Fluorinated Musk Fragrances: The CF_2 Group as a Conformational Bias Influencing the Odour of Civetone and (*R*)-Muscone

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Abstract: The difluoromethylene (CF_2) group has a strong tendency to adopt corner over edge locations in aliphatic macrocycles. In this study, the CF_2 group has been introduced into musk relevant macrocyclic ketones. Nine civetone and five muscone analogues have been prepared by synthesis for structural and odour comparison. X-Ray studies indeed show that the CF_2 groups influence ring structure and they give some insight into the preferred ring conformations, triggering a musk odour as determined in a professional perfumery environment. The historical conformational model of Bersuker *et al*. for musk fragrance generally holds, and structures that become distorted from this consensus, by the particular placement of the CF_2 groups, lose their musk fragrance and become less pleasant.

Introduction

There has been a long interest in the molecular basis of perfumes and fragrances, and particularly, the relationship between molecular shape and the olfactory response.[1] Some of the most iconic fragrances are the musk odorants, a large family of natural and synthetic aliphatic macrocycles that have been widely used for their olfactory and fixative properties.[2] For instance, macrocyclic ketones (**1** and **2**) and lactones (**3**), aromatic nitro derivatives (**4**) or fused bi- and poly(hetero)cyclic compounds (**5**) all produce a well-defined musk odour, despite their structural diversity (Figure 1). This has complicated a rational understanding of structure-odour relationships.[3] In addition, it has been proposed that more than one musk receptor is involved in the recognition of these molecules.[4]

Natural macrocyclic musk odorants, such as **1**-**3**, are medium sized ring lactones and ketones, which are highly aliphatic and display significant conformational freedom. Attempts to constrain such compounds have resulted in limited success in deducing the optimal conformation for maximum odour effect. For example, bridging bonds have been introduced to achieve more rigid structures,[5] but this approach to constrain conformational freedom has resulted in weaker fragrances and has failed to identify clear musk-related conformations.

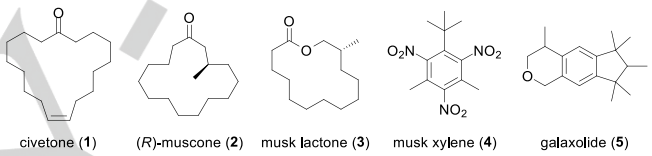

Figure 1. Structures of diverse musk odorants. Macrocycles **1**-**3** are natural products whereas **4** and **5** are synthetic.

The replacement of hydrogen for fluorine is a strategy used for altering the properties of organic compounds, which has been widely practiced in pharmaceuticals research.[6] We have been exploring the role of the CF_2 group[7] in influencing aliphatic macrocyclic ring conformations.[8] For example, X-ray crystal structure analyses of cyclododecanes **6**-**8**, which each contain two CF_2 groups at different locations around the 12-membered ring, have shown that the CF_2 groups only occupy corner positions of these rings in the solid state (Figure 2). For cyclododecanes **6** and **7**, the CF_2 groups stabilise a [3333][9] square conformation, as the fluorines are located at either adjacent or opposite corners of the square. However, in the case of cyclododecane **8**, where the CF_2 groups are positioned 1,6 to each other, this results in considerable distortion of the ring. A square structure for **8** would force one of the CF_2 groups to an edge position, however, this is avoided and the ring distorts to create a new corner and a distorted rectangular conformation. This behaviour can be explained by two factors; the fluorines avoid edge locations because they are slightly larger than hydrogen and there is a steric cost to be paid in projecting a fluorine into the ring, as the fluorine will sterically impact in transannular interactions with internal methylene hydrogens. Also, the C–CF_2–C angle (~118°) is significantly wider than the C–CH_2–C angle (~112°). This angle widening is a general phenomenon which can be rationalised both by Bent's rule[10] and valence shell electron pair repulsions (VSEPR) theory.[11] The angle widening relaxes 1,4-H-H intra-annular interactions across the corner sites. These two factors mutually reinforce a preference for the fluorines to adopt corner locations. These

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observations have extended to the larger C14 and C16 rings, where various placements of CF_2 groups dictate the preferred ring conformation as determined by X-ray structure analyses.[12]

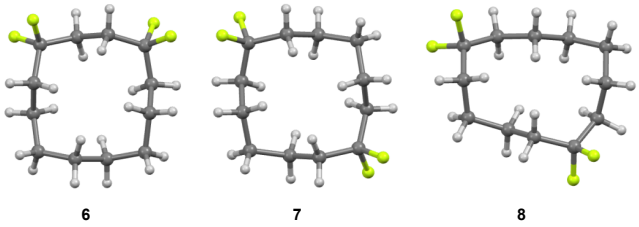
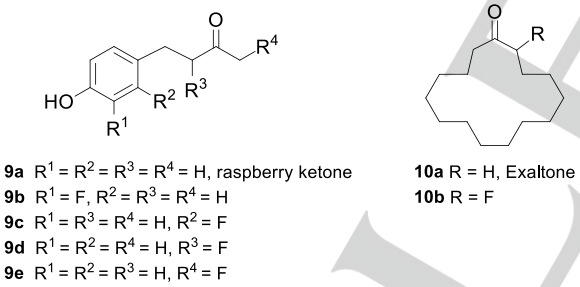


Figure 2. X-ray crystal structures of 1,1,4,4-(**6**), 1,1,7,7-(**7**) and 1,1,6,6-(**8**) tetrafluorocyclododecanes.

There are very few reports on the outcome of replacing hydrogen for fluorine in flavour and fragrance compounds. Schlosser and Michel reported that the smell (and taste) of the raspberry ketone **9a** was not significantly affected by the presence of a fluorine at specific locations (**9b**-**e**), but that the smell was profoundly altered by methyl groups incorporated at the same positions (Figure 3).[13] Also, Schlosser and Michel reported that the musk odour of exaltone **10a** was significantly changed in compound **10b** when an α-hydrogen of the macrocyclic ketone was replaced by a fluorine (Figure 3).[14] The authors suggested that the fluorine may induce a deleterious change in ring conformation, although being adjacent to the ketone it may also have altered the electronic properties of the carbonyl group and its interactions with a receptor.



9a $R^1 = R^2 = R^3 = R^4 = H$, raspberry ketone
9b $R^1 = F$, $R^2 = R^3 = R^4 = H$
9c $R^1 = R^3 = R^4 = H$, $R^2 = F$
9d $R^1 = R^2 = R^4 = H$, $R^3 = F$
9e $R^1 = R^2 = R^3 = H$, $R^4 = F$

10a R = H, Exaltone
10b R = F

Figure 3. Structures of mono-fluorinated odorants.

These observations have led us to explore the impact of the incorporation of CF_2 groups into natural musk macrocycles, with the substituent remote from the carbonyl. We have recently reported such analogues of the 14-membered musk lactone **3**[15] and in that study, a preference for the CF_2 groups to dictate corner positions was obvious in the preferred ring conformations. In order to extend the scope of this study we now describe the synthesis and structure of a range of CF_2 containing analogues of the natural musk ketones, civetone **1** and (*R*)-muscone **2**. These macrocyclic ketones are among the most widely recognised natural fragrances.

Results and Discussion

1. Civetone

Civetone **1** (Figure 1) is a natural pheromone, which was first isolated from the African civet over a hundred years ago by Sack.[16] Civetone **1** has a musk scent and this pleasant olfactory property has made the natural product desirable. However, ethical and conservation concerns have led to protection of the African civet and as a consequence, the macrocycle has received significant synthesis attention.[17] Regarding structure and conformation, *cis*-civetone **1** is a solid at room temperature (m.p. 32 °C),[16] but the conformationally labile nature of the molecule has precluded successful X-ray crystallography. Odd-membered rings are more difficult to crystallise than their even-membered homologues. For civetone **1**, a 2,4-dinitrophenyl hydrazone (DNP) derivative was required to successfully crystallise the macrocycle, and this resolved as two conformers **1a** and **1b** (Figure 4).[18] In each case, the macrocycle adopts a pseudo-rectangular conformation with the hydrazone located at the head of the longer axis (Figure 4). A “straight” alignment of six methylenes defined by a corner at C7 is notable in each polymorph.

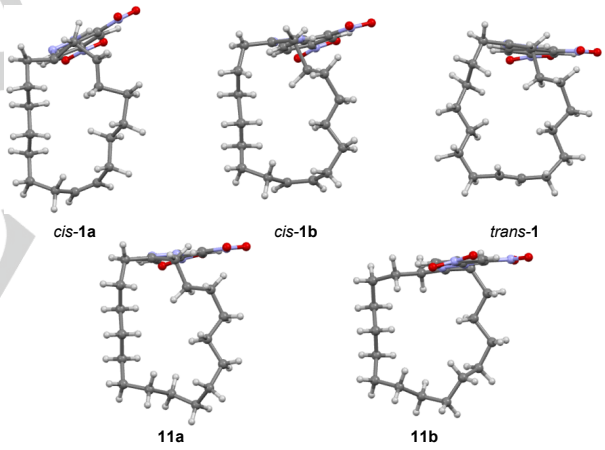
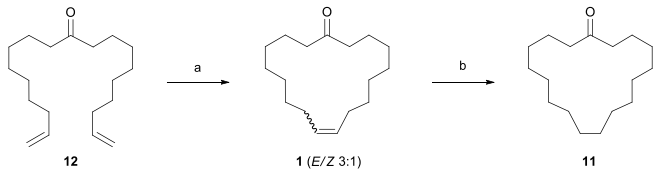


Figure 4. Solid state (X ray) conformers of DNP-hydrazone derivatives of *cis*- and *trans*-civetone **1**, and dihydrocivetone **11**.

The corresponding DNP-hydrazone derivative of the non-natural *trans*-**1** isomer shows a less ordered overall conformation (Figure 4). The linear arrangement of the six methylenes observed in conformers **1a** and **1b** is distorted and the “straight” edge is now composed of seven methylene groups (Figure 4).[19] On the other hand, the natural product dihydrocivetone **11**, with the double bond saturated (Scheme 1), is also a solid compound (m.p. 63 °C),[20] but there is no crystallographic information available. In this project, we prepared a synthetic sample of dihydrocivetone **11** by a ring closing metathesis (RCM)-hydrogenation sequence (Scheme 1), and a suitable crystal of the dihydrocivetone DNP-hydrazone derivative was subjected to X-ray crystallographic analysis. The resultant structure also had two different conformers within the same unit cell, suggesting

that they are close in energy (Figure 4). The first, **11a**, has a similar conformation to the corresponding unsaturated counterparts, **1a** and **1b**, with an edge of six methylenes and corner locations at C7 and C10. The second, **11b**, shows a wider pentagonal shape, with C1 located in a longer edge and with corners at C8 and C11 (Figure 4).



Scheme 1. Synthesis of civetone **1** and dihydrocivetone **11**. Reagents and conditions: (a) Grubbs' 1st generation catalyst (5 mol%), DCM, reflux, 2 h, 33%; (b) H_2, Pd(C) (10 mol%), EtOH, rt, overnight, 60%.

With these structural insights in place, we then addressed CF_2-containing analogues. The fluorinated targets **13**-**21** emerged as candidate compounds for synthesis (Figure 5). They were designed on the assumption that the CF_2 groups would prefer corner locations and that the preferred conformation in the crystalline state will be a low energy conformer. Furthermore, our working hypothesis assumes that the low energy conformers will be relevant in contributing to odour.[21] Some of the analogues **13**-**19** were designed to reinforce the consensus structures that emerged from the crystallography (Figure 4), whereas **20** and **21** were designed to be distorted relative to the consensus structures. It was envisaged that the selective replacement of the CH_2 groups next to the *cis*-double bond of the civetone, by two CF_2 groups could reinforce or mimic the ring constraint induced by the olefin moiety in compounds **13**-**16**. The influence of the carbonyl group location on conformation might also be addressed by the preparation of the regioisomer pairs **13**/**15** and **14**/**16**. Compounds **17**-**19** should reinforce some of the crystallographic conformations by inducing corners in the macrocycle at C7 and C9. Conversely, fluorine substitution of compounds **20** and **21** should lead to distorted conformations by the creation of corners at positions not observed in the structures in Figure 4.

Synthesis. The introduction of the 1,4-di-CF_2 groups during the preparation of **13**-**16** was carried out by difluorination of propargylic ketones[22] and then RCM as the key synthesis steps (Scheme 2). The route started with a 2-iodoxybenzoic acid (IBX) oxidation of commercially-available alcohols **22** and **23** to afford aldehydes **24** and **25**, respectively. Addition of ethynylmagnesium bromide to **24**, followed by oxidation of the intermediate alcohol **26**, gave propargylic ketone **27**. The first *gem*-difluoromethylene group was introduced in a reaction with diethylaminosulfur trifluoride (DAST)[23] at 50 °C. The coupling of volatile alkyne **28** with previously prepared aldehyde **25**, and subsequent oxidation of the intermediate alcohol, gave the second propargylic ketone **30**, which was fluorinated under the same DAST conditions to give tetrafluoro-hydrocarbon **31**. Macrocyclisation was carried out by a RCM reaction with the Grubbs' 1st generation catalyst. The resultant 17-membered macrocycle **32** was obtained in good yield as a mixture of diastereoisomers (*E*/*Z* 2:1). A hydroboration-oxidation sequence afforded a 1:1 inseparable mixture of regioisomeric alcohols. Fortunately, direct oxidation of this mixture generated ketones **33** and **34**, which were readily separated by column chromatography. Interestingly, hydroboration occurred exclusively to the double bond, presumably because the four fluorine atoms deactivated the triple bond to borane attack. Acetylenic ketones **33** and **34** might be considered to be civetone analogues, however, they had no detectable odour. Finally, fluorinated targets **13** and **15** were prepared by partial hydrogenation of **33** and **34** under Lindlar conditions. The saturated dihydrocivetones **14** and **16** were obtained by complete catalytic hydrogenation of **33** and **34**, respectively. Compounds **13**-**16** posessed a faint musk odour relative to our synthetic reference samples of civetone **1** and dihydrocivetone **11**.

Mono-CF_2 civetone analogue **17** was readily synthesised from nonadeca-1,18-dien-10-one **12**[24] in four steps (Scheme 3). The open chain hydrocarbon **35** was obtained in modest yield, by treatment of **12** with DAST. Diene **35** was then subject to an RCM reaction to afford macrocycle **36** as a 1:8 mixture of *cis/trans* isomers. Finally, a hydroboration-oxidation/oxidation sequence of cyclic olefin **36** gave the desired macrocyclic ketone **17**. Symmetry dictates that a single isomer was generated. A pleasant musk odour was observed for dihydrocivetone analogue **17**.

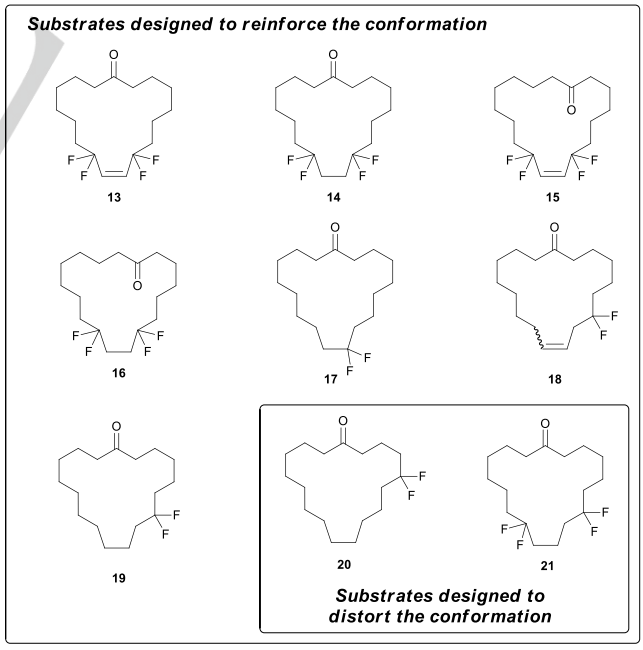
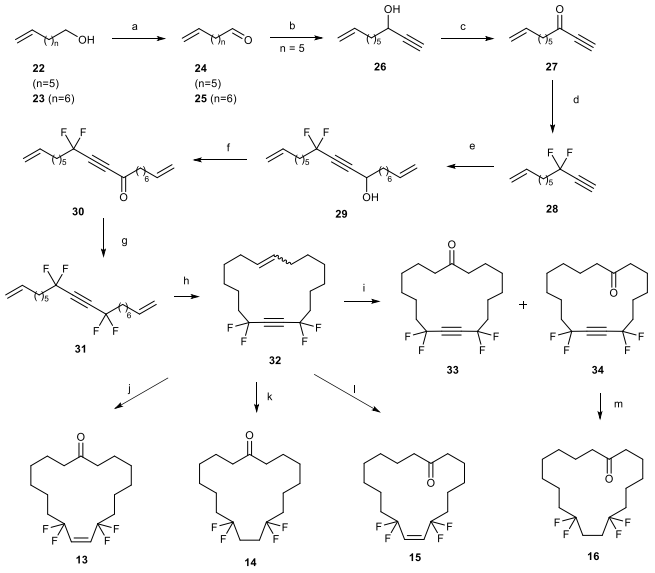
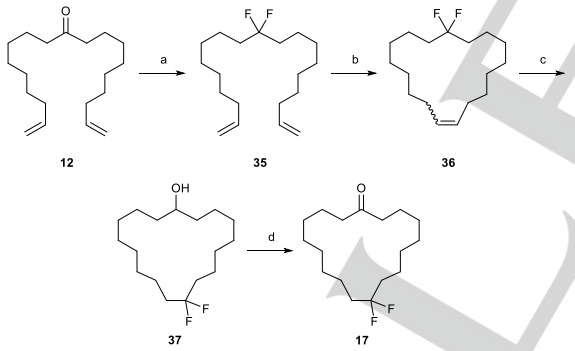


Figure 5. Target civetone analogue structures containing CF_2 groups.



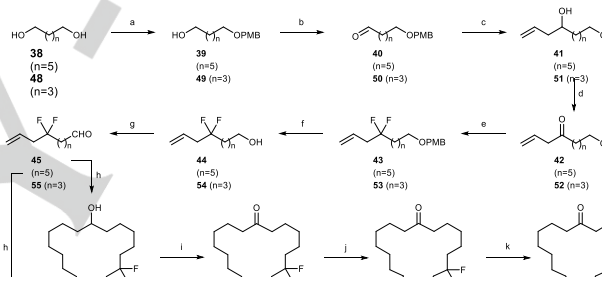
Scheme 2. Synthesis of fluorinated civetone analogues containing the 1,4-di-CF_2 motif. Reagents and conditions: (a) IBX, DMSO, rt, overnight, 97% (n=5), 87% (n=6); (b) Ethynylmagnesium bromide, THF, 0 °C → rt, 3 h, 66%; (c) IBX, DMSO, rt, overnight, 85%; (d) DAST, 50 °C, overnight, 63%; (e) 1) *n*-BuLi, THF, –78 °C → 0 °C, 1 h; 2) **25**, 0 °C → rt, 1 h, 71%; (f) IBX, DMSO, rt, overnight, 82%; (g) DAST, 50 °C, overnight, 69%. (h) Grubbs' 1st generation catalyst (5 mol%), DCM, reflux, 24 h, 83%; (i) 1) $BH_3 \cdot SMe_2$, THF, 0 °C → rt, overnight; 2) EtOH, NaOH, H_2O_2, rt, 4 h; 3) IBX, DMSO, rt, overnight, 36%; (j) H_2, $Pd/BaSO_4$ (10 mol%), quinoline, Py, rt, overnight, 96%; (k) H_2, $Pd/BaSO_4$ (10 mol%), quinoline, Py, rt, overnight, 81%; (l) H_2, Pd(C) (10 mol%), EtOH, rt, overnight, 86%; (m) H_2, Pd(C) (10 mol%), EtOH, rt, overnight, 79%.



Scheme 3. Synthesis of the fluorinated civetone analogue containing a CF_2 group in C9. Reagents and conditions: (a) DAST, 50 °C, 3 days, 27%; (b) Grubbs' 1st generation catalyst (10 mol%), DCM, reflux, 3 h, 38%; (c) 1) $BH_3 \cdot SMe_2$, THF, 0 °C → rt, overnight; 2) EtOH, NaOH, H_2O_2, rt, 4 h; 85%; (d) IBX, DMSO, rt, overnight, 61%.

The syntheses of the mono-CF_2 targets **18** and **19** were achieved following a similar strategy to that of **13**-**16** described above (Scheme 4). Initially, mono-protection of heptane-1,7-diol **38** with the *p*-methoxybenzyl (PMB) group was carried out to generate alcohol **39**, which was then oxidised to aldehyde **40**. Treatment of **40** with allylmagnesium bromide, followed by oxidation of alcohol **41** with IBX afforded homoallylic ketone **42**. This ketone was then treated with DAST to give the difluoro-olefin **43**. Deprotection, followed by oxidation of the released alcohol **44** gave aldehyde **45**. The open chain ketone **47** was then prepared by addition of an in situ generated Grignard reagent, followed by oxidation of the resultant alcohol **46**. RCM of **47** afforded the desired difluorinated civetone **18** as an inseparable mixture of diastereoisomers (*E/Z*, 3:1). Finally, catalytic hydrogenation of the double bond generated *mono*-CF_2 macrocyclic ketone **19**. Both fluorinated compounds **18** and **19** were musk odorants, showing a comparable odour intensity to reference compounds **1** and **11**, respectively.

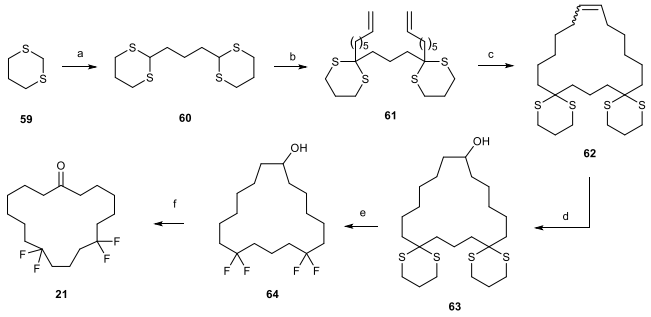
Analogue **20** was prepared as illustrated in Scheme 4, following the same strategy employed for **19**. Compound **20** displayed a distinct floral odour, but without the characteristic musk notes of **1** and **11**.



Scheme 4. Synthesis of fluorinated civetone analogues containing a CF_2 group in C7 and C5. Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 0 °C → 60 °C, overnight, 41% (n=5), 45% (n=3); (b) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C → 0 °C, 1 h, 98% (n=5,3); (c) Allylmagnesium bromide, THF, 0 °C → rt, overnight, 58% (n=5), 46% (n=3); (d) IBX, DMSO, rt, overnight, 85% (n=5), 79% (n=3); (e) DAST, 50 °C, overnight, 43% (n=5), 34% (n=3); (f) DDQ, DCM/H_2O, rt, overnight, 74% (n=5), 78% (n=3); (g) IBX, DMSO, rt, overnight, 98% (n=5), 72% (n=3); (h) 1) 9-Bromonon-1-ene (for n=5) or 11-bromoundec-1-ene (for n=3), Mg (turnings), I_2 (trace), THF, reflux, 6 h; 2) **45** (n=5) or **55** (n=3), rt, overnight, 62% (n=5), 49% (n=3); (i) IBX, DMSO, rt, overnight, 93% (n=5), 81% (n=3); (j) Grubbs' 1st generation catalyst (5 mol%), DCM, reflux, 3 h, 46% (n=5), 64% (n=3); (k) H_2, Pd(C) (10 mol%), EtOH, rt, overnight, 91% (n=5), 87% (n=3).

The final dihydrocivetone target **21** was addressed, using dithiane chemistry by the route shown in Scheme 5. Bis-dithiane **60** was prepared using two equivalents of lithiated 1,3-dithiane **59** and 1,3-dibromopropane. This was followed by a double alkylation using *n*-butyllithium and then two equivalents of 7-bromoheptene, to generate diene **61**. Macrocyclisation of **61** by RCM gave the cyclic *bis*-dithiane **62** (*E/Z* 2:1) in a relatively good yield for such a reaction, perhaps promoted by a Thorpe-Ingold type effect associated with the dithiane motifs.[7c] A hydroboration-oxidation sequence was successfully achieved to obtain the non-symmetrical alcohol **63**. Direct difluorination[25] of **63** with *N*-iodosuccinimide (NIS) and hydrogen fluoride in pyridine (HF·Py), was rather inefficient (14% yield), but afforded the tetrafluorinated alcohol **64**. In an attempt to improve this

fluorination step, a number of protection strategies for the alcohol were explored, but this was unproductive, giving only very complex reaction mixtures. Finally, oxidation of **64** with IBX gave the desired tetrafluorinated civetone **21**. In contrast to the parent civetone **1** and dihydrocivetone **11**, musk notes were not recognised at all for **19**. The odour was significantly modified, having a non-pleasant solvent character (see ESI).[26] The distinctly different olfactory outcome for **20** and **21**, relative to civetone **1**, is consistent with the general hypothesis that these compounds were designed to adopt a distorted macrocyclic ring structure.



Scheme 5. Synthesis of the fluorinated civetone analogue containing the 1,5-di-CF_2 motif. Reagents and conditions: (a) 1) *n*-BuLi, THF, –30 °C, 2 h; 2) 1,3-dibromopropane, –30 °C → rt, overnight, 62%; (b) 1) *n*-BuLi, THF, –30 °C → 0 °C, 2 h; 2) 7-bromohept-1-ene, –30 °C → rt, overnight, 60%; (c) Grubbs' 1st generation catalyst (5 mol%), DCM, reflux, 2 h, 58%; (d) 1) $BH_3{\cdot}SMe_2$, THF, 0 °C → rt, overnight; 2) EtOH, NaOH, H_2O_2, rt, 4 h, 97%; (e) NIS, HF·Py, DCM, –78 °C → rt, overnight, 14%; (f) IBX, DMSO, rt, overnight, 59%.

Structure-odour relationships. The X-ray structures of all of the synthesis targets were acquired, where possible, either as ketones or as their DNP derivatives. Macrocycles **12**-**17**, and **21** were crystalline and X-ray crystal structures were obtained directly for these ketones. Meanwhile, compounds **18**-**20** had to be derivatised to obtain X-ray crystal structure data. The structures for all of these compounds are shown in Figure 6.

As anticipated, the CF_2 groups occupy corner locations in all cases but one (structure DNP-**20**), and the group clearly influences the overall conformation of the macrocycles. The C–CF_2–C angles are significantly wider (114.5°-118.9°) than those usually found in aliphatic chains, a feature previously observed.[7,8,12] Macrocyclic ketones **13** and **15** display almost identical ring conformations (Figure 6) and are very similar to that of civetone **1**. The *cis* double bond is now located directly between the two corners, which are defined by the CF_2 groups at C8 and C11, instead of lying in the arch created by C7-C11 as in *cis*-**1a** and *cis*-**1b** (Figure 4). The main difference between both regioisomers is the location of the carbonyl group in **13** (similar to civetone **1**) and for **15**, displaced to the adjacent carbon on the top edge and pointing in the opposite direction. Dihydrocivetone derivatives **14** and **16** also mimic very closely the dihydrocivetone structure **11a** (Figure 4). The presence of the fluorines at corners C7-C10 in regioisomer **16** reinforces the overall conformation observed for dihydrocivetone **11**. Despite the very clear similarities in the conformation of these four analogues, relative to civetone **1** and dihydrocivetone **11**, only a faint musk odour was observed for all of these compounds. Musk odours were retained but other parameters may impact on odour intensity, such as increasing the molecular mass and reducing volatility with the introduction of four fluorines.[27]

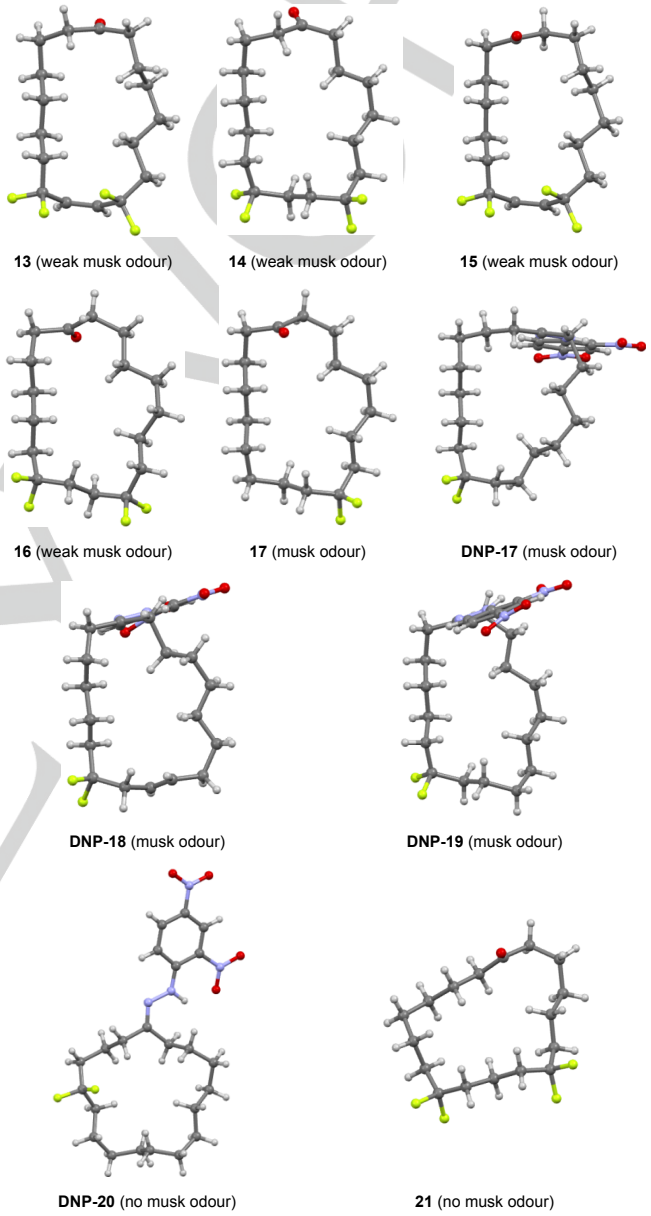


Figure 6. Preferred solid-state conformations of fluorinated civetone derivatives.

In the case of macrocycle **17** (Figure 6), the CF_2 group reinforces a corner at C9 and has the same overall shape found for dihydrocivetone **11a** (Figure 4). Ketone **17** retains an intense musk odour. Although compound **17** was a crystalline solid and an X-ray structure was obtained, the DNP-derivative of **17** was also analysed by X-ray to explore the influence of the hydrazone

motif on ring conformation. These structures are shown in Figure 6. Very different ring conformations are found. The CF_2 groups occupy different corners relative to the long edge of six methylene groups, closer to structure **11b** (Figure 4), suggesting that there is a relatively low energy barrier between these two ring arrangements, however, they retain a similar overall shape.

Strikingly, a very regular, symmetric pentagonal conformation was obtained for the DNP-derivative of **20** (Figure 6). However, the unexpected observation in this case is that the structure locates the CF_2 group at an edge and the carbonyl group (hydrazone) at a corner, a reversal of all other situations so far.[28] It must be assumed that conformations of **20** with the CF_2 at a corner location will impact negatively on an appropriate location for the carbonyl and the ring conformation rearranges as observed. Macrocyclic ketone **20** has no observable musk odour, which is again consistent with not being able to access ring conformations observed for **1** and **11**.

A very different and distinctive conformation in the solid state was found for compound **21** (Figure 6). The presence of the 1,5-di-CF_2 motif was designed to induce a C5 edge into the ring and this has imposed a distorted rectangular structure, quite different from the structures described so far. It is perhaps not surprising that ketone **21** is absent of a detectable musk note.

Some general conclusions on the civetone ring structure, relative to odour can be made. Excluding compounds **20** and **21**, the fluorinated analogues fit with the olfactophore model for musk activity described by Bersuker and co-workers.[29] This model proposed that a musk note requires a pseudo-rectangular structure with a slightly shorter horizontal axis (5-6 Å), a slightly longer vertical axis (6.2-7.2 Å) and the carbonyl (C=O) centered on a horizontal edge (Figure 7). Whilst the conformation of analogues **13**-**19** fits this model well, the distorted conformations of macrocycles **20** and **21** do not.

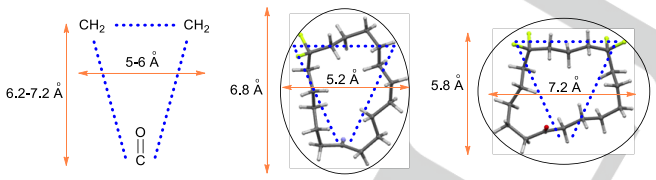


Figure 7. Proposed structural features for macrocyclic musk odorants and ellipsoid-like shape of fluorinated targets **19** and **21** (DNP fragment was omitted to simplify the Figure).

The more intense odour found in the mono-CF_2 derivatives **17**-**19** versus the weak musk character observed for the 1,4-di-CF_2 compounds **13**-**16** could reasonably be due to volatility. A comparative GC experiment was carried out (See ESI) in order to establish the relative volatility of the civetone macrocycles, and there was a tendency towards longer retention times for the tetrafluoroanalogues, particularly the olefins, although the correlation was less distinct for the saturated macrocycles.

2. Muscone

(*R*)-Muscone **2** (Figure 1) was first discovered in 1906, isolated from the male musk deer, Moschus moschiferus.[30] The (*S*) enantiomer is described as having a poorer musk odour.[31] As a key perfumery component, (*R*)-**2** has been the target of a number of total syntheses;[32] however, little work has been carried out on assessing muscone ring conformation and odour. (*R*)-Muscone **2** is a liquid at room temperature, and no X-ray crystallography of the parent macrocycle has been recorded. In 1982, Bernardinelli and Gerdil prepared the DNP-derivative of muscone **2**.[33] X-Ray crystal analysis revealed significant disorder, not unexpected for a 15-membered ring. Deconvolution of the diffraction data led to the conclusion that up to eight closely related, but different ring conformations were adopted by the (*R*)-muscone macrocycle in the solid state (Figure 8), indicative of a very flexible ring system.

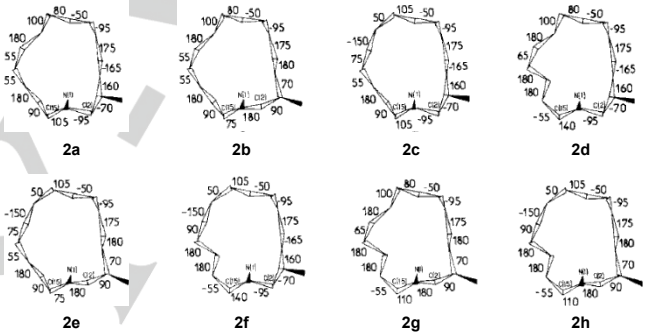
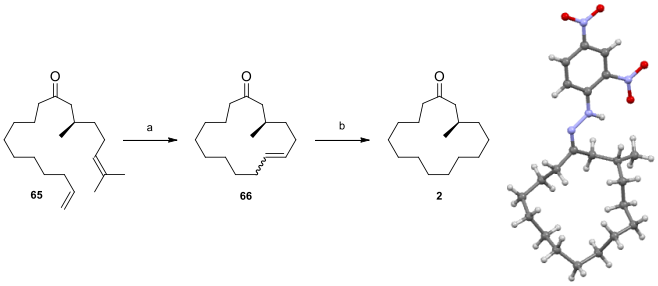


Figure 8. Proposed ring conformations **2a**-**2h** of (*R*)-muscone from Bernardinelli and Gerdil's X-ray study of the (*R*)-muscone-DNP derivative.

As a start point to this study, a sample of (*R*)-muscone **2** was prepared by the route illustrated in Scheme 6, to reinvestigate the X-ray crystal structure analysis. This involved RCM of **65** and then hydrogenation of the resultant olefin **66**, following a previously described protocol.[34] Crystallography of the DNP derivative of (*R*)-2 gave a well resolved structure, as illustrated in Scheme 6.



Scheme 6. Synthesis of (*R*)-muscone **2** and crystal structure of its DNP-hydrazone derivative. Reagents and conditions: (a) Grubbs' 2nd generation catalyst (8 mol%), DCM, reflux, overnight, 30%; (b) H_2, Pd(C) (10 mol%), MeOH, rt, overnight, 95%.

In this structure the macrocycle has a regular pentagonal conformation with corners at the carbonyl group, the stereogenic centre and carbons C6, C9 and C13. Interestingly, none of the predicted structures of Bernardinelli and Gerdil[34] maps onto this structure, although all have a corner located at C-9 and conformers **2b**, **2e**, **2g** and **2h** (Figure 8) locate the methyl group of the stereogenic centre at corner locations. The earlier predictions had corner locations at C7/C12 rather than C6/C13 as is observed in the new crystallographic data. In overview, it may be that all of these structures are close in energy and different crystallographic studies will find various conformations.

It was attractive to explore the incorporation of CF_2 groups into (*R*)-muscone **2** at different locations, but particularly covering C6 to C10, as a strategy to influence and limit the conformational flexibility of the ring. To this end, the difluorinated muscone derivatives **67**-**71** were chosen as synthetic targets (Figure 9). The early X-ray data[33] indicated a corner at C9, thus **68** was selected as a target to stabilise this feature. Structures **67** and **69** were selected to move this corner by one methylene group in each direction, to assess disruption of this feature. Many of the predicted conformations in Figure 8 have one edge which adopts a linear chain of five methylene groups from C-3 (the stereogenic centre) to C-7. For this reason, a CF_2 group was engineered into the design of **70** at C7 to try to stabilise this aspect. In a similar manner, by placing the CF_2 group at the C-6 position in **71**, it should be possible to mimic the conformation of the X-ray structure of the DNP derivative of (*R*)-2 shown in Scheme 6, where only four carbon atoms form the "side" of the structure from C-3 to C-6.

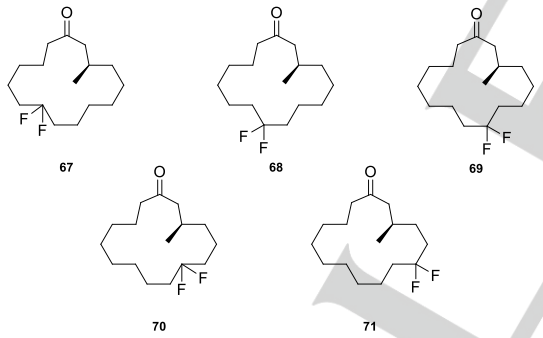
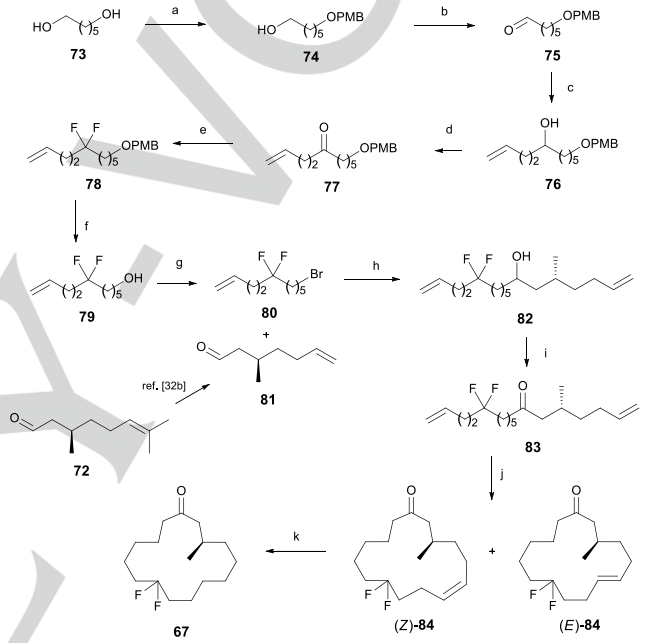


Figure 9. Structures of synthetic (*R*)-muscone targets containing CF_2 groups.

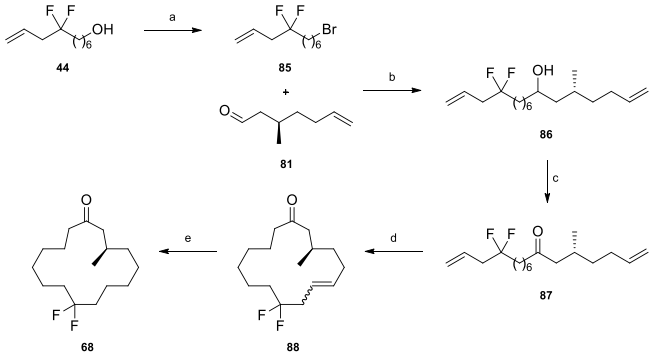
Synthesis. In order to prepare the targets, a ring closing metathesis approach was again adopted, a strategy that has previously been employed for the synthesis of (*R*)-muscone **2**.[33a-f] The stereogenic centre can usefully be contributed from commercially-available (+)-citronellal **72**.

The synthesis of analogue **67** containing a CF_2 group at C10 was carried out as illustrated in Scheme 7. A key early reaction involved the conversion of alcohol **79** to bromide **80** by an Appel reaction.[27] Bromide **80** was then converted into the corresponding Grignard reagent for condensation with aldehyde **81**, itself derived from (+)-citronellal **72** as previously described.[33b] Alcohol **82** was generated as a 1:1 mixture of diastereoisomers, and then oxidation gave ketone **83**. This ketone was subject to a RCM reaction to afford **84** as a separable *E/Z* mixture (1:1). To conclude this synthesis, macrocycles (*E*)-**84** and (*Z*)-**84** were independently hydrogenated to generate difluoro-muscone derivative **67**. Ketone **67** exhibited a weak musk odour but, perhaps surprisingly, the trans-olefin precursor, (*E*)-**84** displayed stronger musky notes. It was interesting to note a total absence of a musk odour when the *cis*-isomer (*Z*)-**84** was assessed, indicating that the configuration of the double bond has a significant influence on the olfactory properties.



Scheme 7. Synthesis of fluorinated muscone analogue containing a CF_2 group in C10. Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 0 °C → 60 °C, overnight, 55%; (b) DMP, DCM, rt, overnight; (c) 1) 4-Bromo-1-butene, Mg (turnings), I_2 (trace), Et2O, reflux, 2 h; 2) 74, 0 °C → rt, overnight, 52% (three steps); (d) DMP, DCM, rt, 2 h; (e) DAST, 50 °C, overnight, 67% (two steps); (f) DDQ, DCM/H_2O, rt, 1 h, 81%; (g) CBr_4, PPh_3, DCM, 0 °C → rt, overnight, 75%; (h) 1) **80**, Mg (turnings), I_2 (trace), Et_2O, reflux, 2 h; 2) **81**, 0 °C → rt, overnight, 43%; (i) DMP, DCM, rt, 1 h; (j) Grubbs' 1st generation catalyst (6 mol%), DCM, reflux, overnight, 52% (two steps); (k) H_2, Pd(C) (10 mol%), MeOH, rt, overnight, 59% from (*Z*)-**84**; 79% from (*E*)-**84**.

The synthesis of muscone **68** was addressed as illustrated in Scheme 8. The previously synthesised alcohol **44** (Scheme 4) was converted to bromide **85** by an Appel reaction, and was then used to prepare the corresponding Grignard reagent for condensation with aldehyde **81**. This coupling gave alcohol **86** as a 1:1 mixture of diastereoisomers. Oxidation to ketone **87** and then an RCM reaction gave macrocyclic ketone **88** as an *E/Z* mixture (2:1). Finally, catalytic hydrogenation of **88** afforded muscone **68**. This compound had a weak musk note relative to our synthetic sample of muscone **2**.

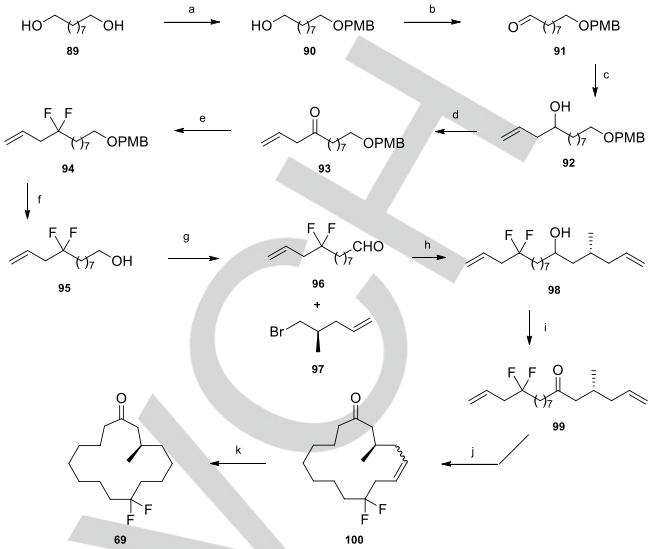


Scheme 8. Synthesis of fluorinated muscone analogue containing a CF_2 group in C9. Reagents and conditions: (a) CBr_4, PPh_3, DCM, 0 °C → rt, overnight, 67%. (b) 1) **85**, Mg (turnings), I_2 (trace), THF, reflux, 6 h; 2) **81**, rt, overnight, 40%; (c) DMP, DCM, rt, 1 h; (d) Grubbs' 1st generation catalyst (6 mol%), DCM, r.t., reflux, overnight, 94% (two steps); (e) H_2, Pd(C) (10 mol%), MeOH, rt, overnight, 41%.

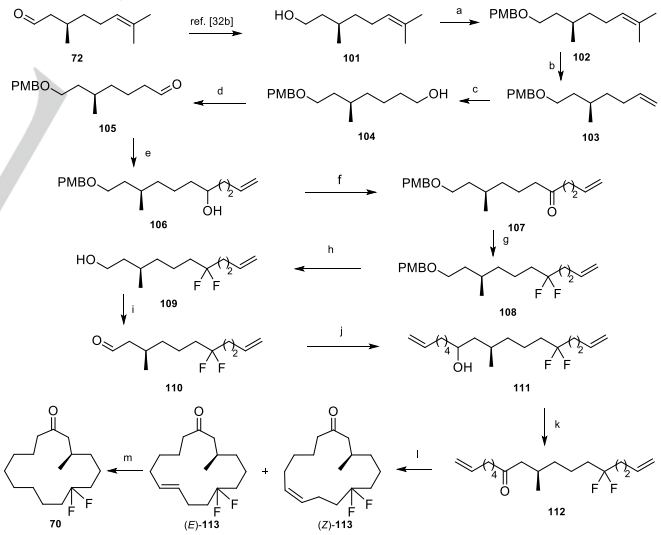
8,8-Difluoromuscone **69** was prepared by coupling fluorinated aldehyde **96** with the enantiopure alkyl bromide **97**,[35] as illustrated in Scheme 9. Aldehyde **96** was obtained in a similar manner to **45** (Scheme 4), but starting from the nonadiol **89**. A Grignard reaction between these entities generated **98**, which was then oxidised to ketone **99**. RCM of **99** with the Hoveyda-Grubbs' 2nd generation catalyst generated macrocycle **100** as an *E/Z* mixture (9:1). Finally, hydrogenation of the olefin gave muscone **69**, which had a good musk profile. The unsaturated precursor **100** (*E/Z*, 9:1) had a nice musky odour too and the perfumers also detected an exaltone aspect with compound **69**.

The synthesis of difluoro muscone derivatives **70** and **71** required modification of the chiral fragment. The preparation of **70** from (*R*)-citronellal **72** is shown in Scheme 10. (*R*)-Citronellol **101**[30b] was PMB protected to give **102**, then ozonolysis followed by a Wittig reaction gave terminal alkene **103**. A hydroboration-oxidation sequence afforded primary alcohol **104**, which was sequentially oxidised and treated with a Grignard reagent derived from 4-bromo-1-butene to give alcohol **106**. This alcohol was oxidised and fluorinated using DAST to generate **108**. Ketone **112** was prepared after PMB deprotection followed by the sequence of reactions used to convert **104** to **107**. Finally, macrocyclisation of **112** by RCM afforded a separable mixture of *E/Z* isomers (5:2) **113** that were hydrogenated to generate the target muscone **70**. This ketone had only a very faint musk odour.

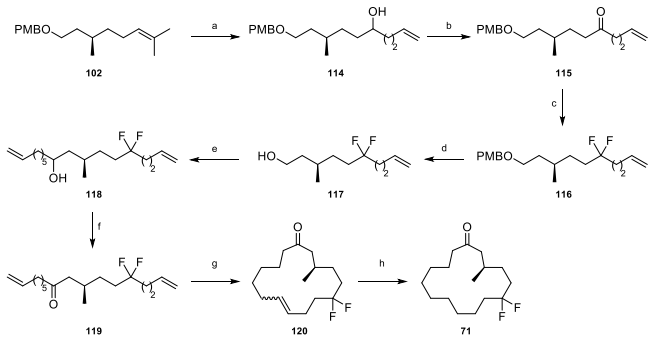
The last compound prepared in this series was muscone **71** as illustrated in Scheme 11. Alkene **102** was subjected to ozonolysis, and the resultant aldehyde was treated with a Grignard reagent derived from 4-bromo-1-butene, to generate alcohol **114**. This alcohol was oxidised to ketone **115** and was then fluorinated with DAST. Deprotection gave alcohol **117**, which was progressed by an oxidation, Grignard reaction, oxidation sequence to give ketone **119**. An RCM reaction generated macrocycle **120** (*E/Z* 3:2) and then hydrogenation gave the target muscone **71**. This molecule had a pleasant musky odour, very similar to synthetic (*R*)-muscone **2**.



Scheme 9. Synthesis of fluorinated muscone analogue containing a CF_2 group in C8. Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 0 °C → 60 °C, overnight, 46%; (b) IBX, DMSO, rt, overnight, 80%; (c) Allylmagnesium bromide, THF, 0 °C → rt, overnight, 44%; (d) IBX, DMSO, rt, overnight, 83%.; (e) DAST, 50 °C, overnight, 63%; (f) DDQ, DCM/H_2O, rt, 1 h, 69%; (g) IBX, DMSO, rt, overnight, 80%.; (h) 1) **97**, Mg (turnings), I_2 (trace), THF, reflux, 4 h; 2) **96**, rt, overnight, 60%; (i) IBX, DMSO, rt, overnight, 95%.; (j) Hoveyda-Grubbs' 2nd generation catalyst (6 mol%), toluene, reflux, overnight, 56%; (k) H_2, Pd(C) (10 mol%), MeOH, rt, overnight, 93%.



Scheme 10. Synthesis of fluorinated muscone analogue containing a CF_2 group in C7. Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 0 °C → 60 °C, overnight, 82%; (b) 1) O_3, DCM, -78 ºC, 30 min.; 2) PPh_3, -78 ºC → rt, overnight; 3) *n*-BuLi, $PMe(Ph)_3Br$, THF, -78 ºC → rt, overnight, 36%; (c) 1) 9-BBN dimer, THF, rt, overnight; 2) EtOH, NaOH, H_2O_2, 0 ºC, 4 h, 99%; (d) DMP, DCM, rt, 2 h; (e) 4-Bromo-1-butene, Mg (turnings), I_2 (trace), THF, reflux, 6 h; 2) **105**, rt, 16 h, 65% (two steps); (f) DMP, DCM, rt, 2 h; (g) DAST, 50 °C, overnight, 70% (two steps); (h) DDQ, DCM/H_2O, rt, 1 h, 74%; (i) DMP, DCM, rt, 1 h, 97%; (j) 1) 6-Bromo-1-hexene, Mg (turnings), I_2 (trace), THF, reflux, 30 min; 2) **110**, 0 °C → rt, overnight, 72%; (k) DMP, DCM, rt, 1 h, 99%; (l) Grubbs' 1st generation catalyst (6 mol%), DCM, reflux, 46 h, 58%; (m) H_2, Pd(C) (10 mol%), MeOH, rt, overnight, 72%.



Scheme 11. Synthesis of fluorinated muscone analogue containing a CF_2 group in C6. Reagents and conditions: (a) 1) O_3, DCM, –78 ºC, 15 min.; 2) PPh_3, –78 ºC → rt, overnight; 3) 4-Bromo-1-butene, Mg (turnings), I_2 (traces), Et_2O, reflux, 2 h; 4) Aldehyde, 0 °C → rt, overnight, 58%; (b) DMP, DCM, rt, 2 h, 96%; (c) DAST, 50 °C, overnight, 64%; (d) DDQ, DCM/H_2O, rt, 1 h, 88%; (e) 1) DMP, DCM, rt, 1 h; 2) 7-Bromo-1-heptene, Mg (turnings), I_2 (trace), Et_2O, reflux, 2 h; 3) Aldehyde, 0 °C → rt, 4 h, 60%; (f) DMP, DCM, rt, 1 h; (g) Grubbs' 1st generation catalyst (6 mol%), DCM, reflux, overnight, 50% (two steps); (h) H_2, Pd(C) (10 mol%), MeOH, rt, overnight, 65%.

Structure-odour relationships. With muscones **67**-**71** in hand, it was of interest to obtain X-ray structural data where possible. Suitable crystals of ketones **67** and **70** were forthcoming, and DNP derivatives of ketones **68** and **69** were successfully prepared. Some of the unsaturated RCM products, such as (*Z*)-**84**, (*E*)-**100** and (*Z*)-**113** also proved amenable to crystallisation. The resultant solid state structures are shown in Figure 10.

It is again clear that the CF_2 groups adopt corner locations and induce some predictable order into the structures. Regarding muscone **67**, a pseudo-rectangular conformation is apparent with corners at C10 (CF_2) and C7 and the methyl group-stereogenic centre is at a corner (Figure 10) similar to the conformers described by Bernardinelli and Gerdil (Figure 8).[34] This feature is also found in the DNP structure of synthetic muscone **2** (Scheme 7). These compounds all have weak musk odours. The RCM product *cis*-olefin **84** is interesting in that it has a regular rectangular structure; however, the carbonyl is unusually pointing into the ring suggesting some significance with respect to its lack of odour. On the other hand, the *trans* olefin (*E*)-**84** has a good musk profile and presumably does not have this endo preference for the carbonyl.

Ketone **70** has a similar conformation to that of **67**, with a corner defined at C7. The carbonyl locates in the middle of an edge. Two conformers **70a** and **70b** were observed in the crystal structure, which differ only around the C10-C11 corner. Conformer **70b** is very similar to that of the unsaturated macrocycle (*Z*)-**113**. The common features between saturated and unsaturated muscones fluorinated at C10 or C7, and the absence of a defined musky character in these derivatives, suggest this squareoid shape is less relevant than that of the more rectangular conformation for olfactory stimulation.

On the other hand, the structure of DNP-**68** showed the corresponding CF_2-corner at C9. This conformation is virtually identical to **2d** proposed by Bernardineli,[34] with the methyl group at an edge. A hint of musk was recognised with ketone **68**.

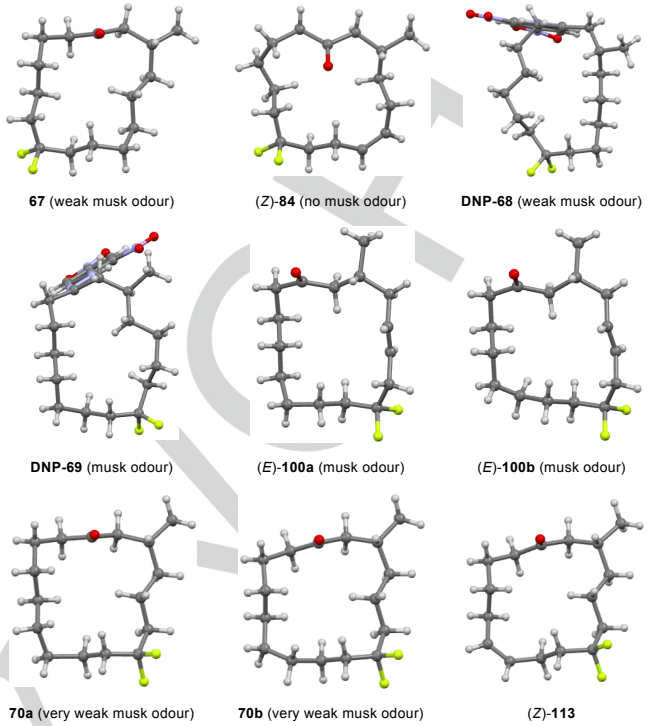
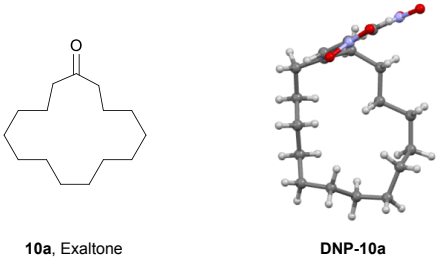


Figure 10. X-Ray structures of fluorinated muscone derivatives.

The structure of the DNP-derivative **69**, has a distorted rectangular conformation as shown in Figure 10, with well defined corners at C11 and C8, and a corner formed at C3 by the stereogenic centre. The overall structure is strikingly similar to the rectangular civetone structures **13**-**19** in Figure 6, although the six methylenes forming the long edge in those compounds is shortened to five in this structure. Ketone **69** exhibits a very good musk profile. The trans isomer (*E*)-**100** was also analysed by X-ray and two different conformers (*E*)-**100a** and (*E*)-**100b** are observed in the unit cell, with a CF_2 corner at C8 as shown in Figure 10. The overall rectangular shape is conserved in (*E*)-**100a**, and in (*E*)-**100b** the corner has moved from C11 to C12, defining a longer five carbon edge. Curiously, both structures have the stereogenic centre at an edge rather than a corner possibly dictated by the *trans* double bond.

It was interesting to find 'exaltone' notes described by the perfumers for compound **69**. Exaltone **10a** (cyclopentanodecanone) is a natural 15-membered ketone structurally related to muscone **2**, but without the stereogenic methyl group at C3 (Figure 11). The X-ray structure of the DNP derivative of **10a** was solved by Fronczek and co-workers in 2008 and is shown in Figure 11.[36] There is clearly a high level of homology between this conformation of exaltone **10a** and the DNP derivative of **69** consistent with their odour relationship. These structures relate to the civetones **13**-**19** in Figure 6 too, with a five, rather than six, carbon long edge, due to the smaller ring size. Presumably, this overall shape could be close to a relevant bioactive conformation for 15-membered musk ketones.



10a, Exaltone **DNP-10a**

Figure 11. X-ray crystal structure of exaltone DNP-derivative.

Conclusions

In summary, a set of fluorinated civetone and muscone analogues with one or more CF_2 groups placed at strategic positions of the ring have been prepared by synthesis. The conformation of all these molecules can be significantly influenced by the location of CF_2 groups. Our study demonstrates that this motif has a clear preference for occupying corner locations across a wider range of more complex and functionalised macrocycles. The majority of the civetone and muscone analogues, and some of the olefin precursors which result from RCM reactions, retain a muskoid scent, as the structures reinforce the conformation of the natural ketones and fit the generalized Bersuker model. However, some structures emerged that do not retain a musk scent, such as **20** and **21** of the civetone class. These compounds clearly have a distorted conformation relative to the parent compounds. Compound (*Z*)-**84** of the muscone class, was also devoid of any distinctive scent, but conspicuously it has a carbonyl group pointing into the ring, the only such example in all of the X-ray structures. Also, there is a tendency for weaker muscone notes as the ring structures deviate from rectangular to square conformations comparing, for example, muscones **69** with **70**. These observations offer structural information which contributes to our understanding of musk odorants. It follows that the utility of this conformational tool could be extended to other macrocycles in order to influence properties in other arenas.

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Keywords: organofluorine chemistry • macrocycles • conformational analysis • musk fragrances • structure-activity relationships

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CF_2-musks ----------

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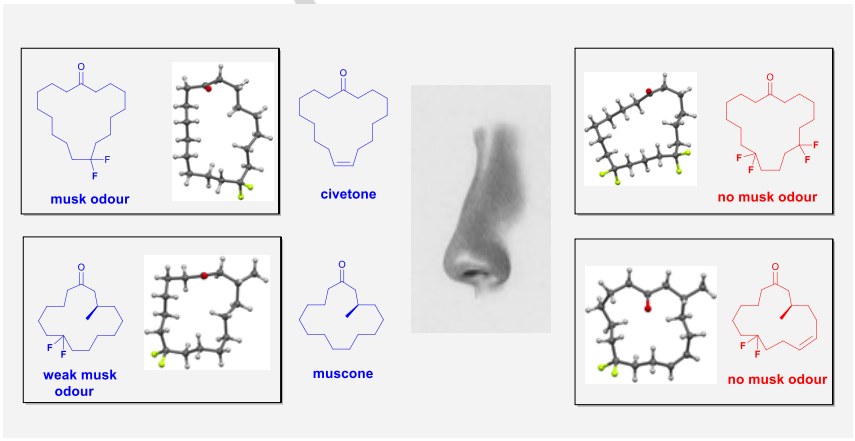
Fluorinated Musk Fragrances: The CF_2 Group as a Conformational Bias Influencing the Odour of Civetone and (*R*)-Muscone



Molecular conformation control: the olfactory properties of two natural musk macrocycles can be selectively modified by placing CF_2 groups in strategic locations. Compounds that retain the musky scent are showing reinforced conformations similar to the natural ketones. However, distorted conformations induced by CF_2 groups are leading molecules without the characteristic musk odour.

Layout 2:

FULL PAPER

Fluorinated Musk Fragances: The CF_2 Group as a Conformational Tool in Civetone and (*R*)-Muscone

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Supporting Information 1

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General Information

All reactions were conducted under an atmosphere of argon using standard vacuum line techniques. All glassware was flamedried and allowed to cool under high vacuum. Reactions with fluorinating reagents (DAST or HF·Py) were carried out in a PTFE flask wich was oven dried and allowed to cool under high vacuum.

All commercially availble reagents were purchased from Acros, Alfa Aesar, Fisher Scientific, Fluorochem or Sigma-Aldrich and used without further purification unless otherwise stated. Dry solvents were obtained from the MBraun SPS-800 Solvent Purification System, by passing the solvent through two drying columns under an argon atmosphere.

Thin layer chromatography (TLC) was performed using Merck TLC silica gel 60 F_{254} aluminium-backed plates. Compounds were visualised by either UV light (254 nm) or by the use of potassium permanganate stain or molybdenum-based stain. Column chromatography was performed using Merck silica gel 60 (40-63 μm).

NMR spectra were acquired on a Bruker Avance III 500 spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz, ^{19}F at 470.6 MHz). Chemical shifts (δ) are reported in parts per million (ppm) and are quoted relative to the residual peak of $CDCl_3$. Coupling constants (J) are given in Hertz (Hz). Signal splitting patterns are described as: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; tt, triplet of triplets; ddt, doublet of doublets of triplets; tdt, triplet of doublets of triplets; q, quartet; quint, quintet; m, multiplet; b, broad; AB, AB system; AA'XX', AA'XX' system.

High and low resolution mass spectra were recorded at the EPSRC National Mass Spectrometry Service, Swansea or at the University of St Andrews by Caroline Horsburgh on a Waters Micromass LCT time of flight mass spectrometer coupled to a Waters 2975 HPLC system. Values are reported as a ratio of mass to charge (m/z).

Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR system.

Single crystal X-ray Diffraction analysis was carried out by Prof Alexandra M. Z. Slawin and Dr David Cordes at University of St Andrews.

Melting points were determined in Pyrex capillaries using a Gallenkamp Griffin Melting Point Apparatus 350 and were uncorrected.

Synthesis and Characterisation

The following compounds were prepared according to previously described procedures: **12**,[1] **22-31**,[2] **39-30**,[3] **49-50**,[4] **60**,[5] **65**,[6] **74-75**,[7] **81**,[6] **90-91**,[8] **97**[9] and **101**.[6]

Civetone (1). Grubbs' 1st generation catalyst (20 mg, 0.02 mmol, 0.05 equiv.) was added to a stirred solution (protected from sunlight) of nonadeca-1,18-dien-10-one **12** (134 mg, 0.48 mmol, 1.0 equiv.) in dry DCM (25 mL) under argon atmosphere at room temperature. The mixture was heated at reflux temperature for 2 h. Then, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (pentane/Et_2O 50:1) gave compound **1** (*E/Z* 3:1 inseparable mixture of diastereoisomers, 40 mg, 33%) as a colourless oil. ***(E)*-1.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.20-1.36 (16H, m, 8 x CH_2), 1.58-1.66 (4H, m, 2 x CH_2), 2.01-2.02 (4H, m, 2 x CH_2), 2.38 (4H, t, *J*(H,H)= 7.1 Hz, 2 x CH_2), 5.28-5.32 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.0 (2 x CH_2), 27.4 (2 x CH_2), 28.3 (2 x CH_2), 28.76 (2 x CH_2), 28.80 (2 x CH_2), 31.9 (2 x CH_2), 42.5 (2 x CH_2), 131.0 (2 x =CH), 213.3 (C=O); IR (thin film) ν (cm^{-1}) = 1703 (C=O); HRMS (CI^+) *m/z* calcd for $C_{17}H_{32}F_2ON$ $[M+NH_4]^+$: 304.2446, found: 304.2449; ***(Z)*-1.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.20-1.36 (16H, m, 8 x CH_2), 1.58-1.66 (4H, m, 2 x CH_2), 2.01-2.02 (4H, m, 2 x CH_2), 2.40 (4H, t, *J*(H,H)= 6.7 Hz, 2 x CH_2), 5.33-5.38 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.8 (2 x CH_2), 26.7 (2 x CH_2), 28.1 (2 x CH_2), 28.2 (2 x CH_2), 28.6 (2 x CH_2), 29.0 (2 x CH_2), 42.4 (2 x CH_2), 130.1 (2 x =CH), 212.6 (C=O). These data are in good agreement with the literature values.[10]

Dihydrocivetone (11). A mixture of 5% Pd/C (17 mg, 0.008 mmol, 0.1 equiv.) in 0.5 mL of absolute EtOH was stirred for a few minutes under a small positive pressure of H_2. A solution of civetone **1** (20 mg, 0.08 mmol, 1.0 equiv.) in 1.0 mL of absolute EtOH was added to the above mixture and the reaction was stirred overnight under H_2 atmosphere at room temperature. Then, the catalyst was removed by filtration through a short pad of celite and washed with Et_2O (56 mL). The solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 15:1) gave compound **11** (12 mg, 60%) as a white solid; m.p. 61-63 ºC (*lit.*[11] 63-64 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.25-1.32 (24H, m, 12 x CH_2), 1.60-1.64 (4H, m, 2 x CH_2), 2.41 (4H, t, *J*(H,H)= 6.8 Hz, 2 x CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.7 (2 x CH_2), 26.8 (2 x CH_2), 27.1 (2 x CH_2), 27.2 (2 x CH_2), 27.5 (2 x CH_2), 27.8 (2 x CH_2), 28.2 (2 x CH_2), 42.4 (2 x CH_2), 212.6 (C=O); IR (thin film) ν (cm^{-1}) = 1706 (C=O); HRMS (CI^+) *m/z* calcd for $C_{17}H_{34}F_2ON$ $[M+NH_4]^+$: 306.2603, found: 306.2606.

8,8,11,11-tetrafluorocycloheptadec-1-en-9-yne (32). Grubbs' 1st generation catalyst (9 mg, 0.01 mmol,

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0.05 equiv.) was added to a stirred solution (protected from sunlight) of 8,8,11,11-tetrafluorononadeca-1,18-dien-9-yne **31** (72 mg, 0.21 mmol, 1.0 equiv.) in dry DCM (10.7 mL) under argon atmosphere at room temperature. The mixture was heated at reflux temperature for 24 h. Then, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes) gave compound **32** (*E/Z* 2:1 inseparable mixture of diastereoisomers, 54 mg, 83%) as a colourless oil. ***(E)*-32.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.25-1.49 (12H, m, 6 x CH_2), 1.51-1.61 (2H, m, CH_2), 2.01-2.18 (8H, m, 4 x CH_2), 5.31-5.43 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.3 (t, *J*(C,F)= 3.7 Hz, CH_2), 23.4 (t, *J*(C,F)= 3.4 Hz, CH_2), 27.0 (CH_2), 27.1 (CH_2), 27.39 (CH_2), 27.41 (CH_2), 29.5 (CH_2), 31.1 (CH_2), 31.6 (CH_2), 38.5 (t, *J*(C,F)= 24.8 Hz, CH_2), 39.0 (t, *J*(C,F)= 25.8 Hz, CH_2), 79.0 (tt, *J*(C,F)= 42.0, 6.4 Hz, ≡C), 79.5 (tt, *J*(C,F)= 42.0, 6.5 Hz, ≡C), 114.5 (t, *J*(C,F)= 237 Hz, CF_2), 114.7 (t, *J*(C,F)= 235 Hz, CF_2), 130.7 (=CH), 131.2 (=CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -84.9 (2F, m, CF_2), -85.4 (2F, m, CF_2); ***(Z)*-32.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.27-1.47 (12H, m, 6 x CH_2), 1.51-1.60 (2H, m, CH_2), 2.00-2.13 (8H, m, 4 x CH_2), 5.41-5.44 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.8 (t, *J*(C,F)= 3.7 Hz, CH_2), 22.5 (t, *J*(C,F)= 3.8 Hz, CH_2), 26.4 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 27.8 (CH_2), 28.0 (CH_2), 29.0 (CH_2), 38.5 (t, *J*(C,F)= 25.0 Hz, CH_2), 38.9 (t, *J*(C,F)= 24.9 Hz, CH_2), 78.9 (tt, *J*(C,F)= 41.7, 6.5 Hz, ≡C), 79.2 (tt, *J*(C,F)= 41.8, 6.7 Hz, ≡C), 114.5 (t, *J*(C,F)= 235 Hz, CF_2), 114.6 (t, *J*(C,F)= 235 Hz, CF_2), 130.0 (=CH), 130.1 (=CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -83.5 (2F, m, CF_2), -83.9 (2F, m, CF_2); HRMS (CI^+) *m/z* calcd for $C_{17}H_{25}F_4$ $[M+H]^+$: 305.1887, found: 305.1889.

8,8,11,11-tetrafluorocycloheptadec-9-yn-1-one (33) and 7,7,10,10-tetrafluorocycloheptadec-8-yn-1-one (34). Borane dimethyl sulfide complex (0.1 mL, 2M solution in THF, 0.19 mmol, 1.25 equiv.) was added to a stirred solution of 8,8,11,11-tetrafluorocycloheptadec-1-en-9-yne **32** (47 mg, 0.15 mmol, 1.0 equiv.) in dry THF (1.6 mL) under argon atmosphere at 0 ºC. The solution was warmed to room temperature and stirred overnight. Then, EtOH (0.1 mL), aq. NaOH (2 M, 0.1 mL) and aq. H_2O_2 (30% w/w, 0.1 mL) were sequentially added and the reaction mixture was stirred for 4 h. After evaporation of the volatiles, H_2O (0.5 mL) was added and the solution was extracted with EtOAc (3 x 3.0 mL). The combined organic layers were washed with brine (3.0 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The intermediate 1:1 mixture of alcohols was dissolved in DMSO (1.5 mL) and IBX (86 mg, 0.31 mmol, 2.0 equiv.) was added at room temperature. The resulting mixture was stirred overnight. Then, H_2O (3.5 mL) and EtOAc (3.5 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 3.5 mL) and brine (3.5 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Separation by column chromatography using silica gel (hexanes/EtOAc 10:1) gave compound **33** (9.0 mg, 18%) as a colourless oil and compound **34** (9.0 mg, 18%) as a colourless oil. **33.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.37 (4H, m, 2 x CH_2), 1.39-1.44 (4H, m, 2 x CH_2), 1.51-1.57 (4H, m, 2 x CH_2), 1.65 (4H, quint, *J*(H,H)= 7.1 Hz, 2 x CH_2), 2.01-2.11 (4H, m, 2 x CH_2), 2.42 (4H, t, *J*(H,H)= 6.8 Hz, 2 x CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.1 (2 x CH_2), 27.8 (2 x CH_2), 23.7 (2 x CH_2), 28.5 (2 x CH_2), 38.6 (t, *J*(C,F)= 25.5 Hz, 2 x CH_2), 42.2 (2 x CH_2), 79.1 (t, *J*(C,F)= 43.4 Hz, 2 x ≡C), 114.4 (t, *J*(C,F)= 235 Hz, 2 x CF_2), 212.3 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -84.4 (4F, s, 2 x CF_2); IR (thin film) ν (cm^{-1}) = 1707 (C=O); HRMS (CI^+) *m/z* calcd for $C_{17}H_{25}F_4O$ $[M+H]^+$: 321.1836, found: 321.1835; **34.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.24-1.31 (2H, m, CH_2), 1.34-1.39 (2H, m, CH_2), 1.40-1.47 (4H, m, 2 x CH_2), 1.48-1.54 (4H, m, 2 x CH_2), 1.64-1.70 (4H, m, 2 x CH_2), 2.01-2.12 (4H, m, 2 x CH_2), 2.43 (2H, t, *J*(H,H)= 6.3 Hz, CH_2), 2.45 (2H, t, *J*(H,H)= 6.8 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.5 (t, *J*(C,F)= 3.8 Hz, CH_2), 22.6 (t, *J*(C,F)= 3.9 Hz, CH_2), 23.0 (CH_2), 24.1 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 28.0 (CH_2), 28.1 (CH_2), 38.62 (t, *J*(C,F)= 24.9 Hz, CH_2), 38.65 (t, *J*(C,F)= 25.2 Hz, CH_2), 41.7 (CH_2), 42.1 (CH_2), 79.1 (2 x ≡C), 114.2 (t, *J*(C,F)= 236 Hz, CF_2), 114.5 (t, *J*(C,F)= 235 Hz, CF_2), 211.8 (C=O); ^{19}F{^{1}H} NMR (470 MHz,

$CDCl_3$) δ = -83.7 (2F, t, J(F,F)= 3.6 Hz, CF_2), -83.9 (2F, t, J(F,F)= 3.5 Hz, CF_2); IR (thin film) ν (cm^{-1}) = 1707 (C=O); HRMS (CI^+) m/z calcd for $C_{17}H_{25}F_4O$ $[M+H]^+$: 321.1836, found: 321.1837.

(*Z*)-8,8,11,11-tetrafluorocycloheptadec-9-en-1-one (13). A mixture of 5% Pd/$BaSO_4$ (6.3 mg) and quinoline (2.1 mg) in 0.9 mL of pyridine was stirred for a few minutes under a small positive pressure of H_2. A solution of 8,8,11,11-tetrafluorocycloheptadec-9-yn-1-one **33** (16 mg, 0.05 mmol, 1 equiv.) in 0.7 mL of pyridine was added to the above mixture after the catalyst turned black. The resulting mixture was stirred overnight under H_2 atmosphere at room temperature. Then, the catalyst was removed by filtration through a short pad of celite and washed with Et_2O (35 mL). The filtrate was washed with sat. aq. $CuSO_4 \cdot 5H_2O$ solution (8.5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 7:1) gave compound **13** (15 mg, 96%) as a white solid; m.p. 64-66 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.23-1.29 (4H, m, 2 x CH_2), 1.33-1.40 (4H, m, 2 x CH_2), 1.44-1.50 (4H, m, 2 x CH_2), 1.62-1.67 (4H, m, 2 x CH_2), 1.92-2.04 (4H, m, 2 x CH_2), 2.43 (4H, t, J(H,H)= 6.5 Hz, 2 x CH_2), 5.69-5.83 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.9 (2 x CH_2), 23.7 (2 x CH_2), 27.9 (2 x CH_2), 28.2 (2 x CH_2), 36.5-37.0 (m, 2 x CH_2), 42.0 (2 x CH_2), 120.9 (t, J(C,F)= 242 Hz, 2 x CF_2), 130.8-131.5 (m, 2 x =CH), 212.2 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -90.8 (4F, s, 2 x CF_2); IR (thin film) ν (cm^{-1}) = 1709 (C=O); HRMS (CI^+) m/z calcd for $C_{17}H_{30}F_4ON$ $[M+NH_4]^+$: 340.2258, found: 340.2256.

8,8,11,11-tetrafluorocycloheptadecan-1-one (14). A mixture of 5% Pd/C (14 mg, 0.007 mmol, 0.1 equiv.) in 0.7 mL of absolute EtOH was stirred for a few minutes under a small positive pressure of H_2. A solution of 8,8,11,11-tetrafluorocycloheptadec-9-yn-1-one **33** (21 mg, 0.06 mmol, 1 equiv.) in 0.7 mL of absolute EtOH was added to the above mixture and the reaction was stirred overnight under H_2 atmosphere at room temperature. Then, the catalyst was removed by filtration through a short pad of celite and washed with Et_2O (46 mL). The solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 10:1) gave compound **14** (18 mg, 86%) as a white solid; m.p. 49-51 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.47 (12H, m, 6 x CH_2), 1.62 (4H, quint, J(H,H)= 7.0 Hz, 2 x CH_2), 1.82-1.92 (4H, m, 2 x CH_2), 1.97-2.03 (4H, m, 2 x CH_2), 2.41 (4H, t, J(H,H)= 6.8 Hz, 2 x CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.3 (t, J(C,F)= 5.1 Hz, 2 x CH_2), 23.3 (2 x CH_2), 27.7 (2 x CH_2), 28.0 (2 x CH_2), 28.8 (tt, J(C,F)= 27.4, 5.0 Hz, 2 x CH_2), 34.8 (t, J(C,F)= 25.4 Hz, 2 x CH_2), 42.2 (2 x CH_2), 125.0 (t, J(C,F)= 241 Hz, 2 x CF_2), 212.0 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -94.1 (4F, s, 2 x CF_2); IR (thin film) ν (cm^{-1}) = 1708 (C=O); HRMS (CI^+) m/z calcd for $C_{17}H_{32}F_4ON$ $[M+NH_4]^+$: 342.2415, found: 342.2415.

(*Z*)-7,7,10,10-tetrafluorocycloheptadec-8-en-1-one (15). A mixture of 5% Pd/$BaSO_4$ (6.5 mg) and quinoline (2.2 mg) in 0.9 mL of pyridine was stirred for a few minutes under a small positive pressure of H_2. A solution of 7,7,10,10-tetrafluorocycloheptadec-8-yn-1-one **34** (17 mg, 0.05 mmol, 1 equiv.) in 0.8 mL of pyridine was added to the above mixture after the catalyst turned black. The resulting mixture was stirred overnight under H_2 atmosphere at room temperature. Then, the catalyst was removed by filtration through a short pad of celite and washed with Et_2O (35 mL). The filtrate was washed with aq. sat. $CuSO_4 \cdot 5H_2O$ (8.6 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 7:1) gave compound **15** (14 mg, 81%) as a white solid; m.p. 61-62 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.23-1.29 (4H, m, 2 x CH_2), 1.32-1.50 (8H, m, 4 x CH_2), 1.62-1.68 (4H, m, 2 x CH_2), 1.93-2.07 (4H, m, 2 x CH_2), 2.41 (2H, t, J(H,H)= 6.7 Hz, CH_2), 2.42 (2H, t, J(H,H)= 6.5 Hz, CH_2), 5.74 (1H, q, J = 13.9 Hz, =CH), 5.83 (1H, q, J(H,H)= 13.7 Hz, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3 (t, J(C,F)= 3.4 Hz, CH_2), 21.8 (t, J(C,F)= 3.5 Hz, CH_2), 23.5 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 36.8 (t, J(C,F)= 26.4 Hz, CH_2), 37.0 (t, J(C,F)= 26.0 Hz, CH_2), 41.4 (CH_2), 42.1 (CH_2), 121.0 (t, J(C,F)= 240 Hz, CF_2), 121.1 (t, J(C,F)= 240 Hz, CF_2), 131.1 (tt, J(C,F)= 31.3, 7.2 Hz, =CH), 131.4 (tt, J(C,F)= 32.1, 6.3 Hz, =CH), 212.0 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -89.6-89.7 (2F, m, CF_2), -92.0-92.1 (2F, m,

CF_2); IR (thin film) ν (cm^{-1}) = 1707 (C=O); HRMS (CI^+) *m/z* calcd for $C_{17}H_{30}F_4ON$ $[M+NH_4]^+$: 340.2258, found: 340.2256.

7,7,10,10-tetrafluorocycloheptadecan-1-one (16). A mixture of 5% Pd/C (12 mg, 0.006 mmol, 0.1 equiv.) in 0.5 mL of absolute EtOH was stirred for a few minutes under a small positive pressure of H_2. A solution of 7,7,10,10-tetrafluorocycloheptadec-8-yn-1-one **34** (18 mg, 0.05 mmol, 1 equiv.) in 0.5 mL of absolute EtOH was added to the above mixture and the reaction was stirred overnight under H_2 atmosphere at room temperature. Then, the catalyst was removed by filtration through a short pad of celite and washed with Et_2O (39 mL). The solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 10:1) gave compound **16** (14 mg, 79%) as a white solid; m.p. 69-70 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.20-1.40 (12H, m, 6 x CH_2), 1.59-1.68 (4H, m, 2 x CH_2), 1.80-2.05 (8H, m, 4 x CH_2), 2.41-2.45 (4H, m, 2 x CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.7 (t, *J*(C,F)= 5.2 Hz, CH_2), 22.4 (t, *J*(C,F)= 5.4 Hz, CH_2), 22.5 (CH_2), 23.5 (CH_2), 27.4 (CH_2), 27.6 (2 x CH_2), 28.2 (CH_2), 28.5 (tt, *J*(C,F)= 27.8, 5.4 Hz, CH_2), 28.9 (tt, *J*(C,F)= 27.2, 5.4 Hz, CH_2), 34.8 (t, *J*(C,F)= 25.1 Hz, CH_2), 35.4 (t, *J*(C,F)= 25.3 Hz, CH_2), 41.9 (CH_2), 42.1 (CH_2), 124.8 (t, *J*(C,F)= 241 Hz, CF_2), 125.2 (t, *J*(C,F)= 240 Hz, CF_2), 211.4 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -93.2 (2F, s, CF_2), -94.5 (2F, s, CF_2); IR (thin film) ν (cm^{-1}) = 1701 (C=O); HRMS (CI^+) *m/z* calcd for $C_{17}H_{32}F_4ON$ $[M+NH_4]^+$: 342.2415, found: 342.2413.

10,10-difluorononadeca-1,18-diene (35). Neat DAST (7.3 mL, 55.7 mmol, 12 equiv.) was added to nonadeca-1,18-dien-10-one **12** (1.29 g, 4.64 mmol) under argon atmosphere. The mixture was heated at 50 °C and stirred for 3 days. Crude reaction was added portionwise to a biphasic mixture of sat. aq. $NaHCO_3$ solution (150 mL) and DCM (100 mL) at 0 °C. The aqueous layer was separated and extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes) gave compound **35** (379 mg, 27%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.30-1.48 (20H, m, 10 x CH_2), 1.75-1.84 (4H, m, 2 x CH_2), 2.05 (4H, q, *J*(H,H)= 7.1 Hz, 2 x CH_2), 4.93-5.02 (4H, m, 2 x =CH_2), 5.82 (2H, ddt, *J*(H,H)= 17.1, 10.2, 6.7 Hz, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.3 (t, *J*(C,F)= 4.4 Hz, 2 x CH_2), 28.8 (2 x CH_2), 28.9 (2 x CH_2), 29.2 (2 x CH_2), 29.3 (2 x CH_2), 33.7 (2 x CH_2), 36.3 (t, *J*(C,F)= 25.1 Hz, 2 x CH_2), 125.4 (t, *J*(C,F)= 240 Hz, CF_2), 139.1 (2 x =CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.6 (2F, s, CF_2); HRMS (EI^+) *m/z* calcd for $C_{19}H_{34}F_2$ $[M]^+$: 300.2628, found: 300.2623.

10,10-difluorocycloheptadec-1-ene (36). Grubbs' 1st generation catalyst (28.3 mg, 0.03 mmol, 0.1 equiv.) was added to a stirred solution (protected from sunlight) of 10,10-difluorononadeca-1,18-diene **35** (103 mg, 0.34 mmol, 1.0 equiv.) in dry DCM (69 mL) under argon atmosphere at room temperature. The mixture was heated at reflux temperature for 3 h. Then, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes) gave compound **36** (*E/Z* 8:1 inseparable mixture of diastereoisomers, 35 mg, 38%) as a colourless oil. ***(E)*-36.** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.32-1.41 (20H, m, 10 x CH_2), 1.75-1.84 (4H, m, 2 x CH_2), 1.86-2.07 (4H, m, 2 x CH_2), 5.33-5.36 (2H, m, 2 x =CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.3 (t, *J*(C,F)= 5.5 Hz, 2 x CH_2), 27.0 (2 x CH_2), 27.6 (2 x CH_2), 28.3 (2 x CH_2), 28.9 (2 x CH_2), 32.4 (2 x CH_2), 34.9 (t, *J*(C,F)= 25.5 Hz, 2 x CH_2), 126.5 (t, *J*(C,F)= 239 Hz, CF_2), 130.8 (2 x =CH); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = -90.9 (2F, s, CF_2); ***(Z)*-36.** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.32-1.41 (20H, m, 10 x CH_2), 1.75-1.84 (4H, m, 2 x CH_2), 1.86-2.07 (4H, m, 2 x CH_2), 5.33-5.36 (2H, m, 2 x =CH);
^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.6 (t, *J*(C,F)= 5.2 Hz, 2 x CH_2), 27.0 (2 x CH_2), 27.6 (2 x CH_2), 28.3 (2 x CH_2), 29.1 (2 x CH_2), 32.4 (2 x CH_2), 34.9 (t, *J*(C,F)= 25.5 Hz, 2 x CH_2), 126.5 (t, *J*(C,F)= 239 Hz, CF_2), 130.1 (2 x =CH); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ = -91.2 (2F, s, CF_2); HRMS (CI^+) *m/z* calcd for $C_{17}H_{25}F_4$ $[M+H]^+$: 305.1887, found: 305.1889.

9,9-difluorocycloheptadecan-1-ol (37). Borane dimethyl sulfide complex (0.13 mL, 2M solution in THF, 0.25 mmol, 1.5 equiv.) was added to a stirred solution of 10,10-difluorocycloheptadec-1-ene **36** (46 mg, 0.17 mmol, 1.0 equiv.) in dry THF (1.7 mL) under argon atmosphere at 0 ºC. The solution was warmed to room temperature and stirred overnight. Then, EtOH (0.13 mL), aq. NaOH (2 M, 0.13 mL) and aq. H_2O_2 (30% w/w, 0.13 mL) were sequentially added and the reaction mixture was stirred for 4 h. After evaporation of the volatiles, H_2O (0.6 mL) was added and the solution was extracted with EtOAc (3 x 4.0 mL). The combined organic layers were washed with brine (4.0 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **37** (42 mg, 85%) as a white solid, which was used without further purification; m.p. 64-65 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.41-1.59 (26H, m, 13 x CH_2), 1.79-1.87 (4H, m, 2 x CH_2), 3.71 (1H, quint, J(H,H)= 5.8 Hz, OCH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.7 (t, J(C,F)= 5.2 Hz, CH_2), 21.9 (t, J(C,F)= 5.3 Hz, CH_2), 23.8 (CH_2), 23.9 (CH_2), 27.2 (CH_2), 27.3 (CH_2), 27.55 (CH_2), 27.58 (CH_2), 27.61 (2 x CH_2), 27.7 (CH_2), 34.7 (t, J(C,F)= 25.7 Hz, CH_2), 34.9 (t, J(C,F)= 24.9 Hz, CH_2), 35.1 (CH_2), 36.1 (CH_2), 70.4 (OCH_2), 126.2 (t, J(C,F)= 240 Hz, CF_2); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -92.3 (2F, s, CF_2); HRMS (EI$^+$) m/z calcd for $C_{17}H_{29}F$ [M-HF]$^+$: 252.2253, found: 252.2252.

9,9-difluorocycloheptadecanone (17). IBX (62 mg, 0.22 mmol, 2 equiv.) was added to a solution of 9,9-difluorocycloheptadecan-1-ol **37** (32 mg, 0.11 mmol, 1.0 equiv.) in DMSO (2.0 mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O (2.6 mL) and EtOAc (2.6 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 2.6 mL) and brine (2.6 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 10:1) gave compound **17** (20 mg, 61%) as a white solid; m.p. 50-51 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.24-1.39 (18H, m, 9 x CH_2), 1.60-1.66 (4H, m, 2 x CH_2), 1.76-1.86 (4H, m, 2 x CH_2), 2.42 (4H, t, J(H,H)= 6.5 Hz, 2 x CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.6 (t, J(C,F)= 5.3 Hz, CH_2), 21.8 (t, J(C,F)= 5.4 Hz, CH_2), 23.4 (CH_2), 23.8 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 27.6 (CH_2), 27.7 (CH_2), 28.0 (2 x CH_2), 28.1 (CH_2), 34.5 (t, J(C,F)= 25.4 Hz, CH_2), 34.8 (t, J(C,F)= 25.5 Hz, CH_2), 42.1 (CH_2), 42.5 (CH_2), 126.3 (t, J(C,F)= 240 Hz, CF_2), 212 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -91.7 (2F, s, CF_2); IR (thin film) ν (cm^{-1}) = 1710 (C=O); HRMS (CI$^-$) m/z calcd for $C_{17}H_{29}F$ [M-H]$^-$: 287.2192, found: 287.2189.

10-(4-methoxybenzyloxy)dec-1-en-4-ol (41). Allylmagnesium bromide (90.5 mL, 1M solution in Et_2O, 90.5 mmol, 1.5 equiv.) was added to a solution of 7-(4-methoxybenzyloxy)heptanal **40** (15.1 g, 60.4 mmol, 1.0 equiv.) in dry THF (215 mL) at 0ºC. The resulting mixture was stirred overnight at room temperature. Then, sat. aq. NH_4Cl solution (107 mL) and Et_2O (54 mL) were sequentially added and the aqueous layer was extracted with Et_2O (3 x 107 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 4:1) gave compound **41** (10.2 g, 58%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.30-1.40 (6H, m, 3 x CH_2), 1.44-1.48 (2H, m, CH_2), 1.56-1.64 (4H, m, 2 x CH_2), 3.44 (2H, t, J(H,H)= 6.7 Hz, CH_2O), 3.64 (1H, bs, OCH), 3.81 (3H, s, MeO), 4.44 (2H, s, CH_2O), 5.13-5.16 (2H, m, =CH_2), 5.79-5.87 (1H, m, =CH), 6.88 (2H, AA'XX', 2 x CH_{Ar}), 7.27 (2H, AA'XX', 2 x CH_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.6 (CH_2), 26.2 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 36.7 (CH_2), 41.9 (CH_2), 55.3 (MeO), 70.1 (CH_2O), 70.6 (OCH), 72.5 (CH_2O), 113.7 (2 x CH_{Ar}), 118.1 (=CH_2), 129.2 (2 x CH_{Ar}), 130.7 (C_{Ar}), 134.9 (=CH), 159.1 (C_{Ar}). HRMS (ESI$^+$) m/z calcd for $C_{18}H_{28}NaO_3$ [M+Na]$^+$: 315.1931, found: 315.1922.

10-(4-methoxybenzyloxy)dec-1-en-4-ona (42). IBX (10.8 g, 38.6 mmol, 1.2 equiv.) was added to a solution of 10-(4-methoxybenzyloxy)dec-1-en-4-ol **41** (9.40 g, 32.2 mmol, 1.0 equiv.) in DMSO (151

mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O (355 mL) and EtOAc (355 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 355 mL) and brine (355 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **42** (7.93 g, 85%) as a colourless oil, which was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.40 (4H, m, 2 x CH_2), 1.55-1.62 (4H, m, 2 x CH_2), 2.44 (2H, t, J(H,H)= 7.4 Hz, CH_2), 3.17 (2H, dt, J(H,H)= 7.1, 1.3 Hz, CH_2), 3.43 (2H, t, J(H,H)= 6.6 Hz, CH_2O), 3.81 (3H, s, MeO), 4.43 (2H, s, CH_2O), 5.12-5.20 (2H, m, =CH_2), 5.92 (1H, ddt, J(H,H)= 17.1, 10.2, 7.0 Hz, =CH), 6.88 (2H, AA'XX', 2 x CH_{Ar}), 7.26 (2H, AA'XX', 2 x CH_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.6 (CH_2), 26.0 (CH_2), 29.0 (CH_2), 29.6 (CH_2), 42.3 (CH_2), 47.7 (CH_2), 55.3 (MeO), 70.0 (CH_2O), 72.5 (CH_2O), 113.7 (2 x CH_{Ar}), 118.7 (=CH_2), 129.2 (2 x CH_{Ar}), 130.6 (C_{Ar}), 130.7 (=CH), 159.1 (C_{Ar}), 209.0 (C=O); HRMS (ESI$^+$) m/z calcd for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 313.1774, found: 313.1767.

1-((7,7-difluorodec-9-en-1-yloxy)methyl)-4-methoxybenzene (43). Neat DAST (14.4 mL, 109.4 mmol, 4.0 equiv.) was added to 10-(4-methoxybenzyloxy)dec-1-en-4-ona **42** (7.93 g, 27.3 mmol, 1.0 equiv.) under argon atmosphere. The mixture was heated at 50 °C and stirred overnight. Crude reaction was added portionwise to a biphasic mixture of sat. aq. $NaHCO_3$ solution (300 mL) and DCM (104 mL) at 0 °C. The aqueous layer was separated and extracted with DCM (3 x 52 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 15:1) gave compound **43** (3.62 g, 43%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.31-1.41 (4H, m, 2 x CH_2), 1.44-1.51 (2H, m, CH_2), 1.55-1.63 (2H, m, CH_2), 1.75-1.85 (2H, m, CH_2), 2.59 (2H, td, J(H,F)= 15.9 Hz, J(H,H)= 7.1 Hz, CH_2), 3.44 (2H, t, J(H,H)= 6.6 Hz, CH_2O), 3.81 (3H, s, MeO), 4.44 (2H, s, CH_2O), 5.18-5.22 (2H, m, =CH_2), 5.80 (1H, ddt, J(H,H)= 16.6, 10.8, 7.1 Hz, =CH), 6.89 (2H, AA'XX', 2 x CH_{Ar}), 7.27 (2H, AA'XX', 2 x CH_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.0 (t, J(C,F)= 4.4 Hz, CH_2), 26.0 (CH_2), 29.1 (CH_2), 29.6 (CH_2), 35.8 (t, J(C,F)= 24.6 Hz, CH_2), 41.1 (t, J(C,F)= 26.6 Hz, CH_2), 55.3 (MeO), 70.0 (CH_2O), 72.5 (CH_2O), 113.7 (2 x CH_{Ar}), 120.0 (=CH_2), 124.3 (t, J(C,F)= 241 Hz, CF_2), 129.2 (2 x CH_{Ar}), 129.8 (t, J(C,F)= 5.8 Hz, =CH), 130.7 (C_{Ar}), 159.1 (C_{Ar}); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.2 (2F, s, CF_2); HRMS (ESI$^+$) m/z calcd for $C_{18}H_{26}F_2NaO_2$ $[M+Na]^+$: 335.1793, found: 335.1786.

7,7-difluorodec-9-en-1-ol (44). DDQ (5.27 g, 23.2 mmol, 2.0 equiv.) was added to a solution of 1-((7,7-difluorodec-9-en-1-yloxy)methyl)-4-methoxybenzene **43** (3.62 g, 11.6 mmol, 1.0 eq) in DCM (93 mL) and water (2.3 mL) at room temperature. The resulting mixture was stirred overnight. Then, aq. sat. $NaHCO_3$ solution (93 mL) was added and the aqueous layer was extracted with DCM (2 x 45 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 7:1) gave compound **44** (1.66 g, 74%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.34-1.42 (4H, m, 2 x CH_2), 1.46-1.52 (2H, m, CH_2), 1.55-1.60 (2H, m, CH_2), 1.76-1.86 (2H, m, CH_2), 2.60 (2H, td, J(H,F)= 15.9 Hz, J(H,H)= 7.1 Hz, CH_2), 3.64 (2H, t, J(H,H)= 6.6 Hz, CH_2O), 5.18-5.22 (2H, m, =CH_2), 5.76 (1H, ddt, J(H,H)= 16.5, 10.8, 7.2 Hz, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.0 (t, J(C,F)= 4.4 Hz, CH_2), 25.5 (CH_2), 29.1 (CH_2), 32.5 (CH_2), 35.6 (t, J(C,F)= 25.0 Hz, CH_2), 41.1 (t, J(C,F)= 26.4 Hz, CH_2), 62.8 (CH_2O), 120.0 (=CH_2), 124.2 (t, J(C,F)= 241 Hz, CF_2), 129.8 (t, J(C,F)= 5.9 Hz, =CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.3 (2F, s, CF_2); HRMS (ESI$^+$) m/z calcd for $C_{18}H_{26}F_2NaO_2$ $[M+Na]^+$: 335.1793, found: 335.1786.

7,7-difluorodec-9-enal (45). IBX (1.18 g, 4.2 mmol, 1.5 equiv.) was added to a solution of 7,7-difluorodec-9-en-1-ol **44** (536 mg, 2.8 mmol, 1.0 equiv.) in DMSO (13.5 mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O (32 mL) and EtOAc (32 mL) were sequentially

added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 32 mL) and brine (32 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **45** (521 mg, 98%) as a colourless oil, which was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.35-1.41 (2H, m, CH_2), 1.48-1.54 (2H, m, CH_2), 1.66 (2H, quint, J(H,H)= 7.4 Hz, CH_2), 1.77-1.87 (2H, m, CH_2), 2.46 (2H, td, J(H,H)= 7.2, 1.4 Hz, CH_2), 2.60 (2H, td, J(H,F)= 15.8 Hz, J(H,H)= 7.2 Hz, CH_2), 5.19-5.23 (2H, m, =CH_2), 5.80 (1H, ddt, J(H,H)= 17.1, 10.2, 7.2 Hz, =CH), 9.78 (1H, bt, J(H,H)= 1.4 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.8 (t, J(C,F)= 4.3 Hz, CH_2), 28.8 (CH_2), 35.6 (t, J(C,F)= 25.1 Hz, CH_2), 41.2 (t, J(C,F)= 26.3 Hz, CH_2), 43.6 (CH_2), 120.1 (=CH_2), 124.1 (t, J(C,F)= 241 Hz, CF_2), 129.7 (t, J(C,F)= 6.0 Hz, =CH), 202.5 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.5 (2F, s, CF_2); HRMS (ESI^+) m/z calcd for $C_{18}H_{26}F_2NaO_2$ $[M+Na]^+$: 335.1793, found: 335.1786.

4,4-difluorononadeca-1,18-dien-10-ol (46). 9-bromonon-1-ene (742 mg, 3.6 mmol, 4.0 equiv.) was added to a suspension of magnesium turnings (87 mg, 3.6 mmol, 4.0 equiv.) and iodine (traces) in dry THF (4.4 mL) under argon atmosphere at room temperature. The reaction was heated at reflux for 6 h. Then, the reaction was cooled to room temperature and was diluted with dry THF (5 mL). A solution of 7,7-difluorodec-9-enal **45** (172 mg, 0.9 mmol, 1.0 equiv.) was added to the above solution and the reaction was stirred overnight. Then, sat. aq. NH_4Cl solution (7.0 mL) and Et_2O (14 mL) were sequentially added and the aqueous layer was extracted with Et_2O (3 x 14 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 10:1) gave compound **46** (177 mg, 62%) as a white solid; m.p. 39-40 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.52 (20H, m, 10 x CH_2), 1.77-1.86 (2H, m, CH_2), 2.05 (2H, q, J(H,H)= 7.1 Hz, CH_2), 2.60 (2H, td, J(H,F)= 15.8 Hz, J(H,H)= 7.2 Hz, CH_2), 3.59 (1H, bs, OCH), 4.92-5.02 (2H, m, =CH_2), 5.19-5.22 (2H, m, =CH_2), 5.76-5.86 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.0 (t, J(C,F)= 4.3 Hz, CH_2), 25.4 (CH_2), 25.6 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.37 (CH_2), 29.44 (CH_2), 29.6 (CH_2), 33.8 (CH_2), 35.8 (t, J(C,F)= 25.1 Hz, CH_2), 37.2 (CH_2), 37.5 (CH_2), 41.1 (t, J(C,F)= 26.9 Hz, CH_2), 71.9 (OCH), 114.1 (=CH_2), 120.0 (=CH_2), 124.2 (t, J(C,F)= 241 Hz, CF_2), 129.8 (t, J(C,F)= 5.8 Hz, =CH), 139.2 (=CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.2 (2F, s, CF_2); HRMS (CI^+) m/z calcd for $C_{19}H_{38}F_2ON$ $[M+NH_4]^+$: 334.2916, found: 334.2916.

4,4-difluorononadeca-1,18-dien-10-one (47). IBX (257 mg, 0.92 mmol, 2 equiv.) was added to a solution of 4,4-difluorononadeca-1,18-dien-10-ol **46** (145 mg, 0.46 mmol, 1.0 equiv.) in DMSO (2.2 mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O (5.3 mL) and EtOAc (5.3 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 5.3 mL) and brine (5.3 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **47** (134 mg, 93%) as a white waxy solid, which was used without further purification; m.p. 27-29 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.25-1.39 (10H, m, 5 x CH_2), 1.45-1.51 (2H, m, CH_2), 1.54-1.61 (4H, m, 2 x CH_2), 1.75-1.85 (2H, m, CH_2), 2.04 (2H, q, J(H,H)= 7.0 Hz, CH_2), 2.38 (2H, t, J(H,H)= 7.8 Hz, CH_2), 2.40 (2H, t, J(H,H)= 7.7 Hz, CH_2), 2.59 (2H, td, J(H,F)= 15.9 Hz, J(H,H)= 7.2 Hz, CH_2), 4.92-5.01 (2H, m, =CH_2), 5.18-5.22 (2H, m, =CH_2), 5.75-5.85 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.8 (t, J(C,F)= 4.4 Hz, CH_2), 23.4 (CH_2), 23.8 (CH_2), 28.82 (CH_2), 28.86 (CH_2), 28.90 (CH_2), 29.17 (CH_2), 29.22 (CH_2), 33.7 (CH_2), 35.7 (t, J(C,F)= 25.5 Hz, CH_2), 41.2 (t, J(C,F)= 26.3 Hz, CH_2), 42.4 (CH_2), 42.8 (CH_2), 114.2 (=CH_2), 120.0 (=CH_2), 124.1 (t, J(C,F)= 242 Hz, CF_2), 129.8 (t, J(C,F)= 5.9 Hz, =CH), 139.1 (=CH), 211.3 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.4 (2F, s, CF_2); HRMS (CI^+) m/z calcd for $C_{19}H_{33}F_2O$ $[M+H]^+$: 315.2494, found: 315.2490.

7,7-difluorocycloheptadec-9-en-1-one (18). Grubbs' 1st generation catalyst (4 mg, 0.005 mmol, 0.05 equiv.) was added to a stirred solution (protected from sunlight) of 4,4-difluorononadeca-1,18-dien-10-one **47** (31 mg, 0.10 mmol, 1.0 equiv.) in dry DCM (5.0 mL) under argon atmosphere at room temperature. The mixture was heated at reflux temperature for 3 h. Then, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 10:1) gave compound **18** (*E/Z* 3:1 inseparable mixture of diastereoisomers, 13 mg, 46%) as a colourless oil. ***(E)*-18.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.21-1.51 (12H, m, 6 x CH_2), 1.60-1.63 (4H, m, 2 x CH_2), 1.72-1.85 (2H, m, CH_2), 2.01-2.08 (2H, m, CH_2), 2.38-2.42 (4H, m, 2 x CH_2), 2.54 (2H, td, *J*(H,F)= 14.5 Hz, *J*(H,H)= 7.2 Hz, CH_2), 5.31-5.36 (1H, m, =CH), 5.51-5.55 (1H, m, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.8 (t, *J*(C,F)= 4.4 Hz, CH_2), 23.8 (2 x CH_2), 27.7 (CH_2), 28.2 (CH_2), 28.4 (CH_2), 28.5 (2 x CH_2), 31.9 (CH_2), 34.7 (t, *J*(C,F)= 25.1 Hz, CH_2), 40.2 (t, *J*(C,F)= 26.4 Hz, CH_2), 41.87 (CH_2), 42.4 (CH_2), 122.5 (t, *J*(C,F)= 6.8 Hz, =CH), 124.9 (t, *J*(C,F)= 242 Hz, CF_2), 136.3 (=CH), 212.7 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -95.9 (2F, s, CF_2); IR (thin film) ν (cm^{-1}) = 1707 (C=O); HRMS (CI^+) *m/z* calcd for $C_{17}H_{32}F_2ON$ $[M+NH_4]^+$: 304.2446, found: 304.2449; ***(Z)*-18.** ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.21-1.51 (12H, m, 6 x CH_2), 1.60-1.63 (4H, m, 2 x CH_2), 1.72-1.85 (2H, m, CH_2), 2.01-2.08 (2H, m, CH_2), 2.38-2.42 (4H, m, 2 x CH_2), 2.60 (2H, td, *J*(H,F)= 15.3 Hz, *J*(H,H)= 7.4 Hz, CH_2), 5.36-5.41 (1H, m, =CH), 5.55-5.61 (1H, m, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.7 (t, *J*(C,F)= 5.0 Hz, CH_2), 23.4 (CH_2), 23.7 (CH_2), 27.1 (CH_2), 27.9 (CH_2), 28.1 (CH_2), 28.31 (CH_2), 28.33 (CH_2), 28.6 (CH_2), 34.1 (t, *J*(C,F)= 26.3 Hz, CH_2), 35.3 (t, *J*(C,F)= 25.3 Hz, CH_2), 41.93 (CH_2), 42.2 (CH_2), 120.8 (t, *J*(C,F)= 6.3 Hz, =CH), 124.9 (t, *J*(C,F)= 242 Hz, CF_2), 134.3 (=CH), 212.1 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -95.1 (2F, s, CF_2).

7,7-difluorocycloheptadecan-1-one (19). A mixture of 5% Pd/C (21 mg, 0.011 mmol, 0.1 equiv.) in 0.9 mL of absolute EtOH was stirred for a few minutes under a small positive pressure of H_2. A solution of 7,7-difluorocycloheptadec-9-en-1-one **18** (32 mg, 0.11 mmol, 1.0 equiv.) in 1.0 mL of absolute EtOH was added to the above mixture and the reaction was stirred overnight under H_2 atmosphere at room temperature. Then, the catalyst was removed by filtration through a short pad of celite and washed with Et_2O (69 mL). The solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 13:1) gave compound **19** (29 mg, 91%) as a white solid; m.p. 50-52 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.40 (18H, m, 9 x CH_2), 1.60-1.66 (4H, m, 2 x CH_2), 1.77-1.89 (4H, m, 2 x CH_2), 2.41 (2H, t, *J*(H,H)= 6.7 Hz, CH_2), 2.43 (2H, t, *J*(H,H)= 6.9 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3 (t, *J*(C,F)= 5.2 Hz, CH_2), 22.1 (t, *J*(C,F)= 5.3 Hz, CH_2), 22.9 (CH_2), 23.8 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 27.8 (CH_2), 28.0 (CH_2), 28.1 (CH_2), 34.6 (t, *J*(C,F)= 25.5 Hz, CH_2), 34.8 (t, *J*(C,F)= 25.6 Hz, CH_2), 42.07 (CH_2), 42.09 (CH_2), 126.1 (t, *J*(C,F)= 240 Hz, CF_2), 211.9 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -92.3 (2F, s, CF_2); IR (thin film) ν (cm^{-1}) = 1707 (C=O); HRMS (CI^+) *m/z* calcd for $C_{17}H_{34}F_2ON$ $[M+NH_4]^+$: 306.2603, found: 306.2606.

8-(4-methoxybenzyloxy)oct-1-en-4-ol (51). Allylmagnesium bromide (81.6 mL, 1M solution in Et_2O, 81.6 mmol, 1.5 equiv.) was added to a solution of 5-(4-methoxybenzyloxy)pentanal **50** (12.1 g, 54.4 mmol, 1.0 equiv.) in dry THF (193 mL) at 0ºC. The resulting mixture was stirred overnight at room temperature. Then, sat. aq. NH_4Cl solution (96 mL) and Et_2O (48 mL) were sequentially added and the aqueous layer was extracted with Et_2O (3 x 96 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 4:1) gave compound **51** (6.57 g, 46%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.40-1.69 (6H, m, 3 x CH_2), 2.11-2.33 (2H, m, CH_2), 3.46 (2H, t, *J*(H,H)= 6.5 Hz, CH_2O), 3.63-3.68 (1H, m, OCH), 3.81 (3H, s, MeO), 4.44 (2H, s, CH_2O), 5.12-5.16 (2H, m, =CH_2), 5.83 (1H, ddt, *J*(H,H)= 16.2, 9.6, 7.9 Hz, =CH), 6.88 (2H, AA'XX', 2 x CH_{Ar}), 7.27

(2H, AA'XX', 2 x CH_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.4 (CH_2), 29.6 (CH_2), 36.5 (CH_2), 41.9 (CH_2), 55.3 (MeO), 69.9 (CH_2O), 70.5 (OCH), 72.6 (CH_2O), 113.7 (2 x CH_{Ar}), 118.1 (=CH_2), 129.2 (2 x CH_{Ar}), 130.6 (C_{Ar}), 134.8 (=CH), 159.1 (C_{Ar}); HRMS (ESI^+) *m/z* calcd for $C_{16}H_{24}NaO_3$ $[M+Na]^+$: 287.1618, found: 287.1610.

8-(4-methoxybenzyloxy)oct-1-en-4-ona (52). IBX (8.36 g, 30.0 mmol, 1.2 equiv.) was added to a solution of 8-(4-methoxybenzyloxy)oct-1-en-4-ol **51** (6.57 g, 24.9 mmol, 1.0 equiv.) in DMSO (118 mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O (274 mL) and EtOAc (274 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 274 mL) and brine (274 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **52** (5.17 g, 79%) as a colourless oil, which was used without further purification; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.58-1.67 (4H, m, 2 x CH_2), 2.47 (2H, t, *J*(H,H)= 7.2 Hz, CH_2), 3.16 (2H, d, *J*(H,H)= 7.0 Hz, CH_2), 3.45 (2H, t, *J*(H,H)= 6.2 Hz, CH_2O), 3.81 (3H, s, MeO), 4.43 (2H, s, CH_2O), 5.12-5.19 (2H, m, =CH_2), 5.92 (1H, ddt, *J*(H,H)= 17.2, 10.2, 7.0 Hz, =CH), 6.88 (2H, AA'XX', 2 x CH_{Ar}), 7.26 (2H, AA'XX', 2 x CH_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.4 (CH_2), 29.1 (CH_2), 42.0 (CH_2), 47.7 (CH_2), 55.3 (MeO), 69.6 (CH_2O), 72.5 (CH_2O), 113.7 (2 x CH_{Ar}), 118.8 (=CH_2), 129.2 (2 x CH_{Ar}), 130.6 (=CH), 130.7 (C_{Ar}), 159.1 (C_{Ar}), 208.7 (C=O); HRMS (ESI^+) *m/z* calcd for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1461, found: 285.1456.

1-((5,5-difluorooct-7-en-1-yloxy)methyl)-4-methoxybenzene (53). Neat DAST (9.2 mL, 70.0 mmol, 4.0 equiv.) was added to 8-(4-methoxybenzyloxy)oct-1-en-4-ona **52** (4.58 g, 17.5 mmol, 1.0 equiv.) under argon atmosphere. The mixture was heated at 50 °C and stirred overnight. Crude reaction was added portionwise to a biphasic mixture of sat. aq. $NaHCO_3$ solution (192 mL) and DCM (64 mL) at 0 °C. The aqueous layer was separated and extracted with DCM (3 x 32 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 15:1) gave compound **53** (1.69 g, 34%) as a colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.54-1.67 (4H, m, 2 x CH_2), 1.78-1.88 (2H, m, CH_2), 2.60 (2H, tdt, *J*(H,F)= 15.8 Hz, *J*(H,H)= 7.1, 1.2 Hz, CH_2), 3.46 (2H, t, *J*(H,H)= 6.2 Hz, CH_2O), 3.82 (3H, s, MeO), 4.44 (2H, s, CH_2O), 5.18-5.22 (2H, m, =CH_2), 5.80 (1H, ddt, *J*(H,H)= 16.4, 10.9, 7.1 Hz, =CH), 6.89 (2H, AA'XX', 2 x CH_{Ar}), 7.26 (2H, AA'XX', 2 x CH_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.0 (t, *J*(C,F)= 4.6 Hz, CH_2), 29.4 (CH_2), 35.7 (t, *J*(C,F)= 25.1 Hz, CH_2), 41.1 (t, *J*(C,F)= 26.2 Hz, CH_2), 55.3 (MeO), 69.5 (CH_2O), 72.6 (CH_2O), 113.8 (2 x CH_{Ar}), 120.0 (=CH_2), 124.2 (t, *J*(C,F)= 241 Hz, CF_2), 129.2 (2 x CH_{Ar}), 129.8 (t, *J*(C,F)= 5.9 Hz, =CH), 130.6 (C_{Ar}), 159.1 (C_{Ar}); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -97.3 (2F, s, CF_2); HRMS (ESI^+) *m/z* calcd for $C_{16}H_{22}F_2O_2Na$ $[M+Na]^+$: 307.1480, found: 307.1475.

5,5-difluorooct-7-en-1-ol (54). DDQ (2.75 g, 12.1 mmol, 2.0 equiv.) was added to a solution of 1-((5,5-difluorooct-7-en-1-yloxy)methyl)-4-methoxybenzene **53** (1.72 g, 6.06 mmol, 1.0 equiv.) in DCM (49 mL) and water (1.2 mL) at room temperature. The resulting mixture was stirred overnight. Then, aq. sat. $NaHCO_3$ solution (49 mL) was added and the aqueous layer was extracted with DCM (2 x 24 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 10:1) gave compound **54** (0.76 g, 78%) as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.49-1.61 (4H, m, 2 x CH_2), 1.76-1.89 (2H, m, CH_2), 2.29 (1H, s, OH), 2.58 (2H, tdt, *J*(H,F)= 15.8 Hz, *J*(H,H)= 7.2, 1.1 Hz, CH_2), 3.61 (2H, t, *J*(H,H)= 6.2 Hz, CH_2O), 5.16-5.20 (2H, m, =CH_2), 5.72-5.83 (1H, m, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.4 (t, *J*(C,F)= 4.6 Hz, CH_2), 32.1 (CH_2), 35.5 (t, *J*(C,F)= 25.0 Hz, CH_2), 41.0 (t, *J*(C,F)= 26.1 Hz, CH_2), 62.2 (CH_2O), 120.0 (=CH_2), 124.1 (t, *J*(C,F)= 241 Hz, CF_2), 129.6 (t,

J(C,F)= 5.9 Hz, =CH); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ = -97.5 (2F, s, CF_2); HRMS (ESI^+) *m/z* calcd for $C_8H_{14}F_2ONa$ $[M+Na]^+$: 187.0905, found: 187.0904.

5,5-difluorooct-7-enal (55). IBX (1.72 g, 6.16 mmol, 2.0 equiv.) was added to a solution of 5,5-difluorooct-7-en-1-ol **54** (505 mg, 3.1 mmol, 1.0 equiv.) in DMSO (15.0 mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O (34 mL) and EtOAc (34 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 34 mL) and brine (34 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **55** (361 mg, 72%) as a colourless oil, which was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.81-1.92 (4H, m, 2 x CH_2), 2.54 (2H, t, *J*(H,H)= 6.4 Hz, CH_2), 2.62 (2H, td, *J*(H,F)= 15.8, *J*(H,H)= 7.2 Hz, CH_2), 5.20-5.24 (2H, m, $=CH_2$), 5.75-5.84 (1H, m, =CH), 9.79 (1H, t, *J*(H,H)= 1.2 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.8 (t, *J*(C,F)= 4.8 Hz, CH_2), 35.0 (t, *J*(C,F)= 25.2 Hz, CH_2), 41.3 (t, *J*(C,F)= 26.0 Hz, CH_2), 43.2 (CH_2), 120.4 ($=CH_2$), 123.9 (t, *J*(C,F)= 241 Hz, CF_2), 129.5 (t, *J*(C,F)= 5.9 Hz, =CH), 201.6 (C=O); $^{19}F\{^{1}H\}$ NMR (470 MHz, $CDCl_3$) δ = -97.8 (2F, s, CF_2); HRMS (ESI^+) *m/z* calcd for $C_8H_{12}F_2O_2Na$ $[M+Na]^+$: 185.0748, found: 185.0745.

4,4-difluorononadeca-1,18-dien-8-ol (56). 11-bromoundec-1-ene (980 mg, 4.2 mmol, 4.0 equiv.) was added to a suspension of magnesium turnings (101 mg, 4.2 mmol, 4.0 equiv.) and iodine (traces) in dry THF (5.0 mL) under argon atmosphere at room temperature. The reaction was heated at reflux for 6 h. Then, the reaction was cooled to room temperature and was diluted with dry THF (15 mL). A solution of 5,5-difluorooct-7-enal **55** (170 mg, 1.1 mmol, 1.0 equiv.) was added to the above solution and the reaction was stirred overnight. Then, sat. aq. NH_4Cl solution (8.2 mL) and Et_2O (17 mL) were sequentially added and the aqueous layer was extracted with Et_2O (3 x 17 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 9:1) gave compound **56** (163 mg, 49%) as a white solid; m.p. 38-39 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.29-1.70 (20H, m, 10 x CH_2), 1.79-1.90 (2H, m, CH_2), 2.05 (2H, q, *J*(H,H)= 7.2 Hz, CH_2), 2.61 (2H, td, *J*(H,F)= 15.9, *J*(H,H)= 7.2 Hz, CH_2), 3.58-3.63 (1H, m, OCH), 4.92-5.02 (2H, m, $=CH_2$), 5.19-5.23 (2H, m, $=CH_2$), 5.76-5.86 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.4 (t, *J*(C,F)= 4.5 Hz, CH_2), 25.6 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.57 (CH_2), 29.63 (CH_2), 33.8 (CH_2), 35.9 (t, *J*(C,F)= 25.1 Hz, CH_2), 36.9 (CH_2), 37.5 (CH_2), 41.1 (t, *J*(C,F)= 26.0 Hz, CH_2), 71.6 (OCH), 114.1 ($=CH_2$), 120.0 ($=CH_2$), 124.2 (t, *J*(C,F)= 241 Hz, CF_2), 129.8 (t, *J*(C,F)= 5.9 Hz, =CH), 139.2 (=CH); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ = -97.3 (2F, s, CF_2); HRMS (ESI^+) *m/z* calcd for $C_{19}H_{34}F_2ONa$ $[M+Na]^+$: 339.2470, found: 339.2468.

4,4-difluorononadeca-1,18-dien-8-one (57). IBX (285 mg, 1.02 mmol, 2 equiv.) was added to a solution of 4,4-difluorononadeca-1,18-dien-8-ol **56** (160 mg, 0.51 mmol, 1.0 equiv.) in DMSO (2.6 mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O 6.2 mL) and EtOAc (6.2 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 6.2 mL) and brine (6.2 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **57** (129 mg, 81%) as a white waxy solid, which was used without further purification; m.p. 27 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.27-1.39 (12H, m, 6 x CH_2), 1.53-1.60 (2H, m, CH_2), 1.73-1.89 (4H, m, 2 x CH_2), 2.01-2.07 (2H, m, CH_2), 2.39 (2H, t, *J*(H,H)= 7.5 Hz, CH_2), 2.47 (2H, t, *J*(H,H)= 6.8 Hz, CH_2), 2.61 (2H, tdt, *J*(H,F)= 15.8 Hz, *J*(H,H)= 7.2, 1.2 Hz, CH_2), 4.92-5.03 (2H, m, $=CH_2$), 5.19-5.23 (2H, m, $=CH_2$), 5.74-5.87 (2H, m, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.4 (t, *J*(C,F)= 4.7 Hz, CH_2), 23.8 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.38 (2 x CH_2), 29.40 (CH_2), 33.8 (CH_2), 35.0 (t, *J*(C,F)= 25.1 Hz, CH_2), 41.1 (t, *J*(C,F)= 26.2 Hz, CH_2), 41.8 (CH_2), 42.8 (CH_2), 114.1 ($=CH_2$), 120.2

(=CH_2), 124.1 (t, *J*(C,F)= 241 Hz, CF_2), 129.6 (t, *J*(C,F)= 5.9 Hz, =CH), 139.2 (=CH), 210.5 (C=O); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ = -97.4 (2F, s, CF_2); HRMS (ESI^+) *m/z* calcd for $C_{19}H_{32}F_2ONa$ $[M+Na]^+$: 337.2313, found: 337.2307.

5,5-difluorocycloheptadec-7-en-1-one (58). Grubbs' 1st generation catalyst (22.5 mg, 0.03 mmol, 0.05 equiv.) was added to a stirred solution (protected from sunlight) of 4,4-difluorononadeca-1,18-dien-8-one **57** (172 mg, 0.55 mmol, 1.0 equiv.) in dry DCM (110 mL) under argon atmosphere at room temperature. The mixture was heated at reflux temperature for 3 h. Then, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 14:1) gave compound **58** (*E/Z* 2:1 inseparable mixture of diastereoisomers, 100 mg, 64%) as a colourless oil. ***(E)*-58**. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.12-1.43 (12H, m, 6 x CH_2), 1.64-1.86 (6H, m, 3 x CH_2), 2.03-2.09 (2H, m, CH_2), 2.37-2.40 (2H, m, CH_2), 2.49-2.53 (2H, m, CH_2), 2.56 (2H, td, *J*(H,F)= 15.0, *J*(H,H)= 7.4 Hz, CH_2), 5.30-5.42 (1H, m, =CH), 5.50-5.56 (1H, m, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.7 (t, *J*(C,F)= 4.6 Hz, CH_2), 23.1 (CH_2), 27.1 (CH_2), 27.3 (CH_2), 28.4 (CH_2), 28.5 (CH_2), 28.62 (CH_2), 28.65 (CH_2), 31.8 (CH_2), 34.4 (t, *J*(C,F)= 25.3 Hz, CH_2), 40.7 (t, *J*(C,F)= 26.4 Hz, CH_2), 42.0 (CH_2), 42.1 (CH_2), 121.8 (t, *J*(C,F)= 6.8 Hz, =CH), 124.7 (t, *J*(C,F)= 242 Hz, CF_2), 136.5 (=CH), 211.0 (C=O); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -97.0 (2F, s, CF_2); IR (thin film) ν (cm^{-1}) = 1704 (C=O); HRMS (ESI^+) *m/z* calcd for $C_{17}H_{28}F_2ONa$ $[M+Na]^+$: 309.2000, found: 309.1998; ***(Z)*-58**. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.12-1.43 (12H, m, 6 x CH_2), 1.64-1.86 (6H, m, 3 x CH_2), 2.03-2.09 (2H, m, CH_2), 2.37-2.40 (2H, m, CH_2), 2.49-2.53 (2H, m, CH_2), 2.61 (2H, td, *J*(H,F)= 15.2, *J*(H,H)= 7.1 Hz, CH_2), 5.30-5.42 (1H, m, =CH), 5.50-5.56 (1H, m, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 16.1 (t, *J*(C,F)= 4.5 Hz, CH_2), 23.2 (CH_2), 26.6 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 28.17 (CH_2), 28.19 (CH_2), 28.65 (CH_2), 28.68 (CH_2), 34.6 (t, *J*(C,F)= 25.3 Hz, CH_2), 35.2 (t, *J*(C,F)= 25.9 Hz, CH_2), 42.19 (CH_2), 42.25 (CH_2), 120.7 (t, *J*(C,F)= 6.1 Hz, =CH), 124.6 (t, *J*(C,F)= 242 Hz, CF_2), 134.7 (=CH), 211.2 (C=O); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -97.6 (2F, s, CF_2).

5,5-difluorocycloheptadecan-1-one (20). A mixture of 5% Pd/C (14 mg, 0.01 mmol, 0.1 equiv.) in 1.1 mL of absolute EtOH was stirred for a few minutes under a small positive pressure of H_2. A solution of 5,5-difluorocycloheptadec-7-en-1-one **58** (18 mg, 0.06 mmol, 1.0 equiv.) in 1.2 mL of absolute EtOH was added to the above mixture and the reaction was stirred overnight under H_2 atmosphere at room temperature. Then, the catalyst was removed by filtration through a short pad of celite and washed with Et_2O (84 mL). The solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 14:1) gave compound **20** (16 mg, 87%) as a white solid; m.p. 52-54 ºC; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.47 (18H, m, 9 x CH_2), 1.60-1.65 (2H, m, CH_2), 1.76-1.90 (6H, m, 3 x CH_2), 2.41 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 2.50 (2H, t, *J*(H,H)= 6.5 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.2 (t, *J*(C,F)= 4.9 Hz, CH_2), 21.6 (t, *J*(C,F)= 5.0 Hz, CH_2), 23.7 (CH_2), 23.78 (CH_2), 26.84 (CH_2), 27.0 (CH_2), 27.26 (CH_2), 27.27 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 28.1 (CH_2), 34.5 (t, *J*(C,F)= 25.6 Hz, CH_2), 35.3 (t, *J*(C,F)= 25.0 Hz, CH_2), 41.8 (CH_2), 42.2 (CH_2), 125.8 (t, *J*(C,F)= 241 Hz, CF_2), 211.4 (C=O); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -94.8 (2F, s, CF_2); IR (thin film) ν (cm^{-1}) = 1707 (C=O); HRMS (ESI^+) *m/z* calcd for $C_{17}H_{30}F_2ONa$ $[M+Na]^+$: 311.2157, found: 311.2152.

1,3-bis(2-(hept-6-en-1-yl)-1,3-dithian-2-yl)propane (61). *n*-BuLi (4.82 mL, 1.5 M solution in hexanes, 7.23 mmol, 2.0 equiv.) was added to a solution of 1,3-di(1,3-dithian-2-yl)propane **60** (1.01 g, 3.61 mmol, 1.0 equiv.) in dry THF (36.1 mL) under argon atmosphere at -30 ºC. The mixture was gradually warmed to 0 ºC and stirred for 2 h. Then, 7-bromohept-1-ene (1.1 mL, 7.23 mmol, 2.0 equiv.) was added dropwise to the above solution at -30 ºC and the mixture was stirred overnight at room temperature. A further aliquot of *n*-BuLi (4.82 mL, 1.5 M solution in hexanes, 7.23 mmol, 2.0 equiv.) was added at -30 ºC and stirred for 2h at room temperature. 7-bromohept-1-ene (1.1 mL, 7.23 mmol, 2.0

equiv.) was added dropwise at -30 ºC and the mixture was stirred overnight at room temperature. A final aliquot of *n*-BuLi (2.41 mL, 1.5 M solution in hexanes, 3.61 mmol, 1.0 equiv.) was added at -30 ºC and stirred for 1h at room temperature. 7-bromohept-1-ene (0.5 mL, 3.61 mmol, 1.0 equiv.) was added dropwise at -30 ºC and the mixture was stirred for 6h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (25 mL) and extracted with Et_2O (4 x 25 mL). The organic extracts were washed with brine (40 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 15:1) gave compound **61** (1.02 g, 60%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.30-1.36 (4H, m, 2 x CH_2), 1.39-1.47 (8H, m, 4 x CH_2), 1.54-1.61 (2H, m, CH_2), 1.86-1.91 (8H, m, 4 x CH_2), 1.94-1.98 (4H, m, 2 x CH_2), 2.04-2.08 (4H, m, 2 x CH_2), 2.80-2.82 (8H, m, 4 x CH_2S), 4.93-5.03 (4H, m, 2 x =CH_2), 5.81 (2H, ddt, *J*(H,H)= 17.0, 10.2, 6.7 Hz, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.0 (CH_2), 23.9 (2 x CH_2), 25.4 (2 x CH_2), 26.0 (4 x CH_2S), 28.7 (2 x CH_2), 29.2 (2 x CH_2), 33.6 (2 x CH_2), 38.1 (2 x CH_2), 38.2 (2 x CH_2), 53.1 (2 x CS_2), 114.3 (2 x =CH_2), 138.9 (2 x =CH); HRMS (CI^+) *m*/*z* calcd for $C_{25}H_{45}S_4$ $[M+H]^+$: 473.2399, found: 473.2394.

1,5,11,15-tetrathiadispiro[5.3.5.12]heptacos-21-ene (62). Grubbs' 1st generation catalyst (44 mg, 0.05 mmol, 0.05 equiv.) was added to a stirred solution (protected from sunlight) of 1,3-bis(2-(hept-6-en-1-yl)-1,3-dithian-2-yl)propane **62** (500 mg, 1.06 mmol, 1.0 equiv.) in dry DCM (53 mL) under argon atmosphere at room temperature. The mixture was heated at reflux temperature for 2 h. Then, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 15:1) gave compound **62** (*E/Z* 2:1 inseparable mixture of diastereoisomers, 275 mg, 58%) as a colourless oil; ***(E)*-62**. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.55 (14H, m, 7 x CH_2), 1.86-2.05 (16H, m, 8 x CH_2), 2.80-2.82 (8H, m, 4 x CH_2S), 5.38 (2H, t, *J*(H,H)= 3.7 Hz, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.9 (CH_2), 23.8 (2 x CH_2), 25.7 (2 x CH_2), 26.0 (4 x CH_2S), 27.9 (2 x CH_2), 28.9 (2 x CH_2), 31.0 (2 x CH_2), 37.1 (2 x CH_2), 37.4 (2 x CH_2), 52.7 (2 x CS_2), 130.8 (2 x =CH); ***(Z)*-62**. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.55 (14H, m, 7 x CH_2), 1.86-2.05 (16H, m, 8 x CH_2), 2.80-2.82 (8H, m, 4 x CH_2S), 5.34 (2H, t, *J*(H,H)= 4.5 Hz, 2 x =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.6 (CH_2), 22.0 (2 x CH_2), 25.4 (2 x CH_2), 25.8 (2 x CH_2), 26.0 (4 x CH_2S), 27.5 (2 x CH_2), 27.9 (2 x CH_2), 37.2 (2 x CH_2), 37.4 (2 x CH_2), 52.6 (2 x CS_2), 130.2 (2 x =CH); HRMS (CI^+) *m*/*z* calcd for $C_{23}H_{41}S_4$ $[M+H]^+$: 445.2086, found: 445.2078.

1,5,11,15-tetrathiadispiro[5.3.5.12]heptacosan-21-ol (63). Borane dimethyl sulfide complex (0.36 mL, 2M solution in THF, 0.72 mmol, 1.25 equiv.) was added to a stirred solution of 1,5,11,15-tetrathiadispiro[5.3.5.12]heptacos-21-ene **62** (256 mg, 0.58 mmol, 1.0 equiv.) in dry THF (6.0 mL) under argon atmosphere at 0ºC. The solution was warmed to room temperature and stirred overnight. Then, EtOH (0.45 mL), aq. NaOH (2 M, 0.45 mL) and aq. H_2O_2 (30% w/w, 0.45 mL) were sequentially added and the reaction mixture was stirred for 4 h. After evaporation of the volatiles, H_2O (2.0 mL) was added and the solution was extracted with EtOAc (3 x 12 mL). The combined organic layers were washed with brine (12 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to gave compound **63** (260 mg, 97%) as a colourless oil, which was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.30-1.57 (20H, m, 10 x CH_2), 1.83-2.00 (12H, m, 6 x CH_2), 2.75-2.85 (8H, m, 4 x CH_2S), 3.66 (1H, quint, *J*(H,H)= 5.3 Hz, OCH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.7 (CH_2), 22.3 (CH_2), 22.8 (CH_2), 23.2 (CH_2), 23.6 (CH_2), 25.66 (CH_2), 25.72 (CH_2), 26.0 (4 x CH_2S), 27.5 (CH_2), 27.9 (CH_2), 28.0 (CH_2), 34.9 (CH_2), 35.9 (CH_2), 37.2 (CH_2), 37.3 (CH_2), 37.66 (CH_2), 37.75 (CH_2), 52.6 (2 x CS_2), 70.9 (COH); HRMS (CI^+) *m*/*z* calcd for $C_{23}H_{41}S_4$ $[M+H]^+$: 445.2086, found: 445.2078.

7,7,11,11-tetrafluorocycloheptadecan-1-ol (64). 70% hydrogen fluoride-pyridine (0.69 mL, 26.5 mmol, 120 equiv.) was added to a stirred solution of *N*-iodosuccinimide (398 mg, 1.77 mmol, 8 equiv.)

in dry DCM (3.5 mL) under argon atmosphere at -78 ºC. The resulting mixture was stirred for 10 min at -78 ºC. Then, a solution of 1,5,11,15-tetrathiadispiro[5.3.5.12]heptacosan-21-ol **63** (102 mg, 0.22 mmol, 1 equiv.) in dry DCM (2.7 mL) was added dropwise to the mixture over 10 min. The reaction mixture was stirred at -78 ºC for 4 h and gradually warmed to room temperature overnight. The crude reaction was added portionwise to a biphasic mixture of sat. aq. $NaHCO_3$ solution (24 mL) and DCM (12 mL) at 0 ºC. The aqueous layer was separated and extracted with DCM (3 x 16 mL). The organic extracts were washed with 10% w/v sat. aq. $Na_2S_2O_3$ solution (2 x 24 mL), brine (24 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 3:1) gave compound **64** (10 mg, 14%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.36-1.56 (20H, m, 10 x CH_2), 1.82-1.97 (8H, m, 4 x CH_2), 3.68-3.71 (1H, m, OCH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.4 (t, J(C,F)= 6.2 Hz, CH_2), 21.16 (t, J(C,F)= 5.8 Hz, CH_2), 21.25 (t, J(C,F)= 5.6 Hz, CH_2), 23.0 (CH_2), 23.1 (CH_2), 27.2 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 34.3 (t, J(C,F)= 25.5 Hz, CH_2), 34.6 (t, J(C,F)= 25.4 Hz, CH_2), 34.7 (CH_2), 34.9 (t, J(C,F)= 26.2 Hz, CH_2), 35.0 (t, J(C,F)= 26.4 Hz, CH_2), 35.9 (CH_2), 70.74 (OCH), 125.5 (t, J(C,F)= 239 Hz, 2 x CF_2); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -92.4-93.5 (2F, AB, CF_2), -92.68-92.69 (2F, AB, CF_2); HRMS (CI^+) m/z calcd for $C_{17}H_{34}F_4ON$ $[M+NH_4]^+$: 344.2571, found: 344.2564.

7,7,11,11-tetrafluorocycloheptadecan-1-one (21). IBX (31 mg, 0.11 mmol, 2.0 equiv.) was added to a solution of 7,7,11,11-tetrafluorocycloheptadecan-1-ol **64** (18 mg, 0.05 mmol, 1.0 equiv.) in DMSO (0.5 mL) at room temperature. The resulting mixture was stirred overnight. Then, H_2O (1.5 mL) and EtOAc (1.5 mL) were sequentially added and the precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with H_2O (2 x 1.5 mL) and brine (1.5 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (hexanes/EtOAc 8:1) gave compound **21** (10 mg, 59%) as a white solid; m.p. 43-45 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.26-1.33 (2H, m, CH_2), 1.37-1.48 (8H, m, 4 x CH_2), 1.51-1.57 (2H, m, CH_2), 1.60-1.67 (4H, m, 2 x CH_2), 1.78-1.97 (8H, m, 4 x CH_2), 2.42 (2H, t, J(H,H)= 6.7 Hz, CH_2), 2.43 (2H, t, J(H,H)= 6.7 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.4 (t, J(C,F)= 5.8 Hz, CH_2), 21.75 (t, J(C,F)= 4.9 Hz, CH_2), 21.85 (t, J(C,F)= 5.1 Hz, CH_2), 22.9 (CH_2), 23.4 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 28.1 (CH_2), 34.1 (t, J(C,F)= 25.4Hz, CH_2), 34.68 (t, J(C,F)= 26.2 Hz, CH_2), 34.70 (t, J(C,F)= 25.6 Hz, 2 x CH_2), 42.0 (CH_2), 42.1 (CH_2), 125.4 (t, J(C,F)= 241 Hz, CF_2), 125.6 (t, J(C,F)= 240 Hz, CF_2), 211.8 (C=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -92.6 (2F, s, CF_2), -93.0 (2F, s, CF_2); IR (thin film) ν (cm^{-1}) = 1705 (C=O); HRMS (ESI^+) m/z calcd for $C_{17}H_{32}F_4ON$ $[M+NH_4]^+$: 342.2415, found: 342.2417.

(*R*)-3-methylcyclopentadec-6-en-1-one (66). Grubbs catalyst (2nd generation, 30 mg, 0.035 mmol, 8 mol%) was added to a solution of (*R*)-2,6-dimethyloctadeca-2,17-dien-8-one **65** (124 mg, 0.42 mmol, 1.0 eq) in dry DCE (400 mL) in a foil covered flask at r.t. under argon. The reaction mixture was heated at 65 °C for 17 h, then cooled to r.t. and the solvent was removed *in vacuo*. Purification of the residue by column chromatography using silica gel (ehtyl acetate/pet.ether 1:30) gave compound **66** (*E/Z* 2:1, inseparable mixture of diastereoisomers, 30 mg, 30%) as a colorless oil; $[\alpha]_D$ -8.2° (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.91 and 0.94 (3H, d, J(H,H)= 6.5 Hz, CH_3), 1.22-1.37 (12H, m, CH_2), 1.58-1.66 (2H, m, CH_2), 2.02-2.15 (6H, m, CH_2), 2.33-2.39 (3H, m, CH_2), 5.33-5.35 (2H, m, CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.8 (CH_3), 23.3 (CH_2), 26.8(CH_2), 27.1 (CH_2), 27.7 (CH_2), 27.9 (CH_2), 28.4 (CH), 29.5 (CH_2), 31.7 (CH_2), 36.5 (CH_2), 42.3 (CH_2), 51.3 (CH_2), 130.7 (=CH), 131.5 (=CH), 212.7 (C=O). These data are in good agreement with the literature values.[6]

(*R*)-Muscone (2). A solution of (*R*)-3-methylcyclopentadec-6-en-1-one **66** (45 mg, 0.19 mmol, 1.0 eq) and palladium on activated carbon (5 wt% on carbon, 40 mg, 10 mol%) in methanol (2 mL) was stirred under a hydrogen atmosphere (1 atm) for 22 h. The reaction mixture was filtered through celite and the

celite was washed with methanol. The solvent was removed *in vacuo* to give (*R*)-muscone **2** (43 mg, 95%) as a colourless oil that was used without further purification. $[\alpha]_D$ -9.8° (c 0.55, $CHCl_3$), [*lit.*[12] $[\alpha]_D$ -12.4° (c 0.76, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.18-1.67 (22H, m, CH_2), 2.03-2.04 (1H, m, CH), 2.19 (1H, dd, *J*(H,H)= 5.2 and 15.0 Hz), 2.37-3.04 (3H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.2 (CH_3), 23.2 (CH_2), 25.2 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 27.2 (CH_2), 27.7 (CH_2), 29.2 (CH), 35.7 (CH_2), 42.2 (CH_2), 50.6 (CH_2), 212.2 (C=O). These data are in good agreement with the literature values.[6]

10-((4-Methoxyphenyl)methoxy)dec-1-en-5-ol (76). Iodine (trace) was added to a suspension of magnesium turnings (1.96 g, 80.6 mmol, 2.0 eq) in dry diethyl ether (80 mL) under argon at r.t. and stirred until the reaction turned colourless. A solution of 4-bromo-1-butene (8.2 mL, 80.6 mmol, 2.0 eq) in dry diethyl ether (20 mL) was added at a rate sufficient to maintain autoreflux and stirred for 30 min after addition was complete. The reaction mixture was diluted with diethyl ether (180 mL), then cooled to 0 °C and a solution of 6-((4-methoxyphenyl)methoxy)hexanal **75** (9.5 g, 40.3 mmol, 1.0 eq) in dry diethyl ether (20 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with sat. ammonium chloride solution (250 mL) and extracted with diethyl ether (2 x 250 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:4) gave compound **76** (6.9 g, 52%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.32-1.65 (11H, m, CH_2, OH), 2.11-2.25 (2H, m, CH_2), 3.45 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 3.59-3.64 (1H, m, CH), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 4.97-5.08 (2H, m, CH_2), 5.85 (1H, ddt, *J*(H,H)= 17.0, 10.2, 6.6, CH), 6.87-6.90 (2H, m, ArH), 7.25-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.7 (CH_2), 26.5 (CH_2), 29.9 (CH_2), 30.3 (CH_2), 36.7 (CH_2), 37.6 (CH_2), 55.5 (CH_3), 70.2 (CH_2), 71.6 (CH), 72.7 (CH_2), 113.9 (CH), 115.0 (CH_2), 129.5 (CH), 130.9 (C), 138.8 (CH), 159.3 (C); HRMS: *m*/*z* calcd for $C_{18}H_{28}Na_1O_3$ $[M+Na]^+$: 315.1931; found: 315.1921.

10-((4-Methoxyphenyl)methoxy)dec-1-en-5-one (77). DMP (10.2 g, 24.1 mmol, 1.2 eq) was added to a solution of 10-((4-methoxyphenyl)methoxy)dec-1-en-5-ol **76** (5.88 g, 20.1 mmol, 1.0 eq) in DCM (300 mL) at r.t. and stirred for 2 h. The reaction mixture was diluted with diethyl ether (200 mL) and sat. $NaHCO_3$ solution (250 mL). Sodium thiosulfate (20 g) was added and the reaction mixture was stirred vigorously for 30 min. The organic layer was separated and washed with brine (300 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give compound **77** (5.8 g) as a colourless oil that was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.33-1.39 (2H, m, CH_2), 1.56-1.64 (4H, m, CH_2), 2.30-2.34 (2H, m, CH_2), 2.41 (2H, t, *J*(H,H)= 7.5 Hz, CH_2), 2.50 (2H, t, *J*(H,H)= 7.6 Hz, CH_2), 3.44 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 4.97-5.05 (2H, m, CH_2), 5.81 (1H, ddt, *J*(H,H)= 16.8, 10.1, 6.6 Hz, CH), 6.87-6.90 (2H, m, ArH), 7.25-7.27 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.8 (CH_2), 26.1 (CH_2), 28.0 (CH_2), 29.7 42.0 (CH_2), 43.0 (CH_2), 55.5 (CH_3), 70.0 (CH_2), 72.8 (CH_2), 114.0 (CH), 115.4 (CH_2), 129.4 (CH), 130.9 (C), 137.4 (CH), 159.3 (C), 210.5 (CO); HRMS: *m*/*z* calcd for $C_{18}H_{26}Na_1O_3$ $[M+Na]^+$: 313.1774; found: 313.1764.

1-(((6,6-Difluorodec-9-en-1-yl)oxy)methyl)-4-methoxybenzene (78). A solution of 10-((4-methoxyphenyl)methoxy)dec-1-en-5-one **77** (5.8 g, 20.1 mmol, 1.0 eq) in DAST (10.6 mL, 80.4 mmol, 4.0 eq) was heated at 50 °C under argon for 18 h. The reaction mixture was cooled to r.t. and poured onto sat. $NaHCO_3$ solution (200 mL). The reaction mixture was extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl

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acetate/pet. ether 1:19) gave compound **78** (4.2 g, 67%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.39-1.54 (4H, m, CH_2), 1.62 (2H, tt, J(H,H)= 7.4, 6.6 Hz, CH_2), 1.77-1.95 (4H, m, CH_2), 2.21-2.26 (2H, m CH_2), 3.45 (2H, t, J(H,H)= 6.5 Hz, CH_2), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 5.00-5.09 (2H, m, CH_2), 5.83 (1H, ddt, J(H,H)= 16.7, 10.2, 6.5 Hz, CH_2), 6.87-6.90 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.4 (t, J(C,F)= 4.5 Hz, CH_2), 26.3 (CH_2), 26.7 (t, J(C,F)= 5.2 Hz, CH_2), 29.8 (CH_2), 35.8 (t, J(C,F)= 25.5 Hz, CH_2), 36.6 (t, J(C,F)= 25.3 Hz, CH_2), 55.5 (CH_3), 70.0 (CH_2), 72.8 (CH_2), 114.0 (CH), 115.4 (CH_2), 125.2 (t, J(C,F)= 240.7 Hz, CF_2), 129.5 (CH), 130.9 (C), 137.3 (CH), 159.3 (C); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -98.2 (2F, s, CF_2); HRMS: m/z calcd for $C_{18}H_{26}F_2Na_1O_2$ $[M+Na]^+$: 335.1793; found: 335.1785.

6,6-Difluorodec-9-en-1-ol (79). DDQ (4.6 g, 20.0 mmol, 1.5 eq) was added to a solution of 1-(((6,6-difluorodec-9-en-1-yl)oxy)methyl)-4-methoxybenzene **78** (4.2 g, 13.4 mmol, 1.0 eq) in DCM (200 mL) and water (2 mL) at r.t. and stirred for 1 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (250 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:19) gave compound **79** (2.1 g, 81%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.39-1.45 (3H, m, CH_2, OH), 1.48-1.55 (2H, m ,CH_2), 1.57-1.63 (2H, m, CH_2), 1.79-1.97 (4H, m, CH_2), 2.22-2.26 (2H, m, CH_2), 3.66 (2H, t, J(H,H)= 6.5 Hz, CH_2), 4.99-5.08 (2H, m, CH_2), 5.83 (1H, ddt, J(H,H)= 16.8, 10.3, 6.4 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.3 (t, J(C,F)= 4.7 Hz, CH_2), 25.8 (CH_2), 26.7 (t, J(C,F)= 5.1 Hz, CH_2), 32.7 (CH_2), 35.8 (t, J(C,F)= 25.7 Hz, CH_2), 36.6 (t, J(C,F)= 25.4 Hz, CH_2), 62.9 (CH_2), 115.4 (CH_2), 125.1 (t, J(C,F)= 240.8 Hz, CF_2), 137.3 (CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -98.3 (2F, s, CF_2); HRMS: m/z calcd for $C_{10}H_{18}F_2Na_1O_1$ $[M+Na]^+$: 215.1218; found: 215.1215.

10-Bromo-5,5-difluorodec-1-ene (80). Carbon tetrabromide (3.7 g, 11.2 mmol, 1.1 eq) and triphenylphosphine (2.9 g, 11.2 mmol, 1.1 eq) were added to a solution of 6,6-difluorodec-9-en-1-ol **79** (1.95 g, 10.1 mmol, 1.0 eq) in dry DCM (200 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 1 h, then warmed to r.t. and stirred for 18 h. The solvent was removed *in vacuo*. Purification of the residue by column chromatography using silica gel (ethyl acetate/pet. ether 1:19) gave compound **80** (1.92 g, 75%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.50-1.55 (4H, m, CH_2), 1.80-0.97 (6H, m ,CH_2), 2.22-2.27 (2H, m, CH_2), 3.42 (2H, t, J(H,H)= 6.7 Hz, CH_2), 5.00-5.09 (2H, m, CH_2), 5.83 (1H, ddt, J(H,H)= 16.8, 10.2, 6.5 Hz, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.7 (t, J(C,F)= 4.7 Hz, CH_2), 26.7 (t, J(C,F)= 5.0 Hz, CH_2), 28.1 (CH_2), 33.8 (CH_2), 35.9 (t, J(C,F)= 25.5 Hz, CH_2), 36.5 (t, J(C,F)= 25.5 Hz, CH_2), 115.5 (CH_2), 125.0 (t, J(C,F)= 240.7 Hz, CF_2), 137.2 (CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -98.5 (2F, s, CF_2).

(5*R*)-13,13-Difluoro-5-methylheptadeca-1,16-diene-7-ol (82). Iodine (trace) was added to a suspension of magnesium turnings (76 mg, 3.1 mmol, 2.0 eq) in dry diethyl ether (5 mL) under argon at r.t. and stirred until the reaction turned colourless. A solution of 10-bromo-5,5-difluorodec-1-ene **80** (0.8 g, 3.1 mmol, 2.0 eq) in dry diethyl ether (5 mL) was added and the reaction was heated at reflux for 2 h. The reaction mixture was cooled to r.t. and diluted with diethyl ether (10 mL), then cooled to 0 °C and a solution of **81** (0.2 g, 1.6 mmol, 1.0 eq) in dry diethyl ether (10 mL) was added. The reaction mixture was stirred at 0 °C for 30 min, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with sat. ammonium chloride solution (60 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:9) gave compound **82** (0.20 g, 43%) as a colourless oil, as a 1:1 mixture of diastereoisomers; $[\alpha]_D$ -2.1° (c 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.92 and 0.93 (3H, d, J(H,H)= 6.0 Hz, CH_3), 1.15-1.72 (14H, m, CH, CH_2, OH), 1.78-1.96 (4H, m, CH_2), 1.99-2.16 (2H, m,

CH_2), 2.22-2.27 (2H, m, CH_2), 3.66-3.73 (1H, m, CH), 4.94-5.08 (4H, m, CH_2), 5.78-5.87 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.3 and 20.4 (CH_3), 22.5 (t, J(C,F)= 4.4 Hz, CH_2), 25.5 and 25.7 (CH_2), 26.7 (t, J(C,F)= 5.1 Hz, CH_2), 29.0 and 29.3 (CH), 29.6 (CH_2), 31.4 and 31.5 (CH_2), 35.8 (t, J(C,F)= 25.7 Hz, CH_2), 36.6 (t, J(C,F)= 25.2 Hz, CH_2), 37.2 (CH_2), 37.8 and 38.4 (CH_2), 45.1 and 45.4 (CH_2), 69.7 and 70.0 (CH), 114.4 and 114.5 (CH_2), 115.4 (CH_2), 125.7 (t, J(C,F)= 240.7 Hz, CF_2), 137.3 (CH), 139.3 (CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -98.2 (2F, s, CF_2); HRMS: m/z calcd for $C_{18}H_{32}F_2Na_1O_1$ $[M+Na]^+$: 325.2313; found: 325.2304.

(5*R*)-13,13-Difluoro-5-methylheptadeca-1,16-diene-7-one (83). DMP (0.38 g, 0.9 mmol, 1.5 eq) was added to a solution of (5*R*)-13,13-difluoro-5-methylheptadeca-1,16-diene-7-ol **82** (0.18 g, 0.6 mmol, 1.0 eq) in DCM (10 mL) at r.t. and stirred for 1 h. The reaction mixture was diluted with diethyl ether (10 mL) and sat. $NaHCO_3$ solution (100 mL). Sodium thiosulfate (0.8 g) was added and the reaction mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was re-extracted with diethyl ether (20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give compound **83** (0.18 g) as a yellow oil that was used without further purification; $[\alpha]_D$ +2.2° (c 0.59, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.90 (3H, d, J(H,H)= 6.5 Hz, CH_3), 1.22-1.42 (4H, m, CH_2), 1.45-1.51 (2H, m, CH_2), 1.56-1.62 (2H, m, CH_2), 1.77-1.95 (4H, m, CH_2), 2.01-2.13 (3H, m, CH_2, CH), 2.20-2.26 (3H, m, CH_2, CH_AH$_B$), 2.37-2.41 (3H, m, CH_2, CH$_A$H$_B$), 4.94-5.08 (4H, m, CH_2), 5.76-5.86 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.9 (CH_3), 22.3 (t, J(C,F)= 4.6 Hz, CH_2), 23.6 (CH_2), 26.7 (t, J(C,F)= 5.1 Hz, CH_2), 29.0 (CH), 29.1 (CH_2), 31.4 (CH_2), 35.8 (t, J(C,F)= 25.5 Hz, CH_2), 36.2 (CH_2), 36.5 (t, J(C,F)= 25.2 Hz, CH_2), 43.2 (CH_2), 50.4 (CH_2), 114.7 (CH_2), 115.4 (CH_2), 125.1 (t, J(C,F)= 241.3 Hz, CF_2), 137.3 (CH), 138.9 (CH), 211.0 (CO); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -98.4 (2F, s, CF_2); HRMS: m/z calcd for $C_{18}H_{30}F_2Na_1O_1$ $[M+Na]^+$: 323.2157; found: 323.2150.

(3*R*)-10,10-Difluoro-3-methylcyclopentadec-6-en-1-one (84). Grubbs catalyst (1st generation, 25 mg, 0.03 mmol, 6 mol%) was added to a solution of (5*R*)-13,13-difluoro-5-methylheptadeca-1,16-diene-7-one **83** (0.16 g, 0.53 mmol, 1.0 eq) in dry DCM (200 mL) in a foil covered flask at r.t. under argon. The reaction mixture was heated at 45 °C for 17 h, then cooled to r.t. and the solvent was removed *in vacuo*. Purification of the residue by column chromatography using silica gel (ethyl acetate/pet. ether 1:49) gave compound **(*E*)-84** (39 mg, 27%) as a pale brown oil and compound **(*Z*)-84** (36 mg, 25%) as a pale brown, waxy solid. **(*E*)-84.** $[\alpha]_D$ +14.4° (c 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, J(H,H)= 6.7 Hz, CH_3), 1.21-1.45 (6H, m, CH_2), 1.52-1.60 (1H, m, CH_AH$_B$), 1.66-1.86 (3H, m, CH_AH$_B$, CH_2), 1.91-2.14 (5H, m, CH_2, CH), 2.15-2.24 (3H, m, CH_AH$_B$, CH_2), 2.35-2.46 (3H, m, CH_AH$_B$, CH_2), 5.39-5.49 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.1 (CH_3), 20.6 (t, J(C,F)= 5.0 Hz, CH_2), 22.5 (CH_2), 26.5-26.6 (m, CH_2), 27.2 (CH_2), 28.9 (CH_2), 29.3 (CH), 35.1 (t, J(C,F)= 25.8 Hz, CH_2), 35.2 (t, J(C,F)= 25.4 Hz, CH_2), 35.6 (CH_2), 41.4 (CH_2), 50.5 (CH_2), 125.9 (t, J(C,F)= 240.3 Hz, CF_2), 129.9 (CH), 131.7 (CH), 212.3 (CO); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -91.2 (1F, d, J(F,F)= 242.5 Hz, CF_AF$_B$), -92.5 (1F, d, J(F,F)= 242.5 Hz, CF$_A$F$_B$); IR (thin film) ν (cm^{-1}) = 1709 (C=O); **(*Z*)-84.** $[\alpha]_D$ -7.3° (c 0.91, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.99 (3H, d, J(H,H)= 6.8 Hz, CH_3), 1.21-1.49 (8H, m, CH_2), 1.57-1.90 (4H, m, CH_2), 1.93-2.15 (5H, m, CH_2, CH), 2.25-2.53 (4H, m, CH_2), 5.35-5.45 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.4 (CH_3), 21.5 (t, J(C,F)= 5.8 Hz, CH_2), 21.8 (CH_2), 21.9 (t, J(C,F)= 5.4 Hz, CH_2), 24.8 (CH_2), 28.4 (CH_2), 29.5 (CH), 34.8 (t, J(C,F)= 25.5 Hz, CH_2), 35.6 (t, J(C,F)= 25.5 Hz, CH_2), 36.6 (CH_2), 41.6 (CH_2), 50.4 (CH_2), 125.9 (t, J(C,F)= 241.1 Hz, CF_2), 128.4 (CH), 130.7 (CH), 211.1 (CO); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -91.5 (1F, d, J(F,F)= 243.6 Hz, CF_AF$_B$), -92.0 (1F, d, J(F,F)= 243.6 Hz, CF$_A$F$_B$); IR (thin film) ν (cm^{-1}) = 1710 (C=O); HRMS: m/z calcd for $C_{16}H_{26}F_2Na_1O_1$ $[M+Na]^+$: 295.1844; found: 295.1839.

(3*R*)-10,10-Difluoro-3-methylcyclopentadecan-1-one (67). A solution of (3*R*,6*E*)-10,10-difluoro-3-methylcyclopentadec-6-en-1-one **84** (20 mg, 0.07 mmol, 1.0 eq) and palladium on activated carbon (10 wt% on carbon, 8 mg, 10 mol%) in methanol (5 mL) was stirred under a hydrogen atmosphere (1 atm) for 22 h. The reaction mixture was filtered through celite and the celite was washed with methanol (20 mL). The solvent was removed *in vacuo* to give compound **67** (12 mg, 59%) as a colourless oil that was used without further purification. The compound solidified upon cooling to -20 ºC; $[\alpha]_D$ -10.6° (c 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.97 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.19-1.49 (14H, CH_2-4,5,6,7,8,12,13), 1.58-1.65 (1H, m, CH_AH$_B$-14), 1.71-1.89 (5H, m, CH_2-9,11, CH$_A$$H_B$-14), 2.02-2.09 (1H, m, CH-3), 2.26 (1H, dd, *J*(H,H)= 15.6, 4.2 Hz, CH_AH$_B$-2), 2.38 (1H, dd, *J*(H,H)= 15.5, 9.1 Hz, CH$_A$$H_B$-2), 2.42-2.51 (2H, m, CH_2-15); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.9 (t, *J*(C,F)= 5.4 Hz, CH_2 C8/12), 21.6 (CH_3), 22.0 (t, *J*(C,F)= 6.3 Hz, CH_2 C8/12), 22.0 (CH_2, C14), 24.7 (CH_2, C5), 26.6 (CH_2, C6), 27.1 (CH_2, C7), 28.2 (CH_2, C13), 29.5 (CH, C3), 34.3 (t, *J*(C,F)= 25.5 Hz, CH_2 C9/11), 34.7 (t, *J*(C,F)= 25.6 Hz, CH_2 C9/11), 35.6 (CH_2, C4), 41.9 (CH_2, C15), 50.4 (CH_2, C2), 126.6 (t, *J*(C,F)= 240.1 Hz, CF_2 C10), 211.4 (CO, C1); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -90.2 (1F, d, *J*(F,F)= 242.7 Hz, CF_AF$_B$), -91.3 (1F, d, *J*(F,F)= 242.7 Hz, CF$_A$$F_B$); IR (thin film) ν (cm^{-1}) = 1711 (C=O); HRMS: *m*/*z* calcd for $C_{16}H_{28}F_2Na_1O_1$ $[M+Na]^+$: 297.2000; found: 297.1995.

10-Bromo-4,4-difluorodec-1-ene (85). Using the same procedure as for **80**, 7,7-difluorodec-9-en-1-ol **44** (4.9 g, 25.4 mmol, 1.0 eq) gave compound **85** (4.36 g, 67%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.33-1.39 (2H, m, CH_2), 1.44-1.56 (4H, m, CH_2), 1.77-1.90 (2H, m, CH_2), 2.60 (2H, td, *J*(H,F)= 15.8 Hz, *J*(H,H)= 7.2 Hz, CH_2), 3.42 (2H, t, *J*(H,H)= 6.8 Hz, CH_2), 5.19-5.23 (2H, m, CH_2), 5.76-5.84 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.1 (t, *J*(C,F)= 4.6 Hz, CH_2), 28.1 (CH_2), 28.7 (CH_2), 32.8 (CH_2), 34.0 (t, *J*(C,F)= 25.2 Hz, CH_2), 41.4 (t, *J*(C,F)= 26.6 Hz, CH_2), 120.3 (CH_2), 124.4 (t, *J*(C,F)= 241.5 Hz, CF_2), 130.0 (t, *J*(C,F)= 5.9 Hz, CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.3 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{10}H_{21}Br_1F_2N_1$ $[M(^{78}Br)+NH_4]^+$: 272.0820; found: 272.0815.

(5*R*)-14,14-Difluoro-5-methylheptadeca-1,16-diene-7-ol (86). Iodine (trace) was added to a suspension of magnesium turnings (406 mg, 16.7 mmol, 4.0 eq) in dry THF (10 mL) under argon at r.t. and stirred until the reaction turned colourless. A solution of 10-bromo-4,4-difluorodec-1-ene **85** (4.26 g, 16.7 mmol, 4.0 eq) in dry THF (10 mL) was added and the reaction was heated at reflux for 6 h. The reaction mixture was cooled to r.t. and diluted with THF (60 mL), then cooled to 0 °C and a solution of (3*R*)-3-methylhept-6-enal **81** (0.53 g, 4.2 mmol, 1.0 eq) in dry THF (20 mL) was added. The reaction mixture was stirred at 0 °C for 30 min, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with sat. ammonium chloride solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:9) gave compound **86** (0.51 g, 40%) as a colourless oil, as a 1:1 mixture of diastereoisomers; $[\alpha]_D$ -0.2° (c 0.84, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.92 (3H, d, *J*(H,H)= 6.6 Hz, CH_3) and 0.93 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.15-1.52 (15H, m, CH_2, OH), 1.57-1.71 (1H, m, CH), 1.76-1.86 (2H, m, CH_2), 1.99-2.16 (2H, m, CH_2), 2.60 (2H, td, *J*(H,F)= 15.8 Hz, *J*(H,H)= 7.1 Hz, CH_2), 3.68-3.71 (1H, m, CH), 4.93-5.04 (2H, m, CH_2), 5.19-5.22 (2H, m, CH_2), 5.76-5.86 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.3 and 20.5 (CH_3), 22.2 (t, *J*(C,F)= 4.4 Hz, CH_2), 25.6 and 25.7 (CH_2), 29.0 and 29.3 (CH), 29.5 and 29.7 (CH_2), 31.4 and 31.5 (CH_2), 35.9 and 36.1 (CH_2), 36.1 (t, *J*(C,F)= 25.0 Hz, CH_2), 37.2 (CH_2), 37.9 and 38.5 (CH_2), 41.4 (t, *J*(C,F)= 26.4 Hz, CH_2), 45.1 and 45.4 (CH_2), 69.8 and 70.1 (CH), 114.4 and 114.5 (CH_2), 120.2 (CH_2), 124.5 (t, *J*(C,F)= 241.3 Hz, CF_2), 130.1 (t, *J*(C,F)= 6.1 Hz, CH), 139.4 (CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.2 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{18}H_{32}F_2Na_1O_1$ $[M+Na]^+$: 325.2313; found: 325.2312.

(5*R*)-14,14-Difluoro-5-methylheptadeca-1,16-diene-7-one (87). Using the same procedure as for **77**, (5*R*)-14,14-difluoro-5-methylheptadeca-1,16-diene-7-ol **86** (0.46 g, 1.5 mmol, 1.0 eq) gave compound **87** (0.45 g) as a yellow oil; $[\alpha]_D$ +2.6° (c 0.54, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.90 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.22-1.42 (6H, m, CH_2), 1.44-1.50 (2H, m, CH_2), 1.54-1.60 (2H, m, CH_2), 1.75-1.85 (2H, m, CH_2), 1.98-2.14 (2H, m, CH_2), 2.20-2.25 (1H, m, CH_AH_B), 2.37-2.41 (3H, m, CH_2, CH_AH_B), 2.60 (2H, td, *J*(H,F)= 15.8 Hz, *J*(H,H)= 7.2 Hz, CH_2), 4.94-5.03 (2H, m, CH_2), 5.18-5.22 (2H, m, CH_2), 5.75-5.84 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.9 (CH_3), 22.1 (CH_2, t, *J*(C,F)= 4.3 Hz), 23.7 (CH_2), 29.0 (CH), 29.2 (CH_2), 31.4 (CH_2), 36.0 (CH_2, t, *J*(C,F)= 24.9 Hz), 36.2 (CH_2), 41.4 (CH_2, t, *J*(C,F)= 26.4 Hz), 43.4 (CH_2), 50.4 (CH_2), 114.7 (CH_2), 120.2 (CH_2), 124.4 (CF_2, t, *J*(C,F)= 241.2 Hz), 130.0 (t, *J*(C,F)= 5.8 Hz, CH), 138.9 (CH), 211.3 (CO); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.3 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{18}H_{30}F_2Na_1O_1$ $[M+Na]^+$: 323.2157; found: 323.2154.

(3*R*)-10,10-Difluoro-3-methylcyclopentadec-6-en-1-one (88). Grubbs catalyst (1st generation, 70 mg, 0.06 mmol, 6 mol%) was added to a solution of (5*R*)-14,14-difluoro-5-methylheptadeca-1,16-diene-7-one **87** (0.46 g, 1.5 mmol, 1.0 eq) in dry DCM (400 mL) in a foil covered flask at r.t. under argon. The reaction mixture was heated at 45 °C for 21 h, then cooled to r.t. and the solvent was removed *in vacuo*. Purification of the residue by column chromatography using silica gel (ethyl acetate/pet. ether 1:49) gave RCM product **88**-1 (186 mg, 45%) as a pale brown solid as a single isomer and RCM product **88**-2 (200 mg, 49%) as a pale brown oil as a 1.0:0.8 mixture of isomers. **RCM product 88-1**; $[\alpha]_D$ -2.2° (c 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.96 (3H, d, *J*(H,H)= 6.6 Hz, CH_3, A), 0.99 (3H, d, *J*(H,H)= 6.8 Hz, CH_3, B), 1.23-1.49 (10H, m, CH_2), 1.57-1.70 (2H, m, CH_2), 1.73-1.85 (2H, m, CH_2), 1.89-1.95 (1H, m, CH, A), 1.98-2.12 (2H, m, CH (B), CH_AH_B), 2.16-2.22 (2H, m, CH_AH_B, CH_AH_B), 2.28-2.48 (3H, m, CH_AH_B, CH_2), 2.51-2.66 (2H, m, CH_2), 5.35-5.43 (1H, m, CH), 5.52-5.58 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.9 (CH_3, A), 20.6 (CH_2, t, *J*(C,F)= 5.0 Hz, A), 21.0 (CH_3, B), 21.8 (CH_2, t, *J*(C,F)= 5.1 Hz, B), 23.0 (CH_2, A), 25.1 (CH_2, B), 26.8 (CH_2, A+B), 27.0 (CH_2, B), 27.3 (CH_2 A), 28.7 (CH, A), 29.4 (CH_2, A), 29.8 (CH, B), 34.3 (CH_2, t, *J*(C,F)= 26.4 Hz, B), 34.6 (CH_2, t, *J*(C,F)= 25.1 Hz, A), 35.1 (CH_2, t, *J*(C,F)= 25.2 Hz, B), 36.0 (CH_2, A), 36.2 (CH_2, B), 39.9 (CH_2, t, *J*(C,F)= 26.7 Hz, A), 41.3 (CH_2, B), 42.3 (CH_2, A), 50.4 (CH_2, B), 51.6 (CH_2, A), 121.6 (CH, t, *J*(C,F)= 6.6 Hz, B), 123.2 (CH, t, *J*(C,F)= 7.1 Hz, A), 125.4 (CF_2, t, *J*(C,F)= 241.6 Hz, B), 125.4 (CF_2, t, *J*(C,F)= 241.3 Hz**,** A), 133.9 (CH, B), 135.8 (CH, A), 212.0 (CO, B), 212.4 (CO, A); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) A: δ = -93.3 (1F, d, *J*(F,F)= 242.2 Hz, CF_AF_B), -94.0 (1F, d, *J*(F,F)= 242.2 Hz, CF_AF_B), B: -93.3 (1F, d, *J*(F,F)= 242.2 Hz, CF_AF_B), -94.2 (1F, d, *J*(F,F)= 242.0 Hz, CF_AF_B); HRMS: *m*/*z* calcd for $C_{16}H_{26}F_2Na_1O_1$ $[M+Na]^+$: 295.1844; found: 295.1841. **RCM product 88-2.** $[\alpha]_D$ +0.4° (c 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.96 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.23-1.51 (10H, m, CH_2), 1.60 (2H, t, *J*(H,H)= 7.2, 6.7 Hz, CH_2), 1.73-1.83 (2H, m, CH_2), 1.89-1.95 (1H, m, CH), 2.04-2.12 (1H, m, CH_AH_B), 2.28-2.34 (2H, m, CH_AH_B, CH_AH_B), 2.39-2.45 (1H, m, CH_AH_B), 2.51-2.60 (2H, m, CH_2), 5.36-5.43 (1H, m, CH), 5.51-5.58 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.9 (CH_3), 20.6 (CH_2, t, *J*(C,F)= 5.0 Hz), 23.0 (CH_2), 26.8 (CH_2), 27.3 (CH_2), 28.7 (CH), 29.4 (CH_2), 34.6 (CH_2, t, *J*(C,F)= 25.1 Hz), 36.0 (CH_2), 39.9 (CH_2, t, *J*(C,F)= 26.7 Hz), 42.3 (CH_2), 51.6 (CH_2), 123.2 (CH, t, J(C,F)= 7.1 Hz), 125.4 (CF_2, t, *J*(C,F)= 241.3 Hz), 135.8 (CH), 212.4 (CO); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -93.3 (1F, d, *J*(F,F)= 242.2 Hz, CF_AF_B), -94.0 (1F, d, *J*(F,F)= 242.2 Hz, CF_AF_B); IR (thin film) ν (cm^{-1}) = 1709; HRMS: *m*/*z* calcd for $C_{16}H_{26}F_2Na_1O_1$ $[M+Na]^+$: 295.1844; found: 295.1840.

(3*R*)-9,9-Difluoro-3-methylcyclopentadecan-1-one (68). A solution of (3*R*)-10,10-difluoro-3-methylcyclopentadec-6-en-1-one **88** (160 mg, 0.59 mmol, 1.0 eq) and palladium on activated carbon (10 wt% on carbon, 63 mg, 10 mol%) in methanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) for 24 h. The reaction mixture was filtered through celite and the celite was washed with methanol (20 mL). The solvent was removed *in vacuo* to give compound **68** (66 mg, 41%) as a colourless oil that

was used without further purification; $[\alpha]_D$ +1.7° (c 0.63, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.97 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.08-1.15 (1H, m, CH_AH_B-14), 1.22-1.44 (13H, CH_AH_B-14, CH_2-5,6,7,11,12,13), 1.56-1.93 (6H, m, CH_2-8,10,14), 1.97-2.07 (1H, m, CH-3), 2.25-2.34 (2H, m, CH_2-2), 2.37-2.51 (2H, m, CH_2-15); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.7 (CH_3), 21.5 (CH_2, t, *J*(C,F)= 5.3 Hz, C11), 21.9 (CH_2, t, *J*(C,F)= 5.5 Hz, C7), 22.2 (CH_2, C14), 24.8 (CH_2, C5), 27.1 (CH_2, C12), 27.3 (CH_2, C13), 27.4 (CH_2, C6), 29.8 (CH, C3), 34.1 (CH_2, t, *J*(C,F)= 25.7 Hz, C8/10), 34.3 (CH_2, t, *J*(C,F)= 25.5 Hz, C8/10), 34.7 (CH_2, C4), 42.0 (CH_2, C15), 51.4 (CH_2, C2), 126.7 (CF_2, t, *J*(C,F)= 240.4 Hz, C9), 212.0 (CO, C1); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -90.8 (1F, d, *J*(F,F)= 243.0 Hz, CF_AF_B), -91.5 (1F, d, *J*(F,F)= 243.0 Hz, CF_AF_B); HRMS: *m*/*z* calcd for $C_{16}H_{28}F_2Na_1O_1$ $[M+Na]^+$: 297.2000; found: 297.1997.

12-(4-methoxybenzyloxy)dodec-1-en-4-ol (92). Allylmagnesium bromide (65.0mL, 1M solution in Et_2O, 65.0 mmol, 1.5 equiv.) was added to a solution of 9-(4-methoxybenzyloxy)nonanal **91** (12.0 g, 43.0 mmol, 1.0 equiv.) in dry THF (200 mL) at 0 ºC. The resulting mixture was stirred overnight at room temperature. Then, sat. aq. NH_4Cl solution (115 mL) and EtOAc (58 mL) were sequentially added and the aqueous layer was extracted with EtOAc (3 x 115 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography using silica gel (pet. ether/EtOAc 10:1) gave compound **92** (6.0 g, 44%) as a colourless oil; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.29-1.35 (12H, m, CH_2), 1.43-1.60 (2H, m, CH_2), 2.14 (1H, br, OH), 3.43 (2H, t, *J*(H,H)= 5.9 Hz, CH_2), 3.65-3.67 (1H, m, CH), 3.80 (3H, s, CH_3), 4.43 (2H, s, CH_2), 5.11-5.15 (2H, m, CH_2), 5.79-5.89 (1H, m, *J*(H,H)= CH), 6.88 (2H, d, *J*(H,H)= 8.0 Hz, ArH), 7.26 (2H, d, *J*(H,H)= 8.0 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.7 (CH_2), 26.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 36.9 (CH_2), 42.0 (CH_2), 55.4 (CH_3), 70.3 (CH_2), 70.7 (CH), 72.6 (CH_2), 113.8 (CH_{Ar}), 118.1 (=CH_2), 129.3 (CH_{Ar}), 130.9 (C_{Ar}), 135.0 (=CH), 159.1 (C_{Ar}); HRMS: *m*/*z* calcd for $C_{20}H_{32}Na_1O_3$ $[M+Na]^+$: 343.2249; found: 343.2235.

12-(4-methoxybenzyloxy)dodec-1-en-4-one (93). IBX (8.1 g, 29 mmol, 1.5 eq) was added to a solution of 12-(4-methoxybenzyloxy)dodec-1-en-4-ol **92** (6.0 g, 19.0 mmol, 1.0 eq) in DMSO (100 mL) at r.t. The reaction mixture was stirred at r.t. for 18 h. The reaction mixture was queched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give compound **93** (5.0 g, 83%) as a yellow oil, which was used without further purification; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.28-1.30 (8H, m, CH_2), 1.57-1.61 (4H, m, CH_2), 2.43 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 3.16 (2H, d, *J*(H,H)= 5.5 Hz, CH_2), 3.44 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 3.80 (3H, s, CH_3), 4.43 (2H, s, CH_2), 5.12-5.19 (2H, m, =CH_2), 5.90-5.94 (1H, m, =CH), 6.87-6.89 (2H, d, *J*(H,H)= 7.9 Hz, ArH), 7.26-7.28 (2H, d, *J*(H,H)= 7.9 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.7 (CH_2), 26.2 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.8 (CH_2), 42.3 (CH_2), 47.7 (CH_2), 55.2 (CH_3), 70.2 (CH_2), 72.5 (CH_2), 113.7 (CH_{Ar}), 118.7 (=CH_2), 129.2 (CH_{Ar}), 130.8 (C_{Ar}), 130.8 (=CH), 137.4 (CH), 159.1 (C_{Ar}), 208.9 (C=O); HRMS: *m*/*z* calcd for $C_{20}H_{30}Na_1O_3$ $[M+Na]^+$: 341.2093; found: 341.2079.

1-((9,9-difluorododec-11-enyloxy)methyl)-4-methoxybenzene (94). A solution of 12-(4-methoxybenzyloxy)dodec-1-en-4-one **93** (3.0 g, 9.4 mmol, 1.0 eq) in DAST (5.0 mL, 37.7 mmol, 4.0 eq) was heated at 50 °C under argon for 18 h. The reaction mixture was cooled to r.t. and poured onto sat. $NaHCO_3$ solution. The reaction mixture was extracted with DCM. The combined organic layers were washed with brine (250 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:10) gave compound **94** (2.0 g, 63%) as a yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.32-1.50 (10H, m, CH_2), 1.59-1.62 (2H, m, CH_2), 1.81-1.84 (2H, m, CH_2), 2.58-2.66 (2H, m CH_2), 3.46 (2H, t, *J*(H,H)= 6.3 Hz, CH_2), 3.83 (3H, s, CH_3), 4.46 (2H, , s, CH_2), 5.21-5.249 (2H, m, =CH_2), 5.80-5.85 (1H, m, CH_2), 6.91 (2H, t,

J(H,H)= 8.5 Hz, ArH), 7.28 (2H, t, *J*(H,H)= 8.5 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 14.2 (CH_2), 22.0 (CH_2), 22.1 (CH_2), 22.1 (CH_2), 22.2 (CH_2),22.3 (CH_2), 22.3 (CH_2), 29.8 (CH_2), 35.9 (t, *J*(C,F)= 25.0 Hz, CH_2), 41.1 (t, *J*(C,F)= 25.0 Hz, CH_2), 55.3 (CH_3), 70.2 (CH_2), 72.5 (CH_2), 113.7 (CH_{Ar}), 120.0 (=CH_2), 124.3 (t, *J*(C,F)= 249.3 Hz, CF_2), 129.2 (CH_{Ar}), 129.9 (t, *J*(C,F)= 7.0 Hz, =CH), 130.8 (C_{Ar}), 159.1 (C_{Ar}); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -97.2 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{20}H_{30}F_2Na_1O_2$ $[M+Na]^+$: 363.2112; found: 363.2096.

9,9-difluorododec-11-en-1-ol (95). DDQ (2.0 g, 8.9 mmol, 1.5 eq) was added to a solution of 1-((9,9-difluorododec-11-enyloxy)methyl)-4-methoxybenzene **94** (2.0 g, 5.9 mmol, 1.0 eq) in DCM (80 mL) and water (0.5 mL) at r.t. and stirred for 1 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:10) gave compound **95** (0.9 g, 69%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.30-1.56 (12H, m, CH_2), 1.72-1.80 (2H, m ,CH_2), 2.53-2.62 (2H, m, CH_2), 3.61 (2H, t, *J*(H,H)= 6.5 Hz, CH_2), 2.60 (2H, dt, *J*(H,F)= 15.8, *J*(H,H)= 7.3 Hz, CH_2), 3.66 (2H, t, *J*(H,H)= 6.5 Hz, CH_2), 5.18-5.22 (2H, m, =CH_2), 5.77-5.84 (1H, m, =CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.0 (t, *J*(C,F)= 4.0 Hz, CH_2), 25.7 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 32.7 (CH_2), 35.9 (t, *J*(C,F)= 24.4 Hz, CH_2), 41.1 (t, *J*(C,F)= 24.4 Hz, CH_2), 62.9 (CH_2), 119.9 (CH_2), 125.4 (t, *J*(C,F)= 241.3 Hz, CF_2), 129.9 (t, *J*(C,F)= 5.7 Hz, CH); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ = -97.2 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{12}H_{22}F_2Na_1O_1$ $[M+Na]^+$: 243.1536; found: 243.1527.

9,9-difluorododec-11-enal (96). IBX (588 mg, 2.1 mmol, 1.5 eq) was added to a solution of 9,9-difluorododec-11-en-1-ol **95** (303 mg, 1.4 mmol, 1.0 eq) in DMSO (15 mL) at r.t. The reaction mixture was stirred at r.t. for 18 h. The reaction mixture was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give **96** (240 mg, 80%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.32-1.48 (8H, m, CH_2), 1.60-1.64 (2H, m ,CH_2), 1.74-1.83 (2H, m, CH_2), 2.43 (2H, t, *J*(H,H)= 7.1 Hz, CH_2), 2.61 (2H, dt, *J*(H,F)= 16.0, *J*(H,H)= 7.1 Hz, CH_2), 5.18-5.21 (2H, m, =CH_2), 5.76-5.83 (1H, m, =CH), 9.78 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.0 (CH_2), 22.0 (CH_2), 28.9 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 35.8 (t, *J*(C,F)= 24.5 Hz, CH_2), 41.1 (t, *J*(C,F)= 24.5 Hz, CH_2), 43.8 (CH_2), 119.9 (=CH_2), 124.2 (t, *J*(C,F)= 232.4 Hz, CF_2), 129.8 (t, *J*(C,F)= 6.4 Hz, =CH), 202.7 (CHO); ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ = -97.3 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{12}H_{20}F_2Na_1O_1$ $[M+Na]^+$: 241.1380; found: 241.1371.

(4*R*)-14,14-Difluoro-4-methylheptadeca-1,16-diene-6-ol (98). A solution of (*R*)-4-(bromomethyl)pent-1-ene **97** (680 mg, 4.2 mmol, 4.0 eq) in dry THF (4 mL) was added to a mixture of magnesium turnings (101 mg, 4.2 mmol, 4.0 eq) and iodine (trace) under argon at r.t. and stirred until the reaction turned colourless. The reaction was heated at reflux for 4 h. The reaction mixture was cooled to r.t. and diluted with THF (4.0 mL), then a solution of 9,9-difluorododec-11-enal **96** (240 mg, 1.1 mmol, 1.0 eq) in dry THF (4.0 mL) was added. The reaction mixture was stirred r.t. for 18 h. The reaction mixture was quenched with sat. ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:10) gave compound **98** (200 mg, 60%) as a colourless oil, as a 1:1 mixture of diastereoisomers; $[\alpha]_D$ -6.2° (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.91 and 0.92 (3H, d, *J*(H,H)= 6.5 Hz, CH_3), 1.29-1.48 (14H, m, CH, CH_2), 1.73-2.18 (4H, m, CH_2), 2.61 (2H, dt, *J*(H,F)= 15.4, *J*(H,H)= 7.1 Hz, CH_2), 2.22-2.27 (2H, m, CH_2), 3.71 (1H, m, CH), 4.98-5.03 (2H, m, =CH_2), 5.17-5.22 (2H, m, =CH_2), 5.76-5.80 (2H, m, =CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.3 and 20.4 (CH_3), 22.2 (t, *J*(C,F)= 4.5 Hz, CH_2), 25.6 and 25.8 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.5 and 29.7 (CH), 38.5 (t, *J*(C,F)= 24.5 Hz, CH_2),

41.0 and 41.3 (CH_2), 41.6 (CH_2), 42.4(t, J(C,F)= 26.2 Hz, CH_2), 44.6 (CH_2), 44.7 (CH_2), 69.8 and 70.1 (CH), 116.0 and 116.7 (=CH_2), 120.1 (=CH_2), 124.4 (t, J(C,F)= 241.4 Hz, CF_2), 130.0 (t, J(C,F)= 6.0 Hz, =CH), 137.3 and 137.5 (=CH); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.2 (2F, s, CF_2); HRMS: m/z calcd for $C_{18}H_{32}F_2Na_1O_1$ $[M+Na]^+$: 325.2319; found: 325.2306.

(4*R*)-14,14-Difluoro-4-methylheptadeca-1,16-diene-6-one (99). IBX (280 mg, 0.99 mmol, 1.5 eq) was added to a solution of (4*R*)-14,14-Difluoro-4-methylheptadeca-1,16-diene-6-ol **98** (200 mg, 0.66 mmol, 1.0 eq) in DMSO (8 mL) at r.t. The reaction mixture was stirred at r.t. for 18 h. The reaction mixture was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give compound **99** (190 mg, 95%) as a colorless oil; $[\alpha]_D$ +5.8° (c 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 0.90 (3H, d, J(H,H)= 6.2 Hz, CH_3), 1.25-1.33 (10H, m, CH_2), 1.52-2.22 (6H, m, CH_2), 2.34-2.42 (2H, m, CH_2), 2.57-2.60 (2H, dt, J(H,F)= 15.8, J(H,H)= 7.3 Hz, CH_2), 4.97-5.22 (4H, m, CH_2), 5.70-5.74 (2H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.9 (CH_3), 22.1 (t, J(C,F)= 4.0 Hz, CH_2), 23.8 (CH_2), 29.0 (CH), 29.2 (CH_2), 29.3 (CH_2), 36.0 (t, J(C,F)= 25.2 Hz, CH_2), 36.2 (CH_2), 41.3 (t, J(C,F)= 23.4 Hz, CH_2), 41.3 (CH_2), 49.5 (CH_2), 116.5 (=CH_2), 120.1 (=CH_2), 126.8 (t, J(C,F)= 242.7 Hz, CF_2), 130.0 (t, J(C,F)= 6.0 Hz, =CH), 136.8 (=CH), 211.1 (C=O); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ = -97.2 (2F, s, CF_2); HRMS: m/z calcd for $C_{18}H_{30}F_2Na_1O_1$ $[M+Na]^+$: 323.2162; found: 323.2148.

(3*R*,5*E*)-8,8-Difluoro-3-methylcyclopentadec-5-en-1-one (100). Hoveyda-Grubbs catalyst (2nd generation, 7.6 mg, 0.012 mmol, 6 mol%) was added to a solution of (4*R*)-14,14-Difluoro-4-methylheptadeca-1,16-diene-6-one **99** (60 mg, 0.2 mmol, 1.0 eq) in dry toluene (80 mL) in a foil covered flask at r.t. under argon. The reaction mixture was heated at 120 °C for 17 h, then cooled to r.t. and the solvent was removed *in vacuo*. Purification of the residue by column chromatography using silica gel (ehtyl acetate/pet.ether 1:25) to give compound **(*E*)-100** (30 mg, 56%) as a colorless oil; $[\alpha]_D$ +5.7° (c 0.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.95 (3H, d, J(H,H)= 6.1 Hz, CH_3), 1.18-1.82 (13H, m, CH_2), 2.14-2.55 (8H, m, CH_2), 5.36-5.52 (2H, m, =CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.7 (t, J(C,F)= 4.2 Hz, CH_2), 19.8 (CH_3), 24.6 (CH_2), 26.0 (CH_2), 26.6 (CH_2), 27.0 (CH_2), 27.9 (CH), 34.4 (t, J(C,F)= 25.2 Hz, CH_2), 39.7 (t, J(C,F)= 27.3 Hz, CH_2), 39.7 (CH_2), 42.1 (CH_2), 48.7 (CH_2), 125.3 (t, J(C,F)= 242.1 Hz, CF_2), 124.1 (=CH), 134.6 (=CH), 211.5 (C=O); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -93.3 (1F, d, J(F,F)= 242.6 Hz, CF_AF_B), -94.3 (1F, d, J(F,F)= 242.6 Hz, CF_AF_B); HRMS: m/z calcd for $C_{16}H_{26}F_2Na_1O_1$ $[M+Na]^+$: 295.1849; found: 295.1832.

(3*R*)-8,8-Difluoro-3-methylcyclopentadecan-1-one (69). A solution of (3*R*,5*E*)-8,8-difluoro-3-methylcyclopentadec-5-en-1-one **100** (30 mg, 0.11 mmol, 1.0 eq) and palladium on activated carbon (5 wt% on carbon, 23 mg, 10 mol%) in methanol (1 mL) was stirred under a hydrogen atmosphere (1 atm) for 22 h. The reaction mixture was filtered through celite and washed with methanol. The solvent was removed *in vacuo* to give compound **69** (28 mg, 93%) as a colourless oil that was used without further purification. $[\alpha]_D$ -3.8° (c 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.94 (3H, d, J(H,H)= 7.5 Hz, CH_3), 1.25-1.42 (14H, m, CH_2), 1.59-1.84 (6H, m, CH_2), 2.17-2.47 (5H, m, CH, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.2 (t, J(C,F)= 5.6 Hz, CH_2), 21.3 (CH_3), 22.5 (t, J(C,F)= 4.8 Hz, CH_2), 23.6 (CH_2), 25.7 (CH_2), 26.6 (CH_2), 26.9 (CH_2), 27.4 (CH_2), 28.3 (CH), 34.2 (t, J(C,F)= 25.5 Hz, CH_2), 34.4 (t, J(C,F)= 24.0 Hz, CH_2), 35.6 (CH_2), 42.4 (CH_2), 50.1 (CH_2), 126.5 (t, J(C,F)= 240.4 Hz, CF_2), 211.8 (C=O); $^{19}F\{^1H\}$ NMR (377 MHz, $CDCl_3$) δ = -91.4 (1F, d, J(F,F)= 241.1 Hz, CF_AF_B), -91.8 (1F, d, J(F,F)= 241.1 Hz, CF_AF_B); HRMS: m/z calcd for $C_{16}H_{28}F_2Na_1O_1$ $[M+Na]^+$: 297.2006; found: 297.1991.

(3*R*)-1-(((3,7-dimethyloct-6-en-1-yl)oxy)methyl)-4-methoxybenzene (102). A solution of α-citronellol **101** (3.5 g, 22.2 mmol, 1.0 eq) in dry DMF (5 mL) was added to a suspension of sodium

hydride (60 % in oil, 0.98 g, 24.4 mmol, 1.1 eq) in dry DMF (5 mL) at 0 ºC under argon and stirred for 15 min. 4-Methoxybenzyl chloride (3.3 mL, 24.4 mmol, 1.1 eq) was added and the reaction mixture was stirred at 0 ºC for 1 h, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with water (100 mL) and extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:19) gave compound **102** (5.0 g, 82%) as a colourless oil; $[\alpha]_D$ +1.7° (c 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.89 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.12-1.20 (1H, m, C*H*$_A$H$_B$), 1.31-1.38 (1H, m, CH$_A$*H*$_B$), 1.39-1.46 (1H, m, C*H*$_A$H$_B$), 1.56-1.63 (1H, m, CH), 1.61 (3H, s, CH_3), 1.63-1.69 (1H, m, CH$_A$*H*$_B$), 1.69 (3H, s, CH_3), 1.91-2.05 (2H, m, CH_2), 3.44-3.52 (2H, m, CH_2), 3.82 (3H, s, CH_3), 4.44 (2H, s, CH_2), 5.09-5.12 (1H, m, CH), 6.87-6.90 (2H, m, ArH), 7.26-7.29 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.9 (CH_3), 19.8 (CH_3), 25.7 (CH_3), 25.9 (CH_2), 29.8 (CH), 36.9 (CH_2), 37.4 (CH_2), 55.5 (CH_3), 68.6 (CH_2), 72.8 (CH_2), 113.9 (CH), 125.1 (CH), 129.4 (CH), 131.0 (C), 131.3 (C), 159.3 (C); HRMS: *m*/*z* calcd for $C_{18}H_{28}Na_1O_2$ $[M+Na]^+$: 299.1982; found: 299.1982.

(3*R*)-1-Methoxy-4-(((3-methylhept-6-en-1-yl)oxy)methyl)benzene (103). Ozone was bubbled through a solution of (3*R*)-1-(((3,7-dimethyloct-6-en-1-yl)oxy)methyl)-4-methoxybenzene **102** (3.3 g, 11.9 mmol, 1.0 eq) in dry DCM (100 mL) at -78 ºC until the solution turned blue to indicate the presence of excess ozone. Oxygen was bubbled through the reaction mixture for a further ten minutes. Triphenylphosphine (3.4 g, 13.1 mmol, 1.1 eq) was added and the reaction mixture was stirred at -78 ºC for 1 h, then warmed to r.t. and left to stir for 18 h. The solvent was removed *in vacuo* and the residue was subjected to a quick purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:9) to give the intermediate aldehyde as a colourless oil that was used without further purification.

n-Butyllithium (2.5 M in hexanes, 12.8 mL, 32.1 mmol, 2.7 eq) was added to a suspension of methyltriphenylphosphonium bromide (12.8 g, 35.7 mmol, 3.0 eq) in dry THF (130 mL) at -78 ºC under argon and stirred for 30 min. A solution of the intermediate aldehyde in dry THF (20 mL) was added and the reaction mixture was stirred at -78 ºC for 4 h, then allowed to warm to r.t. and stirred for a further 16 h. The reaction mixture was quenched with sat. NH_4Cl solution (250 mL) and extracted with diethyl ether (2 x 200 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:39) gave compound **103** (1.05 g, 36%) as a colourless oil; $[\alpha]_D$ +1.3° (c 1.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.90 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.19-1.26 (1H, m, C*H*$_A$H$_B$), 1.38-1.46 (2H, m, CH$_A$*H*$_B$, C*H*$_A$H$_B$), 1.58-1.70 (2H, m, CH$_A$*H*$_B$, CH), 1.99-2.14 (2H, m, CH_2), 3.44-3.52 (2H, m, CH_2), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 4.92-5.03 (2H, m, CH_2), 5.77-5.85 (1H, m, CH), 6.87-6.90 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.7 (CH_3), 29.6 (CH), 31.5 (CH_2), 36.5 (CH_2), 39.6 (CH_2), 55.5 (CH_3), 68.5 (CH_2), 72.8 (CH_2), 113.9 (CH), 114.3 (CH_2), 129.4 (CH), 131.0 (C), 139.4 (CH), 159.3 (C); HRMS: *m*/*z* calcd for $C_{16}H_{24}Na_1O_2$ $[M+Na]^+$: 271.1669; found: 271.1666.

(5*R*)-7-((4-Methoxybenzyl)oxy)-5-methylheptan-1-ol (104). 9-BBN dimer (0.88 g, 3.6 mmol, 1.0 eq) was added to a solution of (3*R*)-1-methoxy-4-(((3-methylhept-6-en-1-yl)oxy)methyl)benzene **103** (0.9 g, 3.6 mmol, 1.0 eq) in dry THF (20 mL) at r.t. under argon and stirred for 18 h. The reaction mixture was cooled to 0 ºC. Ethanol (2.4 mL) was added, followed by NaOH solution (2 N, 2.4 mL) and hydrogen peroxide (30%, 2.4 mL). The reaction mixture was warmed to r.t. and stirred for 4 h. The solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (100 mL) and washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:4) gave compound **104** (0.95 g, 99%) as a colourless oil; $[\alpha]_D$ +0.7° (c 0.73, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.88 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.10-1.21 (1H, m, C*H*$_A$H$_B$), 1.27-1.45 (5H, m, C*H*$_A$H$_B$, CH$_A$*H*$_B$, CH_2,

OH), 1.49-1.69 (4H, m, CH_AH_B, CH_2, CH), 3.43-3.52 (2H, m, CH_2), 3.63 (2H, t, *J*(H,H)= 6.6 Hz, CH_2), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 6.87-6.90 (2H, m, ArH), 7.25-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.8 (CH_3), 23.3 (CH_2), 30.0 (CH), 33.2 (CH_2), 36.9 (CH_2), 37.0 (CH_2), 55.5 (CH_3), 63.2 (CH_2), 72.7 (CH_2), 113.9 (CH), 129.4 (CH), 130.9 (C), 159.3 (C); HRMS: *m*/*z* calcd for $C_{16}H_{26}Na_1O_3$ $[M+Na]^+$: 289.1774; found: 289.1767.

(5*R*)-7-((4-Methoxybenzyl)oxy)-5-methylheptanal (105). Using the same procedure as for **77**, (5*R*)-7-((4-methoxybenzyl)oxy)-5-methylheptan-1-ol **104** (1.6 g, 6.0 mmol, 1.0 eq) gave compound **105** (1.59 g) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.89 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.12-1.22 (1H, m, CH_AH_B), 1.29-1.46 (2H, m, CH_AH_B, CH_AH_B), 1.54-1.74 (4H, m, CH_AH_B, CH_2, CH), 2.39-2.43 (2H, m, CH_2), 3.43-3.52 (2H, m, CH_2), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 6.87-6.90 (2H, m, ArH), 7.25-7.28 (2H, m, ArH), 9.76 (1H, t, *J*(H,H)= 1.9 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.6 (CH_3), 19.7 (CH_2), 29.9 (C), 36.7 (CH_2), 36.8 (CH_2), 44.3 (CH_2), 55.5 (CH_3), 68.4 (CH_2), 72.8 (CH_2), 114.0 (CH), 129.4 (CH), 130.9 (C), 159.3 (C), 203.0 (CO).

(9*R*)-11-((4-Methoxybenzyl)oxy)-9-methylundec-1-en-5-ol (106). Iodine (trace) was added to a suspension of magnesium turnings (0.34 g, 13.8 mmol, 4.0 eq) in dry diethyl ether (10 mL) under argon at r.t. and stirred until the reaction turned colourless. A solution of 4-bromo-1-butene (1.4 mL, 13.8 mmol, 4.0 eq) in dry diethyl ether (10 mL) was added at a rate sufficient to maintain autoreflux and stirred for 30 min after addition was complete. The reaction mixture was diluted with diethyl ether (50 mL), then cooled to 0 °C and a solution of 6-((4-methoxyphenyl)methoxy)hexanal **105** (0.93 g, 3.5 mmol, 1.0 eq) in dry diethyl ether (10 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with sat. ammonium chloride solution (100 mL) and extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:9) gave compound **106** (0.72 g, 65%) as a colourless oil, as a 1:1 mixture of diastereoisomers; $[\alpha]_D$ +2.2° (c 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.88 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.10-1.19 (1H, m, CH_AH_B), 1.25-1.68 (11H, m, CH_AH_B, CH_2, CH), 2.10-2.25 (2H, m, CH_2), 3.43-3.51 (2H, m, CH_2), 3.58-3.65 (1H, bm, CH), 3.81 (3H, s, CH_3), 4.43 (2H, m, CH_2), 4.97-5.08 (2H, m, CH_2), 5.81-5.89 (1H, m, CH), 6.87-6.90 (2H, m, ArH), 7.26-7.29 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.8 and 19.8 (CH_3), 23.1 and 23.2 (CH_2), 30.0 (CH), 30.3 and 30.3 (CH_2), 36.7 and 36.7 (CH_2), 36.9 and 36.9 (CH_2), 37.2 and 37.3 (CH_2), 37.9 and 37.9 (CH_2), 55.5 (CH_3), 68.5 and 68.5 (CH_2), 71.6 and 71.7 (CH), 72.7 (CH_2), 113.9 (CH), 114.9 (CH_2), 129.4 (CH), 130.9 (C), 138.9 (CH), 159.3 (C); HRMS: *m*/*z* calcd for $C_{20}H_{32}Na_1O_3$ $[M+Na]^+$: 343.2244; found: 343.2234.

(9*R*)-11-((4-Methoxybenzyl)oxy)-9-methylundec-1-en-5-one (**107**). Using the same procedure as for **77**, (9*R*)-11-((4-methoxybenzyl)oxy)-9-methylundec-1-en-5-ol **106** (0.70 g, 2.2 mmol, 1.0 eq) gave compound **107** (0.70 g) as a yellow oil; $[\alpha]_D$ +1.9° (c 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.88 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.08-1.15 (1H, m, CH_AH_B), 1.25-1.32 (1H, m, CH_AH_B), 1.37-1.44 (1H, m, CH_AH_B), 1.49-1.67 (4H, m, CH_AH_B, CH_2, CH), 2.30-2.40 (4H, m, CH_2), 2.50 (2H, t, *J*(H,H)= 7.1 Hz, CH_2), 3.43-3.502 (2H, m, CH_2), 3.81 (3H, s, CH_3), 4.43 (2H, s, CH_2), 4.97-5.05 (2H, m, CH_2), 5.77-5.85 (1H, m, CH), 6.87-6.90 (2H, m, ArH), 7.25-7.27 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.7 (CH_3), 24.4 (CH_2), 28.0 (CH_2), 29.9 (CH), 36.7 (CH_2), 36.8 (CH_2), 42.0 (CH_2), 43.3 (CH_2), 55.5 (CH_3), 68.4 (CH_2), 72.8 (CH_2), 113.9 (CH), 115.4 (CH_2), 129.4 (CH), 130.9 (C), 137.4 (CH), 159.3 (C), 210.6 (CO); HRMS: *m*/*z* calcd for $C_{20}H_{30}Na_1O_3$ $[M+Na]^+$: 341.2087; found: 341.2078.

(3*R*)-1-(((7,7-Difluoro-3-methylundec-10-en-1-yl)oxy)methyl)-4-methoxybenzene (108). Using the same procedure as for **78**, (9*R*)-11-((4-methoxybenzyl)oxy)-9-methylundec-1-en-5-one (0.70 g, 2.2

mmol, 1.0 eq) **107** gave compound **108** (0.52 g, 70%) as a colourless oil; $[\alpha]_D$ +2.1° (c 0.92, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.89 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.13-1.21 (1H, m, CH_AH_B), 1.30-1.37 (1H, m, CH_AH_B), 1.39-1.68 (5H, m, CH_2, CH), 1.74-1.96 (4H, m, CH_2), 2.22-2.26 (2H, m, CH_2), 3.44-3.52 (2H, m, CH_2), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 5.00-5.09 (2H, m, CH_2), 5.79-5.87 (1H, m, CH), 6.87-6.90 (2H, m, ArH), 7.26-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.7 (CH_3), 19.9 (CH_2, t, *J*(C,F)= 4.4 Hz), 26.7 (CH_2, t, *J*(C,F)= 5.0 Hz), 29.9 (CH), 35.8 (CH_2, t, *J*(C,F)= 25.7 Hz), 36.9 (CH_2), 36.9 (CH_2, t, *J*(C,F)= 25.4 Hz), 55.5 (CH_3), 68.4 (CH_2), 72.8 (CH_2), 113.9 (CH), 115.4 (CH_2), 125.2 (CF_2, t, *J*(C,F)= 240.5 Hz), 129.4 (CH), 130.9 (C), 137.3 (CH), 159.3 (C); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.2 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{20}H_{30}F_2Na_1O_2$ $[M+Na]^+$: 363.2106; found: 363.2097.

(3*R*)-7,7-Difluoro-3-methylundec-10-en-1-ol (109). Using the same procedure as for **79**, (3*R*)-1-(((7,7-difluoro-3-methylundec-10-en-1-yl)oxy)methyl)-4-methoxybenzene **108** (0.50 g, 1.5 mmol, 1.0 eq) gave compound **110** (0.25 g, 74%) as a colourless oil; $[\alpha]_D$ +1.5° (c 0.55, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.92 (3H, d, *J*(H,H)= 6.7 Hz, CH_3), 1.16-1.23 (1H, m, CH_AH_B), 1.31 (1H, bs, OH), 1.32-1.65 (6H, m, CH_AH_B, CH_2, CH), 1.76-1.97 (4H, m, CH_2), 2.22-2.27 (2H, m, CH_2), 3.65-3.74 (2H, m, CH_2), 4.99-5.09 (2H, m, CH_2), 5.79-5.87 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.6 (CH_3), 19.9 (t, *J*(C,F)= 4.6 Hz, CH_2), 26.7 (t, *J*(C,F)= 5.1 Hz, CH_2), 29.5 (CH), 35.8 (t, *J*(C,F)= 25.6 Hz, CH_2), 36.9 (t, *J*(C,F)= 25.4 Hz, CH_2), 37.0 (CH_2), 40.0 (CH_2), 61.3 (CH_2), 115.4 (CH_2), 125.1 (t, *J*(C,F)= 240.8 Hz, CF_2), 137.3 (CH); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.25 (1F, s, CF_2), -98.26 (1F, s, CF_2); HRMS: *m*/*z* calcd for $C_{12}H_{22}F_2Na_1O_1$ $[M+Na]^+$: 243.1531; found: 243.1526.

(3*R*)-7,7-Difluoro-3-methylundec-10-en-1-al (110). Using the same procedure as for **77**, (3*R*)-7,7-difluoro-3-methylundec-10-en-1-ol **109** (0.22 g, 1.0 mmol, 1.0 eq) gave compound **110** (233 g, 97%) as a yellow oil; $[\alpha]_D$ +2.2° (c 0.65, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.99 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.22-1.31 (1H, m, CH_AH_B), 1.34-1.59 (3H, m, CH_AH_B, CH_2), 1.73-1.99 (4H, m, CH_2), 2.04-2.14 (1H, m, CH), 2.21-2.30 (3H, m, CH_AH_B, CH_2), 2.42 (1H, ddd, *J*(H,H)= 16.4, 5.9, 1.9 Hz, CH_AH_B), 5.00-5.09 (2H, m, CH_2), 5.79-5.87 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.9 (t, *J*(C,F)= 4.5 Hz, CH_2), 20.0 (CH_3), 26.7 (t, *J*(C,F)= 5.0 Hz, CH_2), 28.1 (CH), 35.9 (t, *J*(C,F)= 25.6 Hz, CH_2), 36.7 (CH_2), 36.7 (t, *J*(C,F)= 25.9 Hz, CH_2), 51.2 (CH_2), 115.5 (CH_2), 125.0 (t, *J*(C,F)= 240.5 Hz, CF_2), 137.2 (CH), 202.9 (CO); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.53 (1F, s, CF_2), -98.54 (1F, s, CF_2); ^{19}F NMR (470 MHz, $CDCl_3$) δ = -98.4-(-98.6) (2F, m, CF_2).

(9*R*)-13,13-Difluoro-9-methylheptadeca-1,16-diene-7-ol (111). Iodine (trace) was added to a suspension of magnesium turnings (0.17 mg, 6.8 mmol, 5.0 eq) in dry diethyl ether (5 mL) under argon at r.t. and stirred until the reaction turned colourless. A solution of 6-bromo-1-hexene (0.9 mL, 4.8 mmol, 5.0 eq) in dry diethyl ether (5 mL) was added and the reaction was heated at reflux for 30 min. The reaction mixture was cooled to r.t. and diluted with diethyl ether (20 mL), then cooled to 0 °C and a solution of (3*R*)-7,7-difluoro-3-methylundec-10-en-1-al **110** (0.31 g, 1.4 mmol, 1.0 eq) in dry diethyl ether (10 mL) was added. The reaction mixture was stirred at 0 °C for 30 min, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with sat. ammonium chloride solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:9) gave compound **111** (0.30 g, 72%) as a colourless oil, as a 1:1 mixture of diastereoisomers; $[\alpha]_D$ -2.7° (c 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.92 and 0.93 (3H, d, *J*(H,H)= 6.2 Hz, CH_3), 1.10-1.71 (14H, m, CH, CH_2, OH), 1.76-1.97 (4H, m, CH_2), 2.06-2.09 (2H, m, CH_2), 2.22-2.27 (2H, m, CH_2), 3.66-3.73 (1H, m, CH), 4.94-5.09 (4H, m, CH_2), 5.78-5.87 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.3 and 20.4 (CH_3), 19.8 (t, *J*(C,F)= 4.6 Hz, CH_2) and 19.9 (t, *J*(C,F)= 4.5 Hz, CH_2), 20.4 (CH_2), 25.2 and 25.4 (CH_2), 26.7 (t,

J(C,F)= 4.9 Hz, CH_2), 29.1 (CH_2), 29.3 and 29.6 (CH), 34.0 (CH_2), 35.8 (t, *J*(C,F)= 24.9 Hz, CH_2), 36.4 and 37.9 (CH_2), 36.9 (t, *J*(C,F)= 25.2 Hz, CH_2) and 36.9 (t, *J*(C,F)= 25.5 Hz, CH_2), 37.8 and 38.5 (CH_2), 45.0 and 45.3 (CH_2), 69.7 and 70.0 (CH), 114.6 (CH_2), 115.4 (CH_2), 125.1 (CF_2, t, *J*(C,F)= 240.8 Hz), 137.3 (CH), 139.1 (CH); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.2 (2F, s, CF_2), -98.2 (1F, s, CF_2), -98.3 (1F, s, CF_2); HRMS: *m*/*z* calcd for $C_{18}H_{32}F_2Na_1O_1$ $[M+Na]^+$: 325.2313; found: 325.2304.

(9*R*)-13,13-Difluoro-9-methylheptadeca-1,16-diene-7-one (112). Using the same procedure as for **77**, (9*R*)-13,13-difluoro-9-methylheptadeca-1,16-diene-7-ol **111** (0.28 g, 0.9 mmol, 1.0 eq) gave compound **112** (0.27 g, 99%) as a yellow oil; $[\alpha]_D$ +2.9° (c 0.76, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.90 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.16-1.62 (8H, m, CH_2), 1.74-1.96 (4H, m, CH_2), 1.99-2.10 (3H, m, CH_2, CH), 2.21-2.26 (3H, m, CH_2, CH_AH_B), 2.35-2.40 (3H, m, CH_2, CH_AH_B), 4.94-5.09 (4H, m, CH_2), 5.76-5.87 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.9 (CH_3), 19.9 (CH_2), 23.4 (CH_2), 26.7 (CH_2, t, *J*(C,F)= 4.8 Hz), 28.7 (CH_2), 29.1 (CH), 33.7 (CH_2), 35.9 (CH_2, t, *J*(C,F)= 25.5 Hz), 36.7 (CH_2), 36.7 (CH_2, t, *J*(C,F)= 25.3 Hz), 43.5 (CH_2), 50.3 (CH_2), 114.9 (CH_2), 115.4 (CH_2), 125.0 (CF_2, t, *J*(C,F)= 240.5 Hz), 137.3 (CH), 138.7 (CH), 211.1 (CO); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.2 (1F, d, *J*(F,F)= 239.6 Hz, CF_AF_B), -98.7 (1F, d, *J*(F,F)= 239.6 Hz, CF_AF_B); HRMS: *m*/*z* calcd for $C_{18}H_{30}F_2Na_1O_1$ $[M+Na]^+$: 323.2157; found: 323.2152.

(14*R*)-10,10-Difluoro-14-methylcyclopentadec-6-en-1-one (113). Grubbs catalyst (1st generation, 50 mg, 0.06 mmol, 7 mol%) was added to a solution of (9*R*)-13,13-difluoro-9-methylheptadeca-1,16-diene-7-one **112** (0.25 g, 0.83 mmol, 1.0 eq) in dry DCM (200 mL) in a foil covered flask at r.t. under argon. The reaction mixture was heated at 45 °C for 46 h, then cooled to r.t. and the solvent was removed *in vacuo*. Purification of the residue by column chromatography using silica gel (ethyl acetate/pet. ether 1:49) gave compound **(*Z*)-113** (40 mg, 17%) as a pale brown solid and compound **(*E*)-113** as a pale brown solid. **(*Z*)-113**. $[\alpha]_D$ -6.5° (c 0.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.97 (3H, d, *J*(H,H)= 6.9 Hz, CH_3), 1.21-1.47 (6H, m, CH_2), 1.51-1.58 (1H, m, CH_AH_B), 1.70-1.96 (6H, m, CH, CH_2, CH_AH_B), 2.00-2.25 (5H, m, CH_2, CH_AH_B), 2.35-2.41 (1H, m, CH_AH_B), 2.45-2.52 (2H, m, CH_AH_B, CH_AH_B), 5.35-5.46 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.8 (CH_2, t, *J*(C,F)= 5.3 Hz), 21.5 (CH_2, t, *J*(C,F)= 6.2 Hz), 22.0 (CH_3), 23.4 (CH_2), 26.4 (CH_2), 28.5 (CH_2), 28.7 (CH), 35.3 (CH_2, t, *J*(C,F)= 25.6 Hz), 35.6 (CH_2, t, *J*(C,F)= 25.5 Hz), 36.7 (CH_2), 42.6 (CH_2), 49.6 (CH_2), 125.8 (CF_2, t, *J*(C,F)= 240.4 Hz), 128.7 (CH), 130.4 (CH), 211.2 (CO); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -91.1 (1F, d, *J*(F,F)= 243.1 Hz, CF_AF_B), -93.3 (1F, d, *J*(F,F)= 243.1 Hz, CF_AF_B); IR (thin film) ν (cm^{-1}) = 1702 (C=O); HRMS: *m*/*z* calcd for $C_{16}H_{26}F_2Na_1O_1$ $[M+Na]^+$: 295.1844; found: 295.1841. **(*E*)-113**; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.97 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.23-1.30 (4H, m, CH_2), 1.37-1.56 (4H, m, CH_2),1.57-1.64 (4H, m, CH_2), 1.68-2.10 (7H, m, CH_2, CH), 2.16 (1H, dd, *J*(H,H)= 14.1, 5.4 Hz, CH_AH_B), 2.21-2.25 (2H, m, CH_2), 2.28-2.33 (1H, m, CH_AH_B), 2.39-2.46 (2H, m, CH_AH_B, CH_AH_B), 5.38-5.46 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.6 (CH_2, t, *J*(C,F)= 4.8 Hz), 20.7 (CH_3), 23.9 (CH_2), 26.5 (CH_2, t, *J*(C,F)= 5.1 Hz), 28.3 (CH_2), 29.2 (CH), 31.4 (CH_2), 35.0 (CH_2), 35.5 (CH_2, t, *J*(C,F)= 25.9 Hz), 36.0 (CH_2, t, *J*(C,F)= 25.3 Hz), 42.5 (CH_2), 50.0 (CH_2), 125.8 (CF_2, t, *J*(C,F)= 240.6 Hz), 130.4 (CH), 131.7 (CH), 212.6 (CO); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -91.3 (1F, d, *J*(F,F)= 241.9 Hz, CF_AF_B), -94.2 (1F, d, *J*(F,F)= 241.9 Hz, CF_AF_B); IR (thin film) ν (cm^{-1}) = 1707 (C=O).

(3*R*)-7,7-Difluoro-3-methylcyclopentadecan-1-one (70). A solution of (14*R*)-10,10-difluoro-14-methylcyclopentadec-6-en-1-one **113** (110 mg, 0.40 mmol, 1.0 eq) and palladium on activated carbon (10 wt% on carbon, 43 mg, 10 mol%) in methanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) for 22 h. The reaction mixture was filtered through celite and the celite was washed with methanol (20 mL). The solvent was removed *in vacuo* to give compound **70** (65 mg, 72%) as a colourless oil that was used without further purification; $[\alpha]_D$ -11.9° (c 0.70, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.97 (3H, d, *J*(H,H)= 6.8 Hz, CH_3), 1.23-1.43 (14H, CH_2-4,5,9,10,11,12,13), 1.54-1.60 (1H, m, CH_AH_B-

14), 1.70-1.94 (5H, m, CH_2-6,8, CH_AH_B-14), 2.07-2.14 (1H, m, CH-3), 2.26 (1H, dd, *J*(H,H)= 16.8, 4.7 Hz, CH_AH_B-2), 2.36-2.48 (3H, m, CH_AH_B-2, CH_2-15); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.8 (CH_2, t, *J*(C,F)= 5.6 Hz, C5/9), 20.9 (CH_2, t, *J*(C,F)= 5.4 Hz, C5/9), 21.8 (CH_3), 23.2 (CH_2, C14), 26.2 (CH_2, C5), 26.4 (CH_2, C11/12), 27.0 (CH_2, C11/12), 27.8 (CH_2, C13), 28.3 (CH, C3), 34.2 (CH_2, t, *J*(C,F)= 25.6 Hz, C6/8), 35.2 (CH_2, t, *J*(C,F)= 25.8 Hz, C6/8), 36.2 (CH_2, C4), 40.1 (CH_2, C15), 50.0 (CH_2, C2), 126.5 (CF_2, t, *J*(C,F)= 239.7 Hz, C7), 211.3 (CO, C1); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -90.4 (1F, d, *J*(F,F)= 243.0 Hz, CF_AF_B), -91.5 (1F, d, *J*(F,F)= 243.0 Hz, CF_AF_B); HRMS: *m*/*z* calcd for $C_{16}H_{28}F_2Na_1O_1$ $[M+Na]^+$: 297.2000; found: 297.1997.

(8*R*)-10-((4-Methoxybenzyl)oxy)-8-methyldec-1-en-5-ol (114). Ozone was bubbled through a solution of (3*R*)-1-(((3,6-dimethylhept-5-en-1-yl)oxy)methyl)-4-methoxybenzene **102** (1.73 g, 6.3 mmol, 1.0 eq) in dry DCM (100 mL) at -78 °C until a pale blue colour appeared (approx. 15 min). Oxygen was bubbled through the reaction until the blue colour disappeared. Triphenylphosphine (1.8 g, 6.9 mmol, 1.1 eq) was added and the reaction was stirred at -78 °C for 1 h, then warmed to r.t. and stirred for 18 h. The solvent was removed *in vacuo*. Pentane (150 mL) was added to the residue, causing the precipitation of a white solid. The solid was filtered, the filtrate collected and the solvent removed *in vacuo* to give the intermediate aldehyde as a colourless oil that was used in the next step without purification.

Iodine (trace) was added to a suspension of magnesium turnings (0.54 g, 22.4 mmol, 4.0 eq) in dry diethyl ether (20 mL) under argon at r.t. and stirred until the reaction turned colourless. A solution of 4-bromo-1-butene (2.3 mL, 22.4 mmol, 4.0 eq) in dry diethyl ether (20 mL) was added at a rate sufficient to maintain autoreflux and stirred for 30 min after addition was complete. The reaction mixture was diluted with diethyl ether (60 mL), then cooled to 0 °C and a solution of the aldehyde prepared above (1.4 g, 5.6 mmol, 1.0 eq) in dry diethyl ether (20 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, then warmed to r.t. and stirred for 18 h. The reaction mixture was quenched with sat. ammonium chloride solution (150 mL) and extracted with diethyl ether (200 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:9) gave compound **114** (0.99 g, 58%) as a colourless oil, as a 1:1 mixture of diastereoisomers; $[\alpha]_D$ +1.9° (c 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.89 (3H, d, *J*(H,H)= 6.6 Hz, CH_3) and 0.89 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.11-1.69 (10H, m, CH_2, CH, OH), 2.10-2.25 (2H, m, CH_2), 3.44-3.52 (2H, m , CH_2), 3.55-3.62 (1H, m, CH), 3.81 (3H, s, CH_3), 4.44 (2H, s, CH_2), 4.97-5.08 (2H, m, CH_2), 5.81-5.89 (1H, m, CH), 6.87-6.90 (2H, m, ArH), 7.25-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.8 and 19.9 (CH_3), 30.0 and 30.2 (CH), 30.3 and 30.3 (CH_2), 32.9 and 33.0 (CH_2), 34.9 and 35.0 (CH_2), 36.6 and 36.7 (CH_2), 55.5 (CH_3), 68.4 and 68.5 (CH_2), 71.9 and 72.0 (CH), 72.8 (CH_2), 113.9 (CH), 115.0 (CH_2), 129.5 (CH), 130.9 (C), 138.9 (CH), 159.3 (C); HRMS: *m*/*z* calcd for $C_{19}H_{30}Na_1O_3$ $[M+Na]^+$: 329.2087; found: 329.2086.

(8*R*)-10-((4-Methoxybenzyl)oxy)-8-methyldec-1-en-5-one (115). Using the same procedure as for **77**, (8*R*)-10-((4-methoxybenzyl)oxy)-8-methyldec-1-en-5-ol 114 (0.94 g, 3.1 mmol, 1.0 eq) gave compound **115** (0.89 g, 96%) as a yellow oil that was used without further purification; $[\alpha]_D$ +3.0° (c 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.88 (3H, d, *J*(H,H)= 6.5 Hz, CH_3), 1.39-1.46 (2H, m, CH_AH_B x 2), 1.54-1.67 (3H, m, CH_AH_B x 2, CH), 2.30-2.35 (2H, m, CH_2), 2.36-2.47 (2H, m, CH_2), 2.50 (2H, t, *J*(H,H)= 7.2 Hz, CH_2), 3.44-3.51 (2H, m, CH_2), 3.81 (3H, s, CH_3), 4.41 (1H, d, *J*(H,H)= 11.6 Hz, CH_AH_B), 4.44 (1H, d, *J*(H,H)= 11.6 Hz, CH_AH_B), 4.96-5.05 (2H, m, CH_2), 5.76-5.84 (1H, m, CH), 6.87-6.89 (2H, m, ArH), 7.24-7.27 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.6 (CH_3), 28.0 (CH_2), 29.8 (CH), 30.8 (CH_2), 36.7 (CH_2), 40.7 (CH_2), 42.0 (CH_2), 55.5 (CH_3), 68.3 (CH_2), 72.8 (CH_2), 113.9 (CH), 115.4 (CH_2), 129.4 (CH), 130.8 (C), 137.4 (CH), 159.3 (C), 210.7 (CO); HRMS: *m*/*z* calcd for $C_{19}H_{28}Na_1O_3$ $[M+Na]^+$: 327.1931; found: 327.1932.

(3*R*)-1-(((6,6-Difluoro-3-methyldec-9-en-1-yl)oxy)methyl)-4-methoxybenzene (116). Using the same procedure as for **78**, (8*R*)-10-((4-methoxybenzyl)oxy)-8-methyldec-1-en-5-one **115** (0.94 g, 3.1 mmol, 1.0 eq) gave compound **116** (0.59 g, 64%) as a yellow oil; $[\alpha]_D$ +1.5° (c 0.54, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.90 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.21-1.97 (9H, m, CH, CH_2), 2.21-2.26 (2H, m, CH_2), 3.44-3.53 (2H, m, CH_2), 3.81 (3H, s, CH_3), 4.44 (2H, m, CH_2), 4.99-5.09 (2H, m, CH_2), 5.78-5.88 (1H, m, CH), 6.87-6.91 (2H, m, ArH), 7.25-7.28 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.6 (CH_3), 26.7 (CH_2, t, *J*(C,F)= 5.1 Hz), 29.4 (CH_2, t, *J*(C,F)= 4.1 Hz), 29.8 (CH), 34.2 (CH_2, t, *J*(C,F)= 25.3 Hz), 35.8 (CH_2, t, *J*(C,F)= 25.6 Hz), 36.7 (CH_2), 55.5 (CH_3), 68.2 (CH_2), 72.8 (CH_2), 114.0 (CH), 115.4 (CH_2), 125.3 (CF_2, t, *J*(C,F)= 240.8 Hz), 129.4 (CH), 130.8 (C), 137.3 (CH), 159.3 (C); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -98.7 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{19}H_{28}F_2Na_1O_2$ $[M+Na]^+$: 349.1950; found: 349.1941.

(3*R*)-6,6-Difluoro-3-methyldec-9-en-1-ol (117). Using the same procedure as for **79**, (3*R*)-1-(((6,6-difluoro-3-methyldec-9-en-1-yl)oxy)methyl)-4-methoxybenzene **116** (0.53 g, 1.6 mmol, 1.0 eq) gave compound **117** (0.29 g, 88%) as a colourless oil; $[\alpha]_D$ +0.4° (c 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.93 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.22 (1H, bs, OH), 1.29-1.67 (5H, m, CH_2, CH), 1.76-1.98 (4H, m, CH_2), 2.22-2.27 (2H, m, CH_2), 3.65-3.76 (2H, m, CH_2), 4.99-5.10 (2H, m, CH_2), 5.78-5.8 (1H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.6 (CH_3), 26.7 (CH_2, t, *J*(C,F)= 5.1 Hz), 29.4 (CH_2, t, *J*(C,F)= 4.5 Hz), 29.4 (CH), 34.1 (CH_2, t, *J*(C,F)= 25.1 Hz), 35.8 (CH_2, t, *J*(C,F)= 25.8 Hz), 39.7 (CH_2), 115.4 (CH_2), 125.3 (CF_2, t, *J*(C,F)= 241.2 Hz), 137.3 (CH); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ = -98.8 (2F, s, CF_2); HRMS: *m*/*z* calcd for $C_{11}H_{20}F_2Na_1O_1$ $[M+Na]^+$: 229.1374; found: 229.1370.

(10*R*)-13,13-Difluoro-10-methylheptadec-1,16-dien-8-ol (118). DMP (0.80 g, 1.9 mmol, 1.5 eq) was added to a solution of (3*R*)-6,6-difluoro-3-methyldec-9-en-1-ol **117** (0.26 g, 1.3 mmol, 1.0 eq) in DCM (20 mL) at r.t. and stirred for 1 h. The reaction mixture was diluted with diethyl ether (20 mL) and sat. $NaHCO_3$ solution (20 mL). Sodium thiosulfate (1.6 g) was added and the reaction mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was re-extracted with diethyl ether (30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to give the intermediate aldehyde as a yellow oil that was used without further purification.
Iodine (trace) was added to a suspension of magnesium turnings (0.13 g, 5.2 mmol, 4.0 eq) in dry diethyl ether (5 mL) under argon at r.t. and stirred until the reaction turned colourless. A solution of 7-bromo-1-heptene (0.8 mL, 5.2 mmol, 4.0 eq) in dry diethyl ether (5 mL) was added and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to r.t. and diluted with diethyl ether (10 mL), then cooled to 0 °C and a solution of the aldehyde prepared above (0.26 g, 1.3 mmol, 1.0 eq) in dry diethyl ether (10 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, then warmed to r.t. and stirred for 3 h. The reaction mixture was quenched with sat. ammonium chloride solution (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography using silica gel (ethyl acetate/pet. ether 1:9) gave compound **118** (0.23 g, 60%) as a colourless oil, as a ~1.0:1.4 mixture of diastereoisomers; $[\alpha]_D$ -3.8° (c 0.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.93 (3H, d, *J*(H,H)= 6.6 Hz, CH_3) and 0.94 (3H, d, *J*(H,H)= 6.6 Hz, CH_3), 1.18-1.51 (12H, m, CH_2), 1.58-1.98 (5H, m, CH_2, CH), 2.04-2.08 (2H, m, CH_2), 2.22-2.27 (2H, m, CH_2), 3.65-3.74 (1H, bm, CH), 4.93-5.09 (4H, m, CH_2), 5.78-5.87 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.2 and 20.4 (CH_3), 26.8 (CH_2, t, *J*(C,F)= 4.9 Hz), 28.7 (CH_2, t, *J*(C,F)= 4.4 Hz) and 30.2 (CH_2, t, *J*(C,F)= 4.1 Hz), 29.3 and 29.3 (CH_2), 29.4 and 29.5 (CH), 33.8-34.4 (CH_2, m), 33.9 (CH_2), 35.8 (CH_2, t, *J*(C,F)= 25.6 Hz) and 35.8 (CH_2, t, *J*(C,F)= 25.4 Hz), 38.1 (CH_2), 38.6 (CH_2), 44.8 and 45.0 (CH_2), 69.7 and 67.0 (CH), 114.5 (CH_2), 115.4 (CH_2), 125.3 (CF_2, t, *J*(C,F)= 240.9 Hz)

and 125.3 (CF_2, t, J(C,F)= 240.5 Hz), 137.3 (CH), 139.3 (CH); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.2 (1F, d, J(F,F)= 13.7 Hz, CF_AF_B), -98.3 (1F, d, J(F,F)= 13.7 Hz, CF_AF_B), -98.3 (2F, s); HRMS: m/z calcd for $C_{18}H_{32}F_2Na_1O_1$ $[M+Na]^+$: 325.2313; found: 325.2308.

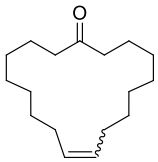
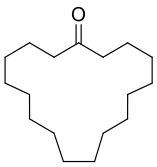
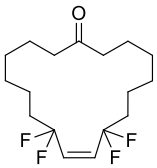
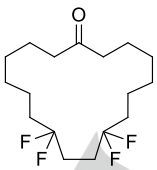
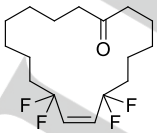
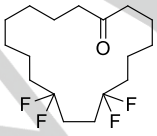
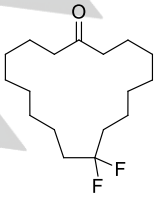
(10*R*)-13,13-Difluoro-10-methylheptadec-1,16-dien-8-one (119). Using the same procedure as for **77**, (10*R*)-13,13-difluoro-10-methylheptadec-1,16-dien-8-ol **118** (0.2 g, 0.66 mmol, 1.0 eq) gave compound **119** (0.2 g) as a yellow oil; $[\alpha]_D$ +1.7° (c 041, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 0.91 (3H, d, J(H,H)= 6.6 Hz, CH_3), 1.23-1.61 (8H, m, CH_2, CH), 1.72-1.97 (4H, m, CH_2), 2.00-2.07 (2H, m, CH_2, CH), 2.21-2.29 (2H, m, CH_2, CH_AH_B), 2.36-2.40 (2H, m, CH_2, CH_AH_B), 4.83-5.09 (4H, m, CH_2), 5.76-5.86 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.8 (CH_3), 26.7 (CH_2, t, J(C,F)= 5.1 Hz), 28.9 (CH), 28.9 (CH_2), 28.9 (CH_2), 29.3 (CH_2, t, J(C,F)= 4.1 Hz), 33.8 (CH_2), 34.2 (CH_2, t, J(C,F)= 25.4 Hz), 35.8 (CH_2, t, J(C,F)= 25.7 Hz), 43.6 (CH_2), 50.1 (CH_2), 114.6 (CH_2), 115.5 (CH_2), 125.1 (CF_2, t, J(C,F)= 240.3 Hz), 137.2 (CH), 139.1 (CH), 210.8 (CO); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -98.4 (2F, s, CF_2); HRMS: m/z calcd for $C_{18}H_{30}F_2Na_1O_1$ $[M+Na]^+$: 323.2157; found: 323.2147.

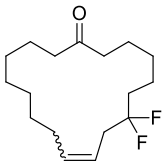
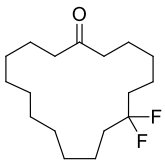
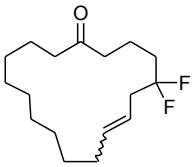
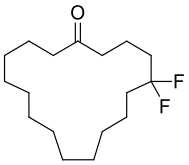
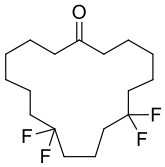
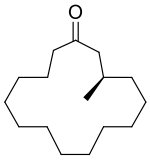
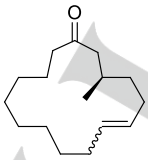
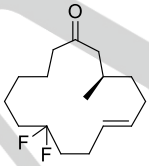
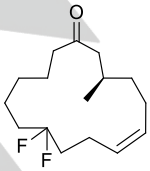
(14*R*)-11,11-Difluoro-14-methylcyclopentadec-7-en-1-one (120). Grubbs catalyst (1st generation, 30 mg, 0.04 mmol, 6 mol%) was added to a solution of (10*R*)-13,13-difluoro-10-methylheptadec-1,16-dien-8-one **119** (0.18 g, 0.60 mmol, 1.0 eq) in dry DCM (250 mL) in a foil covered flask at r.t. under argon. The reaction mixture was heated at 45 °C for 17 h, then cooled to r.t. and the solvent was removed *in vacuo*. Purification of the residue by column chromatography using silica gel (ethyl acetate/pet. ether 1:49) gave compound **120** (82 mg, 50%) as a brown oil, as a *E*:*Z* ~3:2 inseparable mixture of isomers; $[\alpha]_D$ -12.2° (c 0.78, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 1.00 (3H, d, J(H,H)= 6.8 Hz, CH_3 (*E*)), 1.01 (3H, d, J(H,H)= 6.8 Hz, CH_3 (*Z*)), 1.11-1.48 (6H, m, CH_2), 1.56-2.55 (15H, m, CH_2, CH), 5.31-5.44 (2H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.7 (CH_3, *Z*), 21.2 (CH_2, t, J(C,F)= 6.0 Hz, *Z*), 21.5 (CH_3, *E*), 22.8 (CH_2, *Z*), 24.2 (CH_2, *E*), 26.6 (CH_2, t, J(C,F)= 6.2 Hz, *E*), 27.2 (CH_2, *Z*), 27.8 (CH_2, *E*), 28.2 (CH_2, *E*), 28.3 (CH_2, t, J(C,F)= 4.2 Hz, *E*), 28.4 (CH, *E*), 28.6 (CH_2, *Z*), 28.7 (CH_2, *Z*), 29.3 (CH_2, t, J(C,F)= 25.5 Hz, *E*), 30.3 (CH, *Z*), 31.7 (CH_2, *E*), 32.9 (CH_2, t, J(C,F)= 25.7 Hz, *Z*), 33.8 (CH_2, t, J(C,F)= 25.5 Hz, *E*), 35.6 (CH_2, t, J(C,F)= 25.6 Hz, *Z*), 35.7 (CH_2, t, J(C,F)= 25.7 Hz, *E*), 42.1 (CH_2, *E*), 42.8 (CH_2, *Z*), 50.7 (CH_2, *E*), 51.2 (CH_2, *Z*), 125.7 (CF_2, t, J(C,F)= 241.0 Hz, *E*), 125.8 (CF_2, t, J(C,F)= 241.0 Hz, *Z*), 128.7 (CH, *Z*), 130.2 (CH, *E*), 130.5 (CH, *Z*), 132.0 (CH, *E*), 211.7 (CO, *E*), 211.9 (CO, *Z*); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -92.4 (1F, d, J(F,F)= 241.3 Hz, CF_AF_B, (*E*)), -92.4 (1F, d, J(F,F)= 243.3 Hz, CF_AF_B, (*Z*)), -93.0 (1F, d, J(F,F)= 243.3 Hz, CF_AF_B, (*Z*)), -94.0 (1F, d, J(F,F)= 241.3 Hz, CF_AF_B, (*E*)); HRMS: m/z calcd for $C_{16}H_{26}F_2Na_1O_1$ $[M+Na]^+$: 295.1844; found: 295.1832.

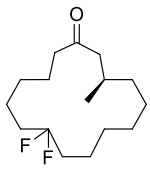
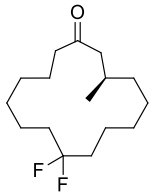
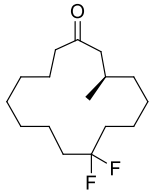
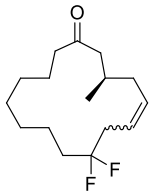
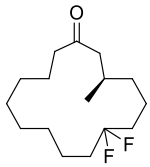
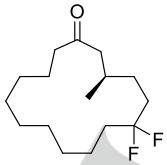
(3*R*)-6,6-Difluoro-3-methylcyclopentadecan-1-one (71). Using the same procedure as for **77**, (14*R*)-11,11-difluoro-14-methylcyclopentadec-7-en-1-one **120** (60 mg, 0.22 mmol, 1.0 eq) gave compound **71** (39.4 mg, 65%) as a colourless oil; $[\alpha]_D$ -2.2° (c 0.51, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 1.00 (3H, d, J(H,H)= 6.9 Hz, CH_3), 1.23-1.41 (14H, CH_2-4,8,9,10,11,12,13), 1.55-1.61 (1H, m, CH_AH_B-14), 1.70-1.93 (5H, m, CH_2-5,7, CH_AH_B-14), 2.06-2.12 (1H, m, CH-3), 2.30 (1H, dd, J(H,H)= 15.3, 3.8 Hz, CH_AH_B-2), 2.37 (1H, dd, J(H,H)= 15.2, 9.7 Hz, CH_AH_B-2), 2.44 (2H, t, J(H,H)= 6.6 Hz, CH_2-15); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.7 (CH_3), 21.4 (CH_2, t, J(C,F)= 5.5 Hz, C8), 22.0 (CH_2, C4), 26.4 (CH_2 x 2), 26.7 (CH_2), 27.0 (CH_2, C13), 27.9 (CH_2, C9), 29.5 (CH, C3), 29.5 (CH_2, C13), 29.5 (CH_2, t, J(C,F)= 6.0 Hz, C4), 32.8 (CH_2, t, J(C,F)= 26.0 Hz, C5), 34.7 (CH_2, t, J(C,F)= 25.3 Hz, C7), 42.3 (CH_2, C15), 50.6 (CH_2, C2), 126.4 (CF_2, t, J(C,F)= 239.5 Hz, C6), 211.4 (CO, C1); $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ = -91.1 (1F, d, J(F,F)= 242.8 Hz, CF_AF_B), -92.1 (1F, d, J(F,F)= 242.8 Hz, CF_AF_B); HRMS: m/z calcd for $C_{16}H_{28}F_2Na_1O_1$ $[M+Na]^+$: 297.2000; found: 297.1988.

Olfactory Properties

A selection of relevant synthetic samples of civetone and muscone was assessed by an expert Perfumer (Dominique Lelièvre) at Givaudan company (Switzerland). A 10% solution in ethanol was prepared for each compound. These solutions were tested 24h and fresh dipped strips with the results shown in the table.

Compound	Structure	Odour description	
		fresh	24h
1 (*E/Z* 3:1)		**Musky**, ketonic, powdery, hot iron facet	Weak, **musky**, ketonic, powdery
11		**Musky**, ketonic, powdery, waxy facet	Weak, **musky**, ketonic, powdery
13		Very weak, **musky**, green off-note	Very weak, **musky**
14		Very weak, **musky**, slightly fatty	Very weak, **musky**, a hint green, powdery
15		Very weak, **musky**, green bell pepper off-note	Very weak, **musky**, slightly powdery
16		Very weak, **musky**, slightly oily	Very weak, **musky**
17		**Musky**, anisic, powdery, waxy	Weak, **musky**, slightly waxy

18 (*E/Z* 3:1)		**Musky**, slightly powdery, waxy	Weak, **musky**, slightly powdery, waxy
19		**Musky**, slightly green, powdery	Weak, **musky**, powdery, slightly animalic, waxy
58		Weak, waxy, lactonic, slightly metallic, rosey	Weak
20		Weak, honey, floral, polish, wax effect	Weak
21		Weak, slight solvent off-note	Weak, hint off green
2		**Musky**, slightly powdery, waxy	Weak, **musky**, slightly powdery, waxy
66 (*E/Z* 2:1)		**Musky**, waxy, hot iron, metallic, rosy, Rosalva like	Weak, a hint of **musky**, powdery, slightly animalic
(*E*)-**84**		**Musky**, slightly waxy, powdery	Weak, **musky**, slightly powdery, waxy, slightly green, parsley leaf
(*Z*)-**84**		Green, waxy, candle wax	Weak, slightly waxy

67		Weak, **musky**	Weak
58		Weak, powdery, anisic, green floral facet	Weak, hint of **musk**, powdery, slightly fatty
69		**Musky**, powdery, Exaltone aspect, slightly fatty, waxy, green	**Musky**, powdery, Exaltone aspect, slightly fatty,
100 (*E/Z* 9:1)		**Musky**, powdery, Exaltone aspect, waxy	**Musky**, powdery, Exaltone aspect
70		Weak, slightly green, hot iron off-note	Weak
71		**Musky**, waxy, slightly green, muscone direction	Weak, **musky**, waxy, green

Relative volatility study of selected civetone derivatives

The relative volatility of the fluorinated civetone analogues was analysed by GC-MS. Samples of compounds **X-X** (~1 mg) were dissolved in 400 μL of chloroform and 1 μL was injected into a programmable temperature vaporising (PTV) injector on the GC operating at a split of 160:1. The GC column used was a relatively non-polar Agilent Technologies J&W DB5-MS (15m x 0.25mm x 0.25mm) using helium as carrier gas at a constant flow of 1.5 mL/min. The GC temperature programme was 100° for 2.1 minutes, increasing at 25°/min up to 320° with a further 3.5 min isothermal at 320°. The injector temperature was 132° on injection and after 1 minute the injector temperature increased at 14.5°/sec to 320° (sample transfer phase). After 1 minute at 320° the temperature increased at 14.5°/sec to 400° and was held at this temperature for a further 2 minutes (injector cleaning phase) before cooling to prepare for the next sample injection. The ion source and GC-MS transfer line temperatures were 200° and 250° respectively and 70 eV EI mass spectra were acquired at 6 scans/sec using the Xcalibur software programme (v. 2.0.7).

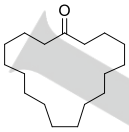
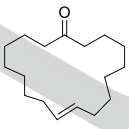
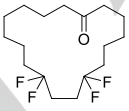
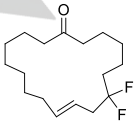
The mass spectra of all of the fluorinated compounds showed molecular ions and M-20, M-20-20 ions for loss of one and two molecules of HF. The spectra of civetone and dihydrocivetone also match with their entries in our mass spectral databases.

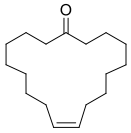
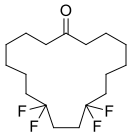
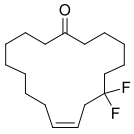
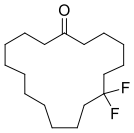
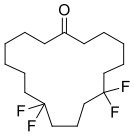
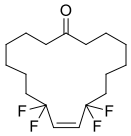
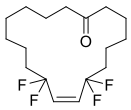
All of the samples gave a single sharp peak, or two for the *E/Z* diastereoisomers, for the expected compound. The variability in retention time is < 0.005 minutes (0.30 seconds), based on repeat analysis of several samples. On the type of GC column used elution order should be based primarily on volatility and molecular mass. The observed retention time are listed below (see table).

According to this data, the relative volatility order for the selected compounds is:

11 > (*E*)-1 > 16 > (*E*)-18 ≈ (*Z*)-1 > 14 > (*Z*)-18 > 19 ≈ 21 > 13 ≈ 15

Although the volatility of all civetone derivatives is quite similar, there are some subtle differences depending on the exact location and number of fluorine atoms and double bonds. Thus, fluorinated compounds are less volatile than their non-fluorinated counterparts. Also in most cases the unsaturated compounds elute later than the saturated equivalents, which suggests additional interaction between the column stationary phase and the double bonds. In particular, the *trans*-derivatives are more volatile than the corresponding *cis*-compounds. On the other hand, saturated 1,4-di-CF_2 derivatives seem to be more volatile than the compound containing the 1,5-di-CF_2 motif but there is no a similiar trend between difluorinated/tretrafluorinated molecules.

Volatility order	Comp.	Structure	M_W (g/mol)	Retention time (min)	ΔRt ($t_n - t_1$) (s)	ΔRt ($t_n - t_{n-1}$) (s)
1st	**11**		252	6.855	–	–
2nd	**(*E*)-1**		250	6.861	0.36	0.36
3rd	**16**		324	6.882	1.62	1.26
4th	**(*E*)-18**		286	6.889	2.04	0.42

5th	**(*Z*)-1**		250	6.893	2.28	0.24
6th	**14**		324	6.907	3.12	0.84
7th	**(*Z*)-18**		286	6.954	5.94	2.82
8th	**19**		288	6.961	6.36	0.42
9th	**21**		324	6.966	6.66	0.30
10th	**13**		322	7.008	9.18	2.52
11th	**15**		322	7.011	9.36	0.18