ChemPubSoc Europe

DOI: 10.1002/chem.201600519

CHEMISTRY
A European Journal
Full Paper

Organic Chemistry

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 structure and odour comparisons. 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 and co-workers 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.

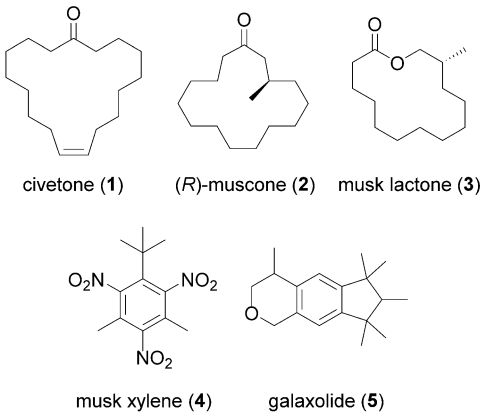

Figure 1. Structures of diverse musk odorants. Macrocycles **1**–**3** are natural products whereas **4** and **5** are synthetic.

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 fluorine atoms 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

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Supporting information for this article can be found under http://dx.doi.org/10.1002/chem.201600519.

CF_2 groups to an edge position, however, this is avoided and the ring distorts to create a new corner and a pseudorectangular conformation. This behaviour can be explained by two factors; the fluorine atoms 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 hydrogen atoms. Also, the C-CF_2-C angle ($\approx 118^\circ$) is significantly wider than the C-CH_2-C angle ($\approx 112^\circ$). 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 fluorine atoms to adopt corner locations. The behaviour extends to 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]

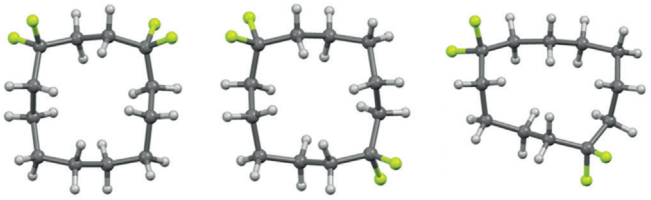
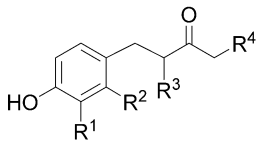


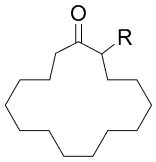
Figure 2. X-ray crystal structures of 1,1,4,4-(**6**), 1,1,7,7-(**7**) and 1,1,6,6-(**8**) tetrafluorocyclododecanes.

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.

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.



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 monofluorinated odorants.

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, in this case C17, 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.

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 study, 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).

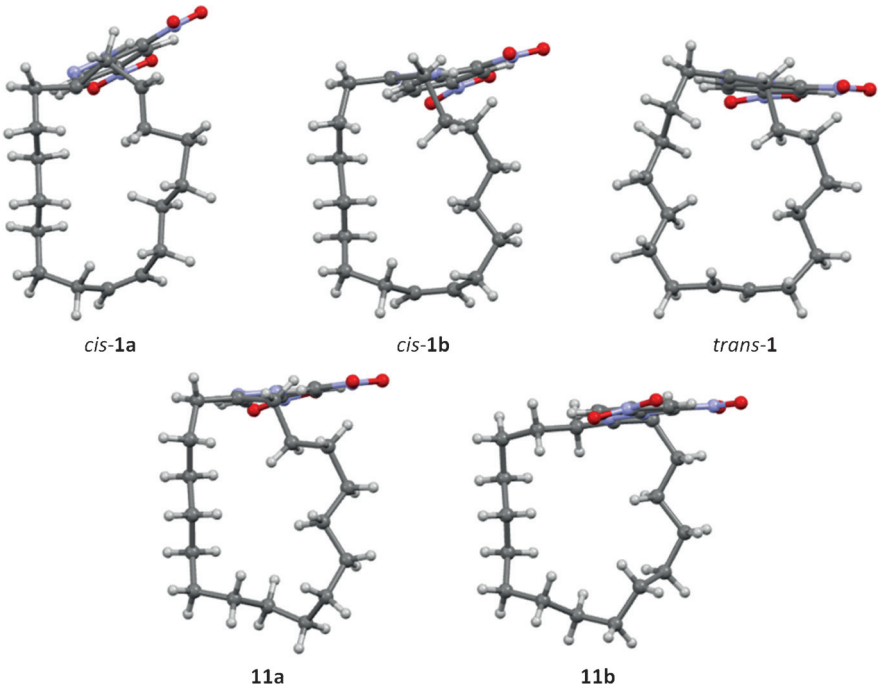
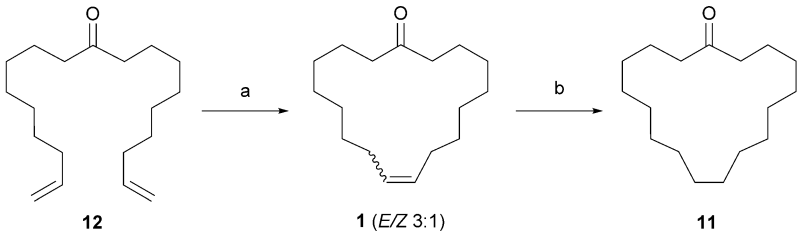


Figure 4. Solid state (X-ray) conformers of DNP-hydrazone derivatives of *cis*- and *trans*-civetone (**1**), and dihydrocivetone (**11**).



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**.

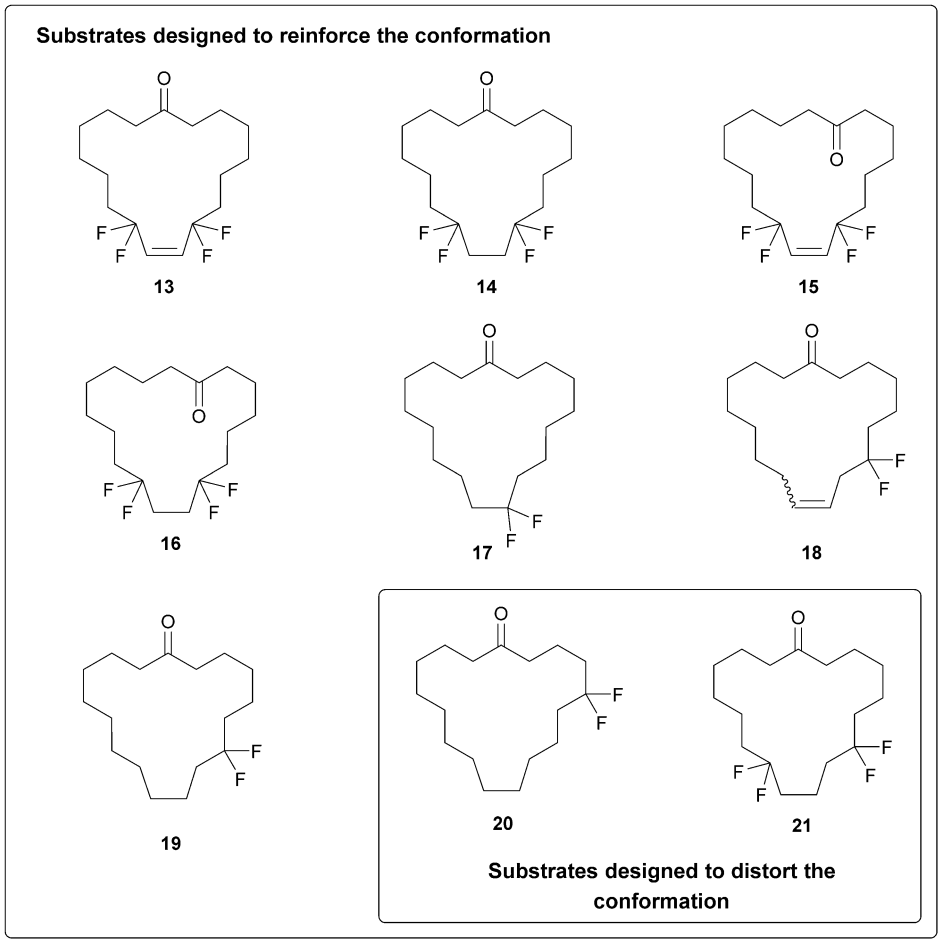


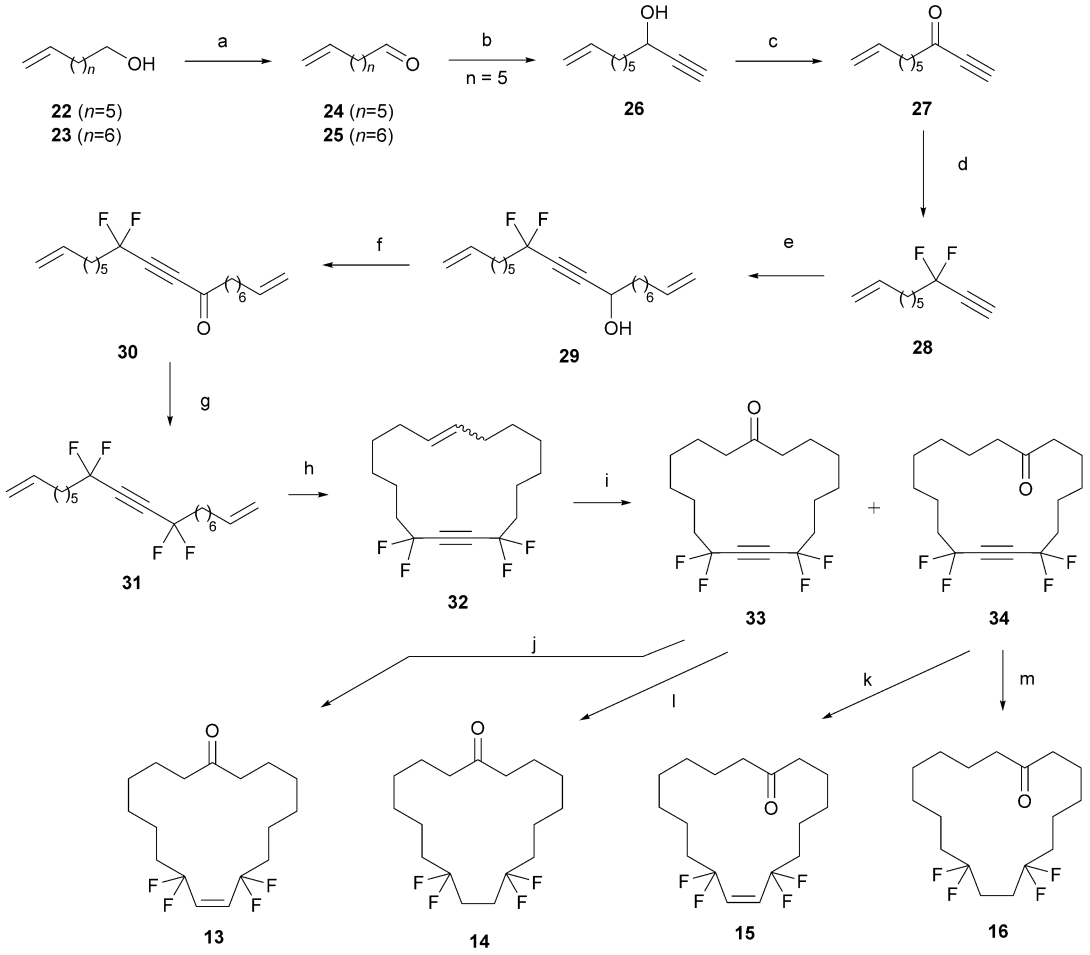
Figure 5. Target civetone analogue structures containing CF_2 groups.

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** possessed a faint musk odour relative to our synthetic reference samples of civetone (**1**) and dihydrocivetone **11**.

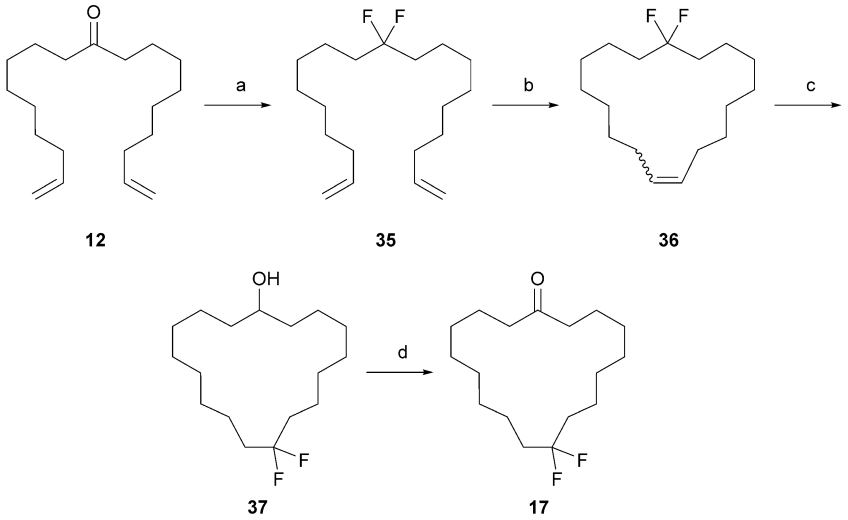
Mono-CF_2 civetone analogue **17** was readily synthesised from nonadeca-1,18-dien-10-one **12**[17b] in four steps (Scheme 3). The open chain hydrocarbon **35** was obtained in modest yield, by treatment of **12** with DAST. Diene **35** was then subject to an RCM reaction to afford macrocycle **36** 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**.

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.

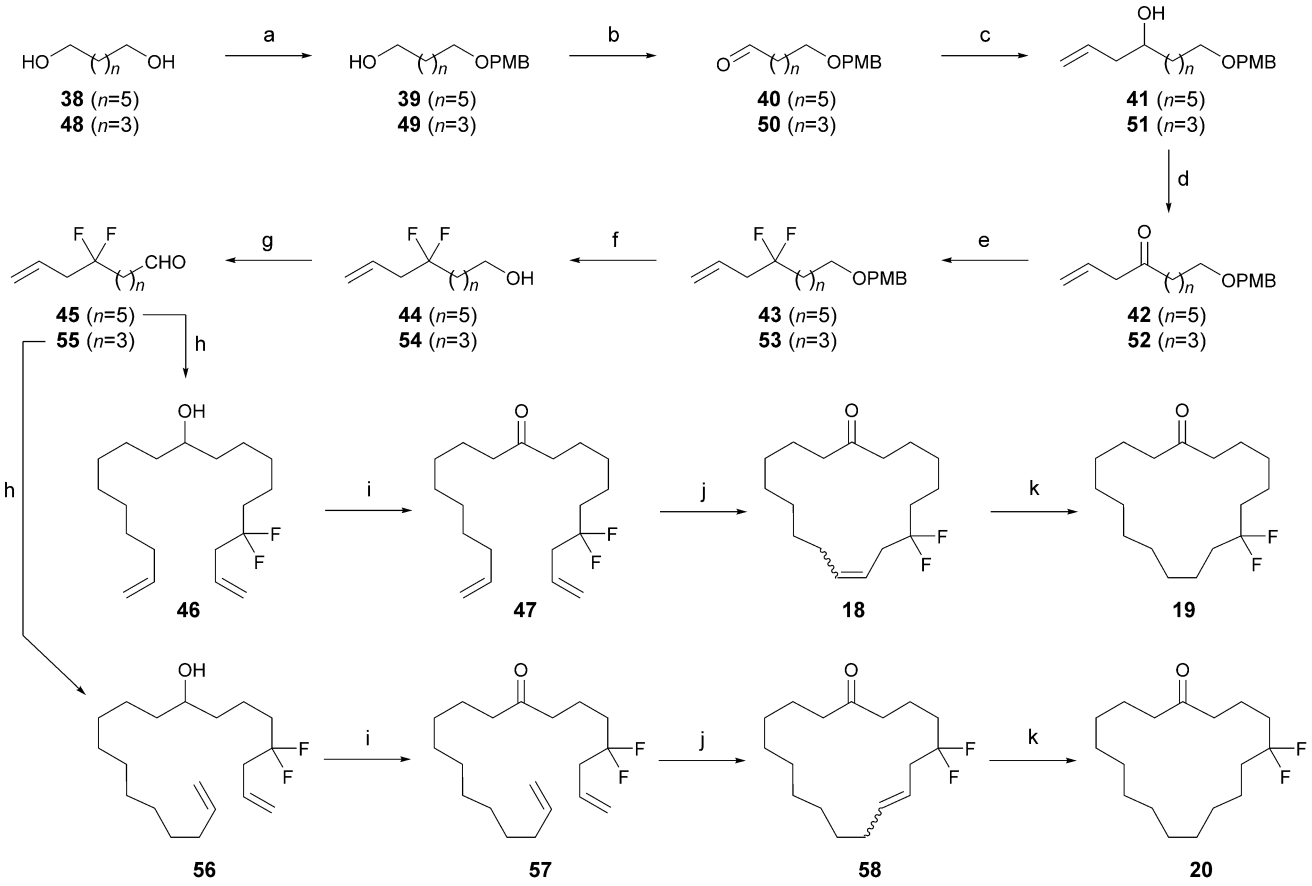
Analogue **20** was prepared as illustrated in Scheme 4, following the same strategy employed for **19**. Compound **20** dis-



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 at 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%.



Scheme 4. Synthesis of fluorinated civetone analogues containing a CF_2 group at 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).

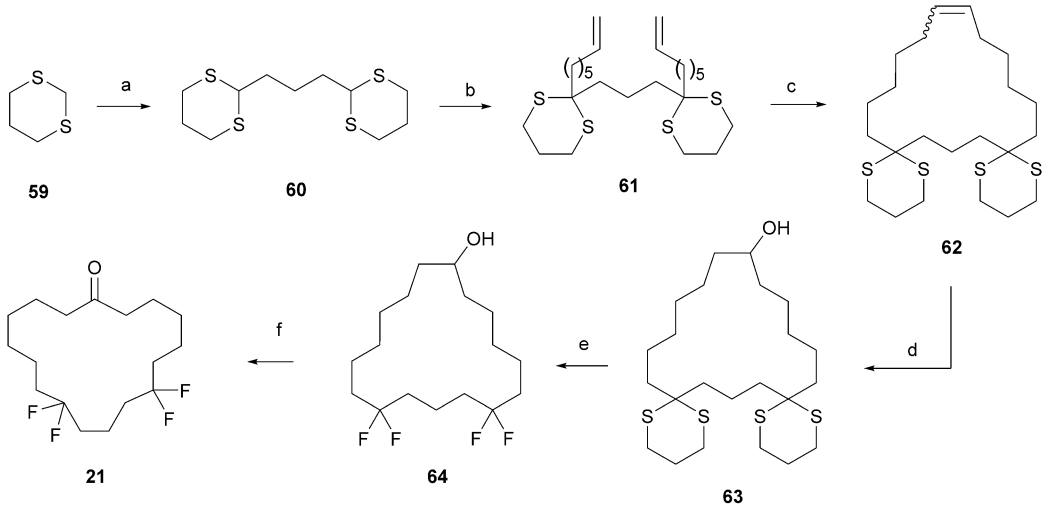
played a distinct floral odour, but without the characteristic musk notes of **1** and **11**.

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[24] 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 the Supporting Information).[25] 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.

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 usu-



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%.

ally 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 fluorine atoms 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 fluorine atoms.[26]

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.[27] 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.[28] 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) centred 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.

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 the Supporting Information) in order to establish the relative volatility of the civetone macrocycles, and there was a tendency towards

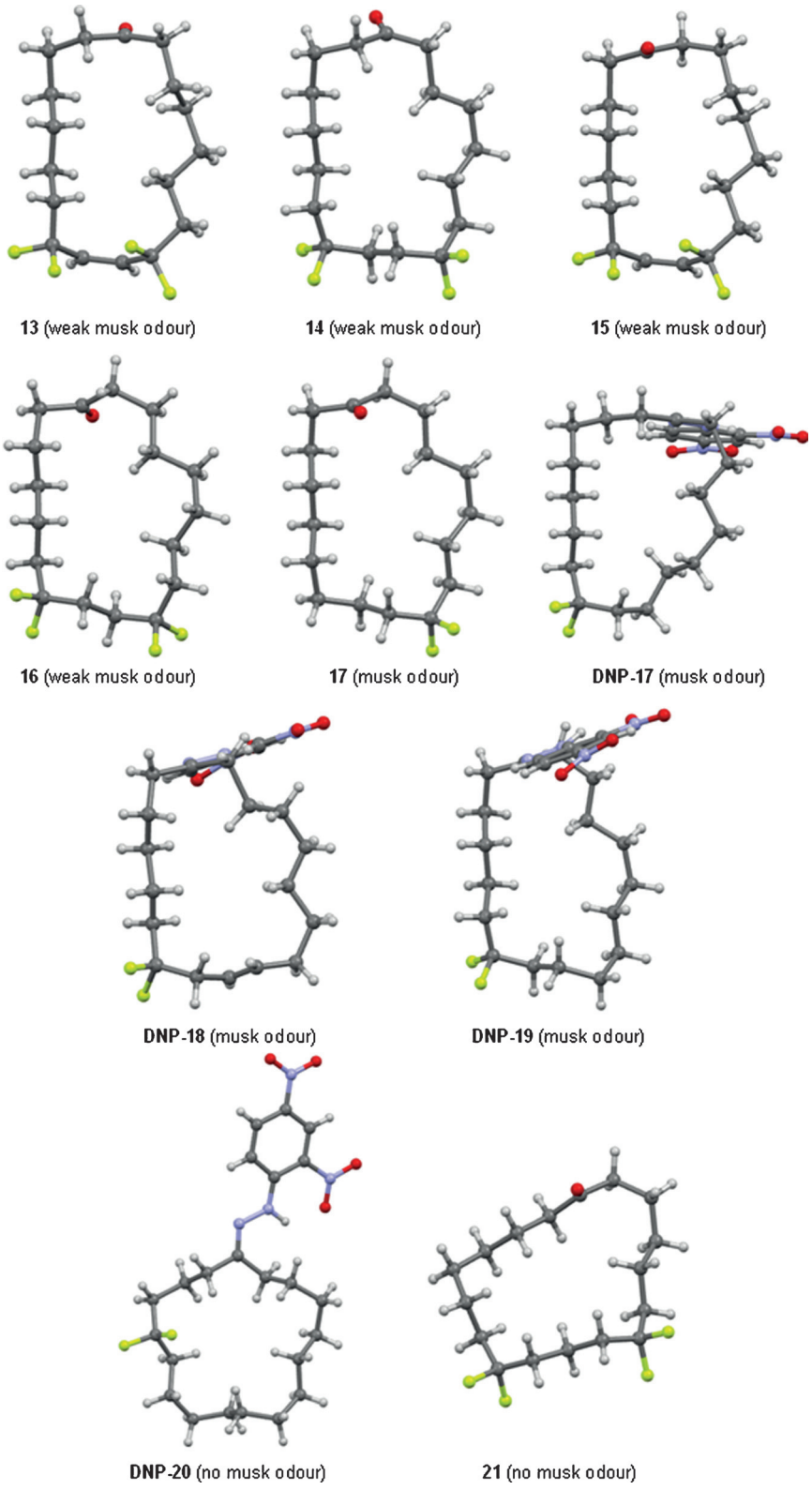


Figure 6. Preferred solid-state conformations of fluorinated civetone derivatives.

longer retention times for the tetrafluoro analogues, 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*.[29] The *S* enan-

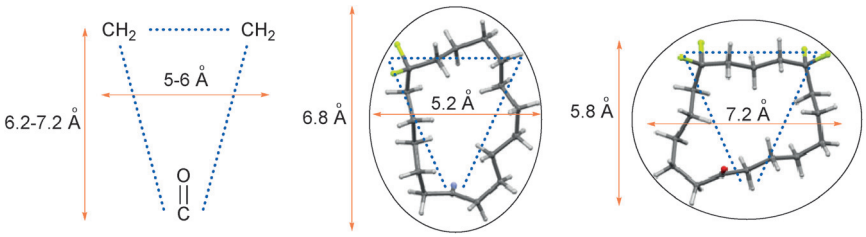


Figure 7. Proposed structural features for macrocyclic musk odorants and ellipsoid-like shape of fluorinated targets **19** and **21** (DNP fragment was omitted to simplify the Figure).

tiomer is described as having a poorer musk odour.[30] As a key perfumery component, (*R*)-**2** has been the target of a number of total syntheses;[31] 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**).[32] 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.

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.[31f] Crystallography of the DNP derivative of (*R*)-**2** gave a well resolved structure, as illustrated in Scheme 6.

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[31f] maps onto this structure, although all have a corner located at C-9 and conformers **2b**, **2e**, **2g** and **2h** (Figure 8) locate the

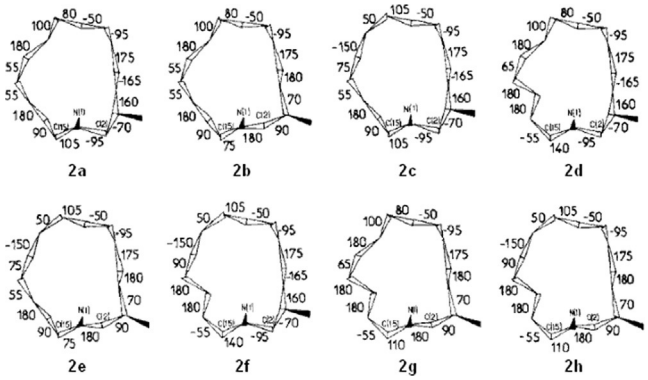
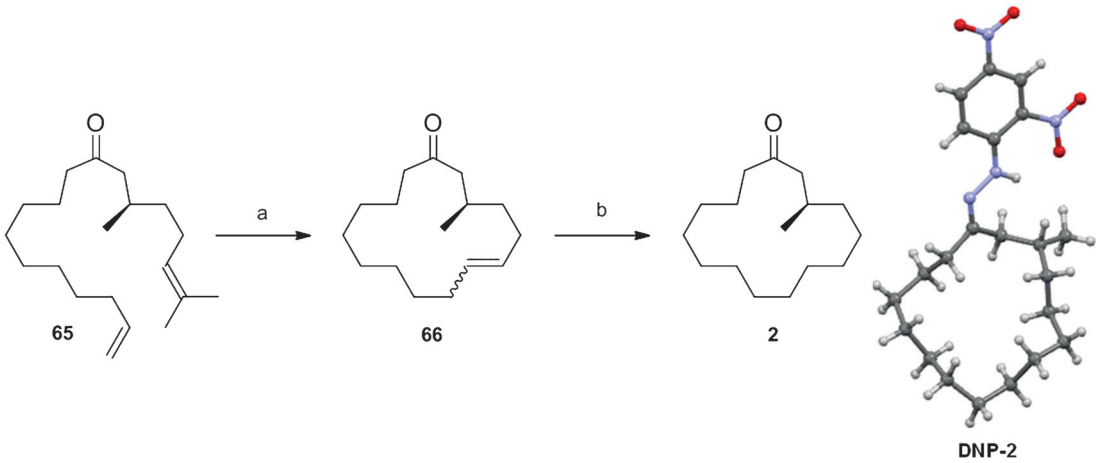


Figure 8. Proposed ring conformations **2a**–**2h** of (*R*)-muscone from Bernardinelli and Gerdil's X-ray study of the (*R*)-muscone-DNP derivative.

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 confor-



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%.

mational 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[32] 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** as shown in Scheme 6, where only four carbon atoms form the "side" of the structure from C-3 to C-6.

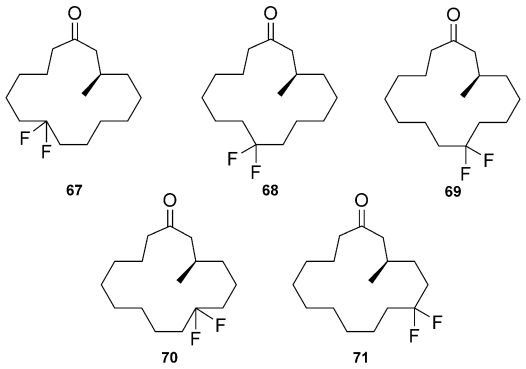


Figure 9. Structures of synthetic (*R*)-muscone targets containing CF_2 groups.

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**).[31a–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. Bromide **80** was then converted into the corresponding Grignard reagent for condensation with aldehyde **81**, itself derived from (+)-citronellal **72** as previously described.[31b] 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.

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 a 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**).

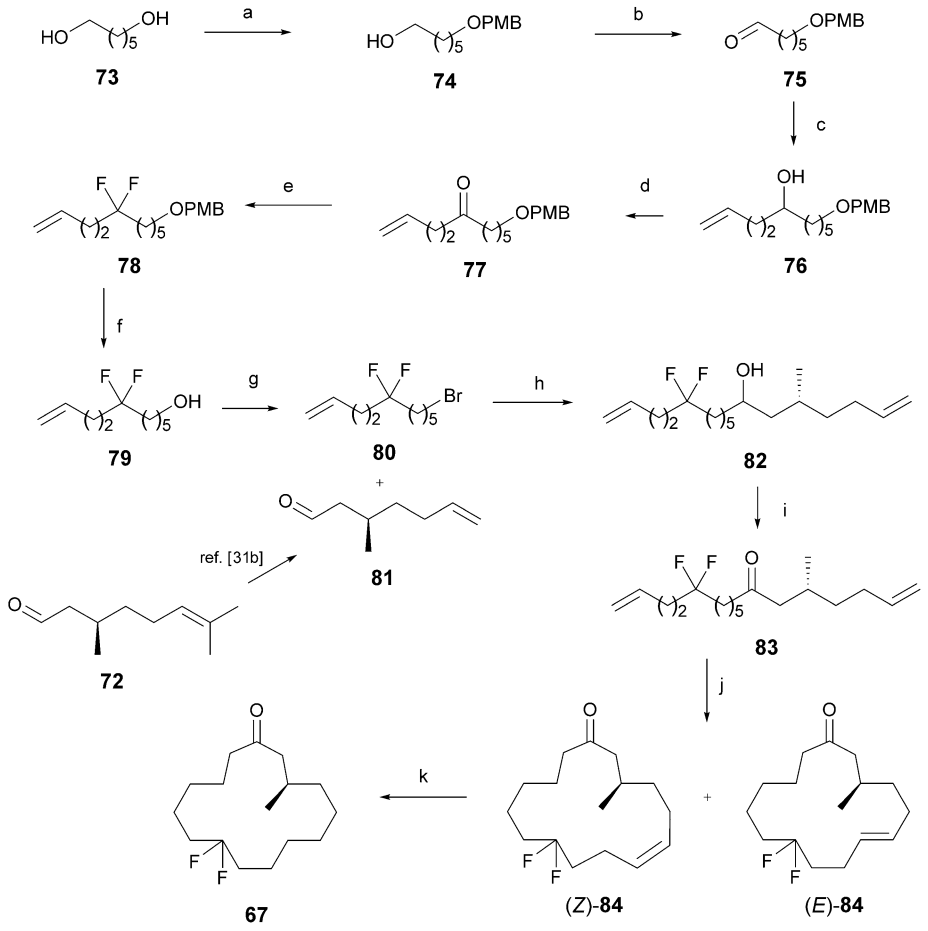
8,8-Difluoromuscone **69** was prepared by coupling fluorinated aldehyde **96** with the enantiopure alkyl bromide **97**,[33] as illustrated in Scheme 9. Aldehyde **96** was obtained in a similar manner to **45** (Scheme 4), but starting from the nonadiol **89**. A Grignard reaction between these entities 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 difluoromuscone 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**[31b] 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.

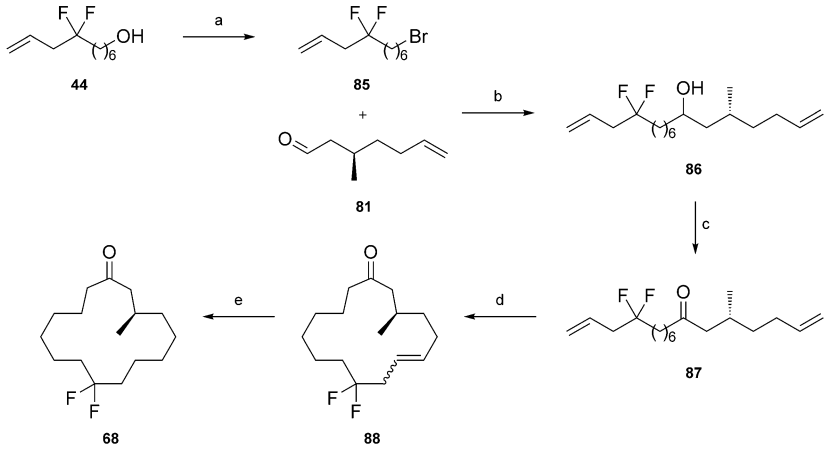
The last compound prepared in this series was muscone **71** as illustrated in Scheme 11. Alkene **102** was subjected to ozonolysis, and the resultant aldehyde was treated with a Grignard reagent derived from 4-bromo-1-butene, to generate alcohol **114**. This alcohol was oxidised to ketone **115** 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**).

Structure–odour relationships

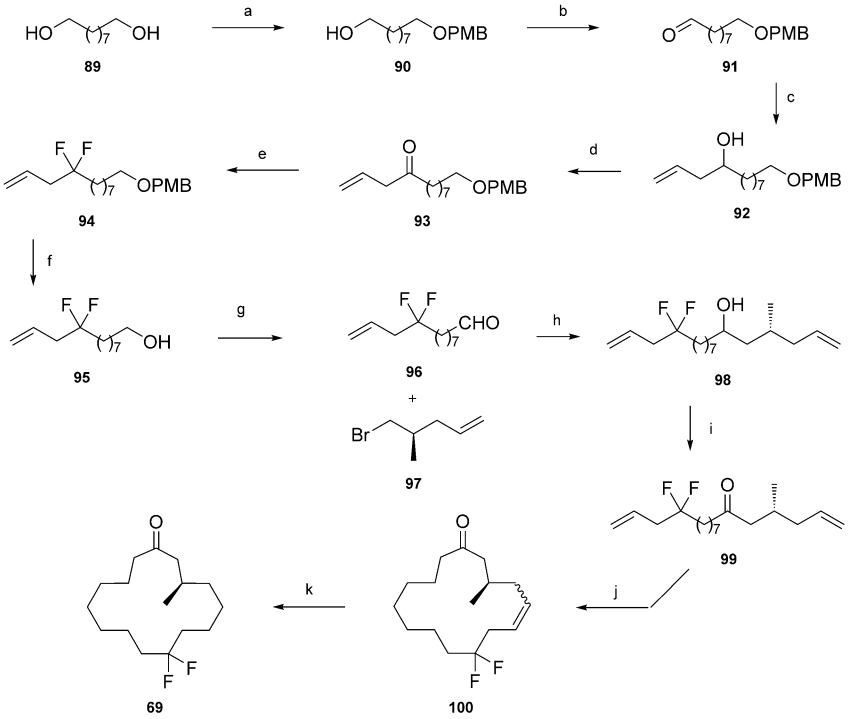
With muscones **67**–**71** in hand, it was of interest to obtain X-ray structural data where possible. Suitable crystals of ketones **67** and **70** were forthcoming, and DNP derivatives of ketones **68** and **69** were successfully prepared. Some of the unsaturated RCM products, such as (*Z*)-**84**, (*E*)-**100** and (*Z*)-**113** also



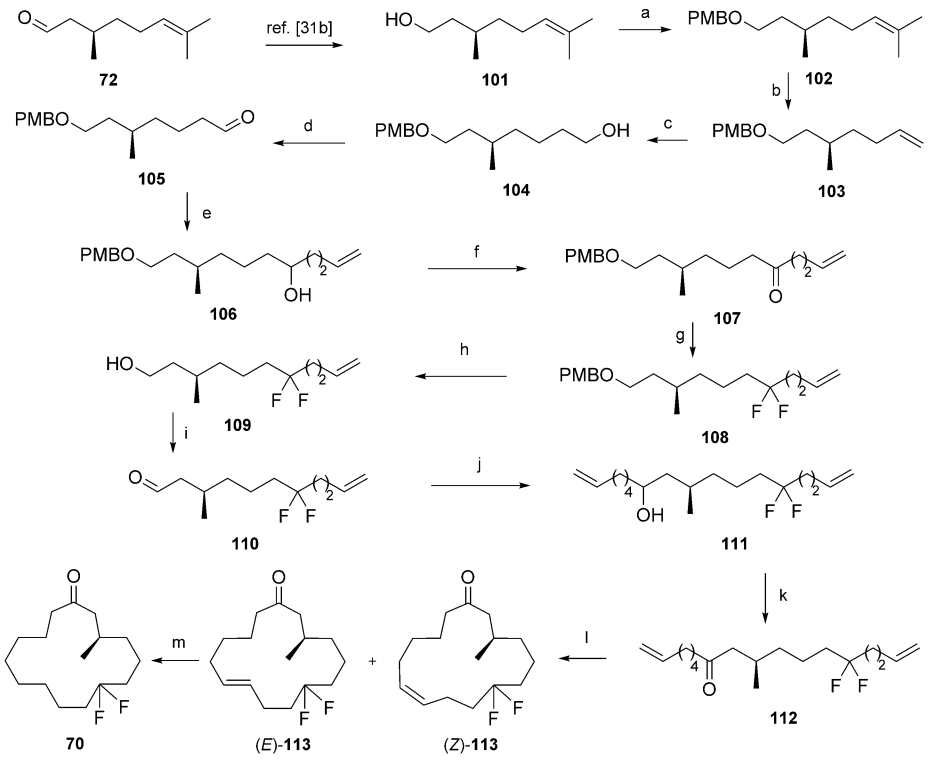
Scheme 7. Synthesis of fluorinated muscone analogue containing a CF_2 group at C10. Reagents and conditions: a) NaH, PMBCl, TBAI, THF, 0 °C→60 °C, overnight, 55%; b) DMP, DCM, RT, overnight; c) 1) 4-Bromo-1-butene, Mg (turnings), I_2 (trace), Et_2O, reflux, 2 h; 2) **75**, 0 °C→RT, overnight, 52% (three 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**.



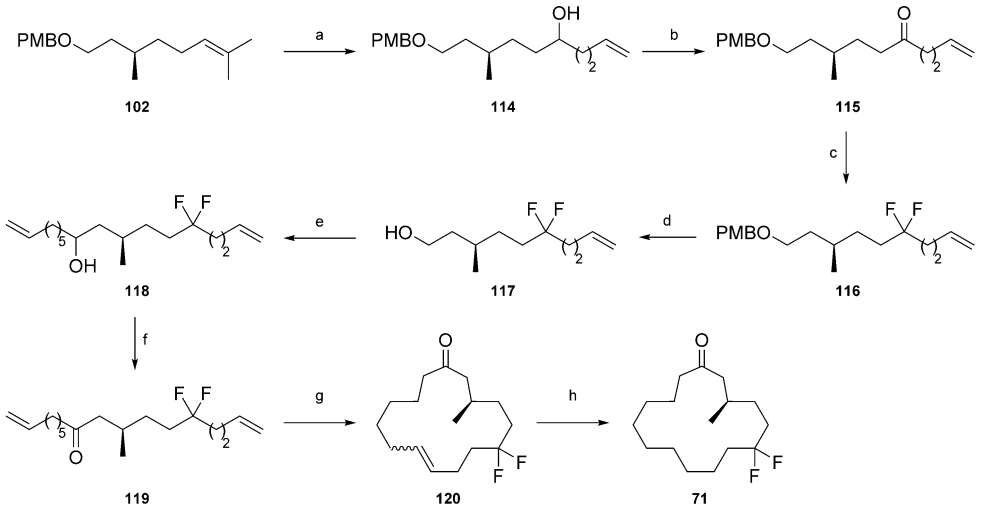
Scheme 8. Synthesis of fluorinated muscone analogue containing a CF_2 group at C9. Reagents and conditions: a) CBr_4, PPh_3, DCM, 0 °C→RT, overnight, 67%; b) 1) **85**, Mg (turnings), I_2 (trace), THF, reflux, 6 h; 2) **81**, RT, overnight, 40%; c) DMP, DCM, RT, 1 h; d) Grubbs' 1st generation catalyst (6 mol%), DCM, RT, reflux, overnight, 94% (two steps); e) H_2, Pd(C) (10 mol%), MeOH, RT, overnight, 41%.



Scheme 9. Synthesis of fluorinated muscone analogue containing a CF_2 group at 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 at C7. Reagents and conditions: a) NaH, PMBCl, TBAI, THF, 0 °C→60 °C, overnight, 82%; b) 1) O_3, DCM, −78 °C, 30 min; 2) PPh_3, −78 °C→RT, overnight; 3) *n*BuLi, $PMe(Ph)_3Br$, THF, −78 °C→RT, overnight, 36%; c) 1) 9-BBN dimer, THF, RT, overnight; 2) EtOH, NaOH, H_2O_2, 0 °C, 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 at C6. Reagents and conditions: a) 1) O_3, DCM, −78 °C, 15 min; 2) PPh_3, −78 °C →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%.

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).[31f] This feature is also found in the DNP structure of synthetic muscone (**2**; Scheme 6). 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,[32] with the methyl group at an edge. A hint of musk was recognised with ketone **68**.

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.[34] 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.

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

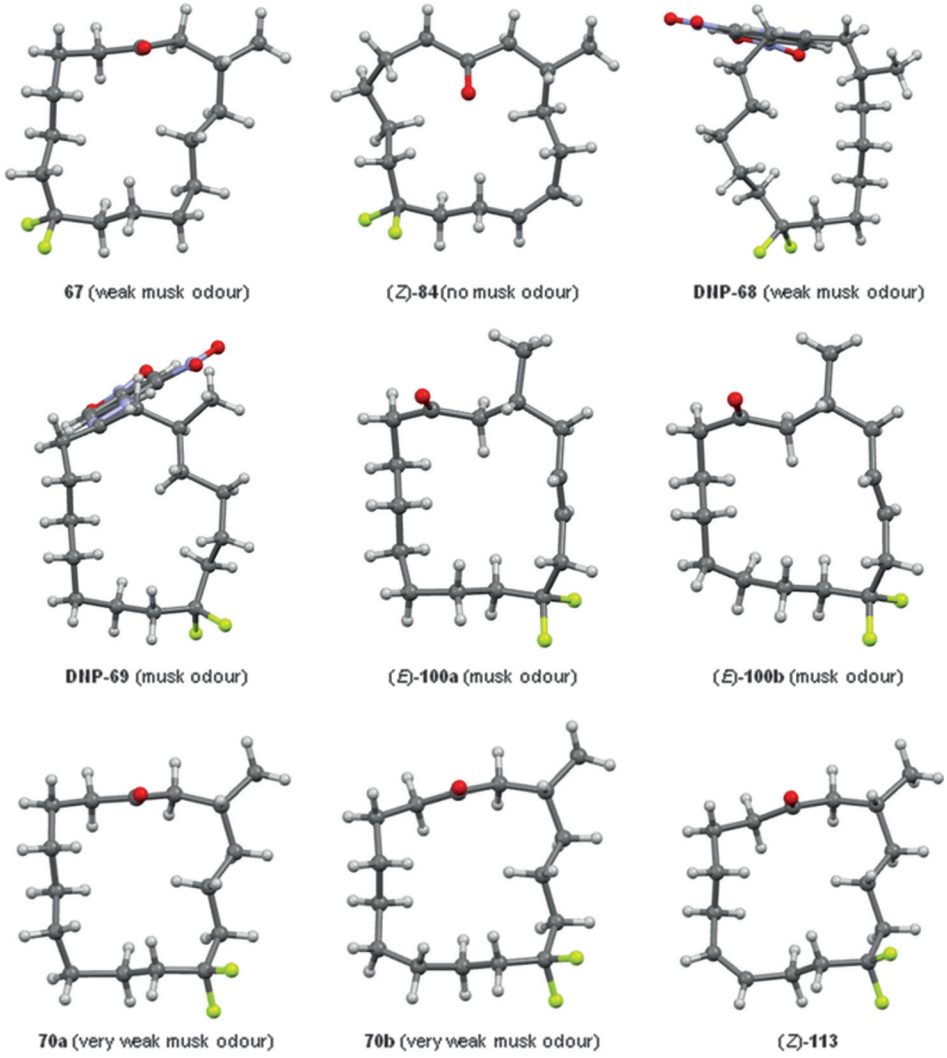


Figure 10. X-ray structures of fluorinated muscone derivatives.

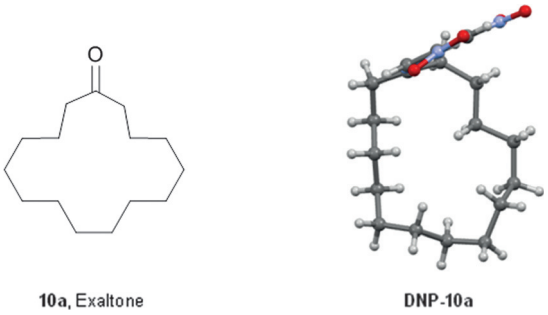


Figure 11. X-ray crystal structure of exaltone DNP-derivative[34].

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.

Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council (EPSRC) and the European Research Council (ERC). We are grateful to Prof. Paul N. Davey and Dominique Lelièvre (Givaudan, Schweiz AG, Dübendorf, Switzerland)

for the olfactory evaluation of the compounds. The authors acknowledge the EPSRC National Mass Spectrometry Facility (Swansea) and Mrs. Caroline Horsburgh (University of St. Andrews) for analytical assistance. M.Y. thanks the China Scholarship Council for financial support. D.O'H. thanks the Royal Society for a Wolfson Research Merit Award.

Keywords: conformation analysis · macrocycles · musk fragrances · organofluorine chemistry · structure–activity relationships

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Received: February 3, 2016
Published online on May 6, 2016