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Synthesis and reactivity of *Z* and *E* functionalized allylic fluorides

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Abstract—The allylic fluorides **1** and **2** are used as models to study the effect of the allylic C–F bond on the diastereoselectivity of reactions occurring on the vicinal double bond, as well as the compatibility of this C–F bond with various reagents. The configurational stability of the *Z* double bonds in enals and enones **1** and **3** is noteworthy. This allowed us to perform various types of reactions (including thermal Diels–Alder cycloadditions) on derivatives **1** with full control of the *Z* geometry.

1. Introduction

The introduction of fluorine atom(s) strongly modifies the physical, chemical and biological properties in a molecule.[1] This explains why fluorinated compounds are intensively studied and used in areas as diverse as pharmaceuticals, agrochemicals and polymers for instance. In fluoro-bioorganic chemistry the replacement of strategic C–H or C–OH bonds by C–F could lead to important informations regarding the structure and mechanism of action of enzymatic systems. It could give as well compounds which are more stable from the chemical point of view and/or have a better bioactivity.[2] Therefore, it is important to control the regio- and stereoselectivity of the fluorination step. Particularly, the difficulties encountered during selective monofluorination in a position vicinal to unsaturated derivatives are well recognized. This is the case for allylic systems and it is particularly true when enantiocontrol is required.[3] For instance the dehydroxyfluorination of allylic alcohols with diethylamino sulfur trifluoride (DAST) is neither regio-, nor stereocontrolled.[4] Several methods have been developed in order to afford a solution to this problem: for instance it is possible to use transition metal complexes of the corresponding π complexed alcohol.[5–7] In the case of allylic alcohols it afforded a complete regio- and stereocontrol, however the required rhenium complexes are expensive derivatives which further, are obtained in a multistep sequence.[8] Therefore other strategies using fluorinated key intermediates have been developed. Davis et al. reported an elegant approach using α-fluorocarbonyls as precursors to a Horner–Wadworth–Emmons olefination process. However such intermediates proved to be very sensitive to basic conditions leading to slight loss of enantiomeric purity.[9] We have reported recently that propargylic routes could be very useful for the stereocontrolled synthesis of monofluorinated allylic derivatives such as **1a** and **2a**.[10] The latter compound was an excellent intermediate for the enantiocontrolled synthesis of fluorinated analogues of bioactive lipids (Fig. 1).[11]

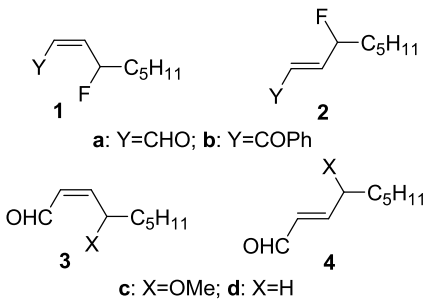

Figure 1.

As part of our program dealing with the development of novel methodologies for the preparation of such chiral fluorides, the purpose of this paper is:

to report an easy and efficient synthesis of corresponding ketones and especially the *Z* isomer **1b**. This led us to prepare also the corresponding *Z* and *E* enals **3** and **4** where fluorine was formally exchanged by a methoxy group or hydrogen. The thermal stability of **1b**, together with the results obtained from **3**, establish that the configurational stability of *Z* enals has been generally underestimated

to extend our previous studies on the steric and electronic effects induced by the C–F bond on the diastereoselectivity of reactions.[12] This will include Diels–Alder,

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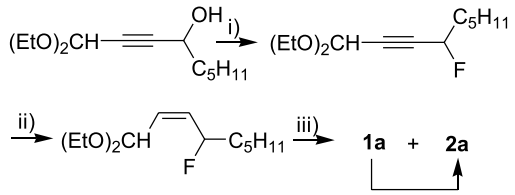
1,2 and 1,4 additions and it will give further information on the compatibility of allylic fluorides with various chemical reagents.

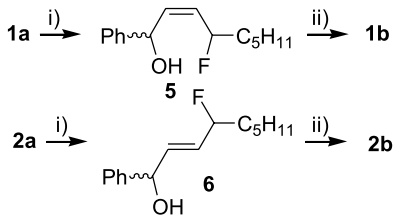
2. Synthesis and thermal stability

We have reported recently the synthesis of **1a** and **2a**, starting from propargylic alcohols: the key steps involved a stereospecific dehydroxyfluorination with DAST at low temperature, followed by a *cis* hydrogenation using Lindlar's catalyst and a deprotection with pure formic acid leading to a 9:1 mixture of **1a** and **2a** separated by chromatography (Scheme 1).[11]



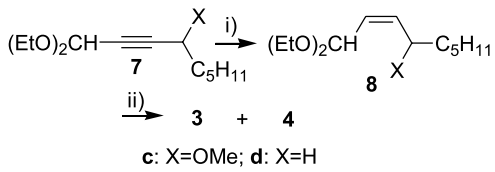
Scheme 1. *Reagents and conditions*: (i) DAST, (ii) H_2, Lindlar; (iii) HCO_2H excess; for details see Ref. 11.

Both isomers were used for the synthesis of the two corresponding ketones: addition of PhLi on **1a** afforded in 91% yield the alcohols **5** as a 1:1 mixture of stereoisomers at the carbinol center, but as exclusive *Z* stereochemistry at the double bond. MnO_2 oxidation of this mixture afforded the ketone **1b** in 86% yield and again without double bond isomerisation. In both cases, the stereochemistry is clearly established by ^1H NMR (J_{H-H}=11.2 Hz). Similar reactions have been performed starting from **2a** affording the *E* isomer **2b** via the allylic alcohols **6** (also obtained as a 1:1 mixture of diastereoisomers). Therefore such allylic fluorides appear compatible with these strong nucleophiles and both the 1,2 addition and the oxidation occur without *Z* to *E* isomerisation (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) PhLi (1.6 equiv.), THF, −50°C, **5** (91%), **6** (82%); (ii) MnO_2 (10 equiv.), CH_2Cl_2, rt, **1b** (86%), **2b** (82%).

The thermal stability of these allylic fluorides, and especially **1a** and **1b**, was of special interest with regard to some synthetic applications such as thermal cycloadditions for instance. To our surprise **1a** was found to be relatively thermally stable: after 24 h at 60°C in benzene, or even in DMSO, there is no evidence for *E* to *Z* isomerisation (NMR control).[13,14] These results led us in a first approach to explore the possible role of the polar C–F bond on this high thermal stability. Therefore, for comparison purposes we prepared the two *Z* enals **3** and **4** where the fluorine has been replaced respectively by OMe and H. The synthesis followed routes similar to the previously used in the preparation of fluorides (Scheme 3). They start from propargylic derivatives **7** which are submitted to a semi hydrogenation with Lindlar's catalyst followed by formolysis. The *Z* enals **3c** and **3d** have been purified by chromatography.

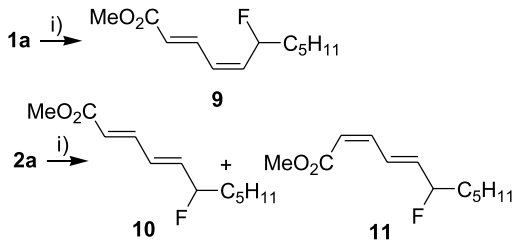


Scheme 3. *Reagents and conditions*: (i) Py (1 equiv.), Lindlar cat. (20% weight), pentane, rt, **8c** (87%), **8d** (99%); (ii) HCO_2H (156 equiv.), CH_2Cl_2, rt, **3c** (46%), **3d** (23%).

Both compounds exhibited a thermal stability similar to compound **1a**: no isomerisation was observed after 3 days in benzene at 60°C! (NMR control). These results first demonstrate that the polar (C–OMe or C–F) bond are not responsible for the good thermal stability; they also clearly establish that the stability of *Z* enals and enones has been largely underestimated and that such compounds have real potentialities in stereoselective synthesis.

3. Reactivity studies

A first series of reactions have been performed using stabilized Wittig reagents and the results are given in Scheme 4. The *Z* enal afforded exclusively the *E*,*Z* diene **9** while the *E* isomer led to a 7:3 mixture of the *E*,*E* and *E*,*Z* dienes **10** and **11**. These isomers could be separated by chromatography.



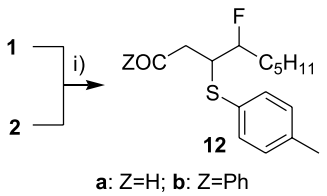
Scheme 4. *Reagents and conditions*: (i) $Ph_3P{=}CHCO_2Me$ (1.2 equiv.), Tol, 75°C, **9** (83%), **10** (45%), **11** (15%).

Therefore, such Wittig type reactions are not only compatible with the allylic fluorides but furthermore, they are stereospecific with regard to the geometry of the starting enal. These results appear of much interest since:

1. They could probably be extended to homochiral derivatives taking into account that starting enals **1a** and **1b** have been obtained previously in optically pure form.[11]
2. They offer a complementary route to the use of dienetricarbonyliron complexes which could afford only the *E*,*E* dienes with the fluorine in allylic position.[5]

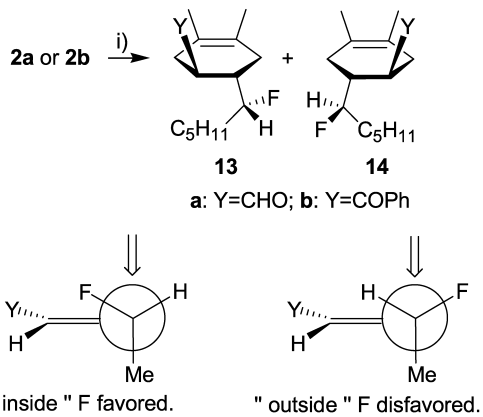
1,4 Addition reactions of thiocresol have been performed on the *E* and *Z* enals and enones **1** and **2**: in both cases they afforded the same inseparable racemic mixture of stereoisomeric adducts **12**. Like in the 1,2 addition there is again

no induction by the allylic C–F bond in these 1,4 additions. It can be noticed also that cuprates appear incompatible with such allylic fluorides since reactions of dimethylcuprate on **1** or **2** led only to decomposition products (Scheme 5).



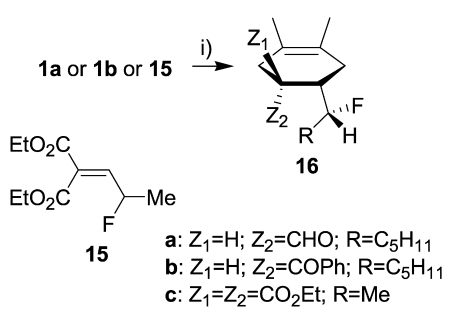
Scheme 5. *Reagents and conditions*: (i) ArSH, THF, Na_2CO_3 (cat), 0°C to rt, **12a** (49%), **12b** (86%).

Next we studied Diels–Alder cycloadditions on alkenes **1** and **2**. Previous experiments have established that for *E* allylic fluoride **2b** the *anti* adduct was the major isomer, with a 76:24 ratio for **13b**–**14b** (Scheme 6).[12]



Scheme 6. *Reagents and conditions*: (i) 2,3 dimethylbutadiene (42 equiv.), reflux, 48 h, **13a** (25%), **14a** (14%), **13b** (62%), **14b** (34%).

For the gemdisubsituted olefin **15** the derivative **16c** was the only compound detected in the crude reaction mixture (Scheme 7). High level computational studies on corresponding transition states have been performed and they have indicated that for the *E* series the transition state with the F'inside' is slightly favored while for the gemdiactivated olefin the TS with the F'outside' was strongly disfavored. The latter result was attributed to the strong electronic repulsion between fluorine and the *cis* ester group which appears in the TS corresponding to the 'inside' F (Scheme 7).[12]



Scheme 7. *Reagents and conditions*: (i) 2,3-dimethylbutadiene (25 equiv.), reflux, **16a** (57%), **16b** (44%), for **16c**, see Ref. 11.

In order to confirm the key role of such a substituent in position *cis* to the allylic fluoride we have performed similar Diels–Alder reactions on *Z* enal **1a** and *Z* enone **1b**; for comparison purposes we did also the same reactions on corresponding *E* isomer **2a**. The results are given in Schemes 6 and 7: starting from **2a** and after 15 h at reflux adducts **13a** and **14a** were obtained as a 2:1 mixture of the *anti* and *syn* isomers (NMR control). The stereochemistry has been established by NMR and by analogy with the data from **13b** and **14b**.[12] In the case of the *Z* isomers **1a** and **1b**, the *syn* adducts **16a** and **16b** were the only isolated compounds. Careful analysis of the crude reaction mixture by ^{19}F NMR excluded the presence of adducts **13a-b** and **14a-b**. Therefore, these reactions are stereospecific with regard to the double bond geometry and this is in agreement with the previous studies establishing that no *Z* to *E* isomerisation of **1a** was occurring after 24 h at 60°C. Further, these results confirm the key role of the electron-withdrawing group *cis* to the allylic C–F bond for the stereoselectivity since we obtain here the same *syn* stereoselectivity than in the case of the fluoride **15**.

4. Conclusion

In summary, we have reported a short and versatile route to *Z* and *E* enals and enones with a fluorine in allylic position. Such *Z* enals, as well as the methoxy analogue and the non-fluorinated derivative have a good thermal stability which allows them to be of further synthetic use in maintaining the stereochemistry of the *Z* double bond. This has been illustrated by 1,2 additions and Wittig reactions; the latter results open new routes to prepare various type of unsaturated or polyunsaturated derivatives with fluorine in allylic position and they would be especially useful in the case of systems containing a *Z* double bond. For the Diels–Alder reactions we could confirm the key role of the substituent *cis* to the allylic fluoride with regard to the *syn* diastereoselectivity. Extension to the preparation of other chiral allylic fluorides is under active study, as well as their application to the preparation of natural product analogues.

5. Experimental

5.1. General

All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen with magnetic stirring. Thin-layer chromatography (TLC) was done on Merck (Art. 1.05554) precoated silica gel 60 F_{254} aluminum sheets (layer thickness 0.2 mm). Visualisation was effected with a UV lamp (254 nm) and/or either by staining with *p*-anisaldehyde/H_2SO_4 solution or by staining with $KMnO_4$ solution. Flash column chromatography was performed using silica gel 60 (Geduran, 40–63 μm, Merck). Solvents were purified as follows: tetrahydrofuran was freshly distilled from sodium benzophenone ketyl under N_2. Diethyl ether and dichloromethane were distilled from P_2O_5 and stored over 3 Å molecular sieves. Triethylamine was distilled from CaH_2. The petroleum ether (PE) used had a boiling range of 30–60°C. NMR spectra were recorded on a Bruker ARX 400 MHz spectrometer. All chemical shifts

are reported in parts per million (δ). ^{1}H NMR (400 MHz) spectra were recorded at rt in $CDCl_3$ or C_6D_6 solutions and referenced to residual $CHCl_3$ (7.27 ppm) or C_6H_6 (7.16 ppm). Fully decoupled ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ or C_6D_6 solutions. The center peaks of $CDCl_3$ (77.0 ppm) and C_6D_6 (128.7 ppm) were used as the internal reference. ^{19}F NMR (376.5 MHz) spectra were recorded in $CDCl_3$ or C_6D_6 solutions using $CFCl_3$ as internal reference. Elemental analyses were performed by the department of microanalyses (C.R.M.P.O.) in Rennes (France). Mass spectra were carried out on a VARIAN MAT 311 spectrometer at the C.R.M.P.O. in Rennes (France).

5.1.1. 4-Fluoro-non-2-(*Z*)-enal (1a) and 4-fluoro-non-2-(*E*)-enal (2a). See Ref. 11.

5.2. 1,2 Additions

5.2.1. 4-Fluoro-1-phenyl-non-2-en-(*Z*)-1-ol (5). To a solution of commercially available phenyllithium (2 M solution in cyclohexane–ether, 70 to 30; 0.7 mL, 1.4 mmol) in 10 mL dry THF and cooled to −50°C was slowly added a solution of aldehyde **1a** (134 mg, 0.85 mmol) in 0.5 mL of dry THF. The reaction mixture was then stirred for 20 min at the same temperature and treated with a saturated solution of NH_4Cl. The product was extracted with ether and the organic layer was dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was chromatographed on silica gel (eluent: pentane/ether, 8/2) to afford a racemic mixture of diastereomers **5** (182 mg, 91% yield). Enriched mixture of one diastereomer allowed the identification of the spectral data of each diastereomer.

1st Diastereomer. Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.36 (m, 4H, Ph), 7.35–7.29 (m, 1H, Ph), 5.88 (dddd, J=11.2, 8.8 Hz, J_{H-F}=2.9 Hz, J=1.1 Hz, 1H, C*H*=CH), 5.66 (dddd, J_{H-F}=12.1 Hz, J=11.1, 8.0, 1.0 Hz, 1H, CH=C*H*), 5.57 (ddd, J=9.0, 3.2, 1.0 Hz, 1H, C*H*OH), 5.39 (dtdd, J_{H-F}=49.5 Hz, J=8.0, 5.1, 1.1 Hz, 1H, C*H*F), 2.16 (d, J=3.2 Hz, 1H, O*H*), 1.92–1.59 (m, 2H, CHFCH_2), 1.57–1.26 (m, 6H, CH_2), 0.92 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.6 (d, J=1.8 Hz), 135.4 (d, J=8.8 Hz), 129.5 (d, J=21.1 Hz), 128.7 (2C), 127.9, 126.1 (2C), 89.1 (d, J=163.2 Hz), 70.1, 35.5 (d, J=22.5 Hz), 31.4, 24.3 (d, J=4.2 Hz), 22.5, 13.9; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −171.38 (dddd, J=49.0, 28.0, 15.3, 14.0 Hz).

2nd Diastereomer. Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.36 (m, 4H, Ph), 7.35–7.29 (m, 1H, Ph), 5.82 (dddd, J=11.1, 9.0 Hz, J_{H-F}=2.7 Hz, J=1.1 Hz, 1H, C*H*=CH), 5.66 (dddd, J_{H-F}=12.1 Hz, J=11.1, 8.0, 1.0 Hz, 1H, CH=C*H*), 5.61 (dd, J=9.0, 3.7 Hz, 1H, C*H*OH), 5.41 (dtdd, J_{H-F}=49.5 Hz, J=8.0, 5.1, 1.1 Hz, 1H, C*H*F), 2.03 (d, J=3.7 Hz, 1H, O*H*), 1.92–1.59 (m, 2H, CHFCH_2), 1.57–1.26 (m, 6H, CH_2), 0.94 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.6 (d, J=1.8 Hz), 135.7 (d, J=8.8 Hz), 129.6 (d, J=19.3 Hz), 128.6 (2C), 127.8, 125.9 (2C), 89.2 (d, J=163.2 Hz), 70.1, 35.7 (d, J=22.5 Hz), 31.5, 24.4 (d, J=4.4 Hz), 22.5, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −172.07 (dddd, J=49.0, 28.0, 15.3, 14.0 Hz); HRMS calcd (EI) 70 eV: for $C_{15}H_{21}OF$ [$M^{+\cdot}$] 236.1576, found 236.158 (2 ppm).

5.2.2. 4-Fluoro-1-phenyl-non-2-(*E*)-en-1-ol (6). To a solution of commercially available phenyllithium (2 M solution in cyclohexane–ether, 70 to 30; 0.7 mL, 1.4 mmol) in 10 mL dry THF and cooled to −60°C was slowly added a solution of aldehyde **2a** (139 mg, 0.88 mmol) in 0.5 mL of dry THF. The reaction mixture was then stirred for 30 min. at the same temperature and treated with a saturated solution of NH_4Cl. The product was extracted with ether and the organic layer was dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was chromatographed on silica gel (eluent: pentane/ether, 8/2) to afford an inseparable racemic mixture of diastereomers **6** (169 mg, 82% yield).

For the two diastereomers. Oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.22 (m, 5H, Ph), 6.01–5.94 (m, 1H, C*H*=CH), 5.93–5.81 (m, 1H, CH=C*H*), 5.29–5.23 (m, 1H, C*H*OH), 5.02–4.83 (m, 1H, C*H*F), 2.00 and 2.01 (2d, J=3.1 Hz, 1H, O*H*), 1.81–1.53 (m, 2H, CHFCH_2), 1.50–1.24 (m, 6H, CH_2), 0.85–0.93 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.3, 134.7 (d, J=11.2 Hz), 129.5 and 129.3 (2d, J=19.3 Hz), 128.6 (2C), 127.94 and 127.93, 126.3 (2C), 93.0 (d, J=166.2 Hz), 74.3, 74.2, 35.3 (d, J=21.7 Hz), 31.50 and 31.49 (2C), 24.5 and 24.4 (2d, J=4.8 Hz), 22.5, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −175.27 (m) and −175.32 (m); HRMS (EI) 70 eV: calcd for $C_{15}H_{21}OF$ [$M^{+\cdot}$] 236.1576, found 236.158 (2 ppm).

5.3. Preparation of the substrates 1b, 2b, 7c, 8c, 3c, 4c, 7d, 8d, 3d and 4d

5.3.1. 4-Fluoro-1-phenyl-non-2-(*Z*)-en-1-one (1b). To a solution of alcohol **5** (159 mg, 0.67 mmol) in 5 mL dry CH_2Cl_2 was added at rt MnO_2 (586 mg, 6.74 mmol). After 6 h stirring, the reaction mixture was filtered through celite® and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel (eluent: pentane/ether, 9/1) to afford the title compound **1b** (135 mg, 86% yield). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–7.95 (m, 2H, Ph), 7.63–7.58 (m, 1H, Ph), 7.53–7.48 (m, 2H, Ph), 6.94 (ddd, J=11.9, 1.5 Hz, J_{H-F}=0.9 Hz, 1H, C*H*=CH), 6.46 (ddd, J_{H-F}=17.7 Hz, J=11.9, 7.3 Hz, 1H, CH=C*H*), 5.85 (ddtd, J_{H-F}=51.7 Hz, J=4.7, 7.3, 1.5 Hz, 1H, C*H*F), 1.90–1.77 (m, 2H, CHFCH_2), 1.62–1.51 (m, 2H, CHFCH$_2$CH_2), 1.44–1.32 (m, 4H, CH_2), 0.93 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7 (d, J=1.6 Hz), 147.2 (d, J=27.3 Hz), 137.5 (d, J=1.0 Hz), 133.2, 128.7 (2C), 128.4 (2C), 123.8 (d, J=10.2 Hz), 91.3 (d, J=160.2 Hz), 34.6 (d, J=22.1 Hz), 31.5, 24.6 (d, J=2.8 Hz), 22.6, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −175.96 (dddd, J=51.4, 27.6, 22.9, 17.7 Hz); HRMS (EI) 70 eV: calcd for $C_{15}H_{19}OF$ [$M^{+\cdot}$] 234.1420, found 234.142 (0 ppm).

5.3.2. 4-Fluoro-1-phenyl-non-2-(*E*)-en-1-one (2b). To a solution of alcohol **6** (150 mg, 0.64 mmol) in 5 mL dry CH_2Cl_2 was added at rt MnO_2 (552 mg, 6.35 mmol). After 4 h stirring, the reaction mixture was filtered through celite® and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel (eluent: pentane/ether, 9/1) to afford the title compound **1b** (122 mg, 82% yield). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01–7.97 (m, 2H, Ph), 7.62–7.57 (m, 1H, Ph), 7.52–7.47 (m, 2H, Ph), 7.18 (ddd, J=15.5, 1.7 Hz, J_{H-F}=0.9 Hz, 1H, C*H*=CH), 7.01 (ddd,

J_{H-F}=21.6 Hz, J=15.5, 3.7 Hz, 1H, CH=C*H*), 5.23 (ddtd, J_{H-F}=48.4 Hz, J=3.7, 6.2, 1.7 Hz, 1H, C*H*F), 1.78 (ddt, J_{H-F}=25.0 Hz, J=6.2, 7.9 Hz, 2H, CHFCH_2), 1.57–1.40 (m, 2H, CHFCH$_2$CH_2), 1.39–1.30 (m, 4H, CH_2), 0.91 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.8, 145.1 (d, J=17.7 Hz), 137.4, 133.1, 128.6 (2C), 128.6 (2C), 123.9 (d, J=9.6 Hz), 91.9 (d, J=175.1 Hz), 34.8 (d, J=20.9 Hz), 31.5, 24.3 (d, J=4.0 Hz), 22.4, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −184.79 (ddt, J=47.0, 22.0, 24.0 Hz); HRMS (EI) 70 eV: calcd for $C_{15}H_{19}OF$ [$M^{+\cdot}$] 234.1420, found 234.142 (0 ppm).

5.3.3. 1,1-Diethoxy-4-methoxy-non-2-yne (7c). To a suspension of sodium hydride (60% dispersion in mineral oil; 0.54 g, 13.5 mmol) in a mixture of 20 mL of dry ether and 1.5 mL of distilled DMSO cooled to 0°C was added a solution of 1,1-Diethoxy-4-hydroxy-non-2-yne (2.05 g, 9.0 mmol) in 4 mL of dry ether. The reaction mixture was then stirred at reflux during 18 h. After cooling at rt, 20 mL of ether and methyl iodide (2.8 mL, 44.9 mmol) were added. The resulting mixture was again stirred at reflux during 10 h. The mixture was then cooled to rt before adding 10 mL of H_2O. The product was extracted with ether and the organic layer was dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was chromatographed on silica gel (eluent: petroleum ether/ether, 9/1) to give the title compound **7c** (1.72 g, 79% yield). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.29 (d, J=1.0 Hz, 1H, (EtO)$_2$C*H*), 3.97 (td, J=6.5, 0.8 Hz, 1H, C*H*OMe), 3.72 (dq, J=10.7, 7.1 Hz, 2H, CH$_3$CH_2O), 3.57 (dq, J=9.3, 7.1 Hz, 2H, CH$_3$CH_2O), 3.37 (s, 3H, OCH_3), 1.74–1.63 (m, 2H, CHOMeCH_2), 1.48–1.37 (m, 2H, CHOMeCH$_2$CH_2), 1.31–1.24 (m, 4H, CH_2); 1.21 (t, J=7.1 Hz, 6H, CH_3CH$_2$O), 0.86 (t, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 91.2, 84.2, 81.1, 71.1, 60.7, 60.7, 56.5, 35.3, 31.4, 24.8, 22.4, 15.0 (2C), 13.9; MS (EI) 70 eV: *m/z* (% rel. int.) 241 (0.7, [M−$^{\cdot}$H]$^+$), 197 (100.0, [M−$^{\cdot}$OEt]$^+$); HRMS (EI) 70 eV: calcd for $C_{14}H_{25}O_3$ [M−$^{\cdot}$H]$^+$ 241.1804, found, 241.181, calcd for $C_{12}H_{21}O_2$ [M−$^{\cdot}$OEt]$^+$ 197.1542, found 197.154.

5.3.4. 1,1-Diethoxy-4-methoxy-non-2-(*Z*)-ene (8c). To a solution of acetal **7c** (0.11 g, 0.43 mmol) and pyridine (35 μL, 0.43 mmol) in 3 mL of pentane at rt was added Lindlar catalyst (20.6 mg, 20% weight). The black suspension was stirred under hydrogen atmosphere. When analysis of an aliquot by NMR showed no starting material (24 h), the reaction mixture was filtered through celite® and concentrated under reduced pressure to obtain 90.6 mg of the title compound **8c**. NMR analysis showed a clean crude product compound, which was used directly for the next steps. (**8c**, 87% yield). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.67 (ddd, J=11.4, 6.6, 1.0 Hz, 1H, C*H*=CH), 5.45 (ddd, J=11.4, 9.3, 1.0 Hz, 1H, CH=C*H*), 5.21 (dd, J=6.6, 1.0 Hz, 1H, (EtO)$_2$C*H*), 3.99 (dt, J=9.3, 5.9 Hz, 1H, C*H*OMe), 3.70–3.56 (m, 2H, CH$_3$CH_2O), 3.57–3.45 (m, 2H, CH$_3$CH_2O), 3.26 (s, 3H, OCH_3), 1.46–1.33 (m, 2H, CHOMeCH_2), 1.33–1.23 (m, 6H, CH_2), 1.21 (t, J=7.1 Hz, 3H, CH_3CH$_2$O), 1.19 (t, J=7.1 Hz, 3H, CH_3CH$_2$O), 0.87 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.3, 130.2, 97.4, 76.9, 60.6, 60.1, 56.2, 35.4, 31.8, 24.8, 22.6, 15.20, 15.17, 14.0; MS (EI) 70 eV: *m/z* (% rel. int.) 212 (6.8, [M−MeOH]$^{+\cdot}$), 199 (53.2, [M−$^{\cdot}$OEt]$^+$); HRMS (EI) 70 eV: calcd for $C_{13}H_{24}O_2$ [M−MeOH]$^{+\cdot}$ 212.1776, found 212.177, calcd for $C_{12}H_{23}O_2$ [M−$^{\cdot}$OEt]$^+$ 199.1698, found 199.170.

5.3.5. 4-Methoxy-non-2-(*Z*)-enal (3c) and 4-methoxy-non-2-(*E*)-enal (4c). A stirred solution of acetal **8c** (0.23 g, 0.9 mmol) in CH_2Cl_2 (10 mL) was reacted with formic acid (5.4 mL, 140.7 mmol). After 5 min at rt, the reaction mixture was neutralized with solid Na_2CO_3 (7.5 g) and diluted with saturated Na_2CO_3 solution. The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. NMR analysis showed a 6/4 *Z*/*E* ratio. Purification of the crude product by flash chromatography on silica gel (petroleum ether/Et_2O, 95/5) gave the two title isomers: *Z* **3c** (74 mg, 46% yield) and *E* **4c** (15.8 mg, 10% yield).

Isomer Z (**3c**). Pale yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.10 (d, J=7.7 Hz, 1H, C*H*O), 6.42 (dd, J=11.5, 8.8 Hz, 1H, CH=C*H*), 6.10 (ddd, J=11.5, 7.7, 1.0 Hz, 1H, C*H*=CH), 4.48 (dtd, J=8.8, 6.8, 1.0 Hz, 1H, C*H*OMe),3.33 (s, 3H, OCH_3), 1.76–1.65 (m, 2H, CHOMeCH_2), 1.59–1.47 (m, 2H, CHOMeCH$_2$CH_2), 1.46–1.22 (m, 4H, CH_2), 0.88 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.1, 152.3, 131.3, 76.7, 56.9, 35.2, 31.6, 24.7, 22.5, 13.9.

Isomer E (**4c**). Pale yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (d, J=7.8 Hz, 1H, C*H*O), 6.69 (dd, J=15.8, 6.1 Hz, 1H, CH=C*H*), 6.25 (ddd, J=15.8, 7.8, 1.0 Hz, 1H, C*H*=CH), 3.86 (qd, J=6.1, 1.1 Hz, 1H, C*H*OMe), 3.33 (s, 3H, OCH_3), 1.70–1.52 (m, 2H, CHOMeCH_2), 1.47–1.24 (m, 6H, CH_2), 0.89 (t, J=6.9 Hz, 3H, CH_3).

5.3.6. 1,1-Diethoxy-non-2-yne (7d). *First step*. Synthesis of non-2-ynal. A solution of octyn (4.35 mL, 29.9 mmol) in anhydrous THF (20 mL) was reacted with *n*-butyllithium (19.9 mL of a 1.6 M solution in hexanes, 31.8 mmol) under nitrogen at −60°C. The solution was stirred for an additional 20 min and anhydrous HMPA (25.4 mL, 144.6 mmol) was added. The temperature was raised to −35°C in 35 min. and then lowered again to −65°C. Freshly distilled DMF (4.5 mL, 57.8 mmol) was added. The reaction mixture was slowly allowed to warm to −16°C in 130 min. and quenched at this temperature by adding aqueous NH_4Cl. The crude product was extracted with Et_2O (3×10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified on silica gel (pentane/Et_2O, 95/5) to give the non-2-ynal (3.37 g, 84%). Pale yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (s, 1H, C*H*O), 2.40 (td, J=7.1, 0.5 Hz, 2H, C≡CCH_2), 1.59 (q, J=7.1 Hz, 2H, CH_2), 1.45–1.36 (m, 2H, CH_2), 1.35–1.25 (m, 4H, CH_2), 0.86 (t, J=7.0 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 99.4, 81.6, 31.1, 28.4, 27.4, 22.4, 19.1, 13.9; MS (EI) 70 eV: *m/z* (% rel. int.) 123 (11.7, [M−$^{\cdot}$CH$_3$]$^+$), 110 (12.2, [M−CO]$^{+\cdot}$), 109 (27.7, [M−$^{\cdot}$CHO]$^+$), 95 (24.1, [M−C$_3$H$_7$]$^+$), 43 (100.0, [C$_3$H$_7$]$^+$); HRMS (EI) 70 eV: calcd for $C_8H_{11}O$ [M−$^{\cdot}$CH$_3$]$^+$ 123.0810, found 123.082.

Second step. A solution of non-2-ynal (49.6 mg, 0.36 mmol), anhydrous triethyl orthoformate (73 μL, 0.43 mmol), *p*-toluenesulfonic acid monohydrate (41 mg,

0.25 mmol) in 5 mL ethyl alcohol was stirred at rt for 29 h. The reaction mixture was neutralized with solid Na_2CO_3 and diluted with water and Et_2O. The phases were separated and the extraction was completed with Et_2O (3×20 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a yellow oil which was subjected to flash chromatography (pentane/Et_2O, 95/5) to afford the compound **7d** (53.2 mg, 70% yield). Pale yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.24 (t, J=1.6 Hz, 1H, $(EtO)_2CH$), 3.72 (dq, J=9.5, 7.1 Hz, 2H, CH_3CH_2O), 3.56 (dq, J=9.5, 7.1 Hz, 2H, CH_3CH_2O), 2.22 (td, J=7.1, 1.6 Hz, 2H, $C{\equiv}CCH_2$), 1.51 (q, J=7.1 Hz, 2H, CH_2), 1.41–1.32 (m, 2H, CH_2), 1.31–1.24 (m, 4H, CH_2), 1.22 (t, J=7.1 Hz, 6H, CH_3CH_2O), 0.87 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 91.4, 86.5, 75.6, 60.5 (2C), 31.2, 28.5, 28.2, 22.5, 18.6, 15.0 (2C), 14.0; MS (EI) 70 eV: m/z (% rel. int.) 211 (0.6, $[M-{\cdot}H]^+$), 183 (0.9, $[M-{\cdot}C_2H_5]^+$), 167 (100.0, $[M-{\cdot}OEt]^+$); HRMS (EI) 70 eV: calcd for $C_{13}H_{23}O_2$ $[M-{\cdot}H]^+$ 211.1698, found 211.170, calcd for $C_{11}H_{19}O$ $[M-{\cdot}OEt]^+$ 167.1436, found 167.144.

5.3.7. 1,1-Diethoxy-non-2-(*Z*)-ene (8d). To a solution of acetal **7d** (40.8 mg, 0.19 mmol) and pyridine (16 μL, 0.19 mmol) in 3 mL of pentane at rt was added Lindlar catalyst (8.2 mg, 20% weight). The black suspension was stirred under hydrogen atmosphere. When analysis of an aliquot by NMR showed no starting material (15 h), the reaction mixture was filtered through celite® and concentrated at reduced pressure to obtain 41.1 mg of the title compound **8d**. NMR analysis showed a clean crude product which was used directly for the next steps. (**8d**, 99% yield). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.62 (dtd, J=11.2, 7.5, 1.1 Hz, 1H, CH=C*H*), 5.46 (ddt, J=11.2, 6.8, 1.6 Hz, 1H, C*H*=CH), 5.20 (dd, J=6.8, 1.1 Hz, 1H, $(EtO)_2CH$), 3.64 (dq, J=9.4, 7.1 Hz, 2H, CH_3CH_2O), 3.50 (dq, J=9.4, 7.1 Hz, 2H, CH_3CH_2O), 2.13 (qd, J=7.5, 1.5 Hz, 2H, CH=CHCH_2), 1.41–1.23 (m, 8H, CH_2), 1.21 (t, J=7.1 Hz, 6H, CH_3CH_2O), 0.87 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.9, 127.1, 97.6, 60.4 (2C), 31.7, 29.3, 28.9, 28.0, 22.6, 15.3 (2C), 14.0; MS (EI) 70 eV: m/z (% rel. int.) 214 (0.4, $M^{+\cdot}$), 169 (22.6, $[M-{\cdot}OEt]^+$); HRMS (EI) 70 eV: calcd for $C_{13}H_{26}O_2$ $M^{+\cdot}$ 214.1933, found 214.192, calcd for $C_{11}H_{21}O$ $[M-{\cdot}OEt]^+$ 169.1592, found 169.160.

5.3.8. Non-2-(*Z*)-enal (3d) and non-2-(*E*)-enal (4d). A stirred solution of acetal **8d** (16.3 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was treated with formic acid (100 μL, 34.2 mmol). After 10 min. at rt, the reaction mixture was neutralized with solid Na_2CO_3 (0.2 g) and diluted with saturated Na_2CO_3 solution. The layers were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. NMR analysis showed a 6/4 *Z*/*E* ratio. Purification of the crude product by flash chromatography on silica gel (pentane/Et_2O, 98/2) gave one pure fraction of the title isomers: *Z* **3d** (2.5 mg, 23% yield) and a mixture of the two isomers *Z* **3d** and *E* **4c** (4.7 mg).

Isomer Z (**3d**). Oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.09 (d, J=8.2 Hz, 1H, C*H*O), 6.65 (dt, J=11.2, 8.2 Hz, 1H, CH=C*H*), 5.97 (ddt, J=11.2, 8.2, 1.6 Hz, 1H, C*H*=CH), 2.61 (qd, J=8.2, 1.6 Hz, 2H, CH=CHCH_2), 1.52 (q, J=7.3 Hz, 2H, CH_2), 1.41–1.25 (m, 6H, CH_2), 0.90 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 153.6, 130.2, 31.5, 29.1, 28.7, 28.0, 22.5, 14.0.

Isomer E (**4d**). Oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (d, J=7.9 Hz, 1H, C*H*O), 6.86 (dt, J=15.6, 6.8 Hz, 1H, CH=C*H*), 6.13 (ddt, J=15.6, 7.9, 1.5 Hz, 1H, C*H*=CH), 2.34 (qd, J=6.8, 1.5 Hz, 2H, CH=CHCH_2), 1.52 (q, J=7.2 Hz, 2H, CH_2), 1.41–1.23 (m, 6H, CH_2), 0.90 (t, J=6.9 Hz, 3H, CH_3).

5.4. Wittig reactions

5.4.1. 6-Fluoro-undeca-2-(*E*),4-(*Z*)-dienoic acid methyl ester (9). To a solution of the aldehyde **1a** (67 mg, 0.42 mmol) in 2 mL of dry toluene was added at rt the (triphenyl-λ^5-phosphanylidene)-acetic acid methyl ester (170 mg, 0.51 mmol). After 14 h of stirring at 75°C, the toluene was removed in vacuo to give a yellow oil. Purification by flash chromatography (pentane/Et_2O, 95/5) afforded the title compound **9** (76 mg, 83% yield). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (ddt, J=15.2, 11.8 Hz, J_{H-F}=J_{H-H}=1.0 Hz, 1H, MeOCOCH=C*H*), 6.24 (tdt, J=11.8 Hz, J_{H-F}=2.1 Hz, J=1.0 Hz, 1H, C*H*=CHCHF), 5.96 (dd, J=15.2 Hz, J_{H-F}=0.8 Hz, 1H, MeOCOC*H*=CH), 5.85 (dddt, J_{H-F}=13.4 Hz, J=11.8, 8.2, 0.8 Hz, 1H, CH=C*H*CHF), 5.42 (dddd, J_{H-F}=48.9 Hz, J=8.2, 5.3, 1.1 Hz, 1H, C*H*F), 3.70 (s, 3H, OCH_3), 1.88–1.74 (m, 1H, CHFC*H*H) and 1.69–1.53 (m, 1H, CHFCH*H*), 1.50–1.25 (m, 6H, CH_2), 0.90 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 138.3, 137.0 (d, J=20.9 Hz), 128.8 (d, J=9.6 Hz), 123.8 (d, J=2.4 Hz), 89.0 (d, J=163.8 Hz), 51.7, 35.6 (d, J=22.5 Hz), 31.5, 24.2 (d, J=4.8 Hz), 22.5, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −174.50 (dddd, J=48.9, 26.4, 15.1, 13.4 Hz); HRMS (EI) 70 eV: calcd for $C_{12}H_{19}O_2F$ $[M^{+\cdot}]$ 214.1369, found 214.138 (2 ppm). Anal. calcd for $C_{12}H_{19}FO_2$: C, 67.26; H, 8.94, found C, 67.17; H, 8.94.

5.4.2. 6-Fluoro-undeca-2-(*E*),4-(*E*)-dienoic acid methyl ester (10) and 6-fluoro-undeca-2-(*Z*),4-(*E*)-dienoic acid methyl ester (11). To a solution of the aldehyde **2a** (45 mg, 0.29 mmol) in 2 mL of dry toluene was added at rt the (Triphenyl-λ^5-phosphanylidene)-acetic acid methyl ester (114 mg, 0.34 mmol). After 15 h of stirring at 70°C, the toluene was removed in vacuo to give a pale yellow oil. NMR analysis of the crude product showed a 7/3 ratio of **10/11**. Purification by flash chromatography (pentane/Et_2O, 95/5) afforded the two title compounds: **10** (28 mg, 45% yield) and **11** (9 mg, 15% yield).

Isomer (2*E*,4*E*) (**10**). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd, J=15.5, 11.2 Hz, 1H, MeOCOCH=C*H*), 6.40 (ddqd, J=15.4, 11.2 Hz, J_{H-H}=J_{H-F}=0.6 Hz, J=1.0 Hz, 1H, C*H*=CHCHF), 6.10 (tdd, J_{H-F}=J_{H-H}=15.4 Hz, J=5.6, 0.6 Hz, 1H, CH=C*H*CHF), 5.95 (dd, J=15.5, 0.6 Hz, 1H, MeOCOC*H*=CH), 5.01 (dqd, J_{H-F}=48.6 Hz, J=5.6, 1.1 Hz, 1H, C*H*F), 3.76 (s, 3H, OCH_3), 1.82–1.57 (m, 2H, CHFCH_2), 1.50–1.25 (m, 6H, CH_2), 0.90 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 143.4 (d, J=1.2 Hz), 139.8 (d, J=18.5 Hz), 128.6 (d, J=12.0 Hz), 122.1 (d, J=2.0 Hz),

92.3 (d, J=169.5 Hz), 51.7, 35.1 (d, J=21.7 Hz), 31.5, 24.3 (d, J=4.4 Hz), 22.5, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −179.32 (ddt, J=48.6, 26.3, 15.4 Hz); HRMS (EI) 70 eV: calcd for $C_{12}H_{19}O_2F$ [$M^{+\cdot}$] 214.1369, found 214.138 (2 ppm). Anal. calcd for $C_{12}H_{19}FO_2$: C, 67.26; H, 8.94, found C, 67.48; H, 9.05.

Isomer (2*Z*,4*E*) (**11**). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (t, J=11.2 Hz, 1H, MeOCOCH=C*H*), 6.32 (dddt, J=15.3, 11.2 Hz, J_{H-F}=1.0 Hz, J=0.5 Hz, 1H, C*H*=CHCHF), 6.08 (td, J_{H-F}=J_{H-H}=15.3 Hz, J=5.6 Hz, 1H, CH=C*H*CHF), 5.90 (dd, J=10.2, 0.5 Hz, 1H, MeOCOC*H*=CH), 4.99 (dqd, J_{H-F}=48.4 Hz, J=5.6, 0.6 Hz, 1H, C*H*F), 3.75 (s, 3H, OCH_3), 1.80–1.54 (m, 2H, CHFCH_2), 1.51–1.25 (m, 6H, CH_2), 0.88 (t, J=7.0 Hz, 3H, CH_3); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −174.47 (dddd, J=48.6, 26.2, 15.0, 13.2 Hz).

5.5. Michael addition reactions

5.5.1. 4-Fluoro-3-*p*-tolylsulfanyl-nonanal (12a). To a solution of enal **1a** (or **2a**) (50 mg, 0.316 mmol) in THF (5 mL) was added, under N_2 at 0°C, thiocresol (100 mg, 0.79 mmol, 2.5 equiv.) and Na_2CO_3 (10 mg). The reaction mixture was allowed to warm to rt and stirred for 10 min. After addition of saturated Na_2CO_3 solution, extraction with ether and washing with water, the organic phase was dried ($MgSO_4$). After removal of the solvents under vacuum, NMR of the crude reaction mixture indicated a 1:1 mixture of the two diastereoisomeric adducts **12a**. Chromatography on SiO_2 using as eluent a 1:9 mixture of ether and petroleum ether afforded 43.7 mg (49% yield) of the mixture of adducts **12a**, as a pale yellow oil. These unstable products have been characterized only by ^{1}H and ^{13}C NMR. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76–9.70 (m, 1H), 7.40–7.10 (m, 4H), 4.62 (ddt, J_{H-F}=47.2, 8.6, 3.7 Hz, 1H, dia 1), 4.49 (dddd, J_{H-F}=48.5, 8.7, 7.3, 3.2 Hz, 1H, dia 2), 3.82–3.68 (m, 1H), 3.62–3.50 (m, 1H), 2.93–2.82 (m, 2H), 2.77–2.66 (m, 2H), 2.35 (s, 3H, dia 1), 2.34 (s, 3H, dia 2), 1.90–1.20 (m, 8H), 0.92–0.86 (m, 3H); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −181.65 (dddd, J=48.9, 33.4, 18.2, 14.2 Hz, dia 1); −182.89 (m, dia 2).

5.5.2. 4-Fluoro-1-phenyl-3-*p*-tolylsulfanyl-nonan-1-one (12b). Starting from **1b** (or **2b**), and using a procedure similar to the preceding one, was prepared the 1:1 diastereoisomeric mixture of adducts **12b** (86% yield), as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0–7.0 (m, 9H), 4.70 (dddd, J_{H-F}=47.8, 8.5, 4.4, 2.8 Hz, 1H, dia 2) 4.59 (dddd, J_{H-F}=48.4, 9.3, 6.4, 3.3 Hz, 1H, dia 1) 4.02–3.82 (m, 1H), 3.52–3.25 (m, 2H), 2.33 (s, 3H, dia1), 2.32 (s, 3H, dia2), 2.0–1.1 (m, 8H); 0.90 (t, J=6.7 Hz, 3H, dia2), 0.87 (t, J=6.7 Hz, 3H, dia1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.8 and 197.5, 138.0 and 137.6, 136.8 and 136.7, 133.4, 133.3, 133.2, 132.7, 95.2 (d, J=176.5 Hz, dia 1), 94.8 (d, J=174.1 Hz, dia2), 48.3 (d, J=20.3 Hz, dia2), 47.6 (d, J=20.1 Hz, dia 1), 40.2 (d, J=1.8 Hz, dia 2), 39.1 (d, J=4.2 Hz, dia 1), 32.7 (d, J=23.8 Hz, dia 1), 32.0 (d, J=20.4 Hz, dia 2), 31.5, 31.4, 25.1 (d, J=4.2 Hz, dia 2), 24.7 (d, J=3.2 Hz, dia 1), 22.5 (d, J=3.4 Hz, dia 1), 21.1 (d, J=3.4 Hz, dia 2), 13.98 and 13.96; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −182.26 (dddd, J=49.4, 33.9, 17.8, 16.0 Hz, dia 1); −186.14 (dddd, J=47.8, 32.7, 25.5, 14.8 Hz, dia 2). HRMS (EI) 70 eV: calcd for $C_{22}H_{27}SO$ [$M-{}^{\cdot}F$]$^+$ 339.1782, found 339.1804.

5.6. Diels–Alder reactions

5.6.1. 6α-(1-Fluoro-hexyl)-3,4-dimethyl-cyclohex-3-ene-β-carbaldehyde (13a) and 6β-(1-fluoro-hexyl)-3,4-dimethyl-cyclohex-3-ene-α-carbaldehyde (14a). A solution of the aldehyde **2a** (49 mg, 0.31 mmol) in 2,3-dimethyl-buta-1,3-diene (1.5 mL, 12.99 mmol) was heated to reflux for 48 h. The excess of 2,3-dimethyl-buta-1,3-diene was removed in vacuo to give a viscous pale yellow oil. The crude product was purified on a flash chromatography (toluene/Et_2O, 99/1) to give a mixture of the two title compounds **13a/14a** (45 mg, ratio: 6/4; as determined by ^{19}F NMR). The two diastereomers were separated by silica gel column chromatography (petroleum ether/ether, 99/1) affording 18 mg of pure **13a** (25% yield) and 11 mg of pure **14a** (14% yield).

More polar, *major diastereomer* **13a**. White solid, mp 38°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.57 (dd, J_{H-F}=5.3 Hz, J=3.2 Hz, 1H, C*H*O), 4.35 (dtd, J_{H-F}=48.7 Hz, J=8.9, 2.4 Hz, 1H, C*H*F), 2.52 (dtd, J=6.0, 8.1, 3.2 Hz, 1H, C*H*CHO), 2.29 (ddt, J=15.1, 8.9 Hz, J_{H-F}=J_{H-H}=8.0 Hz, 1H, C*H*CHF), AB system: ν_A=2.21 (dd, J=15.2, 7.0 Hz, 1H, CH*H*CHCHO) and ν_B=2.01 (dd, J=15.2, 6.6 Hz, 1H, C*H*HCHCHO), 2.01–1.94 (broad peak, 1H, C*H*HCHCHF), 1.70–1.60 (broad peak, 1H, CH*H*CHCHF), 1.65 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.42–1.22 (m, 8H, CH_2), 0.90 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.9 (d, J=2.8 Hz), 123.6, 123.4, 96.1 (d, J=170.3 Hz), 49.4 (d, J=2.8 Hz), 38.7 (d, J=18.5 Hz), 32.7 (d, J=21.7 Hz), 31.6, 31.4 (d, J=8.0 Hz), 29.4, 24.4 (d, J=3.2 Hz), 22.5, 19.0, 18.8, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −179.42 (dddt, J=48.4, 34.1, 20.6, 6.2 Hz); HRMS (EI) 70 eV: calcd for $C_{15}H_{25}OF$ [$M^{+\cdot}$] 240.1889, found 240.187 (6 ppm).

Less polar, *minor diastereomer* **14a**. White solid, mp 42°C, ^{1}H NMR (C_6D_6, 400 MHz) δ 9.43 (dd, J=2.4 Hz, J_{H-F}=1.7 Hz, 1H, C*H*O), 4.50 (ddt, J_{H-F}=48.6 Hz, J=9.3, 3.5 Hz, 1H, C*H*F), 2.34 (dtd, J=5.8, 9.0, 2.5 Hz, 1H, C*H*CHO), 1st AB system: ν_A=1.96 (broad d, J=15.5 Hz, 1H, C*H*HCHCHF), 1.90 (dtdd, J_{H-F}=15.0 Hz, J=9.0, 3.5, 1.4 Hz, 1H, C*H*CHF), 2nd AB system: ν_A=1.85 (broad dd, J=16.9, 8.3 Hz, 1H, C*H*HCHCHO), 1st AB system: ν_B=1.74 (broad d, J=15.5 Hz, 1H, CH*H*CHCHF), 2nd AB system: ν_B=1.66 (broad dd, J=16.9, 5.8 Hz, 1H, CH*H*CHCHO), 1.61–1.49 (m, 2H, CHFCH_2), 1.45 (s, 6H, CH_3), 1.29–1.10 (m, 6H, CH_2), 0.87 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.2, 124.7, 122.9, 94.3 (d, J=170.7 Hz), 48.0 (d, J=3.2 Hz), 38.2 (d, J=20.3 Hz), 31.8 (d, J=21.1 Hz), 31.6, 30.4, 29.6 (d, J=5.2 Hz), 25.2 (d, J=3.8 Hz), 22.5, 19.0, 18.7, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −189.97 (dddd, J=49.6, 36.3, 23.2, 15.3 Hz); HRMS (EI) 70 eV: calcd for $C_{15}H_{25}OF$ [$M^{+\cdot}$] 240.1889, found 240.189 (1 ppm).

5.6.2. [6α-(1-Fluoro-hexyl)-3,4-dimethyl-cyclohex-3-enyl]-β-phenyl-methanone (13b) and [6β-(1-fluoro-hexyl)-3,4-dimethyl-cyclohex-3-enyl]-α-phenyl-methanone (14b). To a solution of the ketone **2b** (539 mg,

0.23 mmol) in 2,3-dimethyl-buta-1,3-diene (1.5 mL, 12.99 mmol) was heated to reflux for 15 h. Then the excess of 2,3-dimethyl-buta-1,3-diene was removed in vacuo to give a viscous pale yellow oil. NMR analysis of the crude product showed a 7/3 ratio of **13b/14b**. The crude product was purified on a flash chromatography (toluene/Et_2O, 99/1) to give the two title compounds: **13b** (44 mg, 62% yield) and **14b** (24 mg, 34% yield).

More polar, *major diastereomer* **13b**. White solid, mp 36°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99–7.95 (m, 2H, Ph), 7.59–7.44 (m, 3H, Ph), 4.38 (dtd, J_{H-F}=48.3 Hz, J=8.0, 3.3 Hz, 1H, C*H*F), 3.64 (dt, J=5.7, 8.9 Hz, 1H, C*H*COPh), 2.50 (dddd, J=16.7, 8.8 Hz, J_{H-F}=7.8 Hz, J=6.0 Hz, 1H, C*H*CHF), 1st AB system: ν_A=2.28 (dd, J=17.0, 8.4 Hz, 1H, C*H*HCHCOPh), 2nd AB system: ν_A=2.15 (dd, J=17.0, 5.6 Hz, 1H, C*H*HCHCHF) and ν_B=2.07 (dd, J=17.0, 5.6 Hz, 1H, CH*H*CHCHF), 1st AB system: ν_B=1.82 (dd, J=17.0, 8.4 Hz, 1H, CH*H*CHCOPh), 1.65 (s, 6H, CH_3), 1.60–1.15 (m, 8H, CH_2), 0.84 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.7, 137.0, 132.8, 128.6 (2C), 128.2 (2C), 124.2, 123.2, 96.5 (d, J=171.1 Hz), 42.9 (d, J=4.8 Hz), 40.5 (d, J=18.5 Hz), 34.6, 32.4 (d, J=21.7 Hz), 32.2 (d, J=6.4 Hz), 31.5, 24.7 (d, J=3.2 Hz), 22.4, 18.9, 18.6, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −179.78 (dddd, J=48.4, 37.5, 20.3, 7.8 Hz).

Less polar, *minor diastereomer* **14b**. White solid, mp 48°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05–8.01 (m, 2H, Ph), 7.61–7.45 (m, 3H, Ph), 4.50 (dqd, J_{H-F}=51.4 Hz, J=4.3, 1.4 Hz, 1H, C*H*F), 3.79 (dt, J=6.1, 10.6 Hz, 1H, C*H*COPh), 2.33–2.00 (m, 5H, CH_2CHCOPh and CH_2CHCHF and C*H*CHF), 1.69 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.58–1.20 (m, 8H, CH_2), 0.88 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.0, 137.2, 133.2, 128.6 (2C), 128.4 (2C), 124.8, 123.9, 94.0 (d, J=169.45 Hz), 43.3 (d, J=3.2 Hz), 39.6 (d, J=19.3 Hz), 36.8, 32.3 (d, J=20.5 Hz), 31.6, 29.3 (d, J=3.2 Hz), 25.4 (d, J=4.8 Hz), 22.5, 19.0, 18.6, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −196.97 (dtd, J=48.9, 32.1, 14.1 Hz).

5.6.3. 6α-(1-Fluoro-hexyl)-3,4-dimethyl-cyclohex-3-ene-α-carbaldehyde (16a). A solution of the aldehyde **1a** (82 mg, 0.52 mmol) in 2,3-dimethyl-buta-1,3-diene (1.5 mL, 12.99 mmol) was heated to reflux for 21 h. The excess of 2,3-dimethyl-buta-1,3-diene was removed in vacuo to give a viscous pale yellow oil. The crude product was purified on a flash chromatography (toluene/Et_2O, 99/1) to give the title compound **16a** (71 mg, 57% yield). White solid, mp 68°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.69 (td, J_{H-F}=2.6 Hz, J=0.6 Hz, 1H, C*H*O), 4.70 (dddd, J_{H-F}=49.0 Hz, J=8.8, 6.2, 3.6 Hz, 1H, C*H*F), 2.56 (dt, J=2.6, 5.4 Hz, 1H, C*H*CHO), AB system: ν_A=2.35 (broad d, J=19.8 Hz, 1H, C*H*HCHCHO) and ν_B=2.22 (broad d, J=19.8 Hz, 1H, CH*H*CHCHO), 2.18 (s, 2H, CH_2CHCHF), 2.08 (ddtd, J_{H-F}=21.8 Hz, J=9.7, 6.2, 3.3 Hz, 1H, C*H*CHF), 1.66 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.62–1.24 (m, 8H, CH_2), 0.90 (t, J=6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.0 (d, J=1.6 Hz), 125.5, 123.1, 96.1 (d, J=168.9 Hz), 48.2 (d, J=4.6 Hz), 40.4 (d, J=20.5 Hz), 32.7, 32.7 (d, J=21.3 Hz), 31.6, 30.3 (d, J=4.0 Hz), 24.7 (d, J=3.8 Hz), 22.5, 19.0, 18.9, 14.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −186.06 (ddt, J=50.7, 31.9, 20.0 Hz); HRMS (EI) 70 eV: calcd for $C_{15}H_{25}OF$ [$M^{+\cdot}$] 240.1889, found 240.188 (1 ppm).

5.6.4. [6α-(1-Fluoro-hexyl)-3,4-dimethyl-cyclohex-3-enyl]-α-phenyl-methanone (16b). A solution of the ketone **1b** (99 mg, 0.42 mmol) in 2,3-dimethyl-buta-1,3-diene (2.5 mL, 21.65 mmol) was heated to reflux for 36 h. The excess of 2,3-dimethyl-buta-1,3-diene was removed in vacuo to give a viscous pale yellow oil. The crude product was purified on a flash chromatography (toluene/Et_2O, 99/1) to give the title compound **16b** (59 mg, 44% yield). White solid, mp 43°C, ^{1}H NMR (C_6D_6, 400 MHz) δ 7.80–7.76 (m, 2H, Ph), 7.14–7.03 (m, 3H, Ph), 4.81 (dtd, J_{H-F}=48.9 Hz, J=7.0, 3.3 Hz, 1H, C*H*F), 3.41 (dt, J=3.4, 6.4 Hz, 1H, C*H*COPh), 1st AB system: ν_A=2.77 (dd, J=17.9, 5.9 Hz, 1H, C*H*HCHCHF) and ν_B=2.30 (broad d, J=18.0 Hz, 1H, CH*H*CHCHF), 2nd AB system: ν_A=2.37 (broad d, J=18.6 Hz, 1H, C*H*HCHCOPh) and ν_B=2.13 (dd, J=18.6, 5.0 Hz, 1H, CH*H*CHCOPh), 2.20 (dtd, J_{H-F}=15.1 Hz, J=7.0, 3.4 Hz, 1H, C*H*CHF), 1.62 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.48–0.85 (m, 8H, CH_2), 0.77 (t, J=7.0 Hz, 3H, CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 201.9, 138.2, 133.3, 129.5 (2C), 129.1 (2C), 126.1, 123.2, 95.2 (d, J=170.1 Hz), 43.1 (d, J=6.6 Hz), 41.8 (d, J=20.7 Hz), 34.6 (d, J=21.7 Hz), 33.7, 33.6 (d, J=5.4 Hz), 32.5, 25.8 (d, J=4.0 Hz), 23.5, 19.8, 19.7, 14.8; ^{19}F NMR (C_6D_6, 376.5 MHz) δ −185.09 (dddd, J=48.2, 32.0, 22.0, 15.2 Hz); HRMS (EI) 70 eV: calcd for $C_{21}H_{29}OF$ [$M^{+\cdot}$] 316.2202, found 316.220 (1 ppm). Anal. calcd for $C_{21}H_{29}FO$: C, 79.70; H, 9.24, found C, 79.63; H, 8.81.

5.6.5. 2-(2-Fluoro-propylidene)-malonic acid diethyl ester (15) and 6α-(1-fluoro-ethyl)-3,4-dimethyl-cyclohex-3-ene-1,1-dicarboxylic acid diethyl ester (16c). See Ref. 12.

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13. If heating is maintained for longer periods the decomposition of **1a** starts, possibly by autocatalytic processes, affording unidentified compounds.
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