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Towards novel difluorinated sugar mimetics; syntheses and conformational analyses of highly-functionalised difluorinated cyclooctenones

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Highly-functionalised difluorinated cyclooctenones were synthesised from trifluoroethanol using either metallated difluoroenol acetal or carbamate chemistry, followed by a [2,3]-Wittig rearrangement or aldol reaction. Efficient RCM reactions afforded the title compounds which showed rather restricted fluxional behaviour by VT ^{19}F NMR. Topological characterisation by molecular modelling and NOESY/ROESY experiments offered a number of challenges, but allowed the identification of two favoured boat–chair conformers which interconverted by pseudorotation with relatively large activation barriers.

Introduction

Medium ring compounds are a synthetic challenge, with eight-membered species posing a particular problem. The combination of Baeyer, Pitzer and transannular strain in the cyclic products, and high conformational flexibility in the acyclic precursors, results in unfavourable enthalpic and entropic contributions to the free energy of activation for the cyclisation reaction.[1] Low effective molarities[2] are the inevitable consequence. However, a range of metal catalysed transformations[3] and other synthetic strategies[4] have been used effectively to gain access to highly functionalised cyclooctanes and their derivatives.

In particular, the commercial availability of ruthenium–alkylidene complexes **1** and **2** (Fig. 1) and the popularisation of their use in ring-closing metathesis (RCM) reactions[5] have made the synthesis of cyclooctane derivatives much more straightforward. Taylor[6] and Crimmins[7] described independently the first annulative uses of the reaction for the formation of oxocenes during syntheses of prelaureatin **3** and (+)-laurencin **4**, respectively, achieving the cyclisations in good yields using relatively high catalyst loadings (10 and 7 mol% in first generation Grubbs' catalyst **1**, respectively). Since these seminal findings were published, there have been many elegant syntheses of natural product-related targets that contain eight-membered[8–10] and other medium ring carbocycles and heterocycles using this approach.[11] Highly-functionalised cyclooctane derivatives have attracted attention, both as ring expanded analogues of saccharides, and as precursors to bicyclic species related to sugars and azasugars. Sinaÿ[12] and van Boom[13] used ring expansion Claisen approaches to synthesise the key carbocycles; the Paris group combined the ideas of the stability of carbasugars with the potential for occupying uncharted conformational space, synthesising **5**, which was shown to be conformationally related to the corresponding glucopyranose by NOE experiments (Fig. 2). The Leiden group developed precursor **6** and exploited transannular strain-relieving nucleophilic attack upon a ketone carbonyl group to close a number of bicyclic systems, which provide

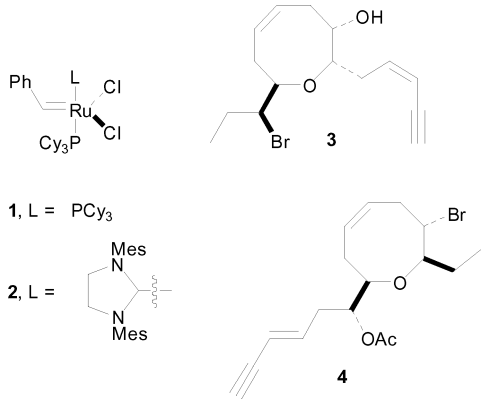

Fig. 1 Grubbs' first and second generation catalysts and eight membered ring-containing natural products approached *via* landmark RCM routes.

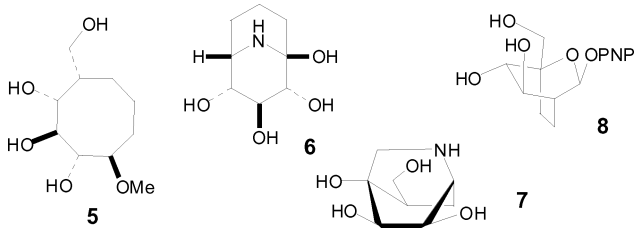

Fig. 2 Carbohydrate mimetics based on cyclooctanic templates.

conformationally-locked analogues of sugars and azasugars in which the exocyclic C–O bond is very slow to cleave.[14] Vasella[15] has also reported bicyclic mimetics of saccharides **7**, while Kirby and Sinaÿ[16] recently synthesised bicyclic molecule **8** which resembles closely the $B_{2,5}$ conformation, a candidate for the one adopted by the glucopyranosyl oxacarbenium ion. All these studies used carbohydrate starting materials to provide most of the functionality in the products and ensure stereocontrol.

We have developed a number of approaches for the synthesis of fluorinated analogues of the molecules of nature from commercial fluorinated starting materials, in which RCM forms a key step.[17] We showed, in preliminary form,[18] how we could use

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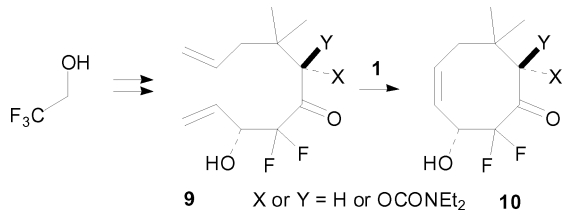
metallated difluoroalkene chemistry to advance trifluoroethanol rapidly to precursors **9** to eight-membered rings and close them *via* RCM to afford difluorinated cyclooctenone templates **10** for stereoselective oxidation reactions (Scheme 1).[19]



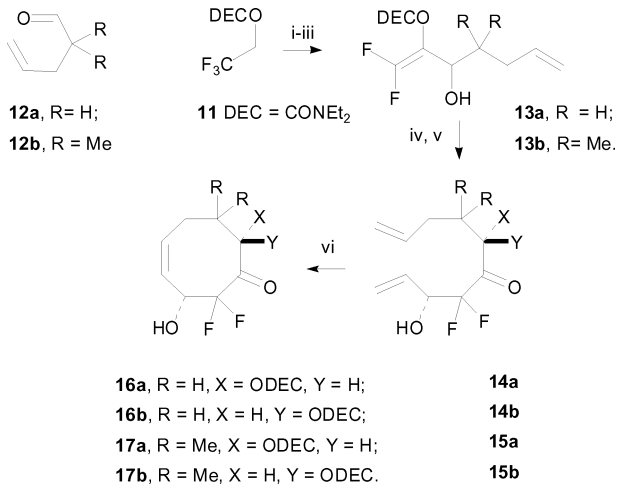
Scheme 1 Highly-functionalised difluorinated cyclooctenones prepared by RCM from trifluoroethanol.

The main issues were concerned with the ways in which the high level of functionality, particularly the highly-electrophilic difluoroketone and the relatively acidic secondary hydroxyl group, would affect the RCM reaction. We were also aware that the conformational analysis of functionalised cyclooctene derivatives was relatively limited[20] and therefore sought to use NMR and molecular modelling synergically to underpin subsequent attempts at transformation, by trying to develop an understanding of the topologies and extent of conformational freedom of these molecules. We now wish to report several cyclooctenone syntheses in full, together with initial conformational analyses based on NMR and electronic structure calculations.

Results and discussion

Synthetic studies

The most direct approach to precursor synthesis started from the *N*,*N*-diethylcarbamate **11** of trifluoroethanol (Scheme 2). Dehydrofluorination/metallation,[21] then addition to **12a** or **12b**, occurred smoothly in the presence of boron trifluoride etherate[22] to afford allylic alcohols **13a** (79%) and **13b** (66%) in good yields on a large scale (up to 100 g or 0.33 mole scale for **13b**). Treatment of the allylic alcohols with *n*-butyllithium afforded the allylic alkoxide, which underwent a transcarbamoylation reaction releasing a difluoroenolate. The addition of acrolein triggered an aldol reaction, and **14a–15b** were isolated in good yields (58 and 64%, respectively) after aqueous work-up. The *anti*- and *syn*-products **15a** and **15b** were separated by flash column chromatography on a multigramme scale using Biotage cartridges, whereas **14a** and **14b** proved inseparable.



Scheme 2 Difluorinated cyclooctenone synthesis based on metallated difluoroenol carbamate chemistry. Reagents and conditions: i, LDA, THF, −78 °C; ii, **12a** or **12b**; iii, $F_3B{\cdot}OEt_2$; iv, *n*-BuLi, THF, −78 to −10 °C; v, acrolein then NH_4Cl; vi, **1** or **2**, Ti(Oi–Pr_4), DCM, reflux (See Table 1).

Table 1 The effect of RCM conditions upon outcome

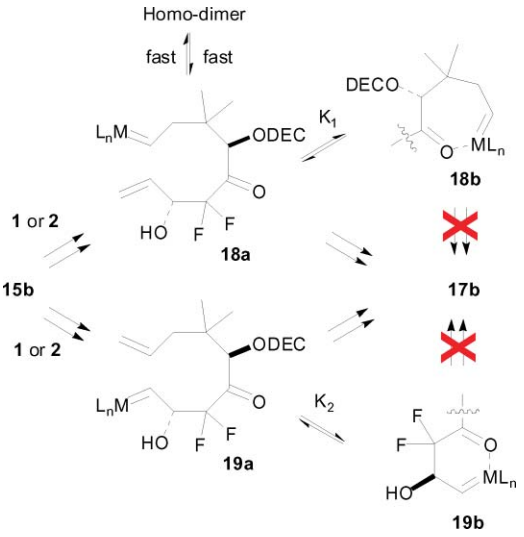
Substrate	Catalyst	Co-catalyst	Time/hours	Yield (%)
15b	5% **1**	No	144	0
15b	5% **1**	Yes	144	77
15b	2.5% **2**	No	72	82
15b	2.5% **2**	Yes	18	75
14a + **14b**	2.5% **2**	Yes	72	63

RCM reactions were carried out at a relatively high substrate concentration (0.01 M) in dichloromethane at reflux, either on the mixture of **14a** and **14b**, or on **15a** and **15b** separately, to afford **16a–17b** in moderate to good yields (Table 1). We were able to separate **16a** and **16b** chromatographically and obtain single crystals of **16b** of sufficient quality for structure elucidation by X-ray crystallography.‡

High dilution conditions are used to favour the formation of the more difficult ring systems (0.003 M by Crimmins during the synthesis of **4**). This makes the preparation of even gram-scale quantities into a non-trivial activity and potentially limits the utility of RCM chemistry rather severely; we were therefore pleased to be able to use higher concentrations. The initial RCMs were slow but no products arising from alkenyl group migration or cross metathesis were observed. First and second generation Grubbs' catalysts **1** and **2** were compared for the RCM of *syn*-**15b** (Table 1); RCM failed completely when **1** was used as the catalyst in the absence of the Ti(IV) co-catalyst.[23] The reaction time shortened (from 7 days to 3 days) when **2** was used as the catalyst in lower loading (2.5 mol%) in the absence of the Ti(IV) co-catalyst, whereas the reaction time shortened to 18 hours (an overall ten-fold reduction) in the presence of the co-catalyst (Table 1).

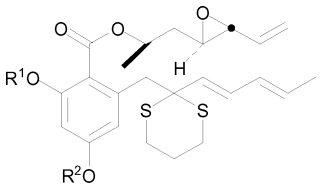
This behaviour is consistent with the lower Lewis acidity of **2**, though it suggests that the ruthenium is still appreciably Lewis acidic in the second generation catalyst.[24] The mechanism of RCM presumably involves the rapid initial formation of **18a** (Scheme 3), which exists in a rapid (though unfavourable) equilibrium with a homodimeric product (products of this type remained undetected in these studies). Cyclisation and formation of chelate **18b** then compete to partition **18a** between productive and unproductive pathways; K_1 is potentially an important determinant of the overall rate of cyclisation. Alternatively, **19a**, which is presumably slower to form, can lead to the formation of 6-membered chelate **19b**.[24] We assume that neither chelate **18b** nor **19b** can progress to a RCM product with a first generation catalyst, unless added Ti(IV) competes for the Lewis basic carbonyl oxygen (and effectively reduces both K_1 and K_2). The driving force for chelate formation is reduced when the presence of the carbene ligand at ruthenium lowers the Lewis acidity of the metal. Substrates **14a–15b** offer a range of ligation sites for Lewis acidic metals; we have shown that the carbamate and an additional carbonyl can chelate tin(IV) quite effectively,[25] and the β-hydroxyketone motif also looks like a good ligand array for Ti(IV). However, it is difficult to see how either of these potential ligands could involve themselves in metal alkylidenes **18** and **19**. Further reductions in catalyst loading were not explored. Scheme 2 ignores irreversible cross metathesis reactions, because we observed no evidence for heterodimeric products at 0.01 M.

‡ Crystallographic data for **16b**: $C_{13}H_{19}F_2NO_4$, crystal size 0.43 × 0.36 × 0.21 mm, M = 291.29, monoclinic, a = 14.5260(9), b = 7.0680(5), c = 13.3397(9) Å, β = 91.5060(10), U = 1369.11(16) Å^3, T = 150(2) K, space group $P2_1/c$, Z = 4, μ(Mo–Kα) = 0.121 mm^{-1}, 9518 reflections measured, 2411 unique, (R_{int} = 0.0198) which were used in all calculations. Final R indices [$F^2 > 2\sigma(F^2)$] $R1$ = 0.0323, w$R2$ = 0.0806; R indices (all data) $R1$ = 0.0342, w$R2$ = 0.0818. Data for **17a** and **17b** were reported previously.[18] CCDC reference number 272798. See http://dx.doi.org/10.1039/b505978j for crystallographic data in CIF or other electronic format.



Scheme 3 Potential modes of ruthenium–alkylidene formation and chelation during RCM.

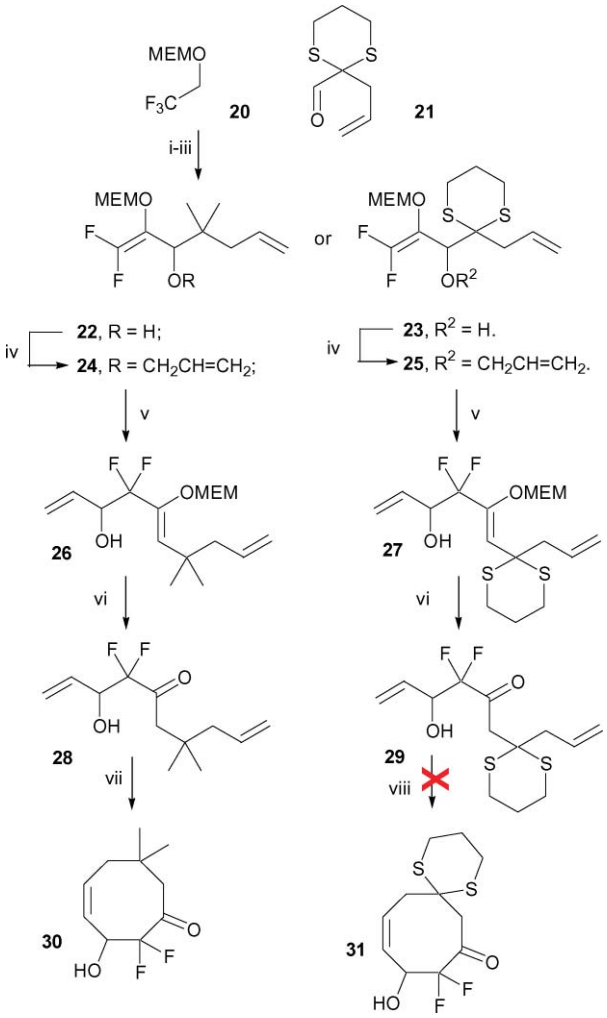
The results in Table 1 also suggest the presence of a modest (less than five-fold) Thorpe–Ingold effect.[26] Murphy and co-workers[27] proposed that a single methyl group placed appropriately could increase RCM yields dramatically; the effect is considerably less clear cut in our system. All the cyclooctenone products showed broadened ^{1}H and ^{19}F NMR spectra at ambient temperature, characteristic of the anticipated fluxional behaviour. These issues are discussed more fully later in the manuscript.



32a, $R^1 = R^2 = Me$;
32b, $R^1 = TBS$, $R^2 = TBDPS$.

This direct sequence can be used to prepare large quantities of cyclooctenones but suffers from the drawback of the reducing conditions required to cleave the carbamate, and the addition of a second stereogenic centre.[28] Nevertheless, the products are interesting substrates from which to learn about conformation and functional group chemistry.

The deletion of the additional stereogenic centre requires a different, and slightly longer synthetic route. Difluoroallylic alcohols **22** and **23** were synthesised in good yields (90 and 71% respectively) using our published procedure[29] from the MEM-ether **20** of trifluoroethanol and pentenals, commercial **12b**, and **21**.[30] The purified alcohols were allylated under phase-transfer conditions to afford ethers **24** and **25** which were progressed without further purification (91 and 70%, respectively). Both underwent a [2,3]-Wittig rearrangement smoothly using our published conditions;[31] complete conversions to **26** and **27** were achieved, though the isolated yields after chromatography were moderate (55 and 30%, respectively, the MEM enol acetals appearing quite sensitive on silica gel). MEM cleavage could be carried out under the usual conditions[32] to afford β-hydroxyketones **28** (65%) and **29** (76%). RCM of **28** was carried out with first generation Grubbs' catalyst initially—the presence of the Ti(IV) co-catalyst was essential, and even then the reaction was slow, requiring 3 days at a substrate concentration of 0.01 M for **28**, but returning a good (78%) yield of product **30**. Dithioketal-containing **29** failed to undergo RCM to **31** even when second-generation catalyst **2** was used at 10 mol% in refluxing toluene. Danishefsky and co-workers[33] reported (10 mol%, 2 mM, 2–5 hours) remarkably efficient closures of highly-substituted **32a** and **32b** (55 and 60%, respectively), in which both alkenyl termini would be expected to react relatively slowly with the catalyst, but we were unable to see any cyclisation to **31**, with **29** returned unchanged even after extended reaction times. We are unable to account for this disappointing outcome;[34] the product would have contained a potentially valuable masked ketone. Nevertheless, the results show two concise and effective routes by which difluorinated cyclooctenones can be synthesised rapidly from readily-available starting materials (Scheme 4).



Scheme 4 [2,3]-Wittig rearrangement-based approach to difluorinated cyclooctenones. Reagents and conditions: i, LDA, THF, −78 °C; ii, **12b** or **21**; iii, NH_4Cl (aq); iv, 50% NaOH, $TBAHSO_4$, allyl bromide; v, LDA, THF, −78 to −30 °C; vi, $SOCl_2$, MeOH; vii, 5% **1**, Ti(Oi–Pr_4), DCM, reflux; viii, see text.

NMR studies

Both ^{1}H and ^{19}F NMR spectra of cyclooctenone products were broad at ambient temperature, requiring VT NMR studies. The proton NMR spectra of **17a, 17b** and **30**, well dispersed at −50 °C, were assigned fully using a combination of COSY, HMQC and HMBC experiments. The ^{19}F NMR spectra resolved into sharp signals at −50 °C; solubility constraints prevented further cooling of the samples. While *cis*-**17a** showed a strongly biased (13 : 1) conformer population at −50 °C, *trans*-**17b**, and less substituted **30** showed more balanced conformer distributions (Table 2). Coalescence temperatures were measured allowing calculation of $\Delta G^{\ddagger}$ for the conformational exchange; the measured values show that **17a** and **17b** are slightly less mobile than the less substituted **30**.

Table 2 Coupling constants, conformer ratios and exchange barriers from VT NMR experiments

Substrate	Ratio	$\Delta G^{\ddagger}$ (kcal mol^{-1})	$^{3}J_{H-F}$ (Hz) major	$^{3}J_{H-F}$ (Hz) minor
16b	1.2 : 1	(—)[c]	21.8	(—)[b]
17a	13 : 1	15.1 ± 0.2[a]	21.5	(—)[b]
17b	1.5 : 1	14.4 ± 0.2[a]	21.9	25.8
30	1.3 : 1	12.1 ± 0.2[a]	20.4	26.1

[a] Averaged from three values which fall within ± 0.2 kcal mol^{-1}. [b] The coupling constant could not be measured. [c] Not attempted.

Less substituted *trans*-**16b** showed similar behaviour to its *gem*-dimethyl analogue **17b** but we were unable to resolve the $^{3}J_{H-F}$ constant in the minor conformer at 223 K and solubility became problematic below this temperature. The spectra for the *cis*-isomer **16a** merely broadened to a single signal at 223 K; the characterisation data reported for this compound were obtained at 50 °C and represent an average of two (or more) conformers.

We sought insight from difluorinated pyran analogues, cyclohexane polyols and cyclohexene diols[17] where we have a number of crystal structures. In functionally related pyrans and cyclohexane polyols which are free to adopt chair conformations, diaxial $^{3}J_{H-F}$ coupling constants reach a maximum of *ca.* 25–26 Hz; in the cyclohexene diols, H–C–C–F dihedral angles of 163 and 169° in the solid state are associated with $^{3}J_{H-F}$ values of 21.4 and 20 Hz in solution, whereas an angle closer to antiperiplanar (175°) results in a larger (24.4 Hz) coupling. Much smaller $^{3}J_{H-F}$ values (<8 Hz) arise where a C–H bond bisects the CF_2 angle (dihedral angles 45–70°).

The $^{3}J_{H-F}$ values obtained for **17b** and **30** clearly suggest that one of the H–C–C–F dihedral angles is close to 180° in the minor conformers and slightly less than that value in the major species.

NOESY experiments should allow the unambiguous assignment of transannular contacts between protons and aid the identification of conformers.

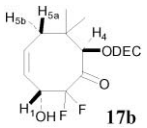
Table 3 shows the summary of the 400 MHz gradient NOESY spectrum of **17b** at 243 K. There are strong cross peaks connecting H-1 and one of the H-6 protons in both conformers, but also weaker cross peaks which appear to indicate NOEs between protons in *different* conformers which are undergoing exchange through ring interconversion. Mixed phase peaks, presumably arising either from overlapped NOE and COSY artefacts, or from subtraction errors were also observed. The NOE may change phase as a function of temperature,[35] complicating the interpretation of these sub-ambient experiments. ROESY experiments[36] were therefore run for **17a** and **30** (the latter is taken as representative of **16b** and **17b** which appear to adopt similar conformations on the basis of the $^{3}J_{H-F}$ values). For *cis*-**17a**, shown by VT ^{19}F NMR to exist as a 13 : 1 mixture of conformers at 212 K, strong ROESY cross peaks (spinlock time 250 ms) connected H-1, H-4 and one of the H-6 protons (Table 4). The spectrum also contains weak signals from the minor conformer and cross peaks arising from environmental exchange were clearly visible.

The ROESY spectrum of **30** is more complex because of the similar populations of conformers (Table 5). The cross peaks which represent a two-stage magnetisation transfer process in which ROE and exchange cross peaks are superimposed, could be reduced significantly by adjustment of the spinlock time. Table 5 summarises the ROESY spectrum with a spinlock time of 250 ms, which shows an extensive set of spurious cross peaks including transferred NOEs between protons in different conformers. Spinlock time reduction to 50 ms minimises these TrNOEs (particularly the H_1 minor/H_{6a} major cross peak) and produces a set of cross peaks correlating H-1, H-4 and one of the H-6 protons in the minor conformer, and H-1 and one of the H-6 protons in the major conformer. The magnetisation transfer experiments and coupling constant analysis suggest clear features, which must be present in the conformational states populated in solution. Molecular modelling was therefore undertaken to obtain further insight.

Electronic structure calculations

Conformational searching was carried out using the PC Spartan[37] Pro 1.0.5 programmes (MMFF94 force field[38]). Families of conformers were inspected for duplicates, then geometry optimisations were performed for all distinct conformers, initially at the AM1 level then using the *ab initio* (RHF) method with the 3-21G*, 6-31G* or 6-31G** basis sets in Spartan. No conformers were excluded for **30** until the optimisation had been carried out at the 6-31G* level; a subset of conformers within 2.5 kcal mol^{-1} of the lowest energy species were then selected for further investigation and comparison. Four conformer types **A–D** (Fig. 3, shown for **30**), which are all boat–chair (C_S) conformers,[20] emerged from the searches and geometry optimisations. We were surprised at the simplicity of this set of conformers; boat–chair species are known to be the most stable for cyclooctane but there is an extensive range of related conformers.[39] These conformers were then identified in the RHF 3-21G* optimised set for **17a** and **17b** and optimised further with

Table 3 Summary of 400 MHz phase sensitive gradient NOESY spectrum for **17b**

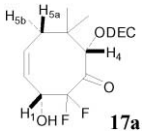


17b

	H_1 minor	H_1 major	H_4 minor	H_4 major	H_{6a} minor	H_{6a} major	H_{6b} minor
H_1 minor							
H_1 major	●						
H_4 minor	—	—					
H_4 major	—	—	●				
H_{6a} minor	●	⊙	—	—			
H_{6a} major	—	●	—	—	●		
H_{6b} minor	—	—	—	—	●	—[b]	
H_{6b} major	—	—	—	—	⊙	●	●

[a] ● = NOESY phase peak, ⊙ = NOESY phase peak; 2 stage magnetisation transfer (NOE + exchange), ● = exchange peak. [b] Not resolved due to signal overlap.

Table 4 Summary of 400 MHz phase sensitive ROESY spectrum for **17a**

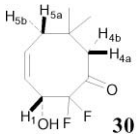


17a

	H_1minor	H_1major	H_4minor	H_4major	H_{6a}minor	H_{6a}major	H_{6b}minor
H_1minor							
H_1major	●						
H_4minor	—[b]	—					
H_4major	—	●	●				
H_{6a}minor	—	—	—[b]	—			
H_{6a}major	—	●	—	●	◉		
H_{6b}minor	—	—	—	—	●	●	
H_{6b}major	—	—	—	—	●	●	—[b]

[a] ● = NOESY phase peak, ◉ = NOESY phase peak; 2 stage magnetisation transfer (NOE + exchange), ● = exchange peak. [b] Too weak to be observed.

Table 5 Summary of 400 MHz phase sensitive ROESY spectrum for **30**



30

	H_1minor	H_1major	H_{4a}minor	H_{4a}major	H_{4b}minor	H_{4b}major	H_{6a}minor	H_{6a}major	H_{6b}minor
H_1minor									
H_1major	●								
H_{4a}minor	—	—							
H_{4a}major	—	●	◉						
H_{4b}minor	—	—	●	●					
H_{4b}major	—	—	●	●	◉				
H_{6a}minor	—	—	—	—	—	—			
H_{6a}major	◉	●	—	●	—	—	—		
H_{6b}minor	●	—	—	—	—	—	●	●	
H_{6b}major	—	—	—	—	—	—	—	●	◉

[a] ● = NOESY phase peak, ◉ = NOESY phase peak; 2 stage magnetisation transfer (NOE + exchange), ● = exchange peak.

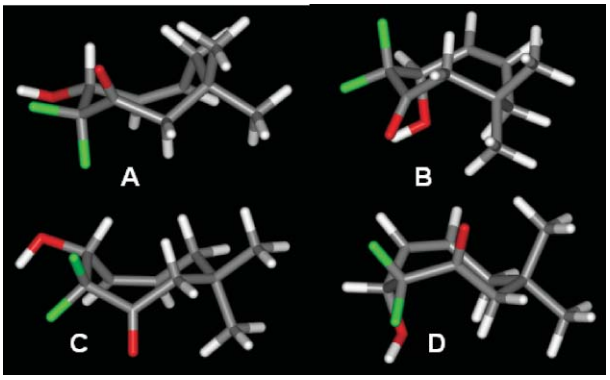


Fig. 3 Four conformers obtained from conformational searching and optimised using electronic structure calculations.

Table 6 Relative energies for the four types of conformer **A–D** for representative cyclooctenones **17a, 17b** and **30**

		Relative energy (kcal mol^{-1})			
	Basis set	**A**	**B**	**C**	**D**
17a	6-31G*	2.698	(**0.000**)	3.795	5.177
	6-31G**	2.676	(**0.000**)	3.763	5.089
	6-31G**[a]	2.679	(**0.000**)	3.762	5.094
17b	6-31G*	(**0.000**)	3.712	0.803	2.123
	6-31G**	(**0.000**)	3.640	0.661	2.100
30	6-31G*	(**0.000**)	0.530	1.630	2.309
	6-31G**	(**0.000**)	0.519	1.651	2.326
	6-31G(d)[b]	(**0.000**)	0.625	1.433	1.827
	6-31G(d) + PCM[b]	(**0.000**)	0.780	0.988	1.616

[a] MOLPRO. [b] Gaussian 98W.

the bigger basis sets. Table 6 summarises the relative energies obtained for each of the four conformers for **17a, 17b** and **30** using the different methods. The optimisations for **17a** were then repeated using MOLPRO[40] with the 6-31G** basis set (RHF). Geometry optimisations were also performed for conformers **A–D** of **30** using the B3LYP method[41] in Gaussian 98W[42] (6-31G(d) basis set). The energies between the four conformers differ strikingly for **17a** and **17b** and are more similar for **30**. The DFT method brings all the energies closer together, an effect which is more pronounced when the PCM method of Tomasi is applied.[43] Conformers **A** and **C** align the polar groups in largely the same direction, whereas **B** and **D** involve some opposition of dipoles suggesting that a relatively polar solvent may favour the former pair of conformers. The calculations suggest an overwhelming conformational preference for **17a**, with more balanced populations for **17b** and **30**, consistent with the VT NMR observations.

Conformational analysis

Consistency between a calculated conformation and more than one piece of NMR data would be more informative than the absolute or even relative energies. The observed values for the $^3J_{H-F}$ coupling constants argue against the presence of types **B** and **D** in solution because both feature the H-1 methine proton

bisecting the CF_2 angle. However, conformers **A** and **C** are supported strongly by the measured $^3J_{H-F}$ coupling constants; for example, for **17b**, the calculated dihedral angles are 172° (**A**, major) and 168° (**C**, minor). Conformers **A** and **C** are also entirely consistent with the results of the ROESY experiments; H-1, H-4 and one of the H-6 protons in the minor conformer **C**, and H-1 and one of the H-6 protons in the major conformer **A**, are clearly well within 3 Å of each other. In the case of **17b, A** and **C** are predicted to be the lowest energy conformers. The ring atoms in the calculated type **C** conformer overlay almost exactly with the crystal structure (Fig. 4). Application of the H–C–C–F Karplus equation[44] to **17b** predicts slightly larger $^3J_{H-F}$ values of 27.2 (**A**) and 28.8 (**C**) Hz, whereas the largest calculated coupling constants for types **B** and **D** are significantly smaller (9.2 and 12.8 Hz respectively).

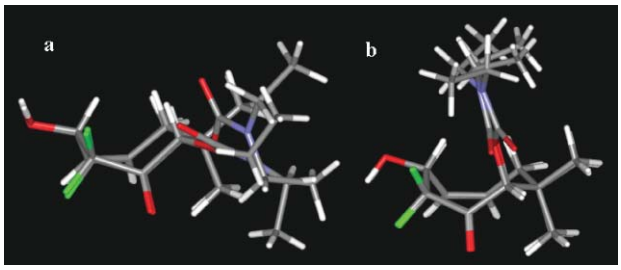


Fig. 4 Overlay of calculated type **C** conformer and crystal structure for a) **17a** and b) **17b**.

In the other cases, the theoretical treatments failed to predict the relative conformer energies correctly. The case of **17a**, where conformer **B** should dominate is particularly striking. Examination of the four conformers for **30** reveals a tension between H···H and H···O transannular interactions; **A** and **C** bring two and three hydrogens respectively into close contact, whereas **B** and **D** oppose one and two hydrogens respectively to the axial hydroxyl group.

The behaviour of **17a** and **17b** is complicated by the additional substituent; the ODEC group can cause additional transannular interactions (the *A*-value of oxygen substituents is subject to a very small second atom effect so that OH and OAc have similar *A*-values[45]), and can cause repulsions with the *gem*-dimethyl group. For **17b**, conformer **C** allows the C-ODEC bond to avoid one of the methyl groups entirely, though only by placing the carbamoyloxy substituent axial; the calculated type **C** conformer overlays reasonably well with the crystal structure (Fig. 5a), while the crystal structures of **16b** and **17b** are also very similar. Obviously packing forces exert influence over the conformations of flexible molecules in the solid state but we believe that the agreement between NMR, calculated and observed molecular structure in the crystal, is significant and suggests that the energies produced by the calculations do not accurately represent the distribution of species in solution. All three calculated type **C** structures overlay with very close correspondence between the ring structures.

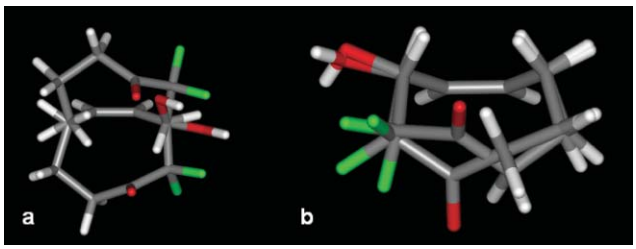


Fig. 5 Overlays a) of **A** and **B** (ring inversion) and b) of **A** and **C** (pseudorotation).

The apparent prevalence of conformer **C** for **17a** is surprising, because conformer A looks better, though it contains a close O···F contact (2.68 Å). Both conformers **A** and **C** maximise attractive *gauche* interactions between C–F and C–O acceptor bonds and potential donors, whereas both bisected conformations contain a pair of acceptor bonds in an antiperiplanar arrangement.[46] It is possible that the theory used has failed to account adequately for the potential magnitude of this effect. The calculated coupling constant for **17a** type **C** (26.4 Hz) agrees quite well with the measured value, whereas the value calculated using the observed molecular structure in the crystal is rather lower (23.5 Hz). The observed coupling constants cannot represent averages given the NOESY/ROESY data obtained at low temperature and the likely nature of the exchange processes. It is more likely that they represent the need for reparameterisation of the Karplus equation for these rather high electron demand environments.

The interconversion(s) of **A** and **C**, (and **B** and **D**) represent pseudorotation, which is slow on the NMR timescale at 223 K (the former can be seen clearly in the exchange peaks in the NOESY and ROESY experiments). The overlay of structures **A** and **B** allows a clear view of the pseudorotation (Fig. 5b) and allows the nature of the exchange in the H-6 and H-4 protons to be understood. **A** and **B**, and **C** and **D** are mutually related by ring inversion (Fig. 5a), which flips the hydroxyl group between equatorial and axial environments in a pseudo-enantiomeric relationship. The typical *A*-value of 0.7 kcal mol^{-1} for a hydroxyl group (a wider range of values is used[45]) is of the same order of magnitude to the differences in energy calculated between **A** and **B** (0.625 kcal mol^{-1}) and **C** and **D** (0.394 kcal mol^{-1}).

The rotation of the carbonyl group onto the upper face causes H_1 to appear at almost 1 ppm lower field and has a similar effect on one of the H_6 protons, so that whereas the lowfield H_6 proton shows the NOE/ROE in the major conformer, it is the highfield H_6 that shows it in the minor species. The H_4 protons exchange between locations with respect to the carbonyl group, producing chemical shift differences up to 1 ppm. Conformational exchange in cyclooctenyl systems has been studied in a limited number of cases with ring inversions and pseudorotations both documented; barriers to inversion exchange of 7.3–8.5 kcal mol^{-1} have been reported, with smaller barriers (*ca.* 5 kcal mol^{-1})[47] for the pseudorotation.[48] We have failed entirely to detect the ring inversion process; the results from 2D NMR experiments and coupling constant analysis identify the exchange which is active at room temperature as the pseudorotation between **A** and **C**. We conclude that conformers **B** and **D** which would be populated by ring inversion lie at energies significantly higher than those predicted by the electronic structure calculations with these small basis sets. All the barriers observed by VT NMR in our systems are considerably bigger than any of those reported in the literature; further studies to elucidate the origins of the barriers to ring interconversion are in progress.

Conclusion

These studies demonstrate the effectiveness of the RCM reaction for the preparation of highly functionalised difluorinated cyclic ketones *via* closure of the difficult cyclooctenyl ring system, and highlight a number of successes and some of the difficulties apparent in carrying out conformational analysis on exchanging conformer systems. The lack of congruence between the NMR observations and the lowest energy conformer identified by the electronic structure calculations is also interesting and suggests that improvements in the choice of model chemistry must be made if systems of this type are to be handled adequately.

Experimental

NMR spectra were recorded on Bruker ARX-250, Bruker DPX-300, Bruker AV-400 or Bruker DRX-400 spectrometers. ^1H and ^{13}C NMR spectra were recorded using the deuterated solvent as

the lock and the residual solvent as the internal reference. ^{19}F NMR spectra were recorded relative to chlorotrifluoromethane as the external standard. The multiplicities of the spectroscopic data are presented in the following manner: app = apparent, s = singlet, d = doublet, t = triplet, pent = pentet, q = quartet, m = multiplet and br = broad. The appearance of complex signals is indicated by app. Homocouplings (H–H, F–F) are given in Hertz and specified by *J*; the nuclei involved in heteronuclear couplings are defined with the observed nucleus given first. Unless stated otherwise, all refer to ^3J couplings. Carbohydrate numbering is used for the products of dihydroxylation reactions to simplify the reading of the NMR data. Chemical ionisation (CI) mass spectra were recorded on a Micromass Prospec or a Kratos Concept 1H spectrometers using ammonia as the reagent gas. Electron impact (EI) spectra were recorded on a Kratos MS-80, a Micromass Prospec or a Kratos Concept 1H spectrometer. Fast atom bombardment (FAB) spectra were recorded on a Kratos Concept 1H spectrometer at about 7 kV using xenon and *m*-nitrobenzyl alcohol as the matrix. GC-MS was carried out on a Perkin Elmer TurboMass spectrometer fitted with a Zebron ZB-5 column (30 m × 0.25 μm) running a 20–350 °C ramp over 27 minutes. Electrospray (ES) mass spectra were recorded on a Micromass LCT or a Micromass Quattro LC spectrometer. High resolution mass spectrometry measurements were carried out either on the Micromass LCT or the Kratos Concept 1H spectrometer using peak matching to suitable reference peaks, depending on the technique used. Thin layer chromatography (TLC) was performed on precoated aluminium silica gel plates supplied by E. Merck, A. G. Darmstadt, Germany (silica gel 60 F_{254}, thickness 0.2 mm, art. 1.05554) or on precoated plastic silica gel plates supplied by Macherey–Nagel (Polygram® SIL G/UV_{254}, thickness 0.25 mm, art. 805 023) or on precoated glass plates supplied by Merck (silica gel 60 F_{254}, art. 1.05715). Visualisation was achieved by UV light and/or potassium permanganate stain. Flash column chromatography was performed using silica gel (Fluorochem, silica gel 60, 40–63 μ, art. 02050017) or using a Biotage flash chromatography system. THF was dried by refluxing with benzophenone over sodium wire until a deep purple color developed and persisted, then distilled and collected by dry syringe as required. Other solvents were dried using a Pure Solv apparatus (Innovative Technologies Inc). All other chemicals were used as received without any further purification. Where required, solvents were degassed by bubbling argon or nitrogen through them for at least 30 minutes. Calculations were performed using PC Spartan Pro 1.0.5 running on an Intel Pentium 4 (2.66 GHz with 1.28 MB RAM) or MOLPRO on a cluster of dual Opteron PCs running Linux.

Preparation of pent-4-enal 12a

Allyl vinyl ether (530 mmol, 44.6 g) was heated at 150 °C in an Ace tube for 16 hours. The reaction mixture was allowed to cool, then distilled to afford the desired pentenal **12a** as a colourless liquid (39.90 g, 90%, 97% by GC). Bp 103–105 °C/760 mmHg (lit.[49] 100 °C/760 mmHg); ν_{max}(film)/cm^{-1} 3080m (C–H), 2979m (C–H), 1917m (C–H), 1825m (C–H), 2725m (C–H), 1725s (C=O); δ_H(250 MHz, $CDCl_3$) 9.99 (1H, t, *J* 1.5, H-1), 6.13–5.97 (1H, m, H-4), 5.32–5.21 (2H, m, H-5), 2.80–2.73 (2H, m, H-2), 2.65–2.56 (2H, m, H-3); δ_c(63 MHz, $CDCl_3$) 202.1, 136.8, 115.9, 43.0, 26.4; spectral data were in agreement with those reported by Murphy *et al.*[49]

Preparation of 2-(*N*,*N*-diethylcarbamoyloxy)-1,1-difluorohepta-1,6-dien-3-ol 13a

n-BuLi (400 mmol, 160 mL of a 2.5 N solution in hexanes) was added dropwise to a cold (−70 °C) solution of diisopropylamine (400 mmol, 56.1 mL) in dry THF (750 mL). After completion of the addition, the mixture was allowed to warm to −30 °C and recooled to −70 °C. A solution of carbamate **11** (200 mmol, 39.8 g) in THF (250 mL) was added at a rate to maintain the temperature between −70 and −60 °C. After completion of the addition, the mixture changed from yellow to purple through orange and red. Pentenal **12a** (220 mmol, 18.5 g) was then added at a rate to maintain the temperature between −70 and −60 °C and the mixture was stirred for 1 hour at −70 °C. Boron trifluoride dimethyl etherate (400 mmol, 51.0 mL) was added in one portion and the reaction mixture was allowed to warm to 0 °C over 2 hours and stirred at this temperature for 1 hour. During this time, the solution turned from purple to yellow through green. The reaction mixture was quenched with ammonium chloride (500 mL of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 × 500 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown oil (54.30 g). Purification by column chromatography (20% diethyl ether in light petroleum) afforded the desired alcohol **13a** as a pale yellow oil (41.61 g, 79%, 98% by GC-MS); R_f (20% ether in light petroleum) 0.22; ν_{max}(film)/cm^{-1} 3448s br (O–H), 3079w (=C–H), 2978s (C–H), 2937s (C–H), 1769 (C=O), 1711s (C=O), 1641m (C=C); δ_H(250 MHz, $CDCl_3$) 5.75 (1H, ddt, J_{trans} 17.0, J_{cis} 10.2, *J* 6.7, H-6), 5.02–4.89 (2H, m, H-7a and H-7b), 4.37–4.31 (1H, m, H-3), 3.65 (1H, br s, –O*H*), 3.28 (4H, q, *J* 7.1, –N(CH_2CH_3)$_2$), 2.15–1.99 (2H, m, H-5), 1.78–1.49 (2H, m, H-4), 1.15–1.05 (6H, m, –N(CH_2CH_3)$_2$); δ_C(65 MHz, $CDCl_3$) 155.2, 155.0 (dd, $^1J_{C-F}$ 293.2, 285.6), 137.9, 115.5, 113.5 (dd, $^2J_{C-F}$ 42.5, 12.0), 66.6, 43.2, 42.6, 33.1, 29.9, 14.3, 13.5; δ_F(235 MHz, $CDCl_3$) −96.3 (1F, d, $^2J_{F-F}$ 51.8), −106.3 (1F, dd, $^2J_{F-F}$ 51.8, $^4J_{F-H}$ 2.6); [HRMS (FAB, $[M + H]^+$) found: 264.14117. Calc. for $C_{12}H_{20}NO_3F_2$: 264.14113]; *m*/*z* (FAB) 264 (20%, $[M + H]^+$), 246 (100).

Preparation of 2-(*N*,*N*-diethylcarbamoyloxy)-1,1-difluoro-4,4-dimethylhepta-1,6-dien-3-ol 13b

As for **13a**, but from *n*-BuLi (394 mmol, 246.3 mL of a 1.6 N solution in hexanes), diisopropylamine (394 mmol, 55.2 mL) in dry THF (750 mL), **11** (197 mmol, 39.24 g) in THF (250 mL), 2,2-dimethyl-4-pentenal (217 mmol, 29.5 mL) and boron trifluoride dimethyl etherate (394 mmol, 50.0 mL). The reaction mixture was quenched with ammonium chloride (750 mL of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 × 750 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil, which was combined with the crude product from a second batch on the same scale to afford a total of 121.0 g of an orange oil. Purification by (Biotage) column chromatography (15% diethyl ether in light petroleum) afforded the desired alcohol **13b** as a pale yellow oil (75.74 g, 66%, 100% by GC); R_f (15% diethyl ether in light petroleum) 0.24; ν_{max}(film)/cm^{-1} 3448s br (O–H), 3075m (=C–H), 2977s (C–H), 2937s (C–H), 1762s (C=O), 1710s (C=O), 1639m (C=C); δ_H(250 MHz, $CDCl_3$) 5.85–5.68 (1H, m, H-6), 5.01 (1H, s, H-7a), 4.98–4.93 (1H, m, H-7b), 4.08 (1H, dd, $^4J_{H-F}$, *J* 1.8, H-3), 3.56 (1H, br s, –O*H*), 3.33–3.19 (4H, m, –N(CH_2CH_3)$_2$), 2.12 (1H, dd, ^2J 13.5, *J* 7.4, H-5a), 1.94 (1H, dd, ^2J 13.5, *J* 7.3, H-5b), 1.15–1.07 (6H, m, –N(CH_2CH_3)$_2$), 0.89 (3H, s, –CH_3), 0.84 (3H, s, –CH_3); δ_C(63 MHz, $CDCl_3$) 155.6 (dd, $^1J_{C-F}$ 292.5, 285.8), 155.4, 135.2, 117.8, 112.2 (dd, $^2J_{C-F}$ 39.7, 11.7), 72.8, 43.7, 43.1, 42.4, 39.0, 23.2, 22.9, 14.3, 13.4; δ_F(235 MHz, $CDCl_3$) −96.2 (1F, d, $^2J_{F-F}$ 53.1), −105.0 (1F, dd, $^2J_{F-F}$ 53.1, $^4J_{F-H}$ 4.0); [HRMS (ES, $[M + Na]^+$ found: 314.1536. Calc. for $C_{14}H_{23}NO_3F_2Na$: 314.1544]; *m*/*z* (ES) 314 (100%, $[M + Na]^+$).

Preparation of 6-(*N*,*N*-diethylcarbamoyloxy)-4,4-difluoro-3-hydroxy-deca-1,9-dien-5-ones *anti*-14a and *syn*-14b

n-BuLi (100 mmol, 40.0 mL of a 2.5 M solution in hexanes) was added dropwise to a cold (−78 °C) solution of alcohol

13a (100 mmol, 26.3 g) in THF (900 mL). After completion of the addition, the mixture was allowed to warm to −10 °C and acrolein (100 mmol, 7.3 mL) was added dropwise as a solution in THF (100 mL). After completion of the addition, the mixture was allowed to warm to 0 °C and stirred at this temperature for 1 hour. The reaction mixture was quenched with ammonium chloride (500 mL of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 × 500 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography (20% ethyl acetate in light petroleum) afforded an inseparable diastereoisomeric mixture (1 : 2) of the desired aldol products *syn*-**14b** and *anti*-**14a** as a pale yellow oil (18.8 g, 58%, 97% by GC-MS); R_f (20% ethyl acetate in light petroleum) 0.28; ν_{max}(film)/cm^{-1} 3399s br (O–H), 3078w (=C–H), 2978s (C–H), 2937s (C–H), 2878s (C–H), 1744s (C=O), 1682s (C=O), 1640m (C=C); δ_H(250 MHz, $CDCl_3$) *syn*/*anti*-mixture: 5.98–5.66 (2H, m, H-2 and H-9), 5.56–5.29 (3H, m, H-1a, H-1b and H-10b), 5.04–4.97 (3H, m, H-10a, H-6 and –O*H*), 4.50–4.32 (1H, m, H-3), 3.32–3.15 (4H, m, –N(CH_2CH$_3$)$_2$), 2.24–1.68 (4H, m, H-7 and H-8), 1.17–1.02 (6H, m, –N(CH$_2$CH_3)$_2$); δ_C(65 MHz, $CDCl_3$) *syn*/*anti*-mixture: 200.0 (dd, $^2J_{C-F}$ 34.1, 21.9), 198.2 (dd, $^2J_{C-F}$ 30.5, 24.9), 155.8, 155.7, 136.8, 136.7, 131.3 (t, $^3J_{C-F}$ 3.1), 130.6 (d, $^3J_{C-F}$ 2.5), 120.5, 120.0, 116.9 (dd, $^1J_{C-F}$ 261.1, 256.6), 116.6, 116.5, 116.4 (dd, $^1J_{C-F}$ 261.4, 259.4), 76.9, 75.9, 73.4 (t, $^2J_{C-F}$ 27.2), 71.8 (dd, $^2J_{C-F}$ 29.0, 23.4), 42.7, 42.2, 29.9, 29.4 (d, $^4J_{C-F}$ 1.5), 29.2 (d, $^4J_{C-F}$ 2.5), 14.2, 14.1, 13.6; δ_F(235 MHz, $CDCl_3$) major diastereoisomer (*anti*-**14a**): −109.8 (1F, d, $^2J_{F-F}$ 256.7), −133.9 (1F, dd, $^2J_{F-F}$ 256.7, $^3J_{F-H}$ 22.5), minor diastereoisomer (*syn*-**14b**): −117.6 (d, $^3J_{F-H}$ 9.3); [HRMS (FAB, [M + H]$^+$) found: 320.16737. Calc. for $C_{15}H_{24}NO_4F_2$: 320.16734; *m*/*z* (FAB) 320 (100%, [M + H]$^+$).

Preparation of 6-(*N*,*N*-diethylcarbamoyloxy)-4,4-difluoro-3-hydroxy-7,7-dimethyldeca-1,9-dien-5-ones *anti*-15a and *syn*-15b

As for **14a**, but from *n*-BuLi (120 mmol, 75 mL of a 1.6 N solution in hexanes), **13b** (29.1 g, 100 mmol) in THF (1 L) and acrolein (132 mmol, 8.8 mL) in THF (100 mL). After completion of the addition, the mixture was allowed to warm to 0 °C and stirred at this temperature for 1 hour. The reaction mixture was quenched with ammonium chloride (1 L of a saturated aqueous solution). The aqueous phase was separated and further extracted with diethyl ether (3 × 750 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale yellow oil, which was combined with the crude product from a second batch on the same scale to afford a total of 100.6 g of a 1 : 1 diastereoisomeric mixture of aldol products *syn*-**15b** and *anti*-**15a** as a pale yellow oil. Purification by (Biotage) column chromatography (1 to 5% ethyl acetate in light petroleum) allowed the separation of the diastereoisomers. *Syn*-**15b** was obtained as a colourless oil (25.06 g, 33%, 98% by GC); R_f (15% ethyl acetate in light petroleum) 0.23; ν_{max}(film)/cm^{-1} 3407s br (O–H), 3078m (=C–H), 2979s (C–H), 2935s (C–H), 2978s (C–H), 1740s (C=O), 1684s (C=O), 1650m (C=C), 1640m (C=C); δ_H(250 MHz, $CDCl_3$) 5.96–5.66 (2H, m, H-2 and H-9), 5.52 (1H, ddd, J_{trans} 17.2, ^2J 1.4, ^4J 1.6, H-1a), 5.36 (dt, J_{cis} 10.6, ^2J 1.4, ^4J 1.4, H-1b), 5.08–4.94 (4H, m, H-10a, H-10b, H-6 and –O*H*), 4.51 (1H, dd, $^3J_{F-H}$ 22.0, *J* 5.4, H-3), 3.32–3.10 (4H, m, –N(CH_2CH$_3$)$_2$), 2.18 (1H, dd, ^2J 13.5, *J* 7.8, H-8a), 2.03 (1H, dd, ^2J 13.5, *J* 6.9, H-8b), 1.16 (3H, t, *J* 7.1, –N(CH$_2$CH_3)$_2$), 1.06–0.95 (9H, m, –N(CH$_2$CH_3)$_2$ and 2 × –CH_3); δ_C(63 MHz, $CDCl_3$) 201.8 (dd, $^2J_{C-F}$ 36.4, 22.2), 155.6, 133.6, 131.2, 120.3, 119.2, 115.3 (dd, $^1J_{C-F}$ 266.8, 256.6), 80.5, 71.7 (dd, $^2J_{C-F}$ 28.7, 22.6), 44.4, 42.8, 42.2, 38.5, 23.5, 23.4, 14.3, 13.6; δ_F(235 MHz, $CDCl_3$) −106.2 (1F, d, $^2J_{F-F}$ 262.7), −132.4 (1F, dd, $^2J_{F-F}$ 262.7, $^3J_{F-H}$ 22.5); [HRMS (TOF ES$^+$) found: 370.1810. Calc. for $C_{17}H_{27}NO_4F_2Na$: 370.1806]; *m*/*z* (ES) 348 (100%, [M + H]$^+$). Then *anti*-**15a** was obtained as a colourless oil (23.54 g, 31%, 100% by GC). R_f (15% ethyl acetate in light petroleum) 0.17; ν_{max}(film)/cm^{-1} 3397s br (O–H), 3078m (=C–H), 2977s (C–H), 2936m (C–H), 2880m (C–H), 1745s (C=O), 1703s (C=O), 1651m (C=C), 1640m (C=C); δ_H(250 MHz, $CDCl_3$) 5.93–5.66 (2H, m, H-2 and H-9), 5.39 (1H, d, J_{trans} 17.0, H-1a), 5.26 (1H, dd, J_{cis} 10.6, ^2J 1.4, H-1b), 5.08–4.94 (3H, m, H-10a, H-10b and H-6), 4.54–4.37 (2H, m, H-3 and –O*H*), 3.30–3.12 (4H, m, –N(CH_2CH$_3$)$_2$), 2.16 (1H, dd, ^2J 13.6, *J* 7.9, H-8a), 2.03 (1H, dd, ^2J 13.6, *J* 7.1, H-8b), 1.14 (3H, t, *J* 7.1, –N(CH$_2$CH_3)$_2$), 1.05–0.95 (9H, m, –N(CH$_2$CH_3)$_2$ and 2 × –CH_3); δ_C(63 MHz, $CDCl_3$) 199.6 (dd, $^2J_{C-F}$ 33.6, 23.9), 155.6, 133.7, 132.1 (dd, $^3J_{C-F}$ 4.6, 1.5), 119.1, 118.8, 116.0 (t, $^1J_{C-F}$ 260.2), 80.0, 74.1 (t, $^2J_{C-F}$ 28.0), 44.4, 42.8, 42.3, 38.7, 23.5, 23.3, 14.4, 13.6; δ_F(235 MHz, $CDCl_3$) −113.6 (1F, dd, $^2J_{F-F}$ 261.4, $^3J_{F-H}$ 11.9), −115.5 (1F, d, $^2J_{F-F}$ 261.4); [HRMS (TOF ES$^+$) found: 370.1798. Calc. for $C_{17}H_{27}NO_4F_2Na$: 370.1806; *m*/*z* (ES) 348 (100%, [M + H]$^+$).

Preparation of 4-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoro-3-oxo-cyclooct-7-en-1-ols *cis*-16a and *trans*-16b

A solution of a diastereoisomeric mixture (2 : 1) of dienes *anti*-**14a** and *syn*-**14b** (15.0 mmol, 4.79 g) and titanium(IV) isopropoxide (4.50 mmol, 1.16 mL) in DCM (1.5 L) was refluxed for 30 minutes. Catalyst **2** (150 μmol, 127 mg) was added as a solution in DCM (5 mL) and the reaction mixture was refluxed for 2 days. Another portion of catalyst **2** (150 μmol, 127 mg) was added as a solution in DCM (5 mL) and the reaction mixture was stirred for an additional day. The mixture was concentrated under reduced pressure to leave a crude diastereoisomeric mixture (1 : 2) as a brown oil (4.53 g). Purification by column chromatography (40% ethyl acetate in light petroleum) allowed the separation of the two diastereoisomers. Major diastereoisomer (*trans*-**16b**) was obtained as a white solid (1.88 g, 43%). R_f (40% ethyl acetate in light petroleum) 0.30; mp 93–94 °C; (found C, 53.17; H, 7.39; N, 4.79; $C_{13}H_{21}F_2NO_4$ requires: C, 53.23; H, 7.22; N, 4.78%); ν_{max}(KBr)/cm^{-1} 3393s br (O–H), 2978m (C–H), 1741s (C=O), 1686s (C=O); δ_H(400 MHz, $CDCl_3$, 323 K) 5.94–5.86 (1H, m, H-8), 5.57–5.52 (1H, m, H-7), 5.41 (1H, dt, *J* 7.0, 3.4, ^4J 3.4, H-4), 5.09–4.98 (1H, m, H-1), 3.38–3.29 (5H, m, –O*H* and –N(CH_2CH$_3$)$_2$), 2.41–1.99 (4H, env., H-5 and H-6), 1.20–1.12 (6H, m, –N(CH$_2$CH_3)$_2$); δ_C(63 MHz, $CDCl_3$) 198.5 (t, $^2J_{C-F}$ 24.6), 154.6, 132.9, 129.5 (d, $^3J_{C-F}$ 5.1), 117.9 (t, $^1J_{C-F}$ 260.9), 75.5, 68.4 (t, $^2J_{C-F}$ 22.1), 42.6, 41.9, 32.4, 22.7, 14.3, 13.6; δ_F(376 MHz, $CDCl_3$, 223 K) major conformer: −107.6 (1F, d, $^2J_{F-F}$ 246.1), −131.5 (1F, dd, $^2J_{F-F}$ 246.1, $^3J_{F-H}$ 21.8), minor conformer: −114.8 (1F, d, $^2J_{F-F}$ 231.7), −128.0 (1F, br d, $^2J_{F-F}$ 231.7); [HRMS (FAB, [M + H]$^+$) found: 292.13608. Calc. for $C_{13}H_{20}NO_4F_2$: 292.13604], *m*/*z* (ES) 292 (100%, [M + H]$^+$). An analytical sample was recrystallised by vapour diffusion to afford colourless cubes, which were used to obtain an X-ray crystal structure of cyclooctenol *trans*-**16b**. The minor diastereoisomer (*cis*-**16a**) was obtained as a pale yellow solid (0.87 g, 20%). R_f (40% ethyl acetate in light petroleum) 0.24; mp 51–52 °C; (found C, 53.37; H, 7.20; N, 4.65; $C_{13}H_{21}F_2NO_4$ requires: C, 53.23; H, 7.22; N, 4.78%); ν_{max}(KBr)/cm^{-1} 3393s br (O–H), 2977m (C–H), 1741s (C=O), 1687s (C=O); δ_H(400 MHz, $CDCl_3$, 323 K) 5.93–5.86 (1H, m, H-8), 5.70–5.55 (1H, m, H-7), 5.33–5.30 (1H, m, H-4), 5.07–4.99 (1H, m, H-1), 3.35–3.29 (5H, m, –N(CH_2CH$_3$)$_2$ and –O*H*), 2.47–1.85 (4H, H-5 and H-6), 1.17–1.13 (6H, m, –N(CH$_2$CH_3)$_2$); δ_C(63 MHz, $CDCl_3$) 196.0 (dd, $^2J_{C-F}$ 27.2, 23.9), 153.4, 132.2, 127.1 (d, $^3J_{C-F}$ 5.6), 115.5 (t, $^1J_{C-F}$ 260.4), 73.0 (d, $^3J_{C-F}$ 2.5), 66.1 (dd, $^2J_{C-F}$ 25.4, 20.9), 41.2, 40.6, 32.3, 22.2, 12.8, 12.3; δ_F(376 MHz, $CDCl_3$, 323 K) major conformer: −106.7 (1F, d, $^2J_{F-F}$ 244.7), −131.3 (1F, dd, $^2J_{F-F}$ 244.7, $^3J_{F-H}$ 18.9), minor conformer: −115.1 (1F, d, $^2J_{F-F}$ 263.0), −119.2 (1F, dd, $^2J_{F-F}$ 263.0, $^3J_{F-H}$ 17.6); [HRMS (FAB, [M + H]$^+$) found: 292.13606. Calc. for $C_{13}H_{20}NO_4F_2$: 292.13604], *m*/*z* (ES) 292 (100%, [M + H]$^+$).

Preparation of *cis*-4-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoro-5,5-dimethyl-3-oxo-cyclooct-7-en-1-ol 17a

Titanium(IV) isopropoxide (4.50 mmol, 1.33 mL) was added to a solution of diene *anti*-**16a** (15.0 mmol, 5.21 g) in dry, degassed DCM (1.5 L) at room temperature. The reaction mixture was refluxed for 1 hour and catalyst **1** (113 μmol, 309 mg) was added as a solution in DCM (10 mL). After 3 days, more catalyst **1** (113 μmol, 309 mg) was added as a solution in DCM (10 mL) and the reaction was refluxed for another 4 days. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford a black solid (5.83 g). The black solid was filtered through a short pad of silica, eluting with 50% ethyl acetate in light petroleum. Fractions containing the product were concentrated under reduced pressure to afford a green solid (3.80 g), which was recrystallised in diethyl ether–light petroleum to afford the desired difluorinated cyclooctenol *cis*-**17a** as colourless cubes (3.31 g, 69%). R_f (50% ethyl acetate in light petroleum) 0.41; mp 117–118 °C; (found: C, 56.22; H, 7.35; N, 4.30; $C_{15}H_{23}F_2NO_4$ requires: C, 56.42; H, 7.26; N, 4.39%); ν_{max}(KBr)/cm^{-1} 3362s br (O–H), 2985m (C–H), 2943m (C–H), 1741s (C=O), 1693s (C=O); δ_H(400 MHz, $CDCl_3$, 323 K) 5.82 (1H, dd, *J* 11.0, 11.0, 11.0, H-7), 5.65 (1H, dd, *J* 11.0, 11.0, H-8), 5.09 (1H, s, H-4), 5.05–4.92 (1H, m, H-1), 3.59 (1H, br s, –O*H*), 3.34–3.14 (4H, m, –N(C*H*$_2$CH$_3$)$_2$), 2.32–2.19 (2H, m, H-6), 1.18–1.04 (9H, m, –N(CH$_2$C*H*$_3$)$_2$ and –C*H*$_3$), 0.97 (3H, s, –C*H*$_3$); δ_C(101 MHz, $CDCl_3$, 323 K) 195.8 (t, $^2J_{C-F}$ 26.0), 154.6, 132.0, 129.1, 116.5 (t, $^1J_{C-F}$ 260.2), 78.9, 67.6 (t, $^2J_{C-F}$ 23.8), 42.2, 41.7, 38.5, 28.4, 20.5, 13.9, 13.3; δ_F(376 MHz, $CDCl_3$, 223 K) major conformer: −102.4 (1F, d, $^2J_{F-F}$ 239.5), −133.4 (1F, dd, $^2J_{F-F}$ 239.5, $^3J_{F-H}$ 21.5), minor conformer: −110.8 (1F, d, $^2J_{F-F}$ 250.3), −110.4 (1F, d, $^2J_{F-F}$ 250.3); *m*/*z* (ES) 320 (46%, [M + H]$^+$). Crystallographic data were reported previously.[18]

Preparation of *trans*-4-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoro-5,5-dimethyl-3-oxo-cyclooct-7-en-1-ol 17b

Method A. Titanium(IV) isopropoxide (4.5 mmol, 1.33 mL), diene *syn*-**15b** (15.0 mmol, 5.21 g) and catalyst **1** (2 × 113 μmol, 2 × 309 mg) were treated as described previously for the preparation of *cis*-**17a** to afford a crude black solid (6.78 g). The black solid was filtered though a short pad of silica eluting with 50% ethyl acetate in light petroleum. Fractions containing the product were concentrated under reduced pressure to afford a green solid (4.02 g), which was recrystallised in diethyl ether–light petroleum to afford the desired difluorinated cyclooctenol *trans*-**17b** as colourless cubes (3.70 g, 77%).

Method B. Titanium(IV) isopropoxide (1.5 mL, 0.44 mL) was added to a solution of diene *syn*-**15b** (5.0 mmol, 1.74 g) in dry degassed DCM (500 mL) and the reaction mixture was refluxed for 1 hour. Catalyst **2** (125 μmol, 106 mg) was added as a solution in dry degassed DCM (5 mL), the reaction mixture was refluxed for an additional 18 hours and concentrated under reduced pressure to leave a brown solid (2.55 g). Work up as described for method A afforded the desired cyclooctenol *trans*-**17b** as colourless cubes (1.20 g, 75%).

Method C. A solution of diene *syn*-**16b** (2.5 mmol, 0.87 g) and catalyst **2** (63 μmol, 53 mg) in dry degassed DCM (250 mL) was refluxed for 3 days and concentrated under reduced pressure to leave a pale brown solid (0.85 g). Work up as described for method A afforded the desired cyclooctenol *trans*-**17b** as colourless cubes (0.65 g, 82%). R_f (50% ethyl acetate in light petroleum) 0.50; mp 118–119 °C; (found: C, 56.47; H, 7.20; N, 4.35; $C_{15}H_{23}F_2NO_4$ requires: C, 56.42; H, 7.26; N, 4.39%); ν_{max}(KBr)/cm^{-1} 3364s br (O–H), 2985m (C–H), 2943m (C–H), 1740s (C=O), 1685s (C=O); δ_H(400 MHz, $CDCl_3$, 243 K) major conformer: 5.90–5.84 (1H, m, H-7), 5.67–5.62 (1H, m, H-8), 4.70 (1H, s, H-4), 4.63 (1H, dd, $^3J_{H-F}$ 24.0, *J* 4.4, H-1), 3.32–3.12 (5H, m, –N(C*H*$_2$CH$_3$)$_3$ and –O*H*), 1.98 (1H, dd, ^2J 14.4, *J* 6.4, H-6a), 1.79 (1H, d, ^2J 14.4, H-6b), 1.15 (3H, s, –C*H*$_3$), 1.12 (3H, t, *J* 8.0, –N(CH$_2$C*H*$_3$)$_2$), 1.08 (3H, s, –C*H*$_3$), 1.05 (3H, t, *J* 7.0, –N(CH$_2$C*H*$_3$)$_2$), minor conformer: 5.85–5.76 (1H, m, H-7), 5.49 (1H, t, *J* 10.0, H-8), 5.28 (1H, br d, $^3J_{H-F}$ 22.0, H-1), 4.96 (1H, s, H-4), 3.41–3.15 (5H, m, –N(C*H*$_2$CH$_3$)$_2$ and –O*H*), 2.60 (1H, dd, ^2J 13.6, *J* 9.6, H-6a), 1.84 (1H, t, ^2J 13.6, H-6b), 1.22 (3H, t, *J* 7.0, –N(CH$_2$C*H*$_3$)$_2$), 1.10 (3H, t, *J* 8.5, –N(CH$_2$C*H*$_3$)$_2$), 1.07 (3H, s, –C*H*$_3$), 0.99 (3H, s, –C*H*$_3$); δ_C(101 MHz, $CDCl_3$, 243 K) major conformer: 198.7 (t, $^2J_{C-F}$ 25.0), 154.9, 129.6, 127.8, 117.0 (t, $^1J_{C-F}$ 260.1), 75.3, 68.1 (t, $^2J_{C-F}$ 22.8), 41.9, 41.5, 38.4, 37.1, 26.5, 22.7, 13.9, 13.4, minor conformer: 194.7 (t, $^2J_{C-F}$ 23.5), 154.1, 132.8, 129.0 (d, $^3J_{C-F}$ 4.2), 116.4 (dd, $^1J_{C-F}$ 263.8, 256.3), 83.6, 67.1 (t, $^2J_{C-F}$ 21.2), 42.9, 42.1, 41.1, 35.0, 28.9, 22.4, 14.1, 13.0; δ_F(376 MHz, $CDCl_3$, 223 K) major conformer: −114.1 (1F, d, $^2J_{F-F}$ 233.5), −126.1 (1F, dd, $^2J_{F-F}$ 235.5, $^3J_{F-H}$ 25.8), minor conformer: −104.1 (1F, $^2J_{F-F}$ 248.5), −130.2 (1F, dd, $^2J_{F-F}$ 248.5, $^3J_{F-H}$ 21.8); *m*/*z* (ES) 320 (38%, [M + H]$^+$). Crystallographic data were reported previously.[18]

Preparation of 1,1-difluoro-2-(2′-methoxyethoxymethoxy)-4,4-dimethylhepta-1,6-dien-3-ol 22

Acetal **20** (30.0 mmol, 5.65 g) was added dropwise to a cold (−78 °C) solution of LDA (prepared by the slow addition of *n*-BuLi (62.9 mmol, 26.0 mL of a 2.42 M solution in hexanes) to a cold (−78 °C) solution of diisopropylamine (63.0 mmol, 8.80 mL) in THF (60 mL) under a nitrogen atmosphere). The reaction was stirred at this temperature for 2 hours and 2,2-dimethyl-4-pentenal (36 mmol, 4.9 mL) was added in one portion. The mixture was allowed to warm to −30 °C over 2 hours and quenched with ammonium chloride (40 mL of a saturated aqueous solution). Water (30 mL) was added and the mixture was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil (7.81 g). Kugelrohr distillation afforded the desired difluoroallylic alcohol **22** (7.56 g, 90%, 98% by GC-MS) as a colourless oil, bp 100 °C/0.1 mmHg; ν_{max}(film)/cm^{-1} 3401m br (O–H), 2934s (C–H), 2892s (C–H), 1639m (C=C); δ_H(300 MHz, $CDCl_3$) 5.80–5.75 (1H, m, H-6), 5.06–5.02 (2H, m, H-7a and H-7b), 5.02 (1H, d, ^2J 6.3, –OC*H*$_a$H$_b$O–), 4.83 (1H, d, ^2J 6.3, –OCH$_a$*H*$_b$O–), 3.96–3.89 (2H, m, –OC*H*$_2$CH$_2$OCH$_3$), 3.79–3.72 (1H, m, H-3), 3.57–3.54 (2H, m, –OCH$_2$C*H*$_2$OCH$_3$), 3.38 (3H, s, –OC*H*$_3$), 3.18 (1H, br s, –O*H*), 2.01 (1H, dd, ^2J 13.5, *J* 7.7, H-5a), 2.14 (1H, dd, ^2J 13.5, *J* 7.7, H-5b), 0.93 (3H, s, –C*H*$_3$), 0.88 (3H, s, –C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 155.0 (dd, $^1J_{C-F}$ 291.6, 285.4), 135.0, 117.5, 98.5 (dd, $^2J_{C-F}$ 4.5, 2.8), 72.6 (t, $^3J_{C-F}$ 2.6), 71.5, 69.0, 59.0, 55.9, 43.5, 39.0 (t, $^4J_{C-F}$ 2.3), 23.1, 22.9; δ_F(282 MHz, $CDCl_3$) −100.3 (1F, d, $^2J_{F-F}$ 66.1), −108.1 (1F, dd, $^2J_{F-F}$ 66.1, $^4J_{F-H}$ 4.5); [HRMS (ES, [M + Na]$^+$) found: 303.1382. Calc. for $C_{13}H_{22}O_4F_2Na$: 303.1384]; *m*/*z* (ES) 303 (100%, [M + Na]$^+$).

Preparation of 1,1-difluoro-2-(2′-methoxyethoxymethoxy)-4,4-[1,3]dithian-2-ylhepta-1,6-dien-3-ol 23

As for **22**, but from *n*-BuLi (9.3 mmol, 3.9 mL of a 2.4 M solution in hexane), diisopropylamine (9.7 mmol, 1.4 mL) in THF (10 mL), ether **20** (4.4 mmol, 830 mg) and aldehyde **21** (5.3 mmol, 1.0 g).[30] The mixture was allowed to warm to −30 °C over 40 min, then quenched with NH_4Cl (10 mL of a saturated aqueous solution). Water (10 mL) was added to the mixture which was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Purification by column chromatography (30% ethyl acetate in hexane) afforded alcohol **23** (1.1 g, 71%, 100% by GC-MS) as a pale yellow oil; R_f (20% ethyl acetate in hexane) 0.33; ν_{max}(film)/cm^{-1} 3436s (OH), 2922s (CH_2), 1750m (C=C) 1637w (C=C); δ_H(300 MHz, $CDCl_3$) 6.00 (1H, ddt, *J* 16.4, 9.7, 7.2, H-6), 5.20–5.09 (4H, m, OC*H*$_2$O, OH and H-7a), 4.96–4.94 (1H, m, H-7b), 4.68 (1H, dd, $^3J_{H-F}$ 3.8, 2.4, H-3), 3.94–3.81 (2H, m, OC*H*$_2$CH$_2$O), 3.59–3.56 (2H, m, OCH$_2$C*H*$_2$O), 3.39 (3H, s, CH_3), 3.04–2.84 (2H, m,

SCH_aH_b), 2.77–2.50 (4H, m, SCH_aH_b and H-5), 2.14–2.01 (1H, m, $SCH_2CH_aH_bCH_2S$), 1.91–1.74 (1H, m, $SCH_2CH_aH_bCH_2S$); δ_C(75 MHz, $CDCl_3$) 156.4 (t, $^1J_{C-F}$ 287.3, C-1), 133.1, 118.5, 113.5 (dd, $^2J_{C-F}$ 33.0, 14.3, C-2), 98.9, 71.6, 68.8, 68.3, 59.1, 53.7, 40.5, 26.3, 25.7, 24.1; δ_F(282 MHz, $CDCl_3$) −96.1 (d, $^2J_{F-F}$ 57.8), −104.4 (dd, $^2J_{F-F}$ 57.8, $^3J_{F-H}$ 3.8); [HRMS EI, $[M]^+$] found: 356.09276. Calc. for $C_{14}H_{22}O_4F_2S_2$: 356.09280); *m/z* (ES) 379 (30, $[M + Na]^+$), 251 (100%, $[M\text{-OMEM}]^+$).

Preparation of 3-allyloxy-1,1-difluoro-2-(2′-methoxyethoxymethoxy)-4,4-dimethylhepta-1,6-diene 24

A mixture of difluoroallylic alcohol **22** (25.8 mmol, 7.25 g), allyl bromide (31 mmol, 2.7 mL), 50% aqueous sodium hydroxide (181 mmol, 9.50 mL) and tetra-*n*-butylammonium hydrogensulfate (1.29 mmol, 430 mg) was stirred at 0 °C for 30 min. The mixture was allowed to warm to room temperature, stirred overnight, quenched with ammonium chloride (30 mL of a saturated aqueous solution), and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the desired ether **24** as a pale yellow oil (7.54 g, 91%), which was used without any further purification. R_f (10% diethyl ether in light petroleum) 0.26; ν_{max}(film)/cm^{-1} 2957s (C–H), 2930s (C–H), 1638m (C=C); δ_H(300 MHz, $CDCl_3$) 5.93–5.72 (2H, m, H-6 and H-2″), 5.26 (1H, dq, J_{trans} 17.3, ^2J 1.5, ^4J 1.5, H-3″a), 5.15 (1H, dq, J_{cis} 5.1, ^2J 1.5, ^4J 1.5, H-3″b), 5.05–4.97 (2H, m, H-7a and H7b), 4.99 (1H, d, ^2J 5.9, $-OCH_aH_bO-$), 4.88 (1H, d, ^2J 5.9, $-OCH_aH_bO-$), 4.13–3.71 (4H, m, $-OCH_2CH_2OCH_3$), 3.62 (1H, dd, $^4J_{H-F}$ 4.1, 2.2, H-3), 3.57–3.51 (2H, m, H-1″), 3.38 (3H, s, $-OCH_3$), 2.16 (1H, dd, ^2J 13.6, ^3J 7.7, H-5a), 2.04 (1H, dd, ^2J 13.6, ^3J 7.7, H-5b), 0.99 (3H, s, $-CH_3$), 0.91 (3H, s, $-CH_3$); δ_C(75 MHz, $CDCl_3$) 156.9 (dd, $^1J_{C-F}$ 293.9, 286.0), 135.0, 134.4, 117.4, 117.0, 112.1 (dd, $^2J_{C-F}$ 33.9, 10.2), 97.2 (dd, $^3J_{C-F}$ 4.0, 2.8), 80.1 (t, $^4J_{C-F}$ 2.8), 71.7, 69.8, 68.3, 59.0, 44.0, 38.5 (t, $^4J_{C-F}$ 1.7), 23.5, 23.1; δ_F(282 MHz, $CDCl_3$) −97.4 (1F, d, $^2J_{F-F}$ 61.7), −108.2 (1F, d, $^2J_{F-F}$ 61.7); [HRMS (ES, $[M + Na]^+$) found: 343.1698. Calc. for $C_{16}H_{26}O_4F_2Na$: 343.1697]; *m/z* (ES) 343 (100%, $[M + Na]^+$).

Preparation of 3-allyloxy-1,1-difluoro-2-(2′-methoxyethoxymethoxy)-4,4-[1,3]dithian-2-ylhepta-1,6-diene 25

As for **24**, from allyl bromide (1.5 mmol, 130 μL), tetrabutylammonium iodide (0.04 mmol, 14.1 mg), NaOH (9.6 mmol, 0.5 mL of a 50% w/v aqueous solution), allyl alcohol **23** (1.4 mmol, 500 mg) and tetrabutylammonium hydrogensulfate (0.07 mmol, 23.8 mg). The reaction mixture was stirred at 0 °C for 20 hours, then diluted with water (2 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave allyl ether **25** (386 mg, 70%, 100% by GC-MS) as a pale yellow oil; R_f (20% diethyl ether in hexane) 0.36; ν_{max}(film)/cm^{-1} 2920w (CH_2), 1742m (C=CF_2), 1637w (C=C); δ_H(300 MHz, $CDCl_3$) 6.08–5.86 (2H, m, H-6 and H-2′), 5.39 (1H, dq, *J* 17.2, ^2J 1.4, ^4J 1.4, H-3a′), 5.22 (1H, br dq, *J* 10.5, ^2J 1.4, ^4J 1.4, H-3b′), 5.15–5.11 (1H, m, H-7a), 5.10–5.05 (2H, m [including 5.06 (1H, d, ^2J 6.0, OCH_aH_bO) H-7b]), 4.95 (1H, br d, ^2J 6.0, OCH_aH_bO), 4.37 (1H, dd, $^4J_{H-F}$ 3.2, 2.0, H-3), 4.20 (1H, ddt, ^2J 12.6, *J* 5.0, ^4J 1.4, H-1a′), 3.96–3.87 (2H, m, OCH_2CH_2O), 3.77 (1H, ddd, ^2J 12.6, *J* 5.7, ^4J 3.9, H-1b′), 3.57–3.56 (2H, m, OCH_2CH_2O), 3.38 (3H, s, CH_3), 3.00–2.84 (2H, m, SCH_aH_b), 2.82–2.78 (1H, br d, ^2J 7.2, H-8a), 2.76–2.64 (3H, m, SCH_aH_b and H-8b), 2.07–1.79 (2H, m, $SCH_2CH_2CH_2S$); δ_C(75 MHz, $CDCl_3$) 157.1 (dd, $^1J_{C-F}$ 293.3, 285.0, C-1), 133.9, 133.5, 118.5, 118.1, 111.3 (dd, $^2J_{C-F}$ 33.8, 12.0, C-2), 97.7, 77.9 (t, $^3J_{C-F}$ 3.0, C-3), 71.6, 70.7, 68.5, 59.7, 55.4, 40.7, 26.6, 26.5, 24.4; δ_F(282 MHz, $CDCl_3$) −95.1 (dd, $^2J_{F-F}$ 58.3, $^4J_{F-H}$ 1.9), −106.0 (d, $^2J_{F-F}$ 58.3); [HRMS EI, $[M]^+$] found: 396.12406. Calc. for $C_{17}H_{26}O_4F_2S_2$: 396.12408); *m/z* (EI) 159 (100%, $[C(SCH_2CH_2CH_2S)CH_2CH{=}CH_2]^+$) 396 (5, $[M]^+$).

Preparation of 4,4-difluoro-5-(2′-methoxyethoxymethoxy)-7,7-dimethyldeca-1,5,9-trien-3-ol 26

A solution of allyl ether **24** (21.3 mmol, 6.83 g) in THF (20 mL) was added dropwise to a cold (−78 °C) solution of LDA (prepared by the slow addition of *n*-BuLi (46.9 mmol, 19.4 mL of a 2.42 M solution in hexanes) to a cold (−78 °C) solution of diisopropylamine (43 mmol, 6.0 mL) in THF (40 mL) under a nitrogen atmosphere). After stirring for 2 hours at −78 °C, the solution was warmed slowly to −30 °C and stirred at this temperature for 18 hours. The reaction mixture was quenched with ammonium chloride (40 mL of a saturated aqueous solution) and allowed to warm to room temperature. Water (30 mL) was added and the mixture was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil. Purification by column chromatography (30% diethyl ether in light petroleum) afforded the alcohol **26** as a yellow oil (2.71 g, 55%). R_f (30% diethyl ether in light petroleum) 0.26; ν_{max}(film)/cm^{-1} 3432m br (O–H), 2959s (C–H), 2929s (C–H), 1668w (C=C), 1639m (C=C); δ_H(300 MHz, $CDCl_3$) 5.95–5.68 (2H, m, H-2 and H-9), 5.46 (1H, d, J_{trans} 17.3, H-1a), 5.40 (1H, s, H-6), 5.33 (1H, d, J_{cis} 10.7 H-1b), 5.04–4.98 (4H, m, H-10a, H-10b, and $-OCH_2O-$), 4.58–4.50 (1H, m, H-3), 3.85–3.81 (2H, m, $-OCH_2CH_2OCH_3$), 3.58–3.55 (2H, m, $-OCH_2CH_2OCH_3$), 3.37 (3H, s, $-OCH_3$), 2.71 (1H, br s, $-OH$), 2.15 (2H, d, *J* 6.6, H-8), 1.13 (3H, s, $-CH_3$), 1.12 (3H, s, $-CH_3$); δ_C(75 MHz, $CDCl_3$) 142.3 (t, $^2J_{C-F}$ 24.9), 135.2, 132.4 (t, $^3J_{C-F}$ 3.1), 128.4 (t, $^3J_{C-F}$ 5.4), 118.7, 118.4 (t, $^1J_{C-F}$ 250.1), 117.1, 98.2, 72.6 (t, $^2J_{C-F}$ 28.5), 71.4, 68.8, 58.8, 47.4, 35.0, 27.8; δ_F(282 MHz, $CDCl_3$) −109.9 (1F, dd, $^2J_{F-F}$ 251.8, $^3J_{F-H}$ 10.1), −112.0 (1F, dd, $^2J_{F-F}$ 251.8, $^3J_{F-H}$ 12.7); [HRMS (ES, $[M + Na]^+$) found: 343.1694. Calc. for $C_{16}H_{26}O_4F_2Na$: 343.1697]; *m/z* (ES) 365 (16%, $[M + 2Na–H]^+$), 343 (100, $[M + Na]^+$).

Preparation of 4,4-difluoro-7-([1,3]dithian-2-yl)-5-(2′-methoxyethoxymethoxy)deca-1,5*Z*,9-trien-3-ol 27

A solution of allyl ether **25** (5.1 mmol, 2.0 g) in THF (5 mL) was added dropwise to a cold (−78 °C) solution of LDA (prepared from *n*-BuLi (10.6 mmol, 5.6 mL of a 1.9 M solution in hexane), diisopropylamine (11.1 mol, 1.6 mL) and THF (10 mL) under a nitrogen atmosphere). After stirring for 2 hours at −78 °C, the solution was warmed slowly to −30 °C over 1.5 hours and stirred at this temperature for 20 hours. The reaction mixture was quenched with NH_4Cl (20 mL of a saturated aqueous solution) and allowed to warm to room temperature. Water (20 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave allylic alcohol **27** (1.3 g) as a yellow oil. Purification by column chromatography (20% ethyl acetate in hexane) afforded allylic alcohol **27** (519 mg, 30%, 100% by GC-MS) as a pale yellow oil; R_f (20% ethyl acetate in hexane) 0.20; ν_{max}(film)/cm^{-1} 3405br w (OH), 2920w (CH_2), 1658w (C=C); δ_H(300 MHz, $CDCl_3$) 6.07–5.87 (2H, m, H-2, H-9), 5.30 (1H, dt, *J* 17.2, ^4J 1.5, H-1a), 5.22 (1H, dt, *J* 10.2, ^4J 1.2, H-1b), 5.15–5.06 (3H, m, OCH_2O and H-10a), 4.96–4.94 (1H, m, H-10b), 4.36 (1H, dd, $^4J_{H-F}$ 3.4, 2.0, H-8a), 4.19 (1H, ddt, *J* 12.6, $^3J_{H-F}$ 5.0, ^4J 1.5, H-3), 3.97–3.86 (2H, m, $OCH_aH_bCH_2O$ and OH), 3.81–3.74 (1H, m, $OCH_2CH_aH_bO$), 3.57–3.54 (2H, m, OCH_2CH_2O), 3.37 (3H, s, CH_3), 3.00–2.65 (6H, m, H-8b and SCH_2), 2.05–1.78 (2H, m, $SCH_2CH_2CH_2S$); δ_C(75 MHz, $CDCl_3$) 157.1 (dd, $^1J_{C-F}$ 292.5, 285.0, C-4), 134.0, 133.5, 118.4, 118.0, 111.4 (dd, $^2J_{C-F}$ 33.0, 11.3, C-5), 96.7, 78.2 (t, $^2J_{C-F}$ 3.5, C-3), 71.6, 70.8, 68.5, 59.1, 55.5, 40.8, 26.6, 26.5, 24.3; δ_C(75 MHz, $CDCl_3$) −95.3 (dd, $^2J_{F-F}$ 57.8, $^4J_{F-H}$ 1.9), −106.0 (d, $^2J_{F-F}$ 57.8); [HRMS EI, $[M]^+$] found: 396.12406. Calc. for $C_{17}H_{26}O_4F_2S_2$: 396.12412); *m/z* (EI) 396 (1, $[M]^+$), 159 (100%, $[C(SCH_2CH_2CH_2S)CH_2CHCH_2]^+$).

Preparation of 4,4-difluoro-3-hydroxy-7,7-dimethyldeca-1,9-dien-5-one 28

Thionyl chloride (6.7 mmol, 0.49 mL) was added dropwise to a cold (0 °C) solution of alcohol **26** (6.70 mmol, 2.15 g) in methanol (50 mL). The mixture was allowed to warm to room temperature and stirred for 4 hours. The methanol was removed under reduced pressure. The residue was taken up in water (50 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a brown oil. Purification by column chromatography (10% diethyl ether in light petroleum) afforded the hydroxyketone **28** as a yellow oil (1.01 g, 65%). R_f (10% diethyl ether in light petroleum) 0.23; ν_{max}(film)/cm^{-1} 3453m br (O–H), 2961s (C–H), 1740s (C=O), 1639m (C=C); δ_H(300 MHz, $CDCl_3$) 5.96–5.69 (2H, m, H-2 and H-9), 5.49 (1H, dt, $^3J_{trans}$ 17.3, ^2J 1.5, ^4J 1.5, H-1a), 5.41 (1H, dt, $^3J_{cis}$ 10.7, ^2J 1.5, ^4J 1.5, H-1b), 5.07–4.97 (2H, m, H-10a and H-10b), 4.61–4.50 (1H, m, H-3), 2.59 (2H, s, H-6), 2.49 (1H, d, ^3J 5.5, –O*H*), 2.13 (2H, dt, ^2J 7.7, ^4J 1.1, H-8), 1.02 (6H, s, –C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 201.2 (dd, $^2J_{C-F}$ 30.0, 27.1), 134.6, 131.5 (t, $^3J_{C-F}$ 2.8), 120.2, 117.9, 114.5 (dd, $^1J_{C-F}$ 261.7, 257.7), 72.0 (dd, $^2J_{C-F}$ 28.3, 24.9), 47.1, 46.0, 33.5, 26.9; δ_F(282 MHz, $CDCl_3$) −113.8 (1F, dd, $^2J_{F-F}$ 274.7, $^3J_{F-H}$ 7.6), −122.8 (1F, dd, $^2J_{F-F}$ 274.7, $^3J_{F-H}$ 15.2); [HRMS (ES, [M + NH_4]$^+$) found: 250.161786. Calc. for $C_{12}H_{22}NO_2F_2$: 250.161864]; *m*/*z* (ES) 343 (100%, [M + Na]$^+$); *m*/*z* (CI) 250 (100%, [M + NH_4]$^+$), 230 (13), 210 (31), 193 (92).

Preparation of 4,4-difluoro-7-([1,3]dithian-2-yl)-3-hydroxy-deca-1,9-diene-5-one 29

Thionyl chloride (0.25 mmol, 18 μL) was added dropwise to a solution of enol ether **27** (0.25 mmol, 100 mg) in MeOH (2.5 mL) at 0 °C. The reaction mixture was stirred at this temperature for 20 hours. The mixture was concentrated *in vacuo*, diluted with water (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Purification by column chromatography (20% ethyl acetate in hexane) afforded diene **29** (60 mg, 76%, 100% by GC-MS) as a pale yellow oil; R_f (20% ethyl acetate in hexane) 0.29; ν_{max}(film)/cm^{-1} 3400br w (OH), 2922w (CH_2), 1659w (C=C); δ_H(300 MHz, $CDCl_3$) 5.96–5.78 (2H, m, H-2 and H-9), 5.50 (1H, dt, *J* 17.2, $^4J_{H-H}$ 1.5, H-1a), 5.42 (1H, dt, *J* 10.5, $^4J_{H-H}$ 1.5, H-1b), 5.18–5.01 (2H, m, H-10), 4.61–4.52 (1H, dt, $^3J_{H-F}$ 15.6, 7.2, H-3), 3.40 (2H, d, $^4J_{F-F}$ 0.9, H-6), 2.97–2.87 (4H, m, H-8 and S*C*H_2*C*H_2*C*H_2S), 2.82–2.73 (2H, m, S*C*H_2*C*H_2*C*H_2S), 2.64 (1H, br s, OH), 2.09–1.98 (1H, m, S*C*H_2*C*H_aH$_b$*C*H_2S), 1.96–1.83 (1H, m, S*C*H_2*C*$H_a$$H_b$*C*$H_2$S); δ_C(75 MHz, $CDCl_3$) 197.2 (dd, $^2J_{C-F}$ 30.8, 27.8, C-5), 131.8, 130.9, 120.6, 119.8, 114.4 (dd, $^1J_{C-F}$ 260.3, 256.5, C-4), 72.0 (dd, $^2J_{C-F}$ 28.5, 25.5, C-3), 49.0, 43.9, 42.6, 26.3 (C × 2), 24.8; δ_F(75 MHz, $CDCl_3$) −113.1 ($^2J_{F-F}$ 273.0, $^3J_{F-H}$ 7.1), −123.0 ($^2J_{F-F}$ 273.0, $^3J_{F-H}$15.6); [HRMS EI, [M]$^+$] found: 308.12240. Calc. for $C_{13}H_{18}O_2F_2S_2$: 308.12242); *m*/*z* (EI) 308 (37, [M]$^+$).

Preparation of 2,2-difluoro-5,5-dimethyl-3-oxo-cyclooct-7-en-1-ol 30

Titanium (IV) *iso*propoxide (0.60 mmol, 0.18 mL) was added to a solution of diene **28** (2 mmol, 0.46 g) in dry degassed DCM (200 mL). This solution was refluxed for 1 hour and catalyst **1** (0.1 mmol, 41 mg) was added as solution in dry degassed DCM (10 mL) and the reaction mixture was further refluxed for 24 hours. Evaporation under reduced pressure of the solvent followed by column chromatography (30% diethyl ether in light petroleum) afforded cyclooctenol **30** as a pale yellow oil (0.32 g, 78%). R_f (30% diethyl ether in light petroleum) 0.23; ν_{max} (film)/cm^{-1} 3444s (O–H), 3033w (=C–H), 2963m (C–H), 2928m (C–H), 2870m (C–H), 1738s (C=O), 1652w (C=C); δ_H (400 MHz, $CDCl_3$, 323 K) 5.90–5.81 (1H, m, H-7), 5.62–5.57 (1H, m, H-8), 4.84–4.72 (1H, m, H-1), 2.78 (1H, br s, –O*H*), 2.50 (1H, dd, ^2J 12.0, $^4J_{H-F}$ 2.7, H-4a), 2.35 (1H, d, ^2J 12.0, H-4b), 1.97 (2H, d, *J* 7.9, H-6), 1.10 (3H, s, –C*H*$_3$), 0.98 (3H, s, –C*H*$_3$); δ_C (101 MHz, $CDCl_3$, 323 K) 198.4 (t, $^2J_{C-F}$ 25.7), 131.8, 129.3 (d, $^3J_{C-F}$ 3.3), 117.3 (t, $^1J_{C-F}$ 258.2), 68.1 (t, $^2J_{C-F}$ 23.2), 47.6, 40.2, 37.7, 30.6, 26.9; δ_H (400 MHz, $CDCl_3$, 223 K) 5.92–5.80 (2H, m, H-8), 5.69–5.60 (1H, m H-7 minor), 5.60–5.29 (1H, m, H-7 major), 5.29–5.12 (1H, m, H-1 major), 4.56 (1H, br. d, $^3J_{H-F}$ 26.1, H-1 minor), 2.96 (1H, d, ^2J 9.8, H-4a minor), 2.87 (1H, d, ^2J 11.2, H-4a major), 2.31 (1H, dd, *J* 12.5, ^2J 9.6, H-6a major), 2.13 (1H, d, ^2J 11.2, H-4b major), 2.04–1.82 (3H, m, H-4b minor, H-6b minor, H-6b major), 1.66 (1H, t, *J*, ^2J 12.5, H-6b minor), 1.11 (6H, s, CH_3), 1.02 (3H, s, CH_3), 0.96 (3H, s, CH_3); δ_F (376 MHz, $CDCl_3$, 223 K) major conformer: −108.3 (1F, d, $^2J_{F-F}$ 240.4), −136.1 (1F, dd, $^2J_{F-F}$ 240.4, $^3J_{F-H}$ 20.3), minor conformer: −115.4 (1F, d, $^2J_{F-F}$ 229.3), −129.1 (1F, dd, $^2J_{F-F}$ 229.3, $^3J_{F-H}$ 26.1); [HRMS (ES, [M + Na]$^+$) found: 227.0860. Calc. for $C_{10}H_{14}O_2F_2Na$: 227.0860]; *m*/*z* (ES) 227 (100, [M + Na]$^+$).

Attempted preparation of 2,2-difluoro-5-([1,3]dithian-2-yl)-3-oxocyclooct-7-en-1-ol 31

A solution of diene **29** (0.24 mmol, 75 mg) and titanium(IV) isopropoxide (0.072 mmol, 21 μL) in toluene (24 mL) was refluxed for 30 minutes. Catalyst **2** (0.012 mmol, 10 mg) was added as a solution in toluene (1 mL) and the reaction was refluxed for 24 hours. Additional second generation Grubbs' catalyst **2** (0.012 mmol, 10 mg) was added and refluxed for 48 hours. At the end of this period, only **29** and no **31** could be identified in the reaction mixture by TLC, ^{19}F NMR and ES-MS.

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