[2,3]-Wittig Rearrangements of Difluoroallylic Ethers. A Facile Entry to Highly Functionalized Molecules Containing a CF_2 Group

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Readily prepared primary, secondary, and tertiary difluoroallylic alcohols, derived from commercially available and inexpensive 2,2,2-trifluoroethanol, have been transformed into a range of difluoroallylic methyl ethers containing appropriate carbanion-stabilizing substituents. The [2,3]-Wittig rearrangements of these difluoroallylic ethers have been achieved cleanly, using lithium diisopropylamide in tetrahydrofuran at −30 °C, in excellent (secondary ether substrates) to good (primary and tertiary ether substrates) yields. Consequently, the approach allows convenient and rapid access to products containing a mid-chain CF_2 group and with a useful level of functionality.

Introduction

The synthesis of highly-functionalized molecules containing a limited number of fluorine atoms remains a significant challenge to synthetic organic chemists. A well-tried approach involves the transformation of suitable functional groups by fluorinating agents.[1] For example, a difluoromethylene (CF_2) group can be introduced by the transformation of a ketonic carbonyl group directly using DAST ((diethylamido)sulfur trifluoride).[2,3] More recent developments have involved the conversions of dithioketals, hydrazones, and oximes to CF_2-containing compounds.[4] The fluorination approach is ideal when a ketonic precursor to the CF_2 compound is readily available. For example, in carbohydrate chemistry, protection and functional group manipulation chemistry has advanced to a stage where almost any ketone is available. The DAST reagent is compatible with many of the commonly-used protecting groups for the hydroxyl function and reacts with densely functionalized aliphatic ketones,[5] unlike many of the newer reagents.[1a,4] However, in complex non-carbohydrate molecules, the installation of the appropriate carbonyl precursor to the CF_2 group may be far from straightforward. There may be additional limitations imposed by the nature of the mechanism of the DAST fluorination reaction. Fluorination with DAST and related species occurs *via* pathways in which the development of positive charge on carbon is well advanced. High electron demand or carbenium ion character leads to the activation of pathways involving elimination, rearrangement, 1,2-hydride shifts, and neighboring group participation.[6]

An alternative strategy uses fluorine-containing building blocks. The introduction of the fluorine atoms is achieved *via* carbon−carbon bond formation to a manipulable fluorine-containing starting material or "building block". The Reformatsky reagent prepared from ethyl bromodifluoroacetate has been used to prepare a wide range of biologically-interesting compounds[7] including antitumour nucleoside Gemcitabine,[8] inhibitors of Renin,[9] Interleukin-1β converting enzyme,[10] human Leukocyte Elastase,[11] and an analogue of arginine.[12] Of the two strategies, the building block approach is potentially more versatile. However, for that potential to be realized to the full, general synthetic methods that allow the elaboration of readily-available fluorine-containing starting materials must be developed.[13] A general building block approach to compounds containing a CF_2 group would be required to address targets in which the fluorine-bearing carbon was located in a range of molecular environments. Scheme 1 outlines our strategic approach based upon trifluoroethanol. Key steps include conversion to a metalated difluoroenol derivative, carbon−carbon bond formation, and transposition of the allylic alcohol products. Excellent precedents existed for both components of the approach. Normant had shown[14] that (2,2-difluoroethenyl)lithium could be used to assemble difluoroallylic alcohols. Nakai and Kobayashi[15] showed

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(1) (a) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505. (b) Mascaretti, O. A. *Aldrichimica Acta* **1993**, *26*, 4758. (c) Mann, J. S. *Chem. Soc. Rev.* **1987**, *16*, 381.

(2) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Hudlicky, M. *Org. React.* **1988**, *35*, 513.

(3) For recent transformations of the carbonyl group with DAST, see: (a) Giardina, G.; Dondio, G.; Grugni, M. *Synlett* **1995**, 55. (b) Ando, K.; Koike, F.; Kondo, F.; Takayama, H. *Chem. Pharm. Bull.* **1995**, *43*, 189. (c) Sabol, J. S.; Brake, N. W.; McDonald, I. A. *Tetrahedron Lett.* **1994**, *35*, 1821.

(4) (a) York, C.; Surya Prakash, G. K.; Wang, Q.; Olah, G. A. *Synlett* **1994**, 425. (b) Tordeux, M.; Boumizane, K.; Wakselman, C. *J. Fluorine Chem.* **1995**, *70*, 207. (c) Motherwell, W. B.; Wilkinson, J. A. *Synlett* **1991**, 191.

(5) (a) El-Lagdach, A.; Matheu, M. I.; Castillón, S.; Bliard, C.; Olesker, A.; Lukacs, G. *Carbohydr. Res.* **1992**, *233*, C1. (b) El-Lagdach, A.; Echarri, R.; Matheu, M. I.; Barrena, M. I.; Castillón, S.; García, J. *J. Org. Chem.* **1991**, *56*, 4556.

(6) (a) Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Stephenson, L.; Youds, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 549. Products arising from neighboring group participation were detected during recent studies on the fluorination of diols with DAST, see: (b) Shellhamer, D. F.; Anstine, D. T.; Gallego, K. M.; Ganesh, B. R.; Hanson, A. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 861. Farina and co-workers have reported some fascinating rearrangements of the taxol skeleton upon exposure to DAST; see: (c) Chen, S. H.; Huang, S.; Wei, J.M.; Farina, V. *J. Org. Chem.* **1993**, *58*, 4520. (d) Chen, S. H.; Huang, S.; Farina, V. *Tetrahedron Lett.* **1994**, *35*, 41.

(7) Welch, J. T. In *Selective Fluorination in Organic and Bio-Organic Chemistry,* ACS Symposium Series 456; Welch, J. T., Ed.; American Chemical Society: Washington DC, 1990; p 182.

(8) Chou, T. S.; Heath, P. C.; Patterson, L. E.; Poteet, L. M.; Lakin, R. E.; Hunt, A. H. *Synthesis* **1992**, 565.

(9) Doherty, A. M.; Sircar, I.; Kornberg, B. E.; Quin, J.; Winters, R. T.; Kaltenbron, S.; Taylor, M. D.; Batley, B. L.; Rapundalo, S. R.; Ryan, M. T.; Painchaud, C. A. *J. Med. Chem.* **1992**, *35*, 2.

(10) Robinson, R. P.; Donahue, K. M. *J. Org. Chem.* **1992**, *57*, 7309.

(11) Bernstein, P. R.; Kosmider, B. J.; Vacek, E. P.; Veale, C. A.; Gomes, B. C. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2175.

(12) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7195.

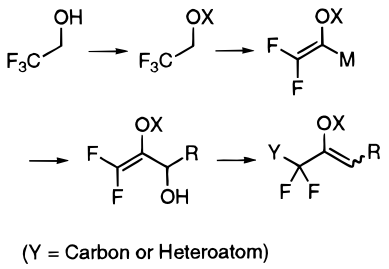
(13) Significant progress is being made in the area, see: (a) Enantiocontrolled Synthesis of Fluoro-organic Compounds; Hayashi, T.; Sholoshonok, V. A., Eds. *Tetrahedron: Asymmetry* **1994**, *5*, 955. (b) Percy, J. M. *Contemp. Org. Synth.* **1995**, in press.

(14) Gillet, J. P.; Sauvêtre, R.; Normant, J. F. *Synthesis* **1986**, 538.

(15) Nakai, T.; Tanaka, K.; Ishihawa, N. *Chem. Lett.* **1976**, 1263.

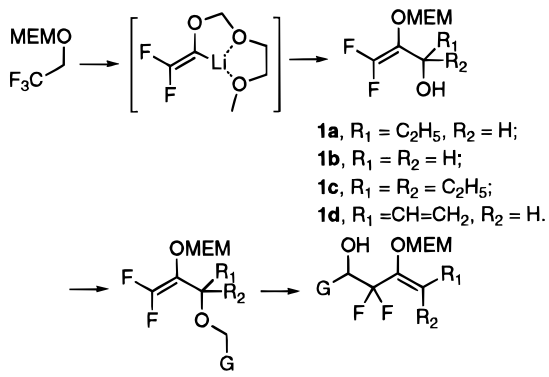
0022-3263/96/1961-0166$12.00/0

Scheme 1



(Y = Carbon or Heteroatom)

Scheme 2



1a, $R_1 = C_2H_5$, $R_2 = H$;
1b, $R_1 = R_2 = H$;
1c, $R_1 = R_2 = C_2H_5$;
1d, $R_1 = CH{=}CH_2$, $R_2 = H$.

that the α-tosyloxy congeners could be prepared from 2,2,2-trifluoroethyl tosylate, and more recently, Ichikawa has published an admirably diverse chemistry based upon a versatile (difluorovinyl)copper reagent generated from the trifluoroethanol derivative.[16] A number of groups had described [3,3]-rearrangements of difluoroallylic alcohols[17] though the literature contained no systematic studies; [2,3]-Wittig rearrangements of difluoroallylic alcohols were unknown.[18] Recently, we published in full our route to difluoroallylic alcohols,[19] reactive substrates for a range of [2,3]- and [3,3]-sigmatropic rearrangement reactions.[20] In this publication, we show how the [2,3]-Wittig rearrangement can be used to prepare highly-functionalized intermediates containing a mid-chain CF_2 group, as illustrated in Scheme 2.

Results and Discussion

All the allylic alcohols (**1a**−**d**) used in the study were prepared using our published procedure.[19] Primary (**1b**) and secondary (**1a**) allylic alcohols were converted to their allyl, benzyl, methallyl, and propargyl ethers using the phase-transfer-catalyzed method described by Schlosser and Strunk[21] and outlined in Table 1. The tertiary allylic alcohol **1c** could not be converted to any of the ethers required for the study using the phase-transfer method. Instead, conversion to the sodium salt in DMF followed by exposure of the alkoxide to the electrophile in the presence of a catalytic amount of tetrabutylammonium iodide[22] gave acceptable yields of the ethers. A similar procedure has been described by Nicolaou and co-workers.[23]

Rearrangements were initiated by adding a THF solution of the ether to a cold (−78 °C) solution of LDA in THF/hexane: Table 2 summarizes our findings. When 1 equiv of LDA was employed, starting material was recovered, whereas the use of 2 equiv of the hindered base led to the isolation of the rearranged products in good yield. Though strong colors were developed at low temperature, indicating that the metalation reactions had commenced, all the reactions required several hours at −30 °C for rearrangement to occur. The allyl ethers were the most reactive; for example, **2a** rearranged completely within 4 h at −30 °C, whereas **3a** required 18 h at the same temperature. The rearrangement of propargyl ethers proved problematic. All the [2,3]-Wittig rearrangements of unprotected propargyl ethers in the literature are presumably dianion rearrangements.[24] LDA is not sufficiently basic to deprotonate the methylene position of a monodeprotonated propargyl ether, resulting in the failure of propargyl ethers **5a** and **5b** to undergo rearrangement under our normal conditions. Alkyllithium reagents are too nucleophilic to be compatible with a difluoroalkene.[25] We therefore prepared the *C*-trimethylsilyl derivative **6a** and were surprised to find that it failed to rearrange under the usual conditions. We were unable to isolate any discrete pure compounds from the product mixture apart from the desilylated propargyl ether **5a**, though GCMS revealed the presence of several compounds that appeared to contain two trimethylsilyl groups. However, we found that the *C*-triisopropyl compounds **7a** and **7b** rearranged smoothly in high yield, suggesting that carbanion attack at silicon may lead to the activation of a multitude of side reactions in the less hindered trimethylsilyl case.

We were unable to detect any products arising from [1,2]-rearrangements[26] in any of the experiments, though performing the rearrangements of the less reactive substrates at higher temperatures (0 °C) led to decomposition[27] and the formation of multiple products. Rearrangement occurred with the appearance of highly characteristic signals in the ^{19}F NMR spectra. The formation

(16) For a recent example, see: Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem.* **1995**, *60*, 2322.

(17) (a) Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P. *Tetrahedron Lett.* **1985**, *26*, 2861. (b) Yuan, W.; Berman, R. I.; Gelb, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 8071. For recent reviews, see: (c) Andreev, V. G.; Kolomiets, A. F. *Usp. Khim.* **1993**, *62*, 594. (d) Purrington, S. T.; Weeks, S. C. *J. Fluorine Chem.* **1992**, *56*, 165. Other transpositions of difluoroallylic alcohols have been described recently, (e) Tellier, F.; Sauvêtre, R. *Tetrahedron Lett.* **1995**, *36*, 4221. Though not pericyclic rearrangements, these results suggest that some very general chemistry is possible from difluoroallylic alcohols. A solvolytic transposition has been reported: (f) Vinson, W. A.; Prickett, K. S.; Spahic, B.; de Montellano, P. R. O. *J. Org. Chem.* **1983**, *48*, 4661.

(18) For a review of the [2,3]-Wittig rearrangement, see: (a) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105. We have published a preliminary account of the reaction of fluorinated compounds: (b) Patel, S. T.; Percy, J. M. *J. Chem. Soc., Chem. Commun.* **1992**, 1477.

(19) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201.

(20) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 11327.

(21) Schlosser, M.; Strunk, S. *Tetrahedron* **1989**, *45*, 2649.

(22) Tomooka, K.; Keong, P.-H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 2789.

(23) Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Dai, W.-M.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1118.

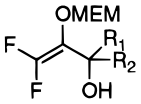
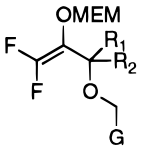
(24) (a) Mikami, K.; Azuma, K.-I.; Nakai, T. *Tetrahedron* **1984**, *40*, 2303. (b) Mikami, K.; Kawamoto, K.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 5799.

(25) In our preliminary account of the [2,3]-Wittig rearrangement, we described an S_N2' alkylation which occurred when **2a** was exposed to *n*-butyllithium. Difluoroallylic acetates are useful substrates in copper-catalyzed S_N2' alkylations of Grignard reagents, see: (a) Tellier, F.; Sauvêtre, R. *J. Fluorine Chem.* **1995**, *70*, 265. (b) Tellier, F.; Sauvêtre, R. *J. Fluorine Chem.* **1993**, *62*, 183.

(26) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett.* **1993**, *34*, 8139.

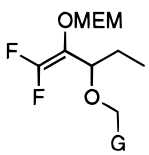
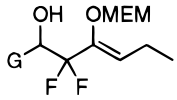
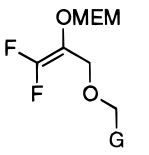
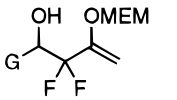
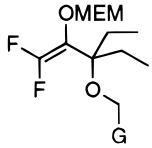
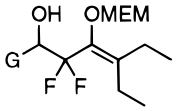
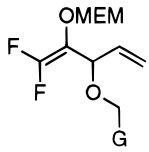
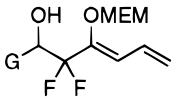
(27) MEM ethers undergo slow cleavage when exposed to alkyllithium reagents in hexane. (a) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. (b) Anderson, R. J.; Adams, K. G.; Chinn, H. R.; Henrick, C. A. *J. Org. Chem.* **1980**, *45*, 2229. Decomposition of this type may contribute to the complexity of the product mixtures formed from slow, high-temperature reactions.

Table 1. Preparation of Difluoroallylic Ethers of Alcohols 1a–d

Entry	Substrate	Product	Yield/%[a]
1	 **1a**, $R_1 = C_2H_5$, $R_2 = H$;	 **2a**, $R_1 = C_2H_5$, $R_2 = H$, G = $CH{=}CH_2$;	93
2		**3a**, $R_1 = C_2H_5$, $R_2 = H$, G = Ph;	65[b]
3		**4a**, $R_1 = C_2H_5$, $R_2 = H$, G = $C(CH_3){=}CH_2$;	69[b]
4		**5a**, $R_1 = C_2H_5$, $R_2 = H$, G = C≡CH;	51
5		**6a**, $R_1 = C_2H_5$, $R_2 = H$, G = $C{\equiv}CSiMe_3$;	30[c]
6		**7a**, $R_1 = C_2H_5$, $R_2 = H$, G = $C{\equiv}CSi\textit{i}Pr_3$.	83[c]
7	**1b**, $R_1 = R_2 = H$;	**2b**, $R_1 = H$, $R_2 = H$, G = $CH{=}CH_2$;	93
8		**3b**, $R_1 = H$, $R_2 = H$, G = Ph;	96
9		**4b**, $R_1 = H$, $R_2 = H$, G = $C(CH_3){=}CH_2$;	48
10		**5b**, $R_1 = H$, $R_2 = H$, G = C≡CH;	82
11		**7b**, $R_1 = H$, $R_2 = H$, G = $C{\equiv}CSi\textit{i}Pr_3$.	78[d]
12	**1c**, $R_1 = R_2 = C_2H_5$;	**2c**, $R_1 = C_2H_5$, $R_2 = C_2H_5$, G = $CH{=}CH_2$;	61[e]
13		**3c**, $R_1 = C_2H_5$, $R_2 = C_2H_5$, G = Ph;	57[e]
14		**4c**, $R_1 = C_2H_5$, $R_2 = C_2H_5$, G = $C(CH_3){=}CH_2$.	27[e]
15	**1d**, $R_1 = CH{=}CH_2$, $R_2 = H$.	**2d**, $R_1 = CH{=}CH_2$, $R_2 = H$, G = $CH{=}CH_2$.	74

[a] Isolated yields after purification. [b] Benzyltriethylammonium chloride was the phase transfer catalyst. [c] Formed by deprotonation of **5a** with LDA and reaction with the appropriate silicon electrophile. [d] Formed by deprotonation of **5b** with LDA and reaction with the appropriate silicon electrophile. [e] Formed by reaction of the sodium salt with the appropriate electrophile in DMF containing TBAI.

Table 2. [2,3]-Wittig Rearrangements of Difluoroallylic Ethers

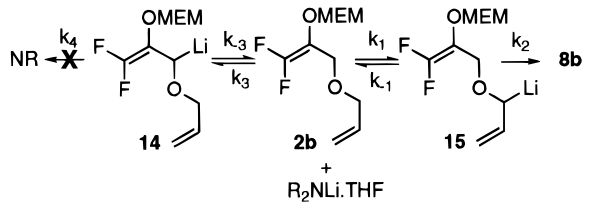
Entry	Substrate	Product	Reaction Time/Hours[a]	Yield/%[b]
1	 **2a**, G = $CH{=}CH_2$;	 **8a**	4	86
2	**3a**, G = Ph;	**9a**	15	76
3	**4a**, G = $C(CH_3){=}CH_2$;	**10a**	15	84
4	**5a**, G = C≡CH;	**11a**	15	[d]
5	**6a**, G = $C{\equiv}CSiMe_3$;	**12a**	15	[c]
6	**7a**, G = $C{\equiv}CSi\textit{i}Pr_3$.	**13a**	4	68
7	 **2b**, G = $CH{=}CH_2$;	 **8b**	4	61
8	**3b**, G = Ph;	**9b**	15	52
9	**4b**, G = $C(CH_3){=}CH_2$;	**10b**	15	58
10	**5b**, G = C≡CH;	**11b**	15	[d]
11	**7b**, G = $C{\equiv}CSi\textit{i}Pr_3$.	**13b**	4	52
12	 **2c**, G = $CH{=}CH_2$;	 **8c**	48	51
13	**3c**, G = Ph;	**9c**	72	70
14	**4c**, G = $C(CH_3){=}CH_2$.	**10c**	72	[d]
15	 **2d**, G = $CH{=}CH_2$.	 **8d**	2	74

[a] Reaction time refers to the time at -30 °C after initial period at -78 °C. [b] Isolated yields after purification. [c] Complex mixture of products formed. [d] No rearrangement; starting material recovered.

of the sp^3-hybridized CF_2 group adjacent to a stereogenic center resulted in diastereotopicity of the two fluorine atoms and the appearance of a large (*ca.* 250 Hz) $^2J_{F-F}$ coupling. The other feature worthy of comment is the appearance of the transposed vinylic methine proton in the ^1H NMR spectra of **2a**–**4a** and **7a**. The signal for these protons appears as a doublet of triplets in which the triplet splitting is effected by the adjacent allylic methylene group. Only one of the fluorine atoms has a visible allylic $^4J_{H-F}$ coupling to the vinylic methine proton. The correct assignment of the ^1H and ^{13}C NMR spectra was confirmed initially by a $^1H-^{13}C$ shift correlation. The *Z*-configuration of the transposed double bond in **8a** is entirely consistent with conventional representations[28] of the envelope [2,3]-Wittig transition state in which alkyl substituents at the allylic carbon atom occupy pseudoequatorial positions. The stereochemical course of the rearrangement was demonstrated by an NOE experiment, irradiating the acetal methylene group in the MEMO group; a positive NOE was detected

(28) Mikami, K.; Nakai, T. *Synthesis* **1991**, 594.

Scheme 3



in the allylic methylene proton signals, rather than at the vinylic methine position.

At the start of the study, we argued that the ethers of difluoroallylic alcohols should be reactive substrates in the [2,3]-Wittig rearrangement. Because the [2,3]-Wittig rearrangement involves the conversion of a moderately stabilized (and therefore reactive) "carbanion" to a more stable alkoxide anion, the reaction should be exothermic, passing through an early transition state.[29] A simple frontier orbital picture of the anionic rearrangement has therefore been applied to predict and rationalize reactivity. Fluorine atom substituents exert a lowering effect upon the orbital energies of alkenes;[30] lowering the energy of the alkene LUMO closes the energetic separation between the acceptor orbital and the carbanion HOMO, accelerating the rearrangement. We predicted that **2d**, which can rearrange through two different vinylic termini, would afford **8d** exclusively upon exposure to our reaction conditions. The isolation of **8d** in 74% yield from the rearrangement appears to confirm our hypothesis.[31]

Secondary allylic alcohols appear to be the best substrates for [2,3]-Wittig rearrangement. The primary alcohol **1b** was converted to the corresponding ethers in good yield, but rearrangements occurred in only moderate yields that were independent of the reactivity of the conjugate base. In all the cases we examined, the material balance was provided by recovered starting ether, even after extended reaction times. The reason for the lower reactivity remains obscure, but it is possible that it may lie in the balance between steric and electronic effects on the deprotonation reaction, Scheme 3. The presence of the two fluorine atoms would be expected to exert an acidifying effect upon the proton (or protons) occupying the allylic position. In the case of the secondary alcohol-derived ether **2a**, kinetic deprotonation occurs in the nonfluorinated allyl group because proton abstraction from the more acidic position is hindered by the ethyl group. When the ethyl group is no longer present as in **2b**, deprotonation at the more acidic methylene position can compete ($k_3 \geq k_1$), leading to the formation of nonproductive "carbanion" **14**. Pre-equilibration to form the more basic **15**, which is then removed by rearrangement, leads to the formation of product **8b**. As products arising from the rearrangements of the nonproductive intermediates are not observed, we conclude that the rearrangements to the fluorinated vinylic terminus are relatively facile ($k_2 \gg k_4$). When the more hindered (but less basic) LTMP[32] was used to trigger rearrangement of **2b**, no deprotonation at the methylene position was observed and only the product of [2,3]-Wittig rearrangement **8b** was isolated in 73% yield. No starting ether **2b** arising from the formation and persistence of nonproductive "carbanion" was recovered. We are performing isotopic labeling studies to confirm this hypothesis and probing the nature of the [2,3]-Wittig transition states by computational methods.[33]

In the case of the ethers of tertiary alcohols, **2c** and **3c** rearranged in moderate yield but methallyl ether **4c** failed to yield any rearranged material, even after 72 h at −30 °C. It is possible that this substrate fails to rearrange because of excessive steric compression in the envelope transition state.[34]

Conclusions

Ethers of difluoroallylic alcohols have been prepared and rearranged efficiently to afford products that contain a CF_2 group embedded within an array of other functional groups. A significant degree of complexity is achieved in a total of four reaction steps from commercially available and inexpensive trifluoroethanol. The reaction sequence demonstrates a significant degree of flexibility and should find applications in the synthesis of structurally complex molecules containing a CF_2 group, a growing area of unnatural product synthesis.

Experimental Section

Tetrahydrofuran was purchased from Fisons, refluxed over sodium−benzophenone ketyl under dry nitrogen, and collected by syringe as required. *n*-Butyllithium was purchased from the Aldrich Chemical Co. as a 1.6 M solution in hexanes. The molarity was determined immediately prior to use by titration against a THF solution of 1,3-diphenyl-2-propanone-*p*-toluenesulfonylhydrazone.[35] Diisopropylamine was distilled from and stored over calcium hydride. Alkyl halides were purchased from Aldrich and distilled before use with the exception of propargyl bromide which was used as supplied. Triisopropylsilyl triflate was purchased from Aldrich and Kugelrohr distilled immediately before use.

General Procedures for the Preparation of Difluoroallylic Ethers. In general, difluoroallylic ethers of 1,1-difluoro-3-hydroxy-2-([methoxyethoxy]methoxy)pent-1-ene (**1a**), 1,1-difluoro-3-hydroxy-2-([methoxyethoxy]methoxy)prop-1-ene (**1b**), and 1,1-difluoro-3-hydroxy-2-([methoxyethoxy]methoxy)penta-1,4-diene (**1d**) were prepared by stirring the appropriate alcohol with a suitable electrophile (1.2 equiv) in 50% aqueous sodium hydroxide (7 equiv), in the presence of a phase-transfer catalyst (0.05 equiv). Difluoroallylic ethers of 3-ethyl-1,1-difluoro-3-hydroxy-2-([methoxyethoxy]methoxy)-pent-1-ene (**1c**) were prepared routinely by treatment of the alcohol with sodium hydride (1.2 equiv) and subsequent reaction of the alkoxide formed with a suitable electrophile (1.2 equiv), in the presence of a catalytic amount of tetrabutylammonium iodide (0.1 equiv).

3-(Allyloxy)-1,1-difluoro-2-([methoxyethoxy]methoxy)-pent-1-ene (2a). A mixture of **1a** (1.50 g, 6.63 mmol), allyl bromide (0.70 mL, 9.63 mmol), 50% aqueous sodium hydroxide (3.70 mL, 46.4 mmol), and tetrabutylammonium hydrogen sulfate (0.11g, 0.33 mmol) was stirred at 0 °C for 30 min. The mixture was allowed to warm to room temperature and stirred

(29) The structure/reactivity relationship discussion is summarized in Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(30) Calculations of HOMO and LUMO energies of fluoroethenes have been performed: Pasto, D. J. *J. Org. Chem.* **1992**, *57*, 1139.

(31) The assignment of the ^{1}H NMR spectrum of **8d** was made with a COSY experiment (see supporting information). None of the alternative product was detectable in the ^{19}F NMR spectrum of the crude product mixture.

(32) Lappert, M. F.; Slade, M. J.; Singh, A.; Atwood, J. L.; Rogers, R. D.; Shakir, R. *J. Am. Chem. Soc.* **1983**, *105*, 302.

(33) Patel, S. T.; Percy, J. M.; Philp, D.; Wilkes, R. D. Manuscript in preparation.

(34) Rearrangements of ethers of simple tertiary allylic alcohols occur with low stereoselectivity because 1,3-repulsions raise the energies of all the possible transition states, converging them. (a) See ref 28. There are exceptions to this general statement which rely on additional organizing interactions. For example, see: (b) Sin, N.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 753.

(35) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

overnight. Saturated aqueous ammonium chloride solution (10 mL) was added, and the mixture was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give **2a** as a pale yellow oil (1.65 g, 93%), which was subjected to rearrangement without further purification: IR (film) 1750, 1647, and 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, 3H, $^3J_{H-H}$ = 7.3 Hz), 1.59−1.80 (m, 2H), 3.36 (s, 3H), 3.58 (t, 2H, $^3J_{H-H}$ = 4.2 Hz), 3.70−3.91 (m, 3H), 4.05 (ddt, 1H, $^2J_{H-H}$ = 13.0 Hz, $^3J_{H-H}$ = 5.0 Hz, 2 × $^4J_{H-H}$ = 1.5 Hz), 4.08 (tdd, 1H, $^3J_{H-H}$ = 12.7 Hz, $^4J_{H-Fcis}$ = 4.9 Hz, $^4J_{H-Ftrans}$ = 1.5 Hz), 4.89 (d, 1H, $^2J_{H-H}$ = 6.1 Hz), 5.00 (d, 1H, $^2J_{H-H}$ = 6.1 Hz), 5.14 (dq, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Hcis}$ = 10.2 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.23 (dq, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Htrans}$ = 14.0 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.79−5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.8, 24.9, 58.9, 68.2, 69.2, 71.6, 76.0, 97.0, 112.3 (dd, $^2J_{C-F}$ = 36.7, 9.7 Hz), 117.1, 134.4, 156.2 (dd, $^1J_{C-F}$ = 284.3, 284.3 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.5 (d, 1F, $^2J_{F-F}$ = 64.1 Hz), −98.3 (d, 1F, $^2J_{F-F}$ = 64.1 Hz); *m/z* (CI, NH_3) 284 (67), 267 (3), 89 (100); HRMS calcd for $C_{12}H_{24}F_2NO_4$ ($[M + NH_4]^+$) 284.16734, found 284.16796.

3-(Benzyloxy)-1,1-difluoro-2-([methoxyethoxy]methoxy)pent-1-ene (3a) was prepared as for **2a** except benzyltriethylammonium chloride was employed as the catalyst and benzyl bromide was the electrophile. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **3a** as a yellow oil (0.49 g, 65%) (R_f 0.46) (Found: C, 61.01; H, 7.22. $C_{16}H_{22}F_2O_4$ requires C, 60.75; H, 7.01): IR (film) 1744 and 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, $^3J_{H-H}$ = 7.6 Hz), 1.58−1.92 (m, 2H), 3.38 (s, 3H), 3.51−3.59 (m, 2H), 3.72−3.83 (m, 1H), 3.86−4.00 (m, 2H), 4.34 (d, 1H, $^2J_{H-H}$ = 11.7 Hz), 4.65 (d, 1H, $^2J_{H-H}$ = 11.7 Hz), 4.95 (d, 1H, $^2J_{H-H}$ = 6.2 Hz), 5.09 (d, 1H, $^2J_{H-H}$ = 6.2 Hz), 7.24−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.9, 25.1, 59.0, 68.3, 70.4, 71.6, 76.2, 97.1, 112.4 (dd, $^2J_{C-F}$ = 36.6, 9.8 Hz), 127.7, 127.9, 128.4, 138.0, 156.4 (dd, $^1J_{C-F}$ = 293.8, 284.7 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.1 (d, 1F, $^2J_{F-F}$ = 61.1 Hz), −98.1 (d, 1F, $^2J_{F-F}$ = 61.1 Hz); *m/z* (CI, NH_3) 317 (100), 105 (30); HRMS (LSIMS) calcd for $C_{16}H_{23}F_2O_4$ ($[M + H]^+$) 317.15644, found 317.15550.

3-(Methallyloxy)-1,1-difluoro-2-([methoxyethoxy]methoxy)pent-1-ene (4a) was prepared as for **2a** except benzyltriethylammonium chloride was employed as the catalyst and 3-chloro-2-methylpropene was the electrophile. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **4a** as a pale yellow oil (0.43 g, 69%) (R_f 0.50): IR (film) 1749, 1655, and 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, $^3J_{H-H}$ = 7.3 Hz), 1.58−1.82 (m, 2H), 1.70 (s, 3H), 3.36 (s, 3H), 3.54 (t, 2H, $^3J_{H-H}$ = 4.2 Hz), 3.70−3.78 (m, 1H), 3.71 (d, 1H, $^2J_{H-H}$ = 13.1 Hz), 3.82−3.90 (m, 2H), 3.94 (d, 1H, $^2J_{H-H}$ = 13.1 Hz), 4.85 (s, 1H), 4.90 (d, 1H, $^2J_{H-H}$ = 6.1 Hz), 4.92 (s, 1H), 5.00 (d, 1H, $^2J_{H-H}$ = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.9, 19.6, 25.0, 59.0, 68.2, 71.6, 72.1, 75.7, 97.0, 112.3 (dd, $^2J_{C-F}$ = 36.7, 9.7 Hz), 112.4, 141.7, 156.3 (dd, $^1J_{C-F}$ = 293.6, 284.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.4 (d, 1F, $^2J_{F-F}$ = 64.1 Hz), −98.4 (d, 1F, $^2J_{F-F}$ = 64.1 Hz); *m/z* (CI, NH_3) 298 (60), 281 (4), 89 (100); HRMS calcd for $C_{13}H_{26}F_2NO_4$ ($[M + NH_4]^+$) 298.18299, found 298.18424.

3-(Propargyloxy)-1,1-difluoro-2-([methoxyethoxy]methoxy)pent-1-ene (5a) was prepared as for **2a** except propargyl bromide was employed as the electrophile. Standard workup and purification by Kugelrohr bulb-to-bulb distillation (ot 70 °C at 0.03 mmHg) gave **5a** as a pale yellow oil (5.70 g, 51%) (Found: C, 54.67; H, 6.77. $C_{12}H_{18}F_2O_4$ requires C, 54.54; H, 6.87.): IR (film) 2116, 1748, and 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, $^3J_{H-H}$ = 7.3 Hz), 1.52−1.79 (m, 2H), 2.36 (t, 1H, $^4J_{H-H}$ = 2.5 Hz), 3.30 (s, 3H), 3.48 (m, 2H), 3.63−3.82 (m, 2H), 3.99 (dd, 1H, $^2J_{H-H}$ = 16.2 Hz, $^4J_{H-H}$ = 2.5 Hz), 4.02−4.09 (m, 1H), 4.10 (dd, 1H, $^2J_{H-H}$ = 16.2 Hz, $^4J_{H-H}$ = 2.5 Hz), 4.83 (d, 1H, $^2J_{H-H}$ = 6.0 Hz), 4.93 (d, 1H, $^2J_{H-H}$ = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.8, 24.8, 55.6, 59.0, 68.3, 71.6, 74.3, 75.7, 79.4, 96.9, 111.8 (dd, $^2J_{C-F}$ = 36.3, 9.9 Hz), 156.4 (dd, $^1J_{C-F}$ = 294.5, 285.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.4 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −97.1 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 282 (40) ($[M + NH_4]^+$), 265 (2), 209 (35), 59 (100).

3-[[(Trimethylsilyl)propargyl]oxy]-1,1-difluoro-2([methoxyethoxy]methoxy)pent-1-ene (6a). To a solution of diisopropylamine (0.29 mL, 2.1 mmol) in THF (1 mL) at −78 °C was added dropwise a 1.6 M solution of *n*-butyllithium in hexanes (1.25 mL, 2.0 mmol). The solution was warmed to 0 °C for 10 min to ensure LDA formation was complete and was subsequently recooled to −78 °C. Ether **5a** (0.26 g, 1.0 mmol) was added dropwise over 5 min. After stirring at −78 °C for 15 min, chlorotrimethylsilane (0.14 mL, 1.0 mmol) was added to the dark brown reaction mixture, which became pale yellow in color instantaneously. The reaction mixture was allowed to warm to −30 °C over 4 h. Standard workup and purification by flash column chromatography, using 10% ethyl acetate/hexane as eluant, gave **6a** as a pale yellow oil (0.10 g, 30%) (R_f 0.40): IR (film) 2176, 1748, and 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 9H), 0.90 (t, 3H, $^3J_{H-H}$ = 7.5 Hz), 1.58−1.81 (m, 2H), 3.37 (s, 3H), 3.54 (t, 2H, $^3J_{H-H}$ = 4.5 Hz), 3.72−3.88 (m, 2H), 4.05 (d, 1H, $^2J_{H-H}$ = 16.0 Hz), 4.06−4.16 (m, 1H), 4.17 (d, 1H, $^2J_{H-H}$ = 16.0 Hz), 4.89 (d, 1H, $^2J_{H-H}$ = 6.0 Hz), 4.99 (d, 1H, $^2J_{H-H}$ = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −0.4, 9.7, 24.7, 56.4, 58.9, 68.2, 71.5, 75.5, 91.3, 96.8, 101.2, 111.9 (dd, $^2J_{C-F}$ = 36.5, 10.2 Hz), 156.1 (dd, $^1J_{C-F}$ = 294.0, 285.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.4 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −97.4 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 354 (50) ($[M + NH_4]^+$), 336 (1), 89 (93), 59 (100).

3-[[(Triisopropylsilyl)propargyl]oxy]-1,1-difluoro-2([methoxyethoxy]methoxy)pent-1-ene (7a). To a solution of diisopropylamine (0.15 mL, 1.1 mmol) in THF (1 mL) at −78 °C was added dropwise a 1.6 M solution of *n*-butyllithium in hexanes (0.63 mL, 1.0 mmol). The solution was warmed to 0 °C for 10 min to ensure LDA formation was complete and was subsequently recooled to −78 °C. Ether **5a** (0.26 g, 1.0 mmol) was added dropwise over 5 min. After stirring at −78 °C for 15 min, triisopropylsilyl triflate (0.30 mL, 1.1 mmol) was added to the dark brown reaction mixture, which became pale yellow in color instantaneously. The reaction mixture was allowed to warm to −30 °C over 4 h. Standard workup and purification by flash column chromatography, using 10% ethyl acetate/hexane as eluant, gave **7a** as a pale yellow oil (0.35 g, 83%) (R_f 0.35): IR (film) 2116, 1749, and 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, $^3J_{H-H}$ = 7.3 Hz), 1.05 (d, 18H, $^3J_{H-H}$ = 7.5 Hz), 1.69 (sept, 3H, $^3J_{H-H}$ = 7.5 Hz), 1.60−1.80 (m, 2H), 3.38 (s, 3H), 3.54−3.60 (m, 2H), 3.73−3.90 (m, 2H), 4.12 (d, 1H, $^2J_{H-H}$ = 16.0 Hz), 4.23 (d, 1H, $^2J_{H-H}$ = 16.0 Hz), 4.25−4.33 (m, 1H), 4.90 (d, 1H, $^2J_{H-H}$ = 6.0 Hz), 5.00 (d, 1H, $^2J_{H-H}$ = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.9, 11.1, 18.5, 24.9, 56.1, 59.0, 68.3, 71.6, 74.7, 87.6, 96.9, 103.0, 111.2 (dd, $^2J_{C-F}$ = 36.4, 10.8 Hz), 155.9 (dd, $^1J_{C-F}$ = 292.3, 285.4 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.4 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −97.4 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 438 (100), 89 (46), 59 (39); HRMS calcd for $C_{21}H_{42}F_2NO_4Si$ ($[M + NH_4]^+$) 438.28512, found 438.28535.

3-(Allyloxy)-1,1-difluoro-2-([methoxyethoxy]methoxy)-prop-1-ene (2b) was prepared as for **2a** except alcohol **1b** was used. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **2b** as a colorless oil (0.56 g, 93%) (R_f 0.37): IR (film) 1760, 1648, and 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.37 (s, 3H), 3.52−3.57 (m, 2H), 3.77−3.83 (m, 2H), 3.96 (dt, 2H, $^3J_{H-H}$ = 5.5 Hz, $^4J_{H-H}$ = 1.6 Hz), 4.09 (d, 1H, $^2J_{H-H}$ = 2.0 Hz), 4.11 (d, 1H, $^2J_{H-H}$ = 2.0 Hz), 4.97 (s, 2H), 5.18 (br d, 1H, $^3J_{H-Hcis}$ = 11.0 Hz), 5.26 (br d, 1H, $^3J_{H-Htrans}$ = 17.1 Hz), 5.80−5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 59.0, 63.6, 68.1, 70.8, 71.6, 95.5, 112.3 (dd, $^2J_{C-F}$ = 38.8, 13.0 Hz), 117.6, 134.1, 155.5 (t, $^1J_{C-F}$ = 288.2 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.0 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −99.3 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 256 (27), 89 (15), 78 (36), 61 (100); HRMS calcd for $C_{10}H_{20}F_2NO_4$ ($[M + NH_4]^+$) 256.13604, found 256.13595.

3-(Benzyloxy)-1,1-difluoro-2-([methoxyethoxy]methoxy)prop-1-ene (3b) was prepared as for **2a** except alcohol **1b** was used and benzyl bromide was the electrophile. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **3b** as a colorless oil (0.14 g, 96%) (R_f 0.38): IR (film) 1763 and

1463 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.38 (s, 3H), 3.52−3.57 (t, 2H, $^3J_{H-H}$ = 4.5 Hz), 3.79−3.86 (t, 2H, $^3J_{H-H}$ = 4.5 Hz), 4.14 (d, 1H, $^2J_{H-H}$ = 2.2 Hz), 4.16 (d, 1H, $^2J_{H-H}$ = 2.2 Hz), 4.52 (s, 2H), 5.00 (s, 2H), 7.26−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.0, 63.7, 68.1, 71.6, 71.9, 95.4, 112.1 (dd, $^2J_{C-F}$ = 38.3, 12.8 Hz), 127.9, 128.4, 137.6, 155.7 (dd, $^1J_{C-F}$ = 292.0, 284.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.7 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −99.1 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 306 (25), 100 (100), 78 (18), 58 (32), 44 (65); HRMS calcd for $C_{14}H_{22}F_2NO_4$ ($[M + NH_4]^+$) 306.15169, found 306.15262.

3-(Methallyloxy)-1,1-difluoro-2-([methoxyethoxy]-methoxy)prop-1-ene (4b) was prepared as for **2a** except alcohol **1b** was used, benzyltriethylammonium chloride was employed as the catalyst, and 3-chloro-2-methylpropene was the electrophile. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **4b** as a pale yellow oil (0.61 g, 48%) (R_f 0.39): (Found: C, 52.48; H, 7.27. $C_{11}H_{18}F_2O_4$ requires C, 52.38; H, 7.19.): IR (film) 1759, 1657, and 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.71 (s, 3H), 3.36 (s, 3H), 3.50−3.57 (m, 2H), 3.77−3.82 (m, 2H), 3.85 (s, 2H), 3.82−3.90 (m, 2H), 4.05 (d, 1H, $^2J_{H-H}$ = 2.2 Hz), 4.06 (d, 1H, $^2J_{H-H}$ = 2.2 Hz), 4.88 (s, 1H), 4.93 (s, 1H), 4.96 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 58.9, 63.4, 68.0, 71.5, 73.7, 95.4, 112.6 (dd, $^2J_{C-F}$ = 39.0, 13.1 Hz), 112.7, 141.5, 155.5 (dd, $^1J_{C-F}$ = 291.8, 284.2 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −110.0 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −99.4 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 270 (51) ($[M + NH_4]^+$), 196 (100), 89 (55), 59 (91), 44 (92).

3-(Propargyloxy)-1,1-difluoro-2-([methoxyethoxy]-methoxy)prop-1-ene (5b) was prepared as for **2a** except alcohol **1b** was used and propargyl bromide was the electrophile. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **5b** as a pale yellow oil (0.11 g, 82%) (R_f 0.43): IR (film) 3288, 2116, 1759, and 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.46 (t, 1H, $^4J_{H-H}$ = 2.5 Hz), 3.40 (s, 3H), 3.54−3.60 (m, 2H), 3.80−3.87 (m, 2H), 4.18 (d, 2H, $^4J_{H-H}$ = 2.5 Hz), 4.22 (d, 1H, $^4J_{H-H}$ = 2.0 Hz), 4.24 (d, 1H, $^4J_{H-H}$ = 2.0 Hz), 4.99 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.9, 59.0, 63.1, 68.1, 71.5, 75.0, 78.9, 95.4, 111.7 (dd, $^2J_{C-F}$ = 38.5, 13.7 Hz), 155.7 (t, $^1J_{C-F}$ = 288.8 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.1 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −98.3 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 254 (45) ($[M + NH_4]^+$), 89 (12), 78 (93), 61 (100).

3-[[(Triisopropylsilyl)propargyl]oxy]-1,1-difluoro-2-([methoxyethoxy]methoxy)prop-1-ene (7b) was prepared as for **7a** except ether **5b** was used. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave **7b** as a pale yellow oil (0.14 g, 78%) (R_f 0.50): IR (film) 3502, 2171, 1758, and 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05−1.08 (m, 21H), 3.39 (s, 3H), 3.54−3.59 (m, 2H), 3.80−3.86 (m, 2H), 4.21 (s, 2H), 4.25 (d, 1H, $^4J_{H-H}$ = 2.2 Hz), 4.26 (d, 1H, $^4J_{H-H}$ = 2.2 Hz), 4.98 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2, 18.5, 57.6, 59.0, 62.6, 68.1, 71.6, 88.4, 95.3, 102.3, 111.8 (dd, $^2J_{C-F}$ = 38.9, 13.8 Hz), 155.8 (dd, $^1J_{C-F}$ = 292.1, 285.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.0 (d, 1F, $^2J_{F-F}$ = 58.0 Hz), −98.4 (d, 1F, $^2J_{F-F}$ = 58.0 Hz); *m/z* (CI, NH_3) 410 (100), 393 (3), 100 (10), 89 (24), 59 (21); HRMS calcd for $C_{19}H_{38}F_2NO_4Si$ ($[M + NH_4]^+$) 410.25382, found 410.25455.

3-(Allyloxy)-3-ethyl-1,1-difluoro-2-([methoxyethoxy]-methoxy)pent-1-ene (2c). A solution of **1c** (0.75 g, 2.95 mmol) in DMF (2 mL) was added dropwise to sodium hydride (0.14 g, 5.90 mmol at 60% dispersion from which the oil had been removed with toluene) in DMF (5 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h, after which time a solution of allyl bromide (0.31 mL, 3.54 mmol) and tetrabutylammonium iodide (0.11 g, 0.29 mmol) in DMF (2 mL) was added dropwise to the orange solution. The reaction mixture was allowed to reach room temperature overnight. Ethyl acetate (30 mL) was added, and the organic layer washed with water (3 × 50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **2c** as a pale yellow oil (0.53 g, 61%) (R_f 0.50): IR (film) 1731, 1648, and 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 6H, $^3J_{H-H}$ = 7.4 Hz), 1.58−1.80 (m, 4H), 3.35 (s, 3H), 3.50−3.56 (m, 2H), 3.75−3.82 (m, 4H), 4.90 (s, 2H), 5.07 (dq, 1H, $^2J_{H-H}$ = 2.0 Hz, $^3J_{H-Hcis}$ = 11.0 Hz, $^4J_{H-H}$ = 1.0 Hz), 5.23 (dq, 1H, $^2J_{H-H}$ = 2.0 Hz, $^3J_{H-Htrans}$ = 17.0 Hz, $^4J_{H-H}$ = 1.0 Hz), 5.76−5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.4, 24.5, 59.0, 63.1, 68.5, 71.6, 81.6, 97.6, 115.7 (dd, $^2J_{C-F}$ = 30.9, 11.7 Hz), 116.1, 134.8, 157.5 (t, $^1J_{C-F}$ = 290.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −102.5 (d, 1F, $^2J_{F-F}$ = 64.1 Hz), −94.1 (d, 1F, $^2J_{F-F}$ = 64.1 Hz); *m/z* (CI, NH_3) 312 (35), 159 (100), 89 (49), 59 (64); HRMS calcd for $C_{14}H_{28}F_2NO_4$ ($[M + NH_4]^+$) 312.19864, found 312.19971.

3-(Benzyloxy)-3-ethyl-1,1-difluoro-2-([methoxyethoxy]-methoxy)pent-1-ene (3c) was prepared as for **2c** except benzyl bromide was employed as the electrophile. Workup as for **2c** and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **3c** as a pale yellow oil (0.39 g, 57%) (R_f 0.45) (Found: C, 63.16; H, 7.88. $C_{18}H_{26}F_2O_4$ requires C, 62.78; H, 7.61.): IR (film) 1730 and 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 6H, $^3J_{H-H}$ = 7.5 Hz), 1.69−1.94 (m, 4H), 3.37 (s, 3H), 3.50−3.55 (m, 2H), 3.78−3.86 (m, 2H), 4.34 (s, 2H), 4.95 (s, 2H), 7.21−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.5, 24.7, 59.0, 64.0, 68.6, 71.6, 81.8, 97.7, 116.0 (dd, $^2J_{C-F}$ = 30.9, 12.1 Hz), 127.3, 127.5, 128.3, 138.7, 157.4 (t, $^1J_{C-F}$ = 290.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −102.3 (d, 1F, $^2J_{F-F}$ = 64.1 Hz), −94.2 (d, 1F, $^2J_{F-F}$ = 64.1 Hz); *m/z* (CI, NH_3) 362 (95), 89 (100), 59 (96); HRMS calcd for $C_{18}H_{30}F_2NO_4$ ($[M + NH_4]^+$) 362.21429, found 362.21490.

3-(Methallyloxy)-3-ethyl-1,1-difluoro-2-([methoxyethoxy]methoxy)pent-1-ene (4c) was prepared as for **2c** except 3-chloro-2-methylpropene was employed as the electrophile. Workup as for **2c** and purification by flash column chromatography, using 10% ethyl acetate/petroleum ether as eluant, gave **4c** as a pale yellow oil (0.24 g, 27%) (R_f 0.50) (Found: C, 58.31; H, 8.39. $C_{15}H_{26}F_2O_4$ requires C, 58.43; H, 8.50.): IR (film) 1731, 1657, and 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, 6H, $^3J_{H-H}$ = 7.5 Hz), 1.64−1.85 (m, 4H), 1.72 (s, 3H), 3.38 (s, 3H), 3.53−3.59 (m, 2H), 3.68 (s, 2H), 3.79−3.85 (m, 2H), 4.81 (br s, 1H), 4.90 (s, 2H), 4.98 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.4, 19.8, 24.7, 59.0, 65.5, 68.5, 71.6, 81.4, 97.7, 111.0, 115.8 (dd, $^2J_{C-F}$ = 30.8, 11.8 Hz), 142.2, 157.4 (t, $^1J_{C-F}$ = 290.4 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −102.5 (d, 1F, $^2J_{F-F}$ = 64.1 Hz), −94.3 (d, 1F, $^2J_{F-F}$ = 64.1 Hz); *m/z* (CI, NH_3) 326 (20), 159 (60), 89 (60), 59 (100); HRMS calcd for $C_{15}H_{30}F_2NO_4$ ($[M + NH_4]^+$) 326.21429, found 326.21438.

3-(Allyloxy)-1,1-difluoro-2-([methoxyethoxy]methoxy)-penta-1,5-diene (2d) was prepared as for **2a** except alcohol **1d** was used. Standard workup and purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave **2d** as a pale yellow oil (0.39 g, 74%) (R_f 0.40): IR (film) 1731, 1648, and 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35 (s, 3H), 3.50 (t, 2H, $^3J_{H-H}$ = 5.0 Hz), 3.70−3.86 (m, 2H), 3.90 (ddt, 1H, $^2J_{H-H}$ = 13.0 Hz, $^3J_{H-H}$ = 5.0 Hz, 2 × $^4J_{H-H}$ = 1.5 Hz), 4.01 (ddt, 1H, $^2J_{H-H}$ = 13.0 Hz, $^3J_{H-H}$ = 5.0 Hz, 2 × $^4J_{H-H}$ = 1.5 Hz), 4.44−4.53 (m, 1H), 4.90 (d, 1H, $^2J_{H-H}$ = 6.5 Hz), 5.00 (d, 1H, $^3J_{H-H}$ = 6.5 Hz), 5.15 (dq, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Hcis}$ = 11.5 Hz), 5.23 (dq, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Htrans}$ = 17.0 Hz, 2 × $^4J_{H-H}$ = 1.5 Hz), 5.24 (dt, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Hcis}$ = 13.0 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.35 (dt, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Htrans}$ = 17.0 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.76−5.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 58.9, 68.3, 69.0, 71.6, 75.1, 97.1, 113.2 (dd, $^2J_{C-F}$ = 36.4, 11.5 Hz), 117.2, 117.8, 134.1, 155.7 (dd, $^1J_{C-F}$ = 293.6, 285.8 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −113.1 (d, 1F, $^2J_{F-F}$ = 61.0 Hz), −102.4 (d, 1F, $^2J_{F-F}$ = 61.0 Hz); *m/z* (CI, NH_3) 282 (25) ($[M + NH_4]^+$), 265 (3), 89 (100), 59 (100).

General Procedure for the [2,3]-Wittig Rearrangement of Difluoroallylic Ethers. A solution of *n*-butyllithium in hexanes (2.0 equiv) was added dropwise to a solution of diisopropylamine (2.2 equiv) in THF (*ca.* 10 mL) at −78 °C. The solution was warmed to 0 °C for 10 min to ensure complete LDA formation and was subsequently recooled to −78 °C. A solution of the appropriate difluoroallylic ether (1.0 equiv) in THF (*ca.* 3 mL) was added dropwise over 5 min. The solution became red-brown in color instantaneously. After stirring at −78 °C for 2 h, the solution was allowed to warm slowly to −30 °C and was maintained at this temperature for a further 2−72 h, depending on the ether substrate used. The reaction

was quenched with a methanolic solution of ammonium chloride (10 mL) and washed with water (20 mL), and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

4,4-Difluoro-3-hydroxy-5-([methoxyethoxy]methoxy)-octa-1,5-diene (8a). Treatment of **2a** with LDA as described above, followed by stirring at −30 °C for 4 h, usual workup, and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **8a** as a yellow oil (1.03 g, 86%) (R_f 0.21) (Found: C, 54.26; H, 7.86. $C_{12}H_{20}F_2O_4$ requires C, 54.13; H, 7.57.): IR (film) 3424, 1750, 1674, and 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3H, $^3J_{H-H}$ = 7.6 Hz), 2.10−2.22 (m, 2H), 2.80 (br s, 1H (OH)), 3.39 (s, 3H), 3.55−3.60 (t, 2H, $^3J_{H-H}$ = 5.0 Hz), 3.80−3.90 (m, 2H), 4.48−4.52 (m, 1H), 5.00 (s, 2H), 5.33 (dt, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Hcis}$ = 10.5 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.49 (dt, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Htrans}$ = 17.1 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.50 (dt, 1H, $^3J_{H-H}$ = 1.5 Hz, $^3J_{H-F}$ = 7.6 Hz), 5.77−5.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 18.8, 59.0, 68.9, 71.6, 72.5, 98.3, 118.2 (t, $^1J_{C-F}$ = 248.6 Hz), 118.9, 122.0 (t, $^3J_{C-F}$ = 5.1 Hz), 132.5, 144.7 (t, $^2J_{C-F}$ = 26.3 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −116.9 (dd, 1F, $^2J_{F-F}$ = 250.2 Hz, $^3J_{H-F}$ = 14.0 Hz), −109.6 (d, 1F, $^2J_{F-F}$ = 250.2 Hz); *m/z* (CI, NH_3) 284 (75), 267 (56), 89 (100), 59 (90); HRMS calcd for $C_{12}H_{24}F_2NO_4$ ($[M + NH_4]^+$) 284.16734, found 284.16684.

1-Phenyl-2,2-difluoro-1-hydroxy-3-([methoxyethoxy]-methoxy)hex-1-ene (9a). Treatment of **3a** with LDA as described above, followed by stirring at −30 °C overnight (15 h), usual workup, and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **9a** as an orange oil (0.075 g, 76%) (R_f 0.19) (Found: C, 60.85; H, 7.25. $C_{16}H_{22}F_2O_4$ requires C, 60.75; H, 7.01.): IR (film) 3423, 1680, and 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H, $^3J_{H-H}$ = 7.6 Hz), 2.06−2.21 (m, 2H), 3.22 (br d, 1H (OH), $^3J_{H-H}$ = 4.0 Hz), 3.38 (s, 3H), 3.59 (t, 2H, $^3J_{H-H}$ = 4.5 Hz), 3.81−3.94 (m, 2H), 5.02 (d, 1H, $^2J_{H-H}$ = 5.0 Hz), 5.05 (d, 1H, $^2J_{H-H}$ = 5.0 Hz), 5.14 (dd, 1H, $^3J_{H-F}$ = 14.7, 9.0 Hz), 5.41 (dt, 1H, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-F}$ = 1.2 Hz), 7.30−7.39 (m, 3H), 7.40−7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 18.7, 59.0, 68.9, 71.6, 75.6 (dd, $^2J_{C-F}$ = 30.7, 26.7 Hz), 98.3, 118.3 (t, $^1J_{C-F}$ = 249.5 Hz), 122.2, 127.8, 127.9, 128.4, 136.3, 144.7 (t, $^2J_{C-F}$ = 26.5 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −116.5 (dd, 1F, $^2J_{F-F}$ = 254.9 Hz, $^3J_{H-F}$ = 13.7 Hz), −109.3 (dd, 1F, $^2J_{F-F}$ = 254.9 Hz, $^3J_{H-F}$ = 9.2 Hz); *m/z* (CI, NH_3) 334 (1) ($[M + NH_4]^+$), 317 (5), 89 (100), 59 (98).

4,4-Difluoro-3-hydroxy-2-methyl-5-([methoxyethoxy]-methoxy)octa-1,5-diene (10a). Treatment of **4a** with LDA as described above, followed by stirring at −30 °C overnight (15 h), usual workup, and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **10a** as a yellow oil (0.084 g, 84%) (R_f 0.14) (Found: C, 55.72; H, 7.82. $C_{13}H_{22}F_2O_4$ requires C, 55.70; H, 7.91.): IR (film) 3404, 1738, 1654, and 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, 3H, $^3J_{H-H}$ = 7.6 Hz), 1.83 (s, 3H), 2.12−2.25 (m, 2H), 2.74 (br s, 1H (OH)), 3.38 (s, 3H), 3.53−3.63 (m, 2H), 3.82−3.89 (m, 2H), 4.50 (q, 1H, $^4J_{H-H}$ = 8.3 Hz), 5.01 (d, 1H, $^2J_{H-H}$ = 6.0 Hz), 5.04 (d, 1H, $^2J_{H-H}$ = 6.0 Hz), 5.09 (t, 1H, $^2J_{H-H}$ = 1.5 Hz, $^5J_{H-F}$ = 1.5 Hz), 5.13 (br s, 1H), 5.56 (dt, 1H, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-F}$ = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 18.8, 18.9, 59.0, 68.9, 71.6, 74.6, 98.3, 116.1, 118.7 (t, $^1J_{C-F}$ = 250.0 Hz), 121.6, 140.7, 145.1 (t, $^2J_{C-F}$ = 26.8 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −115.8 (dd, 1F, $^2J_{F-F}$ = 253.3 Hz, $^3J_{H-F}$ = 15.3 Hz), −108.4 (dd, 1F, $^2J_{F-F}$ = 253.3 Hz, $^3J_{H-F}$ = 6.1 Hz); *m/z* (CI, NH_3) 298 (31), 89 (19), 59 (12); HRMS calcd for $C_{13}H_{26}F_2NO_4$ ($[M + NH_4]^+$) 298.18299, found 298.18146.

4,4-Difluoro-3-hydroxy-5-([methoxyethoxy]methoxy)-1-(triisopropylsilyl)oct-5-en-1-yne (13a). Treatment of **7a** with LDA as described above, followed by stirring at −30 °C for 4 h, usual workup, and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **13a** as a colorless oil (0.13 g, 68%) (R_f 0.30): IR (film) 3405, 2180, 1681, and 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, 3H, $^3J_{H-H}$ = 7.5 Hz), 1.07 (s, 21H), 2.16−2.26 (m, 2H), 2.75 (br d, 1H (OH), $^3J_{H-H}$ = 7.5 Hz), 3.39 (s, 3H), 3.55−3.59 (m, 2H), 3.83−3.88 (m, 2H), 4.74−4.84 (m, 1H), 5.00 (d, 1H, $^2J_{H-H}$ = 5.0 Hz), 5.01 (d, 1H, $^2J_{H-H}$ = 5.0 Hz), 5.62 (dt, 1H, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-F}$ = 1.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.1, 13.7, 18.5, 18.8, 59.0, 64.5, 68.9, 71.6, 89.1, 98.4, 101.5, 116.9 (t, $^1J_{C-F}$ = 249.8 Hz), 122.3, 144.3 (t, $^2J_{C-F}$ = 25.7 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −114.3 (dd, 1F, $^2J_{F-F}$ = 250.4 Hz, $^3J_{H-F}$ = 11.0 Hz), −111.4 (dd, 1F, $^2J_{F-F}$ = 250.4 Hz, $^3J_{H-F}$ = 9.0 Hz); *m/z* (CI, NH_3) 438 (100), 89 (14), 59 (9); HRMS calcd for $C_{21}H_{42}F_2NO_4Si$ ($[M + NH_4]^+$) 438.28512, found 438.28552.

4,4-Difluoro-3-hydroxy-5-([methoxyethoxy]methoxy)-hexa-1,5-diene (8b). Treatment of **2b** with LDA as described above, followed by stirring at −30 °C for 4 h, usual workup, and purification by flash column chromatography, using 40% ethyl acetate/petroleum ether as eluant, gave **8b** as a yellow oil (0.061 g, 61%) (R_f 0.31) (Found: C, 50.53; H, 6.71. $C_{10}H_{16}F_2O_4$ requires C, 50.42; H, 6.77.): IR (film) 3450, 1666, and 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.82 (br d, 1H (OH), $^3J_{H-H}$ = 6.0 Hz), 3.37 (s, 3H), 3.52−3.58 (m, 2H), 3.74−3.80 (m, 2H), 4.42−4.59 (m, 1H), 4.71 (m, 1H), 4.82 (d, 1H, $^2J_{H-H}$ = 3.2 Hz), 5.08 (d, 1H, $^2J_{H-H}$ = 6.5 Hz), 5.14 (d, 1H, $^2J_{H-H}$ = 6.5 Hz), 5.36 (br d, 1H, $^3J_{H-Hcis}$ = 10.5 Hz), 5.49 (br d, 1H, $^3J_{H-Htrans}$ = 17.0 Hz), 5.87−6.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.0, 68.2, 71.6, 72.2, 90.3, 92.9, 117.0 (t, $^1J_{C-F}$ = 247.6 Hz), 119.2, 132.2, 151.7 (t, $^2J_{C-F}$ = 27.0 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −119.5 (dd, 1F, $^2J_{F-F}$ = 256.4 Hz, $^3J_{H-F}$ = 15.3 Hz), −112.7 (dd, 1F, $^2J_{F-F}$ = 256.4 Hz, $^3J_{H-F}$ = 9.2 Hz); *m/z* (CI, NH_3) 256 (39) ($[M + NH_4]^+$), 89 (25), 61 (100).

1-Phenyl-2,2-difluoro-1-hydroxy-3-([methoxyethoxy]-methoxy)but-3-ene (9b). Treatment of **3b** with LDA as described above, followed by stirring at −30 °C overnight (15 h), usual workup, and purification by flash column chromatography, using 40% ethyl acetate/petroleum ether as eluant, gave **9b** as an off-white crystalline solid (0.052 g, 52%) (R_f 0.45): mp 54−55 °C; IR (film) 3450, 1658, and 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.16 (br s, 1H (OH)), 3.38 (s, 3H), 3.53−3.59 (m, 2H), 3.76−3.81 (m, 2H), 4.69 (m, 1H), 4.79 (d, 1H, $^2J_{H-H}$ = 3.5 Hz), 5.03−5.21 (m, 1H), 5.09 (d, 1H, $^2J_{H-H}$ = 6.5 Hz), 5.17 (d, 1H, $^2J_{H-H}$ = 6.5 Hz), 7.33−7.41 (m, 3H), 7.42−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.2, 68.4, 71.7, 73.3, 90.6, 93.1, 117.0 (t, $^1J_{C-F}$ = 248.4 Hz), 128.0, 128.2, 128.7, 136.0, 151.8 (t, $^2J_{C-F}$ = 29.0 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −119.3 (dd, 1F, $^2J_{F-F}$ = 253.3 Hz, $^3J_{H-F}$ = 15.3 Hz), −111.6 (dd, 1F, $^2J_{F-F}$ = 253.3 Hz, $^3J_{H-F}$ = 6.1 Hz); *m/z* (CI, NH_3) 306 (35), 102 (100), 94 (69), 44 (76); HRMS calcd for $C_{14}H_{22}F_2NO_4$ ($[M + NH_4]^+$) 306.15169, found 306.15074.

4,4-Difluoro-3-hydroxy-2-methyl-5-([methoxyethoxy]-methoxy)hexa-1,5-diene (10b). Treatment of **4b** with LDA as described above, followed by stirring at −30 °C overnight (15 h), usual workup, and purification by flash column chromatography, using 40% ethyl acetate/petroleum ether as eluant, gave **10b** as an orange oil (0.26 g, 58%) (R_f 0.40) (Found: C, 52.24; H, 7.21. $C_{11}H_{18}F_2O_4$ requires C, 52.38; H, 7.19.): IR (film) 3436, 1738, 1652, and 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.85 (s, 3H), 2.78 (br d, 1H (OH), $^3J_{H-H}$ = 4.5 Hz), 3.39 (s, 3H), 3.54−3.60 (m, 2H), 3.74−3.84 (m, 2H), 4.40−4.59 (m, 1H), 4.71 (t, 1H, $^2J_{H-H}$ = 3.2 Hz, $^4J_{H-F}$ = 2.2 Hz), 4.83 (d, 1H, $^2J_{H-H}$ = 3.2 Hz), 5.06−5.19 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 59.1, 68.4, 71.7, 74.6, 90.0, 93.3, 116.4, 117.6 (t, $^1J_{C-F}$ = 249.1 Hz), 140.7, 152.3 (t, $^2J_{C-F}$ = 30.7 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ −117.3 (dd, 1F, $^2J_{F-F}$ = 254.1 Hz, $^3J_{H-F}$ = 15.3 Hz), −111.6 (dd, 1F, $^2J_{F-F}$ = 254.1 Hz, $^3J_{H-F}$ = 15.3 Hz); *m/z* (CI, NH_3) 270 (100) ($[M + NH_4]^+$), 94 (53), 59 (18), 44 (24); HRMS calcd for $C_{11}H_{22}F_2NO_4$ ($[M + NH_4]^+$) 270.15169, found 270.15084.

1-(Triisopropylsilyl)-4,4-difluoro-3-hydroxy-5-([methoxyethoxy]methoxy)hex-5-en-1-yne (13b). Treatment of **7b** with LDA as described above, followed by stirring at −30 °C for 4 h, usual workup, and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **13b** as a colorless oil (0.041 g, 52%) (R_f 0.36): IR (film) 3406, 1656, and 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 21H), 3.01 (br d, 1H (OH), $^3J_{H-H}$ = 9.0 Hz), 3.38 (s, 3H), 3.52−3.57 (m, 2H), 3.73−3.81 (m, 2H), 4.70−4.83 (m, 2H), 4.87 (d, 1H, $^2J_{H-H}$ = 3.0 Hz), 5.09 (d, 1H, $^2J_{H-H}$ = 6.5 Hz), 5.14 (d, 1H, $^2J_{H-H}$ = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.1, 18.5, 59.0, 64.0, 68.1, 71.5, 89.2, 90.5, 93.1, 101.1, 115.8 (t, $^1J_{C-F}$ = 248.8 Hz), 151.3 (t, $^2J_{C-F}$ = 27.9 Hz); ^{19}F NMR ($CDCl_3$, 90

MHz) δ −117.2 (dd, 1F, $^2J_{F-F}$ = 250.2 Hz, $^3J_{H-F}$ = 9.2 Hz), −113.4 (dd, 1F, $^2J_{F-F}$ = 250.2 Hz, $^3J_{H-F}$ = 9.2 Hz); *m/z* (CI, NH_3) 410 (100), 94 (15), 58 (62), 44 (33); HRMS calcd for $C_{19}H_{38}F_2NO_4Si$ ($[M + NH_4]^+$) 410.25382, found 410.25488.

6-Ethyl-4,4-difluoro-3-hydroxy-5-([methoxyethoxy]-methoxy)-octa-1,5-diene (8c). Treatment of **2c** with LDA as described above, followed by stirring at −30 °C for 48 h, usual workup, and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **8c** as an orange oil (0.051 g, 51%) (R_f 0.20): IR (film) 3440, 1735, 1655, and 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3H, $^3J_{H-H}$ = 7.5 Hz), 1.01 (t, 3H, $^3J_{H-H}$ = 7.5 Hz), 2.10−2.28 (m, 4H), 2.85 (br d, 1H (OH), $^3J_{H-H}$ = 5.0 Hz), 3.37 (s, 3H), 3.56 (t, 2H, $^3J_{H-H}$ = 4.2 Hz), 3.71−3.90 (m, 2H), 4.42−4.59 (m, 1H), 4.90 (d, 1H, $^2J_{H-H}$ = 6.0 Hz), 4.93 (d, 1H, $^2J_{H-H}$ = 6.0 Hz), 5.34 (br d, 1H, $^3J_{H-Hcis}$ = 10.5 Hz), 5.46 (br d, 1H, $^3J_{H-Htrans}$ = 17.0 Hz), 5.85−6.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.5, 13.6, 21.9, 23.2, 59.0, 68.9, 71.6, 73.8 (t, $^2J_{C-F}$ = 29.1 Hz), 99.1, 118.8, 119.8 (t, $^1J_{C-F}$ = 250.5 Hz), 132.6, 139.9 (t, $^2J_{C-F}$ = 27.0 Hz), 140.2; ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.8 (dd, 1F, $^2J_{F-F}$ = 260.2 Hz, $^3J_{H-F}$ = 13.7 Hz), −104.0 (dd, 1F, $^2J_{F-F}$ = 260.2 Hz, $^3J_{H-F}$ = 6.1 Hz); *m/z* (CI, NH_3) 312 (3), 78 (45), 61 (100); HRMS calcd for $C_{14}H_{28}F_2NO_4$ ($[M + NH_4]^+$) 312.19864, found 312.19857.

1-Phenyl-4-ethyl-2,2-difluoro-1-hydroxy-3-([methoxy-ethoxy]methoxy)hex-3-ene (9c). Treatment of **3c** with LDA as described above, followed by stirring at −30 °C for 72 h, usual workup, and purification by flash column chromatography, using 20% ethyl acetate/petroleum ether as eluant, gave **9c** as an orange oil (0.044 g, 70%) (R_f 0.25): IR (film) 3412, 1660, and 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, $^3J_{H-H}$ = 7.5 Hz), 0.97 (t, 3H, $^3J_{H-H}$ = 7.5 Hz), 1.81−1.93 (m, 2H), 2.08−2.24 (m, 2H), 3.30 (br s, 1H (OH)), 3.40 (s, 3H), 3.59 (t, 2H, $^3J_{H-H}$ = 4.5 Hz), 3.75−3.94 (m, 2H), 4.94 (d, 1H, $^2J_{H-H}$ = 4.0 Hz), 4.97 (d, 1H, $^2J_{H-H}$ = 4.0 Hz), 5.08−5.19 (m, 1H), 7.28−7.40 (m, 3H), 7.40−7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4, 13.4, 21.6, 23.5, 59.1, 69.0, 71.7, 74.8 (t, $^2J_{C-F}$ = 28.3 Hz), 99.2, 120.0 (t, $^1J_{C-F}$ = 251.4 Hz), 127.0, 127.8, 128.0, 128.4, 128.6, 136.2, 139.3 (t, $^2J_{C-F}$ = 27.1 Hz), 140.5; ^{19}F NMR ($CDCl_3$, 90 MHz) δ −109.3 (dd, 1F, $^2J_{F-F}$ = 256.4 Hz, $^3J_{H-F}$ = 12.2 Hz), −104.6 (dd, 1F, $^2J_{F-F}$ = 256.4 Hz, $^3J_{H-F}$ = 6.1 Hz); *m/z* (CI, NH_3) 362 (89) ($[M + NH_4]^+$), 326 (100), 89 (38), 59 (21); HRMS (LSIMS) calcd for $C_{18}H_{26}F_2O_4Na$ ($[M + Na]^+$) 367.16969, found 369.17098.

4,4-Difluoro-3-hydroxy-5-([methoxyethoxy]methoxy)-octa-1,5,7-triene (8d). Treatment of **2d** with LDA as described above, followed by stirring at −30 °C for 2 h, usual workup, and purification by flash column chromatography, using 20% ethyl acetate/hexane as eluant, gave **8d** as an orange oil (0.17 g, 74%) (R_f 0.30): IR (film) 3411, 1754, 1650, and 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35 (s, 3H), 3.54−3.60 (m, 2H), 3.83−3.99 (m, 2H), 4.48−4.81 (m, 1H), 5.09 (s, 2H), 5.25 (br d, 1H, $^3J_{H-Hcis}$ = 11.0 Hz), 5.38 (br d, 1H, $^3J_{H-Htrans}$ = 17.0 Hz), 5.39 (dt, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Hcis}$ = 11.0 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.50 (dt, 1H, $^2J_{H-H}$ = 1.5 Hz, $^3J_{H-Htrans}$ = 17.0 Hz, $^4J_{H-H}$ = 1.5 Hz), 5.58−6.00 (m, 1H), 6.10 (d, 1H, $^3J_{H-H}$ = 11.0 Hz), 6.54−6.76 (m, 1H), O*H* not observed; ^{13}C NMR ($CDCl_3$, 75 MHz) 59.1, 69.1, 71.5, 72.5 (dd, $^2J_{C-F}$ = 31.0, 27.3 Hz), 98.7, 117.3, 118.2 (t, $^1J_{C-F}$ = 250.7 Hz), 118.8 (t, $^3J_{C-F}$ = 5.9 Hz), 119.2, 120.9, 128.9, 132.3; ^{19}F NMR ($CDCl_3$, 90 MHz) δ −121.4 (dd, 1F, $^2J_{F-F}$ = 253.6 Hz, $^3J_{H-F}$ = 12.2 Hz), −113.7 (d, 1F, $^2J_{F-F}$ = 253.6 Hz); *m/z* (CI, NH_3) 282 (13) ($[M + NH_4]^+$), 264 (1), 89 (100), 59 (27).

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Supporting Information Available: ^1H (300 MHz) and ^{13}C NMR spectra (75 MHz) of all compounds; a partial $^1H-^{13}C$ shift correlation experiment of **8a**; a partial COSY experiment of **8d**; ORTEP diagram of **9b** from a single-crystal X-ray structure determination (55 pages). The author has deposited atomic coordinates for **9b** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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