



Cite this: *Org. Biomol. Chem.*, 2016,
14, 211

Fluorine in fragrances: exploring the difluoromethylene (CF_2) group as a conformational constraint in macrocyclic musk lactones[†]

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

The CF_2 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_2 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_2 groups located at the C-6 and C-9 positions, another (**9**) with CF_2 groups at the C-5 and C-9 positions, and a third (**10**) with a CF_2 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_2 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_2 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.

Received 28th September 2015,
Accepted 4th November 2015

DOI: 10.1039/c5ob02023a
www.rsc.org/obc

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 (CF_2) group has received considerably less attention as a group for modifying the properties of organic molecules relative to the $-\text{F}$ and $-\text{CF}_3$ 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

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_2 group avoids an unfavourable edge location.

Natural musks are large conformationally flexible macrocyclic lactones and we were interested to evaluate if the CF_2 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.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.

^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



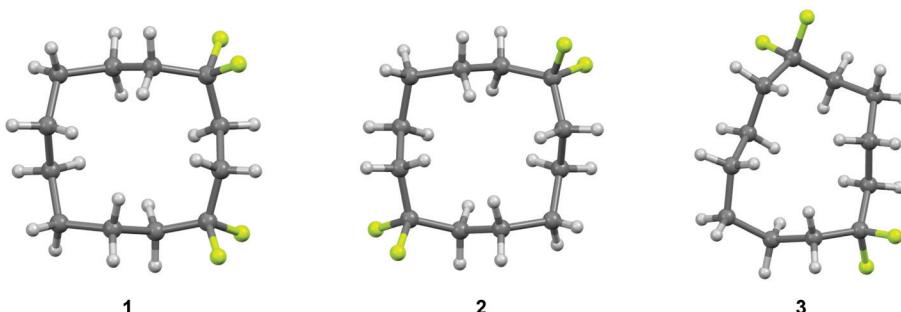


Fig. 1 X-ray crystal structures of 1,1,4,4-(1), 1,1,7,7-(2) and 1,1,6,6-(3) tetrafluorocyclododecanes.^{6a} The CF₂ groups conspicuously adopt corner locations either reinforcing square like structures for **1** and **2** or a inducing a distorted ring for structure **3**.

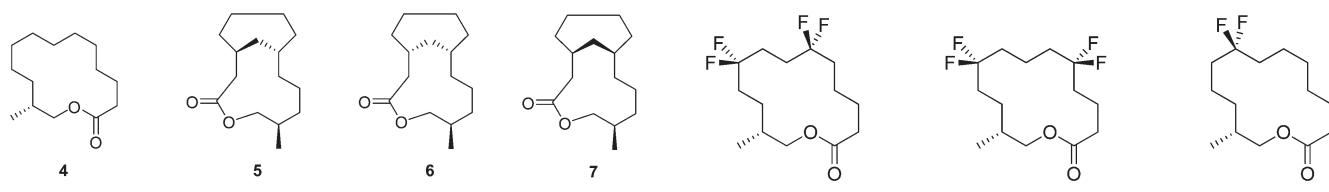


Fig. 2 (12R)-(+)-12-Methyl-13-tridecanolide **4** and bridged musk lactones **5–7**.

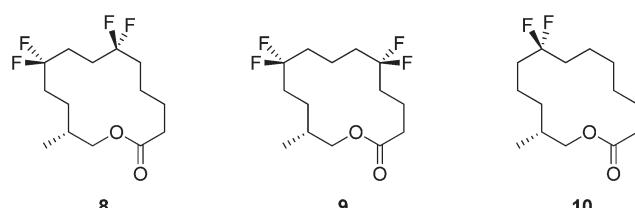


Fig. 4 Target musk lactone analogues **8–10** incorporating CF₂ moieties.

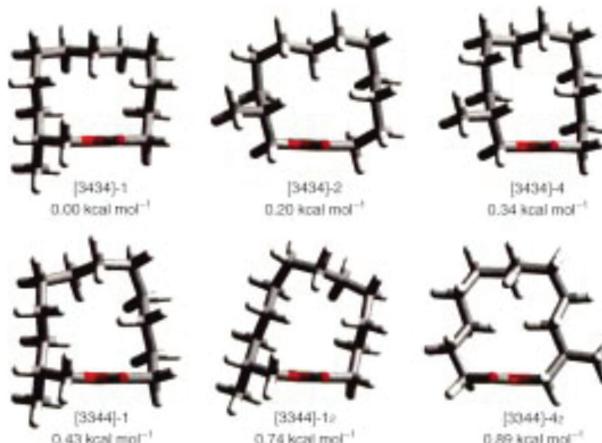


Fig. 3 The six lowest-energy conformations of musk lactone (R)-4 as reported by Kraft and Cadalbert (MM3 force field).¹⁵

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 macrocycle would allow different ground state conformations to be more highly populated, and then different conformations could be assessed for their musk/odour properties.

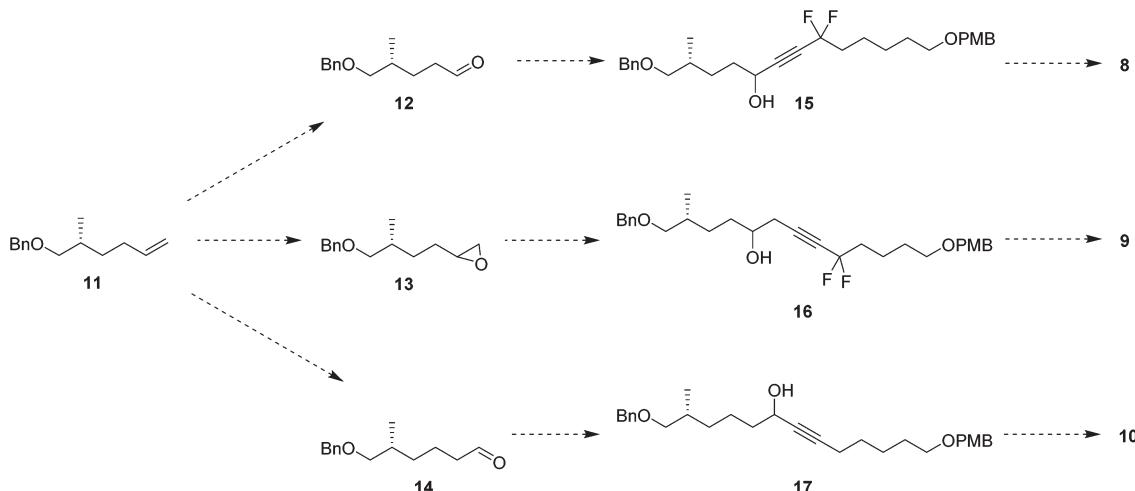
In this respect lactones **8**, **9** and **10** (Fig. 4) were selected for synthesis. In each case we anticipated that they would adopt different Kraft and Cadalbert conformations (Fig. 3). Conformation [3434]-4 has a four carbon edge running along the top of the ring which should be reinforced by the 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

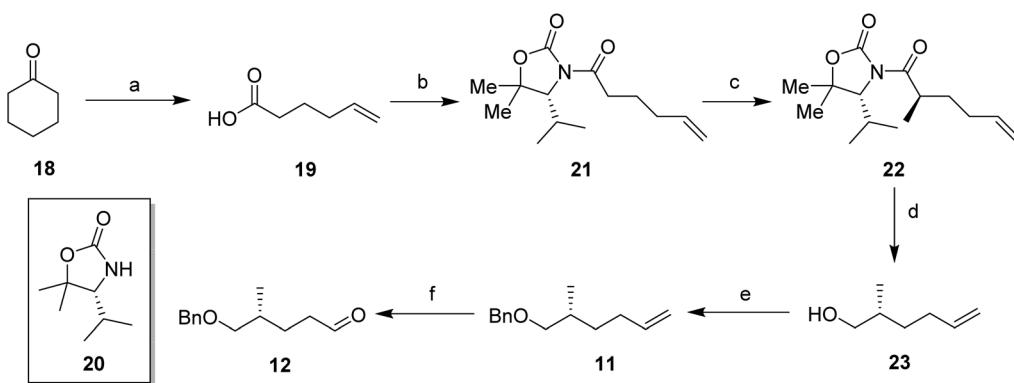
Synthesis

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) H₂O₂, MeOH, 30 min. (ii) FeSO₄·7H₂O, CuSO₄·5H₂O, H₂O, 20%; (b) (i) Oxazolidinone 20, nBuLi, THF, -78 °C, 30 min. (ii) Pivaloyl chloride, NEt₃, THF, 0 °C, 30 min, r.t., 1.5 h, 93%; (c) NaHMDS, MeI, THF, -78 °C, 3 h, 92%, dr >98 : 2; (d) LiAlH₄, Et₂O, 0 °C, 2 h, 66%; (e) NaH, BnBr, DME, r.t.-reflux, 20 h, 94%; (f) (i) O₃, DCM, -78 °C. (ii) PPh₃, -78 °C-r.t., 55%.

(*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 20¹⁹ 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

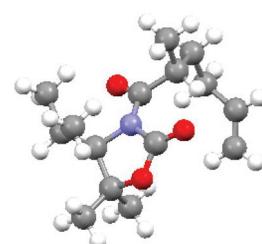
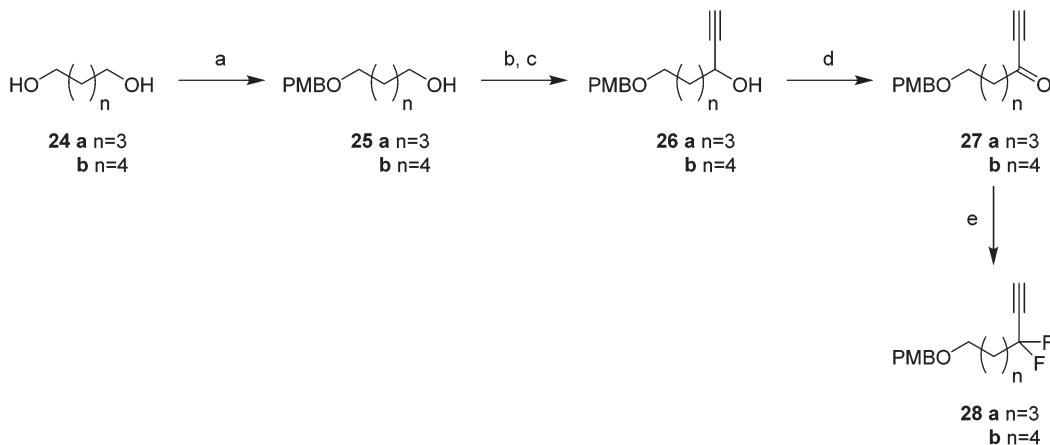


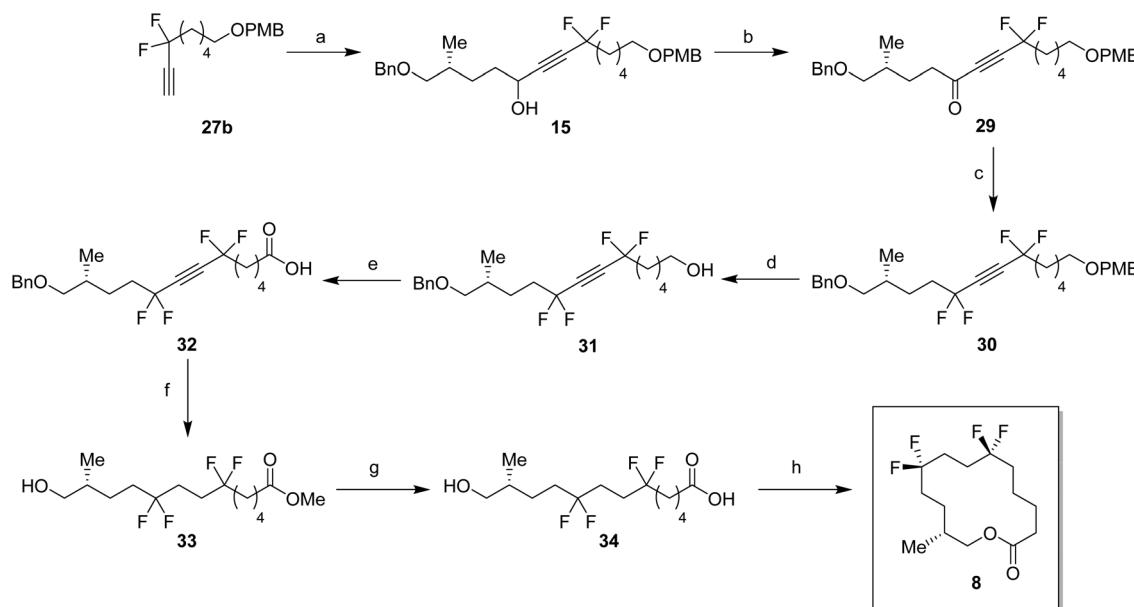
Fig. 5 X-ray crystal structure of compound 22.

(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) *n*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, 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 (*m*CPBA) 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 catalyst,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



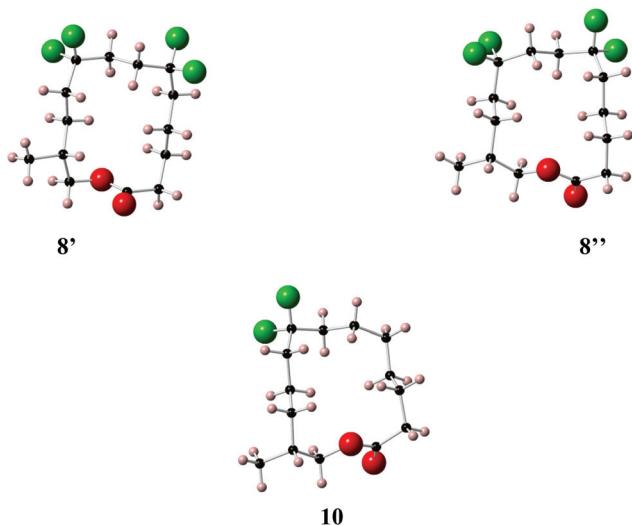
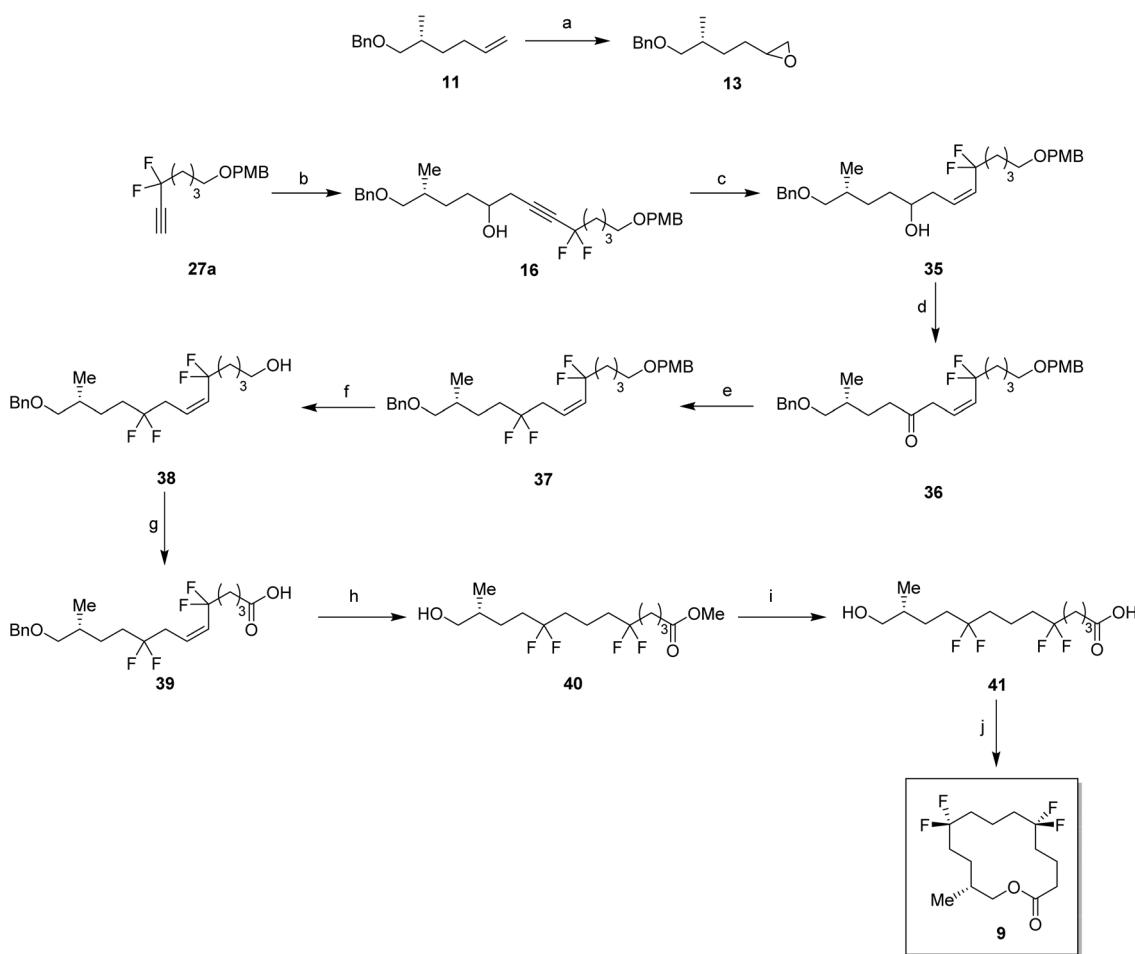
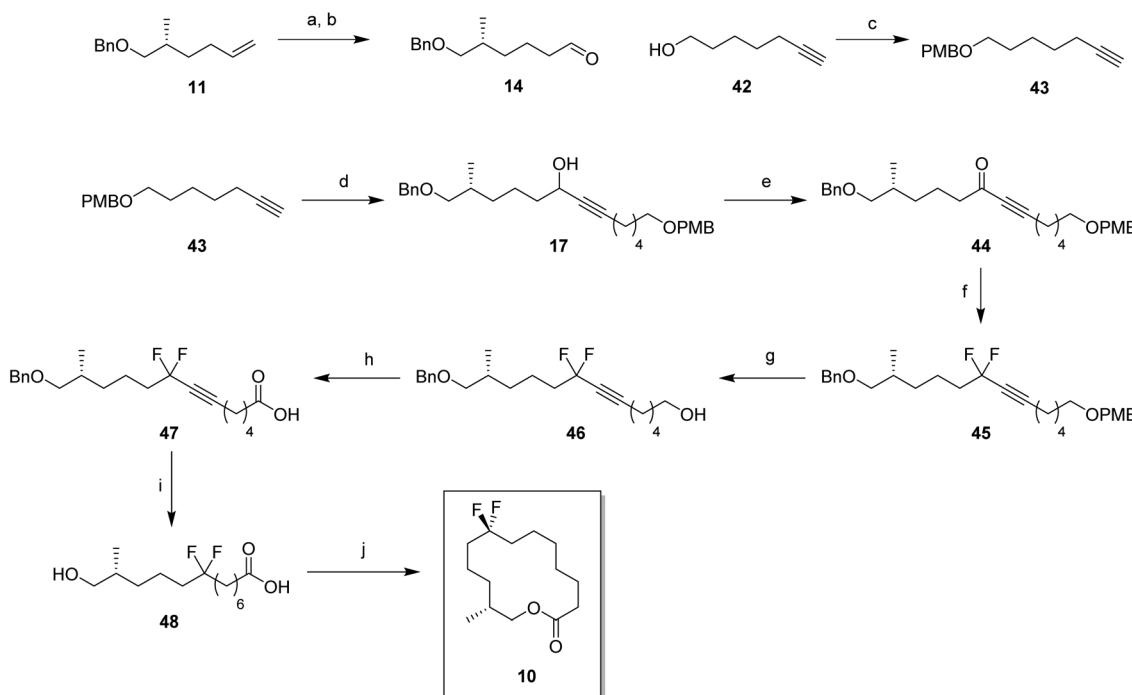


Fig. 6 X-ray crystal structure of musk lactones **8** (two conformers **8'** and **8''** are obvious in the unit cell) and **10**.



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 °C, 15 min. (ii) $\text{BF}_3\text{-OEt}_2$, 15 min. (iii) Epoxide **13**, THF, -78 °C-r.t., 20 h, 60%; (c) palladium (5% on barium sulfate), quinoline, pyridine, H_2 (1 atm), 22 h, 82%; (d) DMP, DCM, r.t., 2 h, 57%; (e) DAST, 50 °C, 18 h, 27%; (f) DDQ, DCM, H_2O , r.t., 2 h, 70%; (g) BAIB, TEMPO, CH_3CN , H_2O , r.t., 18 h, 49%; (h) palladium on carbon (10 wt%), H_2 , MeOH , r.t., 18 h, 59%; (i) LiOH , THF, H_2O , r.t., 3 h, 70%; (j) 2,4,6-Trichlorobenzoyl chloride, 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), 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) *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, 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%.

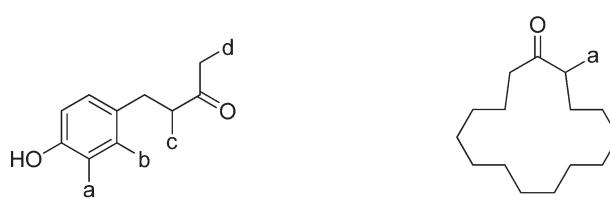
X-ray structures

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



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



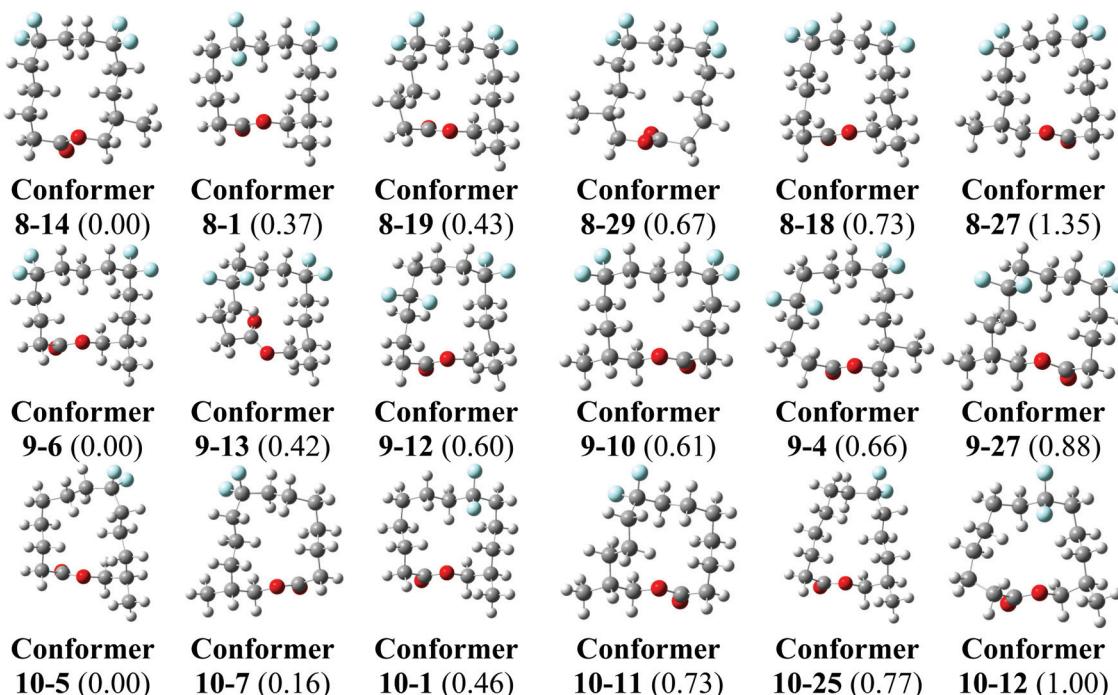


Fig. 7 The calculated lowest energy geometries for **8**, **9** and **10**. Relative Gibbs free energies calculated at the B3LYP-D3/6-311+G** level in kcal mol⁻¹ are given between parenthesis. For full details see ESI.†

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 CF₂ 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 CF_2 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_2 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_2 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.

Acknowledgements

We thank EPSRC for a grant and we thank the EPSRC National Mass Spectrometry Service, Swansea and Mrs Caroline Horsburgh (University of St Andrews) for mass spectrometry analysis. CNvH also thanks the Fluorine Division of the American Chemical Society for a Moissan Summer Undergraduate Fellowship. RAC thank FAPESP for a fellowship (#2015/00975-7) and MB thanks EaStCHEM and the University of St Andrews for support access to a computing facility managed by Dr H. Fruchtl. We thank Prof. Paul Davey and Dominique Lelievre of Givaudan, Schweiz AG, Dübendorf, Switzerland, for facilitating the olfactory assessments.

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. Kerouedan, 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. Anyaram and D. Swern, *Tetrahedron*, 1978, **34**, 1651–1660; oxidation with Dess–Martin Periodinane²³ 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.

