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Fluorinated Furan-2(5*H*)-ones: Reactivity and Stereoselectivity in Diels–Alder Reactions

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3-Fluorofuran-2(5*H*)-one (**1**) and three 3,4-difluorofuran-2(5*H*)-ones **2**–**4**, α,β-unsaturated lactones possessing fluorinated double bonds, were applied as dienophiles in Diels–Alder reactions with normal electron demand using diphenylisobenzofuran or cyclopentadiene as dienes. In the same reactions, furan or 2,3-dimethylbuta-1,3-diene were completely unreactive. Three structural factors of furan-2(5*H*)-ones appeared to have an effect on the reactivity, regioselectivity and diastereoselectivity of the [4+2] cycloadditions: the number of fluorine atoms attached to the double bond and the number and the bulkiness of alkyl substituents at the 5-position of the furan-2(5*H*)-one system. The monofluorinated furan-2(5*H*)-one **1** was generally more reactive than the difluorinated furan-2(5*H*)-ones **2**–**4**. While the reactions of the furan-2(5*H*)-ones **2**–**4** with isobenzofuran exclusively gave *exo* products, those of the monofluorinated lactone **1** led to mixtures of *endo* and *exo* diastereoisomeric [4+2] cycloadducts. All fluorinated furan-2(5*H*)-ones **1**–**4** formed mixtures of diastereoisomeric 1:1 and 1:2 adducts with cyclopentadiene. DFT calculations of the transition states of the above Diels–Alder reactions using the BMK functional, a third-generation hybrid functional tailored for transition state calculations, together with the polarization consistent aug-pc-2 basis set, confirmed the preferential formation of the *exo* adducts from difluorinated furan-2(5*H*)-ones, while for nonfluorinated analogues a small but significant preference for the *endo* adducts was confirmed.

Introduction

Fluorinated furan-2(5*H*)-ones have been shown to be versatile building blocks for syntheses of various types of natural compound analogues (e.g., saccharides,[1a,1b] lignan intermediates,[1c,1d] nucleosides[1e–1h] or manoalide[1i]). Moreover, we and others have investigated Diels–Alder reactions of several mono- and difluorinated alkenes with different types of dienes.[2] Thus, α-fluorostyrene reacted with polyfluorinated cyclohexadienones in Diels–Alder reactions with inverse electron demand to afford fluorinated bicyclo[2.2.2]octenones,[3] while the reaction between this vinyl fluoride and a trifluoromethyl pyranone gave trifluorobenzene derivatives after decarboxylation of the primarily formed cycloadduct.[4] On the other hand, a variety of *p*-substituted α-fluorostyrenes reacted in Diels–Alder reactions with normal electron demand only with the highly reactive diene diphenylisobenzofuran to give mixtures of the *endo*-/*exo*-isomeric [4+2] cycloadducts, but the reactions were rather slow.[5] Activation of the monofluorinated double bond by an adjacent carbonyl function led to better results both with benzyl α-fluoroacrylate,[6,7] and with 2-fluoroalk-1-en-3-ones,[7,8] but these, as well as the reactions of α-fluorostyrenes with different dienophiles, still appeared to take place more slowly than the corresponding reactions of the nonfluorinated parent compounds. The apparently lower reactivities of fluorinated dienophiles are probably caused by increased π-electron densities in the fluorinated double bonds.[5,7]

Several more reactions of this type with activated fluoroolefins such as 2-fluoroacrolein,[9] various α,β-unsaturated α-fluorocarboxylic acid derivatives,[6,7,10] fluorinated *p*-benzoquinones,[11] fluorinated vinyl sulfones[12] and fluorinated vinyl sulfoxides[13] have been reviewed recently.[2,14] Asymmetric [4+2] cycloadditions of α-fluoroacrylate or 2-fluoroalk-1-en-3-ones with cyclopentadiene in the presence of various chiral Lewis acidic titanium complexes have been reported.[8]

The presence of a second fluorine atom at the double bond in α,β-unsaturated carbonyl compounds did not forestall the Diels–Alder reactions. Several perfluoroalk-2-enyl ketones gave the corresponding [4+2] cycloadducts with a selection of 1,3-dienes, for example,[15] as did enol deriva-

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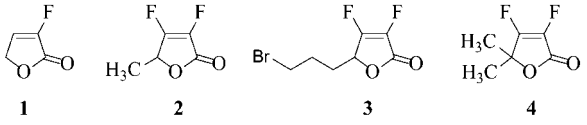
tives of difluoroacetaldehyde with cyclopentadiene.[16] Similar reactions between tetrafluoro-*p*-benzoquinone and various 1,3-dienes have been reported.[11,17]

Recently, we used the Diels–Alder reactions between 2-fluoro- and 2,3-difluoromaleic anhydrides and furan to synthesize fluorinated analogues of the protein phosphatase inhibitor cantharidin.[18] Unfortunately, the anhydride moieties in the products appeared to be very easily hydrolysed to afford dicarboxylic acids exhibiting low bioactivity. With a lactone ring replacing the anhydride the hydrolytic stability of the [4+2] cycloadducts might be increased. Thus, as a continuation of our recent investigations[18,19] we now report our results of Diels–Alder reactions of several mono- and difluorinated furan-2(5*H*)-ones.

Results and Discussion

Diels–Alder Reactions

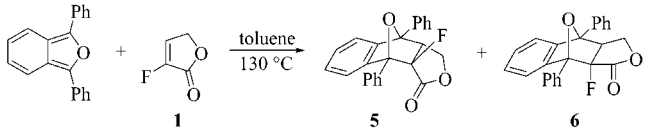
Four furan-2(5*H*)-ones – compounds **1**–**4** (Scheme 1) – were applied in our study. 3-Fluorofuran-2(5*H*)-one[19a] (**1**) and 3,4-difluoro-5,5-dimethylfuran-2(5*H*)-one[19b] (**4**) were prepared by our published procedures, while for the 5-alkyl-3,4-difluorofuran-2(5*H*)-ones (**2** and **3**) a new protocol has been developed.[20] The structures **1**–**4** differ in the number of fluorine atoms attached to the double bond and in the number and size of the substituents at C-5. Therefore it had been presumed that both electronic and steric effects could influence their reactivity and stereoselectivity in [4+2] cycloadditions.



Scheme 1. Fluorinated furan-2(5*H*)-ones **1**–**4** used in [4+2] cycloadditions.

We investigated Diels–Alder reactions of these mono- and difluorinated furan-2(5*H*)-ones with various 1,3-dienes that usually react with various α,β-unsaturated aldehydes or carboxylic acid derivatives.[21] However, none of the furan-2(5*H*)-ones **1**–**4** would react with furan or 2,3-dimethylbuta-1,3-diene in toluene at 150 °C in a sealed tube. When the difluorinated furan-2(5*H*)-ones **2**–**4** were treated with furan in the presence of $TiCl_4$ in dichloromethane[22] even at –20 °C to room temperature, only tar-like products were obtained.

With less reactive dienophiles, the highly reactive diphenylisobenzofuran, a stabilized *ortho*-quinodimethane, has usually been used to effect [4+2] cycloadditions.[23] Also in our case, the reactions of all fluorinated furan-2(5*H*)-ones **1**–**4** with this diene were successful (Scheme 2). The reaction between 3-fluorofuran-2(5*H*)-one (**1**) and this diene in toluene at 130 °C in a sealed tube for 1 day gave a 22:78 mixture of two diastereomeric cycloadducts **5** and **6**. These products were separated by column chromatography and identified spectroscopically as *endo*- and *exo*-4,9-epoxy-9a-fluoro-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]-furan-2(3*H*)-one (**5** and **6**).



Scheme 2. Products of the Diels–Alder reaction between furanone **1** and diphenylbenzofuran.

The structure of the major product was confirmed by X-ray structural analysis (Figure 1) as the *exo* isomer **6** with regard to the lactone ring.

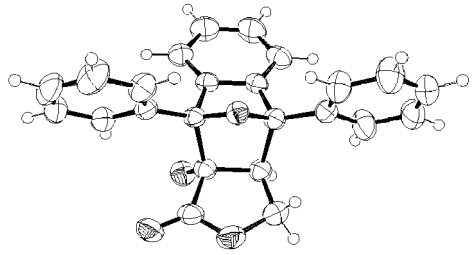


Figure 1. X-ray structure of the *exo*-cycloadduct **6**.

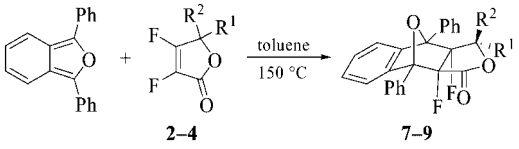
The observed *exo* selectivity contrasts with the general *endo* selectivity of Diels–Alder reactions of dienes such as cyclopentadiene with nonfluorinated dienophiles.[24] Also, the [4+2] cycloaddition of isobenzofuran with maleic anhydride in diethyl ether at 0 °C gave a 3:1 mixture of diastereomers favouring the *endo* isomer.[25] On the other hand, it has already been observed that the reactions of other α-fluoro-α,β-unsaturated carbonyl compounds with cyclopentadiene,[6–8] other 1,3-dienes[11] and particularly with furans led preferably to *exo* isomers.[5,18] However, a 98% *endo* selectivity has recently been reported for the reaction between diphenylisobenzofuran and 2-fluoro-5-(hydroxymethyl)but-2-en-4-olide in acetonitrile at 170 °C for 6 hours.[26] In contrast, the reactions of 3,4-difluoro-5-methyl- (**2**) and 5-(3-bromopropyl)-3,4-difluorofuran-2(5*H*)-one (**3**) with the same diene on heating in toluene at 130 °C in a sealed tube were complete after 2 days. In both reactions, only one of the two possible *exo* products (vide infra) was formed in high yield (Table 1). The reaction between 3,4-difluoro-5,5-dimethylfuran-2(5*H*)-one (**4**) and diphenylisobenzofuran was also completely *exo*-selective, giving the cycloadduct **9** as confirmed by X-ray structure analysis (see electronic supporting information). However, the reaction was very slow, showing only 34% conversion on heating in toluene at 130 °C in a sealed tube for 17 days (Scheme 3).

The stereochemical position of the methyl group in the cycloadduct **7** was assigned by $^{19}F^{1}H$ NOE experiments (cf. Supporting Information), which showed that both fluorine atoms and the methyl group are located on the same side of the five-membered ring. The structure of this product was verified by X-ray crystallography (cf. Figure 2).

Table 1. Results of the Diels–Alder reactions between furan-2(5*H*)-ones **2**–**4** and diphenylisobenzofuran.

Furanone	R^1	R^2	Product	Time /d	% Yield
2	Me	H	7	2	92[a]
3	$BrCH_2CH_2CH_2$	H	8	2	88[a]
4	Me	Me	9	17	18[b]

[a] Conversion 100%. [b] Conversion 34%.



Scheme 3. Products of Diels–Alder reactions between the difluorofuran-2(5*H*)-ones **2**–**4** and diphenylisobenzofuran.

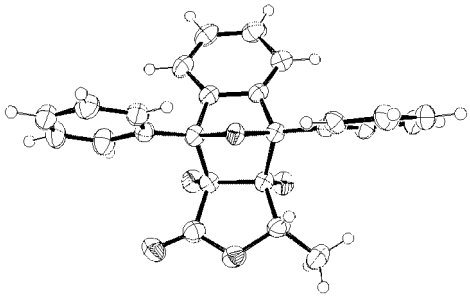
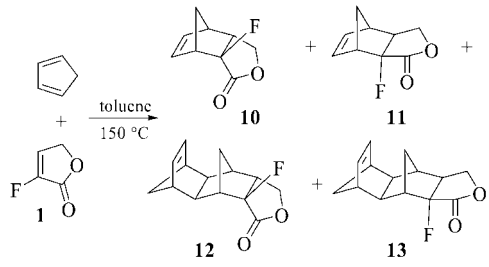


Figure 2. X-ray structure of the *exo*-cycloadduct **7**.

All relevant NMR spectroscopic data for the bromopropyl derivative **8** are very similar to those found for compound **7**. Particularly, the vicinal coupling constants ^3J(H,F) were 13 Hz in both compounds **7** and **8**. On the basis of this close similarity, it can be concluded that compound **8** should have the same stereochemistry as the methyl derivative **7**.

The results of the reactions between fluorinated furan-2(5*H*)-ones **1**–**4** and diphenylisobenzofuran demonstrate two substituent effects that probably determine the stereoselectivity and the reaction rate. The stereoselectivity of the cycloadditions is apparently influenced by the number of fluorine atoms at the double bond. The cycloaddition of the monofluorinated furan-2(5*H*)-one **1** led mainly to the *exo*-annulated isomer **6** (78%) and, furthermore, the reactions of difluorofuran-2(5*H*)-ones **2**–**4** exclusively afforded the *exo*-annulated products (Table 1). The results correlate well with the calculated energies of the transition states of the cycloadditions (vide infra). The reaction rates of cycloadditions of furanones **2**–**4** are strongly influenced by the substituents at the C-5 position: furanones **2**–**3**, possessing only one alkyl group at this position, gave much better yields of the cycloadducts (**7** or **8**) than the geminally dimethylated furan-2(5*H*)-one **4** (Table 1). Apparently, there is a steric interaction between a second substituent R^2 at the 5-position in the lactone ring and the oxygen of the isobenzofuran in the transition state, so the preferred formation of compounds **7** and **8** bearing the additional substituent in the *anti* position relative to the bridging oxygen can be attributed to steric control in the transition state (Scheme 3). The transition state leading to the alternative *exo* product with the substituent in a *syn* orientation relative to the oxygen bridge should be energetically less favourable.

During further attempts to utilize the fluorinated furan-2(5*H*)-ones **1**–**4** in other Diels–Alder reactions we found that these compounds reacted with cyclopentadiene (Scheme 4). The reactions were each carried out in the presence of a fivefold molar excess of this diene at 150 °C in a sealed tube. The conversion of the starting furanone **1** in the reaction with this diene was complete in 60 hours, affording a mixture of four cycloaddition products in a ratio of 49:33:11:7. Structural analysis of this mixture revealed that two types of cycloadducts were formed: a major *endo*/*exo* mixture of 1:1 cycloadducts **10** and **11** (60:40), and an analogous mixture of 1:2 cycloadducts **12** and **13** (60:40), possessing two cycloadded cyclopentadiene units. These 1:2 cycloadducts are very probably formed by a subsequent [4+2] cycloaddition of the primary cycloadducts **10** and **11** with cyclopentadiene.



Scheme 4. Products of the cycloaddition reactions of furanone **1** with cyclopentadiene.

The two 1:1 adducts **10** and **11** were separated from the 1:2 adducts **12** and **13** by column chromatography. Further chromatographic separation to individual stereoisomers failed, and so the *endo* or *exo* configurations could not be unambiguously assigned to one or the other compound. However, by comparison of the differences in fluorine chemical shifts and $^3J_{H,F}$ coupling constants with those for similar compounds[5] it seems justified to assign the corresponding major diastereomers (lower ^{19}F NMR shift, smaller $^3J_{H,F}$ coupling constants) to the *exo* series, while the minor isomers should belong to the *endo* series. Moreover, the $^3J_{H,H}$ coupling constants of H-6 and H-7 of the *endo* and *exo* isomers are also very close to those for Diels–Alder adducts of cyclopentadiene and 4-substituted furan-2(5*H*)-ones.[27] The annulation of the second cyclopentadiene molecule to form the 1:2 adducts is assumed to proceed in an *exo* orientation. This assumption corresponds with earlier findings on cycloadditions between norbornene derivatives and cyclopentadiene.[28]

The formation of the 1:2 adducts of type **12**–**13** was not mentioned in the literature for reactions of nonfluorinated furan-2(5*H*)-one and its 3-methyl derivative with cyclopen-

Table 2. Products of Diels–Alder reactions between mono- and dialkylated difluorofuranones **2**–**4** and cyclopentadiene.

Starting material	R^1	R^2	Time /d	% Conversion	1:1 Cycloadducts[a] Ds_1/Ds_2	Ratio 1:1/1:2 cycloadduct
2	Me	H	10	100	60:40 (**14**)	25:75 (**17**)
3	$BrCH_2CH_2CH_2$	H	10	100	70:30 (**15**)	32:68 (**18**)
4	Me	Me	30	12	78:22 (**16**)	32:68 (**19**)

[a] Ratios were calculated from ^{19}F NMR spectroscopic data.

tadiene in the presence of weak Lewis acids such as bisaluminated triflic amides, which gave 1.1–8.2:1 mixtures of *endo* and *exo* cycloadducts depending on the relative Lewis acidity of the catalyst.[29] Stronger acidic catalysts led to lower selectivity in favour of the *endo* isomers.[30] Additionally, in an asymmetric Diels–Alder reaction between furan-2(5*H*)-one and cyclopentadiene in the presence of Corey's chiral azaborolidinium salts the *endo* product dominated (>90% diastereoselectivity).[31] Furthermore, the reaction between an enantiopure 5-menthyloxy-2-(5*H*)-furanone and cyclopentadiene gave the *endo* cycloadduct with >98% diastereoselectivity.[32]

The reactions between the 5-substituted difluorofuran-2(5*H*)-ones **2**–**4** and cyclopentadiene (Scheme 4) were slower than those of fluorofuran-2(5*H*)-one **1**. The conversions of the monoalkylated furanones **2** and **3** were complete in 10 days at 150 °C, while only 12% of the dimethylated difluorofuranone **4** had been converted in 30 days reaction time under the same conditions. In all cases, mixtures of 1:1 (**14**–**16**) and 1:2 (**17**–**19**) cycloadducts with cyclopentadiene were obtained (Table 2). Both the 1:1 adducts **14** and **15** and the 1:2 adducts **17** and **18** were formed as mixtures of diastereoisomers, but it has not been a trivial matter to decide whether these compounds were *exo*/*endo* isomers with regard to the annulation of the lactone ring or *cis*/*trans* isomers with respect to the position of the alkyl group R^1 relative to the C–F bonds. If it is borne in mind that the 3,4-difluoro-5,5-dimethylfuran-2(5*H*)-one (**4**) reacted very slowly (Table 2), obviously due to steric interaction between the R^2 methyl group and the methylene group of cyclopentadiene in the transition state, it seems more likely that the isomers are *exo*/*endo* isomers with respect to the annulation of the lactone ring. It is interesting to note that obviously only one of the stereoisomers of **15** subsequently reacted with a second molecule of cyclopentadiene to afford the corresponding 1:2 cycloadduct **18**, which was formed as a single stereoisomer. X-ray analysis of the cycloadduct **18** (Figure 3) revealed that this stereoisomer possesses the bromopropyl group (R^1) and both fluorine atoms in an *all-cis* configuration. It is obvious that the 1:2 adduct **18** should be formed from an analogous *all-cis* isomer **14** (Scheme 5).

Two 1:1 and two 1:2 adducts **16** and **19** were also obtained as mixtures of stereoisomers from the reaction of the dimethyl derivative **4** with incomplete conversion even after a very long reaction time (Table 2). Unfortunately, these products could not be isolated as pure compounds, but must be *endo*/*exo* isomers with respect to the annulation of the lactone ring relative to the methylene bridge.

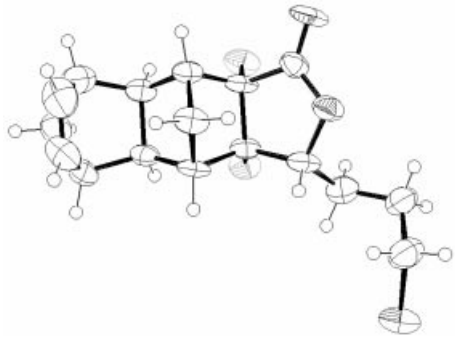
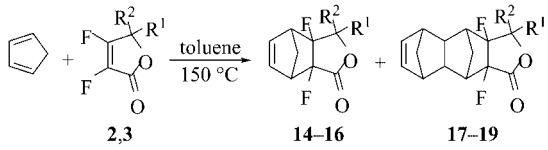


Figure 3. X-ray structure of the all-*cis*-cycloadduct **18**.



Scheme 5. Products of the cycloaddition reactions of furanones **2** and **3** with cyclopentadiene.

All relevant NMR spectroscopic data for the bromopropyl derivative **18** are very close to those for the methyl derivative **17**. On this basis, the same stereochemistry as in **18** can be assigned to the 1:2 cycloadduct **17**. It should be mentioned that in the cycloadditions with cyclopentadiene the observed structural effects of the reacting furanones were the same as those for the cycloadditions with diphenylisobenzofuran. Namely, the decrease in the reactivity of difluorinated lactones **2**–**4** relative to the monofluorinated furanone **1** or of the C-5-dimethylated substrate **4** relative to the monosubstituted furanones **2** and **3** was apparent. From the stereochemical point of view, the difluorinated substrates **2**–**4** again afforded mainly *exo* cycloadducts with respect to the annulation of the tetrahydrofuranone ring in the products **13**–**18**.

In contrast, the thermal Diels–Alder reaction between 5-methylfuran-2(5*H*)-one and cyclopentadiene at 80 °C in toluene gave a 3:1 mixture of two diastereomers in favour of the *endo* isomer bearing the methyl group in the *syn* position relative to the methylene bridge.[33] Moderate Lewis acid catalysts even improve the diastereoselectivity of this reaction to a ratio of about 7:1.[30]

DFT Calculations of Transition State Energies

Experimental results showed that the Diels–Alder reactions of the fluorinated furanones **1**–**4** proceeded with a

stereoselectivity opposite to that displayed by nonfluorinated furanones. To understand the reasons for this better, we decided to calculate relative energies of the transition states leading to the *exo* or *endo* isomers using furan-2(5*H*)-one, 3-fluoro- and 3,4-difluoro-2(5*H*)-furanone as the corresponding dienophiles and cyclopentadiene or isobenzofuran as the dienes. Geometries and energies of starting materials, products and the corresponding transition states were calculated by the DFT method at the mPW1PW91/6-311++G(d,p) level of theory. mPW1PW91 is a second-generation functional, which is less empirical (only one parameter is used) and has substantially better description of systems with noncovalent interactions.[34] Inclusion of zero-point energies (ZPEs) and calculations of Gibbs energies of the transition states corrected to given temperatures in selected cases also afforded results nearly identical with those given below. As a rather apolar solvent (toluene) had been employed, we neglected the solvent effects. The results of calculations agreed well with the experimental results in terms of the preferential formation of the *exo* product from 3,4-difluoro-2(5*H*)-furanone. However, the fact that nonfluorinated furanones form *endo* products almost exclusively was not supported by these calculations (see Figure 4). We therefore attempted to include correlation energy in ab initio calculations by using the perturbation approach at the MP2/6-311++G(d,p) level of theory. Surprisingly, these calculations supported preferential formation of *endo* products for nonfluorinated furanones, but energies of transition states of *endo* and *exo* products in the case of difluorofuranone were nearly equal (Figure 4). These contradictory results are not surprising, as the energy differences vary over the scale of a few kJ mol^{-1}, too subtle to be accurately described by simple methods including electron correlation.

Recently, Rulíšek et al. demonstrated experimentally and theoretically that in the Diels–Alder reaction between furan and maleic anhydride the low thermodynamic stabilities of the cycloadducts and the relatively high and almost energetically equal activation energies of the [4+2] cycloaddition open retro-Diels–Alder reaction channels that overrule the very small kinetic preference for initial formation of the *endo* isomer. In contrast, the activation energies for the reactions between cyclopentadiene and maleic anhydride are

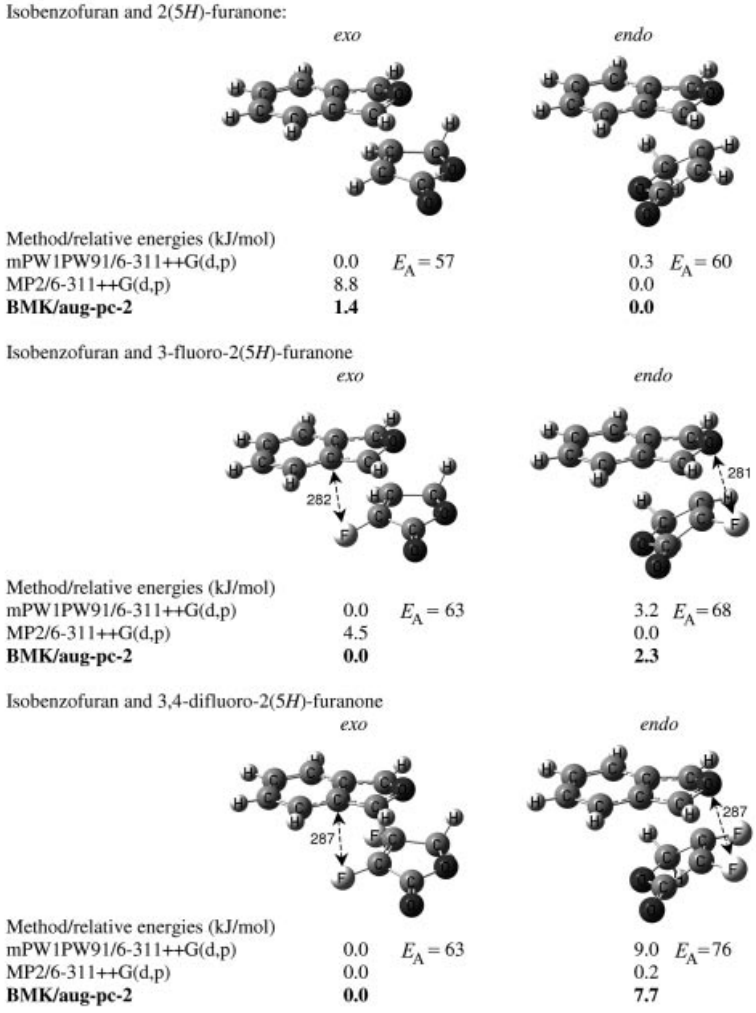
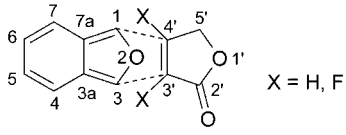


Figure 4. Calculated transition state geometries, relative energies and activation energies for the *endo*- and *exo*-cycloadducts of isobenzofuran with furan-2(5*H*)-one, monofluoro- and difluorofuran-2(5*H*)-ones.

much smaller and differ by 10.8 kJ mol^{-1} in favour of the *endo* transition state. Moreover, the retro-Diels–Alder reactions are almost 40 kJ mol^{-1} higher in energy than in the case of the furan Diels–Alder adducts. Single-point energies of transition states were calculated using high-level ab initio multiconfigurational methods, sufficiently exact to be employed for energetic differences in a kJ scale.[35]

Unfortunately, multiconfigurational treatment of systems including isobenzofuran is too size-prohibitive. However, novel third-generation functionals have been developed recently and were implemented into the last revision of the Gaussian03 program suite. Among them, the BMK functional is specially tailored to provide exact energy values of transition states,[36] provided that a sufficiently flexible basis set is employed. This method is reported to be comparable to or even better than the standard multiconfigurational treatment, with much lower computational costs. We hence recalculated all single-point energies of the transition states at the BMK/aug-pc-2 level of theory (aug-pc-2 is a polarization-consistent basis set that is more exact and economical than other basis sets[37]). Indeed, the results of these calculations agreed well with the experimental data [i.e., for nonfluorinated 2(5*H*)-furanone, *endo* products were predominant both for cyclopentadiene (for computational results including cyclopentadiene see the electronic supporting information) and isobenzofuran as the corresponding dienes, while 3,4-difluorofuran-2(5*H*)-one gave lower energies of the transition state for *exo* products for both dienophiles]. Finally, only small differences were observed for 3-fluorofuran-2(5*H*)-one, the reaction with cyclopentadiene preferring the *endo* pathway, that with isobenzofuran the *exo* pathway (Figure 4). For comparison, activation energies (E_As) relating to the corresponding *endo*- or *exo*-oriented molecular complexes are listed in Figure 4.

It is not easy to find an explanation for the *exo* preference in the case of cyclopentadiene. In the case of furan it can be attributed to the repulsion of the furan oxygen atom and the furan-2(5*H*)-one fluorine atoms at the same side of the formed tricyclic transition state, which makes the *endo* transition state less stable (see Table 3 for the distances between selected atoms in the corresponding transition states). However, the distance between fluorine and oxygen atoms is more than 280 pm [i.e., nearly equal to the sum of the van der Waals distances for fluorine and oxygen (292 pm)]. Another explanation for the observed *exo* preferences, which is not limited to the furan derivatives, can be found, however. Analysis of the electron distribution on the individual atoms of the transition states using the Merz–Singh–Kollman scheme (this is much better than the standard Mullikan description[38]) indicates that significant positive charge is developed at the two inner carbons of the diene system (i.e., C3a and C7a of the heterocyclic system; see Table 4 for MK charges for selected atoms in the corresponding transition states). Hence, the observed lower relative energy of the *exo* transition states of fluorofuranones can be attributed to the attraction of these two carbons and the negatively charged fluorine atoms. Here, the distance between the fluorine atom on the furanone ring and the C_{3a} carbon is about 280–290 pm, significantly smaller than the sum of the van der Waals distances (310 pm). Interestingly, two values of van der Waals radii for fluorine can be found in the literature [i.e., that of Pauli[39] (135 pm) and the newer value of Bondi[40] (147 pm)]. We finally decided to use the newest value of 140 pm, based on Zefirov's work.[41]



More careful examination of the transition states reveals that the electron transfer proceeds in an asynchronic manner with some conjugated addition character, as can be observed from the smaller distance between the C4′ carbon of the furanone ring and the C1 carbon of isobenzofuran. Substitution of the furanone ring with fluorine at the C3′ carbon results in conjugation of the fluorine lone pair with the double bond, significantly reducing its polarity and consequently the conjugated addition character of the Diels–Alder reaction. However, the interaction of fluorine with the C3a carbon of isobenzofuran mentioned above in the case of *exo* transition states removes some electron density

Table 3. Distances between selected atoms in the computed transition states [mPW1PW91/6-311++G(d,p) geometries].

Distance [pm]	*endo* C1–C4′	*endo* C3–C3′	*endo* O2–F3′	*endo* O2–F4′	*exo* C1–C4′	*exo* C3–C3′	*exo* C3a–F3′	*exo* C7a–F4′
Furan-2(5*H*)-one	218.4	230.0	–	–	214.5	236.6	–	–
3-Fluorofuran-2(5*H*)-one	221.8	223.0	282.0	–	213.7	237.8	281.2	–
3,4-Difluorofuran-2(5*H*)-one	213.1	236.1	287.4	305.8	206.4	257.1	287.0	296.2

Table 4. MK charges on selected atoms in the computed transition states.

Charge	*endo* C3	*endo* C3a	*endo* C7a	*endo* C1	*endo* C3′	*endo* C4′	*exo* C3	*exo* C3a	*exo* C7a	*exo* C1	*exo* C3′	*exo* C4′
Furan-2(5*H*)-one	0.01	0.01	0.10	–0.02	–0.37	–0.10	–0.16	0.13	0.16	–0.16	–0.38	0.01
3-Fluorofuran-2(5*H*)-one	–0.09	0.10	0.08	–0.04	0.26	–0.29	–0.17	0.16	0.08	–0.06	0.13	–0.11
3,4-Difluorofuran-2(5*H*)-one	–0.09	0.08	0.18	–0.19	0.11	0.30	–0.07	0.14	0.09	–0.06	0.03	0.37

from it, restoring the original conjugated addition character of the Diels–Alder reaction and thus significantly lowering the corresponding transition state energy (Figure 4, Table 4).

In contrast to ref.[35], the energy barrier for the *retro*-Diels–Alder reaction is more than 150 kJ mol^{-1}, the forward process energy barrier being much lower (ca. 70 kJ mol^{-1}). Therefore these reaction are probably driven kinetically. This explains why *endo* products are formed preferentially in the case of unfluorinated furanone, although the corresponding *exo* products are more stable in all cases calculated for this study.

Conclusions

A series of one monofluorinated (**1**) and three difluorinated (**2**–**4**) furan-2(5*H*)-ones were studied in thermal Diels–Alder reactions with diphenylisobenzofuran or cyclopentadiene. No cycloadducts were obtained in reactions between compounds **1**–**4** and furan or 2,3-dimethylbuta-1,3-diene. Generally, the cycloadditions of the substrates **1**–**4**, which are fluorinated α,β-unsaturated carbonyl systems, were very slow. This observation is in agreement with previous results for the reactions of fluorinated dienophiles and their nonfluorinated parent compounds.[7,8,11] While 4-fluorofuran-2(5*H*)-one (**1**) gave *exo* cycloadducts as the major products with both the dienes, together with minor amounts of the *endo* isomers, all reactions between the 3,4-difluorofuran-2(5*H*)-ones **2**–**4** and diphenylisobenzofuran led exclusively to the *exo* diastereoisomers, in contrast with the general *endo* diastereoselectivity observed with nonfluorinated α,β-unsaturated carbonyl compounds.[21] Furthermore, all furan-2(5*H*)-ones **1**–**4** formed mixtures of diastereoisomeric 1:1 and 1:2 cycloadducts with cyclopentadiene. DFT calculations of the transition state energies, using the recent third-generation functional BMK, of the reactions of furan-2(5*H*)-one, 3-fluorofuran-2(5*H*)-one (**1**) or the model 3,4-difluorofuran-2(5*H*)-one with isobenzofuran or cyclopentadiene gave lower TS energies for the *exo* attachment of 3-fluorofuran-2(5*H*)-one (**1**) and comparable TS energies for the 3,4-difluorofuran-2(5*H*)-ones **2**–**4**, in agreement with the experimental results, while for furan-2(5*H*)-one the *endo*-configured transition state was preferred.

Experimental Section

General Remarks: Unless noted otherwise, all starting materials were obtained from commercial suppliers and used without further purification. Cyclopentadiene was obtained by distillation from commercial dicyclopentadiene.

NMR spectra were recorded on a Bruker WM 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz; ^{19}F, 282 MHz) or a Varian U 600 spectrometer (^{13}C, 150 MHz) in $CDCl_3$. Chemical shifts δ (ppm) refer to tetramethylsilane (^{1}H, 0.0 ppm), $CDCl_3$ (^{13}C, 77.0 ppm) or $CFCl_3$ (^{19}F, 0.0 ppm). For recording of ^{13}C NMR spectra the pulse sequences APT or DEPT were used. Coupling constants (J) are given in Hz. Mass spectra were recorded with a combination of a Varian GC 3400 gas chromatograph and a Finnigan/MAT 8230 mass spectrometer (70 eV, EI).

Computations: DFT calculations were performed using the Gaussian 03W program suite.[42] MP2 and IRC calculations were accomplished by using the PCGAMESS program.[43,44] Vibrational frequencies were calculated for all species to characterize them as minima or transition states. Transition states geometries were found by starting from the corresponding minima on the potential energy surfaces (i.e., complexes of alkenes and dienes on one side and Diels–Alder products on the other side of the potential energy curve), and transition states were estimated using Schlegel's QST3 method.[45] In all cases, the connections of the corresponding transition states and minima were verified by IRC calculations of the simulated reaction pathways. Details of the aug-pc-2 basis set were obtained from supplementary EPAPS document[46] of ref.[47]

Reactions between Fluorinated Furan-2(5*H*)-ones and 1,3-Diphenylisobenzofuran (General Procedure): The appropriate fluorinated furan-2(5*H*)-one (1.5 mmol) and 1,3-diphenylisobenzofuran (430 mg, 1.6 mmol) in toluene (5 mL) were heated in a sealed glass tube at 130 °C for the period of time stated in Table 1. Reactions were monitored by TLC. The solvent was then removed under reduced pressure. After a ^{19}F NMR spectrum of the crude product had been taken, in order to determine the ratio of diastereoisomers, the residue was purified by column chromatography (cyclohexane/ethyl acetate, 10:1). Pure products were obtained by recrystallization.

Reaction between 3-Fluorofuran-2(5*H*)-one (1) and 1,3-Diphenylisobenzofuran: By the above procedure a 78:22 mixture (^{19}F NMR) of two products was obtained as a solid. Yield: 556 mg (95%). $C_{24}H_{17}FO_3$ (372.4): calcd. C 77.41, H 4.60; found C 76.93, H 4.55. By a second chromatographic separation (cyclohexane/ethyl acetate, 5:1) the pure *exo* compound **6** could be separated. Recrystallization from hexane/acetone gave crystals suitable for X-ray structural analysis.

***endo*-4,9-Epoxy-9a-fluoro-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho-[2,3-*c*]furan-2(3*H*)-one (5):** ^{1}H NMR: δ = 3.82–3.95 (m, 2 H), 4.61 (dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.09–8.07 (m, 14 H) ppm. ^{13}C APT NMR: δ = 52.04 (d, $^3J_{C,F}$ = 16.6 Hz, CH), 66.56 (br. s, CH_2), 91.41 (d, $^3J_{C,F}$ = 1.7 Hz, CO), 92.85 (d, $^2J_{C,F}$ = 4.3 Hz, CO), 105.05 (d, $^1J_{C,F}$ = 219.3 Hz, CF), 121.38–132.83 (m, arom. CH), 136.84 (s, arom. C), 139.72 (s, arom. C), 141.36 (d, $^3J_{C,F}$ = 3.4 Hz, arom. C), 146.41 (d, $^3J_{C,F}$ = 1.4 Hz, arom. C), 169.27 (d, $^2J_{C,F}$ = 28.1 Hz, C=O) ppm. ^{19}F NMR: δ = –161.44 (d, $^3J_{H,F}$ = 16.0 Hz, 1 F) ppm.

***exo*-4,9-Epoxy-9a-fluoro-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho-[2,3-*c*]furan-2(3*H*)-one (6):** M.p. 239–241 °C (hexane/acetone). ^{1}H NMR: δ = 3.38 (ddd, $^3J_{H,F}$ = 16.0, $^3J_{H,H}$ = 9.4, $^3J_{H,H}$ = 5.0 Hz, 1 H), 4.07 (ddd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 4.7, $^4J_{H,F}$ = 3.0 Hz, 1 H), 4.42 (dd, $^2J_{H,H}$ = $^3J_{H,H}$ = 9.6 Hz, 1 H), 7.09–7.83 (m, 14 H) ppm. ^{13}C APT NMR: δ = 52.47 (d, $^3J_{C,F}$ = 16.9 Hz, CH), 67.37 (s, CH_2), 91.08 (d, $^2J_{C,F}$ = 25.5 Hz, CO), 92.22 (d, $^3J_{C,F}$ = 4.3 Hz, CO), 101.49 (d, $^1J_{C,F}$ = 214.4 Hz, CF), 125.61–129.14 (m, arom. CH), 131.88 (s, arom. C), 134.79 (s, arom. C), 142.80 (s, arom. C), 146.41 (s, arom. C), 169.49 (d, $^2J_{C,F}$ = 28.1 Hz, C=O) ppm. ^{19}F NMR: δ = –164.82 (dd, $^3J_{H,F}$ = 16.0, $^4J_{H,F}$ = 3.7 Hz, 1 F) ppm. GC MS (EI): m/z (%) = 373.4 (3.5) [M + 1]$^+$, 329.3 (2.8), 314.0 (3.1), 291.5 (4.2), 271.1 (100, retro Diels–Alder), 251.3 (9.9), 193.1 (8.5), 164.0 (1.4), 129.2 (1.4), 91.1 (2.1).

***exo*-4,9-Epoxy-3a,9a-difluoro-3-methyl-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-2(3*H*)-one (7):** Yield: 580 mg (92%). Colourless crystals, m.p. 165–167 °C (hexane/acetone). ^{1}H NMR: δ = 1.46 (dd, $^3J_{H,H}$ = 6.9, $^4J_{H,F}$ = 4.5 Hz, 3 H), 4.78 (dq, $^3J_{H,H}$ =

6.6, $^3J_{H,F}$ = 13.0 Hz, 1 H), 7.53–7.95 (m, 14 H) ppm. ^{13}C DEPT NMR: δ = 15.55 (d, $^2J_{C,F}$ = 22.6 Hz, CH_3), 79.22 (d, $^2J_{C,F}$ = 24.3 Hz, CH), 89.99 (d, $^2J_{C,F}$ = 24.1 Hz, CO), 90.78 (d, $^2J_{C,F}$ = 22.9 Hz, CO), 94.41 (dd, $^1J_{C,F}$ = 224.4, $^2J_{C,F}$ = 13.1 Hz, CF), 98.87 (d, $^1J_{C,F}$ = 229.6, $^2J_{C,F}$ = 11.8 Hz, CF), 122.27–129.15 (m, arom. CH), 131.28 (s, arom. C), 132.64 (s, arom. C), 142.22 (s, arom. C), 142.31 (s, arom. C), 167.18 (d, $^2J_{C,F}$ = 27.5 Hz, C=O) ppm. ^{19}F NMR: δ = –162.09 (br. s, 1 F), –172.32 (m, 1 F) ppm. GC-MS (EI): *m*/*z* (%) = 314.3 (0.2), 270.2 (100, retro-Diels–Alder), 241.2 (9.1), 165.1 (4.8), 127.2 (11.5), 83.0 (20.2). $C_{25}H_{18}F_2O_3$ (404.42): calcd. C 74.25, H 4.49; found C 74.26, H 4.28.

***exo*-3-(3-Bromopropyl)-4,9-epoxy-3a,9a-difluoro-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-2(3*H*)-one (8):** Yield: 696 mg (88%). Colourless crystals, m.p. 144–146 °C (hexane/acetone). ^{1}H NMR: δ = 1.69–1.97 (m, 4 H), 3.19 (m, 2 H), 4.44 (dt, $^3J_{H,H}$ = 6.0, $^3J_{H,F}$ = 13.2 Hz, 1 H), 7.33–7.77 (m, 14 H) ppm. ^{13}C DEPT NMR: δ = 26.94 (s, $CH_2CH_2CH_2$), 28.52 (d, $^3J_{C,F}$ = 10.6 Hz, $CHCH_2$), 32.16 (s, CH_2Br), 81.54 (d, $^2J_{C,F}$ = 22.6 Hz, CH), 90.17 (d, $^2J_{C,F}$ = 24.2 Hz, CO), 90.92 (d, $^2J_{C,F}$ = 24.2 Hz, CO), 94.35 (dd, $^1J_{C,F}$ = 225.8, $^2J_{C,F}$ = 13.6 Hz, CF), 98.87 (d, $^1J_{C,F}$ = 230.2 Hz, CF), 122.39–129.35 (m, arom. CH), 131.32 (s, arom. C), 132.53 (s, arom. C), 142.14 (s, arom. C), 142.40 (s, arom. C), 167.06 (d, $^2J_{C,F}$ = 27.2 Hz, C=O) ppm. ^{19}F NMR: δ = –163.18 (br. s, 1 F), –172.32 (d, $^3J_{H,F}$ = 14.8 Hz, 1 F) ppm. GC-MS (EI): *m*/*z* = 429 (0.5), 270 (100, retro-Diels–Alder), 241 (37.6), 193 (11.5), 165 (26.2), 15.1 (135), 119 (5.5), 77 (15.6), 51 (5.0). $C_{27}H_{21}F_2O_3Br$ (511.36): calcd. C 63.42, H 4.14; found 63.23, H 3.93.

***exo*-4,9-Epoxy-3a,9a-difluoro-3,3-dimethyl-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-2(3*H*)-one (9):** Yield: 117 mg (18%, 34% conversion after two weeks, *m*-fluorotoluene as internal standard, 0.15 mol L^{-1}). Colourless crystals, m.p. 223–225 °C (hexane/acetone). ^{1}H NMR: δ = 1.12 (s, 3 H), 1.53 (d, $^4J_{H,F}$ = 4.7 Hz, 3 H), 7.12–7.81 (m, 14 H) ppm. ^{13}C DEPT NMR: δ = 25.76 (s, CH_3), 26.34 (d, $^3J_{C,F}$ = 14.9 Hz, CH_3), 88.81 (d, $^2J_{C,F}$ = 25.2 Hz, CCH_3), 90.33 (d, $^2J_{C,F}$ = 26.3 Hz, CO), 90.44 (d, $^2J_{C,F}$ = 24.4 Hz, CO), 95.89 (dd, $^1J_{C,F}$ = 224.1, $^2J_{C,F}$ = 12.6 Hz, CF), 98.90 (dd, $^1J_{C,F}$ = 226.7, $^2J_{C,F}$ = 11.2 Hz, CF), 122.22–129.63 (m, arom. CH), 131.47 (s, arom. C), 135.31 (s, arom. C), 142.38 (s, arom. C), 144.41 (s, arom. C), 166.06 (d, $^2J_{C,F}$ = 13.6 Hz, C=O) ppm. ^{19}F NMR: δ = –156.82 (q, $^4J_{H,F}$ = 4.0 Hz, 1 F), –157.79 (br. s, 1 F) ppm. GC MS (EI): *m*/*z* = 341.1 (0.2), 302.0 (0.2), 283.0 (0.4), 270.0 (100, retro-Diels–Alder), 241.1 (7.7), 213.1 (3.4), 193.0 (1.6), 165.0 (4.4), 127.1 (17.0), 105.0 (4.4), 82.9 (31.0), 57.0 (8.3). $C_{26}H_{20}F_2O_3$ (418.44): calcd. C 74.63, H 4.82; found C 74.76, H 5.06.

Reactions between Fluorinated Furan-2(5*H*)-ones and Cyclopentadiene (General Procedure): The furan-2(5*H*)-one (1.5 mmol) and cyclopentadiene (5 g; 7.6 mmol) in toluene (5 mL) were heated in a sealed glass tube at 150 °C for the period of time stated in Table 2. The reactions were monitored by TLC. The solvent was then removed under reduced pressure. After a ^{19}F NMR spectrum of the crude product had been taken, in order to determine the ratio of diastereoisomers, the residue was purified by column chromatography with cyclohexane/ethyl acetate (10:1).

Reaction between 3-Fluorofuran-2(5*H*)-one (1) and Cyclopentadiene: By the general procedure, a crude 82:18 mixture of two mono- (60:40) and two bis (60:40) adducts was formed and was purified by column chromatography (cyclohexane/ethyl acetate, 5:1). The mixture of 1:1 adducts was obtained as a colourless oil, while the mixture of 1:2 adducts was obtained as colourless crystals.

2-Fluoro-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ones (10 and 11): Yield: 192 mg (76%). $C_9H_9FO_2$ (168.17): calcd. C 64.28, H 5.39; found C 64.26, H 5.29. ^{1}H NMR *endo* isomer **10**: δ = 1.98 (dm, $^2J_{H,H}$ = 9.4 Hz, 1 H), 2.05 (dm, $^2J_{H,H}$ = 9.4 Hz, 1 H), 2.99 (ddm, $^3J_{H,F}$ = 27.0, $^3J_{H,H}$ = 8.8 Hz, 1 H), 3.08 (br. s, 1 H), 3.22 (br. s, 1 H), 3.61 (m, 1 H), 4.45 (dd, $^2J_{H,H}$ = 9.9, $^3J_{H,H}$ = 8.5 Hz, 1 H), 6.13 (m, 1 H), 6.41–6.47 (m, 2 H) ppm. ^{1}H NMR *exo* Isomer **11**: δ = 1.55 (dm, $^2J_{H,H}$ = 10.5 Hz, 1 H), 1.67 (dm, $^2J_{H,H}$ = 10.5 Hz, 1 H), 2.40 (ddm, $^3J_{H,F}$ = 19.8, $^3J_{H,H}$ = 8.8 Hz, 1 H), 3.00 (br. s, 1 H), 3.26 (br. s, 1 H), 3.97 (m, 1 H), 4.59 (dd, $^2J_{H,F}$ = 10.2, $^3J_{H,H}$ = 8.5 Hz, 1 H), 6.25–6.27 (m, 1 H), 6.41–6.47 (m, 2 H) ppm. ^{13}C APT NMR *endo* isomer **10**: δ = 46.17 (d, $^2J_{C,F}$ = 16.5 Hz, CH), 46.21 (d, $^2J_{C,F}$ = 22.9 Hz, CH), 48.87 (d, $^3J_{C,F}$ = 2.9 Hz, CH), 50.29 (d, $^2J_{C,F}$ = 25.2 Hz, $CHCH_2O$), 50.56 (d, $^3J_{C,F}$ = 2.0 Hz, CH_2), 69.80 (d, $^3J_{C,F}$ = 2.9 Hz, CH_2O), 103.95 (d, $^1J_{C,F}$ = 209.6 Hz, CF), 138.39 (d, $^3J_{C,F}$ = 2.3 Hz, =CH), 138.87 (s, =CH) ppm. ^{13}C APT NMR *exo* isomer **11**: δ = 43.63 (d, $^3J_{C,F}$ = 2.1 Hz, CH_2), 45.01 (d, $^3J_{C,F}$ = 1.8 Hz, CH), 48.64 (d, $^2J_{C,F}$ = 23.0 Hz, $CHCH_2O$), 70.71 (d, $^3J_{C,F}$ = 2.3 Hz, CH_2O), 104.19 (d, $^1J_{C,F}$ = 203.2 Hz, CF), 133.13 (d, $^3J_{C,F}$ = 8.1 Hz, =CH), 133.13 (d, $^4J_{C,F}$ = 3.0 Hz, =CH) ppm. ^{19}F NMR *endo* isomer **10**: δ = –158.50 (d, $^3J_{H,F}$ = 26.8 Hz, 1 F) ppm. ^{19}F NMR *exo* isomer **11**: δ = –166.40 (d, $^3J_{H,F}$ = 19.8 Hz, 1 F) ppm. GC MS (EI) *endo* isomer **10**: *m*/*z* = 169 (3.2) [M + 1]$^+$, 151 (0.2), 141 (0.4), 123 (0.8), 109 (5.7), 96 (2.4), 83 (5.7), 77 (2.7), 66 (100), 57 (3.6), 51 (2.4), 39 (11.7), 29 (5.7). GC MS (EI) *exo* isomer **11**: *m*/*z* = 169 (8.5) [M + 1]$^+$, 159 (0.4), 149 (0.6), 141 (0.8), 120 (0.8), 109 (7.7), 96 (3.2), 83 (6.1), 77 (2.0), 66 (100), 57 (4.0), 51 (1.6), 39 (13.3), 29 (1.6).

4-Fluoro-6-oxapentacyclo[5.2.2.1.1.0^{2,10}.0^{4,8}]pentadec-12-en-5-ones (12 and 13): Yield: 39 mg (11%). Colourless crystals, m.p. 57–62 °C (cyclohexane). $C_{14}H_{15}FO_2$ (234.27): calcd. C 71.81, H 6.45; found C 71.61, H 6.15. ^{1}H NMR *endo* isomer **12**: δ = 0.54 (dm, $^2J_{H,H}$ = 13.2 Hz, 1 H), 1.32–1.45 (m, 3 H), 1.42 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H), 2.41–3.10 (m, 6 H), 3.81 (dm, $^2J_{H,H}$ = 9.9 Hz, 1 H), 4.54 (dd, $^2J_{H,H}$ = 11.4, $^4J_{H,H}$ = 11.4 Hz, 1 H), 6.06 (m, 1 H) ppm. ^{1}H NMR *exo* isomer **13**: δ = 0.70 (dm, $^2J_{H,H}$ = 10.7 Hz, 1 H), 1.32–1.45 (m, 3 H), 1.44 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H), 2.41–3.10 (m, 6 H), 4.29–4.42 (m, 2 H), 6.02 (m, 1 H) ppm. ^{13}C APT NMR *endo* isomer **12**: δ = 28.89 (d, $^3J_{C,F}$ = 4.0 Hz, CH_2), 38.48–48.82 (m, all CH), 53.22 (s, CH_2), 71.20 (d, $^3J_{C,F}$ = 3.2 Hz, CH_2O), 101.22 (d, $^1J_{C,F}$ = 205.8 Hz, CF), 136.77 (br. s, 2 × =CH), 173.85 (d, $^2J_{C,F}$ = 28.6 Hz, C=O) ppm. ^{13}C APT NMR *exo* isomer **13**: δ = 35.23 (d, $^3J_{C,F}$ = 2.0 Hz, CH_2), 38.48–48.82 (m, all CH), 53.64 (s, CH_2), 66.16 (d, $^3J_{C,F}$ = 2.6 Hz, CH_2O), 104.30 (d, $^1J_{C,F}$ = 203.5 Hz, CF), 136.10 (s, =CH), 136.17 (s, =CH), 172.55 (d, $^2J_{C,F}$ = 27.8 Hz, C=O) ppm. ^{19}F NMR *endo* isomer **12**: δ = –153.98 (d, $^3J_{H,F}$ = 31.1, $^3J_{H,F}$ = 12.1 Hz, 1 F) ppm. ^{19}F NMR *exo* isomer **13**: δ = –176.35 (d, $^3J_{H,F}$ = 21.0 Hz, 1 F) ppm. GC MS (EI) *endo* isomer **12**: *m*/*z* = 235 (11.7) [M + 1]$^+$, 215 (0.4), 197 (0.4), 169 (2.8), 141 (0.8), 128 (1.6), 109 (5.2), 91 (9.7), 83 (3.2), 66 (100), 51 (2.8), 39 (12.5), 29 (1.2). GC MS (EI) *exo* isomer **13**: *m*/*z* = 235 (13.3) [M + 1]$^+$, 207 (0.2), 179 (0.4), 169 (7.7), 159 (0.4), 146 (0.8), 128 (1.6), 103 (6.5), 97 (0.8), 91 (8.1), 77 (3.6), 66 (100), 51 (3.6), 39 (14.5), 29 (1.6).

Reaction between 3,4-Difluoro-5-methylfuran-2(5*H*)-one (2) and Cyclopentadiene: By the above procedure, a 25:75 crude mixture (332 mg) of two mono adducts (60:40) and two bis adducts (73:27) was obtained. After the second column chromatographic separation (cyclohexane/ethyl acetate, 10:1) the pure bis adducts were obtained. The mono adducts could not be isolated in a pure state, but were obtained in a mixture with 15% of the bis adducts.

2,6-Difluoro-5-methyl-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-ones (14a and 14b): Yield: 54 mg (18%, contaminated with 15% of the bis adduct). ^{19}F NMR *endo* isomer **14a**: δ = –172.57 (d, $^3J_{H,F}$ = 7.2 Hz, 1 F), –174.95 (br. s, 1 F) ppm. ^{19}F NMR *exo* isomer **14b**: δ = –168.85 (d, $^3J_{H,F}$ = 8.1 Hz, 1 F), –175.44 (br. s, 1 F) ppm. GC-MS

(EI) *endo* isomer **14a**: *m*/*z* = 200.1 (0.3) [M + 1]$^+$, 180.1 (1.4) [M – HF]$^+$, 155.1 (4.2), 127.0 (11.3), 109.0 (8.5), 101.0 (8.5), 77.0 (5.6), 66.6 (9.9), 66.0 (100). GC-MS (EI) *exo* isomer **14b**: *m*/*z* = 200.1 (0.3) [M + 1]$^+$, 156.1 (1.4), 127.0 (11.3), 109.0 (7.6), 101.0 (7.6), 77.0 (1.9), 66.6 (5.1), 66.0 (100).

4,8-Difluoro-7-methyl-6-oxapentacyclo[5.2.2.1.1.0^{2,10}.0^{4,8}]pentadec-12-en-5-one (17a and 17b): Yield: 204 mg (51%). White waxy solid. $C_{15}H_{16}F_2O_2$ (266.29): calcd. C 68.56, H 6.47; found C 68.33, H 6.38. ^{1}H NMR *endo* isomer **17a**: δ = 0.54 (dm, $^2J_{H,H}$ = 13.2 Hz, 1 H), 1.32–1.45 (m, ds$_1$, ds$_2$, 3 H), 1.42 (d, 3 H, $^3J_{H,H}$ = 6.6 Hz), 2.41–3.10 (m, 6 H), 4.33 (dq, 1 H, $^3J_{H,F}$ = 11.0, $^3J_{H,H}$ = 6.9 Hz), 6.06 (m, 1 H) ppm. ^{1}H NMR *exo* isomer **17b**: δ = 0.70 (dm, $^2J_{H,H}$ = 10.7 Hz, 1 H), 1.32–1.45 (m, 3 H), 1.44 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H), 2.41–3.10 (m, 6 H), 4.42 (dq, $^3J_{H,F}$ = 10.7, $^3J_{H,H}$ = 6.6 Hz, 1 H), 6.02 (m, 1 H) ppm. ^{13}C APT NMR *endo* isomer **17a**: δ = 15.53 (d, $^3J_{C,F}$ = 14.6 Hz, CH_3), 24.64 (dd, $^3J_{C,F}$ = $^3J_{C,F}$ = 5.7 Hz, CH_2), 37.91–48.05 (m, all CH), 53.43 (s, CH_2), 82.91 (d, $^2J_{C,F}$ = 26.9 Hz, *C*HCH$_3$), 93.91 (dd, $^1J_{C,F}$ = 217.8, $^2J_{C,F}$ = 14.6 Hz, CF), 95.29 (dd, $^1J_{C,F}$ = 221.6, $^2J_{C,F}$ = 10.0 Hz, CF), 136.54 (s, =CH), 136.60 (s, =CH), 172.36 (d, $^2J_{C,F}$ = 27.2 Hz, C=O) ppm. ^{13}C APT NMR *exo* isomer **17b**: δ = 17.26 (dd, $^3J_{C,F}$ = 10.3, $^4J_{C,F}$ = 3.2 Hz, CH_3), 27.13 (dd, $^3J_{C,F}$ = $^3J_{C,F}$ = 5.4 Hz, CH_2), 53.76 (s, CH_2), 83.16 (d, $^2J_{C,F}$ = 26.9 Hz, *C*HCH$_3$), 94.00 (dd, $^1J_{C,F}$ = 217.6, $^2J_{C,F}$ = 14.4 Hz, CF), 137.10 (s, =CH), 137.23 (s, =CH), 171.51 (d, $^2J_{C,F}$ = 27.4 Hz, C=O) ppm. ^{19}F NMR *endo* isomer **17a**: δ = –183.61 (dd, $^3J_{H,F}$ = $^3J_{H,F}$ = 8.4 Hz, 1 F), –188.85 (m, 1 F) ppm. ^{19}F NMR *exo* isomer **17b**: δ = –181.49 (dd, $^3J_{H,F}$ = $^3J_{H,F}$ = 9.1 Hz, 1 F), –186.77 (m, 1 F) ppm. GC-MS (EI) *endo* isomer **17a**: *m*/*s* = 266.1 (0.3) [M]$^+$, 201.1 (2.7), 165.1 (1.3), 127 (5.1), 115.1 (5.1), 109.0 (10.8), 77.0 (7.3), 66.0 (100), 65.0 (8.2). GC-MS (EI) *exo* isomer **17b**: *m*/*z* = 266.1 (0.3) [M]$^+$, 212.1 (2.5), 201.1 (3.2), 185.1 (3.2), 181.1 (3.0), 147.1 (57.0), 146.1 (6.3), 129.1 (21.5), 117.1 (22.8), 91.1 (16.5), 77.0 (7.6), 66.0 (100).

Reaction between 5-(3-Bromopropyl)-3,4-difluorofuran-2(5*H*)-one (3) and Cyclopentadiene: By the above procedure, a 21:79 crude mixture (405 mg) of two mono adducts (70:30) and one bis adduct was obtained. After the second column chromatographic separation (cyclohexane/ethyl acetate, 8:1) the pure bis adduct was obtained. The mono adducts could not be isolated in pure state, but were obtained as a 70:30 mixture of two diastereomers.

5-(3-Bromopropyl)-2,6-difluoro-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (15a and 15b): Yield: 46 mg (10%). Colourless crystals, m.p. 43–45 °C (cyclohexane). $C_{11}H_{13}BrF_2O_2$ (307.19): calcd. C 46.93, H 4.27; found C 46.93, H 4.17. ^{1}H NMR *endo* isomer **15a**: δ = 1.42 (dm, $^2J_{H,H}$ = 11.3 Hz, 1 H), 1.75–2.17 (m, 5 H), 3.12 (m, ds$_1$, 1 H), 3.18 (br. s, 1 H), 3.32 (s, 1 H), 4.14 (dt, $^3J_{H,F}$ = 9.1, $^3J_{H,H}$ = 3.9 Hz), 6.42 (m, 2 H) ppm. ^{1}H NMR *exo* isomer **15b**: δ = 1.75–2.17 (m, 5 H), 2.21 (dm, $^2J_{H,H}$ = 9.9 Hz, 1 H), 2.50 (dm, $^2J_{H,H}$ = 9.9 Hz, 1 H), 3.12 (m, 1 H), 3.25 (m, 1 H), 4.14 (dt, $^3J_{H,F}$ = 8.5, $^3J_{H,H}$ = 3.0 Hz), 6.21 (dd, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 3.3 Hz, 1 H), 6.30 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 3.0 Hz, 1 H) ppm. ^{13}C APT NMR *endo* isomer **15a**: δ = 27.99 (d, $^4J_{C,F}$ = 2.9 Hz, $CH_2CH_2CH_2$), 29.22 (d, $^3J_{C,F}$ = 10.9 Hz, OCH*C*H$_2$), 39.69 (br. s, CH_2Br), 47.92 (d, $^2J_{C,F}$ = 21.7 Hz, CH), 49.84 (m, CH_2), 51.01 (d, $^2J_{C,F}$ = 22.3 Hz, CH), 85.00 (d, $^2J_{C,F}$ = 25.2 Hz, OCH), 96.63 (d, $^1J_{C,F}$ = 214.9 Hz, CF), 99.44 (d, $^1J_{C,F}$ = 217.2 Hz, CF), 134.45 (d, $^3J_{C,F}$ = 3.4 Hz, =CH), 135.66 (d, $^3J_{C,F}$ = 2.6 Hz, =CH), 170.32 (d, $^2J_{C,F}$ = 28.4 Hz, C=O) ppm. ^{13}C APT NMR *exo* isomer **15b**: δ = 27.99 (d, $^4J_{C,F}$ = 2.9 Hz, $CH_2CH_2CH_2$), 29.12 (d, $^3J_{C,F}$ = 11.2 Hz, OCH*C*H$_2$), 32.69 (br. s, CH_2Br), 48.47 (d, $^2J_{C,F}$ = 25.4 Hz, CH), 49.84 (m, ds$_1$, ds$_2$, CH_2), 49.86 (d, $^2J_{C,F}$ = 24.6 Hz, CH), 83.79 (d, $^2J_{C,F}$ = 24.4 Hz, OCH), 96.59 (d, $^1J_{C,F}$ = 224.1 Hz, CF), 98.55 (d, $^1J_{C,F}$ = 223.3 Hz, CF), 135.62 (d, $^3J_{C,F}$ = 5.9 Hz, =CH), 136.02 (d, $^3J_{C,F}$ = 6.9 Hz, =CH) ppm. ^{19}F NMR *endo* isomer **15a**: δ = –172.94 (d, $^3J_{H,F}$ = 8.7 Hz, 1 F), –175.39 (br. s, 1 F) ppm. ^{19}F NMR *exo* isomer **15b**: δ = –169.34 (dd, $^3J_{H,F}$ = $^3J_{F,F}$ = 9.9 Hz, 1 F), –176.08 (br. s, 1 F) ppm. GC MS (EI) *endo* isomer **15a**: *m*/*z* = 306/308 (0.2) [M]$^+$, 286/288 (0.2) [M – 20 (– HF)]$^+$, 155.1 (2.8), 128.0 (5.6), 127.0 (24.7), 109.0 (25.0), 101.0 (11.1), 66.0 (100). GC MS (EI) *exo* isomer **15b**: *m*/*z* = 306/308 (0.2) [M]$^+$, 286/288 (0.2) [M – 20 (– HF)]$^+$, 155.1 (1.4), 149.0 (4.2), 127.0 (10.6), 109.0 (8.9), 66.0 (100).

7-(3-Bromopropyl)-4,8-difluoro-6-oxapentacyclo[5.2.2.1.1.0^{2,10}.0^{4,8}]-pentadec-12-en-5-one (18): Yield: 316 mg (56%). Colourless crystals, m.p. 107–109 °C (cyclohexane). ^{1}H NMR: δ = 0.54 (dm, $^2J_{H,H}$ = 13.3 Hz, 1 H), 1.35 (dm, $^2J_{H,H}$ = 8.2 Hz, 1 H), 1.44 (dm, $^2J_{H,H}$ = 8.4 Hz, 1 H), 1.56 (br. s, 1 H), 1.78–2.19 (m, 4 H), 2.50 (br. s, 1 H), 2.61 (m, 2 H), 2.71 (br. s, 1 H), 2.78 (m, 2 H), 3.00–3.02 (m, 2 H), 3.45 (m, 2 H), 4.18 (m, 1 H), 6.04–6.10 (m, 2 H) ppm. ^{13}C APT NMR: δ = 28.23 (d, $^4J_{C,F}$ = 2.9 Hz, $CH_2CH_2CH_2$), 28.73 (d, $^3J_{C,F}$ = 12.6 Hz, OCH*C*H$_2$), 28.82 (s, CH_2Br), 32.72 (s, CH), 37.98 (d, $^3J_{C,F}$ = 8.2 Hz, CH), 38.22 (d, $^3J_{C,F}$ = 8.6 Hz, CH), 44.27 (d, $^2J_{C,F}$ = 18.3 Hz, *C*HCF), 46.27 (s, CH), 46.35 (s, CH), 48.26 (d, $^2J_{C,F}$ = 18.3 Hz, *C*HCF), 53.48 (s, CH_2), 85.42 (d, $^2J_{C,F}$ = 25.7 Hz, OCH), 93.8 (d, $^1J_{C,F}$ = 203.7 Hz, CF), 95.43 (d, $^1J_{C,F}$ = 208.9 Hz, CF), 136.55 (s, =CH), 136.65 (s, =CH) ppm. ^{19}F NMR: δ = –183.54 (m, 1 F), –188.88 (m, 1 F) ppm. GC-MS (EI): *m*/*z* = 372.1/374.0 (0.2) [M]$^+$, 307.0 (1.0), 287.0 (1.5), 165.1 (2.5), 127.0 (7.6), 115.0 (7.8), 109.0 (9.1), 91.1 (16.7), 66.0 (100), 51.0 (3.2), 41.0 (5.1). $C_{17}H_{19}F_2O_2Br$ (373.24): calcd. C 54.71, H 5.13; found C 54.57, H 4.73.

Reaction between 3,4-Difluoro-5,5-dimethylfuran-2(5*H*)-one (4) and Cyclopentadiene: By the above procedure, a 32:68 mixture of two mono adducts (78:22) and two bis adducts (90:10) was obtained. Yield: 45 mg (12% conversion after 30 d). Several column chromatography runs (cyclohexane/ethyl acetate 10:1) gave fractions enriched in mono or bis adducts.

2,6-Difluoro-5,5-dimethyl-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (16a and 16b): ^{19}F NMR *endo* isomer **16a**: δ = –165.98 (m, 1 F), –174.83 (d, $^3J_{F,F}$ = 6.4 Hz, 1 F) ppm. ^{19}F NMR *exo* isomer **16b**: δ = –179.32 (m, 1 F), –185.71 (dm, $^3J_{F,F}$ = 7.2 Hz, 1 F) ppm. GC MS (EI) *endo* isomer **16a**: *m*/*z* = 214.1 (0.3) [M]$^+$, 199.1 (1.3), 194.1 (1.5), 1791 (2.3), 170.1 (10.8), 155.1 (4.4), 149.1 (3.8), 133.0 (7.3), 128.0 (15.2), 127.0 (25.3), 109.0 (7.6), 102.0 (10.1), 77.0 (5.1), 66.0 (100). GC MS (EI) *exo* isomer **16b**: *m*/*z* = 214.1 (0.3) [M]$^+$, 194.1 (1.5), 179.1 (2.3), 170.1 (2.4), 155.1 (3.8), 149.1 (2.5), 133.0 (5.1), 128.0 (8.9), 127.0 (10.8), 109.0 (6.3), 102.0 (5.1), 77.0 (3.8), 66.0 (100).

4,8-Difluoro-7,7-dimethyl-6-oxapentacyclo[5.2.2.1.1.0^{2,10}.0^{4,8}]pentadec-12-en-5-one (19a and 19b): ^{19}F NMR *endo* isomer **19a**: δ = –176.50 (m, 1 F), –183.59 (m, 1F) ppm. ^{19}F NMR *exo* isomer **19b**: δ = –176.87 (m, 1 F), –183.71 (dm, $^3J_{F,F}$ = 8.1 Hz, 1 F) ppm. GC-MS (EI) *endo* isomer **19a**: *m*/*z* = 280.1 (0.4) [M]$^+$, 216.1 (1.3), 215.1 (8.8), 195.1 (8.7), 175.1 (3.6), 155.1 (2.2), 133.0 (4.3), 127.0 (10.1), 115.1 (5.8), 109 (6.5), 91.1 (13.0), 77.0 (7.3), 66.6 (13.0), 66.0 (100), 65.0 (9.4). GC-MS (EI) *exo* isomer **19b**: *m*/*z* = 280.1 (0.4) [M]$^+$, 216.1 (1.0), 215.1 (5.1), 195.1 (5.0), 175.1 (1.3), 129.1 (1.9), 127.0 (4.4), 109.0 (2.8), 91.1 (3.8), 77.0 (2.5), 66.0 (100).

X-Ray Crystallographic Study: Data sets were collected with Enraf–Nonius Mach3 and Nonius KappaCCD diffractometers equipped with a rotating anode generator, with use of Mo radiation. Programs used: data collection EXPRESS (Nonius B.V., 1994) and COLLECT (Nonius B.V., 1998), data reduction RC93 (D. J. Watkin, C. K. Prout, P. M. deQ. Lilley, Chem. Cryst. Lab., Oxford, U.K., 1994) and Denzo-SMN,[48] absorption correction based on

psi-scan-data[49] and SORTAV[50] and Denzo,[51] structure solution SIR92[52] and SHELXS-97,[53] structure refinement CRYSTALS[54] and SHELXL-97,[55] graphics Diamond[56] and SCHAKAL.[57]

***exo*-4,9-Epoxy-9a-fluoro-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho-[2,3-*c*]furan-2(3*H*)-one (6):** Formula $C_{24}H_{17}F_1O_3$, *Mr* = 372.40; colourless crystals 0.2 × 0.3 × 0.3 mm; *a* = 13.46(2), *b* = 9.58(2), *c* = 14.06(2) Å; *α* = 90, *β* = 94.76(2), *γ* = 90°, *V* = 1807.2(53) Å^3, $\rho_{calcd.}$ = 1.3687 g cm^{-3}; μ = 0.792 cm^{-1}; no absorption correction; *Z* = 4, monoclinic, space group $P2_{1/n}$ No.14; λ = 1.54180 Å; *T* = 293 K; 7434 reflections were collected (±*h*, ±*k*, –*l*); $[(\sin\Theta)/\gamma]_{max}$ = 0.63 Å^{-1}; 3718 independent and 3702 observed reflections, 322 refined parameters, *R* = 0.0449, R_w^2 = 0.0481, final difference Fourier ρ = 0.24 (–0.20) e Å^{-3}.

***exo*-4,9-Epoxy-3a,9a-difluoro-3-methyl-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-2(3*H*)-one (7):** Formula $C_{25}H_{18}F_2O_3$, *Mr* = 404.39; colourless crystals 0.25 × 0.20 × 0.05 mm; *a* = 8.322(1), *b* = 10.103(1), *c* = 12.768(1) Å; *α* = 98.78(1), *β* = 94.04(1), *γ* = 111.67°, *V* = 976.49(17) Å^3, $\rho_{calcd.}$ = 1.375 g cm^{-3}; μ = 1.02 cm^{-1}; no absorption correction (0.975 ≤ *T* ≤ 0.995); *Z* = 2, triclinic, space group $P\bar{1}$ (No. 2); λ = 0.71073 Å; *T* = –75 °C; 6951 reflections were collected (±*h*, ±*k*, ±*l*); $[(\sin\Theta)/\gamma]_{max}$ = 0.66 Å^{-1}; 4634 independent and 3212 observed reflections, 272 refined parameters, *R* = 0.047, R_w^2 = 0.109, final difference Fourier ρ = 0.31 (–0.21) e Å^{-3}.

***exo*-4,9-Epoxy-3a,9a-difluoro-3,3-dimethyl-4,9-diphenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-2(3*H*)-one (9):** Formula $C_{26}H_{20}F_2O_3$, *Mr* = 418.42; colourless crystals 0.35 × 0.20 × 0.20 mm; *a* = 9.794(1), *b* = 10.047(1), *c* = 11.329(1) Å; *α* = 68.30(1), *β* = 80.54(1), *γ* = 85.48°, *V* = 021.5(2) Å^3, $\rho_{calcd.}$ = 1.360 g cm^{-3}; μ = 1.00 cm^{-1}; absorption correction (0.966 ≤ *T* ≤ 0.980); *Z* = 2, triclinic, space group $P\bar{1}$ (No. 2); λ = 0.71073 Å; *T* = room temp.; 6951 reflections were collected (±*h*, ±*k*, ±*l*); $[(\sin\Theta)/\gamma]_{max}$ = 0.66 Å^{-1}; 4917 independent and 4048 observed reflections, 282 refined parameters, *R* = 0.040, R_w^2 = 0.112, final difference Fourier ρ = 0.29 (–0.15) e Å^{-3}.

7-(3-Bromopropyl)-4,8-difluoro-6-oxapentacyclo[5.2.2.1.1.0^{2,10}.0^{4,8}]-pentadec-12-en-5-one (18): Formula $C_{17}H_{19}BrF_2O_2$, *Mr* = 373.24; triclinic, space group $P\bar{1}$ (No. 2); colourless crystals 0.05 × 0.20 × 0.30 mm; *a* = 6.450(2), *b* = 10.455(2), *c* = 11.494(2) Å; *α* = 92.17(2), *β* = 96.14(2), *γ* = 92.71(2), *V* = 769.3(3) Å^3, $\rho_{calcd.}$ = 1.612 g cm^{-3}; μ = 3.89 cm^{-1}; λ = 1.54180 Å; *T* = room temp.; 3107 reflections were collected (±*h*, ±*k*, +*l*); $[(\sin\Theta)/\gamma]_{max}$ = 0.61 Å^{-1}; 2938 independent and 2830 observed reflections, 322 refined parameters, *R* = 0.117, R_w^2 = 0.102, final difference Fourier ρ = 1.48 (–1.85) e Å^{-3}.

CCDC-625512 to -625515 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Crystallographical data for **9**, details of $^{19}F\{^1H\}$ NOE experiments and results of calculations of transition states of Diels–Alder reactions between cyclopentadiene and fluorinated dihydrofuranones.

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