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Sequential Desymmetrization–Fluorination: Enantioselective Synthesis of Fluorinated Cyclitols

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Abstract: An asymmetric synthesis of enantioenriched, highly functionalized fluorinated carbocycles has been developed based on an enantioselective Sharpless dihydroxylation of cyclohexadienylsilanes, combined with a diastereoselective electrophilic fluorodesilylation. Several parameters define the level of diastereocontrol for the fluorination step. These include the relative stereochemistry of the starting endocyclic allylsilanes and the structural features of the reactants. As expected for an S_E2' mechanism, the fluorodesilylation occurred with clean transposition of the double bond, with the attack of the electrophilic fluorinating agent taking place preferentially *anti* to the silyl group. For the fluorination step, the best selectivities were observed for the monocyclic *anti*,*syn* benzyl-protected precursors and for the *syn*,*syn* starting allylsilane. Full NMR spectroscopic analysis of the fluorinated monocyclic compounds, which possess an endocyclic double bond flanked by two electronegative groups (the methoxy group and the fluorine substituent) revealed that a subtle combination of steric (1,3-axial/pseudoaxial interaction) and stereoelectronic effects (π–σ* interaction) favours the preferential conformers featuring the methoxy group in a pseudoaxial position.

Keywords: carbocycles · cyclitols · dihydroxylation · electrophilic substitution · fluorine

Introduction

The ongoing interest for fluorine chemistry stems from the unique properties of the C–F bond.[1] As a result, a lot of interest has focused on this research area and more recently on the development of asymmetric fluorination reactions.[2] These fluorinations were mostly applied to the preparation of enantioenriched α-fluorinated carbonyl derivatives featuring one, or more rarely, two stereogenic centres.[3] Consequently, a relatively restricted range of fluorinated targets is accessible when using this chemistry. The quest for efficient methods for the preparation of more complex fluorinated targets is still actively ongoing. We are interested in developing novel routes to enantioenriched fluorinated building blocks other than fluorinated carbonyl derivatives. These compounds could offer alternative functional-group manipulations, thereby broadening the range of accessible fluorocompounds. In this paper, we wish to report the diastereo- and enantioselective synthesis of highly functionalized dihydroxylated fluorinated carbocycles and a detailed study of their structural assignment. The chosen strategy combines a catalytic asymmetric route to enantioenriched organosilanes followed by an electrophilic fluorodesilylation process. This concise approach delivers enantioenriched fluorinated carbocycles featuring endocyclic allylic fluorides, a class of compounds rarely explored in synthesis. Noteworthy exceptions are the fluorinated analogues of shikimic acids, which are of relevance as potential antifungal, antibacterial and antiparasitic agents.[4]

On the basis of relevant precedent from our laboratory,[5] we reasoned that compounds of general structure **I** (Scheme 1) could be prepared by diastereoselective electrophilic fluorodesilylation of the corresponding enantioenriched allylsilanes. A known catalytic asymmetric desymmetrization process will enable the construction of the starting enantioenriched dihydroxylated cyclic allylsilanes. In this strategy, it was anticipated that the silyl group could control the diastereoselectivity of the fluorination process. The presence of the two additional nonsilylated stereogenic carbon atoms can influence the stereochemical outcome of the fluorination and will enable us to determine easily whether the

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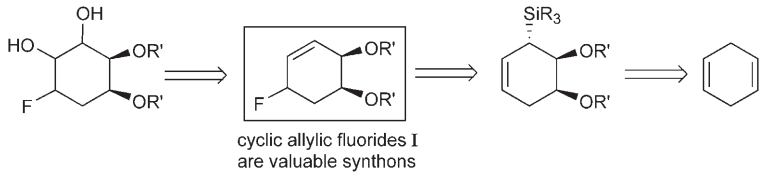
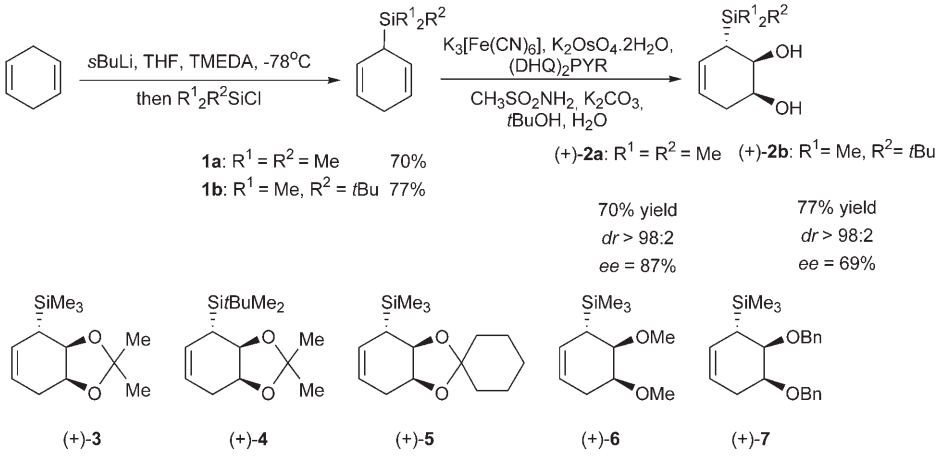


Scheme 1.

approach of the fluorinating reagent takes place preferentially *anti* or *syn* to the silyl group. The cyclic allylic fluorides described herein are versatile building blocks. In this paper, we also report that their derivatisation upon dihydroxylation gives orthogonally protected fluorinated cyclitols. These compounds fall within the category of carbohydrate mimics, which are frequently used as powerful molecular probes for studying the biological function of oligosaccharides present on cell membranes.[6]

Results and Discussion

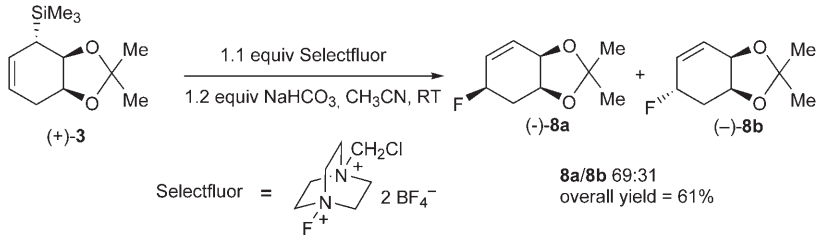
Synthesis of fluorinated carbocycles: The synthesis of representative cyclic allylsilanes was carried out following a reaction sequence developed by Landais et al (Scheme 2, TMEDA = tetramethylethylenediamine).[7] Two cyclohexadienylsilanes were conveniently prepared by metalation of cyclohexa-1,4-diene with *s*BuLi followed by silylation of the resulting carbanion with trimethylsilane chloride or with *tert*-butyldimethylsilane chloride. The desymmetrization of the silyl-2,5-cyclohexadienes **1a** and **1b** was carried out by using an asymmetric Sharpless dihydroxylation in the presence of $(DHQ)_2PYR$ ($(DHQ)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether). Under these conditions, the desired dihydroxylated cyclic allylsilanes were obtained in good yields with complete diastereocontrol. The enantiotopic double bonds were relatively well differentiated, as products (+)-**2a** and (+)-**2b** were formed with enantiomeric excesses of 87 and 69%, respectively. The enantioselective dihydroxylation proceeded, as expected, *anti* to the trimethylsilyl or the *tert*-butyldimethylsilyl groups. We subsequently protected the diols with the objective of accessing a series of monocyclic and bicyclic allylsilanes. It was anticipated that the preferentially reactive conformations of these compounds might differ and could give fluorinated compounds with different levels of diastereocontrol upon electrophilic fluorodesilylation. Compounds **3**–**7** were therefore prepared by using standard procedures, with their 1,2-diols protected as ketals or as ethers.[8]



Scheme 2.

With these compounds in hand, initially we studied the feasibility of the fluorination process. Preliminary attempts on the unprotected diol **2a** proved unsuccessful.[9] We therefore examined the reactivity of the protected diols **3**–**7**. The fluorination of the protected trimethylsilylated precursor (+)-**3** was carried out in acetonitrile at room temperature in the presence of 1.1 equivalents of Selectfluor and 1.2 equivalents of $NaHCO_3$ (Scheme 3).

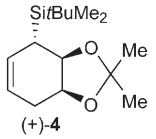
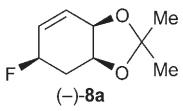
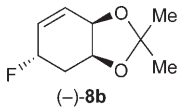
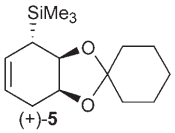
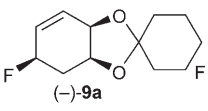
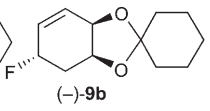
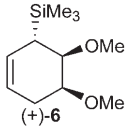
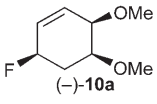
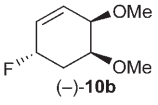
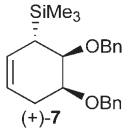
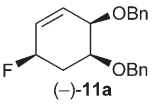
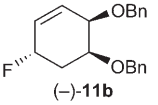
This reaction delivered the allylic fluorides (−)-**8a** and (−)-**8b**, resulting from a clean transposition of the double bond in 61% overall isolated yield (Scheme 3). Up to three days were required for the starting material to be fully consumed. Attempts to reduce the reaction time by heating the reaction mixture were unsuccessful as decomposition was observed under these conditions. The product was formed as a mixture of two diastereomers (*dr* = 69:31). These diastereomers displayed different physicochemical properties and



Scheme 3.

proved to be remarkably easy to separate by simple silica-gel chromatography, enabling full characterization. The data revealed that the major product *syn*,*syn*-(−)-**8a** resulted from addition of the fluorinating reagent *anti* to the trimethylsilyl group, thereby delivering the all-*syn*-fluorinated carbocycle. We subsequently studied the influence of the silyl group and the protecting group on the yield and stereocontrol of the fluorination process (Table 1).

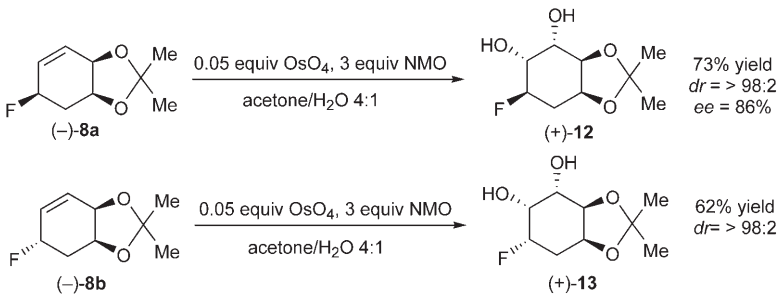
Table 1. Electrophilic fluorination of (+)-**4**–**7**.

Entry	Starting materials	Products		*dr*[a]	Yield [%][b]
1	 (+)-**4**	 (−)-**8a**	 (−)-**8b**	67:33	48
2	 (+)-**5**	 (−)-**9a**	 (−)-**9b**	55:45	60
3	 (+)-**6**	 (−)-**10a**	 (−)-**10b**	80:20[c]	52
4	 (+)-**7**	 (−)-**11a**	 (−)-**11b**	82:18[c]	82

[a] *dr* measured on crude ^{1}H and ^{19}F NMR spectra. [b] Isolated yields. [c] Inseparable diastereomers

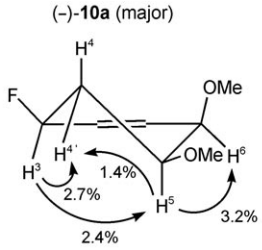
The fluorodesilylation of (+)-**4**, featuring a *tert*-butyldimethylsilyl group instead of a trimethylsilyl group took place with a lower chemical yield of 48%, but with similar diastereocontrol (*dr* = 67:33, entry 1, Table 1). The use of allylsilanes with bulkier silyl groups is therefore not beneficial. The effect of the diol protecting group on both the yield and the diastereomeric ratio was investigated next. The choice of the ketal proved critical as the level of diastereocontrol dropped significantly when the spiro compound (+)-**5** derived from cyclohexanone was reacted with Selectfluor in acetonitrile (entry 2, Table 1). For this electrophilic fluorodesilylation, the two separable diastereomers *syn*,*syn*-(−)-**9a** and *anti*,*syn*-(−)-**9b** were formed in roughly equimolar amounts, with a diastereomeric ratio of 55:45 (entry 2, Table 1). The monocyclic allylsilanes (+)-**6** and (+)-**7**, featuring two methoxy or two benzyloxy groups were also fluorinated successfully under our standard conditions (entries 3 and 4, Table 1). Upon electrophilic fluorodesilylation, the corresponding fluorinated products (−)-**10a**–**b** and (−)-**11a**–**b** were obtained in 52 and 82% yield, respectively. The level of diastereocontrol was higher for these transformations. The two diastereomers (−)-**10a** and (−)-**10b** were formed with a diastereomeric ratio of 80:20. Very similar results were obtained for the fluorination of (+)-**7**, as the two products (−)-**11a** and (−)-**11b** were formed with a *dr* of 82:18. For compounds (−)-**10** and (−)-**11**, the diastereomers could not be separated by silica-gel chromatography. Careful NMR spectroscopic analysis of the mixture of diastereomers revealed that these two transformations delivered the major all-*syn* stereoisomers *syn*,*syn*-(−)-**10a** and *syn*,*syn*-(−)-**11a**, resulting from a preferential approach of the fluorinating agent *anti* with respect to the trimethylsilyl group.

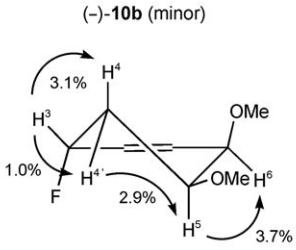
With the pure stereoisomer *syn*,*syn*-(−)-**8a** in hand, we examined the possibility of further functionalisation of the remaining double bond (Scheme 4). A dihydroxylation was performed by using a catalytic amount of osmium tetroxide and stoichiometric amounts of NMO (the "Upjohn" process; NMO = *N*-methylmorpholine-*N*-oxide).[10] This transformation took place with excellent diastereocontrol and afforded compound (+)-**12**, a protected fluorinated analogue of 2-deoxy-*allo*-inositol, in 73% yield and with a *dr* greater than 98:2. The relative stereochemistry of this compound, assigned by NMR spectroscopy and unambiguously confirmed by single crystal X-ray analysis, revealed that the dihydroxylation had occurred solely *anti* with respect to the three existing stereocentres of *syn*,*syn*-(−)-**8a**. The fluorinated compound (+)-**12** was obtained with an enantiomeric excess of 86%, suggesting that no racemisation occurred when the silylated precursor (+)-**2a** was protected, fluorinated and subsequently dihydroxy-



Scheme 4.

lated. As compound (+)-**12** could not be separated by chiral HPLC, its enantiomeric excess was determined by ^{1}H and ^{19}F NMR spectroscopy after quantitative derivatisation with (*R*)-Mosher's acid chloride.[11] Similarly, the minor isomer *anti*,*syn*-(−)-**8b** was submitted to a dihydroxylation and this process delivered in 62% yield the desired product (+)-**13** as a single diastereomer ($dr = > 98{:}2$), resulting from an approach of the osmium tetroxide *anti* to the acetonide group. These results suggested that the fluorinated stereogenic carbon atom has no influence on the stereochemical outcome of the dihydroxylation process.





	1	2	3	4_{syn}	$4'_{anti}$	5	6
F	1.6	9.7	48.2	16.1	6.6	-	-
1		9.7	1.6	-	-	-	4.6
2			2.5	-	~1	-	~1
3				8.5	6.4	1.5	-
4_{syn}					11.7	11.7	-
$4'_{anti}$						3.3	~1
5							3.3

	1	2	3	4_{syn}	$4'_{anti}$	5	6
F	*	*	48.4	24.7	18.0	-	3.5
1		*	*	-	-	-	3.5
2			5.0	-	-	-	~1
3				5.0	6.0	~1	-
4_{syn}					14.0	9.3	-
$4'_{anti}$						2.8	-
5							3.5

Figure 1. Selected steady-state NOE enhancements, ^{1}H–^{1}H and ^{1}H–^{19}F coupling constants for isomers (−)-**10a** (C_6D_6) and (−)-**10b** ($CDCl_3$). The prime notation indicates the H^4 of lowest chemical shift. *: values could not be determined reliably due to the H^1 and H^2 protons of the minor isomer being hidden under those of the major form.

Structural and conformational analysis: Only major diol (+)-**12** was available in the crystalline form and was characterized by X-ray diffraction. Compounds **8**–**13** underwent extensive NMR spectroscopic analysis to determine both the configuration at the position of fluorine substitution and the resulting conformations of the fluorinated products in solution. These analyses were based on equilibrium (steady-state) NOE measurements to enable quantitative intramolecular NOE comparisons to be made, and on the magnitudes of *J*(H,H) and *J*(H,F) coupling constants. Due to the complexity of many ^{1}H multiplet structures, the values of coupling constants derived from direct interpretation of multiplet patterns were confirmed, and where necessary modified, by direct spectrum simulation. Furthermore, to assist in this process, the magnitudes of some heteronuclear ^{1}H–^{19}F coupling constants were first estimated from multiplet peak displacements within ^{1}H–^{1}H COSY crosspeaks and subsequently verified through simulation. Specifically, these *J*(H,F) displacements could be most easily observed within the H^3–H^4 and H^3–H^2 crosspeaks due to the inherently large $^{2}J(H^3,F)$ values. In the case of the bicyclic fluorinated compounds (−)-**8a**–**b** and (−)-**9a**–**b**, the two diastereomers in each case could be separated and the NMR analyses were performed on pure stereoisomers. For compounds (−)-**10a**–**b** and (−)-**11a**–**b**, NMR spectroscopic experiments were performed on mixtures of the two inseparable diastereomers in both cases.

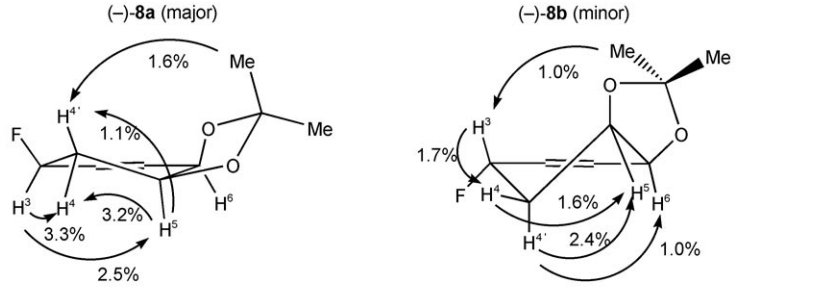
The data for the monocyclic compounds (−)-**10a**–**b** and (−)-**11a**–**b** could be interpreted as adopting conventional half-chair conformations and for clarity of subsequent discussions will be described first. The major isomer (−)-**10a** was analyzed in deuterobenzene, as the H^4 protons were coincident in deuterochloroform which did, however, provide suitable dispersion for the minor isomer (−)-**10b**. The NOE results for (−)-**10a** (Figure 1) indicated H^3 to sit *syn* to H^5, demonstrating the fluorine substituent was itself *syn* to the protected diol functionality. The large H^4–H^5 coupling of 11.7 Hz indicates H^5 adopts an axial position antiperiplanar to the axial H^4_{syn} (throughout the H^4 protons will be described as being *syn* or *anti* with respect to the protected diol moiety) indicative of the half-chair conformation as shown. In this conformation, H^3 adopts the pseudo-axial position and shares a distinctively small H^3–H^2 coupling of 2.5 Hz due to the dihedral angle approaching 90°, with a coupling of 8.5 Hz to H^4_{syn} being consistent with the pseudoaxial-axial arrangement. The near eclipsed relationship between H^4_{syn} and the fluorine is likewise consistent with this proton exhibiting a larger fluorine coupling (16.1 Hz) than $H^{4'}_{anti}$ (6.6 Hz).

The NOE data for the minor isomer (−)-**10b** (Figure 1) now indicated H^3 to be *syn* relative to the methyl ethers and, as expected, the fluorine substitution to have occurred *anti* to the protected diol. The measured coupling constants suggested a similar chair conformation as defined for the major isomer, but with the fluorine now adopting the pseudo-axial position. Thus, H^5 still displayed a relatively large coupling to H^4_{syn} (9.3 Hz) which can only be accounted for with axial geometry, whilst the large $^{3}J(F,H^4_{syn})$ value of 24.7 Hz is likewise consistent with a H^4_{syn}–fluorine axial-pseudo-axial relationship. The H^3 proton consequently displays coupling of similar magnitudes with the H^4_{syn}, $H^{4'}_{anti}$ and H^2 protons; the increase in the coupling with H^2 relative to that observed in the major isomer (5.0 versus 2.5 Hz) is consistent with H^3 now occupying a pseudo-equatorial position.

The NOE and coupling (*J*) data for the major and minor isomers (−)-**11a** and (−)-**11b** collected in $CDCl_3$[8] were very similar to those of the major and minor forms respectively of (−)-**10** and indicate similar substitution configura-

tions and conformations in both the methyl and benzyl ethers, and as such these demand no further discussion. For compounds (−)-**10a–b** and (−)-**11a–b**, it appears that the major determinant for their conformation in solution is the preferential location of the allylic methoxy group in the pseudo-axial position.

Analysis of the NOE data for the bicyclic major isomer (−)-**8a** (Figure 2) clearly indicated that the fluorine substitution had taken place *syn* to the acetonide functionality as for the major isomers above. However, consideration of the coupling constant data suggests that, while the fluorine remains predominantly pseudo-equatorial, slight deviation from the idealized half-chair conformation occurs for this compound. Notably the H^5–$H^{4'}_{syn}$ coupling has reduced to 8.5 Hz (from approximately 11 Hz) and the H^3–$H^{4'}_{syn}$ coupling has also reduced, although less markedly. Furthermore, the increase in the H^5–H^6 coupling to 5.8 Hz (from approximately 3 Hz) suggests that these protons occupy a more eclipsed relationship than in (−)-**10a** or (−)-**11a**, whilst the increase in the F–H^4_{anti} coupling to 16.3 Hz (from approximately 8 Hz) suggests a move toward a more antiperiplanar relationship for these. Taken together, these data indicate a flattening of the cyclohexene half-chair conformation, such that the C^4–C^5–C^6 carbon atoms sit in an almost coplanar geometry (as indicated schematically in Figure 2) and we consider that this may be attributed to the additional conformational constraint imposed by the acetonide protection. The conformational differences appear even more marked for the minor isomer (−)-**8b**. This was studied in both $CDCl_3$ and C_6D_6, the latter removing the troublesome coincidence of H^5 and H^6 observed in $CDCl_3$, although the NMR data suggests that there were no conformational changes observed between these solvents. The NOE data indicate H^3 was *syn*, and, hence, the fluorine atom *anti* to the acetonide. From consideration of the coupling data, it is striking that H^5 no longer exhibited a large diaxial coupling, whereas H^3 and $H^{4'}_{anti}$ did share a large value of 9.1 Hz. In addition, $^3J(H^3,H^2)$ is only 2.5 Hz (similar to the major forms of **10** and **11**) all of which suggested that H^3 occupies the pseudo-axial position. That the fluorine atom must, therefore, be pseudo-equatorial is borne out by the fluorine coupling to the H^4 protons whereby no large axial-pseudoaxial coupling is observed. Furthermore, there exists a NOE between $H^{4'}_{anti}$ and H^6. These data are consistent with (−)-**8b** adopting a half-chair conformation that is inverted with respect to that observed for the isomers of **10** and **11**, as indicated in Figure 2. Presumably this is again, in some part at least, attributable to the influence of the acetonide ring but may also be possibly favoured by the fluorine atom occupying a pseudo-equatorial position, so releasing 1,3-pseudoaxial/axial strain.



	1	2	3	4'$_{syn}$	4$_{anti}$	5	6
F	4.5	9.8	48.2	13.8	16.3	-	-
1		10.2	1.4	-	-	-	~2
2			2.5	0.5	-	-	-
3				7.5	4.8	-	~1.5
4'$_{syn}$					13.2	8.5	~1
4$_{anti}$						4.5	-
5							5.8

	1	2	3	4$_{syn}$	4'$_{anti}$	5	6
F	3.2	11.5	49.4	5.6	14.8	-	-
1		10.4	1.6	-	-	~1.5	~1.5
2			2.3	-	-	~1	~1
3				5.6	9.1	-	~2
4$_{syn}$					13.6	4.4	~1.5
4'$_{anti}$						2.9	-
5							~5

Figure 2. Selected steady-state NOE enhancements, ^1H–^1H and ^1H–^{19}F coupling constants for isomers (−)-**8a** ($CDCl_3$) and (−)-**8b** (C_6D_6). The prime notation indicates the H^4 of lowest chemical shift. For H^5 and H^6, the numerous small, long-range couplings meant that a precise measurement of these could not be established.

The proton spectra collected for the cyclohexylidene protected systems (−)-**9a** and (−)-**9b** bore close similarities with those of the corresponding acetonide-protected isomers, suggesting that the configuration and conformational behaviour of these systems is the same as for the (−)-**8** diastereomers.

The relative stereochemistry of the diol (+)-**12** was determined unambiguously by single-crystal X-ray analysis and showed that the dihydroxylation of the fluorinated acetonide (−)-**8a** had occurred solely in an *anti* fashion with respect to the existing stereocentres (Figure 3).

The solid-state conformation is predominantly that of a chair, with the fluorine atom in an axial position. Some distortion is observed at C^5, however, with C^4–C^5–C^6 occupying a slightly more planar geometry, moving H^4_{anti} and H^6 further apart (Figure 3b) presumably due to the additional conformational constraint imposed by the acetonide. The NMR data (Figure 4) are largely consistent with a distorted chair conformation in acetone but are suggestive of greater flattening of the chair conformation around C^5, as indicated schematically in Figure 4. Thus H^6 shares only a 4.2 Hz coupling with H^1 and displays no 1,3-diaxial NOE to H^4, suggesting this is somewhat removed from the axial position of a cyclohexane chair. In contrast, the fluorine–H^4 couplings are consistent with the fluorine atom holding the axial position and thus it appears that the presence of the acetonide

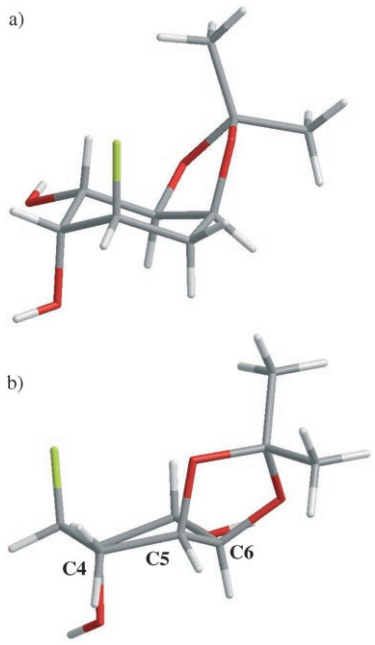
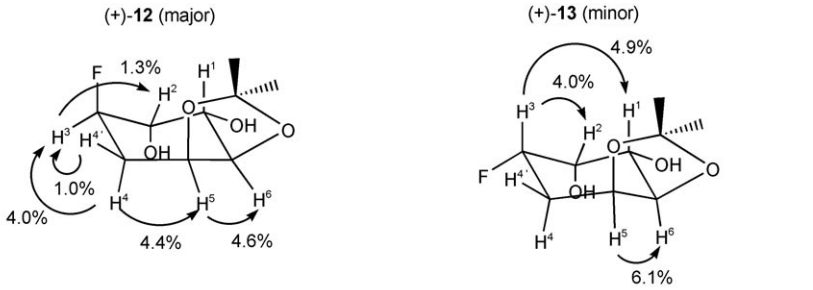


Figure 3. X-ray structure of (+)-**12**. The conformation is predominantly that of a chair (view (a)) with slight distortion bringing C^5 down toward C^4–C^6 (view (b); see text for discussions).



	1	2	3	4'$_{syn}$	4$_{anti}$	5	6
F	3.8	14.9	50.4	18.7	25.9	-	-
1		2.8	-	-	-	-	4.2
2			6.2	-	-	-	-
3				5.4	5.4	-	-
4'$_{syn}$					14.9	5.4	-
4$_{anti}$						5.4	-
5							5.4

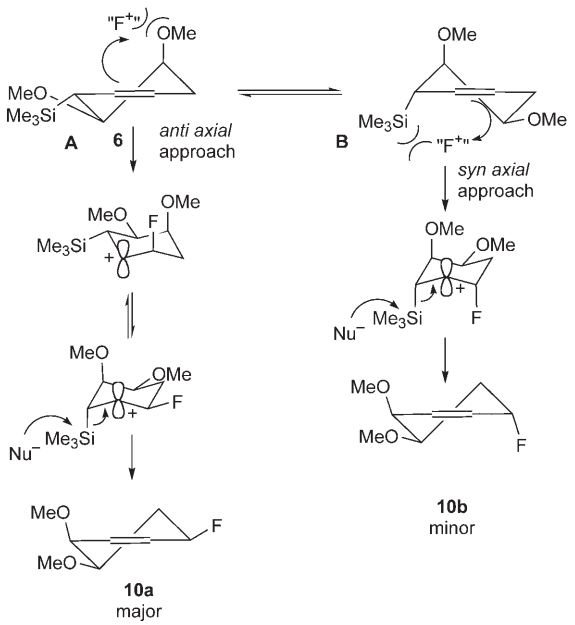
	1	2	3	4'$_{syn}$	4$_{anti}$	5	6
F	~2	11.8	47.4	~2	11.5	2.3	-
1		2.8	-	-	-	-	7.8
2			2.0	~1	-	-	-
3				5.4	11.3	-	-
4'$_{syn}$					13.8	4.7	-
4$_{anti}$						4.6	-
5							5.6

Figure 4. Selected steady-state NOE enhancements, ^{1}H–^{1}H and ^{1}H–^{19}F coupling constants for isomers (+)-**12** ($(CD_3)_2CO$) and (+)-**13** ($(CD_3)_2CO/C_6D_6$). The prime notation indicates the H^4 of lowest chemical shift.

results in a net flattening of the chair around C^4–C^5–C^6 as suggested for the acetonide-protected cyclohexene (−)-**8a**. It appears there may be greater conformational distortion in solution than in the solid state, but we note that in the crystal structure, the hydroxyl group adjacent to the ketal (C^1–OH) forms a hydrogen bond to a ketal oxygen atom (C^6–O) in a neighbouring molecule, while the other hydroxyl group (C^2–OH) forms a hydrogen bond to a hydroxyl oxygen atom (C^1–OH) in a third molecule and that these intermolecular interactions may impart differing conformational constraints in the crystal.

The NOE data of the minor isomer (+)-**13** showed that dihydroxylation of the minor fluorinated acetonide (−)-**8b** had occurred solely *anti* to the acetonide and *syn* with respect to the fluorine atom. Moreover, there existed a significant H^1–H^3 NOE, suggesting the presence of the chair conformation with H^3 axial, also consistent with the sizeable $^3J(H^3,H^4_{anti})$ of 11.3 Hz. The H^1–H^6 coupling of 7.8 Hz again suggests some distortion from an idealized chair with some flattening imposed by the acetonide, but it appears less pronounced than for (+)-**12** above. This suggests that the presence of the axial fluorine atom in (+)-**12** may contribute to greater distortion of the chair conformation in solution due to unfavourable 1,3-diaxial interactions.

Stereochemistry: Allylsilanes are known to react in the presence of electrophiles according to an S_E2' mechanism and are highly selective in the *anti* sense with respect to the silyl group.[12] Although the mechanism of electrophilic fluorination of various nucleophiles with Selectfluor has been the subject of many debates,[13] it is helpful in understanding the site and stereochemical outcome of the fluorinations of compounds (+)-**3**–**7** to postulate the formation of carbocationic intermediates (Scheme 5). With allylsilanes, the β cations are highly stabilized through overlap with the Si–C bonding orbital, thereby defining the site of attack of the electrophile. Accordingly, the fluorinations of (+)-**3**–**7** all proceed with complete regiocontrol, leading to clean double-bond transposition upon desilylation. With an S_E2' mechanism operating, the relatively low reactivity of (+)-**3**–**7** in comparison with other cyclic and acyclic allylsilanes[5] is due to the imperfect alignment of the C–Si bond with the π system, resulting in late stabilization of the developing positive charge towards the carbocationic intermediate. In terms of stereochemical outcome, the best diastereoselectivities were obtained for the fluorination of allylsilanes (+)-**6** and (+)-**7**, which feature two methoxy or benzyloxy groups. The major isomers (−)-**10a** and (−)-**11a** obtained upon fluorodesilylation result from an approach of the fluorinating agent *anti* to the trimethylsilyl group. For cyclohexene (+)-**6** in its half-chair conformation (**A**) with the silyl group on the pseudo-equatorial position, this preferential stereochemical outcome is the result of an axial addition of Selectfluor taking place *anti* to the silyl group. This approach is hampered by



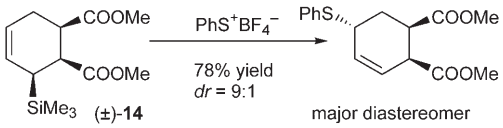
Scheme 5.

an 1,3-diaxial interaction with the methoxy group, leading to erosion of *anti* stereospecificity. If the ring adopts the alternative inverted conformation, which features a pseudo-axial silyl group (**B**), with the reagent approaching the double bond axially, the attack is *syn* to the large silyl group with concomitant unfavourable steric interactions. Not surprisingly, this approach leads to the minor diastereomer. We did not consider the less favourable equatorial attacks for the electrophile as these approaches would lead to twisted intermediates presumably of higher energy.[14] The lower level of diastereocontrol observed for the fluorinations of compounds (+)-**3**–**5** can be rationalized by the additional steric interactions brought about by the ketal group when the approach of Selectfluor is takes place *anti* to the silyl group.

For the major isomer (−)-**10a** with the electronegative fluoro group and methoxy substituent on the allylic position, the structural assignment in solution revealed that the preferential conformer features the methoxy group pseudo-axial and the fluorine atom pseudo-equatorial. This preferential conformer enabled the nonallylic methoxy group to adopt the more favourable equatorial position. For the minor isomer (−)-**10b**, these two substituents are pseudoaxial, enabling favourable interactions with the π-system (π–σ*).[15]

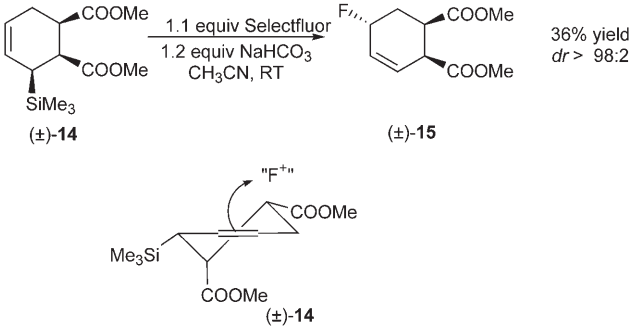
Noteworthy is that the level of diastereocontrol observed for the fluorodesilylations of (+)-**3**–**7** is lower than for electrophilic substitutions, other than fluorinations, reported in the literature on structurally related cyclic all-*syn* allylsilanes.[16] For example, the reaction of phenylsulfenyl chloride on the all-*syn* diester (±)-**14** gave preferentially the desired sulfide resulting from an *anti* addition of the electrophile with respect to the silyl group (*dr* = 9:1) (Scheme 6).

To compare these results with our data, we carried out the electrophilic fluorodesilylation of allylsilane (±)-**14**, which was prepared as a racemate by using, as the key step,



Scheme 6.

an *endo*-selective Diels–Alder cycloaddition from 1-trimethylsilylbutadiene, a procedure developed by Fleming.[16] Upon fluorination of the monocyclic all-*syn* precursor (±)-**14**, the desired product (±)-**15** was isolated in 36% yield and with a *dr* superior to 98:2. The major diastereomer observed for this fluorination resulted from an *anti* axial approach of the fluorinating reagent. This approach is clearly favoured as it is free from unfavourable steric interactions and this is reflected in the very high level of diastereocontrol observed for this electrophilic fluorination (Scheme 7).



Scheme 7.

Conclusion

We have studied the electrophilic fluorodesilylation of various endocyclic allylsilanes. These reactions afforded fluorinated carbocycles featuring allylic fluorides, which can be easily further functionalized. The fluorinations are regioselective and gave products resulting from clean transposition of the double bond. The data revealed that both *anti*,*syn* and all-*syn* allylsilanes are suitable starting materials and delivered the corresponding fluorinated carbocycles in good yields with the level of diastereocontrol dependent on the relative stereochemistry and the geometrical constraints imposed by the starting allylsilanes. The best diastereoselectivity was observed for the fluorination of the all-*syn* allylsilane. The approach of the fluorinating reagent takes place preferentially *anti* to the silyl group as expected for these bimolecular electrophilic substitutions. We have also demonstrated that the dihydroxylation of endocyclic allylic fluorides is feasible and leads to novel highly functionalised, partially protected fluorinated analogues of 2-deoxy-*allo*-inositol. These fluorocompounds, which feature five stereocenters are accessible by using an operationally simple five-step synthesis from 1,4-cyclohexadiene combining a known Sharpless dihydroxylation with an electrophilic fluorodesilylation as the two key steps. The fluorinations presented

herein are the first examples of electrophilic fluorodesilylation of endocyclic allylsilanes. Combined with its robustness, this new synthetic route to fluorinated carbocycles complements other approaches that typically involve nucleophilic fluorination rather than electrophilic fluorination.[17] The products are versatile fluorinated building blocks offering multiple possibilities for further functional-group manipulations of the double bond. A detailed study of the synthetic scope of these new building blocks and related compounds is ongoing in our laboratory.

Experimental Section

General information: ^{1}H NMR spectra were recorded in deuterated solvents by using Bruker DPX200, DPX400, AV400 and AV500 spectrometers, calibrated by using residual protonated solvent as an internal reference. ^{13}C NMR spectra were recorded in deuterated solvents by using Bruker DPX200, DPX400, AV400 and AV500 spectrometers. ^{19}F spectra were recorded on a Bruker AV400 spectrometer. NOE difference experiments were performed at 500 MHz on nondegassed solutions with saturation times totalling 5 s. These were performed with frequency cycling between the individual lines within each multiplet to ensure more even suppression of the wide multiplet structures. NMR spectra were processed in ACD/SpecManager and IUPAC names were obtained by using the ACD/I-lab service. Proton spectrum simulations were performed with the Mestre-C NMR software. Chemical shifts (δ) are quoted in parts per million (ppm) and coupling constants (J) are measured in hertz (Hz). The following abbreviations are used to describe multiplicities s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. Mass spectra were recorded on Micromass GCT (CI), Autospec-oaTof instruments. Optical rotations were determined on a Perkin–Elmer 241 polarimeter in a 1 dm cell. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films on NaCl plates in $CHCl_3$ on a Bruker Tensor 27 FTIR spectrometer. Absorptions are measured in wavenumbers and only peaks of interest are reported. All reactions requiring anhydrous conditions were conducted in dried apparatus under an inert atmosphere of argon or nitrogen. Solvents were dried and purified before use according to standard procedures. All reactions were monitored by TLC using Merck Kiesegel 60 F_{254} plates. Visualisation of the reaction components was achieved by using UV fluorescence (254 nm) and $KMnO_4$ stain. Column chromatography was carried out over Merck silica gel C60 (40–60 μm).

(3*S*,4*S*,7*S*)-2,2-Dimethyl-3,4,7-tetrahydro-1,3-benzodioxol-4-yl(trimethyl)silane ((+)-3): Diol (+)-**2a** (0.325 g, 1.75 mmol) was dissolved in acetone (5 mL) and DMP (DMP = dimethoxypropane, 4 mL). A catalytic amount of *p*TsOH (0.011 g, 0.0525 mmol) was added and the reaction was stirred at room temperature for 2 h. The solvents were evaporated in vacuo and a saturated solution of aq $NaCO_3$ was added. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic layers washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. Column chromatography (hexane/Et_2O 75:25, R_f = 0.5) furnished (+)-**3** as a pale yellow oil (0.337 g, 1.49 mmol, 85 % yield). $[\alpha]_D^{298}$ = +1.1 (c = 0.15 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (dt, J = 5.6, 10 Hz, 1H), 5.62 (dtd, J = 0.8, 5.0, 10.0 Hz, 1H), 4.35 (m, 2H), 2.23 (m, 2H), 1.90 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 0.06 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.2, 120.8, 107.6, 73.8, 72.5, 31.6, 28.3, 27.5, 25.5, −2.5 ppm; IR (neat): $\tilde{\nu}$ = 3031, 1684 cm^{-1}; HRMS (CI): m/z: calcd for $C_{12}H_{22}O_2Si$: 226.1389 $[M]^+$; found: 226.1387.

Trimethyl-(3*S*,4*S*,7*S*)-tetrahydrospiro[1,3-benzodioxole-2,1′-cyclohexan]-4-yl)silane ((+)-5): Diol (+)-**2a** (0.186 g, 1 mmol) was dissolved in cyclohexanone (3 mL) and 1,2-dimethoxyketal (3 mL). A catalytic amount of *p*TsOH (0.006 g, 0.03 mmol) was added and the reaction was stirred at room temperature for 2 h. The solvents were removed in vacuo and saturated aq Na_2CO_3 (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. Column chromatography (hexane/Et_2O 90:10, R_f = 0.3) furnished (+)-**5** as a colourless oil (0.181 g, 0.8 mmol, 80 % yield). $[\alpha]_D^{298}$ = +85.1 (c = 0.255 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (m, 1H), 5.60 (dt, J = 4.4, 10.0 Hz, 1H), 3.85 (m, H), 4.32 (m, 1H), 2.23 (m, 1H), 2.23–2.17 (m, 2H), 1.91 (m, 1H), 1.67–1.55 (m, 8H), 1.42–1.35 (m, 2H), 0.06 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.1, 121.0, 108.2, 73.4, 72.0, 37.3, 35.0, 31.5, 28.8, 25.3, 24.1, 23.8, −2.5 ppm; IR (neat): $\tilde{\nu}$ = 2936, 1675 cm^{-1}; HRMS (CI): m/z: calcd for $C_{15}H_{26}O_2Si$: 267.1780 $[M+H]^+$; found: 267.1788.

[(1*S*,5*S*,6*S*)-5,6-Dimethoxy-2-en-1-yl](trimethyl)silane ((+)-6): Diol (+)-**2a** (0.153 g, 0.82 mmol) in THF (1 mL) was added dropwise to a stirring suspension of NaH (0.1 g, 2.5 mmol) in THF (2 mL) at 0 °C under argon and the mixture was stirred at 0 °C for 30 min. MeI (0.13 mL, 2 mmol) was added and the reaction mixture was stirred for a further 2 h at room temperature. The reaction was quenched with H_2O at 0 °C and extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (40 mL), dried over $MgSO_4$ and the solvent removed in vacuo. Column chromatography (hexane/Et_2O 80:20, R_f = 0.25) furnished (+)-**6** as a colourless oil (0.1 g, 0.53 mmol, 66 % yield). $[\alpha]_D^{298}$ = +88.2 (c = 0.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.57–5.51 (m, 2H), 3.64 (dd, J = 2.0, 3.2 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 2.36–2.26 (m, 2H), 2.05–2.03 (m, 1H), 0.08 ppm (s, 9H); ^{13}C NMR (100 MHz, MeOD): δ = 125.4, 121.3, 77.8, 76.8, 55.9, 55.6, 32.5, 27.2, −3.2 ppm; IR (neat): $\tilde{\nu}$ = 2950, 1639 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{11}H_{22}O_2Si$: 237.1283 $[M+Na]^+$; found: 237.1281.

[5,6-Bis(benzyloxy)cyclohex-2-en-1-yl](trimethyl)silane ((+)-7): Diol (+)-**2a** (0.327 g, 1.75 mmol) in THF (2 mL) was added dropwise to a suspension of NaH (0.2 g, 5.25 mmol) at 0 °C under argon, and the reaction mixture was stirred at 0 °C for 30 min. BnBr (0.52 mL, 4.2 mmol) was added and the reaction was stirred for 3 h at room temperature. The reaction was quenched with H_2O at 0 °C and extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed in vacuo. Column chromatography (hexane/Et_2O 95:5, R_f = 0.25) furnished (+)-**7** as a colourless oil (0.4 g, 1.11 mmol, 63 % yield). $[\alpha]_D^{298}$ = +62.1 (c = 0.69 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 10H), 5.57 (ddd, J = 2.0, 4.4, 10 Hz, 1H), 5.51 (ddd, J = 5.2, 5.5, 10 Hz, 1H), 4.76 (d, J = 12.4 Hz, 1H), 4.70 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 12.8 Hz, 1H), 4.55 (d, J = 12.8 Hz, 1H), 3.88 (m, 1H), 3.59 (ddd, J = 1.6, 5.5, 9.6 Hz, 1H), 2.50 (dddd, J = 2.0, 5.2, 9.6, 16.6 Hz, 1H), 2.30 (ddd, J = 5.2, 5.5, 16.6 Hz, 1H), 2.01 (m, 1H), −0.09 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 138.8, 128.3–121.6, 76.7, 74.9, 71.2, 70.2, 34.6, 27.6, −2.4 ppm; IR (neat): $\tilde{\nu}$ = 3026, 2952, 1642 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{23}H_{30}O_2Si$: 389.1906 $[M+Na]^+$; found: 389.1907.

General procedure for the electrophilic fluorodesilylation of allylsilanes: A solution of the allylsilane (1 equiv) and $NaHCO_3$ (1.2 equiv) in anhydrous CH_3CN (c = 0.1 M) was treated with Selectfluor (1.1 equiv) and the mixture was stirred at room temperature for 3 d. Water was added and the mixture extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo.

(3*S*,5*S*,7*R*)-5-Fluoro-2,2-dimethyl-3,4,5,7-tetrahydro-1,3-benzodioxole (−)-8b and (3*S*,5*R*,7*R*)-5-fluoro-2,2-dimethyl-3, 4,5,7-tetrahydro-1,3-benzodioxole (−)-8a: A mixture of diastereomers in a ratio 1:2.3 was obtained. Column chromatography (hexane/Et_2O 90:10) furnished both the minor compound (−)-**8b** and the major compound (−)-**8a** with an overall 64 % yield.

Minor anti *isomer (−)-**8b***: Yield: 0.124 g, 0.72 mmol; R_f = 0.38 (hexane/Et_2O 90:10); $[\alpha]_D^{298}$ = −11.25 (c = 0.24 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (ddddd, J = 1.0, 1.3, 2.3, 10.4, 11.5, Hz, 1H), 5.80 (ddddd, J = 1.5, 1.5, 1.6, 3.2, 10.4 Hz, 1H), 5.25 (dddddd, J = 1.6, 2.0, 2.3, 5.6, 9.1, 49.4 Hz, 1H), 4.51 (m, 2H), 2.60 (ddddd, J = 1.5, 4.4, 5.6, 5.6, 13.6 Hz, 1H), 1.91 (dddd, J = 2.9, 9.1, 13.6, 14.8 Hz, 1H), 1.37 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.6 (d, 21.6 Hz), 128.8 (d, J = 9.6 Hz), 108.8, 84.9 (d, J = 162.2 Hz), 72.2 (d, J = 11.2 Hz), 71.1 (d, J = 2.8 Hz), 32.3 (d, J = 19.2 Hz), 27.7, 26.3 ppm; ^{19}F {^{1}H} NMR (376 MHz,

$CDCl_3$): $\delta = -179.5$ ppm; IR (neat): $\tilde{\nu} = 2987$, 1648 cm^{-1}; HRMS (EI): m/z: calcd for $C_9H_{13}O_2F$: 173.0978 $[M+H]^+$; found: 173.0975.

Major syn *isomer (−)-**8a***: Yield: 0.232 g, 1.35 mmol; $R_f = 0.25$ (hexane/Et_2O 90:10); $[\alpha]_D^{298} = -14.3$ ($c = 0.175$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.07$ (dddd, $J = 1.4$, 2.0, 4.5, 10.2 Hz, 1H), 6.00 (dddd, $J = 0.5$, 2.5, 9.8, 10.2 Hz, 1H), 5.03 (dddddd, $J = 1.4$, 1.5, 2.5, 4.8, 7.5, 48.2 Hz, 1H), 4.44 (dddd, $J = 1.0$, 1.5, 2.0, 5.8 Hz, 1H), 4.32 (ddd, $J = 4.5$, 5.8, 8.5 Hz, 1H), 2.25 (dddd, $J = 4.5$, 4.8, 13.2, 16.3 Hz, 1H), 2.05 (dddddd, $J = 0.5$, 1.0, 7.5, 8.5, 13.2, 13.8 Hz, 1H), 1.50 (s, 3H), 1.39 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 130.4$ (d, $J = 21.6$ Hz), 127.6 (d, $J = 9.6$ Hz), 84.9 (d, $J = 166.2$ Hz), 71.1 (d, $J = 9.6$ Hz), 70.7 (d, $J = 2.0$ Hz), 32.0 (d, $J = 18.8$ Hz), 28.2, 26.2 ppm; ^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -176.5$ ppm; IR (neat): $\tilde{\nu} = 2987$, 1648 cm^{-1}; HRMS (CI): m/z: calcd for $C_9H_{13}O_2F$: 173.0978 $[M+H]^+$; found: 173.0970.

(3*S*,5*S*,7*R*)-5-Fluoro-3,4,5,7-tetrahydrospriro[1,3-benzodiozole-2,1′-cyclohexane] ((−)-9b) and (3*S*,5*R*,7*R*)-5-fluoro-3,4,5,7-tetrahydrospriro[1,3-benzodiozole-2,1′-cyclohexane] ((−)-9a): A mixture of diastereomers in a ratio of 1:1.3 was obtained. Column chromatography (hexane/Et_2O 95:5) furnished the minor compound (−)-**9b** and the major compound (−)-**9a** with an overall yield of 60%.

Minor anti *isomer (−)-**9b***: Yield: 0.047 g, 0.22 mmol; $R_f = 0.14$ (hexane/Et_2O 95:5); $[\alpha]_D^{298} = -15.8$ ($c = 2.3$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.02$–5.96 (m, 1H), 5.83–5.79 (m, 1H), 5.28–5.12 (m, 1H), 4.52–4.47 (m, 2H), 2.64–2.57 (m, 1H), 1.90 (m, 1H), 1.60–1.52 (m, 8H), 1.41–1.34 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 129.5$ (d, $J = 21.5$ Hz), 129.1 (d, $J = 9.5$ Hz), 109.4, 85.1 (d, $J = 161.6$ Hz), 71.9, 70.7, 37.4, 35.7, 32.4, 25.0, 24.0 ppm; ^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -179.5$ ppm; IR (neat): $\tilde{\nu} = 2934$, 1655 cm^{-1}; HRMS (CI): m/z: calcd for $C_{12}H_{17}O_2F$: 213.1291 $[M+H]^+$; found: 213.1288.

Major syn *isomer (−)-**9a***: Yield: 0.036 g, 0.17 mmol; $R_f = 0.24$; $[\alpha]_D^{298} = -18.6$ ($c = 0.7$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.06$ (td, $J = 2.5$, 10.0 Hz, 1H), 5.98–5.94 (m, 1H), 5.09–4.94 (m, 1H), 4.48–4.44 (m, 1H), 4.31 (ddd, $J = 4.7$, 5.4, 8.4 Hz, 1H), 2.31–2.22, (m, 1H), 2.04 (tt, $J = 8.4$, 13.5 Hz, 1H), 171–1.55 (m, 8H), 1.44–1.35 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 130.7$, 127.5, 110.8, 85.2 (d, $J = 133$ Hz), 70.7, 70 2, 37.9, 35.6, 32.3, 25.0, 24.0 ppm; ^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -177.12$ ppm; IR (neat): $\tilde{\nu} = 2936$, 1654 cm^{-1}; HRMS (CI): m/z: calcd for $C_{12}H_{17}O_2F$: 213.1291 $[M+H]^+$; found: 213.1289.

(3*R*,4*S*,6*R*)-6-Fluoro-3,4-dimethoxycyclohexene ((−)-10a) and (3*R*,4*S*,6*S*)-6-fluoro-3,4-dimethoxycyclohexene ((−)-10b): An inseparable mixture of diastereoisomers in a ratio of 1:4.2 *anti*/*syn* was obtained. Column chromatography (hexane/Et_2O 75:25, $R_f = 0.34$) afforded a mixture of (−)-**10a** and (−)-**10b** as a colourless oil (0.058 g, 0.36 mmol, 52% yield). $[\alpha]_D^{298} = -76.9$ ($c = 0.36$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.08$–6.04 (m, 1H; *syn* and *anti*), 6.20–5.97 (m, 1H; *syn* and *anti*), 5.19 (dddd, $J = 1.0$, 5.0, 6.0, 48.4 Hz, 1H; *anti*), 5.03 (dddd, $J = 1.5$, 6.4, 8.5, 48.2 Hz, 1H; *syn*), 3.90 (dddd, $J = 1.0$, 1.1, 3.3, 4.6 Hz, 1H; *anti*), 3.85 (dq, $J = 1.0$, 3.5 Hz, 1H; *syn*), 3.89 (dddd, $J = 1.0$, 2.8, 3.5, 9.3 Hz, 1H; *anti*), 3.50 (s, 3H; *syn*), 4.37 (s, 3H; *anti*), 3.46 (s, 2H; *anti*), 3.44 (s, 3H; *syn*), 3.42 (dddd, $J = 1.5$, 3.3, 3.3, 11.7 Hz, 1H; *syn*), 2.38 (dddd, $J = 5.0$, 9.3, 14.0. 24.7 Hz, 1H; *anti*), 2.26 (dddd, 8.5, 11.7, 11.7, 16.1 Hz, 1H; *syn*), 2.17 (dddddd, $J = 1.0$, 6.4, 6.6, 11.7, 11.7 Hz, 1H; *syn*), 1.97 ppm (dddd, $J = 2.8$, 6.0, 14.0, 18.0 Hz, 1H; *anti*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 130.3$ (d, $J = 9.9$ Hz; *anti*), 130.2 (d, $J = 20.0$ Hz; *syn*), 128.5 (d, $J = 9.9$ Hz; *anti*), 128.2 (d, $J = 17.9$ Hz; *syn*), 86.3 (d, $J = 166.3$ Hz; *syn*), 86.3 (d, $J = 160.7$; *anti*), 75.2 (d, $J = 14.4$ Hz; *anti*), 74.9 (d, $J = 9.1$ Hz; *syn*), 73.7 (d, $J = 2.4$ Hz; *anti*), 72.9 (d, $J = 1.6$ Hz; *syn*), 57.5 (*syn*), 57.4 (*anti*), 56.9 (*anti*), 56.4 (*syn*), 30.2 (d, $J = 19.9$ Hz; *anti*), 29.4 ppm (d, $J = 18.3$; *syn*); ^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -171.3$ (*syn*), −174.2 (*anti*); IR (neat): $\tilde{\nu} = 2092$, 1642 cm^{-1}; HRMS (ESI): m/z: calcd for $C_8H_{13}FO_2$: 183.0790 $[M+Na]^+$; found: 183.0792.

1,1-[[(1*S*,2*R*,5*R*)-5-Fluorocyclohex-3-ene-1,2-diyl]bis(oxymethylene)]dibenzene ((−)-11a) and 1,1-[[(1*S*,2*R*,5*S*)-5-fluorocyclohex-3-ene-1,2-diyl]-bis(oxymethylene)]dibenzene ((−)-11b): An inseparable mixture of diastereomers in a ratio 1:3.72 *syn*/*anti* was obtained. Column chromatography (hexane/Et_2O 90:10, $R_f = 0.23$) afforded a mixture of (−)-**11a** and (−)-**11b** as a colourless oil (0.35 g, 1.125 mmol, 82% yield). $[\alpha]_D^{298} = -60.4$ ($c = 0.63$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$–7.30 (m, 10H; *syn* and *anti*), 6.04–5.94 (m, 2H; *syn* and *anti*), 5.23 (ddddd, $J = 0.5$, 5.0, 5.0, 6.0, 48.5 Hz, 1H; *anti*), 5.02 (ddddd, $J = 1.3$, 2.5, 6.4, 8.4, 48.2 Hz, 1H; *syn*), 4.76 (d, $J = 12.4$ Hz, 1H; *syn*), 4.75 (d, $J = 12.0$ Hz, 1H; *anti*), 4.71 (d, $J = 12.4$ Hz, 1H; *syn*), 4.67–4.66 (m, 2H; *anti*), 4.68 (d, $J = 12.4$ Hz, 1H; *syn*), 4.61 (d, $J = 12.4$ Hz, 1H; *syn*), 4.09 (t, $J = 3.5$ Hz, 1H; *anti*), 4.03 (dd, $J = 1.0$, 3.0 Hz, 1H; *syn*), 3.99 (dddd, $J = 1.0$, 2.7, 3.5, 9.4 Hz, 1H; *anti*), 3.53 (dddd, $J = 1.3$, 3.0, 3.0, 11.0 Hz, 1H; *syn*), 2.48 (dddd, $J = 5.0$, 9.4, 14.0, 25.3 Hz, 1H; *anti*), 2.38 (dddd, $J = 8.4$, 11.0, 11.7, 16.0 Hz, 1H; *syn*), 2.27 (ddddd, $J = 1.0$, 3.0, 6.4, 7.5, 11.7 Hz, 1H; *syn*), 2.02 ppm (dddd, $J = 2.7$, 6.0, 14.0, 18.2 Hz, 1H; *anti*); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 138.7$ (*syn*), 138.5 (*anti*), 138.4 (*anti*), 138.3 (*syn*), 130.9 (d, $J = 9.9$ Hz; *anti*), 130.1 (d, $J = 20.8$ Hz; *syn*), 128.9 (d, $J = 10.0$ Hz; *syn*), 128.4 (*syn*), 128.3 (d, $J = 1.4$ Hz; *anti*), 128.33 (*anti*), 128.0 (*syn*), 127.9 (*syn*), 127.88 (*anti*), 127.81 (*syn*), 127.7 (*anti*), 127.6 (*anti*), 127.6 (*anti*), 127.6 (*syn*), 127.6 (*anti*), 127.6 (*syn*), 86.6 (d, $J = 160$ Hz; *anti*), 86.6 ppm (d, $J = 166$ Hz; *syn*); ^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -171.8$ (*syn*), −174.0 ppm (*anti*); IR (neat): $\tilde{\nu} = 2984$, 1454, 1027 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{21}FO_2$: 335.1416 $[M+Na]^+$; found: 335.1418.

(3*R*,4*S*,5*R*,6*R*,7*S*)-6-Fluoro-2,2-dimethylhexahydro-1,3-benzodioxole-4,5-diol ((+)-12):[18] The fluorinated acetonide (−)-**8a** (0.23 g, 1.3 mmol) was added to a stirring solution of OsO_4 (0.02 g, 0.065 mmol), NMO (0.45 g, 3.9 mmol), acetone (55 mL) and water (55 mL), and the reaction was stirred at room temperature for 3 d. $NaSO_3$ (1 g) was added and the reaction was stirred for 10 min, before the acetone was removed in vacuo. The remaining mixture was extracted with EtOAc (3×30 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography (hexane/EtOAc 50:50, $R_f = 0.2$) furnished (+)-**12** as a white crystalline solid (0.195 g, 0.95 mmol, 73% yield). 86% *ee* (measured by using Mosher's ester analysis).[11]; m.p. 100–102 °C; $[\alpha]_D^{298} = +0.13$ ($c = 1.49$ in MeOH); ^1H NMR (400 MHz, C_3D_6O): $\delta = 4.70$ (dddd, $J = 5.4$, 5.4, 6.2, 50.4 Hz, 1H), 4.38 (q, $J = 5.4$ Hz, 1H), 4.33 (d, $J = 6.0$ Hz, 1H), 4.21 (d, $J = 4.7$ Hz, 1H), 4.16 (dd, $J = 4.2$, 5.4 Hz, 1H), 4.01 (ddd, $J = 2.8$, 6.2, 14.9 Hz, 1H), 3.92 (ddd, $J = 2.8$, 4.2, 14.9 Hz, 1H), 2.34 (dddd, $J = 5.4$, 5.4, 14.9, 25.9 Hz, 1H), 2.01 (dddd, $J = 5.4$, 5.4, 14.9, 18.7 Hz, 1H), 1.40 (s, 3H), 1.29 ppm (s, 3H); ^{13}C NMR (125 MHz, C_3D_6O): $\delta = 108.9$, 92.1 (d, $J = 172.6$ Hz), 78.6, 72.8 ($J = 5.3$ Hz), 72.0 (d, $J = 21.9$ Hz), 71.7 (d, $J = 8.1$ Hz), 32.1 (d, $J = 20.0$ Hz), 28.2, 25.5 ppm; ^{19}F $\{^1H\}$ NMR (376 MHz, $CDCl_3$): $\delta = -188.63$ ppm; IR (neat): $\tilde{\nu} = 3423$, 3012, 1639 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_{15}FO_4$: 229.0847 $[M+Na]^+$; found: 229.0845.

(3*R*,4*S*,5*R*,6*S*,7*S*)-6-Fluoro-2,2-dimethylhexahydro-1,3-benzodioxole-4,5-diol ((+)-13): The fluorinated acetonide (−)-**8b** (0.4 g, 2.37 mmol) was added to a stirring solution of NMO (0.82 g, 7.11 mmol), OsO_4 (0.038 g, 0.118 mmol), acetone (90 mL) and water (30 mL), and the reaction was stirred at room temperature for 7 d. $NaSO_3$ (1 g) was added and the reaction was stirred for 10 min, before the acetone was removed in vacuo. The remaining mixture was extracted with EtOAc (3×100 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography (hexane/EtOAc 50:50, $R_f = 0.1$) furnished (+)-**13** (0.3 g, 1.47 mmol, 62% yield). M.p. 105–106 °C; $[\alpha]_D^{298} = +26.5$ ($c = 0.2$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.84$ (dddd, $J = 2.0$, 5.4, 11.3, 47.64 Hz, 1H), 4.38 (dddd, $J = 2.3$, 4.6, 4.7, 5.6 Hz, 1H), 4.27 (dddd, $J = 1.0$, 2.0. 2.8, 11.8 Hz, 1H), 4.13 (dd, $J = 5.6$, 7.8 Hz, 1H), 3.65 (ddd, $J = 2.0$, 2.8, 7.8 Hz, 1H), 3.03 (s, 1H), 2.79 (s, 1H), 2.37 (dddd, $J = 4.6$, 11.3, 11.5, 13.8 Hz, 1H), 2.30 (ddddd, $J = 1.0$, 2.0, 4.7, 5.4, 13.8 Hz, 1H), 1.47 (s, 3H), 1.36 ppm (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 109.1$, 85.0 (d, $J = 175.5$ Hz), 78.5, 72.7 (d, $J = 15.3$ Hz), 72.5 (d, $J = 10.0$ Hz), 71.6 (d, $J = 17.6$ Hz), 28.4, 26.7 (d, $J = 22.4$ Hz), 26.0 ppm; ^{19}F $\{^1H\}$ NMR (235 MHz, $CDCl_3$): $\delta = -194.5$ ppm; IR ($CHCl_3$): $\tilde{\nu} = 3424$, 1640, 1215 cm^{-1}; HRMS (ESI): m/z: calcd for $C_9H_{15}O_4F$: 229.0847 $[M+Na]^+$; found: 229.0847.

Dimethyl-5-fluorocyclohex-3-ene-1,2-dicarboxylate ((±)-15): A stirring solution of the allylsilane (0.08 g, 0.35 mmol) in CH_3CN (4 mL) was treated with Selectfluor (0.13 g, 0.38 mmol) and stirred at room temperature for 24 h. H_2O (10 mL) was added and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography (30–40 °C petroleum ether/Et_2O 90:10, $R_f = 0.2$)

furnished the *anti* compound (±)-**15** (0.027 g, 0.13 mmol, 36% yield) as a colourless oil. ^{1}H NMR (500 MHz, C_3D_6O) δ = 6.07 (ddd, J = 3.8, 5.4, 9.7 Hz, 1H), 5.92 (m, 1H), 4.96 (dq, J = 4.0, 48.0 Hz, 1H), 3.58 (m, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.91 (dddd, J = 1.0, 5.4, 5.4, 11.5 Hz, 1H), 2.28–2.13 ppm (m, 2H); ^{13}C NMR (100 MHz, C_3D_6O): δ = 173.4, 173.6, 131.1 (d, J = 10 Hz), 127.3 (d, J = 16 Hz), 84.5 (d, J = 161 Hz), 52.3, 52.1, 42.7 (d, J = 3 Hz), 37.3, 28.9 ppm; ^{19}F {^{1}H} NMR (376 MHz, C_3D_6O): δ = −167.5 ppm; IR ($CDCl_3$): $\tilde{\nu}$ = 2955, 1740, 1437 cm^{-1}; HRMS (CI): m/z: calcd for $C_{10}H_{14}O_4F$: 217.0876 $[M+H]^+$; found: 217.0871.

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[18] CCDC-611642 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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