Journal Name

ARTICLE

Towards 20,20-difluorinated bryostatin

Paul R. Mears[a], Steven Hoekman[a], Claire E. Rye,[a] Fiona P. Bailey,[b] Dominic P. Byrne,[b] Patrick A. Eyers[b] and Eric J. Thomas[a*]

z-CampillosReceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Bryostatins with modified C17-C27 fragments have not been widely studied. The synthesis of 20,20-difluorinated analogues was therefore investigated. Such substitution would inhibit dehydration involving the C19-hydroxyl group and stabilise the ring-closed hemiacetal tautomers. Following preliminary studies, allyldifluorination was used to prepare difluorinated alkenols. Oxidation followed by stereoselective Wittig reactions of the resulting α,α-difluorinated ketones gave (*E*)-α,β-unsaturated esters that were taken through to complete syntheses of the 20,20-difluorinated C17-C27 fragments of bryostatin. These compounds showed modest binding to PKCs. Attempts were also undertaken to synthesise macrocyclic 20,20-difluorinated analogues. During preliminary studies, allyldifluorination was carried out using a 2-alkyl-3-bromo-1,1-difluoropropene.

Introduction

Bryostatins, see bryostatin 1 (**1**) and 10 (**2**) in Fig. 1, are complex marine macrolides that have been intensively investigated because of their potent biological activities.[1] The anticancer activity of bryostatin 1 in particular has been thoroughly studied and other useful clinical indications have been established.[2]

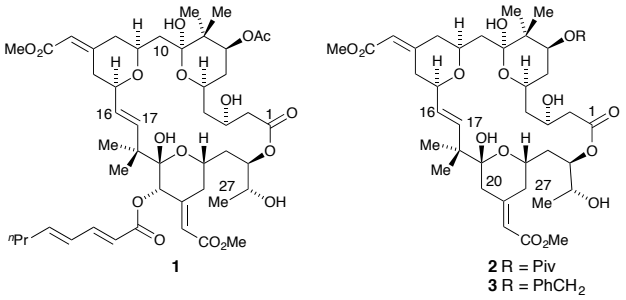


Fig. 1 Structures of representative bryostatins

Unfortunately the isolation of bryostatin from natural sources is still very challenging and so the chemical synthesis of bryostatins has been of considerable interest.[3] Many approaches to their synthesis have been reported in the literature over the years[4] and several total syntheses have now been completed.[5] These equate to outstanding contributions to the chemistry of natural products and highlight the very latest techniques and methodologies of organic synthesis. The early syntheses of these complex targets were substantial achievements in themselves, but they involved many steps with lengthy linear routes, and did not really deliver useful quantities of bryostatins. Recently, however, this situation has changed with a synthesis of bryostatin 1 on a multigramme scale.[6] This development may meet clinical needs and illustrates the power of modern synthetic organic chemistry.

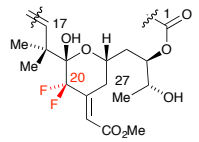
Bryostatins are believed to effect tumour inhibition by binding to the regulatory C1 domain of protein kinase C isotherms (PKCs).[7] Interestingly phorbol esters bind to the same binding site of PKCs yet are tumour promoters.[7] From molecular modelling studies using diacylglycerols (the natural PKC ligands), bryostatin 1 and phorbol esters, Wender postulated that the binding of bryostatin to PKCs involves the C1-carbonyl group together with the C19 and C26 hydroxyl groups with the C3 hydroxyl group helping to maintain the required conformation by forming an intramolecular hydrogen bond.[8] This analysis led to the synthesis of macrocyclic analogues of bryostatins that possessed the C17-C27 fragment of bryostatin 1 so retaining the nanomolar binding to PKCs of the natural products.[9,10] It was then discovered that analogues with different C1-C15 fragments could act as either tumour inhibitors or a tumour promoters so mimicking either bryostatin or the phorbol esters.[10] Our work in this area culminated in a synthesis of the 7-benzyl ether **3** corresponding to bryostatin 10 **2**, the first synthesis of a bryostatin with no oxygenation at C20.[11]

Most of the synthetic analogues with nanomolar binding are complex macrolides with C17-C27 fragments corresponding to those found in the natural products. Despite this feature that leads to potent PKC binding, we chose to investigate the synthesis of analogues of bryostatins in which the structure of the C17-C27 fragment had been modified to see whether any beneficial affects could accrue. One objective was to see whether simpler, non-macrocyclic, compounds could be prepared that retained the potent activity of bryostatins although whether such compounds would be tumour inhibitors

[a] *The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK;* [b]*The Department of Biochemistry, IIB, The University of Liverpool, Liverpool, L69 7ZB, UK.*
* Corresponding author; e-mail: e.j.thomas@manchester.ac.uk.
Electronic Supplementary Information (ESI) includes copies of all the ^{1}H, ^{13}C and ^{19}F NMR spectra reported in this paper. See DOI: 10.1039/x0xx00000x

or tumour promoters was difficult to predict. In particular, it was decided to study the synthesis of bryostatins in which two fluorine substituents had been introduced at C20, for example see structure **4** in Fig. 2. These compounds would retain the structural features that are important for binding, i.e the C1 carbonyl group and the hydroxyl groups at C19 and 26. However the electron withdrawing C20 fluorine substituents would help to stabilise the ring-closed hemi-acetal tautomer. They would also make the 21-methoxycarbonylmethylene group more electrophilic and lead to an increase in the pKa of the anomeric C19 hydroxyl group by about three pKa units. Perhaps most importantly, they would prevent dehydration, i.e. deactivation, involving loss of the C19 hydroxyl group. Fluorinated 2-hydroxytetrahydropyrans have been prepared as surrogates of monosaccharides,[12,13] and analogues of bryostatin with fluorinated B-rings have been synthesized for NMR studies.[14]

We here report full details on our work in this area and preliminary biological data. Some aspects of this work were disclosed in preliminary communications.[15,16]



4

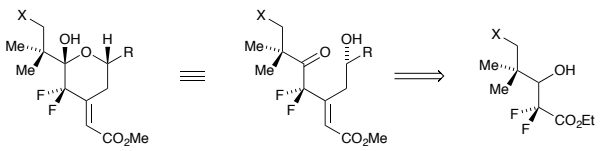
Fig. 2. The 20,20-difluorinated C17-C27 fragment of a bryostatin

Results and discussion

Preliminary investigations

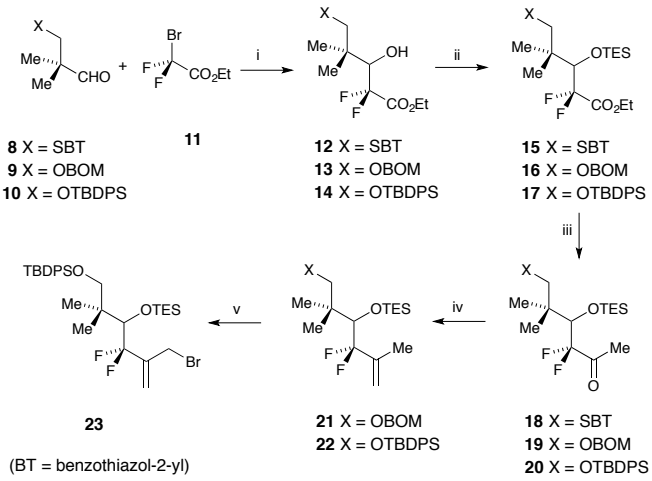
Hydroxyketones **6** are the open-chain tautomers of the fluorinated bryostatin C-ring analogues **5**. The first approach to these compounds was based on elaboration of the β-hydroxyesters **7** prepared from Reformatsky reactions[17,18] of ethyl bromodifluoroacetate as shown in Fig. 3.

The Reformatsky reaction of 3-(2-mercatobenzothiazolyl)-2,2-dimethylpropanal (**8**) with ethyl bromodifluoroacetate **11** using activated copper dust gave the hydroxyester **12**. This was protected as its triethylsilyl ether **13** using triethylsilyl trifluoromethanesulfonate and the ester converted into the corresponding methylketone **18** directly using methyllithium at –78 °C, Scheme 1. An excess of methyllithium at rt gave the corresponding tertiary alcohol (see experimental).



5 **6** **7**

Fig. 3 Outline of the first approach to difluorinated intermediates



8 X = SBT
9 X = OBOM
10 X = OTBDPS

11

12 X = SBT
13 X = OBOM
14 X = OTBDPS

15 X = SBT
16 X = OBOM
17 X = OTBDPS

23

(BT = benzothiazol-2-yl)

21 X = OBOM
22 X = OTBDPS

18 X = SBT
19 X = OBOM
20 X = OTBDPS

Scheme 1 Use of intermediates prepared by Reformatsky reactions of ethyl bromodifluoroacetate Reagents and conditions i, Zn powder, CuCl, THF, rt, 30 min, add **11**, 10 min, add the aldehyde in THF, heat under reflux, 16-36 h (**12**, 83%; **13**, 75%; **14**, 78%); ii, 2,6-lut., TESOTf, DCM, rt, 1-10 d (**15**, 75%; **16**, 85%; **17**, 94%); iii, MeLi, THF, –78 °C, 5.5 h (**18**, 77%; **19**, 86%; **20**, 55%); iv, Ph_3PMeBr, KHMDS, tol., 0 °C, 30 min, add the ketone, rt, 48 h (**21**, 75%; **22**, 73%); v, NBS, $CHCl_3$, hυ, 10 min, heat under reflux 24 h (**23**, <72%).

The intention was to develop the methyl ketone **18** to introduce the required side-chain, see proposed intermediate **6**. However, an attempted aldol condensation with (*E*)-crotonaldehyde gave unchanged starting material and an attempted Wittig reaction to convert the ketone into the corresponding alkene was also unsuccessful. Since these difficulties may have been due to the 2-mercaptobenzothiazole, 3-(benzyloxymethoxy)-2,2-dimethylpropanal (**9**) was taken through to the methylketone **19**. The Wittig reaction with methylene(triphenyl)phosphorane now gave a good yield of the alkene **21** and the same sequence was successful starting with the 3-*tert*-butyldiphenylsilyloxypropanal **10**[19,20] giving the alkene **22**. This was then converted into the allylic bromide **23** under free-radical conditions although on scale-up this reaction was somewhat capricious. The intention had been to use a reaction of the allylic bromide **23** with an aldehyde to assemble intermediates analogous to the target compounds **6**. Although modifications to this synthesis could be envisaged, the relative inaccessability of bromide **23** led to this approach being discontinued, see Scheme 1.

Copper catalysed coupling reactions of bromo- and iodo-difluoroacetates with aryl and alkenyl iodides have been reported.[21,22] This chemistry could lead to a flexible synthesis of the unsaturated difluoroesters **24** from the alkenyl iodides **26**, see Fig. 4. Ozonolysis followed by an (*E*)-selective Horner-Wadsworth-Emmons reaction would introduce the required (*E*)-methoxycarbonylmethylene group. Modification of the ethyl ester should provide the required ketone. Indeed Horner-Wadsworth-Emmons reactions of α,α-difluorinated ketones are known to be (*E*)-selective.[23]

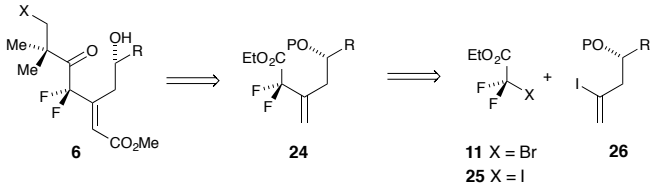
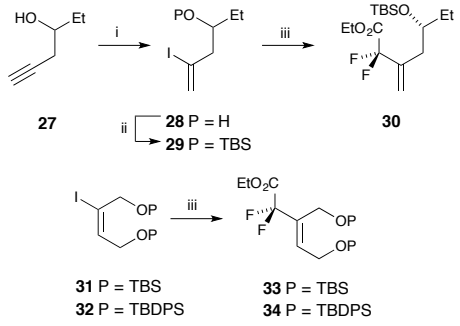


Fig. 4 The proposed use of unsaturated difluorinated esters

To access the intermediate **24** where R = ethyl, the alkenyl iodide **29** was prepared from the alkyne **27** by addition of hydrogen iodide generated *in situ*[24] followed by silylation. However, in our hands, the copper catalysed coupling of this with the iododifluoroester **25** gave only a low yield of the difluorinated alkene **30**. The analogous coupling of the alkenyl iodides **31** and **32** with the iododifluoroester **25** also gave low yields of the products **33** and **34**, Scheme 2, and so this approach was not taken any further.



Scheme 2 Attempted coupling of alkenyl iodides and ethyl iododifluoroacetate Reagents and conditions i, NaI, TMSCl, MeCN, H_2O, rt, 20 min, add **27**, rt, 4 h (80%); ii, TBSCl, imid., DCM, rt, 24 h (75%); iii, **25**, Cu, DMSO, rt, 3 h, add alkenyl iodide, DMSO, rt, 1.25 h (**30**, 8%; **33**, 12%; **34**, 14%).

Allyldifluorination is well known for the introduction of geminal difluorine containing fragments[25] and so the homoallylic difluoroalcohols **36** should be readily accessible from the bromodifluoropropene **37** and aldehydes **38** as shown in Fig. 5. Oxidation and an (*E*)-selective Horner-Wadsworth-Emmons reaction would then provide the unsaturated esters **35** that could be converted into the hydroxyketones **6** by selective modification of the terminal double bond.

The indium powder mediated reaction[25] of 3-bromo-3,3-difluoropropene (**37**) with 3-*tert*-butyldiphenylsilyloxypropanal (**39**) gave a good yield of the difluorinated alkene **40** that was protected as the bis-silyl ether **41**, see Scheme 3. Ozonolysis and

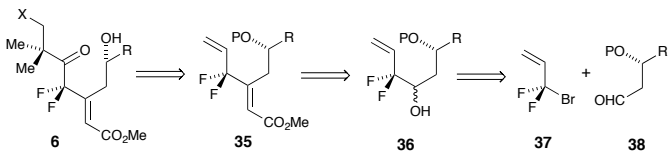
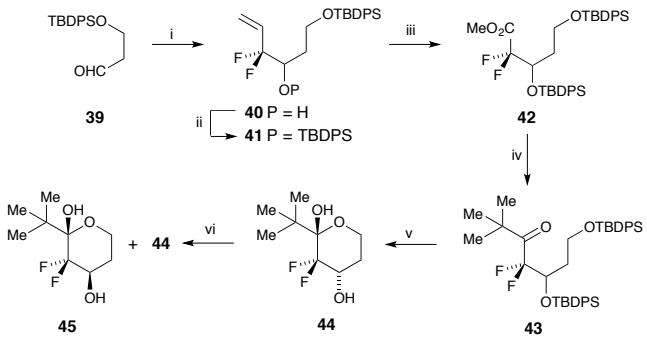


Fig. 5 Use of difluoroallylation in a synthesis of the hydroxyketones **6**



Scheme 3 Preparation of the 2-hydroxytetrahydropyran **44** Reagents and conditions i, In powder, LiI, H_2O, **37**, rt, 10 min, add **39**, THF, rt, 5 h (97%); ii, crude **40**, TBDPSCl, imid., DCM, rt, 48 h (72% from **37**); iii, (a) O_3, DCM, −78 °C, 5 min, add DMS, rt, 3 h (b) ^{t}BuOH, 2-methylbut-2-ene, THF, $NaClO_2$, $Na_2H_2PO_4.2H_2O$, rt, 16 h (c) $TMSCHN_2$, MeOH, tol., rt, 48 h (80% from **41**); iv, ^{t}BuLi, pentane, THF, −78 °C, 5 h (52%); v, TBAF, THF, 0 °C to rt, 15 h (72% after cryst.); vi, C_6D_6, rt, 48 h (**44** : **45** = 40:60).

further oxidation of the resulting aldehyde gave the corresponding acid that was converted into the ester **42** using trimethylsilyldiazomethane. The conversion of ester **42** into the ketone **43** was achieved in one step using *tert*-butyllithium[26] and desilylation using tetrabutylammonium fluoride gave a mixture of two inseparable compounds. On cooling a single product crystallised out from this mixture and was identified as the 3,3-difluoro-2,4-dihydroxytetrahydropyran **44** using X-ray crystallography, see Fig. 6. On standing in solution in deuteriated chloroform (not base-washed), this hemiacetal gave a 40:60 mixture in favour of the second component after 10 min at rt. In benzene-d_6 or in base-washed chloroform, the equilibration took place more slowly but gave a similar mixture of the two compounds, typically within 48 h. Attempts to isolate the second component were unsuccessful as the initially isolated compound **44** tended to crystallise out. However, the IR spectrum of a mixture did not show a carbonyl peak and the ^{1}H NMR spectrum of the mixture was consistent with the second component being the epimer **45**. It would appear that the two hemiacetals equilibrate despite the presence of the geminal fluorine substituents. However, the open chain, hydroxyketone tautomer was not a significant component of the mixture at equilibrium. In the crystalline tautomer **44** the *tert*-butyl and 4-hydroxyl groups are equatorial whereas in the slightly more stable epimer **45**, both hydroxyl groups are axial.

The reaction of prenylmagnesium chloride with the ester **43** gave the ketone **46** that on deprotection gave a mixture of products from which the 2,4-dihydroxytetrahydropyran **47** was isolated by repeated trituration, see Scheme 4. As before in

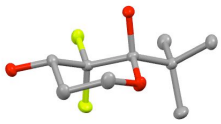
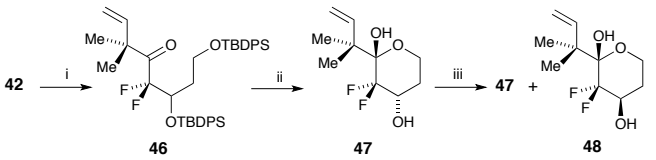


Fig. 6 The structure of the crystalline dihydroxytetrahydropyran **44** as established by X-ray crystallography.



Scheme 4 Synthesis of the 2-hydroxytetrahydropyran **47** Reagents and conditions i, 3-methylbut-2-enylmagnesium chloride, THF, −10 °C, 12 h (66%); ii, TBAF, THF, 0 °C to rt, 15 h (82% afer repeated trituration); iii, C_6D_6, rt, 48 h (**47**:**48** = 60:40).

benzene-d_6, this product was found to equilibrate with a second component identified as the epimeric hemiacetal **48**. In this case, **47**:**48** = 60:40, at equilibrium. Structures were assigned to these products by analogy with the 2,4-hydroxytetrahydropyrans **44** and **45**. In both cases the doublets attributed to the fluorines were significantly more widely separated in their ^{19}F NMR spectra for the crystalline epimers **44** and **47** (see experimental).

It was recognised that 2-substituted 3-bromo-3,3-difluoropropenes **49** could react with aldehydes to give difluoroalkenes **50**, see Fig. 7, and that these might be incorporated into C17-C27 fragments of bryostatin more easily than the less functionalised intermediates **36**, *cf*. Fig. 5. 2-Substituted 3-bromo-3,3-difluoropropenes have been used in palladium-catalysed reactions with aryl boronic acids[27] but their indium mediated reactions with aldehydes have not been investigated.

1-Chloro-1,1-difluorodecan-2-one (**52**) was prepared from from methyl chlorodifluoroacetate (**51**) according to the literature procedure.[28] Conversion into the epoxide **53** was then achieved using di-iodomethane and methyllithium[29] and the epoxide was taken through to the allylic alcohol **54** by treatment with *tert*-butyllithium. This allylic alcohol was converted into 2-bromomethyl-1,1-difluorodecene **55** using *N*-bromosuccinimide and dimethyl sulfide. On heating this allylic bromide in toluene under reflux, isomerisation gave the required 2-(bromodifluoromethyl)decene **56** but only as a mixture with the starting bromide, **55** : **56** = 20 : 80, see Scheme 5. The indium powder mediated reaction of this mixture of allylic bromides with benzaldehyde gave a modest, 50%, yield of the required adduct **57a**. However, better yields were obtained using the bromide **55** and the yield of **57a** improved to 84% in DMF. Indeed the allylic bromide **55** reacted under these conditions with a range of aldehydes to give products **57** in reasonable to excellent yields, see Scheme 5.[16]

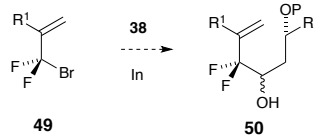
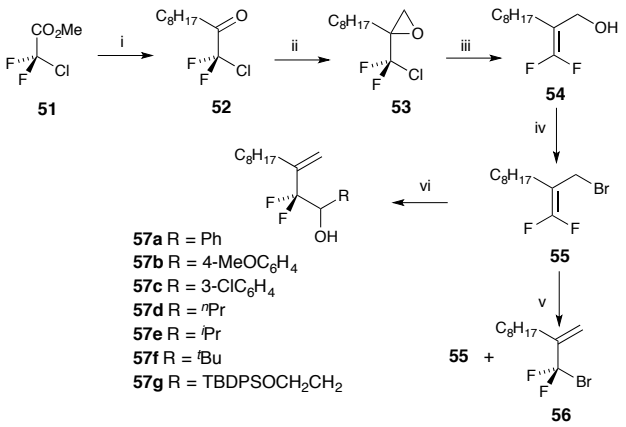


Fig. 7 Posssible reactions of 2-substituted 1-bromo-1,1-difluoropropenes with aldehydes.

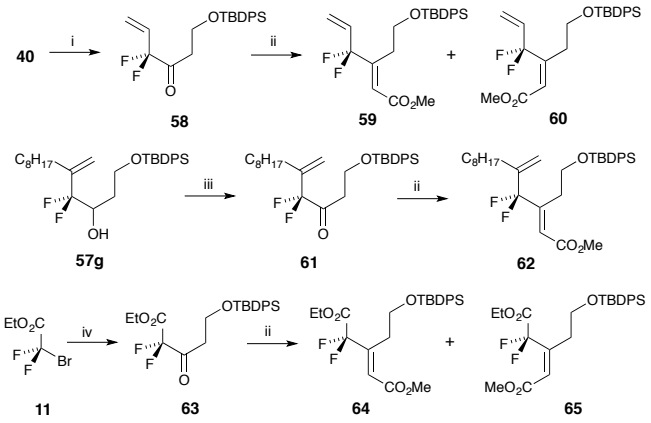


Scheme 5 Chemistry of 2-bromomethyl-1,1-difluorodecene **55** Reagents and conditions i, $C_8H_{17}MgBr$, Et_2O, tol., −78 °C to −20 °C, 10 min (96%); ii, CH_2I_2, MeLi, THF, −78 °C to rt; iii, ^{t}BuLi, pentane, THF, −78 °C to rt, 16 h (44% from **52**); iv, NBS, Me_2S, DCM, 0 °C, 10 min, cool to −20 °C, add **54**, rt, 15 h (63%); v, tol., heat under reflux, 15 h (**55**:**56** = 20:80, 89%); vi, In, DMF, rt, 10 min, add aldehyde, rt, 14 h (**57a**, 84%; **57b**, 65%; **57c**, 93%; **57d**, 98%; **57e**, 68%; **57f**, 47%; **57g**, 91%).

Generally Wittig[30] and Horner-Wadsworth-Emmons reactions[23] of α,α-difluorinated ketones give α,β-unsaturated esters with useful (*E*)-stereoselectivity. However, before embarking on a synthesis of a fluorinated C17-C27 fragment of bryostatin, it was decided to check the stereoselectivity of the introduction of the methoxycarbonylmethylene unit in our system, *cf*. Fig. 5.

Oxidation of the previously prepared alcohols **40** and **57g** gave the ketones **58** and **61**. The ketoester **63** was prepared by oxidation of the alcohol prepared by the samarium di-iodide mediated Reformatsky reaction of ethyl bromodifluoroacetate (**11**) and the protected hydroxypropanal **39**.[31] The Wittig reactions of the ketones **58** and **63** with the stabilised ylid, methoxycarbonylmethylene(triphenyl)phosphorane, were usefully (*E*)-selective, >85:15, with the (*E*)-ester **62** being the only product isolated from ketone **61**, see Scheme 6.

The (*E*)-configuration was assigned to the major products of these reactions using NMR. For example, the vinylic protons in the major and minor products of the reaction with ketone **58** were at δ 6.21 and δ 5.98, respectively, consistent with the vinylic hydrogen being closer to the fluorine substituents in the major isomer. For the minor product, significant nOe enhancement of a 5-hydrogen was observed on irradiation of the vinylic proton consistent with this being the (*Z*)-isomer **60**. The fluorines in the major and minor products were at δ −100.52 and δ −95.73 consistent with the literature[23,30] for analogous difluorinated (*E*)- and (*Z*)-α,β-unsaturated esters. Similar data confirmed the (*E*)-configuration of the major products **62** and **64** from the Wittig reactions of ketones **61** and **63** (see experimental).

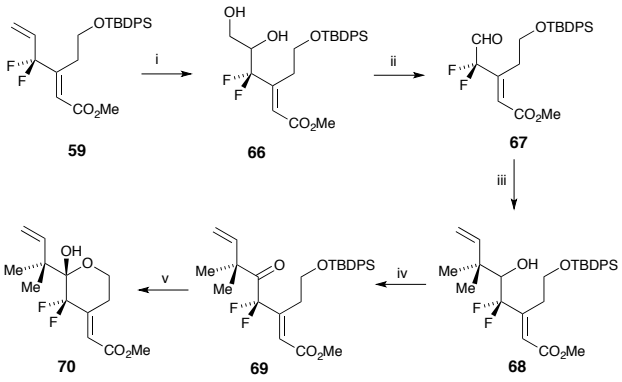


Scheme 6 (*E*)-Selective Wittig reactions of α,α-difluorinated ketones Reagents and conditions i, TPAP, NMO, 4Å sieves, DCM, rt, 16 h (78%); ii, $Ph_3P{=}CHCO_2Me$, tol., 70-90 °C, 6-16 h (**59**, 84%; **60**, 11%; **62**, 48%; **64**, 82%; **65**, 12%); iii, DMSO, $(COCl)_2$, DCM, −78 °C, 30 min, add **57g**, DCM, −78 °C, 45 min, Et_3N, rt, 1 h (61%); iv, (a) SmI_2, **11**, **39**, THF, rt, 10 min (98%) (b) TPAP, NMO, 4Å sieves, DCM, rt, 16 h (63%).

To incorporate the bis-ester **64** into a synthesis of a 2-hydroxytetrahydropyran analogous to the hemiacetal **47** (see Scheme 4), it would be necessary to develop conditions for the regioselective reaction of prenylmagnesium bromide with the ethoxycarbonyl group. It was decided instead to attempt to prepare the corresponding aldehyde by the regioselective oxidative cleavage of the terminal double bond in the diene **59** as the selective cleavage of terminal double bonds in dienes using osmium tetroxide is well known.[32] Although in the case of diene **59**, the terminal double bond will be deactivated towards oxidation by the adjacent fluorine substituents, this is also true for the double bond conjugated to the ester. The dihydroxylation of alkenes with allylic fluorine substituents by osmium tetroxide is known.[32]

In our hands the dihydroxylation of the diene **59** using osmium tetroxide and *N*-methylmorpholine-*N*-oxide in water-acetone was very slow at rt and gave a low yield of diol **66** (29%) together with unchanged starting material. Under more forcing conditions, the yield improved to 44% but side-products that appeared to have been formed by additional hydroxylation of the double bond conjugated to the ester were also detected. The use of ruthenium tetroxide generated *in situ* by the slow addition of sodium periodate to a solution of the alkene and ruthenium(III) chloride[33] gave a 44% yield of the diol **66** together with unchanged starting material. This procedure was quite reliable and side products formed by hydroxylation of the unsaturated ester were not isolated, Scheme 7.

Cleavage of the diol **66** using lead(IV) acetate gave the aldehyde **67**. Rather than react this with a Grignard reagent, the crude aldehyde was added to the prenyl bromide in THF and the mixture transferred to a suspension of zinc powder and titanocene dichloride in THF.[34] This procedure gave a reasonable yield of the alcohol **68** that was oxidised to the ketone **69**. Desilyation using HF.pyridine then gave the required 2-hydroxytetrahydropyran **70**, Scheme 7.



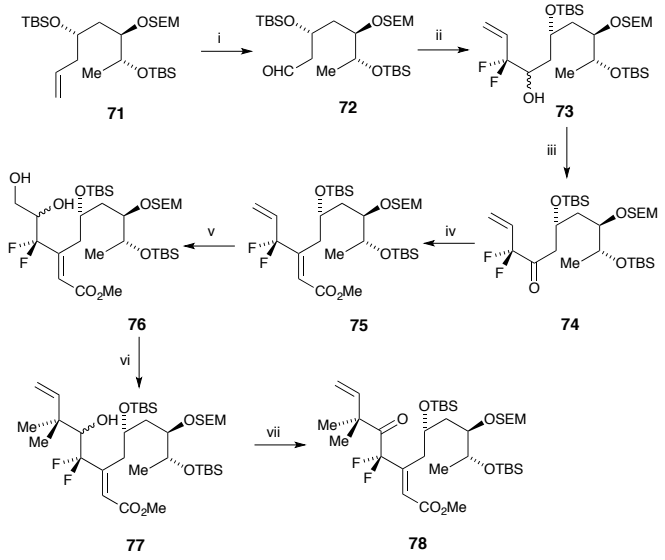
Scheme 7 Synthesis of the 3,3-difluoro-2-hydroxy-4-[(*E*)-methoxycarbonylmethylene]tetrahydropyran **70** Reagents and conditions i, $RuCl_3.H_2O$, EtOAc, MeCN, H_2O, add $NaIO_4$ over 5 h, rt, 39 min (**66**, 44%, recovered **59**, 44%); ii, $Pb(OAc)_4$, $NaHCO_3$, DCM, rt, 30 min; iii, $Me_2C{=}CHCH_2Br$, THF, add to Zn powder, titanocene dichloride (cat.), THF, rt, 2.5 h (65% from **66**); iv, TPAP, NMO, 4Å sieves, DCM, rt, 30 min (87%); v, HF.py., py., THF, rt, 2.5 h (82%).

Structures were assigned to the intermediates in Scheme 7 from spectroscopic data and by analogy with earlier work. The hemiacetal carbon was observed as a double-doublet at δ 99.1 in its proton decoupled ^{13}C NMR spectrum due to slightly different coupling constants ($^2J_{C\text{-}F}$ 30.1, 24.4 Hz) with the axial and equatorial fluorines.

This synthesis had given the 3,3-difluoro-2-hydroxy-4-[(*E*)-methoxycarbonylmethylene]tetrahydropyran **70** in eight steps from 3-*tert*-butyldimethylsilylpropanal **39**. Although the hydroxylation of the alkene **59** was not particularly efficient, it was decided to use the chemistry outlined in Scheme 7 to synthesise a fully substituted C17-C27 fragment of a bryostatin, *cf.* structure **4** in Fig. 2.

Synthesis and chemistry of 2-hydroxy-3,3-difluorotetrahydropyrans analogous to a difluorinated C17-C27 fragment of bryostatin

The known alkene **71**[35] was was ozonolysed with reduction of the intermediate ozonide using triphenylphosphine to give the aldehyde **72**. The indium-mediated difluoroallylation of this aldehyde gave a mixture of the epimers of alcohol **73**. Samples of these were separated for characterisation and the mixture was oxidised to give the ketone **74**. The Wittig reaction of this ketone with methoxycarbonylmethylene(triphenyl)phosphorane was highly stereoselective and gave the required (*E*)-alkene **75** albeit with a small amount of unchanged starting material. Regioselective hydroxylation of the diene **75** was carried out using ruthenium tetroxide, and the resulting diol **76** was taken through to the alcohol **77**, as a mixture of epimers, by cleavage using lead(IV) acetate and reaction of the resulting aldehyde with prenyl bromide mediated by zinc powder and titanocene dichloride. Oxidation of the alcohol **77** then gave the ketone **78**, Scheme 8.

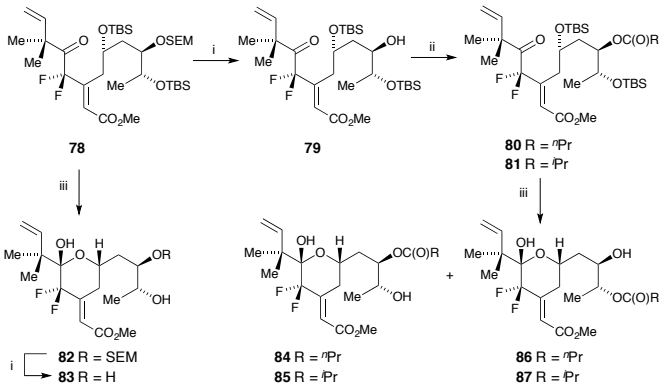


Scheme 8 Synthesis of ketone **78** Reagents and conditions i, O_3, DCM, −78 °C, 5 min, Ph_3P, rt, 3 h (96%); ii, In powder, **37**, rt, 4 h (66%, 53:47); iii, TPAP, NMO, DCM, 4 Å sieves, rt, 16 h (75%); iv, $Ph_3P{=}CHCO_2Me$, tol., 90 °C, 16 h (**75**, 64%; **74**, 10%), v, **75**, $RuCl_3.H_2O$, EtOAc, MeCN, H_2O, add $NaIO_4$ over 9 h (**76**, 55:45, 61%; **75**, 39%); vi, (a) $NaHCO_3$, $Pb(OAc)_4$, DCM, rt, 90 min (b) crude aldehyde and $Me_2C{=}CHCH_2Br$,THF added to Zn dust, titanocene dichloride (cat.), THF, rt, 16 h (**77**, 50:50, 70%); vii, TPAP, NMO, DCM, rt, 16 h (60%).

Selective removal of the 2-(trimethylsilylethoxy)methoxy (SEM) group from the protected hydroxyketone **78** gave the alcohol **79** that was acylated to give the butanoyl and isobutanoyl esters **80** and **81**. Desilylation with *in situ* acetal formation gave mixtures of the esters **84**/**86** and **85**/**87** formed by equilibration of the regioisomers under the reaction conditions, Scheme 9. Selective removal of the *tert*-butyldimethylsilyl groups from the fully protected hydroxyketone **78** gave the hemiacetal **82**. Removal of the SEM-group then gave the corresponding diol **83**.

Structures were assigned to the products in Scheme 9 from spectroscopic data. The hemiacetals **82**-**87** were single compounds (^1H and ^{13}C NMR) with their configurations at C2 assigned on the basis of the anomeric effect. Spin-decoupling and 2D NMR methods were used to distinguish between the different regioisomers (see experimental).

To establish the effect of the C20 geminal fluorine substituents on the PKC binding and biological activity of analogues of bryostatin, it was decided to synthesise a fluorinated macrolide closely related to a non-fluorinated compound that had already been prepared. Amongst the simplest macrocyclic compounds that are known to show potent PKC binding are the salicylic esters **88** prepared by Wender.[36,37] It was therefore decided to prepare a close analogue of this system and the macrodiolide **89** was identified as a suitable target, Fig. 8.



Scheme 9 Synthesis of C20 difluorinated analogues of the C17-C27 fragment of bryostatin Reagents and conditions i, $MgBr_2$, Et_2O, $MeNO_2$, rt, 2-24 h (**79**, 74%; **83**, 70%); ii, RCO_2H, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, rt, 1.5 h, add **79**, DMAP, tol., rt, 16 h (**80**, 80%; **81**, 94%); iii, HF.py., py., THF, 0 °C, 16 h (**82**, 67%; **84**, 42%; **86**, 42%; **85**, 23%; 8**7**, 23%).

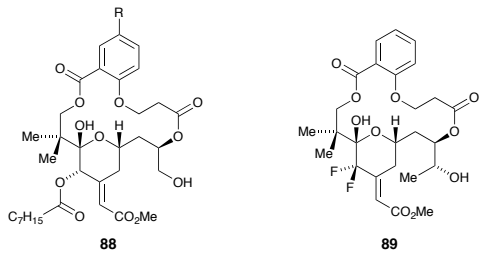
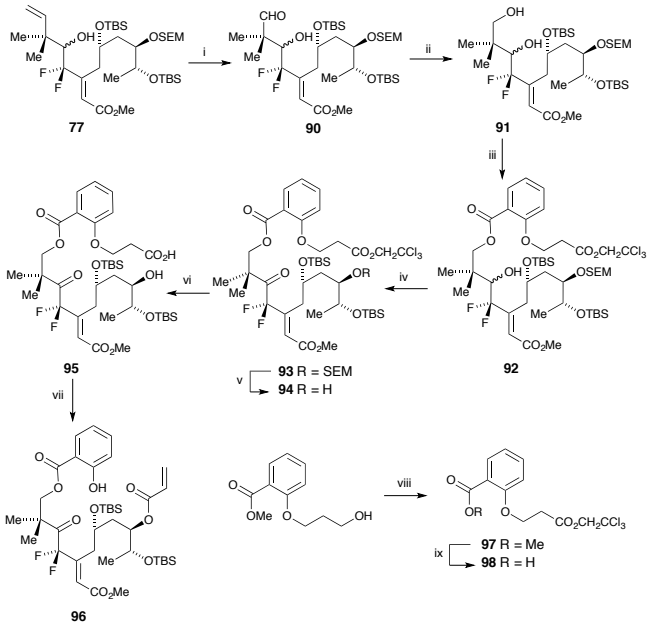


Fig. 8. Simple macrocyclic analogues of bryostatin.

Regioselective hydroxylation of the diene **77** followed by oxidative cleavage of the resulting vicinal diol gave the aldehyde **90**. Reduction using sodium borohydride gave the diol **91** as a mixture of epimers. Regioselective esterification of this diol using the protected salicylic acid **98** gave the ester **92** that was oxidised to give the ketoester **93**. Removal of the SEM ether under standard conditions gave the alcohol **94** and cleavage of this 2,2,2-trichloroethyl ester gave the *seco*-acid **95**. However, an attempted macrocyclisation of this hydroxyacid did not give the required macrodiolide. Instead the major product appeared to have a terminal double bond and was provisionally identified from ^1H NMR data as the acrylate **96** formed by an elimination of the salicylate under the reaction conditions. In Wender's syntheses of the macrodiolides **88**,[36] the assembly of the macrocycle was carried out on intermediates that already had the C-19 hemiacetal functionality intact. In our case, the hemi-acetal was not present in the seco-acid **95**. This meant that the transannular hydrogen bonding found in bryostatins was not able to facilitate macrocyclisation. Unfortunately further studies were not possible and a synthesis of a macrocyclic analogue of a 20,20-difluorinated bryostatin was not completed, see Scheme 10.



Scheme 10 Approaches to the macrodiolide **89** Reagents and conditions i, (a) OsO_4, NMO, ^tBuOH, H_2O, rt, 4 h (b) $Pb(OAc)_4$, Na_2CO_3, DCM, rt, 5 min (82% from **77**); ii, $NaBH_4$, MeOH, 0 °C, 1 h (83%); iii, **98**, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, tol., rt, 1.5 h, add **91**, DMAP, tol., rt, 16 h; iv, TPAP, NMO, 4Å sieves, DCM, rt, 16 h (57% from **91**); v, $MgBr_2$, MeCN, Et_2O, rt, 15 h (65%); vi, Zn, PPTS, THF, reflux, 30 min; vii, 2,4,6-C_6H_2COCl, py., benzene, rt, 45 min, add to DMAP, benzene, 60 °C, 16 h; viii, (a) TEMPO, $PhI(OAc)_2$, MeCN, H_2O, rt, 1 h (b) 2-methyl-but-2-ene, NaH_2PO_4, $NaClO_2$, 0 °C, 1 h (c) Cl_3CCH_2OH, DCC, DMAP, DCM, rt, 16 h (73%); ix, NaI, TMSCl, DCE, 100 °C, 15 h (72%).

PKC Binding studies

Preliminary studies were next carried out into binding of the fluorinated hemiacetals **83**, **84** and **86** to purified PKC proteins. Phorbol esters and bryostatins target individual cysteine-rich zinc finger motifs (C1 and C2 domains) of conventional and novel PKCs, and are believed to lead to allosteric release of the pseudosubstrate region. Thermal profiling has been used to evaluate atypical PKC isozyme destabilisation by small molecules[38] and upon binding, nanomolar to micromolar affinity kinase inhibitors usually induce temperature shifts in the range of 2-10 °C *in vitro*.[39,40] In order to analyse whether bryostatin binding to PKC isozymes can also be evaluated in a thermal shift assay, Sypro Orange, a fluorophore exhibiting enhanced fluorescence when it binds to unfolded protein kinases,[40,41] was employed for real-time thermal profiling with three affinity-tagged purified kinases, namely PKCα, representative of the conventional PKCs, and a known phorbol ester and bryostatin target,[42] PKCζ, an 'atypical' PKC protein that lacks canonical C1 and C2 domains, and PKA, the archetypal Ser/Thr protein kinase from the 'AGC family' to which PKC also belongs. As shown in Fig. 9**A**, all three kinase preparations were essentially pure, making them suited to real-time thermal stability studies in the presence and absence of chemical compounds.

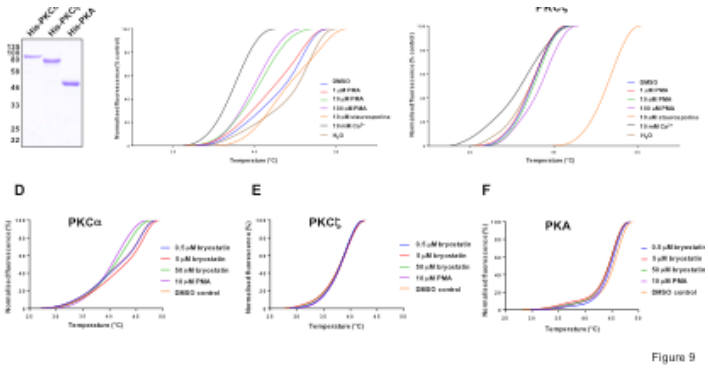


Fig. 9. A novel fluorescence-based PKC thermal shift assay. (A) Analysis of N-terminally 6His affinity-tagged human PKCα (amino acids 1-672), human PKCζ (amino acids 2-592) and full-length murine PKA (1-351). 2 mg of the indicated purified proteins were separated by SDS-PAGE and stained with Coomassie Blue. The positions of a range of molecular mass markers are also shown (kDa). **(B)** Differential scanning fluorimetry reveals PKCα unfolding profiles as a function of temperature in the presence of a series of different compounds. **(C)** PKCζ unfolding profiles evaluated as a function of temperature in the presence of the indicated compounds. Thermal profiling of each kinase in the presence of a range of concentrations of pure commercial bryostatin was assessed using purified (**D**) PKCα, (**E**) PKCζ, or (**F**) PKA catalytic subunit. The final concentration of each kinase in the assays was 5 μM. Triplicate data were fitted to the Boltzmann Equation, and are shown for duplicate experiments. DMSO was the control solvent, and purified phorbol ester (PMA) was the positive control compound employed for PKCα. Similar results were seen in an independent experiment.

PKCα underwent a complex unfolding transition that was influenced markedly in the presence of PMA, which induced a 3°C destabilisation relative to control, consistent with polypeptide domain structural reorganisation. This destabilising effect was even more marked with Ca^{2+} ions, leading to a >6°C change in thermal stability relative to control. In contrast, the broad PKC ATP-binding site inhibitor staurosporine[44] promoted an expected PKCα stabilisation, consistent with interaction with the nucleotide-binding (ATP) site. Based on thermal profiling, little or no destabilisation by PMA was detected for PKCζ, consistent with absence of a C2 domain. In contrast, Ca^{2+} ions markedly destabilised PKCζ, which possesses an atypical Ca^{2+}-binding C1 domain, and staurosporine induced a +9°C stabilisation, in line with its reported nanomolar potency towards this PKC isozyme.[43] We next evaluated the effect of commercial byrostatin on each PKC isozyme, and included PKA, which lacks C1 or C2 domains, as an additional negative control. As shown in Figure 9**D**, bryostatin induced robust destabilisation of PKCα at 10-fold molar compound excess, similar to PMA, but had no detectable effect on PKCζ or PKA. To our knowledge, this is the first time that a thermal shift-assay has been employed to demonstrate bryostatin interaction with PKCα. We next

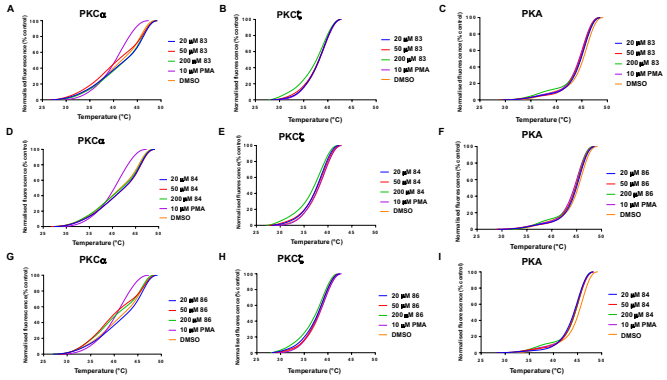


Fig. 10. PKC Thermal shift analysis of fluorinated bryostatins. Real-time thermal stability assay for each kinase was performed in the presence and absence of the indicated concentration of bryostatin analogues **83** (**A**-**C**), **84** (**D**-**F**) or **86** (**G**-**I**). The final concentration of each purified protein kinase was 5 μM. Triplicate data were fitted to the Boltzmann Equation, and are shown for duplicate experiments. DMSO was the control solvent, and PMA was the positive control compound for PKCα. Similar results were seen in independent experiments.

evaluated the effects of compounds **83**, **84** and **86** on temperature-dependent PKC unfolding. As detailed in Fig. 10, **83**had a very subtle destabilising effect on PKCα, but was without effect on PKCζ or PKA, suggestive of a weak interaction. In marked contrast, **86** induced a complex, but dose-dependent bryostatin-like destabilisation of PKCα, but not PKCζ or PKA, suggesting direct binding to a biologically relevant PKCα conformation. No effects of **84** were noted on PKCα, PKCζ or PKA, even at 40-fold molar excess compounds. Together, these data establish a new semi-quantitative assay for rapidly evaluating binding of bryostatins to PKC isozymes, and raise the likelihood that fluorinated compounds such as **86** might possess biological PKCα regulatory activity. Testing this hypothesis will be the focus of future experiments, which will include enzyme based inhibitor assays in-cell thermal stability assays (CETSA) employing endogenous PKC isozymes.

Summary and conclusions

This paper reports the synthesis and preliminary PKC binding studies of a series of hemiacetals that correspond to the C17-C27 fragment of bryostatin. These compounds were selected for study since they retain the key structural features identified as being critical in the nanomolar binding of bryostatin to PKCs yet represent modified C17-C27 fragments that had not been evaluated previously. It was hoped that the two electron-withdrawing fluorine substituents at C20 (bryostatin numbering) would stabilise the ring-closed, hemi-acetal tautomers and inhibit any dehydration involving the crucial C19 hydroxyl group. It was recognised that the fluorine substituents would also increase the acidity of the C19 hydroxyl group by about three pKa units and make the C21 methylene substituent more electrophilic.

In the event, the fluorine containing hemi-acetals **82** – **87** were prepared in *ca.* 10 steps from the known alkene **71**. The key steps in these syntheses were the difluoroallylation of the aldehyde **72** and the (*E*)-selective Wittig reaction of the α,α-difluorinated ketone **74**. During the course of the work other approaches were evaluated including the difluoroallylation using more the complex difluoroalkene **55**. Attempts to complete a synthesis of a difluorinated macrocyclic analogue of a bryostatin could not be concluded because of issues that were encountered in the macrocyclisation of the seco-acid **95**.

The binding of the fluorinated compounds **83**, **84** and **86** with purified human PKCα were studied and very promising early data obtained based on comparative profiling with authentic bryostatin 1. It is hoped that this work will encourage other research workers to develop further analogues of bryostatins of the type presented in this paper with the objective of discovering relatively simple compounds that retain the potent biological activity of bryostatin.

Experimental

General experimental details

Flash column chromatography was performed using Merck silica gel (60H, 230-300 mesh). Base washed siica was prepared by stirring silica in saturated aqueous potassium hydrogen carbonate for 24 h then rinsing with deionised water until the washings were pH 7, followed by rigorous drying in an oven.

Light petroleum refers to the fraction boiling between 40 and 60 °C and was redistilled. Tetrahydrofuran was dried over sodium-benzophenone and was distilled under nitrogen. Dichloromethane was dried over CaH_2 and was distilled. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Mass spectra used electron impact ionisation (EI^+), chemical ionisation using ammonia (CI^+), electrospray ionisation in the positive mode (ES^+), atmospheric pressure chemical ionisation in the positive mode ($APCI^+$) and time of flight MS with electrospray ionisation (TOF ES^+). Low resolution mass spectra were recorded on a Waters SQD2 or on an Agilent 5975C Triple axis spectrometer. High resolution mass spectra were recorded using a Thermo Finnigan MAT95XP or on a Waters QTOF spectrometer. Infra-red spectra were measured using a Bruker Alpha P FTIR spectrometer on NaBr plates, either neat or as evaporated films. Nuclear magnetic resonance spectra were recorded using Bruker Avance 300, Bruker Ultrashield 400 or on Bruker Ultrashield 500 spectrometers at *ca.* 25 °C unless otherwise stated. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts are relative to tetramethylsilane. Residual non-deuteriated solvent was used as the internal standard.

Differential scanning fluorimetry (DSF) was performed with a StepOnePlus Real-Time PCR machine (Life Technologies) using Sypro-Orange dye (Invitrogen) and thermal ramping (0.3 °C in step intervals between 25 and 94°C). PKA catalytic subunit was

purified as described previously.[41] Purified PKC proteins were purchased from MRC-PPU Reagents and Services (University of Dundee), and were diluted to a final concentration of 5 µM in 50 mM Tris/HCl, pH 7.4 and 100 mM NaCl in the presence or absence of the indicated concentrations of ligand (final DMSO concentration was never higher than 4 % v/v). Normalized data were processed using the Boltzmann equation to generate sigmoidal denaturation curves, and these were plotted as previously described.[44] Staurosporine (S-9300), bryostatin 1 (B6697) and phorbol 12-myristate 13-acetate (PMA, P-1680) were all purchased from LC Laboratories and dissolved and diluted in DMSO prior to use.

3-(Benzothiazol-2-ylsulfanyl)-2,2-dimethylpropanal (8). Triphenylphosphine (18 g, 68 mmol) and 2-mercaptobenzothiazole (11.4 g, 68 mmol) was added to neopentyl glycol (10 g, 96 mmol) in THF (150 mL) and the solution cooled to 0 °C. Di-isopropyl azodicarboxylate (13.4 mL) in THF (200 mL) was added dropwise over 1 h and the solution stirred at 0 °C for 2 h and at rt for 16 h. Water (200 mL) was added followed by EtOAc (200 mL) and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic extracts were washed with aqueous NaOH (1 M, 100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:EtOAc) gave 3-(benzothiazol-2-ylsulfanyl)-2,2-dimethylpropanol (14.5 g, 84 %) as a colourless oil, R_f = 0.8 (EtOAc) (Found: Found: M^+ + H, 254.0667. $C_{12}H_{16}NOS_2$ requires M, 254.0668); δ_H (400 MHz, $CDCl_3$) 0.99 (6 H, s, 2 × 2-CH_3), 3.27 and 3.31 (each 2 H, s, 1-H_2 or 3-H_2), 5.10 (1 H, br. s, OH), 7.23 (1 H, td, *J* 8.0, 1.6, ArH), 7.35 (1 H, td, *J* 7.6, 1.6, ArH) and 7.66 and 7.73 (each 1 H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 24.2, 37.5, 42.1, 67.8, 120.9, 121.0, 124.6, 126.3, 134.8, 152.0 and 169.9; *m/z* (ES^+) 276 (M^+ + 23, 100%) and 254 (M^+ + 1, 32).

Dess-Martin periodinone (2.5 g, 5.9 mmol) was added to this alcohol (1.0 g, 3.95 mmol) in DCM (20 mL) and the mixture was stirred at rt for 16 h. Saturated aqueous sodium bisulfite (15 mL) and saturated sodium bicarbonate (15 mL) were added and the mixture stirred until gas evolution stopped. The aqueous layer was extracted with DCM (3 × 20 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (75:25 light petroleum:EtOAc) gave the *title compound* **8** (0.8 g, 81 %) as a yellow oil, R_f = 0.9 (EtOAc) (Found: M^+ + H, 252.0516. $C_{12}H_{14}NOS_2$ requires M, 252.0512); ν_{max}/cm^{-1} 2976, 1774, 1726, 1460, 1428, 1241, 1095, 1017 and 757; δ_H (400 MHz, $CDCl_3$) 1.18 (6 H, s, 2 × 2-CH_3), 3.58 (2 H, s, 3-H_2), 7.22 and 7.33 (each 1 H, t, *J* 8.0, ArH), 7.67 and 7.78 (each 1 H, d, *J* 8.0, ArH) and 9.57 (1 H, s, 1-H); δ_C (100 MHz, $CDCl_3$) 21.3, 31.0, 39.1, 121.1, 121.4, 124.4, 126.1, 135.3, 152.8, 166.7 and 203.7; *m/z* (ES^+) 274 (M^+ + 23, 100%) and 252 (M^+ + 1, 52).

3-(Benzyloxymethyloxy)-2,2-dimethylpropanal (9). Di-isopropylethylamine (3.9 mL, 22 mmol) and chloromethyl benzyl ether (2.0 mL, 14 mmol) were added to neopentyl glycol (3.0 g, 29 mmol) in DCM (30 mL) and the solution was stirred at rt for 16 h. Water (20 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (75:25 light petroleum:EtOAc) gave 3-benzyloxymethoxy-2,2-dimethylpropanol (2.5 g, 81 %) as a colourless oil, R_f = 0.35 (65:35 light petroleum:EtOAc) (Found: M^+ + Na, 247.1306. $C_{13}H_{20}O_3Na$ requires M, 247.1305); ν_{max}/cm^{-1} 3367, 3029, 2879, 1578, 1496, 1457, 1308, 1207, 1041, 1023, 908 and 735; δ_H (400 MHz, $CDCl_3$) 0.95 (6 H, s, 2 × 2-CH_3), 3.45 and 3.47 (each 2 H, s, 1-H_2 or 3-H_2), 4.62 (2 H, s, $PhCH_2$), 4.76 (2 H, s, OCH_2O) and 7.34-7.37 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 21.9, 36.1, 69.6, 71.1, 76.5, 91.6, 127.8, 128.5 and 137.6; *m/z* (ES^+) 247 (M^+ + 23, 100%).

Molecular sieves (7.0 g), NMO (1.65 g, 14 mmol) and TPAP (82 mg, 0.23 mmol) were added to this alcohol (2.1 g, 9.4 mmol) in DCM (20 mL) and acetonitrile (5 mL) and the mixture stirred at rt for 2 h and then filtered through a pad of silica that was washed with DCM (3 × 30 mL) and EtOAc (3 × 30 mL). The filtrate and washings were concentrated under reduced pressure and chromatography of the residue the gave *title compound* **9** (1.52 g, 73 %) as a colourless oil, R_f = 0.6 (65:35 light petroleum:EtOAc); ν_{max}/cm^{-1} 3032**,** 2936, 2877, 1703, 1474, 1455, 1157, 1109, 1044 and 738; δ_H (400 MHz, $CDCl_3$) 1.12 (6 H, s, 2 × CH_3), 3.61 (2 H, s, 3-H_2), 4.58 (2 H, s, $PhCH_2$), 4.74 (2 H, s, OCH_2O), 7.31-7.36 (5 H, m, ArH) and 9.56 (1 H, s, 1-H); δ_C (100 MHz, $CDCl_3$) 19.0, 46.8, 69.5, 72.7, 94.8, 127.8, 127.9, 128.4, 137.6 and 205.0; *m/z* (ES^+) 245 (M^+ + 23, 100%).

Ethyl 5-(2-benzothiazolylsulfanyl)-2,2-difluoro-3-hydroxy-4,4-dimethylpentanoate (12). Acid washed zinc powder (0.9 g, 14 mmol) and copper(I) chloride (cat.) were added to THF (10 mL) under nitrogen and the suspension stirred at rt for 30 min. Ethyl bromodifluoroacetate **11** (1.3 mL, 10 mmol) was added followed, after 10 min, by 3-(2-benzothiazolyl)sulfanyl-2,2-dimethylpropanal **8** (1.7 g, 6.8 mmol) in THF (5 mL). The mixture was stirred under reflux for 16 h then cooled to rt and diluted with EtOAc (20 mL). The black suspension was filtered through a plug of silica that was washed with ether (4 × 40 mL). The filtrate was concentrated under reduced pressure and chromatography of the residue (80:20 light petroleum:ether) gave the *title compound* **12** (2.11 g, 83%) as a yellow oil, R_f = 0.55 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 376.0843. $C_{16}H_{20}NO_3F_2S_2$ requires M, 376.0848); ν_{max}/cm^{-1} 3182, 2956, 1775, 1459, 1428, 1307, 1074, 1004 and 756; δ_H (400 MHz, $CDCl_3$) 0.97 (3 H, t, *J* 8.8, OCH_2CH_3), 1.15 (3 H, d, *J* 5.2, 4-CH_3), 1.23 (3 H, d, *J* 2.8, 4-CH_3), 2.69 and 3.91 (each 1 H, d, *J* 14.4, 5-H), 4.03 (1 H, t, *J* 6.0, 3-H), 4.20-4.06 (2 H, m, OCH_2), 6.66 (1 H, br. d, *J* 8.0, OH), 7.25 and 7.33 (each 1 H, td, *J* 7.5, 1.1, ArH) and 7.68-7.63 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.7, 18.8, 19.5, 36.1, 46.4, 62.5, 71.4 (t, $^2J_{C\text{-}F}$ 22), 117.5 (t, $^1J_{C\text{-}F}$ 251), 120.5, 121.2, 124.9, 126.5, 134.7, 151.6, 164.1 (t, $^2J_{C\text{-}F}$ 30) and 170.4; δ_F (376 MHz, $CDCl_3$) −122.42 and −103.68 (each d, $^2J_{F\text{-}F}$ 246.7); *m/z* (ES^+) 398 (M^+ + 23, 52%) and 376 (M^+ + 1, 100).

Ethyl 5-benzyloxymethoxy-2,2-difluoro-3-hydroxy-4,4-dimethylpentanoate (13). Following the procedure outlined for the synthesis of the hydroxyester **12,** zinc powder (60 mg, 0.9 mmol), copper(I) chloride, ethyl bromodifluoroacetate **11** (0.11

mL, 0.59 mmol) and 3-benzyloxymethoxy-2,2-dimethylpropanal **9** (0.1 g, 0.45 mmol), after heating under reflux for 36 h and chromatography (85:15 light petroleum:EtOAc), gave the *title compound* **13** (0.12 g, 75%) as a colourless oil, R_f = 0.6 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 369.1483. $C_{17}H_{24}O_5F_2Na$ requires M, 369.1485); ν_{max}/cm^{-1} 3458, 2942, 2884, 1759, 1455, 1308, 1045, 910 and 740; δ_H (500 MHz, $CDCl_3$) 1.09 and 1.22 (each 3 H, s, 4-CH_3), 1.37 (3 H, t, *J* 7.5, OCH_2CH_3), 3.40 and 3.83 (each 1 H, d, *J* 7.5, 5-H), 3.93-4.02 (2 H, m, 3-H, OH), 4.36 (2 H, q, *J* 6.2, OCH_2), 4.61 and 4.62 (each 1 H, d, *J* 12.5, PhHC*H*), 4.76 and 4.77 (each 1 H, d, *J* 7.5, OHC*H*O) and 7.33-7.39 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.0, 18.2, 21.0, 24.2, 62.9, 69.9, 76.5, 76.8, 94.8, 117.0 (t, $^1J_{C\text{-}F}$ 261), 127.9, 128.5, 137.3 and 164.0 (t, $^2J_{C\text{-}F}$ 30); δ_F (376 MHz, $CDCl_3$) −124.57 and −105.93 (each d, $^2J_{F\text{-}F}$ 255.7*)*; *m/z* (ES^+) 369 (M^+ + 23, 100%).

Ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-3-hydroxy-4,4-dimethylpentanoate (14). The procedure outlined for the synthesis of the hydroxyester **12** using zinc powder (0.61 g, 9.4 mmol), copper(I) chloride, ethyl bromodifluoroacetate **11** (0.8 mL, 6.1 mmol) and 3-*tert*-butyldiphenylsilyloxy-2,2-dimethylpropanal **10** (1.6 g, 4.7 mmol), after heating under reflux for 36 h, an aqueous extraction using ether (15 mL), water (10 mL) and aqueous hydrogen chloride (1 M, 10 mL), and with extraction of the aqueous layer using ether (3 × 15 mL), gave, after chromatography (90:10 light petroleum:EtOAc), the *title compound* **14** (0.7 g, 78%) as a colourless oil, R_f = 0.7 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 487.2089. $C_{25}H_{34}O_4F_2SiNa$ requires M, 487.2087); ν_{max}/cm^{-1} 3445, 2931, 2858, 1761, 1724, 1428, 1305, 1110, 1071, 820 and 739; δ_H (400 MHz, $CDCl_3$) 1.10 [15 H, s, 2 × 4-CH_3, $SiC(CH_3)_3$], 1.39 (3 H, t, *J* 6.0, OCH_2CH_3), 3.40 and 3.89 (each 1 H, d, *J* 12.0, 5-H), 4.10 (1 H, d, *J* 24.0, 3-H), 4.39 (2 H, q, *J* 8.0, OCH_2), 7.38-7.44 (6 H, m, ArH) and 7.70-7.76 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.9, 19.1, 23.8, 26.5, 26.8, 29.7, 38.0, 62.8, 73.4, 117.0 (t, $^1J_{C\text{-}F}$ 258.0), 127.7, 127.8, 129.6, 130.0, 132.1, 134.8, 135.6, 135.7 and 164.1 (t, $^2J_{C\text{-}F}$ 31.5); *m/z* (ES^+) 487 (M^+ + 23, 100%).

Ethyl 5-(2-benzothiazolyl)sulfanyl-2,2-difluoro-4,4-dimethyl-3-triethylsilyloxypentanoate (15). 2,6-Lutidine (1.3 mL, 11 mmol) and triethylsilyl triflate (1.9 mL, 8.4 mmol) were added to the hydroxyester **12** (2.1 g, 5.6 mmol) in DCM (20 mL) at 0 °C and the mixture stirred at rt for 24 h. Water (20 mL) was added and the aqueous layer was extracted with DCM (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (80:20 light petroleum:EtOAc) gave the *title compound* **15** (2.05 g, 75%) as a yellow oil, R_f = 0.65 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 490.1717. $C_{22}H_{34}NO_3F_2S_2Si$ requires M, 490.1712); ν_{max}/cm^{-1} 2955, 1758, 1459, 1427, 1307, 1082, 994, 830 and 726; δ_H (400 MHz, $CDCl_3$) 0.61-0.66 (6 H, m, 3 × $SiCH_2$), 0.93 (9 H, t, *J* 7.6, 3 × CH_2CH_3), 1.05 and 1.08 (each 3 H, s, 4-CH_3), 1.30 (3 H, t, *J* 6.8, OCH_2CH_3), 3.38 and 3.47 (each 1 H, d, *J* 10.0, 5-H), 4.13 (1 H, m, 3-H), 4.26 (2 H, q, *J* 6.8, OCH_2CH_3), 7.22 (1 H, t, *J* 8.4, ArH), 7.34 (1 H, t, *J* 7.6, ArH), 7.67 (1 H, d, *J* 8.0, ArH) and 7.77 (1 H, d, *J* 8.4, ArH); δ_C (125 MHz, $CDCl_3$) 5.4, 6.9, 13.9, 22.7, 23.3, 39.5, 42.8, 63.1, 76.8, 115.2 (t, $^1J_{C\text{-}F}$ 255.0), 121.0, 121.5, 124.2, 125.9, 135.2, 153.2, 164.2 (t, $^2J_{C\text{-}F}$ 33.2) and 167.3; δ_F (376 MHz, $CDCl_3$) −111.42 and −105.89 (each d, $^2J_{F\text{-}F}$ 263.2*)*; *m/z* (ES^+) 512 (M^+ + 23, 100%) and 490 (M^+ + 1, 61).

Ethyl 5-benzyloxymethoxy-2,2-difluoro-4,4-dimethyl-3-triethylsilyloxypentanoate (16). Following the procedure outlined for the preparation of the silyl ether **15**, the hydroxyester **13** (0.2 g, 0.58 mmol), 2,6-lutidine (0.2 mL, 1.7 mmol) and triethylsilyl triflate (0.2 mL, 0.87 mmol) with stirring for 10 d, after chromatography (85:15 light petroleum:EtOAc) gave the *title compound* **16** (0.24 g, 85%) as a colourless oil, R_f = 0.75 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 483.2337. $C_{23}H_{38}O_5F_2SiNa$ requires M, 483.2349); ν_{max}/cm^{-1} 2972, 2878, 1760, 1455, 1379, 1306, 1086, 1046, 879, 834 and 732; δ_H (500 MHz, $CDCl_3$) 0.65-0.69 (6 H, m, 3 × $SiCH_2$), 0.92-1.03 [15 H, m, 2 × 4-CH_3, 3 × $SiCH_2CH_3$), 1.37 (3 H, t, *J* 7.5, OCH_2CH_3), 3.31 and 3.44 (each 1 H, d, *J* 10.0, 5-H), 4.24-4.34 (3 H, m, 3-H, OCH_2), 4.58 and 4.62 (each 1 H, d, *J* 10.0, PhHC*H*), 4.73 and 4.75 (each 1 H, d, *J* 5.0, OHC*H*O) and 7.32-7.37 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 5.1, 6.8, 13.8, 18.0, 20.5, 21.2, 38.9, 62.7, 69.3, 74.7, 75.1, 94.7, 115.7 (t, $^1J_{C\text{-}F}$ 261), 127.7, 127.8, 128.4, 137.8 and 164.4 (t, $^2J_{C\text{-}F}$ 30); δ_F (376 MHz) −111.35 and −106.22 (each d, $^1J_{F\text{-}F}$ 263.2*)*; *m/z* (ES^+) 483 (M^+ + 23, 75%) and 369 (100).

Ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-4,4-dimethyl-3-triethylsilyloxypentanoate (17). Following the procedure outlined for the preparation of the silyl ether **15**, the hydroxyester **14** (0.2 g, 0.43 mmol), 2,6-lutidine (0.12 mL, 1.0 mmol) and triethylsilyl triflate (0.2 mL, 0.86 mmol) with stirring for 10 days, after chromatography (85:15 light petroleum:EtOAc) gave the *title compound* **17** (0.23 g, 94%) as a colourless oil, R_f = 0.8 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 601.2957. $C_{31}H_{48}O_4F_2Si_2Na$ requires M, 601.2952); ν_{max}/cm^{-1} 2886, 1670, 1432, 1243 and 1032; δ_H (400 MHz, $CDCl_3$) 0.50-0.62 (6 H, m, 3 × $SiCH_2$), 0.88-0.97 (9 H, m, 3 × $SiCH_2CH_3$), 1.07-1.10 [15 H, s, 2 × 4-CH_3, $SiC(CH_3)_3$], 1.34 (3 H, t, *J* 7.0, OCH_2CH_3), 3.30 and 3.50 (each 1 H, d, *J* 12.0, 5-H), 4.27-4.39 (3 H, m, 3-H, OCH_2), 7.38-7.45 (6 H, m, ArH) and 7.64-7.67 (4 H, m, ArH); *m/z* (ES^+) 601 (M^+ + 23, 10%), 565 (50) and 487 (100).

6-(2-Benzothiazolyl)sulfanyl-3,3-difluoro-5,5-dimethyl-4-triethylsilyloxyhexan-2-one (18). Methyllithium (1.0 M, 4.0 mL, 4.0 mmol) was added to the ester **15** (1.3 g, 2.66 mmol) in THF (30 mL) at −78 °C and the solution was stirred at −78 °C for 5.5 h. Water (20 mL) was added followed by ether (20 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:EtOAc) gave the *title compound* **18** (0.93 g, 77%) as a yellow oil, R_f = 0.7 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 460.1617. $C_{21}H_{32}NO_2F_2S_2Si$ requires M, 460.1607); δ_H (400 MHz, $CDCl_3$) 0.61-0.67 (6 H, m, 3 × $SiCH_2$), 0.93 (9 H, t, *J* 8.4, 3 × $SiCH_2CH_3$), 1.03 and 1.05 (each 3 H, s, 5-CH_3), 2.32 (3 H, t, *J* 1.8, 1-H_3), 3.49 and 3.53 (each 1 H, d, *J* 12.0, 6-H), 4.14 (1 H, t, *J* 12.8, 4-H), 7.21 (1 H, td, *J* 8.4, 1.2, ArH), 7.33 (1 H, td, *J* 7.8, 1.2, ArH), 7.67 (1 H, d, *J* 7.8, ArH) and 7.77 (1 H, d, *J* 8.0, ArH); δ_C (100 MHz, $CDCl_3$) 5.1, 6.9, 23.1, 23.5, 26.2, 31.0, 39.4, 42.7, 76.6,

116.9, 121.0, 121.4, 124.2 126.0, 135.3, 153.1, 167.3 and 199.6 (d, $^2J_{C\text{-}F}$ 30); δ_F (376 MHz, $CDCl_3$) −110.73 and −107.56 (each d, $^2J_{F\text{-}F}$ 270.7); *m/z* (ES^+) 482 (M^+ + 23, 100%) and 460 (M^+ + 1, 55).

Methyllithium (1.0 M, 0.07 mL, 0.7 mmol) was added to the ester **15** (0.13 g, 0.27 mmol) in THF (2 mL) at 0 °C and the solution was stirred at rt for 1.5 h. Water (10 mL) was added followed by ether (10 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (80:20 light petroleum:ether) gave 6-(2-benzothiazolyl)sulfanyl-3,3-difluoro-4-triethylsilyloxy-2,5,5-trimethylhexan-2-ol (86 mg, 72%) as a colourless oil, R_f = 0.5 (70:30 light petroleum:EtOAc) (Found: M^+ + H, 476.1922. $C_{22}H_{36}NO_2F_2S_2Si$ requires M, 476.1920); ν_{max}/cm^{-1} 3452, 2954, 1536, 1458, 1428, 1238, 1159, 1070, 1003 and 740; δ_H (500 MHz, $CDCl_3$) 0.44-0.46 (6 H, m, 3 × $SiCH_2$), 0.74 (9 H, t, *J* 10.0, 3 × CH_2CH_3), 1.14 and 1.19 (each 3 H, s, 5-CH_3), 1.28 and 1.31 (each 3 H, s, 1-H_3 or 2-CH_3), 3.01 and 3.86 (each 1 H, d, *J* 15.0, 6-H), 4.15 (1 H, dd, *J* 20.0, 5.0, 4-H), 5.56 (1 H, d, *J* 5.0, OH), 7.22 and 7.34 (each 1 H, t, *J* 10.0, ArH) and 7.66 and 7.73 (each 1 H, d, *J* 10.0, ArH); δ_F (376 MHz, $CDCl_3$) −124.40 and −113.61 (each d, $^2J_{F\text{-}F}$ 225.6); *m/z* (ES^+) 476 (M^+ + 1, 100%).

6-Benzyloxymethyloxy-3,3-difluoro-5,5-dimethyl-4-triethylsilyloxyhexan-2-one (19). Following the procedure outlined for the synthesis of the ketone **18**, the ester **16** (50 mg, 0.11 mmol) in THF (2 mL) and methyllithium (1.0 M, 0.16 mL, 0.16 mmol), after chromatography (90:10 light petroleum: EtOAc) gave the *title compound* **19** (44 mg, 86%) as a yellow oil, R_f = 0.7 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 453.2245. $C_{22}H_{36}O_4F_2SiNa$ requires M, 453.2244); ν_{max}/cm^{-1} 2993, 2864, 1783, 1432, 1304, 1048, 1032 and 728; δ_H (400 MHz, $CDCl_3$) 0.53-0.82 (6 H, m, 3 × $SiCH_2$), 0.93-1.03 (15 H, m, 2 × 5-CH_3, 3 × CH_2CH_3), 2.36 (3 H, s, 1-H_3), 3.34 and 3.37 (each 1 H, d, *J* 8.0, 6-H), 4.26 (1 H, m, 4-H), 4.56 and 4.62 (each 1 H, d *J* 12.0, PhHC*H*), 4.70 and 4.72 (each 1 H, d *J* 8.0, OHC*H*O) and 7.27-7.38 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 5.0, 6.8, 17.9, 20.9, 21.6, 26.0, 38.8, 69.4, 74.2, 74.8 (t, $^2J_{C\text{-}F}$ 24), 94.5, 117.1 (t, $^1J_{C\text{-}F}$ 257.0), 127.7, 127.8, 128.4, 137.7 and 199.4 (t, $^2J_{C\text{-}F}$ 30.5); δ_F (376 MHz, $CDCl_3$) −109.85 and −108.48 (each d, $^2J_{F\text{-}F}$, 270.7); *m/z* (ES^+) 453 (M^+ + 23, 100%).

6-*tert*-Butyldiphenylsilyloxy-3,3-difluoro-5,5-dimethyl-4-triethylsilyloxyhexan-2-one (20). Following the procedure outlined for the synthesis of the ketone **18,** the ester **17** (0.5 g, 0.8 mmol) in THF (20 mL) and methyllithium (1.0 M, 1.3 mL, 1.3 mmol), after chromatography (90:10 light petroleum: EtOAc) gave the *title compound* **20** (0.22 g, 55%) as a colourless oil, R_f = 0.8 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 571.2854. $C_{30}H_{46}O_3F_2Si_2Na$ requires M, 571.2846); ν_{max}/cm^{-1} 2980, 1724, 1423, 1201 and 1109; δ_H (500 MHz, $CDCl_3$) 0.55-0.65 (6 H, m, 3 × $SiCH_2$), 0.92 (9 H, t, *J* 6.0, 3 × $SiCH_2CH_3$), 1.09 (3 H, s, 5-CH_3), 1.12 [9 H, s, $SiC(CH_3)_3$], 1.28 (3 H, s, 5-CH_3), 2.34 (3 H, s, 1-H_3), 3.35 and 3.48 (each 1 H, d, *J* 10.0, 6-H), 4.35 (1 H, t, *J* 10.0, 4-H), 7.37-7.44 (6 H, m, ArH) and 7.66-7.68 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 6.5, 6.9, 19.2, 19.4, 20.9, 26.2, 26.9, 40.1, 70.0, 74.3 (t, $^2J_{C\text{-}F}$ 32), 127.4, 127.6, 134.3, 134.4, 135.1, 135.5, 135.8, 135.9 and 199.8 (t, $^2J_{C\text{-}F}$ 30); *m/z* (ES^+) 571 (M^+ + 23, 100%).

6-Benzyloxymethoxy-3,3-difluoro-4-triethylsilyloxy-2,5,5-trimethylhex-1-ene (21). Potassium hexamethyldisilazide (1.0 M in THF, 0.5 mL, 0.5 mmol) was added to methyl(triphenyl)phosphonium bromide (0.2 g, 0.56 mmol) in toluene (2 mL) at 0 °C and the solution was stirred for 30 min. The ketone **19** (80 mg, 0.19 mmol) in toluene (1 mL) was added and the mixture was stirred at rt for 48 h. Water (2 mL) was added followed by EtOAc (5 mL) and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:ether) gave the *title compound* **21** (60 mg, 75%) as a colourless oil, R_f = 0.9 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 451.2458. $C_{23}H_{38}O_3F_2SiNa$ requires M, 451.2451); ν_{max}/cm^{-1} 2954, 2877, 1455, 1379, 1239, 1159, 1105, 1047, 1025, 1002, 921, 833 and 729; δ_H (500 MHz, $CDCl_3$) 0.65-0.71 (6 H, m, 3 × $SiCH_2$), 0.96-1.03 (15 H, m, 2 × 5-CH_3, 3 × CH_2CH_3), 1.91 (3 H, s, 2-CH_3), 3.31 and 3.41 (each 1 H, d, *J* 10.0, 6-H), 4.05 (1 H, t, *J* 12.0, 4-H), 4.57 and 4.64 (each 1 H, d, *J* 10.0, PhHC*H*), 4.74 and 4.75 (each H, d, *J* 7.0, OHC*H*O), 5.15 and 5.40 (each 1 H, s, 1-H) and 7.28-7.37 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 5.0, 7.0, 19.1, 20.6, 21.1, 30.3, 38.8, 69.3, 75.0, 76.6 (t, $^2J_{C\text{-}F}$ 24.0), 94.7, 116.2 (t, $^3J_{C\text{-}F}$ 9.0), 121.3 (t, $^1J_{C\text{-}F}$ 245.6), 127.7, 127.8, 128.4, 137.9 and 140.6 (t, $^2J_{C\text{-}F}$ 24.0); δ_F (376 MHz, $CDCl_3$) −98.90 and −98.69 (each d, $^2J_{F\text{-}F}$ 244); *m/z* (ES^+) 451 (M^+ + 23, 100%).

6-*tert*-Butyldiphenylsilyloxy-3,3-difluoro-4-triethylsilyloxy-2,5,5-trimethylhex-1-ene (22). Following the procedure outlined for the synthesis of the alkene **21,** methyl(triphenyl)phosphonium bromide (0.16 g, 0.45 mmol) in toluene (2 mL), potassium hexamethyldisilazide (1.0 M in THF, 0.41 mL, 0.41 mmol) and the ketone **20** (84 mg, 0.15 mmol) in toluene (1 mL), after chromatography (90:10 light petroleum:EtOAc) gave the *title compound* **22** (61 mg, 73%) as a colourless oil, R_f = 0.9 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 569.3050. $C_{31}H_{48}O_2F_2Si_2Na$ requires M, 569.3054); ν_{max}/cm^{-1} 2955, 1466, 1107 and 826; δ_H (400 MHz, $CDCl_3$) 0.55-0.67 (6 H, m, 3 × $SiCH_2$), 0.92-0.98 (9 H, m, 3 × $SiCH_2CH_3$), 1.11 (3 H, s, 5-CH_3), 1.13 [9 H, s, $SiC(CH_3)_3$], 1.30 (3 H, s, 5-CH_3), 1.89 (3 H, s, 2-CH_3), 3.40 and 3.51 (each 1 H, d, *J* 8.0, 6-H), 4.09 (1 H, t, *J* 8.0, 4-H), 5.08 and 5.33 (each 1 H, s, 1-H), 7.35-7.48 (6 H, m, ArH) and 7.68-7.73 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 6.9, 7.0, 19.1, 19.3, 20.5, 26.9, 40.3, 70.2, 72.9, 74.1, 116.1, 121.2 (t, $^2J_{C\text{-}F}$ 23), 127.4, 128.6, 129.6, 132.0, 135.7, 137.3 and 140.6; δ_F (376 MHz, $CDCl_3$) −98.9 and −98.2 (t, $^2J_{F\text{-}F}$ 248*J*; *m/z* (ES^+) 569 (M^+ + 23, 20%) and 293 (100).

2-Bromomethyl-6-*tert*-butyldiphenylsilyloxy-3,3-difluoro-4-triethylsilyloxy-5,5-dimethylhex-1-ene (23). *N*-Bromosuccinimide (12 mg, 0.065 mmol) was added to the alkene **22** (30 mg, 0.055 mmol) in chloroform (1 mL). The suspension was exposed to UV light for 10 min and then heated under reflux for 24 h. After cooling to rt, the mixture was concentrated under reduced pressure. Chromatography of the

residue (90:10 light petroleum:EtOAc) gave the *title compound* **23** (25 mg, 72%) as a colourless oil, R_f = 0.9 (70:30 light petroleum:EtOAc) (Found: M^+ + Na, 647.2169. $C_{31}H_{47}O_2{}^{79}BrF_2Si_2Na$ requires M, 647.2159; Found: M^+ + Na, 649.1790. $C_{31}H_{47}O_2{}^{81}BrF_2Si_2Na$ requires M, 649.2159); ν_{max}/cm^{-1} 2956, 2876, 1471, 1428, 1107, 1078, 1006, 822, 739 and 700; δ_H (400 MHz, $CDCl_3$) 0.57-0.64 (6 H, m, 3 × $SiCH_2$), 0.88-0.96 (9 H, m, 3 × $SiCH_2CH_3$], 1.08 [9 H, s, $SiC(CH_3)_3$], 1.11 and 1.27 (each 3 H, s, 5-CH_3), 3.32-3.49 (2 H, m, 6-H_2), 4.06-4.11 (3 H, m, 4-H, 2-CH_2), 5.67-5.70 (2 H, m, 1-H_2), 7.38-7.45 (6 H, m, ArH) and 7.64-7.72 (4 H, m, ArH); δ_F (376 MHz, $CDCl_3$) −98.96 and −91.89 (each d, $^2J_{F\text{-}F}$ 256); *m/z* (ES^+) 649 (M^+ + 23, 20%), 647 (M^+ + 23, 5) and 258 (100).

2-Iodo-4-*tert*-butyldimethylsilyloxyhex-1-ene (29). Trimethylsilyl chloride (0.52 mL, 4.0 mmol) and water (0.037 mL, 2.0 mmol) were added to sodium iodide (0.62 g, 4.0 mmol) in acetonitrile (4 mL) and the yellow suspension was stirred at rt for 20 min. Hex-5-yn-3-ol **27** (0.2 mL, 1.8 mmol) in acetonitrile (1 mL) was added dropwise and the mixture stirred for 4 h. Water (5 mL) was added and the mixture was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to 90:10 light petroleum:EtOAc) gave 5-iodohex-5-en-3-ol **28** (0.33 g, 80%) as a colourless oil, R_f = 0.55 (70:30 light petroleum:EtOAc); ν_{max}/cm^{-1} 3402, 2964, 2933, 1710, 1617, 1461, 1205, 1113, 1021, 979 and 899; δ_H (400 MHz, $CDCl_3$) 1.00 (3 H, t, *J* 8.0, 1-H_3), 1.56 (2 H, m, 2-H_2), 1.63 (1 H, br. s, OH), 2.46 (1 H, dd, *J* 12.0, 8.0, 4-H), 2.56 (1 H, dd, *J* 12.0, 3.0, 4-H'), 3.82 (1 H, m, 3-H) and 5.86 and 6.18 (each 1 H, s, 6-H); δ_C (100 MHz, $CDCl_3$) 9.9, 28.9, 52.4, 71.3, 107.7 and 128.7.

Imidazole (0.21 g, 3.1 mmol) and *tert*-butyldimethylsilyl chloride (0.26 g, 1.7 mmol) were added to 5-iodohex-5-en-3-ol **28** (0.32 g, 1.4 mmol) in DCM (10 mL) and the solution stirred at rt for 24 h. Water (10 mL) was added, the aqueous layer was extracted with DCM (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (90:10 light petroleum:EtOAc) gave the *title compound* **29** (0.36 g, 75%) as a pale yellow oil, R_f = 0.6 (70:30 light petroleum:EtOAc); ν_{max}/cm^{-1} 2956, 2928, 2856, 1618, 1462, 1361, 1252, 1101, 1033, 894, 835 and 774; δ_H (300 MHz, $CDCl_3$) 0.09 and 0.10 (each 3 H, s, $SiCH_3$), 0.87-0.90 [12 H, m, 6-H_3, $SiC(CH_3)_3$], 1.44-1.56 (2 H, m, 5-H_2), 2.47-2.51 (2 H, m, 3-H_2), 3.86 (1 H, m, 4-H) and 5.74 and 6.07 (each 1 H, s, 1-H); δ_C (100 MHz, $CDCl_3$) −4.6, −4.4, 9.2, 18.1, 25.8, 29.1, 52.4, 71.8, 108.7 and 127.8.

Ethyl 5-*tert*-butyldimethylsilyloxy-2,2-difluoro-3-methyleneheptanoate (30). Copper powder (65 mg, 1.02 mmol) was added to a vigorously stirred solution of ethyl 2-iodo-2,2-difluoroacetate **25** (0.025 mL, 0.170 mmol) in anhydrous DMSO (0.20 mL). After 3 h, the alkenyl iodide **29** (19 mg, 0.057 mmol) in anhydrous DMSO (0.20 mL) was added and the mixture stirred 1.25 h. A mixture of ice and saturated aqueous ammonium chloride (1:1, 10 mL) was added followed by ether (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the organic extracts were filtered through Celite® using ether (20 mL). The filtrate was washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using base-washed silica (0.5:99.5 to 1:99 ether:light petroleum) gave the *title compound* **30** (8 mg, 0.024 mmol, 8%) as a colourless oil, R_f = 0.27 (1:99 ether:light petroleum) (Found: M^+ + H, 337.2005. $C_{16}H_{31}O_3F_2Si$ requires M, 337.2005); ν_{max}/cm^{-1} 2958, 2929, 2857, 1768, 1464, 1372, 1292, 1255, 1077, 1006, 837 and 775; δ_H (500 MHz, $CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.90 (3 H, t, *J* 7.0, 7-H_3), 1.35 (3 H, t, *J* 7.0, OCH_2CH_3), 1.40-1.56 (2 H, m, 6-H_2), 2.31 (2 H, d, *J* 6.2, 4-H_2), 3.80 (1 H, pent, *J* 6.2, 5-H), 4.33 (2 H, q, *J* 7.0, OCH_2) and 5.40 and 5.60 (each 1 H, t, *J* 1.9, 3-CH); δ_C (125 MHz, $CDCl_3$) −4.6, −4.5, 9.2, 13.9, 18.0, 25.9, 29.4, 37.7, 63.0, 71.5, 114.0 (t, $^1J_{C\text{-}F}$ 252.1), 120.5 (t, $^3J_{C\text{-}F}$ 8.2), 137.7 (t, $^2J_{C\text{-}F}$ 22.8) and 163.9 (t, $^2J_{C\text{-}F}$ 34.6); δ_F (471 MHz, $CDCl_3$) −106.99 and −105.25 (both d, $J_{F\text{-}F}$ 253.4); *m/e* (ES^+) 359.2 (M^+ + 23, 50%) and 210.2 (100). This capricious reaction required copper powder that was very fine, bronze-pink in colour and extremely lustrous, anhydrous solvent and vigorous stirring, to generate the active copper-reagent species.

This procedure gave ethyl (*E*)-2,2-difluoro-5-*tert*-butyldimethylsilyloxy-3-(*tert*-butyldimethylsilyloxymethyl)pent-3-enoate **33** (3 mg, 0.007 mmol, 12%) as a colourless oil (Found: M^+ + H, 439.2510. $C_{20}H_{41}O_4F_2Si_2$ requires M, 439.2511); ν_{max}/cm^{-1} 2954, 2931, 2886, 2858, 1769, 1472, 1255, 1095, 836 and 778; δ_H (400 MHz, $CDCl_3$) 0.07 and 0.09 (each 6 H, s, 2 × $SiCH_3$), 0.89 and 0.91 [each 9 H, s, $SiC(CH_3)_3$], 1.34 (3 H, t, *J* 7.3, OCH_2CH_3), 4.29 (2 H, s, 3-CH_2), 4.29 (2 H, q, *J* 7.3, OCH_2CH_3), 4.39-4.42 (2 H, m, 5-H_2) and 6.39 (1 H, t, *J* 6.3, 4-H); δ_C (100 MHz, $CDCl_3$) −5.7, −5.3, 13.9, 18.3(2), 25.8, 25.9, 57.4, 59.7, 62.7, 113.0 (t, $^1J_{C\text{-}F}$ 251.1), 130.6 (t, $^2J_{C\text{-}F}$ 21.4), 135.6 (t, $^3J_{C\text{-}F}$ 8.8) and 163.6 (t, $^2J_{C\text{-}F}$ 34.6); δ_F (377 MHz, $CDCl_3$) −106.47; *m/z* (ES^+) 461.3 (M^+ + 23, 100%).

This procedure gave ethyl (*E*)-2,2-difluoro-5-*tert*-butyldiphenylsilyloxy-3-(*tert*-butyldiphenylsilyloxymethyl)pent-3-enoate **34** (4 mg, 0.006 mmol, 14%) as a colourless oil, R_f = 0.39 (5:95 ether:light petroleum); ν_{max}/cm^{-1} 3072, 2957, 2930, 2857, 1769, 1472, 1428, 1290, 1112, 1022, 844, 740 and 702; δ_H (400 MHz, $CDCl_3$) 0.92 and 1.01 [each 9 H, s, $SiC(CH_3)_3$], 1.29 (3 H, t, *J* 7.0, OCH_2CH_3), 4.02 (2 H, s, 3-CH_2), 4.21-4.28 (4 H, m, 5-H_2, OCH_2CH_3), 6.32 (1 H, t, *J* 5.6, 4-H), 7.26-7.44 (12 H, m, ArH) and 7.53 and 7.59 (each 4 H, dd, *J* 8.0, 1.5, ArH); δ_F (377 MHz, $CDCl_3$) −105.74; *m/z* (ES^+) 704.5 (M^+ + 18, 100%).

1-*tert*-Butyldiphenylsilyloxy-4,4-difluorohex-5-en-3-ol (40). 3-Bromo-3,3-difluoroprop-1-ene **37** (0.5 g, 3.18 mmol) was added to a vigorously stirred suspension of indium powder (0.37 g, 3.18 mmol) in deionised water (6.3 mL) and the mixture was stirred for 10 min. The aldehyde **39** (0.70 g, 2.23 mmol) in THF (4.40 mL) was added and the mixture stirred for 5 h. Aqueous hydrogen chloride (10%, 50 mL) and EtOAc (50 mL) were added and the aqueous phase was extracted with EtOAc (3 × 50 mL). The organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum) gave the *title compound* **40** (0.84 g, 2.16 mmol, 97%) as a colourless oil, R_f = 0.78 (50:50 ether:light petroleum) (Found: M^+

+ Na, 413.1715. $C_{22}H_{28}O_2F_2SiNa$ requires M, 413.1724); ν_{max}/cm^{-1} 3435, 3071, 2958, 2931, 2889, 2857, 1472, 1427, 1111, 822, 738 and 701; δ_H (500 MHz, $CDCl_3$) 1.12 [9 H, s, $SiC(CH_3)_3$], 1.81 and 1.92 (each 1 H, m, 2-H), 3.21 (1 H, br. s, OH), 3.92 and 4.00 (each 1 H, m, 1-H), 4.16 (1 H, q, *J* 10.1, 3-H), 5.57 (1 H, d, *J* 11.0, 6-H), 5.77 (1 H, d, *J* 17.4, 6-H'), 6.08 (1 H, m, 5-H), 7.40-7.51 (6 H, m, ArH) and 7.70-7.79 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 19.0, 26.8, 31.8, 62.0, 72.6 (t, $^2J_{C\text{-}F}$ 30.0), 119.8 (t, $^1J_{C\text{-}F}$ 243.9), 120.8 (t, $^3J_{C\text{-}F}$ 10.0), 127.8, 129.9, 130.1 (t, $^2J_{C\text{-}F}$ 25.5), 132.8, 132.9 and 135.5; δ_F (470 MHz, $CDCl_3$) −113.58 (d, $^2J_{F\text{-}F}$ 247.6) and −108.24 (d, $^2J_{F\text{-}F}$ 249.4); *m/z* (ES^+) 413.2 (M^+ + 23, 100%).

1,3-Bis(*tert*-butyldiphenylsilyloxy)-4,4-difluorohex-5-ene (41). 3-Bromo-3,3-difluoroprop-1-ene **37** (0.177 mL, 1.74 mmol) was added to a vigorously stirred suspension of indium powder (0.2 g, 1.74 mmol) and lithium iodide (0.23 g, 1.74 mmol) in deionised water (3.46 mL) and the mixture stirred for 10 min. The aldehyde **39** (0.27 g, 0.867 mmol) in THF (1.73 mL) was added and the reaction mixture stirred for 72 h. Aqueous hydrogen chloride (10%, 30 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil (0.375 g) that was azeotroped with benzene before being taken into DCM (6.0 mL). Imidazole (0.142 g, 2.08 mmol) and *tert*-butyldiphenylsilyl chloride (0.27 mL, 1.04 mmol) were added at 0 °C and the reaction mixture was stirred at rt for 48 h. Saturated aqueous ammonium chloride (30 mL) and DCM (30 mL) were added and the aqueous phase was extracted into DCM (3 × 30 mL). The organic extracts were washed with brine (120 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 ether:light petroleum) gave the *title compound* **41** (0.39 g, 0.622 mmol, 72%) as a colourless oil, R_f = 0.15 (1:99 ether:light petroleum) (Found: M^+ + Na, 651.2896. $C_{38}H_{46}O_2F_2Si_2Na$ requires M, 651.2897); ν_{max}/cm^{-1} 3072, 2959, 2931, 2887, 2858, 1473, 1428, 1112, 822, 740 and 701; δ_H (400 MHz, $CDCl_3$) 0.93 and 1.03 [each 9 H, s, $SiC(CH_3)_3$], 1.72-1.86 (2 H, m, 2-H_2), 3.46 and 3.53 (each 1 H, m, 1-H), 4.03 (1 H, m, 3-H), 5.47 (1 H, d, *J* 11.1, 6-H), 5.61 (1 H, d, *J* 17.4, 6-H'), 5.98 (1 H, m, 5-H), 7.29-7.35 and 7.36-7.44 (each 6 H, m, ArH) and 7.45-7.51 and 7.61-7.66 (each 4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 18.7, 19.3, 26.4, 26.6, 35.1, 59.9, 71.8 (dd, $^2J_{C\text{-}F}$ 32.4, 26.9), 119.9 (t, $^1J_{C\text{-}F}$ 244.6), 120.4 (t, $^3J_{C\text{-}F}$ 9.3), 127.2(2), 129.1, 129.2, 129.3, 129.4, 129.7 (t, $^2J_{C\text{-}F}$ 26.0), 132.0, 133.2, 133.3(2), 135.1, 135.2, 135.6 and 135.8; δ_F (377 MHz, $CDCl_3$) −109.55 and −103.70 (both d, $^2J_{F\text{-}F}$ 247.3); *m/z* (ES^+) 651.4 (M^+ + 23, 100%).

Methyl 2,2-difluoro-3,5-bis(*tert*-butyldiphenylsilyloxy)pentanoate (42). A stream of ozone was bubbled through a solution of alkene **41** (0.34 g, 0.54 mmol) in dry DCM (6.55 mL) at −78 °C for 5 min until a blue colour persisted. The system was purged with oxygen for 10 min, dimethyl sulfide (0.20 mL, 2.72 mmol) was added and the mixture was stirred at rt for 3.5 h. After concentration under reduced pressure, the residue was dissolved in ^{t}BuOH (9.5 mL) and 2-methylbut-2-ene (2 M in THF, 0.63 mL) was added followed by a solution of sodium chlorite (0.295 g, 3.26 mmol) and $Na_2H_2PO_4.2H_2O$ (0.85 g, 5.44 mmol) in distilled water (4.85 mL). After stirring for 16 h, brine (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give an oil (0.39 g), R_f = 0.15 (1:10 ether:light petroleum). The oil was dissolved in anhydrous toluene (4.4 mL) and methanol (1.1 mL) and trimethylsilyl diazomethane (2 M in hexanes, 0.33 mL, 0.66 mmol) was added dropwise before stirring for 48 h. After concentration under reduced pressure, chromatography of the residue (0.5:99.5 to 1:99 ether:light petroleum) gave the *title compound* **42** (0.29 g, 0.436 mmol, 80%) as a colourless oil, R_f = 0.40 (10:90 ether:light petroleum) (Found: M^+ + NH_4, 678.3253. $C_{38}H_{50}NO_4F_2Si_2$ requires M, 678.3241); ν_{max}/cm^{-1} 2957, 2932, 2858, 1764, 1473, 1427, 1105, 821 and 734; δ_H (400 MHz, $CDCl_3$) 0.93 and 1.01 [each 9 H, s, $SiC(CH_3)_3$], 1.89 and 1.96 (each 1 H, dq, *J* 13.0, 6.5, 4-H), 3.42 and 3.51 (each 1 H, dt, *J* 10.5, 6.5, 5-H), 3.77 (3 H, s, OCH_3), 4.40 (1 H, m, 3-H), 7.29-7.44 (12 H, m, ArH) and 7.45-7.50 and 7.61-7.68 (each 4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 19.0, 19.4, 26.7(2), 34.5, 53.0, 59.8, 70.7 (t, $^2J_{C\text{-}F}$ 25.5), 115.2 (t, $^1J_{C\text{-}F}$ 253.9), 127.5, 127.7, 129.5(2), 129.8, 129.9, 132.1, 133.1, 133.6(2), 135.4, 135.5, 135.8, 136.0 and 164.0 (t, $^2J_{C\text{-}F}$ 31.9); δ_F (377 MHz, $CDCl_3$) −117.95 and −111.75 (both d, $^2J_{F\text{-}F}$ 258.9); *m/z* (ES^+) 683.5 (M^+ + 23, 100%).

5,7-Bis(*tert*-butyldiphenylsilyloxy)-4,4-difluoro-2,2-dimethylheptan-3-one (43). *tert*-Butyllithium (1.7 M in pentane, 0.07 mL, 0.119 mmol) was added to the methyl ester **42** (74 mg, 0.112 mmol) in dry THF (2.2 mL) at −78 °C and the solution stirred at −78 °C for 5 h. Saturated methanolic ammonium chloride (5 mL) was added at −78 °C and the mixture was allowed to warm to rt. Water (10 mL) and DCM (10 mL) were added and the aqueous phase was extracted with DCM (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatograpy of the residue (0.5:99.5 ether:light petroleum) gave the *title compound* **43** (40 mg, 0.058 mmol, 52%) as a colourless oil, R_f = 0.24 (1:99 ether:light petroleum) (Found: M^+ + NH_4, 704.3771. $C_{41}H_{56}NO_3F_2Si_2$ requires M, 704.3761); ν_{max}/cm^{-1} 3071, 2959, 2932, 2890, 2858, 1724, 1473, 1427, 1106, 1032, 822 and 739; δ_H (400 MHz, $CDCl_3$) 0.93 and 0.99 [each 9 H, s, $SiC(CH_3)_3$], 1.21 [9 H, s, $C(CH_3)_3$], 1.72-1.87 (2 H, m, 6-H_2), 3.43-3.49 (2 H, m, 7-H_2), 4.54 (1 H, m, 5-H), 7.28-7.43 (12 H, m, ArH) and 7.43-7.50 and 7.66-7.71 (each 4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.0, 19.6, 25.9, 26.7, 26.8, 34.3, 43.7, 60.0, 69.7 (t, $^2J_{C\text{-}F}$ 25.8), 118.2 (t, $^1J_{C\text{-}F}$ 261.7), 127.5, 127.6, 129.4, 129.5, 129.7, 129.8, 132.2, 133.5, 133.6, 133.7, 135.4, 135.5, 135.9, 136.0 and 204.6 (t, $^2J_{C\text{-}F}$ 27.2); δ_F (377 MHz, $CDCl_3$) −111.70 and −109.97 (both d, $^2J_{F\text{-}F}$ 280.4); *m/z* (ES^+) 709.6 (M^+ + 23, 100%).

(2*RS*,4*RS*)-2-*tert*-Butyl-3,3-difluoro-2,4-dihydroxytetrahydro-2*H*-pyran (44). Tetra-*n*-butylammonium fluoride (1 M in THF, 0.70 mL, 0.704 mmol) was added to the ketone **43** (0.23 g, 0.335 mmol) in THF (3.35 mL) at 0 °C and the solution stirred at rt for 15 h. Saturated aqueous ammonium chloride (10 mL), water (10 mL) and EtOAc (20 mL) were added and the aqueous phase was extracted into EtOAc (3 × 20 mL).

The organic extracts were washed with brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum to ether) gave a mixture (^{1}H NMR) of the hemiacetals **44** and **45** (62 mg). Recrystallisation from toluene gave the *title compound* **44** (53 mg, 0.25 mmol, 75%) as white needles, R_f = 0.58 (ether), m.p. = 91-94 °C (Found: C, 51.39; H, 7.64. $C_9H_{16}O_3F_2$ requires C, 51.40; H, 7.70%; Found: M^+ + Na, 233.0956. $C_9H_{16}O_3F_2Na$ requires M, 233.0965); ν_{max}/cm^{-1} 3434, 2965, 2941, 1338, 1093, 1066, 1005, 993, 906, 875 and 752; δ_H (400 MHz, benzene-d_6) 1.10 [9 H, s, C(CH$_3$)$_3$], 1.38 (1 H, t, *J* 1.5, OH), 1.42 (1 H, m, 5-H), 1.64 (1 H, ddq, *J* 2.0, 5.5, 13.5, 5-H'), 1.86 (1 H, br. s, OH), 3.25 (1 H, ddt, *J* 11.5, 5.3, 1.5, 6-H), 3.51 (1 H, m, 6-H') and 4.06 (1 H, m, 4-H); δ_C (100 MHz, benzene-d_6) 26.2 (t, $^4J_{C\text{-}F}$ 3.6), 32.3 (d, $^3J_{C\text{-}F}$ 5.8), 40.0 (t, $^3J_{C\text{-}F}$ 2.9), 58.7, 68.0 (dd, $^2J_{C\text{-}F}$ 22.6, 21.1), 99.7 (dd, $^2J_{C\text{-}F}$ 29.9, 24.1) and 121.3 (dd, $^1J_{C\text{-}F}$ 258.0, 251.4); δ_F (377 MHz, benzene-d_6) −130.11 (d, $^2J_{F\text{-}F}$ 240.0) and −118.89 (d, $^2J_{F\text{-}F}$ 238.7); *m/z* (ES$^-$) 209 ([M-H]$^-$, 100%); (ES$^+$) 233.1 (M^+ + 23, 100%).

After standing in solution in benzene-d_6 for 48 h, the hemiacetal **44** equilibrated with the hemiacetal **45** (^{1}H NMR), **45**:**44** = 60:40 (^{19}F NMR); δ_H (400 MHz, benzene-d_6) hemiacetal **45** 1.15 (1 H, m, 5-H), 1.37 [9 H, s, C(CH$_3$)$_3$], 1.75 (1 H, m, 5-H'), 2.05 (1 H, br. s, OH), 3.30 and 3.56 (each 1 H, m, 6-H) and 3.93 (1 H, t, *J* 12.5, 4-H); δ_C (100 MHz, benzene-d_6) 26.5 (t, $^4J_{C\text{-}F}$ 2.9), 30.7 (d, $^3J_{C\text{-}F}$ 5.1), 40.4 (t, $^3J_{C\text{-}F}$ 2.2), 54.5, 70.2 (dd, $^2J_{C\text{-}F}$ 34.3, 24.1), 100.5 (dd, $^2J_{C\text{-}F}$ 26.2, 24.8) and 117.6 (dd, $^1J_{C\text{-}F}$ 260.2, 253.7); δ_F (377 MHz, benzene-d_6) □115.73 (d, $^2J_{F\text{-}F}$ 252.3) and □113.93 (d, $^2J_{F\text{-}F}$ 253.7). Attempts to separate this mixture by chromatography were unsuccessful.

6,8-Bis(*tert*-butyldiphenylsilyloxy)-5,5-difluoro-3,3-dimethyloct-1-en-4-one (46). 3-Methylbut-2-enylmagnesium chloride (0.31 M in THF, 1.22 mL, 0.38 mmol) was added dropwise to the methyl ester **42** (0.167 g, 0.253 mmol) in dry THF (2.7 mL) at −10 °C and the solution stirred at −10 °C for 12 h. Saturated methanolic ammonium chloride (2.5 mL) was added at −10 °C and the mixture was allowed to warm to rt. Water (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3 × 10 mL) The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0.5:99.5 ether:light petroleum) gave the *title compound* **46** (0.12 g, 0.17 mmol, 66%) as a colourless oil, R_f = 0.58 (10:90 ether:light petroleum) (Found: M^+ + NH_4, 716.3761. $C_{42}H_{56}NO_3F_2Si_2$ requires M, 716.3761); ν_{max}/cm^{-1} 2959, 2931, 2890, 2858, 1726, 1472, 1427, 1390, 1362, 1106, 822 and 739; δ_H (500 MHz, $CDCl_3$) 0.92 and 0.98 [each 9 H, s, SiC(CH$_3$)$_3$], 1.28 and 1.29 (each 3 H, s, 3-CH$_3$), 1.70-1.83 (2 H, m, 7-H$_2$), 3.42-3.50 (2 H, m, 8-H$_2$), 4.47 (1 H, m, 6-H), 5.09-5.12 (2 H, m, 1-H$_2$), 5.94 (1 H, dd, *J* 17.3, 10.4, 2-H), 7.29-7.44 (12 H, m, ArH) and 7.44-7.49 and 7.65-7.69 (each 4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 19.0, 19.6, 23.3, 23.8, 26.7, 26.8, 34.4, 49.7, 60.0, 69.8 (t, $^2J_{C\text{-}F}$ 24.4), 115.5, 118.0 (t, $^1J_{C\text{-}F}$ 260.0), 127.5, 127.6, 129.4, 129.5, 129.7, 129.8, 132.3, 133.5, 133.7(2), 135.4, 135.5, 135.9, 136.0, 139.7 and 201.7 (t, $^2J_{C\text{-}F}$ 28.0); δ_F (471 MHz, $CDCl_3$) −110.70 and −109.98 (both d, $^2J_{F\text{-}F}$ 277.7); *m/z* (ES$^+$) 716.8 (M^+ + 18, 30%).

(2*RS*,4*RS*)-3,3-Difluoro-2,4-dihydroxy-2-(2-methylbut-3-en-2-yl)tetrahydro-2*H*-pyran (47). Tetra-*n*-butylammonium fluoride (1 M in THF, 0.81 mL, 0.81 mmol) was added to the ketone **46** (0.27 g, 0.386 mmol) in THF (3.96 mL) at 0 °C and the solution stirred at rt for 15 h. Saturated aqueous ammonium chloride (10 mL), water (10 mL) and EtOAc (20 mL) were added and the aqueous phase was extracted into EtOAc (3 × 20 mL). The organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum to ether) gave a mixture (^{1}H NMR) of the hemiacetals **47** and **48** (83 mg) as a colourless oil. Repeated trituration with pentane gave the *title compound* **47** (70 mg, 0.315 mmol, 82%) as white needles, R_f = 0.26 (20:80 light petroleum:ether), m.p. 89-94 °C (Found: M^+ + Na, 245.0974. $C_{10}H_{16}O_3F_2Na$ requires M, 245.0965); ν_{max}/cm^{-1} 3436, 2978, 2960, 2934, 2899, 1378, 1093, 1065, 1001, 945, 904, 873, 789 and 752; δ_H (500 MHz, benzene-d_6) 1.30 (3 H, d, *J* 3.8, 1'-H$_3$), 1.39 (3 H, d, *J* 2.2, 2'-CH$_3$), 1.46 (1 H, m, 5-H), 1.71 (1 H, dq, *J* 12.5, 5.5, 5-H'), 2.56 (1 H, br. s, OH), 3.28 (1 H, dd, *J* 11.4, 5.5, 6-H), 3.56 (2 H, m, 6-H', OH), 4.09 (1 H, m, 4-H), 4.92-4.95 (2 H, m, 4'-H$_2$) and 6.07 (1 H, dd, *J* 18.0, 10.4, 3'-H); δ_C (100 MHz, benzene-d_6) 21.7 (dd, $^4J_{C\text{-}F}$ 6.6, 1.5), 24.2 (d, $^4J_{C\text{-}F}$ 6.6), 32.3 (d, $^3J_{C\text{-}F}$ 5.8), 46.5 (d, $^3J_{C\text{-}F}$ 2.9), 58.7, 68.1 (dd, $^2J_{C\text{-}F}$ 21.9, 20.4), 98.4 (dd, $^2J_{C\text{-}F}$ 30.9, 24.3), 115.5, 121.0 (dd, $^1J_{C\text{-}F}$ 260.6, 252.5) and 144.6; δ_F (377 MHz, benzene-d_6) −130.10 (d, $^2J_{F\text{-}F}$ 240.0) and −118.89 (d, $^2J_{F\text{-}F}$ 238.7); *m/z* (ES$^-$) 291.3 (100%) and 221.2 ([M − H]$^-$).

After standing in solution in benzene-d_6 for 48 h, the hemiacetal **47** had equilibrated with the hemiacetal **48**, **47**:**48** = 60:40 (^{19}F NMR); δ_H (400 MHz, benzene-d_6) hemiacetal **48** 1.38 (1 H, m, 5-H), 1.44 and 1.48 (each 3 H, s, 1'-H$_3$ or 2'-CH$_3$), 1.76 (1 H, m, 5-H'), 2.55 (1 H, br. s, OH), 3.31 and 3.67 (each 1 H, m, 6-H), 3.96 (1 H, t, *J* 13.0, 4-H), 5.05-5.14 (2 H, m, 4'-H$_2$) and 6.48 (1 H, dd, *J* 17.5, 11.0, 3'-H); δ_F (377 MHz, benzene-d_6) □115.75 and □114.40 (both d, $^2J_{F\text{-}F}$ 252.4). Attempts to separate this mixture by chromatography were unsuccessful.

2-Difluoromethylenedecan-1-ol (54). Methyllithium (1.6 M in ether, 0.37 mL, 0.60 mmol) was added dropwise to the ketone **52**[28] (68 mg, 0.30 mmol) and di-iodomethane (0.048 mL, 0.60 mmol) in dry THF (1.8 mL) at −78 °C and the mixture allowed to warm to rt over 30 min then cooled to −78 °C. *tert*-Butyllithium (1.7 M in pentane, 5.15 mmol, 3.03 mL) was added and the mixture was stirred at rt for 16 h. Aqueous hydrogen chloride (1 M, 20 mL) and ether (20 mL) were added and the aqueous phase was extracted with ether (3 × 20 mL). The organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 to 5:95 ether:light petroleum) gave the *title compound* **54** (94 mg, 0.46 mmol, 44%) as a colourless oil, R_f = 0.18 (10:90 ether:light petroleum) (Found: M^+, 206.1477. $C_{11}H_{20}OF_2$ requires M, 206.1477); ν_{max}/cm^{-1} 3333, 2955, 2925, 2856, 1746, 1466, 1264, 1001 and 730; δ_H (500 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.0, 10-H$_3$), 1.20-1.35 (10 H, m, 5 × CH$_2$), 1.40-1.48 (2 H, m, 4-H$_2$), 1.96 (1 H, br. s, OH), 2.09 (2 H, m, 3-H$_2$) and 4.14 (2 H, s, 1-H$_2$); δ_C (125 MHz, $CDCl_3$) 14.0, 22.6, 24.4, 27.5, 29.2(2), 29.3,

31.8, 57.7, 90.0 (dd, $^2J_{C\text{-}F}$ 16.4, 13.7) and 154.2 (t, $^1J_{C\text{-}F}$ 288.5); δ_F (377 MHz, $CDCl_3$) −93.14 and −92.87 (both d, $^2J_{F\text{-}F}$ 48.1).

1-Bromo-2-(difluoromethylene)decane (55). Dimethyl sulfide (0.094 mL, 1.280 mmol) was added to *N*-bromosuccinimide (0.185 g, 1.04 mmol) in dry DCM (4.0 mL) at 0 °C and the mixture stirred for 10 min then cooled to −20 °C. The alcohol **54** (0.143 g, 0.693 mmol) in DCM (3 mL) was added and the mixture stirred at rt for 16 h. Saturated aqueous sodium hydrogen carbonate (10 mL) and DCM (10 mL) were added and the aqueous phase was extracted with DCM (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum) gave the *title compound* **55** (0.12 g, 0.435 mmol, 63%) as a colourless oil, R_f = 0.41 (light petroleum); ν_{max}/cm^{-1} 2956, 2925, 2856, 1735, 1465, 1290, 1223, 1188 and 1058; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.0, 10-H_3), 1.25-1.35 (10 H, m, 5 × CH_2), 1.46 (2 H, m, 4-H_2), 2.14 (2 H, m, 3-H_2) and 4.02 (2 H, t, $^4J_{H\text{-}F}$ 1.9, 1-H_2); δ_C (125 MHz, $CDCl_3$) 14.0, 22.6, 25.2, 27.1(m), 27.8 (dd, $^3J_{C\text{-}F}$ 7.4, 1.8), 29.1, 29.2, 29.3, 31.8, 89.0 (dd, $^2J_{C\text{-}F}$ 22.0, 12.9) and 153.9 (t, $^1J_{C\text{-}F}$ 291.2); δ_F (377 MHz, $CDCl_3$) −89.64 and −88.32 (both d, $^2J_{F\text{-}F}$ 35.5).

Following this procedure, *N*-bromosuccinimide (63 mg, 0.36 mmol) in DCM (1.38 mL), dimethyl sulfide (0.032 mL, 0.44 mmol) and the alcohol **54** (49 mg, 0.237 mmol) in DCM (1 mL) with heating the crude product in toluene-d_8 (0.5 mL) under reflux for 16 h gave, after chromatography (light petroleum) a mixture (57 mg, 0.212 mmol, 89%) of the title compound **55** and 2-(bromodifluoromethyl)dec-1-ene **56** as a colourless oil, **55**:**56** = 20:80; ν_{max}/cm^{-1} 2956, 2926, 2856, 1738, 1465, 1131, 1114, 1101, 926 and 895; δ_H (500 MHz, $CDCl_3$) isomer **56** 0.90 (3 H, t, *J* 6.9, 10-H_3), 1.25-1.41 (10 H, m, 5 × CH_2), 1.56 (2 H, m, 4-H_2), 2.28 (2 H, t, *J* 7.9, 3-H_2), 5.17 (1 H, t, $^4J_{H\text{-}F}$ 1.6, 1-H) and 5.60 (1 H, t, $^4J_{H\text{-}F}$ 1.0, 1-H'); δ_C (125 MHz, $CDCl_3$) 14.1, 22.7, 27.4, 29.2(2), 29.2, 29.4, 29.7, 31.8, 114.3 (t, $^3J_{C\text{-}F}$ 7.4), 119.7 (t, $^1J_{C\text{-}F}$ 306.7) and 145.4 (t, $^2J_{C\text{-}F}$ 19.3); δ_F (377 MHz, $CDCl_3$) −48.43.

Difluorinated alcohols 57: general procedure. Indium powder (43 mg, 0.37 mmol) was added to a vigorously stirred solution of 1-bromo-2-(difluoromethylene)decane **55** (50 mg, 0.19 mmol) in DMF (1.0 mL) in a 10 mL Schlenk tube. After 10 min, the aldehyde (0.41 mmol) was added and the mixture stirred for 14 h. Aqueous hydrogen chloride (10%, 10 mL) and ether (10 mL) were added and the aqueous phase was extracted with ether (3 × 30 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to 5:95 ether:light petroleum) gave the alcohols **57** as colourless oils.

2,2-Difluoro-3-methylene-1-phenylundecan-1-ol **57a**. (46 mg, 0.155 mmol, 84%), R_f = 0.14 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 314.2285. $C_{18}H_{30}NOF_2$ requires M, 314.2290; ν_{max}/cm^{-1} 3380, 2954, 2925, 2855, 1455, 1164, 1086, 1060, 1026, 920 and 743; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.0, 11-H_3), 1.23-1.33 (10 H, m, 5 × CH_2), 1.43 (2 H, m, 5-H_2), 1.89-2.00 (2 H, m, 4-H_2), 2.43 (1 H, br. s, OH), 4.93 (1 H, t, $^3J_{H\text{-}F}$ 11.0, 1-H), 5.18 and 5.31 (each 1 H, s, 3-CH), 7.33-7.38 (3 H, m, ArH) and 7.40-7.44 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 27.6, 29.2(2), 29.3, 30.5 (t, $^3J_{C\text{-}F}$ 2.9), 31.8, 75.4 (t, $^2J_{C\text{-}F}$ 30.0), 116.3 (t, $^3J_{C\text{-}F}$ 8.0), 121.2 (t, $^1J_{C\text{-}F}$ 247.2), 127.8, 128.1, 128.6, 136.1 (t, $^3J_{C\text{-}F}$ 2.2) and 142.8 (t, $^2J_{C\text{-}F}$ 22.6); δ_F (471 MHz, $CDCl_3$) −109.53; *m/z* (APCI) 314.2 (M^+ + 18, 100%).

2,2-Difluoro-3-methylene-1-(4-methoxyphenyl)undecan-1-ol **57b**. (40 mg, 0.12 mmol, 65%), R_f = 0.65 (50:50 ether:light petroleum) (Found: $M^+ + NH_4$, 344.2390. $C_{19}H_{32}NO_2F_2$ requires M, 344.2396); ν_{max}/cm^{-1} 3457, 2925, 2855, 1613, 1514, 1464, 1249, 1174, 1062, 1032, 921, 855 and 794; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 7.0, 11-H_3), 1.23-1.35 (10 H, m, 5 × CH_2), 1.43 (2 H, m, 5-H_2), 1.89-2.01 (2 H, m, 4-H_2), 2.48 (1 H, br. s, OH), 3.82 (3 H, s, OCH_3), 4.87 (1 H, t, $^3J_{H\text{-}F}$ 11.4, 1-H), 5.18 and 5.31 (each 1 H, s, 3-CH), 6.89 (2 H, d, *J* 8.9, ArH) and 7.34 (2 H, d, *J* 8.5, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 27.6, 29.2(2), 29.4, 30.5 (t, $^3J_{C\text{-}F}$ 2.9), 31.8, 55.2, 75.1 (t, $^2J_{C\text{-}F}$ 29.9), 113.5, 116.2 (t, $^3J_{C\text{-}F}$ 8.8), 121.2 (t, $^1J_{C\text{-}F}$ 247.2), 128.2 (t, $^3J_{C\text{-}F}$ 2.2), 129.0, 142.9 (t, $^2J_{C\text{-}F}$ 22.6) and 159.8; δ_F (471 MHz, $CDCl_3$) −109.52 and −110.20 (both d, $^2J_{F\text{-}F}$ 244.7); *m/z* (GC/MS-CI) 327 (M^+ + 1).

2,2-Difluoro-3-methylene-1-(3-chlorophenyl)undecan-1-ol **57c**. (60 mg, 0.17 mmol, 93%), R_f = 0.2 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 348.1897. $C_{18}H_{29}NO^{35}ClF_2$ requires M, 348.1900); ν_{max}/cm^{-1} 3428, 2954, 2926, 2855, 1599, 1576, 1467, 1433, 1199, 1163, 1079, 925 and 776; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 6.8, 11-H_3), 1.22-1.36 (10 H, m, 5 × CH_2), 1.44 (2 H, m, 5-H_2), 1.96 (2 H, t, *J* 8.0, 4-H_2), 2.56 (1 H, br. s, OH), 4.90 (1 H, t, $^3J_{H\text{-}F}$ 10.8, 1-H), 5.22 and 5.32 (each 1 H, s, 3-CH), 7.26-7.35 (3 H, m, ArH) and 7.42-7.44 (1 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 27.6, 29.2, 29.4, 30.5 (t, $^3J_{C\text{-}F}$ 2.9), 31.8, 74.8 (t, $^2J_{C\text{-}F}$ 30.0), 116.7 (t, $^3J_{C\text{-}F}$ 8.1), 120.9 (t, $^1J_{C\text{-}F}$ 250.4), 126.0, 128.0, 128.8, 129.3, 134.1, 138.0 (t, $^3J_{C\text{-}F}$ 1.5) and 142.4 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (471 MHz, $CDCl_3$) −109.99 and −108.92 (both d, $^2J_{F\text{-}F}$ 244.7); *m/z* (APCI) 348.2 (M^+ + 18, 100%).

5,5-Difluoro-6-methylenetetradecan-4-ol **57d**. (50 mg, 0.18 mmol, 98%), R_f = 0.23 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 280.2442. $C_{15}H_{32}NOF_2$ requires M, 280.2446); ν_{max}/cm^{-1} 3387, 2959, 2926, 2856, 1466, 1185, 1075, 1029, 964 and 922; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.6, 14-H_3), 0.96 (3 H, t, *J* 7.0, 1-H_3), 1.21-1.38 (10 H, m, 5 × CH_2), 1.38-1.70 (6 H, m, 3 × CH_2), 1.85 (1 H, br. s, OH), 2.04-2.19 (2 H, m, 7-H_2), 3.83 (1 H, q, *J* 9.6, 4-H) and 5.23 and 5.44 (each 1 H, s, 6-CH); δ_C (100 MHz, $CDCl_3$) 13.8, 14.1, 18.8, 22.6, 27.8, 29.2, 29.3, 29.4, 30.5 (t, $^4J_{C\text{-}F}$ 2.9), 31.8, 31.9 (t, $^3J_{C\text{-}F}$ 2.2), 72.3 (t, $^2J_{C\text{-}F}$ 28.7), 115.5 (t, $^3J_{C\text{-}F}$ 8.8), 121.8 (t, $^1J_{C\text{-}F}$ 247.5) and 142.9 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (470 MHz, $CDCl_3$) −112.29 and −111.60 (both d, $^2J_{F\text{-}F}$ 246.3); *m/z* (APCI) 280.2 (M^+ + 18, 100%).

4,4-Difluoro-2-methyl-5-methylenetridecan-3-ol **57e**. (33 mg, 0.126 mmol, 68%), R_f = 0.39 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 280.2443. $C_{15}H_{32}NOF_2$ requires M, 280.2446); ν_{max}/cm^{-1} 3458, 2958, 2926, 2856, 1467, 1264, 1186, 1077, 1021, 907 and 725; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.8, 13-H_3), 0.99 and 1.05 (each 3 H, d, *J* 6.9, 1-H_3 or 2-CH_3), 1.23-1.38 (10 H, m, 5 × CH_2), 1.51 (2 H, m, 7-H_2), 1.82 (1 H, br. s, OH), 1.98 (1 H, m, 2-H), 2.05-2.19 (2 H, m, 6-H_2), 3.66 (1 H, m, 3-H) and 5.22 and 5.47 (each 1 H, s, 5-H); δ_C (100 MHz, $CDCl_3$) 14.1, 16.2 (t, $^4J_{C\text{-}F}$ 2.2), 20.8 (t, $^4J_{C\text{-}F}$ 1.5), 22.6, 27.8, 28.3, 29.2, 29.3, 29.4, 30.4 (t, $^3J_{C\text{-}F}$ 3.0), 31.8, 76.2 (t, $^2J_{C\text{-}F}$ 27.3), 115.1 (t, $^3J_{C\text{-}F}$ 9.6), 122.3 (t, $^1J_{C\text{-}F}$

248.2) and 143.4 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (471 MHz, $CDCl_3$) −109.36 and −108.49 (both d, $^2J_{F\text{-}F}$ 248.2); *m/z* (APCI) 280.2 (M^+ + 18, 100%).

4,4-Difluoro-2,2-dimethyl-5-methylenetridecan-3-ol **57f**. (24 mg, 0.087 mmol, 47%), R_f = 0.29 (10:90 ether:light petroleum) (Found: $M^+ + NH_4$, 294.2602. $C_{16}H_{34}NOF_2$ requires M, 294.2603); ν_{max}/cm^{-1} 3491, 2957, 2925, 2856, 1741, 1714, 1466, 1368, 1166, 1057, 1016 and 922; δ_H (500 MHz, $CDCl_3$) 0.84-0.92 (3 H, m, 13-H_3), 1.07 [9 H, s, $C(CH_3)_3$], 1.23-1.38 (10 H, m, 5 × CH_2), 1.52 (2 H, m, 7-H_2), 1.83 (1 H, br. s, OH), 2.15 (2 H, t, *J* 7.9, 6-H_2), 3.52 (1 H, dd, $^3J_{H\text{-}F}$ 19.9, 6.3, 3-H), 5.21 (1 H, d, $^4J_{H\text{-}F}$ 1.6, 5-CH) and 5.47 (1 H, d, $^4J_{H\text{-}F}$ 2.5, 5-H'); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 26.9 (t, $^4J_{C\text{-}F}$ 2.2), 27.8, 29.2, 29.4(2), 30.5 (dd, $^3J_{C\text{-}F}$ 3.7, 2.2), 31.9, 34.8, 78.1 (dd, $^2J_{C\text{-}F}$ 29.5, 26.5), 114.8 (dd, $^3J_{C\text{-}F}$ 10.3, 8.1), 123.0 (dd, $^1J_{C\text{-}F}$ 253.4, 249.0) and 144.7 (t, $^2J_{C\text{-}F}$ 22.8); δ_F (471 MHz, $CDCl_3$) −111.59 and −100.68 (both d, $^2J_{F\text{-}F}$ 249.9); *m/z* (ES^+) 277.3 (M^+ + 1, 20%).

1-tert-Butyldiphenylsilyloxy-4,4-difluoro-5-methylenetridecan-3-ol **57g**. (85 mg, 0.169 mmol, 91%), R_f = 0.27 (10:90 ether:light petroleum) (Found: M^+ + H, 503.3138. $C_{30}H_{45}O_2F_2Si$ requires M, 503.3151); ν_{max}/cm^{-1} 3471, 2956, 2928, 2856, 1427, 1106, 1084, 936, 822 and 737; δ_H (400 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 8.6, 13-H_3), 1.06 [9 H, s, $SiC(CH_3)_3$], 1.24-1.39 (10 H, m, 5 × CH_2), 1.53 (2 H, m, 7-H_2), 1.81 and 1.88 (each 1 H, m, 2-H), 2.08-2.23 (2 H, m, 6-H_2), 3.09 (1 H, br. s, OH), 3.86 and 3.96 (each 1 H, m, 1-H), 4.20 (1 H, m, 3-H), 5.25 and 5.48 (each 1 H, s, 5-CH), 7.37-7.49 (6 H, m, ArH) and 7.63-7.73 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.1, 19.1, 22.7, 26.8, 27.8, 29.3, 29.4(2), 30.5, 31.7, 31.9, 61.9, 71.3 (t, $^2J_{C\text{-}F}$ 30.7), 115.4 (t, $^3J_{C\text{-}F}$ 9.1), 121.4 (dd, $^1J_{C\text{-}F}$ 248.4, 245.7), 127.8, 129.9, 132.9, 133.0, 135.5(2) and 143.0 (t, $^2J_{C\text{-}F}$ 22.7); δ_F (377 MHz, $CDCl_3$) −114.15 and −110.23 (both d, $^2J_{F\text{-}F}$ 247.3); *m/z* (APCI) 503.3 (M^+ + 1, 100%).

1-*tert*-Butyldiphenylsilyloxy-4,4-difluorohex-5-en-3-one (58). *N*-Methylmorpholine-*N*-oxide (52 mg, 0.446 mmol) and TPAP (5 mg, 0.015 mmol) were added to the alcohol **40** (0.116 g, 0.297 mmol) and 4Å molecular sieves (0.168 g) in dry DCM (2.0 mL) and the mixture stirred for 16 h then concentrated under reduced pressure. Chromatography of the residue (light petroleum to 2:98 ether:light petroleum) gave the *title compound* **58** (90 mg, 0.23 mmol, 78%) as a colourless oil, R_f = 0.43 (10:90 ether:light petroleum) (Found: M^+ + Na, 411.1568. $C_{22}H_{26}O_2F_2SiNa$ requires M, 411.1568); ν_{max}/cm^{-1} 2957, 2931, 2857, 1746, 1427, 1107, 998, 956, 821 and 738; δ_H (500 MHz, $CDCl_3$) 1.05 [9 H, s, $SiC(CH_3)_3$], 2.92 (2 H, t, *J* 6.2, 2-H_2), 4.00 (2 H, t, *J* 6.2, 1-H_2), 5.66 (1 H, d, *J* 11.0, 6-H), 5.85 (1 H, dt, *J* 17.4, 2.5, 6-H'), 6.01 (1 H, m, 5-H), 7.39-7.48 (6 H, m, ArH) and 7.67-7.71 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.7, 39.4, 58.2, 114.3 (t, $^1J_{C\text{-}F}$ 251.2), 123.1 (t, $^3J_{C\text{-}F}$ 9.6), 127.7, 128.3 (t, $^2J_{C\text{-}F}$ 25.1), 129.8, 133.2, 135.5 and 198.2 (t, $^2J_{C\text{-}F}$ 32.4); δ_F (471 MHz, $CDCl_3$) −108.32; *m/z* (ES^+) 427 (M^+ + 39, 25%), 411 (M^+ + 23, 15) and 102 (100).

Methyl (*E*)- and (*Z*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluorohexa-2,5-dienoate (59) and (60). Methoxycarbonylmethylene(triphenyl)phosphorane (0.28 g, 0.844 mmol) was added to the ketone **58** (0.27 g, 0.703 mmol) in dry toluene (2.5 mL) and the mixture heated at 70 °C for 6 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 0.5:99.5 ether:light petroleum) gave the *title compound* **59** (0.26 g, 0.59 mmol, 84%) as a colourless oil, R_f = 0.38 (10:90 ether:light petroleum) (Found: M^+ + Na, 467.1841. $C_{25}H_{30}O_3F_2SiNa$ requires M, 467.1824); ν_{max}/cm^{-1} 2953, 2931, 2857, 1728, 1428, 1258, 1199, 1178, 1106, 1089, 981, 822 and 739; δ_H (400 MHz, $CDCl_3$) 1.05 [9 H, s, $SiC(CH_3)_3$], 2.99 (2 H, t, *J* 6.8, 1'-H_2), 3.70 (3 H, s, OCH_3), 3.81 (2 H, t, *J* 6.8, 2'-H_2), 5.45 (1 H, d, *J* 10.8, 6-H), 5.63 (1 H, dt, *J* 17.4, 2.2, 6-H'), 5.76-5.90 (1 H, m, 5-H), 6.21 (1 H, s, 2-H), 7.37-7.46 (6 H, m, ArH) and 7.66-7.71 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.8, 30.5 (t, $^3J_{C\text{-}F}$ 1.5), 51.5, 62.4, 118.7 (t, $^1J_{C\text{-}F}$ 243.1), 120.9 (t, $^3J_{C\text{-}F}$ 9.6), 121.2 (t, $^3J_{C\text{-}F}$ 8.8), 127.6, 129.6, 131.4 (t, $^2J_{C\text{-}F}$ 28.7), 133.7, 135.6, 149.4 (t, $^2J_{C\text{-}F}$ 25.0) and 165.6; δ_F (471 MHz, $CDCl_3$) −100.52; *m/z* (ES^+) 467.3 (M^+ + 23, 100%). The second fraction was the *title compound* **60** (36 mg, 0.081 mmol, 11%) as a colourless oil, R_f = 0.27 (10:90 ether:light petroleum) (Found: M^+ + Na, 467.1836. $C_{25}H_{30}O_3F_2SiNa$ requires M, 467.1824); ν_{max}/cm^{-1} 2953, 2931, 2857, 1735, 1428, 1240, 1196, 1159, 1105, 997, 822 and 737; δ_H (400 MHz, $CDCl_3$) 1.06 [9 H, s, $SiC(CH_3)_3$], 2.41 (2 H, td, *J* 6.4, 0.8, 1'-H_2), 3.74 (3 H, s, OCH_3), 3.80 (2 H, t, *J* 6.4, 2'-H_2), 5.43 (1 H, d, *J* 11.3, 6-H), 5.63 (1 H, dt, *J* 17.3, 2.8, 6-H'), 5.98 (1 H, s, 2-H), 6.16 (1 H, m, 5-H), 7.36-7.47 (6 H, m, ArH) and 7.63-7.69 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.8, 34.6 (t, $^3J_{C\text{-}F}$ 3.7), 51.8, 61.8, 118.7 (t, $^1J_{C\text{-}F}$ 239.9), 120.1 (t, $^3J_{C\text{-}F}$ 8.8), 122.9 (t, $^3J_{C\text{-}F}$ 5.1), 127.7, 129.7, 132.0 (t, $^2J_{C\text{-}F}$ 27.8), 133.4, 135.6, 142.8 (t, $^2J_{C\text{-}F}$ 27.0) and 166.2; δ_F (377 MHz, $CDCl_3$) −95.73; *m/z* (ES^+) 467.3 (M^+ + 23, 100%) and 462.4 (M^+ + 18, 85).

1-*tert*-Butyldiphenylsilyloxy-4,4-difluoro-5-methylenetridecan-3-one (61). Anhydrous DMSO (51 μL, 0.723 mmol) was added dropwise to oxalyl chloride (31 μL, 0.362 mmol) in dry DCM (1.6 mL) at −78 °C. After 30 min, the alcohol **57g** (91 mg, 0.18 mmol) in dry DCM (1.0 mL) was added. After a further 45 min, triethylamine (0.20 mL, 1.45 mmol) was added and the mixture was stirred at rt for 1 h. Saturated aqueous ammonium chloride (10 mL) and DCM (10 mL) were added and the aqueous phase was extracted into DCM (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0.25:99.75 ether:light petroleum) gave the *title compound* **61** (55 mg, 0.11 mmol, 61%) as a colourless oil, R_f = 0.53 (5:95 ether:light petroleum) (Found: M^+ + Na, 523.2809. $C_{30}H_{42}O_2F_2SiNa$ requires M, 523.2820); ν_{max}/cm^{-1} 2955, 2928, 2857, 1749, 1428, 1106, 927, 822 and 737; δ_H (500 MHz, $CDCl_3$) 0.89 (3 H, t, *J* 6.7, 13-H_3), 1.03 [9 H, s, $SiC(CH_3)_3$], 1.22-1.34 (10 H, m, 5 × CH_2), 1.47 (2 H, m, 7-H_2), 2.08 (2 H, t, *J* 7.6, 6-H_2), 2.88 (2 H, t, *J* 6.0, 2-H_2), 3.97 (2 H, t, *J* 6.0, 1-H_2), 5.32 and 5.55 (each 1 H, s, 5-CH), 7.37-7.47 (6 H, m, ArH) and 7.65-7.70 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 19.1, 22.6, 26.7, 27.5, 29.2, 29.3, 29.4 (t, $^4J_{C\text{-}F}$ 2.2), 31.8, 39.3, 58.0, 116.1 (t, $^1J_{C\text{-}F}$ 251.6), 117.1 (t, $^3J_{C\text{-}F}$ 8.8), 127.7, 129.7, 133.2, 135.5, 140.8 (t, $^2J_{C\text{-}F}$ 21.9) and 198.3 (t, $^2J_{C\text{-}F}$ 31.4); δ_F (471 MHz, $CDCl_3$) −109.74; *m/z* (ES^+) 523.4 (M^+ + 23, 100%).

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-5-methylenetridec-2-enoate (62). Methoxycarbonyl-

methylidene(triphenyl)phosphorane (37 mg, 0.11 mmol) was added to the ketone **61** (32 mg, 0.064 mmol) in toluene (0.23 mL) and the mixture heated at 70 °C for 11 h. After concentration under reduced pressure, chromatography of the residue (0.25:99.75 ether:light petroleum) gave the *title compound* **62** (17 mg, 0.031 mmol, 48%) as a colourless oil, R_f = 0.23 (5:95 ether:light petroleum) (Found: M^+ + Na, 579.3080. $C_{33}H_{46}O_3F_2SiNa$ requires M, 579.3082); ν_{max}/cm^{-1} 2928, 2856, 1729, 1428, 1256, 1200, 1177, 1105 and 739; δ_H (500 MHz, $CDCl_3$) 0.90 (3 H, t, *J* 6.8, 13-H_3), 1.04 [9 H, s, $SiC(CH_3)_3$], 1.21-1.35 (10 H, m, 5 × CH_2), 1.42 (2 H, m, 7-H_2), 1.94 (2 H, t, *J* 7.3, 6-H_2), 2.94 (2 H, t, *J* 7.7, 1'-H_2), 3.70 (3 H, s, OCH_3), 3.76 (2 H, t, *J* 7.7, 2'-H_2), 5.17 and 5.40 (each 1 H, s, 5-CH), 6.22 (1 H, t, *J* 1.8, 2-H), 7.35-7.47 (6 H, m, ArH) and 7.66-7.72 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.1, 19.1, 22.6, 26.7, 27.5, 29.2(2), 29.4, 29.5, 30.7, 31.8, 51.5, 62.4, 115.9 (t, $^3J_{C\text{-}F}$ 8.1), 120.6 (t, $^1J_{C\text{-}F}$ 243.7), 121.3 (t, $^3J_{C\text{-}F}$ 9.0), 127.6, 129.5, 133.7, 135.6, 142.5 (t, $^2J_{C\text{-}F}$ 24.4), 148.9 (t, $^2J_{C\text{-}F}$ 25.3) and 165.6; δ_F (377 MHz, $CDCl_3$) −101.98; *m/z* (ES^+) 579.4 (M^+ + 23, 100%).

Ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-3-oxopentanoate (63). With rigorous exclusion of O_2, SmI_2 (0.1 M in THF, 48 mL, 48 mmol) was added to the aldehyde **39** (0.50 g, 1.6 mmol) and ethyl 2-bromo-2,2-difluoroacetate **11** (0.22 mL, 1.76 mmol) in dry THF (16 mL) and the yellow mixture was stirred at rt for 10 min. Aqueous hydrogen chloride (1 M, 50 mL) was added slowly followed by ether (50 mL). The aqueous phase was extracted with ether (3 × 50 mL) and the organic extracts were washed with saturated aqueous sodium thiosulfate (50 mL) then brine (250 mL) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (0.5:99.5 to 10:90 ether:light petroleum) gave ethyl 5-*tert*-butyldiphenylsilyloxy-2,2-difluoro-3-hydroxypentanoate (0.68 g, 1.57 mmol, 98%) as a colourless oil, R_f = 0.09 (10:90 ether:light petroleum) (Found: M^+ + Na, 459.1797. $C_{23}H_{30}O_4F_2SiNa$ requires M, 459.1779); ν_{max}/cm^{-1} 3476, 3071, 2959, 2931, 2888, 2858, 1759, 1472, 1446, 1307, 1206, 1106, 822 and 738; δ_H (400 MHz, $CDCl_3$) 1.06 [9 H, s, $SiC(CH_3)_3$], 1.39 (3 H, t, *J* 7.0, OCH_2CH_3), 1.87-1.95 (2 H, m, 4-H_2), 3.42 (1 H, br. s, 3-OH), 3.85-4.01 (2 H, m, 5-H_2), 4.39 (2 H, q, *J* 7.0, OCH_2CH_3), 4.44 (1 H, m, 3-H), 7.35-7.50 (6 H, m, ArH) and 7.61-7.75 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 13.9, 19.0, 26.8, 30.8, 61.7, 62.9, 70.9 (dd, $^2J_{C\text{-}F}$ 29.4, 24.8), 114.6 (dd, $^1J_{C\text{-}F}$ 262.6, 252.5), 127.8, 129.9(2), 132.7, 132.8, 135.5(2) and 163.6 (dd, $^2J_{C\text{-}F}$ 33.1, 31.2); δ_F (377 MHz, $CDCl_3$) −123.62 and −114.47 (both d, $^2J_{F\text{-}F}$ 261.2); *m/z* (ES^+) 459.3 (M^+ + 23, 90%) and 102 (100).

N-Methylmorpholine-*N*-oxide (83 mg, 0.71 mmol) and TPAP (8 mg, 0.024 mmol) were added to a suspension of this alcohol (0.21 g, 0.47 mmol) and 4Å molecular sieves (0.27 g) in DCM (2.7 mL) and the mixture stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 0.25:99.75 ether:light petroleum) gave the *title compound* **63** (0.13 g, 0.30 mmol, 63%) as a colourless oil, R_f = 0.29 (10:90 ether:light petroleum) (Found: M^+ + Na, 457.1619. $C_{23}H_{28}O_4F_2SiNa$ requires M, 457.1617); ν_{max}/cm^{-1} 3071, 2957, 2931, 2889, 2857, 1777, 1751, 1428, 1111, 822 and 739; δ_H (500 MHz, $CDCl_3$) 1.04 [9 H, s, $SiC(CH_3)_3$], 1.35 (3 H, t, *J* 7.2, OCH_2CH_3), 2.99 (2 H, t, *J* 6.0, 4-H_2), 4.00 (2 H, t, *J* 6.0, 5-H_2), 4.37 (2 H, q, *J* 7.2, OCH_2CH_3), 7.38-7.48 (6 H, m, ArH) and 7.66-7.71 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.8, 19.1, 26.6, 39.6, 57.8, 63.7, 108.1 (t, $^1J_{C\text{-}F}$ 262.5), 127.7, 129.8, 133.1, 135.5, 161.2 (t, $^2J_{C\text{-}F}$ 30.6) and 195.5 (t, $^2J_{C\text{-}F}$ 28.4); δ_F (471 MHz, $CDCl_3$) −114.16; *m/z* (ES^+) 457.2 (M^+ + 23, 60%).

Methyl (*E*)- and (*Z*)-5-*tert*-butyldiphenylsilyloxy-3-(ethoxycarbonyldifluoromethyl)pent-2-enoate (64) and (65). Methoxycarbonylmethylidene(triphenyl)phosphorane (0.12 g, 0.36 mmol) was added to the ketone **63** (0.13 g, 0.30 mmol) in toluene (1.10 mL) and the mixture stirred at 90 °C for 16 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 2:98 ether:light petroleum) gave the *title compound* **64** (0.12 g, 0.24 mmol, 82%) as a colourless oil, R_f = 0.20 (10:90 ether:light petroleum) (Found: M^+ + Na, 513.1893. $C_{26}H_{32}O_5F_2SiNa$ requires M, 513.1885); ν_{max}/cm^{-1} 2955, 2932, 2858, 1769, 1731, 1279, 1262, 1201, 1181, 1109, 1065, 823 and 740; δ_H (400 MHz, $CDCl_3$) 1.04 [9 H, s, $SiC(CH_3)_3$], 1.29 (3 H, t, *J* 7.3, OCH_2CH_3), 3.06 (2 H, t, *J* 7.2, 4-H_2), 3.70 (3 H, s, OCH_3), 3.78 (2 H, t, *J* 7.2, 5-H_2), 4.26 (2 H, q, *J* 7.3, OCH_2CH_3), 6.33 (1 H, s, 2-H), 7.36-7.46 (6 H, m, ArH) and 7.66-7.70 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.8, 19.1, 26.7, 30.1 (t, $^3J_{C\text{-}F}$ 1.5), 51.6, 62.0, 63.4, 113.1 (t, $^1J_{C\text{-}F}$ 254.9), 123.3 (t, $^3J_{C\text{-}F}$ 8.8), 127.6, 129.6, 133.5, 135.5, 146.0 (t, $^2J_{C\text{-}F}$ 22.1), 162.9 (t, $^2J_{C\text{-}F}$ 33.9) and 165.0; δ_F (377 MHz, $CDCl_3$) −107.08; *m/z* (ES^+) 513.2 (M^+ + 23, 80%), 491.2 (M^+ + 1, 20) and 256.9 (100). The second fraction was the *title compound* **65** (17 mg, 0.035 mmol, 12%) as a colourless oil; δ_H (500 MHz, $CDCl_3$) 1.07 [9 H, s, $SiC(CH_3)_3$], 1.31 (3 H, t, *J* 7.0, OCH_2CH_3), 2.63 (2 H, t, *J* 6.4, 4-H_2), 3.72 (3 H, s, OCH_3), 3.86 (2 H, t, *J* 6.7, 5-H_2), 4.32 (2 H, q, *J* 7.3, OCH_2CH_3), 6.10 (1 H, s, 2-H), 7.37-7.47 (6 H, m, ArH) and 7.66-7.70 (4 H, m, ArH); δ_F (471 MHz, $CDCl_3$) −100.24.

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-5,6-dihydroxyhex-2-enoate (66). Acetonitrile (0.71 mL) and ruthenium(III) chloride hydrate (16 mg, 0.062 mmol) were added to the alkene **59** (0.14 g, 0.31 mmol) in aqueous EtOAc (1:1, 1.42 mL). Sodium periodate (0.066 g, 0.31 mmol) was added in ten equal portions over 5 h and the mixture stirred for a further 30 min before saturated aqueous sodium thiosulfate (10 mL) and EtOAc (10 mL) were added. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 to 50:50 ether:light petroleum) gave recovered alkene **59** (61 mg, 44%) followed by the *title compound* **66** (65 mg, 0.14 mmol, 44%) as a colourless oil, R_f = 0.60 (ether) (Found: M^+ + Na, 501.1898. $C_{25}H_{32}O_5F_2SiNa$ requires M, 501.1885); ν_{max}/cm^{-1} 3401, 2952, 2932, 2889, 2857, 1727, 1428, 1260, 1200, 1105, 1081, 1039, 822 and 738; δ_H (400 MHz, $CDCl_3$) 1.06 [9 H, s, $SiC(CH_3)_3$], 2.85 and 3.07 (each 1 H, dt, *J* 13.6, 6.3, 1'-H), 3.57 (1 H, br. s, OH), 3.69 (3 H, s, OCH_3), 3.82 (2 H, m, 6-H_2), 3.91 (2 H, t, *J* 6.3, 2'-H_2), 4.00 (1 H, m, 5-H), 6.30 (1 H, d, *J* 2.3, 2-H), 7.37-7.48 (6 H, m, ArH) and 7.63-7.70 (4 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.1, 26.8, 30.3, 51.6, 60.6 (dd, $^3J_{C\text{-}F}$ 4.4, 1.5), 63.4, 71.8 (dd, $^2J_{C\text{-}F}$ 32.4, 25.8), 120.6 (dd, $^1J_{C\text{-}F}$ 254.1, 247.5), 122.3 (dd, $^3J_{C\text{-}F}$ 11.1, 8.8), 127.8,

129.9, 132.8, 132.9, 135.5, 135.6, 149.0 (t, $^2J_{C\text{-}F}$ 22.1) and 165.4; δ_F (377 MHz, $CDCl_3$) −117.88 and −107.56 (each d, $^2J_{F\text{-}F}$ 249.0); *m/z* (ES^+) 501.3 (M^+ + 23, 100%).

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-5-hydroxy-6,6-dimethylocta-2,7-dienoate (68). Solid sodium carbonate (39 mg, 0.37 mmol) and lead(IV) acetate (65 mg, 0.15 mmol) were added to the diol **66** (59 mg, 0.12 mmol) in DCM (1.2 mL). The mixture was stirred at rt for 30 min, filtered and concentrated under reduced pressure to give the aldehyde **67** that was azeotroped with benzene. 1-Bromo-3-methylbut-2-ene (0.14 mL, 1.23 mmol) was added to this aldehyde in THF (2.4 mL) and the solution was added to a suspension of zinc dust (80 mg, 1.23 mmol) and titanocene dichloride (3 mg, 0.012 mmol) in THF (2.45 mL) that had been pre-stirred for 5 min. The mixture was stirred for 2.5 h before aqueous hydrogen chloride (10%, 10 mL) and ether (10 mL were added. The aqueous phase was extracted with ether (3 × 30 mL) and the organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum) gave the *title compound* **68** (41 mg, 0.079 mmol, 65%) as a colourless oil, R_f = 0.40 (30:70 ether:light petroleum) (Found: M^+ + Na, 539.2392. $C_{29}H_{38}O_4F_2SiNa$ requires M, 539.2405); ν_{max}/cm^{-1} 3495, 3071, 2957, 2932, 2889, 2858, 1727, 1428, 1261, 1202, 1110, 1072, 916, 823 and 740; δ_H (400 MHz, $CDCl_3$) 1.05 [9 H, s, $SiC(CH_3)_3$], 1.16 (3 H, s, 6-CH_3), 1.18 (3 H, d, *J* 2.0, 6-CH_3), 2.80 (1 H, br. s, OH), 2.85 and 3.06 (each 1 H, dt, *J* 13.4, 6.8, 1'-H), 3.60 (1 H, d, *J* 23.4, 5-H), 3.68 (3 H, s, OCH_3), 3.82-3.90 (2 H, m, 2'-H_2), 5.04-5.11 (2 H, m, 8-H_2), 5.99 (1 H, ddq, *J* 17.4, 10.8, 1.2, 7-H), 6.23 (1 H, d, *J* 2.8, 2-H), 7.36-7.47 (6 H, m, ArH) and 7.65-7.70 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 19.1, 24.1 (t, $^4J_{C\text{-}F}$ 3.6), 24.2, 26.8, 30.9, 41.0, 51.5, 63.3, 76.5 (dd, $^2J_{C\text{-}F}$ 30.9, 26.4), 113.3, 121.4 (dd, $^3J_{C\text{-}F}$ 11.8, 8.2), 122.7 (dd, $^1J_{C\text{-}F}$ 259.3, 249.3), 127.7, 129.7(2), 133.1(2), 135.6(2), 144.1 (d, $^4J_{C\text{-}F}$ 1.8), 150.7 (t, $^2J_{C\text{-}F}$ 21.9) and 165.7; δ_F (377 MHz, $CDCl_3$) −115.62 and −99.51 (each d, $^2J_{F\text{-}F}$ 245.2); *m/z* (ES^+) 539.3 (M^+ + 23, 100%).

Methyl (*E*)-3-(2-*tert*-butyldiphenylsilyloxyethyl)-4,4-difluoro-6,6-dimethyl-5-oxo-octa-2,7-dienoate (69). *N*-Methylmorpholine-*N*-oxide (11 mg, 0.09 mmol) and TPAP (1 mg, 0.003 mmol) were added to a stirred suspension of the alcohol **68** (31 mg, 0.06 mmol) and 4Å molecular sieves (36 mg) in DCM (0.78 mL) and the mixture stirred at rt for 30 min then concentrated under reduced pressure. Chromatography of the residue (2:98 to 10:90 ether:light petroleum) gave the *title compound* **69** (27 mg, 0.053 mmol, 87%) as a colourless oil, R_f = 0.48 (10:90 ether:light petroleum) (Found: M^+ + Na, 537.2264. $C_{29}H_{36}O_4F_2SiNa$ requires M, 537.2249); ν_{max}/cm^{-1} 2932, 2857, 1729, 1428, 1261, 1201, 1109, 1039, 919, 823 and 740; δ_H (500 MHz, $CDCl_3$) 1.03 [9 H, s, $SiC(CH_3)_3$], 1.33 (6 H, s, 2 × 6-CH_3), 2.96 (2 H, t, *J* 7.3, 1'-H_2), 3.69 (3 H, s, OCH_3), 3.74 (1 H, t, *J* 7.3, 2'-H_2), 5.15 (1 H, d, *J* 17.4, 8-H), 5.19 (1 H, d, *J* 10.8, 8-H'), 5.95 (1 H, ddt, *J* 17.4, 10.8, 1.0, 7-H), 6.18 (1 H, t, *J* 1.6, 2-H), 7.36-7.45 (6 H, m, ArH) and 7.65-7.69 (4 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 19.1, 24.0 (t, $^4J_{C\text{-}F}$ 1.8), 26.7, 30.5, 49.7, 51.6, 62.1, 116.1, 116.7 (t, $^1J_{C\text{-}F}$ 257.5), 123.3 (t, $^3J_{C\text{-}F}$ 9.9), 127.6, 129.5, 133.6, 135.6, 139.7, 146.7 (t, $^2J_{C\text{-}F}$ 21.7), 165.0 and 200.5 (t, $^2J_{C\text{-}F}$ 28.9); δ_F (471 MHz, $CDCl_3$) −102.04; *m/z* (ES^+) 537 (M^+ + 23, 100%), 437 (20) and 259 (80).

3,3-Difluoro-2-hydroxy-2-(3-methylbut-1-en-3-yl)-4-[(*E*)-methoxycarbonylmethylene]tetrahydro-4*H*-pyran (70). Hydrogen fluoride.pyridine complex (70% HF, 0.2 mL) was added rapidly to the ketone **69** (34 mg, 0.066 mmol) and pyridine (0.39 mL) in THF (3.9 mL) at 0 °C and the mixture stirred for 2.5 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was stirred at rt for 1 h. After the addition of EtOAc (10 mL), the aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum) gave the *title compound* **70** (15 mg, 0.054 mmol, 82%) as a colourless oil which solidified on cooling, R_f = 0.31 (30:70 ether:light petroleum), m.p. 54-56 °C (Found: C, 56.61; H, 6.64. $C_{13}H_{18}O_4F_2$ requires C, 56.50; H, 6.60%; Found: M^+ + Na, 299.1071. $C_{13}H_{18}O_4F_2Na$ requires M, 299.1071); ν_{max}/cm^{-1} 3515, 2956, 2918, 2850, 1729, 1127 and 1061: δ_H (400 MHz, benzene-d_6) 1.28 (3 H, d, *J* 4.0, 3'-CH_3 or 4'-H_3), 1.37 (3 H, d, *J* 2.5, 4'-H_3 or 3'-CH_3), 2.41 (1 H, dd, *J* 13.4, 6.6, 5-H), 2.46 (1 H, d, *J* 3.5, OH), 3.24 (3 H, s, OCH_3), 3.41 (1 H, dd, *J* 11.1, 6.6, 5-H'), 3.76 and 3.97 (each 1 H, m, 6-H), 4.82-4.93 (2 H, m, 1'-H_2), 6.06 (1 H, dd, *J* 17.9, 10.6, 2'-H) and 6.44 (1 H, dd, *J* 4.0, 2.3, 4-CH); δ_C (125 MHz, benzene-d_6) 21.8 and 24.1 (each d, $^4J_{C\text{-}F}$ 6.3), 28.6 (d, $^3J_{C\text{-}F}$ 2.7), 46.5, 51.3, 60.5, 99.1 (dd, $^2J_{C\text{-}F}$ 30.1, 24.4), 115.4, 117.4 (dd, $^3J_{C\text{-}F}$ 13.5, 6.3), 118.4 (dd, $^1J_{C\text{-}F}$ 263.6, 243.7), 144.5, 148.8 (dd, $^2J_{C\text{-}F}$ 20.8, 18.1) and 166.3; δ_F (377 MHz, benzene-d_6) −119.61 and −105.38 (each d, $^2J_{F\text{-}F}$ 241.5); *m/z* (ES^+) 299.1 (M^+ + 23, 100%).

(3*R*,5*R*,6*R*)-3,6-Bis(*tert*-butyldimethylsilyloxy)-5-(2-trimethylsilylethoxy)methoxyheptanal (72). A stream of ozone was bubbled through the alkene **71** (0.30 g, 0.58 mmol) in DCM (6.3 mL) at −78 °C for 5 min until a blue colour persisted. The system was purged with oxygen for 10 min, triphenylphosphine (0.31 g, 1.16 mmol) was added and the mixture was stirred at r.t. for 3 h. Chromatography of the residue (2:98 to 3:97 ether:light petroleum) gave the *title compound* **72** (0.29 g, 0.56 mmol, 96%), as a colourless oil, R_f = 0.23 (10:90 ether:light petroleum) (Found: M^+ + Na, 543.3352. $C_{25}H_{56}O_5Si_3Na$ requires M, 543.3333); ν_{max}/cm^{-1} 2954, 2928, 2887, 2857, 1726, 1472, 1434, 1250, 1102, 1054, 1033, 810, 774 and 742; δ_H (400 MHz, $CDCl_3$) 0.03 (9 H, s, 3 × $SiCH_3$), 0.06, 0.07, 0.08 and 0.10 (each 3 H, s, $SiCH_3$), 0.88 and 0.89 [each 9 H, s, $SiC(CH_3)_3$], 0.90-1.01 (2 H, m, $SiCH_2$), 1.08 (3 H, d, *J* 6.3, 7-H_3), 1.55 (1 H, m, 4-H), 1.93 (1 H, ddd, *J* 14.4, 7.8, 2.8, 4-H'), 2.53 (1 H, ddd, *J* 15.6, 5.0, 2.0, 2-H), 2.65 (1 H, ddd, *J* 15.9, 5.6, 2.8, 2-H'), 3.49-3.57 (2 H, m, 5-H, OHC*H*CH_2Si), 3.67 (1 H, ddd, *J* 11.3, 9.6, 5.6, O*H*CHCH_2Si), 4.05 (1 H, m, 6-H), 4.35 (1 H, m, 3-H), 4.69 and 4.73 (each 1 H, d, *J* 6.9, OHC*H*O) and 9.84 (1 H, t, *J* 2.8, 1-H); δ_C (100 MHz, $CDCl_3$) −4.8, −4.7, −4.4, −4.3, −1.5, 17.0, 17.9, 18.0, 18.1, 25.8(2), 36.8, 51.7, 65.5, 66.2, 68.8, 79.7, 95.7 and 202.3; *m/z* (ES^-) 557.4 ($[M + 37]^-$, 50%) and 555.4 ($[M + 35]^-$, 100).

(6*S*,8*R*,9*R*)-6,9-Bis(*tert*-butyldimethylsilyloxy)-3,3-difluoro-8-(2-trimethylsilylethoxy)methoxydec-1-en-4-ol (73). Indium powder (49 mg, 0.42 mmol) and 3-bromo-3,3-difluoroprop-1-ene **37** (66 mg, 0.42 mmol) were added to a vigorously stirred solution of the aldehyde **72** (from 73 mg of alkene **71**) in DMF (0.71 mL) and the stirring continued for 4 h. Saturated aqueous ammonium chloride (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 to 5:95 ether:light petroleum) gave the *title compound* **73** (56 mg, 0.094 mmol, 66% from alkene **71**), as a colourless oil, a 53:47 mixture in favour of the less polar diastereoisomer (^{19}F NMR), R_f = 0.19 (10:90 ether:light petroleum) (Found: M^+ + Na, 621.3619. $C_{28}H_{60}O_5F_2Si_3Na$ requires M, 621.3614); ν_{max}/cm^{-1} 2954, 2929, 2858, 1472, 1420, 1250, 1101, 1055, 1032 and 1004; *m/z* (ES^+) 621.4 (M^+ + 23, 30%), 599.4 (M^+ + 1, 20) and 481.3 (100). Repeated chromatography gave a sample of the less polar diastereoisomer; δ_H (400 MHz, $CDCl_3$) 0.03 (9 H, s, 3 × $SiCH_3$), 0.06, 0.07, 0.11 and 0.12 (each 3 H, s, $SiCH_3$), 0.89 and 0.90 [each 9 H, s, $SiC(CH_3)_3$], 0.91-0.97 (2 H, m, $SiCH_2$), 1.10 (3 H, d, *J* 6.0, 10-H_3), 1.67 (1 H, m, 7-H), 1.75-1.89 (2 H, m, 5-H_2), 1.98 (1 H, ddd, *J* 14.4, 6.0, 3.0, 7-H'), 3.45 (1 H, m, 8-H), 3.53 and 3.66 (each 1 H, m, OHC*H*CH_2Si), 3.84 (2 H, d, *J* 2.0, 4-OH), 4.05 (1 H, m, 9-H), 4.16-4.27 (2 H, m, 4-H, 6-H), 4.67 and 4.71 (each 1 H, d, *J* 7.1, OHC*H*O), 5.52 (1 H, d, *J* 11.1, 1-H), 5.71 (1 H, m, 1-H') and 6.03 (1 H, m, 2-H); δ_C (125 MHz, $CDCl_3$) −4.8, −4.7(2), −4.5, −1.5, 17.0, 17.9, 18.0, 18.1, 25.8, 25.9, 35.0, 35.2, 65.4, 69.0, 69.7, 70.7 (t, $^2J_{C\text{-}F}$ 29.8), 80.0, 95.6, 119.9 (dd, $^1J_{C\text{-}F}$ 239.2, 241.9), 120.6 (t, $^3J_{C\text{-}F}$ 9.0) and 130.4 (t, $^2J_{C\text{-}F}$ 25.3); δ_F (377 MHz, $CDCl_3$) −114.86 (d, $^2J_{F\text{-}F}$ 249.7) and −108.30 (d, $^2J_{F\text{-}F}$ 248.3). Further elution gave the more polar diastereoisomer; δ_H (400 MHz, $CDCl_3$) 0.02 (9 H, s, 3 × $SiCH_3$), 0.06, 0.07, 0.09 and 0.10 (each 3 H, s, $SiCH_3$), 0.89 and 0.90 [each 9 H, s, $SiC(CH_3)_3$], 0.91-0.97 (2 H, m, $SiCH_2$), 1.08 (3 H, d, *J* 6.3, 10-H_3), 1.62-1.72 (2 H, m, 7-H, 5-H), 1.87-1.97 (2 H, m, 7-H', 5-H'), 3.47-3.58 (3 H, m, 8-H, OHC*H*CH_2Si, 4-OH), 3.67 (1 H, m, O*H*CHCH_2Si), 3.99-4.12 (3 H, m, 4-H, 6-H, 9-H), 4.69 and 4.73 (each 1 H, d, *J* 6.8, OHC*H*O), 5.52 (1 H, d, *J* 11.1, 1-H), 5.71 (1 H, d, *J* 17.4, 1-H') and 6.02 (1 H, m, 2-H); δ_C (100 MHz, $CDCl_3$) −4.8(2), −4.6, −4.3, −1.5, 16.9, 17.9, 18.0, 18.1, 25.8(2), 36.0, 36.8 (t, $^3J_{C\text{-}F}$ 2.2), 65.7, 68.7, 69.9, 70.9 (t, $^2J_{C\text{-}F}$ 29.9), 80.0, 95.3, 119.9 (dd, $^1J_{C\text{-}F}$ 239.9, 242.1), 120.6 (t, $^3J_{C\text{-}F}$ 8.8) and 130.3 (t, $^2J_{C\text{-}F}$ 25.5); δ_F (377 MHz, $CDCl_3$) −114.45 and −108.07 (both d, $^2J_{F\text{-}F}$ 248.3).

(6*R*,8*R*,9*R*)-6,9-Bis(*tert*-butyldimethylsilyloxy)-3,3-difluoro-8-(2-trimethylsilylethoxy)methoxydec-1-en-4-one (74). *N*-Methylmorpholine-*N*-oxide (19 mg, 0.16 mmol) and TPAP (4 mg, 0.011 mmol) were added to a suspension of a mixture of the diastereoisomers of the alcohol **73** (63 mg, 0.105 mmol) and 4Å molecular sieves (65 mg) in DCM (1.1 mL). The mixture stirred at rt for 16 h then concentrated under reduced pressure. Chromatography of the residue (0.5:99.5 to 5:95 ether:light petroleum) gave the *title compound* **74** as a colourless oil (47 mg, 0.079 mmol, 75%), R_f = 0.59 (10:90 ether:light petroleum) (Found: M^+ + Na, 619.3461. $C_{28}H_{58}O_5F_2Si_3Na$ requires M, 619.3458); ν_{max}/cm^{-1} 2954, 2929, 2887, 2858, 1746, 1472, 1379, 1250, 1099, 1055, 1033, 1004, 938, 859, 831, 810 and 774; δ_H (400 MHz, $CDCl_3$) 0.02 (9 H, s, 3 × $SiCH_3$), 0.03, 0.06(2) and 0.10 (each 3 H, s, $SiCH_3$), 0.85 and 0.88 [each 9 H, s, $SiC(CH_3)_3$], 0.91-1.01 (2 H, m, $SiCH_2$), 1.07 (3 H, d, *J* 6.3, 10-H_3), 1.53 (1 H, m, 7-H), 1.84 (1 H, ddd, *J* 14.4, 6.5, 2.8, 7-H'), 2.84-2.97 (2 H, m, 5-H_2), 3.49-3.59 (2 H, m, 8-H, O*H*CHCH_2Si), 3.66 (1 H, m, OHC*H*CH_2Si), 4.03 (1 H, m, 9-H), 4.37 (1 H, m, 6-H), 4.67 and 4.71 (each 1 H, d, *J* 7.1, OHC*H*O), 5.64 (1 H, d, *J* 10.7, 1-H), 5.83 (1 H, m, 1-H') and 5.97 (1 H, m, 2-H); δ_C (100 MHz, $CDCl_3$) −4.8, −4.7(2), −4.4, −1.5, 17.1, 17.9, 18.0, 18.1, 25.8, 25.9, 36.8, 45.2, 65.5, 66.0, 68.9, 79.7, 95.5, 114.2 (t, $^1J_{C\text{-}F}$ 249.4), 122.9 (t, $^3J_{C\text{-}F}$ 9.5), 128.4 (t, $^2J_{C\text{-}F}$ 25.1) and 198.1 (t, $^2J_{C\text{-}F}$ 31.4); δ_F (377 MHz, $CDCl_3$) −108.87 and −108.03 (each d, $^2J_{F\text{-}F}$ 266.0); *m/z* (ES^+) 619.4 (M^+ + 23, 100%).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-(1,1-difluoropropenyl)-7-(2-trimethylsilylethoxy)methoxynon-2-enoate (75). Methoxycarbonylmethylene(triphenyl)-phosphorane (0.12 g, 0.36 mmol) was added to the ketone **74** (0.18 g, 0.30 mmol) in toluene (1.5 mL) and the mixture heated at 90 °C for 16 h. After allowing to cool to rt, the reaction mixture was concentrated under reduced pressure. Chromatography of the residue (1:99 to 2:98 ether:light petroleum) gave recovered starting material (18 mg, 10%) followed by the *title compound* **75** (0.124 g, 0.19 mmol, 64%) as a clear oil, R_f = 0.37 (10:90 ether:light petroleum) (Found: M^+ + Na, 675.3719. $C_{31}H_{62}O_6F_2Si_3Na$ requires M, 675.3720); ν_{max}/cm^{-1} 2953, 2929, 2887, 2857, 1732, 1250, 1196, 1178, 1100, 1052, 1033, 857, 832, 810 and 774; δ_H (400 MHz, $CDCl_3$) 0.02 (9 H, s, 3 × $SiCH_3$), 0.05, 0.06, 0.07 and 0.08 (each 3 H, s, $SiCH_3$), 0.87 and 0.89 [each 9 H, s, $SiC(CH_3)_3$], 0.90-1.01 (2 H, m, $SiCH_2$), 1.05 (3 H, d, *J* 6.3, 9-H_3), 1.45 (1 H, m, 6-H), 1.73 (1 H, dd, *J* 14.2, 8.3, 6-H'), 2.87 (1 H, dd, *J* 12.8, 6.5, 4-H), 2.98 (1 H, dd, *J* 12.8, 7.6, 4-H'), 3.47-3.56 (2 H, m, 7-H, O*H*CHCH_2Si), 3.68 (1 H, m, OHC*H*CH_2Si), 3.74 (3 H, s, OCH_3), 4.01 (1 H, m, 8-H), 4.12 (1 H, m, 5-H), 4.71 (2 H, s, OCH_2O), 5.53 (1 H, d, *J* 11.0, 3'-H), 5.71 (1 H, d, *J* 17.1, 3'-H'), 5.92 (1 H, m, 2'-H) and 6.20 (1 H, s, 2-H); δ_C (100 MHz, $CDCl_3$) −4.8(2), −4.6, −4.1, −1.5, 17.3, 17.9, 18.0, 18.1, 25.9(2), 35.6, 36.1, 51.5, 65.2, 68.9, 69.1, 80.1, 95.9, 118.9 (t, $^1J_{C\text{-}F}$ 240.7), 120.6 (t, $^3J_{C\text{-}F}$ 8.8), 122.0 (t, $^3J_{C\text{-}F}$ 8.0), 131.8 (t, $^2J_{C\text{-}F}$ 28.4), 149.4 (t, $^2J_{C\text{-}F}$ 24.8) and 165.8; δ_F (377 MHz, $CDCl_3$) −99.44 and −98.74 (each d, $^2J_{F\text{-}F}$ 252.4); *m/*z (ES^+) 675.4 (M^+ + 23, 50%) and 101.4 (100).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-(1,1-difluoro-2,3-dihydroxypropyl)-7-(2-(trimethylsilylethoxy)methoxynon-2-enoate (76). Acetonitrile (0.34 mL) and ruthenium(III) chloride hydrate (40 mg, 0.016 mmol) were added to the alkene **75** (51 mg, 0.078 mmol) in a mixture of EtOAc and water (1:1, 0.34 mL). Sodium periodate (20 mg, 0.094 mmol) was then added in ten equal portions over 9 h. After stirring for a further 30 min, saturated aqueous sodium sulfite (5 mL) and EtOAc (5 mL) were added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 to 40:60 ether:light petroleum) gave recovered alkene **75** (20 mg, 39%) followed by the *title compound* **76** (33

mg, 0.048 mmol, 61%), as a colourless oil, a 55:45 mixture of diastereoisomers (^{19}F NMR), R_f = 0.15 (50:50 ether:light petroleum) (Found: M^+ + Na, 709.3753. $C_{31}H_{64}O_8F_2Si_3Na$ requires M, 709.3775); ν_{max}/cm^{-1} 3394, 2953, 2929, 2894, 2857, 1730, 1472, 1463, 1378, 1250, 1101, 1055, 1033, 834 and 774; δ_H (500 MHz, $CDCl_3$) 0.02 (9 H, s, 3 × $SiCH_3$), 0.05, 0.06(2), 0.07 and 0.08 (each 3 H, s, $SiCH_3$), 0.88 and 0.89 [each 9 H, s, $SiC(CH_3)_3$], 0.90-1.01 (2 H, m, $SiCH_2$), 1.05 (3 H, d, *J* 6.3, 9-H_3), 1.51 (1 H, m, 6-H), 1.77 (0.55 H, ddd, *J* 14.5, 7.9, 1.3, 6-H'), 1.85 (0.45 H, ddd, *J* 14.5, 6.7, 1.6, 6-H'), 2.23 (1 H, br. s, OH), 2.78 (0.45 H, dd, *J* 12.9, 6.3, 4-H), 2.85 (0.55 H, dd, *J* 13.6, 7.9, 4-H), 3.14 (0.55 H, ddd, *J* 13.6, 6.0, 0.7, 4-H'), 3.20 (0.45 H, dd, *J* 12.9, 8.2, 4-H'), 3.46-3.56 (2 H, m, 7-H, O*H*CHCH$_2$Si), 3.67 (1 H, m, OHC*H*CH$_2$Si), 3.75 (3 H, s, OCH_3), 3.78-3.88 (2 H, m, 2'-H, 3'-H), 3.97-4.06 (2 H, m, 8-H, 3'-H'), 4.11 (0.55 H, m, 5-H), 4.24 (0.45 H, dt, *J* 13.3, 6.3, 5-H), 4.71 (1 H, d, *J* 7.0, O*H*CHO), 4.73 (0.45 H, d, *J* 7.0, OHC*H*O), 4.75 (0.55 H, d, *J* 7.0, OHC*H*O) and 6.25 (1 H, s, 2-H); δ_C (125 MHz, $CDCl_3$) −4.8, −4.7, −4.6, −4.1, −4.0, −1.5, 17.1, 17.4, 18.0(2), 18.1, 25.9(2), 35.7, 36.0, 36.5, 51.5, 60.7 (t, $^3J_{C\text{-}F}$ 3.6), 60.9 (dd, $^3J_{C\text{-}F}$ 5.4, 1.8), 65.4, 65.6, 69.0(2), 70.5, 72.5 (dd, $^2J_{C\text{-}F}$ 32.5, 27.1), 73.1 (dd, $^2J_{C\text{-}F}$ 32.5, 25.3), 80.5, 80.6, 95.9, 120.3 (t, $^1J_{C\text{-}F}$ 248.8), 121.0 (dd, $^1J_{C\text{-}F}$ 253.3, 244.2), 122.3 and 123.6 (each dd, $^3J_{C\text{-}F}$ 11.3, 7.7), 147.8 (dd, $^2J_{C\text{-}F}$ 23.5, 20.8), 149.5 (dd, $^2J_{C\text{-}F}$ 24.4, 19.9) and 165.6(2); δ_F (471 MHz, $CDCl_3$) −115.11 (0.55 F, d, $^2J_{F\text{-}F}$ 249.9), −113.55 (0.45 F, d, $^2J_{F\text{-}F}$ 249.9), −107.39 (0.55 F, d, $^2J_{F\text{-}F}$ 249.9) and −107.28 (0.45 F, d, $^2J_{F\text{-}F}$ 248.2); *m/z* (ES^+) 709.4 (M^+ + 23, 70%), 611.2 (50) and 569.3 (100).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-(1,1-difluoro-2-hydroxy-3,3-dimethylpent-4-enyl)-7-(2-trimethylsilylethoxy)methoxynon-2-enoate (77). Solid sodium carbonate (60 mg, 0.56 mmol) and lead(IV) acetate (0.10 g, 0.22 mmol) were added to the diol **76** (0.13 g, 0.186 mmol) in dry DCM (1.9 mL). After stirring at rt for 90 min, the reaction mixture was filtered through Celite® and concentrated under reduced pressure to give an oil that was dissolved in THF (3.8 mL). 1-Bromo-3-methylbut-2-ene (0.22 mL, 1.86 mmol) was added and the solution added to a stirred suspension of zinc dust (0.12 g, 1.86 mmol) and titanocene dichloride (5 mg, 0.02 mmol) in THF (3.8 mL). After stirring for 16 h, aqueous hydrogen chloride (10%, 20 mL) and EtOAc (20 mL) were added. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the organic extracts were washed with brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (3:97 to 5:95 ether:light petroleum) gave the *title compound* **77** (94 mg, 0.13 mmol, 70%) as a colourless oil, a 50:50 mixture of diastereoisomers (^{19}F NMR), R_f = 0.49 (30:70 ether:light petroleum) (Found: M^+ + Na, 747.4294. $C_{35}H_{70}O_7F_2Si_3Na$ requires M, 747.4295); ν_{max}/cm^{-1} 3449, 2954, 2929, 2894, 2857, 1730, 1472, 1463, 1378, 1362, 1251, 1196, 1180, 1151, 1103, 1071, 1057, 1033, 835 and 775; δ_H (400 MHz, $CDCl_3$) 0.02 (9 H, s, 3 × $SiCH_3$), 0.06 and 0.08 (each 6 H, s, 2 × $SiCH_3$), 0.88 and 0.89 [each 9 H, s, $SiC(CH_3)_3$], 0.90-0.98 (2 H, m, $SiCH_2$), 1.03 and 1.05 (each 1.5 H, d, *J* 6.1, 9-H_3), 1.19 and 1.21 (each 3 H, s, 3'-CH_3), 1.50 and 1.75 (each 1 H, m, 6-H), 2.68 (0.5 H, br. s, OH), 2.74 (0.5 H, dd, *J* 12.8, 6.0, 4-H), 2.85 (1 H, m, OH, 4-H), 3.08 (0.5 H, dd, *J* 12.8, 7.0, 4-H'), 3.18 (0.5 H, dd, *J* 12.8, 8.6, 4-H'), 3.44-3.56 (3 H, m, 7-H, 2'-H, O*H*CHCH$_2$Si), 3.68 (1 H, m, OHC*H*CH$_2$Si), 3.73 (3 H, s, OCH_3), 4.04 (1.5 H, m, 8-H, 5-H), 4.12 (0.5 H, m, 5-H), 4.71 and 4.72 (each 1 H, d, *J* 7.0, O*H*CHO), 5.05-5.12 (2 H, m, 5'-H_2), 6.00 (1 H, m, 4'-H) and 6.16 and 6.21 (each 0.5 H, m, 2-H); δ_C (100 MHz, $CDCl_3$) −4.8(3), −4.7, −4.6, −4.1, −4.0, −1.5, 15.3, 17.1, 17.2, 17.9, 18.0, 24.0(2), 24.2, 24.4, 25.8, 25.9(2), 35.4, 35.9, 36.0, 36.3, 41.2, 41.3, 51.4(2), 65.2, 65.3, 65.8, 68.8(2), 69.1, 69.7, 77.2, 78.1 (dd, $^2J_{C\text{-}F}$ 31.4, 25.5), 78.2, 80.4, 80.7, 95.9(2), 112.5, 112.9, 113.4, 113.8, 121.8 (t, $^3J_{C\text{-}F}$ 9.5), 122.4 (dd, $^1J_{C\text{-}F}$ 253.8, 250.9), 122.6 (dd, $^3J_{C\text{-}F}$ 11.7, 7.3), 122.8 (dd, $^1J_{C\text{-}F}$ 257.4, 247.2), 144.1, 144.3, 149.6 (dd, $^2J_{C\text{-}F}$ 23.3, 21.1), 151.1 (dd, $^2J_{C\text{-}F}$ 24.8, 21.2), 165.8 and 165.9; δ_F (377 MHz, $CDCl_3$) −113.53 (0.5 F, d, $^2J_{F\text{-}F}$ 246.9), −112.33 (0.5 F, d, $^2J_{F\text{-}F}$ 245.6), −99.26 (0.5 F, d, $^2J_{F\text{-}F}$ 245.6) and −98.71 (0.5 F, d, $^2J_{F\text{-}F}$ 245.5); *m/z* (ES^+) 753.6 (50%), 747.4 (M^+ + 23, 50) and 608.4 (100).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-(1,1-difluoro-3,3-dimethyl-2-oxopent-4-enyl)-7-(2-trimethylsilylethoxy)methoxynon-2-enoate (78). *N*-Methylmorpholine-*N*-oxide (31 mg, 0.265 mmol) and TPAP (7 mg, 0.02 mmol) were added to a suspension of the alcohol **77** (96 mg, 0.13 mmol) and 4Å molecular sieves (0.11 g) in DCM (0.89 mL) and the mixture was stirred at rt for 16 h then concentrated under reduced pressure. Chromatography of the residue (2:98 to 3:97 ether:light petroleum) gave the *title compound* **78** as a colourless oil (57 mg, 0.079 mmol, 60%), R_f = 0.44 (10:90 ether:light petroleum) (Found: M^+ + Na, 745.4164. $C_{35}H_{68}O_7F_2Si_3Na$ requires M, 745.4139); ν_{max}/cm^{-1} 2953, 2929, 2887, 2857, 1731, 1472, 1362, 1250, 1197, 1180, 1101, 1054, 1033, 832, 809 and 774; δ_H (400 MHz, $CDCl_3$) 0.01 (9 H, s, 3 × $SiCH_3$), 0.05(2) and 0.07(2) (each 3 H, s, $SiCH_3$), 0.86 and 0.88 [each 9 H, s, $SiC(CH_3)_3$], 0.91-0.97 (2 H, m, $SiCH_2$), 1.03 (3 H, d, *J* 6.1, 9-H_3), 1.35 (6 H, s, 2 × 3'-CH_3), 1.41 (1 H, m, 6-H), 1.70 (1 H, dd, *J* 14.2, 8.6, 6-H'), 2.88 (2 H, d, *J* 7.1, 4-H_2), 3.47-3.54 (2 H, m, 7-H, O*H*CHCH$_2$Si), 3.68 (1 H, m, OHC*H*CH$_2$Si), 3.73 (3 H, s, OCH_3), 4.03 (2 H, m, 5-H, 8-H), 4.70 (2 H, s, OCH_2O), 5.17 (1 H, d, *J* 17.6, 5'-H), 5.22 (1 H, d, *J* 10.5, 5'-H'), 5.97 (1 H, dd, *J* 17.4, 10.5, 4'-H) and 6.15 (1 H, s, 2-H); δ_C (125 MHz, $CDCl_3$) −4.8, −4.7, −4.6, −4.1, −1.5, 17.2, 17.9, 18.0, 18.1, 24.1(2), 25.9(2), 35.7, 36.0, 49.8, 51.6, 65.1, 69.0, 69.1, 80.1, 96.0, 116.1, 116.8 (t, $^1J_{C\text{-}F}$ 258.2), 124.0 (t, $^3J_{C\text{-}F}$ 9.0), 139.8, 146.8 (t, $^2J_{C\text{-}F}$ 21.7), 165.2 and 200.4 (t, $^2J_{C\text{-}F}$ 28.9); δ_F (377 MHz, $CDCl_3$) −101.24 and −100.50 (each d, $^2J_{F\text{-}F}$ 267.4); *m/z* (ES^+) 745.4 (M^+ + 23, 100%) and 605.4 (100).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-(1,1-difluoro-3,3-dimethyl-2-oxopent-4-enyl)-7-hydroxynon-2-enoate (79). Nitromethane (0.038 mL, 0.70 mmol) was added to a suspension of magnesium bromide (64 mg, 0.35 mmol) in ether (0.23 mL) followed by the SEM-protected hydroxyketone **78** (18 mg, 0.025 mmol) in ether (0.23 mL), and the mixture stirred at rt for 2 h. Water (10 mL) and EtOAc (10 mL) were added and the aqueous phase extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (3:97 ether:light petroleum) gave the *title compound* **79** (11 mg, 0.019 mmol, 74%) as a

colourless oil, R_f = 0.32 (10:90 ether:light petroleum) (Found: [M-H]$^-$, 591.3346. $C_{29}H_{53}O_6F_2Si_2$ requires M, 591.3349); ν_{max}/cm^{-1} 2954, 2930, 2887, 2857, 1731, 1472, 1463, 1363, 1252, 1197, 1179, 1071, 1036, 1005, 953, 917, 872 and 775; δ_H (400 MHz, $CDCl_3$) 0.03, 0.06, 0.07 and 0.09 (each 3 H, s, $SiCH_3$), 0.87 (18 H, s, 2 × $SiC(CH_3)_3$], 1.14 (3 H, d, *J* 6.1, 9-H_3), 1.36 (6 H, s, 2 × 3'-CH_3), 1.41-1.55 (2 H, m, 6-H_2), 2.28 (1 H, s, OH), 2.83 (1 H, dd, *J* 13.0, 6.4, 4-H), 3.02 (1 H, dd, *J* 12.5, 8.6, 4-H'), 3.50 (1 H, m, 7-H), 3.61 (1 H, m, 5-H or 8-H), 3.73 (3 H, s, OCH_3), 4.20 (1 H, m, 8-H or 5-H), 5.19 (1 H, d, *J* 17.4, 5'-H), 5.23 (1 H, d, *J* 10.8, 5'-H'), 5.98 (1 H, dd, *J* 17.4, 10.8, 4'-H) and 6.14 (1 H, s, 2-H); δ_C (125 MHz, $CDCl_3$) −5.0(2), -4.4, −4.2, 17.9, 18.0, 20.1, 24.0(2), 25.8, 25.9, 35.4, 40.5, 49.8 (t, $^3J_{C\text{-}F}$ 1.8), 51.6, 68.4, 71.7, 71.8, 116.2, 116.8 (t, $^1J_{C\text{-}F}$ 259.1), 123.8 (t, $^3J_{C\text{-}F}$ 9.0), 139.7, 147.4 (t, $^2J_{C\text{-}F}$ 20.8), 165.2 and 200.3 (t, $^2J_{C\text{-}F}$ 28.9); δ_F (376 MHz, $CDCl_3$) −101.50 and −100.00 (each d, $^2J_{F\text{-}F}$ 271.5); *m/z* (ES$^+$) 615.3 (M$^+$ + 23, 55%) and 593.3 (M$^+$ + 1, 100).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-7-butanoyloxy-3-(1,1-difluoro-3,3-dimethyl-2-oxopent-4-enyl)non-2-enoate (80). 2,4,6-Trichlorobenzoyl chloride (0.015 mL, 0.098 mmol) and triethylamine (0.03 mL, 0.22 mmol) were added to butanoic acid (9 μL, 0.1 mmol) in toluene (0.25 mL) and the solution stirred at rt for 1.5 h. The alcohol **79** (29 mg, 0.049 mmol) and DMAP (6 mg, 0.049 mmol) in toluene (0.5 mL) were added and the solution stirred at rt for 16 h. Saturated aqueous ammonium chloride (10 mL) and ether (10 mL) were added and the aqueous phase extracted with ether (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 to 2:98 ether:light petroleum) gave the *title compound* **80** (26 mg, 0.039 mmol, 80%) as a colourless oil, R_f = 0.47 (10:90 ether:light petroleum) (Found: M$^+$ + H, 663.3948. $C_{33}H_{61}O_7F_2Si_2$ requires M, 663.3924); ν_{max}/cm^{-1} 2955, 2930, 2857, 1731, 1472, 1463, 1362, 1251, 1180, 1103, 1072, 1036, 939, 917, 872, 835, 809 and 775; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, $SiCH_3$), 0.05 (6 H, s, 2 × $SiCH_3$), 0.07 (3 H, s, $SiCH_3$), 0.87 and 0.88 [each 9 H, s, $SiC(CH_3)_3$], 0.94 (3 H, t, *J* 7.3, CH_2CH_3), 0.99 (3 H, d, *J* 6.3, 9-H_3), 1.36 (6 H, s, 2 × 3'-CH_3), 1.58 (1 H, m, 6-H), 1.63 (2 H, sext, *J* 7.3, CH_2CH_3), 1.72 (1 H, m, 6-H'), 2.25 [2 H, t, *J* 7.4, $C(O)CH_2$], 2.80 (1 H, dd, *J* 13.0, 6.1, 4-H), 2.92 (1 H, dd, *J* 13.0, 8.5, 4-H'), 3.75 (3 H, s, OCH_3), 3.1-3.96 (2 H, m, 5-H, 8-H), 4.87 (1 H, ddd, *J* 10.5, 4.3, 1.4, 7-H), 5.18 (1 H, d, *J* 17.4, 5'-H), 5.23 (1 H, d, *J* 10.7, 5'-H'), 5.97 (1 H, dd, *J* 17.4, 10.6, 4'-H) and 6.15 (1 H, s, 2-H); δ_C (125 MHz, $CDCl_3$) −5.1, −4.9, −4.8, −4.2, 13.8, 17.8, 17.9(2), 18.3, 24.0, 24.1, 25.8, 25.9, 34.9, 35.7, 36.4, 49.8, 51.7, 67.5, 67.9, 73.5, 116.2, 116.7 (t, $^1J_{C\text{-}F}$ 258.2), 124.0 (t, $^3J_{C\text{-}F}$ 9.0), 139.7, 146.6 (t, $^2J_{C\text{-}F}$ 21.7), 165.2, 173.0 and 200.4 (t, $^2J_{C\text{-}F}$ 28.9); δ_F (377 MHz, $CDCl_3$) −101.13 and −100.29 (each d, $^2J_{F\text{-}F}$ 268.8); *m/z* (ES$^+$) 685.9 (M$^+$ + 23, 100%) and 663.4 (M$^+$ + 1, 70).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-7-(2-methylpropanoyloxy)-3-(1,1-difluoro-3,3-dimethyl-2-oxopent-4-enyl)non-2-enoate (81). Following the procedure outlined for the synthesis of the ester **80**, 2-methylpropanoic acid (0.038 mL, 0.41 mmol) in dry toluene (1.0 mL), 2,4,6-trichlorobenzoyl chloride (0.063 mL, 0.41 mmol), triethylamine (0.11 mL, 0.81 mmol), the alcohol **79** (0.11 g, 0.20 mmol) and DMAP (25 mg, 0.20 mmol) in toluene (2.0 mL), after chromatography (1:99 to 2:98 ether:light petroleum), gave the *title compound* **81** (0.125 g, 0.189 mmol, 94%) as a colourless oil, R_f = 0.54 (10:90 ether:light petroleum), $[\alpha]_D^{20}$ = 0.1 (*c* 1.0, $CHCl_3$) (Found: M$^+$ + H, 663.3920. $C_{33}H_{61}O_7F_2Si_2$ requires M, 663.3924); ν_{max}/cm^{-1} 2954, 2929, 2856, 1731, 1472, 1251, 1195, 1154, 1104, 1070, 1036, 835, 809 and 775; δ_H (500 MHz, $CDCl_3$) 0.02, 0.04(2) and 0.06 (each 3 H, s, $SiCH_3$), 0.86 and 0.87 [each 9 H, s, $SiC(CH_3)_3$], 0.99 (3 H, d, *J* 6.3, 9-H_3), 1.13 and 1.14 (each 3 H, d, *J* 7.0, $CHCH_3$), 1.35 (6 H, s, 2 × 3'-CH_3), 1.59 (1 H, ddd, *J* 14.1, 10.7, 2.9, 6-H), 1.72 (1 H, ddd, *J* 14.5, 9.5, 1.7, 6-H'), 2.49 (1 H, hept, *J* 7.0, 2''-H), 2.79 (1 H, dd, *J* 13.1, 5.8, 4-H), 2.90 (1 H, dd, *J* 13.0, 8.6, 4-H'), 3.73 (3 H, s, OCH_3), 3.89-3.96 (2 H, m, 5-H, 8-H), 4.84 (1 H, ddd, *J* 10.7, 4.1, 1.6, 7-H), 5.17 (1 H, d, *J* 17.4, 5'-H), 5.21 (1 H, d, *J* 10.6, 5'-H'), 5.96 (1 H, dd, *J* 17.4, 10.6, 4'-H) and 6.14 (1 H, s, 2-H); δ_C (125 MHz, $CDCl_3$) −4.9, −4.8, −4.6, −4.0, 17.9, 18.1, 19.0, 19.1, 24.2, 24.3, 25.9, 26.1, 34.3, 34.9, 35.9, 49.9, 51.8, 67.5, 68.0, 73.4, 116.4, 116.9 (t, $^1J_{C\text{-}F}$ 260.0), 124.1 (t, $^3J_{C\text{-}F}$ 9.2), 139.9, 146.6 (t, $^2J_{C\text{-}F}$ 21.8), 165.3, 176.5 and 200.6 (t, $^2J_{C\text{-}F}$ 29.1); δ_F (376 MHz, $CDCl_3$) −101.1 (d, $^2J_{F\text{-}F}$ 268.0) and −100.3 (d, $^2J_{F\text{-}F}$ 268.7); *m/z* (ES$^+$) 685.4 (M$^+$ + 23, 85%) and 663.4 (M$^+$ + 1, 100).

(2*S*,6*S*)-3,3-Difluoro-2-hydroxy-6-[(2*R*,3*R*)-3-hydroxy-2-(2-trimethylsilylethoxy)methoxybutyl]-4-[(*E*)-methoxycarbonylmethylidene]-2-(2-methylbut-3-en-2-yl)tetrahydro-4*H*-pyran (82). Hydrogen fluoride-pyridine complex (0.24 mL) was added to the ketone **78** (57 mg, 0.079 mmol) and pyridine (0.4 mL) in THF (4.0 mL) at 0 °C and the mixture stirred for 16 h. Saturated aqueous sodium hydrogen carbonate (10 mL) was added and the mixture stirred for 1 h. Ethyl acetate (10 mL) was then added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0.1:99.9 to 0.2:99.8 methanol:DCM) gave the *title compound* **82** (26 mg, 0.053 mmol, 67%) as a colourless oil, R_f = 0.41 (4:96 methanol:DCM) (Found: M$^+$ + Na, 517.2435. $C_{23}H_{40}O_7F_2SiNa$ requires M, 517.2409; ν_{max}/cm^{-1} 3394, 2953, 1725, 1674, 1436, 1370, 1280, 1250, 1202, 1178, 1033, 920, 860 and 836; δ_H (500 MHz, benzene-d_6) 0.09 (9 H, s, 3 × $SiCH_3$), 0.89-1.00 (2 H, m, $SiCH_2$), 1.25 (3 H, d, *J* 6.0, 4''-H_3), 1.37 and 1.42 (each 3 H, s, 1'-H_3 or 2'-CH_3), 1.41-1.52 (2 H, m, 1''-H_2), 2.30 (1 H, t, *J* 13.1, 5-H), 2.53 (1 H, s, OH), 3.28 (3 H, s, OCH_3), 3.45-3.53 (3 H, m, 2''-H, 3''-H, O*H*C*H*CH_2Si), 3.68 (1 H, m, OHC*H*CH_2Si), 3.75 (1 H, d, *J* 3.5, OH), 4.18 (1 H, dt, *J* 13.9, 2.2, 5-H'), 4.37 (1 H, br. t, *J* 10.7, 6-H), 4.59 and 4.60 (each 1 H, d, *J* 7.3, OHC*H*O), 5.03 (1 H, dd, *J* 10.7, 1.3, 4'-H), 5.07 (1 H, d, *J* 17.7, 1.3, 4'-H'), 6.29 (1 H, dd, *J* 17.7, 10.7, 3'-H) and 6.50 (1 H, dd, *J* 3.8, 1.9, 4-CH); δ_C (125 MHz, benzene-d_6) −1.3, 18.3, 19.7, 22.8, 23.7, 34.3, 37.6, 46.5, 51.4, 67.1, 67.3, 70.7, 85.6, 98.5, 99.4 (dd, $^2J_{C\text{-}F}$ 30.7, 24.4), 114.0, 117.5 (dd, $^3J_{C\text{-}F}$ 13.5, 6.3), 118.5 (dd, $^1J_{C\text{-}F}$ 264.5, 244.6), 144.8, 149.0 (dd, $^2J_{C\text{-}F}$ 20.8, 18.1) and 166.4; δ_F (471 MHz, benzene-d_6) −121.32 and −104.77 (each d, $^2J_{F\text{-}F}$ 242.9); *m/z* (ES$^+$) 517.3 (M$^+$ + 23, 50%) and 355.1 (100).

(2*S*,6*S*)-3,3-Difluoro-2-hydroxy-6-[(2*R*,3*R*)-2,3-dihydroxybutyl]-4-[(*E*)-methoxycarbonylmethylidene]-2-(2-methylbut-3-en-2-yl)tetrahydro-4*H*-pyran (83). Nitromethane (0.064 mL, 1.189 mmol) was added to a suspension of magnesium bromide (0.11 g, 0.59 mmol) in ether (0.39 mL) followed by the SEM-ether **82** (21 mg, 0.043 mmol) in ether (0.4 mL) and the mixture was stirred at rt for 24 h. Water (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1:99 to 4:96 methanol:DCM) gave the *title compound* **83** (11 mg, 0.03 mmol, 70%) as a colourless oil, R_f = 0.29 (4:96 methanol:DCM) (Found: $[M-H]^-$, 363.1635. $C_{17}H_{25}O_6F_2$ requires M, 363.1619); ν_{max}/cm^{-1} 3397, 2979, 2953, 2926, 1724, 1674, 1437, 1370, 1282, 1204, 1177, 1119, 1066, 1032, 970, 920 and 882; δ_H (400 MHz, benzene-d_6) 1.00 (3 H, d, *J* 6.3, 4''-H_3), 1.31-1.48 (2 H, m, 1''-H_2), 1.39 and 1.45 (each 3 H, s, 1'-H_3 or 2'-CH_3), 2.29 (1 H, t, *J* 13.1, 5-H), 2.76 (1 H, br. s, OH), 3.29 (3 H, s, OCH_3), 3.29 (1 H, m, 3''-H), 3.58 (1 H, m, 2''-H), 4.14 (1 H, dt, *J* 14.1, 2.0, 5-H'), 4.32-4.43 (2 H, m, 6-H, OH), 5.04-5.14 (2 H, m, 4'-H_2), 6.36 (1 H, dd, *J* 17.7, 10.8, 3'-H) and 6.50 (1 H, dd, *J* 3.6, 1.8, 4-CH); δ_C (125 MHz, benzene-d_6) 19.9, 22.9(m), 23.9(m), 34.3, 39.4, 46.4, 51.5, 67.2, 71.6, 73.0, 99.5 (dd, $^2J_{C\text{-}F}$ 30.7, 24.4), 113.9, 117.6 (dd, $^3J_{C\text{-}F}$ 13.5, 6.3), 118.4 (dd, $^1J_{C\text{-}F}$ 264.5, 244.6), 144.6, 148.8 (dd, $^2J_{C\text{-}F}$ 20.8, 18.1) and 166.7; δ_F (377 MHz, benzene-d_6) −121.53 and −104.94 (each d, $^2J_{F\text{-}F}$ 242.9); *m/z* (ES^-) 401.2 ($[M + 37]^-$, 30%) and 399.1 ($[M + 35]^-$, 100) and 363.2 ($[M-H]^-$, 80).

(2*S*,6*S*)-3,3-Difluoro-2-hydroxy-6-[(2*R*,3*R*)-2-butanoyloxy-3-hydroxybutyl]- and (2*S*,6*S*)-3,3-difluoro-2-hydroxy-6-[(2*R*,3*R*)-3-butanoyloxy-2-hydroxybutyl]-4-[(*E*)-methoxycarbonylmethylidene)-2-(2-methylbut-3-en-2-yl)tetrahydro-4*H*-pyrans (84) and (86). Hydrogen fluoride-pyridine complex (0.12 mL) was added to the bis-silyl ether **80** (25 mg, 0.038 mmol) and pyridine (0.2 mL) in THF (1.9 mL) at 0 °C and the mixture stirred for 16 h. Saturated aqueous sodium hydrogen carbonate (10 mL) was added and the mixture was stirred for 1 h. Ethyl acetate (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (40:60 ether:light petroleum) gave the *title compound* **84** (7 mg, 0.016 mmol, 42%) as a colourless oil containing *ca.* 10% of the regioisomer **86**, R_f = 0.41 (4:96 methanol:DCM) (Found: M^+ + Na, 457.2015. $C_{21}H_{32}O_7F_2Na$ requires M, 457.2014); ν_{max}/cm^{-1} 3393, 2972, 2934, 2879, 1724, 1674, 1436, 1368, 1280, 1237, 1178, 1065, 1034, 924 and 882; δ_H (500 MHz, benzene-d_6) 0.71 (3 H, t, *J* 7.3, CH_2CH_3), 0.96 (3 H, d, *J* 6.5, 4''-H_3), 1.37-1.45 (5 H, m, 1''-H_2, 1'-H_3), 1.49 (3 H, s, 2'-CH_3), 1.60-1.63 (2 H, m, CH_2CH_3), 1.94 [2 H, td, *J* 7.7, 4.3, C(O)CH_2], 2.29 (1 H, t, *J* 13.1, 5-H), 3.21 (3 H, s, OCH_3), 3.28 (1 H, s, OH), 3.50 (1 H, m, 3''-H), 3.56 (1 H, m, OH), 4.10 (1 H, t, *J* 10.4, 6-H), 4.19 (1 H, dt, *J* 14.1, 2.2, 5-H'), 5.09 (1 H, dd, *J* 17.7, 1.2, 4'-H), 5.14 (1 H, m, 2''-H), 5.19 (1 H, dd, *J* 10.7, 1.2, 4'-H') and 6.44-6.50 (2 H, m, 4-CH, 3'-H); δ_C (125 MHz, benzene-d_6) 14.0, 19.1, 19.7, 22.3(m), 24.0(m), 34.2, 36.5, 37.0, 46.6 (t, $^3J_{C\text{-}F}$ 2.7), 51.4, 66.7, 69.3, 74.5, 99.7 (dd, $^2J_{C\text{-}F}$ 31.6, 24.4), 114.7, 117.8 (dd, $^3J_{C\text{-}F}$ 13.5, 6.3), 118.3 (dd, $^1J_{C\text{-}F}$ 264.5, 242.8), 144.7, 148.7 (dd, $^2J_{C\text{-}F}$ 21.7, 19.0), 166.4 and 174.3; δ_F (377 MHz, benzene-d_6) −120.93 and −105.01 (each d, $^2J_{F\text{-}F}$ 244.2); *m/z* (ES^+) 457.4 (M^+ + 23, 80%) and 417.4 (M^+ − 17, 100). Further elution gave the *title compound* **86** (7 mg, 0.016 mmol, 42%) as a colourless oil, R_f = 0.35 (4:96 methanol:DCM) (Found: M^+ + Na, 457.2015. $C_{21}H_{32}O_7F_2Na$ requires M, 457.2014); ν_{max}/cm^{-1} 3435, 2955, 2935, 2878, 1724, 1674, 1457, 1436, 1369, 1281, 1245, 1198, 1177, 1117, 1064, 1010, 920, 881 and 823; δ_H (400 MHz, benzene-d_6) 0.80 (3 H, t, *J* 7.4, CH_2CH_3), 0.95 (1 H, br. s, OH), 1.07 (3 H, d, *J* 6.6, 4''-H_3), 1.25-1.43 (8 H, m, 1''-H_2, 1'-H_3, 2'-CH_3), 1.54 (2 H, sext, *J* 7.6, CH_2CH_3), 2.06 [2 H, td, *J* 7.6, 3.0, C(O)CH_2], 2.28 (1 H, t, *J* 13.7, 5-H), 3.27 (3 H, s, OCH_3), 3.56 (1 H, d, *J* 3.2, OH), 3.80 (1 H, dd, *J* 7.1, 3.9, 2''-H), 4.19 (1 H, dt, *J* 14.2, 2.4, 5-H'), 4.39 (1 H, t, *J* 10.5, 6-H), 4.85 (1 H, pent, *J* 6.1, 3''-H), 4.97-5.05 (2 H, m, 4'-H_2), 6.23 (1 H, dd, *J* 17.6, 10.7, 3'-H) and 6.50 (1 H, dd, *J* 3.7, 2.0, 4-CH); δ_C (125 MHz, benzene-d_6) 14.0, 16.3, 19.1, 22.7, 23.9(m), 34.3, 36.7, 38.8, 46.5, 51.5, 67.1, 70.5, 73.6, 99.3 (dd, $^2J_{C\text{-}F}$ 30.7, 24.4), 114.3, 117.6 (dd, $^3J_{C\text{-}F}$ 12.6, 5.4), 118.4 (dd, $^1J_{C\text{-}F}$ 263.6, 244.6), 144.5, 148.6 (dd, $^2J_{C\text{-}F}$ 21.7, 19.0), 166.5 and 173.4; δ_F (377 MHz, benzene-d_6) −121.41 (d, $^2J_{F\text{-}F}$ 242.9) and −105.19 (d, $^2J_{F\text{-}F}$ 241.5); *m/z* (ES^+) 457.4 (M^+ + 23, 100%), 452.4 (M^+ + 18, 60) and 417.3 (M^+ − 17, 45).

(2*S*,6*S*)-3,3-Difluoro-2-hydroxy-6-[(2*R*,3*R*)-3-hydroxy-2-(2-methylpropanoyloxy)butyl]- and (2*S*,6*S*)-3,3-difluoro-2-hydroxy-6-[(2*R*,3*R*)-2-hydroxy-3-(2-methylpropanoyloxy)-butyl]-4-[(*E*)-methoxycarbonylmethylidene)-2-(2-methylbut-3-en-2-yl)tetrahydro-4*H*-pyrans (85) and (87). Following the procedure outlined for the synthesis of the esters **84** and **86**, the hydrogen fluoride-pyridine complex (0.32 mL), the bis-silyl ether **81** (67 mg, 0.101 mmol) and pyridine (0.5 mL) in dry THF (5.1 mL), after chromatography (70:30 ether:light petroleum) gave the *title compound* **85** (10 mg, 0.023 mmol, 23%) as a colourless oil, R_f = 0.34 (70:30 ether:light petroleum); $[\alpha]_D^{20}$ = −54 (*c* 0.50, ether) (Found: M^+ + Na, 457.1993. $C_{21}H_{32}O_7F_2Na$ requires M, 457.2014); ν_{max}/cm^{-1} 3480, 2977, 1724, 1674, 1436, 1369, 1280, 1200, 1067, 1035 and 923; δ_H (400 MHz, benzene-d_6) 0.94 (d, *J* 6.5, 4''-H_3), 0.94 and 0.96 (each 3 H, d, *J* 6.9, $CHCH_3$), 1.41 (3 H, d, *J* 4.0, 1'-H_3), 1.49 (3 H, s, 2'-CH_3), 1.58-1.64 (2 H, m, 1''-H_2), 2.19-2.33 [2 H, m, C(O)CH, 5-H], 3.19 (1 H, d, *J* 3.9, OH), 3.20 (3 H, s, OCH_3), 3.47 (1 H, m, 3''-H), 4.08 (1 H, m, 6-H), 4.18 (1 H, dt, *J* 14.0, 2.4, 5-H'), 5.07 (1 H, dd, *J* 17.6, 1.4, 4'-H), 5.13 (1 H, m, 2''-H), 5.19 (1 H, dd, *J* 10.7, 1.3, 4'-H') and 6.42-6.51 (2 H, m, 4-CH, 3'-H); δ_C (101 MHz, benzene-d_6) 19.1, 19.2, 19.4, 19.7, 21.9(m), 23.7(m), 33.9(m), 34,3, 36.5, 46.3 (t, $^3J_{C\text{-}F}$ 2.5), 51.0, 66.3, 69.0, 73.8, 98.8 (dd, $^2J_{C\text{-}F}$ 31.8, 24.6), 114.5, 117.4 (dd, $^3J_{C\text{-}F}$ 13.2, 6.1), 118.0 (dd, $^1J_{C\text{-}F}$ 267.1, 245.7), 144.4, 148.3 (dd, $^2J_{C\text{-}F}$ 21.4, 18.8), 166.0 and 177.4; δ_F (376 MHz, benzene-d_6) −120.89 and −104.98 (each d, $^2J_{F\text{-}F}$ 243.6); *m/z* (ES^+) 457.2 (M^+ + 23, 10%) and 301.1 (100). Further elution gave the *title compound* **87** (10 mg, 0.023 mmol, 23%) as a white solid, R_f = 0.17 (70:30 ether:light petroleum), m.p. 81 °C, $[\alpha]_D^{20}$ = −49.3 (*c* 0.85, ether) (Found: M^+ + Na, 457.1993. $C_{21}H_{32}O_7F_2Na$ requires M, 457.2014); ν_{max}/cm^{-1} 3435, 2979, 1725, 1674, 1436, 1370, 1281, 1245, 1201,

1178, 1118, 1065, 1011, 920 and 882; δ_H (400 MHz, benzene-d_6) 1.05 (3 H, d, *J* 7.0, CHCH_3), 1.06 (3 H, d, *J* 6.4, 4''-H_3), 1.07 (3 H, d, *J* 7.0, CHCH_3), 1.30-1.39 (4 H, m, 1''-H, 1'-H_3), 1.41 (3 H, s, 2'-CH_3) 1.50 (1 H, ddd, *J* 14.2, 10.2, 2.2, 1''-H'), 2.27 (1 H, m, 5-H), 2.37 [1 H, hept, *J* 7.0, C(O)CH], 2.67 (1 H br. s, OH), 3.29 (3 H, s, OCH_3), 3.79-3.88 (2 H, m, 2''-H, OH), 4.16 (1 H, dt, *J* 14.1, 2.5, 5-H'), 4.38 (1 H, m, 6-H), 4.84 (1 H, m, 3''-H), 5.00-5.09 (2 H, m, 4'-H_2), 6.27 (1 H, dd, *J* 17.6, 10.8, 3'-H) and 6.48 (1 H, dd, *J* 3.9, 2.0, 4-CH); δ_C (101 MHz, benzene-d_6) 15.8, 19.1, 19.2, 22.3(m), 23.5(m), 33.9(m), 34.3, 38.4, 46.1, 51.1, 66.8, 70.2, 73.1, 98.9 (dd, $^2J_{C\text{-}F}$ 31.3, 24.8), 114.1, 117.3 (dd, $^3J_{C\text{-}F}$ 13.1, 6.1), 118.1 (dd, $^1J_{C\text{-}F}$ 264.7, 246.8), 144.1, 148.2 (dd, $^2J_{C\text{-}F}$ 21.4, 18.7), 166.2 and 176.5; δ_F (376 MHz, benzene-d_6) −121.36 and −105.02 (each d, $^2J_{F\text{-}F}$ 241.9); *m/z* (ES^+) 457.2 (M^+ + 23, 100%).

(3*RS*,7*S*,9*R*,10*R*)-7,10-Bis(*tert*-butyldimethylsilyloxy)-4,4-difluoro-3-hydroxy-5-[(*E*)-methoxycarbonylmethylidene]-2,2-dimethyl-9-(2-trimethylsilylethoxy)methoxyundecanal (90). Osmium tetroxide in *tert*-butanol (2.5%, 0.37 mL) and *N*-methylmorpholine-*N*-oxide (46 mg, 0.40 mmol) were added to the diene **77** (0.19 g, 0.26 mmol) in *tert*-butanol-water (1:1, 2.63 mL) and the mixture stirred at rt for 4 h. Saturated aqueous sodium thiosulfate (20 mL) and EtOAc (20 mL) were added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the dihydroxylated intermediate (Found: M^+ + H, 759.4490. $C_{35}H_{73}O_9F_2Si_3$ requires M, 759.4525); *m/e* (ES^+) 781.6 (M^+ + 23, 100%). The residue was dissolved in DCM (2.6 mL) and sodium carbonate (84 mg, 0.79 mmol) and lead(IV) acetate (0.14 g, 0.32 mmol) were added. The reaction mixture was stirred at rt for 5 min, filtered through Celite® and concentrated under reduced pressure. Chromatography of the residue (10:90 to 20:80 ether:light petroleum) gave the *title compound* **90** (0.16 g, 0.22 mmol, 82%) as a colourless oil, a 50:50 mixture of diastereoisomers (^{19}F NMR), R_f = 0.48 (40:60 ether:light petroleum), $[\alpha]_D^{27}$ = −18.8 (*c* 2.0, ether) (Found: M^+ + Na, 749.4049. $C_{34}H_{68}O_8F_2Si_3Na$ requires M, 749.4082); ν_{max}/cm^{-1} 2953, 2929, 2857, 1728, 1472, 1362, 1250, 1180, 1101, 1055, 1031 and 832; δ_H (400 MHz, $CDCl_3$) 0.05 (9 H, s, 3 × $SiCH_3$), 0.05, 0.06, 0.07 and 0.08 (each 3 H, s, $SiCH_3$), 0.87(2) and 0.88(2) [each 4.5 H, s, $SiC(CH_3)_3$], 0.91-0.99 (2 H, m, $SiCH_2$), 1.02 and 1.04 (each 1.5 H, d, *J* 6.3, 11-H_3), 1.22 (3 H, s, 2-CH_3), 1.24 and 1.26 (each 1.5 H, s, 2-CH_3), 1.51 (1 H, m, 8-H), 1.77 (0.5 H, ddd, *J* 14.6, 8.1, 1.3, 8-H'), 1.86 (0.5 H, ddd, *J* 14.4, 6.0, 1.5, 8-H'), 2.65 (0.5 H, dd, *J* 13.4, 6.3, 6-H), 2.80 (0.5 H, dd, *J* 13.6, 8.0, 6-H), 3.17 (0.5 H, dd, *J* 14.4, 6.6, 6-H'), 3.30 (0.5 H, dd, *J* 13.1, 8.8, 6-H'), 3.46 (1 H, m, O*H*CHCH$_2$Si), 3.53 (1 H, m, 9-H), 3.66 (1 H, m, OHC*H*CH$_2$Si), 3.73 and 3.74 (each 1.5 H, s, OCH_3), 3.93 (1.5 H, m, 3-H, OH), 4.00-4.10 (1.5 H, m, 7-H, 10-H), 4.25 (0.5 H, m, 7-H), 4.72, 4.73, 4.74 and 4.76 (each 0.5 H, d, *J* 6.8, OHC*H*O), 6.19 (0.5 H, s, 5-CH), 6.25 (0.5 H, d, *J* 2.8, 5-CH) and 9.55 and 9.56 (each 0.5 H, s, 1-H); δ_C (100 MHz, $CDCl_3$) −4.8, −4.7(2), −4.6, −4.1, −4.0, −1.5, 17.0, 17.1, 18.0, 18.1, 18.7 (t, $^4J_{C\text{-}F}$ 2.0), 18.8 (t, $^4J_{C\text{-}F}$ 2.9), 19.7(m), 19.8(m), 25.8, 25.9(2), 35.3, 35.4, 35.7, 36.5, 49.4(2), 51.5(2), 65.4(2), 68.7, 68.8, 69.0, 70.8, 74.4 (dd, $^2J_{C\text{-}F}$ 33.0, 25.6), 76.0 (dd, $^2J_{C\text{-}F}$ 33.7, 24.9), 80.6, 80.9, 96.0, 121.7(m), 121.7 and 122.8 (each dd, $^1J_{C\text{-}F}$ 257.9, 245.4), 123.3 (dd, $^3J_{C\text{-}F}$ 12.5, 6.6), 148.4 (dd, $^2J_{C\text{-}F}$ 24.2, 21.3), 151.0 (dd, $^2J_{C\text{-}F}$ 25.7, 20.5), 165.7, 165.8, 204.1(m) and 204.3; δ_F (377 MHz, $CDCl_3$) −113.49, −111.92, −99.55 and −98.94 (each 0.5 F, d, $^2J_{F\text{-}F}$ 246.9); *m/z* (ES^+) 749.6 (M^+ + 23, 100%) and 609.4 (60).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-[(2*RS*)-1,1-difluoro-2,4-dihydroxy-3,3-dimethylbutyl]-7-(2-trimethylsilylethoxy)methoxynon-2-enoate (91). Sodium borohydride (9 mg, 0.23 mmol) was added to the aldehyde **90** (0.14 g, 0.19 mmol) in MeOH (2.0 mL) at 0 °C and the mixture stirred for 1 h. Aqueous hydrogen chloride (10%, 10 mL) was added at 0 °C followed by EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 to 30:70 ether:light petroleum) gave the *title compound* **91** (0.12 g, 0.16 mmol, 83%) as a colourless oil, a 50:50 mixture of diastereoisomers (^{19}F NMR), R_f = 0.18 (40:60 ether:light petroleum), $[\alpha]_D^{28}$ = −11.7 (*c* 1.8, ether) (Found: M^+ + H, 729.4387. $C_{34}H_{71}O_8F_2Si_3$ requires M, 729.4419); ν_{max}/cm^{-1} 3415, 2953, 2929, 2886, 2857, 1730, 1472, 1463, 1250, 1179, 1151, 1102, 1055, 1033 and 834; δ_H (400 MHz, $CDCl_3$) 0.01 (9 H, s, 3 × $SiCH_3$), 0.05, 0.06, 0.08 and 0.09 (each 3 H, s, $SiCH_3$), 0.88 and 0.89 [each 9 H, s, $SiC(CH_3)_3$], 0.92-1.00 (2 H, m, $SiCH_2$), 1.02-1.09 (6 H, m, 3'-CH_3, 9-H_3), 1.12 and 1.14 (each 1.5 H, d, *J* 2.6, 3'-CH_3), 1.51 and 1.78 (each 1 H, m, 6-H), 2.72 (0.5 H, dd, *J* 13.1, 6.0, 4-H), 2.86 (0.5 H, dd, *J* 13.4, 7.3, 4-H), 3.12 (0.5 H, dd, *J* 13.4, 6.8, 4-H'), 3.26 (0.5 H, dd, *J* 13.1, 8.6, 4-H'), 3.35 and 3.45 (each 1 H, d, *J* 10.8, 4'-H), 3.47-3.56 (2 H, m, 2'-H, O*H*CHCH$_2$Si), 3.67 (1 H, m, OHC*H*CH$_2$Si), 3.73 (3 H, s, OCH_3), 3.74 (1 H, m, 5-H), 3.81 (0.5 H, d, *J* 3.8, OH), 3.87 (0.5 H, d, *J* 3.5, OH), 3.99-4.04 (1 H, m, 8-H), 4.10 and 4.19 (each 0.5 H, m, 7-H), 4.71 and 4.73 (each 0.5 H, d, *J* 6.8, O*H*CHO), 4.73 (1 H, s, OCH_2O), 6.20 (0.5 H, s, 2-H) and 6.26 (0.5 H, d, *J* 2.6, 2-H); δ_C (100 MHz, $CDCl_3$) −4.8, −4.7(2), −4.6, −4.1, −4.0, −1.5(2), 17.2, 17.3, 18.0, 18.1, 20.1 (t, $^4J_{C\text{-}F}$ 4.4), 20.5 (t, $^4J_{C\text{-}F}$ 3.7), 22.9 (d, $^4J_{C\text{-}F}$ 5.1), 23.5 (d, $^4J_{C\text{-}F}$ 4.4), 26.0(3), 35.6, 35.7, 36.2, 36.3, 38.9, 39.2, 51.4, 65.3, 65.8, 68.9(2), 69.1, 70.1, 72.0 (d, $^5J_{C\text{-}F}$ 2.2), 72.4 (d, $^5J_{C\text{-}F}$ 2.2), 75.6 (dd, $^2J_{C\text{-}F}$ 31.5, 25.6), 78.4 (dd, $^2J_{C\text{-}F}$ 32.2, 25.6), 80.4(2), 95.8, 95.9, 121.8 (t, $^3J_{C\text{-}F}$ 9.5), 122.7 (dd, $^3J_{C\text{-}F}$ 11.7, 6.6), 122.7 and 123.4 (each dd, $^1J_{C\text{-}F}$ 258.2, 245.8), 149.6 (dd, $^2J_{C\text{-}F}$ 23.5, 21.3), 151.3 (dd, $^2J_{C\text{-}F}$ 24.9, 20.5), 165.9 and 166.0; δ_F (377 MHz, $CDCl_3$) −115.99, −114.44, −99.57 and −99.30 (each 0.5 F, d, $^2J_{F\text{-}F}$ 244.2); *m/z* (ES^+) 751.6 (M^+ + 23, 50%) and 611.5 (100).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-{1,1-difluoro-3,3-dimethyl-4-[2-(2,2,2-trichloroethoxycarbonylethoxy)benzoyloxy]-2-oxobutyl}-7-(2-trimethylsilylethoxymethoxy)non-2-enoate (93). 2,4,6-Trichlorobenzoyl chloride (0.018 mL, 0.11 mmol) and triethylamine (0.034 mL, 0.24 mmol) were added to the carboxylic acid **98** (38 mg, 0.11 mmol) in toluene (0.3 mL) and the mixture stirred for 1.5 h. The diol **91** (68 mg, 0.093 mmol) and DMAP (11 mg, 0.093 mmol) in toluene (1.45 mL) were added and the mixture stirred for 16 h. Saturated aqueous ammonium chloride (10 mL) and ether (10 mL) were added and

the aqueous phase was extracted with ether (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the ester **92** (0.10 g) as a mixture of diastereoisomers used without further purification, R_f = 0.38 (40:60 ether:light petroleum).

This ester **92** was taken up in DCM (1.6 mL) and 4Å molecular sieves (75 mg), *N*-methylmorpholine-*N*-oxide (22 mg, 0.17 mmol) and TPAP (5 mg, 0.013 mmol) were added. After stirring at rt for 16 h, the reaction mixture was concentrated under reduced pressure. Chromatography of the residue that had been dry-loaded onto the column (5:95 to 10:90 ether:light petroleum) gave the *title compound* **93** (56 mg, 0.053 mmol, 57% from diol **91**) as a colourless oil, R_f = 0.18 (20:80 ether:light petroleum), $[\alpha]_D^{29}$ = −11.4 (*c* 3.6, ether); ν_{max}/cm^{-1} 2953, 2929, 2857, 1760, 1730, 1602, 1472, 1452, 1370, 1300, 1249, 1153, 1098, 1076, 1051, 1032, 933, 833 and 809; δ_H (400 MHz, $CDCl_3$) 0.01 (9 H, s, 3 × $SiCH_3$), 0.03, 0.04, 0.05 and 0.06 (each 3 H, s, $SiCH_3$), 0.85 and 0.88 [each 9 H, s, $SiC(CH_3)_3$], 0.90-0.99 (2 H, m, $SiCH_2$), 1.03 (3 H, d, *J* 6.4, 9-H_3), 1.38 (6 H, s, 2 x 3'-CH_3), 1.42 (1 H, m, 6-H), 1.70 (1 H, dd, *J* 13.2, 8.1, 6-H'), 2.86-2.95 (2 H, m, 4-H_2), 3.03 (2 H, t, *J* 6.6, C$H_2CO_2CH_2CCl_3$), 3.46 (1 H, m, O*H*CHCH_2Si), 3.52 (1 H, m, 7-H), 3.63 (3 H, s, OCH_3), 3.68 (1 H, ddd, *J* 11.8, 9.8, 5.4, OHC*H*CH_2Si), 3.98-4.10 (2 H, m, 5-H, 8-H), 4.37 (2 H, t, *J* 6.4, OC$H_2CH_2CO_2$), 4.41 (2 H, s, 4'-H_2), 4.70 (2 H, s, OCH_2O), 4.80 (2 H, s, CH_2CCl_3), 6.14 (1 H, s, 2-H), 6.97-7.01 (2 H, m, ArH), 7.47 (1 H, m, ArH) and 7.68 (1 H, dd, *J* 7.6, 1.2, ArH); δ_C (100 MHz, $CDCl_3$) −4.8, −4.7, −4.1, −1.5, 17.1, 17.9, 18.1, 21.9(m), 25.9(2), 34.0, 35.7, 36.0, 47.8, 51.5, 64.1, 65.1, 69.1(2), 69.7, 74.0, 80.2, 94.7, 96.0, 113.5, 116.9 (t, $^1J_{C\text{-}F}$ 257.4), 119.9, 120.8, 124.0 (t, $^3J_{C\text{-}F}$ 8.8), 125.5, 131.7, 133.7, 146.3 (t, $^2J_{C\text{-}F}$ 21.9), 158.1, 165.0, 165.2, 169.3 and 200.6 (t, $^2J_{C\text{-}F}$ 29.9); δ_F (377 MHz, $CDCl_3$) −101.86 and −101.04 (each d, $^2J_{F\text{-}F}$ 271.5); *m/z* (ES^+) 1072 (M^+ + 23, 30%).

Methyl (5*S*,7*R*,8*R*,2*E*)-5,8-bis(*tert*-butyldimethylsilyloxy)-3-{1,1-difluoro-3,3-dimethyl-4-[2-(2,2,2-trichloroethoxycarbonylethoxy)benzoyloxy]-2-oxobutyl}-7-hydroxynon-2-enoate (94). Nitromethane (0.14 mL, 2.52 mmol) was added to a suspension of magnesium bromide (0.23 g, 1.26 mmol) in ether (1.2 mL) followed by the SEM-ether **93** (95 mg, 0.09 mmol) in ether (1.0 mL). After stirring at rt for 15 h, water (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10:90 ether:light petroleum) gave the *title compound* **94** (54 mg, 0.06 mmol, 65%) as a colourless oil, R_f = 0.33 (40:60 ether:light petroleum), $[\alpha]_D^{30}$ = +0.50 (*c* 2.0, ether); ν_{max}/cm^{-1} 2953, 2929, 2856, 1759, 1731, 1601, 1491, 1472, 1452, 1370, 1300, 1250, 1152, 1076 and 952; δ_H (500 MHz, $CDCl_3$) 0.03, 0.05, 0.06 and 0.09 (each 3 H, s, $SiCH_3$), 0.86 and 0.87 [each 9 H, m, $SiC(CH_3)_3$], 1.13 (3 H, d, *J* 6.4, 9-H_3), 1.39 (6 H, s, 2 × 3'-CH_3), 1.45-1.53 (2 H, m, 6-H_2), 2.27 (1 H, br. s, 7-OH), 2.87 (1 H, dd, *J* 12.9, 6.3, 4-H), 2.99 (1 H, dd, *J* 12.3, 8.2, 4-H'), 3.02 (2 H, t, *J* 6.3, C$H_2CO_2CH_2CCl_3$), 3.49 (1 H, m, 7-H), 3.59 (1 H, m, 8-H), 3.65 (3 H, s, OCH_3), 4.22 (1 H, m, 5-H), 4.38 (2 H, t, *J* 6.7, OCH_2CH_2), 4.42 (2 H, s, 4'-H_2), 4.80 (2 H, s, CH_2CCl_3), 6.14 (1 H, s, 2-H), 6.98-7.01 (2 H, m, ArH), 7.47 (1 H, m, ArH) and 7.69 (1 H, dd, *J* 7.9, 1.9, ArH); δ_C (100 MHz, $CDCl_3$) −5.0, −4.4, -4.3, 17.9, 20.1, 21.9 (d, $^4J_{C\text{-}F}$ 2.2), 25.8(2), 34.0, 35.4, 40.6, 47.8, 51.6, 64.1, 68.5, 69.7, 71.7, 71.8, 74.0, 94.7, 113.5, 116.9 (t, $^1J_{C\text{-}F}$ 258.2), 119.9, 120.8, 123.8 (t, $^3J_{C\text{-}F}$ 9.5), 125.5, 131.7, 133.7, 146.8 (t, $^2J_{C\text{-}F}$ 21.9), 158.1, 164.9, 165.2, 169.3 and 200.5 (t, $^2J_{C\text{-}F}$ 29.9); δ_F (471 MHz, $CDCl_3$) −102.07 (d, $^2J_{F\text{-}F}$ 275.9) and −100.55 (d, $^2J_{F\text{-}F}$ 274.2); *m/z* (ES^+) 942 (M^+ + 23, 80%).

Zinc dust (7 mg) and PPTS (14 mg, 0.055 mmol) were added to the ester **94** (20 mg, 0.022 mmol) in THF (0.4 mL) and the mixture heated under reflux for 30 min. Saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted with EtOAc (4 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the acid **95**. This acid was dissolved in benzene (0.26 mL). Pyridine (5 μL, 0.063 mmol) and 2,4,6-trichlorobenzoyl chloride (3 μL, 0.016 mmol) were added and the mixture was stirred for 45 min at rt then added to DMAP (16 mg, 0.13 mmol) in benzene (2.8 mL). The mixture was heated at 60 °C for 16 h then cooled to rt. Saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted with EtOAc (4 × 10 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give an impure product provisionally identified as the acrylate **96** (29 mg); δ_H (400 MHz, $CDCl_3$) 0.05 (12 H, overlapping s, 4 × $SiCH_3$), 1.15 (3 H, d, *J* 7.0, 9-H_3), 1.24 [18 H, s, 2 × $SiC(CH_3)_3$], 1.33 and 1.34 (each 3 H, s, 3'-CH_3), 1.65 (2 H, m, 6-H_2), 2.45 (2 H, m, 4-H_2), 3.47 (1 H, m, 8-H), 3.72 (3 H, s, OCH_3), 3.85 (1 H, m, 5-H), 4.15 (1 H, d, *J* 13.0, 4'-H), 4.27 (1 H, m, 7-H), 4.44 (2 H, m, OH, 4'-H'), 6.19 (1 H, d, *J* 11.0, 3''-H), 6.23 (1 H, m, 2-H), 6.40 (1H, dd, *J* 15.0, 11.0, 2''-H), 6.67 (1 H, d, *J* 15.0, 3''-H'), 7.16 (1 H, d, *J* 6.0, ArH), 7.35 (1 H, t, *J* 6.0, ArH), 7.61 (1 H, m, ArH) and 7.96 (1 H, m, ArH). When the macrocyclisation was attempted at rt, the acrylate **96** was detected by TLC 10 min after adding the mixture to the DMAP.

2-(2,2,2-Trichloroethoxycarbonylethoxy)benzoic acid (98). (2,2,6,6-Tetramethylpiperidin-1yl)oxidanyl **(**TEMPO) (28 mg, 0.18 mmol) and $PhI(OAc)_2$ (0.56 g, 1.728 mmol) were added to methyl 2-(3-hydroxypropoxy)benzoate (0.125 g, 0.594 mmol) in MeCN (12.0 mL) and water (1.9 mL) and the mixture stirred at rt for 1 h. 2-Methylbut-2-ene (3.1 mL, 29.16 mmol), water (0.96 mL) and NaH_2PO_4 (0.713 g, 5.94 mmol) were added. After cooling the mixture to 0 °C, $NaClO_2$ (0.43 g, 4.75 mmol) was added and the deep red solution was stirred for 1 h. Saturated aqueous sodium thiosulfate (20 mL) and EtOAc (20 mL) were added and the aqueous phase was extracted into EtOAc (3 × 20 mL). The organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure. 2,2,2-Trichloroethanol (0.086 mL, 0.89 mmol), DCC (0.185 g, 0.89 mmol) and DMAP (0.11 g, 0.89 mmol) were added to the residue in dry DCM (3.1 mL) and the mixture stirred at rt for 16 h. After concentration under reduced pressure, chromatography of the residue with dry-loading (2:98 to 5:95 EtOAc:light petroleum) gave the ester **97** (0.16 g, 0.44 mmol, 73% as a colourless oil, R_f = 0.56 (40:60 EtOAc:light petroleum) (Found: M^+ + H, 354.9900. $C_{13}H_{14}O_5{}^{35}Cl_3$ requires 354.9907); ν_{max}/cm^{-1}

2951, 1756, 1728, 1601, 1583, 1491, 1453, 1433, 1398, 1304, 1248, 1153, 1133, 1083, 1047, 1026, 912 and 857; δ_H (400 MHz, $CDCl_3$) 3.01 (2 H, t, *J* 6.3, 1-H_2), 3.85 (3 H, s, OCH_3), 4.38 (2 H, t, *J* 6.1, 2-H_2), 4.79 (2 H, s, CH_2CCl_3), 7.00 (2 H, t, *J* 7.8, ArH), 7.45 (1 H, dt, *J* 7.3, 1.7, ArH) and 7.77 (1 H, dd, *J* 8.4, 2.0, ArH); δ_C (100 MHz, $CDCl_3$) 34.2, 51.9, 64.2, 74.0, 94.6, 113.7, 120.7, 120.9, 131.6, 133.4, 157.7, 166.6 and 169.2; *m/z* (ES^+) 376.9 (M^+ + 23, 70% and 355.0 (M^+ + 1, 100).

Sodium iodide (0.265 g, 1.77 mmol) and trimethylsilyl chloride (0.09 mL, 0.71 mmol) were added to this ester **97** (0.126 g, 0.354 mmol) in 1,2-dichloroethane (3.6 mL) and the solution heated at 100 °C for 15 h then cooled and concentrated under reduced pressure. Chromatography of the residue with dry-loading (5:95 to 20:80 EtOAc:light petroleum with 0.1% acetic acid) gave the *title compound* **98** (90 mg, 0.256 mmol, 72%) as a colourless oil, R_f = 0.36 (40:60 EtOAc:light petroleum) (Found: M^+ + H, 340.9749. $C_{12}H_{12}O_5{}^{35}Cl_3$ requires M, 340.9750); δ_H (400 MHz, $CDCl_3$) 3.11 (2 H, t, *J* 6.0, 1-H_2), 4.57 (2 H, t, *J* 6.0, 2-H_2), 4.84 (2 H, s, CH_2CCl_3), 7.08 (1 H, d, *J* 8.3, ArH), 7.16 (1 H, t, *J* 7.5, ArH), 7.58 (1 H, dt, *J* 7.6, 1.8, ArH), 8.16 (1 H, dd, *J* 7.8, 1.8, ArH) and 10.69 (1 H, br. s, CO_2H); δ_C (100 MHz, $CDCl_3$) 33.8, 64.7, 74.2, 94.4, 112.6, 118.2, 122.6, 133.9, 135.0, 156.9, 165.7 and 168.9; *m/z* (ES^+) 364.9, 362.9 (both M^+ + 23, 50%), 225.1 (100).

Acknowledgements

We thank the EPSRC for support (C. E. R.).

Notes and references

1. (a) J. H. Sharp, M. K. Winson and J. S. Porter, *Nat. Prod. Reports*, 2007, **24**, 659; (b) P. A. Wender, *Products in Medicinal Chemistry*, ed. S. Hanessian, Wiley-VCH Verlag GmbH & Co., KgaA, Weinheim, Germany, 2014, 475; (c) H.-B. Yu, F. Yang, F. Sun, G.-Y. Ma, J.-H. Gan, W.-Z. Hu, B.-N. Han, W.-H. Jiao and H.-W. Lin, *J. Nat Prod*., 2014, 77, 2124.
2. (a) B.-F. Ruan and H.-L. Zhu, *Curr. Med. Chem*., 2012, **19**, 2652; (b) K. Irie and R. C. Yanagita, *Chem. Record,* 2014, **14**, 251.
3. (a) S. Ueno, R. C. Yanagita, K. Murakami, A. Murakami, H. Tokuda, N. Suzuki, T. Fujiwara and K. Irie, *Biosci. Biotechnol. Biochem*., 2012, **76**, 1041; (b) D. E. Schaufelberger, M. P. Koleck, J. A. Beutler, A. M. Vatakis, A. B. Alvarado, P. Andrews, L. V. Marzo, G. M. Muschik, J. Roach, J. T. Ross et al., *J. Nat. Prod*., 1991, **54**, 1265.
4. K. J. Hale and S. Manaviazar, *Chem. Asian J*., 2010, **5**, 704.
5. (a) M. Kageyama, T. Tamura, M. H. Nantz, J. C. Roberts, P. Somfrai, D. C. Whritenour and S. Masamune, S. *J. Am. Chem. Soc*., 1990, **112**, 7407; (b) D. A. Evans, P. H. Carter, E. M. Carreira, A. B. Charette, J. A. Prunet and M. Lautens, *J. Am. Chem. Soc*., 1999, **121**, 7540; (c) K. Ohmori, Y. Ogawa, T. Obitsu, Y. Ishikawa, S Nishiyama and S. Yamamura, *Angew. Chem. Int. Ed*., 2000, **39**, 2290; (d) S. Manaviazar, M. Frigerio, G. S. Bhatia, M. G. Hummersone, A. E. Aliev and K. J. Hale, *Org. Lett*., 2006, **8**, 4477; (e) B. M. Trost and G. Dong, *J. Am. Chem. Soc*., 2010, **132**, 16403; (f) G. E. Keck, Y. B. Poudel, T. J. Cummins, A. Rudra and J. A. Covel, *J. Am. Chem. Soc*., 2011, **133**, 744; (g) P. A. Wender and A. J. Schrier, *J. Am. Chem. Soc*., 2011, **133**, 9228; (h) Y. Lu, S. K. Woo and M. J. Krische, *J. Am. Chem. Soc*., 2011, **133**, 13876; (i) Y. Zhang, Q. Guo, X. Sun, J. Lu, Y. Cao, Q. Pu, Z. Chu, L. Gao and Z. Song, *Angew. Chem. Int. Edn*., 2018, **57**, 942.
6. P. A. Wender, C. T. Hardman, S. Ho, M. S. Jeffreys, J. K. Maclaren, R. V. Quiroz, S. M. Ryckbosch, A. J. Shimizu, J. L. Sloane and M. C. Stevens, *Science*, 2017, **358**. 218.
7. M. G. Kazanietz, N. E. Lewin, F. Gao, G. R. Pettit and P. M. Blumberg, *Mol. Pharmacol*., 1994, **46**, 374.
8. P. A. Wender, C. M. Cribbs, K. F. Koehler, N. A. Sharkey, C. L. Herald, Y. Kamano, G. R. Pettit and P. M. Blumberg, *Proc. Natl. Acad. Sci. USA.,* 1988, **85**, 7197.
9. (a) P. A. Wender, J. L. Baryza, C. E. Bennett, F. C. Bi, S. E. Brenner, M. O. Clarke, J. C. Horan, C. Kan, E. Lacôte, B. Lippa, P. G. Nell and T. M. Turner, *J. Am. Chem. Soc*., 2002, **124**, 13648; (b) P. A. Wender, B. A. Loy and A. J. Schrier, *Isr. J. Chem*., 2011, **51**, 453; (c) P. A. Wender, J. L. Baryza, S. E. Brenner, B. A. DeChristopher, B. A. Loy, A. J. Schrier and V. A. Verma, *Proc. Natl. Acad. Sci. USA.,* 2011, **108**, 6721.
10. (a) G. E. Keck, W. Li, M. B. Kraft, N. Kedei, N. E. Lewin and P. M. Blumberg, *Org. Lett*., 2009, **11**, 2277; (b) G. E. Keck, Y. B. Poudel, A. Rudra, J. C. Stephens, N. Kedei, N. E. Lewin, M. L. Peach and P. M. Blumberg, *Angew. Chem. Int. Ed*., 2010, **49**, 4580; (c) G. E. Keck, Y. B. Poudel, A. Rudra, J. C. Stephens, N. Kedei, N. E. Lewin and P. M. Blumberg, *Bioorg. Med. Chem. Lett*., 2012, **22**, 4084; (d) M. B. Kraft, Y. B. Poudel, N. Kedei, N. E. Lewin, M. L. Peach, P. M. Blumberg and G. E. Keck, *J. Am. Chem. Soc*., 2014, **136**, 13202; (e) M. J. Krische, J. M. Ketcham, I. Volchkov, T.-Y. Chen, P. M. Blumberg, N. Kedei and N. E. Lewin, *J. Am. Chem. Soc*., 2016, **138**, 13415.
11. (a) A. P. Green, S. Hardy, A. T. L. Lee and E. J. Thomas, *Org. Biomol. Chem*., 2017, **15**, 9497; (b) A. P. Green, S. Hardy and E. J. Thomas, *Org. Biomol. Chem*., 2017, **15**, 9475; (c) R. Dumeunier, T. Gregson, S. MacCormick, H. Omori and E. J. Thomas, *Org. Biomol. Chem*., 2017, **15**, 2768; (d) M. Ball, A. Baron, B. Bradshaw, M. O'Brien, R. Dumeunier and E. J. Thomas, *Org. Biomol. Chem*., 2016, **14**, 9650.
12. J. L. Roberts, J. Borgese, C. Chan, D. D. Keith and C.-C. Wei, *Heterocycles,* 1993, **35**, 115.
13. (a) B. Linclau, A. J. Boydell, R. S. Timofte, K. J. Brown, V. Vinader and A. C. Weymouth-Wilson, *Org. Biomol. Chem*., 2009, **7**, 803; (b) L. Bonnac, S. E. Lee, G. T. Giuffredi, L. M. Elphick, A. A. Anderson, E. S. Child, D. J. Mann and V. Gouverneur, *Org. Biomol. Chem*., 2010, **8,** 1445.
14. B. A. Loy, A. B. Lesser, D. Staveness, K. L. Billingsley, L. Cegelski and P. A Wender, *J. Am. Chem. Soc*., 2015, **137**, 3678.
15. P. R. Mears and E. J. Thomas, *Tetrahedron Lett*., 2015, **56**, 3975.
16. P. R. Mears and E. J. Thomas, *Tetrahedron Lett*., 2015, **56**, 3980.
17. (a) F. Olimpieri, S. Fustero, A. Volonterio and M. Zanda, *Synthesis,* 2010, 651;
18. J. M. Andrés, M. A. Martínez, P. Pedrosa and A. Pérez-Encabo, *Synthesis,* 1996, 1070.
19. S. Raghavan and K. V. Vinoth, *Org. Biomol. Chem*., 2013, **11**, 2847.

20. H. Sugiyama, F. Yokokawa and T. Shioiri, *Tetrahedron*, 2003, **59**, 6579.
21. C. Guo, X. Yue and F.-L. Qing, *Synthesis*, 2010, 1837.
22. (a) T. Taguchi, O. Kitagawa, T. Morikawa, T. Nishiwaki, H. Uehara, H. Endo and Y. Kobayashi, *Tetrahedron Lett.*, 1986, **27**, 6103; (b) K. Sato, M. Omote, A. Ando and I. Kumadaki, *J. Fluorine Chem.,* 2004, **125**, 509; (c) R. Surmont, G. Verniest, J. W. Thuring, G. Macdonald, F. Deroose and N. De Kimpe, *J. Org. Chem.*, 2010, **75**, 929; (d) K. Sato, R. Kawata, F. Ama, M. Omote, A. Ando and I Kumadaki, *Chem.& Pharm. Bull.*, 1999, **47**, 1013.
23. (a) H. Wang, Y. Zhao, Y. Li and L. Lu, *J. Org. Chem.*, 2006, **71**, 3278; (b) T. Konno, T. Takehana, M. Mishima and T. Ishihara, *J. Org. Chem.,* 2006, **71**, 3545; (c) V. Bizet, X. Pennecoucke, J.-L. Renard and D. Cahard, *J. Fluorine Chem.*, 2013, **152**, 56; (d) J. A. Codelli, J. M. Baskin, N. Agard and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2008, **130**, 11486; (e) N. Shimojuh, Y. Imura, K. Moriyama and H. Togo, *Tetrahedron*, 2011, **67**, 951; (f) H. Nemoto, A. Satoh, K. Fukumoto and C. Kabuto, *J. Org. Chem.*, 1995, **60**, 594.
24. J.-S. Zheng, H.-N. Chang, F.-L. Wang and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 11080.
25. (a) Z.-Y. Yang and D. J. Burton, *J. Org. Chem.*, 1991, **56**, 1037; (b) D. Seyferth, R. M. Simon, D. J. Sepelak and H. A. Klein, *J. Org. Chem.*, 1980, **45**, 2273; (c) D. Seyferth and K. R. Wursthorn, *J. Organomet. Chem.*, 1979, **182**, 455; (d) D. Seyferth, R. M. Simon, D. J. Sepelak and H. A. Klein, *J. Am. Chem. Soc.*, 1983, **105**, 4634; (e) Z.-Y. Yang and D. J. Burton, *J. Fluorine Chem.*, 1989, **44**, 339; (f) M. Kirihara, T. Takuwa, S. Takizawa and T. Momose, *Tetrahedron Lett.*, 1997, **38**, 2853; (g) M. Kirihara, T. Takuwa, S. Takizawa, T. Momose and H. Nemoto, *Tetrahedron*, 2000, **56**, 8275.
26. (a) G. H. Posner, H. J. Kim, M. Kahraman, H. B. Jeon, B. C. Suh, H. Li, P. Dolan and T. W. Kensler, *Bioorg. Med. Chem.*, 2005, **13**, 5569; (b) X. Creary, *J. Org. Chem.*, 1987, **52**, 5020.
27. Q-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230.
28. E. Van Hende, G. Verniest, R. Surmont and N. De Kimpe, *Org. Lett.*, 2007, **9**, 2935.
29. J. M. Concellón, H. Cuervo and R. Fernández-Fano, *Tetrahedron*, 2001, **57**, 8983.
30. T. Eguchi, T. Aoyama and K. Kakinuma, *Tetrahedron Lett.*, 1992, **33**, 5545.
31. J. Fried and E. A. Hallinan, *Tetrahedron Lett.*, 1984, **25**, 2301.
32. (a) H. Wang, Y. Zhao, Y. Li and L. Lu, *J. Org. Chem.*, 2006, **71**, 3278; (b) X.-H. Xu, X.-L. Qiu, X. Zhang and F.-L. Qing, *J. Org. Chem.*, 2006, **71**, 2820.
33. (a) B. Plietker and M. Niggemann, *Org. Lett.*, 2003, **5**, 3353; (b) B. Plietker, *Synthesis*, 2005, **15**, 2453; (c) A. P. Massey, V. S. Pore and B. G. Hazra, *Synthesis*, 2003, **3**, 426.
34. (a) Y. Ding and G. Zhao, *Tetrahedron Lett.*, 1992, **33**, 8117; (b) L. M. Fleury, A D. Kosal, J. T. Masters and B. L. Ashfeld, *J. Org. Chem.*, 2013, **78**, 253.
35. M. Ball, T. Gregson, H. Omori and E. J. Thomas, *Org. Biomol. Chem*., 2017, **15**, 2740.
36. P. A. Wender, Y. Nakagawa, K. E. Near and D. Staveness, *Org. Lett*. 2014, **16**, 5136.
37. P. A. Wender and D. Staveness, *Org. Lett*. 2014, **16**, 5140.
38. H. Zhang, S. Neimanis, L. A. Lopez-Garcia, J. M. Arenciba, S. Amon, A. Stroba, S. Zeuzem, E. Proschak, H. Stark, A. F. Bauer, K. Busschots, K. Busschots, T. J. Jorgensen, M. Engel, J. O. Schulze and R. M. Biondi, *Chem. Biol*., 2014, **21**, 754.
39. A. F. Rudolf, T. Skovgaard, S. Knapp, L. J. Jensen and Berthelsen, *PloS One*, 2014, **9**, 98800.
40. D. M. Foulkes, D. P. Byrne, W. Yeung, S. Shrestha, F. P. Bailey, S. Ferries, C. E. Eyers, K. Keeshan, C. Wells, D. H. Drewry, W. J. Zuercher, N. Kannan and P. A. Eyers, *Sci. Signal*, 2018, **11**, 7951.
41. D. P. Byrne, M. Vonderach, S. Ferries, P. J. Brownridge, C. E. Eyers and P. A. Eyers, *Biochem. J*., 2016, **473**, 3159.
42. H. W. Lee, L. Smith, G. R. Pettit and J. B. Smith, *Mol. Pharmacol*., 1997, 51, 439.
43. D. R. Alessi, *FEBS Lett*., 1997, **402**, 121.
44. J. M. Murphy, Q. Zhang, S. N. Young, M. L. Reese, F. P. Bailey, P. A. Eyers, D. Ungureanu, H. Hammaren, O. Silvennoinen, L. N. Varghese, K. Chen, A. Tripaydonis, N. Jura, K. Fukuda, J. Qin, Z. Nimchuk, M. B. Mudgett, S. Olowe, C. L. Gee, L. Liu, R. J. Daly, G. Manning, J. J. Babon, and I. S. Lucet, *Biochem. J*., 2014, **457**, 323.

