether (9 mL), followed by furan (11 mL) and dry triethylamine (0.94 g, 9.6 mmol). A mixture of trichloro ketone **30** (0.96 g, 4.7 mmol), furan (1.3 mL) and diethyl ether (1 mL) was added dropwise with vigorous stirring at room temperature. After 2 days of stirring, the mixture was poured into water (50 mL) and extracted with diethyl ether (5 × 25 mL). The combined ether layers were washed with brine (40 mL), dried with magnesium sulfate and concentrated in vacuo. The residue (720 mg)

was distilled in a kugelrohr. The distillate, boiling between 90 and 140 °C/0.001 Torr was filtered through silica, eluting with PE/EA, 8:1, and subjected to MPLC (PE/EA, 8:1); 72 fractions of 10 mL were taken. Separation was monitored by TLC on silica (PE/EA, 6:1). The fractions giving spots at R_f = 0.41, 0.39 and 0.33 were collected, and the solvent evaporated:

First fraction (R_f = 0.41): 141 mg, ***endo-endo*-34** according to ^{1}H NMR spectroscopy (Table 1), in addition to 16% of the isomer with R_f = 0.39 (***exo-endo*-34**).

Second fraction (R_f = 0.39): 86 mg, ***exo-endo*-34** according to ^{1}H NMR spectroscopy (Table 1), in addition to 4% of ***endo-endo*-34**.

Third fraction (R_f = 0.33): 23 mg, ***endo-exo*-34** according to ^{1}H NMR spectroscopy (Table 1), with impurities of unknown constitution.

Dechlorination of 34: 2-Isopropyl-2-trifluoroethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (35): Oxabicycle **36** (0.45 g, 1.5 mmol) was dissolved in methanol, which had previously been saturated with ammonium chloride (7 mL). The solution was stirred in an ice bath and a zinc-copper couple[42] (2.0 g) was added in small portions. The mixture was allowed to stir for 16 h. The inorganic solid was filtered and washed with methanol and diethyl ether (8 × 3 mL). The combined filtrates were concentrated with a rotary evaporator, and the residue treated with dichloromethane (3 × 5 mL). After filtration, dichloromethane was evaporated to give 0.2 g (55% yield) of **35** that showed one GLC peak (Carbowax 20 M) at t_R = 14.6 min. EIMS (70eV): *m*/*z* (%) = 264 (100), 249 (13), 221 (12), 196 (24), 181 (12), 179 (36), 155 (62), 154 (37), 139 (33), 123 (13), 121 (10), 83 (21), 82 (18), 81 (57), 71 (53), 68 (11), 55 (32), 53 (16), 43 (64), 41 (24), 39 (18). HRMS: Calcd. for $C_{12}H_{15}F_3O_3$: 264.0976; found 264.0980. IR (film): $\tilde{\nu}$ = 2980 (m, CH), 1715 (s, CO), 1460 (w), 1420 (w), 1285 (s), 1160 (s), 1100 (s), 1040 (m), 970 (s), 890 (w), 860 (m), 810 (w), 735 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2.

Dechlorination of *endo-endo*-34: *endo*-2-Isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (37): Oxabicycle ***endo-endo*-34** (0.20 g, 0.85 mmol) was dissolved in methanol, which had previously been saturated with ammonium chloride (5 mL). The solution was stirred in an ice bath and a zinc-copper couple[42] (2.5 g) was added in small portions. The mixture was allowed to stir for 24 h. The inorganic solid was filtered and washed with methanol. The combined filtrates were concentrated in vacuo, and the residue treated with 6% EDTA disodium salt solution (12 mL). The mixture was extracted with dichloromethane (2 × 5 mL), the extracts dried with magnesium sulfate, filtered and concentrated. The remaining liquid was distilled in a kugelrohr at 120 °C/0.1 Pa to give 0.1 g of oily **37**. IR (film): $\tilde{\nu}$ = 2980 (vs, CH), 2880 (m, CH), 1710 (vs, CO), 1470 (m), 1410 (w), 1410 (w), 1390 (w), 1370 (w), 1355 (w), 1340 (s), 1240 (w), 1180 (s), 1110 (w), 1100 (w), 1090 (w), 1040 (m), 965 (s), 920 (w), 880 (w), 865 (m), 830 (w), 815 (w), 800 (w), 730 (s) cm^{-1}. The ^{1}H and ^{13}C NMR spectra (see Tables 1 and 2) are consistent with reported data.[17]

Reaction of 27 with Sodium Methoxide in Methanol: (2*endo*,4*exo*)-2-Chloro-4-methoxy-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (39a) and (2*exo*,4*exo*)-2-Chloro-4-methoxy-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (39b): A 1 M solution of sodium methoxide in methanol (4 mL, 4 mmol) was added dropwise, while stirring, to a solution of **27** (621 mg, 3 mmol) in dry methanol (5 mL), cooled in an ice bath. The ice bath was then removed, and the mixture was stirred for 2 h at room temperature. Water (20 mL) was added, and the mixture was extracted with diethyl ether (4 × 15 mL). The combined ether extracts were dried with sodium sulfate, filtered and concentrated with a rotary evaporator. The remaining pale-yellow solid was chromatographed on silica (60 g), eluting with PE/EA (5:1). After a fore-run (130 mL), 15-mL fractions were collected, and the separation checked by TLC. Fractions 19–39 contained 536 mg (88%) of **39a** with m.p. 67–69 °C. From the fractions 40–56, a yellow oil was obtained that was rechromatographed on silica (10 g). Elution with PE/EA (5:1) gave 3 mg of **39a** and 41 mg (7%) of **39b**.

(2*endo*,4*exo*)-2-Chloro-4-methoxy-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (39a): $C_9H_{11}ClO_3$ (202.6): calcd. C 53.35, H 5.47, Cl 17.50; found: C 53.32, H 5.45, Cl 17.63. IR (KBr): $\tilde{\nu}$ = 3075 (=C–H), 2980, 2970, 2955, 2935, 2820 (C–H), 1730 (C=O), 1580 (C=C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2.

(2*exo*,4*exo*)-2-Chloro-4-methoxy-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (39b): ^{1}H NMR (250 MHz, $CDCl_3$): Table 1. ^{13}C NMR (62.9 MHz, $CDCl_3$): Table 2.

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