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## Fluorine in fragrances: exploring the difluoromethylene (CF<sub>2</sub>) group as a conformational constraint in macrocyclic musk lactones†

Michael J. Corr,<sup>a</sup> Rodrigo A. Cormanich,<sup>b</sup> Cortney N. von Hahmann,<sup>a</sup> Michael Bühl,<sup>a</sup> David B. Cordes,<sup>a</sup> Alexandra M. Z. Slawin<sup>a</sup> and David O'Hagan<sup>\*a</sup>

The CF<sub>2</sub> group is incorporated into specific positions within the lactone ring of the natural musk lactone, (12*R*)-(+)-12-methyl-13-tridecanolide, a constituent of Angelica root oil, *Angelica archangelica* L. The approach is taken as it was anticipated that CF<sub>2</sub> groups would dictate corner locations in the macrocycle and limit the conformational space available to the lactone. Three fluorine containing lactones are prepared by organic synthesis. One (**8**) has CF<sub>2</sub> groups located at the C-6 and C-9 positions, another (**9**) with CF<sub>2</sub> groups at the C-5 and C-9 positions, and a third (**10**) with a CF<sub>2</sub> group at C-8. Two of the fluorine containing lactones (**8** and **10**) were sufficiently crystalline to obtain X-ray crystal structures which revealed that the CF<sub>2</sub> groups do adopt corner locations. All three lactones were subject to computational analysis at the B3LYP-D3/6-311+G\*\* level to assess the relative energies of different conformers. In all cases, the global minima and most of the lowest energy minima have squared/rectangular geometries and located the CF<sub>2</sub> groups at the corners. The lowest energy structures for **8** and **10** closely approximated the observed X-ray structures, suggesting good convergence of theory and experiment in determining relevant low energy conformations. All three compounds retained a pleasant odour suggesting the rings retained sufficient conformational flexibility to access relevant olfactory conformations.

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## Introduction

The selective replacement of a hydrogen for a fluorine atom is a powerful method for altering the properties of organic compounds, and a strategy that is widely used in bio-organic and medicinal chemistry.<sup>1–3</sup> Generally, this replacement has only a moderate steric effect, but the high electronegativity of the fluorine can have significant electronic influences.<sup>4</sup> The difluoromethylene (CF<sub>2</sub>) group has received considerably less attention as a group for modifying the properties of organic molecules relative to the –F and –CF<sub>3</sub> groups.<sup>5</sup> However, we have recently reported<sup>6–8</sup> that incorporation of a CF<sub>2</sub> group can influence the conformation of organic molecules. In particular, cyclododecanes **1–3** were prepared with varied locations of two difluoromethylene groups (Fig. 1). X-ray crystal structure analysis showed that the CF<sub>2</sub> groups only occupied corner positions. In the case of cyclododecanes **1** and **2**, this stabilises the

square like conformation. However, in the case of cyclododecane **3**, incorporation of the difluoromethylene group 1,6 to each other results in considerable distortion of the ring conformation as the CF<sub>2</sub> group avoids an unfavourable edge location.

Natural musks are large conformationally flexible macrocyclic lactones and we were interested to evaluate if the CF<sub>2</sub> group might limit this conformational flexibility as a tool for exploring preferred conformations responsible for scent. (12*R*)-(+)-12-Methyl-13-tridecanolide **4** is a natural constituent of Angelica root oil, *Angelica archangelica* L.<sup>9</sup> The (*R*)-enantiomer is described as having “a clean, crystal-clear musk top note with strong, elegant woody accents”.<sup>10,11</sup> Macrocyclic **4** possesses a high degree of conformational flexibility and could be expected to adopt a wide variety of conformations, not all of which are likely to be active musk odorants. Several syntheses of (*R*)-**4** have been reported,<sup>10,12–14</sup> but little work has been carried out on determining the active conformations of the musk lactone that contribute to its scent. One such study by Kraft and Cadalbert<sup>15</sup> calculated the six lowest-energy conformations of (*R*)-**4** (Fig. 3), all of which were within 0.9 kcal mol<sup>–1</sup> of each other. In order to impart conformational restriction, they synthesised three musk lactone derivatives **5–7** (Fig. 2), featuring bridging methylene groups. Musk derivatives **5–7** were weaker odorants than the parent (*R*)-**4**, as the authors predicted, but did modify the olfactory properties resulting in slightly differing smell descriptions.

<sup>a</sup>School of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK. E-mail: do1@st-andrews.ac.uk

<sup>b</sup>Chemistry Institute, University of Campinas, Campinas, SP 13083-970, Brazil

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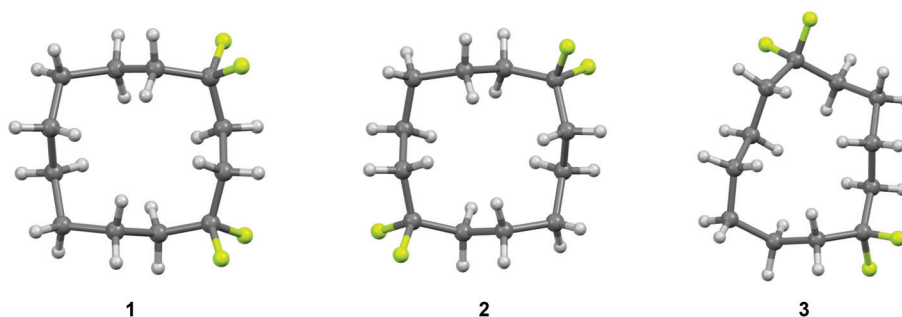


Fig. 1 X-ray crystal structures of 1,1,4,4-(1), 1,1,7,7-(2) and 1,1,6,6-(3) tetrafluorocyclododecanes.<sup>6a</sup> The CF<sub>2</sub> groups conspicuously adopt corner locations either reinforcing square like structures for 1 and 2 or a inducing a distorted ring for structure 3.



Fig. 2 (12*R*)-(+)-12-Methyl-13-tridecanolide 4 and bridged musk lactones 5–7.

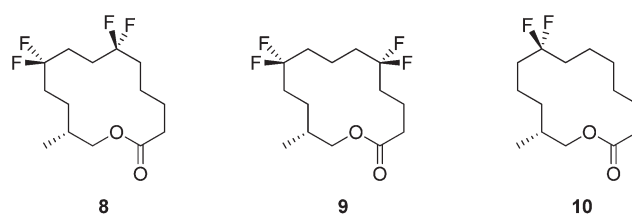


Fig. 4 Target musk lactone analogues 8–10 incorporating CF<sub>2</sub> moieties.

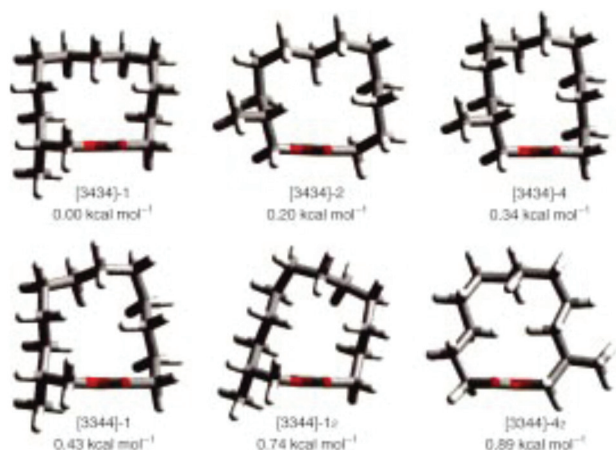


Fig. 3 The six lowest-energy conformations of musk lactone (*R*)-4 as reported by Kraft and Cadalbert (MM3 force field).<sup>15</sup>

As a continuation of the observation that difluoromethylene groups can influence macrocyclic ring conformation, we decided to investigate the synthesis of CF<sub>2</sub> analogues of (12*R*)-(+)-12-methyl-13-tridecanolide 4. The predicted lower energy conformers shown in Fig. 3 are largely rectangular structures with linear edges of four or five methylene groups. It was envisaged that strategic incorporation of CF<sub>2</sub> groups into the macrolide would allow different ground state conformations to be more highly populated, and then different conformations could be assessed for their musk/odour properties.

In this respect lactones 8, 9 and 10 (Fig. 4) were selected for synthesis. In each case we anticipated that they would adopt different Kraft and Cadalbert conformations (Fig. 3). Conformation [3434]-4 has a four carbon edge running along the top of the ring which should be reinforced by the 1,4-CF<sub>2</sub> groups in structure 8. Conformation [3434]-1, the lowest energy Kraft and Cadalbert structure should be reproduced by lactone 9 if the hypothesis holds. Finally the Kraft and Cadalbert structure [3344]-1, which is 0.74 kcal mol<sup>−1</sup> above the ground state structure, is an asymmetric rectangular structure, with a methyl at a corner location, a conformation which should be preferred by lactone 10, which will locate a corner at C-8 of the lactone ring.

## Results and discussion

### Synthesis

In order to prepare the CF<sub>2</sub> containing musk lactones 8–10, a synthesis was devised that would allow their assembly from a common enantiomerically pure chiral fragment (Scheme 1). (*R*)-Olefin 11 was chosen as it could be progressed in three separate directions to aldehyde 12, epoxide 13 and aldehyde 14, respectively. It was envisaged that intermediates 12–14 could then be progressed to the individual musk lactones 8–10. A key strategy for incorporating the CF<sub>2</sub> groups would exploit Grée's method of diethyaminosulfur trifluoride (DAST) treatment of propargylic ketones to generate propargylic difluoromethylene.<sup>16</sup>





**Scheme 1** Planned routes to target lactones **8–10** from (*R*)-olefin **11**.



**Scheme 2** Synthesis of chiral fragments **11** and **12**. Reagents and conditions: (a) (i)  $\text{H}_2\text{O}_2$ , MeOH, 30 min. (ii)  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ ,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ,  $\text{H}_2\text{O}$ , 20%; (b) (i) Oxazolidinone **20**,  $n\text{BuLi}$ , THF,  $-78^\circ\text{C}$ , 30 min. (ii) Pivaloyl chloride,  $\text{NEt}_3$ , THF,  $0^\circ\text{C}$ , 30 min, r.t., 1.5 h, 93%; (c) NaHMDS, MeI, THF,  $-78^\circ\text{C}$ , 3 h, 92%, dr >98 : 2; (d)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ , 2 h, 66%; (e) NaH, BnBr, DME, r.t.-reflux, 20 h, 94%; (f) (i)  $\text{O}_3$ , DCM,  $-78^\circ\text{C}$ . (ii)  $\text{PPh}_3$ ,  $-78^\circ\text{C}$ –r.t., 55%.

(*R*)-Olefin **11** was prepared as shown in Scheme 2. Firstly hexanoic acid **19** was obtained from cyclohexanone **18** by the method reported by Ogibin *et al.*<sup>17</sup> Carboxylic acid **19** was then activated as a mixed anhydride and coupled<sup>18</sup> to (*R*)-oxazolidinone **20**<sup>19</sup> to generate **21**. Asymmetric methylation with iodomethane gave **22** as a single diastereoisomer and the stereochemistry was established by X-ray crystallographic analysis as shown in Fig. 5. Oxazolidinone **22** was then progressed to aldehyde **12** by a sequence of lithium aluminium hydride ( $\text{LiAlH}_4$ ) reduction to give alcohol **23**, benzyl ether formation<sup>20</sup> to give (*R*)-alkene **11** and then ozonolysis.

Attention turned to the synthesis of the propargylic difluoromethylene fragments **28a** and **28b** in Scheme 3. Diols **24a** and **24b** were mono-protected<sup>21</sup> as their 4-methoxybenzyl ethers to give alcohol **25a** and **25b** by modification of a previous procedure.<sup>5</sup> Oxidation to the corresponding aldehydes,<sup>22</sup> followed by reaction with ethynylmagnesium bromide gave propargylic alcohols **26a** and **26b**. Dess–Martin periodinane



**Fig. 5** X-ray crystal structure of compound **22**.

(DMP)<sup>23</sup> oxidation gave propargyl ketones **27**, which were treated with DAST in methodology developed by Grée<sup>16,24,25</sup> to give the required difluoromethylene acetylenes **28a** and **28b**.

With the appropriate fragments in hand, attention turned to the synthesis of lactone **8** (Scheme 4). Lithiation of alkyne **27b** with *n*-butyllithium, and then treatment with, aldehyde **12**





**Scheme 3** Synthesis of difluoro-alkyne fragments **28a** and **28b**. Reagents and conditions: (a) NaH, PMB-Cl, TBAI, THF, 0 °C–reflux, 19 h, **25a** 85%, **25b** 55%; (b) **25a**: DMP, DCM, r.t., 18 h, 100%; **25b**: oxalyl chloride, DMSO,  $\text{NEt}_3$ , DCM,  $-78$  °C–0 °C, 3 h, 100%; (c) ethynylmagnesium bromide, THF,  $-78$  °C–r.t., 18 h, **26a** 71%, **26b** 77%; (d) DMP, DCM, r.t., 2 h, **27a** 85%, **27b** 71%; (e) DAST, 50 °C, 18 h, **28a** 61%, **28b** 51%.



**Scheme 4** Synthesis of musk lactone **8**. Reagents and conditions: (a) (i)  $n\text{BuLi}$ , THF,  $-78$  °C, 30 min. (ii) Aldehyde **12**, THF,  $-78$  °C–r.t., 20 h, 61%; (b) DMP, DCM, r.t., 2 h, 89%; (c) DAST, 50 °C, 18 h, 71%; (d) DDQ, DCM,  $\text{H}_2\text{O}$ , r.t., 2 h, 78%; (e) BAIB, TEMPO,  $\text{CH}_3\text{CN}$ ,  $\text{H}_2\text{O}$ , r.t., 7 h, 58%; (f) palladium on carbon (10 wt%),  $\text{H}_2$ , MeOH, r.t., 18 h, 65%; (g) LiOH, THF,  $\text{H}_2\text{O}$ , r.t., 3 h, 94%; (h) 2,4,6-trichlorobenzoyl chloride,  $\text{NEt}_3$ , THF, r.t., 2.5 h. (ii) 4-DMAP, toluene, r.t., 3.5 h, 54%.

gave alcohol **15** as a 1 : 1 mixture of diastereoisomers. After oxidation,<sup>23</sup> ketone **29** was converted to alkyne **30** with DAST. 4-Methoxybenzyl cleavage<sup>26</sup> and then oxidation with bis-(acetoxy)iodobenzene (BAIB)/TEMPO<sup>27</sup> generated carboxylic acid **32**. Benzyl deprotection could not be achieved under standard conditions, proving resistant to hydrogenation in either ethyl acetate or THF. Hydrogenation in methanol was successful but ester formation occurred to give the saturated methyl ester **33**. This proved satisfactory and then finally ester hydrolysis and macrolactonisation<sup>28</sup> of *seco*-acid **34** gave lactone **8** as a white waxy semi crystalline solid. Lactone **8**

proved amenable to X-ray crystal structure analysis and the structure is shown in Fig. 6.

For the synthesis of lactone **9**, alkene **11** was oxidised with *meta*-perbenzoic acid (*m*CPBA) to give epoxide **13** as a 1 : 1 mixture of diastereoisomers. Ring opening addition of lithiated alkyne **28a**<sup>29</sup> to epoxide **13** gave alcohol **16** in 60% yield. The acetylene could be selectively reduced to the (*Z*)-alkene with a poisoned palladium catalyst,<sup>30</sup> and this gave alkene **35** in 82% yield. This partial reduction was necessary as fluorinations of the ketone from the oxidised acetylene **16** lead to decomposition in reactions with DAST. From here, a similar





Fig. 6 X-ray crystal structure of musk lactones **8** (two conformers **8'** and **8''** are obvious in the unit cell) and **10**.

sequence of reactions as describe for the conversion of **14** to **8** was used to convert alcohol **35** to lactone **9**. This lactone was an oil at room temperature and it was not possible to obtain an X-ray structure.

For the synthesis of lactone **10**, (*R*)-olefin **11** was again used as a starting material but this time converted to aldehyde **14**. This was achieved by hydroboration,<sup>31</sup> followed by oxidation with DMP (Scheme 6). The terminal acetylene **43** was prepared by protection of 6-heptyn-1-ol **42**. A coupling of alkyne **43** and aldehyde **14** gave alcohol **16** in good yield. Following a similar sequence to the conversions in Scheme 4 and Scheme 5, alcohol **17** was converted to *seco*-acid **48**, without having to progress through the corresponding methyl ester. Macrolactonisation<sup>28</sup> of *seco*-acid **48** gave lactone **10** as a white solid. This lactone was also a wax but a suitable crystal was grown which proved amenable to X-ray structure analysis, and the resultant structure is shown in Fig. 6.



**Scheme 5** Synthesis of musk lactone **9**. Reagents and conditions: (a) *m*CPBA, DCM, r.t., 18 h, 55%; (b) (i) *n*BuLi, THF,  $-78^{\circ}\text{C}$ , 15 min. (ii)  $\text{BF}_3\cdot\text{OEt}_2$ , 15 min. (iii) Epoxide **13**, THF,  $-78^{\circ}\text{C}$ –r.t., 20 h, 60%; (c) palladium (5% on barium sulfate), quinoline, pyridine,  $\text{H}_2$  (1 atm), 22 h, 82% (d) DMP, DCM, r.t., 2 h, 57%; (e) DAST,  $50^{\circ}\text{C}$ , 18 h, 27%; (f) DDQ, DCM,  $\text{H}_2\text{O}$ , r.t., 2 h, 70%; (g) BAIB, TEMPO,  $\text{CH}_3\text{CN}$ ,  $\text{H}_2\text{O}$ , r.t., 18 h, 49%; (h) palladium on carbon (10 wt%),  $\text{H}_2$ , MeOH, r.t., 18 h, 59%; (i) LiOH, THF,  $\text{H}_2\text{O}$ , r.t., 3 h, 70%; (j) 2,4,6-Trichlorobenzoyl chloride,  $\text{NEt}_3$ , THF, r.t., 2.5 h. (ii) 4-DMAP, toluene, r.t., 3.5 h, 52%.







**Scheme 6** Synthesis of musk lactone **10**. Reagents and conditions: (a) (i) 9-BBN dimer, THF, 0 °C–r.t., 23 h. (ii) EtOH, NaOH (2 N), H<sub>2</sub>O<sub>2</sub>, 0 °C–r.t., 3 h, 59%; (b) DMP, DCM, r.t., 1 h, 100%; (c) NaH, PMBCL, DMF, 0 °C–r.t., 18.5 h, 87%; (d) (i) *n*BuLi, THF, –78 °C, 30 min. (ii) Aldehyde **14**, THF, –78 °C–r.t., 20 h, 80%; (e) DMP, DCM, r.t., 2 h, 61%; (f) DAST, 50 °C, 18 h, 62%; (g) DDQ, DCM, H<sub>2</sub>O, r.t., 2 h, 88%; (h) BAIB, TEMPO, CH<sub>3</sub>CN, H<sub>2</sub>O, r.t., 7 h, 48%; (i) palladium hydroxide on carbon (20 wt%), H<sub>2</sub>, THF, r.t., 18 h, 46%; (j) (i) 2,4,6-trichlorobenzoyl chloride, NEt<sub>3</sub>, THF, r.t., 2.5 h. (ii) 4-DMAP, toluene, r.t., 3.5 h, 67%.

### X-ray structures

Lactone **8** has two conformers **8'** and **8''**, which are present in a 1 : 1 ratio within the unit cell. It is immediately apparent that the CF<sub>2</sub> groups locate at corner positions, thus the anticipated role of the CF<sub>2</sub> group is as predicted. Also for X-ray structures **8'** and **10** adopt the anticipated Kraft and Cadalbert conformations (Fig. 3). Structure **8'** corresponds to the [3434]-4 structure which has the methyl group at an edge position, and structure **8''** corresponds to the [3344]-1 structure with the methyl group at a corner. Presumably they are close in energy. For lactone **10** the predicted Kraft and Cadalbert [3344]-1 structure is also observed. Lactone **9** is a liquid at room temperature and we could not obtain any X-ray structural data, although we predict that the Kraft and Cadalbert structure [3434]-1, will be relevant (see theory study below).

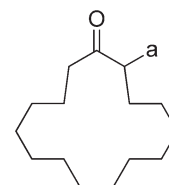
Lactones **8–10** all smell rather similar and all retain a pleasant muskoid odour, with the additional descriptors, 'weak hint of green, powdery'.<sup>32</sup> A distinct smell differential between the compounds proved difficult to discern even for compound **8** despite its having four fluorine atoms. So we could not draw any significant conclusions from the smell analysis, except to conclude that they retained a pleasant odour.

Michel and Schlosser report<sup>33,34</sup> the only other examples that we are aware of where fluorine substitutions for hydrogen have been used as a probe to examine fragrance. They explored several flavour and fragrance compounds and in general found

that there was no significant change in taste or smell when a hydrogen was replaced by a fluorine. For example, for the raspberry ketone **49** a systematic fluorine scan generated analogues **49a–d**, however this resulted in little change to the smell, whereas the same systematic replacement by a methyl has a much more profound effect on the organoleptic properties.<sup>33</sup> They concluded that the fluorine did not induce a significant conformational or steric/shape change in this case, whereas the methyl analogues do. In the case of musk lactone **50** and analogue **50a**, the fluorine located alpha to the ketone made a significant difference in the smell. This was attributed to a conformational change induced by the fluorine, although no conformational analysis was carried out.<sup>34</sup>



- 49** a = H, b = H, c = H, d = H  
**49a** a = F, b = H, c = H, d = H  
**49b** a = H, b = F, c = H, d = H  
**49c** a = H, b = H, c = F, d = H  
**49d** a = H, b = H, c = H, d = F



- 50** a = H  
**50a** a = F



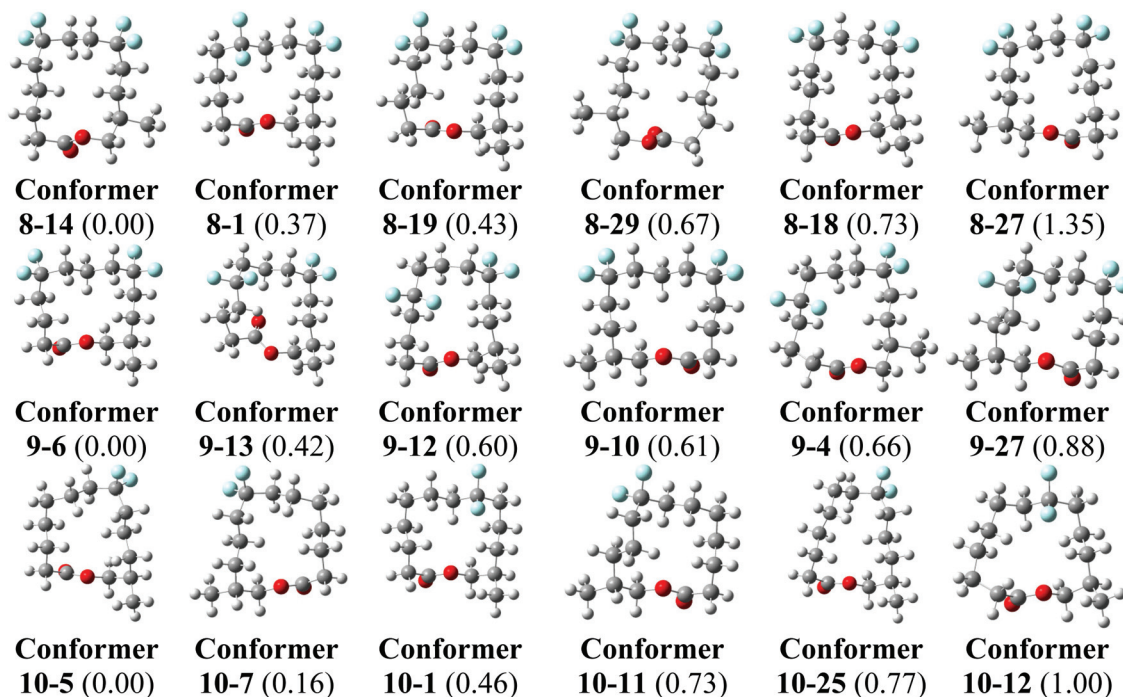


Fig. 7 The calculated lowest energy geometries for **8**, **9** and **10**. Relative Gibbs free energies calculated at the B3LYP-D3/6-311+G\*\* level in kcal mol<sup>-1</sup> are given between parenthesis. For full details see ESI.†

## Computational studies

Theory calculations have been carried out on the three lactones **8–10** in order to explore their conformations further. Minimum energy conformers of the lactones in the gas phase were located through a Monte Carlo conformational search at the MMFF level with the Spartan 14 program,<sup>35</sup> and using an initial temperature of 5000 K in the simulated-annealing algorithm. This procedure found 9650 conformers for lactone **8**, 9714 conformers for lactone **9** and 7948 conformers for lactone **10**. The 30 lowest energy minima in the gas phase for each compound were optimised at the B3LYP-D3/6-311+G\*\* level and frequency calculations were carried out at the same level by using the Gaussian 09 program, Revision D.01.<sup>36</sup> No negative harmonic vibrational frequencies were observed and, hence the conformers are true energy minima. The same frequency calculations were used to obtain thermodynamic corrections affording enthalpies and Gibbs free energies at ambient, standard pressure and temperature for all conformers of **8–10** in the gas phase.

The lowest energy conformers of lactones **8–10** in the gas phase, calculated at the B3LYP-D3/6-311+G\*\* level corrected by Gibbs free energies, are shown in Fig. 7. The 30 lowest energy conformers for each lactone are detailed in the ESI (see Fig. S1–S3 and Tables S1–S3†). The lowest energy conformers for **8** all have square/rectangular ring shapes and all but conformer **8-1** have their CF<sub>2</sub> groups located at corner positions. Notably, the calculated global minimum conformer in the gas

phase matches the experimental X-ray structure **8'** (Fig. 6) and was the anticipated Kraft and Cadalbert structure at the outset. Conformer **8-27**, which emerges as a higher energy conformer (1.35 kcal mol<sup>-1</sup>) in this study, matches the experimental X-ray structure **8''**. That only two calculated conformers, **8-14** and **8-27**, were observed experimentally can be attributed to order and packing in the crystal, where a range of conformers is not expected. Similarly lactone **10** emerges from this study with many low energy conformers, all with square/rectangular ring geometries. Most of them have the CF<sub>2</sub> groups locating at corner locations. Indeed, both the calculated global minimum **10-5** (0.00 kcal mol<sup>-1</sup>) and the second lowest energy conformer **10-7** have squared carbon ring geometries with CF<sub>2</sub> groups at corners (Fig. 7). Conformer **10-7** has a geometry which matches the observed X-ray structure of **10**. Taking structures **8** and **10** together, the outcomes suggest that the computational analysis was able to identify the experimental structures, as low energy stable conformers. These outcomes give some confidence that the calculated lowest energy geometries are relevant experimentally. For lactone **9** we have to rely on theory only. It emerges as a very flexible structure, with many calculated low energy conformers, however it is noteworthy that the lowest energy conformer, **9-6** is almost identical to the anticipated Kraft and Cadalbert [3434]-1 structure for musk lactone. Thus the predictive power of the CF<sub>2</sub>/corner hypothesis holds well.

In summary we have carried out a synthesis and structural study on three CF<sub>2</sub> containing analogues of musk lactone **4**.



The CF<sub>2</sub> group was explored as a design feature to preferentially locate at corner positions of the ring. X-ray structures of lactones **8** and **10** showed this to be the case. In addition the conformations of the lactones **8–10** were explored by detailed computational analysis and this also revealed lowest energy conformers (from many) that had CF<sub>2</sub> at the corner positions. The calculated lowest energy structures matched the X-ray structures for **8'** and **10**. All three of the fluorinated lactones retained a pleasant odour, and it proved difficult to assign a particular analogue to a stronger fragrance. However, even with the CF<sub>2</sub> constraints, it is clear from the conformational analysis that each lactone can access a range of low energy rectangular structures. These structures typically have the lactone moiety in the middle of a flat edge and with the methyl group at the corner of that edge, an arrangement which is presumably consistent with eliciting a fragrance response.

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## References

- 1 K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.
- 2 W. Liu, W. Huang, M.-J. Cheng, R. J. Neilson, W. A. Goddard III and J. T. Groves, *Science*, 2012, **337**, 1322–1325.
- 3 S. Purser, P. R. Moore, S. Swallow and C. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- 4 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
- 5 F. R. Leroux, B. Manteau, J.-P. Vors and S. Pazenok, *Beilstein J. Org. Chem.*, 2008, **4**, 13.
- 6 (a) M. Skibinski, Y. Wang, A. M. Z. Slawin, T. Lebl, P. Kirsch and D. O'Hagan, *Angew. Chem., Int. Ed.*, 2011, **50**, 10581–10584; (b) M. Skibinski, C. A. Urbina-Blanco, A. M. Z. Slawin, S. P. Nolan and D. O'Hagan, *Org. Biol. Chem.*, 2013, **11**, 8209–8213.
- 7 D. O'Hagan, Y. Wang, M. Skibinski and A. M. Z. Slawin, *Pure Appl. Chem.*, 2012, **84**, 1587–1595.
- 8 C. A. Urbina-Blanco, M. Skibinski, D. O'Hagan and S. P. Nolan, *Chem. Commun.*, 2013, **49**, 7201–7203.
- 9 K. Schultz and P. Kraft, *J. Essent. Oil Res.*, 1997, 509–514.
- 10 P. Kraft and W. Tochtermann, *Leibigs Ann. Chem.*, 1994, 1161–1164.
- 11 E. Brenna, C. Fuganti and S. Serra, *Tetrahedron: Asymmetry*, 2003, **14**, 1–42.
- 12 A. Fürstner and K. Langemann, *J. Org. Chem.*, 1996, **61**, 3942–3943.
- 13 A. Fürstner and K. Langemann, *Synthesis*, 1997, 792–803.
- 14 P. Scafato, A. Larocca and C. Rosini, *Tetrahedron: Asymmetry*, 2006, **17**, 2511–2515.
- 15 P. Kraft and R. Cadalbert, *Chem. – Eur. J.*, 2001, **7**, 3254–3262.
- 16 M. Prakesch, E. Kerouredan, D. Grée, R. Grée, J. DeChancie and K. N. Houk, *J. Fluorine Chem.*, 2004, **125**, 537–541.
- 17 Y. N. Ogibin, E. K. Starostin, A. V. Aleksandrov, K. K. Piunitsky and G. I. Nikishin, *Synthesis*, 1994, 901–903.
- 18 J. S. Yadav and N. Rami Reddy, *Tetrahedron*, 2010, **66**, 3265–3274.
- 19 S. D. Bull, S. G. Davies, S. Jones and H. J. Sangane, *J. Chem. Soc., Perkin Trans. 1*, 1999, **4**, 387–398.
- 20 D. F. Taber, R. P. Meagley and D. J. Doren, *J. Org. Chem.*, 1996, **61**, 5723–5728.
- 21 Using a modification of the procedure reported by: R. S. Narayan and B. Borhan, *J. Org. Chem.*, 2006, **71**, 1416–1429.
- 22 Swern oxidation in the case of **24a**; K. Anyram and D. Swern, *Tetrahedron*, 1978, **34**, 1651–1660; oxidation with Dess–Martin Periodinane<sup>23</sup> in the case of **24b**.
- 23 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155–4156.
- 24 M. Prakesch, D. Grée, S. Chandrasekhar and R. Grée, *Eur. J. Org. Chem.*, 2005, 1221–1232.
- 25 Y. Wang, R. Callejo, A. M. Z. Slawin and D. O'Hagan, *Beilstein J. Org. Chem.*, 2014, **10**, 18–25.
- 26 K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa and O. Yonemitsu, *Tetrahedron*, 1986, **42**, 3021–3028.
- 27 J. B. Epp and T. S. Widlanski, *J. Org. Chem.*, 1999, **64**, 293–295.
- 28 I. Paterson, E. A. Anderson, S. M. Dalby, J. Holim and P. Maltas, *Org. Biomol. Chem.*, 2012, **10**, 5873–5886.
- 29 M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391–394.
- 30 W.-C. Sun, C.-S. Ng and G. D. Prestwich, *J. Org. Chem.*, 1992, **57**, 132–137.
- 31 S. Dickschat, E. Helmke and S. Schulz, *Chem. Biodiversity*, 2005, **2**, 318–353.
- 32 Assessed at Givaudan Schweiz AG, Dübendorf, Switzerland.
- 33 M. Schlosser and D. Michel, *Tetrahedron*, 1996, **52**, 99–108.
- 34 D. Michel and M. Schlosser, *Tetrahedron*, 2000, **56**, 4253–4260.
- 35 Y. Shao, L. F. Molnar, Y. Jung, J. Kussmann, C. Ochsenfeld, S. T. Brown, A. T. B. Gilbert, L. V. Slipchenko, S. V. Levchenko, D. P. O'Neill, R. A. DiStasio Jr., R. C. Lochan, T. Wang, G. J. O. Beran, N. A. Besley, J. M. Herbert, C. Y. Lin, T. Van Voorhis, S. H. Chien, A. Sodt, R. P. Steele, V. A. Rassolov, P. E. Maslen,





- P. P. Korambath, R. D. Adamson, B. Austin, J. Baker, E. F. C. Byrd, H. Dachsel, R. J. Doerksen, A. Dreuw, B. D. Dunietz, A. D. Dutoi, T. R. Furlani, S. R. Gwaltney, A. Heyden, S. Hirata, C.-P. Hsu, G. Kedziora, R. Z. Khalliulin, P. Klunzinger, A. M. Lee, M. S. Lee, W. Z. Liang, I. Lotan, N. Nair, B. Peters, E. I. Proynov, P. A. Pieniazek, Y. M. Rhee, J. Ritchie, E. Rosta, C. D. Sherrill, A. C. Simmonett, J. E. Subotnik, H. L. Woodcock III, W. Zhang, A. T. Bell, A. K. Chakraborty, D. M. Chipman, F. J. Keil, A. Warshel, W. J. Hehre, H. F. Schaefer, J. Kong, A. I. Krylov, P. M. W. Gill and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2006, **8**, 3172–3191.
- 36 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09, Revision D.01*, Gaussian, Inc., Wallingford CT, 2009.

