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Fluorine in fragrances: exploring the difluoromethylene (CF₂) group as a conformational constraint in macrocyclic musk lactones†

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

The CF₂ group is incorporated into specific positions within the lactone ring of the natural musk lactone, (12R)-(+)-12-methyl-13-tridecanolide, a constituent of Angelica root oil, *Angelica archangelica* L. The approach is taken as it was anticipated that CF₂ 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 CF₂ groups located at the C-6 and C-9 positions, another (9) with CF₂ groups at the C-5 and C-9 positions, and a third (10) with a CF₂ 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 CF₂ 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 CF₂ 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. $^{1-3}$ Generally, this replacement has only a moderate steric effect, but the high electronegativity of the fluorine can have significant electronic influences. 4 The difluoromethylene (CF₂) group has received considerably less attention as a group for modifying the properties of organic molecules relative to the $^-$ F and $^-$ CF $_3$ groups. 5 However, we have recently reported $^{6-8}$ that incorporation of a CF $_2$ 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 $_2$ groups only occupied corner positions. In the case of cyclododecanes 1 and 2 , this stabilises the

Natural musks are large conformationally flexible macrocyclic lactones and we were interested to evaluate if the CF₂ group might limit this conformational flexibility as a tool for exploring preferred conformations responsible for scent. (12R)-(+)-12-Methyl-13-tridecanolide 4 is a natural constituent of Angelica root oil, Angelica archangelica L.9 The (R)-enantiomer is described as having "a clean, crystal-clear musk top note with strong, elegant woody accents". 10,11 Macrocycle 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, 10,12-14 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 Cadalbert¹⁵ calculated the six lowest-energy conformations of (R)-4 (Fig. 3), all of which were within 0.9 kcal mol⁻¹ 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.

square like conformation. However, in the case of cyclodode-cane 3, incorporation of the difluoromethylene group 1,6 to each other results in considerable distortion of the ring conformation as the CF_2 group avoids an unfavourable edge location.

^aSchool of Chemistry, University of St Andrews, North Haugh, St Andrews, KY16 9ST, UK. E-mail: do1@st-andrews.ac.uk

^bChemistry Institute, University of Campinas, Campinas, SP 13083-970, Brazil † Electronic supplementary information (ESI) available. CCDC 1427901–1427903. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02023a. For access to research data and metadata see DOI: 10.17630/f6dc25c1-c693-4c59-a164-3ccce6e7ef15

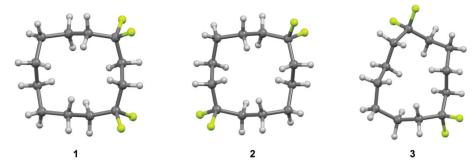


Fig. 1 X-ray crystal structures of 1,1,4,4-(1), 1,1,7,7-(2) and 1,1,6,6-(3) tetrafluorocyclododecanes. 6a The CF₂ groups conspicuously adopt corner locations either reinforcing square like structures for 1 and 2 or a inducing a distorted ring for structure 3.

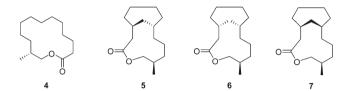


Fig. 2 (12R)-(+)-12-Methyl-13-tridecanolide 4 bridged and musk lactones 5-7.

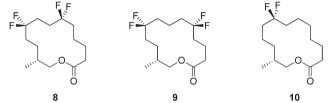


Fig. 4 Target musk lactone analogues 8-10 incorporating CF₂ moieties.

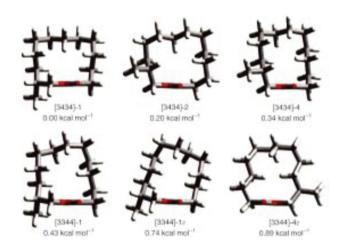


Fig. 3 The six lowest-energy conformations of musk lactone (R)-4 as reported by Kraft and Cadalbert (MM3 force field). 15

As a continuation of the observation that difluoromethylene groups can influence macrocyclic ring conformation, we decided to investigate the synthesis of CF₂ analogues of (12R)-(+)-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 CF2 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-CF₂ 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⁻¹ 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 CF₂ 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 CF₂ groups would exploit Grée's method of diethyaminosulfur trifluoride (DAST) treatment of propargylic ketones to generate propargylic difluoromethylene.16

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) H_2O_2 , MeOH, 30 min. (ii) $FeSO_4 \cdot 7H_2O$, $CuSO_4 \cdot 5H_2O$, H_2O , 20%; (b) (i) Oxazolidinone 20, H_2O_2 , H_2O_3 min. (ii) Pivaloyl chloride, H_2O_3 , H_2O_3 ,

(R)-Olefin **11** was prepared as shown in Scheme 2. Firstly hexenoic acid **19** was obtained from cyclohexanone **18** by the method reported by Ogibin $et\ al.^{17}$ Carboxylic acid **19** was then activated as a mixed anhydride and coupled¹⁸ to (R)-oxazolidinone **20** ¹⁹ 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 (LiAlH₄) reduction to give alcohol **23**, benzyl ether formation²⁰ 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-protected²¹ as their 4-methoxybenzyl ethers to give alcohol **25a** and **25b** by modification of a previous procedure.⁵ Oxidation to the corresponding aldehydes,²² 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)²³ oxidation gave propargyl ketones 27, which were treated with DAST in methodology developed by Grée^{16,24,25} 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, NEt₃, 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) nBuLi, 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, H₂O, r.t., 2 h, 78%; (e) BAIB, TEMPO, CH₃CN, H₂O, r.t., 7 h, 58%; (f) palladium on carbon (10 wt%), H₂, MeOH, r.t., 18 h, 65%; (g) LiOH, THF, H₂O, r.t., 3 h, 94%; (h) 2,4,6-trichlorobenzoyl chloride, NEt₃, 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,²³ ketone 29 was converted to alkyne 30 with DAST. 4-Methoxybenzyl cleavage²⁶ and then oxidation with bis-(acetoxy)iodobenzene (BAIB)/TEMPO²⁷ 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 macrolactonisation²⁸ 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 (mCPBA) to give epoxide 13 as a 1:1 mixture of diastereoisomers. Ring opening addition of lithiated alkyne 28a 29 to epoxide 13 gave alcohol 16 in 60% yield. The acetylene could be selectively reduced to the (Z)alkene with a poisoned palladium catayst,30 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

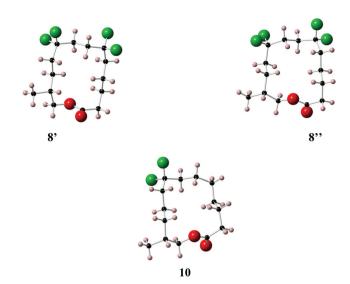


Fig. 6 X-ray crystal structure of musk lactones 8 (two conformers 8' and 8" are obvious in the unit cell) and 10.

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, 31 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. Macrolactonisation²⁸ 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) mCPBA, DCM, r.t., 18 h, 55%; (b) (i) nBuLi, THF, -78 °C, 15 min. (ii) BF₃·OEt₂, 15 min. (iii) Epoxide 13, THF, -78 °C-r.t., 20 h, 60%; (c) palladium (5% on barium sulfate), quinoline, pyridine, H2 (1 atm), 22 h, 82% (d) DMP, DCM, r.t., 2 h, 57%; (e) DAST, 50 °C, 18 h, 27%; (f) DDQ, DCM, H₂O, r.t., 2 h, 70%; (g) BAIB, TEMPO, CH₃CN, H₂O, r.t., 18 h, 49%; (h) palladium on carbon (10 wt%), H₂, MeOH, r.t., 18 h, 59%; (i) LiOH, THF, H₂O, r.t., 3 h, 70%; (j) 2,4,6-Trichlorobenzoyl chloride, NEt₃, 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), H₂O₂, 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) nBuLi, THF, -78 °C, 30 min. (ii) Aldehyde 14, THF, -78 °Cr.t., 20 h, 80%; (e) DMP, DCM, r.t., 2 h, 61%; (f) DAST, 50 °C, 18 h, 62%; (q) DDQ, DCM, H₂O, r.t., 2 h, 88%; (h) BAIB, TEMPO, CH₃CN, H₂O, r.t., 7 h, 48%; (i) palladium hydroxide on carbon (20 wt%), H2, THF, r.t., 18 h, 46%; (j) (i) 2,4,6-trichlorobenzoyl chloride, NEt3, 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 CF₂ groups locate at corner positions, thus the anticipated role of the CF2 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'. 32 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^{33,34} 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.³³ 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. 34

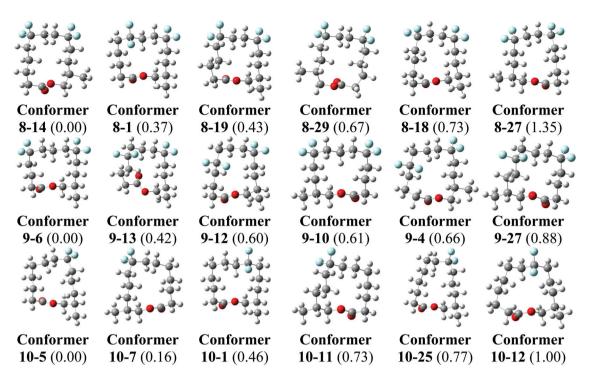


Fig. 7 The calculated lowest energy geometries for 8, 9 and 10. Relative Gibbs free energies calculated at the B3LYP-D3/6-311+G** level in kcal mol⁻¹ are given between parenthesis. For full details see ESI.†

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, 35 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.01.³⁶ 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_2 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⁻¹) 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 CF2 groups locating at corner locations. Indeed, both the calculated global minimum 10-5 (0.00 kcal mol⁻¹) and the second lowest energy conformer 10-7 have squared carbon ring geometries with CF2 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 CF₂/corner hypothesis holds well.

In summary we have carried out a synthesis and structural study on three CF₂ containing analogues of musk lactone 4.

The CF₂ 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 CF₂ 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 CF₂ 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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