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Synthetic Approaches to Hydroazulenes and Guaianes through [4 + 3] Cycloadditions of Oxyallyl Intermediates

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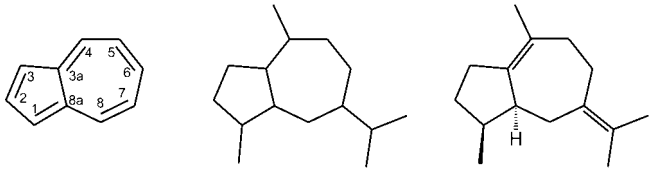
Building blocks for syntheses of guaiane and secoguaiane sesquiterpenoids were prepared by the title reaction. 4-(3-Methylfuran-2-yl)butan-2-one (**1**) was obtained in five steps from methyl 3-methylfuran-2-carboxylate (**4**), and treatment of **1** with pentachloroacetone and sodium 2,2,3,3-tetrafluoropropoxide in 2,2,3,3-tetrafluoropropan-1-ol produced a [4 + 3] cycloadduct that was dechlorinated without prior isolation to give the oxabicyclic diketone **2** in a low yield. A better route to diketone **2** was via the oxabicycle **10b**, prepared in a high yield from 2-(but-3-en-1-yl)-3-methylfuran (**9**) and pentachloroacetone, followed by dechlorination. Treatment of **2** with dilute methanolic potassium hydroxide resulted in the cleavage of the oxa bridge, with formation of 3,8-dimethylazulen-4-ol (**11**). Catalytic hydrogenation of **2** afforded the saturated oxabicyclic diketone **14**, intramolecular aldol condensation of which gave the tricycle **15**. The oxa bridge of the oxatricyclic enone **15** was cleaved by hydrogenolysis in the presence of palladium/carbon catalyst to give the 6-hydroxydecahydroazulen-4-one **16**. Treatment of isobutyl trichloromethyl ketone (**20**) with furan **9** and sodium trifluoroethoxide in trifluoroethanol eventually gave the 2-chlorooxabicycle **22**. This solvolysis product was dechlorinated to furnish the oxabicyclic trifluoroethoxy ketone **24** as a single product that was subjected to the sequence of transformations used for **10b**. X-ray structure analysis of the resulting saturated diketone **26** established the *endo* configuration of the isopropyl group. Finally, aldol cyclization of **26** furnished the guaiane derivative **27**.

Introduction

Many sesquiterpenoids can be formally regarded as derivatives of hydrogenated azulene (**A**); a sub-class of these contains the *guaiane* skeleton (**B**), such as the hydrocarbon β-bulnesene (**C**). A variety of approaches to construct this fused 5,7 ring system[1,2] and to synthesize representative natural products of this family have been elaborated.[3]



A **B** **C**

Apart from the utilization of rearrangement reactions of – for example – decalin precursors, most of the synthesis strategies for such hydroazulenes (also named bicyclo[5.3.0]-decanes) have started with the five-membered ring and elaborated the seven-membered ring by ring enlargement (e.g. 6 → 7) or isomerization reactions.[4–8]

Though the annulation of a cyclopentane ring ("cyclopentannulation") to a preformed seven-membered ring has been used for syntheses of *pseudo*guaianes,[9–11] this approach had, to the best of our knowledge, rarely been applied to the synthesis of guaianes. Rigby et al. made use of the "conjugate" 1,8-addition found with tropone and thus succeeded in total syntheses of the guaianolides *rac*-dehydrocostus lactone, estafiatin and grosshemin,[12] while Deprés et al. found that 7-methylcycloheptatriene would undergo a regio- and stereoselective cycloaddition with dichloroketene, ring expansion of the [2 + 2] cycloadduct with diazomethane giving a hydroazulenone that served as a versatile building block for oxygenated guaianes.[13] A ring-closing metathesis annulation sequence starting with 6-isopropenyl-3-methylcyclohept-2-enone [prepared from (–)-(*R*)-carvone by ring expansion] was utilized by Brocksom et al.[14]

[4 + 3] Cycloadditions of furans with oxyallyl intermediates afford 8-oxabicyclo[3.2.1]oct-6-en-3-ones, which can be viewed as oxa-bridged cycloheptenones and so might also be useful for guaiane syntheses. Approaches to *pseudo*guaianes by cyclopentannulation starting with a few selected 8-oxabicycles have been described by the groups of Mann and Nicholas.[15,16]

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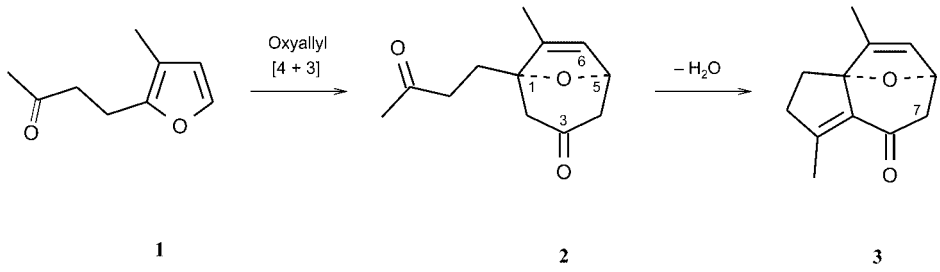
[‡] X-ray analysis.
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1. Plan of a guaiane synthesis based on a [4 + 3] cycloaddition and an intramolecular aldol reaction.

Since the beginning of our investigations of oxyallyl cycloadditions, we have examined potential applications to syntheses in the field of sesquiterpenes with 5,7-fused rings. Here we report results of studies we began in the 1980s, which resulted in building blocks for guaianes and secoguaianes that might encourage other workers to follow up this route.[17–19]

One of the oldest methods for syntheses of cyclopentenones is the well-known intramolecular aldol condensation (Hunsdiecker cyclization),[20] used for cyclopentannulation on various four-, five- and six-membered carbocycles.[21] Intramolecular aldol condensation of a cyclopropano-fused cycloheptanone, for example, was used by Saha et al. for a synthesis of cyclocolorenone.[22]

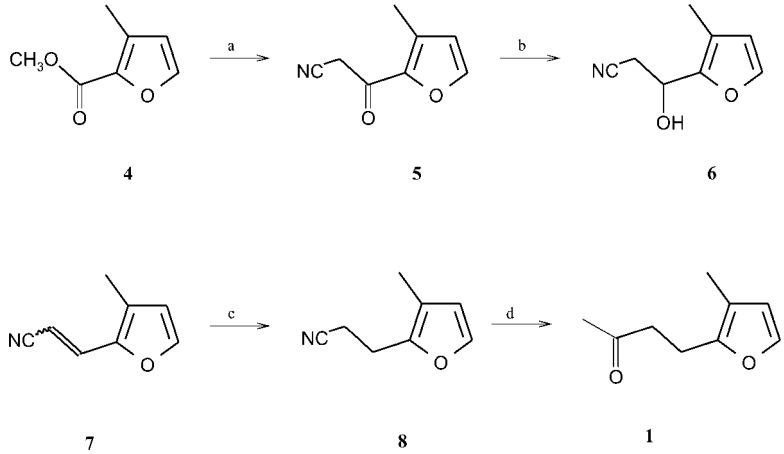
Given an 8-oxabicyclo[3.2.1]oct-6-en-3-one as scaffold for the functionalized cycloheptane ring, we felt that an intramolecular aldol reaction in the diketone **2** should furnish the oxatricyclic enone **3**. The high functionality of **3** should later allow the introduction of a side chain at C-7 and various oxygen substituents at different positions (Scheme 1).

Results and Discussion

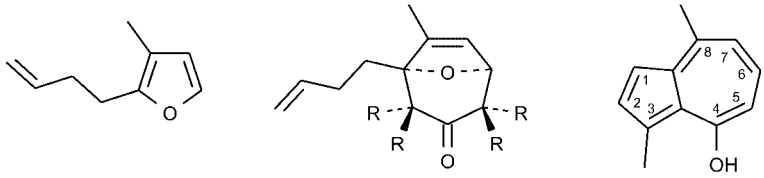
Our first approach to the diketone **2** was through oxyallyl cycloaddition with the furan **1**, itself accessible from methyl 3-methylfuran-2-carboxylate (**4**), available on a multigram scale by an Organic Synthesis procedure.[23] Claisen condensation of the ester **4** with acetonitrile in the presence of sodium hydride gave the β-oxo nitrile **5** in 79% yield (Scheme 2). Reduction of the carbonyl group was attempted with sodium borohydride in ethanol. To our surprise, when we allowed the components to react at ambient temperature without cooling and tolerating a slight warming, apart from the expected β-hydroxy nitrile **6** (61% yield), a mixture of (*E*,*Z*)-propenenitriles **7** was formed as byproducts (18% yield). This prompted us to carry out the reaction with final heating at reflux, which directly afforded the (*E* + *Z*)-propenenitriles **7** in a 78% yield. Finally, hydrogenation of the α,β-unsaturated carbonitrile moiety was effected with magnesium in methanol (74% yield).[24] Conversion of the saturated nitrile **8** into the methyl ketone **1** was achieved in a 59% yield with methylmagnesium iodide in the presence of $Ni(acac)_2$.[25,26]

For the [4 + 3] cycloaddition of the functionalized furan **1** we generated the oxyallyl intermediate from pentachloroacetone and sodium 2,2,3,3-tetrafluoropropoxide in 2,2,3,3-tetrafluoropropan-1-ol.[27] The expected tetrachloro-substituted oxabicycle was not isolated but was dechlorinated immediately to deliver the oxabicycle **2**, though in only 17% yield.[28]

Our second approach started with 2-(but-3-en-1-yl)-3-methylfuran (**9**); as we have reported previously, the [4 + 3] cycloaddition in this case gave the oxabicycle **10a** with a butenyl side chain at C-1 (87% yield), and dechlorination gave **10b** in 74% yield.[28a] In a multigram experiment



Scheme 2. Synthesis of the furan **1**. Reagents and conditions: a) acetonitrile, NaH, MTBE, reflux, 79%. b) $NaBH_4$, ethanol, room temp., 61%. c) Mg, methanol, 0 °C → room temp., 74%. d) CH_3MgI, toluene, $Ni(acac)_2$, room temp., 59%.



9 **10a:** R = Cl **11**
10b: R = H

(100 mmol) the yield could be improved to 95%. Finally, we were able to transform the furan **9** into **10b** in a 95% total yield on a multigram scale, omitting the isolation of the tetrachloride **10a**.

The introduction of the second carbonyl group in good yield was effected by a palladium-catalyzed Wacker oxidation[29] of the terminal C=C double bond of **10b**. However, acetoxymercuration followed by Jones oxidation proved to be more convenient to obtain compound **2** (72% yield).[30]

Classical intramolecular aldol condensations of 1,4-diketones (γ-diketones) are known to proceed under mild conditions, such as with fairly dilute alkali hydroxides (the Hunsdiecker procedure).[20] When we treated the oxabicyclic diketone **2** with KOH in methanol (5%) at room temperature, the expected enone **3** was isolated in a 26% yield after a reaction time of 26 h, together with unreacted **2** (19%). To our surprise, a violet colour developed during this reaction, and we hypothesized that an azulene might have been formed. On repeating the reaction in methanol at reflux, we were able to isolate the violet product. Its UV/Vis spectrum, recorded in methanol, was consistent with the absorptions described for 4-hydroxy- and 4-methoxyazulene.[31,32]

An attempt to confirm the structure by NMR spectroscopy in a $CDCl_3$ solution gave – at first sight – a confusing result (vide infra). However, a ^{13}C NMR spectrum of a hexadeuterioacetone solution showed the expected twelve resonances, which were assigned by the DEPT technique to five quaternary, five tertiary and two methyl carbon atoms. A broad "hill" observed in the ^1H NMR spectrum at δ = 10.1 ppm supported the presence of an enolic hydroxy group; two methyl singlets at δ = 2.72 and 2.82 ppm and multiplets between δ = 6.66 and 7.22 ppm were consistent with formula **11**. The yield of the compound was 36%.

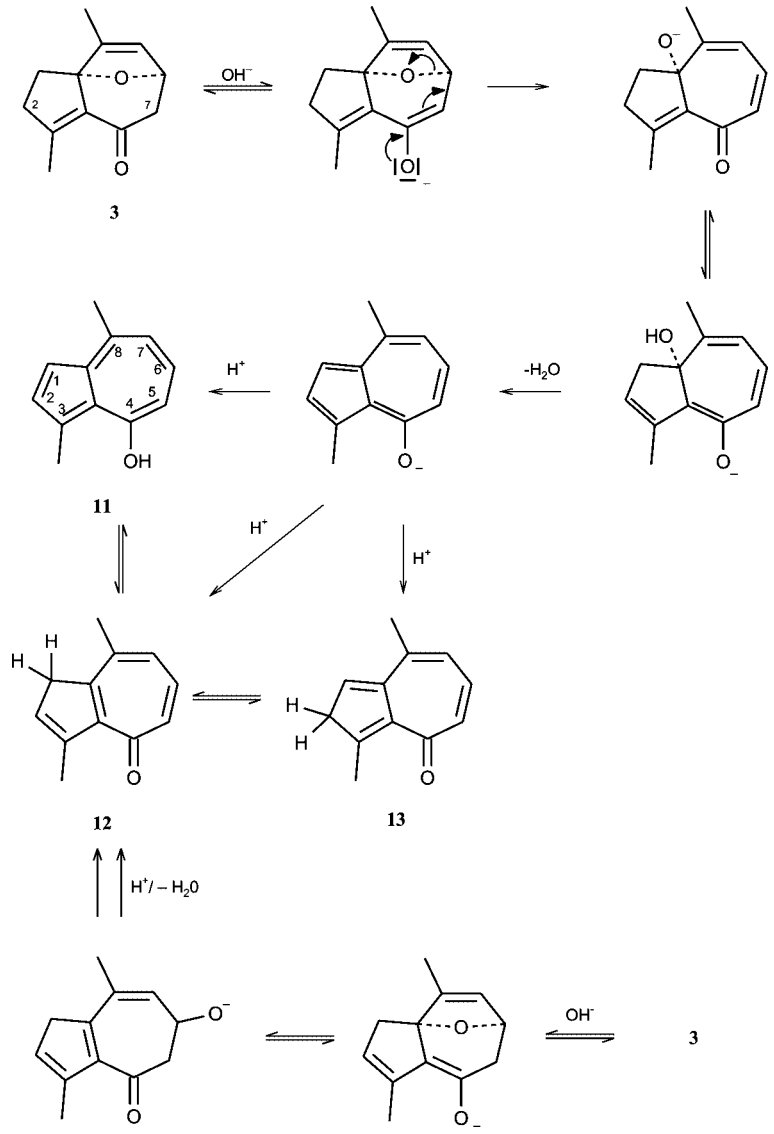
On closer inspection of the NMR spectra of a $CDCl_3$ solution, we came to the conclusion that the dimethyl-substituted azulenol **11** was accompanied by a keto tautomer (**12** or **13**), in line with the analogous findings of Reid et al.[32] and of Japanese workers[33] for 4-hydroxyazulene. Apart from the resonances due to **11**, among them a broad peak in the ^1H NMR spectrum at δ = 9.40 ppm for the proton of the enolic hydroxy group from **11**, supported by a signal in the ^{13}C NMR spectrum at δ = 163.8 ppm, resulting from the "phenolic" carbon atom (C-4) of azulenol **11**, a resonance at δ = 185.0 ppm in the ^{13}C NMR spectrum can be attributed to the carbonyl carbon atom of a tropone[34] (in addition to signals between δ = 113.8 and 153.5 ppm), thus pointing to the "cyclopentenotropone" **12**. However, the multiplicity of signals resulting from the protons of the methylene group and the methyl group at C-3 are in better accordance with tautomer **13**. According to the integrals of the ^1H NMR spectrum the percentage amount of azulenol **11** in the equilibrium mixture was ca. 50%.

In the cleavage of the ether bridge in tricycle **3**, deprotonation at C-2 or at C-7 can be imagined as the first step (Scheme 3). We prefer the latter, since an analogue of **3** bearing two methyl groups at C-2 (aldehyde **D**, Scheme 4) – synthesised as a building block for sesquiterpenes of the lactarane family – also forms a cyclopentenotropone (**F**) on treatment with boiling MeOH/KOH.[35] On the other hand, when enolization at C-7 is impossible, as in the case of compound **26** → **27** (see below), no cleavage was observed. Finally, the reactions resemble the cleavage of oxabicyclic oxo acetals to form β-tropolones.[36]

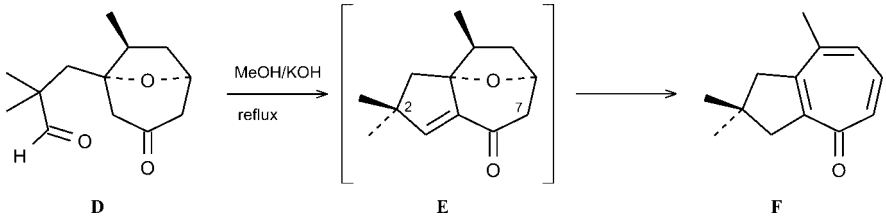
Although the formation of an azulenol by cleavage of **3** was striking and interesting as a novel approach to these isomers of naphthalenols, and might open the door for attachment of an appendix at the "*ortho*" position (C-5) of **11**, we preferred to execute the aldol cyclization with the *saturated* diketone (**14**). It was anticipated[37,38] that heterogenous catalytic hydrogenation of **2** should proceed stereospecifically from the easily accessible α-face of the bicycle, thus establishing a β configuration of the methyl group at C-7. Indeed, hydrogenation in the presence of Pd/C in methanol gave a single product, consistent with formula **14**. Our presumption that the methyl group at C-7 of **14** should be β was eventually corroborated by the X-ray structure analysis of the analogous saturated oxabicycle **26**, described below.

On treatment of **14** with potassium hydroxide in methanol, the Hunsdiecker cyclization was effected smoothly (80% yield), giving a single stereoisomer (**15**), without any byproducts. The ^1H NMR spectrum shows a doublet at δ = 0.90 ppm (J = 7.0 Hz) and a finely split singlet at δ = 2.12 ppm, indicating the methyl groups at C-4 and C-1, respectively, along with the bridgehead proton (6-H, δ = 4.59 ppm, multiplet). The conjugated enone unit is indicated by IR absorptions at 1680 and 1630 cm^{-1} and by the chemical shifts in the ^{13}C NMR spectrum (δ = 134.3, 153.6, 197.0 ppm).

With the goal of also adjusting the methyl group at C-1 in a stereochemically defined fashion, we also subjected tricycle **15** to catalytic hydrogenation, expecting saturation of



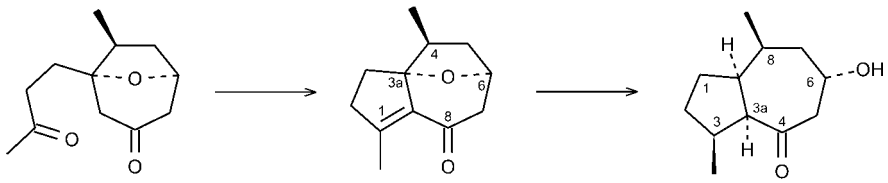
Scheme 3. Proposed formation mechanism and tautomerism of the azulenol **11**.



Scheme 4. Formation of tropone **F** by intramolecular aldol reaction and ether cleavage.

the enone C=C double bond. To our surprise, *four* equivalents of hydrogen were taken up in the presence of Pd/C in methanol. The IR spectrum indicated that the product contained a hydroxy group in addition to a carbonyl group, whilst the resonance of the quaternary carbon atom C-3a in oxatricycle **15** (Scheme 5) was lacking in the ^{13}C NMR spectrum. It may be concluded that hydrogenolysis of the allylic C-3a–oxygen bond had taken place to afford a hydroazulenone, such as diastereomer **16**.

House et al. reported comprehensive investigations into *cis*- and *trans*-fused perhydroazulen-4-ones (**17**, **18**), among other bicyclic systems.[39,40] By examining the ^1H NMR spectra they found characteristic differences in the chemical shifts of the protons at the "fused" carbon atom C-3a: the

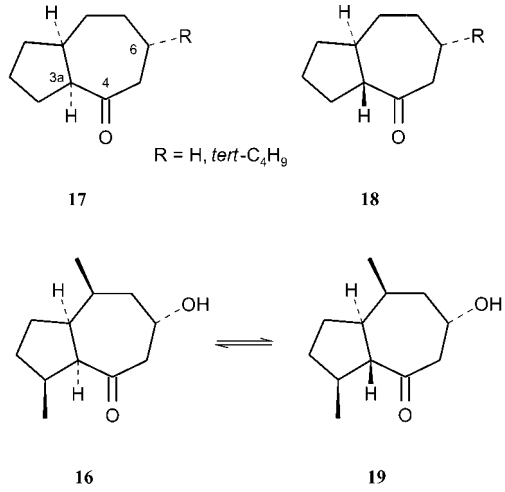


14 15 16

Scheme 5. Formation and hydrogenolysis of the oxatricycle **15**.

3a-H protons in the *trans* isomers (**18**) show high-field shifts (δ = 2.80 ppm) in relation to the *cis* isomers (**17**), which give rise to resonances between δ = 3.0 and 3.3 ppm.

We found a triplet at δ = 2.83 ppm for the proton at C-3a of **16**. On the assumption that the methyl group at C-3, due to its deshielding effect, should cause a high-field shift on neighbouring protons, the ^{1}H NMR spectroscopic data are consistent with *cis* fusion.



R = H, *tert*-C_4H_9

17 18

16 19

In order to substantiate this assignment we subjected **16** to a base-catalyzed equilibration at C-3a in methanolic sodium methoxide solution. This treatment resulted in a mixture of **16** and a new compound that could be separated by MPLC. In agreement with the results of House et al.,[39,40] signals in the region of δ = 3 ppm were absent, and thus indicated the formation of the *trans*-fused ketol **19**.

Installation of the Isopropyl Group

In order to complete the guaiane skeleton by a convergent [4 + 3] cycloaddition strategy, we intended to replace the oxyallyl moiety generated from pentachloroacetone by an *isopropyl*-substituted intermediate.[41–44] Apart from stereoselectivity, this raises the question of regioselectivity.

In exploring the reactions between 2-methylfuran and various dichloro ketones we had observed that the 1,4-dialkyl substitution pattern was preferred: a regioselectivity of >16:1 had been found in the reaction with dichloromethyl isobutyl ketone in the presence of $LiClO_4$/Et_3N/diethyl ether.[45] In the hope that regioselectivity and yield would be higher with the corresponding trichloro ketone **20** (Scheme 6) and sodium 2,2,2-trifluoroethoxide (NaTFE) in 2,2,2-trifluoroethanol (TFE), we investigated the reaction between **20** and furan **9**. (Moreover, the trichloroketone **20** is easier to prepare on a multigram scale than the dichloromethyl analogue.[46])

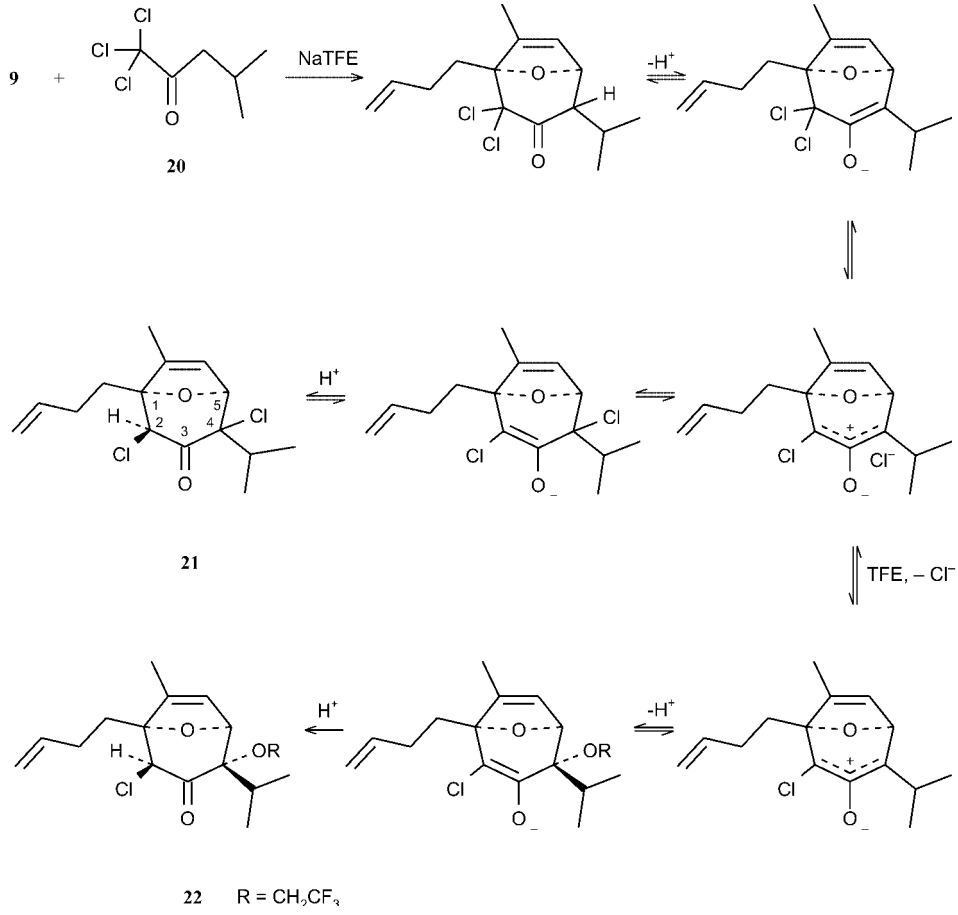
The reaction between the furan **9** and **20** in the presence of NaTFE in TFE proved to be more sluggish than that with pentachloroacetone. At room temperature, the peak corresponding to **20** in the GLC had not vanished after 5 h and, moreover, unreacted furan **9** was still present, though a 15% excess of **20** had been used. In addition, in order to produce an enduring basic reaction, more than 2 equiv. of NaTFE had to be used. According to the GLC, *two* products producing peaks in the range of retention times expected for oxabicyclic compounds were formed. When we kept the reaction mixture at reflux for several days, only one of these product peaks remained. Obviously trichloro ketone **20** was reacting in the same manner as with unsubstituted furan.[44]

The unstable (under these conditions) product could be identified as the 2,4-dichlorooxabicycle **21** by allowing the compounds to react at a lower temperature (0 °C). With the goal of directing the reaction course towards the "stable" compound, we added 2 equiv. of NaTFE solution very slowly at 0 °C and stirred the mixture in an ice bath until trichloro ketone **20** was no longer detectable by GLC. The mixture was then heated at reflux and the solvolysis product **22** was isolated in 78% yield after extraction, adsorptive filtration and distillation.

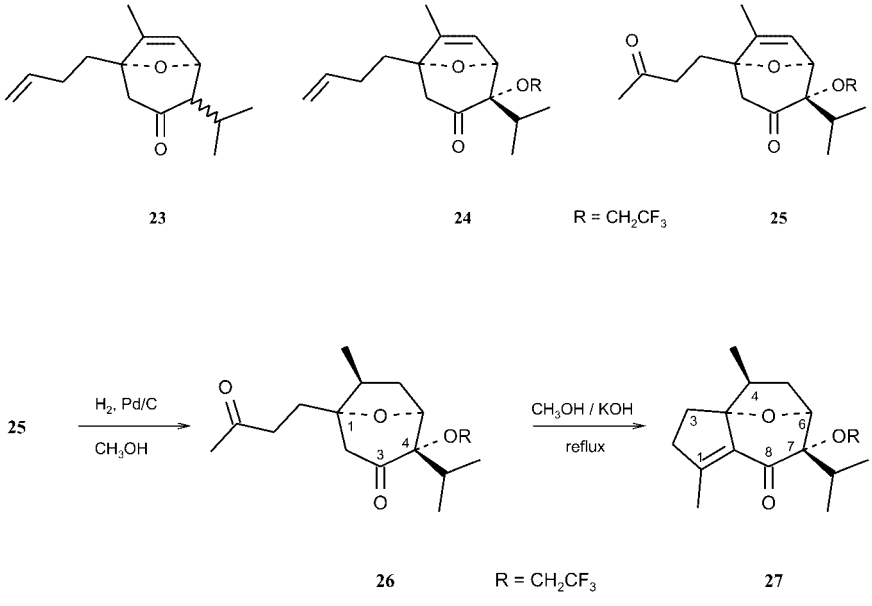
The oxabicycles **21** and **22** were dechlorinated by treatment with zinc/copper couple in methanolic ammonium chloride solution. Whereas the latter compound (**22**) furnished a single product (**24**) in a 99% yield, the dehalogenation of **21** gave a mixture of *endo* and *exo* isomers (3:1, **23**).

Having obtained **24** by way of a reaction cascade with a notable regio- and stereoselectivity, we subjected this trifluoroethoxy bicycle to oxymercuration and subsequent oxidation. The formed unsaturated diketone **25** was hydrogenated (Scheme 7). In order to establish the configuration at C-4, an X-ray structure analysis of the saturated oxabicycle **26** was accomplished (Figure 1) and indeed confirmed the *endo* configuration of the isopropyl group.

Finally, aldol cyclization of **26** furnished the guaiane derivative **27** in 89% yield. In summary, a highly functionalized guaiane was assembled in 55% total yield from furan **9** and trichloromethyl ketone **20**.



Scheme 6. Proposed mechanism of the reaction between furan **9** and trichloromethyl ketone **20** in the presence of sodium 2,2,2-trifluoroethoxide/2,2,2-trifluoroethanol.



Scheme 7. Hydrogenation and intramolecular aldol cyclization of oxabicycle **25**.

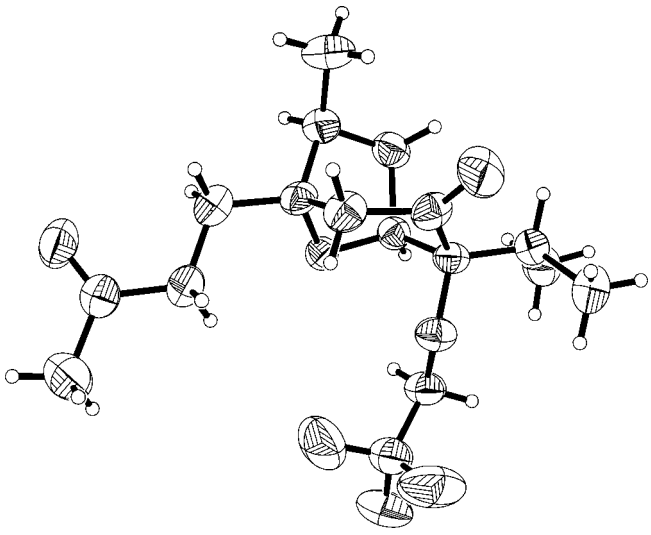


Figure 1. X-ray structure of the hydrogenation product **26**.[47]

Conclusion

[4 + 3] Cycloadditions between 2-(but-3-en-1-yl)-3-methylfuran (**9**) and oxyallyl intermediates generated from pentachloroacetone or isobutyl trichloromethyl ketone open a route to highly functionalized 8-oxabicyclo[3.2.1]-oct-6-en-3-ones, which can be transformed into hydroazulene derivatives with useful functionalities. Moreover, a novel approach to 4-hydroxyazulenes through base-induced cleavage of the 8-oxa bridge was found. Compounds **23**–**25** represent building blocks containing the complete secoguaiane skeleton.

Experimental Section

General Remarks: IR: Perkin–Elmer 457. UV/Vis: Beckman Acta M series. NMR: Varian T 60 for 60 MHz ^{1}H NMR spectra, Bruker WP 80 for 80 MHz ^{1}H NMR spectra, Bruker AC 250 for 62.9 MHz ^{13}C NMR and 250 MHz ^{1}H NMR spectra, and Bruker CXP 300 for 75.47 MHz ^{13}C NMR spectra and 300 MHz ^{1}H NMR spectra. TMS was used as 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, centres of the multiplets are given. EIMS: Varian MAT 711 with SS 100 data system. Analytical TLC: precoated sheets, Polygram Sil G/UV$_{254}$ (silica), distributed by Macherey–Nagel & Co, Düren, Germany; detection by UV extinction, or by spraying with vanillin/H_2SO_4 solution, followed by warming. Gas chromatography (GLC): Hewlett Packard 5710 A with 2.3 m glass columns packed with 5% Carbowax on Chromosorb G or 5% OV 101 on Gaschrom Q; nitrogen (30 mL min^{-1}) as carrier gas. Capillary gas chromatograms were obtained with a Carlo–Erba Fractovap GI instrument with a 20 m glass column coated with OV 1701; hydrogen was used as carrier gas. In all cases a flame ionization detector (FID) was used. Preparative column chromatography: silica 60 (40–63 μm), distributed by Macherey–Nagel & Co, Düren, Germany. MPLC: column length 20 cm, diameter 2.5 cm, packed with Lichroprep Si 60®, particle size 15–25 μm (Merck). For chromatography, dry petroleum ether (PE) was distilled (b.p. 40–65 °C). Ethyl acetate (EA) was dried with calcium chloride, distilled, and kept dry over molecular sieves (4 Å). Melting points were determined with a Büchi 510 apparatus, Büchi Laboratoriumstechnik AG, Flawil/Switzerland, and are not corrected. Elemental analyses were performed by the service of the Institut für Organische Chemie, University of Stuttgart. Diethyl ether and *tert*-butyl methyl ether (MTBE) were dried by heating at reflux over sodium wire followed by distillation. Acetonitrile was dried by stirring with powdered calcium hydride, distilled and stored over molecular sieves (3 Å). Methanol was dried by heating at reflux with magnesium turnings and distillation.[48] For sodium trifluoroethoxide/trifluoroethanol (NaTFE/TFE) and sodium 2,2,3,3-tetrafluoropropoxide reagents see ref.[28a] and ref.[27], respectively. Pentachloroacetone was commercially available at the time when the experiments were performed; for preparations, see ref.[49] Zinc/copper couple was prepared by Le Goff's method.[50] EDTA was available from Merck as the disodium salt dihydrate (Titriplex III®). Jones reagent[51] was prepared by dissolving anhydrous CrO_3 (26.7 g) in a mixture of water (40 mL) and concentrated sulfuric acid (23 mL); this solution was made up to 100 mL with water in a graduated flask.

3-Methyl-β-oxo-2-furanpropanenitrile (5): A suspension of sodium hydride in mineral oil (Weissöl) (80%, 36 g, ca. 1.2 mol) was diluted with dry *tert*-butyl methyl ether (400 mL), and the mixture was heated under dry argon. A mixture of acetonitrile (63 mL, 1.2 mol) and *tert*-butyl methyl ether (40 mL) was added dropwise to the magnetically stirred boiling mixture, followed by methyl 3-methylfuran-2-carboxylate (**4**,[23] 56 g, 0.4 mol) in *tert*-butyl methyl ether (80 mL); each addition took 20 min. The mixture was heated at reflux for 15 h, while hydrogen gas evolved. The mixture was then cooled with an ice bath, and an aqueous solution of sodium carbonate (400 mL of saturated sodium carbonate solution + 400 mL of water) was added cautiously with stirring (vigorous evolution of hydrogen gas!). The layers were separated, and the organic layer was extracted with sodium carbonate solution (4 × 200 mL, prepared by diluting a saturated Na_2CO_3 solution with an equal volume of water). The aqueous layers were combined, cooled in an ice bath and acidified with concd. hydrochloric acid to pH = 1.5 with magnetic stirring. The mixture was extracted with diethyl ether (5 × 600 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in a rotary evaporator. The remaining crude product (49.1 g) was purified by sublimation at 70 °C/0.05 Torr to give the title compound (47.3 g, 79%). A more rapid purification was effected by recrystallization from 96% ethanol; 200 mL was needed for crystallization of 28.73 g of a raw product from another preparation. Analytically pure **5** (21.28 g) with m.p. 93–94 °C was obtained after drying in vacuo (oil pump). ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, 3-CH_3), 4.00 (s, 2 H, CH_2), 6.52 (d, J = 2 Hz, 1 H, 4-H), 7.54 (d, J = 2 Hz, 1 H, 5-H) ppm. ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 11.7 (+, 3-CH_3), 29.4 (–, α-CH_2), 113.9 (C_q, CN), 116.7 (+, C-4), 134.0 (C_q, C-3), 146.2 (+, C-5), 146.3 (C_q, C-2), 177.1 (C_q, β-CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2250 (CN), 1665 (C=O), 1575 cm^{-1} (C=C). $C_8H_7NO_2$ (149.1): calcd. C 64.42, H 4.73, N 9.39; found C 64.46, H 4.80, N 9.11.

β-Hydroxy-3-methyl-2-furanpropanenitrile (6): Oxo nitrile **5** (5.00 g, 33.5 mmol) was added portionwise to a stirred solution of sodium borohydride (1.91 g, 50.5 mmol) in ethanol (96%, 100 mL); hydrogen gas evolved and the mixture warmed slightly. The mixture was stirred at room temperature for 74 h, treated with saturated aqueous ammonium chloride solution (250 mL) and extracted with diethyl ether (5 × 100 mL). The combined extracts were dried with magnesium sulfate and concentrated. The residue was taken up in

a few mL of dichloromethane and filtered through silica (80 g) by elution with dichloromethane. After a forerun consisting of (*E* + *Z*) isomers of **7** (9:1, according to ^{1}H NMR, 0.79 g, 18% yield, see below), compound **6** (3.07 g, 61%) was eluted. ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, 3-CH_3), 2.89 (d, J = 7 Hz, 2 H, CH_2), 3.11 (br. d, J = 5.5 Hz, 1 H, OH, vanishes after shaking the sample with D_2O), 5.05 [dt, J = 7, 5.5 Hz, 1 H, C*H*(OH)], 6.26 (d, J = 2 Hz, 1 H, 4-H), 7.35 (d, J = 2 Hz, 1 H, 5-H) ppm. IR (film): $\tilde{\nu}$ = 3420 (br., OH), 3150, 3120, 2960, 2925, 2240 (CN) cm^{-1}. $C_8H_9NO_2$ (151.2): calcd. C 63.57, H 6.00, N 9.27; found C 63.30, H 6.16, N 9.47.

(*E* + *Z*)-3-Methyl-2-furanpropenenitrile (7). Procedure a): Thionyl chloride (6 mL) was added to a solution of hydroxy nitrile **6** (2.36 g, 15.6 mmol) in pyridine (31 mL). When the exothermic reaction had subsided, the dark mixture was quenched by addition of ice/water (100 g) and extracted with diethyl ether (4 × 80 mL). The extract was washed with a saturated aqueous $NaHCO_3$ solution (6 × 20 mL), dried with magnesium sulfate and concentrated in vacuo. The remaining liquid was distilled in a kugelrohr at 70–90 °C/0.001 Torr; efficient cooling of the recipient bulb is necessary. According to the ^{1}H NMR spectrum, the distillate (1.37 g, 66%) consisted of (*E* + *Z*)-**7** in a 2:1 ratio. ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.15 (s, 3-CH_3), 5.13 [d, J = 12 Hz, (*Z*)-α-H], 5.63 [d, J = 16 Hz, (*E*)-α-H], 6.36 (d, J = 2 Hz, 4-H), 7.40 [d, J = 2 Hz, (*E*)-5-H], 7.51 [d, J = 2 Hz, (*Z*)-5-H] ppm. IR (film): $\tilde{\nu}$ = 3140, 3115, 3060, 2220 (CN), 1620, 1565 (C=C) cm^{-1}. C_8H_7NO (133.2): calcd. C 72.17, H 5.30, N 10.52; found C 72.43, H 5.35, N 10.22. **Procedure b):** Oxo nitrile **5** (5.94 g, 40 mmol) was added portionwise to a stirred solution of sodium borohydride (2.27 g, 60 mmol) in ethanol (96%, 120 mL); hydrogen gas evolved and the mixture warmed slightly. It was heated at reflux for 2 h, cooled, and concentrated in vacuo in a rotary evaporator. Saturated aqueous ammonium chloride solution (80 mL) was added cautiously to the residue (gas evolution!), followed by diethyl ether (40 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 40 mL). The combined extracts were dried with magnesium sulfate and concentrated, and the remaining liquid was distilled in a kugelrohr at 80–100 °C/0.05 Torr. According to a GLC (Carbowax, 80→220 °C, 8 K min^{-1}), the distillate (4.41 g, ca. 78% yield) consisted of (*E*)-**7** (76%), (*Z*)-**7** (11%) and 3-(3-methyl-2-furyl)propanenitrile (**8**, 9%, see below). This product was used without further purification for the following preparation (of **8**).

3-Methyl-2-furanpropanenitrile (8): Magnesium turnings (22.5 g, 925 mmol) were added with stirring and continued cooling to an ice-cooled solution of **7** (3.09 g, 23.2 mmol) in dry methanol (230 mL). The reaction started after a short induction period with evolution of (hydrogen) gas and decolouration of the pale yellow solution. (***Caution:*** The reaction may get out of control, especially on preparation at a larger scale!). After 1 h, the ice bath was removed, and the mixture was warmed up (25 °C). When the exothermic reaction had subsided (2.2 h), the flask was cooled with an ice bath. A mixture of saturated aqueous ammonium chloride solution (250 mL), water (200 mL) and concd. hydrochloric acid (150 mL) was added dropwise to the very viscous contents. The resulting clear solution was extracted with diethyl ether (5 × 150 mL), and the combined organic layers were dried with magnesium sulfate and concentrated in a rotary evaporator. The remaining liquid was distilled in a kugelrohr at 60–80 °C/0.001 Torr to give analytically pure **8** (2.31 g, 74%). ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, CH_3), 2.45–3.15 (m, 4 H, CH_2), 6.24 (d, J = 2 Hz, 1 H, 4-H), 7.32 (d, J = 2 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 9.7 (CH_3), 16.7 (α-CH_2), 22.4 (β-CH_2), 113.1 (C-3), 116.2 (C-4), 118.9 (CN), 141.1 (C-2), 146.6 (C-5) ppm. IR (film): $\tilde{\nu}$ = 3140, 3105, 2240 (CN), 1505 cm^{-1}. C_8H_9NO (135.2): calcd. C 71.09, H 6.71, N 10.36; found C 70.83, H 6.98, N 10.24.

4-(3-Methyl-2-furyl)butan-2-one (1): A Grignard solution was prepared under dry argon in a pre-dried three-necked flask from magnesium turnings (1.82 g, 75 mmol), dry diethyl ether (10 mL) and methyl iodide (6.9 mL, 111 mmol). Dry toluene (50 mL) was added, and the mixture was distilled (oil bath). When the temperature of the bath had reached 85 °C, the mixture was cooled with stirring. A solution of dry nickel(II) acetylacetonate in toluene (5%, 5.4 mL) was then added; the mixture became dark and warm while a slight gas evolution occurred. After 38.7 h of stirring at room temperature, the mixture was cooled with an ice bath. A mixture of ice (50 g) and concd. hydrochloric acid (10 mL) was added, and the solution was extracted with diethyl ether (4 × 25 mL). The combined extracts were dried with magnesium sulfate and concentrated in a rotary evaporator, and the remaining liquid was distilled in a kugelrohr at 90–120 °C/0.2 Torr to give oily **1** (2.70 g, 59%). ^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.97 (s, 3 H, furyl-CH_3), 2.13 (s, 3 H, $COCH_3$), 2.80 (s, 4 H, CH_2), 6.13 (d, J = 2 Hz, 1 H, 4-H), 7.19 (d, J = 2 Hz, 1 H, 5-H) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3100, 3000, 2960, 2920, 2865, 1710 cm^{-1} (C=O). $C_9H_{12}O_2$ (152.2): calcd. C 71.03, H 7.95; found C 70.92, H 8.09.

7-Methyl-1-(3-oxobutyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (2): A solution (1 M) of sodium 2,2,3,3-tetrafluoropropoxide in 2,2,3,3-tetrafluoropropan-1-ol was prepared;[27] 12.5 mL of this was added to **1** (3.80 g, 25 mmol), and the mixture was cooled in an ice bath. With magnetic stirring, pentachloroacetone (2.88 g, 12.5 mmol) was added dropwise over 2 min. The ice bath was then removed and the mixture was stirred at room temperature. After 1.5 h, spotting on wet pH indicator paper showed neutrality of the solution. The mixture was diluted with diethyl ether (100 mL) and the precipitated sodium chloride was allowed to settle. After filtration, the solution was concentrated in a rotary evaporator. A saturated solution of ammonium chloride in methanol (110 mL) was added to the residue. With magnetic stirring, zinc/copper couple (20 g)[50] was added in portions and the mixture was stirred for 40 h. Undissolved zinc and inorganic salts were filtered off, and the filtrate was concentrated in a rotary evaporator. Dilute hydrochloric acid, prepared from water (100 mL) and concd. HCl (5 mL), was added, and the mixture was extracted with diethyl ether (4 × 30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and dried with magnesium sulfate, and the solvent was removed in a rotary evaporator. The residue was chromatographed on silica (80 g); elution with PE/EA (2:1) gave unreacted **1** (1.75 g, 46%). Elution was continued with pure EA, which gave crude **2** (0.55 g), which was purified by distillation in an oil bath (60–70 °C) onto a cooled finger at 0.07 Torr; colourless deposit (0.44 g, 17% **2**), m.p. 51–53 °C. The m.p. rose to 53.5–54.5 °C after recrystallization from petroleum ether. ^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.70 (split br. s, 3 H, 7-CH_3), 1.8–2.95 [m, 8 H, CH_2, surmounted by an s at 2.18 ppm (3 H, CH_3CO)], 4.94 (m, 1 H, 5-H), 5.84 (m, 1 H, 6-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 11.8 (7-CH_3), 28.1 (*C*H_3CO), 30.0 (CH_2), 37.6 (CH_2), 44.7 (C-4), 50.1 (C-2), 76.0 (C-5), 86.3 (C-1), 128.4 (C-6), 143.2 (C-7), 205.9 (C-3), 207.8 (CH_3*C*O) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2990, 2940, 1705 (CO) cm^{-1}. EIMS (70 eV): *m*/*z* (%) = 208 (55) [M$^+$] from $C_{12}H_{16}O_3$, 190 (9), 166 (12), 165 (9), 151 (64), 150 (11), 133 (12),123 (16), 121 (16), 109 (40), 108 (97), 107 (11), 99 (19), 95 (53), 79 (14), 67 (23), 43 (100). HRMS: calcd. for $C_{12}H_{16}O_3$ 208.10995; found 208.1100.

1-(But-3-enyl)-7-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (10b): A mixture of 2-(but-3-enyl)-3-methylfuran (**9**,[52] 24.8 g, 182 mmol) and pentachloroacetone (46.1 g, 200 mmol) was cooled in an ice

bath. With magnetic stirring, an NaTFE solution (c = 2 mol L^{-1}, 100 mL) was added dropwise, not allowing the temperature of the reaction mixture to exceed 8–11 °C. This took 1.5 h, and sodium chloride precipitated, together with a proportion of the yellow solid product **10a**.[28a] After completion of the addition, the ice bath was removed and stirring was continued at room temperature for 1 h. A GLC indicated that **9** had disappeared, and a test with wet pH indicator paper showed an alkaline reaction. The mixture was poured into brine (200 mL). Small amounts of water and dichloromethane were added to dissolve the solid, and the mixture was extracted with dichloromethane (5 × 80 mL). The combined organic layers were washed with brine, and the washing solution was extracted with dichloromethane (2 × 50 mL). The dichloromethane solutions were combined and concentrated in a rotary evaporator. The remaining yellow solid (60.8 g) was dissolved in methanol that had previously been saturated with ammonium chloride (700 mL). Zinc/copper couple (191 g, 2.90 mol) was added *in portions* (!) with magnetic stirring. ***Caution:*** This reaction may be violent! Addition should be leisurely, and boiling of the solvent should be moderated by a reflux condenser. When the exothermic reaction had subsided, the mixture was stirred at room temperature for 15 h and then heated at reflux for a further 6 h. When the mixture had reached room temperature, the inorganic solid was filtered off and washed with methanol. The combined filtrates were poured into an ice-cold solution of EDTA disodium salt dihydrate (8%, 1.5 L) and extracted with dichloromethane (8 × 200 mL). The organic solutions were combined, filtered, and concentrated in a rotary evaporator. The remaining yellowish-brown oil was distilled with a 20 cm Vigreux column. The colourless distillate with b.p. 78 °C/0.01 Torr (33.0 g, 95% yield) solidified at room temperature (ca. 25 °C). The NMR spectra were in agreement with those of a sample from our first experiments.[28a]

7-Methyl-1-(3-oxobutyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (2). Procedure a): A solution of **10b** (1.92 g, 10 mmol) in DMF/water (1:1, 10 mL) was added dropwise at room temperature to a solution of $PdCl_2$ (40 mg) and $CuCl_2$ (40 mg) in a mixture of DMF (30 mL) and water (30 mL). The mixture was vigorously stirred under oxygen, with monitoring of the progress of the reaction by GLC (OV 101). After several hours, the reaction came to a standstill, so more $PdCl_2$ and $CuCl_2$ were added (50 mg each) and stirring was continued. The conversion was essentially complete after repetition of the addition four times over 5 d. The mixture was poured into hydrochloric acid (3 M, 50 mL) and extracted with diethyl ether (4 × 30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL) and dried with magnesium sulfate. The diethyl ether was removed in a rotary evaporator; according to a GLC, the remaining pale yellow solid (1.14 g of **2**, 55% yield) was contaminated with a small amount of the primary product **10b**. Crystallization from petroleum ether gave an analytically pure sample with m.p. 54 °C. A second experiment, however, with addition of $PdCl_2$ (100 mg) and $CuCl_2$ (1.35 g, 10 mmol) in one portion, afforded **2** (1.49 g, 72%) after 5 d of reaction time as a pale-yellow solid, but also contaminated with a small amount of the primary product **10b** (GLC). **Procedure b):** Mercuric acetate (4.0 g, 12.6 mmol) and 1-(but-3-enyl)-7-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**10b**, 18.5 g, 96 mmol) were dissolved in a mixture of acetone (75 mL) and water (10 mL) with magnetic stirring at room temperature. After 20 min, the mixture was cooled down to 0 °C, and Jones' reagent (60 mL) was added dropwise over 45 min, the temperature not being allowed to exceed 10 °C. The cooling bath was removed and stirring was continued at room temperature for 45 min. The mixture was poured into water (200 mL) and extracted with diethyl ether (200 mL). The aqueous layer was extracted with more diethyl ether (5 × 100 mL), and the combined diethyl ether extracts were washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL) and dried with magnesium sulfate. Compound **2** (14.34 g, 72%) with m.p. 54 °C was obtained after evaporation of the solvent. ^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.73 (fine-split s, 3 H, 7-CH_3), 1.83–2.85 [m, surmounted by an s at 2.20 ppm (11 H, CH_2 and butyl-4-H)], 4.93 (s, 1 H, 5-H), 5.85 (m, 1 H, 6-H) ppm. IR (KBr): $\tilde{\nu}$ = 3060 (C=C–H), 2960, 2930, 2890, 2850 (C–H), 1700 (C=O), 1640 (C=C) cm^{-1}. $C_{12}H_{16}O_3$ (208.3): calcd. C 69.21, H 7.74; found C 68.99, H 7.73.

1,4-Dimethyl-2,3,3a,6,7,8-hexahydro-3a,6-epoxyazulen-8-one (3): A solution of KOH in methanol was prepared (5%, 20 mL). Diketone **2** (420 mg, 2 mmol) was added, and the mixture was stirred under argon for 26 h. The solution was then poured into cold dilute hydrochloric acid (2.5 g of concd. HCl dissolved in 100 g of ice/water) and extracted with diethyl ether (50 mL and 4 × 25 mL). The combined violet extracts were washed with saturated aqueous $NaHCO_3$ solution (5 mL), dried with magnesium sulfate and concentrated in a rotary evaporator. The residue (320 mg) was chromatographed on silica (20 g) by elution with PE/EA (1:1). The first fractions contained the title compound **3** (100 mg, 26%), which was distilled in a kugelrohr at 120–130 °C/0.005 Torr. The sample solidified in the refrigerator, m.p. 42–44 °C. The further fractions contained unreacted **2** (80 mg, 19%). ^{13}C NMR/off-resonance (75.47 MHz, $CDCl_3$): δ = 196.2 (s, C-8), 150.8 (s, C-1), 145.3 (s, C-4), 135.6 (s, C-8a), 126.2 (d, C-5), 96.05 (s, C-3a), 76.6 (d?, C-6), 42.3 (t, C-7), 36.8 (t, C-3?), 28.4 (t, C-2?), 16.2 (q, 1-CH_3), 11.2 (q, 4-CH_3) ppm. IR (CCl_4): $\tilde{\nu}$ = 3060, 2960, 2945, 2910, 2855, 2835, 1685, 1635 cm^{-1}. $C_{12}H_{14}O_2$ (190.2): calcd. C 75.76, H 7.42; found C 75.62, H 7.69.

3,8-Dimethylazulen-4-ol (11): A solution of **2** (2.90 g, 13.9 mmol) in methanol (10 mL) was added dropwise with magnetic stirring to a boiling solution (reflux condenser) of methanolic KOH (5%, 20 mL) over 1 h. The mixture was then heated at reflux for a further 45 min; a blue-violet colour developed. The mixture was cooled and concentrated in a rotary evaporator. The mixture was acidified by cautious addition of hydrochloric acid (1 M, 40 mL), and extracted with diethyl ether (6 × 20 mL). The combined diethyl ether extracts were washed neutral with saturated $NaHCO_3$ and brine. After drying with magnesium sulfate, the solvent was removed in a rotary evaporator, and the remaining viscous, violet mass was chromatographed on silica (80 g) by elution with PE/EA (9:5). Compound **11** (850 mg, 36%) was isolated from the collected coloured fractions and recrystallized from a little *n*-hexane to give brownish-violet needles with m.p. 97 °C. ^{1}H NMR (250 MHz, [D_6]-acetone): δ = 2.72 (s, 3 H, 3?-CH_3), 2.82 (s, 3 H, 8?-CH_3), 6.66 (d, $^3J_{6,7}$ = 9.9 Hz, 1 H, 7-H), 6.80 (d, $^3J_{5,6}$ = 11.0 Hz, 1 H, 5-H), 7.15 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 7.21 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, 2-H), 7.22 (dd, $^3J_{5,6}$ = 11.0 Hz, $^3J_{6,7}$ = 10.0 Hz, 1 H, 6-H), 10.10 (br. s, 1 H, 4-OH) ppm. Analysis was made by first order. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.37 (d, J = 0.8 Hz), 2.46 (4 equidistant lines, "J" = 1.8 Hz), 2.79 (s, from azulenol **11**), 2.94 (s, from **11**) [CH_3 from keto and enol tautomers], 3.36 (5 nearly equidistant lines, "J" = 1.9–2.0 Hz, CH_2 from keto tautomer **12** or **13**), 6.41 (4 lines with "J" = 1.5–1.7 Hz), 6.67 (d, J = 9.9 Hz, from **11**), 6.80 (d?, "J" = 6.5 Hz?, overlapped by a d, J = 11.1 Hz, at 6.83 ppm from **11**), 7.0–7.3 (m, 5 H, from **11** and 4 H from keto tautomer **12** or **13**), 9.40 (br. s, 1 H, OH from **11**). From the peak integrals a 1:1 ratio was calculated. ^{13}C NMR/DEPT (62.9 MHz, [D_6]acetone): δ = 18.3 (+, 3-CH_3), 24.8 (+, 8-CH_3), 113.9 (+, CH), 115.7 (+, CH), 120.4 (+, CH), 123.4 (C_q), 127.7 (C_q), 133.8 (+, CH), 135.6 (+, CH), 137.3 (C_q), 146.6 (C_q), 164.7 (C_q, C-4) ppm. ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 17.5 (+), 17.9 (+), 24.4 (+), 24.9 (+) (CH_3), 43.0 (–, CH_2), 113.8 (+), 114.8 (+), 120.0 (+), 129.8

(+), 133.1 (+), 133.4 (+), 135.0 (+), 135.2 (+), 138.7 (+) (CH), 122.3 (C_q), 126.4 (C_q), 136.2 (C_q), 142.8 (C_q), 146.05 (C_q), 146.3 (C_q), 151.5 (C_q), 153.45 (C_q), 163.8 (C_q) (C-4 from **11**), 185.0 (C_q) (C-4 from **12** or **13**) ppm. IR (KBr): $\tilde{\nu}$ = very br. band extending from 3200 to 1700 (OH), surmounted by peaks at 2960 and 2920, 1612, 1570, 1535, 1505 cm^{-1}. IR ($CDCl_3$): $\tilde{\nu}$ = very br. band extending from ca. 3700 to ca. 2200 (OH) cm^{-1}, surmounted by peaks at 3590 (OH), 3070 (C=C–H), 2980, 2970, 2960, 2930, 2880 (C–H), 1620 (C=O), 1570, 1550, 1540, 1510 (C=C) cm^{-1}. UV/Vis (methanol): λ_{max} (lg ε) = 252 (3.57), 284 (3.65), 309 (3.11), 344 (2.78) nm. EIMS (70 eV): *m*/*z* (%) = 173 (13), 172 (100) [M^+] from $C_{12}H_{12}O$, 171 (56), 157 (45), 143 (11), 129 (37), 128 (42), 127 (12), 115 (12), 76 (12). HRMS: calcd. for $C_{12}H_{12}O$ 172.0886; found 172.0886. $C_{12}H_{12}O$ (172.1): calcd. C 83.69, H 7.02; found C 83.58, H 7.07.

(7β)-7-Methyl-1-(3-oxobutyl)-8-oxabicyclo[3.2.1]octan-3-one (14): A suspension of Pd/C catalyst (10%, 600 mg) in a solution of **2** (14.30 g, 68.8 mmol) in methanol (70 mL) was shaken under hydrogen. When the hydrogen uptake was complete (1.5 h), the catalyst was filtered off and the filtrate was concentrated in a rotary evaporator. The crude product was used directly for the preparation of **15**. A sample for analysis was obtained in 95% yield by kugelrohr distillation at 110 °C/0.03 Torr. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 15.2 (7-CH_3), 30.0 (*C*H_3CO), 31.1 (CH_2), 37.8 (CH_2), 38.7 (C-6), 41.3 (C-7), 48.3 (C-4), 49.3 (C-2), 73.2 (C-5), 84.5 (C-1), 207.8, 207.9 (C-3 and butyl-C-3) ppm. IR (film): $\tilde{\nu}$ = 2955, 2870 (C–H), 1715 (C=O) cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$): δ = 0.98 (d, J = 7 Hz, 3 H, 7-CH_3), 0.90–2.75 (m, surmounted by an s at 2.18 ppm, 14 H in toto, CH_2, 7-H and butenyl-4-H), 4.51–4.80 (m, 1 H, 5-H) ppm. EIMS (20 eV): *m*/*z* (%) = 210 (39) [M^+], 167 (100), 152 (37), 99 (52). EIMS (70 eV): *m*/*z* (%) = 210 (12) [M^+], 167 (58), 152 (22), 99 (100), 43 (65). CIMS (CH_4, 70 eV): *m*/*z* (%) = 251 (7) [M·$C_3H_5^+$], 239 (18) [M·$C_2H_5^+$], 211 (85) [MH^+], 193 (100) [MH^+ – H_2O], 175 (13), 169 (23), 151 (31), 99 (12). $C_{12}H_{18}O_3$ (210.3): calcd. C 68.55, H 8.63; found C 68.41, H 8.91.

(3aα,4ß,6α)-1,4-Dimethyl-2,3,4,5,6,7-hexahydro-8*H*-3a,6-epoxyazulen-8-one (15): A solution of **14** (14.2 g, 67.5 mmol) in methanol (50 mL) was added dropwise with magnetic stirring to a boiling solution (reflux condenser) of methanolic KOH (5%, 100 mL) over 30 min. The mixture was then heated at reflux for a further 45 min, cooled and concentrated in a rotary evaporator. The mixture was acidified by cautious addition of hydrochloric acid (1 M, 200 mL) and extracted with diethyl ether (200 mL). The aqueous layer was extracted with more diethyl ether (5×100 mL), and the combined diethyl ether extracts were washed with saturated aqueous $NaHCO_3$ solution (80 mL) and brine (80 mL). After drying with magnesium sulfate, the solution was concentrated and distilled in a kugelrohr at 80–90 °C/0.001 Torr to give **15** (10.5 g, 81%) as a colourless liquid that solidified on storage. A sample for analysis was sublimed, m.p. 47 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, J = 7.0 Hz, 3 H, 4-CH_3), 1.14–1.22 (m, 1 H, 5β-H), 2.03–2.12 (m, surmounted by a fine-split s at 2.12 ppm, 4 H, 1-CH_3, 3?-H), 2.20–2.57 (m, 6 H, 2-,3?-,4-,5- and 7-H), 2.65 (dd, 1 H, A part of an ABM sub-spectrum from 7-H, centred at 2.65 ppm, $^2J_{7\alpha,7\beta}$ = 17.2 Hz and J = 5.2 Hz, the lines are finely split), 4.59 (finely split t, $^3J_{5\beta,6}$ = $^3J_{6,7\alpha}$ = 6.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR/off-resonance (76.47 MHz, $CDCl_3$): δ = 14.1 (q, 4-CH_3), 15.8 (q, 1-CH_3), 32.1 (t, C-3 or C-2), 36.2 (t, C-2 or C-3), 38.5 (t, C-5), 43.2 (d, C-4), 49.1 (t, C-7), 73.4 (d, C-6), 95.1 (s, C-3a), 134.3 (s, C-8a), 153.6 (s, C-1), 197.0 (s, C-8) ppm. IR (KBr): $\tilde{\nu}$ = 2950, 2890, 2830 (C–H), 1680 (C=O), 1630 (C=C) cm^{-1}. $C_{12}H_{16}O_2$ (192.3): calcd. C 74.97, H 8.39; found C 75.17, H 8.46. EIMS (70 eV): *m*/*z* (%) = 164 (65), 149 (25), 123 (100), 67 (16), 41 (15). EIMS (20 eV): *m*/*z* (%) = 192 (1) [M^+], 164 (100), 149 (22), 123 (53). MS (CI, CH_4, 70 eV): *m*/*z* (%) = 233 (7) [M·$C_3H_5^+$], 221 (23) [M·$C_2H_5^+$], 193 (100) [MH^+], 175 (10), 164 (11), 151 (15), 147 (11).

(3β,3aα,6α,8β,8aα)-6-Hydroxy-3,8-dimethyl-2,3,3a,5,6,7,8,8a-octahydroazulen-4(1*H*)-one (16): A suspension of Pd/C catalyst (20 mg) in a solution of **15** (270 mg, 1.41 mmol) in methanol (10 mL) was shaken under hydrogen. When the hydrogen uptake was complete (30 min), the catalyst was filtered off and the filtrate concentrated in a rotary evaporator. The remaining liquid was dried by oil-pump vacuum to give **16** (265 mg) as a colourless oil. A sample for analysis was distilled in a kugelrohr at 120 °C/0.001 Torr. However, no satisfying combustion analysis could be obtained. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 and 0.99 (each d, J = 7.1 and 7.0 Hz, 6 H, 3-CH_3 and 8-CH_3), 1.41–1.55 (m, 1 H, 7-H), 1.68–1.81 (m, 4 H), 1.84–2.02 (m, 1 H), 2.18–2.40 (m, 3 H, 3a-H), 2.65 (d, $^3J_{5,6}$ = 4.5 Hz, the line at higher field is split with 0.5 Hz, 2 H, 5-H), 2.83 (t, $^3J_{3,3a}$ = $^3J_{3a,8a}$ = 8.0 Hz, 3a-H and OH), 4.17 (br. quint, $^3J_{5,6}$ = $^3J_{6,7} \approx$ 4.5 Hz, 1 H, 6-H) ppm. ^{13}C NMR/off-resonance (75.47 MHz, $CDCl_3$): δ = 16.3 (q, 8-CH_3), 22.5 (t, C-1), 23.9 (q, 3-CH_3), 27.9 (d, C-3), 32.8 (t, C-2), 38.6 (m, consisting of a d and t, C-7, C-8), 46.0 (d, C-8a), 51.1 (t, C-5), 62.7 (d, C-3a or C-6), 65.9 (d, C-6 or C-3a), 212.5 (s, C-4) ppm. IR (film): $\tilde{\nu}$ = 3600–3160 (br., OH), 2950, 2920, 2855, 1680 (C=O) cm^{-1}. EIMS (70 eV): *m*/*z* (%) = 196 (14) [M^+], 141 (74), 123 (65), 109 (74), 95 (44), 81 (100), 69 (39), 67 (51), 55 (38) and many weaker peaks with intensities <35%. HRMS: calcd. for $C_{12}H_{20}O_2$: 196.1463; found 196.1464.

Equilibration of (3β,3aα,6α,8β,8aα)-6-Hydroxy-3,8-dimethyl-2,3,3a,5,6,7,8,8a-octahydroazulen-4(1*H*)-one (16) – (3β,3aβ,6α,8-β,8aα)-6-Hydroxy-3,8-dimethyl-2,3,3a,5,6,7,8,8a-octahydroazulen-4(1*H*)-one (19): A suspension of Pd/C catalyst (17 mg) in a solution of **15** (202 mg, 1.05 mmol) in methanol (10 mL) was shaken under hydrogen. When the hydrogen uptake was complete (17 min), the catalyst was filtered off and the filtrate concentrated in a rotary evaporator. The remaining liquid was dissolved in methanol (10 mL) and sodium methoxide (15 mg) was added. The mixture was stirred for 17 h and concentrated in vacuo, and the residue was taken up in hydrochloric acid (1 M, 10 mL) and extracted with diethyl ether (4×5 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL), and dried with magnesium sulfate. A GLC (OV 1701, 50→300 °C, 5 K min^{-1}) showed **16** (t_r = 24.7 min) and equilibration product **19** (t_r = 25.7 min) in a 37:67 ratio. A sample of this mixture (140 mg) was subjected to MPLC on silica by elution with PE/EA (1:1) to give **16** (25 mg) and **19** (45 mg) as colourless oils. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.6 Hz, 3 H, 3- or 8-CH_3), 1.06 (d, J = 7.0 Hz, 3 H, 8- or 3-CH_3), 1.10–1.21 (m, 1 H), 1.45–1.54 (m, 1 H), 1.67–1.84 (m, 4 H), 1.92–1.99 (m, 1 H), 2.07–2.22 (m, 3 H), 2.31–2.41 (m, 1 H), 2.54 (A part of an ABM sub-spectrum from 7-H, $^2J_{5,5}$ = 17.8 Hz, the lines are further split with $^3J_{5,6}$ = 10.8 Hz, 1 H, 5-H), 2.77 (B part of ABM sub-spectrum from 7-H with $^2J_{7,7}$ = 17.8 Hz, the lines are further split, 1 H, 5-H′), 4.29 (br. t, $^3J_{5,6}$ = $^3J_{6,7}$ = 10.8 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 12.8 (8-CH_3), 19.7 (3-CH_3), 29.6, 32.0, 33.7, 35.3 (C-1, C-2, C-3, C-7), 46.8, 46.9 (C-8a, C-8), 52.9 (C-5), 58.8 (C-3a), 64.0 (C-6), 209.9 (C-4) ppm. EIMS (70 eV): *m*/*z* (%) = 196 (12) [M^+], 178 (29), 109 (100), 82 (34), 81 (47), and many weaker peaks. HRMS: calcd. for $C_{12}H_{20}O_2$ 196.1463; found 196.1461.

1-(But-3-enyl)-2,4-dichloro-4-isopropyl-7-methyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one (21): A mixture of 2-(but-3-enyl)-3-methylfuran (2.72 g, 20.0 mmol, **9**) and 1,1,1-trichloro-4-methylpentan-2-one (4.10 g, 20.2 mmol, **20**) was cooled to –20 °C. With magnetic stirring, an NaTFE/TFE solution (c = 2.0 mol L^{-1}, 10.0 mL) was

added at –20 °C over 15 min. The mixture was warmed up to 0 °C (2 h) and then stirred at this temperature for 2.5 d, whereupon the mixture turned red. A spot of a sample on wet pH indicator paper showed a neutral reaction. The mixture was poured into brine (150 mL), and the flask was rinsed with water (50 mL) and extracted with diethyl ether (4 × 20 mL). The combined extracts were washed with brine (20 mL), dried with magnesium sulfate and concentrated in a rotary evaporator. The last part of the solvent was removed by stirring in vacuo (oil pump) at 50 °C. The remaining yellow oil (5.73 g, ca. 94%) was identified as **21** by the following spectra. For analysis and spectra, a sample was purified by chromatography on silica by elution with PE/EA (30:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.01 (quint, $^4J_{6,7\text{-}CH3} = {}^3J_{5,6}$ = 1.8 Hz, 1 H, 6-H), 5.88 (ddt, $^3J_{3,4Z}$ = 17.1 Hz, $^3J_{3,4E}$ = 10.2 Hz, $^3J_{2,3}$ = 6.4 Hz, 1 H, butenyl-3-H), 5.10 (ddt, $^3J_{3,4Z}$ = 17.1 Hz, $^2J_{4Z,4E} = {}^4J_{2,4Z}$ = 1.5 Hz, 1 H, butenyl-4-H$_Z$), 5.02 (dt, $^3J_{3,4E}$ = 10.2 Hz, $^4J_{2,4E}$ = 1.3 Hz, 1 H, butenyl-4-H$_E$), 4.88 (m, 1 H, 5-H), 4.69 (s, 1 H, 2-H), 2.67 (sept, ^3J = 6.7 Hz, 1 H, isopropyl-1-H), 2.0–2.5 (m, 4 H, butenyl-1-H and -2-H), 1.87 (finely split s, 3 H, 7-CH_3), 1.13 (d, ^3J = 6.5 Hz, 3 H, isopropyl-CH_3), 0.89 (d, ^3J = 6.8 Hz, 3 H, isopropyl-CH_3) ppm. ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 14.4 (+, 7-CH_3), 16.4 (+), 17.9 (+) (isopropyl-CH_3), 27.25 (–), 31.3 (–) (butenyl-C-1 and -C-2), 32.2 (+, isopropyl-C-1), 69.1 (+, C-2), 81.5 (+, C-5), 84.9 (C_q, C-1), 91.8 (C_q, C-4), 115.2 (–, butenyl-C-4), 127.9 (+, C-6), 137.4 (+, butenyl-C-3), 145.4 (C_q, C-7), 194.0 (C_q, C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3090, 3070 (C=C–H), 2980, 2940, 2930, 2880 (C–H), 1735 (C=O), 1640 (C=C) cm^{-1}. $C_{15}H_{20}Cl_2O_2$ (303.2): calcd. C 59.42, H 6.65, Cl 23.38; found C 58.97, H 6.61, Cl 23.34.

1-(But-3-enyl)-4-*endo*-isopropyl-7-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (23n) and 1-(But-3-enyl)-4-*exo*-isopropyl-7-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-on (23x) by Dechlorination of 21: Crude product **21** (5.50 g, as described before) was dissolved in methanol saturated with ammonium chloride (70 mL). Zinc/copper couple (19.1 g, 292 mmol) was added portionwise with stirring at room temperature. After 1 h, the mixture was heated at reflux overnight, then cooled, and filtered. The filtrate was poured into a stirred ice-cold aqueous solution of EDTA disodium salt dihydrate (8%, Titriplex III, 170 mL). The emulsion was extracted with diethyl ether (5 × 30 mL), and the extracts were combined, washed with brine (30 mL) and dried with magnesium sulfate. The solvent was evaporated in vacuo, and the remaining dark brown oil (3.8 g) was distilled in a kugelrohr at 120–140 °C/0.005 Torr. According to the NMR spectra, the distillate, a pale yellow oil (2.00 g, 45% relating to furan **3**) consisted of **23n** and **23x** in a ratio of 3:1 (75:25). ^{1}H NMR (250 MHz, $CDCl_3$): Major product (75%-component, **23n**): δ = 5.86 (ddt, $^3J_{3,4Z}$ = 17.1 Hz, $^3J_{3,4E}$ = 10.2 Hz, $^3J_{2,3}$ = 6.6 Hz, 1 H, butenyl-3-H), 5.76 (m, 1 H, 6-H), 5.05 (ddt, $^3J_{3,4Z}$ = 17.1 Hz, $^2J_{4Z,4E} = {}^4J_{2,4Z}$ = 1.7 Hz, 1 H, butenyl-4-H$_Z$), 4.97 (ddt, $^3J_{3,4E}$ = 10.2 Hz, $^2J_{4E,4Z} = {}^4J_{2,4E}$ = 1.7 Hz, 1 H, butenyl-4-H$_E$), 4.92 (ddd, J = 1.3 Hz, $^3J_{5,6}$ = 1.3 Hz, $^3J_{4exo,5}$ = 4.0 Hz, 1 H, 5-H), 2.48 (d, $^2J_{2exo,2endo}$ = 14.8 Hz, 1 H, 2-H$_{exo}$), 2.43 (dd, $^3J_{4exo,5}$ = 4.1 Hz, $^3J_{4exo,\text{isopropyl-1-H}}$ = 7.2 Hz, 1 H, 4-H$_{exo}$), 2.31–2.19 (m, surmounted by a d at 2.26 ppm with $^2J_{2endo,2exo}$ = 14.8 Hz, 2 H, 2-H$_{endo}$, butenyl-1-H or -2-H), 2.10–1.93 (m, surmounted by an oct at 1.99 ppm with ^3J = 6.9 Hz, 2 H, isopropyl-1-H, butenyl-1-H or -2-H), 1.85–1.70 (m, surmounted by a finely split s at 1.70 ppm, 5 H, 7-CH_3, butenyl-1-H or -2-H), 1.05 (d, ^3J = 6.7 Hz, 3 H, isopropyl-CH_3), 0.88 (d, ^3J = 7.0 Hz, 3 H, isopropyl-CH_3) ppm. IR (film): $\tilde{\nu}$ = 3080 (C=C–H), 2970, 2960, 2920, 2880 (C–H), 1705 (C=O), 1640 (C=C) cm^{-1}. EIMS (70 eV): m/z (%) = 234 (20) [M$^+$] from $C_{15}H_{22}O_2$, 193 (70), 191 (55), 151 (15), 149 (25), 137 (20), 136 (15), 135 (80), 134 (38), 133 (12), 126 (12), 121 (15), 119 (13), 117 (14), 109 (36), 108 (15), 107 (14), 105 (16), 96 (17), 95 (100), 93 (14), 91 (16), 85 (28), 83 (25), 81 (12), 79 (18), 69 (75), 67 (13), 57 (12), 55 (28), 53 (12), 43 (21), 41 (52), 39 (20). HRMS: calcd. for $C_{15}H_{22}O_2$: 234.1620; found 234.1618. Minor product (25%-component **23x**): δ = 5.86 (ddt, $^3J_{3,4Z}$ = 17.1 Hz, $^3J_{3,4E}$ = 10.2 Hz, $^3J_{2,3}$ = 6.6 Hz, 1 H, butenyl-3-H), 5.76 (m, 1 H, 6-H), 5.05 (ddt, $^3J_{3,4Z}$ = 17.1 Hz, $^2J_{4Z,4E} = {}^4J_{2,4Z}$ = 1.7 Hz, 1 H, butenyl-4-H$_Z$), 4.97 (ddt, $^3J_{3,4E}$ = 10.2 Hz, $^2J_{4E,4Z} = {}^4J_{2,4E}$ = 1.7 Hz, 1 H, butenyl-4-H$_E$), 4.85 (m, 1 H, 5-H), 2.48 (d, $^2J_{2exo,2endo}$ = 14.8 Hz, 1 H, 2-H$_{exo}$), 2.26 (d, $^2J_{2endo,2exo}$ = 14.8 Hz, 1 H, 2-H$_{endo}$) 1.99 (oct, ^3J = 7.0 Hz, 1 H, isopropyl-1-H), 2.8–1.70 (m, 5 H, 4-H$_{endo}$, butenyl-1-H and -2-H), 1.70 (finely split s, 3 H, 7-CH_3), 1.06 (d, ^3J = 6.6 Hz, 3 H, isopropyl-CH_3), 0.91 (d, ^3J = 6.8 Hz, 3 H, isopropyl-CH_3) ppm. ^{13}C NMR/DEPT (62.90 MHz, $CDCl_3$): δ = 12.1 (+, 7-CH_3), 19.9 (+), 22.6 (+) (isopropyl-CH_3 from **23n**), 21.0 (+), 21.6 (+) (isopropyl-CH_3 from **23x**), 24.6 (+, isopropyl-C-1 from **23n**), 27.65 (–), 33.7 (–, butenyl-C-1 and -C-2), 28.0 (+, isopropyl-C-1 from **23x**), 49.6 (–, C-2), 61.1 (+, C-4), 78.3 (+, C-5), 87.6 (C_q, C-1), 114.7 (–, butenyl-C-4), 126.6 (+, C-6), 138.2 (+, butenyl-C-3), 144.2 (C_q, C-7), 207.3 (C_q, C-3) ppm.

1-(But-3-enyl)-2-chloro-4-*endo*-isopropyl-7-methyl-4-*exo*-(2,2,2-trifluoroethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (22): A mixture of 2-(but-3-enyl)-3-methylfuran (4.22 g, 31.0 mmol, **9**) and 1,1,1-trichloro-4-methylpentan-2-one (6.10 g, 30.0 mmol, **20**) was cooled to 0 °C. With magnetic stirring, an NaTFE/TFE solution (c = 2.0 mol L^{-1}, 30.0 mL, 60 mmol) was added at 0 °C over 15 min. A solid precipitated from the yellow reaction mixture. The mixture was stirred at 0 °C for 3 d. A GLC (80→250 °C, 8 K min^{-1}) showed, apart from the peak of unreacted furan **9** (t_R = 4.2 min), two peaks at t_R = 17.6 and 19.0 min. The mixture was then heated at reflux for 3 d, whereupon the peak at t_R = 19.0 min vanished. The mixture was poured into brine (500 mL), and extracted with dichloromethane (5 × 100 mL). The combined extracts were washed with brine (100 mL), dried with magnesium sulfate and concentrated in a rotary evaporator. The remaining liquid was filtered through alumina (400 g, activity grade III) by elution with PE/EA (20:1). The filtrate was concentrated and distilled in a kugelrohr at 110 °C/0.005 Torr to give **22** (8.60 g, 78%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, ^3J = 7.1 Hz, 3 H, isopropyl-CH_3), 1.06 (d, ^3J = 7.0 Hz, 3 H, isopropyl-CH_3), 1.89 (t, J = 1.3 Hz, 3 H, 7-CH_3), 1.80–2.35 (m, 4 H, butenyl-1-H and -2-H), 2.25 (sept, ^3J = 7.0 Hz, 1 H, isopropyl-1-H), 3.70 (dq, $^2J_{Ha,Hb}$ = 11.1 Hz, $^3J_{Ha,F}$ = 8.3 Hz, 1 H, –OCH$_a$H$_b$CF$_3$), 4.00 (dq, $^2J_{Ha,Hb}$ = 11.1 Hz, $^3J_{Hb,F}$ = 8.4 Hz, 1 H, –OCH$_b$H$_a$CF$_3$), 4.72 (s, 1 H, 2-H$_{exo}$), 4.85 (s, 1 H, 5-H), 5.01 (d, split downfield part, $^3J_{3,4E}$ = 10.3 Hz, $^2J_{4Z,4E}$ = 1.5 Hz, 1 H, butenyl-4-H$_E$), 5.09 (dd, $^3J_{3,4Z}$ = 17.2 Hz, $^2J_{4Z,4E}$ = 1.5 Hz, 1 H, butenyl-4-H$_Z$), 5.82–5.93 (m, surmounted by a finely split s at 5.83 ppm, 2 H, 6-H and butenyl-3-H) ppm. ^{13}C NMR/off-resonance (75.47 MHz, $CDCl_3$): δ = 14.5 (q, 7-CH_3), 16.6, 18.6 (q, isopropyl-CH_3), 28.2 (d, isopropyl-C-1), 27.1, 31.6 (t, butenyl-C-1 and -C-2), 62.7 (qt, $^2J_{CF}$ = 35.1 Hz, –OCH$_2$CF$_3$), 66.3 (d, C-2), 80.2 (d, C-5), 87.95, 90.4 (s, C-1, C-4), 115.15 (t, butenyl-C-4), 123.6 (q, $^1J_{CF}$ = 277.8 Hz, –CF$_3$), 125.6 (d, C-6), 137.65 (d, butenyl-C-3), 146.3 (s, C-7), 196.8 (s, C-3) ppm. IR (film): $\tilde{\nu}$ = 3090 (C=C–H), 3010, 2980, 2960, 2940, 2910, 2890, 2860 (C–H), 1730 (C=O), 1645 (C=C) cm^{-1}. EIMS (70 eV): m/z (%) = 366 (12) [M$^+$], 351 (14), 330 (10), 231 (13), 211 (20), 195 (15), 167 (14), 155 (11), 154 (100), 153 (11), 139 (17), 136 (11), 135 (64), 95 (45), 91 (13), 83 (16), 79 (11), 77 (10), 71 (45), 67 (15), 65 (10), 55 (34), 53 (12), 43 (49), 41 (33), 39 (13). HRMS: calcd. for $C_{17}H_{22}ClF_3O_3$ 366.1212; found 366.1211.

1-(But-3-enyl)-4-*endo*-isopropyl-7-methyl-4-*exo*-(2,2,2-trifluoroethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (24): Zinc/copper couple (1.44 g, 22.0 mmol) was added with stirring at room temperature

to a solution of **22** (500 mg, 1.37 mmol) in methanol saturated with ammonium chloride (6 mL). The mixture was then heated at reflux for 2 h, after which the GLC peak of **22** had vanished. The mixture was cooled, poured into a stirred ice-cold aqueous solution of EDTA (8%, 170 mL), and extracted with dichloromethane (4×20 mL). The combined extracts were washed with brine and dried with magnesium sulfate. The solvent was evaporated in vacuo, and the remaining oil was filtered through silica (5 g) by elution with PE/EA (10:1). A pure, nearly colourless oil (**24**, 450 mg, 99%) was isolated from the eluate. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87, 1.01 (d, ^3J = 7.0 Hz, 6 H, isopropyl-CH_3), 1.67–2.67 (m, 4 H, butenyl-1-H and -2-H), 1.75 (t, J = 1.4 Hz, 3 H, 7-CH_3), 2.15 (sept, ^3J = 7.0 Hz, 1 H, isopropyl-1-H), 2.30 (d, $^2J_{2endo,2exo}$ = 16.5 Hz, 1 H, 2-H$_{endo}$), 2.64 (d, $^2J_{2exo,2endo}$ = 16.5 Hz, 1 H, 2-H$_{exo}$), 3.79 (dq, $^2J_{Ha,Hb}$ = 11.5 Hz, $^3J_{Ha,F}$ = 8.6 Hz, 1 H, –OC$_{HaHb}$CF$_3$), 3.90 (dq, $^2J_{Hb,Ha}$ = 11.5 Hz, $^3J_{Hb,F}$ = 8.6 Hz, 1 H, –OC$_{HbHa}$CF$_3$), 4.83 (finely split s, 1 H, 5-H), 4.98 (ddd, $^3J_{3,4E}$ = 10.1 Hz, $^4J_{2,4E}$ = 3.0 Hz, $^2J_{4Z,4E}$ = 1.4 Hz, 1 H, butenyl-4-H$_E$), 5.05 (ddd, $^3J_{3,4Z}$ = 17.1 Hz, $^4J_{2,4Z}$ = 3.3 Hz, $^2J_{4Z,4E}$ = 1.4 Hz, 1 H, butenyl-4-H$_Z$), 5.79 (finely split s, 1 H, 6-H), 5.78–5.91 (m, 1 H, butenyl-3-H) ppm. ^{13}C NMR/off-resonance (75.47 MHz, $CDCl_3$): δ = 12.2 (q, 7-CH_3), 16.4 (q), 18.3 (q) (diastereotopic isopropyl-CH_3), 28.7 (d, isopropyl-C-1), 27.4 (t), 33.7 (t) (butenyl-C-1 and -C-2), 47.25 (t, C-2), 62.8 (qt, $^2J_{CF}$ = 34.7 Hz, –OCH_2CF_3), 81.1 (d, C-5), 85.05 (s), 86.7 (s) (C-1, C-4), 114.8 (t, butenyl-C-4), 123.9 (q, $^1J_{CF}$ = 277.8 Hz, –CF_3), 124.7 (d, C-6), 138.1 (d, butenyl-C-3), 147.2 (s, C-7), 204.7 (s, C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3090, 3080 (C=C–H), 2980, 2970, 2950, 2930, 2880, 2860 (C–H), 1710 (C=O), 1640 cm^{-1} (C=C). EIMS (20 eV): m/z (%) = 332 (64) [M$^+$], 294 (18), 249 (55), 197 (25), 193 (10), 154 (14), 149 (11), 136 (21), 135 (100), 134 (11), 133 (12), 105 (10), 97 (12), 95 (34), 83 (12), 71 (82), 57 (13), 43 (20). HRMS: calcd. for $C_{17}H_{23}F_3O_3$: 332.1599; found 332.1595.

4-*endo*-Isopropyl-7-methyl-1-(3-oxobutyl)-4-*exo*-(2,2,2-trifluoroethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (25): 1-(But-3-enyl)-4-isopropyl-7-methyl-4-(2,2,2-trifluorethoxy)-8-oxabicyclo[3.2.1]-oct-6-en-3-one (**24**, 3.1 g, 9.30 mmol) and mercuric acetate (0.39 g, 1.22 mmol) were dissolved in a mixture of acetone (7.3 mL) and water (1 mL) with magnetic stirring at room temperature. After 30 min, the mixture was cooled down to 0 °C, and Jones' reagent (5.8 mL, equivalent to 15.5 mmol of CrO_3) was added dropwise over 30 min. The cooling bath was removed and stirring was continued at room temperature for 1 h. The mixture was poured into water (20 mL) and extracted with diethyl ether (5×10 mL). The combined diethyl ether extracts were washed with saturated aqueous $NaHCO_3$ solution (2×10 mL) and brine (10 mL), and dried with magnesium sulfate. After evaporation of the solvent (rotary evaporator, then oil pump), a colourless solid (2.67 g, 82% **25**) was obtained. This product was used without purification for the following preparations. For analysis and spectra a sample was recrystallized from a little diethyl ether, which gave colourless, rhombic crystals with m.p. 88–89 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 and 0.96 (d, ^3J = 7.0 Hz, 6 H, diastereotopic isopropyl-CH_3), 1.70 (finely split s, 3 H, 7-CH_3), 1.93 (m, appearing as a dd, 2 H, butyl-2-H), 2.12 (sept, ^3J = 7.0 Hz, 1 H, isopropyl-1-H), 2.13 (s, 3 H, butyl-4-H), 2.2–2.8 [m, surmounted by an AB sub-spectrum at δ_A = 2.57 (2-H$_{exo}$), δ_B = 2.28 (2-H$_{endo}$) ppm, J_{AB} = 16.6 Hz = $^2J_{2endo,2exo}$, 4 H, 2-H$_{endo}$, 2-H$_{exo}$, butyl-1-H], 3.75 (dq, $^2J_{Ha,Hb}$ = 11.5 Hz, $^3J_{Ha,F}$ = 8.5 Hz, 1 H, –OC$_{Ha}$H$_b$CF$_3$), 3.88 (dq, $^2J_{Ha,Hb}$ = 11.5 Hz, $^3J_{Hb,F}$ = 8.5 Hz, 1 H, –OC$_{Hb}$H$_a$CF$_3$), 7.78 (finely split s, 1 H, 5-H), 5.77 (t, J = 1.7 Hz, 1 H, 6-H) ppm. ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 12.0 (+, 7-CH_3), 16.2 (+), 18.3 (+) (isopropyl-CH_3), 27.9 (–), 37.3 (–) (butyl-C-1 and -C-2), 28.3 (+), 30.0 (+) (isopropyl-C-1, butyl-C-4), 47.0 (–, C-2), 62.5 (–, q, $^2J_{C,F}$ = 34.7 Hz, –OCH_2CF_3), 80.95 (+, C-5), 84.9 (C_q), 86.1 (C_q) (C-1, C-4), 123.8 (C_q, q, $^1J_{C,F}$ = 278 Hz, –CF_3), 124.9 (+, C-6), 146.65 (C_q, C-7), 204.2 (C_q, C-3), 207.9 (C_q, butyl-C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3090 (C=C–H), 3020, 2975, 2950, 2920, 2890 (C–H), 1710 (C=O), 1650 (C=C) cm^{-1}. $C_{17}H_{23}F_3O_4$ (348.4): calcd. C 58.61, H 6.65; found C 58.41, H 6.61.

4-*endo*-Isopropyl-7-methyl-1-(3-oxobutyl)-4-*exo*-(2,2,2-trifluoroethoxy)-8-oxabicyclo[3.2.1]octan-3-one (26): A spatula tip of Pd/C catalyst (10%) was added to a solution of **25** (0.35 g, 1.00 mmol) in dry methanol (50 mL), and the suspension was shaken under hydrogen. When the hydrogen uptake was complete (2 h), the catalyst was filtered off and the filtrate concentrated in a rotary evaporator. The white solid product (345 mg, 98% **26**) was used directly for the following reaction (**26** → **27**). A sample for analysis and spectra was recrystallized from hexane, which gave colourless needles with m.p. 96.3 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.94 (d, ^3J = 7.1 Hz, 3 H), 0.95 (d, ^3J = 7.3 Hz, 3 H, diastereotopic isopropyl-CH_3), 1.03 (d, ^3J = 6.8 Hz, 3 H, 7-CH_3), 1.1–1.3, 1.7–2.1, 2.2–2.8 [m, surmounted by a s at 2.17, and an AB sub-spectrum at δ_A = 2.70 (2-H$_{exo}$), δ_B = 2.26 (2-H$_{endo}$) ppm, J_{AB} = 14.8 Hz = $^2J_{2endo,2exo}$, 13 H, isopropyl-1-H, 6-H, 7-H, butyl-1-H, -2-H, -4-H, 2-H$_{endo}$, 2-H$_{exo}$], 3.77 (dq, $^2J_{Ha,Hb}$ = 10.7 Hz, $^3J_{Hb,F}$ = 8.4 Hz, 1 H, –OC$_{Ha}$H$_b$CF$_3$), 4.17 (dq, $^2J_{Ha,Hb}$ = 10.7 Hz, $^3J_{Hb,F}$ = 8.5 Hz, 1 H, –OC$_{Hb}$H$_a$CF$_3$), 4.56 (dd, $^3J_{5,6Ha}$ = 8.7 Hz, $^3J_{5,6Hb}$ = 2.4 Hz, 1 H, 5-H) ppm. ^{13}C-NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 14.5 (+, 7-CH_3), 17.4 (+), 18.05 (+) (diastereotopic isopropyl-CH_3), 27.6 (+), 29.9 (+) (butyl-C-4, isopropyl-C-1), 30.2 (–, butyl-C-1), 34.1 (–), 37.8 (–) (C-6, butyl-C-2), 41.5 (+, C-7), 44.5 (–, C-2), 62.4 (–, q, $^2J_{C,F}$ = 34.9 Hz, –OCH_2CF_3), 75.6 (+, C-5), 85.3 (C_q), 85.5 (C_q) (C-1, C-4), 123.8 (C_q, q, $^1J_{C,F}$ = 278.0 Hz, –CF_3), 204.8 (C_q, C-3), 207.9 (C_q, butyl-C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2970, 2940, 2890 (C–H), 1720, 1710 (C=O), 1280, 1160, 1110 cm^{-1}. $C_{17}H_{25}F_3O_4$ (350.4): calcd. C 58.28, H 7.19; found C 58.39, H 7.27.

X-ray Crystallographic Study:[47] A crystal of **26** (0.5×0.2×0.1 mm) was selected. The compound crystallised in space group $P2_1/c$ with Z = 4 molecules per unit cell. For the X-ray crystal structure determination a Nicolet P3 four-circle diffractometer with a graphite monochromator was used, at 293 K. The X-ray source was monochromatic Mo-K_α radiation, wavelength 71.073 pm. The lattice constants were a = 1003.73(0.14), b = 1868.04(0.30), c = 1021.23(0.12) pm, β = 110.770(9)°, determined from the 2θ values of 25 automatically centred reflexes (20.00° < 2θ < 25.00°) by the least-squares method; the crystal lattice was monoclinic. The intensity data were taken in the Wyckoff-scan mode with a 0.8° angle range and scan rates between 1.0 and 29.3° min^{-1}, depending on reflex intensity. Thus, up to a maximum scattering angle of $2\theta_{max}$ = 50°, 3145 independent reflexes were found; among these 1850 with $I_{obs} > 2\sigma(I_{obs})$ were classified as "observed". The raw data were scaled from three check reflexes – the largest deviation was 4% – and subjected to Lorentz and polarisation correction. A structure model was obtained by direct methods (SHELXS-97)[53] and refined by the least-squares method in full-matrix procedure (SHELXL-97).[54] For the refinement all data were used. Thus, 3145 reflexes contributed to refinement of 218 parameters (scaling factor, position parameter, anisotropic temperature factors for C, O, and F atoms, H atoms were calculated in riding mode) up to $R1$ [$I > 2\sigma(I)$] = 0.0836 and $_wR2$ (all data) = 0.1569, respectively, with $1/w = \sigma^2(F_o)^2 + (0.0404 \cdot P^2) + 1.33 \cdot P$, where $P = [\mathrm{Max}(F_o^2,0) + 2 \cdot F_c^2]/3$. The estimated overall standard deviation of an observation with a weighting factor of one was σ = 1.085. The refinement converged with a residual electron density of 0.19 e A^{-3} and –0.16 e A^{-3}, respectively, detected in the difference Fourier map.

(3aα,4ß,6α,7α)-7-Isopropyl-1,4-dimethyl-7-(2,2,2-trifluoroethoxy)-2,3,4,5,6,7-hexahydro-8*H*-3a,6-epoxyazulen-8-one (27): A solution of **26** (175 mg, 0.50 mol) in methanol (1 mL) was added dropwise by syringe with magnetic stirring to a boiling solution of methanolic KOH (5%, 0.8 mL) over 20 min. The mixture was then heated at reflux for a further 45 min, cooled and poured into a solution of hydrochloric acid (1 M, 1.5 mL) in ice-cold water (20 mL) and extracted with diethyl ether (3×20 mL). The combined diethyl ether extracts were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), and dried with magnesium sulfate. TLC on silica (SIL G/UV_{254}, Macherey–Nagel), developed with PE/EA (1:1), showed a spot with R_f = 0.68 under UV light, while **26** had R_f = 0.58. The solution was concentrated in a rotary evaporator, and the remaining yellow oil (162 mg) was filtered through silica (10 g) by elution with PE/EA (4:1). After evaporation of the solvent, the liquid was distilled in a kugelrohr at 100 °C/0.005 Torr to give **27** (147 mg, 89%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (d, ^3J = 6.9 Hz, 3 H), 0.95 (d, ^3J = 7.1 Hz, 3 H) (diastereotopic isopropyl-CH_3), 1.12 (d, ^3J = 6.8 Hz, 3 H, 4-CH_3), 1.3–1.4, 2.0–2.6 (m, surmounted by an s at 2.13 ppm, 11 H, 1-CH_3, 2-H, 3-H, 4-H, 5-H, isopropyl-1-H), 3.80 (dq, $^2J_{Ha,Hb}$ = 11.6 Hz, $^3J_{Ha,F}$ = 8.7 Hz, 1 H, –$OCH_aH_bCF_3$), 3.89 (dq, $^2J_{Ha,Hb}$ = 11.6 Hz, $^3J_{Hb,F}$ = 8.7 Hz, 1 H, –$OCH_bH_aCF_3$), 4.4–4.6 (m, 1 H, 6-H) ppm. ^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ = 14.0 (+, 4-CH_3), 16.2 (+, 1-CH_3), 17.2 (+), 19.0 (+) (diastereotopic isopropyl-CH_3), 29.0 (+, isopropyl-C-1), 31.9 (–), 33.8 (–) (C-2, C-3), 37.2 (–, C-5), 41.8 (+, C-4), 63.0 (–, q, $^2J_{C,F}$ = 34.7 Hz, –OCH_2CF_3), 79.1 (+, C-6), 84.6 (C_q, C-7), 95.4 (C_q, C-3a), 123.9 (C_q, q, $^1J_{C,F}$ = 277.8 Hz, –CF_3), 134.0 (C_q, C-8a), 157.5 (C_q, C-1), 195.3 (C_q, C-8) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2965, 2940, 2920, 2890, 2850 (C–H), 1710, 1675 (C=O), 1615 (C=C), 1280, 1155, 1110 cm^{-1}. $C_{17}H_{23}F_3O_3$ (332.4): calcd. C 61.44, H 6.97; found C 61.20, H 7.08.

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