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Trisubstituted cyclooctene synthesis at the limits of relay ring-closing metathesis: a racemic difluorinated analogue of fucose

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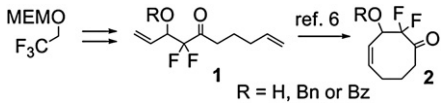
ABSTRACT

A telescoped sequence based on metallated enol acetal chemistry allowed the efficient delivery of a ring-closing metathesis (RCM) precursor, which was used to form a cyclooctenone product with a trisubstituted alkenyl group in moderate yield, though a high loading of second generation Grubbs' pre-catalyst was required. A relay RCM (RRCM) precursor was synthesised to deliver the key alkylidene at a higher rate; the catalyst loading required was high, and increasing the reaction temperature simply resulted in the loss of the cyclising alkylidene by a non-productive cross-metathesis pathway. We were forced to use high dilution conditions to suppress the unwanted CM and secure the cyclooctenone product. The cyclooctenone product could be progressed to analogues of fucose and 6-deoxyidose by UpJohn dihydroxylation.

1. Introduction

RCM has proved a spectacularly useful tool in the hands of chemists synthesising natural products and their analogues.[1] The reaction tolerates dense and diverse functionality and can deliver rings of a wide range of sizes. We have used the reaction to make fluorinated analogues of monosaccharides[2] and that work has led us to explore the synthesis of substituted cyclooctenes **2** from trifluoroethanol.[3] We used these as precursors to conformationally-locked monosaccharide analogues (Scheme 1).[4]



Scheme 1. Outline scheme showing elaboration of trifluoroethanol to cyclooctenone **2**.

The formation of eight-membered rings from acyclic precursors has proved challenging to many cyclisation methodologies because a combination of enthalpic and entropic effects usually results in a significantly positive free energy of reaction, and usually, low reaction rates.[5] Cyclooctane is strained (strain energy 9.4 kcal mol^{-1})[6] and (in the absence of conformational restraint) cyclisation can require the loss of free rotation around up to 7 rotatable bonds depending on the type of cyclisation, resulting in a significantly negative ΔS^0 and $\Delta S^{\ddagger}$ for the reaction. Cyclooctene formation is easier because the product ring is less strained (strain energy 5.1 kcal mol^{-1}) than cyclooctane; the replacement of sp^3 centres reduces the number of hydrogen atoms involved in repulsive transannular interactions. However, the same entropic issues arise. Despite a number of early reports of failure,[7] the synthesis of cyclooctenes by RCM methods is becoming much more common.[8] Crimmins[9] and Taylor[10] independently achieved the first non-annelative syntheses of oxocenes en route to Laureatin-type natural products and there have been many subsequent reports of effective reactions.[11,12] However, the formation of products in which the alkene is trisubstituted is still relatively unusual, though there have been notable recent successes[13] by the groups of Wicha,

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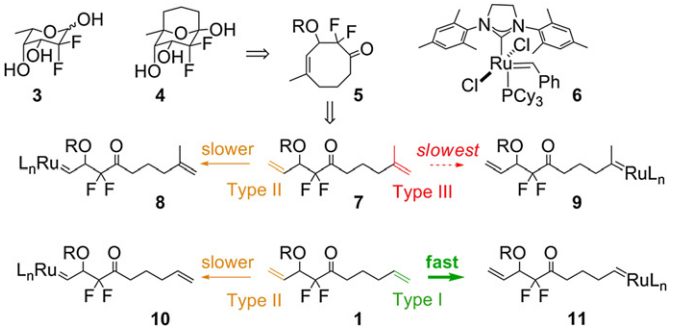
Chavan and Tori. We showed that cyclooctene-forming RCM reactions can occur with surprisingly high effective molarities (EM)[14] as we developed our approach to difluorinated bicyclic analogues of monosaccharides.[4] We wished to extend the approach to include species **4**, which resembles fucose **3**, a key monosaccharide in human glycobiology,[15] for which **5** would be a key precursor. RCM had delivered related cyclooctenones **2** in good yield; however, RCM to **5** posed a sterner challenge. Whereas the first step in the RCM of **1** would be cross-metathesis with the Type I alkene (the alkenes are classified according to their propensity to homodimerise with Grubbs' second generation pre-catalyst **6**)[16] terminus to afford **11** (rather than **10**), precursor **7** presents more substituted alkenes to the 14-electron catalytic species (Scheme 2).



Scheme 2. Sequence of events in RCM of **1** and **7**.

Alkenes with a 1,1-disubstitution pattern are classified as Type III so we would expect the sequence of events shown in Scheme 2, with **8** the key intermediate rather than **9**. The additional methyl group could then slow cyclisation through a steric effect; it would appear that the system we propose to explore is tensioned against both formation of a cyclising alkylidene with a reasonable lifetime, and the subsequent cyclisation. This seemed like an interesting test of the limits of an RCM-based approach.

2. Results and discussion

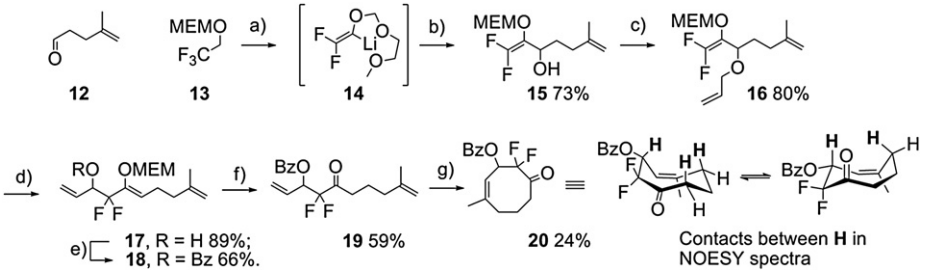
2.1. Synthesis and deployment of the RCM precursor

The sequence described by Baker et al.[17] was used to prepare substituted pentenal **12** from methallyl alcohol (Scheme 3). The aldehyde was trapped with metallated difluoroenol acetal **14** (prepared from the MEM ether of trifluoroethanol **13** according to our published method). The allylic alcohol **15** was distilled (Kugelrohr), then allylated to **16** under the usual phase transfer catalysed conditions. These steps were carried out without the purification of intermediates, as in our published[14] synthetic route to **2** (though samples were purified for characterisation). The [2,3]-Wittig rearrangement affording **17** was followed by benzoylation to **18** and enol acetal methanolysis; we chose the benzoate at this stage because of the volatility of **2** (R=H, which made isolation difficult) and the high effective molarity observed in the cyclisation of the benzoate of **2** (R=Bz). Ketone **19** was purified by flash column chromatography at this stage. RCM was attempted with 20–33 mol % loadings of **6** (added in 5% portions over time) with the Ti(IV) co-catalyst in DCM at 10 mM, and the reaction was monitored by ^{19}F NMR. We were unable to secure conversions of **19** exceeding 40%, an unacceptable outcome in view of the high loading of catalyst required. Carrying out the reaction in hot toluene[18] failed to improve matters, with only a ca. 30% conversion of **19**. Our best isolated purified yield of **20** (24% based on a 10+5+5 mol% loading of **6** over 12 days, an unacceptably slow reaction) represents an impractically high loading of the pre-catalyst. The overall yield for the six-step sequence from **12** was then 5%. The ^{19}F NMR and ^{1}H NOESY spectra of benzoate **20** showed the population of the boat-chair conformers observed for the less substituted cyclooctenes. While sacrificial loadings of pre-catalyst have been tolerated in total syntheses terminated by RCM steps, we wished to use **5** more economically, if possible; we also wished to avoid the purification difficulties caused by very high loadings of pre-catalyst. To accelerate the formation of the cyclising alkylidene, we sought to deploy Hoye's relay method[19], which relies on the rapid formation of cyclopentene to overcome barriers to alkylidene formation.[20]

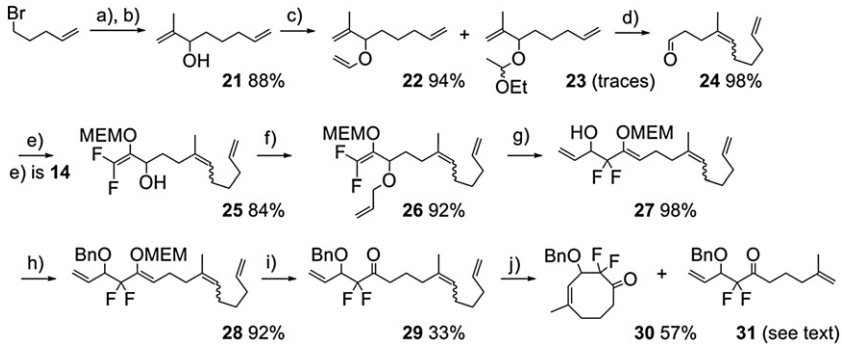
2.2. Synthesis and deployment of the relay RCM precursor

Aldehyde **24** was constructed according to literature methods; the conversion of pentenyl bromide to the Grignard reagent, according to the method of Hudlicky et al.,[21] and trapping with methacrolein, was a critical step. Alcohol **21** could be obtained in high yield on a multigram scale (Scheme 4). Transvinylation afforded a mixture of allyl vinyl ether **22** (as a mixture of diastereoisomers) and traces of acetal **23**; Claisen rearrangement secured the enal **24** (81% over three steps), which we could intercept with metallated enol acetal **14** to afford **25**, as described for **12**.

Our established methodology was then used to develop **27** (via [2,3]-Wittig rearrangement product **26**), which was benzylated to **28** (the benzyl protecting group is much more useful for product elaboration because it does not migrate, though the benzyl ether of **6** cyclised with rather lower EM than the corresponding benzoate), and ketone **29** was released. Once again, material was brought through the steps preceding the ketone without purification (only intermediates with satisfactory ^{1}H and ^{19}F NMR spectra were progressed), with careful flash column chromatography only before relay RCM (RRCM). The RRCM was attempted with 15 mol % **20** and the Ti(IV) co-catalyst at 2.5 mM in DCM and the reaction was followed by ^{19}F NMR of aliquots. The conversion reached 40% after 22 h at reflux and a new product could be seen clearly; a further portion of catalyst (15 mol % GII) was added and after a further 24 h, diene **29** had been consumed completely. Cyclooctenone **30** was



Scheme 3. Preparation and RCM of precursor **19**. Reagents and conditions: (a) 2.0 LDA, THF, −78 °C; (b) **12**, then NH_4Cl/MeOH; (c) NaOH, $TBAHSO_4$, allyl bromide, 0 °C to rt; (d) 2.0 LDA, THF, −100 to −40 °C; (e) Bz_2O, PVP, DCM, rt; (f) $SOCl_2$, MeOH, 0 °C to rt. g) **6** (10 + 5 + 5 mol%), Ti(O*i*-Pr)$_4$, DCM, reflux.



Scheme 4. Preparation and RRCM of precursor **29**. Reagents and conditions: (a) Mg, OEt_2, reflux; (b) methacrolein; (c) $Hg(OCOCF_3)_2$, ethyl vinyl ether, reflux; (d) 150 °C, μW; (e) **14**, then NH_4Cl/MeOH; (f) NaOH, $TBAHSO_4$, allyl bromide, 0 °C to rt; (g) 2.0 LDA, THF, −100 to −40 °C; (h) NaH, THF then TBAI, BnBr, 0 °C to rt; (i) $SOCl_2$, MeOH, 0 °C to rt; (j) **6** (15 mol %+15 mol %), $Ti(O^iPr)_4$, $CHCl_3$, reflux.

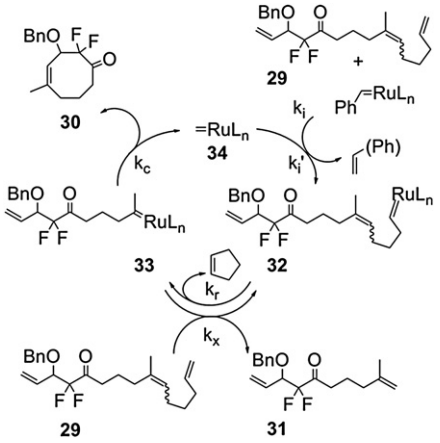
obtained in 57% yield after treatment of the crude product with PS-thiol resin and flash column chromatography. The overall yield for the six-step sequence from **24** was then 13%. The catalyst loading is high but we were unable to reduce it significantly and still achieve complete conversion of the starting material.

We had found that RCMs of derivatives of **6** in 1,2-dichloroethane were fast and clean, so we attempted RRCM of **29** in that solvent, and in chloroform, at reflux. The results were interesting; the ^{19}F NMR spectrum of the crude product from both reactions suggested that starting material had been recovered unchanged. However, the ^1H NMR spectrum told a different story, indicating the presence of a simplified species from which the relay system had been extruded. Two broad singlets arising from a terminal C(Me)=CH_aH_b system could be seen clearly in the ^1H NMR spectrum, replacing the triplet from the alkene signal of the mid-chain C(Me)=C*H*CH_2 group. The new spectrum was consistent with the formation of **31** by cross-metathesis with RRCM precursor; full characterisation confirmed the identification.

While we had succeeded in increasing the concentration of key alkylidene **33** in solution (Scheme 5), the secondary effect was the diversion of the reaction away down an intermolecular pathway. We believe that this pathway is cross-metathesis with the relay precursor **29** to afford more **32** and return the much less reactive **31** to the reaction mixture. This was not what we expected under the relatively dilute conditions used for the reaction. The rate limiting step is clearly cyclisation (k_c) and there are two possible additional consequences; firstly, methylidene **34** must carry the chain (k_i') after the first initiation by the benzylidene (k_i) and it is possible that the cross-metathesis step between **29** and **33** (k_x) becomes a more significant pathway as **34** decomposes.[22] Secondly, the relay step (k_r) is assumed to be fast and irreversible but the k_x step effectively runs this step in reverse and may establish an equilibrium for the relay step. That higher levels of benzylidene presumably postpone the establishment of this equilibrium was our initial hypothesis. However, in small scale experiments run over 24 h, varying the catalyst loading from 10 to 12.5 or 15 mol % had no effect on the ratio of **30**:**31**, whereas the concentration of **29** is influential (Fig. 1a). A plot of **30**:**31** versus 1/[**29**] (Fig. 1b) was approximately linear and of slope 1.4×10^{-4} M; this represents an estimate of k_C/k_X, which corresponds to an approximate effective molarity of 0.14 mM.

In these small scale experiments, we were only able to obtain **30** as the major product when the concentration was lowered to 0.12 mM but the conversion was now below 20%.

In our system, the use of the relay method makes the nature of first-formed alkylidene unambiguous—it must be type **9** rather than **8**. The diversion of the key alkylidene in this way was unforeseen and indicates that the fate of the alkylidene, which must cyclise to deliver the product ring system must be considered explicitly when more difficult ring closures are being planned; rapid initiation is no guarantee of a successful RCM outcome.



Scheme 5. Competing RRCM and disarming cross-metathesis processes.

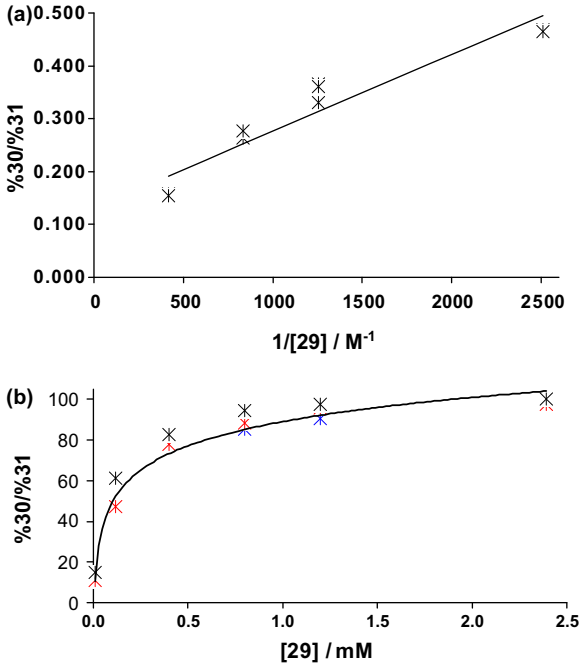
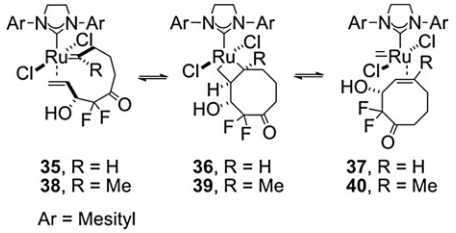


Figure 1. (a) Conversion plot for **29** at different concentrations and loadings of **6** (blue crosses 10%, black crosses 12.5%, red crosses 15%) and (b) cyclisation versus cross-metathesis (estimation of effective molarity) for **29** (multiple points at 10–15% loadings of **6**).

2.3. Electronic structure calculations on intermediate ruthenium complexes

We sought additional insight from electronic structure calculations. Though the B3LYP functional[23,24] has been shown to provide unreliable absolute energies for intermediates on RCM pathways,[25] it can be used to generate reasonable geometries and to order the energies of the intermediate complexes correctly.[26] We built a product η^2-complex (Scheme 6, we have examined alcohols for conformational simplicity and economy) based on the known low energy boat-chair conformation of **2** and related species, and tracked it back through the metallocyclobutane to the initial η^2-complex; a similar complex was constructed for **5**. While this does not constitute an exhaustive exploration of the conformational space available to these cyclising systems, it does allow a like-for-like comparison using an experimentally-detected product conformation.



Scheme 6. Equilibrating ruthenium complex intermediates in the RRCM.

Table 1
Calculated (B3LYP/LACVP*/6-31G(d)) electronic energies for intermediate ruthenium complexes

Complex	E_{rel} (kcal mol^{-1})	Complex	E_{rel} (kcal mol^{-1})
35	(0.00)	**38**	(0.00)
36	−2.4	**39**	+3.7
37	+0.4	**40**	−1.8

We then optimised the geometries (B3LYP/LACVP*/6-31G(d)) of the products from alkylidenes **9** and **11**, at the initial η^2- (**35** from **11**, **38** from **9**), metallocyclobutane (**36** from **11**, **39** from **9**) and product η^2-complex (**37** from **11**, **40** from **9**) stages in Spartan'06 (Table 1).[27,28]

These calculations suggest that it is much more difficult for the methylated system to progress from the initial cyclic η^2-complex to the metallocyclobutane; the difference in ΔE is a substantial 6 kcal mol^{-1} (this approximates to an enthalpic difference between the two complexes).

Metallocyclobutane formation and breakdown have often been invoked as alternative rate-determining steps; in this case, it looks like the formation of metallocyclobutane **39** must occur against a strongly unfavourable equilibrium constant, and presumably with a significant additional barrier. The presence of the additional methyl group causes changes in the geometry of all the complexes; Figure 2a and b shows the overlay of the cyclic η^2-complexes **35** (yellow backbone) and **38** (blue backbone), and Figure 2c and d the metallocyclobutanes **36** (yellow backbone) and **39** (blue backbone). The tilt in the alkylidene plane, which is required to accommodate the additional methyl group forces the entire backbone to move, and turns the η^2-coordinated alkene on its axis. In the absence of transition structures and full frequency calculations, we cannot estimate or predict the relative cyclisation rates of the two systems, but we must point out the significant effect that the methyl group is predicted to have on the relative energies of the intermediates on the cyclisation pathway. The literature contains little that allows the effect of the α-methyl group to be evaluated; Ulman and Grubbs found that the α-methyl group suppressed cross-metathesis with the first-generation alkylidene completely,[29] and while the RCM of α-methyl analogue **42** of diethyl diallylmalonate **41**, is described[30] as 'more demanding than the corresponding RCM of diethyl diallylmalonate'[31], due to steric effects, the difference in the concentration/time profiles for cyclisation catalysed by **6** is minimal. Figure 3 shows the data taken from Vougioukalakis and Grubbs.[30]

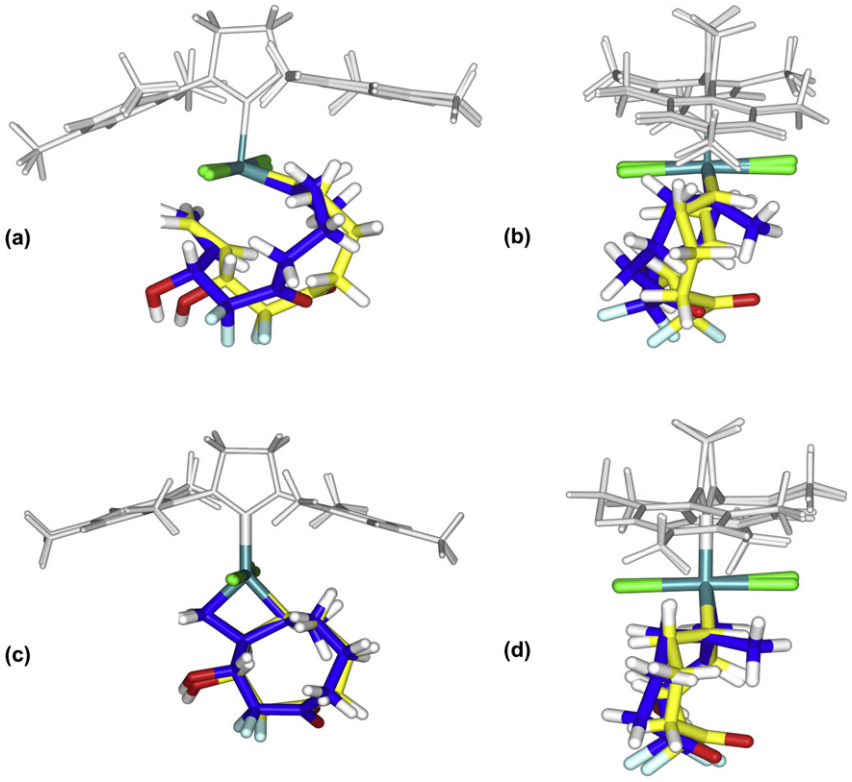


Figure 2. Overlays of optimised structures for (a) and (b) **35** (yellow) and **38** (blue), and (c) and (d) **36** (yellow) and **39** (blue).

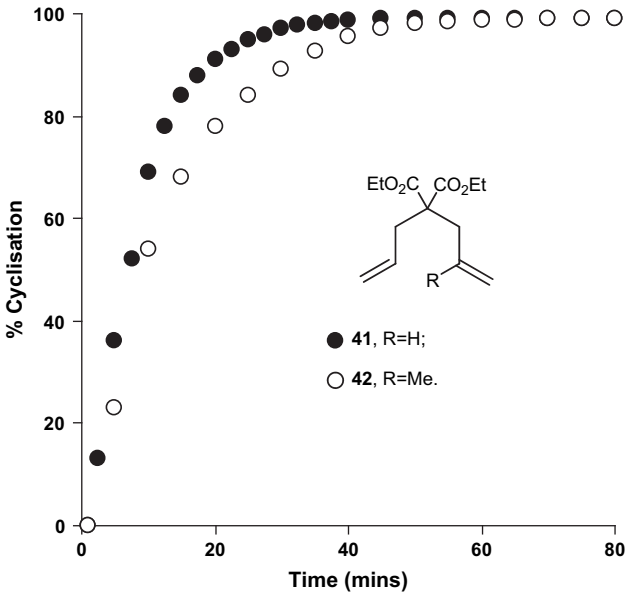


Figure 3. Conversion/time profiles for the appearance of cyclopentene product from the cyclisation of **41** (closed circles) and **42** (open circles) catalysed by **6** (1 mol % **6**, [substrate] 0.1 M, CD_2Cl_2, 303 K).[30]

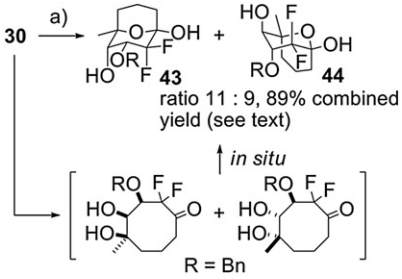
The effect would be expected to be nil or small here because cyclisation is not the rate-determining step in cyclopentene formation from **41**.

In our system, cyclisation is definitely rate-determining and the α-methyl group is attached to the Ru=C bond; we can estimate its effect at approximately 1000-fold by comparing the EM for the cyclisations of **11** (R=Bn, EM=0.17 M)[14] and the approximate EM for the cyclisation from **29** (EM=0.14 mM).

Finally, we should comment on the order of events chosen for the electronic structure calculations. It is also possible that the alkylidene formed unambiguously via the relay entry, cross-metathesises with the other terminal alkenyl group to afford **8** and **10** in Scheme 2; Hoye and Zhao[32] inter alia[33] present evidence that alkylidene transfer is accelerated by a free allylic hydroxyl group. The systems we have synthesised have the allylic hydroxyl group protected so we do not expect this to be a competitive pathway. The possibility forms the subject of current investigation via electronic structure calculations.

2.4. Characterisation and elaboration of cyclooctenone 30

Cyclooctenone **30** was a crystalline solid and monocrystals of sufficient quality for structure elucidation by X-ray were obtained. The conformation in the crystal is of the familiar boat-chair form characterised rigorously for **2** and the NOESY spectra of benzyl ether **30** (and benzoate **20**) suggested strongly that this was also



Scheme 7. UpJohn dihydroxylation and spontaneous cyclisation of cyclooctenone **30**. Reagents and conditions: (a) OsO_4/*t*-BuOH, NMO, acetone, water.

the major conformation in $CDCl_3$ solution.[3,4] Dihydroxylation of **30** was carried out under UpJohn conditions[34] to afford a mixture of diols **43** and **44** (the dihydroxyketone undergoes transannular hemiketal formation), which were characterised by their NMR spectra ($^3J_{H-F}$ values allow the two series to be distinguished as described previously). The diols could be separated partially by flash column chromatography and we used preparative HPLC to isolate samples of **43** and **44** of microanalytical purity (Scheme 7).

Of these, **43** is a protected fucopyranose analogue, while **44** is a protected 6-deoxyidopyranose analogue. We have described the successful debenzylation of related sugar analogues under standard hydrogenolysis conditions.[4]

3. Conclusions

As expected, the RCM of **19** to trisubstituted cyclooctenone **20** was slow and required a high loading of pre-catalyst **6**. Embedding the target cyclisation within an RRCM precursor achieved a modest gain in cyclisation efficiency, as cross metathetical disarming of the key alkylidene competed strongly. The slow cyclisation arises from a powerful steric effect exerted by the α-methyl group in the key alkylidene. The RRCM educt was used to prepare a locked difluoro analogue of a fucosyl sugar via UpJohn dihydroxylation.

4. Experimental

4.1. General

NMR spectra were recorded on Bruker DPX-300, DRX-400, AV-400 or DPX-500 spectrometers. ^{1}H NMR spectra were recorded at 300, 400, and 500 MHz, ^{13}C NMR spectra at 75 and 100 MHz, and ^{19}F spectra at 282 and 376 MHz. ^{1}H and ^{13}C NMR spectra were recorded using the deuterated solvent as the internal reference. ^{19}F NMR spectra were recorded relative to an external standard of fluorotrichloromethane. Unless otherwise stated, couplings, *J*, refer to $^3J_{H-H}$ couplings and are given in Hertz. The nuclei involved in other homonuclear, or heteronuclear couplings are defined with the observed nucleus given first. Thin layer chromatography (TLC) was performed on precoated aluminium silica gel plated supplied by E. Merck, A.G. Darmstadt, Germany (silica gel 60 F254, thickness 0.2 mm, art. 1.05554) and compounds were visualised with UV light or a potassium permanganate stain. Flash column chromatography was carried out with solvent gradients on Biotage Horizon (with pre-packed cartridges) or Buchi Sepacore (with self-packed or Biotage Snap™ cartridges) instruments. Preparative HPLC was carried out on a Perkin Elmer Quaternary LC pump module 200Q/410 with Series 200 Autosampler and Waters Spherisorb S5 ODS2 column (250×20 mm, 5 μm) (5 mL min^{-1}, 260 nm detection wavelength). GC analyses were carried out using a Perkin Elmer Autosystem XL instrument, using a standard PE-5 column (injector 250 °C, start temperature 40 °C, ramp rate 10 °C min^{-1}, end temperature 280 °C) or a Finnegan Pro GC–MS system, using the same temperature ramping programme, running a 20–350 °C ramp over 27 min on a 30 m×0.25 μm ZB-5 column. Low resolution mass spectral data were collected either on a Finnegan Pro GC–MS system, using electron impact ionisation or on a Finnegan Pro electrospray system (by manual injection), using methanol or acetonitrile as solvents. Chemical ionisation (CI) mass spectra were recorded using ammonia as the reagent gas. High resolution mass spectra were recorded by the EPSRC Mass Spectrometry service by either electrospray or chemical ionisation, where polyethyleneimine was used as a reference compound. Infra-red analyses were carried out on a Perkin Elmer IR spectrometer, using KBr discs. Crystals for X-ray analysis were grown by vapour diffusion. Solvents were dried using a Pure Solv apparatus (Innovative Technologies Inc). For RCM reactions, the solvents were degassed by

sparging with nitrogen before use. Diisopropylamine was distilled from calcium hydride and stored over calcium hydride under an atmosphere of nitrogen before use. SPE tubes were Stratospheres tubes (supported thiol) supplied by Varian. *n*-Butyllithium was titrated with *tert*-butanol (1 M in xylene) using 4-phenylbenzylidene benzylamine as indicator in a dry THF/diisopropylamine medium under argon according to the method of Duhamel and Plaquevent.[35]

4.2. Synthesis of RCM precursor and cyclisation to 20

4.2.1. 1,1-Difluoro-2-(2′-methoxy-ethoxymethoxy)-6-methyl-hepta-1,6-dien-3-ol ***15***. Lithium diisopropylamide was prepared by the slow addition of *n*-BuLi (50 mmol, 21.01 mL of a 2.38 M solution in hexane) to a cold (−78 °C) stirred solution of diisopropylamine (55 mmol, 7.73 mL) in THF (25 mL) under a nitrogen atmosphere. The solution was then warmed to room temperature for 15 min giving a pale yellow solution, then re-cooled to −78 °C. Acetal **13** (25 mmol, 4.7 g) was added dropwise over 20 min at −78 °C. The orange/brown solution was stirred at this temperature for 40 min and 4-methyl-pent-4-enal **12**[17] (37.5 mmol, 3.68 g, 1.5 equiv) was added in a steady stream over 1 min. The mixture was allowed to warm to −40 °C over 3 h and quenched with ammonium chloride (3 mL of a saturated aqueous solution). Water (50 mL) was added and the mixture was extracted with diethyl ether (3×50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a yellow oil. The material could be taken on without purification. Distillation (Kugelrohr, bp 115 °C/0.05 mmHg) afforded alcohol **15** (as a colourless oil). Yield 4.85 g, 73% (93% by GC, t_R (GC) 15.01 min); R_f (30% ethyl acetate/hexane) 0.16; ν_{max} (film) 3434br, 2937br, 1751s, 1648w, 1451w, 1279s, 1236s, 1111w, 1138w, 889s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.01 (d, 1H, ^2J 6.6), 4.88 (d, 1H, ^2J 6.6), 4.72 (s, 1H), 4.70 (s, 1H), 4.30–4.19 (m, 1H), 3.97 (ddd, 1H, ^2J 10.7, J 6.3, 3.6), 3.77 (ddd, 1H, ^2J 10.7, J 5.4, 3.1), 3.64–3.55 (m, 2H), 3.40 (s, 3H), 3.29 (d, 1H, J 8.5), 2.06 (q, 2H, J 7.6), 1.92–1.70 (m, 2H), 1.73 (s, 3H); δ_C (75 MHz, $CDCl_3$) 154.6 (dd, $^1J_{C-F}$ 292.0, 285.9), 144.7, 117.8 (dd, $^2J_{C-F}$ 36.9, 9.8), 110.1, 97.8 (t, $^3J_{C-F}$ 3.4), 71.4, 68.3, 66.7 (t, $^3J_{C-F}$ 2.6), 58.8, 33.5, 31.6, 21.2; δ_F (282 MHz, $CDCl_3$) −100.4 (d, 1F, $^2J_{F-F}$ 64.0), −110 (d, 1F, $^2J_{F-F}$ 64.0); m/z (CI^+) 284 (66%, $[M+NH_4]^+$), 277 (22), 268 (24), 229 (21), 214 (61), 196 (43), 181 (100), 179 (92), 167 (83), 142 (43), 99 (92), 94 (84); HRMS (ES^+): calcd $[M+NH_4]^+$ 284.1668; found 284.1669.

4.2.2. 3-Allyloxy-1,1-difluoro-2-(2′-methoxy-ethoxymethoxy)-6-methyl-hepta-1,6-diene ***16***. A mixture of difluoroallylic alcohol **15** (17.5 mmol, 4.65 g), and allyl bromide (21.0 mmol, 1.76 mL), was added to vigorously stirred sodium hydroxide (122.4 mmol, 6.48 mL of a 50% aqueous solution), and tetra-*n*-butylammonium hydrogensulfate (0.87 mmol, 0.30 g) at 0 °C in one portion over 1 min. The mixture was stirred at this temperature for 1 h (a white suspension was formed after 10 min), then allowed to warm to room temperature overnight. The yellow-white suspension was quenched with ammonium chloride (5 mL of a saturated aqueous solution), and extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford ether **16** as a pale yellow oil, which was used without purification. Yield 4.28 g, 80% (97% GC, t_R (GC) 15.26 min); R_f (30% ethyl acetate/hexane) 0.46; ν_{max} (film) 3077w, 2932s, 2359w, 1749s, 1648s, 1451s, 1375w, 1280s, 1235s, 1117s, 1042s, 952s, 890s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.88 (dddd, 1H, J 17.2, 10.4, 6.2, 5.1), 5.27 (dq, 1H, J 17.2, ^4J 1.7, ^2J 1.7), 5.17 (ddd, 1H, J 10.4, ^4J 3.0, ^2J 1.4), 5.03 (d, 1H, ^2J 6.1), 4.94 (d, 1H, ^2J 6.1), 4.71 (br s, 1H), 4.70 (br s, 1H) 4.09 (ddt, 1H, ^2J 12.5, J 5.1, ^4J 1.4), 4.00 (tdd, 1H, J 7.0, $^4J_{H-F}$ 3.7, 2.3), 3.93–3.74 (m, 3H), 3.56 (t, 2H, J 5.3), 3.38 (s, 3H), 2.10–2.00 (m, 2H), 1.97–1.66 (m, 2H), 1.72 (s, 3H); δ_C NMR (75 MHz, $CDCl_3$) 156.0 (dd, $^1J_{C-F}$ 293.8, 284.7), 144.8, 134.3, 117.2, 112.3 (dd, $^2J_{C-F}$ 36.7, 10.1), 110.3, 97.0 (dd, $^4J_{C-F}$ 4.1, 2.5), 74.0 (t, $^3J_{C-F}$ 3.2), 71.5, 69.2, 68.2 (d, $^6J_{C-F}$ 1.8), 58.9, 33.4, 29.7 (t, $^4J_{C-F}$ 1.9), 22.2; δ_F (282 MHz, $CDCl_3$), −97.9 (dd, 1F, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 2.3), −109.6 (dd, 1F, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.7); m/z (CI^+) 324 (100%, $[M+NH_4]^+$), 286 (12), 277 (26), 236 (15), 219 (26), 196 (19), 181 (23), 179 (34), 165 (34), 94 (24), 52 (81); HRMS (ES^+): calcd $[M+NH_4]^+$ 324.1981; found 324.1979.

4.2.3. 4,4-Difluoro-5-(2-methoxy-ethoxymethoxy)-9-methyl-deca-1,5,9-trien-3-ol ***17***. Lithium diisopropylamide was prepared as for **15** from *n*-BuLi (26.70 mmol, 11.56 mL of a 2.31 M solution in hexane) and diisopropylamine (29.37 mmol, 4.13 mL) in THF (133 mL). A solution of ether **16** (13.35 mmol, 4.09 g) in dry THF (26 mL) was added dropwise at −100 °C over 20 min to the stirred LDA solution under a nitrogen atmosphere. The pale pink solution was stirred at this temperature for 30 min before being allowed to warm to −40 °C over 4 h. During warming, the solution changed colour to yellow then through orange to brown and finally black. The reaction was quenched with ammonium chloride (2 mL of a saturated methanolic solution); the black colour was discharged and an orange/red solution was observed. The layers were separated and the aqueous phase was extracted with diethyl ether (3×50 mL). The original organic layer and the combined organic extracts were washed with brine (2×25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford alcohol **17**. Yield 3.64 g, 89% (95% conversion by GC, t_R (GC) 17.54 min), which was used without further purification; the following data were obtained from a small sample purified by flash chromatography (silica gel, 30% diethyl ether/hexane); R_f (30% diethyl ether/hexane) 0.20; ν_{max} (film) 3436br, 2919s, 1749w, 1643w, 1443s, 1167w, 1114w, 1038s, 938w, 885w cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.91 (ddd, 1H, J 17.2, J 10.6, J 5.5), 5.56 (td, 1H, J 7.4, ^4J 1.3), 5.48 (apparent dt, 1H, J 17.2, ^4J 1.5, ^2J 1.5), 5.33 (apparent dt, 1H, ^3J 10.6, ^4J 1.5, ^2J 1.5), 5.03 (d, 1H, ^2J 5.9), 5.01 (d, 1H, ^2J 5.9) 4.76–4.74 (m, 1H), 4.71–4.68 (m, 1H), 4.50 (dddt, 1H, J_{H-F} 14.2, 8.8, J 5.5, ^4J 1.5), 3.88–3.84 (m, 2H), 3.60–3.56 (m, 2H), 3.38 (s, 3H), 2.39–2.29 (m, 2H), 2.10 (t, 2H, J 7.5), 1.72 (s, 3H); δ_C (75 MHz, $CDCl_3$) 155.2 (dd, $^2J_{C-F}$ 27.5, 25.2), 144.6, 132.5 (dd, $^3J_{C-F}$ 3.6, 2.3), 120.0 (t, $^3J_{C-F}$ 5.0), 118.8, 118.2 (dd, $^1J_{C-F}$ 250.2, 249.2), 110.6, 98.2, 72.4 (dd, $^3J_{C-F}$ 30.4, 27.6), 71.5, 68.8, 59.0, 36.9, 23.4, 22.3; δ_F (282 MHz, $CDCl_3$), −110.1 (dd, 1F, $^2J_{F-F}$ 253.1, $^3J_{H-F}$ 8.8), −115.6 (dd, 1F, $^2J_{F-F}$ 253.1, $^3J_{H-F}$ 14.2); m/z (CI^+) 324 (33%, $[M+NH_4]^+$), 268 (5), 200 (8), 184 (10), 167 (10), 149 (7), 122 (14), 108 (47), 94 (100), 89 (13), 72 (11), 58 (25); HRMS (ES^+): calcd $[M+NH_4]^+$ 324.1981; found 324.1979.

4.2.4. 3-Benzoyloxy-4,4-difluoro-5-(2′-methoxy-ethoxymethoxy)-9-methyl-deca-1,5,9-triene ***18***. Poly(vinylpyridine) (9.96 mmol 9.96 g at 1 mequiv g^{-1}), followed by benzoic anhydride (9.66 mmol, 2.57 g), and DMAP (3.86 mmol, 0.47 g) were added to a solution of alcohol **17** (9.66 mmol, 2.96 g) in DCM (100 mL), and resulting suspension was swirled for 18 h at room temperature. The poly(vinylpyridine) was removed by filtration, and the solution was washed with $NaHCO_3$ (30 mL), then brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford ester **18** as an orange brown oil, which was used without purification. Yield 2.63 g, 66% (100% by GC, t_R (GC) 23.28 min); R_f (50% diethyl ether/hexane) 0.43; ν_{max} (film) 2919s, 1730s, 1449m, 1265s, 1114s, 1032w, 944w, 890w, 712s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.07 (dd, 2H, J 8.4, ^4J 1.4), 7.58 (t, 1H, J 7.5), 7.44 (t, 2H, J 7.5), 6.02–5.89 (m, 2H), 5.61 (t, J 7.6, 1H), 5.53 (dd, 1H, J 15.9, ^2J 1.2), 5.42 (dd, 1H, J 9.5, ^2J 1.2), 5.01 (s, 2H), 4.68–4.66 (m, 1H), 4.64–4.63 (m, 1H), 3.87 (t, 1H, J 4.9), 3.86 (t, 1H, J 4.5), 3.57 (dd, 2H, J 4.9, 4.5), 3.38 (s, 3H), 2.37–2.27 (m, 2H), 2.02 (t, 2H, J 7.5), 1.65 (s, 3H); δ_C (75 MHz, $CDCl_3$) 164.8, 144.6 (t, $^2J_{C-F}$ 25.4), 144.3, 133.4, 129.9, 129.5, 128.9, 128.4, 121.4, 120.5 (t, $^3J_{C-F}$ 5.1), 117.3 (dd, $^1J_{C-F}$ 251.1, 249.5), 110.6, 98.2, 72.8 (dd, $^2J_{C-F}$ 31.7, 27.0), 71.6, 69.8, 59.0, 36.8, 32.2, 22.3; δ_F (282 MHz, $CDCl_3$) −110.8 (dd, 1F, $^2J_{F-F}$ 253.4, $^3J_{H-F}$ 11.2), −112.4 (dd, 1F, $^2J_{F-F}$ 253.4, $^3J_{H-F}$ 12.6);

m/*z* (CI^+) 428 (100%, $[M+NH_4]^+$), 374 (3), 340 (5), 308 (7), 288 (12), 228 (12), 139 (23), 122 (10), 94 (22), 52 (68); HRMS (ES^+): calcd $[M+NH_4]^+$ 428.2243; found 428.2243.

4.2.5. 3-Benzoyloxy-4,4-difluoro-9-methyl-5-oxo-deca-1,9-diene ***19***. Thionyl chloride (6.41 mmol, 0.470 mL) was added to a stirred solution of enol ether **18** (6.41 mmol, 2.63 g) in methanol (65 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 18 h after which the solvent was removed under reduced pressure. The resulting paste was dispersed in water (50 mL) and extracted with diethyl ether (4×40 mL). The combined organic extracts were washed with $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil, which was purified by flash chromatography (silica gel, 5% diethyl ether/hexane) to afford ketone **19** as a clear oil. Yield 1.22 g, 59% (94% by GC, t_R (GC) 19.23 min); R_f (30% diethyl ether/hexane) 0.54; ν_{max} (film) 3459br, 2935s, 1742s, 1649m, 1602m, 1452s, 1263s, 1107s, 891m, 712s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.04 (dd, 2H, *J* 8.4, ^4J 1.4), 7.61 (t, 1H, *J* 7.5), 7.46 (t, 2H, *J* 7.5), 6.05–5.88 (m, 2H), 5.58 (dd, 1H, ^3J 16.0, ^2J 1.0), 5.52 (dd, 1H, *J* 9.3, ^2J 1.0), 4.71 (td, 1H, ^4J 1.4, ^2J 0.9), 4.64 (dd, 1H, ^4J 2.2, ^2J 0.9), 2.72 (t, 2H, *J* 7.2), 2.00 (t, 2H, *J* 7.2), 1.76 (pentet, 2H, *J* 7.2), 1.66 (s, 3H); δ_C (75 MHz, $CDCl_3$) 199.8 (dd, $^2J_{C-F}$ 29.9, 28.1), 164.3, 144.3, 133.7, 129.8, 128.9, 128.6, 127.6, 122.7 (dd, $^3J_{C-F}$ 3.1, 2.3), 114.2 (dd, $^1J_{C-F}$ 261.6, 256.1), 111.0, 72.4 (dd, $^2J_{C-F}$ 29.7, 25.1), 36.9, 36.5, 22.0, 20.1; δ_F (282 MHz, $CDCl_3$) −113.7 (dd, 1F, $^2J_{F-F}$ 274.0, $^3J_{H-F}$ 8.9), 118.8 (dd, 1F, $^2J_{F-F}$ 274.0, $^3J_{H-F}$ 14.6); *m*/*z* (CI^+) 340 (100%, $[M+H^+]$), 323 (13), 200 (22), 183 (22), 139 (10), 105 (9), 52 (80); HRMS (ES^+): calcd $[M+NH_4]^+$ 323.1453; found 323.1454.

4.2.6. 3-Benzoyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-en-1-one ***20***. A solution of freshly purified ketone **19** (1.00 mmol, 323 mg), and $Ti(O^iPr)_4$ (0.33 mmol, 0.100 mL) in freshly degassed DCM (100 mL) was refluxed under an atmosphere of nitrogen for 30 min, then pre-catalyst **6** (0.1 mmol, 85 mg, 10 mol%) was added. The solution was refluxed for 12 days with two further additions of catalyst (each 0.05 mmol, 42 mg, 5 mol%) and $Ti(O^iPr)_4$ (each 0.3 mmol, 90 mL) after 55 and 134 h, until a conversion of approximately 50% was observed by ^{19}F NMR of aliquots. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, 10% diethyl ether/hexane) to afford cyclooctenone **20** as a yellow oil. Yield 70 mg, 24% (99% by GC, t_R (GC) 20.15 min); ν_{max} (film) 2937s, 2361s, 1731s, 1601w, 1452s, 1271s, 1095s, 1027w, 968w, 710s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06–8.02 (m, 2H), 7.56–7.49 (m, 1H, *J* 7.5), 7.43–7.36 (m, 2H), 6.21 (ddd, 1H, J_{H-F} 19.8, *J* 8.3, ^4J 3.5), 5.28 (d, 1H, *J* 8.3), 2.71 (dddd, 1H, *J* 12.6, 10.7, ^2J 3.6, ^4J 2.1), 2.60–2.50 (m, 1H), 2.45 (td, 1H, *J* 13.3, ^2J 5.2), 2.11 (ddd, 1H, *J* 13.3, ^2J 5.2, ^4J 2.7), 2.07–1.95 (m, 1H), 1.86–1.74 (m, 1H), 1.70 (s, 3H); δ_C (100 MHz, $CDCl_3$) 199.6 (dd, $^2J_{C-F}$ 26.2, 24.6), 165.3, 144.6, 133.6, 130.0, 129.1, 128.5, 118.9 (d, $^3J_{C-F}$ 5.1), 116.5 (dd, $^1J_{C-F}$ 263.1, 260.3), 68.9 (dd, $^2J_{C-F}$ 23.9, 18.6), 37.0, 32.9, 26.6, 24.2; δ_F (282 MHz, $CDCl_3$, 323 K) −111.1 (d, 1F, $^2J_{F-F}$ 238.8), 132.0 (dd, 1F, $^2J_{F-F}$ 238.8, $^3J_{H-F}$ 21.1); *m*/*z* (CI^+) 312 (100%, $[M+NH_4]^+$), 294 (5), 174 (23), 172 (88), 154 (39), 137 (19), 105 (21), 52 (94); HRMS (ES^+): calcd $[M+NH_4]^+$ 312.1406; found 312.1403.

4.3. Synthesis of RRCM precursor and cyclisation to 30

4.3.1. 2-Methyl-octa-1,7-dien-3-ol ***21***. A solution of 5-bromopent-1-en (167.7 mmol, 25 g) in diethyl ether (85 mL) was added dropwise over 1 h to stirred suspension of magnesium turnings (209.6 mmol, 5.09 g) in diethyl ether (17 mL). The reaction mixture was stirred and began to reflux, developing a black colour as the Grignard reagent formed. The mixture was stirred at reflux until almost all of the magnesium had been consumed (3 h). The black solution was cooled to 0 °C and methacrolein (192.9 mmol, 15.88 mL) was added dropwise over 30 min, then the solution was stirred for a further 30 min at this temperature. The reaction was quenched with water (50 mL); a precipitate was formed and the mixture was diluted further with water (100 mL). The precipitate was collected and washed at the pump with diethyl ether (500 mL). The phases in the filtrate were separated and the aqueous layer was extracted with diethyl ether (2×50 mL). The organic washings and extracts were combined and washed with $NaHCO_3$ (30 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *under reduced pressure*. The residue was distilled (Kugelrohr, 20 °C/0.5 mmHg) to afford alcohol **21** as a pale yellow oil. Yield 20.80 g, 88% (98% by GC, t_R (GC) 8.61 min), which was used without purification; R_f (30% ether/hexane) 0.45; bp 40–42 °C/0.075 mmHg; ν_{max} (film) 3348br, 2936s, 1641m, 1441m, 994s, 908s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.81 (ddt, 1H, *J* 17.1, *J* 10.2, *J* 6.6), 5.03–4.91 (m, 3H), 4.85 (s, 1H), 4.07 (t, 1H, *J* 6.5), 2.09 (dt, 2H, *J* 7.1, 6.6), 1.72 (s, 3H), 1.61–1.33 (m, 5H); δ_C (75 MHz, $CDCl_3$) 147.5, 138.6, 114.5, 110.9, 75.6, 33.9, 33.5, 25.0 17.3; *m*/*z* (EI^+) 139 (1%, $[M-H]^+$), 125 (8), 96 (15), 71 (94), 43 (100); HRMS (ES^+): calcd $[M+NH_4]^+$ 139.1117; found 139.1115.

4.3.2. 2-Methyl-3-(vinyloxy)-octa-1,7-diene ***22***. Mercury(II) bis(trifluoroacetate) (1.44 mmol, 633 mg) was added to a solution of alcohol **21** (148.3 mmol, 20.8 g) in ethyl vinyl ether (250 mL). The solution was refluxed for 22.5 h, then the solvent was removed *under reduced pressure* to give a pale yellow oil. Acetal **23** was removed by distillation (Kugelrohr, 15 °C at 0.5 mmHg) to afford ether **22** as a pale yellow oil. Yield 23.07 g, 94% (98% by GC, t_R (GC) 8.81 min), which was used without further purification. For analysis a small sample was purified by flash chromatography on silica gel eluted with 5% ether/hexane; R_f (5% ether/hexane) 0.66; ν_{max} (film) 2935s, 2360w, 1639s, 1443w, 1377w, 1195s, 909s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.29 (dd, 1H, *J* 14.0, *J* 6.6), 5.80 (ddt, 1H, *J* 17.1, *J* 10.2, *J* 6.9), 5.06–4.90 (m, 4H), 4.30 (dd, 1H, *J* 14.0, ^2J 1.3), 4.09 (dd, 1H, *J* 7.0, 6.1), 3.99 (dd, 1H, *J* 6.6, ^2J 1.3), 2.13–2.04 (m, 2H, *J* 6.9, ^4J 1.3), 1.78–1.30 (env., 4H) 1.68 (s, 3H); δ_C (75 MHz, $CDCl_3$) 150.5, 144.2, 138.5, 114.7, 113.2, 88.6, 83.6, 33.5, 32.7, 24.8, 16.9; a molecular ion could not be obtained for this compound (by ES, EI, CI or FAB). Traces of acetal 23 are revealed by the presence of peaks between 3.7 and 3.5 ppm, arising from the $-OCH_aH_bCH_3$ protons.

Compounds **24**–**29** are mixtures of *E* and *Z*-alkene diastereoisomers. As these mixtures converge on single compounds **30** or **31**, extensive deconvolution of the spectra has not been undertaken.

4.3.3. 4-Methyl-deca-4,9-dienal ***24***. Ether **23** (118.0 mmol, 19.57 g) was divided into batches (4×5 g), which were crimp-capped in microwave tubes, each containing a stirrer bead. The tubes were sealed and irradiated in the cavity of a CEM Explorer microwave instrument at 150 °C for 10 min, until conversion to aldehyde **24** was complete (by ^1H NMR of aliquots). The tubes were cooled and opened and their contents, aldehyde **24** was used without purification. Yield 19.2 g, 98% (95% by GC, t_R (GC) 11.88 min (major), 11.60 (minor)); R_f (10% ether/hexane) 0.41; δ_H (400 MHz, $CDCl_3$) 9.78 (t, 1H, *J* 1.8, minor), 9.76 (t, 1H, *J* 2.0, major), 5.80 (ddt, 1H, *J* 17.1, 10.2, 6.7), 5.16 (t, 1H, *J* 7.2), 5.00 (d, 1H, *J* 17.1), 4.94 (d, 1H, *J* 10.2), 2.54–2.46 (m, 2H), 3.33 (t, 2H, *J* 7.6), 2.08–1.96 (m, 4H), 1.69 (m, 3H, minor), 1.61 (m, 3H, major), 1.42 (quintet, 2H, *J* 7.6); δ_C (100 MHz, $CDCl_3$) 202.6, 202.2, 138.8, 138.7, 133.1, 133.0, 126.6, 125.5, 114.5, 114.4, 42.3, 42.1, 33.4, 33.3, 31.8, 29.1, 28.9, 27.3, 27.2, 24.3, 23.0, 16.1; *m*/*z* (CI^+) 167 (23%, $[M+H]^+$), 149 (14), 122 (13), 81 (15), 52 (50); HRMS (ES^+): calcd $[M+NH_4]^+$ 167.1430; found 167.1431.

4.3.4. 1,1-Difluoro-2-(2′-methoxy-ethoxymethoxy)-6-methyl-dodeca-1,6,11-trien-3-ol ***25***. Lithium diisopropylamide was prepared as for **15** from *n*-BuLi (60.00 mmol, 20.69 mL, of a 2.90 M solution in

hexane) and diisopropylamine (66.00 mmol, 9.28 mL) in THF (35 mL) under nitrogen.

Alcohol **25** was prepared as for **15** from acetal **13** (30.00 mmol, 5.03 mL) and aldehyde **24** (36.00 mmol, 6.55 g). The same reaction conditions and work-up afforded **25** as a red/brown oil, which was used without purification. Yield 8.42 g, 84% (90% by GC, t_R (GC) 19.80 min (major), 19.36 (minor)). A sample was purified by flash chromatography (silica gel, 0–20% ethyl acetate/hexane gradient) to afford alcohol **25** as a yellow oil; R_f (20% ethyl acetate/hexane) 0.16; ν_{max} (film) 3437br, 2930s, 1752m, 1637w, 1443w, 1237w, 1112s, 732m cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.77 (ddt, 1H, *J* 17.1, 10.2, 6.6), 5.12 (t, 1H, *J* 6.9), 5.01–4.74 (m, 4H), 4.19 (br s, 1H), 3.97–3.53 (m, 4H), 3.36 (s, 3H), 2.07–1.93 (m, 6H), 1.85–1.60 (m, 2H) 1.60 (s, 3H), 1.44–1.34 (quintet, 2H, *J* 7.4); δ_C (75 MHz, $CDCl_3$) 154.6 (dd, $^1J_{C-F}$ 292.0, 286.0), 138.9, 134.1, 124.9, 118.1 (dd, $^2J_{C-F}$ 36.8, 9.9), 114.3, 97.9 (dd, $^4J_{C-F}$ 4.2, 3.0), 71.4, 68.4, 66.8 (dd, $^3J_{C-F}$ 3.0, 1.8), 59.0, 35.5, 33.3, 32.0, 28.9, 27.3, 15.8; δ_F (282 MHz, $CDCl_3$) −100.2 (d, 1F, $^2J_{F-F}$ 63.5, minor), −100.3 (d, 1F, $^2J_{F-F}$ 63.5, major), −109.6 (dd, 1F, $^2J_{F-F}$ 63.5, $^4J_{H-F}$ 3.3 minor), −109.7 (dd, 1F, $^2J_{F-F}$ 63.5, $^4J_{H-F}$ 3.0 major); *m*/*z* (ES^+) 335 (5%, $[M+H]^+$), 321 (8), 280 (11), 229 (6), 188 (100), 115 (15), 89 (12); HRMS (ES^+): calcd $[M+NH_4]^+$ 335.2028; found 335.2027.

*4.3.5. 3-Allyloxy-1,1-difluoro-2-(2′-methoxy-ethoxymethoxy)-6-methyl-dodeca-1,6,11-triene **26**.* Alcohol **26** was prepared as for **16** from alcohol **25** (25.19 mmol, 8.415 g), allyl bromide (30.2 mmol, 2.63 mL), sodium hydroxide (140.00 mmol, 7.41 mL of a 50% aqueous solution), and tetra-*n*-butylammonium hydrogensulfate (2.52 mmol, 0.854 g). The same reaction conditions and work-up afforded **26** as a pale yellow oil. Yield 8.66 g, 92% (84% by GC, t_R (GC) 20.44 min (major), 20.00 min (minor)). A sample was purified by flash chromatography on silica gel eluted with 10% diethyl ether/hexane to give **26** as a yellow oil; R_f (10% diethyl ether/hexane) 0.39; ν_{max} (film) 2929s, 1749m, 1640m, 1452w, 1231w, 1131s, 914w cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.94–5.74 (env., 2H), 5.31–4.88 (env., 7H), 4.08 (ddt, 1H, ^2J 12.6, *J* 5.0, 1.5), 4.00–3.74 (m, 4H), 3.59–3.55 (m, 2H), 3.39 (s, 3H), 2.09–1.66 (env., 8H), 1.59 (s, 3H), 1.47–1.36 (m, 2H); δ_C (75 MHz, $CDCl_3$) for both diastereoisomers: 155.0 (dd, $^1J_{C-F}$ 293.8, 284.8), 138.9, 134.4, 134.0, 117.1, 114.3, 112.4 (dd, $^2J_{C-F}$ 36.5, 9.6), 97.1 (dd, $^4J_{C-F}$ 3.8, 2.6), 71.6, 69.2, 68.2 (d, $^5J_{C-F}$ 1.8), 59.0; for major diastereoisomer 125.1, 74.0 (t, $^3J_{C-F}$ 3.3), 35.3, 33.3, 30.0, 27.3, 15.8: for minor diastereoisomer 125.8, 74.3 (t, $^3J_{C-F}$ 3.0), 33.3, 30.1, 29.2, 29.0, 27.5, 27.1, 23.2; δ_F (282 MHz, $CDCl_3$) −97.6 (dd, 1F, $^2J_{F-F}$ 36.3, $^4J_{H-F}$ 3.5, minor), −97.7 (dd, 1F, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.5 major), −109.3 (dd, 1F, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.5, minor), −109.5 (dd, 1F, $^2J_{F-F}$ 63.3, $^4J_{H-F}$ 3.5 major); *m*/*z* (CI^+) 392 (97%, $[M+NH_4]^+$), 251 (19), 233 (21), 182 (20), 122 (64), 94 (100); HRMS (ES^+): calcd $[M+NH_4]^+$ 392.2607; found 392.2611.

*4.3.6. Preparation of 4,4-difluoro-5-(2-methoxy-ethoxymethoxy)-9-methyl-pentadeca-1,5,9,14-tetraen-3-ol **27**.* Lithium diisopropylamide was prepared as for **15** from *n*-BuLi (46.07 mmol, 15.89 mL, of a 1.9 M solution in hexane) and diisopropylamine (50.69 mmol, 7.12 mL) in THF (230 mL) under nitrogen.

Alcohol **26** was prepared as for **16** from ether **26** (23.04 mmol, 8.662 g) in THF (23 mL), which was added dropwise to the LDA at −100 °C over 15 min; a pale pink colour formed and the solution was stirred and allowed to warm to −70 °C over 1.5 h, then to −40 °C over 3 h. The same quenching conditions and work-up afforded alcohol **27** as a red-brown oil, which was used without purification. Yield 8.53 g, 98% (>95% conversion by ^{19}F NMR and GC t_R (GC) 22.13 min (major), 21.85 min (minor)). A sample was purified by flash chromatography (silica, pre-washed with 5% triethylamine in 30% diethyl ether/hexane, eluting with 30% diethyl ether/hexane) to afford **27** as a yellow oil; R_f (30% ether/hexane) 0.11; ν_{max} (film) 3420br, 2922s, 1640w, 1458w, 1116s, 910s, 733s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.92 (ddd, 1H, *J* 17.2, 10.5, 5.6), 5.80 (ddt, 1H, *J* 17.1, 10.1, 6.6), 5.55 (td, 1H, *J* 7.4, ^4J 1.3), 5.48 (app. dt, 1H, *J* 17.2, ^2J 1.5), 5.34 (app. dt, 1H, *J* 10.5, ^2J 1.5), 5.15 (td, 1H, *J* 7.2, ^4J 1.0), 5.04–4.91 (m, 4H), 4.56–4.44 (m, 1H), 3.90–3.80 (m, 2H), 3.60–3.55 (m, 2H), 3.38 (s, 3H), 2.79 (br d, 1H, *J* 6.0), 2.34–2.23 (m, 2H), 2.12–1.95 (m, 6H), 1.68 (d, 3H, ^4J 1.0, minor), 1.59 (s, 3H, major), 1.42 (quintet, 2H, *J* 7.4); δ_C (100 MHz, $CDCl_3$) for both diastereoisomers: 145.2 (dd, $^2J_{C-F}$ 27.6, 25.2), 139.0, 133.9, 132.5 (dd, $^3J_{C-F}$ 3.2, 2.4), 118.8, 118.2 (dd, $^1J_{C-F}$ 250.4, 247.2), 72.4 (dd, $^2J_{C-F}$ 30.8, 27.5), 71.5, 68.8, 59.0, 27.3; for major diastereoisomer 125.4, 120.2 (t, $^3J_{C-F}$ 5.2), 114.4, 98.2, 38.8, 33.3, 28.9, 23.8, 15.8; for minor diastereoisomer 126.3, 120.0 (t, $^3J_{C-F}$ 5.1), 114.4, 98.3, 33.4, 31.0, 29.2, 23.7, 23.1; δ_F (282 MHz, $CDCl_3$) −109.7 (dd, 1F, $^2J_{F-F}$ 253.5, $^3J_{H-F}$ 9.0, minor), −109.8 (dd, 1F, $^2J_{F-F}$ 253.0, $^3J_{H-F}$ 8.5, major), −115.7 (dd, 1F, $^2J_{F-F}$ 253.0, $^3J_{H-F}$ 14.2, major), −115.9 (dd, 1F, $^2J_{F-F}$ 253.5, $^3J_{H-F}$ 14.7, minor); *m*/*z* (CI^+) 392 (100%, $[M+NH_4]^+$), 299 (9), 142 (38), 122 (31), 94 (92); HRMS (ES^+): calcd $[M+NH_4]^+$ 392.2607; found 392.2606.

*4.3.7. 3-Benzyloxy-4,4-difluoro-5-(2′-methoxy-ethoxymethoxy)-9-methyl-pentadeca-1,5,9,14-tetraene **28**.* A solution of alcohol **27** (22.67 mmol, 8.53 g) in THF (70 mL) was added cautiously to a suspension of NaH (68.1 mmol, 2.72 g of a 60% suspension in mineral oil, pre-washed with dry hexane (3×50 mL)) in THF at 0 °C under nitrogen. The mixture was stirred at this temperature for 45 min while hydrogen evolved. tetra-*n*-Butylammonium iodide (2.27 mmol, 0.837 g), followed by benzyl bromide (24.94 mmol, 2.96 mL) were added, and the reaction allowed to warm to room temperature over 3 h, and stirred overnight. The reaction was quenched by the cautious addition of water (150 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (3×150 mL) and the combined original organic layer and extracts were washed with brine (2×100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford ether **28** as a brown oil, which was used without purification. Yield 9.72 g, 92%. A sample was purified by flash chromatography (silica, pre-washed with 5% triethylamine in 10% diethyl ether/hexane, eluted with 10% diethyl ether/hexane) to afford **28** as a yellow oil; R_f (10% diethyl ether/hexane) 0.11; ν_{max} (film) 2927s, 2358 m, 1682w, 1640w, 1454, 1116, 938m, 853s, 736s, 699s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.26 (m, 5H), 5.94–5.75 (m, 2H), 5.58 (td, 1H, *J* 7.3, ^4J 1.2), 5.50–5.41 (m, 2H), 5.16 (br t, 1H, *J* 7.2), 5.06–4.93 (env., 4H), 4.68 (d, 1H, ^2J 11.8), 4.54 (d, 1H, ^2J 11.8), 4.28–4.17 (m, 1H), 3.82–3.77 (m, 2H), 3.55 (dd, 2H, *J* 5.1, 4.2), 3.39 (s, 3H), 2.36–2.25 (m, 2H), 2.11–1.95 (m, 6H), 1.70 (br s, 3H, minor), 1.61 (s, 3H, major), 1.49–1.38 (m, 2H); δ_C (75 MHz, $CDCl_3$) for both diastereoisomers: 145.0 (dd, $^2J_{C-F}$ 26.9, 25.1), 138.9, 137.6, 134.1, 131.1 (dd, $^3J_{C-F}$ 3.6, 1.8), 128.3, 127.8, 127.7, 118.1 (dd, $^1J_{C-F}$ 250.7, 245.3), 114.4, 79.0 (dd, $^2J_{C-F}$ 31.4, 26.0), 71.6, 71.4, 68.7, 59.0, 38.9, 33.4, 23.8; for major diastereoisomer 125.2, 121.4, 120.1 (t, $^3J_{C-F}$ 5.4), 98.2, 29.0, 15.9; for minor diastereoisomer 126.1, 121.4, 120.0 (t, $^3J_{C-F}$ 5.4), 98.2, 31.1, 29.2, 27.3, 23.2; δ_F (282 MHz, $CDCl_3$) −108.3 (dd, 2F, $^2J_{F-F}$ 254.5, $^3J_{H-F}$ 9.0, both diastereoisomers), −114.3 (dd, 1F, $^2J_{F-F}$ 254.5, $^3J_{H-F}$ 13.7, major), −114.6 (dd, 1F, $^2J_{F-F}$ 254.5, $^3J_{H-F}$ 14.2, minor); *m*/*z* (ES^+) 487 (31%, $[M+Na]^+$), 482 (52), 389 (12), 123 (26), 91 (100); HRMS (ES^+): calcd $[M+NH_4]^+$ 487.2630; found 487.2632. This product was too involatile for GC analysis.

*4.3.8. 3-Benzyloxy-4,4-difluoro-9-methyl-pentadeca-1,8,13-trien-5-one **29**.* Ketone **29** was prepared as for **19** from thionyl chloride (20.95 mmol, 1.52 mL) and a solution of **28** (20.95 mmol, 9.719 g) in methanol (200 mL) at 0 °C. The solution was allowed to warm to room temperature over 2 h and stirred for 18 h. The same reaction conditions and work-up afforded ketone **29** as a pale yellow oil. Yield 2.59 g, 33% (95% by GC, t_R (GC) 23.36 min (major), 22.97 min (minor)); R_f (5% diethyl ether/hexane) 0.23; ν_{max} (film) 2928.5s, 2359m, 1741s, 1640w, 1454m, 1101s, 910m, 736s, 698s cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.24 (m, 5H), 5.96–5.77 (m, 2H), 5.59–5.48 (m, 2H), 5.15 (t, 1H, *J* 7.2), 5.08–4.96 (m, 2H), 4.65 (d, 1H, ^2J 11.5), 4.42 (d, 1H, ^2J 11.5), 4.30 (dt, 1H, $^3J_{H-F}$ 16.6, *J* 6.7), 2.67 (t, 2H, *J* 7.3),

2.12–1.97 (m, 6H), 1.75–1.68 (5H, env. containing), 1.75 (pentet, 2H, *J* 7.4), 1.59 (s, 3H), 1.45 (pentet, 2H, *J* 7.6); δ_C (75 MHz, $CDCl_3$) for both diastereoisomers, 236.8, 208.9 (dd, $^2J_{C-F}$ 31.7, 25.1), 129.6 (dd, $^3J_{C-F}$ 3.6, 1.2), 128.3, 128.0, 128.0, 123.2, 115.0 (dd, $^1J_{C-F}$ 262.1, 253.7), 114.4, 79.3 (dd, $^2J_{C-F}$ 31.1, 23.9), 71.4, 38.7; for major diastereoisomer 239.9, 234.1, 125.5, 37.7, 33.4, 29.0, 27.4, 20.6, 15.7; for minor diastereoisomer 238.8, 234.2, 126.2, 38.0, 30.7, 29.3, 27.3, 23.1, 20.7; δ_F (282 MHz, $CDCl_3$) (−110.1)–(111.1) (m incl. app. d, 2F, $^2J_{F-F}$ 263.5, both diastereoisomers), −124.0 (dd, 2F, $^2J_{F-F}$ 263.5, $^3J_{H-F}$ 16.6, both diastereoisomers); *m*/*z* (CI^+) 394 (100%, $[M+NH_4]^+$), 268 (10), 216 (8), 142 (12), 108 (17); HRMS (ES^+): calcd $[M+NH_4]^+$ 394.2552; found 394.2549.

4.3.9. 3-Benzyloxy-2,2-difluoro-5-methyl-cyclooct-4Z-enone ***30***. Ketone **30** was prepared as for **20** from ketone **29** (1.28 mmol, 482 mg), $Ti(O^iPr)_4$ (0.422 mmol, 0.126 mL) in degassed DCM (512 mL) and pre-catalyst **6** (0.192 mmol, 163 mg, 15%) at reflux over 18 h. The ^{19}F NMR spectrum of an aliquot showed conversion was incomplete and a further portion of pre-catalyst was added (0.192 mmol, 163 mg, 15%) and the solution was refluxed for a further 24 h. The solvent was removed under reduced pressure and the residue was taken up in diethyl ether (5 mL), filtered and concentrated under reduced pressure. The residue was taken up in methanol (1 mL) then eluted through a Stratospheres SPE tube, eluting with methanol (5×2 mL). The solution was concentrated under reduced pressure to afford a brown oil, which was purified by flash chromatography (silica gel, 20% diethyl ether/hexane) to give cyclooctenone **30** as clear blocks. Yield 203 mg, 57% (92% by GC, t_R (GC) 19.56 min); R_f (20% diethyl ether/hexane) 0.28; mp 69–71 °C; ν_{max} (KBr) 2936w, 1742s, 1667w, 1448m, 1060s, 864m, 730s, 697s cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.31 (m, 5H), 5.33 (br d, 1H, *J* 8.0), 4.79 (d, 1H, ^2J 12.0), 4.67 (d, 1H, ^2J 12.0), 4.59 (ddd, 1H, J_{H-F} 20.1, *J* 8.0, $^3J_{H-F}$ 4.3), 2.67–2.49 (m, 2H)*, 2.15–2.11 (m, 2H), 2.01–1.92 (m, 1H), 1.86–1.76 (env. 4H, containing 1.78 (s, 3H)); δ_C (100 MHz, $CDCl_3$) 200.4 (dd, $^2J_{C-F}$ 27.2, 24.8), 144.0, 137.1, 128.5, 128.1, 128.0, 121.4 (d, $^3J_{C-F}$ 5.6), 117.7 (dd, $^1J_{C-F}$ 263.6, 258.8), 73.5 (dd, $^2J_{C-F}$ 23.2, 19.2), 71.8, 36.8, 32.6, 26.4, 24.3; δ_F (376 MHz, 363 K, toluene) −111.0 (d, 1F, $^2J_{F-F}$ 240.3), −129.6 (dd, 1F, $^2J_{F-F}$ 240.3, $^3J_{H-F}$ 19.2). Anal. Calcd (%) for $C_{18}H_{23}F_2O_3N$ C, 68.56; H, 6.47. Found: C, 68.54; H, 6.55. *m*/*z* (ES^+) 281 (50%, $[M+NH_4]^+$), 132 (13), 91 (61); HRMS (ES^+): calcd $[M+Na]^+$ 303.1167; found 303.1168. *In the $\{^{19}F\}^1H$ NMR spectrum, these signals appear as 2.61 (ddd, 1H, *J* 12.5, ^2J 10.5, 4.0) and 2.53 (ddd, 1H, ^2J 10.9, *J* 6.9, 4.0). The *J* values are averages arising from conformational exchange.

Crystal data: $C_{16}H_{18}F_2O_2$, crystal size 0.33×0.29×0.25 mm^3, *M*=280.31, monoclinic, *a*=12.837(4) Å, *b*=7.615(3) Å, *c*=15.535(5) Å, *α*=90°, *β*=112.153(6)°, *γ*=90°, *U*=1406.5(8) $Å^3$, *T*=150(2) K, space group *P*2(1)/*n*, *Z*=4, *μ*(Mo-K*α*)=0.103 mm^{-1}, 9739 reflections measured, 2473 [*R*(int)=0.1222], which were used in all calculations. Final *R* indices [$F^2>\sigma(F^2)$] *R*1=0.0609, *wR*2=0.1387; *R* indices (all data) *R*1=0.0752, *wR*2=0.1468.

4.3.10. 3-Benzyloxy-4,4-difluoro-9-methyl-5-oxo-deca-1,9-diene ***31***. This compound was prepared as for **30** from **29** (0.32 mmol, 119 mg) and $Ti(O^iPr)_4$ (0.082 mmol, 25 μL) in dried degassed chloroform (110 mL) and pre-catalyst **6** (0.0.031 mmol, 27 mg, 15%) at reflux over 24 h. The solvent was evaporated under reduced pressure, then taken up in diethyl ether (2 mL), filtered and evaporated under reduced pressure. ^1H and ^{19}F NMR analysis of the crude product revealed the presence of a new product (major) and 30 (minor) at this point. The residue was taken up in methanol (2 mL) and eluted through a pre-conditioned (with methanol) Thiol-SP SPE tube. The solvent was evaporated under reduced pressure and the product was purified by flash chromatography on silica gel eluted with diethyl ether/hexane (0–10% gradient) to afford **31** as a pale yellow oil. Yield 19 mg, 20%; R_f (10% diethyl ether/hexane) 0.20; ν_{max} (film) 3462br, 2937s, 1738s, 1646m, 1608m, 1452s, 1263s, 1109s, 891m, 718s cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37–7.29 (m, 5H), 5.87 (ddd, 1H, *J* 17.4, 10.4, 7.6), 5.55 (d, 1H, *J* 10.4), 5.50 (d, 1H, *J* 17.4), 4.73 (br s, 1H), 4.66 (br s, 1H), 4.63 (d, 1H, ^2J 11.6), 4.39 (d, 1H, ^2J 11.6), 4.27 (dt, 1H, J_{H-F} 16.4, *J* 7.6), 2.76–2.62 (m, 2H), 2.01 (t, 2H, *J* 7.4), 1.75 (t, 2H, *J* 7.4), 1.69 (br s, 3H); δ_C (1250 MHz, $CDCl_3$) 201.8 (dd, $^2J_{C-F}$ 31.2, 25.2), 144.7, 136.8, 129.6 (d, $^2J_{C-F}$ 2.7), 128.4, 128.1, 127.9, 127.0, 123.2, 115.0 (dd, $^1J_{C-F}$ 261.7, 253.8), 110.7, 79.4 (dd, $^2J_{C-F}$ 30.6, 24.0), 71.4, 37.7, 36.7, 22.1, 20.2; δ_F (376 MHz, $CDCl_3$) −110.7 (dd, 1F, $^2J_{F-F}$ 263.3, J_{H-F} 7.6), −124.0 (dd, 1F, $^2J_{F-F}$ 263.3, J_{H-F} 16.4); *m*/*z* (ES^+) 347 (18%, $[M+K]^+$), 331 (31, $[M+Na]^+$) 242 (100), 91 (61); HRMS (ES^+): calcd $[M+NH_4]^+$ 326.1926; found 326.1924; t_R (GC) 19.71 min.

4.3.11. Small scale RRCM reactions. Stock solutions of **29** (30.1 mg, 0.080 mmol) and titanium tetra isopropoxide (7 μL, 0.023 mmol) in dry chloroform (1 mL), and pre-catalyst **6** (5.1 mg, 0.006 mmol) were prepared immediately before use. Carousel reaction tubes were charged with the appropriate volumes of stock solution of **29** and Ti reagent and additional chloroform (up to 20 mL) was added by syringe. The solutions were heated at reflux for 30 min before addition of the stock solution of **6**. Reactions were heated at reflux for 24 h then the solvent was removed under reduced pressure. The residue was taken up in diethyl ether (5 mL), filtered and concentrated under reduced pressure. The residues were dissolved in $CDCl_3$ for ^1H NMR spectroscopic analysis.

4.4. Cyclooctenone transformation

4.4.1. 3R-Benzyloxy-2,2-difluoro-9-oxa-1R*,5S*-methyl-5S*-bicyclo[3.3.1]nona-1R*,4R*-diol 41 and 3R*-benzyloxy-2,2-difluoro-9-oxa-1S*,5R*-methyl-5R*-bicyclo[3.3.1]nona-1S*,4S*-diol* ***42***. Osmium tetroxide (0.03 mmol, 0.41 mL of a 2.5% solution in *t*-BuOH) was added to a solution of cyclooctenone **30** (0.649 mmol, 182 mg) and NMO (1.198 mmol, 152 mg) in a mixture of water (0.813 mL) and acetone (1.6 mL) at 0 °C. The reaction was stirred at this temperature for 6 h until consumption of starting material was observed by TLC. The reaction was quenched by the addition of $Na_2S_2O_5$ (5 mL) and then stirred for 18 h. Water (15 mL) was added and the mixture was extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a mixture of **41** and **42** (11:9 by ^{19}F NMR) as a light grey paste (182 mg, 89%), which was purified by flash chromatography on silica gel eluted with ethyl acetate/hexane 30% 4CV then 30–50% 10CV to afford (in order of elution) **44** as a white solid (5 mg, 2%); R_f (50% ethyl acetate/hexane) 0.25; mp 56–58 °C; ν_{max} (KBr) 3422br, 2937w, 1456w, 1338w, 1217w, 1129m, 1083s, 1019s, 985s, 911m, 753s, 699s cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45–7.33 (m, 5H), 4.93 (d, 1H, ^2J 11.5), 4.69 (d, 1H, ^2J 11.5), 3.98 (ddd, 1H, J_{H-F} 12.8, 6.7, *J* 4.4), 3.67–3.65 (m, 1H, $\{^{19}F\}^1H$ simplifies to 3.66 (dd, *J* 7.2, 4.4)), 3.33 (br s, 1H), 2.22–2.14 (m, 1H), 2.07–1.97 (m, 1H), 1.88–1.83 (m, 1H), 1.75–1.55 (m, 3H), 1.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 137.2, 128.6, 128.2, 127.9, 118.3 (dd, $^1J_{C-F}$ 268.4, 250.8), 95.8 (dd, $^2J_{C-F}$ 29.2, 19.9), 80.5 (dd, $^2J_{C-F}$ 29.8, 17.5), 77.6, 75.1 (d, $^4J_{C-F}$ 2.3), 72.6 (t, $^3J_{C-F}$ 3.5), 31.4, 28.9 (d, $^3J_{C-F}$ 1.8), 25.5, 16.3; δ_F (376 MHz, $CDCl_3$) −110.2 (dd, 1F, $^2J_{F-F}$ 258.6, J_{H-F} 12.8), (−123.5)–(−124.3) (m inc. app. d, $^2J_{F-F}$ 258.6, 1F). Anal. Calcd (%) for C, 61.14; H, 6.41. Found C, 61.31; H, 6.57. *m*/*z* (ES^-) 313 (29%, $[M-H]^-$), 293 (20), 205 (18), 185 (100), 182 (34), 123 (15), 59 (91); HRMS (ES^+): calcd $[M+Na]^+$ 332.1668; found 332.1666; t_R (HPLC, reverse phase, 40% H_2O in MeOH) 23.3 min; followed by a mixture of **44** and **43** (141 mg, 69%), then **43** as a white solid (36 mg, 18%); R_f (50% ethyl acetate/hexane) 0.35; mp 125–127 °C; δ_H (400 MHz, $CDCl_3$) 7.42–7.34 (m, 5H), 4.91 (d, 1H, ^2J 11.7), 4.80 (d, 1H, ^2J 11.7), 4.10 (ddd, 1H, $^3J_{H-F}$ 20.5, 7.6, *J* 4.4), 3.63 (ddd, 1H, *J* 4.4, $^3J_{H-F}$ 4.3, ^4J 2.8), 2.06–1.99 (m, 1H), 1.87–1.79 (m, 1H), 1.75–1.61 (m, 2H), 1.56–1.45 (m, 2H), 1.39

(s, 3H); δ_C (100 MHz, $CDCl_3$) 136.6, 128.7, 128.5, 128.2, 117.7 (dd, $^1J_{C-F}$ 258.4, 254.9), 94.7 (dd, $^2J_{C-F}$ 26.6, 20.1), 76.6, 74.5 (dd, $^2J_{C-F}$ 19.9, 17.5), 73.1 (d, $^4J_{C-F}$ 1.8), 72.8 (dd, $^3J_{C-F}$ 7.6, 1.8), 30.7, 27.4 (d, $^3J_{C-F}$ 1.8), 25.6, 18.8; δ_F (376 MHz, $CDCl_3$) (−116.4)–(−117.1) (m inc. app. d, 1F, $^2J_{F-F}$ 248.8), −124.0 (dddd, 1F, $^2J_{F-F}$ 248.8, $^3J_{H-F}$ 20.5, $^4J_{H-F}$ 6.1, 2.8); Anal. Calcd (%) for C, 61.14; H, 6.41. Found C, 61.25; H, 6.38. m/z (CI^+) 332 (100%, $[M+NH_4]^+$), 242 (47), 206 (6), 108 (20), 91 (11), 52 (28); HRMS (ES^+): calcd $[M+Na]^+$ 332.1668; found 332.1672; t_R (HPLC, reverse phase, 40% H_2O in MeOH) 17.6 min. Preparative HPLC (ODS, 40% H_2O in MeOH) allows full separation of **43** and **44**.

Supplementary data

CCDC 737582 (for **30**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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