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Synthesis of *exo*-methylenedifluorocyclopentanes as precursors of fluorinated carbasugars by 5-*exo*-dig radical cyclization

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ABSTRACT

The synthesis of polyhydroxylated 1,1-difluoro-5-methylenecyclopentanes is described. The sequence involves an addition of $PhSeCF_2TMS$ to a tartrate-derived aldehyde or its corresponding *tert*-butanesulfinylimines followed by a radical cyclization. The use of a benzyl protected substrate led to an unproductive 1,5-hydrogen transfer after cyclization but the desired compound was eventually obtained from the unprotected substrate. A hydroboration/oxidation sequence was investigated on these 1,1-difluoro-5-methylenecyclopentanes as it would provide fluorinated carbasugars, a new and promising class of glycomimetics. Unfortunately, this reaction was poorly efficient and its regioselectivity not the expected one.

Presentation of the research group:
The group entitled "Synthesis of fluorinated biomolecules" is part of the COBRA laboratory UMR-CNRS-6014 located in Mont-Sain-Aignan. The group is headed by Xavier Pannecoucke (Pr. INSA-Rouen), with 6 permanent co-workers: Jean-Philippe Bouillon (Pr. Univ-Rouen), Dominique Cahard (DR CNRS), Samuel Couve-Bonnaire (lecturer INSA-Rouen), Philippe Jubault (Pr. INSA-Rouen), Eric Leclerc (CR CNRS) and Jean-Charles Quirion (Pr. INSA-Rouen).
Our research interests are dealing with the development of new methodologies in fluorine chemistry and their application to the synthesis of fluorinated biomolecules.
Methodological studies:

Enantioselective electrophilic fluorination and trifluoromethylation (chiral reagents, organometallic catalysis and organocatalysis).
Diethylzinc/Ethyldibromofluoroacetate: an original association for the synthesis of new fluorinated scaffolds.

Fluorinated biomolecules and applications:

- Fluorinated glycomimetics (C-glycosides and carba-sugars).
- Fluoroalkene as amide bond mimic: Asymmetric synthesis of fluorinated dipeptide analogues and synthesis of alkaloid analogues.
- Fluorinated polyfunctional cyclopropanes as therapeutic agents.
- Synthesis of trifluoromethylated heterocycles from perfluoroketene dithioacetals and γ-ketothioesters, for pharmaceutical applications.

1. Introduction

The development of new nucleoside analogues remains 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]. The use of a

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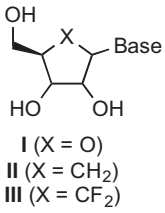
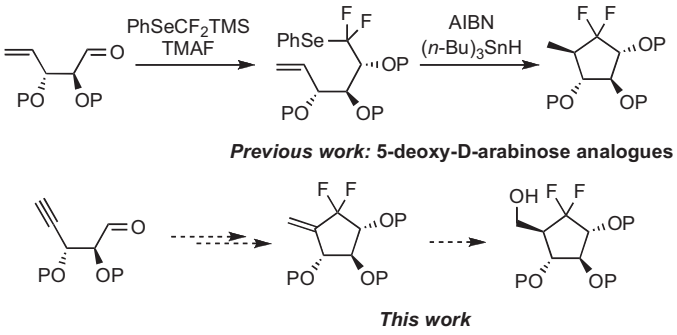


Fig. 1. Nucleoside and analogues.



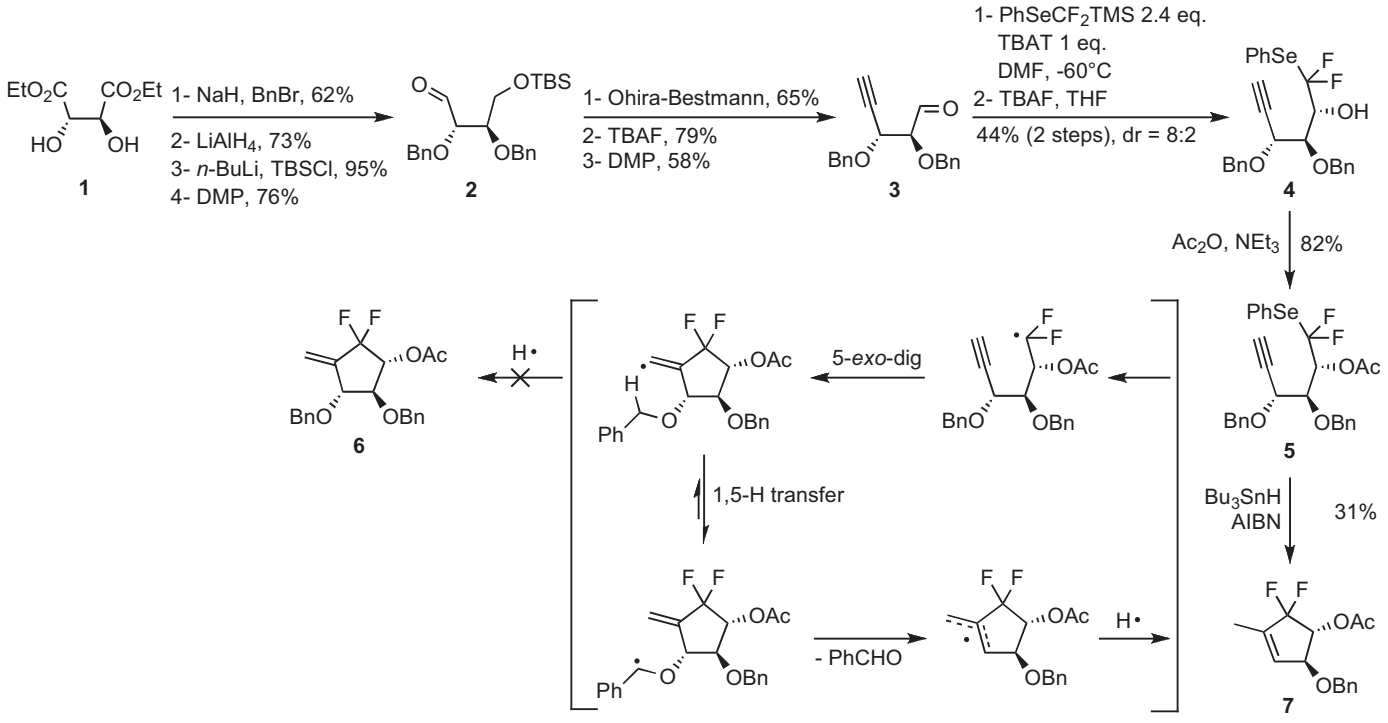
Scheme 1. General retrosynthetic scheme.

standard sugar backbone (**I**, X = O, Fig. 1) with modifications either on the base or on the substituents of the carbohydrate ring led to several powerful anticancer or antiviral drugs (5-fluorouracil, gemcitabine, azidothymidine, zalcitabine). Carbocyclic nucleosides (**II**, X = CH_2, Fig. 1) have more recently emerged in this field and several lead compounds have been discovered (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.

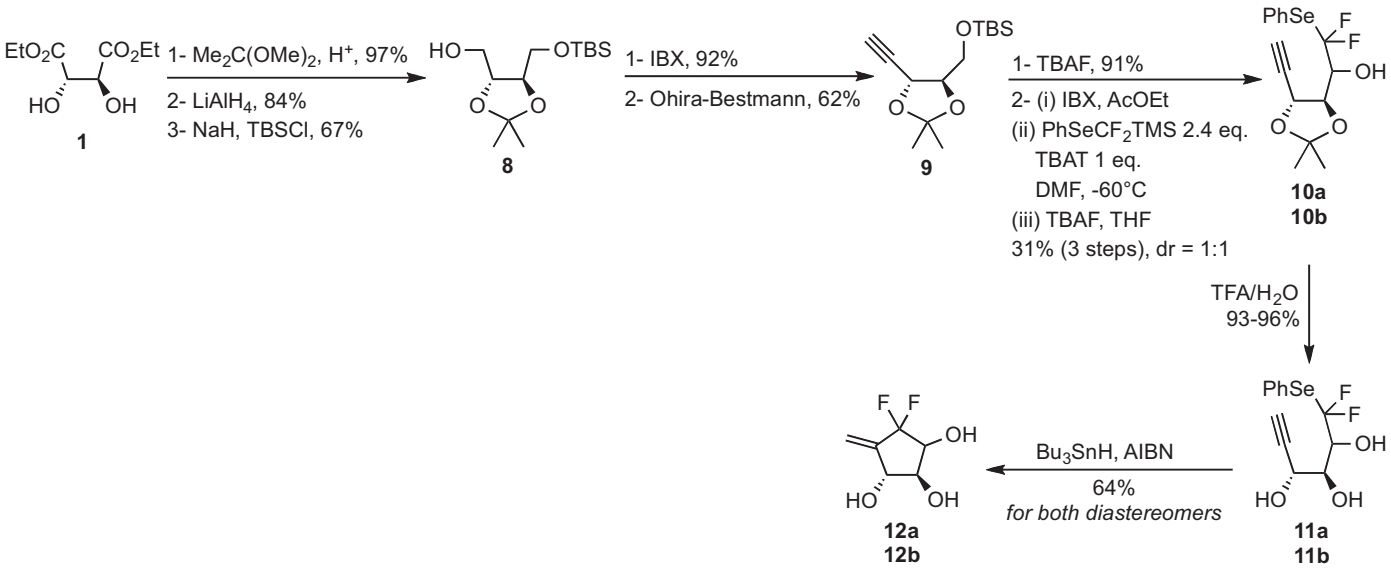
The fluorination of various positions on the base or on the pentose backbone has been widely studied, especially the replacement of the hydroxyl group in 2-position of the sugar backbone which is known to slow down the metabolic cleavage of the N-glycosidic bond and gave rise to efficient drugs (gemcitabine, clorofarabine) [3]. We were to our part interested in the synthesis of CF_2-carbocyclic nucleosides **III**, in which the intracyclic oxygen atom is replaced by a CF_2 group. Such compounds were indeed only scarcely described and no general method for their preparation was provided (Scheme 1) [4,5]. The stereoelectronic properties of the fluorine atom (strong electronegativity, small size) might nevertheless reasonably impart to these surrogates better mimicking abilities than the apolar CH_2 group [3b] The synthesis of fluorinated carbanucleosides obviously required a general method to prepare fluorocarbocyclic analogues of pentoses. We already reported a synthetic route to 5-deoxy-CF_2-carbasugars based on a 5-*exo*-trig reductive radical cyclization of a precursor obtained from an addition of $PhSeCF_2TMS$ to the corresponding aldehyde (Scheme 1) [6]. One of the ways to obtain exact analogues of sugars using the same strategy was to perform a 5-*exo*-dig radical cyclization on a similar substrate featuring a terminal triple bond. The resulting *exo*-methylenedifluorocyclopentane could indeed be adequately functionalized to provide the desired CF_2-carbasugar (Scheme 1). We wish to report herein the work which has been achieved using such an approach.

2. Results and discussion

The benzyl-protected ynal **3** was prepared from D-diethyltartrate **1** using modifications of the literature procedures (Scheme 2). Aldehyde **2** was obtained, according to Marshall's procedure, by benzylation, complete reduction, monoprotection with a *tert*-butyldimethylsilyl (TBS) group and oxidation with Dess–Martin periodinane (DMP) of **1** [7]. The triple bond was introduced using the Ohira–Bestmann reagent [8] and the remaining alcohol was deprotected. Aldehyde **3** was obtained after another Dess–Martin oxidation and subjected to the fluoride-promoted addition of



Scheme 2. First synthesis with a benzyl-protected substrate.

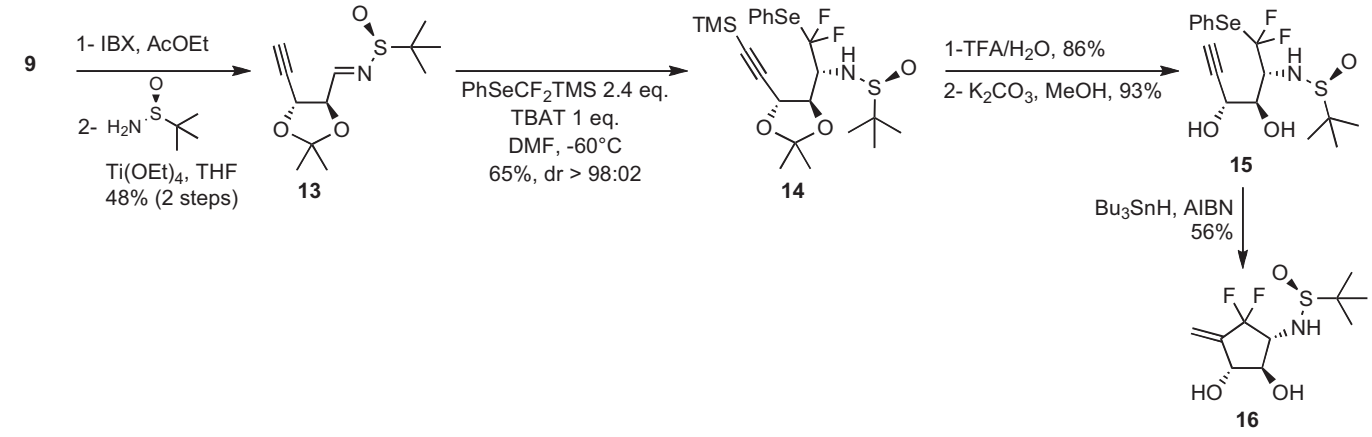


Scheme 3. Synthesis of an *exo*-methylene-1,1-difluoro-2,3,4-*tris*(hydroxy)-cyclopentane.

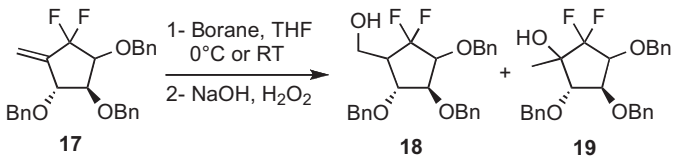
$PhSeCF_2TMS$ [9]. The two-step sequence involving a subsequent deprotection of the OH/OTMS mixture obtained from the addition provided the desired compound **4** in moderate yield and with the usual diastereoselectivity [6]. Up to that point, the only marked difference compared to our previous work on enals concerns the fluoride source that was used for the addition. Indeed, the addition proceeded smoothly on most of the enals using TMAF in DCM whereas this ynal required the use of TBAT in DMF as a promoter in order to obtain satisfactory yields. The radical precursor **5** was obtained after acetylation of **4** and subjected to the standard reductive radical cyclization conditions [6,10]. Unfortunately, compound **7** was obtained in 31% yield instead of the expected 5-*exo*-dig radical cyclization product **6**. The formation of **7** can be explained by a favorable 1,5-hydrogen transfer which takes place after the cyclization and prevent the reduction to **6**. The resulting stabilized benzylic radical undergoes an irreversible fragmentation reaction that yields benzaldehyde and an allylic radical. A final reduction of the latter with tin hydride affords **7** through a process that has already been reported on a non-fluorinated similar substrate [11].

This result was nonetheless encouraging since the targeted 5-*exo*-dig radical cyclization did occur despite subsequent degradation reactions. As the benzyl-protecting group is responsible for the hydrogen transfer and the fragmentation, it immediately appeared that a simple switch in the protecting groups should solve the problem. A synthesis of the acetonide-protected aldehyde was thus performed using a sequence similar to the previous one [12]. Alcohol **8** was prepared according to the literature procedure in three steps from **1** [12a,13]. The reported synthesis of **9** was slightly modified, using an IBX oxidation instead of the Swern reaction (Scheme 3) [12b,13]. A subsequent deprotection and another IBX oxidation afforded a moderately stable ynal which was not purified and directly subjected to the $PhSeCF_2TMS$ addition/deprotection sequence. Compound **10** was obtained in 31% yield over three steps from **9**. Surprisingly, the usual 8:2 diastereoselectivity dropped to 1:1 on this compound. The reason for this loss of selectivity remains unclear but is probably related to the conformational rigidity associated with an acetonide protecting group for this particular C-2/C-3 relative configuration [6]. The two diastereomers **10a** and **10b** could however be separated and the acetonide group has been removed on each one of them prior to cyclization. Compounds **11a** and **11b** underwent an efficient radical cyclization to provide the expected *exo*-methylenedifluorocyclopentanes **12a** and **12b** in 64% yield for both compounds (Scheme 3).

A similar sequence was applied to the *tert*-butanesulfinylimine **13** derived from the same aldehyde. Alcohol **9** was again oxidized with IBX and the crude aldehyde condensed with Ellman's



Scheme 4. Synthesis of an *exo*-methylene-2-amino-3,4-*bis*(hydroxy)-1,1-difluorocyclopentane.



	18	19
BH_3.THF	9%	35%
thexylborane	3%	12%
9-BBN	/	/

Scheme 5. Hydroboration of an *exo*-methylenedifluorocyclopentane.

auxiliary to afford **13** in 48% overall yield. The $PhSeCF_2TMS$ addition was performed according to the reported procedure [10f] to afford **14** in 65% yield and as a single diastereomer (Scheme 4). The silylation of the triple bond was not anticipated and might result from the weak stability of the N–Si bond of the first intermediate: an equilibration and a transfer of the silicon group from the sulfinamide to the alkyne might take place. The higher stability of the O–Si bond prevent this side-reaction in the case of **4** and **10**. This high diastereoselectivity (matched case) is in agreement with the previously reported results obtained on eneimines [6b]. The triple bond was however silylated during the process and a complete deprotection was thus performed prior to the cyclization which proceeded smoothly to afford **16** in 56% yield (Scheme 4).

Having in hand functionalized *exo*-methylenedifluorocyclopentanes, our next move was to investigate the hydroboration/oxidation of the double bond in order to prepare fluorocarbocyclic analogues of arabinose. The hydroboration of the unprotected compounds **12** with BH_3.THF either led to incomplete conversion or to degradation of the starting material when an excess of reagent was used. Both diastereomers were thus benzylated and compounds **17** were subjected to a hydroboration/oxidation sequence which provided alcohols **18** and **19** in low yields (Scheme 5). Surprisingly, a Markovnikov-type regioselectivity was observed for this reaction since **19** was the major compound. The use of sterically hindered boranes such as thexylborane or 9-BBN only led to a loss of reactivity without improving the regioselectivity. It has already been reported in the literature that a CF_2 group α to the double bond could favor this type of regioselectivity and that the Markovnikov regioisomer could even be the exclusive one when electrophilic boranes such as $HBCl_2$ are used [14]. However, the steric hindrance of C-4 and the boranes which were used should have led to a classical anti-Markovnikov regioselectivity and this result remains puzzling, even in light of the literature reports.

3. Conclusion

An efficient preparation of polyfunctionalized 1,1-difluoro-5-methylenecyclopentanes has thus been carried out. The synthetic pathway involves an addition of $PhSeCF_2TMS$ to tartrate-derived aldehydes or *tert*-butanesulfinylimines featuring a terminal triple bond followed by a reductive 5-*exo*-dig radical cyclization. The $PhSeCF_2TMS$ addition proceeded in agreement with our previous reports except for the aldehyde derived from **9** for which no diastereoselectivity was observed. The reductive 5-*exo*-dig radical cyclization was efficient in all cases despite an undesired 1,5-hydrogen transfer in the case of **6** which changed the course of the reaction to afford **7** instead of the expected compound. These *exo*-methylenedifluorocyclopentanes appeared as a nice entry to fluorocarbocyclic analogues of pentoses but, to our disappointment, the final and crucial hydroboration/oxidation sequence was a failure. Poor yields and an unexpected regioselectivity were indeed obtained and another route to fluorocarbocyclic analogues of pentoses and nucleosides has thus to be disclosed. Work is currently in progress in our laboratory to bring solutions to this synthetic challenge.

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 pre-packed 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 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 a FT-IR Spectrometer. Optical rotations were measured at 20 °C and with λ = 589 nm; concentrations are expressed in cg mL^{-1}.

4.2. (2S,3R)-2,3-Bis(benzyloxy)pent-4-ynal (3)

To a flask containing **2** [7] (522 mg, 1.26 mmol) were added Bestmann–Ohira reagent (362 mg, 1.89 mmol, 1.5 equiv.), MeOH (20 mL) and K_2CO_3 (348 mg, 2.52 mmol, 2 equiv.) in one portion. The resulting suspension was stirred at room temperature overnight where after saturated aqueous NH_4Cl was added. The resulting solution was extracted with Et_2O, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (cyclohexane/EtOAc 95:05) to afford (2*S*,3*R*)-2,3-bis(benzyloxy)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-pent-1-yne (336 mg, 65%) as a colorless oil. Rf = 0.51 (5% EtOAc in cyclohexane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 10H), 4.84 (d, J = 11.7 Hz, 1H), 4.78 (dd, J = 16.7 Hz, J = 11.6 Hz, 2H), 4.55 (d, J = 11.7 Hz, 1H), 4.30 (dd, J = 10.7 Hz, J = 2.11 Hz, 1H), 3.93–3.88 (m, 1H), 3.81–3.71 (m, 1H), 3.65 (dd, J = 10.3 Hz, J = 5.3 Hz, 1H), 2.51 (d, J = 2.1 Hz, 1H), 0.88 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9, 138.0, 128.7, 128.6, 128.5, 128.3, 128.0, 127.8, 81.7, 80.9, 75.5, 74.0, 71.3, 69.0, 63.3, 26.2, 18.6, −5.1. IR (neat) ν_{max} 3306, 2929, 1094 cm^{-1}. MS (ESI+): m/z = 428.13 ([M+H_2O]$^+$). Anal. Calcd. for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 72.78; H, 8.29. To a solution of (2*S*,3*R*)-2,3-bis(benzyloxy)-4-{[*tert*-butyl(dimethyl)silyl]oxy}pent-1-yne (1.5 g, 3.7 mmol) in dry THF (45 mL) was added a solution of TBAF (1 M in THF, 4.5 mL, 4.5 mmol, 1.2 equiv.). The mixture was then stirred at room temperature for 1 h, then water was added and the product 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 column chromatography (cyclohexane/EtOAc 90:10 then 85:15) to afford (2*R*,3*R*)-2,3-bis(benzyloxy)pent-4-yn-1-ol (840 mg, 91%) as a colorless oil. Rf = 0.33 (20% EtOAc in cyclohexane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 10H), 4.87 (d, J = 8.4 Hz, 1H), 4.84

(d, J = 8.4 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.33 (dd, J = 5.9 Hz, J = 2.2 Hz, 1H), 3.94–3.86 (m, 1H), 3.83–3.78 (m, 1H), 3.76–3.70 (m, 1H), 2.58 (d, J = 2.1 Hz, 1H), 2.07 (dd, J = 6.8 Hz, J = 5.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.3, 137.6, 128.8, 128.3, 128.2, 80.6, 77.6, 76.6, 73.9, 71.4, 70.2, 62.6. IR (neat) ν_{max} 3418, 3287, 2874, 1072 cm^{-1}. MS (ESI+): m/z = 314.43 ($[M+H_2O]^{+}$[1,30]), 615.00 ($[2M+Na]^{+}$). Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.09; H, 7.03. To a solution of (2*R*,3*R*)-2,3-bis(benzyloxy)pent-4-yn-1-ol (1.0 g, 3.4 mmol) in CH_2Cl_2 (10 mL) at room temperature was added Dess–Martin reagent (15 wt% in CH_2Cl_2, 8.5 mL, 3.9 mmol, 1.1 equiv.). After 1 h the reaction mixture was diluted with ether and a solution of $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ was poured into the flask. After 10 min stirring, the two layers were separated and the ether layer was washed with saturated aqueous $NaHCO_3$. The combined aqueous phases were extracted twice with ether, and the combined ether extracts were dried over $MgSO_4$ and concentrated. The crude residue was then purified by flash column chromatography (cyclohexane/EtOAc 90:10 then 80:20) to afford the desired product **3** (862 mg, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.39–7.27 (m, 10H), 4.86–4.75 (m, 3H), 4.55 (d, J = 15.6 Hz, 1H), 4.45 (dd, J = 4.3 Hz, J = 2.3 Hz, 1H), 3.94 (dd, J = 4.4 Hz, J = 1.5 Hz, 1H), 2.63 (d, J = 2.3 Hz, 1H).

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

To a solution of aldehyde **3** (862 mg, 2.93 mmol) and $PhSeCF_2TMS$ (1.96 g, 7.03 mmol, 2.4 equiv.), with suspended MS 4 Å, in dry DMF (20 mL) at −60 °C was added TBAT (1.57 g, 2.93 mmol, 1 equiv.). The reaction mixture was allowed to stir at −60 °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 the crude residue in dry THF (50 mL) was added a solution of TBAF (1 M in THF, 5.86 mL, 5.86 mmol, 2 equiv.). The mixture was then stirred at room temperature 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/EtOAc (gradient from 99:01 to 90:10) and the two diastereomers could be separated to afford **4** (486 mg) and the minor (2*R*,3*R*,4*R*) diastereomer (156 mg, 44% overall) as yellow oils. Rf = 0.30 (10% EtOAc in cyclohexane). $[\alpha]_D$ = −11.5 (c 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 7.3 Hz, 2H), 7.43–7.28 (m, 13H), 4.94 (d, J = 10.7 Hz, 1H), 4.87 (d, J = 11.9 Hz, 1H), 4.71 (d, J = 10.7 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.36 (dd, J = 8.0 Hz, J = 2.2 Hz, 1H), 4.34–4.24 (m, 1H), 4.07 (d, J = 8.0 Hz, 1H), 3.24 (d, J = 10.7 Hz, 1H), 2.57 (d, J = 2.2 Hz, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −79.3 (dd, J = 209.0 Hz, J = 8.1 Hz, 1F), −82.7 (dd, J = 209.5 Hz, J = 15.6 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.7, 137.5, 129.8, 129.5, 128.8, 128.7, 128.4, 128.3, 128.2, 127.3 (t, J = 300.2 Hz), 124.0, 79.5, 77.6, 75.5, 73.3 (dd, J = 26.2 Hz, J = 23.8 Hz), 71.9, 71.3. Anal. Calcd. for $C_{26}H_{24}F_2O_3Se$: C, 62.28; H, 4.82. Found: C, 61.95; H, 5.07.

4.4. (2R,3S,4R)-2-Acetoxy-3,4-bis(benzyloxy)-1,1-difluoro-1-phenylselanyl-hex-5-yne (5)

To a solution of compound **4** (486 mg, 0.97 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (0.23 mL, 1.68 mmol, 1.7 equiv.), DMAP (15 mg, 0.12 mmol, 0.1 equiv.) and Ac_2O (0.18 mL, 1.94 mmol, 2 equiv.). The mixture was stirred at room temperature for 1 h, then water was added and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was then purified by flash chromatography using cyclohexane/EtOAc (95:05) as eluent to afford the desired product **5** (430 mg, 82%) as a pale yellow oil. Rf = 0.12 (5% EtOAc in cyclohexane). $[\alpha]_D$ = −41.7 (c 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.44–7.28 (m, 13H), 5.78 (td, J = 10.8 Hz, J = 2.1 Hz, 1H), 4.94–4.75 (m, 3H), 4.47 (d, J = 11.4 Hz, 1H), 4.25 (dd, J = 7.3 Hz, J = 2.1 Hz, 1H), 4.15 (dd, J = 7.3 Hz, J = 2.1 Hz, 1H), 2.54 (d, J = 2.1 Hz, 1H), 2.14 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −76.7 (dd, J = 215.9 Hz, J = 11.0 Hz, 1F), −78.1 (dd, J = 215.9 Hz, J = 11.0 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6, 137.9, 137.8, 137.7, 137.5, 137.0, 129.9, 129.4, 129.0, 128.7, 128.6, 128.4, 128.3, 128.2, 124.8 (t, J = 300.0 Hz), 124.0, 79.3, 77.6, 77.0, 75.4, 72.5 (t, J = 25.7 Hz), 71.6, 70.1, 21.2. IR (neat) ν_{max} 3285, 3063, 2871, 1760, 1217, 1071 cm^{-1}. MS (ESI+): m/z = 562.07 ($[M+H_2O]^{+}$). Anal. Calcd. for $C_{28}H_{26}F_2O_4Se$: C, 61.88; H, 4.82. Found: C, 61.63; H, 5.07.

4.5. (4S,5R)-5-(O-Acetyl)-4-(O-benzyl)-1,1-difluoro-2-methylcyclopent-2-en-4,5-diol (7)

To a solution of compound **5** (100 mg, 0.18 mmol) in *t*-BuOH (4 mL) was added AIBN (9 mg, 0.06 mmol, 0.3 equiv.). The mixture was then degassed, heated at 80 °C and a degassed solution of Bu_3SnH (74 μL, 0.28 mmol, 1.5 equiv.) in *t*-BuOH (2 mL) was added dropwise via a syringe pump over 45 min. After 1 h, the solvent was evaporated and the crude residue was purified by flash chromatography using cyclohexane/EtOAc (99:01 then 98:02) as eluent to afford product **7** (16 mg, 31%) as a pale yellow oil. Rf = 0.41 (10% EtOAc in cyclohexane). $[\alpha]_D$ = +72.0 (c 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 5.91 (s, 1H), 5.32 (ddd, J = 11.4 Hz, J = 5.2 Hz, J = 3.1 Hz, 1H), 4.60 (dd, 2H), 4.48–4.45 (m, 1H), 2.15 (s, 3H), 1.60 (s, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −97.0 (ddd, J = 259.0 Hz, J = 10.7 Hz, J = 9.0 Hz, 1F), −110.8 (dd, J = 257.8 Hz, J = 3.1 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 137.7, 133.4 (t, J = 8.7 Hz), 128.9, 128.4, 128.2, 124.8 (t, J = 249.6 Hz), 82.0 (d, J = 4.4 Hz), 78.4 (dd, J = 27.3 Hz, J = 19.3 Hz), 72.3, 20.9, 10.6. IR (neat) ν_{max} 2925, 1757, 1234, 1096 cm^{-1}. MS (ESI+): m/z = 300.13 ($[M+H_2O]^{+}$). Anal. Calcd. for $C_{15}H_{16}F_2O_3$: C, 63.82; H, 5.71. Found: C, 63.79; H, 6.05.

4.6. (2R,3S,4S) and (2S,3S,4S)-3,4-(O-isopropylidene)-1,1-difluoro-1-(phenylselanyl)-hex-5-yn-2,3,4-triol (10)

To a solution of compound **9** (1.6 g, 5.9 mmol) in dry THF (50 mL) was added a solution of TBAF (1 M in THF, 7.1 mL, 7.1 mmol, 1.2 equiv.) and the mixture was stirred at room temperature for 1 h. Water was then added and the product 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 column chromatography (cyclohexane/EtOAc 90:10 then 80:20) to afford (2*R*,3*R*)-2,3-(*O*-isopropylidene)pent-4-yn-1-ol(840 mg, 91%) as a colorless oil. Rf = 0.22 (20% EtOAc in cyclohexane). $[\alpha]_D$ = +13.8 (c 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (dd, J = 7.6 Hz, J = 2.2 Hz, 1H), 4.18 (dt, J = 6.6 Hz, J = 2.7 Hz, 1H), 3.90 (dd, J = 12.4 Hz, J = 3.1 Hz, 1H), 3.68 (dd, J = 12.4 Hz, J = 3.7 Hz, 1H), 2.55 (d, J = 2.2 Hz, 1H), 1.90 (br s, 1H), 1.50 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 111.0, 82.2, 80.9, 75.2, 66.5, 61.0, 27.0, 26.3. IR (neat) ν_{max} 3434, 3290, 2990, 2937, 1384, 1216, 1068 cm^{-1}. MS (EI): m/z = 141.1 ($[M-CH_3]^{+}$). Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.51; H, 7.85. (2*R*,3*R*)-2,3-(*O*-Isopropylidene)pent-4-yn-1-ol (200 mg, 1.28 mmol) was dissolved in EtOAc (8 mL). IBX (1.08 g, 3.84 mmol, 3 equiv.) was added and the mixture was refluxed for 7 h (TLC cyclohexane/EtOAc 80:20). The reaction was filtered through a sintered glass funnel to remove the excess IBX and its byproducts and washed with EtOAc. The solvent was removed under reduced

pressure to give the crude aldehyde (217 mg, quantitative yield) as a colorless oil. This unstable aldehyde was used for the next step without further purification. To a solution of aldehyde (200 mg, 1.28 mmol) and $PhSeCF_2TMS$ (859 mg, 3.07 mmol, 2.4 equiv.), with suspended MS 4 Å, in dry DMF (20 mL) at −60 °C was added TBAT (685 mg, 1.28 mmol, 1 equiv.). The reaction mixture was allowed to stir at −60 °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 the crude residue in dry THF was added a solution of TBAF (1 M in THF, 2.56 mL, 2 equiv.). The mixture was then stirred at room temperature 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/EtOAc (gradient from 99:01 to 90:10) as eluent to afford the separated (2*S*,3*R*,4*R*) and (2*R*,3*R*,4*R*) diastereomers **10a** and **10b** (63 mg and 71 mg respectively, 31% overall) as yellow oils. **10a**: Rf = 0.19 (10% EtOAc in cyclohexane). $[\alpha]_D$ = +27.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 2H), 7.46–7.33 (m, 3H), 4.61 (dd, *J* = 7.7 Hz, *J* = 2.1 Hz, 1H), 4.40 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H), 3.96–3.85 (m, 1H), 2.91 (d, *J* = 10.7 Hz, 1H), 2.57 (d, *J* = 1.8 Hz, 1H), 1.52 (s, 3H), 1.47 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −79.6 (dd, *J* = 212.9 Hz, *J* = 8.2 Hz, 1F), −81.6 (dd, *J* = 213.1 Hz, *J* = 14.3 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.8, 130.0, 129.6, 126.3 (t, *J* = 168.5 Hz), 112.3, 79.6, 77.6, 76.0, 72.2 (t, *J* = 25.0 Hz), 67.8, 26.8, 26.6. Anal. Calcd. for $C_{15}H_{16}F_2O_3Se$: C, 49.87; H, 4.46. Found: C, 50.10; H, 4.34. **10b**: Rf = 0.13 (10% EtOAc in cyclohexane). $[\alpha]_D$ = +9.4 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.46–7.33 (m, 3H), 4.90 (dd, *J* = 5.9 Hz, *J* = 2.1 Hz, 1H), 4.50 (t, *J* = 5.0 Hz, 1H), 4.18–4.08 (m, 1H), 2.67 (d, *J* = 4.7 Hz, 1H), 2.53 (d, *J* = 2.1 Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −78.5 (dd, *J* = 215.1 Hz, *J* = 7.9 Hz, 1F), −82.8 (dd, *J* = 214.9 Hz, *J* = 15.5 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.8, 130.1, 129.9, 129.8, 129.6, 129.5, 123.7 (t, *J* = 149.3 Hz), 111.4, 82.1, 80.4, 74.7, 74.3 (dd, *J* = 26.7 Hz, *J* = 22.5 Hz), 66.3 (d, *J* = 2.7 Hz), 27.0, 25.9. IR (neat) ν_{max} 3435, 3299, 1060 cm^{-1}. MS (EI): *m*/*z* = 362.0 ([M]$^+$), 347.0 ([M−CH_3]$^+$]. Anal. Calcd. for $C_{15}H_{16}F_2O_3Se$: C, 49.87; H, 4.46. Found: C, 49.96; H, 4.57.

4.7. 1,1-Difluoro-1-(phenylselanyl)-hex-5-yne-2,3,4-triol (11)

A solution of compound **10** (204 mg, 0.56 mmol) in a mixture of TFA (0.47 mL) and H_2O (0.12 mL) was stirred at room temperature for 3 h. The mixture was then concentrated under reduced pressure, co-evaporated twice with $CHCl_3$ and lyophilized overnight. The crude residue was then purified by flash chromatography using CH_2Cl_2/MeOH (gradient from 100:00 to 98:2) as eluent to afford the desired product **11** (174 mg, 96%) as a white solid. **11a**: Rf = 0.19 (5% MeOH in CH_2Cl_2). $[\alpha]_D$ = −14.6 (*c* 1.2, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 7.74 (d, *J* = 6.9 Hz, 2H), 7.47–7.35 (m, 3H), 4.35 (dd, *J* = 8.3 Hz, *J* = 2.2 Hz, 1H), 4.22 (t, *J* = 11.0 Hz, 2H), 3.89 (d, *J* = 8.2 Hz, 1H), 2.92 (d, *J* = 2.2 Hz, 1H). ^{19}F NMR (282.5 MHz, CD_3OD) δ −79.4 (dd, *J* = 210.5 Hz, *J* = 10.9 Hz, 1F), −80.5 (dd, *J* = 210.2 Hz, *J* = 11.2 Hz, 1F). ^{13}C NMR (75.5 MHz, CD_3OD) δ 139.3, 131.2, 130.9, 129.6 (t, *J* = 298.1 Hz), 126.5, 84.0, 77.0, 75.0 (t, *J* = 24.2 Hz), 74.4 (d, *J* = 2.9 Hz), 65.5. Anal. Calcd. for $C_{12}H_{12}F_2O_3Se$: C, 44.87; H, 3.77. Found: C, 45.11; H, 3.75. **11b**: Rf = 0.29 (5% MeOH in CH_2Cl_2). $[\alpha]_D$ = −12.0 (*c* 1.4, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 7.74 (d, 2H), 7.43–7.30 (m, 3H), 4.66 (t, *J* = 2.1 Hz, 1H), 4.07 (q, *J* = 10.0 Hz, 1H), 3.83 (dd, *J* = 8.5 Hz, *J* = 2.2 Hz, 1H), 2.83 (d, *J* = 2.3 Hz, 1H). ^{19}F NMR (282.5 MHz, CD_3OD) δ −77.6 (dd, *J* = 205.0 Hz, *J* = 10.9 Hz, 1F), −81.0 (dd, *J* = 206.3 Hz, *J* = 10.2 Hz, 1F). ^{13}C NMR (75.5 MHz, CD_3OD) δ 139.3, 131.0, 130.9, 130.8, 129.8 (t, *J* = 299.8 Hz), 127.1, 85.1, 75.9 (t, *J* = 22.1 Hz), 75.2, 75.0, 64.1. IR (neat) ν_{max} 3296, 1061 cm^{-1}. MS (EI): *m*/*z* = 322.0 ([M]$^+$). Anal. Calcd. for $C_{12}H_{12}F_2O_3Se$: C, 44.87; H, 3.77. Found: C, 45.02; H, 3.80.

4.8. (2R,3S,4S) and (2S,3S,4S)-1,1-difluoro-5-methylenecyclopentane-2,3,4-triol (12)

The same procedure as for the preparation of **7** was applied to **11a** and **11b**. In each case, the crude residue was purified by flash chromatography using CH_2Cl_2/MeOH (95:05 then 80:20) as eluent to afford **12a** or **12b** (64%) as a pale yellow oil. **12a**: Rf = 0.24 (5% MeOH in CH_2Cl_2). $[\alpha]_D$ = +84.5 (*c* 1.2, MeOH). ^{1}H NMR (300 MHz, MeOD) δ 5.81 (dt, *J* = 5.9 Hz, *J* = 3.0 Hz, 1H), 5.66 (dt, *J* = 5.3 Hz, *J* = 2.7 Hz, 1H), 4.20–4.17 (m, 1H), 3.83 (td, *J* = 11.9 Hz, *J* = 9.2 Hz, 1H), 3.63 (td, *J* = 8.4 Hz, *J* = 2.5 Hz, 1H). ^{19}F NMR (282.5 MHz, MeOD) δ −104.5 (dd, *J* = 251.7 Hz, *J* = 12.2 Hz, 1F), −106.0 (ddt, *J* = 252.4 Hz, *J* = 11.5 Hz, *J* = 3.7 Hz, 1F). ^{13}C NMR (75.5 MHz, MeOD) δ 147.5 (dd, *J* = 21.0 Hz, *J* = 19.7 Hz), 120.5 (t, *J* = 251.1 Hz), 118.0, 81.0 (d, *J* = 6.3 Hz), 78.2 (dd, *J* = 23.7 Hz, *J* = 19.7 Hz), 74.8 (t, *J* = 3.7 Hz). IR (neat) ν_{max} 3271, 1045 cm^{-1}. MS (CI+): *m*/*z* = 167 ([M+H]$^+$). Anal. Calcd. for $C_6H_8F_2O_3$: C, 43.38; H, 4.85. Found: C 43.54; H, 4.82. **12b**: Rf = 0.23 (10% MeOH in CH_2Cl_2). $[\alpha]_D$ = +20.3 (*c* 0.8, MeOH). ^{1}H NMR (300 MHz, MeOD) δ 5.77 (dt, *J* = 5.3 Hz, *J* = 2.7 Hz, 1H), 5.63 (dt, *J* = 5.3 Hz, *J* = 2.7 Hz, 1H), 4.45–4.41 (m, 1H), 4.02 (q, *J* = 4.7 Hz, 1H), 3.79 (dt, *J* = 8.7 Hz, *J* = 4.4 Hz, 1H). ^{19}F NMR (282.5 MHz, MeOD) δ −96.2 (d, *J* = 259.0 Hz, 1F), −110.9 (d, *J* = 258.0 Hz, 1F). ^{13}C NMR (75.5 MHz, MeOD) δ 148.8 (t, *J* = 20.9 Hz), 122.6 (dd, *J* = 258.0 Hz, *J* = 245.5 Hz), 118.6, 77.5, 76.9 (t, *J* = 2.7 Hz), 75.0 (dd, *J* = 30.7 Hz, *J* = 18.1 Hz). Anal. Calcd. for $C_6H_8F_2O_3$: C, 43.38; H, 4.85. Found: C 43.41; H, 4.79.

4.9. N-{[(4R,5R)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]methylene}-2-methylpropane-2-sulfinamide (13)

Compound **9** (156 mg, 1.0 mmol) was dissolved in EtOAc (6.5 mL). IBX (839 mg, 3.0 mmol, 3 equiv.) was added and the mixture was refluxed for 7 h (TLC cyclohexane/EtOAc 80:20). The reaction was filtered through a sintered glass funnel to remove the excess IBX and its byproducts and washed with EtOAc. The solvent was removed under reduced pressure to give the crude aldehyde (217 mg, quantitative yield) as a colorless oil. This unstable aldehyde was used in the next step without further purification. To a solution of aldehyde (154 mg, 1.00 mmol) and $Ti(OEt)_4$ (0.50 mL, 2.00 mmol, 2 equiv.) in 5 mL of anhydrous THF was added (*S*)-2-methyl-2-propanesulfinamide (121 mg, 1.00 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 EtOAc. The filtrate was then washed with 10 mL of saturated aqueous NaCl and the aqueous layer extracted with EtOAc. 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/EtOAc85:15) to afford the desired product **13** (123 mg, 48% over 2 steps) as a yellow oil. Rf = 0.42 (40% EtOAc in cyclohexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, *J* = 3.8 Hz, 1H), 4.84–4.76 (m, 2H), 2.60 (d, *J* = 2.1 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.23 (s, 9H).

4.10. (S_S,2R,3R,4S)-2-tert-Butanesulfinamido-3,4-(O-isopropylidene)-6-trimethylsilyl-1,1-difluoro-1-phenylselanyl-hex-5-yne (14)

To a solution of **13** (709 mg, 2.76 mmol) and $PhSeCF_2TMS$ (1.85 g, 6.62 mmol, 2.4 equiv.), with suspended MS 4 Å, in dry DMF (22 mL) at −60 °C was added TBAT (1.49 g, 2.76 mmol, 1 equiv.).

The reaction mixture was allowed to stir at −60 °C for 2 h. A saturated solution of NH_4Cl and water were then added and the aqueous layer was extracted with EtOAc. The combined organic layers were then washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was then purified by flash chromatography using cyclohexane/EtOAc (gradient from 99:01 to 90:10) as eluent to afford product **14** (960 mg, 65%) as a yellow oil. Rf = 0.52 (30% EtOAc in cyclohexane). $[\alpha]_D$ = +40.3 (*c* 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.0 Hz, 2H), 7.45–7.32 (m, 3H), 4.88 (d, *J* = 8.5 Hz, 1H), 4.44 (d, *J* = 8.1 Hz, 1H), 4.32 (d, *J* = 8.3 Hz, 1H), 3.84–3.74 (m, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.30 (s, 9H), 0.16 (s, 9H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −76.7 (dd, *J* = 207.3 Hz, *J* = 10.3 Hz, 1F), −78.1 (dd, *J* = 208.3 Hz, *J* = 12.4 Hz, 1F). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.7, 135.3 (t, *J* = 386.5 Hz), 129.9, 129.5, 124.0, 111.8, 99.9, 93.5, 77.4, 68.1, 60.9 (t, *J* = 24.2 Hz), 57.4, 27.0, 26.9, 23.0, 0.1. IR (neat) ν_{max} 3295, 2961, 2186, 1171, 1077 cm^{-1}. MS (ESI+): *m*/*z* = 537.8 ($[M+H]^+$), 1074.8 ($[2M+H]^+$). Anal. Calcd. for $C_{22}H_{33}F_2NO_3SSeSi$: C, 49.24; H, 6.20; N, 2.61; S, 5.98. Found: C, 49.30; H, 6.22; N, 2.69; S, 5.96.

4.11. *N*-{(2*R*,3*R*)-1-[Difluoro(phenylseleno)methyl]-2,3-dihydroxypent-4-yn-1-yl}-2-methylpropane-2-sulfinamide (15)

A solution of compound **14** (870 mg, 1.62 mmol) in a mixture of TFA (1.44 mL) and H_2O (0.36 mL) was stirred at room temperature for 3 h. The mixture was then concentrated under reduced pressure, co-evaporated twice with $CHCl_3$ and lyophilized overnight. The crude residue was then purified by flash chromatography using CH_2Cl_2/MeOH (97:03) as eluent to afford the desired product (690 mg, 86%) as a yellow oil. To a solution of this compound (657 mg, 1.32 mmol) was added K_2CO_3 (274 mg, 1.99 mmol, 1.5 equiv.) in MeOH (9 mL). After 1 h at room temperature, a saturated solution of NH_4Cl was added and the aqueous phases were extracted three times with EtOAc. The combined organic phases were then washed with water, brine, dried over $MgSO_4$ filtered and concentrated under reduced pressure to give the desired product **15** (520 mg, 93%) as a solid. Rf = 0.40 (4% MeOH in CH_2Cl_2). $[\alpha]_D$ = −41.9 (*c* 0.8, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 7.73–7.70 (m, 2H), 7.48–7.37 (m, 3H), 4.43 (dd, *J* = 9.0 Hz, *J* = 2.1 Hz, 1H), 4.09 (t, *J* = 11.3 Hz, 1H), 4.02 (d, *J* = 9.0 Hz, 1H), 2.98 (d, *J* = 2.1 Hz, 1H), 1.33 (s, 9H). ^{19}F NMR (282.5 MHz, CD_3OD) δ −77.1 (dd, *J* = 207.3 Hz, *J* = 11.3 Hz), −77.9 (dd, *J* = 207.3 Hz, *J* = 11.3 Hz). ^{13}C NMR (75.5 MHz, CD_3OD) δ 139.3, 131.5, 131.1, 129.0 (t, *J* = 299.8 Hz), 126.2, 83.8, 77.8, 73.3, 65.5, 65.2 (t, *J* = 23.1 Hz), 59.2, 23.9. IR (neat) ν_{max} 3372, 3264, 1048 cm^{-1}. MS (ESI+): *m*/*z* = 426.1 ($[M+H]^+$), 870.7 ($[2M+Na]^+$). Anal. Calcd. for $C_{16}H_{21}F_2NO_3SSe$: C, 45.28; H, 4.99; N, 3.30; S, 7.56. Found: C, 45.32; H, 4.97; N, 3.24; S, 7.63.

4.12. (S_S,2*R*,3*R*,4*S*)-2-tert-Butanesulfinamido-1,1-difluoro-5-methylenecyclopentane-3,4-diol (16)

The same procedure as for the preparation of **7** was applied to **15**. Purification of the crude material by flash chromatography using CH_2Cl_2/MeOH (gradient from 96:04 to 70:30) as eluent to afford **16** (56%) as a pale yellow solid. Rf = 0.38 (10% MeOH in CH_2Cl_2). $[\alpha]_D$ = +90.2 (*c* 1.3, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 5.82 (dt, *J* = 4.5 Hz, *J* = 2.6 Hz, 1H), 5.69 (dt, *J* = 5.1 Hz, *J* = 2.6 Hz, 1H), 4.27 (dt, *J* = 2.6 Hz, *J* = 2.3 Hz, 1H), 3.74 (td, *J* = 10.0 Hz, *J* = 1.5 Hz, 1H), 3.58 (td, *J* = 14.1 Hz, *J* = 11.3 Hz, 1H), 1.31 (s, 9H). ^{19}F NMR (282.5 MHz, CD_3OD) δ −99.2 (dd, *J* = 255.8 Hz, *J* = 16.5 Hz, 1F), −102.9 (dd, *J* = 253.7 Hz, *J* = 11.4 Hz, 1F). ^{13}C NMR (75.5 MHz, CD_3OD) δ 147.3 (dd, *J* = 20.9 Hz, *J* = 19.8 Hz), 120.3 (dd, *J* = 254.2 Hz, *J* = 248.2 Hz), 118.5 (d, *J* = 2.2 Hz), 79.4 (d, *J* = 6.0 Hz), 75.3 (t, *J* = 3.8 Hz), 67.7 (dd, *J* = 21.4 Hz, *J* = 19.2 Hz), 58.9, 23.9. IR (neat) ν_{max} 3394, 1681, 1044 cm^{-1}. MS (EI): *m*/*z* = 269 ($[M]^+$). Anal. Calcd. for $C_{10}H_{17}F_2NO_3S$: C, 44.60; H, 6.36; N, 5.20; S, 11.91. Found: C, 44.57; H, 6.38; N, 5.24; S, 11.93.

4.13. (2*R*,3*S*,4*S*) and (2*S*,3*S*,4*S*)-2,3,4-tris(*O*-benzyl)1,1-difluoro-5-methylenecyclopentane-2,3,4-triol (17)

To a solution of 12 (20 mg, 0.11 mmol) in DMF (2 mL) were added NaH (95% in mineral oil, 11 mg, 0.46 mmol), (n-Bu)$_4$NI (4 mg, 0.01 mmol) and BnBr (0.070 mL, 0.55 mmol) and the mixture was stirred overnight. A saturated solution of NH_4Cl was added and the aqueous phases were extracted three times with Et_2O. The combined organics were washed with water, dried over $MgSO_4$ and evaporated. Purification by column chromatography (10% EtOAc in cyclohexane) afforded **17** as a colorless oil (21 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 15H), 5.95–5.90 (m, 1H), 5.67–5.64 (m, 1H), 4.88 (d, *J* = 12.1 Hz, 1H), 4.62–4.47 (m, 6H), 4.12–4.05 (m, 1H), 3.96–3.90, 5.95–5.90 (m, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −90.7 (ddd, *J* = 255.8 Hz, *J* = 8.2 Hz, *J* = 4.1 Hz, 1F), −111.4 (ddd, *J* = 255.8 Hz, *J* = 5.2 Hz, *J* = 3.1 Hz, 1F).

4.14. Representative procedure for the hydroboration reactions

To a solution of **17** (11 mg, 0.03 mmol) in THF (1 mL) at 0 °C was added dropwise a solution of BH_3.THF (1 M in THF, 0.08 mL, 0.08 mmol). The reaction was monitored by TLC (20% EtOAc in cyclohexane) and three more equivalents of BH_3.THF were added if necessary. The reaction was usually complete in 1 h 30 min after which time NaOH (3 M in water, 0.06 mL, 0.18 mmol) and hydrogen peroxide (35% in water, 0.03 mL, 0.03 mmol) were added and the mixture stirred for 45 mn. Extraction with CH_2Cl_2, drying over $MgSO_4$ and filtration afforded the crude mixture that was purified by column chromatography (gradient from 1 to 15% EtOAc in cyclohexane) to yield **19** (4 mg, 35%) and **18** (1 mg, 9%). **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 15H), 4.88 (d, *J* = 11.9 Hz, 1H), 4.72–4.59 (m, 4H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.04–3.92 (m, 2H), 3.84–3.76 (m, 1H), 1.30 (d, *J* = 3.2 Hz, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −110.1 (ddd, *J* = 243.4 Hz, *J* = 7.2 Hz, *J* = 4.1 Hz, 1F), −125.8 (ddd, *J* = 243.4 Hz, *J* = 11.3 Hz, *J* = 6.2 Hz, 1F). **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (m, 15H), 4.87 (d, *J* = 12.1 Hz, 1H), 4.65–4.44 (m, 5H), 4.24–4.19 (m, 1H), 4.05–3.88 (m, 4H), 2.97–2.89 (m, 1H), 1.9 (bs, 1H). ^{19}F NMR (282.5 MHz, $CDCl_3$) δ −105.6 to −105.8 (m, 2F).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.02.015.

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