Tetrahedron: *Asymmetry* 20 (2009) 910–920

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric de novo synthesis of fluorinated D-glucitol and D-mannitol analogues

Guy T. Giuffredi, Sophie Purser, Marcin Sawicki, Amber L. Thompson, Véronique Gouverneur *

Chemistry Research Laboratory, University of Oxford, Mansfield Road, OX1 3TA Oxford, UK

ARTICLE INFO

Article history:
Received 16 February 2009
Accepted 6 March 2009
Available online 1 April 2009

Dedicated to Professor George W. F. Fleet at the occasion of his 65th birthday

ABSTRACT

A highly efficient *anti*-S_E2' electrophilic fluorination of enantioenriched allylsilanes a subsequent dihydroxylation of the resulting allylic fluorides were used as key steps for the synthesis of three fluorinated carbohydrate analogues, 1,5-di-*O*-benzyl-2-deoxy-2-fluoro-D-glucitol, 2,6-di-*O*-benzyl-5-deoxy-5-fluoro-L-glucitol and 1,5-di-*O*-benzyl-2-deoxy-2-fluoro-D-mannitol. A new catalytic asymmetric route to 1-benzyloxy-4-trimethylsilyl-but-3-yn-2-ol, a common precursor to two advanced allylsilanes, is also described featuring a Noyori asymmetric transfer hydrogenation reaction.

1. Introduction

The chemical modification of carbohydrates is a well-established strategy to probe the origin of the specificity in recognition processes with proteins or nucleic acids. Fluorinated carbohydrates are important analogues since the fluorine substituents affect hydrogen-bonding interactions while maintaining key structural features of the parent compounds. Carbohydrate modifications involve the chemoselective replacement of hydroxyl groups or the endocyclic oxygen atom by fluorine substituents or CF_2 groups.[1] For example, fluorinated sialic acid derivatives have served as important mechanistic probes for kinetic and crystal structural studies of sialidases and sialyl transferases for elucidation of their catalytic mechanistic profile.[2] In more extreme sugar mimesis, more heavily fluorinated sugars with advantageous properties were studied.[3] The hexafluorinated glucose derivative 1-hydroxy-5-hydroxymethyl-2,2,3,3,4,4-hexafluorooxane was found to cross the erythrocyte membrane with a faster rate compared to D-glucose, due to enhanced specific binding to the transport protein.[3c,3d] For further experimentation in this field, complex fluorinated carbohydrate analogues resulting from multi-site chemical modifications may be required, rendering synthetic protocols based on the manipulation of natural sugars increasingly difficult to apply. Despite the fact that asymmetric de novo syntheses complement enzymatic approaches and offer the flexibility one might need for the preparation of more disguised fluorinated sugars, this strategy is not frequently used especially when the target structures feature the fluorine substituents on stereogenic centres.[3a,4] Previous investigations from this laboratory have shown that allylsilanes are suitable substrates for the introduction of fluorine on an allylic position.[5] The fluorodesilylation of various homochiral allylsilanes combined with key dihydroxylation events has offered synthetic routes to novel enantioenriched mono- and difluorinated cyclitols.[6] In these syntheses, the silyl group served the purpose of enhancing the reactivity of the alkene and of controlling the regio- and stereoselective installation of the fluorine substituents. With the long-term aim of preparing multi-site modified enantioenriched fluorinated sugar mimics, our primary objective was to validate the first asymmetric synthesis of fluorinated carbohydrates starting from allylsilanes. We selected fluorinated D-glucitol and D-mannitol analogues as our first targets and envisaged that these may be accessible from the appropriately functionalised acyclic allylsilanes (Fig. 1).

2. Results and discussion

Our retrosynthetic analysis to access **1** and **2** is based on the use of the enantioenriched isomeric *syn*- and *anti*-allylsilanes (2*R*,3*R*,4*E*)-**3** and (2*R*,3*S*,4*E*)-**3** for the stereocontrolled introduction of the allylic fluorine substituent (Scheme 1). Recently, we have reported that an efficient transfer of chirality from the silylated to the fluorinated stereocentre is observed upon electrophilic fluorination of structurally related racemic allylsilanes.[7] We therefore anticipated that synthetically useful stereocontrol will be observed upon fluorodesilylation of (2*R*,3*R*,4*E*)-**3** and (2*R*,3*S*,4*E*)-**3**, with the configuration of the newly formed fluorinated carbon programmed in line with an *anti*-S_E2' mechanism.[8] Dihydroxylation of the resulting allylic fluorides should lead to our targets. This retrosynthesis was also driven by the availability of robust synthetic routes to these advanced intermediates. Panek et al. have reported that the Ireland–Claisen [3,3]-sigmatropic rearrangement of optically active *Z*- and *E*-vinylsilanes led to structurally related *syn*-and *anti*-crotylsilanes, respectively, in high yields with an excellent

* Corresponding author.
E-mail address: veronique.gouverneur@chem.ox.ac.uk (V. Gouverneur).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.03.001

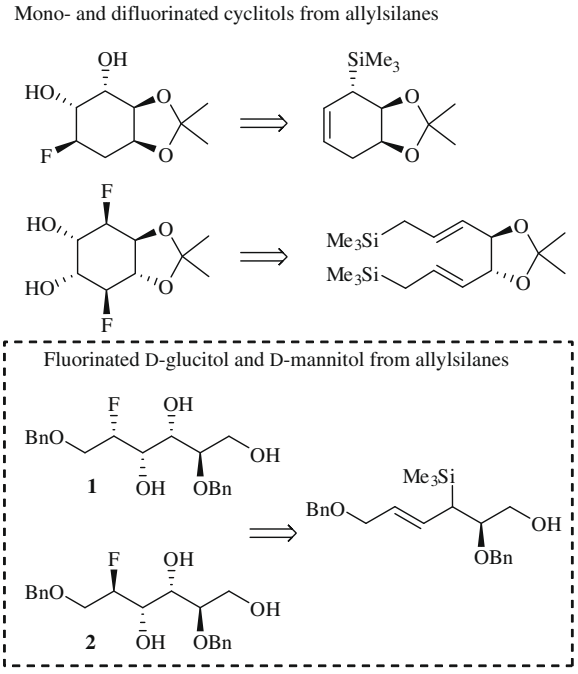
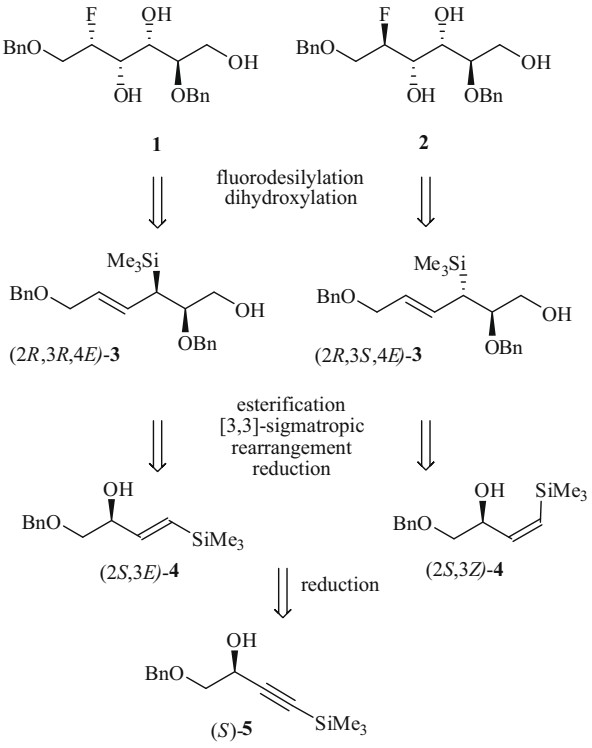


Figure 1. Fluorinated cyclitol and carbohydrate analogues from allylsilanes.

level of stereocontrol.[9] This work led us to consider the use of the vinylsilanes (2*S*,3*E*)-**4** and (2*S*,3*Z*)-**4** as precursors to *syn*-(2*R*,3*R*,4*E*)-**3** and *anti*-(2*R*,3*S*,4*E*)-**3**, respectively. Both vinylsilanes can be prepared from the propargylic alcohol (*S*)-**5**. Key aspects of the suggested de novo asymmetric synthesis are the development of an alternative catalytic asymmetric route for the preparation of (*S*)-**5** and the level and sense of stereocontrol for the fluorination and the dihydroxylation. The synthesis and reactivity

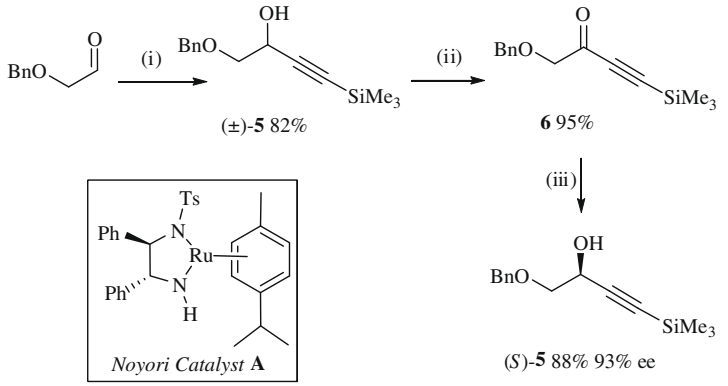


Scheme 1. Retrosynthetic analysis of **1** and **2**.

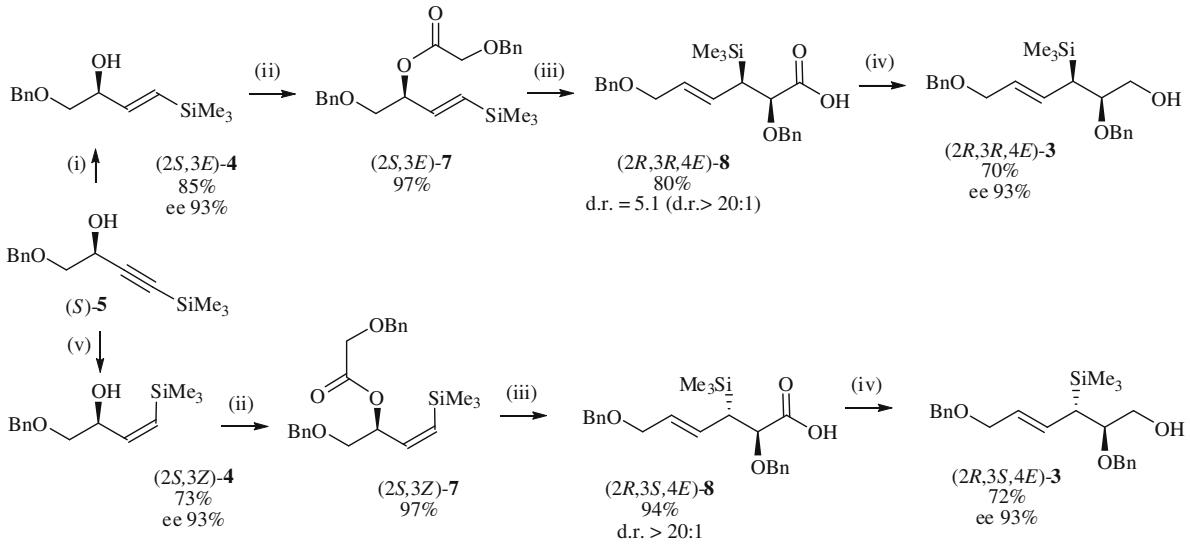
of enantioenriched allylsilanes (2*R*,3*R*,4*E*)-**3** and (2*R*,3*S*,4*E*)-**3** were not considered in our previous work.[7]

Our study began with the validation of an alternative route to access the silylated propargylic alcohol (*S*)-**5**, a common precursor to both allylic alcohols (2*S*,3*E*)-**4** and (2*S*,3*Z*)-**4** (Scheme 2).[9d,10] Based on the literature precedents,[11] we selected an asymmetric catalytic reduction of ynone **6** to install the stereogenic centre within (*S*)-**5**. Ynone **6** was obtained in 95% yield by oxidation of (±)-**5** using freshly prepared IBX. Deprotonation of trimethylsilylacetylene with *n*-BuLi in THF followed by addition of 2-(benzyloxy)acetaldehyde[12] afforded (±)-**5** in 82% yield. The reduction of ynone **6** was performed using a Noyori asymmetric transfer hydrogenation reaction in the presence of the chiral ruthenium catalyst **A**. This catalyst was prepared following the literature procedure.[13] It was used successfully in thoroughly degassed isopropyl alcohol to reduce **6**. This catalytic asymmetric transfer hydrogenation delivered the propargylic alcohol (*S*)-**5** in 83% yield and 93% ee. The enantiomeric excess was measured by chiral stationary phase HPLC against the racemic reference (±)-**5**. At this stage, the absolute configuration of compound (*S*)-**5** was assigned by analogy with the stereochemical outcome observed for the reduction of structurally related ynones using the same catalyst **A**.[11] This assignment was confirmed in the next stage of the synthesis by comparing the $[\alpha]_D^{20}$ value of the reduced allylic alcohol (2*S*,3*E*)-**4** {$[\alpha]_D^{25} = -4.3$ (*c* 1.1, $CHCl_3$)} with the literature data since this is a known compound {$[\alpha]_D^{25} = -1.9$ (*c* 1.1, $CHCl_3$)}.[14]

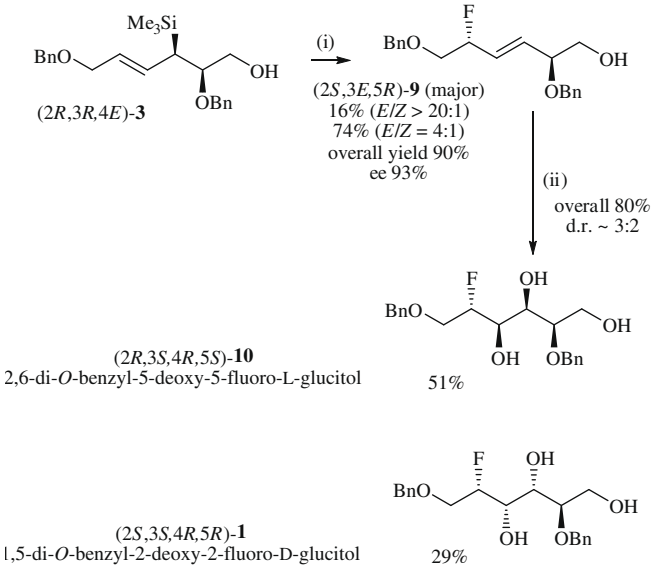
With (*S*)-**5** in hand, we studied its conversion into one or the other diastereomeric allylsilanes **3** (Scheme 3). To programme the desired stereochemistry of the fluorinated centre within targets **1** and **2**, it was necessary to access both the allylsilanes (2*R*,3*R*,4*E*)-**3** and (2*R*,3*S*,4*E*)-**3**, since the fluorodesilylation is expected to operate via an *anti*-S_E2' mechanism. These novel allylsilanes were prepared based on the literature protocols.[9a] The conversion of (*S*)-**5** into (2*R*,3*R*,4*E*)-**3** commenced with a sodium bis-(2-methoxyethoxy)aluminium hydride-mediated reduction leading to the allylic alcohol (2*S*,3*E*)-**4**, which was isolated in 85% yield. The enantiomeric excess of this compound was determined by the ^{19}F NMR of the corresponding Mosher ester and found to be 93%, a result indicating that no racemisation occurred upon reduction. Subsequent esterification with 2-benzyloxy acetic acid using DCC and DMAP delivered (2*S*,3*E*)-**7** in 97%. Treatment of this ester with LiHMDS and TMSCl provided the *Z*-*O*-silylketene acetal intermediate, the *Z* geometry being dictated by the strong chelating ability of the glycolate oxygen upon enolisation. Subsequent [3,3]-sigmatropic rearrangement of this in situ-formed *Z*-*O*-silylketene acetal afforded the hexenoic acid (2*R*,3*R*,4*E*)-**8** in 80% isolated yield. The diastereomeric ratio of the purified product is excellent (dr > 20:1). Analysis of the ^1H NMR of the crude mixture indicated the presence of a minor diastereomer (dr = 5:1). To access (2*R*,3*S*,4*E*)-**8**, we performed a similar esterification and Ireland–Claisen rearrangement with the *Z*-vinylsilane (2*S*,3*Z*)-**4**, a compound prepared in 73% yield by reduction with BH_3·THF and freshly distilled cyclohexene in THF (ee = 93%). Esterification and rearrangement using conditions similar to the ones applied to (2*S*,3*E*)-**4** were successful and high yielding steps. The acid (2*R*,3*S*,4*E*)-**8** was isolated in 94% yield as a single diastereomer (dr of crude and purified material was >20:1). The relative stereochemistry of both (2*R*,3*R*,4*E*)-**8** and (2*R*,3*S*,4*E*)-**8** was assigned by analogy with the literature based on the distinctive vicinal coupling constants $^3J_{2,3}$ ($^3J_{2,3}$ = 7.1 Hz for *syn*-(2*R*,3*R*,4*E*)-**8** and $^3J_{2,3}$ = 3.2 Hz for *anti*-(2*R*,3*S*,4*E*)-**8**). Reduction of (2*R*,3*R*,4*E*)-**8** and (2*R*,3*S*,4*E*)-**8** with $LiAlH_4$ in Et_2O afforded the alcohols (2*R*,3*R*,4*E*)-**3** and (2*R*,3*S*,4*E*)-**3** in good yields. The enantiomeric excesses of these allylsilanes **3** were found to be 93%.



Scheme 2. Reagents and conditions: (i) trimethylsilylacetylene, *n*-BuLi, THF, −78 °C then 0 °C; (ii) IBX, DMSO–THF (1:5), rt, 16 h; (iii) 8 mol % Catalyst **A**, *i*-PrOH, 30 °C, 16 h.



Scheme 3. Reagents and conditions: (i) sodium bis(2-methoxyethoxy)-aluminium hydride, Et_2O, 0 °C–rt, 16 h; (ii) benzyloxyacetic acid, DMAP, DCC, CH_2Cl_2, 0 °C–rt, 16 h; (iii) LiHMDS, THF, −78 °C, 1 h, then TMSCl, −78 °C–rt, 16 h; (iv) $LiAlH_4$, Et_2O, 0 °C, 3 h; (v) BH_3·THF complex, freshly distilled cyclohexene, THF, 0 °C, 3 h, then AcOH, 0 °C, 16 h.



Scheme 4. Reagents and conditions: (i) Selectfluor, $NaHCO_3$, MeCN, rt, 16 h; partial separation of the two stereoisomers by silica gel filtration (ii) OsO_4, NMO, CH_2Cl_2–H_2O 3:1, rt, **3 d**; separation by silica gel chromatography.

The next task was to perform the fluorodesilylation and subsequent dihydroxylation. First we focused our attention on the reactivity of (2*R*,3*R*,4*E*)-**3** (Scheme 4). The fluorination was performed at room temperature in acetonitrile with 1.5 equiv of 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) and with 1 equiv of $NaHCO_3$. The resulting *anti*-allylic fluoride **9** was isolated in 90% overall yield as a 4:1 mixture of *E*:*Z* isomers. Purification by short plug silica gel filtration delivered an analytically pure sample of the sole diastereoisomer (2*S*,3*E*,5*R*)-**9** (16% yield), which was used for the subsequent step. Dihydroxylation of (2*S*,3*E*,5*R*)-**9** was performed using 5 mol % OsO_4 with three equiv of the co-oxidant NMO in a 3:1 mixture of CH_2Cl_2 and H_2O. This oxidation delivered two diastereomers in a ~3:2 ratio indicating that the fluorine and the benzyloxy substituent are inducing an opposite sense of stereocontrol. Silica gel chromatography allowed for the separation of these two products that were isolated in 51% and 29% yields. We were able to unambiguously assign by X-ray crystallography followed by single crystal ^1H and ^{19}F NMR the relative stereochemistry of the major stereoisomer **10**, namely 2,6-di-*O*-benzyl-5-deoxy-5-fluoro-L-glucitol **10**. Esterification of the minor isomer (±)-**1** with *p*-nitrobenzoyl chloride gave compound (±)-**11**, which was found suitable for X-ray crystallography. This analysis confirmed that the minor diastereomer formed upon dihydroxylation is 2-deoxy-2-fluoro-D-glucitol doubly protected by benzyl groups at positions 1 and 5. It is

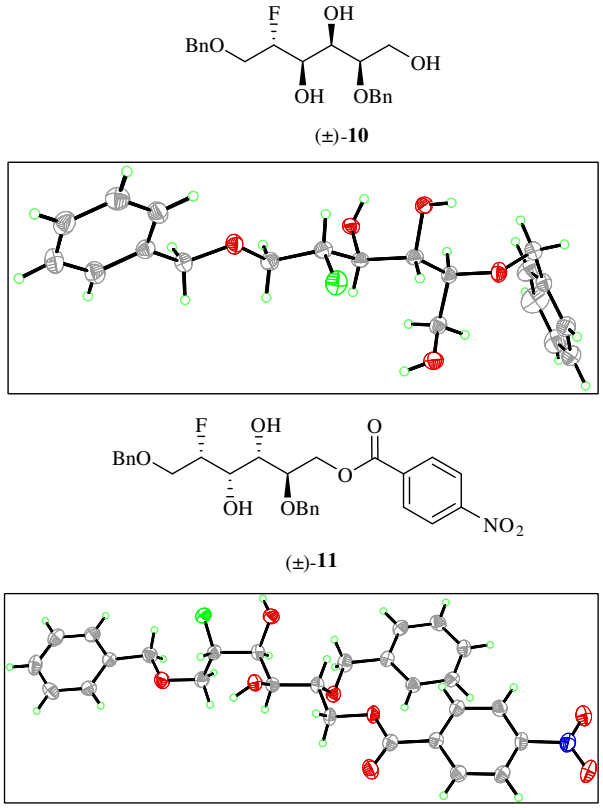


Figure 2. X-ray crystallography of (±)-**10** and (±)-**11**.

interesting to note that the compounds (±)-**10** and (±)-**11** adopt significantly different conformations in the solid state. Importantly, these data unambiguously demonstrate that the fluorodesilylation proceeded, as anticipated, with the approach of the electrophilic fluorinating reagent Selectfluor *anti* with respect to the silyl group (*anti*-S_E2' mechanism) (Fig. 2).

With the successful preparation of (2*S*,3*S*,4*R*,5*R*)-**1**, the fluorination and subsequent dihydroxylation of the allylsilane (2*R*,3*S*,4*E*)-**3** were next examined (Scheme 5). Upon fluorodesilylation using our standard conditions, the *syn*-allylic fluoride (2*S*,3*E*,5*S*)-**9** was formed in 83% yield. Two diastereomers were detected in the crude reaction mixture, the *E*-isomer being formed predominantly (*E*:*Z* ratio = 12:1). The dihydroxylation gave 1,5-di-*O*-benzyl-2-deoxy-2-fluoro-D-mannitol (2*R*,3*S*,4*R*,5*R*)-**2** in 96% yield (dr = 11:1). The excellent level of stereocontrol observed for the dihydroxylation of (2*S*,3*E*,5*S*)-**9** indicates that the two stereogenic centres of the *syn*-allylic fluoride (2*S*,3*E*,5*S*)-**9** both direct an *anti*-delivery of OsO_4. Although X-ray analysis was not possible for (2*R*,3*S*,4*R*,5*R*)-**2**, esterification of (±)-**2** with *p*-nitrobenzoyl chloride led to compound (±)-**12**, a crystal of which was found suitable for X-ray crystallography. This analysis confirmed unambiguously the structure and relative stereochemistry of (±)-**12** and, by default, of (2*R*,3*S*,4*R*,5*R*)-**2** (Fig. 3).

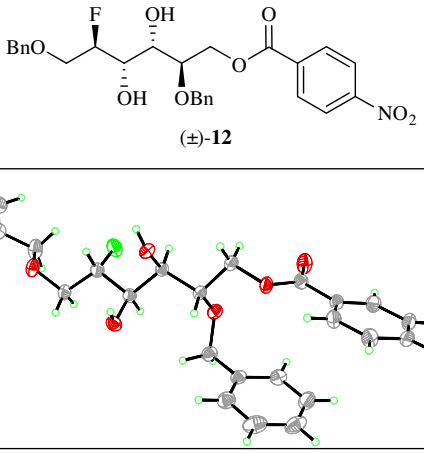
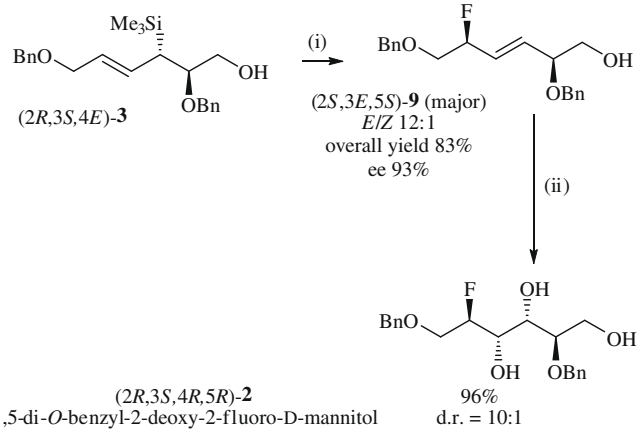


Figure 3. X-ray crystallography of ester (±)-**12**.



Scheme 5. Reagents and conditions: (i) Selectfluor, $NaHCO_3$, MeCN, rt, 16 h; (ii) OsO_4, NMO, CH_2Cl_2–H_2O 3:1, rt, **2 d**.

3. Conclusions

In conclusion, we have validated the first asymmetric de novo synthesis of three fluorinated carbohydrate analogues, 1,5-di-*O*-benzyl-2-deoxy-2-fluoro-D-glucitol **1**, 2,6-di-*O*-benzyl-5-deoxy-5-fluoro-L-glucitol **10**, and 1,5-di-*O*-benzyl-2-deoxy-2-fluoro-D-mannitol **2**. This work advances our understanding of the fluorodesilylation reaction since we have confirmed that the electrophilic fluorination of allylsilanes featuring a stereogenic silylated carbon operates with a stereochemical outcome in line with a stereoselective *anti*-S_E2' mechanism. This result is consistent with the sense of stereocontrol observed upon fluorination of allenylsilanes.[8] In addition, the work reported herein sets solid foundations for the synthesis of more complex fluorinated carbohydrates. The main advantage of our approach is its intrinsic flexibility since functional alterations are possible at several levels. Carboxylic acids other than 2-benzyloxy acetic acid may be used and processes other than dihydroxylations may allow for alternative functionalisations of the allylic fluorides.

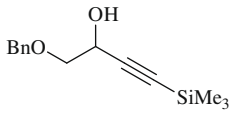
4. Experimental

4.1. General procedures

All ^1H NMR spectra were recorded in deuterated solvents using Bruker DPX200, DPX400, AV400 and AV500 spectrometers, calibrated using residual protonated solvents as an internal reference. ^{13}C NMR spectra were recorded in deuterated solvents using Bruker DPX400, AV400 and AV500 spectrometers with a carbon-13 cryoprobe. ^{19}F spectra (both with and without proton decoupling were recorded on a Bruker AVANCE AV400 spectrometer. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling

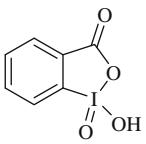
constants (J) are reported in units of hertz (Hz). The following abbreviations are used to describe multiplicities, s = singlet, d = doublet, t = triplet, q = quartet, br = broad m = multiplet. Low resolution mass spectra were recorded on Micromass GCT (CI) AutospecoaTof instruments. High resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTof spectrometer using positive electrospray ionisation (EI^+). 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 neat or in solution in $CHCl_3$ or CH_2Cl_2 on a Bruker Tensor 27 FTIR spectrometer. Absorptions are measured in wavenumbers (cm^{-1}) and only peaks of interest are reported. Melting points of solids were measured on a Griffin apparatus and are uncorrected. 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 F254 plates. Visualisations of the reaction components were achieved using UV fluorescence (254 nm) and $KMnO_4$ stain. Column chromatography was carried out over Merck Silica Gel C60 (40–60 μm).

4.2. 1-(Benzyloxy)-4-(trimethylsilyl)but-3-yn-2-ol (±)-5[15]



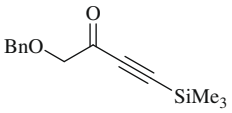
n-BuLi (130 mL of a 2.5 M solution in hexanes, 325 mmol) was added to a solution of trimethylsilylacetylene (39.5 mL, 280 mmol) in THF (450 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. A solution of freshly prepared 2-(benzyloxy)acetaldehyde (42.5 g, 280 mmol) in THF (110 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 5 min, then at 0 °C for 2 h. H_2O was added at 0 °C and the mixture was extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with brine (1 L), dried over $MgSO_4$ and the solvent was removed in vacuo. Purification by column chromatography (60–40 petrol ether–Et_2O, 60:40, R_f = 0.5) furnished the racemic propargylic alcohol (±)-**5** as a colourless oil (57.1 g, 230 mmol, 82% yield). ν_{max} (film) 3416 (br, O–H), 3064, 2959, 2864 (C–H), 2175 (C≡C); δ_H (400 MHz, $CDCl_3$) 0.20 (9H, s, $Si(CH_3)_3$), 3.57 (1H, dd, J 9.9, 7.6 Hz, CH_AOBn), 3.67 (1H, dd, J 9.9, 3.5 Hz, CH_BOBn), 4.58 (1H, dd, J 7.6, 3.4 Hz, $CHOH$), 4.59 (1H, d, J 12.3 Hz, CH_APh), 4.66 (1H, d, J 12.3 Hz, CH_BPh), 7.26–7.41 (5H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$) -0.2 ($Si(CH_3)_3$), 62.3 (CHOH), 73.4 (CH_2OBn), 73.5 (CH_2Ph), 90.6 ($CSi(CH_3)_3$), 102.9 ($CCHOH$), 127.6, 128.30, 128.7 (C_{Harom}), 137.6 (C_{arom}); m/z (ESI^+) 271.3 $[M+Na]^+$.

4.3. 2-Iodoxybenzoic acid[16]



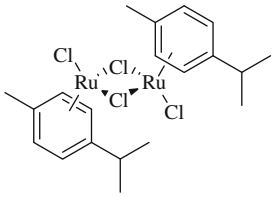
2-Iodobenzoic acid (50 g, 200 mmol) was added to a solution of oxone® (181 g, 290 mmol) in H_2O (650 mL) and the reaction mixture was mechanically stirred at 70 °C for 3 h. The suspension was cooled to 0 °C and stirred slowly for a further 1.5 h. The mixture was filtered, and the filtered was washed with cooled H_2O (500 mL) and acetone (200 mL) to furnish iodobenzoic acid (IBX) as a white solid (49.5 g, 177.4 mmol, 89% yield). Melting point was not recorded due to the explosive nature of the compound (lit.[17] 233 °C); ν_{max} (film) 1640 (C=O); δ_H (400 MHz, DMSO-d_6) 7.84 (1H, t, J 7.8 Hz, $CH(CH)_2$), 7.98 (1H, t, J 7.8 Hz, $CH(CH)_2$), 8.01 (1H, d, J 7.8 Hz, $CHCHC$), 8.15 (1H, d, J 7.8 Hz, $CHCHC$); δ_C (101 MHz, DMSO-d_6) 125.9, 131.0, 131.3, 132.3, 133.8, 147.4, 168.4; m/z (ESI^+) 263.2 $[M-OH]^-$.

4.4. 1-(Benzyloxy)-4-(trimethylsilyl)but-3-yn-2-one 6



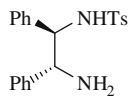
To a stirred solution of IBX (38 g, 136 mmol) in DMSO (180 mL), (±)-**5** (22.5 g, 90 mmol) in THF (900 mL) was added and the reaction mixture was stirred at room temperature for 16 h. H_2O (20 mL) was added and the resulting precipitate was filtered. The filtrate was extracted with EtOAc (3 × 300 mL) and the combined organics were washed with brine (600 mL), dried over $MgSO_4$ and the solvent was removed in vacuo at room temperature. Filtration through a short plug of silica gel (EtOAc) furnished **6** as a yellow oil (21.1 g, 86 mmol, 95% yield). ν_{max} (film) 3032 (C–H), 2152 (C≡C), 1737 (C=O); δ_H (400 MHz, $CDCl_3$): 0.25 (9H, s, $Si(CH_3)_3$), 4.24 (2H, s, CH_2OBn), 4.68 (2H, s, CH_2Ph), 7.30–7.48 (5H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$): −0.9 ($Si(CH_3)_3$), 73.4 (CH_2Ph), 74.7 (CH_2OBn), 101.3 ($CSi(CH_3)_3$), 102.6 (CCO), 128.0, 128.1, 128.5 (C_{Harom}), 137.0 (C_{arom}), 184.7 (CO); HRMS (ESI^+) $C_{14}H_{18}O_2Si^+$ ($[M+Na]^+$) requires 269.0968; found 269.0968.

4.5. Di-μ-chloro-bis[chloro(η^6–1-isopropyl-4-methylbenzene)ruthenium(II)][11]



A solution of ruthenium(III) chloride hydrate (5.0 g, 21.5 mmol) in EtOH (250 mL) was treated with α-phellandrene (25 mL) and heated at 120 °C for 4 h. The solution was cooled to room temperature and the solid filtered to furnish di-μ-chloro-bis[chloro(η^6-1-isopropyl-4-methyl-benzene)ruthenium(II) as a red-brown crystalline solid (4.5 g, 13.7 mmol, 64% yield). ν_{max} (film) 3050 (C–H); δ_H (400 MHz, $CDCl_3$): 1.28 (12H, d, J 7.0 Hz, $CH(CH_3)_2$), 2.16 (6H, s, CCH_3), 2.92 (2H, septet, J 7 Hz, $CH(CH_3)_2$), 5.34 (4H, d, J 6.3 Hz, $CHCCH_3$), 5.48 (4H, d, J 6.3 Hz, $CHCCH(CH_3)_2$); δ_C (101 MHz, $CDCl_3$): 18.9 (CCH_3), 22.1 ($CH(CH_3)_2$), 30.6 ($CH(CH_3)_2$), 80.3 ($CHCCH_3$), 81.4 ($CHCCH(CH_3)_2$), 96.7, 101.2 (C_{arom}); m/z (ESI^-) 576.93 $[M-Cl]^-$.

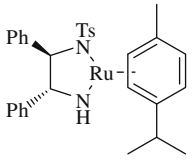
4.6. *N*-[(1*R*,2*R*)-2-Amino-1,2-diphenylethyl]methanesulfonamide[11]



Anhydrous NEt_3 (2.5 mL) was added to a solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (5.0 g, 24 mmol) in THF (190 mL) at 0 °C prior to the addition of a solution of *p*-TsCl (4.9 g, 26 mmol) in THF (50 mL) over 30 min at the same temperature. The mixture was stirred at 0 °C for 16 h. The solvent was removed in vacuo and satd $NaHCO_3$ (sat.) (200 mL) was added. The mixture was extracted

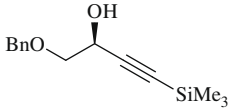
with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were washed with brine (400 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Purification by column chromatography (EtOAc, R_f = 0.4) furnished *N*-[(1*R*,2*R*)-2-amino-1,2-diphenylethyl]methanesulfonamide as a white solid (7.4 g, 20 mmol, 86% yield): MP 127–128 °C, (lit.[18] 125–126 °C); $[\alpha]_D^{25} = -17.4$ (*c* 1.3, $CHCl_3$), {lit.[18] $[\alpha]_D^{25} = -36.7$ (*c* 1.0, $CHCl_3$), other literature values vary considerably}; ν_{max} (film) 3365 (br, N–H), 2254 (C–H), 1601 (S=O); δ_H (400 MHz, $CDCl_3$): 2.33 (3H, s, CH_3), 4.14 (1H, d, *J* 5.2 Hz, C*H*NH_2), 4.39 (1H, d, *J* 5.2 Hz, C*H*NHTs), 6.98 (2H, d, *J* 8.2 Hz, *CH*CH_3), 7.09–7.25 (10H, m, H_{arom}), 7.32 (2H, d, *J* 8.2 Hz, $CHCSO_2$); δ_C (101 MHz, $CDCl_3$): 21.4 (CH_3), 60.5 ($CHNH_2$), 63.1 (CHNHTs), 126.5, 126.8, 127.0, 127.4, 127.5, 128.2, 128.4, 129.1 (C_{Harom}), 137.5, 139.2, 141.4, 142.5 (C_{arom}); MS *m/z* (ESI^+) 367.2 $[M+H]^+$.

4.7. (1*R*,2*R*)-(−)-*N*-Tosyl-1,2-diphenylethane-1,2-diamine[η^6-1-isopropyl-4-methylbenzene)-ruthenium(II)] A[11]



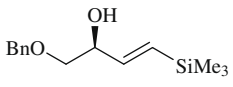
A mixture of di-μ-chloro-bis[chloro(η^6-1-isopropyl-4-methylbenzene)ruthenium(II) (1.8 g, 2.8 mmol), *N*-[(1*R*,2*R*)-2-amino-1,2-diphenylethyl]methanesulfonamide (2.0 g, 5.5 mmol) and KOH (2.3 g, 41 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 5 min. Then H_2O (30 mL) was added and the mixture was stirred until the colour changed from orange to deep purple. The organic layer was washed with H_2O, dried over CaH_2 and the solvent was removed in vacuo to furnish catalyst **A** as a deep purple solid (3.13 g, 5.2 mmol, 94% yield): δ_H (400 MHz, toluene-d_8) 1.09 (6H, d, *J* 7.0 Hz, CH(C*H*$_3$)$_2$), 1.89 (3H, s, TsCC*H*$_3$), 2.05 (3H, s, C*H*$_3$), 2.37 (1H, m, C*H*(CH$_3$)$_2$), 3.91 (1H, d, *J* 4.0 Hz, C*H*NH), 4.71 (1H, d, *J* 4.0 Hz, CHNTs), 4.94 (2H, d, *J* 5.0 Hz, RuCH), 5.22 (2H, d, *J* 5.0 Hz, RuCH), 6.42 (1H, br s, NH), 6.70 (2H, d, *J* 8.0 Hz, TsCH), 7.00–7.23 (10H, m, H_{arom}), 7.49 (2H, d, *J* 8.0 Hz, TsCH), *m/z* (ESI^+) 601.1 $[M+H]^+$.

4.8. (2*S*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-yn-2-ol (*S*)-5[15]



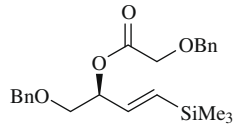
Catalyst **A** (3.00 g, 5.0 mmol) was added to a solution of **6** (14.8 g, 60 mmol) in degassed IPA (700 mL) and the reaction mixture was stirred at 30 °C for 16 h. The solvent was removed in vacuo. Purification by column chromatography (40–60 petrol ether–Et_2O, 80:20, R_f = 0.3) furnished (*S*)-**5** as a pale yellow oil (13.1 g, 53 mmol, 88% yield): 93% ee (Major 8.8 min, Minor 10.1 min, Chirapak AD, hexane–IPA 97:3, 207 nm, flow rate 1 mL/min. The ee has been confirmed by Mosher esterification); $[\alpha]_D^{25} = +3.9$ (*c* 1.0, CH_2Cl_2), {lit.[15] $[\alpha]_D^{30} = +7.3$ (*c* 1.0, $CHCl_3$), 93% ee}; all other data were identical to (±)-**5**.

4.9. (2*S*,3*E*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-en-2-ol-(−) (2*S*,3*E*)-4[14]



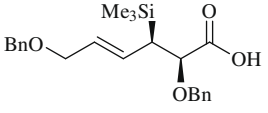
A solution of (*S*)-**5** (4.0 g, 16 mmol) in Et_2O (10 mL) was added to sodium bis-(2-methoxyethoxy)aluminium hydride (65% w/t in toluene, 9.0 mL, 28 mmol) in Et_2O (10 mL) at 0 °C, the reaction was allowed to warm to room temperature and the reaction mixture was stirred for 16 h. Then 1 M H_2SO_4 (32 mL) was added at 0 °C and the mixture was extracted with Et_2O (3 × 30 mL) and the combined organics were washed with brine, dried over $MgSO_4$ and the solvent was removed in vacuo to obtain pure product (2*S*,3*E*)-**4** as a pale yellow oil (3.4 g, 13.6 mmol, 85% yield, *E*:*Z* > 20:1): 93% *ee* (determined by Mosher esterification); $[\alpha]_D^{25} = -4.3$ (*c* 1.1, $CHCl_3$, {lit.[14] $[\alpha]_D^{25} = -1.9$ (*c* 1.1, $CHCl_3$)}; ν_{max} (film) 3440 (br, O–H), 3031, 2954, 2897 (C–H), 1621 (C=C); δ_H (400 MHz, $CDCl_3$) 0.08 (9H, s, Si(CH$_3$)$_3$), 2.49 (1H, s, OH), 3.36 (1H, dd, *J* 9.6, 8.5 Hz, CH_AOBn), 3.57 (1H, dd, *J* 9.6, 3.3 Hz, CH_BOBn), 4.33–4.39 (1H, m, C*H*OH), 4.59 (2H, s, CH_2Ph), 6.00–6.04 (2H, m, C*HCH*Si), 7.29–7.41 (5H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$) −1.4 (Si(CH$_3$)$_3$), 73.0 (CH_2OBn), 73.3 (CH_2Ph), 73.9 (CHOH), 127.8, 127.8, 128.5 (C_{Harom}), 131.7 (CHSi), 137.9 (C_{arom}), 143.5 (*C*HCOH), *m/z* (ESI^+) 268.2 $[M+NH_4]^+$, 309.2 $[M+CH_3CN+NH_4]^+$.

4.10. (2*S*,3*E*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-en-2-yl (benzyloxy)acetate (2*S*,3*E*)-7



To a solution of (2*S*,3*E*)-**4** (2.95 g, 11.8 mmol), 2-benzyloxy acetic acid (1.78 mL, 12.4 mmol) and DMAP (0.14 mg, 1.2 mmol) in CH_2Cl_2 (28 mL), was added a solution of DCC (2.5 g, 12.2 mmol,) in CH_2Cl_2 (10 mL) at 0 °C and the reaction left to warm to room temperature over 16 h with out removal of the cooling bath. The reaction mixture was filtered through a short pad of silica (hexane–EtOAc, 90:10) and furnished (2*S*,3*E*)-**7** as a pale yellow oil (4.56 g, 11.4 mmol, 97% yield): R_f = 0.4 (hexane–Et_2O 75:25); $[\alpha]_D^{21} = +21.3$ (*c* 1.1, CH_2Cl_2); ν_{max} (film) 3031, 2954, 2862 (C–H), 1757 (C=O), 1621 (C=C); δ_H (400 MHz, $CDCl_3$) 0.09 (9H, s, Si(CH$_3$)$_3$), 3.59 (1H, dd, *J* 10.9, 6.3 Hz, CH_AOBn), 3.62 (1H, dd, *J* 10.9, 4.6 Hz, CH_BOBn), 4.20 (2H, s, CH_2CO_2), 4.53 (1H, d, *J* 12.1 Hz, CH_APh), 4.61 (1H, d, *J* 12.1 Hz, CH_BPh), 4.67 (2H, s, CH_2Ph), 5.64 (1H, dddd, *J* 8.1, 6.3, 4.6, 1.8 Hz, CHOR), 5.61–5.98 (2H, m, C*HCH*Si), 7.21–7.41 (10H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$) −1.4 (Si(CH$_3$)$_3$), 67.2 (CH_2CO_2), 71.1 (CH_2OBn), 73.1 (CH_2Ph), 73.3 (CH_2Ph), 74.9 (CHOR), 127.6, 127.7, 128.0, 128.1, 128.4, 128.5 (C_{Harom}), 133.9 (CHSi), 137.2, 137.9 (C_{arom}), 139.6 (*C*HCOR), 169.7 (CO_2); HRMS (ESI^+) $C_{23}H_{30}O_4Si^+$ ($[M+Na]^+$) requires 421.1806; found 421.1807.

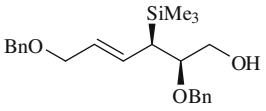
4.11. (2*R*,3*R*,4*E*)-2,6-Bis(benzyloxy)-3-(trimethylsilyl)hex-4-enoic acid (2*R*,3*R*,4*E*)-8



At first, LiHMDS 1 M in THF (20 mL, 20 mmol) was added dropwise to a solution of (2*S*,3*E*)-**7** (4.4 g, 11 mmol) in THF (110 mL) at −78 °C and the reaction mixture was stirred for 1 h. Chlorotrimethylsilane (2.1 mL, 17 mmol) was added dropwise and the reaction left to warm to room temperature over 16 h without removing the cooling bath. 10% HCl (50 mL) was added at 0 °C and the mixture extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and the solvent was removed in vacuo to afford a crude mixture of 5:1 *E*/*Z*. Purification by column chromatography (CH_2Cl_2–MeOH, 90:10, R_f = 0.6) furnished (2*R*,3*R*,4*E*)-**8** as a pale yellow oil (3.5 g, 8.9 mmol, 80% yield; *E*/*Z* > 20:1): $[\alpha]_D^{21} = +15.0$ (*c* 1.0, CH_2Cl_2); ν_{max} (film) 3031, 2952 (C–H), 1720 (C=O); δ_H (400 MHz, CD_2Cl_2) 0.08

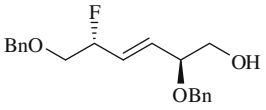
(9H, s, $Si(CH_3)_3$), 2.28 (1H, dd, *J* 9.9, 7.1 Hz, CHSi), 3.99 (1H, dd, *J* 12.6, 6.1 Hz, CH_AOBn), 4.03 (1H, dd, *J* 12.6, 5.6 Hz, CH_BOBn), 4.14 (1H, d, *J* 7.1 Hz, CHOBn), 4.49 (1H, d, *J* 11.1 Hz, $CHOCH_APh$), 4.50 (2H, s, CH_2OCH_2Ph), 4.68 (1H, d, *J* 11.1 Hz, $CHOCH_BPh$), 5.56 (1H, dt, *J* 15.4, 5.9 Hz, $CHCH_2OBn$), 5.67 (1H, dd, *J* 15.4, 9.9 Hz, *CH*CHSi), 7.29–7.41 (10H, m, H_{arom}), 8.57 (1H, br s, OH); δ_C (101 MHz, CD_2Cl_2) −1.7 ($Si(CH_3)_3$), 38.2 (CHSi), 71.0 (CH_2OBn), 71.7 (CH_2OCH_2Ph), 72.9 ($CHOCH_2Ph$), 80.5 (*C*HOBn), 127.4, 127.9, 128.2, 127.4, 128.7 (C_{Harom}), 128.7 (*C*HCHSi), 128.8 (C_{Harom}), 131.3 ($CHCH_2OBn$), 137.6 139.0 (C_{arom}), 176.9 (CO_2); HRMS (ESI^+) $C_{23}H_{30}O_4Si^+$ ([M+Na]$^+$) requires 421.1806; found 421.1807.

4.12. (2*R*,3*R*,4*E*)-2,6-Bis(benzyloxy)-3-(trimethylsilyl)hex-4-en-1-ol (2*R*,3*R*,4*E*)-3



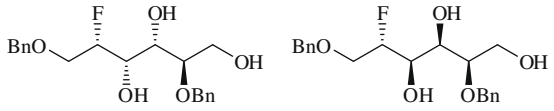
At first, $LiAlH_4$ (1.9 g, 40 mmol) in Et_2O (100 mL) was cooled to 0 °C and a solution of (2*R*,3*R*,4*E*)-**8** (3.2 g, 8 mmol) in Et_2O (100 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 3 h. Then NH_4Cl sat. (16 mL) was added. The resulting suspension was then dried over $MgSO_4$, filtered and the solvent removed in vacuo. Purification by column chromatography (40–60 petrol ether–Et_2O, 80:20, R_f = 0.1) furnished (2*R*,3*R*,4*E*)-**3** as a colourless oil (2.2 g, 5.6 mmol, 70% yield, *E*/*Z* > 20:1): $[\alpha]_D^{25} = -12.6$ (*c* 1.0, CH_2Cl_2); ν_{max} (film) 3425 (O-H), 3088, 3063, 3030, 2949 (C–H), 1656 (C=C); δ_H (400 MHz, $CDCl_3$) 0.07 (9H, s, $Si(CH_3)_3$), 2.26 (1H, dd, *J* 10.0, 6.9 Hz, CHSi), 2.38 (1H, br s, OH), 3.66–3.73 (2H, m, *CH*OBn, CH_AOH), 3.74–3.81 (1H, m, CH_BOH), 4.03 (2H, d, *J* 5.4, CH_2OBn), 4.51 (2H, s, CH_2OCH_2Ph), 4.55 (1H, d, *J* 11.2 Hz, $CHOCH_APh$), 4.61 (1H, d, *J* 11.2 Hz, $CHOCH_BPh$), 5.55 (1H, dt, *J* 15.2, 6.3 Hz, $CHCH_2OBn$), 5.65 (1H, dd, *J* 15.2, 10.0 Hz, *CH*CHSi), 7.28–7.39 (10H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$) -1.6 ($Si(CH_3)_3$), 35.8 (CHSi), 62.7 (CH_2OH), 70.9 (CH_2OBn), 71.1 (CH_2OCH_2Ph), 71.5 ($CHOCH_2Ph$), 80.8 (CHOBn), 126.9 (*C*HCHSi), 127.6, 127.7, 127.8, 128.0, 128.4, 128.5 (C_{Harom}), 132.0 ($CHCH_2OBn$), 138.1, 138.4 (C_{arom}); HRMS (ESI^+) $C_{23}H_{32}O_3Si^+$ ([M+Na]$^+$) requires 407.2013; found 407.2010.

4.13. (2*S*,3*E*,5*R*)-2,6-Bis(benzyloxy)-5-fluorohex-3-en-1-ol (2*S*,3*E*,5*R*)-9



At first, (2*R*,3*R*,4*E*)-**3** (1.7 g, 4.4 mmol) and $NaHCO_3$ (0.36 g, 4.4 mmol) in acetonitrile (45 mL) were treated with Selectfluor (2.3 g, 6.6 mmol) and the reaction mixture was stirred at room temperature for 16 h. Et_2O (30 mL) was added and the mixture was filtered. The organic phases were washed with H_2O (30 mL), dried over $MgSO_4$ and the solvent was removed in vacuo to give crude products A and B in a 85:15 ratio. Short plug silica filtration (50:50 hexane–Et_2O, then 100% Et_2O, R_f = 0.1 (hexane–Et_2O 50:50)) furnished pure (2*S*,3*E*,5*R*)-**9** as a colourless oil (0.3 g, 0.8 mmol, 16% yield) and a 80:20 mixture of A and B (1.1 g, 3.3 mmol, 74%). $[\alpha]_D^{21} = -31.2$ (*c* 1.0, CH_2Cl_2); For the major *E* isomer ν_{max} (film) 3425 (O-H), 3088, 3063, 3031, 2866 (C–H), 1604 (C=C); δ_H (400 MHz, $CDCl_3$) 2.18 (1H, br s, OH), 3.56–3.68 (4H, m, CH_2OBn, CH_2OH), 3.97–4.05 (1H, m, CHOBn), 4.42 (1H, d, *J* 11.7 Hz, $CHOCH_APh$), 4.62 (2H, s, CH_2CH_2Ph), 4.62 (1H, d, *J* 11.9 Hz, $CHOCH_BPh$), 5.15 (1H, ddd, *J* 49, 5.3, 4.0 Hz, CHF), 5.80 (1H, ddm, *J* 15.8, 6.9 Hz, *CH*CHOBn), 5.90 (1H, dddm, *J* 15.8, 14.9, 5.4 Hz, *CH*CHF), 7.27–7.40 (10H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$) 65.1 (CH_2OH), 70.8 (CH_2OCH_2Ph), 71.9 (d, *J* 23 Hz, CH_2OBn), 73.5 ($CHOCH_2Ph$), 79.7 (CHOBn), 91.4 (d, *J* 172 Hz, CHF), 127.8, 127.9, 127.9, 128.5, 128.5 (C_{Harom}), 129.4 (d, *J* 19 Hz, *C*HCHF), 131.0 (d, *J* 11 Hz, *C*HCHOBn), 139.28, 139.40 (C_{arom}); δ_F (376 MHz, $CDCl_3$) −183.4 (dtd, *J* 48, 25, 14 Hz); HRMS (ESI^+) $C_{20}H_{23}FO_3^+$ ([M+Na]$^+$) requires 353.1523; found 353.1525.

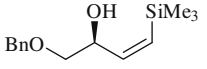
4.14. 1,5-Di-*O*-benzyl-2-deoxy-2-fluoro-D-glucitol (2*S*,3*S*,4*R*,5*R*)-1 and 2,6-di-*O*-benzyl-5-deoxy-5-fluoro-L-glucitol (2*R*,3*S*,4*R*,5*S*)-10



At first, (2*S*,3*E*,5*R*)-**9** (260 mg, 0.8 mmol) and NMO (280 mg, 2.4 mmol) in CH_2Cl_2 (6 mL) and H_2O (2 mL) were treated with OsO_4 (9 mg, 0.04 mmol) and the reaction mixture was stirred at room temperature for 3 days. Then Na_2SO_3 (0.2 g) was added and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was extracted with EtOAc (3 × 30 mL) and the combined organics were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed in vacuo to furnish (2*R*,3*S*,4*R*,5*S*)-**10** and (2*S*,3*S*,4*R*,5*R*)-**1** in a 60:40 ratio. Purification by column chromatography (40–60 petrol ether–EtOAc 50:50) gave an (2*R*,3*S*,4*R*,5*S*)-**10** as a pale yellow solid (145 mg, 0.4 mmol, 51%) and (2*S*,3*S*,4*R*,5*R*)-**1** as a white solid (82 mg, 0.2 mmol, 29%).

(2*R*,3*S*,4*R*,5*S*)-**10**: mp = 88–89 °C; $[\alpha]_D^{25} = -2.0$ (*c* 1.3, MeOH); ν_{max} ($CHCl_3$) 3283 (O-H); δ_H (400 MHz, MeOD) 3.64 (1H, dt, *J* 5.4, 4.6 Hz, CHOBn), 3.71–3.98 (6H, m, CH_2OBn, CH_2OH, 2 × *CH*OH), 4.59 (2H, s, CH_2OCH_2Ph), 4.66 (1H, d, *J* 11.5 Hz, $CHOCH_APh$), 4.67 (1H, dm, *J* 48 Hz, CHF), 4.74 (1H, d, *J* 11.5 Hz, $CHOCH_BPh$), 7.24–7.44 (10H, m, H_{arom}); δ_C (101 MHz, MeOD) 60.5 (CH_2OH), 68.5 (d, *J* 24 Hz, *C*HCF), 69.0 (d, *J* 3.3 Hz, *C*HCHOBn), 69.9 (d, *J* 20 Hz, CH_2OBn), 72.7 (CHOBn), 73,4 (CH_2OBn), 71.6 (CHOBn), 91.7 (d, *J* 175 Hz, CHF), 127.7, 127.7, 127.8, 128.1, 128.3, 128.4 (C_{Harom}), 138.5, 139.0 (C_{arom}); δ_F (376 MHz, MeOD) -194.4 (dtdd, *J* 48, 28, 5.7, 2.5 Hz); HRMS (ESI^+) $C_{20}H_{25}F_1O_5^+$ ([M+Na]$^+$) requires 387.1578; found 387.1577. (2*S*,3*S*,4*S*,5*R*)-**1**: R_f (40–60 petrol ether:EtOAc 50:50) = 0.25; mp = 58–60 °C; $[\alpha]_D^{25} = +2.6$ (*c* 0.4, MeOH); ν_{max} ($CHCl_3$) 3440 (O–H), 2935 (C–H); δ_H (400 MHz, MeOD) 3.63–3.68 (1H, m, CHOBn), 3.71–3.97 (5H, m, CH_2OBn, CH_2OH, *CH*CHOBn), 4.16 (1H, ddd, *J* 16.1, 6.8, 2.0 Hz, *CH*CHF), 4.53 (1H, d, *J* 11.8 Hz, CH_2OCH_APh), 4.59 (1H, d, *J* 11.8 Hz, CH_2OCH_BPh), 4.61 (1H, d, *J* 11.1 Hz, $CHOCH_APh$), 4.74 (1H, dddd, *J* 48, 6.6, 4.8, 2.8 Hz, CHF), 4.76 (1H, d, *J* 11.1 Hz, $CHOCH_BPh$), 7.23–7.42 (10H, m, H_{arom}); δ_C (101 MHz, MeOD) 61.0 (CH_2OH), 69.5 (d, *J* 22 Hz, CH_2OBn), 69.6 (d, *J* 29 Hz, *C*HCF), 69.6 (d, *J* 3.5 Hz, *C*HCHOBn), 72.6 (CHOBn), 73,5 (CH_2OBn), 71.6 (CHOBn), 94.7 (d, *J* 172 Hz, CHF), 127.6, 127.7, 127.9, 128.0, 128.3, 128.4 (C_{Harom}), 138.3, 139.0 (C_{arom}); δ_F (376 MHz, MeOD) −199.3 (dddd, *J* 48, 28, 24, 16 Hz); HRMS (ESI^+) $C_{20}H_{25}FO_5^+$ ([M+Na]$^+$) requires 387.1578; found 387.1582.

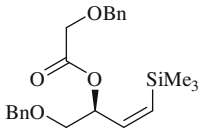
4.15. (2*S*,3*Z*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-en-2-ol (2*S*,3*Z*)-4



Freshly distilled cyclohexene (4.2 mL, 72 mmol) was added dropwise over 10 min to a solution of BH_3 (1 M in THF, 72 mL, 72 mmol) under argon at 0 °C. The reaction mixture was stirred for 1 h at 0 °C before the dropwise (15 min) addition of a solution of (*S*)-**5** (8.8 g, 36 mmol) in THF (36 mL). The reaction mixture was stirred at 0 °C until everything is dissolved and warmed to room

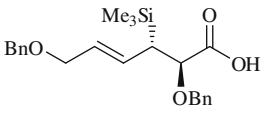
temperature. After 1 h at this temperature acetic acid (14.7 mL, 145 mmol) was added and the mixture stirred for 16 h. Et_2O (100 mL) and water (100 mL) were added and the aqueous phase was extracted with ether (3 × 100 mL). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Purification by column chromatography (hexane–EtOAc 80:20, R_f = 0.41) furnished (2*S*,3*Z*)-**4** as a colourless oil (6.6 g, 26 mmol, 73% yield, *E*/*Z* > 1:20, 93% ee (determined by Mosher esterification). $[\alpha]_D^{21} = +55.7$ (*c* 1.3, CH_2Cl_2), ν_{max} (film) 3433 (br, O–H), 3032, 2955, 2860 (C–H), 1613 (C=C); δ_H (400 MHz, $CDCl_3$): 0.14 (9H, s, $Si(CH_3)_3$), 3.40 (1H, dd, *J* 9.6, 8.4 Hz, CH_AOBn), 3.49 (1H, dd, *J* 9.6, 8.4 Hz, CH_BOBn), 4.49 (1H, tdd, *J* 8.3, 3.4, 0.8 Hz, *CH*OH), 4.57 (1H, d, *J* 12.0 Hz, CH_APh), 4.61 (1H, d, *J* 12.0 Hz, CH_BPh), 5.78 (1H, dd, *J* 14.4, 0.8 Hz, *CH*Si), 6.22 (1H, dd, *J* 14.4, 8.4 Hz, *CH*CHOH), 7.34 (5H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$): 0.3 ($Si(CH_3)_3$), 71.1 (CHOH), 73.4 (CH_2Ph), 73.9 (CH_2OBn), 127.8, 127.9, 128.5 (C_{Harom}), 134.2 (CHSi), 137.8 (C_{arom}), 145.1 (*CH*CHOH); HRMS (ESI^+) $C_{14}H_{22}O_2Si^+$ ($[M+Na]^+$) requires 273.1281; found 273.1281.

4.16. (2*S*,3*Z*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-en-2-yl (benzyloxy)acetate (2*S*,3*Z*)-7



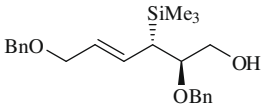
To a solution of (2*S*,3*Z*)-**4** (5.9 g, 23.5 mmol), 2-benzyloxy acetic acid (3.54 mL, 24.7 mmol) and DMAP (0.29 mg, 2.4 mmol) in CH_2Cl_2 (57 mL), was added a solution of DCC (5.0 g, 24.2 mmol) in CH_2Cl_2 (19 mL) at 0 °C and the reaction left to warm to room temperature over 16 h without removal of the cooling bath. The reaction mixture was filtered through a short pad of silica (hexane–EtOAc, 90:10) and furnished (2*S*,3*Z*)-**7** as a pale yellow oil (9.09 g, 22.7 mmol, 97% yield): R_f = 0.4 (hexane–Et_2O, 75:25); $[\alpha]_D^{21} = +21.3$ (*c* 1.1, CH_2Cl_2); ν_{max} (film) 3032, 2954, 2862 (C–H), 1755 (C=O), 1613 (C=C); δ_H (400 MHz, $CDCl_3$): 0.2 (9H, s, $Si(CH_3)_3$), 3.54 (1H, dd, *J* 10.8, 3.7 Hz, CH_AOBn), 3.61 (1H, dd, *J* 10.8, 7.4 Hz, CH_BOBn), 4.13 (2H, s, CH_2CO_2R), 4.55 (1H, d, *J* 12.2 Hz, CH_APh), 4.61 (1H, d, *J* 12.2 Hz, CH_BPh), 4.64 (2H, s, CH_2Ph), 5.77 (1H, dddd, *J* 9.1, 7.4, 3.7, 0.5 Hz, *CH*OR), 5.87 (1H, dd, *J* 14.4, 0.5 Hz, *CH*Si), 6.21 (1H, dd, *J* 14.4, 9.1 Hz, *CH*CHOH), 7.35 (10H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$): 0.0 ($Si(CH_3)_3$), 67.2 (CH_2CO_2R), 71.6 (CH_2OBn), 73.1 (CH_2Ph), 73.2 (CH_2Ph), 73.7 (CHOR), 73.4 (CH_2Ph), 127.7, 127.7, 128.0, 128.1, 128.4, 128.5 (C_{Harom}), 136.2 (CHSi), 137.2, 137.8 (C_{arom}), 141.0 (*CH*CHOR), 169.6 (CO_2R); HRMS (ESI^+) $C_{23}H_{30}O_4Si^+$ ($[M+Na]^+$) requires 421.1806; found 421.1787.

4.17. (2*R*,3*S*,4*E*)-2,6-Bis(benzyloxy)-3-(trimethylsilyl)hex-4-enoic acid (2*R*,3*S*,4*E*)-8



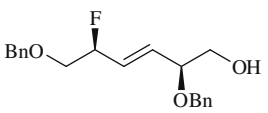
At first, (2*S*,3*Z*)-**7** (8.9 g, 22 mmol) in THF (220 mL) was cooled to −78 °C, then LiHMDS 1 M in THF (40 mL, 40 mmol) was added drop wise and the reaction mixture was stirred for 1 h at −78 °C. Chlorotrimethyl silane (4.3 mL, 34 mmol) was added drop wise and the reaction left to warm to room temperature over 16 h without removing the cooling bath. Then 10% HCl (100 mL) was added at 0 °C and the mixture was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Purification by column chromatography (CH_2Cl_2–MeOH, 90:10, R_f = 0.6) furnished (2*R*,3*S*,4*E*)-**8** as a pale yellow oil (8.4 g, 21 mmol, 94% yield): $[\alpha]_D^{21} = -11.3$ (*c* 1.0, CH_2Cl_2); ν_{max} (film) 3031, 2954, 2866 (C–H), 1746 (C=O), 1605 (C=C); δ_H (400 MHz, $CDCl_3$): 0.01 (9H, s, $Si(CH_3)_3$), 2.10 (1H, dd, *J* 10.7, 3.2 Hz, *CH*Si$(CH_3)_3$), 3.98 (1H, ddd, *J* 12.2, 6.7, 1.1 Hz, CH_AOBn), 4.01 (1H, ddd, *J* 12.2, 6.3, 1.1 Hz, CH_BOBn), 4.16 (1H, d, *J* 3.2 Hz, *CH*COOH), 4.30 (1H, d, *J* 11.1 Hz, $CHOCH_APh$), 4.46 (2H, s, CH_2OCH_2Ph), 4.69 (1H, d, *J* 11.1 Hz, $CHOCH_BPh$), 5.51 (1H, dt, *J* 15.5, 6.5 Hz, *CH*CH_2OBn), 5.85 (1H, dd, *J* 15.5, 10.7 Hz, *CH*CHCH_2OBn), 7.34 (10H, m, H_{arom}), 7.90 (1H, br s, COOH); δ_C (101 MHz, $CDCl_3$): −2.4 ($Si(CH_3)_3$), 38.2 (*CH*Si$(CH_3)_3$), 70.7 (CH_2OBn), 70.9 (CH_2OCH_2Ph), 72.7 ($CHOCH_2Ph$), 78.4 (*CH*OBn), 127.2 (*CH*CH_2OBn), 127.5, 127.9, 128.4, 128.5 (C_{Harom}), 130.6 (*CH*CHCH_2OBn), 137.1, 138.3 (C_{arom}), 176.9 (CO_2H); HRMS (ESI^+) $C_{23}H_{30}O_4Si^+$ ($[M+Na]^+$) requires 421.1806; found 421.1810.

4.18. (2*R*,3*S*,4*E*)-2,6-Bis(benzyloxy)-3-(trimethylsilyl)hex-4-en-1-ol (2*R*,3*S*,4*E*)-3



At first, $LiAlH_4$ (3.9, 100 mmol) in Et_2O (250 mL) was cooled to 0 °C and a solution of (2*R*,3*S*,4*E*)-**8** (8.2 g, 21 mmol) in Et_2O (250 mL) was added drop wise and the reaction mixture was stirred at 0 °C for 3 h. Then NH_4Cl sat. (40 mL) was added. The resulting suspension was then dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography (40–60 petrol ether–Et_2O, 80:20, R_f = 0.1) furnished (2*R*,3*S*,4*E*)-**3** as a colourless oil (5.9 g, 15 mmol, 72% yield): $[\alpha]_D^{21} = -22.1$ (*c* 1.0, CH_2Cl_2); ν_{max} (film) 3423 (O-H), 3063, 3030, 2951 (C–H), 1654 (C=C); δ_H (400 MHz, $CDCl_3$): 0.07 (9H, s, $Si(CH_3)_3$), 1.91 (1H, br s, OH), 1.98 (1H, dd, *J* 10.7, 3.8 Hz, *CH*Si$(CH_3)_3$), 3.73 (3H, m, CH_2OH, *CH*OBn), 4.03 (2H, d, *J* 6.3 Hz, CH_2OBn), 4.48 (1H, d, *J* 12.0 Hz, CH_2OCH_APh), 4.57 (1H, d, *J* 12.0 Hz, CH_2OCH_BPh), 4.60 (1H, d, *J* 11.1 Hz, $CHOCH_APh$), 4.67 (1H, d, *J* 11.1 Hz, $CHOCH_BPh$), 5.55 (1H, dt, *J* 15.4, 6.4 Hz, *CH*CH_2OBn), 5.84 (1H, ddt, *J* 15.4, 10.7, 1.1 Hz, *CH*CHCH_2OBn), 7.35 (10H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$): −2.0 ($Si(CH_3)_3$), 37.1 (*CH*Si$(CH_3)_3$), 64.3 (*CH*OBn), 71.1 (CH_2OBn), 71.5 ($CHOCH_2Ph$), 72.2 (CH_2OCH_2Ph), 80.1 (CHOH); 126.5 (*CH*CH_2OBn), 127.5, 127.6, 127.7, 127.8, 128.3, 128.4 (C_{Harom}), 132.3 (*CH*CHCH_2OBn), 138.5, 138.5 (C_{arom}); HRMS (ESI^+) $C_{23}H_{32}O_3Si^+$ ($[M+Na]^+$) requires 407.2013; found 407.2015.

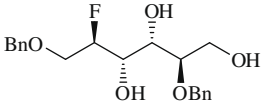
4.19. (2*S*,3*E*,5*S*)-2,6-Bis(benzyloxy)-5-fluorohex-3-en-1-ol (2*S*,3*E*,5*S*)-9



At first, (2*R*,3*S*,4*E*)-**3** (4.8 g, 12 mmol) and $NaHCO_3$ (1.05 g, 4.4 mmol) in acetonitrile (125 mL) were treated with Selectfluor (6.7 g, 19 mmol) and the reaction mixture was stirred at room temperature for 16 h. Then Et_2O (100 mL) was added and the mixture was filtered. The organic phases were washed with H_2O (100 mL), dried over $MgSO_4$ and the solvent was removed in vacuo. Short plug silica filtration (hexane–Et_2O, 50:50, R_f = 0.1 then 100% Et_2O) furnished pure (2*S*,3*E*,5*S*)-**9** as a colourless oil (3.5 g, 11 mmol, 83% yield, *E*:*Z* 12:1). $[\alpha]_D^{21} = -38.4$ (*c* 1.1, CH_2Cl_2); ν_{max} (film) 3440 (O-H), 3088, 3064, 3021, 2866 (C–H), 1605 (C=C); δ_H (400 MHz, $CDCl_3$) 2.10 (1H, br s, OH), 3.58 (1H, dd, *J* 11.6, 6.9 Hz, CH_AOH), 3.62 (1H, dd, *J* 11.6, 4.6 Hz, CH_AOH), 3.68 (2H, dd, *J* 23.3, 4.8 Hz, CH_2OBn), 4.02 (1H, dtm, *J* 7.0, 4.9 Hz, *CH*OBn), 4.43 (1H, d, *J* 11.7 Hz, $CHOCH_APh$), 4.61

(1H, d, *J* 12.5 Hz, CH_2OCH_APh), 4.64 (1H, d, *J* 12.5 Hz, CH_2OCH_BPh), 4.66 (1H, d, *J* 11.7 Hz, $CHOCH_BPh$), 5.15 (1H, ddt, *J* 48, 5.5, 4.8 Hz, CHF), 5.81 (1H, ddm, *J* 15.9, 7.2 Hz, *CH*CHOBn), 5.90 (1H, ddd, *J* 15.9, 13.9, 5.5 Hz, CHCF), 7.28–7.40 (10H, m, H_{arom}); δ_C (101 MHz, $CDCl_3$) 65.2 (d, *J* 1.5 Hz, COH), 70.8 ($CHOCH_2Ph$), 71.8 (d, *J* 22.8 Hz, CH_2OBn), 73.5 (CH_2OCH_2Ph), 91.4 (d, *J* 172 Hz, CHF), 127.8, 127.9, 127.9, 128.5, 128.5, 128.5 (C_{Harom}), 129.6 (d, *J* 19.2 Hz, *C*HCHF), 131.0 (d, *J* 10.3 Hz, *C*HCHOBn), 137.6, 137.9 (C_{arom}); δ_F (376 MHz, $CDCl_3$), −183.1 (dddd, *J* 48, 23.3, 13.9, 2.1 Hz); HRMS (ESI^+) $C_{20}H_{23}FO_3^+$ ([M+Na]$^+$) requires 353.1523; found 353.1525.

4.20. 1,5-Di-*O*-benzyl-2-deoxy-2-fluoro-D-mannitol (2*R*,3*S*,4*R*,5*R*)-2

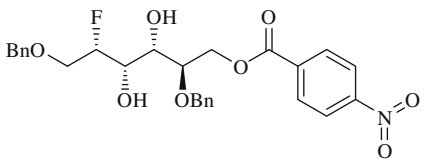


(2*S*,3*E*,5*S*)-**9** (2.0 g, 6 mmol) and NMO (2.1 g, 18 mmol) in CH_2Cl_2 (60 mL) and H_2O (20 mL) was treated with OsO_4 (76 mg, 0.3 mmol) and the reaction mixture was stirred at room temperature for 2 days. Na_2SO_3 (2 g) was added and the reaction mixture was stirred at room temperature for 30 min. The mixture was extracted with EtOAc (3 × 100 mL) and the combined organics were washed with brine (150 mL), dried over $MgSO_4$ and the solvent was removed in vacuo to furnish (2*R*,3*S*,4*R*,5*R*)-**2**. Purification by column chromatography (40–60 petrol ether–EtOAc, 50:50) furnished (2*R*,3*S*,4*R*,5*R*)-**2** as a pale white solid (2.1 g, 5.8 mmol, 96%, dr 11:1). Mp: 92–96 °C; $[\alpha]_D^{25} = +20.4$ (*c* 0.5, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3383 (O–H), 3089, 3064, 3032, 2934, 2872 (C–H); δ_H (400 MHz, MeOD) 3.59–3.65 (1H, m, CHOBn), 3.75–4.00 (5H, m, CH_2OBn, CH_2OH, *CH*OH), 4.10 (1H, dd, *J* 9.0, 0.9 Hz, *CH*CHF), 4.60 (2H, s, CH_2OCH_2Ph), 4.61 (1H, d, *J* 11.3 Hz, $CHOCH_APh$), 4.68 (1H, ddmd, *J* 48, 5.4, 2.1 Hz, CHF), 4.77 (1H, d, *J* 11.3 Hz, $CHOCH_BPh$), 7.22–7.41 (10H, m, H_{arom}); δ_C (101 MHz, MeOD) 61.1 (CH_2OH), 67.7 (d, *J* 25 Hz, *C*HCF), 68.3 (d, *J* 2.7 Hz, *C*HCHOBn), 70.1 (d, *J* 20 Hz, CH_2OBn, 72.60 (CHOBn), 73,5 (CH_2OBn), 79.6 (CHOBn), 91.6 (d, *J* 175 Hz, CHF), 127.6, 127.7, 127.8, 128.0, 128.3, 128.4 (C_{Harom}), 138.5, 139.0 (C_{arom}); δ_F (376 MHz, MeOD) −193.4 (dtdd, *J* 48, 28, 4.6, 2.5 Hz, F_{major}), −195.1 (dtt, *J* 48, 24, 21 Hz, F_{minor}); HRMS (ESI^+) $C_{20}H_{25}FO_5^+$ ([M+Na]$^+$) requires 387.1578; found 387.1578.

4.21. General procedure: esterification of primary alcohols

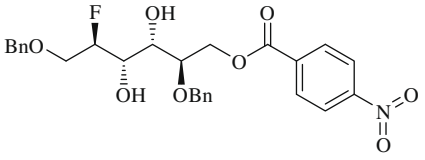
A solution of 4-nitrobenzoyl chloride (49 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of primary alcohol (70 mg, 0.27 mmol), triethylamine (0.16 ml, 1.3 mmol, 5 equiv) and DMAP (7 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. CH_2Cl_2 (2 mL) and NH_4Cl sat. (2 mL) was added and the organic layer was washed subsequently with sodium bicarbonate (2 mL of a saturated aqueous solution) and water (2 mL), dried over $MgSO_4$, filtered and the solvent removed in vacuo. Purification by column chromatography (hexane–EtOAc, 50:50) furnished the corresponding nitrobenzoic esters as white solids.

4.21.1. 1,5-Di-*O*-benzyl-2-deoxy-2-fluoro-6-*O*-(4-nitrobenzoyl)-glucitol (±)-11



R_f = 0.34 (hexane–EtOAc; 50:50); mp (crystal): 77–80 °C; ν_{max} (CH_2Cl_2) 3540 (O–H), 3055, 2984, 2953, 2864 (C–H), 1724 (C=O) 1532 (N=O); δ_H (400 MHz, $CDCl_3$) 2.87 (1H, br s, OH), 2.95 (1H, br s, OH), 3.78–3.87 (2H, m, CH_2OBn), 3.89–3.92 (2H, m, *CH*OH*CH*OBn), 4.20 (1H, dd, *J* 19.4, 4.9 Hz, *CH*OHCHF), 4.54 (1H, dm, *J* 11.9 Hz, CH_AOR), 4.56 (1H, d, *J* 11.8 Hz, CH_2OCH_APh), 4.62 (1H, d, *J* 11.8 Hz, CH_2OCH_BPh), 4.65 (1H, d, *J* 11.4 Hz, $CHOCH_APh$), 4.77 (1H, d, *J* 11.4 Hz, $CHOCH_BPh$), 4.80 (1H, ddt, *J* 47, 8.9, 4.1 Hz, CHF), 4.85 (1H, dm, *J* 11.9 Hz, CH_BOR), 7.27–7.35 (10H, m, H_{arom}), 8.15 (2H, d, *J* 9.0 Hz, H_{aromNO_2}), 8.25 (2H, d, *J* 9.0 Hz, H_{aromNO_2}); δ_C (101 MHz, $CDCl_3$): 64.2 (CH_2OR), 68.9 (d, *J* 20 Hz, *C*HCHF), 69.0 (d, *J* 23 Hz, CH_2OBn), 69.9 (d, *J* 3.6 Hz, *C*HCHOBn), 72.9 ($CHOCH_2Ph$), 73.8 (CH_2OCH_2Ph), 77.0 (CHOBn), 93.8 (d, *J* 174 Hz, CHF), 123.6 (H_{aromNO_2}), 127.7, 128.0, 128.0 128.1, 128.5, 128.5 (C_{Harom}), 130.7 (H_{aromNO_2}), 135.3 (H_{aromNO_2}), 137.2 137.5 (C_{arom}), 150.5 (CNO_2), 164.7 (CO_2); δ_F (376 MHz, $CDCl_3$) −200.0 (dddd, *J* 47, 25, 22, 19 Hz); HRMS (ESI^+) $C_{27}H_{28}FNO_8^+$ ([M+Na]$^+$) requires 536.1691; found 536.1694.

4.21.2. 1,5-Di-*O*-benzyl-2-deoxy-2-fluoro-6-*O*-(4-nitrobenzoyl)-mannitol (±)-12

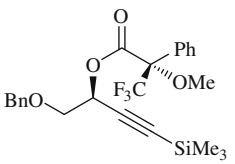


Dr 89: 11; R_f = 0.35 (hexane–EtOAc; 50:50); mp (crystal): 118–122 °C ν_{max} (CH_2Cl_2) 3550 (O-H), 3055, 2984, 2953, 2871 (C–H), 1727 (C=O) 1530 (N=O); δ_H (400 MHz, $CDCl_3$) 2.90 (2H, br s, OH), 3.72–3.98 (4H, m, CH_2OBn, *CHCH*OBn), 4.20 (1H, dd, *J* 8.0, 7.9 Hz, *CH*OHCHF), 4.57 (1H, dd, *J* 12.1 Hz, CH_AOR), 4.58 (1H, d, *J* 12.0 Hz, CH_2OCH_APh), 4.62 (1H, d, *J* 12.0 Hz, CH_2OCH_BPh), 4.63 (1H, d, *J* 11.6 Hz, $CHOCH_APh$), 4.68 (1H, ddt, *J* 47, 8.1, 4.1 Hz, CHF), 4.77 (1H, d, *J* 11.6 Hz, $CHOCH_BPh$), 4.82 (1H, dd, *J* 12.1, 2.9 Hz, CH_BOR), 7.27–7.35 (10H, m, H_{arom}), 8.16 (2H, d, *J* 9.0 Hz, H_{aromNO_2}), 8.26 (2H, d, *J* 9.0 Hz, H_{aromNO_2}); δ_C (101 MHz, $CDCl_3$): 64,2 (CH_2OR), 68.4 (d, *J* 3.6 Hz, *C*HCHOBn), 68.5 (d, *J* 25 Hz, *C*HCHF), 69.2 (d, *J* 22 Hz, CH_2OBn), 72.8 ($CHOCH_2Ph$), 73.8 (CH_2OCH_2Ph), 77.4 (CHOBn), 90.7 (d, *J* 175 Hz, CHF), 123.6 ($C_{HaromNO_2}$), 127.2, 128.0, 128.1 128.1, 128.5, 128.6 (C_{Harom}), 130.8 ($C_{HaromNO_2}$), 135.2 (C_{aromNO_2}), 137.4 137.4 (C_{arom}), 150.6 (CNO_2), 164.8 (CO_2); δ_F (376 MHz, $CDCl_3$) -194.3 (dddd, *J* 47, 28, 21, 7.9 Hz), -200.7 (dddd, *J* 47, 28, 20, 18 Hz); HRMS (ESI^+) $C_{27}H_{28}FNO_8^+$ ([M+Na]$^+$) requires 536.1691; found 536.1695.

4.22. General procedure: Mosher esterification

A solution of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (2.8 equiv) in DCM (0.5 mL) was added to a solution of alcohol (10 mg, 1 equiv), Et_3N (5 equiv) and catalytic DMAP (>1 mg) in DCM (0.8 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. Dichloromethane (2 mL) and NH_4Cl sat. (2 mL) were added and the organic layer was washed subsequently with $NaHCO_3$ sat. (2 mL) and water (2 mL), dried over $MgSO_4$, filtered and the solvent removed in vacuo to afford analytically pure Mosher esters.

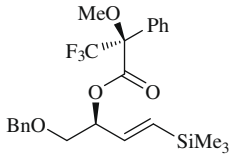
4.22.1. (2*S*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-yn-2-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



Dr 96.5: 3.5; R_f = 0.64 (hexane–EtOAc; 80:20); $[\alpha]_D^{25} = +40.2$ (*c* 1.0, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3065, 3032, 2953, 2857 (C–H), 1742

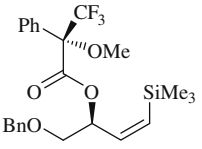
(C=O), 2171 (C≡C); δ_H (400 MHz, $CDCl_3$) 0.18 (9H, s, $Si(CH_3)_3$), 3.61 (3H, s, OCH_3), 3.67–3.74 (2H, m, CH_2OBn), 4.45 (1H, d, *J* 11.9 Hz, CH_APh), 4.49 (1H, d, *J* 11.9 Hz, CH_BPh), 5.88 (1H, dd, *J* 7.7, 4.4 Hz, *C*HOR), 7.21–7.45 (8H, m, H_{arom}), 7.58 (2H, d, *J* 7.6 Hz, H_{arom}); δ_C (101 MHz, $CDCl_3$): 0.4 ($Si(CH_3)_3$), 55.5 (d, *J* 1.4 Hz, OCH_3), 65.3 (CHOR), 70.9 (*C*H_2OBn), 73.1 (*C*H_2Ph), 93.3 (CSi), 98.0 (*C*CHOR), 124.5 (q, *J* 289 Hz, CF_3), 127.8, 127.9, 128.1, 128.7, 128.8, 130.0 (C_{Harom}), 132.7, 137.9 (C_{arom}), 166.0 (CO_2); δ_F (376 MHz, $CDCl_3$) −71.2 (3.5%), −71.7 (96.5%); HRMS (ESI^+) $C_{24}H_{27}F_3O_4Si^+$ ([M+Na]$^+$) requires 487.1523; found 487.1520.

4.22.2. (2*S*,3*E*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-en-2-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



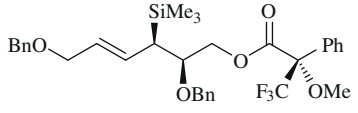
Dr 96.5: 3.5; R_f = 0.66 (hexane–EtOAc; 80:20); $[\alpha]_D^{25}$ = +46.3 (*c* 1.0, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3065, 3032, 2956, 2860 (C–H), 1750 (C=O), 1600 (C=C); δ_H (400 MHz, $CDCl_3$) 0.07 (9H, s, $Si(CH_3)_3$), 3.55 (3H, d, *J* 1.1 Hz, OCH_3), 3.57 (1H, d, *J* 3.4 Hz, CH_AOBn), 3.59 (1H, s, CH_BOBn), 4.45 (1H, d, *J* 11.9 Hz, CH_APh), 4.49 (1H, d, *J* 11.9 Hz, CH_BPh), 5.77–5.82 (1H, mdd, *J* 5.7, 0.7 Hz, CHOR), 5.99 (1H, dd, *J* 18.9, 5.7 Hz, *C*HCHOR), 6.10 (1H, dd, *J* 18.9, 0.7 Hz, CHSi) 7.22–7.41 (8H, m, H_{arom}), 7.56 (2H, d, *J* 7.5 Hz, H_{arom}); δ_C (101 MHz, $CDCl_3$) 1.6 ($Si(CH_3)_3$), 55.4 (OCH_3), 71.0 (*C*H_2OBn), 73.0 (*C*H_2Ph), 76.8 (CHOR), 123.2 (q, *J* 317 Hz, CF_3), 127.5, 127.6, 127.7, 128.3, 128.4, 129.5 (C_{Harom}), 132.3 (C_{arom}), 136.1 (CHSi), 137.8 (C_{arom}), 138.4 (*C*HCHOR), 165.8 (CO_2); δ_F (376 MHz, $CDCl_3$) −71.4 (3.5%), −71.5 (96.5%); HRMS (ESI^+) $C_{24}H_{29}F_3O_4Si^+$ ([M+Na]$^+$) requires 489.1679; found 489.1678.

4.22.3. (2*S*,3*Z*)-1-(Benzyloxy)-4-(trimethylsilyl)but-3-en-2-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



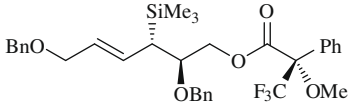
Dr 97.3:2.7; R_f = 0.66 (hexane–EtOAc; 80:20); $[\alpha]_D^{25}$ = +45.8 (*c* 1.1, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3065, 3032, 2954, 2852 (C–H), 1748 (C=O), 1604 (C=C); 0.21 (9H, s, $Si(CH_3)_3$), 3.50 (1H, dd, *J* 10.9, 3.4 Hz, CH_AOBn), 3.56 (3H, d, *J* 0.9 Hz, OCH_3), 3.56 (1H, dd, *J* 10.9, 8.0 Hz, CH_BOBn), 4.45 (1H, d, *J* 12.1 Hz, CH_APh), 4.50 (1H, d, *J* 12.1 Hz, CH_BPh), 5.93 (1H, d, *J* 14.4 Hz, CHSi), 5.96 (1H, ddd, *J* 9.7, 8.0, 3.4 Hz, CHOR), 6.22 (1H, dd, *J* 14.4, 9.7 Hz, *C*HCHOR), 7.21–7.42 (8H, m, H_{arom}), 7.56 (2H, d, *J* 7.7 Hz, H_{arom}); δ_C (101 MHz, $CDCl_3$) -0.1 ($Si(CH_3)_3$), 55.5 (OCH_3), 71.5 (*C*H_2OBn), 73.1 (*C*H_2Ph), 75.5 (CHOR), 123.4 (q, *J* 288 Hz, CF_3), 127.5, 127.5, 127.6, 128.2, 128.3, 129.5 (C_{Harom}), 132.4 (C_{arom}), 137.5 (CHSi), 137.7 (C_{arom}), 139.8 (*C*HCHOR), 165.6 (CO_2); δ_F (376 MHz, $CDCl_3$) −71.5 (2.7%), −71.7 (97.3%); HRMS (ESI^+) $C_{24}H_{29}F_3O_4Si^+$ ([M+Na]$^+$) requires 489.1679; found 489.1679.

4.22.4. (2*R*,3*R*,4*E*)-2,6-Bis(benzyloxy)-3-(trimethylsilyl)hex-4-en-1-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



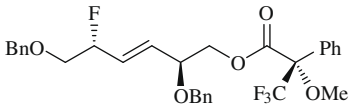
Dr 97:3; R_f = 0.55 (hexane–EtOAc; 80:20); $[\alpha]_D^{25}$ = +24.3 (*c* 1.0, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3065, 3032, 2952, 2851 (C–H), 1750 (C=O), 1656 (C=C); δ_H (400 MHz, $CDCl_3$) 0.09 (9H, s, $Si(CH_3)_3$), 2.03 (1H, dd, *J* 9.8, 8.5 Hz, CHSi), 3.52 (3H, d, *J* 1.0 Hz, OCH_3), 3.76 (1H, ddd, *J* 8.5, 5.4, 2.4 Hz, CHOBn), 4.25 (1H, dd, *J* 11.7, 5.3 Hz, CH_AOR), 4.37 (1H, d, *J* 10.9 Hz, CHOCH_BPh), 4.49 (2H, s, CH_2OCH_2Ph), 4.61 (1H, d, *J* 10.9 Hz, CHOCH_BPh), 4.80 (1H, dd, *J* 11.7, 2.6 Hz, CH_BOR), 5.30 (2H, s, CH_2OBn), 5.47 (1H, dt, *J* 15.4, 5.7 Hz, C*H*CH_2OBn), 5.56 (1H, dd, *J* 15.4, 9.8 Hz, *CH*CHSi), 7.21–7.41 (13H, m, H_{arom}), 7.55 (2H, d, *J* 7.4 Hz, H_{arom}); δ_C (101 MHz, $CDCl_3$); −1.5 ($Si(CH_3)_3$), 53.4 (CH_2OR) 55.5 (OCH_3), 66.6 ($CHOCH_2$Ph), 71.6, 71.9 (*C*H_2OCHPh), 78.6 (CHOBn), 122.7 (q, *J* 329 Hz, CF_3), 127.1 (CHSi), 127.4, 127.6, 127.6, 127.7, 128.0, 128.2, 128.4, 128.4, 129.6 (C_{Harom}), 131.6 (*C*HCH_2OBn), 132.2, 137.8, 138.4 (C_{arom}), 166.6 (CO_2); δ_F (376 MHz, $CDCl_3$) −71.4 (3.0%), −71.4 (97.0%); HRMS (ESI^+) $C_{33}H_{39}F_3O_5Si^+$ ([M+Na]$^+$) requires 623.2411; found 623.2399.

4.22.5. (2*R*,3*S*,4*E*)-2,6-Bis(benzyloxy)-3-(trimethylsilyl)hex-4-en-1-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



Dr 97.0:3.0; R_f = 0.55 (hexane–EtOAc; 80:20); $[\alpha]_D^{25}$ = +11.0 (*c* 0.7, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3065, 3032, 2953, 2851 (C–H), 1750 (C=O), 1655 (C=C); δ_H (400 MHz, $CDCl_3$) 0.09 (9H, s, $Si(CH_3)_3$), 1.79 (1H, dd, *J* 10.6, 2.8 Hz, CHSi), 3.53 (3H, d, *J* 0.9 Hz, OCH_3), 3.84 (1H, ddd, *J* 6.1, 5.3, 2.8 Hz, CHOBn), 4.25 (1H, ddd, *J* 12.3, 6.4, 1.0 Hz, CH_AOR), 4.02 (1H, ddd, *J* 12.3, 6.4, 1.0 Hz, CH_BOR), 4.37 (1H, dd, *J* 11.3, 5.8 Hz, CH_AOBn), 4.38 (1H, d, *J* 11.2 Hz, CHOCH_BPh), 4.46 (1H, dd, *J* 11.3, 5.3 Hz, CH_BOBn), 4.47 (1H, d, *J* 11.9 Hz, CH_2OCH_APh), 4.50 (1H, d, *J* 11.9 Hz, CH_2OCH_APh), 4.60 (1H, d, *J* 11.2 Hz, CHOCH_BPh), 5.47 (1H, dt, *J* 15.4, 6.4 Hz, C*H*CH_2OBn), 5.78 (1H, dd, *J* 15.4, 10.7 Hz, *CH*CHSi), 7.21–7.41 (13H, m, H_{arom}), 7.53 (2H, d, *J* 7.4 Hz, H_{arom}); δ_C (101 MHz, $CDCl_3$); -2.3 ($Si(CH_3)_3$), 55.5 (OCH_3), 68.6 (CH_2OR), 70.9 ($CHOCH_2$Ph), 71.4 (CH_2OCH_2Ph), 72.4 (*C*H_2OBn), 76.7 (CHOBn), 123.5 (q, *J* 289 Hz, CF_3), 127.3 (CHSi), 127.5, 127.5, 127.6, 127.7, 128.3, 128.4, 128.5, 128.6, 129.7 (C_{Harom}), 130.5 (*C*HCH_2OBn), 132.1, 138.1, 138.5 (C_{arom}), 166.4 (CO_2); δ_F (376 MHz, $CDCl_3$) −71.3 (97.0%), −71.3 (3.0%); HRMS (ESI^+) $C_{33}H_{39}F_3O_5Si^+$ ([M+Na]$^+$) requires 623.2411; found 623.2412.

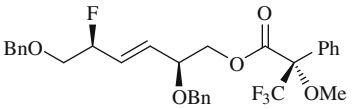
4.22.6. (2*S*,3*E*,5*R*)-2,6-Bis(benzyloxy)-5-fluorohex-3-en-1-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



Dr 96.0:4.0; R_f = 0.45 (hexane–EtOAc; 80:20); $[\alpha]_D^{25}$ = +16.0 (*c* 0.7, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3065, 3032, 2918, 2852 (C–H), 1751 (C=O), 1648 (C=C); δ_H (400 MHz, $CDCl_3$) 3.52 (3H, d, *J* 1.0 Hz, OCH_3), 3.58 (2H, dd, *J* 21.5, 5.8 Hz, *C*H_2OBn), 4.16–4.22 (1H, m, CHOBn), 4.35 (1H, dd, *J* 11.3, 4.4 Hz, CHOCH_APh), 4.36 (1H, dd, *J* 11.3, 7.9 Hz, CHOCH_BPh), 4.40 (1H, d, *J* 11.7 Hz, CH_AOR), 4.56 (1H, d, *J* 11.7 Hz, CH_BOR), 4.59 (1H, d, *J* 12.1 Hz, CH_2OCH_APh), 4.61 (1H, d, *J* 12.1 Hz, CH_2OCH_BPh), 5.12 (1H, ddt, *J* 48, 10.1, 5.6 Hz, CHF), 5.78 (1H, dddd, *J* 15.9, 6.6, 2.3, 1.2 Hz, *CH*CHOBn), 5.91 (1H, dddd, *J* 15.9, 14.7, 5.6, 1.1 Hz, *CH*CHF), 7.21–7.42 (13H, m, H_{arom}), 7.54 (2H, d, *J* 7.4 Hz, H_{arom}); δ_C (101 MHz, $CDCl_3$) 55.5 (d, *J* 1.5 Hz, OCH_3), 67.5 (d, *J* 1.5 Hz, $CHOCH_2$Ph), 71.0 (CH_2OR), 71.7 (d, *J* 23 Hz, CH_2OBn), 73.4 (CH_2OCH_2Ph), 76.3 (CHOBn), 91.2 (d, *J* 172 Hz, CHF), 123.1 (q, *J* 289 Hz, CF_3), 127.4, 127.6, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 129.6 (C_{Harom}), 129.7 (d, *J* 10.1 Hz,

*C*HCHOBn), 130.0 (d, *J* 22 Hz, *C*HCHF) 132.1, 137.6, 137.9 (C_{arom}), 166.4 (CO_2); δ_F (376 MHz, $CDCl_3$) −71.6 (96%, CF_3), −71.6 (4%, CF_3), −184.2 (dtdd, *J* 48, 24.1, 14.7, 2.3 Hz, CHF); HRMS (ESI^+) $C_{30}H_{30}F_4O_5^+$ ($[M+Na]^+$) requires 569.1922; found 569.1901.

4.22.7. (2*S*,3*E*,5*S*)-2,6-Bis(benzyloxy)-5-fluorohex-3-en-1-yl (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



Dr 96.5:3.5; R_f = 0.45 (hexane–EtOAc; 80:20); $[\alpha]_D^{25} = +12.9$ (*c* 0.9, CH_2Cl_2); ν_{max} (CH_2Cl_2) 3065, 3032, 2953, 2862 (C–H), 1751 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 3.52 (3H, d, *J* 1.0 Hz, OCH_3), 3.58 (2H, dd, *J* 23.8, 4.8 Hz, CH_2OBn), 4.14–4.22 (1H, m, CHOBn), 4.34 (1H, dd, *J* 11.4, 4.1 Hz, CHOCH_APh), 4.39 (1H, dd, *J* 11.4, 7.3 Hz, CHOCH_BPh), 4.40 (1H, d, *J* 11.7 Hz, CH_AOR), 4.57 (1H, d, *J* 11.7 Hz, CH_BOR), 4.58 (1H, d, *J* 12.1 Hz, CH_2OCH_APh), 4.62 (1H, d, *J* 12.1 Hz, CH_2OCH_BPh), 5.11 (1H, ddt, *J* 48, 9.7, 4.7 Hz, CHF), 5.77 (1H, dddd, *J* 15.8, 6.9, 2.3, 1.4 Hz, *C*HCHOBn), 5.90 (1H, dddd, *J* 15.8, 14.6, 5.5, 0.8 Hz, *C*HCHF), 7.22–7.42 (13H, m, H_{arom}), 7.54 (2H, d, *J* 7.4 Hz, H_{arom}); δ_C (101 MHz, $CDCl_3$) 55.5 (OCH_3), 67.5 (CHOCH_2Ph), 70.9 (CH_2OR), 71.7 (d, *J* 23 Hz, CH_2OBn), 73.5 (CH_2OCH_2Ph), 76.3 (CHOBn), 91.2 (d, *J* 174 Hz, CHF), 123.1 (q, *J* 289 Hz, CF_3), 127.4, 127.6, 127.7, 127.8, 127.9, 128.4, 128.4, 128.5, (C_{Harom}), 129.7 (d, *J* 10.5 Hz, *C*HCHOBn), 129.6 (C_{Harom}), 130.1 (d, *J* 20 Hz, *C*HCHF) 132.1, 137.6, 137.6 (C_{arom}), 166.4 (CO_2); δ_F (376 MHz, $CDCl_3$) −71.6 (96%, CF_3), −71.6 (4%, CF_3), −184.3 (dtd, *J* 48, 24.0, 14.8 Hz, CHF); HRMS (ESI^+) $C_{30}H_{30}F_4O_5^{+*}$ ($[M+Na]^+$) requires 569.1922; found 569.1919.

4.23. Single-crystal X-ray diffraction, compounds 1, 11 and 12

Crystals of 2,6-di-*O*-benzyl-5-deoxy-5-fluoro- glucitol **10** were grown by recrystallisation from EtOAc/hexane and a crystal having dimensions approximately 0.13 × 0.18 × 0.45 nm was used.

1,5-Di-*O*-benzyl-2-deoxy-2-fluoro-6-*O*-(4-nitrobenzoyl)-glucitol **11** were grown by recrystallisation from EtOAc/hexane and a crystal having dimensions approximately 0.16 × 0.32 × 0.35 nm was used.

1,5-Di-*O*-benzyl-2-deoxy-2-fluoro-6-*O*-(4-nitrobenzoyl)-mannitol **12** were grown by recrystallisation from EtOAc/hexane and a crystal having dimensions approximately 0.10 × 0.20 × 0.54 nm was used.

In all three cases, a typical single crystal was chosen and was mounted on a hair using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems Cryostream N2 open flow cooling device.[17] Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated Mo Kα radiation, λ = 0.71073 Å) to a maximum resolution of 0.77 Å. Intensity data were processed using the DENZO-SMN package and were corrected for absorption and other effects using SCALEPACK.[18]

The systematic absences in the intensity data were examined to determine the space group ($P2_1/n$ for **10** and **12** and $P2_1/c$ for **11**). In each case, the structure was solved using the direct-methods program SIR92,[19] which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS[20] program suite to refine coordinates and anisotropic thermal parameters of all non-hydrogen atoms (Figs. 2 and 3). Hydrogen atoms were located in the difference map and refined before being added to the model using a riding constraint. Crystallographic data (excluding structure factors) for all structures have been deposited with the Cambridge Crystallographic Data Centre (CCDC 721663–721665) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We thank the Berrow Foundation for a Scholarship to GTG, the EPSRC, AstraZeneca as well as the European Community (MRTN-CT-2003-505020) for generous financial support.

References

1. (a) Dax, K.; Albert, M.; Ortner, J.; Paul, B. *J. Carbohydr. Res.* **2000**, *327*, 47; (b) Deleuze, A.; Menozzi, C.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 6680.
2. (a) Chokhawala, H. A.; Cao, H.; Yu, H.; Chen, X. *J. Am. Chem. Soc.* **2007**, *129*, 10630; (b) Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Chem. Commun.* **1999**, 1525; (c) Watts, A. G.; Withers, S. G. *Can. J. Chem.* **2004**, *82*, 1581.
3. (a) Timofte, R. S.; Linclau, B. *Org. Lett.* **2008**, *10*, 3673; (b) Linclau, B.; Boydell, A. J.; Timofte, R. S.; Brown, K. J.; Vinader, V.; Weymouth-Wilson, A. C. *Org. Biomol. Chem.* **2009**, *7*, 803; (c) Kim, H. W.; Rossi, P.; Shoemaker, R. K.; DiMagno, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 9082; (d) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem* **2004**, *5*, 622.
4. (a) Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.* **2004**, *2*, 528; (b) Masuda, T.; Shibuya, S.; Arai, M.; Yoshida, S.; Tomozawa, T.; Ohno, A.; Yamashita, M.; Honda, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 669; (c) Davis, F. A.; Qi, H.; Sundarababu, G. *Tetrahedron* **2000**, *56*, 5303.
5. (a) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3219; (b) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26.
6. (a) Purser, S.; Odell, B.; Claridge, T. D. W.; Moore, P. R.; Gouverneur, V. *Chem. Eur. J.* **2006**, *12*, 9176; (b) Purser, S.; Claridge, T. D. W.; Odell, B.; Moore, P. R.; Gouverneur, V. *Org. Lett.* **2008**, *10*, 4263.
7. Sawicki, M.; Kwok, A.; Tredwell, M.; Gouverneur, V. *Beil. J. Org. Chem.* **2007**, *3*, 34.
8. Carroll, L.; McCullough, S.; Rees, T.; Claridge, T. D. W.; Gouverneur, V. *Org. Biomol. Chem.* **2008**, *6*, 1731.
9. (a) Sato, T.; Tsunekawa, H.; Kohama, H.; Fujisawa, T. *Chem. Lett.* **1986**, *15*, 1553; (b) Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431; (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293; (d) Masse, C. E.; Knight, B. S.; Stavropoulos, P.; Panek, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 6040.
10. (a) Panek, J. S.; Sparks, M. A. *Tetrahedron: Asymmetry* **1990**, *1*, 801; (b) Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, T. *J. Org. Chem.* **1990**, *55*, 5324.
11. Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219.
12. 45 g 2-(Benzyloxy)acetaldehyde was prepared following the procedure of: Early, W. G.; Jacobsen, J. E.; Madin, A.; Meier, G.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18046.
13. Haak, K.-J.; Hashiguchi, S.; Akio, F.; Ikariya, F.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285.
14. Masato, K.; Hiroshi, K.; Fumie, S. *Chem. Lett.* **1987**, 2163–2166.
15. Takano, S.; Setoh, M.; Yamada, O.; Ogasawara, K. *Synthesis* **1993**, 1253.
16. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
17. Cosier, J.; Glazer, A. M. *J. Appl. Crystallogr.* **1986**, *19*, 105.
18. Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode. In *Methods Enzymol.*; Carter, C. W., Sweet, R. M., Eds.; Academic Press, 1997; Vol. 276,.
19. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
20. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.