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# A Two-Directional Approach to Enantiopure 1,4-Difluoro-cyclohexenes: Synthesis of Difluorinated Cyclitol Analogues

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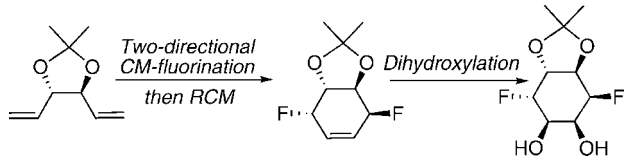
## ABSTRACT




**Enantiopure 1,4-difluoro-cyclohexenes were prepared from readily available acetonide-protected (3*S*,4*S*)-hexa-1,5-diene-3,4-diol. In a two-directional mode, a double cross-metathesis reaction using allyltrimethylsilane as the olefinic partner, followed by electrophilic fluorination, afforded diastereomeric acetonide-protected 3,6-difluoro-octa-1,7-diene-4,5-diols. These dienes were found to be suitable substrates for ring-closing metathesis, delivering cyclohexenes featuring fluorine atoms on the two allylic positions flanking the double bond. Upon dihydroxylation, novel difluorinated cyclitol analogues were formed.**

The inclusion of fluorine into organic molecules can induce dramatic changes in their conformation, reactivity, and physical properties. As a result, fluorinated compounds have been used frequently in the pharmaceutical and agrochemical industry as well as in material science.[1] Fluorinated building blocks are consequently in great demand, inclusive of functionalized molecules that feature the fluorine on a stereogenic center. Alkenes and alkynes flanked by fluorine substituents emerged as highly versatile molecules that can be manipulated in various ways.[2] The reactivity of difluorinated alkenes of general structure A with the fluorine installed on the two allylic positions has been scarcely explored, a notable exception being the work of O' Hagan and co-workers.[3] In the context of a detailed conformational study, these compounds were used as intermediates for the enantioselective synthesis of all-*syn*, *anti*-*syn*-*anti*, and *syn*-*syn*-*anti* four vicinal fluorine motifs. Rapid progress in this area is hampered by the difficulties associated with the preparation of these difluorinated alkenes, especially when stereocontrol at the two fluorinated allylic positions is required. O' Hagan et al. successfully prepared enantioenriched acyclic *syn*-1,4-difluoro-alk-2-enes from allylic fluorides relying on a cross homometathesis process.[3] This chemistry is intrinsically limited to the preparation of

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(2) Pacheco, M.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943–1981.

(3) (a) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z *J. Am. Chem. Soc.* **2006**, *128*, 16422–16423. (b) Hunter, L.; Slawin, A. M. Z.; Kirsh, P.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7887–7890.

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symmetrical *syn* derivatives.[4] In recognition of the importance of these compounds, we have reported that *syn*-1,4-difluoro-alk-2-enes were accessible upon electrophilic fluorodesilylation of monofluorinated (*E*)-allylsilanes in the presence of Selectfluor.[5] This approach allowed for the preparation of unsymmetrical derivatives. To date, no syntheses of the corresponding cyclic *anti*- and *syn*-1,4-difluorocycloalkenes B are known, and therefore, no information is available on their reactivity or physical properties. These compounds have however been identified as minor products of three isolated and distinct transformations, the fluorination of cyclopentadiene, of epoxycyclopentene, and of benzene (Figure 1).[6]

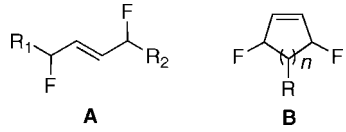
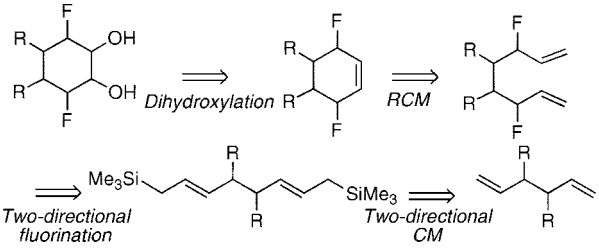



**Figure 1.** Alkenes flanked by two fluorine substituents.

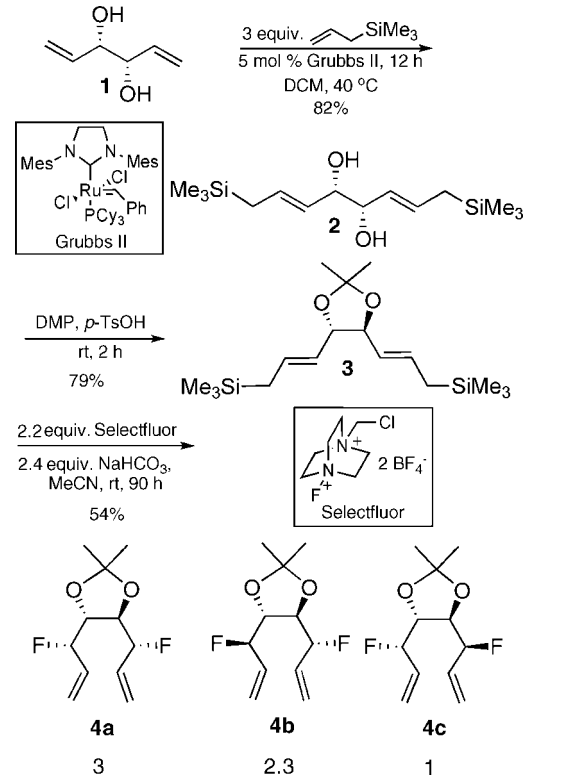
In this communication, we report the first synthesis of enantiopure 1,4-difluorocyclohexenes, and we demonstrate that these novel molecules are precursors of difluorinated cyclitols. In our retrosynthetic analysis, 1,4-difluorinated cyclohexenes might be formed upon ring closing metathesis of an acyclic 3,6-difluoro-octa-1,7-diene, a compound featuring two allylic fluoride groups. Given the accessibility of allylic fluorides from allylsilanes, an unprecedented two-directional electrophilic fluorination of a bis-silylated diene was chosen to prepare the acyclic difluorinated precursor necessary for the ring closure. A double cross-metathesis was planned to access the bis-silylated diene (Scheme 1).

**Scheme 1.** Retrosynthetic Analysis




As the chemistry was designed with the view to access difluorinated cyclitols, the sequence commenced with the known two-step synthesis of (3*S*,4*S*)-hexa-1,5-diene-3,4-diol **1** from D-mannitol (Scheme 2).[7] With diol **1** in hand, the

**Scheme 2.** Two-Directional Synthesis of 3,6-Difluoro-1,7-dienes




first reaction to be validated was the two-directional cross-metathesis process. Double cross-metathesis reactions are not common in the literature. Cossy et al. reported that unprotected 1,5-dien-3-ol underwent double cross-metathesis in the presence of 3 equiv of acrolein, but under identical reaction conditions, the corresponding acetyl- and TBS-protected diene led to chemoselective single cross-metathesis despite the presence of an excess of olefinic partner.[8] With this in mind, the unprotected diol **1** was reacted with 3 equiv of allyltrimethylsilane in the presence of 5 mol % of Grubbs second-generation catalyst. Pleasingly, double cross-metathesis took place and afforded after 12 h the desired bis-silylated dienol **2** in 82% yield.

The two-directional fluorination of **2** was attempted next. When the fluorodesilylation was carried out in the presence of 2.2 equiv of Selectfluor and 2.4 equiv of $NaHCO_3$ in acetonitrile, the desired product was formed in only 11% yield. This experiment suggested that the presence of the unprotected hydroxy groups is likely to be detrimental for the fluorination to proceed efficiently. The acetonide-protected bisallylsilane **3** was therefore prepared and isolated in 79% yield as a mixture of the two geometrical isomers *EE* and *EZ* present in a 3:1 ratio. Compound **3** was subjected

(4) For an early example of homometathesis of racemic allylic fluoride, see: Thibaudeau, S.; Fuller, R.; Gouverneur, V. *Org. Biomol. Chem.* **2004**, *2*, 1110–1112.

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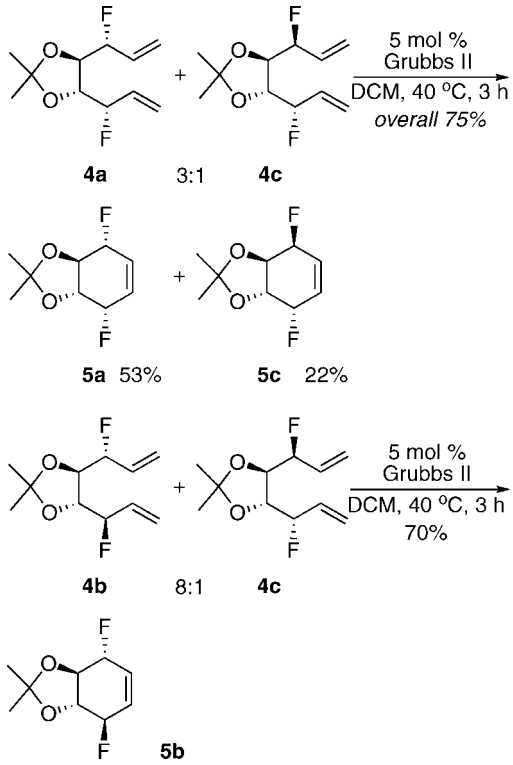
(8) (a) Bouzbouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451–1454. (b) Bouzbouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465–3467.

to the crucial fluorodesilylation applying the reaction conditions used for the fluorination of **2**. Pleasingly, the reaction did proceed successfully delivering the three diastereomeric 3,6-difluorinated-1,7-dienes **4a**, **4b**, and **4c** in 54% overall yield. The low level of selectivity was not unexpected since the bis-silylated diene does not feature stereogenic silylated centers.[5] Partial separation by silica gel chromatography delivered two fractions (each containing two diastereomers) that were not further purified prior to the subsequent ring-closing event.

**Scheme 3.** RCM of Dienes **4a**−**c**




Our next goal was to validate the RCM (Scheme 3). Upon treatment with 5 mol % of Grubbs second-generation catalyst, we found that a 3:1 mixture of **4a** and **4c** underwent smooth metathesis to afford the separable ring-closed products **5a** and **5c** in 75% overall yield. Compound **5c** was crystalline, and its structure was confirmed by single-crystal X-ray analysis.[9] Under similar conditions, an 8:1 mixture of **4b** and **4c** delivered the difluorinated tetrahydrobenzodioxole **5b** in 70% isolated yield. For this transformation, the ring-closed product derived from minor **4c** was not recovered after purification.

With stereoisomers **5a**−**c** in hand, a detailed study was carried out to probe their characteristic spectroscopic data. Fluorine configurations and ring conformations for **5a**−**c** were determined from analysis of $^{1}H-^{1}H$, $^{1}H-^{19}F$, and $^{19}F-^{19}F$ coupling constants combined with $^{1}H-^{1}H$ NOESY data (Figure 2).

(9) See details in Supporting Information.

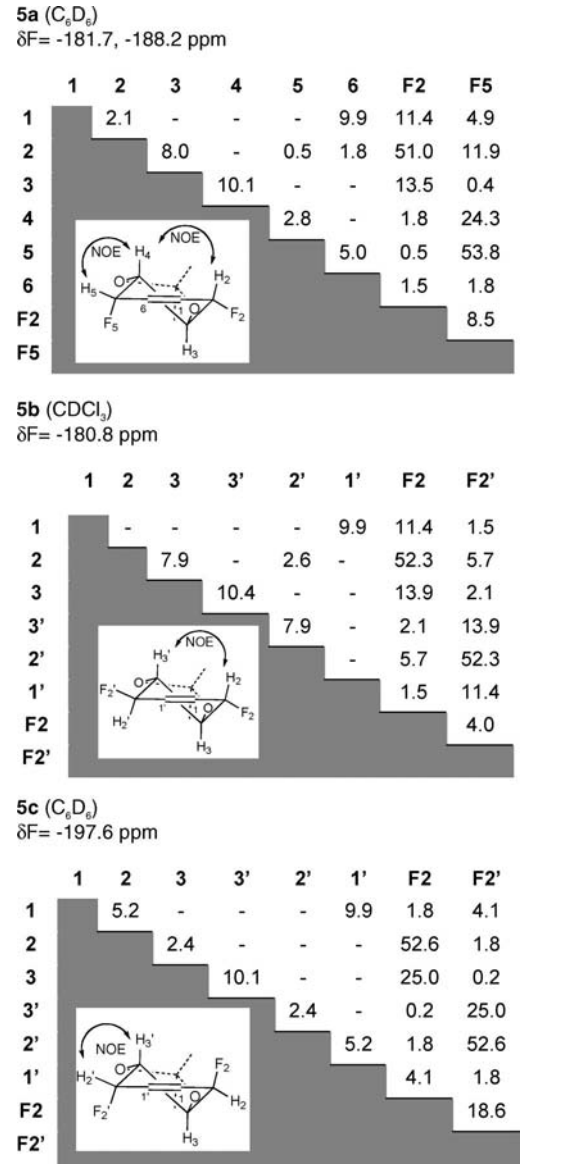



**Figure 2.** Selected $^{1}H$ and $^{19}F$ NMR data for **5a**−**c**. Tables show coupling constants in hertz. When no values are given, $J \sim 0$ Hz.

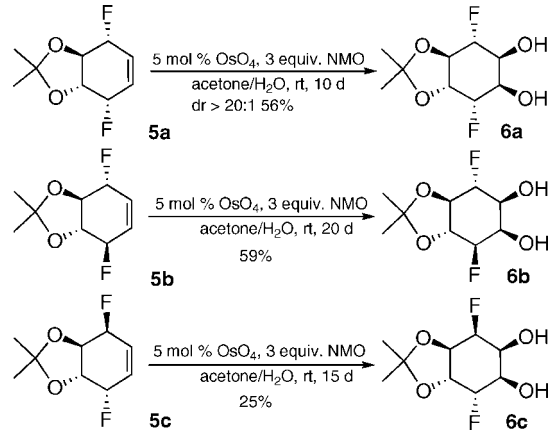
Initial assessments of $J_{HH}$ coupling constants were made from the fully $^{19}F$-decoupled $^{1}H$ data, prior to consideration of the $^{19}F$-coupled spectra. While the $^{1}H\{^{19}F\}$ spectrum of asymmetric **5a** was amenable to direct analysis, the C2-symmetric molecules **5b** and **5c** required spin system simulation, as did all $^{19}F$-coupled proton spectra. For all three systems **5a**−**c**, the resulting NMR data were consistent with the anticipated half-chair conformations (Figure 2). The proton relationships were clearly delineated from their vicinal $^{3}J_{HH}$ coupling constants and NOE interactions, with the corresponding $^{3}J_{HF}$ couplings providing complimentary evidence. Thus, the proton−fluorine axial−pseudoaxial geometries observed for **5a** and **5c** correlated with correspondingly high $^{3}J_{HF}$ values of $\sim$ 24 Hz, whereas the alternative axial−pseudoequatorial relationships in **5a** and **5b** displayed $^{3}J_{HF}$ closer to 14 Hz. Also noteworthy as being sensitive to

the substituent's configurations are the long-range five-bond fluorine−fluorine couplings across the alkene. When both fluorines occupy the pseudoaxial positions (**5c**), the $^5J_{FF}$ coupling increases to ∼19 Hz, while this decreases to ∼4 Hz when both are pseudoequatorial (**5b**). An intermediate value of 8.5 Hz was observed for **5a**. This favored axial−pseudoaxial coupling pathway is also reflected, but to a lesser degree, in the corresponding long-range $^5J_{HH}$ proton−proton couplings. The data are in line with the ones previously reported on structurally related monofluorinated cyclohexenes.[10]

The next stage of the synthesis of difluorinated cyclitol analogues required selective dihydroxylation of **5a**−**c** (Scheme 4). Treatment with 5 mol % of $OsO_4$ and 3 equiv of the co-oxidant NMO (Upjohn conditions)[11] gave the required diols **6a**−**c** in moderate yields. The substitution pattern of **5b** and **5c** naturally led to a single diastereomeric product, and we were pleased to find that the hydroxylation of the non C2-symmetric cyclohexene **5a** led to the formation of a single diastereomer resulting from an anti approach with respect to the fluorine substituents.

In summary, this work has validated the first enantioselective synthesis of cyclohexenes flanked on the two allylic positions by fluorine substituents, an unexplored class of compounds. Successful dihydroxylation of these building blocks delivered novel deoxyfluoro-*myo*-inositols that may be regarded as highly valuable compounds to intervene with the phosphatidylinositol cycle.[12] Alternative functional manipulation of these difluorinated cyclohexenes may allow access to additional high value targets, such as for example cyclohexanes featuring four stereodefined vicinal fluorine motifs.

**Scheme 4.** Dihydroxylation of Difluorocyclohexenes **5a**−**c**

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**Supporting Information Available:** Experimental procedures and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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