A Novel Synthesis of 2-Alkoxy-3-hydroxytropones and 2,7-Dihydroxytropones from Dialkoxy-8-oxabicyclo[3.2.1]oct-6-en-3-ones

Hartmut Zinser,[a][‡] Sonja Henkel,[a][‡‡] and Baldur Föhlisch*[a]

Keywords: Acetals / Cleavage reactions / Ketones / Solvolysis / Tautomerism

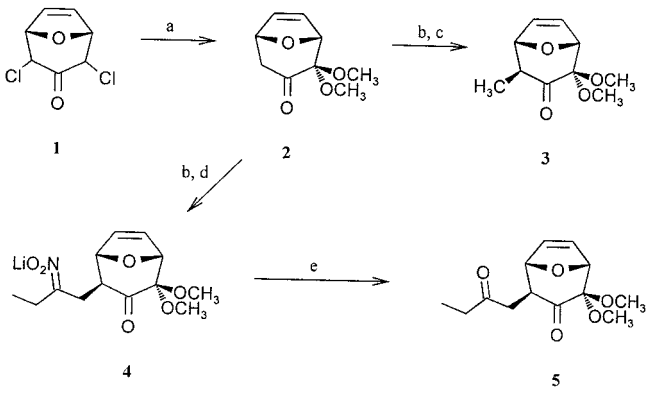
Trichloro-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones **6** and **7** are solvolysed by methanolic sodium methoxide to form the bicyclo[3.2.1] α,α-dimethoxy ketones **13** and **14**, with preservation of one chloro substituent. In the case of **6a**, prolonged reaction time with an excess of methanolic sodium methoxide provides a trimethoxy-substituted oxanorbornene aldehyde **19** through ring contraction. Treatment of the mixture of **13** and **14** with zinc and aqueous acetic acid affords dechlorinated α-oxo acetals **15** and **16**. Starting with the [4+3] cycloadducts derived from 2-methylfuran and tetrachloroacetones (**6b** and **7b**), the same procedure, but with use of ethanol or trifluoroethanol, results in the corresponding ethoxy- and trifluoroethoxy acetals. These compounds can be converted into the oxabicyclic compounds **15**, which undergo cleavage of the ether bridge on heating with KOH in methanol, thus providing 2-alkoxy-3-hydroxytropones **20**, which can be dealkylated to give the 2,7-dihydroxytropones (7-hydroxytropolones) **29**. The lithium enolate generated from the α-oxo acetal **15a** can be *exo*-alkylated with methyl iodide. Michael addition with 2-nitro-1-butene followed by a Nef reaction furnishes the bicyclic dioxo acetal **5**. Treatment of **5** with basic methanol results in an epoxyazulenone derivative **26**, and a hydroxytropone **20f**, which is in equilibrium with the cyclic hemiacetal form **28**.

Introduction

Recently, we reported our finding that 2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**1**) undergoes solvolysis in methanol/methoxide to form 2,2-dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**), resulting in the 1,3-transposition of substituents through an enolization/ionization mechanism.[1,2] In the course of another study,[3] we were interested in utilizing the enolate generated from the bicyclic α-oxo acetal **2**, with the ultimate goal of cleaving the ether bridge of the oxabicyclic compound. This report describes our results, which include some unexpected observations.

Results and Discussion

As expected, the lithium enolate prepared from **2** with LDA/THF was methylated using a conventional protocol (MeI, HMPA), resulting in the 4-methyl-bicyclic compound **3** (Scheme 1). Since alkylations of oxabicyclic enolates prefer to occur on the *exo* face,[4] the configuration at C-4 should be 4-*exo*.[4] This was proved by the low-field chemical shift of the methyl group (δ_H = 1.42 ppm; δ_C = 15.8 ppm), and the small coupling constant between 4-H and the bridgehead proton 5-H ($J_{4,5}$ = 0.7 Hz).



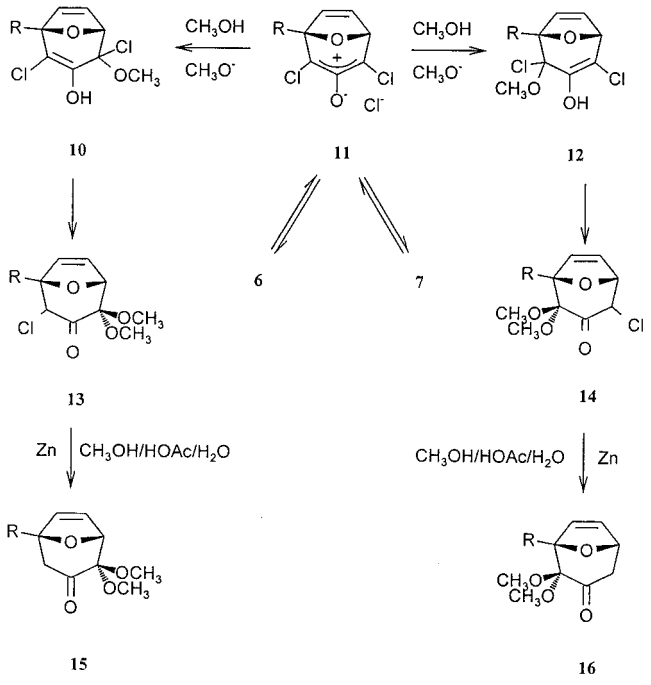
Scheme 1. Formation and alkylation of **2**: a) CH_3ONa/CH_3OH, 38%; b) LDA, THF; c) CH_3I, HMPT, 82%; d) 2-nitrobut-1-ene; e) 3 M H_2SO_4, H_2O/CH_3OH, 64%

A functionalized side chain could be attached by treating the lithium enolate with 2-nitro-1-butene.[5] We did not attempt to isolate the expected nitronate **4** or the corresponding nitro compound (i.e. the Michael adduct), but instead immediately subjected the reaction mixture to the conditions of a Nef reaction.[6] The dioxo acetal **5** was isolated in a 64% yield. The NMR spectra indicated that the configuration of **5** was also *exo*.

[a] Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: (internat.) + 49-(0)711-6854269
E-mail: baldur.foehlisch@po.uni-stuttgart.de
[‡] Taken from the Diploma thesis and doctoral dissertation of H. Zinser, Univ. Stuttgart, 1994 and 1999, respectively.
[‡‡] X-ray analysis.

  DOI: 10.1002/ejoc.200300600

Unfortunately, our preparation of the starting material **2** from the dichloro-substituted bicyclic compound **1** gave an unsatisfying yield.[1] Instead of trying to optimize this reaction, we investigated the alcoholysis of the oxabicyclic α,α,α′-trichloro analogues, expecting better stabilization of the intermediate(s), e.g. **11** (Scheme 2), by the additional chloro substituent.

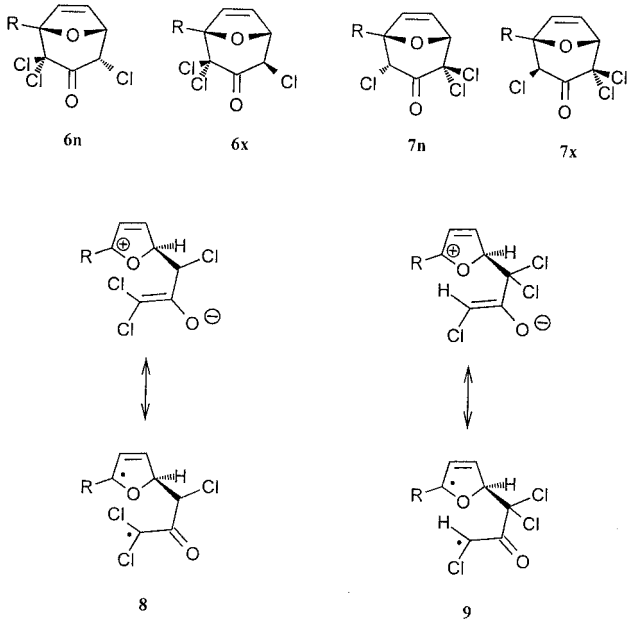


Scheme 2. Methanolysis and dechlorination of trichloro-8-oxabicyclo[3.2.1]oct-6-en-3-ones **6**, **7**

Synthesis of Trichlorooxabicyclic Compounds

The *endo*-configured oxabicyclic compounds **6an** and **6bn** have previously been obtained in a 45−54% yield by the [4+3] cycloaddition reactions of furan and 2-methylfuran (respectively) with the oxyallyl intermediate generated from 1,1,3,3-tetrachloroacetone in methanol/triethylamine.[7] Hoping for improved yields, we instead used trifluoroethanol/sodium trifluoroethoxide (TFE/NaTFE).[8] In cases when the furan component was readily available, it was used in excess (Table 1). Indeed, furan itself gave the known 4-*endo*-bicyclic compound **6an** in a 72% yield, purified by adsorptive filtration and crystallization; we did not check the mother liquor for other products such as the 4-*exo* epimer.

Four diastereomeric oxabicyclic compounds (**6n**, **6x**, **7n**, **7x)** could be envisaged to arise from the [4+3] cycloaddition of a 2-substituted furan with a trichlorooxyallyl intermediate.



With 2-methylfuran, two major products were formed in the ratio of ca. 70:30. A third product (< 5%) was detected by GLC, but we were unable to isolate it. The main product, obtained in pure form by recrystallization from methanol, proved to be **6bn**.[7] Repeated chromatography (MPLC) of the mother liquor furnished a small amount of the minor product. Its structure was unequivocally proved by an X-ray crystal structure analysis, which showed that the 2-*endo* regioisomer, namely 2,4,4-trichloro-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**7bn**, Figure 1), was formed too.[9]

It should be noted that the "unsymmetrical" isomer of 1,1,3,3-tetrachloroacetone (namely, 1,1,1,3-tetrachloroacetone), would be expected to form the same trichlorooxyallyl intermediate(s), and hence should furnish the same oxabicyclic compounds with 2-methylfuran. Indeed, the regioisomers **6bn** and **7bn** were formed in a 67% yield with a ratio of 67:33, i.e. practically the same result.

2-Isopropylfuran and 2-(benzyloxymethyl)furan, on reaction with 1,1,3,3-tetrachloroacetone, also gave a mixture of regioisomers **6** and **7**. In all the cases studied, the bicyclic compounds **6** are favoured, but the regioselectivity is low

Table 1. Synthesis of trichloro-8-oxabicyclo[3.2.1]oct-6-en-3-ones **6** and **7** from 1,1,3,3-tetrachloroacetone and furans with sodium trifluoroethoxide/trifluoroethanol

6, **7**	R	Equiv. of furan	Combined yield (**6** + **7**) [%]	Ratio **6**/**7**
a	H	5	72	–
b	CH_3	5	65	2.3:1
c	*i*-C_3H_7	0.83	62	3.4:1
d	$BnOCH_2$	1.8	78	1.2:1

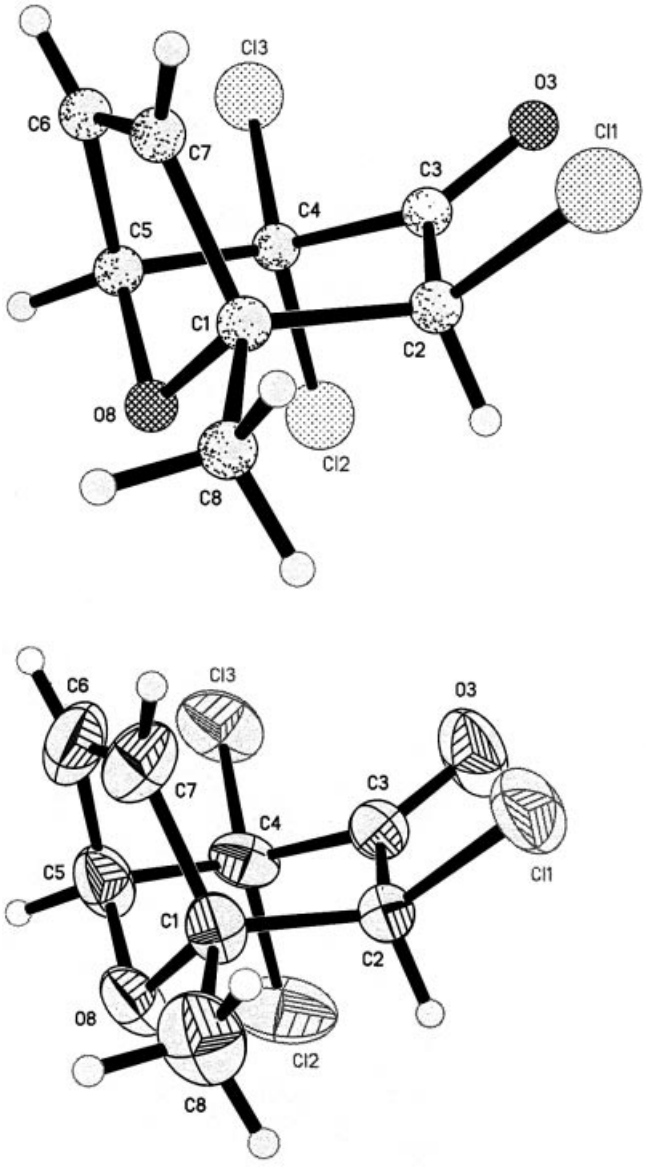


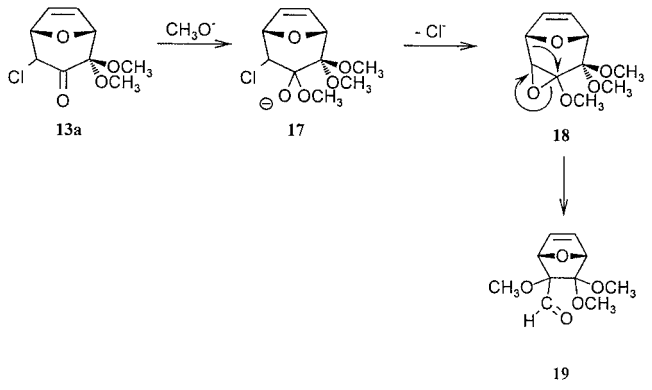
Figure 1. X-ray structure of (2-*endo*)-2,4,4-trichloro-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**7bn**); see also ref.[9]

(Table 1). It should be noted that a vicinal relationship between the substituents (R and geminal Cl_2) would be expected to induce more torsional strain in **6** than in **7**; that is, the latter would be thermodynamically more stable. The fact that **6** is nevertheless favoured points to a stepwise cycloaddition in which the intermediate(s) **8** are more stable than **9**.[10]

Solvolysis of Trichlorooxabicyclic Compounds and Dechlorination

The trichlorobicyclic compound **6an** was treated with methanolic sodium methoxide at 0 °C. After 2.5 h, a mixture of the *endo*- and *exo*-chlorodimethoxy ketones **13a** was obtained in a 93% combined yield (Scheme 2). The ^1H NMR spectrum of the major isomer showed a doublet at $\delta = 4.79$ ppm with $J = 4.5$ Hz, consistent with the $J_{4,5}$ coupling in **1** and **6an**, thus proving the formula as **13an**. For the minor isomer, a high-field shift was observed ($\delta = 3.93$ ppm), and the small coupling constant (0.9 Hz) clearly indicates a 4-*endo* proton (**13ax**). The fact that only two chloro substituents are displaced by methoxy groups is in line with the enolization/ionization mechanism postulated for the reaction **1** → **2**.[1] As for the epimerization at C-4, protonation of the chloroenol(ate) intermediate at equilibrium is possible from both faces of the molecule.

After allowing the bicyclic trichloro ketone **6an** to react with an excess of methanolic sodium methoxide at room temperature for several days, we found that all the chloro substituents were displaced by methoxy groups. However, the product contained an aldehyde functionality and three methoxy groups, as verified by the NMR spectrum ($\delta_H = 9.60$, 3.39, 3.36 and 3.26 ppm). Presumably, the oxo acetal **13a** is attacked by methoxide at the carbonyl group with the formation of an epoxide. The latter would undergo a dyotropic rearrangement with ring contraction to form the oxanorbornene derivative **19** (Scheme 3).



Scheme 3. Proposed rearrangement mechanism of the chloro acetal **13a**

In analogy to the behaviour of the dichloride **1**,[1] alcoholysis of the regioisomers **6b**–**d** and **7b**–**d** was expected to proceed via the same intermediate, i.e. the ion pair **11** (Scheme 2). Hence, and because separation of **6** and **7** proved to be cumbersome, the trichlorobicyclic compounds were subjected to alcoholysis as a regioisomeric mixture, except for **6a**. To avoid separation of the *endo* and *exo* isomers of the dialkoxychlorobicyclic compounds **13** and **14**, the methanolic product mixture was treated with aqueous acetic acid and dehalogenated immediately with zinc pow-

Table 2. Dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-ones **15** and **16** formed by methanolysis and dechlorination of trichlorobicyclic compounds **6** and **7**

15, **16**	R^1	Combined yield (**15** + **16**) [%]	Ratio **15**/**16**
a (**15a** = **2**)	H	97	–
b	CH_3	95	2:1
c	i-C_3H_7	93	> 19:1
d	$BnOCH_2$	75	8.4:1

der, thus affording the dialkoxy ketones **15** and **16** (Table 2).

In contrast to the preferred 1,2-position of substituents in the starting materials **6b**−**d**, in this case the favoured products had the substituents in a 1,4-relationship, that is in the "opposite" orientation. Obviously, the oxyallyl intermediate **11** preferentially associates with alcohol molecules at the less hindered (C-4) position. The regioselectivity seems to be influenced by steric interactions of the substituent R and the alcohol molecule, as indicated by the **15/16** ratio (Table 2).

In the case of **6b**, we also replaced methanol by ethanol and 2,2,2-trifluoroethanol, in the presence of the corresponding sodium alkoxides. The ratio of the regioisomeric α,α-dialkoxy ketones **15b/16b** (with C_2H_5 or CF_3CH_2, instead of CH_3), produced in a 96% yield after dechlorination with zinc, was 3.1:1 and 5.1:1, i.e. higher than with methanol (see the Exp. Sect.).

Synthesis of β-Tropolones by Cleavage of Dialkoxybicyclic Compounds

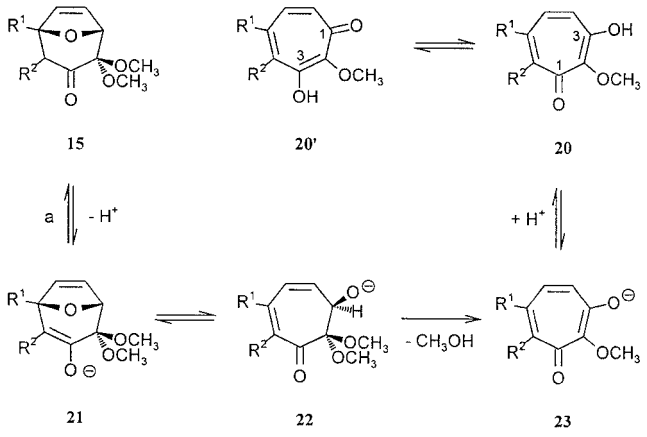
The pioneering work of Noyori et al. on the transformation of 2- or 3-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one into isopropyl-substituted tropones and α-tropolones[11] has initiated the development of improved procedures for the synthesis of troponoids by cleavage of the bicyclic ether functionality.[4b,12−14]

Our attempts to cleave the oxygen bridge in **2** by TMSOTf/TEA,[12] $ZrCl_4$/piperidine[14] and $TiCl_4$/TEA[15] gave unsatisfactory results. Surprisingly, it appeared that a very simple protocol was sufficient; refluxing **15a** (= **2**) with 10% methanolic KOH solution, followed by acidification with mineral acid, gave a solid product in 84% yield with empirical formula $C_8H_8O_3$ (as deduced from the mass spectrum and combustion analysis), thus indicating the elimination of 1 equiv. of CH_3OH.

The IR spectrum of the solid (as a KBr mull) shows an extended band between ca. 3500 and 1800 cm^{-1}, with peaks at 3010 and 2920 cm^{-1}. The first sharp peaks (of medium intensity) at 1625 cm^{-1} are inconsistent with the value expected for the carbonyl absorption of a carboxylic acid, but in line with a hydroxytropone structure (**20a**). Further indications of this structure were provided by the strong absorptions at 1570, 1535 and 1500 cm^{-1}.[16]

Unambiguous proof of the structure came from the ^1H NMR solution spectrum ($CDCl_3$) which indicates an "enolic" hydroxy group (δ = 7.40 ppm) and the presence of one methoxy group (δ = 4.03 ppm). A symmetrical multiplet, presumably of an AA′BB′ type, centered at δ = 7.05 ppm (cf. δ = 7.04 ppm reported for 3-hydroxytropone[17]), is in accordance with a rapid tautomeric equilibrium through intermolecular proton transfer between the hydroxy and oxo groups (**20a** ⇄ **20a′**). This degenerate isomerization leads to averaged signals in the NMR spectra (C_{2v} pseudosymmetry). However, only three out of the four lines expected from the sp^2 carbon nuclei in the ^{13}C NMR spectrum of **20a** were found. Obviously, the intensities of the averaged signals of the quaternary carbon atoms C-1 and C-3 were too low to be observed.

The cleavage of the ether bridge in **2** can be rationalized by the mechanism shown in Scheme 4. In a protic solvent, formation of the enolate derived from **15a** (= **2**) is reversible, and a second equilibrium is established, which results in the formation of the "oxidocycloheptadienone" **22**. Irreversible elimination of one molecule of methanol gives the delocalized β-tropolonate anion **23**.



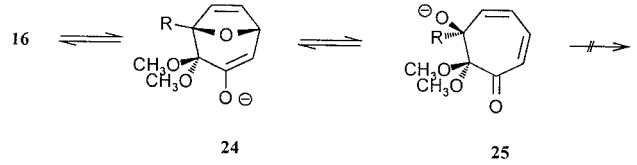
Scheme 4. Cleavage of oxabicyclic oxo acetals **15**: a) KOH, CH_3OH, 65 °C

Similar treatment of the 1-substituted 4,4-dialkoxy ketones **15b**−**d** furnished the 6-substituted 3-hydroxy-2-methoxytropones **20b**−**d** in high yields (Table 3). In analogy to **20a**, the solution NMR spectra showed a reduced number of resonances (i.e. averaged signals), due to the rapid tautomerism between **20** and **20′**. Likewise, the intensity of the averaged signals of the quaternary carbon atoms C-1 and C-3 was too low to be observed.

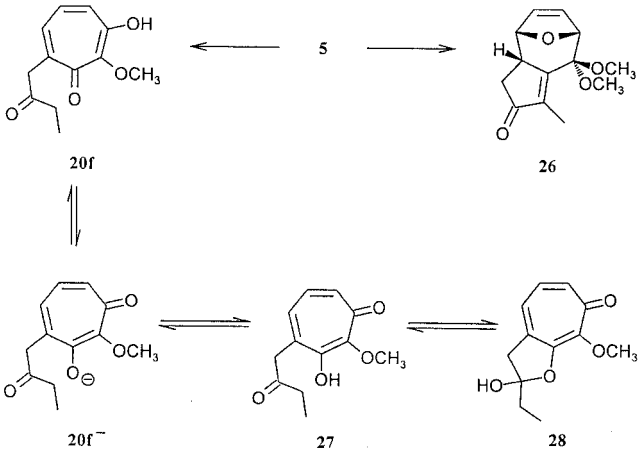
Table 3. Synthesis of 2-alkoxy-3-hydroxytropones **20** by cleavage of 2,2-dialkoxybicyclic compounds

Compound	Reaction time	Product	R^1	R^2	Yield [%]
15a = 2	16 h	**20a**	H	H	85
15b	16 h	**20b**	CH_3	H	84
15c	24 h	**20c**	*i*-C_3H_7	H	78
15d	16 h	**20d**	$BnOCH_2$	H	58
3	12 h	**20e**	H	CH_3	88
5	8 h	**20f**	H	2-oxobutyl	72

The minor alcoholysis products **16b**−**d** did not react under these conditions. Evidently, elimination of methanol is not possible from the cleavage product **25**, which is in equilibrium with **24** and **16**. Hence, when the mixtures from alcoholysis **15** + **16** were treated with water, unchanged **16** could be separated easily from the anions **23** by extraction of the alkaline aqueous phase. Undoubtedly, this separation protocol is preferable to chromatography of the mixtures of **15** and **16**.



However, in contrast, the oxabicyclic compounds **3** and **5**, bearing a substituent in α-position to the carbonyl group (Scheme 1), were transformed to the corresponding hydroxytropones **20e** and **20f** in good yield. In the case of **5**, an oxabicyclic by-product **26** was found, which proved to arise from an intramolecular aldol condensation of this 1,4-diketone (Scheme 5). This epoxyazulenone **26** was formed preferentially on reaction with methanolic KOH under "mild" conditions (room temperature, 3 d) in a 68% yield. Refluxing a solution of **5** in methanolic sodium methoxide for 6 h gave the tropone **20f** as the main product (72% yield), with 16% of **26**.



Scheme 5. Intramolecular aldol condensation versus cleavage of the diketone **5**

Regarding the structure of the compound assigned to formula **20f**, spectroscopy showed that it can exist in rapidly interconverting forms. No absorption in the range expected for the carbonyl band of the oxobutyl side chain was present in the IR spectrum of solid **20f** (cf. **5**: 1715 and 1735 cm^{-1}). This observation, together with the presence of a strong absorption at 3120 cm^{-1}, is consistent with the cyclic hemiacetal form **28**. Obviously the tautomeric form **27**, or rather its anion **20f⁻**, undergoes ring closure (Scheme 5).

The NMR spectra of a [D_6]acetone solution of this mixture were consistent with a rapid equilibrium between the tautomers **20f** and **27** and the hemiacetal **28**, the latter comprising 45% of the mixture. In the ^{13}C NMR spectrum, resonances at δ = 110.9 and 180.2 ppm indicate the "acetalic" carbon atom and the "troponoid" carbonyl carbon atom, respectively. In [D_6]DMSO solution, the exchange is so rapid that no carbon resonances from the tropone nucleus were found. The ^1H NMR spectrum showed a few, very broad signals. Unfortunately, the solubility in $CDCl_3$ was too low to obtain satisfying spectra.

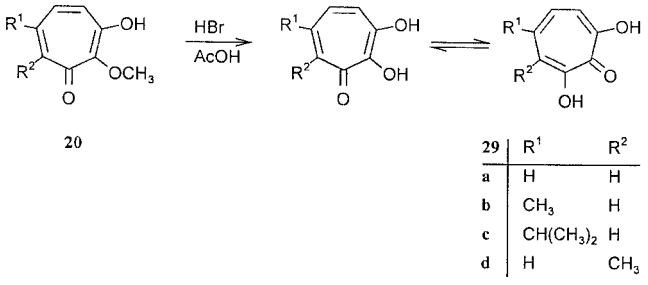
The cleavage of the ethyl and trifluoroethyl oxo acetals prepared from **6b** + **7b** by heating with 10% methanolic KOH led to the ethoxy and trifluoroethoxy analogues of **20b**, in 82 and 90% yield, respectively (see the Exp. Sect.). In other words, the alkoxy substituents were preserved, in accordance with the mechanism shown in Scheme 4.

Demethylation of the Methoxytropones

4-Methyl- and 4-isopropyl-7-methoxy-(α)-tropolone, isomers of the β-tropolones **20b** and **20c**, respectively, have previously been demethylated by HBr/acetic acid to give 2,7-dihydroxy-4-methyltropone (**29b**) and 2,7-dihydroxy-4-isopropyltropone (**29c**).[18] The latter is the natural product β-thujaplicinol, which was isolated from the heartwood of the Western red cedar (*Thuja plicata* Donn.), and other species of the family *Cupressaceae*.[19,20] We therefore treated the methoxytropones **20a**−**c** and **20e** with HBr/acetic acid, and obtained the 7-hydroxytropolones **29a**−**d** in very good yields (> 94%) (Table 4). Banwell's synthesis[18] used expensive organostannanes and palladium catalysts, but our methodology avoids this. However, the present approach hinges on the availability of the substituted furans needed for the [4+3] cycloadducts. A drawback is formation of the "wrong" oxabicyclic compounds **16**, that result in diminished yields of the alkoxytropones **20**.

Table 4. Synthesis of hydroxytropolones **29** by demethylation of 2-alkoxy-3-hydroxytropones **20**

Compound	R^1	R^2	Yield [%]
29a	H	H	94
29b	CH_3	H	> 99
29c	*i*-C_3H_7	H	96
29d	H	CH_3	97



Scheme 6. Demethylation of 3-hydroxy-2-methoxytropones **20**

Conclusions

The cleavage of the α-oxo acetal **2** and its analogues with the formation of 3-hydroxytropones opens a novel route to 2-alkoxy-3-hydroxytropones, which can be dealkylated to give dihydroxytropones. The former are structural isomers of the natural products MY3-469[21] and β-thujaplicinol methyl ether.[22] Several hydroxytropones, among them **20a**, are reported to exhibit interesting pharmacological

properties.[21,23−25] As for the preparation of α-oxo acetals, it is not unreasonable that optimization of the reaction of dichlorooxabicyclic ketones (e.g. **1**) would simplify the hydroxytropone synthesis.

Experimental Section

General Remarks: IR spectra were recorded with a Perkin−Elmer 457 instrument. NMR spectra were recorded with a Bruker AC 250 spectrometer (for 62.9 MHz ^{13}C NMR and 250 MHz ^{1}H NMR spectra) and a Bruker ARX 500 spectrometer (for 500 MHz ^{1}H NMR spectra and 125.8 MHz ^{13}C NMR spectra). Tetramethylsilane was used as an internal standard; the solvents are specified in the text. For higher-order ^{1}H NMR spectra that could not be fully analyzed, chemical shift ranges or, in the case of symmetrical signals, centers of the multiplets (mc) are given. EIMS were recorded with a Varian MAT 711 spectrometer with data system SS 100. Analytical TLC was performed on precoated sheets [Polygram Sil G/UV$_{254}$(silica)], distributed by Macherey−Nagel & Co. (Düren, Germany). Detection was by UV extinction, or by spraying with $KMnO_4$ or vanillin/H_2SO_4 solution, followed by warming. Preparative column chromatography employed Silica 60 (40−63 μm), distributed by Macherey−Nagel & Co. (Düren, Germany). Melting points were determined with a Büchi 510 apparatus from Büchi Laboratoriumstechnik AG (Flawil, Switzerland), and are not corrected. Elemental analyses were performed at the Institut für Organische Chemie, University of Stuttgart. Dry petroleum ether (PE) was distilled (b.p. 40−65 °C). Ethyl acetate (EA) was dried with calcium chloride, distilled, and kept dry over 4-Å molecular sieves. Methanol was dried by refluxing with magnesium turnings, followed by distillation. Ethanol was dried with sodium and diethyl phthalate, followed by distillation. Tetrahydrofuran (THF) was dried with sodium and distilled in presence of benzophenone indicator. Sodium trifluoroethoxide/trifluoroethanol (NaTFE/TFE) was prepared according to the literature method.[8c]. Hexamethylphosphoric acid triamide (HMPA) and diisopropylamine were dried with and distilled from powdered calcium hydride. For the preparation of lithium diisopropylamide (LDA), a 1.6 M solution of *n*-butyllithium in hexane (Merck) was used. Furan and 2-methylfuran (Merck, Fluka) were stored over KOH pellets and distilled from KOH prior to use. 2-Isopropylfuran and 2-(benzyloxymethyl)-furan were prepared according to literature procedures.[26,27] 1,1,3,3-Tetrachloroacetone (1,1,3,3-TeCA) was prepared from 1,1,3-trichloroacetone (Merck, Fluka) and sulfuryl chloride;[28] for an alternative preparation see ref.[29] 1,1,1,3-Tetrachloroacetone (1,1,1,3-TeCA) was obtained by chlorination of 1,1,1-trichloroacetone.[30]

(4-*exo*)-2,2-Dimethoxy-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (3): A solution of LDA (4.9 mmol) in THF (10 mL) was prepared under nitrogen and cooled to 0 °C. With magnetic stirring, a solution of **2** (753 mg, 4.09 mmol) in dry THF (8 mL) was added, and stirred for 30 min. Using a syringe, HMPA (700 μL, 4.0 mmol) was added rapidly, followed by methyl iodide (400 μL, 6.4 mmol), and stirring continued at 0 °C for 2.5 h. The reaction mixture was quenched with 0.5 M HCl (20 mL) and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with saturated solutions of $NaHCO_3$ (15 mL) and NaCl (15 mL) and dried with Na_2SO_4. The solvent was removed in a rotary evaporator, and the remaining yellow oil subjected to chromatography on silica (40 g). Elution with EA/PE (1:7) furnished 665 mg (82%) of **3**, as a colourless oil that solidified on standing. Recrystallization form MTBE/hexane gave a colourless solid with m.p. 37−39 °C. $C_{10}H_{14}O_4$ (198.2): calcd. C 60.59, H 7.12; found C 60.56, H 7.10. IR (KBr): $\tilde{\nu}$ = 3060 (w, =C−H), 2960, 2930, 2890, 2820 (m, C−H), 1715 (s, C=O), 1590 cm^{-1} (w, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 7.4 Hz, 3 H, CH_3), 2.40 (dq, *J* = 7.4, 0.7 Hz, 1 H, H-4), 3.29 (s, 3 H, *endo*-OCH_3), 3.43 (s, 3 H, *exo*-OCH_3), 4.67 (s, 1 H, H-5), 4.95 (d, *J* = 1.8 Hz, 1 H, H-1); AB subspectrum centered at δ = 6.29, with δ_A = 6.37 and δ_B = 6.21 (J_{AB} = 6.0 Hz; the lines of the A-part are split into a dd with *J* = 1.8, 0.5 Hz; the lines of the B-part are split into doublets with *J* = 1.8 Hz, 6-H and 7-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.8 (4-CH_3), 49.5 (C-4), 49.6 (*endo*-OCH_3), 50.8 (*exo*-OCH_3), 80.4 (C-5) 83.0 (C-1), 99.8 (C-2), 129.8 (C-7), 136.2 (C-6), 204.3 (C-3) ppm.

(4-*exo*)-2,2-Dimethoxy-4-(2-oxobutyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (5): A solution of LDA (5.2 mmol) in THF (15 mL) was prepared under nitrogen and cooled to −40 °C. With magnetic stirring, a solution of **2** (800 mg, 4.35 mmol) in dry THF (10 mL) was added. The mixture was stirred for 30 min, and a solution of 2-nitro-1-butene[31] (600 mg, 5.94 mmol) in dry THF (1 mL) was added. The mixture was warmed to 0 °C (2 h) and then stirred for 30 min at this temperature. A solution of concd. H_2SO_4 (10.0 mL) in methanol/water (2:1, 50 mL) was prepared. With vigorous stirring, the THF reaction mixture was added slowly to the acid, which became turquoise-green in colour. When the colour had faded, stirring was continued for 30 min. Ice-cold water (50 mL) and diethyl ether (50 mL) were added, and the layers separated. The aqueous layer was saturated with NaCl and extracted with diethyl ether (4 × 50 mL). The combined diethyl ether extracts were washed with saturated solutions of $NaHCO_3$ (30 mL) and NaCl (30 mL), and dried with Na_2SO_4. The solvent was evaporated, and the remaining orange-coloured oil subjected to chromatography on silica (100 g), eluting with EA/PE (1:7). The colourless oil (**5**, 710 mg, 64%) obtained after evaporation solidified on standing. Recrystallization from MTBE/hexane gave a colourless solid with m.p. 55−56 °C. $C_{13}H_{18}O_5$ (254.3): calcd. C 61.41, H 7.13; found C 61.37, H 7.11. IR (KBr): $\tilde{\nu}$ = 3070, 3060 (m, =C−H), 2980, 2950, 2920, 2890, 2860, 2820 (ms, C−H), 1735, 1715 (s, C=O), 1580 cm^{-1} (w, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 2.46 (q, *J* = 7.3 Hz, 2 H, CH_2CH_3), 2.81 (ddd, *J* = 11.0, 3.0, 0.7 Hz, 1 H, H-4) ppm; AB subspectrum centered at δ = 2.92, with δ_A = 3.20 and δ_B = 2.63 (*J* = 18.1 Hz; the lines of the A-part are split into doublets with *J* = 11.0 Hz; the lines of the B-part are split into doublets with *J* = 3.0 Hz, 4n-H and 4x-H), 3.31 (s, 3 H, *endo*-OCH_3), 3.45 (s, 3 H, *exo*-OCH_3), 4.78 (d, *J* = 0.6 Hz, 1 H, H-5), 4.91 (d, *J* = 1.8 Hz, 1 H, H-1) ppm; AB subspectrum centered at δ = 6.31, with δ_A = 6.41 and δ_B = 6.20 (*J* = 6.1 Hz; the lines of the A-part are split into a dd with *J* = 1.6, 0.5 Hz; the lines of the B-part are split into doublets with *J* = 1.6 Hz, 6-H and 7-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.8 (CH_2CH_3), 36.1 (CH_2CH_3), 41.2 (CH_2 at C-4), 49.8 (C-4), 50.2 (*endo*-OCH_3), 50.5 (*exo*-OCH_3), 80.1 (C-5), 80.6 (C-1), 99.6 (C-2), 129.9 (C-7), 136.2 (C-6), 203.6 (C-3), 208.3 (C=O) ppm.

(4-*endo*)-2,2,4-Trichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (6an): 1,1,3,3-TeCA (19.60 g, 100 mmol) was mixed with furan (34.0 g, 500 mmol) and TFE (5 mL) and cooled in an ice bath. A 2 M solution of NaTFE in TFE (50 mL, 100 mmol) was added dropwise with vigorous magnetic stirring over 2 h. The mixture was stirred for a further 30 min and then diluted with water (50 mL) and dichloromethane (50 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with brine (2 × 40 mL), dried

with Na_2SO_4 and concentrated in a rotary evaporator. Recrystallization of the remaining brown solid gave 13.51 g (59%) of **6an**. The brown residue from the mother-liquor was filtered through silica (40 g), eluting with EA/PE (1:5). The residue of the eluate was recrystallized from methanol, giving a further 2.89 g of **6an**. Total yield 16.40 g (72%) **6an** as a pale yellow solid that was pure enough (> 99%) for further reactions. Colourless crystals with m.p. 87−88 °C were obtained by sublimation at 70 °C/0.001 Torr (ref.[7] 88−89 °C). IR (KBr): $\tilde{\nu}$ = 3080 (m−w, =C−H), 2920 (m, C−H), 1745 cm^{-1} (s, C=O). ^1H NMR (250 MHz, $CDCl_3$): AB subspectrum centered at δ = 5.14, with δ_A = 5.15 (H-4) and δ_B = 5.13 (H-5) (J_{AB} = 4.6 Hz; the lines of the B-part are split into doublets with J = 1.4 Hz); δ = 5.16 (d, J = 1.7 Hz, 1 H, H-1), AB subspectrum centered at δ = 6.56, with δ_A = 6.63 (H-7) and δ_B = 6.51 (H-6) (J_{AB} = 6.0 Hz; the lines of the A-part are split into doublets with J = 1.8 Hz; the lines of the B-part are split into doublets with J = 1.2 Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 61.7 (C-4), 82.65 (C-5), 85.1 (C-2), 87.4 (C-1), 132.9 and 134.9 (C-6 and C-7), 186.2 (C-3) ppm.

Reaction of 1,1,3,3-TeCA with 2-Methylfuran: (4-*endo*)-2,2,4-Trichloro-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (6bn) and (2-*endo*)-2,4,4-Trichloro-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (7bn)

Method a): 1,1,3,3-TeCA (7.8 g, ca. 40 mmol) was mixed with 2-methylfuran (18 mL, 200 mmol) and cooled in an ice bath to 0 °C. A 2 M solution of NaTFE in TFE (20 mL, 40 mmol) was added dropwise with vigorous magnetic stirring over 45 min. The mixture was stirred at 0 °C for further 2 h, and then diluted with water (40 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried with Na_2SO_4 and concentrated in a rotary evaporator. The brown residue was filtered through silica (40 g), eluting with PE/EA (3:1). The residue from the eluate was recrystallized from PE/EA, giving 4.45 g (46%) of pale yellow crystals, a mixture of isomers **6bn** and **7bn** (70:30), according to the NMR spectra. Fractional crystallization from methanol gave 750 mg (8%) of colourless rhombic crystals (**6bn**) with m.p. 91−94 °C (ref.[7] 93−94 °C). **6bn:** ^1H NMR (250 MHz, $CDCl_3$): δ = 1.77 (s, 1-CH_3), AB subspectrum with δ_A = 5.14 (H-4), δ_B = 5.08 (H-5) (J_{AB} = 4.5 Hz, centre at δ = 5.11 ppm). The lines of the B part are duplicated with J = 1.7 Hz. AB subspectrum with δ_A = 6.51 (H-6), δ_B = 6.32 (H-7) (J_{AB} = 5.9 Hz, centre at δ = 6.41 ppm). The lines of the A part are duplicated with J = 1.6 Hz. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.5 (1-CH_3), 61.2 (C-4), 82.5 (C-2), 90.3 (C-1), 91.7 (C-5), 134.15 and 136.5 (C-6 and C-7), 186.6 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3080, 2990, 2970, 2930 (CH), 1755 with shoulder at 1740 cm^{-1} (C=O). The fractions enriched with the isomer **7bn** (280 mg) were subjected to MPLC on silica using a 20 cm column, diameter 2.5 cm, packed with LiChroprep Si 60, 15−25 mμ (Merck). Elution was made with PE/EA (4:96) under pressure (10 bar). The residue of the eluates that contained pure **7bn** (32 mg) was dissolved in $CDCl_3$ to record the NMR spectra. **7bn:** ^1H NMR (250 MHz, $CDCl_3$): δ = 1.69 (s, 1-CH_3), 4.90 (s, 1 H, H-2), 5.14 (d, $J_{5,6}$ = 1 Hz, 1 H, H-5), 6.39 (mc, 2 H, H-6, H-7) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.55 (1-CH_3), 67.5 (C-2), 84.6 (C-1), 87.1 (C-4), 89.7 (C-5), 132.05 and 138.0 (C-6, C-7), 186.4 (C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3090, 2960, 2910 (CH), 1750, 1730 cm^{-1} (C=O) cm^{-1}.

X-ray Crystallographic Study of 6bn:[9] The $CDCl_3$ solution was transferred to a small test tube (5 × 0.5 cm) and concentrated slowly. The compound crystallized with space group $P2_12_12_1$ with Z = 4 molecules/unit cell and had m.p. 120−121 °C. A crystal (1.0 × 0.9 × 0.8 mm) was selected and fixed onto a thin glass capillary. For the X-ray crystal structure determination a Nicolet P3 four-circle diffractometer equipped with a graphite monochromator was used, at 293 K. The X-ray source was monochromatic Mo-K_α radiation, wavelength 71.069 pm. The lattice constants were a = 702.49(10), b = 1040.24(14), c = 1329.06(17) pm, determined from the 2θ values of 30 automatically centered reflexes (30° < 2θ < 35°) by means of the least-squares method;[32] the crystal lattice was orthorhomic. The intensity data were taken in the Wyckoff-scan mode with a 1° angle range and scan rates between 1.0 and 29.3 °/min, depending on reflection intensity. Thus, up to a maximum scattering angle $2\theta_{max.}$ = 55°, 1637 independent reflections were found; among these 1552 with $I_{obsd.} > 3\sigma(I_{obsd.})$ were classified as "observed". The raw data were scaled from three check reflections − the largest deviation was 3% − and subjected to a Lorentz and polarization correction. By means of direct methods (SHELX 86)[33] a structure model was obtained that was refined by the full-matrix least-squares procedure. In addition to the observed data further reflexes with intensities $> 4\sigma(I_{obsd.})$ were used. Thus 1577 reflexes contributed to refinement of 147 parameters (scaling factor, position parameter, anisotropic temperature factors for C, O, and Cl atoms, isotropic temperature factors for H atoms) up to R = 0.030 and R_w = 0.034, respectively, with $1/w = 0.1 + \sigma(F)^2 + 10^{-4}F + 10^{-6}F^2 + (3 \times 10^{-5})F^3$. The estimated overall standard deviation of an observation with weight one was σ = 1.11.

Method b): 1,1,3,3-TeCA (1.96 g, 10 mmol) was mixed with 2-methylfuran (4.1 g, ca. 50 mmol) and cooled in an ice bath to 0 °C. A 1 M solution of NaTFE in TFE (10 mL, 10 mmol) was added dropwise with vigorous magnetic stirring over 1 h. The mixture was stirred at 0 °C for further 30 min, and then diluted with water (30 mL) and dichloromethane (30 mL). The layers were separated, and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated in a rotary evaporator. The brown residue was filtered through silica (50 g), eluting with PE/EA (10:1). The residue from the eluate was recrystallized from methanol, giving 1.57 g (65%) of a mixture of isomers **6bn** and **7bn** (2:1), according to the ^1H NMR spectrum. This mixture was used for preparation of the oxo acetals **15b** and **16b** (see below).

Reaction of 1,1,1,3-Tetrachloroacetone with 2-Methylfuran: A mixture of 1,1,1,3-tetrachloroacetone[30] (2.85 g, 14.5 mmol) and 2-methylfuran (5.95 g, 72.5 mmol) was treated with a 2 M NaTFE solution in TFE for 2 h, as described for 1,1,3,3-TeCA (see above, first experiment). The same workup afforded 1.78 g (51%) of an isomeric mixture of **6bn**+**7bn** in the ratio of 67:33, according to the ^1H NMR spectrum.

Reaction of 1,1,3,3-TeCA with 2-Isopropylfuran: (4-*endo*)-2,2,4-Trichloro-1-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (6cn) and (2-*endo*)-2,4,4-Trichloro-1-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (7cn): Prepared from 2-isopropylfuran[26] (880 mg, 8.0 mmol) in TFE (8 mL), and 1,1,3,3-TeCA (1.88 g, 9.6 mmol) with 1 M NaTFE solution in TFE (9.6 mL, 9.6 mmol), as described for **6b**. The solution of base was added over 45 min, followed by 30 min of stirring. The brown, oily product was subjected to chromatography on silica (100 g), eluting with EA/PE (1:10). The regioisomers **6cn** (1.03 g) and **7cn** (307 mg) were obtained with yields of 48% and 14%, respectively. After recrystallization from methanol the isomers showed m.p. 72 °C (**6cn**) and 98 °C (**7cn**). **6cn:** $C_{10}H_{11}Cl_3O_2$ (269.6): calcd. C 44.56, H 4.11, Cl 39.46; found C 44.59, H 4.16, Cl 40.41. IR (KBr): $\tilde{\nu}$ = 3080 (s, =C−H), 2960, 2920, 2860 (m, C−H), 1750 (s, C=O), 1590 cm^{-1} (s, C=C). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.9 Hz, 3 H, CH_3), 1.20 (d, J = 7.0 Hz, 3 H, CH_3), 2.71 [sept, J = 6.9 Hz, 1 H, CH(CH_3)$_2$] ppm; AB subspectrum

centered at δ = 5.11, with δ_A = 5.13 (H-4) and δ_B = 5.09 (H-5) (J_{AB} = 4.6 Hz; the lines of the B-part are split into doublets with J = 1.5 Hz); AB subspectrum centered at δ = 6.41, with δ_A = 6.49 (H-6) and δ_B = 6.34 (H-7) (J_{AB} = 6.0 Hz; the lines of the A-part are split into doublets with J = 1.4 Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.7 and 20.2 (diastereotopic CH_3), 29.9 [*C*H(CH_3)$_2$], 61.3 (C-4), 82.2 (C-5), 90.6 (C-1), 96.0 (C-2), 133.7 and 134.6 (C-6 and C-7), 186.9 (C-3) ppm. **7cn:** IR (KBr): ṽ = 3090 (w, =C−H), 2960, 2850 (m, C−H), 1740 (s, C=O), 1590 cm^{-1} (w, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08 (d, J = 6.9 Hz, 3 H, CH_3), 1.27 (d, J = 7.0 Hz, 3 H, CH_3), 2.74 [sept, J = 6.9 Hz, C*H*(CH_3)$_2$], 4.15 (d, J = 1.0 Hz, H-2), 5.06 (mc, H-5) ppm; AB subspectrum centered at δ = 6.39, with δ_A = 6.45 (H-7) and δ_B = 6.32 (H-6) (J_{AB} = 6.0 Hz; the lines of the B-part are split into a dd with J = 1.8 Hz and 0.6 Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.5 (CH_3), 20.05 (CH_3) (diastereotopic CH_3), 30.5 [*C*H(CH_3)$_2$], 56.3 (C-2), 82.6 (C-5), 88.0 (C-1), 95.6 (C-4), 132.5 and 135.3 (C-6 and C-7), 190.3 (C-3) ppm.

Reaction of 1,1,3,3-TeCA with 2-Benzyloxymethylfuran: (4-*endo*)-1-Benzyloxymethyl-2,2,4-trichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (6dn) and (2-*endo*)-1-Benzyloxymethyl-2,4,4-trichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (7dn): Prepared from 2-(benzyloxymethyl)-furan[27] (1.69 g, 9.0 mmol) in TFE (10 mL) and 1,1,3,3-TeCA (980 mg, 5.0 mmol) with 1 M NaOTFE solution in TFE (5 mL, 5 mmol), as described for **6b**. The time taken for the addition was 45 min, followed by 30 min of stirring. The brown, oily product was subjected to chromatography on silica (50 g), eluting with EA/PE (1:10). Separation was not successful; according to the ^{1}H NMR the oil obtained (1.48 g, ca. 78%) consisted of the regioisomers **6dn** and **7dn**, in the ratio of 1.2:1, and impurities (ca.10%). This impure product mixture was used for the methanolysis procedure described below. IR ($CDCl_3$): ṽ = 3080, 3050, 3020 (mw, =C−H), 2930, 2910, 2850 (m, C−H), 1765 (s, C=O), 1590 cm^{-1} (w, C=C). **6dn:** ^{1}H NMR (500 MHz, $CDCl_3$): AB subspectrum with δ_A = 4.08, δ_B = 4.27 (J_{AB} = 11.4 Hz, diastereotopic CH_2OBn); AB subspectrum with δ_A = 4.72, δ_B = 4.60 (J_{AB} = 12.1 Hz, diastereotopic PhCH_2); AB subspectrum centered at δ = 5.15, with δ_A = 5.16 (H-5) and δ_B = 5.14 (H-4) (J_{AB} = 4.5 Hz; the lines of the A-part are split into doublets with J = 1.7 Hz); AB subspectrum centered at δ = 6.49, with δ_A = 6.55 (H-6) and δ_B = 6.42 (H-7) (J_{AB} = 5.9 Hz; the lines of the A-part are split into doublets with J = 0.9 Hz), 7.25−7.40 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 61.3 (C-4), 67.2 (*C*H$_2$OBn), 73.9 (Ph*C*H$_2$), 82.4 (C-5), 87.6 (C-2), 92.0 (C-1), 128.0, 128.48 and 128.50 (phenyl-C), 133.5 and 134.4 (C-6 and C-7), 186.0 (C-3) ppm. **7dn:** ^{1}H NMR (500 MHz, $CDCl_3$): AB subspectrum with δ_A = 3.76, δ_B = 3.99 (J_{AB} = 11.2 Hz, diastereotopic CH_2OBn); AB subspectrum with δ_A = 4.70, δ_B = 4.62, J_{AB} = 12.1 Hz (diastereotopic PhCH_2); 5.20 (d, J = 1.7 Hz, 1 H, H-5), 5.31 (s, 1 H, H-2) ppm; AB subspectrum centered at δ = 6.39, with δ_A = 6.45 (H-6) and δ_B = 6.32 (H-7) (J_{AB} = 6.0 Hz; the lines of the A-part are split into doublets with J = 1.8 Hz); 7.25−7.40 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 62.8 (C-2), 68.5 (*C*H$_2$OBn), 73.9 (Ph*C*H$_2$), 87.5 (C-5), 89.4 (C-4), 93.9 (C-1), 127.7, 127.9 and 127.95 (phenyl-C), 133.9 and 137.3 (C-6 and C-7), 186.9 (C-3) ppm.

Reaction of 6a with Sodium Methoxide: (4-*endo*)- and (4-*exo*)-4-Chloro-2,2-dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (13a): A 1 M solution of sodium methoxide in methanol (22 mL) was added dropwise with stirring over 2 h to a cooled solution (0 °C) of **6a** (2.275 g, 10.0 mmol) in dry methanol (50 mL). The mixture was stirred for further 30 min, diluted with water (50 mL) and extracted with dichloromethane (4 × 25 mL). The combined extracts were washed with brine, dried with Na_2SO_4 and concentrated in a rotary evaporator. The remaining yellow oil became crystalline and was recrystallized from diethyl ether/pentane, giving 1.46 g (67%) of **13an** as a colourless solid with m.p. 56−57 °C. Chromatography of the mother liquor on silica (50 g) with EA/PE (1:5) gave a further 370 mg (17%) of **13an** and 196 mg (9%) of **13ax** with m.p. 73−74 °C. $C_9H_{11}ClO_4$ (218.6): calcd. C 49.44, H 5.07, Cl 16.22; found C 49.66, H 5.13, Cl 16.27. **13an:** IR (KBr): ṽ = 3080 (m, =C−H), 2980, 2960, 2920, 2830, 2820 (ms, C−H), 1745 (s, C=O), 1585 cm^{-1} (m, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.38 (s, 3 H, *endo*-OCH_3), 3.52 (s, 3 H, *exo*-OCH_3), 4.79 (d, J = 4.5 Hz, 1 H, H-4), 4.96 (d, J = 1.7 Hz, 1 H, H-1), 5.05 (dd, J = 4.5, 1.6 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.39, with δ_A = 6.46 (H-7) and δ_B = 6.33 (H-6) (J_{AB} = 6.1 Hz; the lines of the A-part are split into doublets with J = 1.8 Hz, the B-part with 1.6 Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 50.6 (*endo*-OCH_3), 51.1 (*exo*-OCH_3), 62.8 (C-4), 80.7 (C-5), 82.5 (C-1), 102.7 (C-2), 132.7 and 133.4 (C-6 and C-7), 194.45 (C-3) ppm. **13ax:** IR (KBr): ṽ = 3070 (m, =C−H), 2970, 2940, 2920, 2810 (m, C−H), 1735 (s, C=O), 1585 cm^{-1} (m, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.35 (s, 3 H, *endo*-OCH_3), 3.44 (s, 3 H, *exo*-OCH_3), 3.93 (d, J = 1.1 Hz, 1 H, H-4), 5.01 (s, 1 H, H-5), 5.05 (d, J = 1.8 Hz, 1 H, H-1) ppm; AB subspectrum centered at δ = 6.37, with δ_A = 6.39 (H-7) and δ_B = 6.34 (H-6) (J_{AB} = 6.1 Hz; the lines of the A-part are split into doublets with J = 1.8 Hz, the B-part with J = 1.5 Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 49.5 (*endo*-OCH_3), 51.5 (*exo*-OCH_3), 56.6 (C-4), 80.7 (C-5), 82.6 (C-1), 100.4 (C-2), 132.55 and 133.55 (C-6 and C-7), 194.6 (C-3) ppm.

2,3,3-Trimethoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-carbaldehyde (19): A solution of 2 M sodium methoxide in methanol (6.0 mL) was added with stirring over 10 min to a cooled (0 °C) solution of **6an** (455 mg, 2.0 mmol) in dry methanol (6 mL). Stirring was continued for a further 30 min. The ice bath was then removed, and the mixture stirred at room temperature for 5 d. Water (20 mL) was added, and the mixture extracted with dichloromethane (5 × 20 mL). The combined extracts were washed with brine, dried with Na_2SO_4 and concentrated in a rotary evaporator. The remaining pale yellow oil was chromatographed on silica (20 g). Elution with PE/EA (2:1) gave 160 mg (37%) of **19** as a colourless solid with m.p. 100−110 °C. $C_{10}H_{14}O_5$ (214.2): calcd. C 56.07, H 6.59; found C 55.99, H 6.56. IR (KBr): ṽ = 2940, 2910, 2820, 2710 (ms, C−H), 1720 (s, C=O), 1570 cm^{-1} (C=C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.26 (s, 3 H, CH_3O at C-2), 3.36 (s, 3 H, *endo*-OCH_3 at C-3), 3.39 (s, 3 H, *exo*-OCH_3 at C-3), 4.93 (s, 1 H, H-1), 5.22 (s, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.59, with δ_A = 6.62 and δ_B = 6.56 (J_{AB} = 5.8 Hz; the lines of the A-part are split into doublets with J = 1.9 Hz, the B-part with 1.7 Hz, 5-H and 6-H); 9.60 (s, 1 H, C*H*O) ppm. ^{13}C NMR/DEPT (125.8 MHz, $CDCl_3$): δ = 50.4 (CH_3O at C-2), 51.5 (*endo*-OCH_3 at C-3), 53.8 (*exo*-OCH_3 at C-3), 78.6 (C-1), 80.2 (C-5), 88.4 (C_q, C-2), 110.6 (C_q, C-3), 133.3 and 135.5 (C-5 and C-6), 199.25 (*C*HO) ppm.

Methanolysis and Dechlorination of 6an: 2,2-Dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (2): A 2 M solution of sodium methoxide in methanol (6 mL, 12 mmol) was added with stirring over 10 min to a cooled solution (0 °C) of **6an** (1.138 g, 5 mmol) in dry methanol (15 mL). After stirring for further 30 min, acetic acid (1 mL) and water (3 mL) were added, and the ice bath removed. With continuous stirring, zinc dust (3.0 g, 46 mmol) was added in portions. After 18 h of stirring at room temperature, the heterogeneous mixture was filtered through a sintered glass frit. The filtrate was diluted with water (30 mL) and extracted with dichloromethane (5 × 100 mL). The combined extracts were washed with saturated solu-

tions of $NaHCO_3$ and NaCl and dried with Na_2SO_4. The solvent was evaporated in vacuo, and the remaining pale yellow oil filtered through silica (15 g). Elution with EA/PE (1:5) afforded 890 mg (97%) of **2**, as a colourless solid. The ^{13}C NMR and ^1H NMR spectra were in agreement with that reported,[1] and showed practically no impurities. Recrystallization from MTBE/hexane gave a solid with m.p. 49−50 °C.

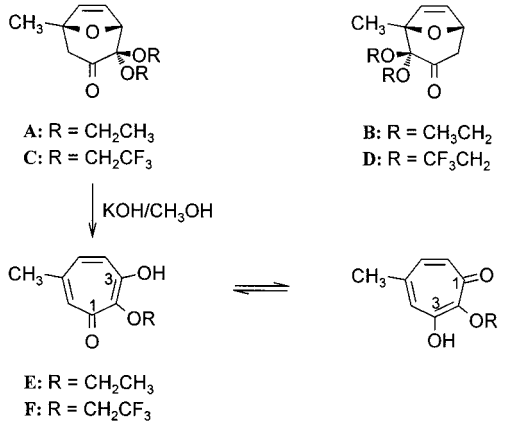
Methanolysis and Dechlorination of 6b+7b: 2,2-Dimethoxy-5-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (15b) and 2,2-Dimethoxy-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (16b): Prepared from the regioisomeric mixture **6bn+7bn** (723 mg, 3.0 mmol) in dry methanol (10 mL) and 2 M sodium methoxide solution in methanol (4.0 mL, 8.0 mmol), followed by zinc dust (2.0 g, 31 mmol), as described for **6an → 2**. The colourless, oily product was chromatographed on silica (100 g). Elution with EA/PE (1:8) afforded 374 mg (63%) of colourless solid **15b** and 190 mg (32%) of oily, colourless **16b**. The main isomer **15b** was recrystallized from MTBE/pentane; m.p. 52 °C. **15b:** $C_{10}H_{14}O_4$ (198.2): calcd. C 60.59, H 7.12; found C 60.33, H 7.23. IR (KBr): $\tilde{\nu}$ = 3080 (w, =C−H), 2980, 2960, 2950, 2920, 2810 (m, C−H), 1730 (s, C=O), 1590 cm^{-1} (w, C=C). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.51 (s, 3 H, CH_3) ppm; AB subspectrum centered at δ = 2.59, with δ_A = 2.78 (4x-H) and δ_B = 2.39 (4n-H) (J_{AB} = 15.3 Hz); 3.32 (s, 3 H, *endo*-OCH_3), 3.46 (s, 3 H, *exo*-OCH_3), 4.95 (d, *J* = 1.1 Hz, 1 H, H-1), 6.14 (mc, 2 H, H-6 and H-7) ppm. ^{13}C NMR/off-resonance (62.9 MHz, $CDCl_3$): δ = 22.5 (5-CH_3), 50.0 (*endo*-OCH_3), 50.45 (CH_2, C-4), 50.9 (*exo*-OCH_3), 80.6 (CH, C-1), 85.0 (C_q, C-5), 99.1 (C_q, C-2), 129.7 (CH, C-7), 139.1 (CH, C-6) (C-6 and C-7), 201.0 (C_q, C-3) ppm. **16b:** IR (film): $\tilde{\nu}$ = 2960, 2920, 2820 (m, C−H), 1725 cm^{-1} (s, C=O). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.54 (s, 3 H, CH_3) ppm; AB subspectrum centered at δ = 2.64, with δ_A = 2.88 (4x-H) and δ_B = 2.40 (4n-H) (J_{AB} = 15.8 Hz; the lines of the A-part are split into doublets with *J* = 4.8 Hz, the B-part with 1.1 Hz); 3.37 (s, 3 H, *exo*-OCH_3), 3.48 (s, 3 H, *endo*-OCH_3), 4.97 (dd, *J* = 4.8, 1.3 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.16, with δ_A = 6.28 (H-6) and δ_B = 6.05 (H-7) (J_{AB} = 5.9 Hz; the lines of the A-part are split into doublets with *J* = 1.7 Hz) ppm. ^{13}C NMR/off-resonance (62.9 MHz, $CDCl_3$): δ = 17.2 (1-CH_3), 45.6 (CH_2, C-4), 52.2 (*endo*-OCH_3), 53.5 (*exo*-OCH_3), 78.2 (CH, C-5), 88.7 (C_q, C-1), 101.9 (C_q, C-2), 135.0 (CH), 135.3 (CH) [C-6 and C-7], 202.65 (C_q, C-3) ppm.

Methanolysis and Dechlorination of 6cn+7cn: 1-Isopropyl-4,4-dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (15c): Prepared from the regioisomeric mixture **6cn+7cn** (1.16 g, 4.32 mmol) in dry methanol (15 mL) and 2 M NaOMe solution in MeOH (5.0 mL, 10.0 mmol), followed by zinc dust (2.0 g, 31 mmol), as described for **6an → 2**. The yellow oily product was filtered through silica (20 g). Elution with EA/PE (1:7) gave 904 mg (93%) of **15c** as a colourless solid. Recrystallization from hexane gave crystals with m.p. 46−47 °C. $C_{12}H_{18}O_4$ (226.3): calcd. C 63.70, H 8.02; found C 63.66, H 7.99. IR (KBr): $\tilde{\nu}$ = 3080 (w, C−H), 2950, 2920, 2880, 2820 (m, C−H), 1725 (s, C=O), 1590 cm^{-1} (s, C=C). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.97 (d, 3 H, CH_3, *J* = 6.9 Hz), 1.00 (d, *J* = 6.9 Hz, 3 H, CH_3), 2.01 [dt, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$] ppm; AB subspectrum centered at δ = 2.58, with δ_A = 2.73 (2x-H) and δ_B = 2.43 (2n-H) (J_{AB} = 15.2 Hz); 3.31 (s, 3 H, *endo*-OCH_3), 3.45 (s, 3 H, *exo*-OCH_3), 4.97 (d, *J* = 1.8 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.17, with δ_A = 6.20 (H-7) and δ_B = 6.17 (H-6) (J_{AB} = 6.0 Hz; the lines of the B-part are split into doublets with *J* = 1.8 Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.3 (CH_3), 17.6 (CH_3), 32.9 [$CH(CH_3)_2$], 46.9 (C-2), 49.9 (*endo*-OCH_3), 51.0 (*exo*-OCH_3), 80.35 (C-5), 91.0 (C-1), 99.3 (C-4), 129.8 (C-6), 136.5 (C-7), 201.7 (C-3) ppm.

Methanolysis and Dechlorination of 6dn+7dn: 1-Benzyloxymethyl-4,4-dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (15d) and 1-Benzyloxymethyl-2,2-dimethoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (16d): Prepared from the crude regioisomeric mixture **6dn+7dn** (1.48 g, ca. 3.9 mmol) in dry methanol (15 mL) and a 2 M NaOMe solution in MeOH (4.0 mL), followed by zinc powder (2.0 g, 31 mmol), as described for **6an → 2**. The colourless, oily product was chromatographed on silica (50 g). Elution with EA/PE (1:7) gave 802 mg (67%) of solid colourless **15d** and 120 mg (8%) of colourless, oily **16d**. The main isomer **15d** was recrystallized from MTBE/hexane: m.p. 46−48 °C. **15d:** $C_{17}H_{20}O_5$ (304.3): calcd. C 67.09, H 6.62; found C 67.13, H 6.62. IR (KBr): $\tilde{\nu}$ = 2980, 2960, 2930, 2890, 2850 2820, 2780 (wm, C−H), 1735 cm^{-1} (s, C=O). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.39 (d, *J* = 15.4 Hz, 1 H, *endo*-H-2), 2.86 (d, *J* = 15.4 Hz, 1 H, *exo*-H-2), 3.32 (s, 3 H, *endo*-OCH_3), 3.46 (s, 3 H, *exo*-OCH_3) ppm; AB subspectrum centered at δ = 3.66, with δ_A = 3.68 and δ_B = 3.64 (J_{AB} = 10.5 Hz, diastereotopic CH_2OBn); 4.62 (s, 2 H, OCH_2Ph), 5.01 (d, *J* = 1.8 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.22, with δ_A = 6.23 (H-7) and δ_B = 6.21 (H-6) (J_{AB} = 6.0 Hz; the lines of the B-part are split into doublets with *J* = 1.8 Hz); 7.26−7.34 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 46.3 (C-2), 50.1 (*endo*-OCH_3), 50.9 (*exo*-CH_3), 71.3 (CH_2OBn), 73.6 (PhCH_2), 80.7 (C-5), 87.4 (C-1), 99.4 (C-4), 127.7, 128.4 and 130.4 (phenyl-C), 127.8 (C-6), 136.5 (C-7), 200.8 (C-3) ppm. **16d:** IR ($CDCl_3$): 3010 (w, =C−H), 2950, 2920, 2900, 2830 (m, C−H), 1725 cm^{-1} (s, C=O). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.42 (dd, *J* = 16.1, 1.0 Hz, 1 H, *endo*-H-4), 2.90 (dd, *J* = 16.1, 4.9 Hz, 1 H, *exo*-H-4), 3.36 (s, 3 H, *endo*-OCH_3), 3.44 (s, 3 H, *exo*-OCH_3) ppm; AB subspectrum centered at δ = 3.94, with δ_A = 4.02 and δ_B = 3.86 (J_{AB} = 11.2 Hz, diastereotopic CH_2OBn); AB subspectrum centered at δ = 4.63, with δ_A = 4.69 and δ_B = 4.57 (J_{AB} = 12.4 Hz, diastereotopic PhCH_2); 5.07 (d, *J* = 5.0 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.27, with δ_A = 6.34 (H-6) and δ_B = 6.21 (H-7) (J_{AB} = 6.0 Hz; the lines of the A-part are split into doublets with *J* = 1.5 Hz); 7.26−7.36 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 45.8 (C-4), 54.0 (OCH_3), 67.65 (CH_2OBn), 73.8 (PhCH_2), 78.0 (C-5), 92.3 (C-1), 102.05 (C-2), 127.6, 127.65 and 128.4 (phenyl-C), 132.5 (C-7), 135.6 (C-6), 202.5 (C-3) ppm.

Ethanolysis and Dechlorination of (6bn+7bn): 2,2-Diethoxy-5-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (A) and 2,2-Diethoxy-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (B): The mixture of regioisomers **6bn+7bn** (483 mg, 2.0 mmol, see above) in dry ethanol (10 mL) was treated with 1 M ethanolic sodium ethoxide (5.0 mL, 5.0 mmol), followed by zinc powder (2.0 g, 31 mmol), as described for **6an**. The colourless oil obtained after usual workup was chromatographed on silica (50 g). Elution with EA/PE (1:8) gave 326 mg (72%) of solid **A** and 110 mg (24%) of oily **B.** The main regioisomer **A** was recrystallized from MTBE/hexane and showed m.p. 63−65 °C. **A:** $C_{12}H_{18}O_4$ (226.3): calcd. C 63.70, H 8.02; found C 63.55, H 8.13. IR (KBr): $\tilde{\nu}$ = 3070 (m, =C−H), 2990, 2950, 2910, 2880, 2840 (m, C−H), 1730 (s, C=O), 1590 cm^{-1} (w, C=C). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.233 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3), 1.236 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.50 (s, 3 H, 1-CH_3) ppm; AB subspectrum centered at δ = 2.59, with δ_A = 2.79 (4x-H) and δ_B = 2.39 (4n-H) (J_{AB} = 15.2 Hz); AB part of an ABX_3 subspectrum from *endo*-OCH_2CH_3, with δ_A = 3.45, δ_B = 3.18 (J_{AB} = 9.4, J_{AX} = J_{BX} = 7 Hz); AB part of an ABX_3 subspectrum from *exo*-OCH_2CH_3, with δ_A = 3.91, δ_B = 3.65 (J_{AB} = 9.6, J_{AX} = J_{BX} = 7 Hz); 4.93 (d, *J* = 1.3 Hz, 1 H, H-1), 6.13 (mc, 2 H, H-6 and H-7) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.1 (*endo*-OCH_2CH_3), 15.6 (*exo*-OCH_2CH_3), 22.6 (5-CH_3), 50.6 (C-4), 57.9 (*endo*-OCH_2CH_3), 58.7 (*exo*-OCH_2CH_3), 81.2 (C-1), 84.9 (C-5), 99.2 (C-

2), 130.2 (C-7), 138.85 (C-6), 201.4 (C-3) ppm. **B:** IR (film): $\tilde{\nu}$ = 3070 (m, =C−H), 2960, 2920, 2880 (s, C−H), 1725 (s, C=O), 1590 cm^{-1} (w, C=C). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.22 (m, overlapping t, 6 H, OCH_2CH_3), 1.53 (s, 3 H, 1-CH_3), 2.38 (dd, J = 16.0, 1.1 Hz, 1 H, *endo*-H-4) 2.87 (dd, J = 15.9, 4.8 Hz, 1 H, *exo*-H-4), 3.44−3.51 (m, 1 H, OCH_2CH_3), 3.65−3.79 (m, 3 H, OCH_2CH_3), 4.95 (d, J = 5.0 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.15, with δ_A = 6.26 (H-6) and δ_B = 6.05 (H-7) (J_{AB} = 5.9 Hz; the lines of the A-part are split into doublets with J = 1.6 Hz) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.3 (*endo*-OCH_2CH_3), 15.9 (*exo*-OCH_2CH_3), 16.9 (1-CH_3), 45.8 (C-4), 59.7 (*endo*-OCH_2CH_3), 61.3 (*exo*-OCH_2CH_3), 78.1 (C-5), 88.9 (C-1), 101.9 (C-2), 135.0 and 135.3 (C-6 and/or C-7), 203.4 (C-3) ppm.



Trifluoroethanolysis and Dechlorination of (6b+7b): 1-Methyl-4,4-bis(2,2,2-trifluoroethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (C) and 1-Methyl-2,2-bis(2,2,2-trifluoroethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (D): The mixture of regioisomers **6bn**+**7bn** (725 mg, 3.0 mmol, see above) in dry TFE (15 mL) was treated with a 1 M solution of sodium trifluoroethoxide in TFE (5.0 mL, 5.0 mmol) for 6 h, as described for **6an**. Then the filtered mixture was treated with acetic acid (0.5 mL) and concentrated in vacuo. The liquid (ca. 2 mL) was diluted with methanol (10 mL) and water (1 mL); zinc powder (2.0 g, 31 mmol) was then added. After 24 h of stirring at room temperature, the heterogeneous mixture was filtered through a sintered glass frit. The filtrate was diluted with water (30 mL) and extracted with dichloromethane (5 × 100 mL). The combined extracts were washed with saturated solutions of $NaHCO_3$ and NaCl and dried with Na_2SO_4. The solvent was evaporated in vacuo, and the remaining colourless oil filtered through silica (40 g). Elution with EA/PE (1:10) afforded 805 mg (80%) of **C**, and 157 mg (16%) of colourless oily **D**. The main regioisomer **C** was recrystallized from MTBE; m.p. 59−60 °C. **C:** IR (KBr): $\tilde{\nu}$ = 3080 (w, =C−H), 2960 (m, C−H), 1740 cm^{-1} (s, C=O). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.53 (s, 3 H, 1-CH_3), 2.40 (d, J = 15.1 Hz, 1 H, *endo*-H-2), 2.85 (d, J = 15.2 Hz, 1 H, *exo*-H-2) ppm; AB part of an ABX_3 subspectrum from *endo*-OCH_2CF_3, with δ_A = 4.15, δ_B = 4.03 (J_{AB} = 10.8, J_{AX} = J_{BX} = 8.2−8.3 Hz); AB part of an ABX_3 subspectrum from *exo*-OCH_2CF_3, with δ_A = 4.51, δ_B = 4.25 (J_{AB} = 12.3, J_{AX} = J_{BX} = 8.6 Hz); 4.84 (d, J = 2.0 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.17, with δ_A = 6.19 (H-6) and δ_B = 6.15 (H-7) (J_{AB} = 6.0 Hz; the lines of the B-part are split into doublets with J = 1.8 Hz) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.3 (1-CH_3), 50.1 (C-2), 60.2 (q, J = 35.8 Hz, *endo*-OCH_2CF_3), 62.1 (q, J = 35.3 Hz, *exo*-OCH_2CF_3), 79.7 (C-5), 85.8 (C-1), 99.1 (C-4), 123.4 (q, J = 277 Hz, *endo*-OCH_2CF_3), 123.5 (q, J = 277 Hz, *exo*-OCH_2CF_3), 129.2 (C-7), 139.95 (C-6), 199.5 (C-3) ppm. **D:** $C_{12}H_{12}F_6O_4$ (334.2): calcd. C 43.13, H 3.62; found C 43.11, H 3.67. IR (film): $\tilde{\nu}$ = 3070 (w, =C−H), 2970, 2950, 2930, 2880 (m, C−H), 1730 (s, C=O), 1590 cm^{-1} (w, C=C). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, 1-CH_3), 2.47 (d, J = 16.5 Hz, 1 H, *endo*-H-4), 2.89 (dd, J = 16.7, 5.1 Hz, 1 H, *exo*-H-4) ppm; AB part of an ABX_3 subspectrum from *endo*-OCH_2CF_3, with δ_A = 4.18, δ_B = 4.03 (J_{AB} = 11.1, J_{AX} = J_{BX} = 8.1−8.2 Hz); AB part of an ABX_3 subspectrum from *exo*-OCH_2CF_3, with δ_A = 4.29, δ_B = 4.26 (J_{AB} = 12, J_{AX} = J_{BX} = 8.5−8.6 Hz); 5.02 (d, J = 5.2 Hz, 1 H, H-5), 6.06 (d, J = 5.9 Hz, 1 H, H-7), 6.35 (dd, J = 5.9, 1.6 Hz, 1 H, H-6) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 16.2 (1-CH_3), 46.0 (C-4), 62.9 (q, J = 35.5 Hz, *endo*-OCH_2CF_3), 63.3 (q, J = 35.9 Hz, *exo*-OCH_2CF_3), 78.2 (C-5), 88.6 (C-1), 100.4 (C-2), 121.6 (CF_3), 134.5 and 136.15 (C-6 and/or C-7), 202.5 (C-3) ppm.

Cleavage of 2: 3-Hydroxy-2-methoxycyclohepta-2,4,6-trienone (20a): A solution of **2** (368 mg, 2.0 mmol) in 10% methanolic KOH (15 mL) was refluxed for 16 h. The mixture was diluted with water (20 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were shaken with an aqueous 0.5 M KOH solution (10 mL), and the dichloromethane solution discarded. The basic aqueous solutions were combined, cooled in an ice-bath, acidified with dilute hydrochloric acid (1:2 v/v, 10 mL) and extracted with dichloromethane (5 × 20 mL). The combined extracts were washed with brine and dried with Na_2SO_4. After filtration, the solvent was evaporated and the remaining brown oil subjected to sublimation at 60−100 °C/0.001 Torr. The resulting yellow-orange solid was recrystallized from EA/hexane, affording pale-yellow **20a** (260 mg, 85%) with m.p. 113−115 °C (dec.). $C_8H_8O_3$ (152.15): calcd. C 63.16, H 5.30; found C 62.91, H 5.32. EIMS (70 eV): *m/z* (%) = 152 (100) [$M^{+\cdot}$], 134 (8) [M − H_2O], 121 (31) [M − OCH_3], 109 (32) [M − CH_3 − CO], 104 (12), 81 (24), 76 (17). IR (KBr): $\tilde{\nu}$ = 3050 (br. s, O−H), 1625 (m, C=O), 1570, 1535, 1500 cm^{-1} (s, C=C). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.03 (s, 3 H, OCH_3), 7.05 [mc, AA′BB′ subspectrum with centers at δ_A = 7.13 (H-4, H-5) and δ_B = 6.98 (H-3, H-6)], 7.40 (br. s, 1 H, O−H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 59.2 (OCH_3), 131.9 (C-5 and C-6), 135.0 (C-4 and C-7), 150.1 (C-2) ppm.

3-Hydroxy-2-methoxy-6-methylcyclohepta-2,4,6-trienone (20b): Prepared from **15b** (200 mg, 1.01 mmol) with 10% methanolic KOH (15 mL). Sublimation of the brown residue at 60−80 °C/0.001 Torr gave a yellow oil which solidified in the air, forming a pale yellow hydrate of **20b** (156 mg, 84%) with m.p. 88−94 °C. Drying over P_4O_{10} gave an oil again. $C_9H_{10}O_3{\cdot}H_2O$ (184.2): calcd. C 58.69, H 6.56; found C 59.13, H 6.64. IR ($CDCl_3$): $\tilde{\nu}$ = 3450 (m, O−H), 2980, 2920, 2820 (wm, C−H), 1645 (m, C=O), 1585, 1560, 1545, 1520 cm^{-1} (s, C=C). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.1 (very br., H_2O), 2.32 (d, J = 0.8 Hz, 3 H, CH_3), 4.00 (s, 3 H, OCH_3), 6.83−7.04 ppm; ABC subspectrum from H-4, H-5 and H-7: an AB analysis gives δ_A = 7.01 (H-4), δ_B = 6.86 (H-5) (J_{AB} = 12.2 Hz; the lines of the B-part are split into doublets with J = 1.6 Hz), δ_C = 7.00 (s, 1 H, H-7); 7.15 (br. s, 1 H, OH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.25 (CH_3), 59.2 (OCH_3), 133 (br., C-5), 135.5 (C-4 and C-7), 143.0 (C-6), 148.9 (C-2) ppm.

3-Hydroxy-6-isopropyl-2-methoxycyclohepta-2,4,6-trienone (20c): Prepared from **15c** (679 mg, 3.0 mmol) with 10% methanolic KOH (20 mL) over 24 h, as described for **2**. The resulting brown oil was sublimed at 60−120 °C/0.001 Torr to afford a yellow solid. Recrystallization from MTBE/pentane gave **20c** (458 mg, 78%) as a yellow solid with m.p. 89−90 °C. $C_{11}H_{14}O_3$ (194.2): calcd. C 68.02, H 7.26; found C 67.91, H 7.23. IR (KBr): $\tilde{\nu}$ = 3000 (br. s, O−H), 2950, 2910 (m, C−H), 1630 (m, C=O), 1575, 1540, 1520 cm^{-1} (s,

C=C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (d, J = 6.9 Hz, 6 H, CH_3), 2.76 [sept, J = 6.9 Hz, C*H*(CH_3)$_2$], 4.01 (s, 3 H, OCH_3), 6.90−7.10 ppm; ABC subspectrum from H-4, H-5 and H-7: an AB analysis gives δ_A = 7.08 (H-4), δ_B = 6.90 (H-5) (J_{AB} = 12.5 Hz; the lines of the B-part are split into doublets with J = 1.3 Hz), δ_C = 7.06 (s, 1 H, H-7); 7.33 (br. s, 1 H, OH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.8 (CH_3), 37.8 [*C*H(CH_3)$_2$], 59.1 (OCH_3), 133.7 (C-7 and C-4), 148.9 (C-5 and C-6), 152.8 (C-2) ppm.

6-Benzyloxymethyl-3-hydroxy-2-methoxycyclohepta-2,4,6-trienone (20d): Prepared from **15d** (400 mg, 1.31 mmol) with 10% methanolic KOH (15 mL) over 12 h, as described for **2**. After filtration and evaporation of the solvent in vacuo, the resulting yellow oil was purified by chromatography on silica (20 g). Elution with PE/EA (1:1) followed by pure EA gave 220 mg (58%) of a brownish, smeary solid that formed a crystalline hydrate of **20d** in the air, with m.p. 85−95 °C. $C_{16}H_{16}O_4$·H_2O (290.3): calcd. C 65.91, H 6.46; found C 66.19, H 6.25. IR (KBr): ṽ = 3400 (br. s, O−H), 2920 (m, C−H), 1650, 1640 (m, C=O), 1570, 1510 cm^{-1} (s, C=C). ^{1}H NMR (250 MHz, [D$_6$]acetone): δ = 2.93 (br. s, H_2O), 3.87 (s, 3 H, −OCH_3), 4.45 (d, J = 1.1 Hz, 2 H, C*H*$_2$OBn), 4.61 (s, 2 H, PhC*H*$_2$O), 6.96−7.43 ppm; ABC subspectrum from H-4, H-5 and H-7 and multiplet from C_6H_5: discrete signals δ = 7.00 (s, 2 H) and 7.10 (m, 1 H) can be assigned to H-4 + H-5, and H-7, resp.); 8.84 (br. s, HO) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]acetone): δ = 59.0 (OCH_3), 73.0 (*C*H_2OBn), 74.1 (O*C*H_2Ph), 128.5, 128.6 and 129.2 (phenyl-C), 133 (br., C-5 and C-6), 139.1 (C-7 and C-4), 150.4 (C-2) ppm.

3-Hydroxy-2-methoxy-7-methylcyclohepta-2,4,6-trienone (20e): Prepared from **3** (520 mg, 2.62 mmol) with 10% methanolic KOH (25 mL) as described for **2**. Sublimation of the resulting yellow oil at 60−80 °C/0.001 Torr gave oily **20e**, which solidified in the air, forming a hydrate. Recrystallization from acetone/water afforded 425 mg (88%) as a pale yellow solid with m.p. 88−92 °C. $C_9H_{10}O_3$·H_2O (184.2): calcd. C 58.69, H 6.57; found C 58.94, H 6.59. IR (KBr): ṽ = 3480, 3220 (s, O−H), 1620 (m, C=O), 1570, 1520, 1495 cm^{-1} (s, C=C). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 2.25 (s, 3 H, CH_3), 3.0 (very br., H_2O), 3.87 (s, 3 H, OCH_3), 6.90−6.98 ppm; ABC subspectrum from H-4, H-5 and H-7: an AB analysis gives δ_A = 6.96 (H-4) and δ_B = 6.92 (H-5) (J_{AB} = 11.8 Hz; the lines of the B-part are split into doublets with J = 8.4 Hz), δ_C = 7.23 (d, J = 8.4 Hz, 1 H, H-6) ppm. ^{13}C NMR (125.8 MHz, [D$_6$]acetone): δ = 23.4 (CH_3), 59.3 (OCH_3), 122.9 (C-4 and C-7), 130 (br., C-1, C-3), 131.0 (C-5), 132.5 (C-6), 150.3 (C-2) ppm.

2-Ethoxy-3-hydroxy-6-methylcyclohepta-2,4,6-trienone (E): Prepared from **A** (250 mg, 1.11 mmol) with 10% methanolic KOH (15 mL), as described for **2**. The brown residue was sublimed at 60−80 °C/0.001 Torr to afford a yellow oil, which solidified in the air, forming a hydrate. Recrystallization from acetone/water gave 180 mg of **E** (82%), a pale yellow solid with m.p. 87−94 °C. $C_{10}H_{12}O_3$·H_2O (198.2): calcd. C 60.59, H 7.12; found C 60.35, H 7.13. IR (KBr): ṽ = 3400 (br. s, O−H), 2980, 2960 (m, C−H), 1630 (m, C=O), 1570, 1510 cm^{-1}(s, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.1 (br., H_2O), 2.32 (d, J = 1.0 Hz, 3 H, 6-CH_3), 4.34 (q, J = 7.1 Hz, 2 H, C*H*$_2$$CH_3$), 6.82−7.04 ppm; ABC subspectrum from H-4, H-5 and H-7: an AB analysis gives δ_A = 7.01 (H-4), δ_B = 6.86 (H-5) (J_{AB} = 12 Hz; the lines of the B-part are split into doublets with J = 1.6 Hz), δ_C = 7.00 (s, 1 H, H-7); 7.21 (br. s, 1 H, HO) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.7 (CH_2*C*H_3), 26.2 (6-CH_3), 67.3 (*C*$H_2$$CH_3$), 133.6 (b, C-5), 135.4 (C-4 and C-7), 142.8 (C-6), 147.8 (C-2) ppm.

3-Hydroxy-6-methyl-2-(2,2,2-trifluoroethoxy)cyclohepta-2,4,6-trienone (F): Prepared from **C** (752 mg, 2.25 mmol) with 10% methanolic KOH (25 mL) over 4 h, as described for **2**, with the same workup. A grey solid remained after evaporation of the extracts. Recrystallization from acetone gave 473 mg (90%) of **F** as a pale yellow solid with m.p. 155−157 °C. $C_{10}H_9F_3O_3$ (198.2): calcd. C 51.29, H 3.87; found C 51.29, H 3.88. IR (KBr): ṽ = 3450 (br., m, O−H), 1645 (m, C=O), 1520, 1505 cm^{-1} (s, C=C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, CH_3), 4.69 (q, J = 8.6 Hz, 2 H, C*H*$_2$$CF_3$), 6.85 (br. s, 1 H, HO), 6.85−7.03 ppm; ABC subspectrum from H-4, H-5 and H-7: an AB analysis gives δ_A = 7.01 (H-4), δ_B = 6.90 (H-5) (J_{AB} = 12.9 Hz), δ_C = 7.00 (s, 1 H, H-7) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.35 (CH_3), 67.5 (q, J = 34.6 Hz, *C*$H_2$$CF_3$), 122.5 (C-5), 124.75 (C-4), 136.25 (C-7), 143 (C-6), 146.7 (C-2) ppm.

Reaction of 5 with Methanolic KOH Solution: (5α,8α,8aβ)-4,4-Dimethoxy-3-methyl-5,8-epoxy-1,2,4,5,8,8a-hexahydroazulen-2-one (26): A solution of **5** (254 mg, 1.0 mmol) in 1 M KOH solution (50 mL) was stirred under nitrogen at room temperature for 3 d. The mixture was cooled to 0 °C and neutralized by slowly adding 2 M HCl (25 mL). The mixture was concentrated to half its original volume in a rotary evaporator and extracted with dichloromethane (5 × 20 mL). The combined extracts were washed with brine and dried with Na_2SO_4. After filtration and evaporation in vacuo, the remaining brown oil was chromatographed on silica (20 g). Elution with EA/PE (1:2) gave 162 mg (68%) of **26** as a colourless solid. For combustion analysis it was recrystallized from MTBE/hexane; m.p. 93−95 °C. $C_{13}H_{16}O_4$ (236.3): calcd. C 66.09, H 6.83; found C 66.06, H 6.94. IR (KBr): ṽ = 2970, 2950 (m, C−H), 1710 (C=O), 1635 cm^{-1} (w, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87 (d, J = 2.1 Hz, 3 H, 3-CH_3) ppm; AB part of an ABX subspectrum with δ_A = 2.51, δ_B = 1.79 (J_{AB} = 18.4 Hz, 1-H_2C); the X part, with δ_X = 3.18 (H-8a), shows 9 lines due to coupling with H-8 and 3-CH_3; 3.26 (s, 3 H, *endo*-OCH_3), 3.41 (s, 3 H, *exo*-OCH_3), 4.87 (dd, J = 4.1, 1.5 Hz, 1 H, H-8), 4.94 (d, J = 1.8 Hz, 1 H, H-5) ppm; AB subspectrum centered at δ = 6.25, with δ_A = 6.31 (H-6), δ_B = 6.19 (H-7) (J_{AB} = 6.1 Hz; the lines of the A-part are split into doublets with J = 1.8 Hz, the B-part with 1.5 Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 9.6 (3-CH_3), 35.9 (C-1), 40.8 (C-8a), 48.3 (*endo*-OCH_3), 51.2 (*exo*-OCH_3), 80.9 and 81.1 (C-5 and C-8), 100.2 (C-4), 131.3 and 132.8 (C-6 and C-7), 142.9 (C-3), 163.4 (C-3a), 207.8 (C-2) ppm.

Cleavage of 5: 3-Hydroxy-2-methoxy-7-(2-oxobutyl)cyclohepta-2,4,6-trienone (20f, 27, 28) and 2-Ethyl-2,3-dihydro-2-hydroxy-8-methoxy-7*H*-cyclohepta[*b*]furan-7-one (26): A solution of **5** (254 mg, 1.0 mmol) in 1 M methanolic NaOMe (50 mL) was refluxed under nitrogen for 6 h. The mixture was cooled to 0 °C and acidified by slowly adding 2 M HCl (26 mL). The mixture was concentrated to half its original volume in a rotary evaporator and extracted with dichloromethane (5 × 20 mL). The combined extracts were washed with brine, dried with Na_2SO_4, and the solvent was evaporated in vacuo. The remaining brown oil was chromatographed on silica (20 g). Elution with EA/PE (1:2) gave 38 mg (16%) of **26** (see the preceding experiment). Elution with acetone/EA (1:9) then gave 160 mg of a brown solid (**20f**, **27**, **28**; 72%), which was recrystallized from acetone; m.p. 112 °C (dec.). $C_{12}H_{14}O_4$ (222.2): calcd. C 64.85, H 6.35; found C 64.69, H 6.46. IR (KBr): ṽ = 3120 (s, O−H), 2960, 2920 (s, C−H), 1625 (C=O), 1580, 1520 cm^{-1} (s, C=C). The peak integrals of a 500 MHz ^{1}H NMR spectrum of this substance in [D$_6$]acetone solution showed that 55% of the compound was present in the open-chain form (**20f**, **27**), and 45% as the cyclic hemiacetal **28**. **20f**, **27:** ^{1}H NMR: δ = 1.00 (t, J = 7.3 Hz, 3 H,

CH_2CH_3), 2.60 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 3.69 (s, 2 H, 7-CH_2), 3.79 (s, 3 H, OCH_3); 6.87−7.05 (m, H-4, H-5 and H-6) ppm. **28:** ^{1}H NMR: δ = 1.06 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 2.02 (m, CH_2CH_3, partly superimposed with the [D$_6$]acetone peak), 2.85 (br. s, OH) ppm; AB subspectrum centered at δ = 3.28, with δ_A = 3.40 and δ_B = 3.16 (J_{AB} = 17.6 Hz, 3-H_2C); 3.83 (s, 3 H, OCH_3), 6.92−7.05 (m, 3 H, H-4, H-5 and H-6) ppm. From the ^{13}C NMR spectrum (125.8 MHz, [D$_6$]acetone) the following signals were tentatively assigned: δ = 8.1 (CH_2CH_3, **20f**, **27**), 8.8 (CH_2CH_3, **28**), 33.2 (CH_2CH_3, **20f**, **27**), 36.2 (CH_2CH_3, **28**), 43.4 (7-CH_2, **20f**), 49.9 (C-3, **28**), 58.8, 58.9 (OCH_3 from **20f**, **27** and/or **28**), 110.9 (C-1, **20f**, **27**), 125.4, 133.0, 139.25, (C-4, C-5 and C-6, **28**), 142.2 (C-8, **28**), 149.4 (C-3a, **28**), 159.0 (C-8a, **28**), 180.2 (C-7, **28**), 207.35 (C=O, **20f**, **27**) ppm.

2,7-Dihydroxycyclohepta-2,4,6-trienone (29a): A 33% solution of HBr in glacial acetic acid (5 mL) was added slowly to a solution of **20a** (152 mg, 1.0 mmol) in glacial acetic acid (2 mL). The mixture was heated to 60 °C for 1 h. The volatile components were then evaporated in vacuo. The dark, tarry residue was sublimed at 60−100 °C/0.01 Torr, resulting in a yellow solid that was resublimed at 60−70 °C/0.01 Torr. The isolated product (130 mg, 94%) had an intense wood odour, and showed decomposition at the melting point (> 133 °C) (ref.[34] 136 °C). Despite the deficiency in melting point, the ^{13}C NMR spectrum was consistent with the data reported for **29a**, apart from negligible differences due to the different solvent (CD_3OD)[35]. IR (KBr): $\tilde{\nu}$ = 3230 (s, OH), 1605 (m, C=O), 1520 cm^{-1} (br. s, C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35 [m, AA′BB′ subspectrum with centers at δ_A = 7.52 (H-4, H-5) and δ_B = 7.20 (H-3, H-6)], 8.34 (br., 2 H, OH) ppm. For an analyis of the ^{1}H NMR spectrum in [D$_6$]acetone see ref.[36] ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 121.2 (CH, C-3, C-6), 130.0 (CH, C-4, C-5), 160.05 (C_q, C-2, C-7), 169.2 (C_q, C-1) ppm.

2,7-Dihydroxy-4-methylcyclohepta-2,4,6-trienone (29b): A 33% solution of HBr in glacial acetic acid (5 mL) was added slowly to a solution of **20b** (120 mg, 0.72 mmol) in acetic acid (2 mL). The mixture was heated to 90 °C for 30 min. The volatile components were then evaporated in vacuo. The remaining brown solid was sublimed at 60−80 °C/0.001 Torr affording 110 mg (> 99%) of **29b** as a solid with m.p. 131−132 °C (ref.[18] 132.5−133.5 °C). The ^{13}C NMR spectrum was consistent with the data reported for **29b**, apart from negligible differences due to the different solvent ($CDCl_3$).[18] IR (KBr): $\tilde{\nu}$ = 3220 (s, O−H), 1605 (m, C=O), 1515 cm^{-1} (s, C=C). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 2.39 [s, 3 H, CH_3, AB subspectrum centered at δ = 7.13, with δ_A = 7.27 (H-6) and δ_B = 7.00 (H-5), J_{AB} = 10.8 Hz; the lines of the B-part are split into doublets with J = 0.7 Hz], 7.31 (d, J = 1.5 Hz, 1 H, H-3) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 25.6 (4-CH_3), 120.5 (C-6), 122.35 (C-3?), 128.5 (C-5?), 139.3 (C-4), 158.15 (C-2), 159.5 (C-7), 167.4 (C-1) ppm.

2,7-Dihydroxy-4-isopropylcyclohepta-2,4,6-trienone (β-Thujaplicinol, 29c): Prepared from **20c** (194 mg, 1.0 mmol) in acetic acid (3 mL) and 33% HBr in glacial acetic acid (5 mL), as described for **29b**. The dark, tarry residue was sublimed at 60−100 °C/0.001 Torr to give 173 mg (96%) of a smeary yellow solid that was recrystallized from MTBE/hexane. Yield: 145 mg (81%) of **29c** with m.p. 54−55 °C (ref.[19] 57.5−58 °C). The IR spectrum (KBr) essentially corresponded with the figure shown in ref.[19] The ^{1}H NMR (250 MHz, $CDCl_3$) spectrum was fully consistent with the data reported for the "viscous, red-brown" oily **29b**;[18] moreover, the resonance for the two HO protons appeared as a broad signal at δ = 8.3. Minor deviations were found for the 62.9 MHz ^{13}C NMR spectrum.[18] ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.9 (CH_3), 38.6 [4-$CH(CH_3)_2$], 121.2 (C-6), and 121.8 (C-3), 128.4 (C-5), 152.5 (C-4), 158.3 (C-2) and 159.8 (C-7), 166.9 (C-1) ppm.

2,7-Dihydroxy-3-methylcyclohepta-2,4,6-trienone (29d): Prepared from **20e** (112 mg, 0.67 mmol) with a 33% solution of HBr in glacial acetic acid (5 mL), as described for **29b**. The brown solid product was sublimed at 60−80 °C/0.001 Torr, giving 99 mg (97%) of a colourless, hygroscopic solid. After recrystallization from acetone/water, the m.p. was 111−113 °C. The spectra were in agreement with structure **29d**; however, a satisfying combustion analysis of **29d** could not be obtained. IR (KBr): $\tilde{\nu}$ = 3200 (s, O−H), 1605, 1580 (m, C=O), 1520, 1500 cm^{-1} (s, C=C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, 3-CH_3) ppm; ABC subspectrum of H-4, H-5 and H-6, a first-order analysis gave 7.06 ("t", J = 10.1−10.5 Hz, 1 H, H-5), 7.41 ("d, J = 10.1 Hz", 1 H, H-4), 7.19 ("d, J = 10.7" 1 H, H-6); 7.9 (very br., 2 H, OH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.1 (CH_3), 119.5 (C-6), 127.8 (C-4), 133.0 (C-3), 133.6 (C-5), 158.1 (C-7?), 159.1 (C-2?), 167.4 (C-1) ppm. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3 H, 3-CH_3), 6.96 (br. s, 2 H, OH) ppm; ABC subspectrum of H-4, H-5 and H-6, a first-order analysis gave 7.03 ("t, J = 10.2 Hz", 1 H, H-5), 7.20 ("d, J = 10.4 Hz", 1 H, H-4), 7.31 ("dd, J = 10.2, 1.5 Hz", 1 H, H-6) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO): δ = 20.9 (CH_3), 119.6 (C-6), 126.8 (C-4), 131.4 (C-3), 132.4 (C-5), 158.7 and 158.9 (C-2 and C-7), 166.75 (C-1) ppm. $C_8H_8O_3 \cdot H_2O$ (170.2): calcd. C 56.47, H 5.92; found C 58.72, H 5.39. EIMS (70 eV): *m/z* (%) = 152 (100) [$M^{+\cdot}$], 124 (24) [M − CO], 106 (6), [M − CO − H_2O], 78 (19). HRMS: calcd. for $C_8H_8O_3$ 152.0473; found 152.0469.

Acknowledgments

We thank the analytical and spectroscopic service of the Institute of Organic Chemistry for spectra and elemental analyses, especially Jochen Rebell (NMR), and Dr. Wolfgang Frey for help with the X-ray data. Thomas Haisch made an experimental contribution.

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Received September 25, 2003

