Tetrahedron 66 (2010) 3963–3972

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of difluorinated carbocyclic analogues of 5-deoxypentofuranoses and 1-amino-5-deoxypentofuranoses: en route to fluorinated carbanucleosides

Gaëlle Fourrière, Nathalie Van Hijfte, Jérôme Lalot, Guy Dutech, Bruno Fragnet, Gaël Coadou, Jean-Charles Quirion, Eric Leclerc *

Université et INSA de Rouen, CNRS, UMR 6014 C.O.B.R.A.–IRCOF, 1 rue Tesnière, 76821 Mont Saint-Aignan Cedex, France

ARTICLE INFO

Article history:
Received 17 November 2009
Received in revised form 25 February 2010
Accepted 22 March 2010
Available online 27 March 2010

Keywords:
Nucleosides
Carbasugars
Fluorine
Radical cyclization

ABSTRACT

The synthesis of difluorinated carbocyclic analogues of 5-deoxypentofuranoses and 1-amino-5-deoxypentofuranoses is described. The sequence involves an addition of $PhSeCF_2TMS$ to carbohydrate-derived aldehydes or their corresponding *tert*-butanesulfinylimines followed by a radical cyclization. Optimized conditions for the $PhSeCF_2TMS$ addition to α-chiral aldehydes have been disclosed and its unusual diastereoselectivity is discussed. Application of the sequence using Ellman's auxiliary allows a more direct access to 1-aminopentose analogues with a complete control of the pseudo-anomeric center configuration.

1. Introduction

Although being a long-standing strategy, the development of new nucleoside analogues is still a productive approach for the development of antitumoral or antiviral agents. Indeed, these agents may act as inhibitors of various enzymes involved in the cell or viral replication processes. Depending on their degree of phosphorylation, inhibition of thymidilate synthetase, ribonucleotide reductase or DNA polymerases may occur, these nucleoside analogues acting either as competitive inhibitors or alternate substrates.[1] Analogues possessing a standard sugar backbone (X=O, Fig. 1) but including modifications either on the base or in the backbone substitutions gave rise to several powerful anticancer or antiviral drugs (5-fluorouracil, gemcitabine, azidothymidine, zalcitabine). On the other hand, carbocyclic nucleosides ($X=CH_2$, Fig. 1) have acquired in recent years a growing importance in this field, leading to the discovery of several lead compounds (entecavir, abacavir, aristeromycin).[2] Unfortunately, all these compounds may suffer from a lack of selectivity or bioavailability (and thus from a certain toxicity) and the need for new analogues with greater activities and/or lowered side effects has therefore increased.

The fluorination of various positions on the base or on the pentose backbone has been widely studied. 5-Fluorouracil (5-FU) or prodrugs delivering 5-FU (Floxuridine, Capecitabine,…) are, for example, widely used as antitumoral agents. The replacement of the hydroxy group in 2-position of the sugar backbone is also known to slow down the metabolic cleavage of the *N*-glycosidic bond and gave rise to efficient drugs (gemcitabine, clorofarabine).[3] However, the synthesis of CF_2-carbocyclic nucleosides **I**, in which the intracyclic oxygen atom is replaced by a CF_2 group, is only scarcely described and no general method for their preparation is provided (Scheme 1).[4,5] The strong electronegativity and the small size of the fluorine atoms

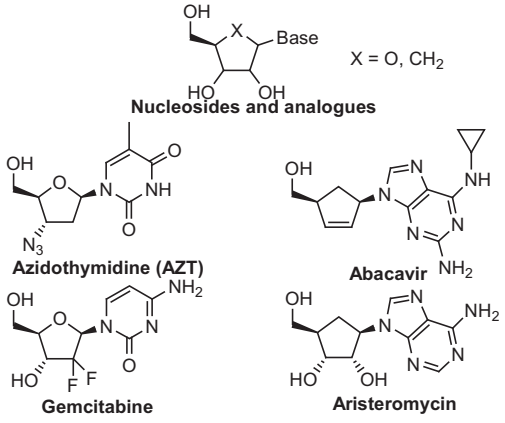

Figure 1. Nucleoside and carbanucleoside drugs.

* Corresponding author. Tel.: +33 235522901; e-mail address: eric.leclerc@insa-rouen.fr (E. Leclerc).

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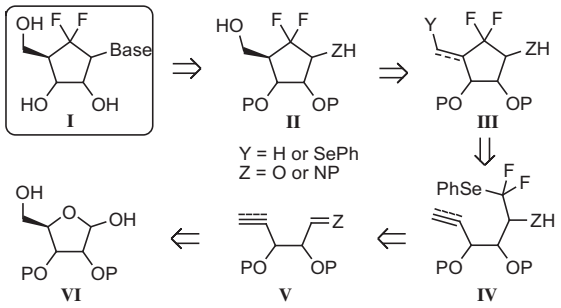
doi:10.1016/j.tet.2010.03.079

could however impart to these surrogates better mimicking abilities than an apolar CH_2 group.[3b] Our current interest in the synthesis of CF_2-glycosides prompted us to devise a synthetic plan for the preparation of such fluorocarbocyclic analogues of pentoses and nucleosides.[6] Our aim was to develop a general strategy allowing the synthesis of **II** for various carbohydrate series using the same reaction sequence. Our approach, as displayed on Scheme 1, is based on the use of difluorocyclopentane **III** as the key intermediate. Compounds of type **III** feature an exocyclic double bond or a phenylselanylmethyl moiety at C-5, which would allow the introduction of the hydroxy group. This intermediate would be obtained through a 5-*exo* radical cyclization of a difluoromethyl radical onto a double or triple bond, through an atom-transfer or reductive process. The radical precursor **IV** would be readily prepared by addition of $PhSeCF_2TMS$ on the pentose-derived aldehyde or its corresponding *tert*-butanesulfinylimine **V**.



Scheme 1. General retrosynthetic scheme.

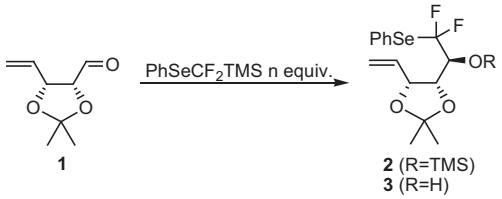
Our first efforts focused on the achievement of a diastereoselective addition of $PhSeCF_2TMS$ to easily prepared carbohydrate-derived aldehydes featuring an exocyclic double bond and on the validation of our strategy through a reductive radical cyclization leading to 5-deoxypentose analogues. First results were disclosed in a preliminary communication and we wish to present herein a full and detailed report of this study, which also include additional examples, the addition of $PhSeCF_2TMS$ to *tert*-butanesulfinylimines and the subsequent radical cyclization of the adducts.[7]

2. Results and discussion

2.1. Addition of $PhSeCF_2TMS$ to aldehydes

Aldehyde **1** was prepared according to a literature procedure involving a Zn-promoted reductive elimination of a D-ribose-derived iodide.[8] The addition of $PhSeCF_2TMS$ to this substrate was examined using various conditions reported in the literature (Table 1). If the fluoride-promoted addition of $PhSeCF_2TMS$ to aromatic aldehydes is well established,[9] the use of easily enolizable α-chiral aldehydes is poorly documented. Our first attempts were direct applications of the method described by Qing using a catalytic amount of TBAF in THF.[9a] If addition products **2** and **3** were indeed isolated using this method (Table 1, entry 1), a significant amount of by-products resulting from the base-promoted enolization of the aldehyde were also detected. Lowering the reaction temperature or the amount of TBAF did not improve this result. We thus turned our attention to a Lewis acid-based method, which was recently reported.[9d] The use of $Cu(OAc)_2$/dppe as an activator indeed allowed us to isolate **2** as the sole product, but in moderate yield and diastereoselectivity (Table 1, entry 2). The use of TMAF as the promoter in CH_2Cl_2 at low temperature eventually led to **2** in higher yield and with an acceptable diastereoselectivity (Table 1, entry 3).[9c] No by-products were detected despite the large excess of nucleophile (3 equiv) and of fluoride source (3 equiv), which were first required to complete the reaction at −78 °C. These amounts were efficiently reduced to 1.5 equiv and 1 equiv, respectively (Table 1, entry 4). However, a mixture of the TMS ether **2** and of the free alcohol **3** is obtained in that case.

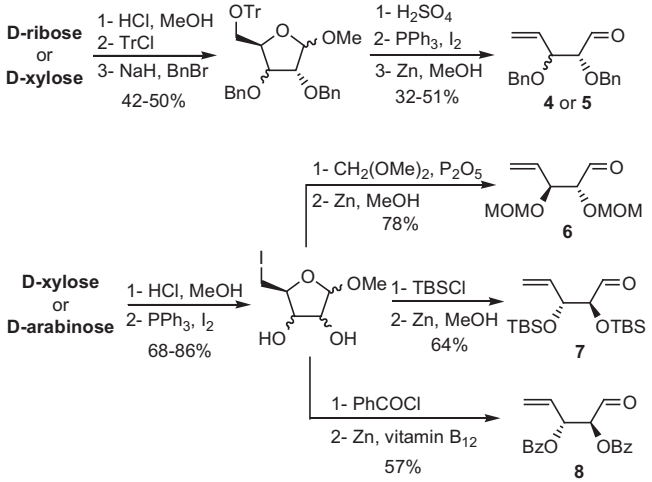
Table 1
Optimization of the addition of $PhSeCF_2TMS$



Entry	*n*	Conditions	**2**[a] (%)	**3**[a] (%)	dr[b]
1	1	TBAF 0.1 equiv, THF, −20 °C	26	27	9:1
2	2.5	$Cu(OAc)_2$/dppe 0.1 equiv, DMF, rt	47	—	7:3
3	3	TMAF 3 equiv, DCM, −78 °C	58	—	8:2
4	1.5	TMAF 1 equiv, DCM, −78 °C	36	27	8:2

TBAF=tetrabutylammonium fluoride; dppe=1,2-bis(diphenylphosphino)ethane; TMAF=tetramethylammonium fluoride.
[a] Isolated yields.
[b] Diastereomeric ratios for **2**, estimated from the ^1H or ^{19}F NMR spectra of the crude mixture.

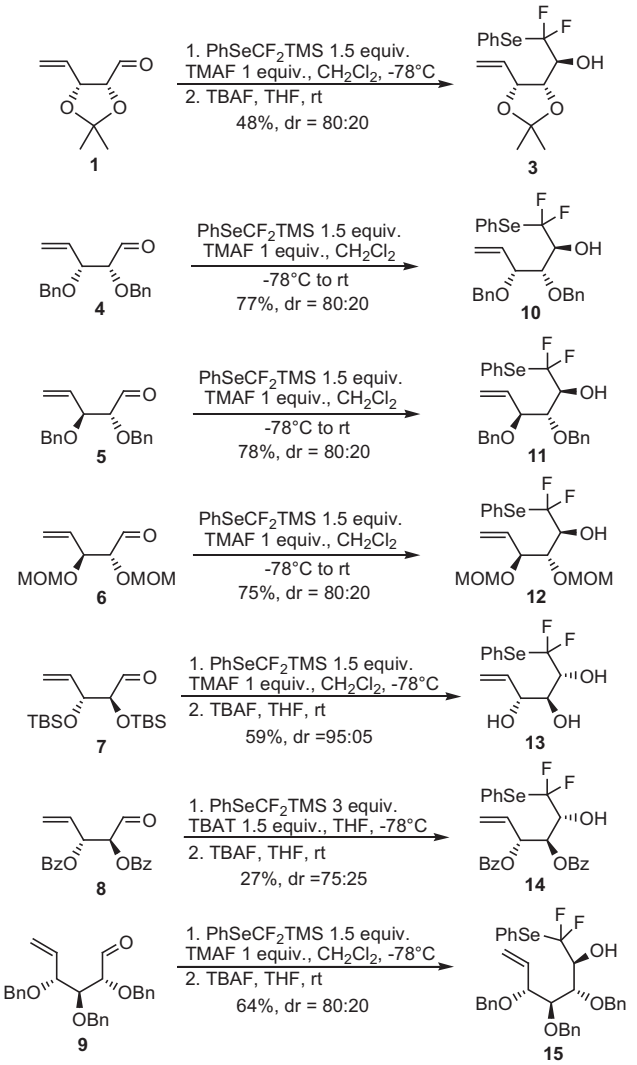
TMAF thus appeared as the appropriate mediator for this reaction and we decided to apply this method to a wide range of aldehydes obtained from various carbohydrates and diversely protected. Aldehydes **4**–**9** were thus prepared using procedures from the literature or slight modifications of the reported syntheses, which always involved a Zn-promoted reductive elimination of a carbohydrate-derived iodide as the key-step (Scheme 2).[10]



Scheme 2. Preparation of aldehydes **4**–**9**.

The addition of $PhSeCF_2TMS$ was then examined on each of these substrates. The use of only a slight excess of reagents requires a two-step procedure to convert the isolated OH/OTMS mixture to the free alcohol **3** (Scheme 3). Worthy of note is the fact that, for benzyl- or MOM-protected aldehydes such as **4**–**6**, a warm-up to rt is sufficient to afford alcohols **10**–**12** in high yield. The TBS-protected arabinose derivative **7** led to the fully deprotected addition product **13** in appreciable yield thanks to the two-step procedure mentioned earlier. One exception to the TMAF-mediated reaction is the benzoyl-protected arabinose derivative **8**. The addition product **14** could

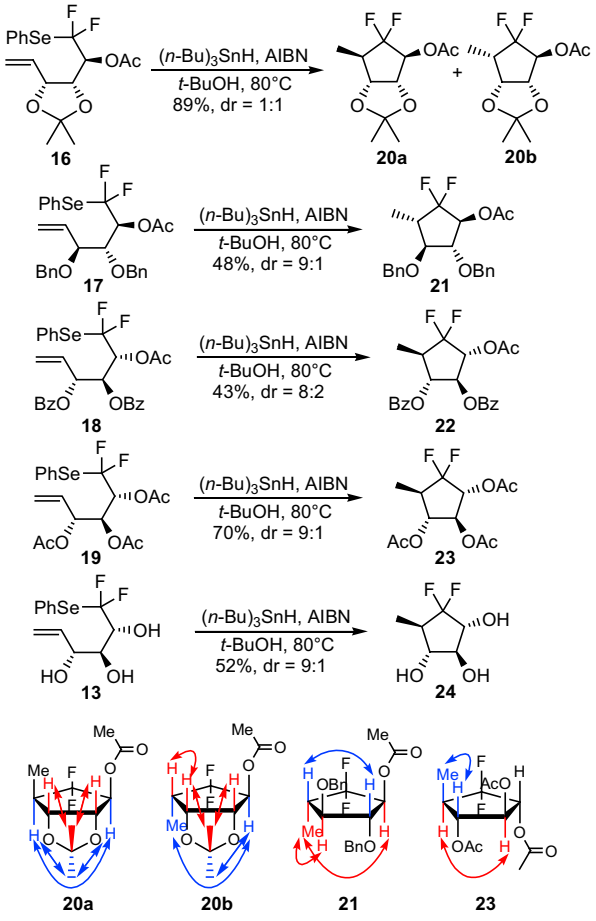
indeed be isolated only in low yield and using TBAT as the fluoride source (Scheme 3), indicating that the electrophilicity of such protecting groups was inappropriate in this reaction. Finally, the glucose-derived aldehyde **9** could be also converted to alcohol **15** thanks to the two-step procedure.[11] Diastereomeric ratios (estimated from ^{1}H or ^{19}F NMR spectra of the crude mixture) were always in the 80:20 range, except for the TBS-protected aldehyde **7** for which an almost complete diastereoselectivity is observed. The relative configuration of each major diastereomer, which is displayed on Scheme 2 was not determined at that stage.



Scheme 3. Addition of $PhSeCF_2TMS$ under optimized conditions.

2.2. Radical cyclization

Having in hands several precursors, we then investigated the crucial 5-*exo-trig* radical cyclization. A classical, reductive tin hydride-mediated cyclization was first performed as it would allow us to demonstrate our synthetic strategy.[4a,4b,12] Moreover, the 5-deoxypentose analogues, which would be obtained from such a reaction, if less valuable than the exact analogues, remain interesting original structures with only few precedents in the literature. Compounds **3**, **11**, **13**, and **14** obtained from the addition reactions were thus acetylated and engaged in reductive radical cyclizations (Scheme 4). Complete conversion of the starting material was generally observed within 2 h and cyclized compounds **20**–**24** were obtained in moderate to high yields. No direct reduction of the substrate was ever observed, which could have explained the moderate yields obtained for **21**, **22**, and **24**. The reaction conditions appeared compatible with all the protecting groups, which were tested (esters, ethers, and acetonide). Not surprisingly, the cautious acetylation of the free hydroxy groups from **3**, **11**, **13**, and **14** proved unnecessary, as illustrated by the successful cyclization of the unprotected arabinose derivative **13** (Scheme 4). The diastereoselectivity of the reaction (estimated from ^{1}H or ^{19}F NMR spectra of the crude mixture) is strongly dependant on the substrate (vide infra). Finally, a 6-*exo-trig* radical cyclization of compound **15** was also attempted but the cyclized compound was obtained only in low yield and with a low purity.



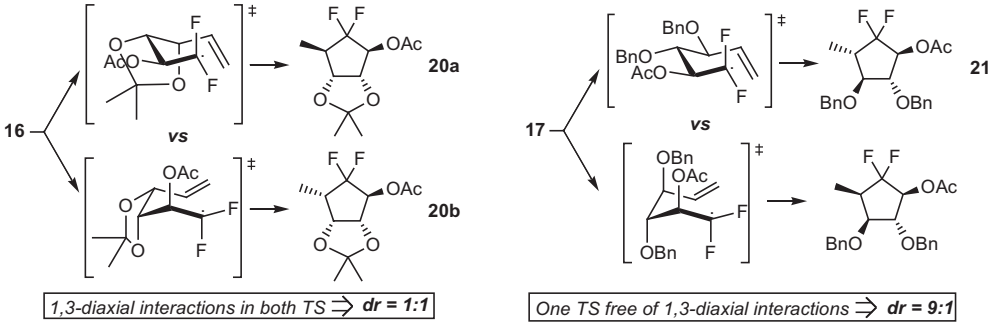
Scheme 4. Synthesis of the 5-deoxypentose CF_2-carbocyclic analogues.

Compound **21** was deacetylated and subjected to a Mitsunobu reaction using N^3-benzoylthymine as the nucleophile.[4d] Disappointingly, the expected pseudo-nucleoside could not be obtained from this reaction on a sterically hindered substrate.

2.3. Stereochemical outcome of the addition and cyclization reactions

The relative configurations of the cyclized compounds **20**, **21**, and **23** were easily determined thanks to NOESY NMR experiments and the configuration of **22** and **24** was deduced from these results (Scheme 4: the colored arrows stand for the observed NOESY correlations). This work provided answers to the stereochemical outcome of both the $PhSeCF_2TMS$ addition and the radical cyclization. The latter proceeds according to the well-known Beckwith–Houk

transition state.[13] A strong diastereoselectivity was therefore observed in the reaction of the xylose and arabinose derivatives **17** and **19** for which an 'all equatorial' transition state is possible (Scheme 5). On the other hand, an equimolar mixture of the two



Scheme 5. Stereoselectivity of the radical cyclization.

C-5 epimers **20a** and **20b** was obtained from the ribose derivative **16**. Both transition states leading to these compounds indeed suffer from at least one non-bonding 1,3-diaxial interaction (Scheme 5).

The stereochemical outcome of the addition of $PhSeCF_2TMS$ to aldehydes **1** and **4**–**9** was less expected. *anti*-Felkin adducts are indeed obtained as the major diastereomers whereas the addition of fluoroalkylsilane reagents to α-chiral aldehydes is often poorly diastereoselective except for α-dibenzylaminoaldehydes for which a Felkin selectivity is observed.[14] If a chelated transition state can be considered for the reactions promoted by $Cu(OAc)_2$ and dppe (Table 1, entry 2), such a model is irrelevant regarding the fluoride-promoted additions. However, Portella's group observed similar results in the addition of fluoroalkylsilane reagents to other highly functionalized carbohydrate-derived aldehydes.[15] These authors suggested that the unusual bulkyness of the postulated hypervalent fluorosilicon intermediate and of the electrophile could give rise to non-classical transition states. The models grounded on stabilizing hyperconjugation, either from the Anh/Eisentein or Cieplak interpretation, imply conformations, which might indeed be disfavored due to the steric hindrance of both partners (Fig. 2).[16] Two transition states are therefore proposed, which account for the observed selectivity and allow the minimization of steric interactions (Fig. 2). **A** is a Felkin model in which the bulky substituent takes the place of the electronegative one.[17] This conformation has been determined to be the most stable one from an energy minimization study of aldehyde **7** performed using the Discover/Insight II software (Fig. 2). However, reasoning on the most stable conformation of the substrate might be misleading for reactions on highly flexible aldehydes. Alternatively, transition state **B**, which is similar to the one proposed by Portella, clearly minimizes the steric hindrance despite an unusual *gauche* conformation. Moreover, the relative orientations of the C–OR bond and the incoming nucleophile offer supplemental stabilization thanks to dipole moment minimization.[18]

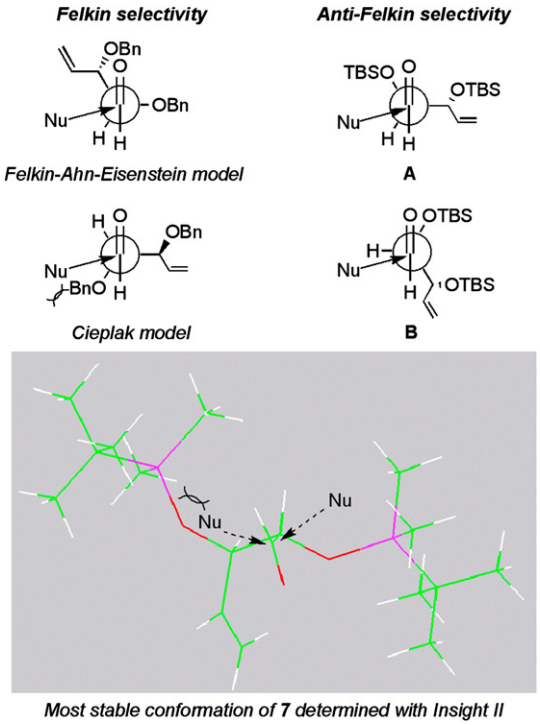
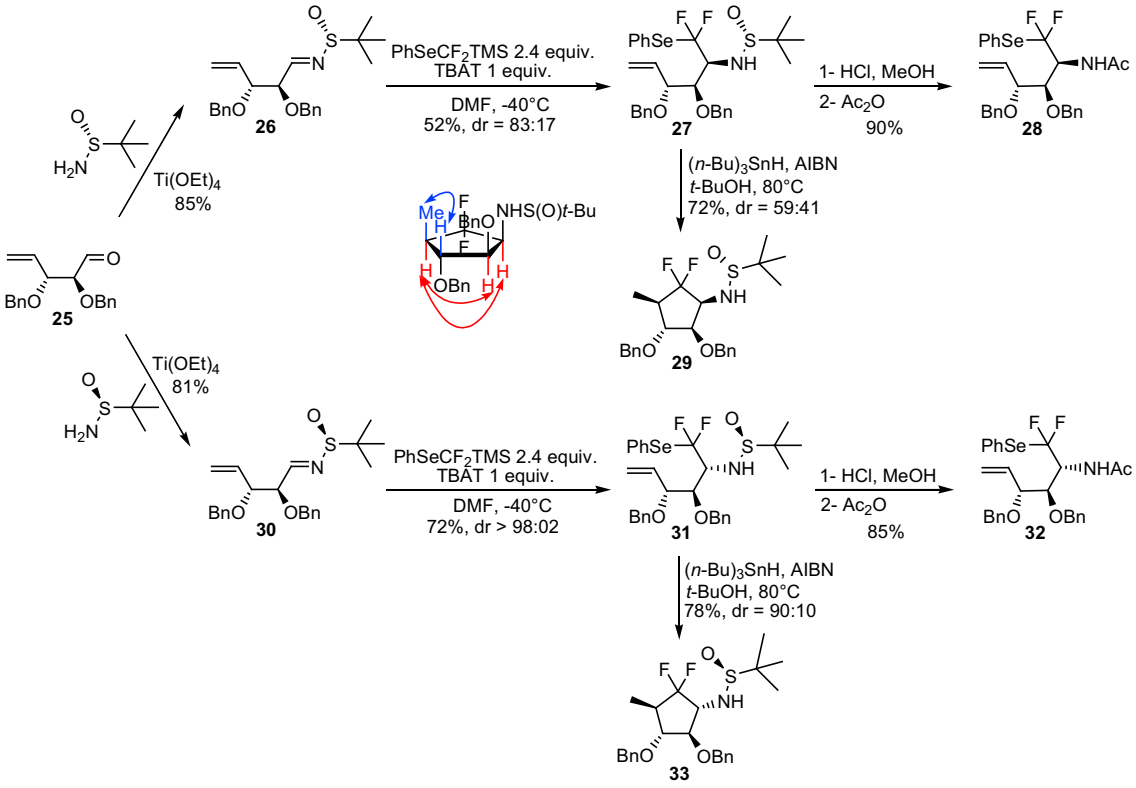


Figure 2. Diastereoselectivity of the $PhSeCF_2TMS$ addition.

2.4. Addition of $PhSeCF_2TMS$ to *tert*-butanesulfinylimines and cyclization

In order to provide a more direct access to nucleoside analogues and to control at will the configuration of the pseudo-anomeric center, a similar sequence was performed on *tert*-butanesulfinylimines **26** and **30** (Scheme 6). The addition of $PhSeCF_2TMS$ proceeded smoothly according to the procedure developed by Hu, using TBAT as a promoter.[12f] A mismatched diastereoselectivity (dr=83:17) was observed in the case of **26** and the matched case was obtained for **30** (dr >98:02, only one diastereomer detected in the ^1H and ^{19}F NMR spectra of the crude mixture). It has been unambiguously demonstrated, thanks to a simple hydrolytic cleavage of the sulfinamide group, that the C-2 configuration of each major diastereomer was exclusively controlled by the chiral auxiliary. Indeed, acetamides **28** and **32** displayed different ^1H, ^{13}C, and ^{19}F NMR data, indicating they were diastereomers, which could only differ by their C-2 configuration. Moreover, the observed match/mismatch cases were in agreement with what could be predicted from the literature.[12f,19] Indeed, the stereochemical outcome of nucleophilic additions using this chiral auxiliary is well established and, when confronted to the selectivity that we previously observed for the corresponding aldehydes, implies a matched diastereoselectivity for **30**. The reductive radical cyclization of addition products **27** and **31** afforded the corresponding 5-deoxypentofuranose analogues **29** and **33** in good yield. The relative configuration of **29** was again determined thanks to NOESY correlations and the predicted stereoselectivity for the $PhSeCF_2TMS$ addition was thus confirmed. Signal overlaps in the ^1H NMR spectrum of **33** did not allow us to draw conclusions from NOESY experiments. However, if the change of C-2 configuration is admitted,



Scheme 6. Addition to sulfinylimines and cyclization.

the depicted relative configuration for **33** can be deduced from the high selectivity of the radical cyclization. Indeed, in that case, a transition state placing all substituents in pseudo-equatorial position is possible, leading to **33** with the represented C-5 configuration. This assumption is confirmed by the low diastereoselectivity obtained for the cyclization of **27**, in which the C-2 configuration requires to place at least one substituent in pseudo-axial position for both possible transition states.

An attempt was made to convert compound **33** to the corresponding pyrimidyl nucleoside using a known procedure.[4c] After cleavage of the sulfinyl auxiliary, the free amine function was allowed to react with 3-ethoxy-2-propenoyl isocyanate. Unfortunately, no reaction occurred, which might be due to the steric hindrance and weak nucleophilicity of this substrate.

3. Conclusion

An efficient preparation of difluorinated carbocyclic 5-deoxypentofuranose and 1-amino-5-deoxypentofuranose analogues has thus been carried out. The synthetic pathway involves an addition of $PhSeCF_2TMS$ to carbohydrate-derived aldehydes or *tert*-butanesulfinylimines featuring a terminal double bond followed by a reductive 5-*exo*-*trig* radical cyclization. The $PhSeCF_2TMS$ addition exhibited an interesting, though unusual, diastereoselectivity and the use of Ellman's auxiliary appeared to be the method of choice for a rapid access to 1-aminopentose analogues with a total control of the pseudo-anomeric center. An efficient method for a future synthesis of pentofuranose and nucleoside surrogates has been secured thanks to this study. Indeed, performing a similar sequence using a phenylselanyl group transfer radical cyclization with the same substrates or a reductive 5-*exo*-*dig* radical cyclization of similar precursors featuring a terminal triple bond should allow us to achieve this goal. More work devoted to the conversion of the carbasugars to nucleoside analogues should also be performed. These strategies are currently under investigation and results in this area will be reported in due course.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry THF, DMF, or CH_2Cl_2 were obtained by drying over Na/benzophenone (THF) or barium oxide (DMF) or P_2O_5 (CH_2Cl_2) and distillation. All reagents were purchased from commercial sources and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates using UV light as a visualizing agent and an ethanolic solution of phosphomolybdic acid, *p*-anisaldehyde or potassium permanganate, and heat as developing agents. Chromatographic purifications were carried out using silica gel columns (60, particle size 0.040–0.063 mm or 0.070–0.200 mm) or automated equipment with prepacked silica cartridges. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a 300 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. The NOESY experiments were recorded on a 400 or 500 MHz instrument. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, app=apparent. Mass spectrometry (MS) experiments were performed using electrospray ionization (ESI). IR spectra were recorded on an FT-IR spectrometer. Optical rotations were measured at 20 °C and with λ=589 nm; concentrations are expressed in cg mL^{-1}.

4.2. (2*S*,3*R*,4*R*)-3,4-*O*-Isopropylidene-1,1-difluoro-1-phenylselanyl-hex-5-en-2,3,4-triol (3)

To a solution of aldehyde **1** (1.11 g, 3.74 mmol) and $PhSeCF_2TMS$ (1.57 g, 5.60 mmol, 1.5 equiv), with suspended MS 4 Å, in dry

CH_2Cl_2 (20 mL) at −78 °C was added TMAF (350 mg, 3.74 mmol, 1 equiv). The reaction mixture was allowed to stir at −78 °C for 1 h. Water was then added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash chromatography using cyclohexane/AcOEt (97:3) as eluent to afford the desired addition product as its TMS ether (1.62 g, 63%). To a solution of this mixture of diastereomers (400 mg, 0.92 mmol) in dry THF was added a solution of TBAF (1 M in THF, 1.1 mL, 1.2 equiv). The mixture was then stirred at rt for 1 h. Water was then added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash chromatography using cyclohexane/AcOEt (95:05 then 90:10) as eluent to afford the separated (2*S*,3*R*,4*R*) (**3**) and (2*R*,3*R*,4*R*) diastereomers (215 mg and 40 mg, respectively, 76% overall) as yellow oils. R_f=0.52 (20% AcOEt in cyclohexane). $[\alpha]_D$ +3.4 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 2H, Ar), 7.44–7.30 (m, 3H), 5.94 (ddd, *J*=17.8, 10.1, 8.1 Hz, 1H), 5.40–5.27 (m, 2H), 4.71 (t, *J*=7.9 Hz, 1H), 4.51 (d, *J*=7.5 Hz, 1H), 3.85 (dt, *J*=14.9, 8.8 Hz, 1H), 3.07 (d, *J*=9.7 Hz, 1H), 1.56 (s, 3H), 1.40 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −79.1 (dd, *J*=210.1, 8.0 Hz, 1F), −82.2 (dd, *J*=210.5, 15.1 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.6, 133.9, 129.7, 129.4, 127.3 (t, *J*=300.7 Hz), 124.0, 120.9, 109.8, 79.7, 74.4 (d, *J*=3.4 Hz), 72.2 (t, *J*=24.7 Hz), 26.9, 24.7. IR (neat) ν_{max} 3411, 3060, 2988, 2924, 2851, 1713, 1580 cm^{-1}. MS (ESI$^+$): *m*/*z*=381.93 ([M+H_2O]$^+$). Anal. Calcd for $C_{15}H_{18}F_2O_3Se$: C, 49.60; H, 4.99. Found: C, 49.39; H, 4.78.

4.3. (2*S*,3*R*,4*R*)-3,4-Bis(*O*-benzyl)-1,1-difluoro-1-phenylselanyl-hex-5-en-2,3,4-triol (10)

To a solution of aldehyde **4** (1.11 g, 3.74 mmol) and $PhSeCF_2TMS$ (1.57 g, 5.60 mmol, 1.5 equiv), with suspended MS 4 Å, in dry CH_2Cl_2 (20 mL) at −78 °C was added TMAF (350 mg, 3.74 mmol, 1 equiv). The reaction mixture was allowed to stir at −78 °C for 1 h 30 min, warmed up to −40 °C for 1 h and then to rt for 1 h. Water was then added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography using cyclohexane/AcOEt (98:2) as eluent afforded the pure (2*S*,3*R*,4*R*) diastereomer **10** and a mixture of the (2*S*,3*R*,4*R*) and (2*R*,3*R*,4*R*) diastereomers (1.460 g overall, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 2H), 7.35 (m, 13H), 5.87 (ddd, 1H, *J*=16.5, 11.0, 7.3 Hz), 5.43 (m, 2H), 4.66 (m, 3H), 4.38 (d, 1H), 4.21 (m, 1H), 3.99 (t, 1H, *J*=7.3 Hz), 3.88 (d, 1H, *J*=7.0 Hz), 3.36 (d, 1H, *J*=9.5 Hz). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −76.68 (dd, *J*=215.8, 10.3 Hz), −78.55 (dd, *J*=215.7, 11.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.7, 135.3, 128.5, 127.7 (t, *J*=299.7 Hz), 124.2 (d, *J*=2.3 Hz), 120.8, 80.3, 77.6 (d, *J*=2.2 Hz), 74.4, 72.8 (dd, *J*=23.0, 3.0 Hz), 70.9. MS (ESI$^+$): *m*/*z*=522.1 ([M+H_2O]$^+$).

4.4. (2*S*,3*R*,4*S*)-3,4-Bis(*O*-benzyl)-1,1-difluoro-1-phenylselanyl-hex-5-en-2,3,4-triol (11)

The same procedure was applied to **5** (1.1 g, 3.7 mmol). Purification by flash column chromatography using cyclohexane/AcOEt (98:2 then 95:5) as eluent afforded the pure (2*S*,3*R*,4*S*) (**11**) and the pure (2*R*,3*R*,4*S*) diastereomers, and a mixture of both (1 g, 155 mg and 310 mg, respectively, 78% overall) as colorless oils. R_f=0.25 (5% AcOEt in cyclohexane). $[\alpha]_D$ −14.4 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J*=7.1 Hz, 2H), 7.62–7.37 (m, 13H), 5.90 (ddd, *J*=16.4, 11.3, 7.7 Hz, 1H), 5.51 (s, 1H), 5.44 (d, *J*=7.0 Hz, 1H), 4.90 (dd, *J*=48.1, 10.4 Hz, 2H), 4.61 (dd, *J*=66.2, 11.9 Hz, 1H), 4.28–4.06 (m, 3H), 3.50 (d, *J*=10.1 Hz, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −79.9 (dd, *J*=208.8, 7.5 Hz, 1F), −83.1 (dd, *J*=208.8, 15.5 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.3, 137.8, 137.6, 134.5, 129.6, 129.3, 128.6 (×2), 128.2, 128.0, 127.9, 127.7, 127.6 (t, *J*=298.9 Hz), 124.1, 121.0, 81.8, 76.9 (d, *J*=1.7 Hz), 74.9, 72.7 (t, *J*=23.9 Hz), 70.9. IR (neat) ν_{max} 3521, 3063, 3032, 2870, 1579 cm^{-1}. MS (ESI$^+$): *m*/*z*=522.1 ([M+H_2O]$^+$). HRMS (CI$^+$) calcd for $C_{26}H_{27}F_2O_3Se$ ([M+H]$^+$) *m*/*z* 505.1094, found 505.1093.

4.5. (2*S*,3*R*,4*S*)-3,4-Bis(*O*-methoxymethyl)-1,1-difluoro-1-phenylselanyl-hex-5-en-2,3,4-triol (12)

The same procedure was applied to **6** (0.885 g, 4.3 mmol). Purification by column chromatography (10% EtOAc in cyclohexane) afforded the pure (2*S*,3*R*,4*S*) diastereomer (**12**) and a mixture of the (2*S*,3*R*,4*S*) and (2*R*,3*R*,4*S*) diastereomers (1.341 g overall, 75%). R_f=0.33 (20% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H), 7.21–7.12 (3H, m), 5.62 (ddd, *J*=16.7, 10.3, 7.8 Hz, 1H), 5.17–5.08 (m, 2H), 4.61–4.34 (m, 8H), 4.07–4.01 (m, 1H), 3.98–3.86 (m, 1H), 3.82–3.78 (m, 1H), 3.21 (s, 3H), 3.12 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −77.7 (dd, *J*=207.7, 6.9 Hz, 1F), −84.2 (dd, *J*=207.7, 17.2 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.6, 134.0, 129.3, 127.5 (t, *J*=298.9 Hz), 120.1, 98.2, 94.3, 77.6, 75.7, 72.2 (dd, *J*=26.1, 22.7 Hz), 56.8, 55.9. MS (ESI$^+$): *m*/*z*=435.1 ([M+Na]$^+$). Anal. Calcd for $C_{16}H_{22}F_2O_5Se$: C, 46.72; H, 5.39. Found: C, 46.68; H, 5.38.

4.6. (2*R*,3*S*,4*R*)-1,1-Difluoro-1-phenylselanyl-hex-5-ene-2,3,4-triol (13)

To a solution of aldehyde **7** (1.69 g, 4.9 mmol) and $PhSeCF_2TMS$ (2.06 g, 7.40 mmol, 1.5 equiv), with suspended MS 4 Å, in dry CH_2Cl_2 (150 mL) at −78 °C was added TMAF (459 mg, 4.90 mmol, 1 equiv). The reaction mixture was allowed to stir at −78 °C for 1 h. Water was then added and the aqueous layer was extracted with CH_2Cl_2. The collected organics were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To a solution of the obtained crude residue in dry THF (20 mL) was added a solution of TBAF (1 M in THF, 12.3 mL, 5 equiv). The mixture was stirred at rt for 1 h and water was added. The aqueous phase was extracted with CH_2Cl_2 and organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography using CH_2Cl_2/MeOH (99:1) as eluent to afford the pure (2*R*,3*S*,4*R*) diastereomer **13** and a mixture of the (2*R*,3*S*,4*R*) and (2*S*,3*S*,4*R*) diastereomers (146 mg and 233 mg, respectively, 59% over two steps) as white solids. R_f=0.36 (4% MeOH in CH_2Cl_2). $[\alpha]_D$ −9.9 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J*=7.78 Hz, 2H), 7.45–7.31 (m, 3H), 5.81 (ddd, *J*=17.4, 10.4, 7.0 Hz, 1H), 5.35 (d, *J*=32.2 Hz, 1H), 5.30 (d, *J*=25.4 Hz, 2H), 4.25–4.11 (m, 1H), 3.91 (d, *J*=6.7 Hz, 2H), 3.71 (br s, 1H), 3.34 (br s, 1H), 2.99 (br s, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −78.7 (dd, *J*=211.2, 10.4 Hz, 1F), −81.9 (dd, *J*=213.3, 14.5 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.7, 136.1, 135.9, 129.9, 129.5, 127.3 (t, *J*=300.5 Hz), 123.9, 120.6, 119.9, 74.6, 73.6 (t, *J*=24.6 Hz), 70.9 (d, *J*=2.4 Hz). IR (neat) ν_{max} 3504, 3154, 2844, 1955, 1881, 1646, 1580 cm^{-1}. GC–MS: *m*/*z*=341.9 ([M+H_2O]$^+$). Anal. Calcd for $C_{12}H_{14}F_2O_3Se$: C, 44.59; H, 4.37. Found: C, 44.77; H, 4.25.

4.7. (2*R*,3*S*,4*R*)-3,4-Bis(*O*-benzoyl)-1,1-difluoro-1-phenylselanyl-hex-5-en-2,3,4-triol (14)

To a solution of aldehyde **8** (1.75 g, 5.40 mmol) and $PhSeCF_2TMS$ (4.52 g, 16.19 mmol, 3 equiv), with suspended MS 4 Å, in dry THF (200 mL) at −78 °C was added TBAT (4.37 g, 8.10 mmol, 1.5 equiv). The reaction mixture was allowed to stir at −78 °C for 1 h. Water was then added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To a solution of this crude product in dry THF (30 mL) was added

a solution of TBAF (1 M in THF, 2.6 mL, 1.2 equiv) and the mixture was stirred at rt for 1 h. Water was then added and the aqueous layer was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash chromatography using cyclohexane/AcOEt (95:5 then 9:1) as eluent to afford the pure (2*R*,3*S*,4*R*) (**14**) and the pure (2*S*,3*S*,4*R*) diastereomers and a mixture of both (384 mg, 17 mg and 200 mg, respectively, 27% overall, over two steps) as pale orange solids. R_f=0.16 (10% EtOAc in cyclohexane). $[\alpha]_D$ +39.9 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (q, *J*=7.4 Hz, 4H), 7.67 (d, *J*=7.4 Hz, 2H), 7.53–7.48 (m, 2H), 7.43–7.29 (m, 7H), 5.97–5.85 (m, 3H), 5.57 (d, *J*=17.4 Hz, 1H), 5.40 (d, *J*=9.9 Hz, 1H), 4.28 (dt, *J*=16.9, 8.6 Hz, 1H), 3.15 (d, *J*=10.1 Hz, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −79.4 (dd, *J*=213.2, 8.2 Hz, 1F), −83.8 (dd, *J*=215.7, 14.1 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.7, 165.4, 137.7, 133.7, 133.5, 131.8, 130.0, 129.7, 129.6, 129.5, 128.7 (2C), 126.5 (t, *J*=300.3 Hz), 123.5, 122.3, 74.5, 73.0 (t, *J*=25.4 Hz), 70.7. IR (neat) ν_{max} 3475, 3063, 1733, 1713, 1601 cm^{-1}. MS (ESI$^+$): *m*/*z*=549.93 ([M+H_2O]$^+$). Anal. Calcd for $C_{26}H_{22}F_2O_5Se$: C, 58.76; H, 4.17. Found: C, 58.80; H, 4.13.

4.8. (2*S*,3*R*,4*S*,5*R*)-3,4,5-Bis(*O*-benzyl)-1,1-difluoro-1-phenylselanyl-hept-6-en-2,3,4-tetraol (15)

The same two-step procedure used for **1** was applied to aldehyde **9**. Purification by flash column chromatography using cyclohexane/AcOEt (98:2 then 95:5) as eluent afforded the major (2*S*,3*R*,4*S*,5*R*) diastereomer **15** and a mixture of the (2*S*,3*R*,4*S*,5*R*) and (2*R*,3*R*,4*S*,5*R*) diastereomers (63% yield overall). R_f=0.29 (10% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J*=7.0 Hz, 2H), 7.32–7.21 (m, 28H), 5.89 (ddd, *J*=17.5, 10.6, 7.2 Hz, 1H), 5.27 (m, 2H), 4.76–4.57 (m, 5H), 4.34 (d, *J*=11.9 Hz, 1H), 4.15–3.95 (m, 3H), 3.38 (d, *J*=9.4 Hz, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −77.5 (dd, *J*=207.3, 6.2 Hz, 1F), −82.8 (dd, *J*=207.3, 16.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 137.7, 137.5, 137.3 (2C); 134.71, 129.3–127.7 (m, 7C), 127.3 (t, *J*=300.0 Hz); 118.9, 81.4, 79.1, 75.6 (d, *J*=2.7 Hz), 74.9, 74.5 (2C), 72.5 (t, *J*=25.0 Hz), 70.4. MS (ESI$^+$): *m*/*z*=642.20 ([M+H_2O]$^+$). Anal. Calcd for $C_{26}H_{22}F_2O_5Se$: C, 65.49; H, 5.50. Found: C, 65.51; H, 5.46.

4.9. (2*S*,3*R*,4*R*,5*R*)- and (2*S*,3*R*,4*R*,5*S*)-2-*O*-Acetyl-3,4-*O*-isopropylidene-1,1-difluoro-5-methylcyclopentane-2,3,4-triol (20a and 20b)

To a solution of **16** (324 mg, 0.80 mmol) in *t*-BuOH (28 mL) was added AIBN (39 mg, 0.02 mmol, 0.3 equiv). The mixture was then degassed, heated at 80 °C, and a degassed solution of Bu_3SnH (320 μL, 1.20 mmol, 1.5 equiv) in *t*-BuOH (15 mL) was added dropwise via a syringe pump over 45 min. AIBN (39 mg, 0.02 mmol, 0.3 equiv) was added every 30 min until total consumption of the starting material (followed by NMR ^{19}F), usually within 2 h. The solvent was then evaporated and the crude residue was purified by flash chromatography using cyclohexane/AcOEt (95:5 then 9:1) as eluent to afford the pure (2*S*,3*R*,4*R*,5*S*) (**20b**) and the pure (2*S*,3*R*,4*R*,5*R*) (**20a**) diastereomers, and a mixture of both (70 mg, 85 mg and 25 mg, respectively, 89% overall) as pale yellow oils. Compound **20a**: R_f=0.30 (20% AcOEt in cyclohexane). $[\alpha]_D$ +15.4 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (d, *J*=9.4 Hz, 1H), 4.52–4.46 (m, 1H), 4.30–4.23 (m, 1H), 2.53–2.33 (m, 1H), 2.15 (s, 3H), 1.51 (s, 3H), 1.29 (s, 3H), 1.19 (d, *J*=7.1 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −106.6 (dt, *J*=237.2, 8.1 Hz, 1F), −122.9 (dtt, *J*=237.4, 16.5, 2.8 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6, 126.4 (dd, *J*=262.2, 256.4 Hz), 113.3, 81.5 (d, *J*=6.9 Hz), 80.7 (d, *J*=6.3 Hz), 78.0 (dd, *J*=27.6, 17.8 Hz), 44.8 (t, *J*=22.0 Hz), 27.1, 24.9, 20.9, 10.3 (d, *J*=5.7 Hz). IR (neat) ν_{max} 3490, 2986, 2941, 1761 cm^{-1}. MS (ESI$^+$): *m*/*z*=268.1 ([M+H_2O]$^+$). Anal. Calcd for $C_{12}H_{14}F_2O_3Se$: C, 52.80; H, 6.44. Found: C, 52.67; H, 6.51. Compound **20b**: R_f=0.20 (20% AcOEt in cyclohexane). $[\alpha]_D$ −15.2 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (d, *J*=9.4 Hz, 1H), 4.62 (dt, *J*=6.4, 4.5 Hz, 1H), 4.45 (dd, *J*=6.4, 4.5 Hz, 1H), 2.53–2.32 (m, 1H), 2.11 (s, 3H), 1.46 (s, 3H), 1.29 (s, 3H), 1.18 (d, *J*=7.0 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −112.5 (ddd, *J*=245, 25.3, 9.3 Hz, 1F), −115.8 (dq, *J*=246.2, 4.3 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.1, 126.4 (dd, *J*=262.6, 256.6 Hz), 111.9, 81.3 (d, *J*=4.4 Hz), 78.4 (d, *J*=11.5 Hz), 76.5 (dd, *J*=36.2, 19.2 Hz), 41.9 (t, *J*=21.9 Hz), 26.1, 24.4, 21.0, 5.8 (d, *J*=4.4 Hz). MS (ESI$^+$): *m*/*z*=268.2 ([M+H_2O]$^+$).

4.10. (2*S*,3*R*,4*S*,5*S*)-2-*O*-Acetyl-3,4-bis(*O*-benzyl)-1,1-difluoro-5-methylcyclopentane-2,3,4-triol (21)

The same procedure was applied to **17** (50 mg; 0.09 mmol). Purification by column chromatography using cyclohexane/AcOEt (97:3) as eluent afforded the desired product (17 mg, 48%) as a colorless oil. Only the major (2*S*,3*R*,4*S*,5*S*) diastereomer **21** was isolated. R_f=0.14 (5% EtOAc in cyclohexane). $[\alpha]_D$ +8.8 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.24 (m, 10H), 5.18 (dt, *J*=12.9, 2.7 Hz, 1H), 4.74–4.55 (m, 4H), 3.92 (dt, *J*=5.3, 3.8 Hz, 1H), 3.60 (ddd, *J*=9.8, 5.5, 1.5 Hz, 1H), 2.48–2.26 (m, 1H), 2.14 (s, 3H), 1.18 (d, *J*=6.8 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −111.7 (ddd, *J*=242.7, 13.1, 10.1 Hz, 1F), −113.5 (ddt, *J*=243.2, 11.0, 3.2 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6, 138.1, 137.6, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 123.0 (dd, *J*=263.8, 251.7 Hz), 86.3 (d, *J*=2.3 Hz), 84.7 (d, *J*=8.6 Hz), 76.3 (dd, *J*=35.6, 19.5 Hz), 73.1, 72.6, 43.4 (t, *J*=21.8 Hz), 21.0, 9.3 (d, *J*=5.2 Hz). IR (neat) ν_{max} 2884, 1755 cm^{-1}. MS (ESI$^+$): *m*/*z*=452.3 ([M+H_2O+2Na+2H]$^+$), 426.2 ([M+2H_2O]$^+$), 408.2 ([M+H_2O]$^+$). Anal. Calcd for $C_{22}H_{24}F_2O_4$: C, 67.68; H, 6.20. Found: C, 67.45; H, 6.22.

4.11. (2*R*,3*S*,4*R*,5*R*)-2-*O*-Acetyl-3,4-bis(*O*-benzoyl)-1,1-difluoro-5-methylcyclopentane-2,3,4-triol (22)

The same procedure was applied to **18** (57 mg; 0.10 mmol). Purification by column chromatography using cyclohexane/AcOEt (95:5 then 9:1) as eluent afforded the desired product (18 mg, 43%) as a pale yellow oil and as a mixture of diastereomers. Only the analytical data of the major (2*R*,3*S*,4*R*,5*R*) diastereomer **22** are provided. R_f=0.27 (10% EtOAc in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10–8.01 (m, 4H), 7.63–7.55 (m, 2H), 7.52–7.38 (m, 4H), 5.62–5.57 (m, 1.5H), 5.48–5.37 (m, 1.5H), 2.80–2.60 (m, 1H), 2.20 (s, 3H), 1.30 (d, *J*=7.1 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −111.4 (ddd, *J*=243.1, 18.4, 11.7 Hz, 1F), −112.5 (ddq, *J*=243.2, 13.4, 2.1 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.4, 166.0, 165.8, 133.9, 133.8, 133.7, 130.4, 130.3, 130.2, 130.1, 129.4, 129.2, 128.9, 128.8, 122.6 (dd, *J*=261.2, 254.2 Hz), 79.3 (d, *J*=5.1 Hz), 78.7 (t, *J*=3.0 Hz), 76.3, 76.0, 75.8, 75.6, 74.6 (d, *J*=7.0 Hz), 43.8 (t, *J*=23.7 Hz), 9.6 (d, *J*=5.2 Hz). IR (neat) ν_{max} 2982, 1760, 1729, 1602 cm^{-1}. MS (ESI$^+$): *m*/*z*=858.87 ([2M+Na]$^+$). Anal. Calcd for $C_{22}H_{20}F_2O_6$: C, 63.16; H, 4.82. Found: C, 63.20; H, 4.79.

4.12. (2*R*,3*S*,4*R*,5*R*)-1,1-Difluoro-2,3,4-tri(*O*-acetyl)-5-methylcyclopentane-2,3,4-triol (23)

The same procedure was applied to **19** (100 mg, 0.22 mmol). Purification by column chromatography using cyclohexane/AcOEt (95:5 then 9:1) as eluent afforded the pure (2*R*,3*S*,4*R*,5*R*) diastereomer **23** and a mixture of the (2*R*,3*S*,4*R*,5*R*) and (2*R*,3*S*,4*R*,5*S*) diastereomers (16 mg and 30 mg, respectively, 70% overall) as pale yellow oils. R_f=0.31 (20% EtOAc in cyclohexane). $[\alpha]_D$ +6.1 (*c* 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25–5.17 (m, 2H), 4.94 (dd, *J*=9.5, 5.7 Hz, 1H), 2.56–2.35 (m, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.17 (d, *J*=6.91 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −111.6 (ddd, *J*=243.8, 19.7, 11.9 Hz, 1F), −112.9 (dt, *J*=244.0, 3.3 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.6, 170.3, 169.4, 125.9 (t, *J*=297.4 Hz), 76.5, 76.2, 75.9, 75.6, 75.5, 43.3 (t, *J*=23.6 Hz), 20.8, 20.7, 20.5, 9.0 (d, *J*=4.9 Hz). IR (neat) ν_{max} 3486, 2947, 1756 cm^{-1}. MS (ESI$^+$): *m*/*z*=318.2 ([M+Na]$^+$), 332.07

([M+K]$^+$). HRMS (CI$^+$) calcd for $C_{12}H_{17}F_2O_6$ ([M+H]$^+$) m/z 295.0993, found 295.1004.

4.13. (2*R*,3*S*,4*R*,5*R*)-1,1-Difluoro-5-methylcyclopentane-2,3,4-triol (24)

The same procedure was applied to **13** (100 mg; 0.31 mmol). Purification by column chromatography using CH_2Cl_2/MeOH (98:2) as eluent afforded the desired product (27 mg, 52%) as an unseparable mixture of diastereomers and as a colorless oil. Only the analytical data of the major (2*R*,3*S*,4*R*,5*R*) diastereomer **24** are provided. R_f=0.23 (10% MeOH in CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ 3.73–3.66 (m, 1H), 3.63–3.58 (m, 1H), 3.35–3.26 (m, 1H), 2.14–1.92 (m, 1H), 1.09 (d, J=7.1 Hz, 3H). ^{19}F NMR (282.5 MHz, CD_3OD) δ −108.86 (dt, J=226.1, 9.6 Hz, 1F), −110.21 (dt, J=277.1, 15.0 Hz, 1F). ^{13}C NMR (75.5 MHz, CD_3OD) δ 124.7 (dd, J=256.4, 254.2 Hz), 82.7 (dd, J=2.8, 2.6 Hz), 82.0, 79.6, 78.8 (d, J=5.3 Hz), 78.3 (dd, J=4.1, 3.1 Hz), 45.8 (t, J=22.1 Hz), 10.1 (dd, J=5.7, 2.7 Hz). IR (neat) ν_{max} 3292, 2928, 2632, 2537, 1728, 1585 cm^{-1}. MS (ESI$^+$): m/z=186.23 ([M+H_2O] $^+$). Anal. Calcd for $C_6H_{10}F_2O_3$: C, 42.86; H, 5.99. Found: C, 42.43; H, 5.94.

4.14. (R_S)- and (S_S)-*N*-[(2*R*,3*R*)-2,3-Bis(benzyloxy)pent-4-enylidene]-*tert*-butanesulfinamide (26 and 30)

To a solution of aldehyde **25** (317 mg, 1.07 mmol) and Ti(OEt)$_4$ (0.45 mL, 2.14 mmol, 2 equiv) in 5 mL of anhydrous THF was added (*R*) or (*S*)-2-methyl-2-propanesulfinamide (130 mg, 1.07 mmol, 1 equiv) and the mixture was refluxed for 1 h. Saturated aqueous NaCl (5 mL) was then added under vigorous stirring, and the suspension formed was filtered through Celite and washed with AcOEt. The filtrate was then washed with 10 mL of saturated aqueous NaCl and the aqueous layer extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash chromatography (cyclohexane/AcOEt 95:5 then 90:10) to afford the desired product (362 mg, 85% for **26**, 345 mg, 81% for **30**). Compound **26**: R_f=0.48 (5% EtOAc in cyclohexane). [α]$_D$ −189.7 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J=5.1 Hz, 1H), 7.40–7.20 (m, 10H), 5.93–5.84 (ddd, J=17.5, 10.1, 7.4 Hz, 1H), 5.39 (d, J=4.1 Hz, 1H), 5.33 (s, 1H), 4.73 (d, J=12.1 Hz, 1H), 4.63 (d, J=11.9 Hz, 1H), 4.55 (d, J=12.1 Hz, 1H), 4.42 (d, J=11.9 Hz, 1H), 4.33 (t, J=5.1 Hz, 1H), 4.12 (t, J=6.4 Hz, 1H), 1.17 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.0, 138.1, 137.8, 134.1, 128.8, 128.2, 128.1, 127.9, 120.2, 81.6, 80.4, 72.7, 71.0, 57.9, 22.2. IR (neat) ν_{max} 3030, 2866, 1622, 1207 cm^{-1}. MS (ESI$^+$) m/z=400.13 ([M+H]$^+$), 417.07 ([M+H_2O]$^+$). Anal. Calcd for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.51. Found: C, 69.16; H, 7.25; N, 3.68. Compound **30**: R_f=0.46 (5% EtOAc in cyclohexane). [α]$_D$ +77.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J=4.7 Hz, 1H), 7.33–7.18 (m, 10H), 5.92–5.80 (ddd, J=18.2, 10.6, 7.5 Hz, 1H), 5.28 (d, J=3.0 Hz, 1H), 5.24 (d, J=10.7 Hz, 1H), 4.71 (d, J=12.0 Hz, 1H), 4.60 (d, J=12.1 Hz, 1H), 4.48 (d, J=12.1 Hz, 1H), 4.34 (d, J=12.0 Hz, 1H), 4.18 (t, J=4.7 Hz, 1H), 4.02 (t, J=4.7 Hz, 1H), 1.15 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.3, 137.7, 137.4, 134.2, 128.4, 120.0, 81.1, 80.9, 72.7, 70.7, 56.9, 22.6. IR (neat) ν_{max} 3031, 2928, 1625, 1274 cm^{-1}. MS (ESI$^+$) m/z=400.13 ([M+H]$^+$), 417.07 ([M+H_2O]$^+$). Anal. Calcd for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.51. Found: C, 69.12; H, 7.27; N, 3.45.

4.15. (R_S,2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-*tert*-butanesulfinamido-1,1-difluoro-1-phenylselanyl-hex-5-ene (27)

To a solution of **26** (200 mg, 0.50 mmol) and $PhSeCF_2TMS$ (335 mg, 1.20 mmol, 2.4 equiv) in 4 mL of anhydrous DMF at −40 °C was added TBAT (270 mg, 0.50 mmol, 1 equiv). After 2 h stirring at −40 °C, saturated aqueous NH_4Cl (4 mL) was added at this temperature and the mixture was extracted with AcOEt (3×5 mL). The combined organic layers were washed with water (4×10 mL) then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash chromatography using cyclohexane/AcOEt (95:05 to 90:10) as eluent to afford the desired product as an unseparable mixture of diastereomers (157 mg, 52%, dr=83:17). Only the analytical data of the major (R_S,2*S*,3*R*,4*R*) diastereomer **27** are provided. R_f=0.40 (30% EtOAc in cyclohexane). [α]$_D$ −62.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J=7.0 Hz, 2H), 7.34–7.15 (m, 13H), 6.05–5.94 (ddd, J=18.6, 10.4, 8.3 Hz, 1H), 5.29–5.14 (m, 2H), 5.01 (d, J=7.1 Hz, 1H), 4.67 (d, J=12.1 Hz, 1H), 4.47 (t, J=12.1 Hz, 2H), 4.18–4.14 (m, 2H), 4.02–3.91 (m, 1H), 3.77 (t, J=4.5 Hz, 1H), 0.96 (s, 9H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −74.3 (dd, J=197.7, 11.4 Hz, 1F), −75.4 (dd, J=197.7, =12.4 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.3, 134.7, 129.2, 128.6, 128.5, 128.4, 126.8 (t, J=301.0 Hz), 124.3, 120.3, 82.4, 78.8, 73.1, 71.1, 62.5 (t, J=12.6 Hz), 56.7, 22.6. IR (neat) ν_{max} 3296, 3031, 2868, 1216, 1173 cm^{-1}. MS (ESI$^+$) m/z=608.13 ([M+H]$^+$). HRMS (CI$^+$) calcd for $C_{30}H_{36}F_2NO_3SSe$ ([M+H]$^+$) m/z 608.1549, found 608.1552.

4.16. (S_S,2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-*tert*-butanesulfinamido-1,1-difluoro-1-phenylselanyl-hex-5-ene (31)

The same procedure was applied to **30** (200 mg; 0.50 mmol). Purification by column chromatography using cyclohexane/AcOEt (95:05 then 90:10) as eluent afforded the desired product **31** (219 mg, 72%, dr >98:02). R_f=0.52 (30% EtOAc in cyclohexane). [α]$_D$ +9.3 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J=8.0 Hz, 2H), 7.34–7.15 (m, 13H), 5.67–5.63 (m, 2H), 5.42–5.38 (m, 1H), 5.04 (d, J=10.5 Hz, 1H), 4.69 (d, J=10.5 Hz, 1H), 4.63 (d, J=8.1 Hz, 1H), 4.52 (d, J=11.1 Hz, 1H), 4.39 (d, J=11.1 Hz, 1H), 4.32 (m, 1H), 3.95–3.92 (m, 1H), 3.89–3.79 (m, 1H), 1.21 (s, 9H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −76.0 (dd, J=197.8, 11.3 Hz, 1F), −77.0 (dd, J=197.8, 12.4 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.4, 137.3, 134.3, 129.2, 128.3, 127.3 (t, J=300.0 Hz), 122.9, 83.6, 77.0, 75.1, 71.3, 62.1 (t, J=23.8 Hz), 57.1, 22.8. IR (neat) ν_{max} 3306, 2958, 2868, 1255, 1179 cm^{-1}. MS (ESI$^+$) m/z=608.13 ([M+H]$^+$). HRMS (CI$^+$) calcd for $C_{30}H_{36}F_2NO_3SSe$ ([M+H]$^+$) m/z 608.1548, found 608.1544.

4.17. (R_S,2*S*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-*tert*-butanesulfinamido-1,1-difluoro-5-methylcyclopentane (29)

To a degassed solution of **27** (100 mg, 0.165 mmol) and AIBN (8.2 mg, 0.05 mmol, 0.3 equiv) in 4 mL of *t*-BuOH was added over 1 h under reflux a degassed solution of Bu_3SnH (70 μL, 0.247 mmol, 1.5 equiv) in 2 mL of *t*-BuOH. AIBN (0.3 equiv) was added each 30 min until total consumption of the starting material (followed by ^{19}F NMR). The solvent was then evaporated and the crude residue obtained was purified by flash chromatography (cyclohexane/AcOEt 95:5 to 80:20) to afford the desired product (46 mg, 72%) as a colorless oil and as a mixture of diastereomers. R_f=0.52 (30% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.23 (m, 10H), 4.75 (d, J=18.8 Hz, 1H), 4.71 (d, J=18.8 Hz, 1H′), 4.59–4.48 (m, 2H+2H′), 4.41 (d, J=18.8 Hz, 1H), 4.36 (d, J=18.8 Hz, 1H′), 4.14–3.97 (m, 3H+3H′), 3.70 (d, J=6.1 Hz, 1H′), 3.53 (d, J=7.2 Hz, 1H), 2.58–2.49 (m, 1H′), 2.32–2.06 (m, 1H), 1.25 (s, 9H+9H′), 1.16 (d, J=7.1 Hz, 3H), 1.06 (d, J=7.1 Hz, 3H′). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −101.3 (d, J=250.8 Hz), −105.8 (d, J=235.8 Hz), −106.6 (d, J=234.1 Hz), −120.3 (d, J=232.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.6, 136.5, 136.3, 136.2, 128.9, 128.8, 128.7, 128.6, 128.4 (2C), 128.2 (2C), 128.0, 127.9, 126.1 (t, J=256.1 Hz), 86.9 (d, J=7.2 Hz), 80.6, 80.5, 80.4, 80.3, 80.2, 80.0, 73.0 (2C), 72.4, 72.3, 61.6 (d, J=19.1 Hz), 61.2 (d, J=19.1 Hz), 60.8 (d, J=19.1 Hz), 60.5 (d, J=19.1 Hz), 56.8, 56.7, 43.7 (t, J=21.8 Hz), 41.9 (t, J=23.0 Hz), 22.8, 11.0 (d, J=6.9 Hz), 7.3 (d, J=7.4 Hz). MS (ESI$^+$): m/z=452.20 ([M+H]$^+$), 903.0 ([2M+H]$^+$). Anal. Calcd for

$C_{24}H_{31}F_2NO_3S$: C, 63.83; H, 6.92; N, 3.10; S, 7.10. Found: C, 63.91; H, 7.26; N, 3.09; S, 6.78.

4.18. (*S*S,2*S*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-*tert*-butanesulfinamido-1,1-difluoro-5-methylcyclopentane (33)

The same procedure was applied to **31** (100 mg, 0.165 mmol). Purification by column chromatography using cyclohexane/AcOEt (95:5 to 80:20) to afford **33** (50 mg, 78%) as a colorless oil and as a mixture of diastereomers. Only the analytical data of the major (*S*S,2*S*,3*R*,4*R*,5*R*) diastereomer **33** are provided. R_f=0.19 (20% AcOEt in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J=7.8 Hz, 2H), 7.38–7.28 (m, 8H), 4.88 (d, J=11.6 Hz, 1H), 4.66 (d, J=11.6 Hz, 1H), 4.58 (s, 2H), 3.87–3.77 (m, 2H), 3.59–3.55 (m, 1H), 3.42 (d, J=6.6 Hz, 1H), 2.38–2.23 (m, 1H), 1.22 (s, 9H), 1.14 (d, J=7.9 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −103.9 to −104.0+−104.7 to −104.9 (m, 1F), −109.8 (dt, J=234.6, 8.6 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 137.8, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.3, 124.8 (dd, J=258.9, 253.3 Hz), 86.3 (d, J=5.8 Hz), 85.6 (dd, J=5.5, 2.6 Hz), 73.1, 72.6, 63.8 (dd, J=26.6, 19.1 Hz), 57.0, 43.7 (dd, J=23.0, 20.8 Hz), 22.7, 12.7 (dd, J=6.5, 3.9 Hz). MS (ESI$^+$): m/z=452.13 ([M+H]$^+$). Anal. Calcd for $C_{24}H_{31}F_2NO_3S$: C, 63.83; H, 6.92; N, 3.10; S, 7.10. Found: C, 63.87; H, 6.88; N, 3.09; S, 7.01.

4.19. (2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-1,1-difluoro-1-phenylselanyl-2-acetamido-hex-5-ene (28)

To a solution of **27** (200 mg, 0.33 mmol) in 4.5 mL of anhydrous MeOH was added HCl (4 M in dioxane, 83 μL, 1 equiv) every hour until total consumption of the starting material. After concentration, the crude residue (196 mg, 0.39 mmol) was dissolved in 10 mL of anhydrous CH_2Cl_2 then Et_3N (0.11 mL, 0.78 mmol, 2 equiv), DMAP (6 mg, 0.05 mmol, 0.12 equiv), and Ac_2O (0.073 mL, 0.78 mmol, 2 equiv) were added. After 1 h 30 min stirring at rt, water was added. The aqueous layer was then extracted with CH_2Cl_2 and the combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash chromatography (cyclohexane/AcOEt 95:05 to 80:20) to afford **28** (161 mg, 90% overall). R_f=0.42 (30% EtOAc in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J=7.9 Hz, 2H), 7.37–7.16 (m, 13H), 7.02 (d, J=9.2 Hz, 1H), 5.90 (ddd, J=18.2, 10.1, 8.0 Hz, 1H), 5.29–5.13 (m, 2H), 5.10–4.91 (m, 1H), 4.54 (d, J=11.7 Hz, 1H), 4.43 (d, J=10.6 Hz, 1H), 4.28 (d, J=10.3 Hz, 1H), 4.14 (d, J=10.3 Hz, 2H), 3.65 (s, 1H), 1.68 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −77.0 (dd, J=197.7, 7.2 Hz, 1F), −78.8 (dd, J=197.7, 19.6 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 137.9, 137.5, 137.0, 135.4, 130.3, 129.7, 129.3, 128.9, 128.5, 124.6 (t, J=300.4 Hz), 120.1, 83.7, 77.1, 72.9, 71.9, 55.0 (dd, J=24.9, 20.7 Hz), 23.6. IR (neat) ν_{max} 3397, 3031, 2868, 1686 cm^{-1}. MS (ESI$^+$) m/z=562.80 ([M+H_2O]$^+$), 546 ([M+H]$^+$). Anal. Calcd for $C_{28}H_{29}F_2NO_3Se$: C, 61.76; H, 5.37; N, 2.57. Found: C, 61.74; H, 5.23; N, 2.53.

4.20. (2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-1,1-difluoro-1-phenylselanyl-2-acetamido-hex-5-ene (32)

The same procedure was applied to **31** (200 mg, 0.33 mmol). Purification by column chromatography using cyclohexane/AcOEt (95:05 to 80:20) afforded **32** (152 mg, 85% overall). R_f=0.28 (30% EtOAc in cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J=7.0 Hz, 2H), 7.34–7.14 (m, 13H), 6.23 (d, J=9.6 Hz, 1H), 5.72 (ddd, J=15.6, 10.0, 7.6 Hz, 1H), 5.40 (d, J=1.9 Hz, 1H), 5.34 (d, J=3.3 Hz, 1H), 4.88 (d, J=10.2 Hz, 1H), 4.81 (dt, J=16.4, 7.4 Hz, 1H), 4.65 (dd, J=12.8, 10.3 Hz, 2H), 4.39 (d, J=11.8 Hz, 1H), 4.08 (d, J=7.6 Hz, 1H), 3.87 (t, J=7.5 Hz, 1H), 2.01 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −76.2 (dd, J=197.7, 8.2 Hz, 1F), −78.4 (dd, J=197.7, 16.5 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 138.4, 137.8, 137.5, 134.0, 129.7, 129.4, 128.7, 128.6 (2C), 128.3, 127.9, 126.8 (t, J=301.4 Hz), 121.1, 81.1, 75.0, 71.1, 54.2 (dd, J=24.7, 22.4 Hz), 23.5. IR (neat) ν_{max} 3433, 3031, 2867, 1689 cm^{-1}. MS (ESI$^+$) m/z=562.80 ([M+H_2O]$^+$), 546 ([M+H]$^+$). HRMS (CI$^+$) calcd for $C_{28}H_{30}F_2NO_3Se$ ([M+H]$^+$) m/z 546.1359, found 546.1363.

Acknowledgements

We thank the Centre National de la Recherche Scientifique (CNRS) and the Région Haute-Normandie for a PhD grant to G.F. We also thank Dr. Pedro Lameiras, Sophie Guillard, and Pr. Hassan Oulyadi (LRMN, COBRA UMR 6014, Mont Saint-Aignan, France) for the NOESY experiments.

Supplementary data

Copies of ^{1}H, ^{19}F, ^{13}C NMR spectra for most compounds as well as copies of NOESY spectra for **20a**, **20b**, **21**, **23**, and **29** are provided. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.03.079.

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