

High pressure chiral recognition experiments – a route to homochiral 4-fluorocyclohexenones

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This paper is dedicated to Professor Binne Zwanenburg – a great colleague and a good friend – on the occasion of his 70th birthday

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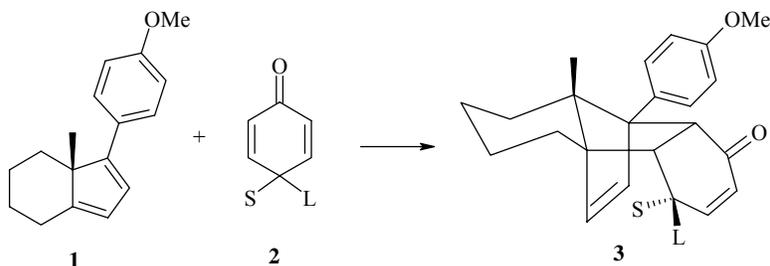
Abstract

4-Fluorocyclohexadienones, prepared by an improved Jacquesy-process, were shown to undergo highly face-selective Diels-Alder reactions with the homochiral cyclopentadiene **1**. Some of the diastereoselective transformations, quite unique rearrangements of α -hydroxy compounds resulting from nucleophilic attack to the carbonyl group as well as selected Retro-Diels-Alder reactions, are reported.

Keywords: Asymmetric synthesis, chiral recognition, cycloadditions, high pressure chemistry, fluorocompounds

Introduction

In recent papers, we communicated the potential of the homochiral cyclopentadiene **1**¹ for sequential diastereoselective cycloadditions,^{2, 3} kinetic resolution⁴ and differentiation of enantiotopic double bonds.^{4, 5, 6, 7} In the latter case, cycloadditions with cyclohexadienones of type **2** were shown to follow the very obvious pathway which places the small residue “S” into the α -endo-position (Scheme 1).



Scheme 1

With various disubstituted cyclohexadienones as well as spiro-cyclohexadienones this was shown to be a highly selective and absolutely reliable transformation,⁷ which however, due to immediate formation of phenols, cannot be exercised with $S = H$.

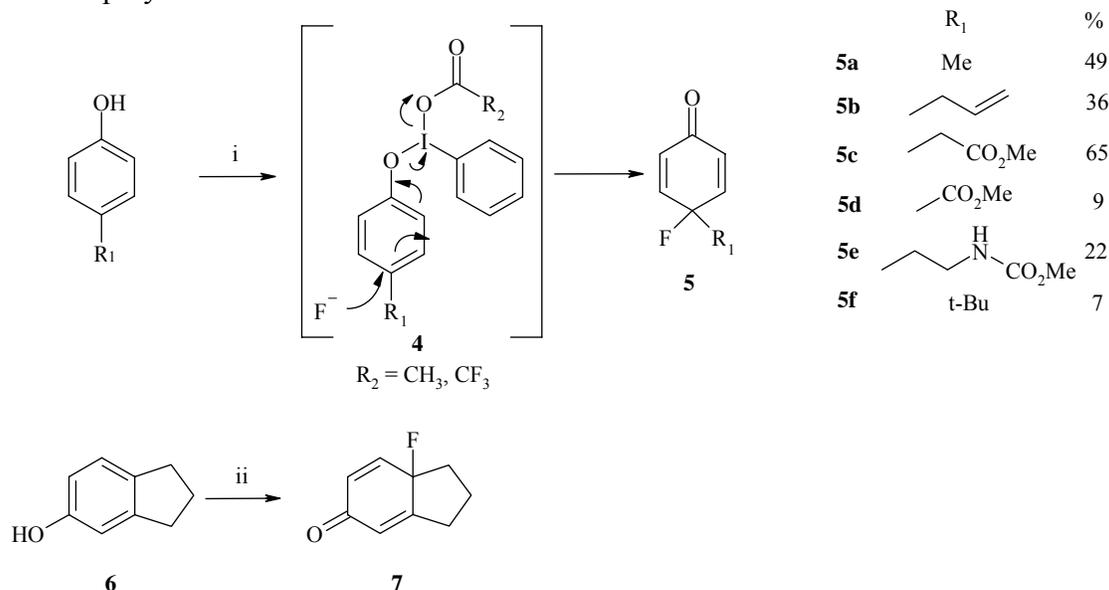
In such a situation with a need for a non-enolizable hydrogen replacement with comparable space demand the fluorine is the candidate of choice.⁸ The special influence of this electron attracting substituent on cycloaddition rates⁷ and biological activity,^{9, 10, 11} that has been reported for various cyclohexenone- and spiro-cyclohexenone derivatives,¹² certainly enhances the motivation for these investigations.

Results and Discussion

Preparation of dienophiles

Looking for a simple and broadly applicable route to fluorinated cyclohexadienones of type **5**, we selected the method published by Jacquesy et. al.¹³ employing bis-trifluoroacetoxy iodobenzene (PIFA) as oxidant and pyridinium poly-hydrogenfluoride (PPHF) as nucleophile. The reaction probably proceeds through intermediate **4** (Scheme 2).

Unfortunately, in our hands even the quite simple methyl derivative **5a** could only be obtained in 34 %. In addition to low yields and bad reproducibility we also observed the formation of phenol dimers and of typically dark brown polymers formed in phenol oxidations.¹⁴ We therefore in some cases chose bis-acetoxy iodobenzene (PIDA) as the weaker oxidant and inverse addition in order to maintain a low stationary phenol concentration (see experimental). Under these conditions, we consistently obtained acceptable yields for **5a**, **5c**, **5e** and **7** together with limited polymer formation.



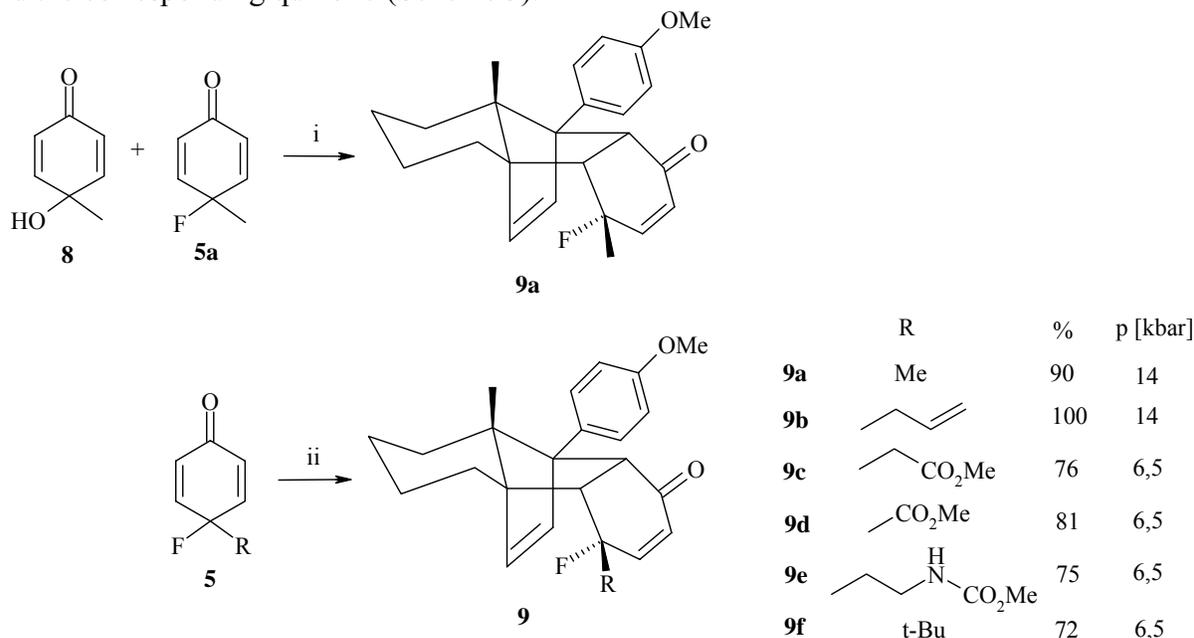
Scheme 2. i: Ar-I(OR)₂, PPHF, CH₂Cl₂; ii: PIDA, PPHF, CH₂Cl₂, 0 °C, 55 min, 47 %.

Since we deal with simple starting materials the optimization process was stopped at this stage. It should be noted that with these modifications even the bicyclic fluoride **7** and the *tert*-butyl derivative **5f** are accessible, however, in the case of **5f** only in 7 % yield. These data clearly demonstrate that the presence of an acceptor group (see **5d**) as well as space demanding substituents (**5e**, **5f**) lower the yield of the transformation.

As expected, all these cyclohexadienones (**5a-5f**) suffer from air oxidation and photo-degradation. However, they can be kept for months if they are stored in the refrigerator at 0 °C under argon.

Cycloaddition experiments

With a good selection of dienophiles available, we focused on a detailed investigation of their cycloaddition behaviour. In order to demonstrate the rate enhancing effects of the fluoro atom⁷ we started with a high pressure competition experiment employing methyl derivative **5a**, which had already been shown to undergo high yielding, diastereoselective cycloadditions at 6,5 kbar,⁵ and the corresponding quinol **8** (Scheme 3).



Scheme 3. i: 1, 14 kbar, RT, 6 d; ii: 1, 6.5-14 kbar, CH₂Cl₂, RT, 7-14 d.

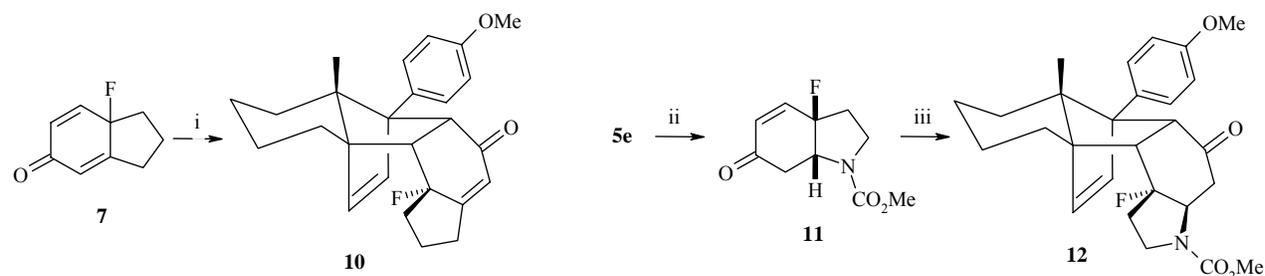
Although this competition experiment was run at 14 kbar for six days, only the fluoro derivative **9a** was formed and proved to be identical to the product obtained earlier at 6,5 kbar. Therefore the cycloadditions with **5b-5f** could be run at both pressures and both cases smoothly provided the corresponding adducts **9b-9f** in good to excellent yields.

A special observation that was particularly made starting from **5b** and **5c** deserves further comments. In some cases without any detectable reason or predictability, no cycloaddition took place at all and the whole material was completely destroyed leading to a black suspension.

Assuming the formation of radicals to be responsible for these undesired processes, we tried a few radical scavengers and were finally successful with the addition of 4-N-acetylamino tetramethylpiperidin-N-oxyl (TEMPO),¹⁵ which leads to perfectly reproducible yields for **9a**, **9b** and **9c** as given in Scheme 3.

HPLC- as well as NMR-data proved all the cycloadducts to be single stereo- and regioisomers. Similarities to the well established data of **9a**⁵ together with NOE measurements (see experimental) indicated the configuration as portrayed in Scheme 3.

Finally, we also studied the Diels-Alder chemistry of the two bicyclic dienophiles **7** and **11**. While **7** resulted directly from the fluorination process (see Scheme 2), **11** was prepared from **5e** via an intramolecular Michael addition (Scheme 4).



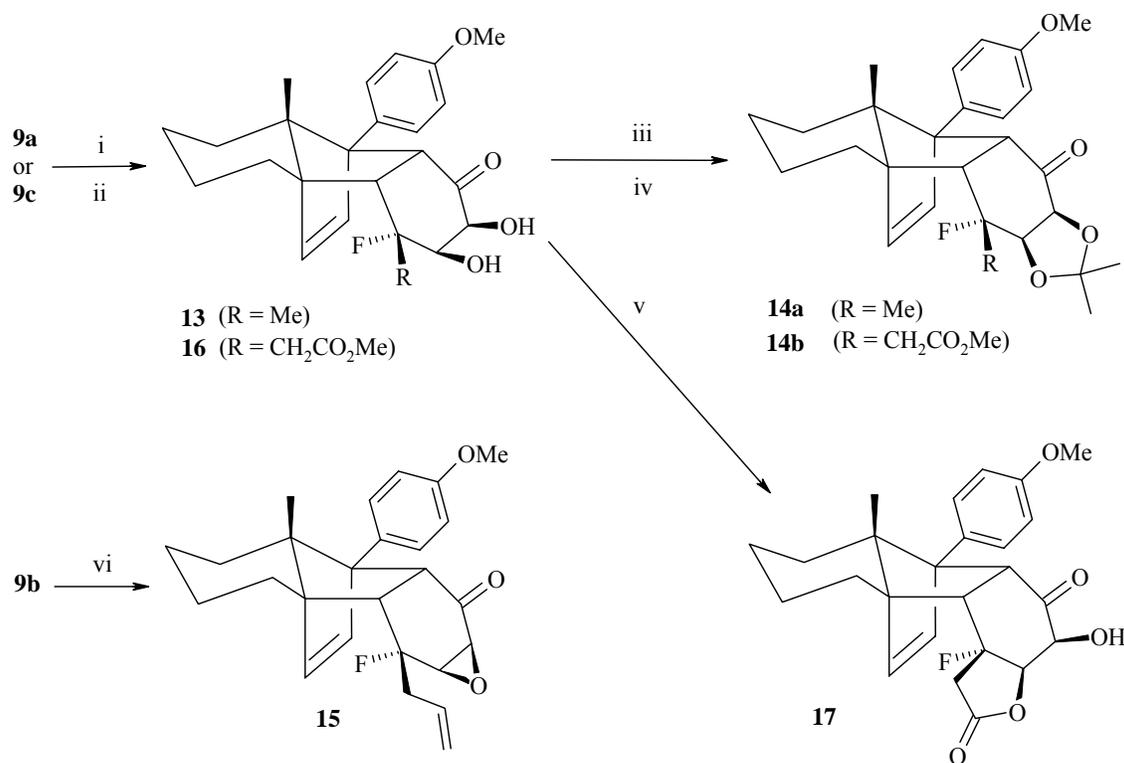
Scheme 4. i: **1**, 6.5 kbar, CH₂Cl₂, RT, 9 d, 14%; ii: NaHCO₃, H₂O, DMSO, overnight, 66 %; iii: **1**, 14 kbar, CH₂Cl₂, RT, 14 d, 36 %.

In both cases the yields at 6,5 kbar are low (starting from **11** only 4 % cycloadduct). Therefore, we repeated this cycloaddition at 14 kbar for a fortnight and obtained 36 % of cycloadduct **12** instead. Taking into consideration that a kinetic resolution is undergone starting from the racemic mixture **11** the yield was clearly improved. The retro process with the material thus obtained provides excellent yields of enantiomerically pure **11**, affording a simple route to homochiral fluorinated alkaloid building blocks.

Selective transformations of cycloadducts

It had been observed in numerous cases before that the special endo-configuration of adducts **9**, **10** and **12** together with their conformational rigidity result in completely diastereoselective β -approach - in electrophilic as well as nucleophilic attack to the cyclohexenone moiety.^{4, 5}

For instance this could be shown for the “flash-dihydroxylation”¹⁶ of **9a** which can be followed by ketal formation and also for the chemo- and diastereoselective nucleophilic epoxidation¹⁷ of the allyl derivative **9b** (Scheme 5).

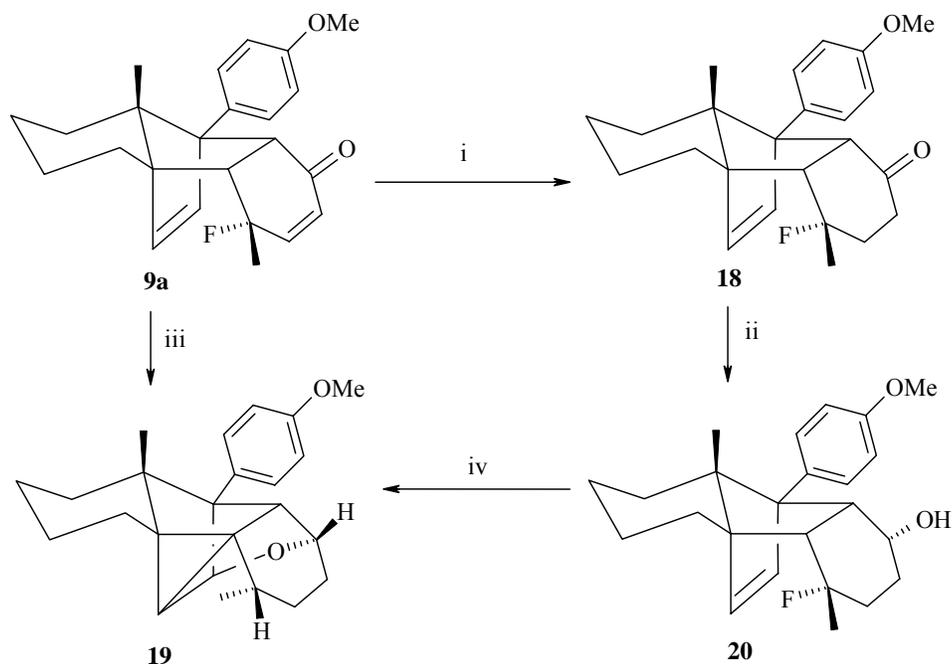


Scheme 5. i: **9a**, RuCl₃, NaIO₄, EtOAc, CH₃CN, RT, 40 min, 71 %; ii: **9c**, RuCl₃, NaIO₄, EtOAc, CH₃CN, RT, 40 min, 71 %; iii: **13**, 2-methoxypropene, p-TsOH, DMF, RT, overnight, 99 %; iv: **16**, 2,2-dimethoxypropane, p-TsOH, DMF, 100 °C, 1 h, 73 %; v: **16**, HCl, THF, RT, 5 d, 22 %; vi: H₂O₂, NaOH, THF, MeOH, RT, 40 min, 97 %.

Interestingly, the ester derivative **9c** gave different results when we tried to apply the flash-hydroxylation – ketal formation sequence. Although hydroxylation worked as expected, ketalisation, which leads to nearly quantitative yields with methyl derivative **14a**, never exceeded 73 % in this case. As prolonged treatment in the presence of acid led to the regeneration of diene **1**, we assume hydrogen fluoride elimination, followed by a retro-Diels-Alder process and aromatization. The reasonable and quite useful formation of lactone **17** was observed on treatment with HCl in tetrahydrofuran, albeit in low yield.

Things became more complicated when we turned to nucleophilic attack to the unsaturated carbonyl group of **9a**.

As expected, treatment with just one equivalent of L-Selectride in toluene at -78 °C led to the saturated ketone **18** in high yield (Scheme 6). Subsequent reduction with K-Selectride gave rise to the α -carbinol **20** exclusively. However, the reduction of **9a** with 2,2 equivalents of L-Selectride did not even provide a trace of the desired product. To our surprise, the high yield reaction product turned out to be polycyclic ether **19**, which obviously had been formed under extrusion of hydrogen fluoride.



Scheme 6. i: L-Selectride 1 eq., toluene, $-78\text{ }^{\circ}\text{C}$, 15 min, 86 %; ii: K-Selectride, toluene, $-78\text{ }^{\circ}\text{C}$, 15 min, 64 %; iii: L-Selectride 2.2 eq., toluene, $-78\text{ }^{\circ}\text{C}$, 15 min, 82 %; iv: LiPF_6 , CH_2Cl_2 , RT, 5 min, 49 %.

This unusual and on the first glance certainly unexpected structure was confirmed by the facts that no fluoro atom was present anymore, that a hydroxyl group was missing, and that the NMR-signal of the methyl group in the six-membered ring showed up as a doublet, giving rise to the assumption that the fluoro atom had been replaced by hydrogen. Additionally, the double bond in the five-membered ring had disappeared. An X-ray analysis finally proved structure **19** (Figure 1).

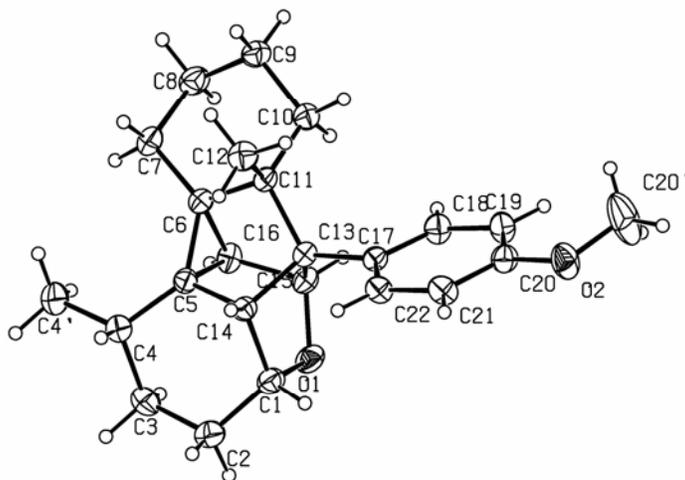
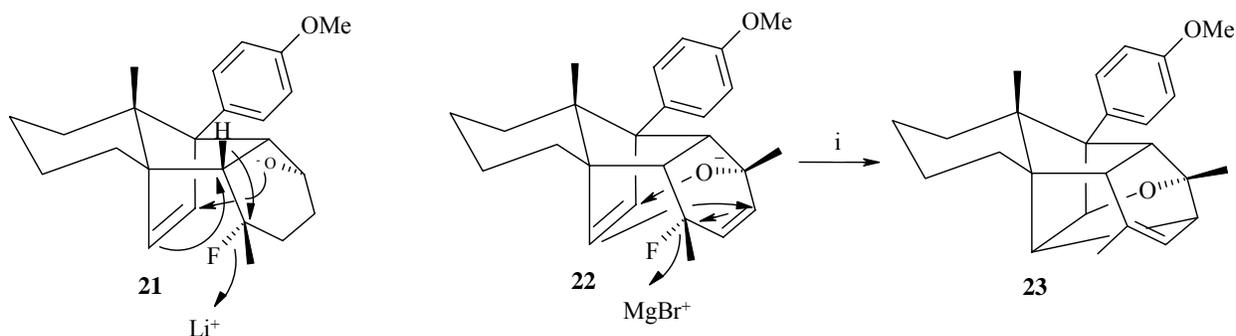


Figure 1. X-ray structure of **19**.

The importance of the lithium counterion for this strange behaviour is clearly demonstrated by the fact that ether formation was also noticed during L-Selectride reduction of the saturated ketone **18**, proving this compound to be an intermediate en route to **19**. On the other hand, K-Selectride reduction of this ketone uneventfully led to the secondary alcohol **20**, which on treatment with lithium hexafluorophosphate in dichloromethane was finally converted to ether **19** again.

Obviously, the lithium cation in inert solvents like toluene or dichloromethane operates as a Lewis acid coordinating with the fluorine, which triggers the rearrangement (see **21**, Scheme 7). Assuming that formation of ether **19** is due to the combined action of a Lewis acid and a hydride donor and that the Lewis acid behaviour of the counterion determines the fate of the fluoro atom, one had of course to check on Grignard reagents. Those reagents represent a combination of Lewis acid and nucleophile which on predictable 1,2-addition to the unsaturated ketone **9a** should result in a highly reactive tertiary, allylic fluoride (see **22**).

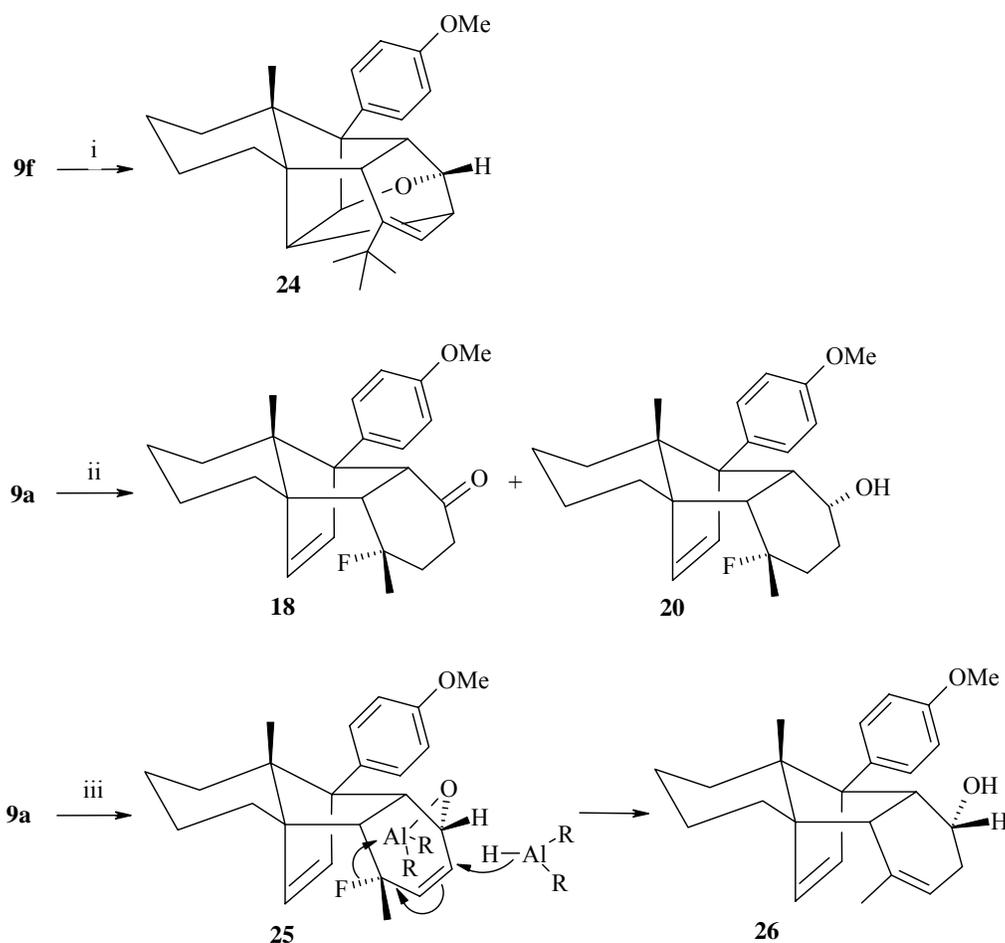


Scheme 7. i: MeMgBr, THF, $-78\text{ }^{\circ}\text{C}$, 5 min, 68 %.

Accordingly, we were not surprised to again isolate 68 % of a non-fluorinated compound after performing the Grignard reaction at $-78\text{ }^{\circ}\text{C}$. As NMR data of this reaction product clearly point to the cyclic ether **23**, we assume in this case S_{N}' -substitution of the fluoride anion (see **22**).

A very similar cyclisation took place in the lithium aluminium hydride reduction of the *tert*-butyl derivative **9f** leading to the cyclic ether **24** (Scheme 8). Although run with a huge excess of lithium aluminium hydride, ether formation in the case of **24** was a much slower process than the Grignard reaction described above. Additionally, it proved to be a specialty of the sterically hindered *tert*-butyl compound **9f**, which obviously only leads to intramolecular S_{N}' -substitution of the fluoro atom. In contrast **9a** under similar conditions gave rise to a mixture of ketone **18** (66 %) and carbinol **20** (34 %) in quantitative yield via an intermolecular 1,4 – 1,2 hydride addition sequence. These results obtained with a Lewis base reducing agent were compared with the outcome in the case of the Lewis acid reagent DIBAL. Here again S_{N}' -substitution dominates the process leading to the homoallylic alcohol **26**. It can be assumed that Lewis acid

assistance from the aluminium alcoholate formed in the reduction step (see **25**) is responsible for the outcome of this reaction.



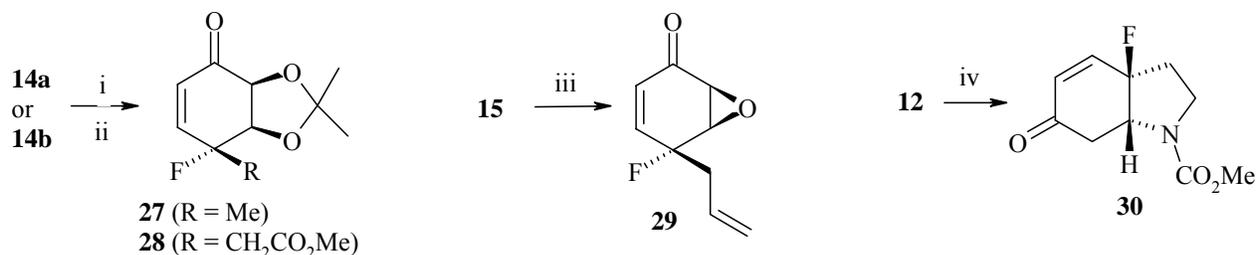
Scheme 8. i: LAH 20 eq., THF, reflux, 1 d, 38 %; ii: LAH 1,2 eq., THF, RT, 5 min, 66 % **18** and 34 % **20**; iii: DIBAL 2.2 eq., toluene, -78 °C, 15 min, 76 %.

Although we are presenting only a comparatively small selection of results obtained on nucleophilic attack to the carbonyl system it demonstrates the enormous impact of the fluorine on the outcome of this process. Minor changes in the starting material as well as in the reagent may lead to a complete change in the reaction pathway. It would certainly need a profound and detailed investigation of all options to arrive at safe rules and predictions.

Retro Diels-Alder chemistry

Since all the cycloadducts described so far can be obtained with perfect face selectivity and undergo any subsequent transformation with very high diastereoselectivity, one could expect homochiral fluorine substituted cyclohexenones from their thermal retro Diels-Alder processes.

While compounds with free hydroxyl groups like **13** and **16** failed completely during Retro-Diels-Alder processes, good to excellent yields could be obtained starting from protected derivatives **14a**, **14b** and **15** (Scheme 9).



Scheme 9. i: **14a**, $2 \cdot 10^{-2}$ mbar, 350 °C, 76 %; ii: **14b**, $2 \cdot 10^{-2}$ mbar, 350 °C, 69 %; iii: $2 \cdot 10^{-2}$ mbar, 350 °C, 70 %; iv: $2 \cdot 10^{-2}$ mbar, 350 °C, 100 %.

It is worth to mention that the indolinone adduct **12**, although suffering from poor yields in its preparation, surprisingly undergoes the retro process in quantitative yield.

Conclusions

All cycloadditions employing diene **1** and the fluorocyclohexadienones **5a-5f**, **7**, and **11** have been shown to proceed with excellent regio- and face-selectivity to provide in all cases a single homochiral Diels-Alder adduct.

Subsequent oxidation reactions at the remaining double bond were characterised by exclusive β -attack leading to reaction products that could be transformed easily into homochiral cyclohexenones in a thermal Retro Diels-Alder reaction.

While these oxidations parallel those with non-fluorinated compounds, diastereoselective nucleophilic attack to the unsaturated carbonyl group led to hydroxyl intermediates, which rearranged under formation of cyclic ethers and under extrusion of the fluoride anion.

Experimental Section

General Procedures. All solvents were distilled before use. Column chromatography was performed on silica gel (Baker, 30-60 μ m) with the indicated eluent. High pressure of 14 kbar was achieved with a high pressure apparatus from Hofer. Reactions with 6,5 kbar were performed with a high pressure apparatus from Nova Swiss using the pneumatic pump 550.0441-A. FVP (flash vacuum pyrolysis) was carried out in an apparatus presented by Seybold und Jersak¹⁹. Melting points were determined with a melting point apparatus from Gallenkamp and are not corrected. IR-spectra were recorded with a Perkin-Elmer FT 1710 spectrometer. The

wave numbers ν of the characteristic bands are given in cm^{-1} . The intensities are abbreviated as follows: s (strong), m (middle) and w (weak). NMR spectra were recorded on a Bruker AM 400 (400 MHz for ^1H , 100 MHz for ^{13}C), WP 200 (200 MHz for ^1H) and Varian Gemini 200 BB (188 MHz for ^{19}F) spectrometer. Chemical shifts (δ in ppm) are given from internal CHCl_3 (7.26) for ^1H NMR and $^{13}\text{CDCl}_3$ (77.0) for ^{13}C NMR. Coupling constants J are presented in Hz. Multiplicities for ^1H NMR are abbreviated as follows: s (singlet), d (doublet), tr (triplet), q (quartet), m (multiplet). Broad signals are marked with a br. The number of protons is electronically integrated. Multiplicities for ^{13}C NMR have been obtained by using the DEPT (Distortionless Enhancement by Polarisation Transfer) technique. The signals are named as follows: p = primary, s = secondary, t = tertiary and q = quaternary carbon atoms. Mass spectra (MS) were determined on a Finnigan MAT 312 at an ionisation potential of 70eV and the indicated temperature. Intensities are in relative relation to the base peak. Mass spectra (HRMS) were performed on a VG AUTOSPEC spectrometer using the peak-matching method. FAB (fast atomic bombardment)-spectra were determined with a VG AUTOSPEC in a m-nitrobenzyl alcohol matrix at low resolution. Intensities are given relative to the base peak.

3-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-3aH-indene (1). For preparation and spectroscopic data, see lit.¹.

4-Fluoro-4-methylcyclohexa-2,5-dienone (5a). Phenyliodine diacetate (PIDA) (28.6 g, 90.22 mmol) was dissolved in CH_2Cl_2 (1050 ml) and pyridinium poly-hydrogen fluoride (PPHF) (17.34 ml) was added. A solution of p-cresol (7.5 g, 69.4 mmol) in CH_2Cl_2 (340 ml) was prepared and added dropwise to the PIDA/PPHF-mixture at 0 °C over a period of 45 minutes. The mixture was stirred for another 10 minutes at 0 °C, then the reaction was stopped by addition of solid potassium carbonate. The stirred suspension was allowed to warm to room temperature, filtered, and the solvent was evaporated under reduced pressure. The crude product was chromatographed on silica gel with petroleum ether/ Et_2O (5:1) to give **5a** (4.292 g, 49 %) as a yellow oil. ^{19}F -NMR (188 MHz, CDCl_3): $\delta = -146.0$ (s, 1F); For further spectroscopic data, see lit.¹³

4-Allyl-4-fluorocyclohexa-2,5-dienone (5b). PPHF (0.56 ml) was added to a solution of p-allylphenol (301 mg, 2.24 mmol) in CH_2Cl_2 (80 ml) followed by portion wise addition of bis-trifluoroacetoxy iodobenzene (PIFA) (1.235 g, 2.912 mmol). The reaction was quenched with solid potassium carbonate after 30 minutes of stirring at room temperature. The suspension was stirred for an additional five minutes, filtered, and concentrated in vacuo. Flash chromatography on silica gel with petroleum ether/ Et_2O (13:1) afforded **5b** (123 mg, 36 %) as a yellow liquid. IR (CHCl_3 , cm^{-1}): 3084 (w), 3028 (w), 2944 (w), 2912 (w), 1676 (s), 1640 (s), 1384 (m), 1224 (s), 928 (s), 856 (s); ^1H NMR (200 MHz, CDCl_3): $\delta = 2.64$ (dd, 16/8 Hz, 2H); 5.18 (m, 2H); 5.71 (m, 1H); 6.25 (d, 10 Hz, 2H); 6.88 (dd, 10/6 Hz, 2H); Exact mass Calcd.: 152.0638, found: 152.0638.

Methyl(1-fluoro-4-oxocyclohexa-2,5-dien-1-yl)acetate (5c). The reaction was performed according to the preparation of **5a** with PIDA (2.481 g, 7.8 mmol) in CH_2Cl_2 (80 ml), PPHF

(1.5 ml), methyl (4-hydroxyphenyl)acetate (1 g, 6 mmol) in CH₂Cl₂ (40 ml), and a flash chromatography on silica gel with petroleum ether/Et₂O (5:1). **5c** (722 mg, 65 %) was obtained as a yellow oil. IR (CHCl₃): ν = 3040 (w), 2956 (w), 1720 (s), 1680 (s), 1640 (m), 1436(m), 1172 (m) cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ = 2.91 (d, 17 Hz, 2H); 3.72 (s, 3H); 6.29 (d, 9 Hz, 2H), 7.06 (dd, 6/9 Hz, 2H); Exact mass Calcd.: 184.0536, found: 184.0537.

Methyl 1-fluoro-4-oxocyclohexa-2,5-diene-1-carboxylate (5d). The reaction was performed according to the preparation of **5a** with bis-trifluoroacetoxy pentafluorophenylidane (662 mg, 1.3 mmol) in CH₂Cl₂ (13 ml), PPHF (0.25 ml), methyl 4-hydroxybenzoate (152 mg, 1 mmol) in CH₂Cl₂ (7 ml), and a flash chromatography on silica gel with petroleum ether/Et₂O (3:1). **5d** (16 mg, 9 %) was obtained as a white solid. IR (CHCl₃, cm⁻¹): 3040 (w), 2956 (w), 1764 (s), 1676 (s), 1640 (m), 1436 (m), 1256 (s), 1036 (s), 852 (m); ¹H NMR (200 MHz, CDCl₃): δ = 3.83 (s, 3H); 6.42 (d, 10 Hz, 2H); 6.92 (dd, 10/7 Hz, 2H); Exact mass Calcd.: 170.0379, found: 170.0379.

Methyl 2-(1-fluoro-4-oxocyclohexa-2,5-diene-1-yl)ethylcarbamate (5e). The reaction was performed according to the preparation of **5a** with PIDA (5.666 g, 17.862 mmol) in CH₂Cl₂ (185 ml), PPHF (3.436 ml), methyl 2-(4-hydroxyphenyl)ethylcarbamate (2.683 g, 13.74 mmol) in CH₂Cl₂ (90 ml), and a flash chromatography on silica gel with petroleum ether/Et₂O (5:1). **5e** (773 mg, 22 %) was obtained as a white solid. IR (CHCl₃, cm⁻¹): 3456 (m), 3000 (w), 2956 (w), 1724 (s), 1676 (s), 1640 (m), 1516 (s), 1236 (s); ¹H NMR (400 MHz, CDCl₃): δ = 2.14 (dtr, 17/7 Hz, 2H); 3.32 (m, 2H); 3.67 (s, 3H); 4.80 (mbr, 1H); 6.27 (d, 10 Hz, 2H); 6.92 (dd, 10/7 Hz, 2H); Exact mass Calcd.: 213.0801, found: 213.0802.

4-tert-Butyl-4-fluorocyclohexa-2,5-dienone (5f). The reaction was performed according to the preparation of **5b** with *p*-tert-butylphenol (5 g, 33.3 mmol), CH₂Cl₂ (666 ml), PPHF (8.32 ml), PIDA (13.937 g, 43.29 mmol), and a flash chromatography on silica gel with petroleum ether/Et₂O (10:1). **5f** (381 mg, 7 %) was obtained as a yellow liquid. IR (CHCl₃, cm⁻¹): 2972 (m), 1676 (s), 1636 (s), 1504 (w), 1368 (m), 1172 (m), 992 (m); ¹H NMR (400 MHz, CDCl₃): δ = 1.06 (d, 1 Hz, 9H); 6.29 (d, 10 Hz, 2H); 7.00 (dd, 7/10 Hz, 2H); Exact mass Calcd.: 168.0953, found: 168.0950.

7a-Fluoro-1,2,3,7a-tetrahydro-5H-inden-5-one (7). The reaction was performed according to the preparation of **5a** with PIDA (3.073 g, 9.689 mmol) in CH₂Cl₂ (100 ml), PPHF (1.86 ml), 5-indanol (1 g, 7.453 mmol) in CH₂Cl₂ (50 ml), and a flash chromatography on silica gel with petroleum ether/Et₂O (10:1). **7** (537 mg, 47 %) was obtained as a yellow oil. For spectroscopic data, see Lit.¹³

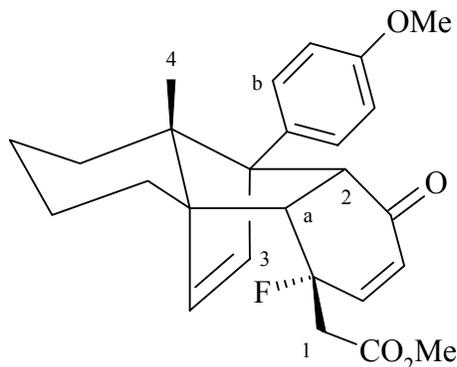
4-Hydroxy-4-methylcyclohexa-2,5-dien-1-one (8). For preparation and spectroscopic data, see Lit.⁷

4-Fluoro-4-methylcyclohexa-2,5-dienone adduct (9a). Dienone **5a** (50 mg, 0.396 mmol), diene **1** (105 mg, 0.436 mmol), TEMPO (93 mg, 0.436 mmol) and CH₂Cl₂ (0.5 ml) were sealed in a Teflon tube and exposed to a pressure of 14 kbar for 14 days. After evaporating the solvent under reduced pressure and flash chromatography on silica gel with petroleum ether/Et₂O (5:1) **9a**

(130 mg, 90 %) was obtained as a white solid. ^{19}F -NMR (188 MHz, CDCl_3): $\delta = -141.7$ (s, 1F); For further spectroscopic data, see Lit.⁵

4-Allyl-4-fluorocyclohexa-2,5-dienone adduct (9b). The reaction was performed according to the preparation of **9a** with dienone **5b** (200 mg, 1.314 mmol), diene **1** (348 mg, 1.445 mmol), TEMPO (308 mg, 1.445 mmol), CH_2Cl_2 (1.3 ml) over a period of 7 d at 14 kbar followed by a flash chromatography on silica gel with petroleum ether/ Et_2O (5:1). **9b** (513 mg, 100 %) was obtained as a white foam. IR (CHCl_3 , cm^{-1}): 3000 (w), 2928 (m), 2864 (w), 1668 (s), 1640 (w), 1612 (w), 1516 (s), 1252 (s), 1180 (s); ^1H NMR (200 MHz, CDCl_3): $\delta = 0.45$ (dbr, 13 Hz, 1H); 0.81 (s, 3H); 1.03-1.71 (m, 5H); 1.84 (dtrbr, 13/4 Hz, 1H); 2.28 (dbr, 10 Hz, 1H); 2.51 (m, 2H); 2.88 (d, 9 Hz, 1H); 3.67 (dd, 9/5 Hz, 1H); 3.80 (s, 3H); 5.14 (m, 1H); 5.23 (m, 1H); 5.66 (m, 1H); 5.82 (d, 12 Hz, 1H); 5.84 (d, 6 Hz, 1H); 6.06 (dd, 6/4 Hz, 1H); 6.47 (dd, 12/11 Hz, 1H); 6.88 (d, 9 Hz, 2H); 7.31 (d, 9 Hz, 2H); FAB-MS: m/z (%) = 392 (M^+ , 3), 240 (100, diene **1**).

Methyl(1-fluoro-4-oxocyclohexa-2,5-dien-1-yl)acetate adduct (9c). The reaction was performed according to the preparation of **9a** with dienone **5c** (1.872 g, 10.165 mmol), diene **1** (2.687 g, 11.182 mmol), TEMPO (2.385 g, 11.182 mmol), CH_2Cl_2 (10 ml) over a period of 10 d at 6.5 kbar followed by a flash chromatography on silica gel with petroleum ether/ Et_2O (3:1). **9c** (3.263 g, 76 %) was obtained as a white solid, mp 91.6 °C. IR (CHCl_3 , cm^{-1}): 3000 (w), 2952 (m), 2928 (m), 2864 (w), 1740 (s), 1672 (s), 1612 (w), 1516 (s), 1248 (s), 1180 (s); ^1H NMR (200 MHz, CDCl_3): $\delta = 0.46$ (dbr, 13 Hz, 1H); 0.83 (s, 3H); 1.12-1.72 (m, 5H); 1.85 (dtrbr, 14/4 Hz, 1H); 2.27 (dbr, 13 Hz, 1H); 2.86 (dd, 14/2 Hz, 2H); 3.11 (dd, 8/3 Hz, 1H); 3.67 (s, 3H); 3.78 (d, 8 Hz, 1H); 3.80 (s, 3H); 5.85 (dd, 10/2 Hz, 1H); 5.86 (d, 5 Hz, 1H); 6.05 (dd, 5/6 Hz, 1H); 6.51 (dd, 13/10 Hz, 1H); 6.87 (d, 9 Hz, 2H); 7.32 (dd, 9/9 Hz, 2H); NOE-experiment:



Irradiation: NOE:
 H-a +6,0 % (H-1), +10,2 % (H-4)
 H-b +9,0 % (H-2), +8,2 % (H-3), +2,5 % (H-4).
 Exact mass Calcd.: 424.2049, found: 424,2052.

Methyl 1-fluoro-4-oxocyclohexa-2,5-diene-1-carboxylate adduct (9d). The reaction was performed according to the preparation of **9a** with dienone **5d** (52 mg, 0.297 mmol), diene **1**

(81 mg, 0.327 mmol), CH₂Cl₂ (0.5 ml) over a period of 7 d at 6.5 kbar followed by a flash chromatography on silica gel with petroleum ether/Et₂O (3:1). **9d** (101 mg, 81 %) was obtained as a white solid, mp 139.9 °C. IR (CHCl₃, cm⁻¹): 3000 (w), 2956 (m), 2936 (m), 2864 (w), 1756 (s), 1672 (s), 1636 (w), 1516 (s), 1252 (s), 1032 (m); ¹H NMR (400 MHz, CDCl₃): δ = 0.48 (dbr, 13 Hz, 1H); 0.83 (s, 3H); 1.12-1.49 (m, 4H); 1.64 (dbr, 13 Hz, 1H); 1.85 (dtrbr, 13/4 Hz, 1H); 2.28 (ddbr, 13/2 Hz, 1H); 3.15 (d, 8 Hz, 1H); 3.80 (s, 6H); 3.90 (dd, 8/4 Hz, 1H); 5.89 (d, 6 Hz, 1H); 5.95 (d, 10 Hz, 1H); 6.07 (dd, 6/3 Hz, 1H); 6.42 (dd, 13/10 Hz, 1H); 6.88 (d, 9 Hz, 2H); 7.32 (d, 9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 15.26 (p); 21.03 (s); 23.72 (s); 27.40 (s); 28.42 (s); 47.17 (t, doublet 20 Hz); 49.94 (t); 53.58 (p); 55.18 (p); 61.64 (q); 62.39 (q); 71.17 (q); 93.02 (q, doublet 190 Hz); 2x 113.13 (t); 2x 128.60 (q); 129.13 (t), 134.23 (t); 136.27 (t); 138.60 (t); 140.85 (t, doublet 31 Hz); 158.41 (q); 170.48 (q, doublet 29 Hz); 197.69 (q); Exact mass Calcd.: 410.1893, found: 410.1878.

Methyl 2-(1-fluoro-4-oxocyclohexa-2,5-diene-1-yl)ethylcarbamate adduct (9e). The reaction was performed according to the preparation of **9a** with dienone **5e** (141 mg, 0.661 mmol), diene **1** (175 mg, 0.727 mmol), CH₂Cl₂ (0.7 ml) over a period of 14 d at 6.5 kbar followed by a flash chromatography on silica gel with petroleum ether/Et₂O (1:3). **9e** (226 mg, 75 %) was obtained as a colorless oil. IR (CHCl₃, cm⁻¹): 3456 (m), 3000 (w), 2956 (m), 2928 (m), 2860 (w), 1720 (s), 1672 (s), 1526 (s), 1240 (s); ¹H NMR (400 MHz, CDCl₃): δ = 0.45 (dbr, 13 Hz, 1H); 0.83 (s, 3H); 1.12-2.32 (m, 9H); 2.89 (d, 8 Hz, 1H); 3.33 (m, 2H); 3.67 (s, 3H); 3.75 (dd, 8/5 Hz, 1H); 4.84 (m, 1H); 5.81 (d, 10 Hz, 1H); 5.84 (d, 6 Hz, 1H); 6.52 (dd, 10/11 Hz, 1H); 6.88 (d, 9 Hz, 2H); 7.30 (d, 9 Hz, 2H); FAB-MS: m/z (%) = 453 (M⁺, 2), 240 (100, diene **1**).

4-tert-Butyl-4-fluorocyclohexa-2,5-dienone adduct (9f). The reaction was performed according to the preparation of **9a** with dienone **5f** (50 mg, 0.297 mmol), diene **1** (79 mg, 0.327 mmol), CH₂Cl₂ (0.5 ml) over a period of 14 d at 6.5 kbar followed by a flash chromatography on silica gel with petroleum ether/Et₂O (5:1). **9f** (87 mg, 72 %) was obtained as a white foam. IR (CHCl₃, cm⁻¹): 2960 (s), 2928 (s), 2864 (m), 1668 (s), 1612 (w), 1516 (s), 1248 (m), 1180 (m); ¹H NMR (200 MHz, CDCl₃): δ = 0.44 (dbr, 13 Hz, 1H); 0.85 (d, 1 Hz, 3H); 0.96 (d, 1 Hz, 9H); 1.08-1.73 (m, 5H); 1.85 (m, 1H); 2.26 (m, 1H); 3.01 (d, 8 Hz, 1H); 3.63 (dd, 8/6 Hz, 1H); 3.80 (s, 3H); 5.81 (d, 6 Hz, 1H); 5.91 (dd, 10/2 Hz, 1H); 6.03 (dd, 6/4 Hz, 1H); 6.46 (dd, 14/10 Hz, 1H); 6.88 (d, 9 Hz, 2H); 7.33 (dd, 9/10 Hz, 2H); FAB-MS: m/z (%) = 408 (M⁺, 1), 240 (100, diene **1**).

7a-Fluoro-1,2,3,7a-tetrahydro-5H-inden-5-one adduct (10). The reaction was performed according to the preparation of **9a** with dienone **7** (241 mg, 1.584 mmol), diene **1** (419 mg, 1.742 mmol), CH₂Cl₂ (2 ml) over a period of 9 d at 6.5 kbar followed by a flash chromatography on silica gel with petroleum ether/Et₂O (5:1). **10** (86 mg, 14 %) was obtained as a yellow foam. IR (CHCl₃, cm⁻¹): 3000 (m), 2956 (s), 2932 (s), 2868 (m), 1652 (s), 1612 (m), 1516 (s), 1252 (s); ¹H NMR (400 MHz, CDCl₃): δ = 0.47 (dbr, 13 Hz, 1H); 0.86 (s, 3H); 1.08-2.95 (m, 13H); 3.06 (dd, 31/8 Hz, 1H); 3.80 (s, 3H); 3.86 (d, 8 Hz, 1H); 5.81 (d, 6 Hz, 1H); 5.90 (m, 2H); 6.88 (d, 10 Hz, 2H); 7.33 (d, 10 Hz, 2H); Exact mass Calcd.: 372.2089 (M⁺-HF), found: 372.2084 (M⁺-HF).

Methyl 3a-fluoro-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate (11). Carbamate **5e** (1.85 g, 8.677 mmol) was dissolved in DMSO (260 ml) and saturated aqueous sodium

bicarbonate solution (37 ml) was added. The suspension was stirred overnight at 40 °C. After cooling to room temperature, the mixture was partitioned between water and Et₂O. The aqueous layer was separated, neutralized with 2 N HCl, and extracted four times with Et₂O. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The following flash chromatography on silica gel with petroleum ether/Et₂O (1:1) gave **11** (1,215 g, 66 %) as a white solid, mp 65.2 °C. IR (CHCl₃, cm⁻¹): 3028 (m), 2956 (m), 2900 (w), 1692 (s), 1452 (s), 1392 (s), 1236 (s), 1124 (s), 948 (s); ¹H NMR (400 MHz, CDCl₃): δ = 2.23 (m, 2H); 2.44 (m, 1H); 3.15 (dd, 16/7 Hz, 1H); 3.70 (m, 2H); 3.74 (s, 3H); 4.42 (m, 1H); 6.11 (d, 11 Hz, 1H); 6.89 (dd, 11/10 Hz, 1H); Exact mass Calcd.: 213.0801, found: 213.0804.

Methyl 3a-fluoro-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate adduct (12). The reaction was performed according to the preparation of **9a** with hydroindole **11** (100 mg, 0.47 mmol), diene **1** (124 mg, 0.517 mmol), CH₂Cl₂ (0.5 ml) over a period of 14 d at 14 kbar followed by a flash chromatography on silica gel with petroleum ether/Et₂O (1:3). **12** (76 mg, 36 %) was obtained as a white solid. IR (CHCl₃, cm⁻¹): 3000 (w), 2956 (m), 2928 (m), 2864 (w), 1692 (s), 1612 (w), 1516 (m), 1456 (s), 1392 (s), 1248 (m), 1228 (m); ¹H NMR (400 MHz, CDCl₃): δ = 0.45 (dbr, 13 Hz, 1H); 0.79 (s, 3H); 1.14-2.37 (m, 10H); 2.79 (dd, 17/8 Hz, 1H); 2.95 (m, 1H); 3.46 (m, 2H); 3.68 (s, 3H); 3.75 (d, 10 Hz, 1H); 3.79 (s, 3H); 4.02 (m, 1H); 6.21 (d, 6Hz, 1H); 6.31 (dd, 6/3 Hz, 1H); 6.87 (d, 10 Hz, 2H); 7.23 (dd, 10/11 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 15.31 (p); 21.13 (s); 23.74 (s); 26.91 (s); 27.38 (s); 37.25 (s, doublet 25 Hz); 41.98 (s); 46.42 (s); 49.82 (t); 52.45 (p); 54.58 (t); 55.16 (p); 59.94 (t); 62.09 (q); 62.87 (q); 68.59 (q); 101.63 (q, doublet 76 Hz); 2x 113.28 (t); 2x 128.49 (t); 129.10 (q); 136.90 (t); 139.37 (t); 155.00 (q); 158.34 (q); 208.93 (q); Exact mass Calcd.: 453.2315, found: 453.2325.

Diol adduct (13). For preparation and spectroscopic data, see Lit.¹³.

Acetonide adduct (14a). To a solution of diol adduct **13** (102 mg, 0.255 mmol) and a catalytic amount of p-toluenesulfonic acid in dry DMF (5 ml) 2-methoxypropene (120 μl, 1.275 mmol) was added at 0 °C. The reaction was stirred over night at room temperature and then diluted with Et₂O. The organic layer was washed two times with brine, dried over MgSO₄, and filtered. Concentration in vacuo and subsequent flash chromatography on silica gel with petroleum ether/Et₂O (3:1) provided **14a** (111 mg, 99%) as a white solid, mp 163.9 °C. IR (CHCl₃, cm⁻¹): 2996 (s), 2936 (s), 1728 (s), 1612 (w), 1516 (s), 1464 (m), 1380 (s), 1292 (s), 1180 (s), 1072 (s); ¹H NMR (400 MHz, CDCl₃): δ = 0.60 (dbr, 13 Hz, 1H); 0.79 (s, 3H); 1.10-1.70 (m, 5H); 1.38 (s, 3H); 1.57 (s, 3H); 1.70 (s, 3H); 2.05 (dtrbr, 10/4 Hz, 1H); 2.20 (dbr, 13 Hz, 1H); 3.00 (dd, 34/10 Hz, 1H); 3.79 (s, 3H); 4.14 (d, 8 Hz, 1H); 4.28 (d, 10 Hz, 1H); 4.30 (dd, 8/5 Hz, 1H); 5.95 (dd, 9/6 Hz, 1H); 6.16 (d, 6 Hz, 1H); 6.85 (d, 10 Hz, 2H); 7.15 (d, 10 Hz, 2H); Exact mass Calcd.: 440.2363, found: 440.2368.

Acetonide adduct (14b). Diol **16** (200 mg, 0.44 mmol) in dry DMF (8 ml), 2,2-dimethoxypropane (4 ml) and a catalytic amount of p-toluenesulfonic acid were heated for 1 hour at 100 °C. The work-up procedure started by diluting with Et₂O, washing with water followed by washing with brine. After drying the organic layer over MgSO₄, filtering and evaporating the solvent under reduced pressure the crude product was purified by flash

chromatography on silica gel with petroleum ether/Et₂O (3:1) to afford **14b** (158 mg, 73 %) as a white foam. IR (CHCl₃, cm⁻¹): 2992 (m), 2932 (s), 2856 (m), 1732 (s), 1612 (w), 1516 (s), 1436 (w), 1384 (m), 1252 (s), 1180 (s); ¹H NMR (200 MHz, CDCl₃): δ = 0.60 (dbr, 13 Hz, 1H); 0.78 (s, 3H); 1.0-2.27 (m, 7H); 1.40 (d, 10 Hz, 3H); 1.60 (d, 12 Hz, 3H); 2.80 (m, 3H); 3.72 (s, 3H); 3.79 (s, 3H); 4.14 (d, 8 Hz, 1H); 4.32 (d, 10 Hz, 1H); 4.82 (dd, 8/6 Hz, 1H); 5.95 (dd, 9/6 Hz, 1H); 6.20 (d, 6Hz, 1H); 6.85 (d, 9 Hz, 2H); 7.14 (d, 9 Hz, 2H); FAB-MS: m/z (%) = 498 (M⁺, 6), 240 (100, diene **1**).

Epoxide adduct (15). Adduct **9b** (230 mg, 0.586 mmol) was dissolved in a MeOH/THF-mixture (49 ml/15 ml) and cooled to 0 °C. A second solution of NaOH (293 mg, 7.325 mmol) in 30 % aqueous H₂O₂ (15 ml) was prepared at 0 °C and dropped portion wise to the adduct solution. After stirring for 40 minutes at room temperature the reaction was stopped by diluting with CH₂Cl₂ and washed with ice-cold Fe(II)SO₄-solution (2x). The combined aqueous phases were extracted three times with CH₂Cl₂ and the combined organic extracts were dried over MgSO₄. After filtration and concentration in vacuo a flash chromatography on silica gel with petroleum ether/Et₂O (1:1) afforded **15** (231 mg, 97 %) as a white foam. IR (CHCl₃, cm⁻¹): 2932 (s), 2856 (m), 1716 (s), 1612 (w), 1516 (s), 1464 (w), 1444 (w), 1248 (s), 1180 (m); ¹H NMR (400 MHz, CDCl₃): δ = 0.56 (dbr, 13 Hz, 1H); 0.75 (s, 3H); 1.10-1.60 (m, 4H); 1.67 (dbr, 13 Hz, 1H); 1.99 (dtrbr, 9/4 Hz, 1H); 2.16 (dbr, 13 Hz); 2.69-2.98 (m, 3H); 3.30 (d, 4 Hz, 1H); 3.49 (dd, 4/1 Hz, 1H); 3.79 (s, 3H); 3.89 (dd, 11/1 Hz, 1H); 5.29 (m, 1H); 5.33 (m, 1H); 5.93 (dd, 13/6 Hz, 1H); 5.97 (m, 1H); 6.12 (d, 6 Hz, 1H); 6.84 (d, 10 Hz, 2H); 7.12 (d, 10 Hz, 2H); Exact mass Calcd.: 408.2101, found: 408.2106.

Diol adduct (16). Adduct **9c** (1 g, 2.356 mmol) was dissolved in ethyl acetate (20 ml) and acetonitrile (20 ml). A solution of RuCl₃·3H₂O (35 mg, 0.133 mmol) and NaIO₄ (608 mg, 3.534 mmol) in water (5 ml) was added at 0 °C. After 40 minutes of stirring at room temperature, the reaction was quenched by addition of a saturated aqueous Na₂S₂O₃-solution (24 ml). The mixture was stirred for another five minutes and extracted three times with EtOAc. Drying of the combined organic layers over MgSO₄, filtration, evaporation of the solvent under reduced pressure and flash chromatography on silica gel with petroleum ether/Et₂O (1:2) afforded **16** (770 mg, 71 %) as a white solid. IR (CHCl₃, cm⁻¹): 3572 (w), 3457 (w), 2932 (m), 2856 (w), 1732 (s), 1708 (s), 1612 (w), 1516 (s), 1440 (m), 1252 (s); ¹H NMR (200 MHz, CDCl₃): δ = 0.53 (dbr, 13 Hz, 1H); 0.80 (s, 3H); 1.04-2.02 (m, 6H); 2.24 (dbr, 13 Hz, 1H); 2.60-3.23 (m, 5H); 3.52 (sbr, 1H); 3.74 (s, 3H); 3.81 (s, 3H); 3.92 (dd, 8/4 Hz, 1H); 4.13 (dd, 3/2 Hz, 1H); 4.41 (dd, 2/4 Hz, 1H); 5.97 (d, 6 Hz, 1H); 6.27 (dd, 6/13 Hz, 1H); 6.88 (d, 9 Hz, 2H); 7.30 (d, 9 Hz, 2H); FAB-MS: m/z (%) = 458 (M⁺, 5), 240 (100, diene **1**).

Lactone adduct (17). A solution of diol adduct **16** (50 mg, 0.109 mmol) in THF (2.5 ml) was treated with 6 N HCl (1 ml). After 5 days of stirring at room temperature, the reaction was neutralized with NaOH (240 mg). The aqueous layer was extracted three times with Et₂O. After separation of the organic layer, drying over MgSO₄, filtration and flash chromatography on silica gel with petroleum ether/Et₂O (1:1) **17** (10 mg, 22 %) was obtained as a white solid. IR (CHCl₃, cm⁻¹): 3587 (w), 3545 (w), 2936 (m), 2860 (w), 1792 (m), 1760 (m), 1732 (m), 1612

(w), 1516 (s), 1252 (s); ^1H NMR (400 MHz, CDCl_3): δ = 0.48 (dbr, 13 Hz, 1H); 0.83 (s, 3H); 1.16-2.25 (m, 7H); 2.96 (dd, 29/18 Hz, 1H); 3.26 (dd, 40/18 Hz, 1H); 3.57 (dd, 10/10 Hz, 1H); 4.04 (m, 1H); 4.40 (m, 2H); 5.75 (d, 3 Hz, 1H); 6.09 (dd, 9/6 Hz, 1H); 6.19 (d, 6 Hz, 1H); 6.89 (d, 10 Hz, 2H); 7.20 (d, 10 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 15.02 (p); 21.06 (s); 23.43 (s); 26.68 (s); 28.43 (s); 45.33 (s, doublet 27 Hz); 50.81 (t, doublet 20 Hz); 54.64 (p); 61.84 (q); 62.25 (q); 75.32 (t); 86.38 (t, doublet 28 Hz); 100.70 (q, doublet 185 Hz); 2x 113.18 (t); 2x 128.04 (t); 131.45 (q); 138.21 (t); 138.90 (t); 159.13 (q); 173.93 (q); 208.56 (q); FAB-MS: m/z (%) = 426 (M^+ , 6), 240 (72, diene **1**).

Ketone adduct (18). To a solution of adduct **9a** (50 mg, 0.136 mmol) in dry toluene (2 ml) L-Selectride (1 M in THF) (130 μl , 0.136 mmol) was added at -78 $^\circ\text{C}$. The reaction was stirred for 15 minutes followed by addition of a saturated aqueous NH_4Cl -solution. The suspension was warmed to room temperature and partitioned between water and Et_2O . The aqueous layer was separated, neutralized with 2N HCl and extracted three times with Et_2O . The combined organic extracts were washed with brine, dried over MgSO_4 and filtered. Concentration in vacuo and a flash chromatography on silica gel with petroleum ether/ Et_2O (3:1) afforded **18** (43 mg, 86 %) as a white solid. IR (CHCl_3 , cm^{-1}): 3000 (m), 2936 (s), 2856 (m), 1704 (s), 1612 (w), 1516 (s), 1464 (w), 1444 (w), 1380 (w), 1248 (s); ^1H NMR (400 MHz, CDCl_3): δ = 0.50 (dbr, 13 Hz, 1H); 0.77 (s, 3H); 1.08-2.31 (m, 11H); 2.63 (dd, 30/10 Hz, 1H); 3.62 (d, 10 Hz, 1H); 3.79 (s, 3H); 6.02 (dd, 10/6 Hz, 1H); 6.05 (d, 6 Hz, 1H); 6.86 (d, 10 Hz, 2H); 7.18 (d, 10 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 16.34 (p); 21.48 (s); 23.52 (s); 27.89 (s); 28.46 (p, doublet 27 Hz); 28.54 (s); 53.74 (t, doublet 19 Hz); 54.46 (t); 55.32 (p); 60.01 (q); 61.14 (q); 66.01 (q); 94.06 (q, doublet 198 Hz); 2x 113.34 (t); 2x 128.23 (t); 131.14 (q); 135.38 (t); 139.44 (t); 157.89 (q); 210.87 (q); Exact mass Calcd.: 368.2152, found: 368.2139.

Cyclic ether (19). The reaction was performed according to the preparation of **18** with adduct **9a** (50 mg, 0.14 mmol), L-Selectride (1 M in THF) (301 μl , 0.308 mmol), dry toluene (2 ml) over a period of 15 minutes at -78 $^\circ\text{C}$ followed by a flash chromatography on silica gel with petroleum ether/ Et_2O (3:1). **19** (39 mg, 82 %) was obtained as a white solid. IR (CHCl_3 , cm^{-1}): 3000 (m), 2956 (s), 2928 (s), 2852 (m), 1612 (w), 1516 (s), 1464 (m), 1248 (s); ^1H NMR (200 MHz, CDCl_3): δ = 3.76 (s, 3H); 3.81 (d, 7Hz, 3H); 1.00-2.20 (m, 14H); 2.43 (d, 2 Hz, 1H); 3.79 (s, 3H); 4.08 (m, 1H); 4.70 (m, 1H); 6.86 (d, 10 Hz, 2H); 7.14 (d, 10 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ = 16.52 (p); 18.20 (p); 21.33 (s); 22.79 (s); 25.64 (t); 25.99 (s); 29.32 (s); 31.38 (t); 31.82 (s); 32.98 (s); 33.37 (q); 41.26 (q); 51.23 (t); 55.20 (p); 74.68 (t); 85.69 (t); 2x 113.64 (t); 127.93 (q); 2x 129.54 (t); 158.33 (q); Exact mass Calcd.: 350.2246, found: 350.2246.

Alcohol adduct (20). Ketone adduct **18** (50 mg, 0.136 mmol) in dry toluene (1 ml) was treated with K-Selectride (298 μl , 0.299 mmol) at -78 $^\circ\text{C}$. The mixture was warmed to 0 $^\circ\text{C}$ and quenched with a 10 %-NaOH-solution (0.4 ml). After subsequent portion wise addition of a 30 % aqueous H_2O_2 -solution (0.32 ml) stirring for three hours followed. The reaction mixture was extracted three times with Et_2O and the combined organic layers were washed with a saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ -solution followed by treatment with brine. Evaporation of the solvent and flash chromatography on silica gel with petroleum ether/ Et_2O (3:1) afforded **20** (32 mg,

64 %) as a white solid, mp 103.8 °C. IR (CHCl₃, cm⁻¹): 3572 (m), 3000 (m), 2932 (s), 2856 (m), 1612 (m), 1516 (s), 1244 (s), 1180 (s); ¹H NMR (200 MHz, CDCl₃): δ = 0.47 (dbr, 13 Hz, 1H); 0.80 (s, 3H); 1.07-2.39 (m, 13H); 1.50 (d, 22 Hz, 3H); 3.15 (dd, 10/6 Hz, 1H); 3.79 (s, 3H); 4.08 (m, 1H); 5.97 (dd, 11/6 Hz, 1H); 6.20 (dd, 6/2 Hz, 1H); 6.88 (d, 10 Hz, 2H), 7.25 (d, 10 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 16.9 (p); 21.1 (s); 23.9 (s); 28.0 (s); 29.1 (p); 33.2 (s); 47.8 (t); 53.0 (t); 55.1 (p); 60.6 (q); 62.1 (q); 65.5 (q); 65.9 (t); 97.1 (q); 2x 113.6 (t); 2x 128.2 (t); 131.1 (q); 135.2 (t); 137.1 (t); 158.0 (q); Exact mass Calcd.: 370.2308, found: 370.2305.

Cyclic ether (23). Adduct **9a** (300 mg, 0.819 mmol) was dissolved in dry THF (26 ml). At room temperature a MeMgBr-solution (3 M in Et₂O) (270 μl, 0.819 mmol) was dropped to the adduct solution. The reaction was stopped after 5 minutes by addition of a saturated aqueous NH₄Cl-solution. After diluting the suspension with water and Et₂O the aqueous layer was separated and extracted three times with Et₂O. The combined organic extracts were dried over MgSO₄, filtered, and the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel with petroleum ether/Et₂O (10:1) afforded **23** (212 mg, 68 %) as a colorless oil. IR (CHCl₃, cm⁻¹): 3000 (m), 2964 (s), 2936 (s), 2864 (s), 1612 (w), 1512 (s), 1464 (w), 1444 (w), 1380 (m), 1252 (s), 1180 (m), 1036 (m); ¹H NMR (400 MHz, CDCl₃): δ = 0.76 (s, 3H); 1.20 (s, 3H); 1.22-1.63 (m, 8H); 1.79 (d, 2 Hz, 3H); 1.94 (d, 6 Hz, 1H); 2.04 (m, 1H); 2.23 (m, 1H); 2.40 (d, 6 Hz, 1H); 3.79 (s, 3H); 5.01 (dd, 5/1 Hz, 1H); 5.76 (m, 1H); 6.85 (d, 10 Hz, 2H); 7.22 (d, 10 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 18.49 (p); 18.61 (p); 21.48 (s); 21.65 (s); 22.19 (p); 24.78 (s); 34.28 (s); 55.12 (p); 42.02 (t); 46.96 (q); 49.83 (t); 49.90 (t); 50.09 (t); 57.53 (q); 73.71 (q); 86.89 (t); 90.29 (q); 2x 113.41 (t); 119.11 (t); 2x 128.19 (t); 132.55 (q); 136.70 (q); 157.84 (q); Exact mass Calcd.: 362.2246, found: 362.2243.

Cyclic ether (24). To adduct **9f** (52 mg, 0.127 mmol) in dry THF (1 ml) was added a suspension of LAH (100 mg, 2.54 mmol) in THF (1 ml). The mixture was refluxed over night before being quenched with a 0,1 N NaOH-solution at 0 °C. The volume was increased with water and the mixture was dissolved with an excess of 2 N citric acid. The aqueous layers were extracted twice with Et₂O and twice with CH₂Cl₂. After drying the combined organic extracts with brine and MgSO₄, a flash chromatography on silica gel with petroleum ether/Et₂O (5:1) afforded **24** (20 mg, 38 %) as a colorless oil. IR (CHCl₃, cm⁻¹): 3000 (m), 2964 (s), 2948 (s), 2864 (m), 1612 (w), 1512 (s), 1464 (w), 1252 (s), 1180 (m), 1036 (m); ¹H NMR (200 MHz, CDCl₃): δ = 0.85 (s, 3H); 1.04 (s, 9H); 1.10-1.66 (m, 8H); 1.98 (trbr, 5 Hz, 1H); 2.25 (trbr, 6 Hz, 1H); 2.58 (dd, 6/2 Hz, 1H); 2.77 (dbr, 6 Hz, 1H); 3.79 (s, 3H); 4.00 (m, 1H); 5.14 (dbr, 5 Hz, 1H); 5.74 (dd, 7/2 Hz, 2H); 6.86 (d, 9 Hz, 2H); 7.25 (d, 9 Hz, 2H); FAB-MS: m/z (%) = 390 (M⁺, 91).

Homoallylic alcohol adduct (26). Adduct **9a** (500 mg, 1.357 mmol) was dissolved in dry toluene (15 ml) and treated with DIBAL (1,2 M in toluene) (2.488 ml, 2.985 mmol) at -78 °C. The reaction was warmed to room temperature and a saturated aqueous NH₄Cl-solution was added. The mixture was treated with a K₂CO₃-methanol paste and allowed to stir for an additional 5 minutes. The suspension was partitioned between water and Et₂O then the aqueous layer was separated and extracted three times with Et₂O. Subsequent drying of the combined organic layers over MgSO₄, filtration and concentration of the solution with the rotary evaporator

provided the crude product. Purification by flash chromatography on silica gel with petroleum ether/Et₂O (3:1) afforded **26** (382 mg, 80 %) as a white foam. IR (CHCl₃, cm⁻¹): 3584 (m), 3000 (m), 2928 (s), 2856 (m), 1612 (w), 1512 (s), 1252 (s), 1180 (s); ¹H NMR (200 MHz, CDCl₃): δ = 0.34 (dbr, 13 Hz, 1H); 0.86 (s, 3H); 1.05-2.20 (m, 10H); 1.80 (sbr, 3H); 2.62 (dbr, 9 Hz, 1H); 3.56 (dd, 9/7 Hz, 1H); 3.80 (s, 3H); 4.11 (m, 1H); 5.30 (m, 1H); 5.94 (d, 6 Hz, 1H); 6.23 (d, 6 Hz, 1H); 6.88 (d, 9 Hz, 2H); 7.34 (d, 9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 14.95 (p); 21.02 (s); 23.60 (s); 24.34 (p); 27.67 (s); 27.89 (s); 33.22 (s); 47.03 (t); 50.37 (t); 55.12 (p); 59.70 (q); 62.00 (q); 66.03 (q); 69.55 (t); 2x 113.46 (t); 120.38 (t); 2x 128.19 (t); 129.40 (q); 131.63 (q); 137.12 (t); 137.31 (t); 158.00 (q); FAB-MS: m/z (%) = 350 (M⁺, 4), 240 (100, diene **1**).

(3aS,7R,7aR)-7-Fluoro-2,2,7-trimethyl-7,7a-dihydro-1,3-benzodioxol-4(3aH)-one (27). Acetonide adduct **14a** (298 mg, 0.676 mmol) was pyrolyzed at 2*10⁻² mbar and 350 °C. The educt evaporated between 165 °C and 220 °C from the flask into the pyrolysis-tube. The crude product was collected in a flask behind the pyrolysis-tube cooled with liquid nitrogen. The flash chromatographic purification on silica gel with petroleum ether/Et₂O (5:1) gave **27** (103 mg, 76 %) as a yellow oil. IR (CHCl₃, cm⁻¹): 2988 (m), 2936 (w), 2896 (w), 1696 (s), 1452 (w), 1376 (m), 1224 (s), 1080 (s); ¹H NMR (400 MHz, CDCl₃): δ = 1.38 (s, 3H); 1.43 (s, 3H); 1.65 (d, 25 Hz, 3H); 4.51 (d, 5 Hz, 1H); 4.55 (ddd, 12/6/2 Hz, 1H); 6.16 (dd, 11/4 Hz, 1H); 6.75 (ddd, 11/5/2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 23.98 (p, doublet 22 Hz); 25.71 (p); 27.16 (p); 74.24 (t); 78.36 (t, doublet 37 Hz); 89.63 (q, doublet 161 Hz); 110.86 (q); 129.72 (t); 146.06 (t); 194.78 (q); Exact mass Calcd.: 200.0849, found: 200.0843.

Methyl [(3aR,4R,7aS)-4-fluoro-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-yl]acetate (28). The reaction was performed according to the preparation of **27** with acetonide adduct **14b** (250 mg, 0.501 mmol) at an evaporation temperature of approx. 150-240 °C and a flash chromatography on silica gel with petroleum ether/Et₂O (5:1). **28** (89 mg, 69 %) was obtained as a yellow oil. IR (CHCl₃, cm⁻¹): 2992 (m), 2952 (w), 1740 (s), 1700 (s), 1436 (m), 1376 (m), 1228 (s); ¹H NMR (400 MHz, CDCl₃): δ = 1.37 (s, 3H); 1.43 (s, 3H); 2.39 (dd, 25/16 Hz, 1H); 2.58 (dd, 18/16 Hz, 1H); 3.76 (s, 3H); 4.02 (d, 6 Hz, 1H); 4.27 (ddd, 13/6/2 Hz, 1H); 6.24 (dd, 11/3 Hz, 1H); 7.06 (ddd, 11/4/2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 25.61 (p); 27.04 (p); 41.25 (s, doublet 25 Hz); 52.04 (p); 74.13 (t); 77.37 (t, doublet 37 Hz); 88.65 (q, doublet 167 Hz); 111.07 (q); 130.42 (t); 143.45 (t); 168.49 (q); 194.46 (q); Exact mass Calcd.: 258.0904, found: 258.0909.

(1S,5R,6R)-5-Allyl-5-fluoro-7-oxabicyclo[4.1.0]hept-3-en-2-one (29). The reaction was performed according to the preparation of **27** with epoxide adduct **15** (216 mg, 0.529 mmol) at an evaporation temperature of approx. 150-250 °C and a flash chromatography on silica gel with petroleum ether/Et₂O (30:1). **29** (62 mg, 70 %) was obtained as a yellow oil. IR (CHCl₃, cm⁻¹): 3084 (w), 3028 (w), 2984 (w), 2936 (w), 2912 (w), 1696 (s), 1640 (w), 996 (m); ¹H NMR (200 MHz, CDCl₃): δ = 2.25 (m, 2H); 3.01 (dd, 4/2 Hz, 1H); 3.08 (m, 1H); 4.98 (m, 2H); 5.97 (m, 1H); 6.05 (m, 1H); 6.51 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 41.48 (s); 52.54 (t); 56.65 (t, doublet 43 Hz); 87.94 (q, doublet 168 Hz); 121.08 (s); 128.27 (t); 129.45 (t); 141.58 (t);

192.14 (q); MS (RT): m/z (%) = 168 (M^+ , 2), 151 (7), 145 (18), 139 (32), 127 (56), 119 (28), 112 (35), 99 (100).

Methyl (3aR,7aR)-3a-fluoro-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate (30).

The reaction was performed according to the preparation of **27** with hydroindole adduct **12** (133 mg, 0.293 mmol) at an evaporation temperature of approx. 150-200 °C and a flash chromatography on silica gel with petroleum ether/Et₂O (1:3). **30** (63 mg, 100 %) was obtained as a colorless oil. IR (CHCl₃, cm⁻¹): 3000 (m), 2956 (m), 2900 (w), 1692 (s), 1452 (s), 1392 (s), 1356 (m), 1072 (s); ¹H NMR (400 MHz, CDCl₃): δ = 2.26 (m, 2H); 2.45 (m, 1H); 3.13 (dd, 17/6 Hz, 1H); 3.64 (m, 2H); 3.73 (s, 3H); 4.42 (m, 1H); 6.10 (d, 10 Hz, 1H); 6.89 (dd, 10/4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 33.77 (s); 34.74 (s); 42.24 (s); 44.93 (s); 52.79 (p); 62.18 (t, doublet 23 Hz); 96.72 (q, doublet 83 Hz); 130.67 (t); 143.56 (t); 155.10 (q); 195.33 (q); Exact mass Calcd.: 213.0801, found: 213.0793.

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