Systematic Synthesis of Multifluorinated α,α-Difluoro-γ-lactones through Intramolecular Radical Cyclization

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Carbon radicals from allyl *O*-(trimethylsilyl)-α-bromo-α,α-difluoroacetal can cyclize onto the olefinic part regiospecifically to give γ-lactols in good yield. The lactols are then converted to the corresponding α,α-difluoro-γ-lactones. Systematic synthesis of multifluorinated-α,α-difluoro-γ-lactones has thus been accomplished through intramolecular radical cyclization as a key reaction. Semiempirical MO calculation study suggested a unique nature of α,α-difluoroacetate in that complete delocalization of the electrons in the SOMO orbital of α,α-difluoroacetyl radical occurred; this caused unsuccessful cyclization. To apply the present radical reaction, the first synthesis of both enantiomers of difluoroeldanolide, analogues of the sex pheromone of the male African sugarcane borer, has been demonstrated. Electrophysiological tests revealed that the difluorinated analogues were as active as the natural eldanolide on the olfactory receptors.

Introduction

Partially fluorinated analogues of biologically important compounds demonstrated dramatic changes and distinctive modifications in their biological activities;[1] this makes efficient methods for the synthesis of selectively fluorinated compounds ever more necessary.[2,3] Most work, however, has focused on monofluorination of molecules, and only limited examples have been reported on introduction of the *gem*-difluoromethylene moiety.[1] Because it is believed that difluoromethylene moiety acts similarly to ether-oxygen in vivo, interesting biological activity is anticipated for analogues of α,α-difluorinated biomolecules; many types of partially difluorinated analogues of biomolecules have thus been synthesized such as amino acids,[4] vitamin D_3,[5] nucleotides,[6] prostaglandins,[7] fatty acids,[7] and insect pheromones.[8] We focused on the synthesis of α,α-difluoro-γ-lactones because a significant class of γ-lactone compounds has been found among biologically active molecules.[1,9]

Free-radical intramolecular cyclization of olefins is of paramount importance in organic synthesis for the construction of five- or six-membered rings.[10] However, limited examples were reported to provide α-halo- or α,α-dihalo-γ-lactone derivatives by radical reaction,[11] and there was no successful example of synthesizing α,α-difluoro-γ-lactone using the radical cyclization method when we began this project; Barth and O-Yang reported that only the starting material was recovered when allyl α,α-difluoro-α-iodeacetate was reacted with hexabu-

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(2) A recent review of the synthetic of geminaldifluoromethylene compounds, see: Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619.

(3) Synthetic methods for difluoromethyl compounds has progressed extensively recently. For examples, see. (a) Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1997**, *53*, 14749. (b) Taguchi, T.; Kurishita, M.; Shibuya, A.; Aso, K. *Tetrahedron* **1997**, *53*, 9497. (c) Okano, T.; Ishihara, H.; Takakura, N.; Tsuge, H.; Eguchi, S.; Kimoto, H. *J. Org. Chem.* **1997**, *62*, 7192. (d) Weigel, J. A. *J. Org. Chem.* **1997**, *62*, 6108. (e) Crowley, P. J.; Percy, J. M.; Stansfield, K. *Chem. Commun.* **1997**, 2033. (f) Serelis, A. K.; Simpson, G. W. *Tetrahedron Lett.* **1997**, *38*, 4277. (g) Xu, Y.; Dolbier, W. R. Jr.; Rong, X. X. *J. Org. Chem.* **1997**, *62*, 1576. (h) Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T. *Tetrahedron Lett.* **1997**, *38*, 2853. (i) Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 1447. (j) Ocampo, R.; Dolbier, W. R. Jr.; Bartberger, M. D.; Paredes, R. *J. Org. Chem.* **1997**, *62*, 109. (k) Iseki, K.; Oishi, S.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9081. (l) Hara, S.; Chen, S.-Q.; Hoshio, T.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1996**, *37*, 8511. (m) Crowley, P. J.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett.* **1996**, *37*, 8233. (n) Fujita, T.; Fuchigami, T. *Tetrahedron Lett.* **1996**, *37*, 4725. (o) Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 822.

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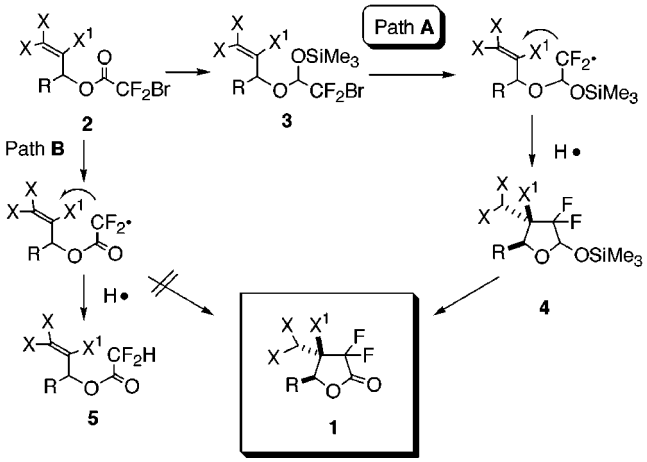
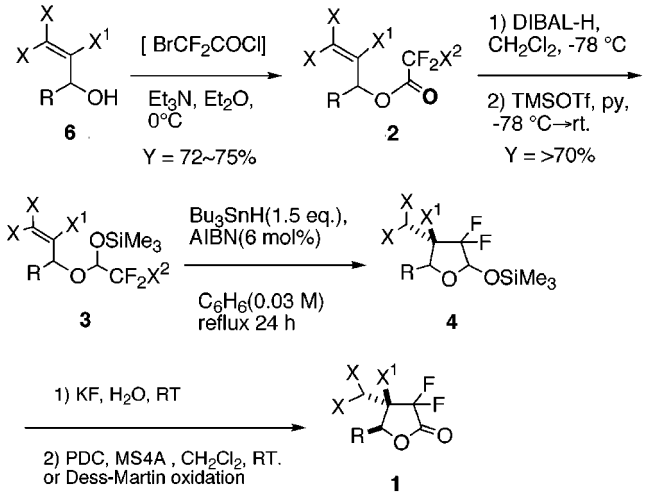
Scheme 1. Synthesis of α,α-Difluoro-γ-lactone through Intramolecular Radical Cyclization Protocol



Scheme 2. Synthesis of α,α-Difluoro-γ-lactones through Intramolecular Radical Cyclization



tylditin under irradiation conditions of a sunlamp.[12] We also tried to synthesize γ-lactone **1** directly from allyl α-bromo- or α-iodo-α,α-difluoroacetate via radical cyclization, but all efforts failed (path B in Scheme 1). Desired compound **1** was obtained only when carbon radicals from allyl *O*-(trimethylsilyl)-α-bromo-α,α-difluoroacetals **3** were subjected to the reaction (path A in Scheme 1).[13] In this paper, we describe full details of the results of investigation on the systematic synthesis of multifluorinated α,α-difluoro-γ-lactones using a free-radical intramolecular cyclization strategy.

Results and Discussion

1. Synthesis of Multifluorinated α,α-Difluoro-γ-lactones. Esters of α-radical species have reportedly been considered unsuitable for C-C bond formation because of their stable nature.[11] Cyclization of allyl α-bromo-α,α-difluoroacetate **2a** (R = $PhCH_2CH_2$; X, X^1 = H) has been attempted using tributylstannylhydride (Bu_3SnH) as reductant in the presence of radical initiators such as azobisisobutyronitrile (AIBN) or triethylborane[14] in benzene, in toluene, or in xylene under various temperature conditions, but the only product identified was the reduction compound **5a** (R = $PhCH_2CH_2$; X, X^1 = H). Significant amounts of an unidentified complex mixture were obtained if the reaction was performed at elevated temperature, such as under xylene reflux conditions. Radical reaction using atom transfer method also gave no cyclized compound but afforded complex mixtures.[15] We then tried electro-reductive intramolecular cyclization of esters **2a**,[16] but no desired lactone **1a** was obtained, though we found an interesting reaction that reductive cleavage of the acyl group occurred to provide corresponding alcohol **6a** when the reaction was carried out with zinc−zinc electrode.[17] Transition metal supported radical cyclization of **2a** was also investigated using $RuCl_2(PPh_3)_2$,[18a] Cu(bpy)Cl,[18b] and CuBr/Fe;[18c] however, none of the desired cyclized product was obtained.

Radical cyclization of the α-bromoacetal method was developed as an indirect but efficient route to γ-lactones by Ueno et al.[20a] and Stork et al.[20b] These results strongly suggested to us that increasing flexibility of the intermediate radical species would probably solve the problem in this project, and therefore α-bromoacetal was next subjected to the radical reaction. As anticipated, the desired cyclic acetal was obtained for the first time through this route, though the original Ueno−Stork-type acetals, *O*-ethyl- or *O*-butylacetal radicals, gave the corresponding cyclized compounds in very low yield of less than 10%. We finally found that *the use of O-(trimethylsilyl) (TMS) acetal was essential for efficient cyclization*, and the intramolecular radical addition of α,α-difluoro-*O*-TMS-acetals **3a** onto olefin was accomplished regiospecifically to give the corresponding five-membered lactols **4a** in good yield.[13a] The lactols **4a** were then converted to the desired α,α-difluoro-γ-lactones **1a** by PDC oxidation (Scheme 2).

Various types of new difluoroanalogues of γ-lactones **1** were synthesized through the present radical cyclization methodology (Table 1). To a benzene solution of *O*-TMS-acetal **3a** (R = $PhCH_2CH_2$; X, X^1 = H; X^2 = Br) and 6 mol % of AIBN was slowly added a benzene solution of 1.5 equiv of tributyltinhydride (Bu_3SnH) over 5 h under reflux conditions. The reaction mixture was heated to reflux for an additional 4 h and then cooled to room temperature. After evaporation, silica gel flash column chromatography using hexanes−ethyl acetate (200:1 to 50:1) as eluent afforded cyclized product **4a** in 62% yield. This step finished regiospecifically to provide

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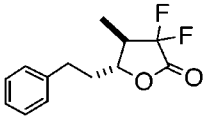
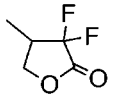
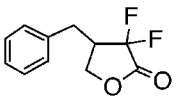
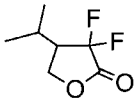
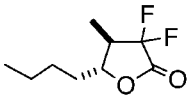
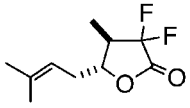
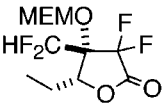
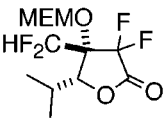
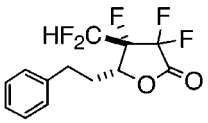
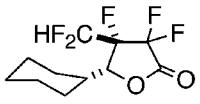
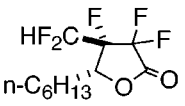
Table 1. Synthesis of α,α-Difluoro-γ-lactones 1 through Intramolecular Radical Cyclization Protocol[a]

Entry	TMS acetal **3** (R)	Lactol **4** Yield	Lactone **1**	Yield of **1**	Ratio[b] *trans*-**1** / *cis*-**1**
1	**3a** (R=$PhCH_2CH_2$, X= H, X^1= H, X^2= Br)	75% (75%)[c]		72%[d]	92 : 8
2	**3b** (R= H, X= H, X^1= H, X^2= Br)	57%		47%[d]	--------
3	**3c** (R= H, X=Ph, X= H, X^1= H, X^2= Br)	62%		95%[d]	--------
4	**3d** (R= H, X=Me, X= Me, X^1= H, X^2= Br)	68%		79%[d]	--------
5	**3e** (R= n-C_4H_9, X= H, X^1= H, X^2 = Br)	78%		81%[d]	92 : 8
6	**3f** (R= *i*-Butenyl X= H, X^1= H, X^2= Br)	74% (72%)[c]		74%[d]	98 : 2
7	**3g** (R= Et, X= F, X^1= OMEM, X^2= Br)	65% (0%)[c]		52%[d]	72 : 28[f]
8	**3h** (R= *i*-Pr, X= F, X^1= OMEM, X^2= Br)	70%		64%[d]	82 : 18[f]
9	**3i** (R= $PhCH_2CH_2$, X, X^1 = F, X^2= Br)	78% (0%)[c]		53%[e], 24%[d]	98 : 2[f]
10	**3j** (R= *c*-Hexyl, X, X^1 = F, X^2= Br)	59%		55%[e]	95 : 5[f]
11	**3k** (R= n-C_6H_{14}, X, X^1 = F, X^2= Br)	50%		55%[e]	98 : 2[f]

[a] *n*-Bu_3SnH, AIBN (10 mol %), C_6H_6, reflux. [b] Determined by capillary GC analysis (MS ϕ0.25 × 25 m). [c] Yield of corresponding α-chloro-α,α-difluoroacetate **3aa**. [d] Results of PDC oxidation. [e] Results of Dess−Martin oxidation. [f] In accordance with the nomenclature, it should be cited as *cis*-**1**:*trans*-**1**.

only five-membered lactol; and no six-membered lactol was obtained. TMS = lactol **4a** was then treated with tetrabutylammonium fluoride (TBAF) at room temperature for 12 h to provide the deprotected lactol which was used immediately for oxidation without further purification. PDC oxidation of the lactol in CH_2Cl_2 in the presence of molecular sieves 4A powder at room temperature for 6 h[21] and subsequent purification using silica gel flash column gave the desired α,α-difluoro-γ-lactone **1a** in 72% yield (Table 1, entry 1). Lactone **1a** was also obtained from α-chloro-α,α-difluoroacetal **3aa** (R = $PhCH_2CH_2$; X, X^1 = H; X^2 = Cl) in 40% overall yield. Six types of new α,α-difluoro-γ-lactones **1a**−**f** were obtained by the same

(21) Chidambaram, N.; Bhat. S.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 5013.

sequence (Table 1, entries 1−6). The most important point of the present reaction is that radical cyclization occurred regiospecifically. Neither six-membered lactol nor intermolecular coupling products formed.

This strategy was applicable for the synthesis of five more highly fluorinated types of γ-lactones **1g**−**k**. The starting fluoroallyl alcohol **6** was prepared by the method of Percy et al.[22] Trifluoroethanol was initially converted to the corresponding methoxyethoxymethyl ether (MEM) which was then treated with *n*-BuLi at −78 °C in THF to form corresponding vinyllithium species;[24] this then reacted with propionaldehyde to release **6g**[22b] and **6h** in 83% and 88% yield, respectively. Alcohol **6g** was converted to α-bromo-α,α-difluoroacetate **2g**, which was prepared in situ from the corresponding sodium salts and oxalic chloride in the presence of triethylamine in ether at 0 °C in 75% yield. Using 1,1,1,2-tetrafluoroethane as starting material, another types of fluoro allyl alcohols, **6i**−**k**, were similarly prepared.[22,23] Starting esters **2i**−**k** were thus prepared through the same reaction sequences in 72−75% yield and then were converted to *O*-TMS-acetal by DIBAL reduction and subsequent treatment with TMSOTf in the presence of pyridine as base in more than 70% yield. Synthesis of highly fluorinated α,α-difluoro-γ-lactones **1g**−**k** was accomplished through the present radical cyclization protocol, though it was essential to use Dess−Martin oxidation[24] instead of PDC oxidation in the last step for these compounds. Synthesis of five new types of α,α-difluoro-γ-lactones, **1g**−**k**, has thus been accomplished through the radical cyclization methodology (Table 1, entries 7−11). Direct radical cyclization of ester **2g** or **2i** was again attempted using AIBN as radical initiator in the presence of Bu_3SnH or Et_3SiH under benzene or toluene reflux conditions. None of the desired γ-lactone **1g** or **1i** was obtained, and only complex mixtures were produced. Therefore, the present methodology was confirmed as the best way to synthesize these types of highly fluorinated α,α-difluoro-γ-lactones through intramolecular radical reaction.

Trimethylsilyl group of **4g** was deprotected by treatment with tetrabutylammonium fluoride (TBAF) and the subsequent PDC oxidation provided corresponding γ-lactone **1g** as a separable mixture (*cis*-**1g**:*trans*-**1g** = 72:28) (Table 1, entry 7). Each isomer was isolated by silica gel flash column chromatography, and the stereochemistry was assigned by the NOE experiment of **1g** in ^1H NMR analysis; strong NOE (15%) was observed between CF_2H group at 4-position with 5-H in *cis*-**1g**, while none was observed in *trans*-**1g**. The stereochemistry of **1i** obtained was tentatively assigned as cis-form by NOE experiment in ^1H NMR analysis; strong NOE (12%) was observed between CF_2H group at 3-position with 4-H in **1i**, while the opposite isomer has not yet been isolated. As mentioned, α,α-difluoro-γ-lactone, *trans*-**1a**, was obtained by radical cyclization of 1-(2-phenyl)ethylprop-2-enyl-α-bromo-α,α-difluoro-*O*-(trimethylsilyl)acetal (**4a**) (Table 1, entry 1). Isomer of *cis*-**4i** must be the thermodynamically favored form because both have the same geometry of *trans*-**4a** if the fluorine atom corresponds to the hydrogen atom. In fact, MM2 calculation of **4i** suggested that (4,5-cis)-isomers are sterically more stable than corresponding (4,5-trans)-isomers.[25] This well agrees with the rule hypothesized by Yadav et al.:[26] they discussed a guiding factor for the trans disposition of C-methyl group and the adjacent side chain during intramolecular radical cyclization.

It was interesting that radical cyclization products were obtained when both *O*-(trimethylsilyl)-α-bromo-α,α-difluoroacetal **3a** and *O*-(trimethylsilyl)-α-chloro-α,α-difluoro **3aa** were subjected, while no desired cyclized acetal was produced when chloroacetal, **3ia**, was subjected to the reaction; neither cyclized products nor unreacted starting acetal **3ia** was recovered, and only the complex mixtures were obtained. These results might be explained by the differences in reactivity between β-methyl radical and β-difluoromethyl radical. The β-methyl radical, which was generated from radical cyclization of acetal **3a**, was converted to the methyl group quickly by reduction with Bu_3SnH, while reduction of the stable difluoromethyl radical, which was derived from acetal **3i**, proceeded slowly; further reaction caused by highly reactive chlorine radical, appeared to form a complex mixture, though we have no direct evidence to confirm this.

Various types of α,α-difluoro-γ-lactones were thus synthesized through the present radical cyclization using stoichiometric quantities of Bu_3SnH as reducing agent. However, the growing concern about tin toxicity is providing a powerful incentive to discover processes utilizing tin compounds as catalyst, and several methods employing Bu_3SnH in this capacity have been developed.[27,28] Among methods which use tin as catalysis, the system of $(Bu_3Sn)_2O$−PMHS (TMSO−$(SiHMeO)_n$−TMS)−BuOH developed by G. Fu and colleagues[28d,e] was considered to the best one from the standpoints of cost, reagent stability, and broad applicability. The technique was found applicable to our radical cyclization after optimization of the reaction conditions. We encountered a serious problem of the reaction quitting at low conversion using that system, though the desired cyclized compound **4a** was indeed obtained. Fortunately, this was solved by the addition of radical initiator (5 mol % of AIBN) eight times at 4 h intervals during the reaction, and 7.5 mol % of $(Bu_3Sn)_2O$ was added to the reaction mixture 24 h after the reaction had begun. We thus succeeded in reducing the amount of tin reagent significantly and accomplished the synthesis of α,α-difluoro-γ-lactone **1a** as follows: treatment of trimethylsilylacetal **3a** with 15 mol % of $(Bu_3Sn)_2O$ (7.5 mol %, two times), 5 equiv of PMHS, 5.5 equiv of *n*-BuOH, and 40 mol % AIBN (5 mol % added every 4 h) in toluene at 80 °C for 32 h provided the desired cyclized compound **4a**, then subse-

(22) (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201. (b) Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron* **1995**, *51*, 10289. (c) Crowley, P. J.; Percy, J. M.; Stansfield, K. *Tetrahedron Lett.* **1996**, *37*, 8233. (d) Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1997**, *53*, 14749.

(23) Tellier, F.; Sauvétre, R. *Tetrahedron Lett.* **1993**, *34*, 7565.

(24) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(25) CS Chem3D Pro was employed to calculate the steric energy of four isomers of **3a**. Calculations suggested that both (4,5-cis)-isomers are sterically more stable than corresponding (4,5-trans)-isomers; these well agreed with the experimental results.

(26) (a) Yadav. J. S.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1989**, 1824. (b) Yadav. J. S.; Shekaram, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, 843. (c) Yadav. J. S.; Praveen Kumar, T. K.; Maniyan, P. P. *Tetrahedron Lett.* **1993**, *34*, 2965.

(27) Pioneer examples for this field, see: (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

(28) (a) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4. (b) Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751. (c) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 7070. (d) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949. (e) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2796.

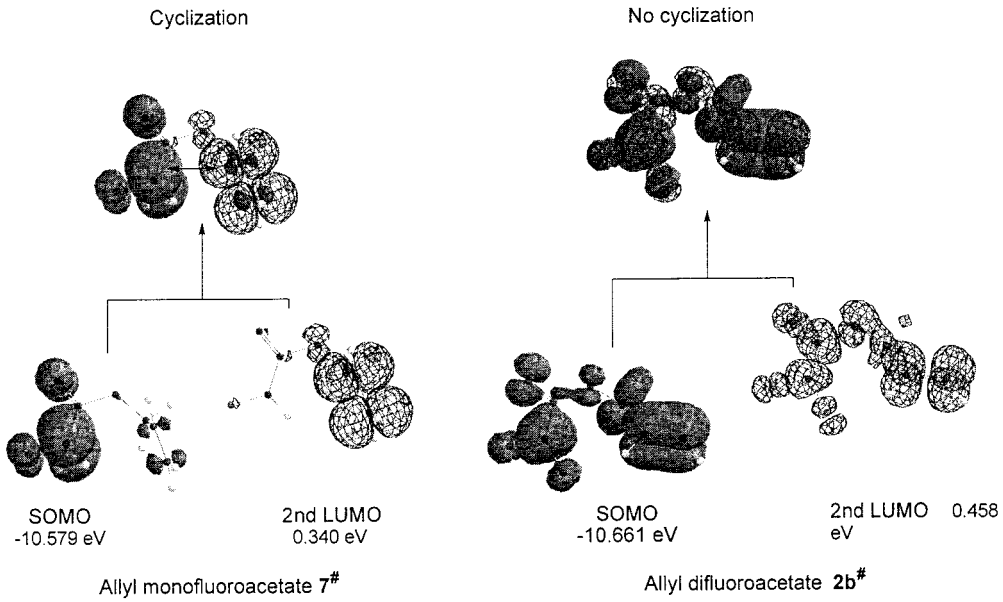
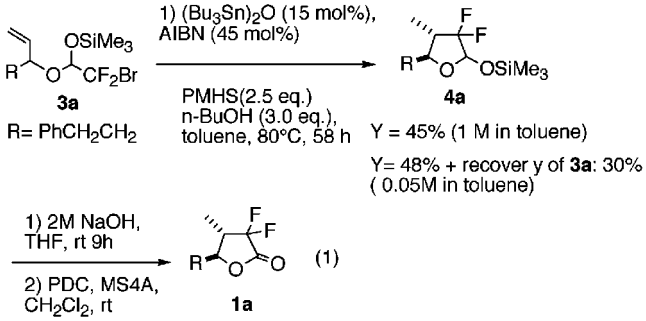


Figure 1. Possibility of cyclization depending on radical species.

quent alkaline treatment (2 M NaOH) released desilylated lactol which was finally converted to the desired γ-lactone **1a** by PDC oxidation in 40% overall yield from **3a** (eq 1).



Conformation of the starting radical species has been proposed to be quite important in radical cyclization,[15a,26] and our experimental results clearly upheld this idea. Because *O*-(trimethylsilyl)acetal radical species are free from the restriction of geometry, this factor must be essential to the intramolecular radical cyclization of stable radical species such as difluoromethyl radicals.[29] The results reported by Uneyama et al. strongly supported the importance of this factor in that the cyclization was achieved efficiently to give the corresponding lactum in more than 90% yield when *N*,*N*-bisallyl α-bromo-α,α-difluoroacetamide was subjected to the corresponding radical cyclization.[30]

To better understand the differences in the reactivity between radicals of α,α-difluoroacetate and corresponding *O*-(trimethylsilyl)acetal, semiempirical (PM3) calculations were made of radical species of allyl α-fluoroacetate **7**, allyl α,α-difluoroacetate **2b**, and allyl α,α-difluoro-*O*-(trimethylsilyl)acetal **3b**.[31] The calculation estimated the conformational energy differences between the two limiting conformers; stable forms of all radical species were S-trans-forms, which were believed to be unfavorable for the cyclization, though the differences in heat of the formation energy between S-trans-forms, **7**‡, **2b**‡, and **3b**‡, and S-cis-forms, **7**#, **2b**#, and **3b**#, were not great (1.32−3.86 Kcal/mol).[32] Because cyclization products were obtained from monofluoroacetate **7**[12] and difluoroacetal **3b**, we found these results confusing.

Fortunately, detailed investigation of the MO calculation revealed that our experimental results could be well explained by the differences in the spin density and delocalization of electrons on the SOMO orbital of the olefinic part of these radical species. The calculation suggested very low spin density of difluoromethyl radical of **2b** to be 0.910 (S-cis-**2b**#) and 0.907 (S-trans-**2b**‡), respectively; this explains their low reactivity and stable nature of the difluoromethyl radicals.[31] As anticipated, MO calculation suggested much higher spin density of *O*-(trimethylsilyl)acetal radical of S-cis-**3b**# and S-trans-**3b**‡: 0.922 and 0.923, respectively. High reactivity of the α-radical of α,α-difluoro-*O*-(trimethylsilyl)acetal is thus well explained by the calculation. SOMO (−10.579 eV) and second LUMO (0.340 eV) orbitals of S-cis-form of monofluoroacetate **7**# suggest that these harmonize well and the cyclization is allowable (Figure 1). On the contrary, those from **2b**# do not match because electrons of the SOMO (−10.661 eV) orbital of **2b**# are completely delocalized, so that no cyclization occurred from the radical species derived from **2b** even though it took the S-cis-form of **2b**# (Figure 1).

We attempted to calculate allyl dichloroacetate and allyl dibromoacetate and observed, interestingly, that the complete delocalization of electrons on the SOMO orbital of the olefinic part took place only on the difluoroacetate radical: thus difluoromethyl radical species have a very special electron nature. This special nature of the electron state of the olefinic part of **2b**# seems due to the influence

(29) (a) Asai, H.; Uneyama, K. *Chem. Lett.* **1995**, 1123. (b) Qiu, Z.-M.; Burton, D. J. *J. Org. Chem.* **1995**, *60*, 5570. (c) Buttle, L. A.; Motherwell, W. B. *Tetrahedron Lett.* **1994**, *35*, 3995.

(30) Uneyama et al. recently demonstrated successful intramolecular radical cyclization of corresponding bisallyl α,α-difluoroamides: Uneyama, K.; Yanagiguchi, T.; Asai, H. *Tetrahedron Lett.* **1997**, *38*, 7763.

(31) MacSpartan Plus was employed for MO (PM3) calculation.

(32) Results of MO (PM3) calculation (heat of formation): S-cis-**7**#, −83.83 kcal/mol; S-trans-**7**‡, −85.15 kcal/mol; S-cis-**2b**#, −133.54 kcal/mol; S-trans-**2b**‡, −135.79 kcal/mol; S-cis-**3b**#, −207.58 kcal/mol; S-trans-**3b**‡, −211.44 kcal/mol.

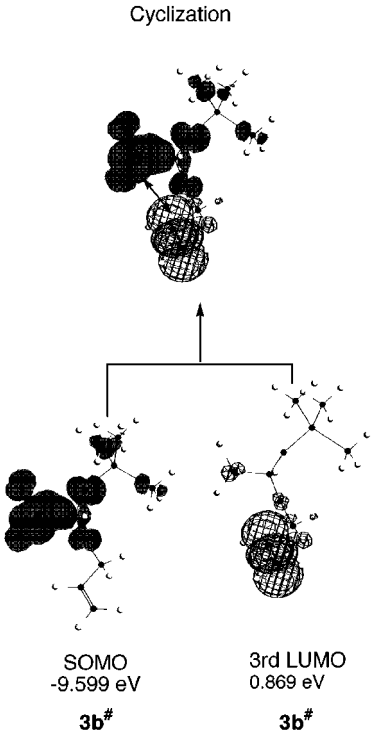


Figure 2. Successful cyclization of the radical species derived from α,α-difluoro-*O*-(trimethylsilyl)acetal.

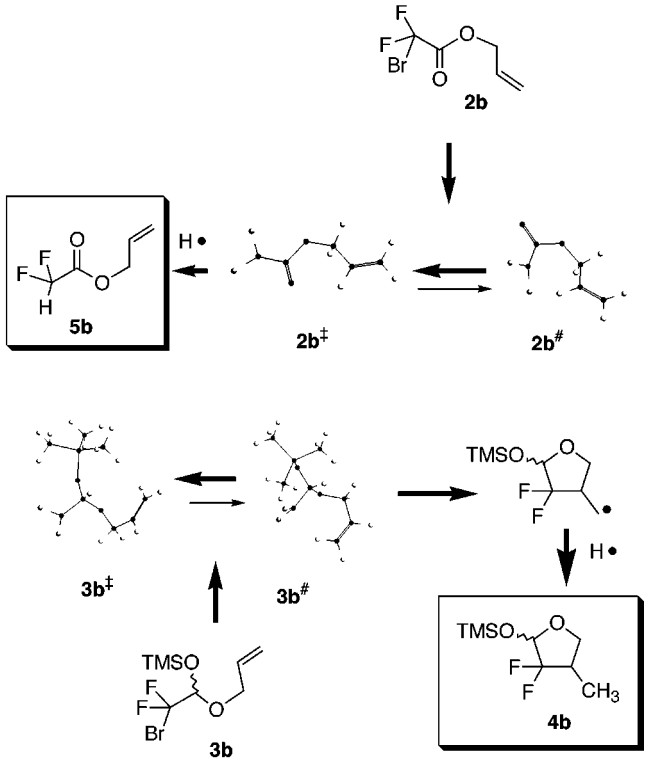


Figure 3. Plausible mechanism of the radical cyclization.

of both the low level of the SOMO orbital and the "electric-steric effect" at α-position by the two fluorine atoms substituted. SOMO (−9.588 eV) and LUMO orbitals of **3b‡** (S-trans) are also not suitable for cyclization. However, SOMO (−9.599 eV) and third LUMO (0.869 eV) from **3b#** (S-cis) were found to match well, so that cyclization might occur through the transition state as illustrated in Figure 2.

From these results of MO calculation, a plausible mechanism for the present radical cyclization is proposed as illustrated in Figure 3. The differences of heat formation energy between S-trans-form, **2b‡** and **3b‡**, and S-cis-form, **2b#** and **3b#**, are not large so that these two forms are convertible under the reaction conditions. Cyclized product **4b** is thus derived from **3b#**, because reactivity of the radical is enhanced by the trimethylsilyl substituent of its electron-donating nature. On the other hand, radical species derived from **2b** give no desired cyclized product **1b** but afford the reduction product **5b**, because neither of the transition states of **2b‡** and **2b#** was suitable for the cyclization.

2. Synthesis of Optically Active α,α-Difluoroeldanolide. The difluoromethylene group is well-known as an isoelectronic and isosteric substitute for oxygen in phosphate analogues.[33] Such species, therefore, mimic the tetrahedral transition states related to the hydrolytic action of proteases and esterases, so that enzyme inhibition can be caused by difluorinated molecules when the nucleophilic hydroxyl group is part of the active site.[33] Geminal difluoromethylene group has been considered as an ether-oxygen equivalent from the standpoint of biological activity and therefore to express unique biological activity.[34] Schlosser et al. reported the strong similarity in properties between some fluorinated compounds and their hydrogen containing sources (F/H transposition) and contrasted this with the more dramatic effect of replacing a hydrogen with a methyl group.[35] The exceptional size of fluorine minimizes the steric hindrance of the difluoromethylene group, but steric interactions need to be considered in conjunction with electronic factors when assessing the relations of *gem*-difluorination.[35] With the important feature of *gem*-difluoromethylene compounds in mind, we chose α,α-difluoroeldanolide, (3*R*,4*R*)-**1f**, as our target molecule for synthesizing difluorinated analogues of the natural bioactive compound, eldanolide, (3*S*,4*R*)-**8**, which is known to be a sex pheromone of the male African sugarcane borer, *Eldana saccharina*.[26b,36,37]

Synthesis of α,α-difluoroeldanolide, (3*R*,4*R*)-**1f**, was accomplished using alcohol (*R*)-**6f** (>99% ee) as the starting material (Scheme 3). Compound (*R*)-**6f** was converted to α-chloro-α,α-difluoroacetate (*R*)-**2fa** {$[\alpha]_D^{22}$ +9.6 (*c* 1.29, $CHCl_3$)} in 94% yield. Ester (*R*)-**2fa** was then reduced to the corresponding acetal by DIBAL in CH_2Cl_2 at −78 °C, and subsequent treatment with (trimethylsilyl)-*O*-triflate (TMSOTf) in the presence of pyridine gave *O*-TMS-acetal **3fa** in 92% yield. To a benzene solution of the acetal **3fa** and AIBN (10 mol %) was slowly

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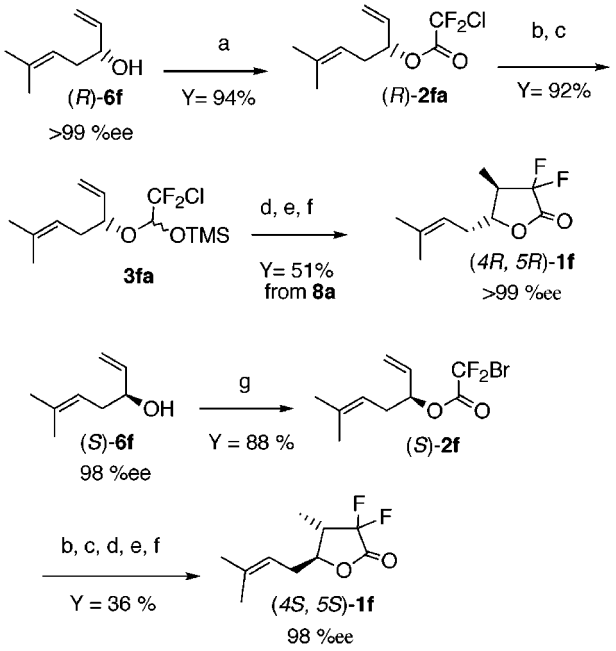
(34) Chambers, R. D.; Jaouhari, R.; O'Hagan, D. *Tetrahedron* **1989**, *45*, 5101.
(35) Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99.
(36) (a) Vigneron, J. P.; Méric, R.; Larchevêue, M.; Debal, A.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron Lett.* **1982**, *23*, 5051. (b) Vigneron, J. P.; Mic, R.; Larchevêue, M.; Debal, A.; Lallemand, J. Y.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521.
(37) For some syntheses of optically active eldanolide, see: (a) Angert, H.; Czerwonka, R.; Reissig, H.-U. *Liebigs Ann.* **1996**, 259. (b) Paulsen, H.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5667. (c) Suzuki, Y.; Mori, W.; Ishizone, H.; Naito, K.; Honda, T. *Tetrahedron Lett.* **1992**, *33*, 4931. (d) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810. (e) Uematsu, T.; Uemura, T.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 587, and references therein.

Scheme 3. Synthesis of Both Enantiomers of Difluoroeldanolide[a]



[a] Key: (a) $ClCF_2CO_2Li$, $(COCl)_2$, Et_3N, Et_2O, 0 °C; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) TMSOTf, Py, −78 °C → rt; (d) *n*-Bu_3SnH, AIBN, benzene, reflux; (e) KF, H_2O, rt; (f) PDC, MS4A, CH_2Cl_2, rt; (g) $BrCF_2CO_2Li$, $(COCl)_2$, Et_3N, Et_2O, 0 °C.

added a benzene solution of tributyltinhydride (2.2 equiv) over 5 h under reflux conditions. The reaction mixture was heated to reflux for an additional 4 h and then cooled to room temperature. After evaporation, silica gel flash column chromatography using hexane/ethyl acetate (200:1 to 50:1) as eluent gave the cyclized product. This step finished regiospecifically to provide only five-membered lactol; no six-membered lactol was obtained. TMS-lactol was then treated with 1.0 M THF solution of tetrabutylammonium fluoride (TBAF) at room temperature for 21 h to provide the deprotected lactol which was used immediately for oxidation without further purification. PDC oxidation of the lactol in CH_2Cl_2 in the presence of molecular sieves 4A powder at room temperature for 6 h, and subsequent purification using silica gel flash column gave the desired γ-lactone (3*R*,4*R*)-**1f** $\{[\alpha]_D^{23}$ +62.4 (*c* 1.17, EtOH)} in 51% overall yield from **2fa**. Optical purity of the final product (3*R*,4*R*)-**1f** was confirmed by GC analysis as >99% ee because no signal of the enantiomer was observed using chiral column (Chiraldex G-Ta). Thus, the starting optical purity was exactly retained during these reaction sequences. Using this protocol, the antipode of α,α-difluoroeldanolide (3*S*,4*S*)-**1f** $\{[\alpha]_D^{22}$ −63.3 (*c* 1.15, EtOH)} was also synthesized from 98% ee of (*S*)-**6f**. We thus accomplished the first synthesis of optically active α,α-difluoroeldanolide through intramolecular radical cyclization protocol and *Pseudomonas cepacia* lipase (PCL)-catalyzed enantioselective acylation.

The biological activity of eldanolide, fluorinated eldanolide and their antipodes was compared by electroantennography. Increasing doses were tested on female antennae according to standard procedures.[38] As previously reported,[39] both enantiomers of eldanolide elicited strong EAG responses, the difluoroeldanolide (4*S*,5*R*)-(+)-**1f** being slightly but significantly more active than

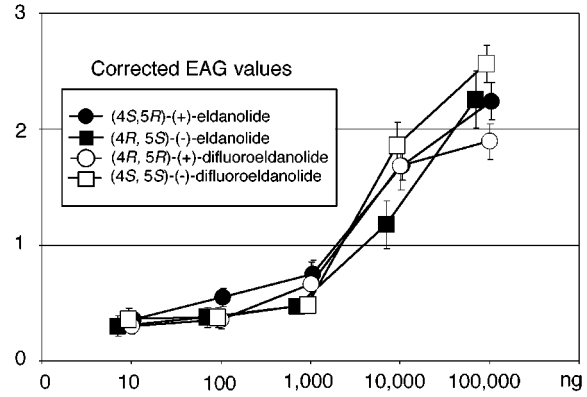


Figure 4.

natural eldanolide. We initially anticipated that α,α-difluoro analogue would lose its pheromone activity because it has been believed that substitutions at the polar group of lepidoptera pheromone molecules result in reduced recognition by the olfactory receptors. To our surprise, the difluoroanalogues showed dose−response curves very similar to those of natural eldanolide (Figure 4). Substituting fluorine for hydrogen results in pheromone analogues whose intrinsic activity varies according to the number of substitutions and their position. Generally, substitutions at the polar group of lepidoptera pheromone molecules result in reduced recognition by the olfactory receptors[40] and may produce potent inhibitors of the pheromone catabolizing enzymes[41] present in the olfactory tissues. Although the lactone moiety has been believed important to distinguish a molecule by olfactory receptors, these results show that this idea should now be reconsidered. This decreased affinity for the receptor contradicts our results and makes the fluoroeldanolides good candidates for investigation of the interaction between eldanolide and its receptor sites. In other lepidoptera species, whose pheromones are straight chain compounds, in vitro trifluoromethyl ketone (TFMK) analogues are good inhibitors of the hydrolysis of the acetate pheromone in its alcohol moiety by antennal esterases. They also inhibit the transformation of the alcohol into the aldehyde. In vivo, TFMKs have very low intrinsic activity on the receptor, and they decrease the EAG, single cell responses, and behavior, when passed over the antenna during the test of the pheromone or after topical application. Those effects are not well explained by an inhibition of the pheromone catabolism (one would expect an increase in response due to more pheromone being available), but rather show a direct interaction with the receptor itself. The pathways for the catabolism of eldanolide in the olfactory tissues and the

(38) For an example of EAG experiment for insect pheromones, see: Lucas, P.; Renou, M.; Tellier, F.; Hammoud, A.; Audemard, H.; Descoins, C. *J. Chem. Ecol.* **1994**, *20*, 489.

(39) (a) Vigneron, J. P.; Méric, R.; Larchevêue, M.; Debal, A.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron Lett.* **1982**, *23*, 5051. (b) Vigneron, J. P.; Méric, R.; Larchevêue, M.; Debal, A.; Lallemand, J. Y.; Kunesch, G.; Zagatti, P.; Gallois, M. *Tetrahedron* **1984**, *40*, 3521.

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(41) Graham, S. M.; Prestwich, G. D. *J. Org. Chem.* **1994**, *59*, 2956. Duran, I.; Parilla, A.; Feixas, J.; Guerrero, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2953. Rosell, G.; Herrero, S.; Guerrero, A. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 227.

enzymes involved are totally unknown, but the activity of the difluoroeldanolides makes them very different from the TFMKs.

Conclusion

In conclusion, this paper describes an efficient general route to access a variety of new multifluorinated α,α-difluoro-γ-lactones. We succeeded in synthesizing optically active α,α-difluoro analogues of natural pheromone, and they showed unexpected biological activity; the essence of fluorine chemistry is found in such "unpredictable reactivity" of fluorinated compounds. The importance of the development of efficient methods for the synthesis of selectively fluorinated compounds has thus greatly increased. Because optically active α,α-difluoro-γ-lactones can be synthesized using the present methodology, we hope that our technique will be widely used in the field of synthetic organic chemistry for the design of new fluorinated molecules.

Experimental Section

General Procedures. Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Wako gel C-300 and Wako gel B5F were used for flash column chromatography and thin-layer chromatography (TLC), respectively. Chemical shifts are expressed in δ value (ppm) downfield from tetramethylsilane (TMS) in $CDCl_3$ as an internal reference. ^{19}F NMR spectra were reported in ppm downfield from C_6F_6 as an internal reference.

Synthesis of γ-Lactones. (3*R,4*S**)-2,2-Difluoro-3-methyl-6-phenylhexan-4-olide (1a).** To a solution of **4a** (130 mg, 0.413 mmol) in dry THF (1.5 mL) was added 0.5 mL of TBAF (0.5 mmol, 1.0 M in THF) at room temperature. After 11 h of stirring, the mixture was diluted with ether and washed brine. The organic layer was dried over anhydrous $MgSO_4$. After removal of the solvent by evaporation, 85 mg of lactol was obtained. The lactol was dissolved in dry CH_2Cl_2 containing 300 mg of powdered MS4A, and PDC (404 mg, 1.052 mmol) was added at room temperature. After 6 h of stirring, the mixture was filtered through a short column of Florisil. Silica gel flash column chromatography (hexane/ethyl acetate = 20:1) gave lactone **1a** as a colorless oil in 72% yield (56.7 mg, 0.236 mmol): bp 100 °C/1.0 mmHg (Kugelrohr); R_f 0.40 (hexane/ethyl acetate = 7:1); ^1H NMR (200 MHz, $CDCl_3$) 1.21 (3H, d, J = 6.8 Hz), 1.89−2.22 (2H, m), 2.24−2.56 (1H, m), 2.71−3.04 (2H, m), 4.16 (1h, dt, J = 9.0 Hz, 3.3 Hz), 7.21−7.39 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 7.49 (d, J_{C-F} = 7.6 Hz), 31.14, 35.06, 42.83 (t, J_{C-F} = 20.6 Hz), 81.74 (d, J_{C-F} = 8.1 Hz), 115.56 (dd, J_{C-F} = 259.6, 251.3 Hz), 126.38, 128.31, 128.62, 139.91, 165.12 (dd, J_{C-F} = 34.1, 32.0 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 41.13 (1F, dd, J = 274.9, 20.9 Hz), 47.30 (1F, dd, J = 274.9, 12.4 Hz); IR (neat) 3030, 2940, 1810, 1460, 1340, 700 cm^{-1}. Anal. Calcd for $C_{13}H_{14}F_2O_2$: C, 64.00; H, 5.87. Found: C,64.00; H, 5.87.

(3*S,4*S**)-2,2,3-Trifluoro-3-(difluoromethyl)-6-phenylhexan-4-olide (1i).** To a boiling solution of silyl acetal **3i** (1.87 g, 4.2 mmol) and AIBN (21 mg, 0.125 mmol) in benzene (20.0 mL) was added a benzene (65 mL) solution of Bu_3SnH (1.75 mL, 6.3 mmol) dropwise over 7 h, and the mixture was stirred for an additional 3 h under reflux conditions. After being cooled to room temperature, a KF-saturated aqueous solution (40 mL) was added to the reaction mixture at room temperature and stirred for 15 min. The reaction mixture was extracted with ether. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness, and silica gel flash column chromatography (hexane/ethyl acetate = 50:1) gave *O*-TMS-lactol **4i** (1.20 g, 3.3 mmol) as a colorless liquid in 78% yield. This compound was immediately used for the further reaction. To a solution of lactol **4i** (450 mmg, 1.22 mmol) in THF (1.8 mL) was added a THF (1.8 mL) solution of tetrabutylammonium fluoride (1.8 mmol) at room temperature, and the mixture was stirred for 12 h under ambient atmosphere. The reaction mixture was diluted with ether (20 mL) and washed with water and brine. The organic layer was dried over $MgSO_4$ and evaporated to afford desilylated lactol (470 mg) which was then used immediately for the following Dess−Martin oxidation. A dichloromethane (8.1 mL) solution of the crude lactol (450 mg) was added to Dess−Martin periodinane (1.03 g, 2.44 mmol), and the mixture was stirred for 26 h at room temperature. The reaction was quenched by addition of 10% $Na_2S_2O_3$ solution (2 mL), and the mixture was extracted with ethyl acetate. The combined organic layers were dried, concentrated under vacuo, and chromatographed on silica gel (hexanes/ethyl acetate = 12:1−3:1) and gave lacton **1i** (190 mg, 0.65 mmol) as a coloress oil in 53% yield. Lactone (*cis*)-(3*S**,4*S**)-**1i**: bp 100 °C/5.0 mmHg (Kugelrohr); R_f 0.61 (hexane/ethyl acetate = 7:1); ^1H NMR (200 MHz, $CDCl_3$) 2.02−2.18 (2H, m), 2.70 (1H, dt, J = 14.1, 8.3 Hz), 2.92 (1H, ddd, J = 14.1, 8.5, 5.1 Hz), 4.66 (1H, ddd, J = 18.3, 10.0, 3.4 Hz), 5.99 (1H, dt, J = 7.3, 52.4 Hz), 7.11−7.30 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 29.53 (d, J_{C-F} = 6.6 Hz), 30.66, 77.16, 90.69 (dddt, J_{C-F} = 207.0, 24.3, 18.0, 24.3 Hz), 109.71 (ddt, J_{C-F} = 29.1, 3.5, 249.9 Hz), 122.87 (dd, J_{C-F} = 408.5, 397.3 Hz), 126.76, 128.41, 128.82, 139.03, 160.63 (dd, J_{C-F} = 31.8, 30.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −39.32 to 38.98 (1F, m), 28.35 (1F, ddt, J = 313.3, 52.2, 9.2 Hz), 30.72 (1F, ddt, J = 308.9, 50.2, 6.4 Hz), 36.11 (1F, dd, J = 294.7, 8.5 Hz), 39.00 (1F, ddd, J = 297.7, 15.3, 7.5 Hz); IR (neat) 3030, 2935, 1826(CO), 1267, 1167 cm^{-1}. Anal. Calcd for $C_{13}H_{11}F_5O_2$: C, 53.07; H, 3.77. Found: C, 53.15; H, 3.87.

Using the same procedure, new γ-lactones **1** were synthesized. Dess−Martin oxidation gave better yield than PDC oxidation when lactols **4i**, **4j**, and **4k** were subjected.

2,2-Difluoro-3-methylbutan-4-olide(1b): bp 110 °C/760 mmHg (Kugelrohr); R_f 0.17 (hexane/ethyl acetate = 4:1); ^1H NMR (200 MHz, $CDCl_3$) 1.23 (3H, dd, J = 7.0, 1.3 Hz), 2.65−2.95 (1H, m), 4.00 (1H, t, J = 8.5 Hz), 4.52 (1H, t, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 8.49 (d, J_{C-F} = 7.2 Hz), 37.04 (t, J_{C-F} = 21.4 Hz), 70.13 (d, J_{C-F} = 7.6 Hz), 114.96 (dd, J_{C-F} = 257.1 Hz, 253.5 Hz), 165.51 (t, J_{C-F} = 31.6 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 39.46 (1F, dd, J = 274.9, 17.0 Hz), 46.41 (1F, dd, J = 275.0, 13.1 Hz); IR (neat) 2980, 1810, 1460, 1350, 1220, 1105, cm^{-1}. Anal. Calcd for $C_5H_6F_2O_2$: C, 44.13; H, 4.44. Found: C, 44.53; H, 4.76.

3-Benzyl-2,2-difluorobutan-4-olide(1c): bp 67 °C/7.0 mmHg (Kugelrohr); R_f 0.44 (hexane/ethyl acetate = 4:1); ^1H NMR (200 MHz, $CDCl_3$) 2.70 (1H, dd, J = 13.5, 9.6 Hz), 2.82−3.10 (1H, m), 3.13 (1H, dd, J = 13.5, 5.4 Hz), 4.08 (2H, dd, J = 9.3, 8.1 Hz), 4.31 (1H, dd, J = 9.4, 7.5 Hz), 7.14−7.34 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$,) 30.17 (d, J_{C-F} = 6.2 Hz), 43.50 (t, J_{C-F} = 20.3 Hz), 65.58 (d, J_{C-F} = 7.3 Hz), 114.60 (dd, J_{C-F} = 256.9, 251.8 Hz), 127.25, 128.53, 128.98, 135.85, 165.35 (dd, J_{C-F} = 33.1, 32.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 41.51 (1F, dd, J = 276.0, 17.1 Hz), 47.88 (1F, dd, J = 276.0, 12.6 Hz); IR (neat) 3032, 1812, 1496, 1455, 1117, 992, cm^{-1}. Anal. Calcd for $C_{11}H_{10}F_2O_2$: C, 62.26; H, 4.75. Found: C, 62.82; H, 4.92.

2,2-Difluoro-3-isopropylbutan-4-olide (1d): bp 60 °C/7.5 mmHg (Kugelrohr); R_f 0.43 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, $CDCl_3$) 0.92 (3H, d, J = 6.7 Hz), 1.10 (3H, dd, J = 6.5, 1.3 Hz), 1.93−2.12 (1H, m), 2.22−2.53 (1H, m), 4.05 (1H, t, J = 9.5 Hz), 4.50 (1H, t, J = 8.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$,) 19.54, 20.16, 25.28 (d, J_{C-F} = 5.1 Hz), 48.19 (t, J_{C-F} = 19.9 Hz), 68.41 (d, J_{C-F} = 9.1 Hz), 114.91 (dd, J_{C-F} = 259.5, 251.3 Hz), 165.86 (dd, J_{C-F} = 34.5, 32.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 41.42 (1F, dd, J = 280.4, 21.2 Hz), 50.98 (1F, dd, J = 279.1, 12.9 Hz); IR (neat) 2971, 1815, 1473, 1365, 1208, 1106, cm^{-1}. Anal. Calcd for $C_7H_{10}F_2O_2$: C, 51.22; H, 6.14. Found: C, 51.43; H, 6.56.

(3*R,4*S**)-2,2-Difluoro-3-methyloctan-4-olide (1e):** bp 55 °C/3.0 mmHg (Kugelrohr); R_f 0.47 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.90 (3H, t, J = 6.8 Hz), 1.19 (3H, d, J = 6.9 Hz), 1.26−1.77 (6H, m), 2.17−2.49 (1H, m),

4.12 (1H, dt, J = 8.5, 3.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$,) 7.53 (d, J_{C-F} = 7.6 Hz), 13.64, 22.20, 27.02, 32.88, 42.78 (t, J_{C-F} = 20.5 Hz), 82.93 (d, J_{C-F} = 8.0 Hz), 115.70 (dd, J_{C-F} = 259.6, 251.1 Hz), 165.28 (dd, J_{C-F} = 33.9, 31.8 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 41.23 (1F, dd, J = 274.7, 21.0 Hz), 47.30 (1F, dd, J = 275.0, 13.2 Hz); IR (neat) 2950, 1810, 1460, 1320, 1210, cm^{-1}. Anal. Calcd for $C_9H_{14}F_2O_2$: C, 56.24; H, 7.34. Found: C, 56.69; H, 7.61.

(3*R,4*S**)-2,2-Difluoro-7,3-dimethyl-6-octen-4-olide (1f):** bp 75 °C/2.2 mmHg (Kugelrohr); R_f 0.39 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.18 (3H, dd, J = 6.9, 1.2 Hz), 1.61 (3H, s), 1.71 (3H, s), 2.22−2.59 (3H, m), 4.17 (1H, dt, J = 8.8, 5.5 Hz), 5.05−5.15 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$,) 7.71 (d, J_{C-F} = 7.7 Hz), 17.93, 25.75, 31.00, 41.70 (t, J_{C-F} = 20.6 Hz), 82.53 (d, J_{C-F} = 8.0 Hz), 115.73 (dd, J_{C-F} = 259.6, 251.1 Hz), 115.94, 137.19, 165.27 (dd, J_{C-F} = 34.0, 32.0 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 41.65 (1F, dd, J = 274.7, 21.0 Hz), 47.38 (1F, dd, J = 274.9, 12.6 Hz); IR (neat) 2922, 1811, 1460, 1337, 1213, cm^{-1}. Anal. Calcd for $C_{10}H_{14}F_2O_2$: C, 58.81; H, 6.91. Found: C, 57.44; H, 7.03.

***cis*-(3*S**,4*S**)-3-(Difluoromethyl)-2,2-difluoro-3-((methoxyethoxy)methoxyhexan-4-olide (1g):** bp 90 °C/3.8 mmHg (Kugelrohr); R_f 0.32 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.08 (3H, t, J = 16.5 Hz), 1.60−1.96 (2H, m), 3.38 (3H, s), 3.55−3.95 (4H, m), 4.71−4.74 (1H, m), 4.93−5.24 (2H, m), 6.52 (1H, t, J = 53.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$,) 9.56, 22.74, 58.88, 68.23, 71.19, 77.19−79.00 (m), 80.66 (dd, J_{C-F} = 6.8 Hz, 4.4 Hz), 93.30 (d, J_{C-F} = 4.8 Hz), 112.21 (ddt, J_{C-F} = 250.6, 247.1, 3.6 Hz), 162.10 (t, J_{C-F} = 31.0 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 29.19 (1F, ddd, J = 305.5, 54.3, 7.1 Hz), 31.30 (1F, ddd, J = 305.9, 53.4, 12.2 Hz), 40.43 (1F, dd, J = 288.9, 12.2 Hz), 47.48 (1F, dd, J = 289.3, 6.8 Hz); IR (neat) 2939, 1820, 1462, 1236, 1163 cm^{-1}. Anal. Calcd for $C_{11}H_{16}F_4O_5$: C, 43.43; H, 5.30. Found: C, 43.47; H, 5.46.

***trans*-(3*S**,4*R**)-3-(Difluoromethyl)-2,2-difluoro-3-((methoxyethoxy)methoxy)hexan-4-olide (1g):** bp 90 °C/3.8 mmHg (Kugelrohr); R_f 0.26 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.14 (3H, t, J = 7.4 Hz), 1.81−2.05 (2H, m), 3.38 (3H, s), 3.52−3.57 (2H, m), 3.66−3.74 (1H, m), 3.84−3.93 (1H, m), 4.57 (1H, dd, J = 9.8, 4.3 Hz), 4.98 (1H, d, J = 8.0 Hz), 5.18 (1H, d, J = 7.9 Hz), 6.32 (1H, t, J = 52.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$,) 10.59, 22.53, 58.88, 68.33, 77.19−79.00 (m), 83.39 (d, J_{C-F} = 2.3 Hz), 93.06, 113.05 (tt, J_{C-F} = 249.8, 3.7 Hz), 161.91 (t, J_{C-F} = 30.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 31.27 (2F, dd, J = 51.9, 6.8 Hz), 39.71 (1F, dd, J = 284.9, 6.8 Hz), 41.30 (1F, dd, J = 285.4, 6.8 Hz); IR (neat) 2941, 1823, 1462, 1096 cm^{-1}. Anal. Calcd for $C_{11}H_{16}F_4O_5$: C, 43.43; H, 5.30. Found: C, 43.54; H, 5.28.

(3*S,4*S**)-3-(Difluoromethyl)-2,2-difluoro-3-((methoxyethoxy)methoxy)-3-methylhexan-4-olide (1h):** bp 70 °C/5.0 mmHg (Kugelrohr); R_f 0.40 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.98 (3H, d, J = 6.6 Hz), 1.04 (3H, d, J = 6.8 Hz), 2.09−2.26 (1H, m), 3.34 (3H, s), 3.51 (2H, t, J = 4.0 Hz), 3.57−3.70 (1H, m), 3.82−3.93 (1H, m), 4.53 (1H, d, J = 6.6 Hz), 4.92 (1H, d, J = 8.0 Hz), 5.19 (1H, d, J = 9.4 Hz), 6.51 (1H, t, J = 53.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$,) 17.39, 19.44, 28.08, 58.89, 68.30, 71.18, 78.00−79.58 (m), 83.58 (dd, J = 7.3, 3.8 Hz), 93.27 (d, J = 5.3 Hz), 112.39 (t, J = 248.1 Hz), 114.21 (dd, J = 250.3, 246.2 Hz), 162.09 (t, J = 31.2 Hz); ^{19}F NMR(188 MHz, $CDCl_3$) 31.24 (1F, d, J = 51.9 Hz), 31.36 (1F, dd, J = 63.6, 11.9 Hz), 41.39 (1F, ddd, J = 289.9, 10.0, 6.1 Hz), 48.01 (1F, d, J = 289.9 Hz); IR (neat) 2947, 1809, 1475, 1398, 1371, 1237 cm^{-1}. Anal. Calcd for $C_{12}H_{18}F_4O_5$: C, 45.29; H, 5.70. Found: C, 45.33; H, 5.81.

(3*S,4*S**)-4-Cyclohexyl-3-(difluoromethyl)-2,2,2-trifluorobutan-4-olide (1j):** bp 60 °C/4.5 mmHg (Kugelrohr); R_f 0.44 hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.12−1.44 (5H, m), 1.68−2.03 (6H, m), 4.57 (1H, dd, J = 17.6, 7.2 Hz), 6.16 (1H, dt, J = 53.0, 5.0 Hz,); ^{13}C NMR (50 MHz, $CDCl_3$) 25.20, 25.41, 25.65, 27.81, 28.90, 37.23 (d, J = 3.9 Hz), 81.92 (d, J = 21.2 Hz), 91.59 (ddt, J = 207.1, 26.0, 17.4 Hz), 110.54 (ddt, J = 251.1, 34.9, 3.4 Hz), 160.81 (t, J = 31.1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −35.65 to −35.20 (1F, m), 29.01 (1F, ddt, J = 311.3, 51.9, 12.2 Hz), 31.86 (1F, ddt, J = 308.6 Hz, 57.7, 11.9 Hz), 37.13 (1F, ddt, J = 298.8, 13.6, 7.5 Hz), 40.27 (1F, d, J = 299.4 Hz); IR (neat) 2935, 2858, 1826, 1454, 1171 cm^{-1}. Anal. Calcd for $C_{11}H_{13}F_5O_2$: C, 48.54; H, 4.81. Found: C, 48.61; H, 4.77.

(3*S,4*S**)-3-(Difluoromethyl)-2,2,3-trifluorodecan-4-olide (1k):** bp 70 °C/2.5 mmHg (Kugelrohr); R_f 0.58 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.90 (3H, t, J = 6.8 Hz), 1.25−1.92 (10H, m), 4.79 (1H, ddd, J = 18.6, 8.8, 4.3 Hz), 6.15 (1H, dt, J = 52.5, 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 13.95, 22.43, 24.91, 27.97 (d, J_{C-F} = 7.0 Hz), 28.62, 31.37, 78.59 (d, J_{C-F} = 21.7 Hz), 109.85 (ddt, J_{C-F} = 248.0, 29.5, 2.7 Hz), 160.75 (dd, J_{C-F} = 33.1, 30.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −38.84 to −38.79 (1F, m), 28.72 (1F, ddt, J = 311.3, 51.9, 9.2 Hz), 30.70 (1F, ddt, J = 308.3, 51.2, 6.4 Hz), 36.20 (1F, dd, J = 294.4, 8.8 Hz), 38.55 (1F, ddd, J = 297.1, 17.0, 9.2 Hz); IR (neat) 2931, 2862, 1826, 1468, 1265, 1169 cm^{-1}. Anal. Calcd for $C_{11}H_{15}F_5O_2$: C, 48.18; H,5.51 Found: C, 48.00; H, 5.59.

Lactol 4a (mixture of diastereomers): bp 100 °C/4.0 mmHg (Kugelrohr); R_f 0.63 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.12−0.13 (9H, m), 0.96−1.03 (3H, m) 1.76−1.88 (2H, m), 1.88−2.35 (1H, m), 2.48−2.85 (2H, m), 3.58 (0.5H, dt, J = 4.6, 4.1 Hz), 3.85 (0.5H, dd, J = 12.7, 6.5 Hz), 5.02 (0.5H, d, J = 6.9 Hz), 5.17 (0.5H, d, J = 6.5 Hz), 7.08−7.24 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 0.23, 0.39, 7.45 (d, J_{C-F} = 7.3 Hz), 11.67 (d, J_{C-F} = 7.7 Hz), 31.75, 31.85, 36.21, 37.39, 40.39 (t, J_{C-F} = 21.3 Hz), 43.91 (t, J_{C-F} = 23.4 Hz), 81.96 (d, J_{C-F} =8.3 Hz), 83.12−83.27 (m), 95.60 (dd, J_{C-F} = 41.1, 26.2 Hz), 97.12 (dd, J_{C-f} = 43.7, 23.8 Hz), 125.94, 126.45 (dd, J_{C-F} = 261.6, 247.5 Hz), 128.35, 128.41, 141.50, 141.64; ^{19}F NMR (188 MHz, $CDCl_3$) 36.79 (0.5F, ddd, J = 229.4, 23.3, 6.8 Hz), 38.46 (0.5F, d, J = 233.1 Hz), 38.74 (0.5F, dd, J = 229.4, 10.4 Hz), 61.15 (0.5F, ddd, J = 232.9, 24.3, 6.4 Hz); IR (neat) 2950, 1600, 1450, 1365, 1250 cm^{-1}. Anal. Calcd for $C_{16}H_{24}F_2O_2Si$: C, 61.12; H, 7.69. Found: C, 61.55; H, 7.65.

Lactol 4b (mixture of diastereomers): bp 50 °C/45 mmHg (Kugelrohr); R_f 0.62 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.19 (9H, s), 1.08−1.16 (3H, m), 2.35−2.60 (1H, m), 3.49−3.80 (1H, m), 4.15−4.25 (1H, m), 5.08−5.19 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) −0.01, −0.04, 7.78−8.06 (m) 12.13 (dd, J_{C-F} = 7.4, 4.4 Hz), 35.67 (dt, J_{C-F} = 37.2, 22.3 Hz), 37.85 (dd, J_{C-F} = 24.4, 22.2 Hz), 70.98−72.31 (m), 72.23 (t, J_{C-F} = 3.8 Hz), 96.05(dd, J_{C-F} = 37.9, 29.2 Hz), 96.90 (dd, J_{C-F} = 43.7, 24.3 Hz), 125.45 (dd, J_{C-F} = 261.9, 255.3 Hz), 126.08 (dd, J_{C-F} = 266.1, 245.8 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 36.18 (0.5F, d, J = 233.8 Hz), 36.83 (0.5F, d, 20.0 Hz), 37.04 (0.5F, dd, J = 20.0, 4.9 Hz), 59.09 (0.5 F, ddd, J = 233.9, 23.2, 6.6 Hz); IR (neat) 2975, 1460, 1255, 1040 cm^{-1}. Anal. Calcd for $C_8H_{16}F_2O_2Si$: C, 45.69; H, 7.67. Found: C, 45.78; H, 7.68.

Lactol 4c (mixture) of diastereomers: bp 90 °C/2.6 mmHg (Kugelrohr); R_f 0.63 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.10 (3H, s), 0.22 (6H, s) 2.62−3.12 (3H, m), 3.65−4.11 (2H, m), 5.12 (0.5H, d, J = 5.8 Hz), 5.21 (0.5H, d, J = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) −0.01, 30.73 (d, J_{C-F} = 6.2 Hz), 33.42 (dd, J_{C-F} = 6.7, 3.7 Hz), 41.77 (t, J_{C-F} = 21.2 Hz), 44.42 (dd, J_{C-F} = 23.3, 21.0 Hz), 69.99 (d, J_{C-F} = 7.9 Hz), 70.39 (t, J_{C-F} = 3.7 Hz), 96.28 (dd, J_{C-F} = 39.3, 27.2 Hz), 97.10 (dd, J_{C-F} = 40.9, 23.6 Hz), 125.23 (dd, J_{C-F} = 262.1, 248.6 Hz), 126.47, 126.53, 128.56, 128.61, 138.48, 138.65; ^{19}F NMR (188 MHz, $CDCl_3$) 37.97 (0.5F, d, J = 233.4 Hz), 38.29 (0.5F, dd, J = 230.4, 10.9 Hz), 39.91 (0.5F, ddd, J = 230.4, 20.2 Hz, 5.6 Hz), 60.31 (0.5 F, ddd, J = 234.7, 22.8, 6.8 Hz); IR (neat) 2950, 1600, 1450, 1365, 1250 cm^{-1}. Anal. Calcd for $C_{14}H_{20}F_2O_2Si$: C, 58.71; H, 7.04. Found: C, 58.89; H, 7.02.

Lactol 4d (mixture of diastereomers): bp 60 °C/7.5 mmHg (Kugelrohr); R_f 0.49 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.17 (4.5 H, s), 0.18 (4.5 H, s), 0.84−0.95 (3H, m), 1.03−1.09 (3H, m), 1.79−1.98 (1H, m), 1.98−2.43 (1H, m), 3.62−3.71 (0.5H, m), 3.86 (0.5 H, t, J = 9.5 Hz), 4.01−4.10 (0.5H, m), 4.20 (0.5H, t, J = 8.8 Hz), 5.05 (0.5H, dd, J = 7.3, 1.9 Hz), 5.21 (0.5H, d, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) −0.10, 20.45, 20.62, 21.09, 21.45, 25.93, 26.02, 46.36 (t, J_{C-F} = 20.6 Hz), 51.01 (t, J_{C-F} = 22.1 Hz), 69.28 (dd, J_{C-F} = 4.6, 2.2 Hz), 69.95 (d, J_{C-F} = 9.8 Hz), 96.79 (dd, J_{C-F} =

41.7, 25.5 Hz), 97.98 (dd, J_{C-F} = 43.8, 22.9 Hz), 125.72 (dd, J_{C-F} = 258.1, 246.5 Hz), 125.92 (dd, J_{C-F} = 265.9, 249.4 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 38.91 (0.5F, ddd, J = 233.0, 24.4, 7.8 Hz), 39.10 (0.5F, dd, J = 238.7, 11.4 Hz), 43.42 (0.5F, dd, J = 232.6, 9.2 Hz), 62.45 (0.5 F, ddd, J = 237.5, 21.5 Hz); IR (neat) 2963, 1477, 1385, 1253 cm^{-1}. Anal. Calcd for $C_{10}H_{20}F_2O_2Si$: C, 50.39; H, 8.46. Found: C, 50.24; H, 8.49.

Lactol 4e (mixture of diastereomers): bp 50 °C/2.0 mmHg (Kugelrohr); R_f 0.68 (hexane/ethyl acetate = 50:1), repeated development; ^{1}H NMR (200 MHz, $CDCl_3$) 0.09 (9 H, s), 0.82 (3H, t, J = 6.9 Hz), 0.98 (1.5H, d, J = 6.9 Hz), 1.00 (1.5H, dd, J = 7.5 Hz, 2.2 Hz), 1.20−1.56 (6H, m), 1.78−2.29 (1H, m), 3.48−3.58 (0.5H, m), 3.79 (0.5 H, q, J = 6.3 Hz), 4.96 (0.5H, d, J = 7.0 Hz), 5.12 (0.5H, d, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) −0.04, 0.09, 7.47 (d, J_{C-F} = 6.6 Hz), 11.70 (d, J_{C-F} = 7.8 Hz, 3.6 Hz), 13.93, 22.61, 22.66, 27.61, 27.70, 34.13, 35.29, 40.46 (t, J_{C-F} = 21.1 Hz), 43.93 (t, J_{C-F} = 22.6 Hz), 82.80 (d, J_{C-F} = 8.4 Hz), 83.95 (t, J_{C-F} = 3.9 Hz), 95.55 (dd, J_{C-F} = 40.7, 26.4 Hz), 97.10 (dd, J_{C-F} = 43.7 Hz, 24.0 Hz), 125.76 (dd, J_{C-F} = 261.9 Hz, 247.8 Hz), 126.30 (dd, J_{C-F} = 266.2 Hz, 246.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 36.88 (0.5F, dd, J = 229.7, 10.7 Hz) 38.57 (0.5F, d, J = 232.6 Hz), 38.83 (0.5F, dd, J = 229.7, 10.7 Hz), 61.41 (0.5 F, ddd, J = 232.6, 24.6, 6.7 Hz); IR (neat) 2970, 1460, 1255, 1110 cm^{-1}. Anal. Calcd for $C_{12}H_{24}F_2O_2Si$: C, 54.10; H, 9.08. Found: C, 53.91; H, 9.12.

Lactol 4f (mixture of diastereomers): bp 75 °C/2.5 mmHg (Kugelrohr); R_f 0.68 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.10 (4.5H, s), 0.11 (4.5H, s), 0.98 (1.5H, d, J = 6.9 Hz), 1.00 (1.5H, dd, J = 7.2, 2.2 Hz), 1.55 (3H, s), 1.64 (3H, s), 1.84−2.19 (1H, m), 2.24 (2H, t, J = 6.2 Hz), 3.59 (0.5H, dt, J = 9.3, 6.0 Hz), 3.85 (0.5H, dt, J = 6.3, 6.4 Hz), 4.97 (0.5H, d, J = 6.7 Hz), 5.03−5.14 (1H, m), 5.13 (0.5H, d, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) −0.03, 0.10, 7.57 (d, J_{C-F} = 6.4 Hz), 11.81 (d, J_{C-F} = 7.7 Hz), 17.94, 25.74, 32.66, 33.88, 39.83 (t, J_{C-F} = 21.1 Hz), 43.14 (t, J_{C-F} = 22.6 Hz), 82.68 (d, J_{C-F} = 8.0 Hz), 83.79 (t, J_{C-F} = 3.8 Hz), 95.53 (dd, J_{C-F} = 40.3, 26.7 Hz), 97.12 (dd, J_{C-F} = 43.5, 24.2 Hz), 118.61, 119.11, 125.75 (dd, J_{C-F} = 261.4, 248.3 Hz), 126.28 (dd, J_{C-F} = 266.1, 247.0 Hz), 134.25, 134.63; ^{19}F NMR (188 MHz, $CDCl_3$) 37.04 (0.5F, ddd, J = 229.6, 23.0, 6.8 Hz), 38.71 (0.5F, d, J = 229.2 Hz), 38.85 (0.5F, dd, J = 229.2, 9.8 Hz), 61.15 (0.5F, ddd, J = 232.4, 24.4, 6.1 Hz); IR (neat) 2962, 1461, 1370, 1253, 1109 cm^{-1}. Anal. Calcd for $C_{13}H_{24}F_2O_2Si$: C, 56.08; H, 8.69. Found: C, 56.45; H, 8.84.

Lactol 4g (mixture of diastereomers): bp 90 °C/5.0 mmHg (Kugelrohr); R_f 0.69 (hexane/ethyl acetate = 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.10−0.19 (9H, m), 0.84 (1.5H, t, J = 7.4 Hz), 0.99 (1.5H, t, J = 7.6 Hz), 1.58−1.73 (2H, m), 3.38 (3H, s), 3.54−3.58 (2H, m), 3.61−3.92 (2H, m), 4.13−4.36 (1H, m), 4.89−5.21 (3H, m), 5.78−6.60 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) −0.19, −0.10, −0.02, 9.86, 10.17, 10.31, 22.38, 23.08, 27.43, 58.97, 67.79, 68.16, 69.74, 69.81 (t, J_{C-F} = 3.2 Hz), 11.81 (d, J_{C-F} = 7.7 Hz), 17.94, 25.74, 32.66, 33.88, 39.83 (t, J_{C-F} = 21.1 Hz), 71.45−71.57 (m), 79.01, 80.58−80.73 (m), 81.84, 92.62 (d, J_{C-F} = 23.1 Hz), 94.20 (dd, J_{C-F} = 18.5, 6.2 Hz), 95.73 (dd, J_{C-F} = 40.8, 20.1 Hz), 95.63 (dd, J_{C-F} = 42.7, 22.8 Hz), 97.67 (t, J_{C-F} = 3.2 Hz), 97.95 (t, J_{C-F} = 3.0 Hz), 113.33 (t, J_{C-F} = 248.4 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 31.26−61.09 (4F, m); IR (neat) 2962, 1461, 1370, 1253, 1109 cm^{-1}. Anal. Calcd for $C_{13}H_{24}F_2O_2Si$: C, 56.08; H, 8.69. Found: C, 56.45; H, 8.84.

Lactol 4h (mixture of diastereomers): bp 80 °C/8.0 mmHg (Kugelrohr); R_f 0.68 and 0.63 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.18 (9H, s), 0.94 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.6 Hz), 1.88−2.17 (1H, m), 3.37 (3H, s), 3.51−3.93 (5H, m), 4.88−5.21 (3H, m), 6.34 (1H, t, J = 53.9 Hz); ^{13}C NMR for the major isomer (50 MHz, $CDCl_3$) −0.02, 18.96, 19.52, 28.57, 58.94, 67.96, 71.39, 81.54, 93.13 (d, J_{C-F} = 6.7 Hz), 94.36−95.75 (m), 113.34 (dt, J_{C-F} = 247.0, 18.6 Hz), 121.60 (ddd, J_{C-F} = 268.8, 259.2, 7.0 Hz), 122.26 (dd, J_{C-F} = 275.3, 251.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 31.26−61.09 (4F, m); IR (neat) 2980, 1475, 1390, 1255, 1083 cm^{-1}. Anal. Calcd for $C_{15}H_{28}F_4O_5Si$: C, 45.91; H, 7.19. Found: C, 46.45; H, 7.24.

Lactol 4i (mixture of diastereomers): bp 110 °C/5.5 mmHg (Kugelrohr); R_f 0.61 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.23 (4.5 H, s), 0.25 (4.5H, s), 1.88−2.28 (2H, m), 2.62−3.00 (2H, m), 4.22−4.55 (1H, m), 5.24 (0.5H, d, J = 8.3 Hz), 5.31 (0.5H, dd, J = 6.4, 2.7 Hz), 5.67−6.29 (1H, m), 7.20−7.35 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) −0.24, −0.09, 29.80 (d, J_{C-F} = 9.1 Hz), 31.12−31.30 (m), 31.59 (d, J_{C-F} = 9.1 Hz), 76.16−78.14 (m), 94.60−96.42 (m), 107.00−116.60 (m), 126.17, 126.24, 128.39, 128.52, 140.57, 140.69;^{19}F NMR (188 MHz, $CDCl_3$) −43.04 (0.5F, d, J = 481.5 Hz), −37.11 to −36.34 (0.5F, m), 26.13−41.77 (4F, m); IR (neat) 2962, 1255, 1095 cm^{-1}. Anal. Calcd for $C_{16}H_{21}F_5O_2Si$: C, 52.16; H, 5.75. Found: C, 52.37; H, 5.64.

Lactol 4j (mixture of diastereomers): bp 80 °C/4.0 mmHg (Kugelrohr); R_f 0.49 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.20−0.21 (9 H, m), 0.98−1.38 (5H, m), 1.55−1.98 (6H, m), 4.00 (0.5H, d, J = 6.6 Hz), 4.10 (0.5H, d, J = 6.7 Hz), 5.16 (0.5H, dd, J = 6.8, 0.9 Hz), 5.21 (0.5H, dd, J = 6.1, 2.8 Hz), 5.99 (1H, dt, J = 52.6, 11.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) −0.25, 25.72, 25.89, 26.20, 28.27, 29.39, 37.59 (d, J_{C-F} = 5.6 Hz), 80.41 (dd, J_{C-F} = 20.7, 4.7 Hz), 94.51 (dd, J_{C-F} = 38.1, 23.6 Hz), 111.70 (ddt, J_{C-F} = 246.3, 25.1, 3.2 Hz), 120.50 (ddd, J_{C-F} = 284.2, 259.1, 15.1 Hz);^{19}F NMR (188 MHz, $CDCl_3$) −46.04 (0.5F, s), −33.50 (0.5F, s), 28.34−41.53 (4F, m); IR (neat) 2962, 1255, 1095 cm^{-1}. Anal. Calcd for $C_{14}H_{23}F_5O_2Si$: C, 48.54; H, 6.69. Found: C, 48.69; H, 6.82.

Lactol 4k (mixture of diastereomers): bp 70 °C/3.7 mmHg (Kugelrohr); R_f 0.7 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.20 (9 H, s), 0.89 (3H, t, J = 6.5 Hz), 1.25−1.38 (8H, m), 1.50−1.84 (2H, m), 4.18−4.33 (1H, m), 5.18 (0.5H, d, J = 8.3 Hz) 5.25 (0.5H, dd, J = 6.5, 2.7 Hz), 5.68−6.32 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) −0.15, 13.98, 22.53, 25.32, 25.25, 28.93, 30.03 (d, J_{C-F} = 9.0 Hz), 31.61, 78.98 (d, J_{C-F} = 21.1 Hz), 95.70 (dd, J_{C-F} = 40.2, 23.1 Hz), 111.15 (ddt, J_{C-F} = 247.0, 27.0, 6.9 Hz), 120.52 (ddd, J_{C-F} = 277.6, 250.6, 19.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −36.57 to −36.41 (1F, m), 26.12−41.85 (4F, m); IR (neat) 2960, 1468, 1255, 1095 cm^{-1}. Anal. Calcd for $C_{14}H_{25}F_5O_2Si$: C, 48.26; H, 7.23. Found: C, 48.45; H, 7.61.

5-Phenyl-1-penten-3-yl Difluoroacetate (5a). Difluoroacetate **5a** was obtained in 60−70% yield when ester **2a** was subjected to the radical reaction under the same reaction conditions described before: bp 70 °C/3.0 mmHg (Kugelrohr); R_f 0.62 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.99−2.29 (2H, m), 2.75 (2H, t, J = 7.9 Hz), 5.34−5.50 (3H, m), 5.82−5.99 (1H, m), 5.92 (1H, t, J = 53.4 Hz), 7.22−7.41 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 31.13, 35.36, 77.36, 106.69 (t, J_{C-F} = 249.5 Hz), 118.85, 126.19, 128.30, 128.53, 134.46, 140.57, 161.82 (t, J_{C-F} = 28.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 35.19 (2F, d, J = 52.2 Hz); IR (neat) 3025, 2930, 1792, 1765, 1500, 1230 cm^{-1}. Anal. Calcd for $C_{13}H_{14}F_2O_2$: C, 64.99; H, 5.87. Found: C, 64.94; H, 5.91.

Synthesis of Substrates for the Radical Cyclization. 1,1,2-Trifluoro-5-phenyl-1-penten-3-yl Bromodifluoroacetate (2i). To a solution of lithium 2-bromo-2,2-difluoroacetate (2.97 g, 16.4 mmol) in ether (15 mL) was added an ether (7.0 mL) solution of oxalyl chloride (2.08 g, 16.4 mmol) at 0 °C dropwise, and the mixture was stirred for 1.5 h at the same temperature. To this solution was added an ether (5.0 mL) solution of 1,1,2-trifluoro-5-phenyl-1-penten-3-ol (**6i**) (1.78 g, 8.23 mmol) and triethylamine (3.45 mL, 24.8 mmol) at 0 °C. After 1.5 h of stirring at the same temperature, the mixture was filtered through a short column of silica gel and evaporated to dryness. Silica gel flash column chromatography (hexanes/ethyl acetate = 50:1) gave **2i** (2.38 g, 6.4 mmol) as a colorless liquid in 77% yield: bp 100 °C/6.0 mmHg (Kugelrohr); R_f 0.7 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 2.18−2.50 (2H, m), 2.77 (2H, t, J = 7.8 Hz), 5.58 (1H, dtt, J = 25.2, 7.4, 2.2 Hz), 7.22−7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 30.93, 31.05, 71.08 (dt, J_{C-F} = 22.0, 3.3 Hz), 108.27 (t, J_{C-F} = 314.6 Hz), 125.55 (ddd, J_{C-F} = 238.8, 49.6, 17.4 Hz), 126.7, 128.22, 128.78, 139.15, 153.61 (ddd, J_{C-F} = 294.2, 283.1, 43.7 Hz), 158.57 (t, J_{C-F} = 32.1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −27.43 (1F, ddd, J = 115.5, 33.6, 25.1 Hz), 48.58 (1F, dd, J = 114.8, 62.6 Hz), 64.68 (1F, dd, J = 62.7, 33.6 Hz), 100.68 (2F, s); IR (neat) 3030, 2931, 1792, 1776, 1286,

1128 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrF_5O_2$: C, 41.85; H, 2.70. Found: C, 42.09; H, 2.83.

Using the same procedure, esters **2** were obtained in greater than 80% yield.

5-Phenyl-1-penten-3-yl Bromodifluoroacetate (2a): bp 80 °C/3.5 mmHg (Kugelrohr); R_f 0.67 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.84−2.16 (2H, m), 2.57−2.67 (2H, m),5.21−5.35 (2H, m),5.77 (1H, ddd J = 17.5, 10.6, 6.8 Hz),7.06−7.25 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 31.04, 35.44, 78.94, 108.81 (t, J_{C-F} = 314.7 Hz), 119.30, 126.26, 126.30, 128.57, 133.85, 140.37, 158.75 (t, J_{C-F} = 31.2 Hz); ^{19}F NMR-(188 MHz, $CDCl_3$) 100.96 (2F, s); IR (neat) 2925, 1770, 1500, 1290, cm^{-1}. Anal. Calcd for $C_{13}H_{13}BrF_2O_2$: C, 48.93; H, 4.11. Found: C, 48.89; H, 4.23.

5-Phenyl-1-penten-3-yl Chlorodifluoroacetate (2aa): bp 80 °C/5.0 mmHg; R_f 0.6 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.84−2.15 (2H, m) 2.49−2.73 (2H, m) 5.21−5.33 (3H, m) 5.67−5.84 (1H, m) 7.05−7.25 (5H, m); ^{13}CNMR (50 MHz, $CDCl_3$) 31.04, 35.43, 79.04, 116.94 (t, J = 299.2 Hz), 119.32, 126.28, 128.30, 128.58, 133.90, 140.35, 158.37; ^{19}F NMR (188 MHz, $CDCl_3$) 36.10−40.08 (m), 97.52 (2F, s); IR (neat) 2930, 1770, 1450, 1300, 1160 cm^{-1}. Anal. Calcd for $C_{13}H_{13}ClF_2O_2$: C, 56.84; H, 4.77. Found: C, 56.90; H, 4.78.

Allyl Bromodifluoroacetate (2b): bp 80 °C/6.0 mmHg (Kugelrohr); R_f 0.71 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 4.82 (2H, d, J = 5.8 Hz), 5.35−5.49 (2H, m), 5.96 (1H, ddt, J = 16.8, 10.8, 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 68.42, 108.62 (t, J_{C-F} = 312.3 Hz), 120.66, 129.64, 159.28 (t, J_{C-F} = 28.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 94.75 (2F, s); IR (neat) 2950, 1775, 1450, 1365, 1165 cm^{-1}. Anal. Calcd for C_5H_5-BrF_2O_2: C, 27.93; H, 2.34. Found: C,27.87; H, 2.33.

Cinnamyl Bromodifluoracetate (2c): bp 103 °C/5.0 mmHg (Kugelrohr); R_f 0.53 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 4.90 (2H, dd, J = 6.7, 1.3 Hz), 6.21 (1H, dt, J = 15.9, 6.70 Hz), 6.69 (1H, d, J = 15.9 Hz), 7.16−7.36 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 68.69, 108.74 (t, J_{C-F} = 312.5 Hz), 120.19, 126.84, 128.67, 128.70, 135.48, 136.88, 159.43 (t, J_{C-F} = 31.3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 100.46 (2F, s); IR (neat) 3025, 1770, 1650, 1450, 1380, 1160 cm^{-1}. Anal. Calcd for $C_{11}H_9BrF_2O_2$: C, 45.39; H,3.12. Found: C, 45.59; H, 3.23.

Isopropenyl Bromodifluoroacetate (2d): bp 35 °C/3.3 mmHg (Kugelrohr); R_f 0.69 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.76 (3H, s), 1.79 (3H, s), 4.82 (2H, dd, J = 6.7, 1.3 Hz), 5.34−5.45 (1H,m);^{13}C NMR (50 MHz, $CDCl_3$) 18.09, 25.76, 65.03, 108.93 (t, J_{C-F} = 314.5 Hz), 116.23, 142.49, 159.59 (t, J_{C-F} = 31.0 Hz); ^{19}F NMR(188 MHz, $CDCl_3$) 10126 (2F, s); IR (neat) 2977, 2921, 1774, 1673, 1295 cm^{-1}. Anal. Calcd for $C_7H_9BrF_2O_2$: C, 34.59; H,3.73. Found: C, 34.89; H, 3.73.

1-Hepten-3-yl Bromodifluoroacetate (2e): bp 50 °C/2.5 mmHg (Kugelrohr); R_f 0.86 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.91 (3H, t, J = 7.0 Hz), 1.25−1.38 (4H, m), 1.68−1.82 (2H, m), 5.26−5.41 (3H, m), 5.82 (1H, ddd, J = 17.3, 10.4, 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 13.83, 22.25, 26.91, 33.50, 79.82, 108.90 (t, J_{C-F} = 314.6 Hz), 118.85, 134.26, 158.87 (t, J_{C-F} = 31.1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 100.99 (2F, s); IR (neat) 2975, 1775, 1460, 1170 cm^{-1}. Anal. Calcd for $C_9H_{13}BrF_2O_2$: C, 39.87; H, 4.83. Found: C, 39.89; H, 4.23.

6-Methyl-1,5-heptadien-3-yl Bromodifluoroacetate (2f): bp 65 °C/3.0 mmHg (Kugelrohr); R_f 0.70 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.62 (3H, s), 1.70 (3H, s), 2.34−2.56 (2H, m), 5.02−5.12 (1H, m), 5.25−5.40 (3H, m), 5.84 (1H, ddd, J = 17.5, 10.4, 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 17.91, 25.76, 32.81, 79.27, 108.89 (t, J_{C-F} = 314.6 Hz), 117.20, 118.71, 134.01, 136.07, 158.80 (t, J_{C-F} = 31.1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 101.05 (2F, s); IR (neat) 2927, 1775, 1451, 1297, 1169 cm^{-1}. Anal. Calcd for $C_{10}H_{13}BrF_2O_2$: C, 42.42; H, 4.63. Found: C, 42.10; H, 4.85.

6-Methyl-1,5-heptadien-3-yl Chlorodifluoroacetate (2fa): bp 60 °C/3.0 mmHg (Kugelrohr); R_f 0.73 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.53 (3H, s), 1.71 (3H, s), 2.31−2.58 (2H, m), 5.02−5.13 (1H, m), 5.25−5.40 (3H, m), 5.85 (1H, ddd, J = 17.3, 10.5, 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 17.83, 25.74, 32.83, 79.34, 116.97 (t, J_{C-F} = 301.0 Hz), 117.15, 118.72, 134.03, 136.12, 158.48 (t, J_{C-F} = 34.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 97.80 (2F, s); IR (neat) 2919, 1778, 1302, 1171, 1133 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClF_2O_2$: C,50.33; H,5.49. Found: C, 50.13; H, 5.95.

1,1-Difluoro-2-((methoxyethoxy)methoxy)-1-penten-3-yl Bromodifluoroacetate (2 g): bp 80 °C/4.0 mmHg (Kugelrohr); R_f 0.71 (hexane/ethyl acetate = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.95 (3H, t, J = 7.5 Hz), 1.80−2.03 (2H, m), 3.37 (3H, s), 3.54 (2H, t, J = 4.6 Hz), 3.71−3.91, (2H, m), 4.93 (1H, d, J = 6.3 Hz), 4.97 (1H, d, J = 6.3 Hz), 5.49 (1H, ddt, J = 2.6, 1.8, 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 9.27, 23.62, 59.00, 68.62, 71.44, 76.09 (dd, J_{C-F} = 5.1 Hz, 2.8 Hz), 97.63 (t, J_{C-F} = 3.4 Hz), 108.57 (t, J_{C-F} = 314.7 Hz), 111.75 (dd, J_{C-F} = 36.0, 15.7 Hz), 155.93 (dd, J_{C-F} = 294.5, 290.5 Hz), 158.62 (t, J_{C-F} = 31.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 57.97 (1F, d, J = 51.3 Hz), 67.09 (1F, d, J = 51.3 Hz), 100.89 (2F, d, J = 13.6 Hz); IR (neat) 2884, 1780, 1750, 1290, 1128, cm^{-1}. Anal. Calcd for $C_{11}H_{15}BrF_4O_5$: C, 34.48; H, 3.95. Found: C, 35.09; H, 3.73.

1,1-Difluoro-4-methyl-1-penten-3-yl Bromodifluoroacetate (2h): bp 80 °C/2.3 mmHg (Kugelrohr); R_f 0.63 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.95 (3H, d, J = 6.8 Hz), 1.02 (3H, d, J = 6.6 Hz), 2.20−2.39 (1H, m), 3.36 (3H, s), 3.54 (2H, t, J = 4.6 Hz), 3.69−3.90 (2H, m), 4.92 (1H, d, J = 6.1 Hz), 4.96 (1H, d, J = 6.0 Hz), 5.21 (1H, dt, J = 10.0, 2.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 18.07, 18.51, 29.13, 59.00, 68.62, 71.46, 79.72 (dd, J_{C-F} = 4.8, 3.0 Hz), 97.60 (t, J_{C-F} = 12.2 Hz), 108.55 (t, J_{C-F} = 312.7 Hz), 111.49 (dd, J_{C-F} = 36.3, 15.6 Hz), 156.13 (dd, J_{C-F} = 294.4, 290.1 Hz), 158.62 (t, J_{C-F} = 31.5 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 57.67 (1F, d, J = 51.8 Hz), 66.86 (1F, d, J = 51.9 Hz), 100.65 (1F, d, J = 158.0 Hz), 101.62 (1F, d, J = 156.2 Hz); IR (neat) 2980, 1780, 1748, 1470, 1297, 955 cm^{-1}. Anal. Calcd for $C_{12}H_{17}BrF_4O_5$: C, 34.30; H, 4.45. Found: C, 35.94; H, 4.39.

1,1,2-Trifluoro-5-phenyl-1-penten-3-yl Chlorodifluoroacetate (2ia): bp 90 °C/6.0 mmHg (Kugelrohr); R_f 0.7 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 2.08−2.36 (2H, m), 2.63 (2H, t, J = 7.8 Hz), 5.45 (1H, dtt, J = 25.2, 7.5, 2.3 Hz), 7.06−7.27 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 30.91, 31.00, 71.15 (dt, J_{C-F} = 22.0, 3.4 Hz), 116.61 (t, J_{C-F} = 300.8 Hz), 125.65 (ddd, J_{C-F} = 238.7, 49.6, 17.3 Hz), 126.70, 128.21, 128.78, 139.12, 153.61 (ddd, J_{C-F} = 294.2, 283.0, 43.6 Hz), 158.25 (t, J_{C-F} = 34.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −27.49 (1F, ddd, J = 115.3, 33.6, 24.8 Hz), 48.64 (1F, dd, J = 114.6, 62.1 Hz), 64.75 (1F, dd, J = 62.7, 33.6 Hz), 97.81 (2F, s); IR (neat) 2928, 1793, 1778, 1322, 1173 cm^{-1}. Anal. Calcd for $C_{13}H_{10}ClF_5O_2$: C, 47.51; H, 3.07. Found: C, 47.09; H, 3.03.

1-Cyclohexyl-2,3,3-trifluoro-2-propenyl Bromodifluoroacetate (2j): bp 70 °C/4.0 mmHg (Kugelrohr); R_f 0.66 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.87−1.41 (5H,m), 1.67−2.15 (6H, m), 5.29 (1H, ddt, J = 26.4, 9.9, 2.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 25.13, 25.28, 25.83, 28.23, 28.75, 37.41, 75.68 (dt, J_{C-F} = 19.3, 3.2 Hz), 108.30 (t, J_{C-F} = 314.5 Hz), 124.41 (ddd, J_{C-F} = 239.6, 50.0, 17.1 Hz), 154.15 (ddd, J_{C-F} = 293.8, 282.0, 43.7 Hz), 158.80 (t, J_{C-F} = 32.0 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −26.88 (1F, ddd, J = 115.3, 33.2, 26.8 Hz), 47.07 (1F,dd, J = 115.0, 65.1 Hz), 64.12 (1F, dd, J = 65.3, 33.1 Hz), 100.86 (2F,s); IR (neat) 2935, 2858, 1793, 1776, 1452, 1271, 1126 cm^{-1}. Anal. Calcd for $C_{11}H_{12}$-BrF_5O_2: C, 37.63; H, 3.44. Found: C, 37.57; H, 354.

1,1,2-Trifluoro-1-nonen-3-yl Bromodifluoroacetate (2k): bp 80 °C/4.0 mmHg (Kugelrohr); R_f 0.80 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.5 Hz), 1.25−1.40 (8H, m), 1.85−1.98 (2H, m), 5.57 (1H, dddt, J = 25.3, 2.9, 1.8, 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 13.91, 22.43, 24.70, 28.55, 29.39, 31.44, 71.79 (dt, J_{C-F} = 22.1, 3.4 Hz), 108.33 (t, J_{C-F} = 314.5 Hz), 125.06 (ddd, J_{C-F} = 239.2, 49.7, 17.1 Hz), 153.65 (ddd, J_{C-F} = 294.1, 282.4, 43.9 Hz), 158.70 (t, J_{C-F} = 32.0 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −27.46 (1F, ddd, J = 114.3, 33.2, 24.8 Hz), 47.68 (1F,dd, J = 115.0, 64.4 Hz), 64.10 (1F, dd, J = 64.4, 33.6 Hz), 100.70 (2F,s); IR (neat) 2931, 2862, 1793, 1776, 1467, 1286, 1130 cm^{-1}. Anal. Calcd for $C_{11}H_{14}$-BrF_5O_2: C, 37.41; H, 4.00. Found: C, 37.78; H, 4.21.

Bromodifluoroacetaldehyde 1,1,2-Trifluoro-5-phenyl-1-pentene-3-yl *O*-(Trimethylsilyl)acetal (3i). To a solution of ester **2i** (2.27 g, 6.08 mmol) in dichloromethane (15.0 mL)

was added a toluene (4.97 mL) solution of DIBAL (7.35 mmol) at −78 °C over 10 min, and the mixture was stirred for 3 h at the same temperature. To this were added a pyridine (1.5 mL, 18.55 mmol) and a dichloromethane (5.0 mL) solution of trimethyl-*O*-triflate (2.03 g, 9.13 mmol) dropwise over 5 min at −78 °C. This solution was allowed to warm to 0 °C over 6 h with stirring. The reaction was quenched by 1 h of stirring with potassium fluoride (1.4 g, 4 equiv) and water (0.45 mL) at room temperature. Silica gel flash column chromatography (hexanes/ethyl acetate = 50:1) gave **3i** (1.97 g, 4.4 mmol) as a colorless liquid in 72% yield. Mixture of diastereomers of **3i**: bp 90 °C/4.5 mmHg (Kugelrohr); R_f 0.73 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.19 (4.5 H, s), 0.22 (4.5 H, s), 2.01−2.40 (2H, m), 2.78 (1H, t, J = 7.3 Hz), 2.79 (1H, t, J = 7.5 Hz), 4.25−4.38 (0.5 H, m), 4.38−4.51 (0.5 H, m), 4.74−4.78 (1H, m), 7.21−7.38 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) −0.10, 1.90, 31.13, 31.21, 32.51, 32.69, 68.30 (d, J_{C-F} = 21.3 Hz), 71.71 (d, J_{C-F} = 21.4 Hz), 93.17 (t, J_{C-F} = 31.1 Hz), 95.41 (t, J_{C-F} = 30.3 Hz), 121.52 (t, J_{C-F} = 310.2 Hz), 122.17 (t, J_{C-F} = 310.6 Hz), 126.25, 126.32, 128.30, 128.52, 128.59, 140.32, 154.7 (ddd, J_{C-F} = 527.3, 277.8, 26.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −25.94 (0.5F, ddd, J = 115.6, 33.2, 27.1 Hz), −24.87 (0.5F, ddd, J = 115.0, 31.9, 27.5 Hz), 43.32 (0.5F, dd, J = 115.5, 74.1 Hz), 43.39 (0.5 F, dd, J = 115.6, 76.0 Hz), 61.82 (0.5F, dd, J = 74.4, 32.7 Hz), 62.65 (0.5F, dd, J = 74.9, 33.2 Hz), 98.02−101.07 (2F, m); IR (neat) 2962, 1784, 1259, 1128 cm^{-1}. Anal. Calcd for $C_{16}H_{20}BrF_5O_2$ Si: C, 42.96; H, 4.51. Found: C, 42.66; H, 4.79.

Using the same procedure, *O*-(trimethylsilyl)-acetals **3** were synthesized as mixtures of diastereomers.

Bromodifluoroacetaldehyde 5-Phenyl-1-penten-3-yl *O*-(Trimethylsilyl)acetal (3a). Mixture of diastereomers (ca. 1:1): bp 90 °C/1.7 mmHg (Kugelrohr); R_f 0.58 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.15 (4.5H, s), 0.16 (4.5H, s) 1.73−2.20 (2H, m), 2.59−2.88 (2H, m) 3.98−4.08 (1H, m), 4.71−4.77 (1H, m) 5.18−5.43 (2H, m) 7.17−7.30 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 0.23, 0.40, 31.12, 31.21, 36.81, 36.86, 81.31, 92.72 (t, J_{C-F} = 30.4 Hz), 94.97 (t, J_{C-F} = 30.3 Hz), 118.19, 118.92, 123.04 (t, J_{C-F} = 311.0 Hz), 125.80, 128.86, 128.29, 128.37, 128.58, 137.37, 138.06, 141.55; ^{19}F NMR (188 MHz, $CDCl_3$) 98.39−101.20 (2F, m); IR (neat) 2950, 1600, 1495, 1360, 1255, 1120 cm^{-1}. Anal. Calcd for $C_{16}H_{23}BrF_2O_2$ Si: C, 48.86; H, 5.89. Found: C, 48.57; H, 5.40.

Bromodifluoroacetaldehyde Allyl *O*-(Trimethylsilyl)-acetal (3b): bp 100 °C/43 mmHg (Kugelrohr); R_f 0.73 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.23 (9H, s), 4.07−4.33 (2H, m), 4.77 (1H, dd, J = 4.5, 3.5 Hz), 5.22−5.39 (2H, m), 5.82−6.01 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 0.18, 68.87, 95.22 (t, J_{C-F} = 30.0 Hz), 118.18, 122.00 (t, J_{C-F} = 308.3 Hz), 133.11; ^{19}F NMR (188 MHz, $CDCl_3$) 99.50 (2F, dd, J = 245.2, 163.2 Hz); IR (neat) 2975, 1460, 1420, 1365, 1255, 1225, 1130 cm^{-1}. Anal. Calcd for $C_8H_{15}BrF_2O_2$ Si: C, 33.23; H, 5.23. Found: C, 33.57; H, 5.40.

Bromodifluoroacetaldehyde Cinnamyl *O*-(Trimethylsilyl)acetal (3c): bp 105 °C/4.5 mmHg (Kugelrohr); R_f 0.53 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.07 (9H, s), 4.20 (2H, ddd, J = 30.3, 12.7, 5.9 Hz), 4.67 (1H, dd, J = 4.7, 3.5 Hz), 6.09 (1H, dt, J = 16.1, 6.0 Hz), 6.48 (1H, d, J = 16.0 Hz), 7.09−7.25 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 68.74, 95.23 (t, J_{C-F} = 30.1 Hz), 122.05 (t, J_{C-F} = 310.1 Hz), 124.15, 126.56, 128.02, 128.60, 133.65, 136.15; ^{19}F NMR (188 MHz, $CDCl_3$) 98.91 (1F, dd, J = 166.0, 4.2 Hz), 100.22 (1F, dd, J = 165.2, 2.8 Hz); IR (neat) 3050, 2975, 1500, 1450, 1255 cm^{-1}. Anal. Calcd for $C_{14}H_{19}BrF_2O_2$ Si: C, 46.03; H, 5.24. Found: C, 47.16; H, 5.49.

Bromodifluoroacetaldehyde Isopropenyl *O*-(Trimethylsilyl)acetal (3d): bp 75 °C/3.0 mmHg (Kugelrohr); R_f 0.69 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.22 (9H, s), 1.68 (3H, s), 1.76 (3H, s),4.10−4.29 (2H, m), 4.77 (1H, dd, J = 4.6, 3.7 Hz), 5.30−5.38 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 68.74, 95.23 (t, J_{C-F} = 30.1 Hz), 122.05 (t, J_{C-F} = 310.1 Hz), 0.15, 18.09, 25.73, 64.85, 95.29 (t, J_{C-F} = 29.8 Hz), 119.51, 122.24 (t, J_{C-F} = 310.5 Hz), 138.47; ^{19}F NMR (188 MHz, $CDCl_3$) 99.64 (2F, dd, J = 222.8, 164.5 Hz); IR (neat) 2962, 1675, 1447, 1365 cm^{-1}. Anal. Calcd for $C_{10}H_{19}BrF_2O_2$ Si: C, 37.86; H, 6.04. Found: C, 38.26; H, 6.13.

Bromodifluoroacetaldehyde 1-Hepten-3-yl *O*-(Trimethylsilyl)acetal (3e). Mixture of diastereomers (ca. 1:1): bp 75 °C/2.5 mmHg (Kugelrohr); R_f 0.80 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.19 (4.5H, s), 0.21 (4.5H, s), 0.89 (3H, t, J = 7.0 Hz), 1.25−1.75 (6H, m), 3.94−4.05 (1H, m), 4.71−4.78 (1H, m), 5.16−5.29 (2H, m), 5.60−5.87 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 0.43, 13.94, 22.45, 37.13, 34.87, 78.39, 82.23, 93.03 (t, J_{C-F} = 30.3 Hz), 94.94 (t, J_{C-F} = 29.9 Hz), 117.83, 118.46, 122.14 (t, J_{C-F} = 307.5 Hz), 123.19 (t, J_{C-F} = 311.0 Hz),137.78, 138.46; ^{19}F NMR (188 MHz, $CDCl_3$) 98.33−101.11 (2F, m); IR (neat) 2950, 1250, 1130, 840 cm^{-1}. Anal. Calcd for $C_{12}H_{23}BrF_2O_2$ Si: C, 41.74; H, 6.71. Found: C, 42.35; H, 6.86.

Bromodifluoroacetaldehyde 6-Methyl-1,5-heptadien-3-yl *O*-(Trimethylsilyl)acetal (3f). Mixture of diastereomers (ca. 1:1): bp 75 °C/3.2 mmHg (Kugelrohr); R_f 0.68 (hexane/ethyl acetate = 10:1);^{1}H NMR (200 MHz, $CDCl_3$) 0.18 (4.5H, s), 0.20 (4.5H, s), 1.59 (3H, s), 1.68 (3H, s), 2.16−2.47 (2H, m), 3.22 (1H, dd, J = 14.0, 7.3 Hz), 4.72−4.79 (1H, m), 5.06−5.29 (3H, m), 5.69 (0.5H, ddd, J = 17.1, 10.5, 8.1 Hz), 5.79 (0.5H, ddd, J = 17.3, 10.2, 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 0.33, 0.41, 17.96, 18.03, 25.75, 33.92, 34.12, 78.62, 81.70, 93.25 (t, J_{C-F} = 30.2 Hz), 95.07 (t, J_{C-F} = 29.9 Hz), 117.73, 118.82, 118.90, 122.05 (t, J_{C-F} = 308.9 Hz), 122.98 (t, J_{C-F} = 311.0 Hz),134.09, 134.17, 137.37, 138.01; ^{19}F NMR (188 MHz, $CDCl_3$) 98.20−100.99 (2F, m); IR (neat) 2963, 1424, 1377, 1254, 1129 cm^{-1}. Anal. Calcd for $C_{13}H_{23}BrF_2O_2$ Si: C, 43.70; H, 6.49. Found: C, 44.03; H, 6.58.

Chlorodifluoroacetaldehyde 6-Methyl-1,5-heptadien-3-yl *O*-(Trimethylsilyl)acetal (3fa). Mixture of diastereomers (ca. 1:1): bp 75 °C/3.2 mmHg (Kugelrohr); R_f 0.73 (hexane/ethyl acetate = 7:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.19 (4.5H, s), 0.21 (4.5H, s), 1.60 (3H, s), 1.70 (3H, s), 2.16−2.49 (2H, m), 4.00 (1H, dd, J = 13.9, 7.2 Hz), 4.89−4.94 (1H, m), 5.06−5.16 (1H, m), 5.17−5.30 (2H, m), 5.60−5.89 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 0.28, 0.36, 17.93, 18.00, 25.74, 33.92, 34.11, 78.73, 81.77, 92.64 (t, J_{C-F} = 32.2 Hz), 94.47 (t, J_{C-F} = 31.9 Hz), 117.68, 118.70, 118.81, 118.85, 126.78 (t, J_{C-F} = 295.8 Hz), 127.44 (t, J_{C-F} = 297.6 Hz), 134.11, 134.18, 137.33, 138.00; ^{19}F NMR (188 MHz, $CDCl_3$) 92.58−95.02 (2F, m); IR (neat) 2965, 1255, 1130, 846 cm^{-1}. Anal. Calcd for $C_{13}H_{23}ClF_2O_2$ Si: C, 49.91; H, 7.41. Found: C, 49.99; H, 7.29.

Bromodifluoroacetaldehyde 1,1-Difluoro-2-((methoxyethoxy)methoxy)-1-penten-3-yl *O*-(Trimethylsilyl)acetal (3g). Mixture of diastereomers (ca. 1:1): bp 80 °C/6.0 mmHg (Kugelrohr); R_f 0.67 (hexane/ethyl acetate = 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.19 (4.5H, s), 0.20 (4.5H, s), 0.90 (1.5H, t, J = 7.4 Hz), 0.91 (1.5H, t, J = 7.5 Hz), 1.56−1.91 (2H, m), 3.36 (3H, s), 3.54 (1H, t, J = 4.6 Hz), 3.55 (1H, t, J = 4.8 Hz), 3.68−3.94 (2H, m), 4.11−4.29 (1H, m), 4.72−4.77 (1H, m), 4.90−5.10 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) −0.26, −0.07, 9.56, 9.75, 24.63, 25.02, 58.95, 68.40, 71.55, 73.27 (t, J_{C-F} = 3.2 Hz), 76.48 (t, J_{C-F} = 3.5 Hz), 93.23 (t, J_{C-F} = 31.3 Hz), 95.71 (t, J_{C-F} = 30.6 Hz), 97.15, 97.78 (t, J_{C-F} = 2.9 Hz) 112.80 (dd, J_{C-F} = 36.6, 11.1 Hz), 114.38 (dd, J_{C-F} = 36.8, 12.2 Hz), 122.12 (t, J_{C-F} = 307.9 Hz), 155.34 (dd, J_{C-F} = 296.2, 287.4 Hz), 156.07 (dd, J_{C-F} = 295.0, 284.4 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 53.08 (0.5F, d, J = 42.1 Hz), 53.41 (0.5F, d, J = 40.0 Hz), 63.26 (0.5F, d, J = 63.4 Hz), 65.05 (0.5F, d, J = 62.7 Hz), 98.54−101.34 (2F, m); IR (neat) 2967, 1752, 1254, 1123 cm^{-1}. Anal. Calcd for $C_{14}H_{25}BrF_4O_5Si$: C, 36.77; H, 5.51. Found: C, 35.82; H, 5.36.

Bromodifluoroacetaldehyde 1,1-Difluoro-4-methyl-1-penten-3-yl *O*-(Trimethylsilyl)acetal (3h). Mixture of diastereomers (ca. 1:1): bp 85 °C/4.0 mmHg (Kugelrohr); R_f 0.63 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) (major isomer) 0.19 (9H, s), 0.86 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.6 Hz), 1.97−2.15 (1H, m), 3.36 (3H, s), 3.54 (2H, t, J = 4.5 Hz), 3.66−3.93 (2H, m), 4.68 (1H, t, J = 2.8 Hz), 4.90 (1H, d, J = 5.9 Hz), 4.99 (1H, d, J = 5.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) (major isomer) −0.09, 18.43, 19.45, 29.68, 58.97, 68.32 (d, J_{C-F} = 1.6 Hz), 76.96 (t, J_{C-F} = 3.4 Hz), 92.67 (t, J_{C-F} = 31.7 Hz), 97.12, 111.54 (dd, J_{C-F} = 36.8, 10.7 Hz),

122.32 (t, J_{C-F} = 308.2 Hz), 156.45 (dd, J_{C-F} = 295.2, 283.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) (major isomer) 52.81 (1F, d, J = 63.4 Hz), 65.11 (1F, d, J = 63.4 Hz), 99.51−102.10 (2F, m); IR (neat) 2978, 1750, 1473, 1371, 1240, 1128 cm^{-1}. Anal. Calcd for $C_{15}H_{27}BrF_4O_5$ Si: C, 38.22; H, 5.77. Found: C, 38.60; H, 5.86.

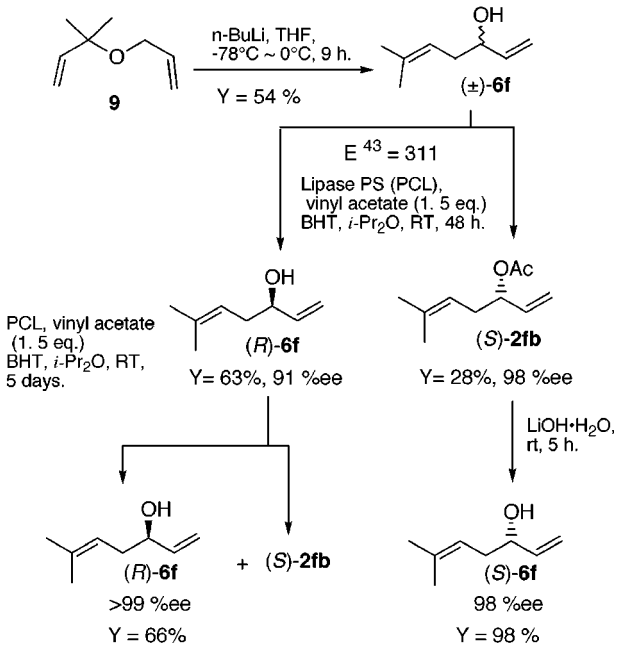
Chlorodifluoroacetaldehyde 1,1,2-Trifluoro-5-phenyl-1-penten-3-yl *O*-(Trimethylsilyl)acetal (3ia). Mixture of diastereomers (ca. 1:1): bp 90 °C/4.5 mmHg (Kugelrohr); R_f 0.75 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.06 (4.5 H, s), 0.09 (4.5 H, s), 1.90−2.30 (2H, m), 2.65 (1H, t, J = 7.9 Hz), 4.14−4.24 (0.5 H, m), 4.24−4.40 (0.5 H, m), 4.78 (1H, t, J = 3.1 Hz), 7.10−7.30 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) −0.25, −0.17, 31.11, 31.16, 32.69, 32.49, 68.63 (dt, J_{C-F} = 24.0, 2.8 Hz), 71.70 (d, J_{C-F} = 21.2 Hz) 92.62 (t, J_{C-F} = 33.0 Hz), 94.78 (t, J_{C-F} = 32.0 Hz), 127.44 (dt, J_{C-F} = 297.2, 27.2 Hz), 126.25, 126.32, 126.41, 128.29, 128.46, 128.52, 128.59, 140.28, 153.72; ^{19}F NMR (188 MHz, $CDCl_3$) −26.20 (0.5F, ddd, J = 116.0, 33.6, 26.0 Hz), −24.95 (0.5F, ddd, J = 116.0, 32.3, 27.5 Hz), 43.08 (0.5F, dd, J = 74.3, 16.3 Hz), 43.70 (0.5 F, dd, J = 73.9, 15.6 Hz), 61.85 (0.5F, dd, J = 75.3, 32.9 Hz), 62.74 (0.5F, dd, J = 75.6, 33.2 Hz), 92.5−95.2 (2F, m); IR (neat) 2961, 1783, 1258, 1128 cm^{-1}. Anal. Calcd for $C_{16}H_{20}ClF_5O_2$ Si: C, 42.96; H, 4.51. Found: C, 42.66; H,4.79.

Bromodifluoroacetaldehyde 1-Cyclohexyl-2,3,3-trifluoro-2-propenyl *O*-(Trimethylsilyl)acetal (3j). Mixture of diastereomers (ca. 1:1): bp 80 °C/8.0 mmHg (Kugelrohr); R_f 0.74 and 0.61 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.20 (4.5H, s), 0.21 (4.5H, s), 0.83−1.30 (6H, m), 1.62−2.20 (5H, m), 3.88−4.10 (1H, m), 4.70 (1H, t, J = 3.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) (major isomer only) −0.08, 25.45, 25.56, 26.16, 28.43, 29.45, 38.69, 73.81 (dt, J_{C-F} = 20.3, 2.1 Hz), 95.54 (t, J_{C-F} = 30.4 Hz), 122.42 (t, J_{C-F} = 310.8 Hz), 125.85 (ddd, J_{C-F} = 245.5, 48.8, 14.3 Hz), 154.22 (ddd, J_{C-F} = 293.7, 276.9, 44.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −27.30 (0.5F, dt, J = 113.9, 29.5 Hz), −23.87 (0.5F, dt, J = 116.0, 30.3 Hz), 40.87 (0.5F, dd, J = 113.6, 83.1 Hz), 41.93 (0.5F, dd, J = 116.7, 76.0 Hz), 58.87 (0.5F, dd, J = 81.1, 31.2 Hz), 61.77 (0.5F, dd, J = 77.3, 32.2 Hz), 98.04−101.16 (2F, m); IR (neat) 2931, 2856, 1784, 1452, 1259 cm^{-1}. Anal. Calcd for $C_{14}H_{22}BrF_5O_2$ Si: C, 39.54; H, 5.21. Found: C, 40.89; H, 5.09.

Bromodifluoroacetaldehyde 1,1,2-Trifluoro-1-nonen-3-yl *O*-(Trimethylsilyl)acetal (3k). Mixture of diastereomers (ca. 1:1): bp 70 °C/4.0 mmHg (Kugelrohr); R_f 0.73 and 0.66 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.20 (4.5H, s), 0.21 (4.5H, s), 0.88 (3H, m), 1.25−1.42 (8H, m), 1.63−1.94 (2H, m), 4.23−4.45 (1H, m), 4.71−4.76 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) (major isomer only) −0.08, 13.97, 22.50, 24.97, 28.76, 31.05, 31.57, 72.60 (d, J_{C-F} = 21.6 Hz), 95.42 (t, J_{C-F} = 30.2 Hz), 122.32 (t, J_{C-F} = 310.9 Hz), 126.44 (ddd, J_{C-F} = 242.5, 49.6, 13.1 Hz), 153.585 (ddd, J_{C-F} = 293.3, 277.4, 44.8 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −26.28 (0.5F, ddd, J = 115.6, 33.2, 25.8 Hz), −25.21 (0.5F, ddd, J = 116.0, 33.6, 27.5 Hz), 42.45 (0.5F, dd, J = 116.0, 76.3 Hz), 42.55 (0.5F, dd, J = 116.0, 76.3 Hz), 61.37 (0.5F, dd, J = 76.3, 32.6 Hz), 62.05 (0.5F, dd, J = 77.0, 32.9 Hz), 98.89−100.94 (2F, m); IR (neat) 2958, 2860, 1783, 1460, 1257, 1128 cm^{-1}. Anal. Calcd for $C_{14}H_{24}BrF_5O_2$ Si: C, 39.35; H, 5.66. Found: C, 39.80; H,5.14.

1,1,2-Trifluoro-5-phenyl-1-penten-3-ol (6i). To a solution of 1,1,1,2-tetrafluoroethane (12.2 mmol) in THF (5.3 mL) was added a hexane solution of n-BuLi (22.3 mmol, 1.6M) dropwise for 10 min at −100 °C, and the resulting solution was gradually warmed to −78 °C over 1 h with stirring. To this solution was added a THF (5 mL) solution of phenetylaldehyde (1.34 g, 9.9 mmol) at −78 °C, and the mixture was warmed to −50 °C over 1 h. The reaction was quenched by addition of methanol (3 mL), diluted with ethyl acetate (10 mL), and washed with 5 mL of brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. Silica gel flash column chromatography (hexanes−ethyl acetate = 10:1 to 5:1) gave **6i** as a colorless liquid in 82% yield (1.78 g, 8.2 mmol): bp 85 °C/2.5 mmHg (Kugelrohr); R_f 0.20 (hexane/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$) 1.97−2.26 (2H, m), 2.40 (1H, brd, J = 6.2 Hz, OH), 2.75 (2H, t, J = 7.8 Hz), 4.41 (1H, dddt, J = 26.5, 3.7, 1.7, 7.3 Hz), 7.22−7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 31.42, 34.24, 65.17 (dt, J_{C-F} = 21.8, 2.3 Hz), 126.19, 128.29, 128.50, 128.82 (ddd, J_{C-F} = 239.3, 49.8, 13.1 Hz), 140.52, 152.76 (ddd, J_{C-F} = 291.5, 277.3, 45.5 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −28.03 (1F, ddd, J = 115.0, 31.4, 27.3 Hz), 42.08 (1F, dd, J = 114.3, 78.0 Hz), 59.42 (1F, dd, J = 78.5, 32.4 Hz); IR (neat) 3350, 3028, 2950, 1307, 1259 cm^{-1}. Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 61.22; H, 5.17.

Scheme 4. Synthesis of Optically Active 6-Methylhept-1,5-dien-2-ol (6)



Using the same procedure, fluoroallyl alcohols **6g**, **6h**, **6j**, and **6k** were synthesized. All spectra of **6g** for ^{1}H and ^{13}C NMR coincided with those in reference 22a.

1,1-Difluoro-2-((methoxyethoxy)methoxy)-4-methyl-1-penten-3-ol (6h): bp 80 °C/2.3 mmHg (Kugelrohr); R_f 0.23 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.81 (3H, d, J = 5.8 Hz), 1.03 (3H, d, J = 5.8 Hz), 1.76−1.94 (1H, m), 3.18 (1H, brs, OH), 3.36 (3H, s), 3.52−3.57 (2H, m), 3.68−3.77 (2H, m), 3.57−3.98 (1H, m), 4.83 (1H, d, J = 6.6 Hz), 4.97 (1H, d, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 18.59, 19.07, 31.52, 58.88, 68.36, 71.35, 72.90 (d, J_{C-F} = 2.6 Hz), 97.93 (t, J_{C-F} = 3.5 Hz), 117.84 (dd, J_{C-F} = 37.0, 10.0 Hz), 154.97 (dd, J_{C-F} = 290.1, 283.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) 51.34 (1F, d, J = 64.8 Hz), 61.20 (1F, d, J = 65.5 Hz); IR (neat) 3452, 2960, 1751, 1469, 1234, 1030 cm^{-1}. Anal. Calcd for $C_{10}H_{18}F_2O_4$: C, 49.99; H, 7.55. Found: C, 50.04; H, 7.59.

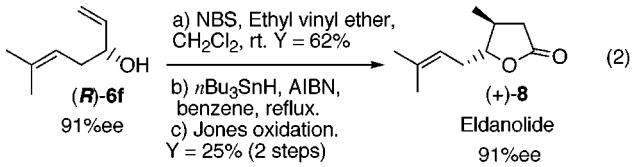
1-Cyclohexyl-2,3,3-trifluoro-2-propenol (6j): bp 60 °C/4.0 mmHg (Kugelrohr); R_f 0.43 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.82−1.36 (5H, m), 1.59−1.80 (5H, m), 1.95−2.08 (1H, m), 2.53 (1H, s, OH), 3.99 (1H, dddd, J = 27.9, 8.8, 4.0, 2.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 25.52, 25.58, 26.12, 28.61, 29.25, 40.17, 70.50 (dt, J_{C-F} = 21.1 Hz, 2.2 Hz), 128.20 (ddd, J_{C-F} = 239.4, 50.5, 12.6 Hz), 153.34 (ddd, J_{C-F} = 290.9, 276.0, 45.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −27.30 (1F, dt, J = 113.6, 29.3 Hz), 40.84 (1F, dd, J = 111.9, 78.3 Hz), 58.79 (1F, dd, J = 80.4, 31.9 Hz); IR (neat) 3349, 2929, 2855, 1789, 1452, 1254 cm^{-1}. Anal. Calcd for $C_9H_{13}F_3O$: C, 55.66; H, 6.75. Found: C, 55.85; H, 6.99.

1,1,3-Trifluoro-1-nonen-3-ol (6k): bp 70 °C/8.0 mmHg (Kugelrohr); R_f 0.48 (hexane/ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.6 Hz), 1.28−1.40 (6H, m), 1.67−1.81 (4H, m), 4.37 (1H, dddt, J = 26.7 Hz, 3.7 Hz, 1.8 Hz, 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 13.90, 22.50, 25.22, 28.83, 31.61, 32.82, 65.94 (dt, J_{C-F} = 22.0, 2.3 Hz), 128.91 (ddd, J_{C-F} = 239.2, 49.9, 12.6 Hz), 152.91 (ddd, J_{C-F} = 291.2, 276.5, 45.5 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) −28.48 (1F, ddd, J = 113.4, 32.4, 26.6 Hz), 41.23 (1F, dd, J = 114.3, 80.4 Hz), 58.80 (1F,

dd, $J = 80.4$, 31.8 Hz); IR (neat) 3340, 2930, 2861, 1789, 1468, 1258 cm^{-1}. Anal. Calcd for $C_9H_{15}F_3O$: C, 55.09; H, 7.71. Found: C, 54.85; H, 7.88.

Synthesis of Difluoroeldanolide. Preparation of Optically Active Allyl Alcohol 6f via Lipase-Catalyzed Reaction (Scheme 4). To a THF (240 mL) solution of 15.2 g (120 mmol) of 1-methyl-3-butenyl allyl ether (**9**)[42] was added n-BuLi (89.0 mL, 144 mmol, 1.62 M in hexane) at −78 °C, and the mixture was allowed to warm to 0 °C with 9 h of stirring under argon atmosphere. Silica gel flash coloumn chromatography of the crude products gave (±)-**6f**[26b] (8.15 g, 64.5 mmol) in 54% yield. Enantioselective acylation of (±)-**6f** was achieved using *Pseudomonas cepacia* lipase (PCL) in organic media; the mixture of (±)-**6f** (6.88 g, 54.5 mmol), PCL (1.38 g), 2,6-di-*tert*-butyl-4-methylphenol (BHT) (240.2 mg, 1.09 mmol, 2 mol %) vinyl acetate (7/54 mL, 81.8 mmol) in diidopropyl ether (180 mL) was stirred at room temperature for 48 h. The mixture was filtered through a glass-sintered filter to remove the lipase, and the filtrate was evaporated and chromatographed on silica gel flash column to give (*S*)-(+)-**2fb** (2.72 g, 16.3 mmol, 28%) and (*R*)-(−)-**6f** (3.92 g, 31.1 mmol, 63%), respectively. Enantiomeric excess of acetate (*S*)-**2fb** was determined by capillary GC analysis with the chiral phase Chiraldex G-Ta to be 98.2% ee. Acetate (*S*)-**2fb** obtained (2.72 g, 16.2 mmol) was hydrolyzed at room temperature for 5 h with lithium hydroxide monohydrate (1.02 g, 24.25 mmol) in a mixed solvent (THF/water/methanol = 32 mL/11 mL/5.5 mL) to give optically active alcohol (S)-**6f** (2.01 g, 15.9 mmol) in 98% yield. The optical purity of (*R*)-**6f** was not sufficient (91% ee) at the first stage of resolution, so alcohol (*R*)-**6f** (91%ee) was subjected to PCL-catalyzed acylation for 5 days at room temperature. Optically pure (*R*)-**6f** (>99% ee) was thus obtained in 42% overall yield from racemic (*R*)-**6f** (Scheme 4). Optical purity of (*R*)-**6f** was confirmed by GC analysis to be >99% ee since no signal of the enantiomer was observed using chiral column (Chiraldex G-Ta).

Because optical rotation values of (*R*)-**6f** and (*S*)-**2fb** have not been reported, absolute configuration of these compounds was confirmed by converting alcohol (*R*)-(−)-**6f** ($[\alpha]_D^{23}$ −21.7 (*c* 0.90, EtOH), 91% ee) to natural eldanolide, (4*S*,5*R*)-(+)-**8** ($[\alpha]_D^{22}$ + 53.9 (*c* 0.70, EtOH), lit.[37c] +57.8°), in 25% overall yield through Ueno−Stork-type radical cyclization and subsequent Jones oxidation (eq 2).[20a,b] Absolute configuration of the starting alcohol (−)-**6f** was thus confirmed as (*R*)-form.



(2)

Eldanolide 8:[37] ^{1}H NMR (200 MHz, $CDCl_3$) 1.06 (3H, d, J = 6.4 Hz), 1.57 (3H, s), 1.66 (3H, s), 2.15 (1H, dd, J = 16.2, 8.8 Hz), 2.15−2.35 (1H, m), 2.35−2.40 (1H, m), 2.61 (2H, dd, J = 9.0, 5.9 Hz), 3.99 (1H, dt, J = 6.1, 5.9 Hz), 5.18 (tq, J = 5.9, 1.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 17.65, 17.89, 25.74, 32.08, 35.02, 37.01, 65.79, 87.06, 117.88, 135.39, 176.53.

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Supporting Information Available: IR, ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra for new lactones, **1a**−**k** (44 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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