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A regio- and stereoisomeric study of allylic alcohol fluorination with a range of reagents

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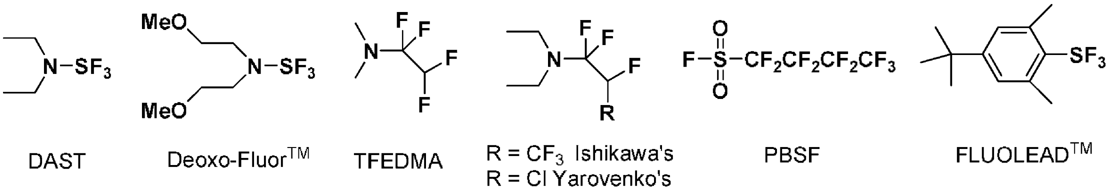
ABSTRACT

A range of dehydroxyfluorination reagents was reacted with separate diastereoisomers of a chiral allylic alcohol to explore both the regio- and stereoselectivity ratios of direct versus allylic fluorination. The allylic alcohol stereoisomers gave the same predominant fluorinated diastereoisomer indicating that the reaction proceeds with a significant S_N1 component *via* an allylic carbocation intermediate, which is quenched by fluoride ion, predominantly from the least hindered face. None of the reagents displayed very high regio- or stereoselectivity, although in all cases the allylic fluorination products predominated.

1. Introduction

The presence of fluorine in licensed drugs continues to be significant [1–3] and pharmaceutical products are increasingly emerging with fluorine both attached to aromatic rings but increasingly with fluorine at a stereogenic centre [4]. Dehydroxyfluorination is an important reaction in this context and it is particularly attractive if conditions can be found to convert an enantiomerically pure alcohol in a stereospecific manner to an enantiomerically pure organo-fluorine product. However often these reactions proceed *via* a partial S_N1 type reaction course and they can be subject to some loss in stereointegrity. Dehydroxyfluorinations are mediated with a range of reagents, although the first widely utilised reagent in this context was diethylamine sulfurtrifluoride (DAST), the more user-friendly form of SF_4, which became commercially available in the 1980s [5]. Subsequently Deoxo-Fluor^{TM} has emerged [6] as a second-generation DAST reagent which is finding wide utility because it is more heat stable and less hazardous for large-scale conversions than DAST. Other reagents such as Ishikawa's [7] and Yarovenko's [8] reagents have been explored in dehydroxyfluorinations, but they have not found wide utility, and perfluoro-1-butanesulfonyl fluoride (PBSF) has been reported for this transformation [9]. Most recently, tetrafluoroethyldimethylamine (TFEDMA) was introduced as a commercially available reagent and the scope and limitations of this reagent are still emerging [10]. The novel new fluorinating reagent with high stability and ease of handling, FLUOLEAD^{TM}, is an alternative to current fluorinating reagents [11].



In a synthetic programme in our laboratory we required to fluorinate the diastereoisomers of allylic alcohol **1** (**a** and **b**) for conversion to **2** (**a** and **b**) as illustrated in Scheme 1. This substrate has a number of complicating features with respect to the

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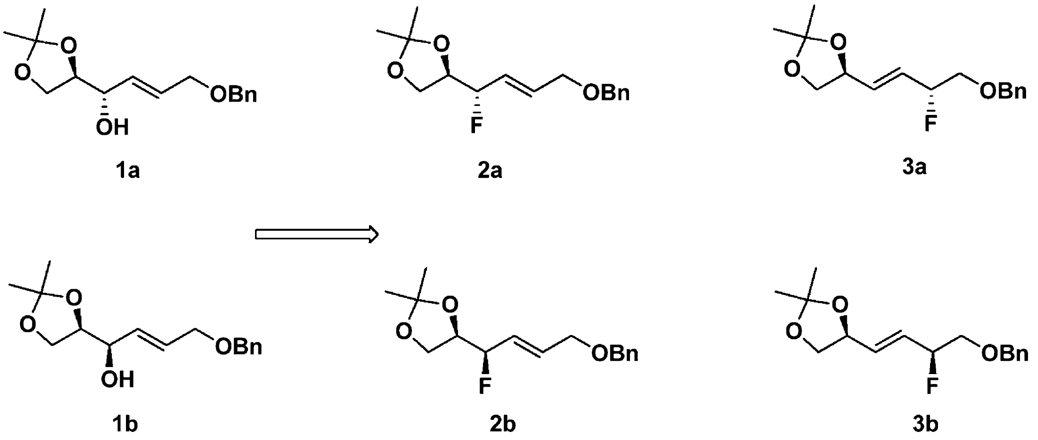


Scheme 1. Diastereoisomers **1a** and **1b** can generate four different isomeric products as a result of dehydroxyfluorination progressing either by direct or allylic fluorination.

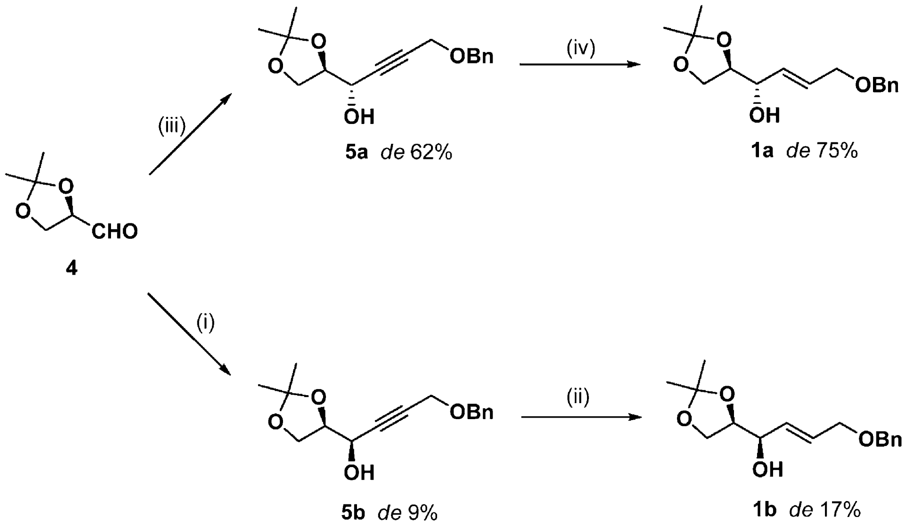
dehydroxyfluorination reaction. Firstly fluorination can proceed either by direct substitution of OH for F to give **2**, or by an allylic substitution reaction [12] to generate product **3**. Also for each reaction course there is two stereochemical outcomes, thus diastereoisomers **1a** and **1b** can give rise to a mixture of four products, **2a**/**2b**, and/or **3a**/**3b**. In this paper we report the outcomes of the regio- and stereoselectivity of fluorination reactions of **1a** and **1b** with DAST, Deoxo-Fluor™, TFEDMA, PBSF and FLUOLEAD™.

2. Results and discussion

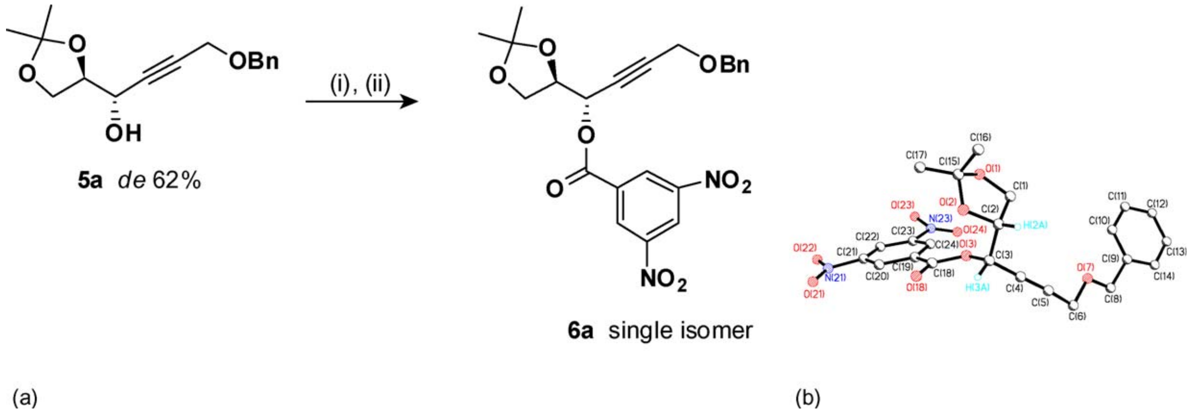
Mixtures of diastereoisomers **1a** and **1b** were prepared but with different diastereoisomeric biases. The *syn* addition of lithium acetylide to aldehyde (*R*)-**4** was conducted under conditions designed to promote chelation-control [13] as illustrated in Scheme 2. This generated **5b** as the major isomer, but with low diastereoselectivity (*de* 9%, determined by chiral GC-FID). A similar reaction was explored under non-chelation conditions using titanium tri-isopropoxychloride, to promote *anti*-selective addition [14] as illustrated in Scheme 2. This gave **5a** in much higher diastereoisomeric excess (*de* 62%, determined by chiral GC-FID). The two product mixtures of **5a**/**5b** were then transformed separately by propargylic reduction to the corresponding allylic alcohols **1a**/**1b** using $LiAlH_4$ [15] as illustrated in Scheme 2. These allylic alcohol reductions gave exclusively the *E*-olefins. The relative stereochemistry of diastereoisomers **5a** and **5b** required to be assigned. This was achieved by preparing the dinitrobenzoyl esters **6** as illustrated in Scheme 3. The esters were crystalline and the relative stereochemistry of the major isomer **6a** derived from **5a** was determined by X-ray structure analysis (Scheme 3).

Dehydroxyfluorination reactions were then conducted on the product mixtures **1a**/**1b**, using the five fluorination reagents, and the resultant ratios of **2a**/**2b** and **3a**/**3b** are summarised in Scheme 4 and Table 1. All give very modest regio- and stereoselectivity. During the preparation of fluorosphingosine derivatives, De Jonghe et al. studied the fluorination of a similar motif [16] using DAST at −78 °C, also with modest selectivity. However in our case only a very low conversion was obtained at −78 °C with DAST, Deoxo-Fluor™ and TFEDMA and conversion was only moderately improved at 0 °C. Thus for these three reagents warmer reactions temperatures were necessary. Fluorination with PBSF reagent was found to be very unreactive, even after prolonged heating and the use of a large excess of reagent. Reaction of FLUOLEAD™ at 0 °C proved efficient in terms of conversion, but gave a similar product profile to the other more established reagents that were investigated.

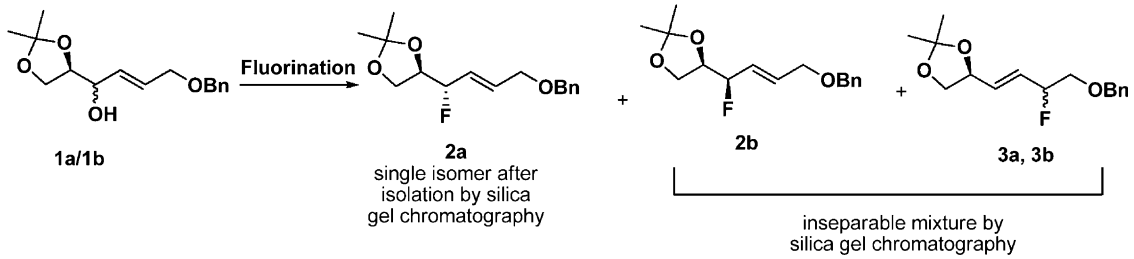
It is apparent that regioisomers **3** predominate over regioisomers **2** in all of these reactions. In the case of direct fluorination to give **2**, the major isomer is **2a** in all cases despite the stereochemical bias of both starting diastereoisomer mixtures of **1a**/**1b**. Consequently it is concluded that dehydroxyfluorination proceeds with a significant S_N1 type component to the reaction



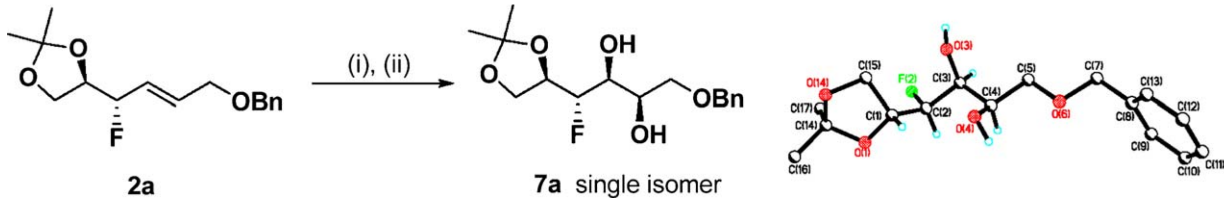
Scheme 2. Reagents and conditions: (i) benzyl propargyl ether, *n*-BuLi, THF, −78 °C, then **4**, 4 h, 81%; (ii) $LiAlH_4$, hexanes, reflux, 2 h, 45%; (iii) Benzyl propargyl ether, *n*-BuLi, $ClTi(Oi\text{-}Pr)_3$, THF, −78 °C, then **4**, 4 h, 82%; (iv) $LiAlH_4$, hexanes, reflux, 2 h, 55%.



Scheme 3. (a) Reagents and conditions: (i) 3,5-dinitrobenzoyl chloride, pyridine, 0 °C then RT, 16 h; (ii) crystallisation in absolute ethanol, 70%. (b) X-ray structure of **6a**.



Scheme 4. Fluorination of allylic alcohol **1a**/**1b** gave **2a** and the inseparable mixture of isomers **2b**/**3a**/**3b**.



Scheme 5. Synthesis and X-ray structure of **7a**: (i) AD-mix-β, t-BuOH/H_2O, 0 °C then RT, 3 days; (ii) crystallisation from Et_2O, 37%.

pathway, with a bias for fluoride attack predominantly to one face of a reaction intermediate. The configuration of this predominant isomer was determined after conducting a Sharpless dihydroxylation [17] reaction on **2a** to generate the crystalline derivative **7a** for X-ray structure analysis (Scheme 5). The X-ray structure clearly shows that there is an *anti* relationship between the C–F bond and the vicinal acetonide ether C–O bond in stereoisomer **2a**.

To complete the stereochemical analysis of this reaction the diastereoisomer preference for the allylic substituted products **3a**/**3b** was explored. TFEDMA reaction on **1a** (*de* 75%) resulted in a diastereoisomeric ratio of 1:0.7 (determined by ^{19}F NMR) for **3a**:**3b** with a slight bias in favour of the *syn* diastereoisomer **3b**. The stereochemistry of **3b** was again determined after Sharpless dihydroxylation of an inseparable mixture of **2b**/**3a**/**3b**. Silica gel chromatography purified a 1:0.7 diastereoisomeric mixture of diols favouring **8b** [18]. These stereoisomers were converted directly to their corresponding cyclic sulfates [19] **9a** and **9b** (Scheme 6) and diastereoisomers **9a** and **9b** were successfully separated by flash chromatography. The minor isomer **9a** was crystallised and the corresponding X-ray derived structure is illustrated in Scheme 6. By inference the major isomer formed in the allylic fluorination reaction of **1a** (*de* 75%) is therefore **3b**.

The diastereofacial preference exhibited by reacting these dehydroxyfluorinating reagents (Table 1) with **1a** and **1b** is

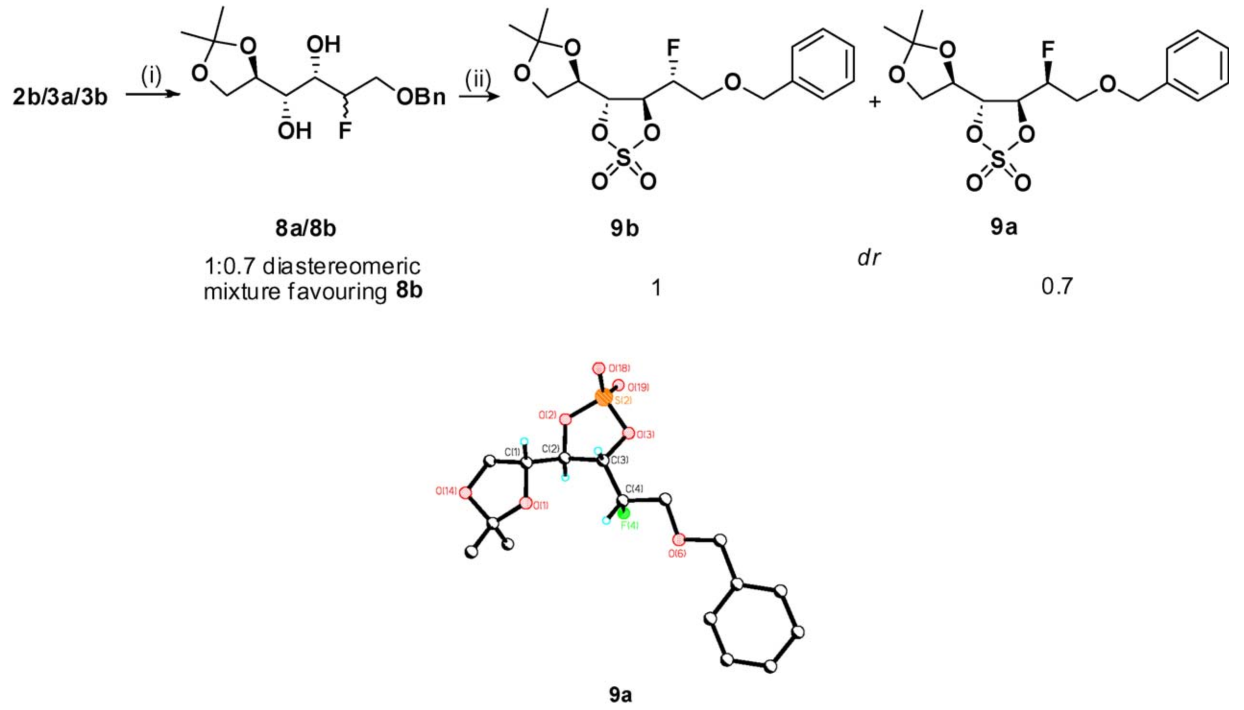
Table 1
Influence of the dehydroxyfluorinating agent on direct or allylic fluorination of **1a**/**1b** in DCM as a solvent.

Fluorinating agent	Temp. (time)	Major allylic alcohol substrate, *de* (%)	Ratio[a], **2a**/**2b**/**3a**/**3b**	Yield (%)[b]	
				(**2a**)	(**2b**,**3a**,**3b**)
TFEDMA	RT (1 h)	**1a**, 75%	2.0/1.0/2.9/4.2	11	44
DAST	RT (4.5 h)	**1a**, 75%	1.5/1.0/2.2/2.7	11	45
Deoxo-Fluor™	55 °C (3.5 h)	**1a**, 75%	1.2/1.0/1.7/3.7	9	48
TFEDMA	RT (1 h)	**1b**, 17%	2.5/1.0/3.7/3.9	13	46
DAST	RT (4.5 h)	**1b**, 17%	1.5/1.0/2.1/2.2	12	44
Deoxo-Fluor™	55 °C (3.5 h)	**1b**, 17%	1.5/1.0/2.6/2.7	10	44
FLUOLEAD™	0 °C (40 min)[c]	**1a**/**1b** *dr* 1:1	1.9/1.0/2.6/2.8	ND[c]	ND[c]

[a] Ratio in the crude mixture determined by ^{19}F NMR spectroscopy.

[b] Determined after two rounds of chromatography.

[c] Not determined. Product ratios determined by ^{19}F NMR only, although the conversion was high.



Scheme 6. Reagents and conditions: (i) AD-mix-β, t-BuOH/H_2O, 0 °C then RT, 3 days, 60%; (ii) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C, 30 min, then $SOCl_2$, pyridine, DCM, 0 °C, 2.5 h, 61%. X-ray structure establishes the absolute configuration of **9a** and by inference both **3a** and **3b**.

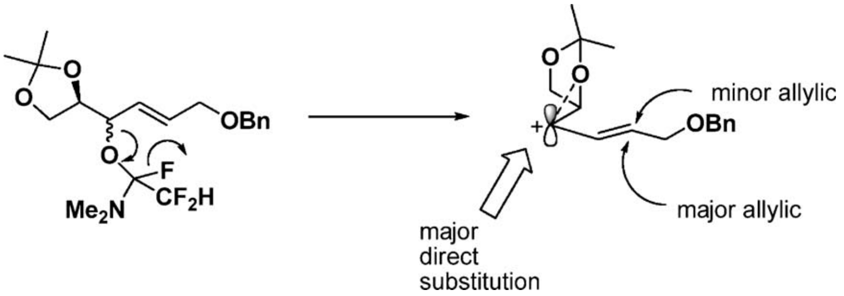


Fig. 1. Fluorination of **1a**/**1b** generates a carbocation intermediate (shown for TFEDMA) which is stabilised both by the allylic double bond and the adjacent ether oxygen, which shields one face of the carbocation from fluoride ion attack.

consistent with a significant S_N1 component to the reaction mechanism. Presumably a combination of steric and electronic effects associated with the acetonide and its proximate ether oxygen influences facial attack to an intermediate carbocation as illustrated in Fig. 1.

Allylic fluorination also showed a significant, but much reduced facial bias consistent with this mechanistic model. In conclusion we have explored a dehydroxyfluorination reaction on substrate **1a**/**1b** which is prone to both direct and allylic substitution. The particular case studied explored several fluorinating reagents. The stereochemical preference of both direct substitution by fluoride and allylic fluorination was explored by recourse to solving X-ray structures of appropriate product derivatives.

3. Experimental

3.1. General experimental procedures

All reagents were obtained from commercial sources and were used without further purification. Dry tetrahydrofuran, dichloromethane and hexane were obtained from the Solvent Purification System MB SPS-800. All moisture sensitive reactions were carried out under a positive pressure of N_2 using oven-dried glassware. Reaction temperatures below 0 °C were maintained using a bath-cooling apparatus LP Technology RP-100-CD. Thin layer chromatography (TLC) was performed using Macherey-Nagel Polygram Sil G/UV_{254} plastic plates; visualisation was achieved by inspection under UV light (255 nm) or by the staining with a solution of basic potassium permanganate or phosphomolybdic acid. Column chromatography was performed using silica gel 60 (40–63 μm) from Apollo Scientific Ltd. Low-resolution and high-resolution mass spectra were recorded using a Micromass GCT (time-of-flight), high performance, orthogonal acceleration spectrometer coupled to an Agilent Technologies 6890N GC system. Electrospray mass spectrometry (ESMS) was performed on a high performance orthogonal acceleration TOF mass spectrometer, coupled to a Waters 2975 HPLC. Only major peaks are reported and intensities are quoted as percentages of the base peak. NMR spectra were recorded on either a Bruker AV-300 or a Bruker AV-400 spectrometers. Samples were prepared in $CDCl_3$. For ^1H and ^{13}C NMR calibration was carried out on the residual solvent signal at 7.26 (^1H) and 77.16 (^{13}C). For ^{19}F NMR, $CFCl_3$ as an external reference was used. Optical rotations were measured using a Perkin-Elmer Model 341 polarimeter $[\alpha]_D$ values are determined at 589 nm and 25 °C and reported in $10^{-1} \times cm^2\,g^{-1}$. The measurement of diastereomeric excess was conducted by Chiral Gas Chromatography (FID) and ^{1}H NMR spectroscopy. Chiral GC column: Chiral Betadex^{TM}, Supelco, Beta Dex 225, fused silica capillary column, ($60 \times 0.25 \times 0.25$ μm film thickness).

3.2. (R)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (4)

Saturated aqueous $NaHCO_3$ (2 cm^3) was added to a stirred solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (3.3 g, 13 mmol) in CH_2Cl_2 (30 cm^3) while maintaining the temperature below 25 °C. Sodium metaperiodate (5.3 g, 25 mmol) was then added over a 20 min period with vigorous stirring and the reaction was allowed to proceed for 4 h while the temperature was maintained below 30 °C. The solution was then decanted from the solid and the remaining solid was stirred with additional CH_2Cl_2 (10 cm^3) for 5 min and it was again decanted from the solid. The CH_2Cl_2 solutions were combined and concentrated in vacuo and then distilled under reduced pressure (67–72 °C, 30 mmHg) giving **4** as a colourless oil (1.46 g, 67%).

$[\alpha]_D + 76.2^\circ$ (c 1.3, benzene), lit. [20] $[\alpha]_D + 73.1^\circ$ (c 1.3, benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 7.3 Hz, 4.8 Hz, 1.9 Hz, 1H), 4.10 (dd, *J* = 8.8, 7.3 Hz, 1H), 4.02 (dd, *J* = 8.8, 4.8 Hz, 1H), 1.41 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8 (CHO), 111.2 (C), 79.8 (CH), 65.5 (CH_2), 26.2 (CH_3), 25.1 (CH_3); MS (CI+) *m/z* 131.07 [M–Na]$^+$ (100); HRMS (CI+) $C_6H_{10}O_3H^+$ requires *m/z* 131.0708, found 131.0704.

3.3. (R)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (5b)

n-BuLi (1.6 M in *n*-hexane, 9.63 cm^3, 15.4 mmol) was added to a stirred solution of benzyl propargyl ether (2.27 cm^3, 15.4 mmol) in dry THF (19 cm^3) at −78 °C. After stirring at −78 °C for 1.5 h, a solution of **4** (1.0 g, 7.7 mmol) in THF (8 cm^3) was added dropwise to the mixture and the reaction stirred for 4 h at −78 °C. The reaction mixture was then poured into saturated aqueous NH_4Cl (50 cm^3) at −78 °C. Water (70 cm^3) was added and the reaction mixture was extracted with Et_2O (3× 110 cm^3). The Et_2O extract was successively washed with water and brine, then dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified over silica (9:1 hex:EtOAc → 3:1) to give the desired alcohol **5b** (1.723 g, 81%, *de* 9% determined by chiral GC-FID) as a clear oil.

Data for major diastereoisomer (**5b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 4.58 (s, 2H), 4.37 (dt, *J* = 8.8, 1.7 Hz, 1H), 4.28–3.86 (m, 5H), 2.70 (brs, OH), 1.46 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3 (C) 128.6 (CH), 128.2 (CH), 128.0 (CH), 110.6 (C), 83.9 (C), 82.3 (C), 78.7 (CH), 71.8 (CH), 66.2 (CH_2), 64.3 (CH), 57.4 (CH_2), 26.9 (CH_3), 25.3 (CH_3); MS (ESI, +ve) *m/z* 299.11 [M–Na]$^+$ (55), 259 [M–H–H_2O]$^+$ (100); HRMS (ES+) $C_{16}H_{20}O_4Na^+$ requires *m/z* 299.1260, found 299.1259.

3.4. (S)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol (5a)

n-BuLi (1.6 M in *n*-hexane, 13.88 cm^3, 22.2 mmol) was added dropwise to a solution of benzyl propargyl ether (3.27 cm^3, 22.2 mmol) in THF (21.0 cm^3) at −78 °C. After 30 min, Ti(O*i*-Pr)$_3$Cl (1 M in *n*-hexane, 41.0 cm^3, 22.2 mmol) was added and the flask warmed to −60 °C. To maintain solubility, additional THF (41 cm^3) was added and the solution was stirred for 90 min prior to re-cooling to −78 °C. Compound **4** (1.44 g, 11.1 mmol) was then added in one portion and the mixture stirred for 4 h prior to quenching with saturated NH_4Cl (70 cm^3) at −78 °C. Water (100 cm^3) was added and the reaction mixture was extracted with Et_2O (3× 150 cm^3). The product was purified over silica gel (9:1 hex:EtOAc → 3:1) to give the desired alcohol **5a** (2.52 g, 82%, *de* 9% determined by chiral GC-FID) as a clear oil.

Data for major diastereoisomer (**5a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 4.58 (s, 2H), 4.52 (dt, *J* = 4.4, 1.7 Hz, 1H), 4.28–3.86 (m, 5H), 2.56 (brs, OH), 1.47 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4 (C) 128.6 (CH), 128.2 (CH), 128.0 (CH), 110.3 (C), 83.9 (C), 82.4 (C), 77.9 (CH), 71.8 (CH), 65.4 (CH_2), 62.7 (CH), 57.4 (CH_2), 26.5 (CH_3), 25.2 (CH_3); MS (ESI, +ve) *m/z* 299.11 [M–Na]$^+$ (55), 259 [M–H–H_2O]$^+$ (100); HRMS (ES+) $C_{16}H_{20}O_4Na^+$ requires *m/z* 299.1260, found 299.1259.

3.5. (S)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ynyl 3,5-dinitrobenzoate (6a)

3,5-Dinitrobenzoyl chloride (0.482 g, 2.0 mmol) was added to a solution of **5a** (0.515 g, 1.8 mmol, *de* 62%) in dry pyridine (29 cm^3) at 0 °C. After stirring for 16 h at ambient temperature the reaction mixture was poured into ice water and extracted into Et_2O (3× 70 cm^3). The product was purified over silica gel (9:1 hex:EtOAc → 5:1) to give **6a** which was recrystallised from absolute ethanol (0.593 g, 70%).

mp 86–88 °C (from EtOH), $[\alpha]_D + 38.8^\circ$ (c 0.5, $CHCl_3$); ν_{max} (KBr plate)/cm^{-1} 2923, 1764, 1629, 1545, 1459, 1345, 1273, 1153, 1074, 721; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (t, 1H, *J* = 2.1 Hz), 9.21 (d, 2H, *J* = 2.1 Hz), 7.39–7.27 (m, 5H), 5.88–5.83 (m, 1H), 4.58 (s, 2H), 4.55–4.46 (m, 1H), 4.27–4.15 (m, 4H), 1.38 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 (C), 148.9 (C), 137.2 (C), 133.4 (C), 129.8 (CH), 128.7 (CH), 128.2 (CH), 122.9 (CH), 111.0 (C), 84.9 (C), 79.6 (C), 76.3 (CH), 72.1 (CH_2), 66.6 (CH), 65.6 (CH_2), 57.3 (CH_2), 26.5 (CH_3), 25.0 (CH_3); MS (ESI, +ve) *m/z* 493.06 [M–Na]$^+$ (100); HRMS (ESI, +ve) $C_{23}H_{22}N_2O_9Na^+$ requires *m/z* 493.1223, found 493.1218.

3.6. (R, E)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1, 3-dioxolan-4-yl) but-2-en-1-ol (1b)

A solution of **5b** (1.62 g, 5.86 mmol, *de* 9%) in *n*-hexane (6.5 cm^3) was added to a suspension of $LiAlH_4$ (0.3 g, 7.62 mmol) in *n*-hexane (13 cm^3) at 0 °C. The reaction mixture was heated under reflux for 2 h and was then quenched by dropwise addition of water (10 cm^3). The mixture was filtered and the resultant precipitate was washed with Et_2O (3× 75 cm^3). The combined organics were dried ($MgSO_4$) and the product purified over silica gel (9:1 hex:EtOAc → 3:1) to give alcohol **1b** (0.734 g, 45%, *de* 17% determined by chiral GC-FID) as a clear oil.

Data for major diastereoisomer (**1b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 5.98–5.89 (m, 1H), 5.78–5.67 (m, 1H), 4.51 (s, 2H), 4.33–4.27 (m, 1H), 4.13–4.07 (m, 1H), 4.05–4.02 (m, 2H), 3.99–3.87 (m, 2H), 2.25 (brs, OH), 1.45 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2 (C), 130.5 (CH), 130.4 (CH), 128.5 (CH), 127.8 (CH), 127.8 (CH), 110.0 (C), 78.8 (CH), 73.4 (CH), 72.4 (CH_2), 69.9 (CH_2), 66.0 (CH_2), 26.9 (CH_3), 25.4 (CH_3); MS (ESI, +ve) *m/z* 301.08 [M–Na]$^+$ (100); HRMS (ES+) $C_{16}H_{22}O_4Na^+$ requires *m/z* 301.1416, found 301.1421.

3.7. (S,E)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (1a)

A solution of **5a** (2.431 g, 8.79 mmol, *de* 62%) in *n*-hexane (10 cm^3) was added to a suspension of $LiAlH_4$ (0.450 g, 11.9 mmol) in *n*-hexane (20 cm^3) at 0 °C. The reaction mixture was heated under reflux for 2 h and was quenched by dropwise addition of water (15 cm^3). The mixture was filtered and the precipitate washed with Et_2O (3× 100 cm^3). The combined organics were dried ($MgSO_4$) and evaporated and the product purified over silica gel (9:1 hex:EtOAc → 3:1) to give alcohol **1a** (1.346 g, 55%, *de* 75%, determined by chiral GC-FID) as a clear oil.

Data for major diastereoisomer (**1a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 5.98–5.89 (m, 1H), 5.78–5.67 (m, 1H), 4.51 (s, 2H), 4.33–4.27 (m, 1H), 4.13–4.07 (m, 1H), 4.05–4.02 (m, 2H), 3.99–3.87 (m, 2H), 2.25 (brs, OH), 1.44 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2 (C), 130.4 (CH), 129.4 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 109.5 (C), 78.2 (CH), 71.3 (CH), 72.4 (CH_2), 70.1 (CH_2), 64.9 (CH_2), 26.5 (CH_3), 25.2 (CH_3); MS (ESI, +ve) *m*/*z* 301.08 [M–Na]$^+$ (100); HRMS (ES+) $C_{16}H_{22}O_4Na^+$ requires *m*/*z* 301.1416, found 301.1421.

3.8. (R)-4-((S,E)-4-(Benzyloxy)-1-fluorobut-2-enyl)-2,2-dimethyl-1,3-dioxolane (**2a**), (R)-4-((R,E)-4-(benzyloxy)-1-fluorobut-2-enyl)-2,2-dimethyl-1,3-dioxolane (**2b**), (S)-4-((R,E)-4-(benzyloxy)-3-fluorobut-1-enyl)-2,2-dimethyl-1,3-dioxolane (**3a**) and (S)-4-((S,E)-4-(benzyloxy)-3-fluorobut-1-enyl)-2,2-dimethyl-1,3-dioxolane (**3b**)

3.8.1. General procedure for the reaction of allylic alcohol **1a**/**1b** mixtures with TFEDMA

A solution of allylic alcohol **1a**/**1b** (5.0 mmol, 10 cm^3) in CH_2Cl_2 was added to a solution of TFEDMA (5.5 mmol, 10 cm^3) in CH_2Cl_2 at 0 °C in a polythene vessel. After addition the reaction mixture was brought to ambient temperature and stirred for 1 h and the progress of the reaction was monitored by TLC. The reaction was worked up by adding saturated $NaHCO_3$ solution and the product was extracted into CH_2Cl_2 (3× 150 cm^3). Purification by chromatography (6:1 hex:EtOAc → 3:1) gave **2a** and an inseparable mixture of isomers **2b**/**3a**/**3b**. Stereoisomer ratios and yields are given in Table 1.

3.8.2. General procedure for the reaction of allylic alcohol **1a**/**1b** mixtures with Deoxo-Fluor™

A solution of Deoxo-Fluor™ (7.5 mmol, 50%) in THF was added to a solution of **1a**/**1b** (5.0 mmol) in CH_2Cl_2 (20 cm^3) at 0 °C. After addition the reaction mixture was heated to 55 °C for 3.5 h and the progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to ambient temperature and was then worked up by adding saturated aqueous $NaHCO_3$ solution. The product was extracted into CH_2Cl_2 (3× 150 cm^3) and was purified by silica gel chromatography eluting with a hexane/ethyl acetate gradient (10:1 hex:EtOAc → 3:1). This gave **2a** and an inseparable mixture of isomers **2b**/**3a**/**3b**. Stereoisomer ratios and yields are given in Table 1.

3.8.3. General procedure for the reaction of allylic alcohol **1a**/**1b** mixtures with DAST™

DAST™ (neat, 7.5 mmol) was added to a solution of **1a**/**1b** (5.0 mmol) in dry CH_2Cl_2 (20 cm^3) at 0 °C. After addition the reaction mixture was brought to ambient temperature and stirred for 4.5 h and the progress of the reaction was monitored by TLC. The reaction was worked up by adding saturated aqueous $NaHCO_3$ solution and the product was extracted into CH_2Cl_2 (3× 150 cm^3) and purified by silica gel chromatography (hexane/ethyl acetate gradient (6:1 hex:EtOAc → 3:1). This gave **2a** and an inseparable mixture of isomers **2b**/**3a**/**3b**. Stereoisomer ratios and yields are given in Table 1.

3.8.4. General procedure for the reaction of allylic alcohol **1a**/**1b** mixtures with FLUOLEAD™

To a solution of FLUOLEAD™ (1.2 mmol in 2.2 cm^3 of dry CH_2Cl_2) in a polyethylene vessel at 0 °C was added a solution of allylic alcohol **1a**/**1b** (1.1 mmol in 2.2 cm^3 of dry CH_2Cl_2). After addition the reaction mixture was stirred at 0 °C for 40 min. The progress of the reaction was monitored by TLC. The reaction mixture was worked up by slowly adding saturated aqueous $NaHCO_3$ solution and the crude product was extracted into CH_2Cl_2 (3× 20 cm^3). Evaporation of solvents in vacuo gave a product that was analysed directly by ^{19}F NMR spectroscopy. Stereoisomer ratios are given in Table 1.

Data for **2a**: $[\alpha]_D$–7.6° (c 1.0, $CHCl_3$), ν_{max} (KBr plate)/cm^{-1} 1215, 1115, 1071, 972; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.37–7.27 (m, 5H), 6.00 (m, 1H), 5.84 (m, 1H), 4.87 (dm, *J* = 47.9 Hz, 1H), 4.54 (s, 2H), 4.15 (m, 1H), 4.10–4.04 (m, 3H), 3.98 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 132.1 (d, *J* = 11.6 Hz, CH), 138.3 (C), 128.8 (CH), 128.1 (CH), 127.0 (d, *J* = 18.6 Hz, CH), 120.0 (CH), 109.9 (C), 91.9 (d. *J* = 173.0 Hz, CH), 76.9 (d, *J* = 27.7 Hz, CH), 72.8 (CH_2), 69.9 (CH_2), 65.8 (d. *J* = 4.2 Hz, CH_2), 26.8 (CH_3), 25.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –187.95 (dm, *J* = 47.9 Hz, 1F); ^{19}F {^{1}H dec} NMR (282 MHz, CDCl3) δ –187.95 (s, 1F); MS (ESI, +ve) *m*/*z* 303.07 [M–Na]$^+$ (100); HRMS (ESI, +ve) $C_{16}H_{21}FO_3Na^+$ requires *m*/*z* 303.1372, found 303.1378.

Data for inseparable mixture of isomers **2b**/**3a**/**3b**: ν_{max} (KBr plate)/cm^{-1} 1215, 1115, 1071, 972; ^{19}F NMR (282 MHz, $CDCl_3$) δ –183.48 (dm, 48.3 Hz, 1F), –183.87 (m, 1F), –184.63 (m, 1F); ^{19}F {^{1}H dec} NMR (282 MHz, $CDCl_3$) δ –183.48 (s, 1F), –183.87 (s, 1F), –184.63 (s, 1F); MS (ESI, +ve) *m*/*z* 303.04 [M–Na]$^+$ (100); HRMS (ESI, +ve) $C_{16}H_{21}FO_3Na^+$ requires *m*/*z* 303.1372, found 303.1375.

3.9. (1S,2S,3R)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-fluorobutane-2,3-diol (**7a**)

Methanesulfonamide (0.041 g, 0.43 mmol) was added to a solution of AD-mix-β (0.602 g) in *tert*-butyl-alcohol (2.3 cm^3) and water (2.3 cm^3). A solution of **2a** (0.120 g, 0.43 mmol) in *tert*-butyl-alcohol (2.3 cm^3) was then added and the resulting mixture was stirred at 0 °C for 1 h and then at ambient temperature for 3 days. Solid Na_2SO_3 (0.662 g) was added and the mixture stirred for 30 min. The product was then extracted into Et_2O (3× 20 cm^3) and the combined organic layers were washed with 2 M KOH (20 cm^3) and concentrated. The product was purified over silica gel (9:1 hex:EtOAc → 4:1) and **7a** was recrystallised from Et_2O (0.05 g, 37%).

mp 94–96 °C (from Et_2O); $[\alpha]_D$ +1.9° (c 0.6, $CHCl_3$), ν_{max} (KBr plate)/cm^{-1} 3456, 2727, 1700, 1265, 1225, 1161, 1138, 1115, 1054, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 4.58 (s, 2H), 4.57–4.44 (dm, *J* = 46.0 Hz, 1H), 4.44–4.37 (m, 1H), 4.14 (ddd, *J* = 8.7, 6.5, 6.2 Hz, 1H), 4.06 (ddd, *J* = 8.7, 5.5, 5.3 Hz, 1H), 4.03–3.95 (m, 1H), 3.90 (dddd, *J* = 11.2, 6.1, 4.7, 1.7 Hz, 1H), 3.65 (d, *J* = 5.3 Hz, 1H), 3.08 (d, *J* = 4.7 Hz, 1H), 2.88 (d, *J* = 5.9 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7 (C), 128.7 (CH), 128.1 (CH), 128.0 (CH), 110.2 (C), 91.2 (d, *J* = 176.8, CH), 74.3 (d, *J* = 27.3, CH), 73.8 (CH_2), 72.2 (CH_2), 71.6 (d, *J* = 23.3, CH), 68.4 (d, *J* = 5.4 Hz, CH), 65.9 (d. *J* = 4.7 Hz, CH_2), 26.5 (CH_3), 25.3 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ –198.37 (ddd, *J* = 46.0, 13.0, 11.2 Hz, 1F); ^{19}F {^{1}H dec} NMR (470 MHz, $CDCl_3$) δ –198.37 (s, 1F); MS (ESI, +ve) *m*/*z* 337.19 [M–Na]$^+$ (100); HRMS (ESI, +ve) $C_{16}H_{23}FO_5Na^+$ requires *m*/*z* 337.1427, found 337.1431.

3.10. (1S,2S,3R)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-fluorobutane-1,2-diol (**8b**)

The mixture of isomers **2b**/**3a**/**3b** (0.468 g, 1.7 mmol) was treated as described in Section 3.9 and the product was extracted into CH_2Cl_2 (3× 70 cm^3) and purified over silica gel eluting with hexane/ethyl acetate (9:1 hex:EtOAc → 3:1) to give the desired diols **8a**/**8b** as a 1:0.7 diastereomeric mixture (0.321 g, 60%) favouring **8b**.

3.11. (1R,2R,3S)-4-(Benzyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-fluorobutane [1,3,2] dioxolane 2,2-dioxide (**9b**) and (1R,2R,3S)-4-(benzyloxy)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-fluorobutane-[1,3,2] dioxolane 2,2-dioxide (**9a**)

$SOCl_2$ (0.125 cm^3, 1.7 mmol) was added to a solution of **8b** (0.447 g, 1.4 mmol, *dr* 1:0.7) in CH_2Cl_2 (65 cm^3) and pyridine (0.17 cm^3, 2.1 mmol) and the mixture was stirred at 0 °C for

30 min. Saturated $CuSO_4$ (aq) (35 cm^3) was then added and the product extracted into CH_2Cl_2 (3× 70 cm^3). The organics were dried ($MgSO_4$) and concentrated and then dissolved in CH_3CN (50 cm^3). The solution was cooled to 0 °C and then $NaIO_4$ (0.764 g, 3.5 mmol), $RuCl_3{\cdot}3H_2O$ (1 mol.%) and H_2O (35 cm^3) were added and the heterogeneous mixture was stirred vigorously at 0 °C for 3 h. Et_2O (140 cm^3) was then added and the organic layer was washed with 5% aqueous $NaHCO_3$ (50 cm^3) and dried ($MgSO_4$). The product was purified over silica gel (9:1 hex:EtOAc → 4:1) to give **9b** (0.322 g, 61%) as an oil and **9a** as a white crystalline solid (0.141 g, 27%).

Data for **9a**: mp 38–40 °C (from Et_2O); $[\alpha]_D$ +30.5 (c 0.63, $CHCl_3$), ν_{max} (KBr plate)/cm^{-1} 3090, 3066, 3033, 2990, 1881, 1812, 1734, 1606, 1396, 1261, 1213, 1061, 986, 953, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H), 5.07–4.76 (m, 3H), 4.62 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.8, 1H), 4.37 (m, 1H), 4.19 (dd, J = 9.6, 6.0 Hz, 1H), 4.07 (d, J = 9.6, 3.1 Hz, 1H), 3.89–3.67 (m, 2H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1 (C), 128.8 (CH), 128.4 (CH), 128.1 (CH), 111.3 (C), 88.1 (d, J = 184.3, CH), 82.7 (d, J = 18.7, CH), 79.5 (d, J = 5.4 Hz, CH), 74.8 (CH), 74.1 (CH_2), 67.1 (CH_2), 26.9 (CH_3), 24.9 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −206.85 (dddd, J = 45.8, 24.6, 18.2, 11.8 Hz, 1F; ^{19}F {^1H dec} NMR) (470 MHz, $CDCl_3$) δ −206.85 (s, 1F); MS (ESI, +ve) m/z 399.09 $[M{-}Na]^+$ (100); HRMS (ESI, +ve) $C_{16}H_{21}O_7FSNa^+$ requires m/z 399.0888, found 399.0886.

Data for **9b**: $[\alpha]_D$ +23.1 (c 1.9, $CHCl_3$), ν_{max} (KBr plate)/cm^{-1} 3090, 3066, 3033, 2990, 1881, 1812, 1734, 1606, 1396, 1261, 1213, 1061, 986, 953, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 5.16 (ddd, J = 11.0, 6.2, 4.0 Hz, 1H), 4.94 (ddt, J = 46.0 Hz, 6.2 Hz, 5.3, 4.1 Hz), 4.83–4.76 (m, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.9, 1H), 4.43 (ddd, J = 9.5, 6.2, 3.4 Hz, 1H), 4.18 (dd, J = 9.5, 6.2 Hz, 1H), 4.03 (dd, J = 9.5, 3.4 Hz, 1H), 3.84 (ddd, J = 18.0, 11.5, 4.1, 1H), 3.79 (ddd, J = 27.0, 11.5, 4.1, 1H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1 (C), 128.7 (CH), 128.3 (CH), 127.9 (CH), 111.2 (C), 89.0 (d, J = 179.6, CH), 81.1 (d, J = 4.1, CH), 80.2 (d, J = 29.0, CH), 74.0 (CH_2), 73.8 (CH), 67.1 (d, J = 22.6 Hz, CH_2), 66.4 (CH_2), 26.7 (CH_3), 24.9 (CH_3); ^{19}F NMR (470 MHz, $CDCl_3$) δ −198.42 (dddd, J = 46.0, 27.0, 18.0, 11.0 Hz, 1F); ^{19}F {^1H dec} NMR (470 MHz, $CDCl_3$) δ −198.42 (s, 1F); MS (ESI, +ve) m/z 399.11 $[M{-}Na]^+$ (100); HRMS (ESI, +ve) $C_{16}H_{21}O_7FSNa^+$ requires m/z 399.0888, found 399.0890.

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