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Highly-functionalised difluorinated cyclohexane polyols *via* the Diels–Alder reaction: regiochemical control *via* the phenylsulfonyl group†

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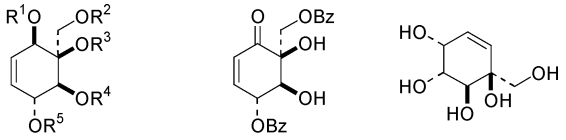
A difluorinated dienophile underwent cycloaddition reactions with a range of furans to afford cycloadducts which could be processed regio- and stereoselectively *via* episulfonium ions, generated by the reaction between their alkenyl groups and phenylsulfenyl chloride. The oxabicyclic products were oxidised to the phenylsulfonyl level and ring opened *via* $E1_cB$ or reductive desulfonative pathways to afford, ultimately, difluorinated cyclohexene or cyclohexane polyols.

Introduction

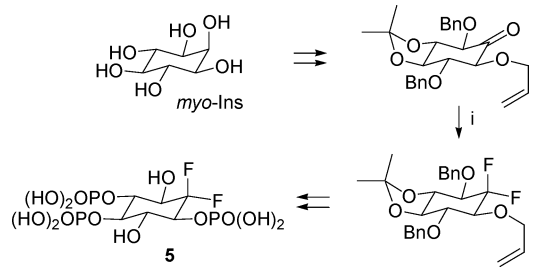
The furan Diels–Alder reaction is one of the most concise and powerful methods for the construction of six-membered carbocycles with high information content,[1] yet the cycloaddition remains under-used for the synthesis of fluorinated analogues of the molecules of nature. Cyclohexane polyols (cyclitols, conduritols and (hydroxymethyl)conduritols), abound in Nature, and vary widely in structure, occurrence and importance. For example, the cyclitols (cyclohexanehexitols) are vital components of the second messenger system, which controls cell proliferation and growth, smooth muscle contraction, inflammatory cellular events, and a range of other processes.[2] The conduritols and (hydroxymethyl)conduritols are more complex structurally and considerably less common;[3] those which show interesting biological activities include ferrudiol **1**, zeylenol **2**, tonkinenin A **3** and piperonol B **4**, all of which are used widely in Chinese traditional medicine for the treatment of digestive disorders.[4]



1, R^1, R^2, R^5= Bz, R^3, R^4= H; **2**, R^2, R^5 = Bz, R^1, R^3, R^4 = H. **3** **4**

The parent pentitol structures in **1** and **2** contain an alkenyl and a hydroxymethyl group; two of the hydroxyl groups are allylic while of the remaining two, one is tertiary, whereas **3** has five distinct oxygen functionalities. This level of functional group density and diversity is both attractive and synthetically challenging.

Mono- and di-fluorinated cyclitols have proved to be useful biological probes of phosphatidylinositol metabolism, and have commanded the attention of a number of groups.[5] There are two strategies available for the synthesis of fluorinated cyclitol analogues. Fluorinations with DAST ((diethylamino)sulfur trifluoride) or DeoxoFluor,[6] which transform hydroxyl or ketonic carbonyl groups with the incorporation of one or two fluorine atoms, are very well established. There are many successful examples in the literature, particularly from readily-available natural product starting materials.[7] For example, Potter and Sawyer were able to synthesise **5** from readily-available *myo*-inositol *via* a concise route (Scheme 1) in which the axial hydroxyl group (at the carbon which becomes C-2) could be isolated and transformed to a ketonic carbonyl.[8]



Scheme 1 Reagents and conditions: i, 4.0 DAST, rt, 5 hours, 79%.

However, this transformative approach does have a number of significant limitations. Though there are some interesting examples of selective fluorinations of unprotected or lightly-protected substrates with DAST,[9] extensive functional or protecting group manipulations are usually required to present a single group to the reagent, and even then, the course of fluorination reactions can be unpredictable.[10] Fluorinations of carbonyl groups with DAST involve transition states in which electron demand is relatively high, leading to the activation of pathways such as neighbouring group participation, group shifts, and elimination reactions. Complex mixtures of products can result, though some imaginative solutions have been developed to minimise competing pathways.[11] The combination of the high potential for side reactions and the lack of any obvious and abundant starting materials for fluorination approaches to analogues of **1–4** (apart from quinic acid, which has formed the basis for a number of syntheses of (hydroxymethyl)conduritols, and difluorinated shikimic acid analogues[12]) ensures that building block or *de novo* routes are of considerable potential interest and importance.[13]

Given the tremendous utility of the Diels–Alder reaction for the construction of highly-functionalised six-membered carbocycles, the development of the reaction for the elaboration of fluorinated dienes[14] and dienophiles[15] to analogues of cyclitols, conduritols and (hydroxymethyl)conduritols would seem to be an important activity, especially for the synthesis

† Electronic supplementary information (ESI) available: full synthesis and characterisation data for additional intermediates and products. See http://dx.doi.org/10.1039/b507131c

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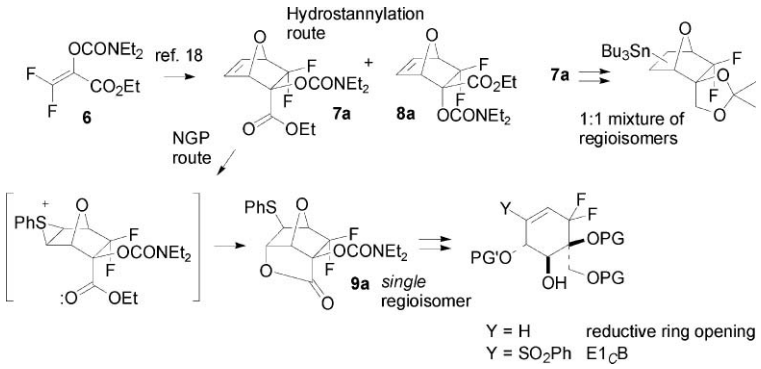


Scheme 2

of *gem*-difluorinated compounds where this methodology is under-used. In the only paper describing a successful furan Diels–Alder reaction of a difluorinated dienophile, Wakselman[16] and co-workers reported an attempted route to difluorinated analogues of shikimic acid which involved the synthesis of ethyl 2,2-difluoroacrylate, and the Lewis acid-catalysed cycloaddition reaction with furan. Unfortunately, the difluorinated oxa[2.2.1]bicycloheptene cycloadducts could not be ring opened with retention of the two fluorine atoms. Instead, a phenolic product was formed. Building on this seminal contribution, we prepared[17] dienophile **6** and developed the Lewis acid-catalysed cycloaddition reaction with furans. Faced with rather unsatisfactory outcomes from the application of Lautens' ring opening methodology to our cycloadducts (Scheme 2),[18] we explored an approach pioneered by the Lausanne and Madrid groups,[19] in which a reaction with a sulfur electrophile triggers neighbouring group participation to gain control of the chemistry of the rather electronically symmetrical alkenyl group.

Ring-opening reactions of oxabicyclo[2.2.1]heptanes can be triggered by the generation of a carbanionic centre β-to one of the bridging C–O bonds; the (phenylsulfonyl) group is an effective controller of this process, and there exists further potential for reductive cleavage of the C–S bond to be coupled with the strain-relieving C–O bond breaking step. We therefore began a campaign to advance our cycloadducts through to a range of very highly-functionalised difluorinated cyclohexanes and cyclohexenes, related to the (hydroxymethyl)conduritols, using an intramolecular nucleophilic interception of an episulfonium ion in a key controlling step.

We described the efficient preparation and some subsequent reactions of **9a** in our communication.[20] In this manuscript, we wish to describe, in full, the outcomes of our study, in which we have explored the effect of furan substitution and the effect of cycloadduct stereochemistry upon the feasibility of this Diels–Alder based strategy, effectively setting a new benchmark in the synthesis of densely-functionalised difluorinated cyclohexane derivatives from inexpensive and sustainable fluorinated starting materials.

Results and discussion

The cycloadducts were progressed as either separated racemic *endo*- or *exo*-diastereoisomers, or as mixtures when inseparable (Scheme 3, Table 1).

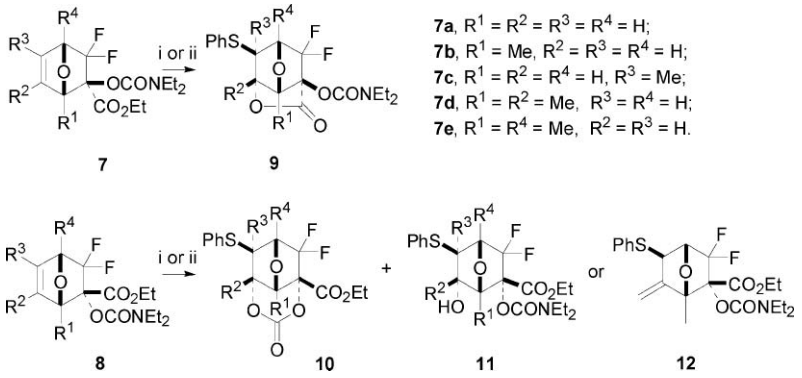
Ester **7a** failed to react with the NCS–thiophenol reagent combination[21] but a smooth reaction occurred with freshly-prepared phenylsulfenyl chloride,[22] and crystalline lactone **9a** could be isolated in excellent (89%) yield on a 20 g scale. Slightly lower yields of lactone could be obtained using the more convenient *in situ* method of Suzuki *et al.* (PhSSPh, SO_2Cl_2, DCM).[23]

The product from the former procedure could usually be induced to crystallize upon trituration with hexane, whereas those obtained using the *in situ* method required short column chromatography. The *exo*-cycloadduct **7b** also offers the prospect of neighbouring group participation by the carbamate; treatment with freshly-distilled PhSCl in dry chloroform afforded a mixture of **10b** and **11b**, even after non-aqueous work-up. Interception of the episulfonium ion **13** delivers an

Table 1

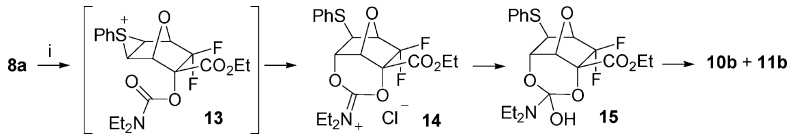
	Lactone from *endo*		Products from *exo*			
Cycloadducts	Lactone	(%)		(%)		(%)
7a	**9a**	89				
8a			**10a**	0	**11a**	20
7b + **8b**	**9b**	44				
			10b	11	**11b**	27
7c	**9c**	70	(—)	(—)	(—)	(—)
7d + **8d**	**9d**[a]		(—)	95[a]	(—)	(—)
	(—)	(—)	**12**[a]		(—)	(—)
7e	**9e**	40	(—)	(—)	(—)	(—)
8e	(—)	(—)	(—)	(—)	**11e**	22

[a] **9d** and **12** were obtained as an inseparable mixture; the yield is an estimate based on the NMR ratio of 1 : 1.5.



7a, $R^1 = R^2 = R^3 = R^4 = H$;
7b, $R^1 = Me$, $R^2 = R^3 = R^4 = H$;
7c, $R^1 = R^2 = R^4 = H$, $R^3 = Me$;
7d, $R^1 = R^2 = Me$, $R^3 = R^4 = H$;
7e, $R^1 = R^4 = Me$, $R^2 = R^3 = H$.

Scheme 3 Reagents and conditions: i, PhSCl, $CHCl_3$, rt; ii, PhSSPh, SO_2Cl_2, DCM, rt.



Scheme 4 Reagents and conditions: i, PhSCl, $CHCl_3$, rt; ii, PhSSPh, SO_2Cl_2, DCM.

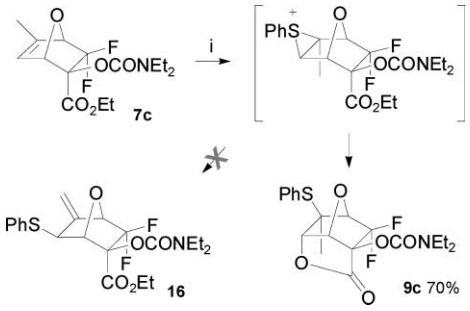
electrophilic intermediate **14**; the tetrahedral intermediate **15**, which results from the attack of water can partition between cyclic carbonate **10b** and β-phenylthio alcohol **11b**, presumably upon reaction with water from the silica used to separate the products (Scheme 4).

The *endo*- and *exo*-cycloadducts from 2-methylfuran **7b** and **8b** are inseparable by chromatography, but treatment with phenylsulfenyl chloride generated *in situ* affords lactone **9b** (44%), cyclic carbonate **10b** (11%) and β-phenylthio alcohol **11b** (27%) which can be separated. X-Ray crystal structures were solved for **10b** and **11b** to obtain unambiguous proof of constitution and relative configuration. Similar behaviour was observed with the inseparable mixture of *endo*- and *exo*-cycloadducts with 2,5-dimethylfuran to afford **9e** (40%), and **11e** (22%).

In the case of 2,3-dimethylfuran, the *endo*-component **7d** of the cycloadduct mixture forms the lactone **9d**, whereas the *exo*-cycloadduct **8d** is transformed to allylic sulfide **12** *via* proton loss from the episulfonium ion. Episulfonium ion ring opening with proton loss was observed before by Bialecki and Vogel.[24] We observed none of the allylic sulfide from the *endo*-cycloadduct indicating that formation of the 5-membered lactone is fast on the timescale of episulfonium ion ring opening, but that formation of the six-membered cyclic carbonate cannot compete with proton loss. Though the carbamoyloxy group is Lewis basic, the extra degree of rotational freedom appears to be enough to lower the rate below that of the eliminative ring opening (there are additional issues with restricted rotation in the carbamoyloxy group which may impede access to conformations from which cyclisation can occur).

Cycloaddition between **6** and 3-methylfuran occurs stereoselectively (54%, *endo–exo* 8 : 1) and with a single regiochemical outcome **7c** and **8c**, consistent with the development of a carbenium ion or free radical character during the course of a highly asynchronous reaction. The HMBC spectra for both stereoisomers show a $^3J_{C-H}$ cross peak correlating the bridgehead proton next to the CF_2 group and the carbon of the allylic methyl group; the identity of **7c** was confirmed by X-ray crystallography. Treatment of **7c** with phenylsulfenyl chloride in dry chloroform afforded lactone **9c** exclusively despite the development of an eclipsing interaction between the *endo*-methyl group and lactone C–O bonds. The ^{1}H NMR spectra of **9c** features a clear $^5J_{H-F}$ coupling[25] (3.6 Hz), demonstrated unambiguously by a $\{^{19}F\}^1H$ NMR experiment, consistent with the mutual proximity of the methyl group protons and one of the fluorine atoms.

Episulfonium ring opening with proton loss to afford **16** (which avoids the development of the eclipsing interaction) exists as a viable alternative pathway, but we saw no evidence of this reaction (Scheme 5).



Scheme 5 Reagents and conditions: i, PhSCl, $CHCl_3$, rt.

Reduction, protection and oxidation

Lactones, cyclic carbonates, β-phenylthio alcohols and allylic sulfides **9–12** (and mixtures thereof) could be reduced with DIBAL-H, or more economically and conveniently, with excess lithium aluminium hydride. The ester and carbamate groups were reduced in one pot. Attempting the reduction with sodium borohydride returned a relatively complex mixture of products, which we were unable to simplify by altering reaction times. The direct cleavage of the carbamate is pleasing, meaning that there was no need to explore more complex and costly carbamates.[26] The 1,2-diols were protected selectively as the acetonides and the secondary hydroxyl group was benzylated in each case to afford **22–23** (Scheme 6, Table 2).

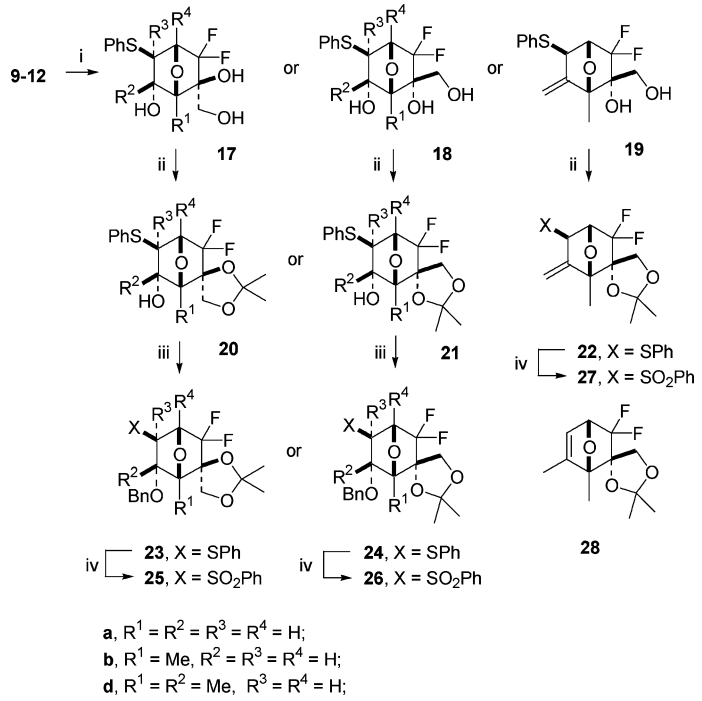
For example, from lactone **9a**, the three steps were performed to afford sulfide **23a** in an overall yield of 62% without purification, apart from trituration of the crude products with hexane. A similar sequence was launched from **11a**; the triol was purified by chromatography delivering satisfactory NMR spectra but was then taken through the next three steps after trituration alone, ultimately delivering **26a** in microanalytical purity after short column chromatography in 54% overall yield from **18a**. Table 2 summarises all the outcomes from these sequences.

Acetonide formation occurred very slowly from **19** and the product was more fragile than any of the other acetonides, suggesting that significant strain is caused when the exocyclic alkene, the bridgehead methyl group and the acetonide are brought together. Purified *m*CPBA was used routinely for the oxidations of sulfides **22–24** to the sulfones **25–27**, delivering high yields of products, which were easy to purify. Inspection of the crystal structure of sulfone **27** (Fig. 1) (*vide infra*) suggests some close contacts between protons, particularly between one of the methylene protons in the acetonide and the bridgehead methyl group (2.11 Å between the protons, 2.69 Å from the

Table 2

Precursor	Diol/triol	(%)	Acetonide	(%)	Benzyl ether	(%)	Sulfone	(%)
9a	**17a**	80	**20a**	73	**23a**	70	**25a**	89
10a/11a	**18a**	67	**21a**	100[b]	**24a**	100[b]	**26a**	54
9b	**17b**	93	**20b**	95	**23b**	86	**25b**	94
10b/11b	**18b**	79	(na)	(na)	(na)	(na)	(na)	(na)
9d/12	**17d**	68	**20d**	89	**23d**	93	**25d**	91
	19	76	**22**	20[a]	(na)	(na)	**27**	78

[a] The reaction was very slow and could not be driven to completion. [b] Estimated on the basis of recovered mass and satisfactory ^{1}H NMR spectrum.



Scheme 6 Reagents and conditions: i, $LiAlH_4$, THF, 0 °C to reflux; ii, acetone, $CuSO_4$ (anhyd), $TsOH{\cdot}H_2O$, rt; iii, NaH, THF, 0 °C then BnBr,TBAI, rt; iv, *m*CPBA, NaH_2PO_4, DCM, rt.

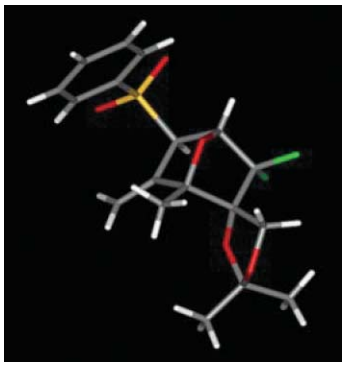
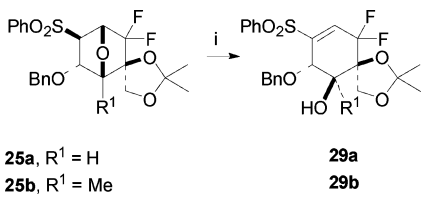


Fig. 1 Crystal structure of **27**; $=CH\cdots H_3C$ = 2.42 Å, $CH_3\cdots H_aH_bC$ = 2.11 Å.

centroid of the methyl carbon). There is also a relatively short contact between the bridgehead methyl and one of the protons in the exocyclic alkene (2.42 Å between the protons, 2.75 Å from the methyl group centroid). These close contacts may account for the slow formation of **22** and its lability.

E1$_C$B ring opening and vinylsulfone chemistry

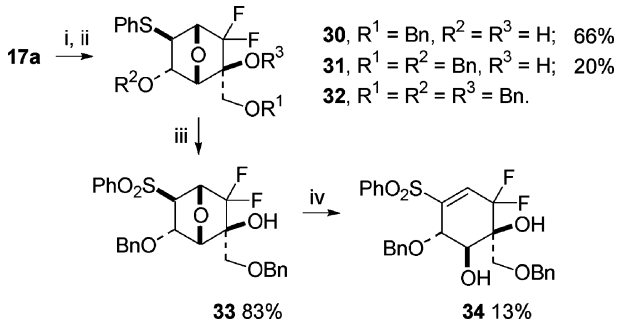
This part of the sequence was straightforward; treatment of sulfone **25a** with *n*-BuLi in THF at −78 °C for one hour, followed by warming to −30 °C and quenching, resulted in ring opening to **29a** in good yield (89%) (Scheme 7).[27] Exposure of **25b** to the same conditions afforded **29b** (87%) after E1$_C$B ring opening.



Scheme 7 Reagents and conditions: i, *n*-BuLi, THF, −78 °C to −30 °C, then H_2O and warm to rt.

These results are pleasing because there is considerable potential for the conjugate bases of **29a** and **29b** to react further through dehydrofluorination or S_N2' displacement of the fluoride ion, both pathways leading ultimately to thermodynamically favourable aromatisation.

A strategy involving a lower degree of protection was also attempted (Scheme 8). Exposure of triol **17a** to sodium hydride and a large excess of benzyl bromide gave dibenzylated compound **31** in low yield; even with large excesses of sodium hydride and benzyl bromide, the major product was the diol **30** in which only the primary hydroxyl group had been benzylated though we were also able to observe and isolate some **31** (confirming the structural assignment by X-ray crystallography).[20]

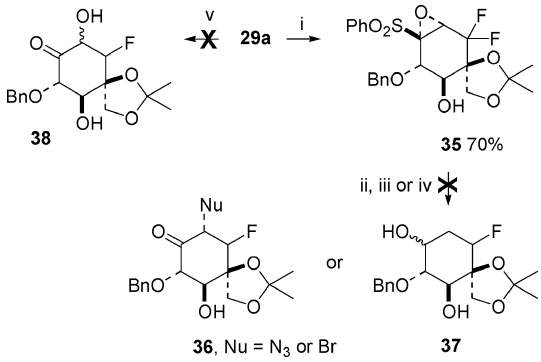


Scheme 8 Reagents and conditions: NaH, THF, 0 °C; ii, BnBr, TBAI, rt; iii, *m*CPBA, NaH_2PO_4, DCM, rt; iv, *n*-BuLi, THF, −78 °C to −30 °C, then H_2O and warm to rt.

The tertiary hydroxyl group resisted all attempts at benzylation as **32** was undetectable. Steric crowding on the lower face of the molecule, which is clearly considerable, must be exacerbated by the benzylation of the primary hydroxyl group. Acetonide formation starts easily on the primary hydroxyl group, capture of the tertiary hydroxyl is now intramolecular and the steric bulk of the acetonide, once formed is pinned away from the secondary hydroxyl allowing efficient benzylation.

Oxidation of **31** to sulfone **33** also proceeded smoothly but ring opening of the sulfone required a larger excess (4 equiv.) of *n*-BuLi than expected, and the yield of the corresponding vinylsulfone **34** was much lower than that for **29a** or **29b**.[28] The difference does not arise because the anionic or dianionic conjugate bases of **33** are insoluble in the reaction medium because the reaction was homogeneous throughout. Because of this discouraging result, we did not progress diol **30** through a similar sequence.

Disappointingly, the vinylsulfone products have proved intractable to date, as reported in our preliminary communication (Scheme 9).[20] We were able to prepare epoxide **35** in good yield, but found it resistant to nucleophilic ring opening



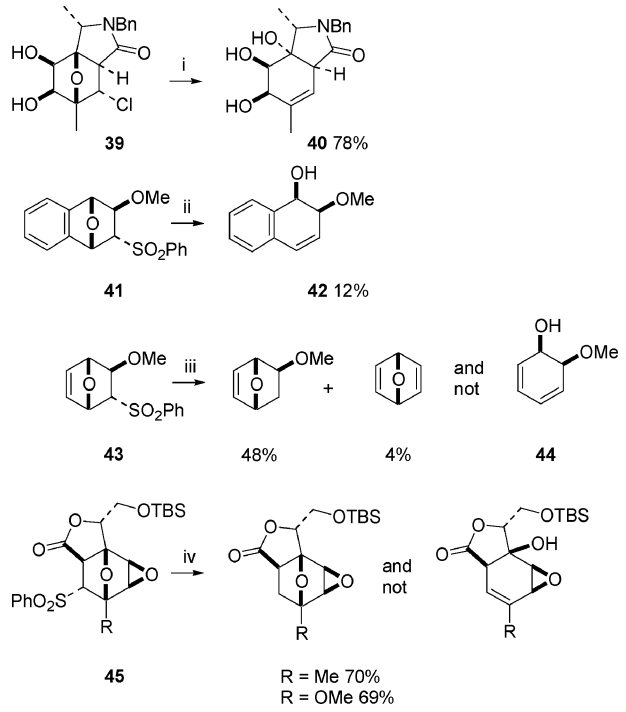
Scheme 9 Reagents and conditions: i, H_2O_2, NaOH, MeOH, rt; ii NaN_3, DMF, rt to 80 °C; $MgBr_2{\cdot}OEt_2$, THF, rt; iii, DIBAL-H, THF–PhMe, rt; iv, RuO_2, $NaIO_4$, MeCN–H_2O, rt; or OsO_4, NMO, *t*-BuOH–acetone–water.

under a range of conditions (azide ion or $MgBr_2$, leading to **36** or DIBAL-H affording **37**).[29]

The unreactivity with nucleophiles may be an effect of the adjacent CF_2 centre; substitutions next to CF_2 are often rather slow because of electronic repulsions between the fluorine atoms and the incoming nucleophile. Bäckvall *et al.*[30] and Fuchs *et al.*[31] reported dihydroxylation reactions of vinylsulfones leading to hydroxyketones (**38** was the anticipated product here) but sulfone **29a** was recovered unchanged after 14 days under the Bäckvall conditions. Presumably the compound is too electron deficient for the oxidation to occur at any meaningful rate. These disappointing outcomes demanded a different approach to ring opening.

Reductive desulfonative ring opening

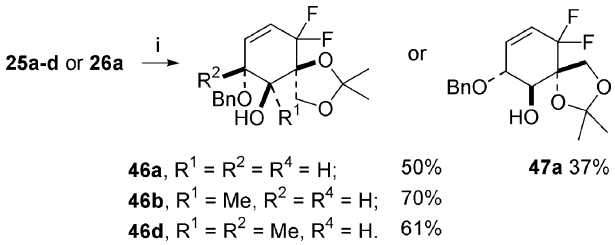
Reductive desulfonation with cleavage of a β C–O bond is the key step in Julia–Lythgoe or Julia–Paris–Kocienski olefination; leaving groups are hydroxide or carboxylate anions, with the latter used most often.[32] The oxabicyclo[2.2.1]heptanyl core is strained, and relief of strain facilitates reactions which cleave the normally strong C–O bond. We wondered if we could exploit strain relief to remove the phenylsulfonyl group and open the bicyclic system in the same step. The precedents were not encouraging; though Jung and Street[33] (Scheme 10) had combined a reductive dechlorination of **39** with ring-opening to **40**, Rickborn and Mirsadeghi[34] found that ring-opening to **42** was only a minor pathway following the exposure of **41** to amalgam conditions, while **43** failed to afford any ring-opened material **44**, a result amplified by Jung and Truc[35] with **45**.



Scheme 10 Reagents and conditions: i, Na, THF, rt; ii, 12 eq. Na(Hg), 4 : 1 DMF–MeOH, rt; iii, Na(Hg), MeOH; iv, Na(Hg), MeOH–THF, rt.

We were pleased to find that conditions based on the convenient method of Lee and co-workers[36] were effective for the conversion of **25a**, **25b** and **25d** to the corresponding cycloalkenes **46a**, **46b** and **46d** respectively in moderate to good yields (Scheme 11). The THF co-solvent was used because the substrates dissolved sparingly in neat ethanol.

In all cases, the cycloalkene was the only fluorinated reaction product visible in the ^{19}F NMR spectrum. We observed neither the simple desulfonation product, nor any alkene formed by loss of the phenylsulfonyl and benzyloxy groups. There was no



Scheme 11 Reagents and conditions: i, Mg, $HgCl_2$, EtOH–THF, 0 °C.

evidence of reductive defluorination of the ring opened products. The reaction was used to prepare gram quantities of **46a**. There was a remarkable and unexplained difference between the rate of consumption of **25a** and **26a** under these conditions. Whereas the reaction of **25a** had occurred fully after 5 hours, **26a** required the addition of more of the magnesium/mercuric reagent (23 mole% for **25a**, 70 mole% for **26a**), sonication and an extended reaction time (7 days) to reach completion, forming **47a**.[37]

The appearance of the methine proton next to the benzyloxy group requires some comment. In both **46a** and **47a**, this proton appears as a ddq, simplifying to a dt in the $\{^{19}F\}^1H$ NMR spectrum. There is a large apparent $^5J_{H-F}$ in both cases (9.0 Hz for **46a**, 9.4 Hz for **47a**). Though there is precedent for values of this size (for example between *trans*-related H-3 and H-6 protons in 1,4-cyclohexadiene where $^5J_{H-H}$ = 8–10 Hz), we were surprised to see large $^5J_{H-F}$ coupling constants in such electron deficient molecules. Conformational searching was carried out for **46a** and **47a**, producing two conformers for the former and an unique species for the latter. Geometry optimisation (RHF 6-31-G*//AM1)[38] produced structures with identical ring conformations and near antiparallel arrangements of the relevant C–H and C–F bonds (Fig. 2).

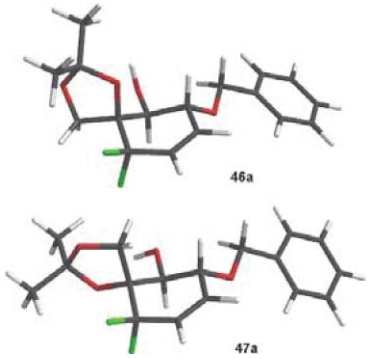


Fig. 2 Calculated structures for **46a** (lowest energy conformer) and **47a** (sole conformer found) showing an antiparallel C–H/C–F relationship.

The stereoelectronic aspects of the ring-opening reaction require some comment. Vogel and co-workers[1] point out the stereoelectronic difficulty involved in ring opening when an sp^2 carbanionic centre is generated at C(2) on the 7-oxanorbornanyl skeleton as shown in **48**. Considerable distortion is required for donation into the C(1)–O(7) σ* so that C-2 can provide the β-carbon of an enolate, without $E1_cB$ ring-opening occurring.[39]

Sulfonyl-stabilised carbanions are much more labile in terms of ease of bridging C–O cleavage; the sp^2 representation is used for α-aryl and alkylsulfonyl carbanions both with and without additional stabilisation. Epimerisation of *endo*- and *exo*-sulfones appears to be rapid at low temperature; ring opening occurs from either starting diastereoisomer even at low temperature, consistent with the generally higher stabilities of enolates.[40] An sp^3-type carbanion developed in the *endo* orientation should be capable of more effective overlap with the C(1)–O(7) σ* than the *exo* sp^3-type carbanion. King, Payne and co-workers[41] have explored the stereoelectronic basis of β-alkoxy substitutent effects on the rates of deprotonation of a wide range of alkyl phenyl sulfones including **49** and **50**. Estimated H–C–C–O

dihedral angles are shown in Fig. 3 while **51** represents the ideal conformational arrangement for generalised anomeric stabilisation of the incipient carbanion by delocalisation into the β C–O σ*.

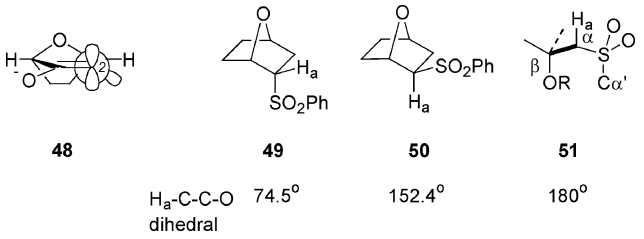
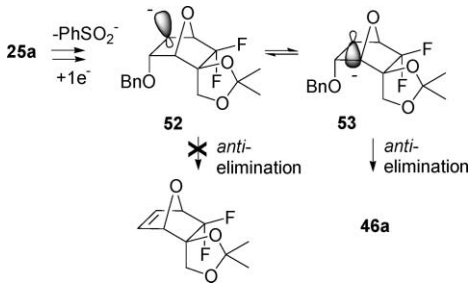


Fig. 3 Critical stereoelectronic relationships defined by the oxanorbornanyl skeleton.

The mechanism[42] of the reductive ring opening presumably involves initial formation of an unstabilised carbanion **52**, which can either lose the conjugate base of benzyl alcohol, ring open through a *syn*-elimination, or undergo inversion to **53** and progress through an orbital alignment closer to antiperiplanar (Scheme 12).

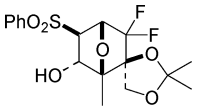


Scheme 12

The former seem unlikely given the lack of strain relief or the near orthogonality of the relevant orbitals (like the arrangement in **49**), so carbanion inversion to **53** must be much faster than protonation, even in an alcohol solvent. It seems surprising that **41**, **43** and **45** which all lead *directly* to the better-aligned *endo* sp^3-type carbanion (like **53**), fail to ring open, whereas **25a–d** and even **26a**, which lead to the orthogonal carbanion and therefore require inversion, undergo the ring opening reaction without protodesulfonation. It would seem more logical for reductive desulfonation to occur with *inversion*: **25a–d** and **26a** would then afford carbanions which could progress, whereas **41**, **43** and **45** would yield non-productive species, which would protonate more rapidly than they could ring open. This idea cannot be tested fully through the data available currently in the literature but there is remarkable consistency between the hypothesis and all the outcomes we have found reported in the literature.

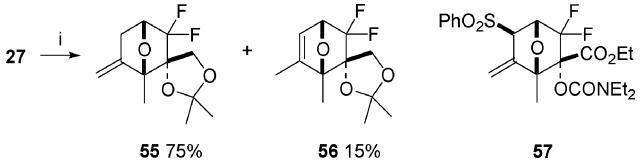
It is very difficult to see how the relative configuration of a remote quaternary centre can exert such a powerful effect on the reductive desulfonation reaction. The observation that the reduction of **26a** can be kept active for 8 days without any detectable simple desulfonation, suggests the remote quaternary centre exerts a powerful effect over the electron-accepting properties of the phenylsulfonyl group.

Though the desulfonative ring opening reaction is carried out in a protic solvent, it failed to occur to any appreciable extent when the adjacent hydroxyl group was exposed. Oxidation of **20b** afforded sulfone **54**; ring opening was attempted but **54** was returned unchanged. Presumably the hydroxyl group is ionised under the reaction conditions and the presence of the electron-rich oxygen perturbs the electron-acceptor properties of the sulfur atom inhibiting the reaction.



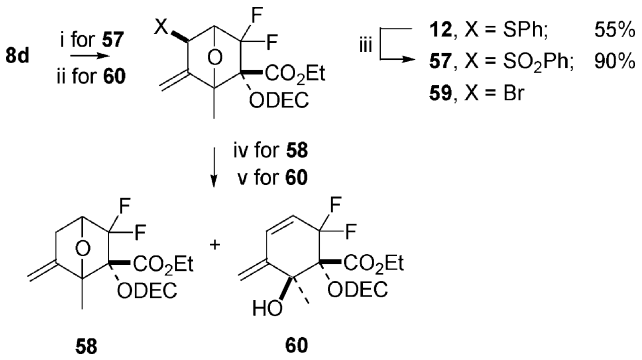
54

Allylic sulfone **27** did not ring open under these conditions; instead, desulfonation occurred exclusively to afford **55**, with some alkenyl group migration, presumably *via* the allylic carbanion forming known **56** (Scheme 13).[18]



Scheme 13 Reagents and conditions: i, Mg, $HgCl_2$, EtOH–THF, 0 °C.

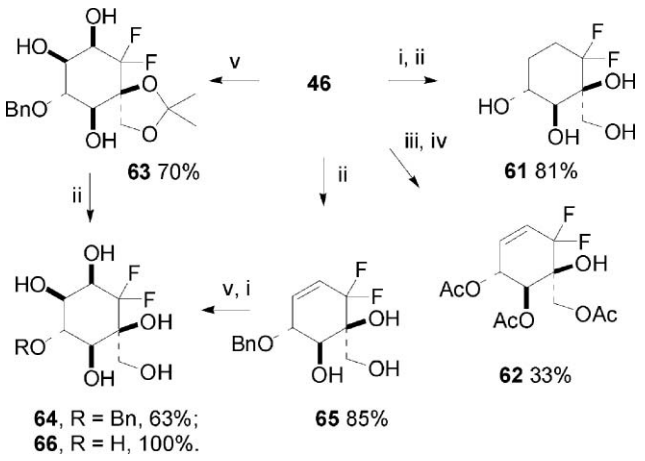
The additional stabilisation of the carbanion (which is now allylic) would be expected to slow down the ring-opening step resulting in protonation rather than elimination.[43] We also prepared sulfone **57** from *exo*-cycloadduct **8d** believing that the slightly higher level of electron demand in this compound would make the bridging oxygen a better leaving group and facilitate ring-opening but again, reductive desulfonation to **58** and **8d** was the dominant pathway. Exocyclic alkene **58** was prepared in larger quantities for characterisation *via* bromination of **8d** to afford **60**, and reduction with zinc in DMF which formed **59** (44%) and **8d** (36%) as a separable mixture (Scheme 14).



Scheme 14 Reagents and conditions: i, PhSSPh, SO_2Cl_2, DCM; ii, Br_2, MeCN, rt; iii, $MnSO_4$, H_2O_2, $NaHCO_3$, MeCN, rt; iv, Mg, $HgCl_2$, EtOH–THF, 0 °C; v, Zn, DMF, sonication, rt.

Educt processing

The goal of this chemistry is the synthesis of densely-functionalised difluorinated cyclohexane polyols so we progressed representative educt **46** through a number of further transformations and deprotections (Scheme 15). Exposure to hydrogen over palladium resulted in reduction of the alkenyl group and cleavage of the benzyl ether; the acetonide was removed in acidic methanol to reveal tetrol **61**. Alternatively, exposure of **46a** to excess boron trichloride,[44] resulted in cleavage of the acetonide and benzyl ether. As this product was difficult to purify satisfactorily (presumably borate esters are formed rather readily), it was triacetylated to afford **62**. We were also able to dihydroxylate **46a**,[45] then cleave the acetonide from **63** to afford **64**. However, reversing the order of these two steps resulted in a twofold more rapid dihydroxylation reaction *via* **65**. The sense of stereoselection in the dihydroxylation reaction is assumed using the Kishi model[46] which has proved reliable in related structures.[47] The benzyl ether could then be hydrogenolysed successfully to release **66**.



Scheme 15 Reagents and conditions: i, H_2, 5% Pd–C, EtOH; ii, Amberlyst-15, MeOH; iii, BCl_3, DCM, −78 °C to rt; iv, Ac_2O, pyridine, rt; v, OsO_4, NMO, *t*-BuOH–acetone–water.

Conclusion

We have for the first time constructed highly-functionalised difluorinated cyclohexenes and cyclohexane polyols from trifluoroethanol, using a Diels–Alder reaction that admits a range of alkylfurans. Sulfur electrophile chemistry allowed regiochemical control, while ring-opening was achieved through reductive cleavage of the carbon–sulfur bond. The route delivers the polyols successfully; the main methodological challenges now lie in understanding the relationship between cycloaddition reactivity and component structure, and in developing highly *endo*- or *exo*-selective cycloadditions through which the flux of materials through these pathways can be maximised.

Experimental

General experimental

NMR spectra were recorded on Bruker ARX-250, Bruker DPX-300, Bruker AC-300 or Bruker DRX-400 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded using the deuterated solvent as the lock and the residual solvent as the internal reference. ^{19}F NMR spectra were recorded relative to chlorotrifluoromethane as the external standard. The multiplicities of the spectroscopic data are presented in the following manner: app. = apparent, s = singlet, d = doublet, t = triplet, pent. = pentet, q = quartet, m = multiplet and br = broad. The appearance of complex signals is indicated by app. Homocouplings (H–H, F–F) are given in Hertz and specified by *J*; the nuclei involved in heteronuclear couplings are defined with the observed nucleus given first. Unless stated otherwise, all refer to ^3J couplings. Chemical ionisation (CI) mass spectra were recorded on a Micromass Prospec or a Kratos Concept 1H spectrometer using ammonia as the reagent gas. Electron impact (EI) spectra were recorded on a Kratos MS-80, a Micromass Prospec or a Kratos Concept 1H spectrometer. Fast atom bombardment (FAB) spectra were recorded on a Kratos Concept 1H spectrometer at about 7 kV using xenon and *m*-nitrobenzyl alcohol as the matrix. GC-MS was carried out on a Perkin Elmer TurboMass spectrometer fitted with a Zebron ZB-5 column (30 m × 0.25 μm) running a 20–3500 C ramp over 27 minutes. Electrospray (ES) mass spectra were recorded on a Micromass LCT or a Micromass Quattro LC spectrometer. High resolution mass spectrometry measurements were carried out either on the Micromass LCT or the Kratos Concept 1H spectrometer using peak matching to suitable reference peaks, depending on the technique used. Thin Layer Chromatography (TLC) was performed on precoated aluminium silica gel plates supplied by E. Merck, A.G. Darmstadt, Germany (Silica gel 60 F254, thickness 0.2 mm, Art. 1.05554) or on precoated plastic silica gel plates supplied by Macherey-Nagel (Polygram® SIL G/UV254, thickness 0.25 mm, Art. 805 023) or on precoated glass plates supplied by Merck (Silica gel 60 F254, art. 1.05715). Visualisation was achieved by UV light and/or potassium permanganate stain. Flash column chromatography was performed using silica gel (Fluorochem, Silica gel 60, 40–63 μ, Art. 02050017) or using a Biotage flash chromatography system. THF was dried by refluxing with benzophenone over sodium wire until a deep purple color developed and persisted, then distilled and collected by dry syringe as required. Other solvents were dried using a Pure Solv apparatus (Innovative Technologies Inc). All other chemicals were used as received without any further purification.

Representative procedures are described in the Experimental section; full characterisation details for all other compounds are in the electronic supplementary information (ESI).† Cycloadditions with furan, 2-methylfuran and 2,3-dimethylfuran, preparations of **9a**, **17a**, **28a** and **43** were carried out according to our published procedures.[18] Phenylsulfenyl chloride was prepared *in situ* according to the procedure of Suzuki and co-workers.[23] Conformational searching and geometry optimisations were carried out using MacSpartan Pro.[38]

Crystallographic experimental

Crystallographic data for 7c. $C_{15}H_{21}F_2NO_5$, crystal size 0.32 × 0.25 × 0.18 mm, $M = 333.33$, orthorhombic, $a = 9.319(2)$, $b = 12.579(3)$, $c = 27.029(7)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90$ deg, $U = 3168.3(14)$ Å^3, $T = 150(2)$ K, space group *Pbca*, $Z = 8$, μ(Mo–Kα) = 0.119 mm^{-1}, 21124 reflections measured, 2784 unique, ($R_{int} = 0.0268$) which were used in all calculations. Final *R* indices [$F^2 > 2\sigma(F^2)$] $R1 = 0.0338$, $wR2 = 0.0820$; *R* indices (all data) $R1 = 0.0395$, $wR2 = 0.0849$.‡

Crystallographic data for 9a. $C_{18}H_{19}F_2NO_5S$, crystal size 0.38 × 0.29 × 0.13 mm, $M = 399.40$, monoclinic, $a = 10.4325(7)$, $b = 11.7993(8)$, $c = 14.7171(10)$ Å, $\alpha = 90$, $\beta = 92.0510(10)$, $\gamma = 90$ deg, $U = 1810.5(2)$ Å^3, $T = 150(2)$ K, space group $P2(1)/n$, $Z = 4$, μ(Mo–Kα) = 0.229 mm^{-1}, 13859 reflections measured, 3555 unique, ($R_{int} = 0.0353$) which were used in all calculations. Final *R* indices [$F^2 > 2\sigma(F^2)$] $R1 = 0.0386$, $wR2 = 0.1049$; *R* indices (all data) $R1 = 0.0443$, $wR2 = 0.1079$.‡

Crystallographic data for 10b. $C_{17}H_{16}F_2O_6$, crystal size 0.33 × 0.30 × 0.88 mm, $M = 386.36$, monoclinic, $a = 9.9999(5)$, $b = 8.3226(4)$, $c = 19.8783(10)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90$ deg, $U = 1648.65(14)$ Å^3, $T = 150(2)$ K, space group $P2(1)/c$, $Z = 4$, μ(Mo–Kα) = 0.251 mm^{-1}, 11548 reflections measured, 2900 unique, ($R_{int} = 0.0194$) which were used in all calculations. Final *R* indices [$F^2 > 2\sigma(F^2)$] $R1 = 0.0309$, $wR2 = 0.0796$; *R* indices (all data) $R1 = 0.0336$, $wR2 = 0.0816$.‡

Crystallographic data for 11b. $C_{21}H_{27}F_2NO_6S$, crystal size 0.32 × 0.25 × 0.18 mm, $M = 459.50$, monoclinic, $a = 8.806(2)$, $b = 22.250(6)$, $c = 11.795(3)$ Å, $\alpha = 90$, $\beta = 98.871(4)$, $\gamma = 90$ deg, $U = 2283.2(10)$ Å^3, $T = 150(2)$ K, space group $P2(1)/c$, $Z = 4$, μ(Mo–Kα) = 0.194 mm^{-1}, 16416 reflections measured, 4020 unique, ($R_{int} = 0.0273$) which were used in all calculations. Final *R* indices [$F^2 > 2\sigma(F^2)$] $R1 = 0.0406$, $wR2 = 0.1051$; *R* indices (all data) $R1 = 0.0485$, $wR2 = 0.1097$.‡

Crystallographic data for 27. $C_{18}H_{20}F_2O_5S$, crystal size 0.32 × 0.25 × 0.18 mm, $M = 386.40$, monoclinic, $a = 17.875(3)$, $b = 6.5609(12)$, $c = 15.029(3)$ Å, $\alpha = 90$, $\beta = 93.158(3)$, $\gamma = 90$ deg, $U = 1759.9(6)$ Å^3, $T = 150(2)$ K, space group $P2(1)/c$, $Z = 4$, μ(Mo–Kα) = 0.231 mm^{-1}, 12099 reflections measured, 3096 unique, ($R_{int} = 0.0728$) which were used in all calculations. Final *R* indices [$F^2 > 2\sigma(F^2)$] $R1 = 0.0611$, $wR2 = 0.1416$; *R* indices (all data) $R1 = 0.0929$, $wR2 = 0.1545$.‡

‡ CCDC reference numbers 272665–272670. See http://dx.doi.org/10.1039/b507131c for crystallographic data in CIF or other electronic format.

Crystallographic data for 46b. $C_{18}H_{22}F_2O_4$, crystal size 0.32 × 0.25 × 0.18 mm, M = 340.36, monoclinic, a = 10.5327(18), b = 11.552(2), c = 16.158(3) Å, α = 75.465(3), β = 68.790(3), γ = 71.827(3) deg, U = 1720.2(5) Å^3, T = 150(2) K, space group $P2(1)/c$, Z = 4, μ(Mo–Kα) = 0.194 mm^{-1}, 12601 reflections measured, 6014 unique, (R_{int} = 0.0204) which were used in all calculations. Final R indices [$F^2 > 2\sigma(F^2)$] $R1$ = 0.0381, $wR2$ = 0.0923; R indices (all data) $R1$ = 0.0459, $wR2$ = 0.0968.‡

Synthetic experimental

Ethyl *exo*-2-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-5-methyl-7-oxabicyclo[2.2.1]hept-5-enyl-2-*endo*-carboxylate 7c and ethyl *endo*-2-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-5-methyl-7-oxabicyclo[2.2.1]hept-5-enyl-2-*exo*-carboxylate 8c. Tin(IV) chloride (1 mmol, 0.12 mL) was added to a solution of **6** (1 mmol, 0.25 g), 3-methylfuran (2 mmol, 0.16 g), in DCM (3 mL) under an atmosphere of nitrogen. After 45 minutes at 0 °C, the reaction was quenched with water (10 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford a brown oil which was purified by column chromatography (Biotage 25 M, gradient 8% diethyl ether to 33% diethyl ether in hexane) to afford *endo*-**7c** as colourless cubes (0.16 g, 48%); mp 55–57 °C; R_f (50% diethyl ether in hexane) 0.29; (Found C, 54.22; H, 6.53; N, 4.26; $C_{15}H_{21}F_2NO_5$ requires: C, 54.05; H, 6.35; N, 4.20%); δ_H (400 MHz, $CDCl_3$) 6.41 (1H, t, J 1.4, HC=C), 5.18 (1H, s, CHOCHCF$_2$), 4.53 (1H, d, $^3J_{H-F}$ 5.7, CHOCHCF$_2$), 4.28–4.14 (2H, m, OCH_2CH$_3$), 3.47–3.25 (4H, m, NCH_2CH$_3$), 1.94 (3H, d, J 1.4, C=CCH_3), 1.24 (3H, t, J 7.2, OCH$_2$CH_3), 1.21 (3H, t, J 7.2, NCH$_2$CH_3), 1.13 (3H, t, J 7.2, NCH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 165.4, 154.0, 141.5 (d, $^3J_{C-F}$ 4.0), 130.7, 123.8 (dd, $^1J_{C-F}$ 281.8, 261.4), 85.2 (d, $^3J_{C-F}$ 4.1), 83.9 (t, $^2J_{C-F}$ 26.8), 82.3 (dd, $^2J_{C-F}$ 27.2, 12.9), 61.7, 42.2, 42.1, 13.9, 13.8, 13.7, 13.4; δ_F (376 MHz, $CDCl_3$) −107.9 (d, $^2J_{F-F}$ 226.3), −112.7 (dd, $^2J_{F-F}$ 226.3, $^3J_{F-H}$ 5.7); m/z (ES +) 334 (94%, M + 1), 314 (14), 288 (4), 252 (100), 118 (8), 100 (78): and *exo*-**8c** as a colourless oil (0.012 g, 6%); R_f (50% diethyl ether in light petroleum) 0.21; δ_H (400 MHz, $CDCl_3$) 6.02 (1H, dd, J 3.2, 2.0, HC=C), 5.62 (1H, s, CHOCHCF$_2$), 4.57 (1H, d, $^3J_{H-F}$ 5.7, CHOCHCF$_2$), 4.33–4.24 (2H, m, OCH_2CH$_3$), 3.37–3.14 (4H, m, NCH_2CH$_3$), 1.97 (3H, d, J 1.6, C=CCH_3), 1.30 (3H, t, J 7.2, OCH$_2$CH_3), 1.13 (3H, t, J 6.0, NCH$_2$CH_3), 1.12 (3H, t, J 6.0, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 166.0, 153.2, 144.4 (d $^3J_{C-F}$ 4.5), 129.6, 123.0 (dd $^1J_{C-F}$ 262.0, 277.1), 84.3, 82.9 (t, $^2J_{C-F}$ 26.4), 79.9 (dd, $^2J_{C-F}$ 27.6, 14.0), 62.1, 42.3, 42.1, 13.9, 13.8, 13.7, 13.4; δ_F (282 MHz, $CDCl_3$) −108.6 (dd, $^2J_{F-F}$ 227.1, $^3J_{F-H}$ 5.7), −110.9 (d, $^2J_{F-F}$ 227.1); m/z (ES) 334 (100%, [M + H]$^+$), 217 (3), 159 (18), 118 (30), 100 (6).

This minor product was not characterized further.

Ethyl *exo*-2-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-1,4-dimethyl-7-oxabicyclo[2.2.1]hept-5-enyl-2-*endo*-carboxylate 7e and ethyl *endo*-2-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-1,4-dimethyl-7-oxabicyclo[2.2.1]hept-5-enyl-2-*exo*-carboxylate 8e. Were prepared as for **7c** and **8c** from enoate **6** (2 mmol, 0.5 g), 2,5-dimethyl furan (4 mmol, 0.43 mL), and $SnCl_4$ (0.5 mmol, 0.5 mL of a 1 M solution in DCM) in DCM (5 mL). After 30 minutes at 0 °C, the reaction was quenched with water (5 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford a brown oil. Purification by column chromatography (20% ethyl acetate in hexane) afforded an inseparable mixture of cycloadducts **7e** and **8e** (1.9 : 1) as a colourless oil (0.66 g, 96%); R_f (20% ethyl acetate in hexane) 0.35; δ_H (300 MHz, $CDCl_3$) 6.33 (1H, d, J 5.4, HC=CH (major cycloadduct)), 6.25–6.19 (3H, m, HC=CH), 4.21 (2H, q, J 7.2, OCH_2CH$_3$ (minor stereoisomer)), 4.10 (2H, q, J 7.2, OCH_2CH$_3$ (major stereoisomer)), 3.34–3.12 (4H, m, N(CH_2CH$_3$)$_2$), 1.50 (3H, s, CH$_3$), 1.46 (3H, s, CH$_3$), 1.24–1.03 (9H, m, OCH$_2$CH_3, N(CH$_2$CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 165.8, 165.0, 154.1, 153.2, 141.2, 140.5, 136.7, 136.3, 123.6 (t, $^1J_{C-F}$ 273.6), 122.8 (dd, $^1J_{C-F}$ 278.0, 270.1), 90.7, 90.6, 86.6 (t, $^2J_{C-F}$ 26.7), 86.4 (dd, $^2J_{C-F}$ 22.6, 15.6), 83.0 (dd, $^2J_{C-F}$ 22.6, 15.6), 61.4, 60.3, 42.4, 42.1, 14.9, 13.9, 13.3, 11.6, [signals for C1, and five CH$_3$ environments are coincident for both diastereoisomers]; δ_F (282 MHz, $CDCl_3$) (−104.0)–(−105.4) (br, m), −106.4 (d, $^2J_{F-F}$ 220.6), −117.6 (d, $^2J_{F-F}$ 220.6), (−117.5)–(−118.0) (br, m); [HRMS (ES, [M + H]$^+$) Found 348.1616. Calc. for $C_{16}H_{24}F_2NO_5$ 348.1617]; m/z (ES) 348 (100%, [M + H]$^+$), 252 (68), 100 (35).

Ethyl 2*S-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-6*S**-hydroxy-5*R**-phenylsulfanyl-7-oxabicyclo[2.2.1]-1*S**-heptane-2-carboxylate 11a.** Sulfuryl chloride (5.7 mmol, 0.46 mL) was added dropwise to a solution of diphenyl disulfide (5.7 mmol, 1.24 g) in CH_2Cl_2 (1 mL), the solution was stirred at room temperature for one hour before *exo*-**8a** (3.8 mmol, 1.2 g) in CH_2Cl_2 (1 mL) was added dropwise. The resulting orange solution was stirred at room temperature for 48 hours before the solvent was removed *in vacuo* to afford an orange solid which was purified by column chromatography (50% diethyl ether in hexane) to afford **11a** (0.33 g, 20%) as a white solid; mp 133–135 °C; R_f (50% diethyl ether in hexane) 0.16; δ_H (300 MHz, $CDCl_3$) 7.42–7.25 (5H, m, Ar), 5.26 (1H, d, J 5.1 CHOH), 4.41 (1H, d, $^3J_{H-F}$ 7.7, CHCF$_2$), 4.36–4.25 (3H, m, CHOCH, OCH_2CH$_3$), 3.57 (1H, d, J 5.1, CHSPh), 3.51–3.23 (4H, m, N(CH_2CH$_3$)$_2$), 2.79 (1H, s, OH), 1.30 (3H, t, J 7.05, NCH$_2$CH_3), 1.24 (3H, t, J 7.20, OCH$_2$CH_3), 1.11 (3H, t, J 7.05, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 165.5 (d $^3J_{C-F}$ 5.3), 154.3, 134.4, 130.1, 129.33, 127.2, 121.5 (dd $^1J_{C-F}$ 278.1, 262.3), 84.4 (t $^2J_{C-F}$ 25.3), 81.7 (dd, $^2J_{C-F}$ 27.9, 15.1), 81.3, 78.9, 62.4, 48.7 (d, $^3J_{C-F}$ 4.5), 42.2, 42.1, 13.9, 13.7, 12.2; δ_F (282 MHz, $CDCl_3$) −105.2 (dd, $^2J_{F-F}$ 230.7, $^3J_{F-H}$ 7.7), −119.8 (d, $^2J_{F-F}$ 230.7); [HRMS (EI, M$^+$) Found 445.1379. Calc. for $C_{20}H_{25}F_2NO_6S$ 445.1371]; m/z (ES) 463 (16%, M + [H$_2$O]$^+$), 446 (100). Single crystals were grown by diffusion of diethyl ether into hexane, this afforded colourless needles from which a crystal structure was obtained.

3,3-Difluoro-2*R-(hydroxymethyl)-1*S**-methyl-5*R**-phenylsulfanyl-7-oxabicyclo[2.2.1]-7*S**-heptane-2,6*S**-diol 17b.** A solution of lactone **9b** (5.3 mmol, 2.2 g) in THF (7 mL) was added to a suspension of lithium aluminium hydride (31.8 mmol, 1.2 g) in THF (42 mL) at 0 °C under an atmosphere of nitrogen. The suspension was refluxed overnight; after cooling, the excess lithium aluminium hydride was destroyed carefully by the addition of water (10 mL) then dilute HCl (20 mL of a 1 M aqueous solution). The resulting solution was neutralised with aqueous sodium hydroxide (5 mL of a 0.5 M aqueous solution) and extracted with ethyl acetate (6 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid which was triturated with hexane to yield triol **17b** (1.6 g, 93%) as cubes; mp 98–100 °C; R_f (60% ethyl acetate in light petroleum) 0.40; (Found: C, 53.07; H, 5.18; $C_{14}H_{16}F_2O_4S$ requires: C, 52.82; H, 5.07%); ν_{max} (film)/cm^{-1} 3425 w br (OH), 3250 m br (OH), 1106 m (CO), 1077s (CO), 731 (C–H def.), 658 (C–H def.); δ_H (300 MHz, CD_3COCD_3) 7.45–7.25 (5H, m, Ar), 5.61 (1H, br, OH), 4.49 (1H, br, OH), 4.18 (1H, dd, $^3J_{H-F}$ 8.7, 2.0, CHCF$_2$), 4.06 (1H, d, ^2J 12.0, CH_aCH$_b$O), 3.88 (1H, d, J 4.7, CHOH), 3.81 (1H, dt, ^2J 12.0, $^4J_{H-F}$ 2.3, CH$_a$CH_bO), 3.61–3.58 (1H, m, CHSPh), 2.85 (1H, br, OH), 1.44 (3H, s, CH_3); δ_C (75 MHz, CD_3COCD_3) 135.9, 130.0, 129.7, 127.1, 125.4 (t, $^1J_{C-F}$ 265.7), 91.3 (d, $^3J_{C-F}$ 6.0), 84.2 (t, $^2J_{C-F}$ 26.8), 83.5, 80.9 (dd, $^2J_{C-F}$ 23.2, 16.1), 61.6 (d, $^3J_{C-F}$ 7.4), 50.7 (d, $^3J_{C-F}$ 3.2), 15.2; δ_F (282 MHz, CD_3COCD_3), −111.9 (dd, $^2J_{F-F}$ 230.3, $^3J_{F-H}$ 8.7), −112.7 (d, $^2J_{F-F}$ 230.3); m/z (ES) 317 (100%, [M − H]).

3,3-Difluoro-2*R-(hydroxymethyl)-5*R**-phenylsulfanyl-7-oxabicyclo[2.2.1]-1*S**,7*S**-heptane-2,6*S**-diol acetone acetal 20a.** Amberlyst-15 (0.02 g) was added to a solution of triol **17a**

(1.6 mmol, 0.49 g) in 2,2-dimethoxy propane (4 mL) and the mixture was stirred at room temperature under an atmosphere of nitrogen for 24 hours. After filtration, the mixture was concentrated *in vacuo* to afford a yellow solid which was triturated with hexane to afford acetonide **20a** (0.4 g, 73%) as a white solid; mp 117–120 °C; R_f (50% diethyl ether in light petroleum) 0.26; (Found: C, 55.81; H, 5.21; S, 9.21; $C_{16}H_{18}F_2O_4S$ requires: C 55.80; H, 5.27; S, 9.31%); δ_H (300 MHz, $CDCl_3$) 7.41–7.24 (5H, m, Ar), 4.46–4.28 (4H, env. H-1, H-4, H-6, CH_aH_bO), 4.09 (1H, dt, J 10.7, $^4J_{H-F}$ 3.1, CH_aCH_bO), 3.51–3.49 (1H, m, H-5), 2.32 (1H, d, J 4.8, OH), 1.49 (2H, s, CH_3), 1.39 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 134.2, 130.3, 129.5, 127.4, 123.2 (dd, $^1J_{C-F}$ 271.3, 266.8), 110.1, 86.2 (dd, $^2J_{C-F}$ 27.1, 16.4), 85.6 (d, $^3J_{C-F}$ 5.7), 84.3 (dd, $^2J_{C-F}$ 28.3, 26.6), 77.2, 64.5 (d, $^3J_{C-F}$ 7.9), 50.6 (dd, $^3J_{C-F}$ 5.1, 2.8), 26.0, 25.4; δ_F (282 MHz, $CDCl_3$) −109.4 (dd, $^2J_{F-F}$ 229.8, $^3J_{F-H}$ 8.3), −120.7 (d, $^2J_{F-F}$ 229.8); [HRMS (ES, M^+ + Na) Found: 367.0775. Calc. for $C_{16}H_{18}F_2O_4SNa$ 367.0798]; m/z (ES) 367 (100%, $[M + Na]^+$).

6*S-Benzyloxy-3,3-difluoro-2*R**-(hydroxymethyl)-5*R**-phenylsulfanyl-7-oxabicyclo[2.2.1]-1*S**,7*S**-heptan-2-ol acetone acetal 23a.** A solution of alcohol **20a** (2.3 mmol, 0.78 g) in THF (1 mL), was added slowly to a suspension of sodium hydride (2.3 mmol, 0.12 g of 60% dispersion, from which the mineral oil had been removed by washing with hexane) in THF at 0 °C under an atmosphere of nitrogen. The resulting orange suspension was stirred at 0 °C for one hour before tetra n-butylammonium iodide (0.2 mmol, 0.015 g) and benzyl bromide (3.2 mmol, 0.4 mL) were added in one portion. The mixture was allowed to warm to room temperature and stirred for 18 hours before being cautiously quenched with water (5 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow solid (0.9 g), which was triturated with hexane to afford acetonide **23a** (0.70 g, 70%) as a white solid; mp 87–90 °C; R_f (50% diethyl ether in light petroleum) 0.54; (Found: C, 63.67; H, 5.57; S, 7.26; $C_{23}H_{24}F_2O_4S$ requires: C 63.58; H, 5.57; S, 7.38%); ν_{max} (mull)/cm^{-1} 3067 m (Ar C–H), 2980 m (C–H), 2916 m (C–H), 2879 m (C–H), 1455 m (C–C), 1442 m (C–C), 1235 m (C–O), 1170 m br (C–O), 1091 m br (C–O), 736 m (Ar C–H), 690 m (Ar C–H); δ_H (300 MHz, $CDCl_3$) 7.41–7.25 (10H, env. Ar), 4.56–4.33 (5H, env. H-1, H-4, H-6, CH_aCH_bO, OCH_aCH_bPh), 4.07–4.01 (2H, env. CH_aCH_bO, OCH_aCH_bPh), 3.58–3.56 (1H, m, H-5), 1.49 (3H, s, CH_3), 1.38 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 136.7, 134.1, 130.9, 129.5, 128.7, 128.3, 127.8, 127.7, 123.2 (dd $^1J_{C-F}$ 271.8, 265.6), 110.2, 86.3 (dd, $^2J_{C-F}$ 26.8, 16.7), 85.0 (dd, $^2J_{C-F}$ 28.8, 26.6), 84.7 (d, $^3J_{C-F}$ 5.7), 83.7, 73.6, 64.6 (d, $^3J_{C-F}$ 7.4), 48.6 (dd, $^3J_{C-F}$ 5.4, 2.6), 26.1, 25.4; δ_F (282 MHz, $CDCl_3$) −109.2 (dd, $^2J_{F-F}$ 230.2, $^3J_{F-H}$ 8.9), −120.0 (d, $^2J_{F-F}$ 230.2); [HRMS (ES, M^+ + Na) Found: 457.1278. Calc. for $C_{23}H_{24}F_2O_4SNa$ 457.1261]; m/z (ES) 457 (100%, $[M + Na]^+$).

6*S-Benzyloxy-3,3-difluoro-2*R**-(hydroxymethyl)-5*R**-phenylsulfonyl-7-oxabicyclo[2.2.1]-1*S**,7*S**-heptan-2-ol acetone acetal 25a.** A solution of sulfide **23a** (1.35 mmol, 0.58 g) in DCM (2 mL) was added to a suspension of *m*CPBA (2.8 mmol, 0.48 g) and sodium dihydrogen phosphate (2.8 mmol, 0.33 g) in DCM (11 mL). The resulting colourless solution was stirred at room temperature for 30 minutes, during which time a white precipitate formed. The mixture was quenched with saturated aqueous sodium bicarbonate (10 mL) and diluted with ethyl acetate (20 mL). The phases were separated and the organic layer was washed with aqueous sodium bicarbonate (6 × 10 mL) before being dried ($MgSO_4$) and concentrated *in vacuo* to afford sulfone **25a** (0.56 g, 89%) as a white solid; mp 137–139 °C; R_f (50% diethyl ether in light petroleum) 0.23; (Found C, 59.35; H, 4.94; $C_{23}H_{24}F_2O_6S$ requires: C, 59.22; H, 5.19%); ν_{max} (mull)/cm^{-1} 2950 m (C–H), 1447 m (C–C), 1309 m (C–O), 1137s (C–O), 1086s (C–O), 711 w (Ar C–H), 730 w (Ar C–H), 690 w (Ar C–H); δ_H (300 MHz, $CDCl_3$) 7.90–7.24 (10H, env. Ar), 4.72–4.27 (6H, env., H-1, H-4, H-6, OCH_2Ar, CH_aH_bO), 3.97 (1H, dt, J 10.7, $^4J_{H-F}$ 3.1, CH_aH_bO), 3.60–3.59 (1H, m, H-5), 1.43 (3H, s, CH_3), 1.32 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 137.2, 136.3, 134.6, 129.7, 128.8, 128.7, 128.4, 128.0, 122.8 (dd, $^1J_{C-F}$ 272.7, 267.6), 110.3, 86.2 (dd, $^2J_{C-F}$ 27.1, 16.4), 84.3 (d, $^3J_{C-F}$ 5.1), 81.0 (dd, $^2J_{C-F}$ 31.9, 26.9), 78.2, 73.7, 67.7 (dd, $^3J_{C-F}$ 5.1, 2.8), 64.4 (d, $^3J_{C-F}$ 6.8), 26.0, 25.2; δ_F (282 MHz, $CDCl_3$) −110.5 (dd, $^2J_{F-F}$ 228.9, $^3J_{F-H}$ 7.6), 118.4 (d, $^2J_{F-F}$ 228.9); [HRMS (ES, M^+ + Na) Found: 489.1169. Calc. for $C_{23}H_{24}F_2O_6SNa$ 489.1159]; m/z (ES) 489 (100%, $[M + Na]^+$).

3*S-Benzyloxy-6,6-difluoro-1*S**-(hydroxymethyl)-4-phenylsulfonyl-cyclohex-4-en-1,2*S**-diol acetone acetal 29a.** *n*-Butyllithium (0.5 mmol, 0.3 mL of a 1.7 M solution in hexanes) was added slowly to a solution of sulfone **25a** in THF at −78 °C under an atmosphere of nitrogen. After stirring at this temperature for 30 minutes, the reaction was quenched with water (5 mL) and allowed to warm to room temperature before being extracted with ethyl acetate (6 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to afford a pale yellow solid (0.23 g) which was triturated with hexane to yield alcohol **29a** (0.21 g, 89%) as a white solid; mp 132–134 °C; R_f (50% diethyl ether in light petroleum) 0.26; ν_{max} (mull)/cm^{-1} 3448s br (OH), 2991 w (C–H), 1450 m (C–C), 1106 m (C–O), 1062 m (C–O), 757 w (Ar C–H), 686 w (Ar C–H); δ_H (300 MHz, $CDCl_3$) 7.75–7.72 (2H, m, Ar), 7.53–7.47 (1H, m, Ar), 7.33–7.26 (5H, m, Ar), 7.19–7.14 (2H, m, Ar), 6.91 (1H, dt, J 1.8, $^4J_{H-F}$ 6.4, H-9), 4.86 (1H, d, ^2J 11.0, OCH_aH_bPh), 4.79 (1H, d, ^2J 11.0, OCH_aH_bPh), 4.66–4.60 (1H, m, H-7), 4.26 (1H, d, ^2J 9.6, H-4), 4.16 (1H, d, ^2J 9.6, H-4), 3.88 (1H, br s, H-6), 2.27 (1H, br s, OH), 1.45 (3H, s, CCH_3), 1.43 (3H, s, CCH_3); δ_C (75 MHz, $CDCl_3$) 148.7 (dd, $^3J_{C-F}$ 12.4, 10.2), 139.9, 137.4, 133.7, 131.4 (dd, $^2J_{C-F}$ 37.0, 26.9), 129.0, 128.5, 128.1, 128.0, 116.0 (dd, $^1J_{C-F}$ 252.1, 239.6), 112.8, 77.2 (d, $^2J_{C-F}$ 63.9), 77.1, 75.5, 73.8 (d, $^3J_{C-F}$ 4.0), 65.4 (d, $^3J_{C-F}$ 2.8), 26.6, 25.5; δ_F (282 MHz, $CDCl_3$) −93.8 (d, $^2J_{F-F}$ 293.7), −110.3 (dd, $^2J_{F-F}$ 293.7, $^3J_{F-H}$ 6.4); [HRMS (ES, M^+ + Na) Found: 489.1170. Calc. for $C_{23}H_{24}F_2O_6SNa$ 489.1159]; m/z (ES) 489 (100%, $[M + Na]^+$). Satisfactory elemental analysis could not be obtained.

3,3-Difluoro-2*R-(benzyloxymethyl)-6*S**-hydroxy-5*R**-phenylsulfanyl-7-oxa-bicyclo[2.2.1]-1*S**,7*S**-heptan-2-ol acetone acetal 30 and 6*S**-benzyloxy-3,3-difluoro-2*R**-(benzyloxymethyl)-5*R**-phenylsulfanyl-7-oxabicyclo[2.2.1]-1*S**,7*S**-heptan-2-ol 31.** A solution of triol **17a** (11.5 mmol, 3.5 g), in THF (18 mL), was added slowly to a suspension of sodium hydride (57.5 mmol, 1.38 g of 60% dispersion, from which the mineral oil had been removed by washing with hexane) in THF (70 mL) at 0 °C under an atmosphere of nitrogen. The resulting white suspension was stirred at 0 °C for one hour before TBAI (0.42 g, 10 mol%) and benzyl bromide (34.5 mmol, 4.1 mL) were added in one portion. The mixture was allowed to warm to room temperature and stirred for 4 hours before being quenched cautiously with water (20 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil which was purified by column chromatography (30% diethyl ether in light petroleum) to afford alcohol **31** (1.1 g, 20%) as a colourless oil; R_f (30% diethyl ether in light petroleum) 0.20; ν_{max} (film)/cm^{-1} 3532s br (OH), 3062s (Ar C–H), 3030s (Ar C–H), 2870s (C–H), 1481s (C–C), 1454s (C–C), 1439 m (C–C), 1119s br (C–O), 738s (Ar C–H), 697s (Ar C–H); δ_H (300 MHz, $CDCl_3$) 7.23–7.05 (15H, env. Ar), 4.36–4.32 (5H, env., OCH_2Ph, OCH_2Ph, CH_aH_bO), 4.21–4.18 (1H, m, H-6), 3.95–3.80 (3H, env., H-1, H-4, CH_aH_bO), 3.70–3.66 (1H, m, H-5), 3.49 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 137.7, 137.0, 134.3, 130.4, 129.3, 128.4, 128.2, 127.9, 127.7, 127.6, 127.5, 127.2, 124.0 (dd, $^1J_{C-F}$ 270.7, 265.6), 85.8 (dd, $^2J_{C-F}$ 28.3, 26.6), 85.6 (d, $^3J_{C-F}$ 5.1), 84.3, 80.3 (dd, $^2J_{C-F}$ 24.6, 17.2), 73.5, 68.3, 68.2, 48.3 (dd, $^3J_{C-F}$ 5.4, 3.1); δ_F (282 MHz, $CDCl_3$) −113.1 (dd, $^2J_{F-F}$ 234.6, $^3J_{F-H}$ 6.4), −117.1 (d, $^2J_{F-F}$ 234.6); [HRMS (ES, $[M + Na]^+$) Found: 507.1438.

Calc. for $C_{27}H_{26}F_2O_4SNa$ 507.1418]; *m/z* (ES) 507 (100%, $[M + Na]^+$): and diol **30** (2.6 g, 66%); R_f (30% diethyl ether in light petroleum) 0.05; mp 99–100 °C; (Found: C, 61.14; H, 4.93; $C_{20}H_{20}F_2O_4S$ requires: C, 60.90; H, 5.11%); ν_{max} (film)/cm^{-1} 3382 s (O–H), 1115 s (C–O), 1086 s (C–O), 1022 s (C–O), 744 s (C–H def.), 731 s (C–H def.), 690 s (C–H def.), 656 s (C–H def.); δ_H (300 MHz, $CDCl_3$) 7.39–7.27 (10H, m, Ar), 4.62–4.54 (2H, m, CH_aH$_b$Ph, CH$_a$$H_b$Ph), 4.42–4.38 (1H, m, C*H*SPh), 4.33 (1H, d, $^3J_{H-F}$ 8.5, C*H*CF$_2$), 4.07–4.02 (3H, m, C*H*OH, C*H*CO, OCH_aH$_b$), 3.63–3.61 (1H, m, OCH$_a$$H_b$), 3.18 (1H, br s, OH), 2.11 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 136.6, 134.0, 130.7, 129.4, 128.7, 128.3, 127.8, 127.6, 124.0 (dd, $^1J_{C-F}$ 269.3, 266.9), 86.1 (dd, $^2J_{C-F}$ 28.7, 26.3), 85.3 (d, $^3J_{C-F}$ 6.0), 84.0, 81.5 (dd, $^2J_{C-F}$ 25.1, 16.7), 73.9, 61.4 (d, $^3J_{C-F}$ 7.2), 48.1 (d, $^3J_{C-F}$ 8.4); δ_F (282 MHz, $CDCl_3$) −112.9 (dd, $^2J_{F-F}$ 236.0, $^3J_{F-H}$ 8.5), −124.4 (d, $^2J_{F-F}$ 236.0); *m/z* (ES) 395 (100%, $[M + H]^+$).

6*S-Benzyloxy-3,3-difluoro-2*R**-(benzyloxymethyl)-5*R**-phenylsulfonyl-7-oxabicyclo[2.2.1]-1*S**,7*S**-heptan-2-ol 33.** A solution of sulfide **31** (1.9 mmol, 0.94 g) in DCM (4 mL) was added to a solution of *m*CPBA (5.7 mmol, 0.98 g) and sodium dihydrogen phosphate (5.7 mmol, 0.68 g) in DCM (20 mL). The resulting colourless solution was stirred at room temperature for 2 hours. During this time, a white precipitate formed. The mixture was quenched with saturated aqueous sodium bicarbonate (10 mL) and diluted with ethyl acetate (20 mL), the phases were separated and the organic layer was washed with aqueous sodium bicarbonate (6 × 15 mL) before being dried ($MgSO_4$) and concentrated *in vacuo* to afford sulfone **33** (0.81 g, 83%) as colourless cubes; mp 105–108 °C; R_f (40% diethyl ether in light petroleum) 0.13; (Found: C, 62.77; H, 4.95; $C_{27}H_{26}F_2O_6S$ requires: C, 62.78; H, 5.07%); ν_{max} (film)/cm^{-1} 3520 w, br, (OH), 1306 s (C–H), 1157 s (C–H), 1083 s (C–H), 751 s (C–H def.), 719 s (C–H), 690 s (C–H), 672 s (C–H); δ_H (250 MHz, $CDCl_3$) 7.90–7.87 (2H, m, Ar), 7.73–7.67 (1H, m, Ar), 7.61–7.55 (2H, m, Ar), 7.34–7.21 (8H, m, Ar), 7.15–7.12 (2H, m, Ar), 4.75 (1H, d, $^3J_{F-H}$ 7.4, C*H*CF$_2$), 4.53–4.44 (5H, m, C*H*OBn, 2 × OC$H_a$$H_b$Ph), 4.38–4.35 (1H, m, C*H*SO$_2$Ph), 3.87 (1H, dd, ^2J 10.2, $^4J_{F-H}$ 1.7, CH_aH$_b$OBn), 3.69 (1H, dt, ^2J 10.2, $^4J_{F-H}$ 2.4, CH$_a$$H_b$OBn), 3.65 (1H, d, *J* 4.4, C*H*CHOBn), 3.39 (1H, s, br, O*H*); δ_C (76 MHz, $CDCl_3$) 137.7, 137.6, 136.8, 135.0, 130.1, 129.2, 129.0, 128.9, 128.8, 128.7, 128.4, 128.2, 123.9 (dd, $^1J_{C-F}$ 271.5, 267.0), 85.6 (d, $^3J_{C-F}$ 5.1), 82.0 (dd, $^2J_{C-F}$ 31.7, 26.7), 80.9 (dd, $^2J_{C-F}$ 24.8, 17.1), 79.2, 74.2, 74.1, 68.1 (d, $^3J_{C-F}$ 6.2), 67.9; δ_F (235 MHz, $CDCl_3$) −114.8 (dd, $^2J_{F-F}$ 232.3, $^3J_{F-H}$ 6.6), −121.3 (d, $^2J_{F-F}$ 232.3); *m/z* (ES) 515 (4%, $[M + H]^+$), 155 (100).

Single crystals were grown by vapour diffusion (diethyl ether into light petroleum).

5*S-Benzyloxy-2,2-difluoro-3*S**-(benzyloxymethyl)-6-phenylsulfonylcyclohex-6-en-3,4*S**-diol 34.** *n*-Butyllithium (2 mmol, 0.76 mL of a 2.6 M solution in hexane) was added slowly to a solution of sulfone **33** (0.5 mmol, 0.26 g), in THF (2 mL) at −78 °C under an atmosphere of nitrogen. The reaction was stirred at −78 °C for 1 hour, then was warmed from −78 °C to −30 °C and quenched cautiously with water (1 mL). It was allowed to warm to room temperature before being extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were dried and concentrated *in vacuo* to afford a dark liquid, which was purified by column chromatography to yield alcohol **33** (0.034 g, 13%) as a white powder; mp 108–110 °C; R_f (50% diethyl ether in light petroleum) 0.15; ν_{max} (film)/cm^{-1} 3358 w br (OH), 2868 w (C–H), 1305 m (C–C), 1145 s (C–O), 1052 s (C–O), 727 m (C–H def.), 682 m (C–H def.); δ_H (250 MHz, $CDCl_3$) 7.73–7.70 (1H, m, Ar), 7.50–7.45 (2H, m, Ar), 7.38–7.24 (12H, m, Ar), 6.88 (1H, dt, *J* 7.9, $^3J_{H-F}$ 1.9, C*H*CF$_2$), 4.90 (1H, d, ^2J 10.8, OCH_aH$_b$Ph), 4.76 (1H, d, ^2J 10.8, OCH$_a$$H_b$Ph), 4.67–4.61 (1H, m, C*H*OBn), 4.59 (2H, s, CH$_2$OC$H_a$$H_b$Ph), 4.02 (1H, br, s, C*H*OH), 3.90 (1H, dd, ^2J 10.2, $^3J_{H-F}$ 2.4, CH_aH$_b$OBn), 3.85 (1H, dd, ^2J 10.2, $^3J_{H-F}$ 1.5, CH$_a$$H_b$OBn), 3.35 (1H, br, s, OH), 2.76 (1H, br, s, OH); δ_C (75.5 MHz, $CDCl_3$) 148.4 (t, $^3J_{C-F}$ 11.1), 140.2, 137.9, 137.2, 133.9, 131.1 (dd, $^2J_{C-F}$ 37.9, 26.5), 129.3, 129.1, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 117.4 (dd, J_{C-F} 251.0, 241.3), 77.2, 75.8, 75.7 (d, $^3J_{C-F}$ 3.6), 75.6 (dd, $^2J_{C-F}$ 26.5, 19.3), 74.6, 68.9 (d, $^3J_{C-F}$ 4.2); δ_F (235 MHz, $CDCl_3$), −95.8 (dd, $^2J_{F-F}$ 295.1, $^3J_{F-H}$ 5.9), −111.8 (dd, $^2J_{F-F}$ 295.1,$^3J_{F-H}$ 7.5); [HRMS (FAB) Found: 517.14966. Calc. for $C_{27}H_{27}F_2O_6S$ 517.14964]; *m/z* (ES) 515 (5%, $[M - H]^+$), 141 (100). Satisfactory microanalysis could not be obtained for this compound.

5*S-Benzyloxy-2,2-difluoro-3*S**-(hydroxymethyl)-6*R**-phenylsulfonyl-7-oxabicyclo[4.1.0]-1*R**-heptan-3,4*S**-diol acetone acetal 35.** Hydrogen peroxide (0.25 mL of 30% solution) and sodium hydroxide (0.06 mL of a 1M solution) were added to a solution of vinyl sulfone **29a** (0.1 g, 0.21 mmol) in methanol (1 mL) at room temperature. The resulting white suspension was stirred at room temperature for 2 hours before being diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford a colourless oil which was purified by column chromatography to afford epoxide **35** as a white solid (0.07 g, 70%); mp 144–146 °C; R_f (50% diethyl ether in hexane) 0.76; (Found: C, 57.19; H 4.94; $C_{23}H_{24}O_7F_2S$ requires: C 57.26; H 5.01%); δ_H (250 MHz, $CDCl_3$) 7.93 (2H, d, *J* 8.0, Ar*H*), 7.62 (1H, dt, *J* 7.5, 1.5, Ar*H*), 7.48–7.42 (2H, m, Ar*H*), 7.34–7.30 (3H, m, Ar*H*), 7.15–7.11 (2H, m, Ar*H*), 4.80 (1H, d, *J* 6.2, C*H*OBn), 4.71 (1H, d, ^2J 11.4, OCH_aH$_b$Ph), 4.64 (1H, d, ^2J 11.4, OCH$_a$$H_b$Ph), 4.28 (1H, d, *J* 5.1, C*H*CF$_2$), 4.20 (1H, dd, ^2J 9.5, 0.7, CH_aH$_b$OC(CH$_3$)$_2$), 4.15 (1H, d, ^2J 9.5, CH$_a$$H_b$OC(CH$_3$)$_2$), 3.74 (1H, dd, *J* 6.2, 3.3, C*H*OH), 2.23 (1H, s, O*H*), 1.49 (6H, s, C(CH$_3$)$_2$); δ_C (63 MHz, $CDCl_3$) 137.4, 137.1, 129.7, 129.4, 128.8, 128.3, 127.9, 115.3 (t, $^1J_{C-F}$ 252.5), 112.7, 83.2 (dd, $^2J_{C-F}$ 26.5, 19.3), 76.0, 74.3, 71.3, 65.8, 58.7 (dd, $^2J_{C-F}$ 51.1, 31.3), 27.0, 25.6; δ_F (235 MHz, $CDCl_3$) −108.4 (dd, $^2J_{F-F}$ 276.6, $^3J_{F-H}$ 5.3), −110.3 (d, $^2J_{F-F}$ 276.6); *m/z* (ES) 481 (13%, $[M - H]^-$), 465 (3), 449 (3), 3918 (4), 375 (5), 297 (6), 255 (8), 141 (100).

3*S-Benzyloxy-6,6-difluoro-1*S**-(hydroxymethyl)-cyclohex-4-en-1,2*S**-diol acetone acetal 46a.** A solution of sulfone **25a** (2.2 mmol, 1.04 g), in THF (8 mL) was added to a suspension of magnesium (20 mmol, 0.5 g) and $HgCl_2$ (0.5 mmol, 0.13 g) in ethanol (8 mL); the mixture was stirred at 0 °C for 5 hours. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (6 × 20 mL), the combined extracts were dried ($MgSO_4$), filtered and concentrated. The residue was purified by trituration with hexane to afford **46a** as a white solid (0.73 g, 50%); mp 83–85 °C; R_f (50% diethyl ether in hexane) 0.42; δ_H (400 MHz, $CDCl_3$) 7.40–7.32 (5H, m, Ar), 6.20 (1H, dq, *J* 10.5, 2.0, *H*C=CHCF$_2$), 5.82 (1H, ddt, 10.5, $^4J_{H-F}$ 6.3, ^4J 2.0, HC=C*H*CF$_2$), 4.76 (1H, d, ^2J 11.6, OCH_aH$_b$Ph), 4.72 (1H, d, ^2J 11.6, OCH$_a$$H_b$Ph), 4.37 (1H, dd, ^2J 9.3, $^4J_{H-F}$ 1.0, CH_aH$_b$OC), 4.32 (1H, d, ^2J 9.3, CH$_a$$H_b$OC), 4.26 (1H, ddq, $^5J_{H-F}$ 9.0, *J* 7.5, 2.0, C*H*OBn), 3.93–3.87 (1H, m*, C*H*OH), 2.45 (1H, d, *J* 3.7, O*H*), 1.51 (3H, s, CH$_3$), 1.46 (3H, s, CH$_3$); δ_C (75 MHz, $CDCl_3$) 137.7, 135.4 (t, $^3J_{C-F}$ 11.3), 128.6, 128.1, 127.9, 122.8 (dd, $^2J_{C-F}$ 33.6, 25.3), 117.2 (dd, $^1J_{C-F}$ 248.0, 235.2), 112.3, 84.0 (dd, $^2J_{C-F}$ 30.2, 19.6), 77.8, 72.4, 72.3, 65.3 (d, $^3J_{C-F}$ 3.8), 26.5, 25.4; δ_F (282 MHz, $CDCl_3$) −90.7 (dd, $^2J_{F-F}$ 284.1, $^5J_{F-H}$ 9.0), −112.4 (dd, $^2J_{F-F}$ 284.1, $^3J_{F-H}$ 6.3); [HRMS (CI) ($M^+ + NH_4$) Found: 344.1671. Calc. for $C_{17}H_{24}O_4NF_2$ 344.1668]; *m/z* (ES) 325 (35%, $[M - H]^-$) 217 (56), 199 (10), 107 (37). *The signal at 3.91–3.90 simplifies to 3.91 (1H, dd, *J* 7.4, 3.7) in the $\{^{19}F\}^1H$ spectrum. Satisfactory elemental analysis could not be obtained for this compound.

Ethyl 2*S-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-1*S**-methyl-6-methylene-5*R**-phenylsulfanyl-7-oxa-bicyclo[2.2.1]-4*S**-heptane-2-carboxylate 12.** A solution of phenylsulfenyl chloride (17.3 mL of a 2 M solution in dichloromethane, 34.6 mmol), made *in situ*,[23] was added dropwise to a solution of

exo cycloadduct **8d** (11.5 mmol, 4 g) in DCM (64 mL) at 0 °C under an atmosphere of nitrogen. The solution was warmed to room temperature and stirred for 72 hours. The solvent was removed *in vacuo* affording an orange solid which was purified through a short column of silica gel (eluant 30% diethyl ether in hexane) to yield sulfide **12** as a fine yellow powder (2.9 g, 55%); mp 54–55 °C; R_f (30% diethyl ether in light petroleum) 0.31; (Found: C, 58.15; H, 5.6; N 3.03; $C_{22}H_{27}F_2NO_5S$ requires: C, 58.01; H, 5.97; N 3.07%); ν_{max} (film)/cm^{-1} 2975 w (C–H), 1755 s (C=O), 1712 s (C=O), 1280 (C–O), 1256 s (C–O), 1169 s (C–O), 1044 s (C–O), 738 s (C–H def.), 689 m (C–H def.); δ_H (300 MHz, $CDCl_3$) 7.37–7.33 (2H, m, Ar), 7.30–7.19 (3H, m, Ar), 5.39 (1H, d, ^2J 1.8 C=CH_aH$_b$), 5.22 (1H, d, ^2J 1.8 C=CH$_a$$H_b$), 4.35 (1H, d, $^3J_{H-F}$ 6.7, CHCF$_2$), 4.20 (2H, q, J 7.1, OCH_2CH$_3$), 4.16, (1H, s, CHSPh), 3.23–3.12 (4H, m, N(CH_2CH$_3$)$_2$), 1.71 (3H, s, CH_3), 1.21 (3H, t, J 7.1, OCH$_2$CH_3), 1.04 (6H, q, J 7.0, N(CH$_2$CH_3)$_2$); δ_C (300 MHz, $CDCl_3$) 164.1, 152.8, 147.3, 134.1, 131.5, 129.3, 127.7, 122.2 (t, $^1J_{C-F}$ 271.1), 112.8, 92.2, 82.7 (dd, $^2J_{C-F}$ 34.7, 31.0), 81.8 (t, $^2J_{C-F}$ 25.1), 61.9, 48.8, 42.4, 42.1, 16.4, 14.0, 13.9, 13.4; δ_F (282 MHz, $CDCl_3$) −(108.1)–(−104.3) (br), (−114.0)–(−108.8) (br); m/z (ES) 456 (100%, [M + H]$^+$), 457 (57).

Ethyl 2*S-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-1*S**-methyl-6-methylene-5*R**-phenylsulfonyl-7-oxa-bicyclo[2.2.1]-4*S**-heptane-2-carboxylate 57.** Manganic sulfate (0.15 mmol, 0.025 g) followed by hydrogen peroxide (1 mL of 30% aqueous solution) and sodium hydrogen carbonate (9 mL of a 0.2 M aqueous solution) were added to a solution of sulfide **12** (0.5 mmol, 0.23 g) in CH_3CN (13 mL). The mixture was stirred at room temperature for 24 hours, then quenched with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid which was triturated with hexane to yield sulfone **57** (0.22 g, 90%) as a white powder; mp 135–137 °C; R_f (30% diethyl ether in light petroleum) 0.12; (Found: C, 54.00; H, 5.39; N 2.75; $C_{22}H_{27}F_2NO_7S$ requires: C, 54.20; H, 5.58; N 2.87%); ν_{max} film/cm^{-1} 2961 w (C–H), 1755 s (C=O), 1716 s (C=O), 1283 s (C–O), 1259 s (C–O), 1137 s (C–O), 1081 s (C–O), 756 s (C–H def.), 688 s (C–H def.); δ_H (300 MHz, $CDCl_3$) 7.75–7.72 (2H, m, Ar), 7.60–7.43 (3H, m, Ar), 5.83 (1H, d, ^2J 1.7, C=CH_aH$_b$), 5.27 (1H, d, ^2J 1.7, C=CH$_a$$H_b$), 4.92–4.87 (1H, m, C$HCF_2$), 4.17–4.10 (3H, m, C$HSO_2Ph, OCH_2CH_3$), 3.21–3.10 (4H, m, N(C$H_2CH_3$)$_2$), 1.31 (3H, s, C$H_3$), 1.15 (3H, t, J 7.1, OCH$_2$CH_3), 1.03 (6H, q, J 7.0, N(CH$_2$CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 163.5, 152.6, 140.5, 136.5, 134.3, 130.1, 128.8, 121.7 (t, $^1J_{C-F}$ 272.3), 115.6, 92.2, 82.5 (t, $^2J_{C-F}$ 20.9), 79.1 (t, $^2J_{C-F}$ 29.3), 67.6 (t, $^3J_{C-F}$ 3.6), 62.0, 42.4, 42.1, 15.9, (2 peaks coincident) at 13.9, 13.3; δ_F (376 MHz, C_7D_8, 373 K) −106.4 (dd, $^2J_{F-F}$ 231.6,$^3J_{F-H}$ 8.4), −112.0 (d, $^2J_{F-F}$ 231.6); m/z (ES) 488 (100%, [M + H]$^+$), 489 (28).

3,3-Difluoro-5*R-bromo-2*S**-(*N*,*N*-diethylcarbamoyloxy)-1*S**-methyl-6-methylene-7-oxa-bicyclo[2.2.1]-4*S**-heptane-2*R**-carboxylate 59.** A solution of bromine (11.5 mmol, 45 mL of a 1.0 M solution in CH_3CN) was added dropwise to *exo* cycloadduct **8d** (5 mmol, 1.72 g) in CH_3CN (45 mL) at room temperature under an atmosphere of nitrogen. The solution was stirred overnight at room temperature, then quenched with sodium sulfite (20 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to leave an orange solid which was purified by column chromatography (30% diethyl ether in light petroleum) to afford **59** (1.93 g, 91%) as cubes; mp 68–70 °C; R_f (30% diethyl ether in light petroleum) 0.34; (Found: C, 45.22; H, 5.36; N, 3.27; $C_{16}H_{22}BrF_2NO_5$ requires: C, 45.08; H, 5.20; N 3.29%); ν_{max} (film)/cm^{-1} 2975 w (C–H), 1744 s (C=O), 1711 s (C=O), 1280 s (C–O), 1260 s (C–O), 1170 s (C–O), 754 s (Ar C–H), 653 s (Ar C–H); δ_H (300 MHz, $CDCl_3$) 5.52 (1H, s, C=CH_aH$_b$), 5.28 (1H, s, C=CH$_a$$H_b$), 4.80 (1H, s, C$H$Br), 4.59 (1H, t, $^3J_{H-F}$ 3.2, CHCF$_2$), 4.22 (2H, q, J 7.1, OCH_2CH$_3$), 3.26–3.10 (4H, m, N(CH_2CH$_3$)$_2$), 1.74 (3H, s, CH_3), 1.23 (3H, t, J 7.1, OCH$_2$CH_3), 1.04 (6H, t, J 7.1, N(CH$_2$CH_3)$_2$); δ_C (300 MHz, $CDCl_3$) 163.9, 152.7, 149.1, 121.5 (t, $^1J_{C-F}$ 272.3), 115.7, 92.2, 85.5 (t, $^2J_{C-F}$ 26.9), 82.3 (t, $^2J_{C-F}$ 20.9), 62.0, 43.9 (t, $^3J_{C-F}$ 4.5), 42.4, 42.0, 16.6, 14.0, 13.9, 13.3; δ_F (282 MHz, $CDCl_3$) −106.0 (br. d, $^2J_{F-F}$ 220.3), (−108.2)–(−113.6) (br); m/z (ES) 428 (100%, [(^{81}Br) M + H]$^+$), 426 (100, [(^{79}Br) M + H]$^+$).

Attempted preparation of ethyl 3,3-difluoro-2*S-diethylcarbamoyloxy-1*S**-methyl-6-methylene-cyclohex-4-en-1-ol-2-carboxylate 60; preparation of 58.** A solution of alkene **59** (2.7 mmol, 1.15 g) in dry DMF (7 mL) was added to zinc metal (4.05 mmol, 0.26 g) at room temperature under an atmosphere of argon. The reaction was sonicated for 10 hours then it was filtered to remove the zinc powder, concentrated *in vacuo* to afford a yellow liquid which was purified by flash column chromatography (Biotage) (gradient from 8% to 30% diethyl ether in light petroleum) to yield alkene **58** (0.41 g, 44%) as pale white cubes; mp 45–46 °C; R_f (30% diethyl ether in light petroleum) 0.30; (Found: C, 55.65; H, 6.54; N, 3.94; $C_{16}H_{24}F_2NO_5$ requires: C, 55.32; H, 6.67; N, 4.03%); ν_{max} (film)/cm^{-1} 2986 w (C–H), 1753 m (C=O), 1708 s (C=O), 1424 m (C–O), 1278 s (C–O), 1041 s (C–O); δ_H (300 MHz, $CDCl_3$) 5.02 (1H, t, J 2.0, C=CH_aH$_b$), 4.97 (1H, t, J 2.4, C=CH$_a$$H_b$), 4.50–4.46 (1H, m, C$HCF_2$), 4.22 (2H, q, J 7.1, OCH_2CH$_3$), 3.26–3.10 (4H, m, N(CH_2CH$_3$)$_2$), 2.57–2.53 (2H, m, C$H_a$$H_b$CHCF$_2$), 1.73 (3H, s, br, C$H_3$), 1.22 (3H, t, J OCH$_2$CH_3), 1.05 (6H, q, J 7.0, N(CH$_2$CH_3)$_2$); δ_C (300 MHz, $CDCl_3$) 164.3, 153.0, 146.2, 122.8 (t, $^1J_{C-F}$ 270.5), 108.4, 91.8, 83.0 (t, $^2J_{C-F}$ 20.3), 77.5 (t, $^2J_{C-F}$ 26.9), 61.7, 42.3, 42.0, 32.3, 16.2, 13.9, 13.8, 13.3; δ_F (282 MHz, $CDCl_3$) −105.9–(−108.7) (br), −110.4–(−114.7) (br); [HRMS (+FAB) Found: 348.16216. Calc. for $C_{16}H_{24}F_2NO_5$ 387.10778]; m/z (ES$^+$) 348 (100%, [M + H]$^+$), 349 (81), 303 (7), 302 (37); and *exo* cycloadduct **8d** (0.34 g, 36%).

6,6-Difluoro-1*S-(hydroxymethyl)-cyclohexane-1,2*S**,3*S**-triol 61.** A suspension of **46a** (0.25 mmol, 0.08 g) and 10% palladium on carbon (0.1 g) in ethanol (10 mL) was stirred under an atmosphere of hydrogen for 20 hours at room temperature. The hydrogen was removed and the mixture filtered through celite before the solvent was removed to afford a colourless oil (0.05 g). R_f (ethyl acetate) 0.47; δ_H (300 MHz, $CDCl_3$) 4.35 (1H, d, ^2J 9.0, CH_aH$_b$O), 4.16 (1H, d, ^2J 9.0, CH$_a$$H_b$O), 3.69 (1H, dt, J 10.4, 1.8, CH(OH)CH$_2$), 3.37 (1H, dd, J 9.3, 3.3, CH(OH)CH(OH)CH$_2$), 2.79 (2H, br s, 2 × OH), 2.19–2.18 (4H, m, CH_2CH_2CF$_2$), 1.47 (3H, s, CH$_3$), 1.43 (3H, s, CH$_3$); δ_C (75 MHz, $CDCl_3$) 121.8 (dd, $^1J_{C-F}$ 254.1, 245.4), 112.3, 83.6 (t, $^2J_{C-F}$ 26.4), 74.4 (d, $^3J_{C-F}$ 4.5), 70.9, 65.7, 28.1 (t, $^2J_{C-F}$ 23.8), 26.6, 25.9, 25.5 (d, $^3J_{C-F}$ 7.6); δ_F (282 MHz, $CDCl_3$) −109.1 (ddd, $^2J_{F-F}$ 252.7, $^3J_{H-F}$ 27.0, 11.6), −110.2 (d, $^2J_{F-F}$ 252.7).

The crude diol was dissolved in methanol (10 mL), Amberlyst-15 was added and the mixture heated at 50 °C for 8 hours. The Amberlyst-15 was removed by filtration and the solvent removed *in vacuo* to afford **61** as a colourless oil (0.04 g, 81%). δ_H (400 MHz, $CDCl_3$) 3.91 (1H, dd, ^2J 11.7, $^4J_{H-F}$ 1.0, CH_aH$_b$O), 3.83–3.76 (2H, m, (includes 3.82 d, ^2J 11.7, CH$_a$$H_b$O) C$H$OHCH$_2$), 3.47 (1H, dd, J 7.6, $^4J_{H-F}$ 2.8, CHC(OH)CH$_2$OH), 2.23 (1H, ddt, J 14.4, 4.8, $^3J_{H-F}$ 35.4, CH$_a$H$_b$CH_aH$_b$CF$_2$), 1.95–1.84 (2H, m, CH_aH$_b$CH$_2$CF$_2$, CH$_2$CH$_a$$H_bCF_2$), 1.51–1.40 (1H, m, CH$_a$$H_bCH_2CF_2$); δ_C (100 MHz, $CDCl_3$) 123.7 (dd, $^1J_{C-F}$ 252.5, 227.5), 74.6 (d, $^3J_{C-F}$ 6.0), 74.5 (t, $^2J_{C-F}$ 23.5), 69.3, 60.7, 27.7 (t, $^2J_{C-F}$ 24.0), 26.0 (d, $^3J_{C-F}$ 10.0); δ_F (282 MHz, $CDCl_3$) −111.7 (d, $^2J_{F-F}$ 250.8), 113.2 (ddd, $^2J_{F-F}$ 250.8, $^3J_{F-H}$ 33.4, 19.6); [HRMS (ES, [M + NH$_4$]$^+$) Found 216.1041. Calc. for $C_7H_{16}F_2NO_4$ 216.1042]; m/z (ES) 198 (2%, M$^-$), 197 (28), 177 (12), 157 (37), 127 (11), 111 (42), 97 (100).

2*S,3*S**-Diacetoxy-6,6-difluoro-1*S**-(acetoxymethyl)-cyclohex-4-en-1-ol 62.** BCl_3 (9 mmol, 9 mL of a 1 M solution in hexanes) was added slowly to a solution of alcohol **46a** (1.8 mmol, 0.6 g) in CH_2Cl_2 (100 mL) at −78 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was recooled to −78 °C before being quenched with methanol (5 mL), allowed to warm to room temperature and stirred for 24 hours. The solvent was removed and the resulting brown oil (0.273 g) was used without further purification. Pyridine (2.5 mmol, 0.2 mL) was added to a solution of the crude tetraol (0.273 g) in acetic anhydride (2 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 4 days, before being quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with cold sodium hydrogen carbonate solution (3 × 10 mL) and cold HCl (3 × 10 mL of 0.1 M solution) before being dried ($MgSO_4$), filtered and concentrated to afford a yellow oil which was purified by Biotage (25 M, 70% diethyl ether in hexane) to afford triacetate **62** as a colourless oil (0.2 g, 33%); R_f (70% diethyl ether in hexane) 0.16; δ_H (400 MHz, $CDCl_3$) 6.03 (1H, dt, *J* 10.4, 2.3, *H*C=CHCF$_2$), 5.86–5.80 (1H, m, *H*C=CHCF$_2$), 5.76–5.66 (1H, m, HC=CHC*H*OAc), 5.40 (1H, dd, *J* 8.2, 1.4, C=CHCH(OAc)C*H*OAc), 4.45 (1H, dd, *J* 12.0, $^4J_{H-F}$ 3.2, CH_aH$_b$O), 4.27 (1H, dt, J 12.0, $^4J_{H-F}$ 1.9, CH$_a$$H_b$O), 3.68 (1H, s, O*H*); δ_C (75 MHz, $CDCl_3$) 171.2, 170.3, 169.9, 133.3 (t $^3J_{C-F}$ 11.7), 123.2 (dd, $^2J_{C-F}$ 33.2, 24.9), 117.8 (dd, $^1J_{C-F}$ 245.4, 241.6), 74.9 (dd, $^2J_{C-F}$ 27.2, 21.4), 71.5 (d, $^3J_{C-F}$ 3.8), 70.3, 62.2, 20.7, 20.6, 20.5; δ_F (282 MHz, $CDCl_3$) −95.1 (dd, $^2J_{F-F}$ 287.2, $^3J_{F-H}$ 6.5), −113.6 (d, $^2J_{F-F}$ 287.2); [HRMS (ES, M$^+$ + NH$_4^+$) Found 340.1202. Calc. for $C_{13}H_{20}F_2NO_7$ 340.1202]; *m*/*z* (ES) 321 (8%, [M − H]$^-$), 279 (10), 261 (100), 241(6), 219 (9), 199(16), 179 (18), 139 (55). The signal at 5.86–5.80 appeared as: 5.83 (1H, dt, *J* 10.4, 1.8, *H*C=CHCF$_2$) in the {^{19}F}^{1}H spectrum.

3*S-Benzyloxy-6,6-difluoro-1*S**-(hydroxymethyl)-cyclohexane-1,2*S**,4*S**,5*R**-triol acetone acetal 63.** Osmium tetroxide (5 mol%, 0.28 mL of a 2.5% solution in ^{t}BuOH) was added to a solution of alcohol **46a** (0.67 mmol 0.22 g) in acetone–water (2 mL, 4 : 1, v/v) at 0 °C, followed by the addition of NMO (6 mmol, 0.31 g). The yellow solution was stirred for 1 week at room temperature to afford a dark liquid that was purified by flash column chromatography (Biotage, 40% ethyl acetate in light petroleum) to yield triol **63** (0.17 g, 70%), as a pale yellow oil; R_f (40% ethyl acetate in light petroleum) 0.2; (Found: C, 56.75; H, 6.15; $C_{17}H_{22}F_2O_6$ requires: C 56.66; H, 6.15%); ν_{max} (film)/cm^{-1} 3454 w br (OH), 2939 w (C–H), 1218 m (C–O), 1072s, br, (C–O), 734 m (C–H def.), 698 m (C–H def.); δ_H (250 MHz, CD_3COCD_3) 7.44 (2H, d, *J* 6.7, Ar), 7.36–7.24 (3H, m, Ar), 4.94 (1H, d, ^2J 11.3, OCH_aH$_b$Ph), 4.85 (1H, d, ^2J 11.3, OCH$_a$$H_b$Ph), 4.26 (1H, dd, ^2J 9.1, $^4J_{H-F}$ 1.5, OCH_aH$_b$), 4.17 (1H, d, ^2J 9.1, OCH$_a$$H_b$), 4.05–3.98 (1H, m, C*H*CF$_2$), 3.86 (1H, t, *J* 8.9, C*H*OBn), 3.74–3.68 (1H, m, C*H*CHCF$_2$), 3.62–3.58 (1H, m, C*H*CCF$_2$), 2.88 (3H, s, br, O*H*), 1.44 (6H, s, C*H*$_3$); δ_C (75 MHz, CD_3COCD_3) 139.4, 128.0, 127.6, 127.2, 118.6 (dd, $^1J_{C-F}$ 263.9, 243.5), 112.3, 84.5 (dd, $^2J_{C-F}$ 27.5, 20.3), 79.9, 74.3, 72.3 (dd, $^2J_{C-F}$ 31.7, 20.9), 71.0 (d, $^3J_{C-F}$ 7.2), 70.4 (d, $^3J_{C-F}$ 7.2), 66.2, 25.8 (d, $^5J_{C-F}$ 2.4), 25.5; δ_F (282 MHz, CD_3COCD_3) −111.6 (br d, $^2J_{F-F}$ 268.2), −120.9 (d, $^2J_{F-F}$ 268.2); [HRMS (EI$^+$) Found: 360.13852. Calc. for $C_{17}H_{22}O_6F_2$ 360.13845]; *m*/*z* (ES) 359 (100%, [M − H]$^+$), 301 (34).

3*S-Benzyloxy-6,6-difluoro-1*S**-(hydroxymethyl)-cyclohex-4-ene-1,2*S**-diol 65.** Amberlyst-15 (2.1 g) was added to a solution of acetonide **46a** (1.2 mmol, 0.33 g) in methanol (12 mL) at 50 °C. After heating for 24 hours, the Amberlyst was removed by filtration and washed with methanol (2 × 3 mL). The washings were combined with the original methanolic solution. Removal of the solvent afforded triol **65** as a white powder (0.29 g, 85%); mp 84–85 °C; R_f (40% ethyl acetate in light petroleum) 0.13; (Found: C, 58.83; H, 5.47; $C_{14}H_{16}F_2O_4$ requires: C, 58.74; H, 5.63%); ν_{max} (film)/cm^{-1} 3444 m br (OH), 3345 m br (OH), 1152 m (CO), 1012 s (CO), 1043 s (CO), 736 (Ar C–H), 695 (Ar C–H); δ_H (300 MHz, CD_3COCD_3) 7.44–7.26 (5H, m, Ar), 6.24 (1H, dq, *J* 10.3, $^3J_{H-F}$ 2.3, C*H*=CHCF$_2$), 5.74 (1H, m, *J* 10.3, =C*H*CF$_2$), 4.78–3.90 (9H, env. [including 4.06 (1H, dd, ^2J 11.5, $^4J_{H-F}$ 2.4, CH_aH$_b$), 3.92 (1H, d, ^2J 11.5, CH$_a$$H_b$)], C*H*OBn, C*H*OH, O*H*, OC$H_a$$H_b$Ph); δ_C (75 MHz, CD_3COCD_3) 139.0, 135.9 (dd, $^3J_{C-F}$ 13.2, 10.8), 128.2, 127.7, 127.4, 122.0 (dd, $^2J_{C-F}$ 33.5, 25.1), 119.6 (dd, $^1J_{C-F}$ 244.7, 235.2), 77.5, 75.1 (dd, $^2J_{C-F}$ 27.5, 19.1), 74.2 (d, $^3J_{C-F}$ 4.8), 72.1, 61.3 (d, $^3J_{C-F}$ 4.8); δ_F (282 MHz, CD_3COCD_3) −94.8 (dd, $^2J_{F-F}$ 282.4, $^3J_{F-H}$ 9.5), −113.7 (ddd, $^2J_{F-F}$ 282.4, $^3J_{F-F}$ 7.6, $^4J_{F-H}$ 1.9); *m*/*z* (ES) 285 (8%, [M − H]$^+$), 217 (100).

3*S-Benzyloxy-6,6-difluoro-1*S**-(hydroxymethyl)-cyclohexane-1,2*S**,4*S**,5*R**-triol 64.** Osmium tetroxide (5 mol%, 0.1 mL of a 2.5% sol in ^{t}BuOH) was added to a solution of triol **65** (0.2 mmol 0.062 g) in acetone–water (0.6 mL, 4 : 1, v/v) at 0 °C, followed by the addition of NMO (1 mmol, 0.12 g). The yellow solution was stirred for 4 days at room temperature then Na_2SO_3 (1.0 mmol, 0.13 g) was added to destroy any excess of OsO_4 and the mixture was stirred for a further 30 minutes. The resulting solution was extracted with ethyl acetate (5 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a dark liquid which was purified by flash column chromatography (Biotage, gradient from 25%–100% ethyl acetate in hexane) to yield tetrol **64** (0.04 g, 63%), as a white solid; mp 130–131 °C; R_f (100% ethyl acetate) 0.39; (Found C, 52.50; H, 5.63; $C_{14}H_{18}F_2O_6$ requires: C, 52.50; H, 5.66%); ν_{max}(film)/cm^{-1} 3351 s br (OH), 2926 w (C–H), 1105 s (C–O), 1069 s (C–O), 1019 s (C–O), 731 m (C–H def.), 700 s (C–H def.); δ_H (300 MHz, $(CD_3)_2SO$) 7.51–7.48 (2H, m, Ar), 7.41–7.28 (3H, m, Ar), 5.97 (1H, d, $^3J_{H-F}$ 6.4, O*H*), 5.14 (1H, d, ^3J 7.3, O*H*), 5.02 (1H, s, O*H*), 4.95 (1H, d, ^3J 7.3, O*H*), 4.86 (2H, s, br, OCH_aH$_b$Ph, OCH$_a$$H_b$Ph), 4.69 (1H, t, *J* 5.9, C*H*OBn), 3.93–3.85 (1H, m, C*H*CF$_2$), 3.78–3.63 (3H, m, CH_aH$_b$OH, C*H*CHOBn, O*H*), 3.56–3.50 (2H, m, CH$_a$$H_b$OH, C*H*CHCF$_2$); δ_C (100 MHz, CD_3COCD_3) 139.6, 127.9, 127.6, 127.1, (dd, $^1J_{C-F}$ 262.0, 244.5), 80.1, 76.2 (dd, $^2J_{C-F}$ 24.0, 20.8), 74.5, 73.3 (dd, $^2J_{C-F}$ 31.1, 21.6), 71.9 (d, $^3J_{C-F}$ 6.4), 70.7 (d, $^3J_{C-F}$ 9.6), 61.1 (two Ar–H environments are coincident); δ_F (282 MHz, CD_3COCD_3) −115.7 (d, $^2J_{F-F}$ 268.2), −121.5(d, $^2J_{F-F}$ 268.2); [HRMS (FAB) Found: 321.11495 Calc. for $C_{14}H_{19}F_2O_6$ 321.11497]; *m*/*z* (ES) 319 (100%, [M − H]$^-$), 279 (25), 249 (38).

Tetrol 64 by deprotection of 63. Amberlyst-15 (2.6 g) was added to a solution of acetonide **63** (1.0 mmol, 0.36 g) in methanol (17 mL) at 50 °C. After heating for 24 hours, the Amberlyst was removed by filtration and washed with methanol (2 × 3 mL). The washings were combined with the original methanolic solution; removal of the solvent afforded pentol **64** as a white powder (0.24 g, 75%); mp 130–131 °C. Spectral data were identical to those reported previously.

6,6-Difluoro-1*S-(hydroxymethyl)-cyclohexane-1,2*S**,3*S**,4*S**,5*R**-tetrol 66.** A suspension of **64** (0.37 mmol, 0.12 g) and 10% palladium on carbon (0.04 g) in methanol (15 mL) was stirred under an atmosphere of hydrogen for 12 hours at room temperature. The hydrogen was removed and the mixture filtered through celite before the solvent was removed to afford **66** as a colourless oil (0.09 g, 100%). R_f (100% ethyl acetate) 0.06; δ_H (300 MHz, $CDCl_3$) 4.10–3.65 (4H, envelope, [including 3.90 (1H, app. br. d, ^2J 11.7, CH_aH$_b$) and 3.73 (1H, app. br. d, ^2J 11.7, CH$_a$$H_b$)], 2 × C*H*OH), 3.61–3.48 (2H, m, 2 × C*H*OH); δ_C (75 MHz, CD_3OD) 120.3 (dd, $^1J_{C-F}$ 262.4, 245.8), 77.4 (t, $^2J_{C-F}$ 23.0), 74.6 (dd, $^2J_{C-F}$ 32.1, 22.3), 71.4 (d, $^3J_{C-F}$ 6.6), 70.8, 70.2 (d, $^3J_{C-F}$ 8.6), 62.0; δ_F (282 MHz, CD_3OD) −115.8 (d, $^2J_{F-F}$ 271.8), −122.3 (d, $^2J_{F-F}$ 271.8); [HRMS (EI, M$^+$) Found 230.0598. Calc. for $C_7H_{12}F_2O_6$ 230.0596]; *m*/*z* (ES) 229 (100%, [M − H]$^-$), 189 (47), 171 (49), 159 (79), 141 (48).

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