JOC*Article*

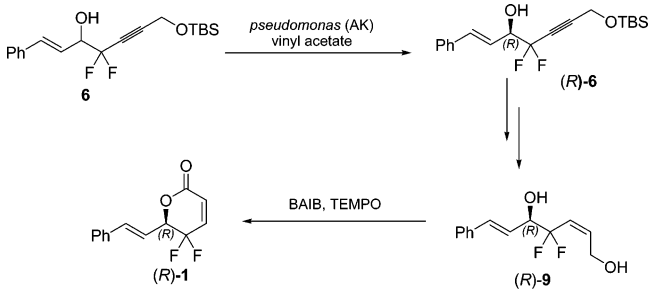
# An Efficient and General Route to *gem*-Difluoromethylenated α,*β*-Unsaturated *δ*-Lactones: High Enantioselective Synthesis of *gem*-Difluoromethylenated Goniothalamins

Zheng-Wei You,† Zhong-Xing Jiang,† Bing-Lin Wang,† and Feng-Ling Qing*,†,‡

*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 354 Fenglin Lu, Shanghai 200032, China, and Institute of Biological Sciences and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China*

*flq@mail.sioc.ac.cn*

*Received May 17, 2006*




An efficient and general strategy to *gem*-difluoromethylenated α,*β*-unsaturated *δ*-lactones in high yields from various aldehydes (including aliphatic, aromatic, α,*β*-unsaturated, and sterically hindered aldehydes) has been developed. This methodology was successfully applied for the preparation of two enantiomers of *gem*-difluoromethylenated goniothalamins (*S*)-**1** and (*R*)-**1**. *gem*-Difluoropropargylation of cinnamaldehyde followed by the resolution of resulting homopropargylic alcohols mediated by lipase from *Pseudomonas* (AK) gave alcohols (*R*)-**6** and (*S*)-**6**. Selective hydrogenation of the triple bond of (*S*)-**6** and (*R*)-**6** to double bond with Lindlar catalyst in the presence of quinoline afforded the expected product (*S*)-**8** and (*R*)-**8**, respectively. Deprotection of (*S*)-**8** and (*R*)-**8** followed by oxidation of the resulting 1,5-diols with catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and excess bis-acetoxyiodobenzene (BAIB) provided the target molecules *gem*-difluoromethylenated goniothalamins (*S*)-**1** and (*R*)-**1** in high yields, respectively.

## Introduction

α,*β*-Unsaturated *δ*-lactone **A** is a common structural unit of natural products with medicinal interest,[1] such as Goniothalamin,[2] Forstriecin,[3] and (+)-Boronolide,[4] and is also a versatile building block for complex natural products synthesis (Figure 1).[5] It has been revealed by structure−activity relationship studies that the α,*β*-unsaturated *δ*-lactone structure plays a key role in the bioactivities of many natural products, because such a structure unit is an excellent potential Michael acceptor for nucleophilic amino acid residues of the natural receptors interacting with these compounds.[2c,3b,4]

* To whom correspondence should be addressed. Fax: 86-21-64166128.
† Shanghai Institute of Organic Chemistry.
‡ Donghua University.

(1) For a review see: Davies-Coleman, M. T.; Rivett, D. E. A. *Prog. Chem. Org. Nat. Prod.* **1989**, *55*, 1−33.

(2) (a) de Fatima, A.; Kohn, L. K.; Antonio, M. A.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2005**, *13*, 2927−2933. (b) Chen, W.-Y.; Wu, C.-C.; Lan, Y.-H.; Chang, F.-R.; Teng, C.-M.; Wu, Y.-C. *Eur. J. Pharmacol.* **2005**, *522*, 20−29. (c) de Fatima, A.; Kohn, L. K.; Antonio, M. A.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2006**, *14*, 622−631. (d) Chan, K. M.; Rajab, N. F.; Ishak, M. H. A.; Ali, A. M.; Yusoff, K.; Din, L. B.; Inayat-Hussain, S. H. *Chem.-Biol. Interact.* **2006**, *159*, 129−140.

(3) (a) Lewy, D. S.; Gauss, C. M.; Soenen, D. R.; Boger D. L. *Curr. Med. Chem.* **2002**, *9*, 2050−2032. (b) Buck, S. B.; Hardouin, C.; Ichikawa, S.; Soenen, D. R.; Gauss, C.-M.; Hwang, I.; Swingle, M. R.; Bonness, K. M.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 15694−15695. (c) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 17111−17117.

(4) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935−3941 and references therein.

(5) For recent examples see: (a) Nicolaou, K. C.; Pihko, P. M.; Bernal, F.; Frederick, M. O.; Qian, W.; Uesaka, N.; Diedrichs, N.; Hinrichs, J.; Koftis, T. V.; Loizidou, E.; Petrovic, G.; Rodriquez, M.; Sarlah, D.; Zou, N. *J. Am. Chem. Soc.* **2006**, *128*, 2244−2257. (b) Khalaf, J. K.; Datta, A. *J. Org. Chem.* **2005**, *70*, 6937−6940. (c) Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2004**, *69*, 6294−6304.

10.1021/jo061012r CCC: $33.50 
Published on Web 08/16/2006

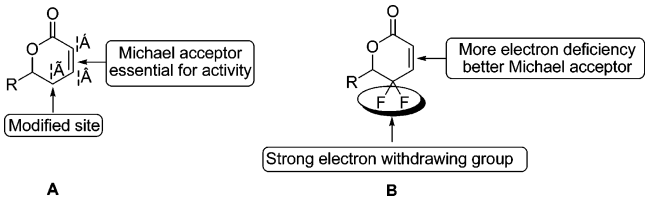
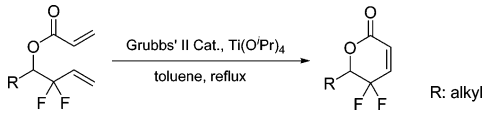



**FIGURE 1.** Design of *gem*-difluoromethylenated α,*β*-unsaturated *δ*-lactone **B**.

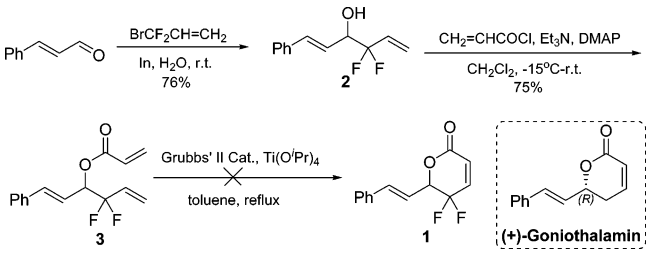
**SCHEME 1**



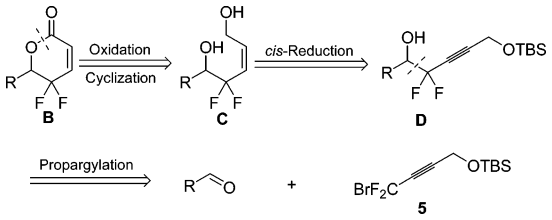

The strong electronegativity and relatively small size of fluorine atoms combined with the chemical inertness of C−F bonds make fluorine substitution a powerful tool for medicinal chemistry studies.[6] Special attention has been paid to the *gem*-difluoromethylene group ($CF_2$) because many compounds with this structure exhibit extraordinary biological activities and potential pharmaceutical applications.[7] With a long-term interest in the development of site-specific fluorine substitution methodologies and synthesis of fluorinated bioactive compounds, we intended to introduce *gem*-difluoromethylene group ($CF_2$), a strong electron-withdrawing group, to α,*β*-unsaturated *δ*-lactones **A** at the *γ*-position (Figure 1). Thus, the conjugated double bond of resulting **B** would be much more electron deficient than that of **A**, making it a better candidate to enhance the reactivity of the conjugated double bond as a Michael acceptor with minimum steric change.

Although there are a few reports concerning the difluoromethylenated lactones or closely related compounds in the literature,[8] it is still desirable to develop new facile synthetic methodologies to prepare such difluoromethylenated lactone **B**. Recently, we also developed an efficient procedure to synthesize *γ*,*γ*-*gem*-difluoromethylenated α,*β*-unsaturated *δ*-lactone **B** using ring-closing metathesis (RCM) reaction as the key step (Scheme 1).[9] We attempted to apply this methodology to the synthesis of *gem*-difluoromethylenated goniothalamin **1**, a representative natural α,*β*-unsaturated *δ*-lactone displaying cytotoxic activity against various cancerous cell lines.[2] Accordingly, indium-mediated allylation of cinnamaldehyde with 3-bromo-3,3-difluoropropene[10] followed by acryloylation of the resulting alcohol **2** afforded acryloyl ester **3** in good yield (Scheme 2). Although the RCM reaction has been employed to construct goniothalamin successfully,[11] the RCM reaction of acryloyl ester **3** under the same reaction conditions shown in

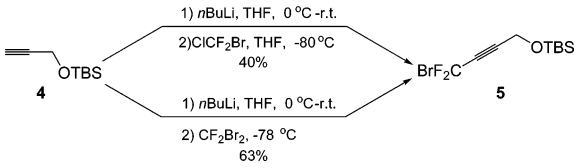
**SCHEME 2**



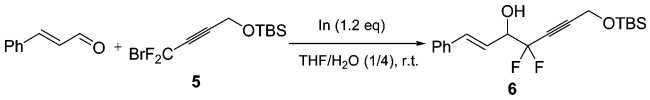

**SCHEME 3**



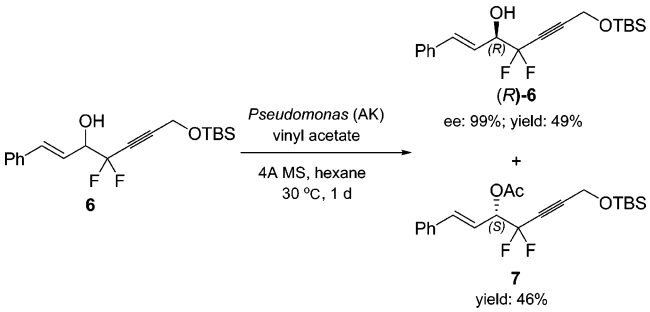

**SCHEME 4**




**SCHEME 5**




**SCHEME 6**




Scheme 1 failed to give the expected compound **1**. It may be that the electron-rich double bond next to phenyl was more reactive under RCM reaction conditions than the other electron-deficient terminal doubles. In addition, because of the strictly anhydrous and oxygen-free conditions of RCM reaction and the high cost of Grubbs' II catalyst, we were eager to explore new approaches for the synthesis of *γ*,*γ*-*gem*-difluoromethylenated α,*β*-unsaturated *δ*-lactones.

## Results and Discussion

A new strategy to *γ*,*γ*-*gem*-difluoromethylenated α,*β*-unsaturated *δ*-lactone **B** was outlined in Scheme 3. Lactone **B** could be obtained from the corresponding 1,5-diol **C** via an oxidation-lactone formation. Compound **C** could be prepared from homopropargyl alcohol **D** via selective hydrogenation. The reaction of aldehyde with fluorine-containing building block **5** should provide the intermediate **D**.

(6) (a) Ojima, I. *ChemBioChem* **2004**, *5*, 628−635. (b) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643. (c) Strunecká, A.; Patoèka, J.; Connett, P. *J. Appl. Biomed.* **2004**, *2*, 141−150.

(7) (a) Percy, J. M. *Chim. Oggi.* **2004**, *22*, 18−20. (b) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683.

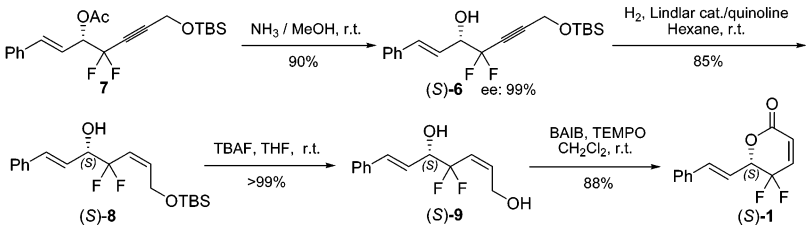
(8) For examples see: (a) Chupp, J. P.; Molyneaux, J. M. *J. Heterocycl. Chem.* **1989**, *26*, 1771−1780. Hu, Q.-S.; Hu, C.-M. *J. Fluorine Chem.* **1997**, *83*, 87−88. (c) Peng, W.; Zhu, S. *Tetrahedron* **2003**, *59*, 4395−4404.

(9) You, Z.-W.; Wu, Y.-Y.; Qing, F.-L. *Tetrahedron Lett.* **2004**, *45*, 9479−9481.

(10) Kirihara, M.; Takuwa., T.; Takizawa, S.; Momose, T.; Nemoto, H. *Tetrahedron* **2000**, *56*, 8275−8280.

(11) (a) Gruttadauria, M.; Meo, P. L.; Noto, R. *Tetrahedron Lett.* **2004**, *45*, 83−85. (b) Sundby, E.; Anthonsen, T.; Hansen, T. V. et al. *Tetrahedron* **2004**, *60*, 521−524.

**SCHEME 7**



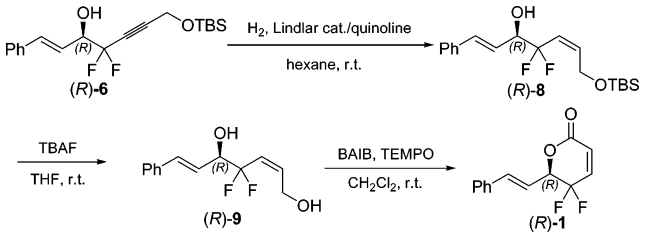

Fried and co-workers had reported the preparation of compound **5** in 40% yield from the reaction of lithium acetylide with $ClCF_2Br$ (Scheme 4).[12] We found that the yield could be improved to 63% when $CF_2Br_2$ was used instead of $ClCF_2Br$. Compound **5** could be prepared in 40 g scale with this procedure.

We then explored the synthesis of *gem*-difluoromethylenated goniothalamin **1** starting from the *gem*-difluoropropargylation of cinnamaldehyde with compound **5**. Several years ago, Hammond and co-workers described that treatment of triisopropylsilyldifluorobromopropyne (TIPS−C≡C−$CF_2Br$) with indium and carbonyl electrophile in THF/$H_2O$ (1:4) at room temperature gave only propargyl-containing products.[13] We were pleased to find that the reaction of cinnamaldehyde with **5** in the presence of indium under Hammond's reaction conditions provided the expected compound **6** in 85% yield (Scheme 5).

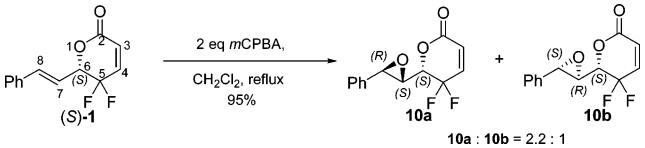
With racemic *gem*-difluoromethylenated propargyl alcohol **6** in hand, the resolution of racemic **6** into optically active alcohols was investigated. The resolution of racemic alcohols through lipase-catalyzed transesterification is a widely used methodology and has been successfully applied to *gem*-difluoromethylenated alcohols.[14] As the resolution of homopropargylic alcohols mediated by lipase from *Pseudomonas* (AK) was highly enantioselective,[15] we first examined *Pseudomonas* (AK) for its ability to mediate the transesterification of racemic **6**. Delightfully, the acylation of **6** with vinyl acetate in the presence of 0.5 mass equiv of *Pseudomonas* (AK) and 4 Å molecular sieves in hexane at 30 °C afforded (*R*)-**6** in 99% ee and 49% yield, and compound **7** was isolated in 46% yield (Scheme 6). The absolute configurations of compounds (*R*)-**6** and **7** were determined by X-ray crystal structure of compound **10b**.

Deacylation of **7** with LiOH or $K_2CO_3$ led to partial defluorination, and only a small amount of expected (*S*)-**6** was isolated (Scheme 7). Fortunately, treatment of **7** with $NH_3$/MeOH gave (*S*)-**6** in 90% yield and 99% ee. Initial attempts to hydrogenate the triple bond of (*S*)-**6** to cis double bond in the presence of Lindlar catalyst were not successful, leading to a complex inseparable mixture. Interestingly, the selective hydrogenation proceeded smoothly in the presence of both Lindlar catalyst and quinoline to provide the expected product (*S*)-**8** in 85% yield. Deprotection of (*S*)-**8** with *n*-$Bu_4NF$ (TBAF) gave

**SCHEME 8**




**SCHEME 9**




cyclization precursor (*S*)-**9** in quantitative yield. Recently, Forsyth and co-workers described the oxidation of 1,5-diols to δ-lactones with catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and excess bis-acetoxyiodobenzene (BAIB).[16] Accordingly, treatment of (*S*)-**9** with 0.2 equiv of TEMPO and 3 equiv of BAIB in $CH_2Cl_2$ at room temperature afforded the target molecule (*S*)-**1** in 88% yield.

In the same way, *gem*-difluoromethylenated (−)-goniothalamin (*R*)-**1** was also synthesized from (*R*)-**6** in 68% yield over three steps without isolation of the intermediates (*R*)-**8** and (*R*)-**9** (Scheme 8).

To evaluate the potential ability of **1** for further synthetic transformation and to determine the absolute configuration of **1**, epoxidation of (*S*)-**1** was carried out. Reaction of (*S*)-**1** with *m*-chloroperoxybenzoic acid (2.0 equiv) in $CH_2Cl_2$ under reflux afforded *gem*-difluoromethylenated goniothalamin epoxides **10a** and **10b** in the ratio of 2.2:1 (determinated by $^{19}F$ NMR before column chromatography) in 95% yield (Scheme 9).[17] The optical rotation and NMR spectra of **10b** were the same as we reported previously.[18] The absolute configuration of **10b** was determined by the X-ray crystallographic analysis.[18] Therefore, compound **10b** was assigned the 6*S*, 7*R*, 8*S* configuration as shown in Scheme 8 and the absolute configuration of **1** was further confirmed.

To demonstrate the efficiency and viability of our developed methodology, the synthesis of a series of *gem*-difluoromethylenated α,β-unsaturated δ-lactones was then carried out. As shown in Table 1, *gem*-difluoropropargylation reaction of

(12) (a) Kwok, P.-Y.; Muellner, F. W.; Chen, C.-K.; Fried, J. *J. Am. Chem. Soc.* **1987**, *109*, 3684−3692. (b) Rim, I.; Cantacuzene, D.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1063.

(13) Wang, Z. G.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547−6552.

(14) For related exmaples see: (a) Itoh, T.; Kudo, K.; Tanaka, N.; Sakabe, K.; Takagi, Y.; Kihara, H. *Tetrahedron Lett.* **2000**, *41*, 4591−4595. (b) Kirihara, M.; Kawasaki, M.; Katsumata, H.; Kakuda, H.; Shiro, M.; Kawabata, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2283−2289. (c) Itoh, T.; Kudo, K.; Yokota, K.; Tanaka, N.; Hayase, S.; Renou, M. *Eur. J. Org. Chem.* **2004**, 406−412. (d) Kaneda, T.; Komura, S.; Kitazume, T. *J. Fluorine Chem.* **2005**, *126*, 17−26.

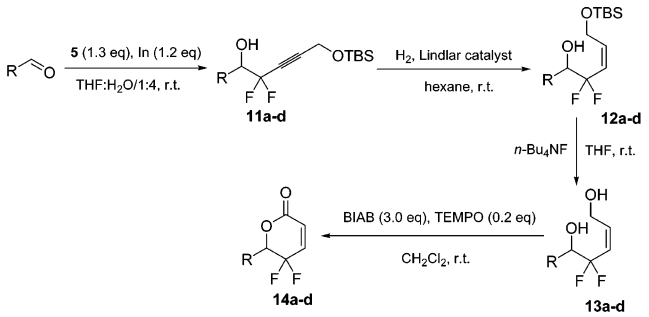
(15) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129−6139.

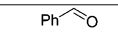
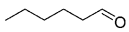
(16) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57−59.

(17) (a) Goh, S. H.; Ee, G. C. L.; Chuah, C. H.; Wei, C. *Aust. J. Chem.* **1995**, *48*, 199−205. (b) Peng, X.; Li, A.; Shen, H.; Wu, T.; Pan, X. *J. Chem. Res. Synop.* **2002**, 330−332. (c) Lan, Y.-H.; Chang, F.-R.; Yu, J.-H.; Yang, Y.-L.; Chang, Y.-L.; Lee, S.-J.; Wu, Y.-C. *J. Nat. Prod.* **2003**, *66*, 487−490.

(18) You, Z.-W.; Zhang, X.-G.; Qing, F.-L. *Synthesis*, **2006**, 2533−2542.

**TABLE 1. Synthesis of *gem*-Difluoromethylenated α,β-Unsaturated δ-Lactones 14a−d**




| Entry | Aldehyde | **11** (Yield) | **12** (Yield) | **13** (Yield) | **14** (Yield) |
|---|---|---|---|---|---|
| 1 |  | **11a** (83%) | **12a** (>99%) | **13a** (94%) | **14a** (92%) |
| 2 |  | **11b** (80%) | **12b** (>99%) | **13b** (95%) | **14b** (96%) |
| 3 |  | **11c** (74%) | **12c** (96%) | **13c** (90%) | **14c** (82%) |
| 4 |  | **11d** (77%) | **12d** (92%) | **13d** (88%) | **14d** (85%) |

aldehydes (including aliphatic, aromatic, α,β-unsaturated, and sterically hindered aldehydes) afforded the corresponding alcohols **11** in good yields. It is noteworthy that quinoline was not required in the selective hydrogenation of compounds **11** and the over-reduction could be avoided by carefully monitoring the reaction mixture by $^{19}$F NMR.[19] Removal of the TBDMS protective group of **12** with TBAF followed by oxidative-lactone formation in the presence of BAIB and TEMPO gave the desired *gem*-difluoromethylenated α,β-unsaturated δ-lactones **14** in excellent yields.

## Conclusion

An efficient and general strategy to *gem*-difluoromethylenated α,β-unsaturated δ-lactones from various aldehydes under mild conditions in high yield was developed. This new approach had entirely overcome the shortcomings of the early one to construct the fluorinated unsaturated lactone structure unit via RCM reaction. All the reactions were carried out at room temperature and were insensitive to moisture and atmosphere. Furthermore, the last three steps could be performed in sequence without isolation of the intermediates. Using this strategy combined with lipase-catalyzed enantioselective acylation, *gem*-difluoromethylenated goniothalamin (*S*)-**1** and (*R*)-**1** were readily stereoselectively prepared in high enantiomer purity (99% ee) and good yield, where the RCM reaction sequences were troublesome. The generality and effectiveness of the strategy to construct *gem*-difluoromethylenated δ-lactones were well demonstrated by successful synthesis of various δ-substitution δ-lactones **14a−d** from corresponding aldehydes in high yield (52−73% over four steps).

## Experimental Section

$^{19}$F NMR spectra were reported in ppm relative to $FCCl_3$ as outside standard and low field as positive.

**(*E*)-4,4-Difluoro-1-phenylhexa-1,5-dien-3-ol (2).** To a suspension of cinnamaldehyde (2.74 g, 20.7 mmol) and indium powder (3.57 g, 31.1 mmol) in $H_2O$ (200 mL) was added 3-bromo-3,3-difluoropropene (4.88 g, 31.1 mmol) at room temperature. After stirring for 16 h, the reaction mixture was quenched with 1 M HCl aqueous solution (20 mL) and was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 5:1) to afford **2** (3.29 g, 76% yield) as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.25−7.42 (m, 5H), 6.76 (d, $J$ = 15.9 Hz, 1H), 6.19 (dd, $J$ = 16.1, 6.5 Hz, 1H), 6.00 (ddd, $J$ = 23.1, 17.4, 11.1 Hz, 1H), 5.70−5.78 (m, 1H), 5.55 (d, $J$ = 11.1 Hz, 1H), 4.45−4.55 (m, 1H), 2.28 (d, $J$ = 4.2 Hz, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ −108.7 (dt, $J$ = 248.0, 10.1 Hz, 1F), −110.7 (dt, $J$ = 249.3, 10.3 Hz, 1F).

**(*E*)-4,4-Difluoro-1-phenylhexa-1,5-dien-3-yl acrylate (3).** A solution of fresh-distilled acryloyl chloride (0.23 mL, 2.8 mmol) in dry $CH_2Cl_2$ (2 mL) was added dropwise to a solution of **2** (199 mg, 0.95 mmol), triethylamine (0.40 mL, 2.8 mmol), and DMAP (12 mg, 1 mol %) in dry $CH_2Cl_2$ (5 mL) at −15 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and was stirred for 2 h. Then, the mixture was quenched with a saturated solution of $NaHCO_3$ and was extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 20:1) to afford **3** (188 mg, 75% yield) as a yellowish oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.27−7.42 (m, 5H), 6.78 (d, $J$ = 15.9 Hz, 1H), 6.50 (dd, $J$ = 17.3, 1.4 Hz, 1H), 6.19 (dd, $J$ = 17.4, 10.5 Hz, 1H), 6.14 (d, $J$ = 7.2 Hz, 1H), 5.93 (dd, $J$ = 10.5, 1.2 Hz, 1H), 5.89−6.06 (m, 1H), 5.77−5.80 (m, 1H), 5.71−5.74 (m, 1H), 5.56 (d, $J$ = 10.8 Hz, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ −106.5 (dt, $J$ = 249.4, 9.4 Hz, 1F), −110.1 (dt, $J$ = 250.8, 11.4 Hz, 1F); IR (thin film) $\upsilon_{max}$ 3031, 2962, 1735, 1654, 1635, 1580, 1498, 1451, 1406, 1261, 1178 cm$^{-1}$; MS (ESI): $m/z$ = 282.1 $[M + NH_4]^+$, 287.1 $[M + Na]^+$; Anal. Calcd for $C_{15}H_{14}F_2O_2$: C, 68.17; H, 5.34. Found: C, 68.25, H, 5.20.

***tert*-Butyldimethyl(prop-2-ynyloxy)silane (4).** To a solution of fresh-distilled propargyl alcohol (56.2 g, 1.0 mol), imidazole (75.1 g, 1.1 mol) and DMAP (1.22 g, 1 mol %) in DMF (400 mL) was added TBSCl (159 g, 1.1 mol) at room temperature. After stirring for 17 h, the reaction mixture was quenched with water and was filtered through Celite, and the filter cake was washed with $Et_2O$. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. Vacuum distillation (25 Torr) provided **4** (160 g, 94% yield) as a colorless liquid (57−63 °C): $^1$H NMR (300 MHz, $CDCl_3$) δ 4.31 (d, $J$ = 2.4 Hz, 2H), 2.39 (t, $J$ = 2.4 Hz, 1H), 0.91 (s, 9H), 0.13 (s, 6H).

**(4-Bromo-4,4-difluorobut-2-ynyloxy)(*tert*-butyl)dimethylsilane (5).** To a solution of **4** (23.1 g, 0.14 mol) in dry THF (380 mL) was added BuLi (93 mL, 1.6 M solution in hexane) dropwise over 1 h at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 h before being cooled to −78 °C. Then, $CF_2Br_2$ (85.4 g, 0.41 mol) was added. After stirring for 2.5 h at −78 °C, the reaction mixture was quenched with a saturated solution of $NH_4Cl$ and was extracted with petroleum ether. The combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. Vacuum distillation (1 Torr) provided **5** (25.7 g, 63% yield) as a yellow liquid (55−59 °C): $^1$H NMR (300 MHz, $CDCl_3$) δ 4.45 (t, $J$ = 4.1 Hz, 2H), 0.92 (s, 9H), 0.14 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) δ −32.6 (t, $J$ = 4.1 Hz, 2F).

**(*E*)-7-(*tert*-Butyldimethylsilyloxy)-4,4-difluoro-1-phenylhept-1-en-5-yn-3-ol ((±)-6).** To a stirred suspension of cinnamaldehyde (2.99 g, 22.6 mmol) and **5** (8.81 g, 29.4 mmol) in $H_2O$/THF (70 mL, 4/1, v/v) was added indium power (3.12 g, 27.2 mmol) at room temperature. After stirring for 22 h, the reaction mixture was quenched with a saturated solution of $NH_4Cl$ and was filtered through Celite, and the filter cake was washed with ethyl acetate.

(19) Manthati, V. L.; Gree, D.; Gree, R. *Eur. J. Org. Chem.* **2005**, 3825−3829.

The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 10:1) to afford ±±)-**6** (6.80 g, 85%) as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.38−7.42 (m, 2H), 7.24−7.35 (m, 3H), 6.82 (d, $J$ = 15.9 Hz, 1H), 6.24 (dd, $J$ = 16.1, 6.5 Hz, 1H), 4.48−4.58 (m, 1H), 4.38 (t, $J$ = 4.5 Hz, 2H); 2.84 (br s, 1H), 0.88 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 135.9, 135.4, 128.6, 128.4, 126.9, 122.3 (t, $J$ = 3.1 Hz), 113.4 (t, $J$ = 238.4 Hz), 88.4 (t, $J$ = 6.8 Hz), 75.6 (t, $J$ = 39.7 Hz), 75.1 (t, $J$ = 29.3 Hz), 51.3 (t, $J$ = 2.0 Hz), 25.7, 18.2, −5.2; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −94.9 to −95.0 (m, 2F); IR (thin film) $\upsilon_{max}$ 3417, 3030, 2957, 2932, 2860, 2258, 1656, 1579, 1498, 1473, 1465, 1257, 1106 cm$^{-1}$; MS (ESI): $m/z$ = 370.2 [M + $NH_4$]$^+$, 375.2 [M + Na]$^+$; HRMS (MALDI): $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{26}F_2NaO_2Si$: 375.1562; found: 375.1574.

**(*R*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-4,4-difluoro-1-phenylhept-1-en-5-yn-3-ol ((*R*)-6) and (*S*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-4,4-difluoro-1-phenylhept-1-en-5-yn-3-yl acetate (7).** To a solution of alcohol (±)-**6** (6.87 g, 19.5 mmol) and vinyl acetate (8.74 mL, 94.6 mmol) in hexane (240 mL) was added the lipase (3.44 g, 0.5 mass equiv), activated 4 Å molecular sieves (3.44 g, 0.5 mass equiv) at room temperature. After stirring for 24 h at 30 °C, the reaction mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 20:1) to afford (*R*)-**6** (3.37 g, 49% yield, 99% ee) and compound **7** (3.57 g, 46%) both as yellow oils. Compound (*R*)-**6**: Chiral HPLC (Chiralcel AD-H, 10% 2-propanol in hexane, 250 × 4.6 mm, 254 nm, 0.7 mL/min), $t_R$ = 9.24 min (minor), $t_R$ = 10.95 min (major); $[\alpha]^{26}_D$ = −13.6 (*c* 1.79, $CHCl_3$). Compound **7**: $[\alpha]^{26}_D$ = +71.1 (*c* 1.68, EtOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.43−7.45 (m, 2H), 7.27−7.39 (m, 3H), 6.85 (d, $J$ = 15.9 Hz, 1H), 6.20 (dd, $J$ = 15.9, 7.5 Hz, 1H), 5.78 (dd, $J$ = 17.3, 8.6 Hz, 1H), 4.42 (t, $J$ = 4.5 Hz, 2H), 2.18 (s, 3H), 0.93 (s, 9H), 0.14 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 169.1, 137.9, 135.5, 128.8, 128.7, 127.0, 119.0, 111.6 (t, $J$ = 237.9 Hz), 88.4 (t, $J$ = 6.7 Hz), 75.5 (t, $J$ = 39.3 Hz), 74.7 (t, $J$ = 31.0 Hz), 51.2, 25.7, 20.8, 18.2, −5.2; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −93.4 to −93.5 (m, 2F); IR (thin film) $\upsilon_{max}$ 3031, 2958, 2860, 2257, 1757, 1655, 1580, 1498, 1473, 1225, 1106 cm$^{-1}$; MS (ESI): $m/z$ = 412.1 [M + $NH_4$]$^+$, 417.1 [M + Na]$^+$; HRMS (MALDI): $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{28}F_2NaO_3Si$: 417.1668; found: 417.1674.

**(*S*,*E*)-7-(*tert*-Butyldimethylsilyloxy)-4,4-difluoro-1-phenylhept-1-en-5-yn-3-ol ((*S*)-6).** A saturated solution of $NH_3$ in MeOH (35 mL) was added to **7** (2.79 g, 7.1 mmol) at room temperature. After stirring for 4 h, the reaction mixture was concentrated carefully by rotary evaporation under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to afford (*S*)-**6** (2.24 g, 90%, 99% ee (determined by HPLC)) as a yellow oil: $[\alpha]^{21}_D$ = +12.6 (*c* 1.11, $CHCl_3$).

**(*S*,1*E*,5*Z*)-7-(*tert*-Butyldimethylsilyloxy)-4,4-difluoro-1-phenylhepta-1,5-dien-3-ol ((*S*)-8).** To a solution of (*S*)-**6** (1.24 g, 3.5 mmol) in hexane (35 mL) was added Lindlar catalyst (201 mg) and quinoline (194 mg) at room temperature. The suspension was stirred for 2 h before hydrogenation. After stirring for another 2.5 h under hydrogen atmosphere, $^{19}$F NMR indicated the absence of starting material (*S*)-**6.** The reaction mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 20:1) to afford (*S*)-**8** (1.06 g, 85%) as a yellow oil: $[\alpha]^{25}_D$ = −8.75 (*c* 2.17, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.26−7.43 (m, 5H), 6.80 (d, $J$ = 15.9 Hz, 1H), 6.21 (dd, $J$ = 15.9, 6.3 Hz, 1H), 5.97−6.07 (m, 1H), 5.48−5.64 (m, 1H), 4.44−4.55 (m, 3H), 2.47 (br s, 1H), 0.91 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 140.8 (t, $J$ = 4.4 Hz), 136.1, 134.7, 128.6, 128.3, 126.8, 123.2 (dd, $J$ = 4.4, 2.9 Hz), 120.6 (t, $J$ = 244.9 Hz), 120.2 (t, $J$ = 26.1 Hz), 74.7 (t, $J$ = 30.0 Hz), 60.0 (t, $J$ = 3.7 Hz), 25.9, 18.3, −5.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −101.5 to −102.5 (m, 1F), −103.1 to −104.1 (m, 1F); IR (thin film) $\upsilon_{max}$ 3396, 3031, 2931, 2859, 1664, 1473, 1257, 1098 cm$^{-1}$; MS (ESI): $m/z$ = 377.2 [M + Na]$^+$; HRMS (MALDI): $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{28}F_2NaO_2Si$: 377.1719; found: 377.1733.

**(*S*,2*Z*,6*E*)-4,4-Difluoro-7-phenylhepta-2,6-diene-1,5-diol ((*S*)-9).** A solution of TBAF in THF (1 M, 1.8 mL) was added to a solution of (*S*)-**8** (570 mg, 1.6 mmol) in THF (10 mL). After stirring for 12 h, the reaction mixture was concentrated and purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 1:1) to afford (*S*)-**9** (386 mg, quantitive yield) as a colorless oil: $[\alpha]^{25}_D$ = +21.6 (*c* 2.42, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.23−7.39 (m, 5H), 6.75 (d, $J$ = 16.5 Hz, 1H), 6.18 (dd, $J$ = 15.9, 6.3 Hz, 1H), 6.00−6.09 (m, 1H), 5.51−5.65 (m, 1H), 4.48 (dd, $J$ = 15.6, 9.3 Hz, 1H), 4.29−4.39 (m, 2H), 3.01 (br s, 2H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 138.6 (t, $J$ = 4.9 Hz), 135.9, 134.7, 128.7, 128.4, 126.8, 123.1 (dd, $J$ = 4.9, 1.9 Hz), 122.4 (t, $J$ = 25.9 Hz), 120.6 (t, $J$ = 245.1 Hz), 74.4 (t, $J$ = 31.0 Hz), 58.9 (t, $J$ = 3.6 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −100.7 (ddd, $J$ = 254.6, 13.7, 10.3 Hz, 1F), −102.9 (ddd, $J$ = 253.5, 13.5, 11.3 Hz, 1F); IR (thin film) $\upsilon_{max}$ 3356, 3030, 2885, 1660, 1600, 1496, 1450, 1029 cm$^{-1}$; MS (ESI): $m/z$ = 258.2 [M + $NH_4$]$^+$, 263.1 [M + Na]$^+$, 279.2 [M + K]$^+$; HRMS (MALDI): $m/z$ [M + Na]$^+$ calcd for $C_{13}H_{14}F_2NaO_2$: 263.0854; found: 263.0861.

**(*S*,*Z*)-5,5-Difluoro-6-styryl-5,6-dihydropyran-2-one ((*S*)-1).** To a solution of (*S*)-**9** (321 mg, 1.3 mmol) in $CH_2Cl_2$ (14 mL) was added bis-acetoxyiodobenzene (1.29 g, 4.0 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (42 mg, 20 mol %) at room temperature. After stirring for 3 h, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and was extracted with $CH_2Cl_2$. The combined organic extracts were washed with saturated solutions of $NaHCO_3$, $NH_4Cl$, and brine; dried over anhydrous $Na_2SO_4$; filtered; and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to afford (*S*)-**1** (278 mg, 88%) as a white solid: Mp = 90−92 °C; $[\alpha]^{24}_D$ = +111.7 (*c* 0.980, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.43−7.46 (m, 2H), 7.29−7.39 (m, 3H), 6.90 (d, $J$ = 15.6 Hz, 1H), 6.82−6.89 (m, 1H), 6.35 (d, $J$ = 9.9 Hz, 1H), 6.26 (dd, $J$ = 15.9, 6.9 Hz, 1H), 5.12−5.22 (m, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 160.2 (t, $J$ = 2.5 Hz), 137.9, 137.8 (t, $J$ = 29.4 Hz), 135.2, 129.0, 128.8, 127.1, 126.6 (t, $J$ = 9.1 Hz), 117.1 (t, $J$ = 2.5 Hz), 112.1 (t, $J$ = 241.9 Hz), 80.2 (t, $J$ = 30.2 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −106.6 to −108.8 (m, 2F); IR (KBr) $\upsilon_{max}$ 3065, 2920, 2852, 1742, 1645, 1452, 1106 cm$^{-1}$; MS (ESI): $m/z$ = 254.1 [M + $NH_4$]$^+$, 259.1 [M + Na]$^+$; HRMS (EI): $m/z$ M$^+$ calcd for $C_{13}H_{10}F_2O_2$: 236.0649; found: 236.0647.

**(*R*,*Z*)-5,5-Difluoro-6-styryl-5,6-dihydropyran-2-one ((*R*)-1).** To a solution of (*R*)-**6** (278 mg, 0.79 mmol) in hexane (8 mL) was added Lindlar catalyst (45 mg) and quinoline (43 mg) at room temperature. The suspension was stirred for 2 h before hydrogenation. After stirring for another 3 h under hydrogen atmosphere, $^{19}$F NMR indicated the absence of starting material (*R*)-**6**. The reaction mixture was filtered; washed with 1 M HCl, saturated $NaHCO_3$, and brine; dried over anhydrous $Na_2SO_4$; and concentrated to afford crude (*R*)-**8** as a yellow oil. The crude (*R*)-**8** was dissolved in THF (4 mL) followed by treatment with a solution of TBAF in THF (1 M, 0.87 mL) at room temperature. After stirring for 12 h, the solvent was removed under reduced pressure. The resulting oil was dissolved in ethyl acetate, washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated to afford crude (*R*)-**9** as a yellow oil. The crude (*R*)-**9** was dissolved in $CH_2Cl_2$ (8 mL), followed by treatment with bis-acetoxyiodobenzene (760 mg, 2.4 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (25 mg, 20 mol %) at room temperature. After stirring for 3 h, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ and was extracted with $CH_2Cl_2$. The combined organic extracts were washed with saturated $NaHCO_3$, $NH_4Cl$, and brine; dried over anhydrous $Na_2SO_4$; filtered; and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 10:

1) to afford (*R*)-**1** (126 mg, 68% for three steps) as a white solid: Mp = 89−91 °C; $[\alpha]^{22}_D = -108.2$ (*c* 2.00, $CHCl_3$).

**(*S*)-5,5-Difluoro-6-((2*S*,3*R*)-3-phenyloxiran-2-yl)-5,6-dihydropyran-2-one (10a) and (*S*)-5,5-Difluoro-6-((2*R*,3*S*)-3-phenyloxiran-2-yl)-5,6-dihydropyran-2-one (10b).** To a solution of (*S*)-1 (214 mg, 0.91 mmol) in $CH_2Cl_2$ (4.5 mL) was added *m*-CPBA (313 mg, 1.8 mmol) at room temperature. After stirring at reflux for 20 h, the reaction mixture was quenched with 5% $Na_2S_2O_3$ solution and was extracted with $CH_2Cl_2$. The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to afford **10a** (132 mg) and **10b** (65 mg) in 95% total yield as both white solids. Compound **10a**: $[\alpha]^{22}_D = +122.6$ (*c* 1.37, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.29−7.41 (m, 5H), 6.88 (ddd, *J* = 10.3, 8.0, 2.3 Hz, 1H), 6.35 (dd, *J* = 10.2 Hz, 1H), 4.58 (dt, *J* = 18.9, 5.1 Hz, 1H), 4.07 (d, *J* = 1.5 Hz, 1H), 3.47 (dd, *J* = 5.1, 1.8 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 159.2 (t, *J* = 2.3 Hz), 137.6 (dd, *J* = 32.1, 25.4 Hz), 135.2, 128.9 (t, *J* = 20.1 Hz), 128.7 (t, *J* = 19.9 Hz), 126.6 (dd, *J* = 10.1, 8.2 Hz), 125.8 (t, *J* = 19.9 Hz), 112.2 (dd, *J* = 245.8, 240.2 Hz), 78.0 (dd, *J* = 31.9, 28.0 Hz), 56.5 (d, *J* = 4.5 Hz), 55.5; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −106.6 (dd, *J* = 292.0, 18.5 Hz, 1F), −110.0 (dt, *J* = 291.0, 6.7 Hz, 1F). Compound **10b**: $[\alpha]^{26}_D = -123.0$ (*c* 0.895, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.34−7.42 (m, 3H), 7.26−7.30 (m, 2H), 6.79 (dddd, *J* = 10.2, 6.4, 3.8, 1.3 Hz, 1H), 6.38 (d, *J* = 10.2 Hz, 1H), 4.83−4.90 (m, 1H), 4.01 (d, *J* = 2.1 Hz, 1H), 3.42 (dd, *J* = 4.6, 2.3 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 159.0 (t, *J* = 2.2 Hz), 135.5 (dd, *J* = 30.8, 26.8 Hz), 134.9, 129.0 (t, *J* = 20.0 Hz), 128.7 (t, *J* = 19.9 Hz), 127.5 (t, *J* = 10.0 Hz), 125.8 (t, *J* = 20.5 Hz), 112.5 (dd, *J* = 242.7, 241.4 Hz), 76.9 (dd, *J* = 31.4, 28.0 Hz), 57.3 (t, *J* = 5.2 Hz), 54.1; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −92.6 (ddd, *J* = 291.4, 9.7, 3.2 Hz, 1F), −110.6 (ddt, *J* = 291.3, 6.2, 2.4 Hz, 1F).

Compounds **11a**−**d** were prepared from corresponding aldehydes using the same procedure of preparation of alcohol (±)-**6**.

**5-(*tert*-Butyldimethylsilyloxy)-2,2-difluoro-1-phenylpent-3-yn-1-ol (11a).** Colorless oil (205 mg, 83%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.48−7.51 (m, 2H), 7.35−7.45 (m, 3H), 4.93 (t, *J* = 8.9 Hz, 1H), 4.34 (t, *J* = 4.5 Hz, 2H), 2.43 (br s, 1H), 0.88 (s, 9H), 0.07 (s, 6H);$^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 135.4, 129.0. 128.2, 127.9, 113.6 (t, *J* = 238.1 Hz), 88.8 (t, *J* = 13.4 Hz), 76.3 (t, *J* = 58.4), 75.7 (t, *J* = 75.7 Hz), 51.2 (t, *J* = 2.0 Hz), 25.7, 18.2, −5.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −94.2 to −94.3 (m, 2F); IR (thin film) $\upsilon_{max}$ 3396, 3038, 2932, 2860, 2258, 1496, 1473, 1456, 1199, 1062, 781, 701 cm$^{-1}$; MS (ESI): *m*/*z* = 344.1 $[M + NH_4]^+$; HRMS (EI): *m*/*z* $[M^+ - HF]$ calcd for $C_{17}H_{23}FO_2Si$: 306.1451; found: 306.1461.

**5-(*tert*-Butyldimethylsilyloxy)-1-(2,6-dichlorophenyl)-2,2-difluoropent-3-yn-1-ol (11b).** Colorless oil (715 mg, 80%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.16−7.39 (m, 3H), 5.75−5.87 (m, 1H), 4.36 (t, *J* = 4.5 Hz, 2H), 4.08 (d, *J* = 12.9 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 137.2, 134.4, 130.4, 130.3, 129.0, 113.0 (t, *J* = 241.3 Hz), 88.5 (t, *J* = 6.3 Hz), 75.9 (t, *J* = 38.6 Hz), 74.8 (t, *J* = 29.5 Hz), 51.3 (t, *J* = 1.9 Hz). 25.7 (t, *J* = 20.2 Hz), 18.2, −5.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −90.3 to −91.4 (m, 1F), −91.6 to −92.6 (m, 1F); IR (thin film) $\upsilon_{max}$ 3568, 3455, 3081, 2957, 2931, 2257, 1582, 1564, 1473, 1438, 1101 cm$^{-1}$; MS (ESI): *m*/*z* = 395.2 $[M + H]^+$, 412.1 $[M + NH_4]^+$, 417.1 $[M + Na]^+$; HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}Cl_2F_2NaO_2Si$: 417.0626; found: 417.0628.

**(*E*)-8-(*tert*-Butyldimethylsilyloxy)-5,5-difluorooct-2-en-6-yn-4-ol (11c).** Yellowish oil (630 mg, 74%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.87−5.99 (m, 1H), 5.50−5.58 (m, 1H), 4.38 (t, *J* = 4.4 Hz, 2H), 4.24−4.30 (m, 1H), 2.73 (d, *J* = 3.9 Hz, 1H), 1.74−1.76 (m, 3H), 0.89 (s, 9H), 0.11 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 132.8, 124.8 (t, *J* = 2.9 Hz), 113.4 (t, *J* = 237.3 Hz), 88.0 (t, *J* = 6.6 Hz), 75.8 (t, *J* = 39.3 Hz), 75.0 (t, *J* = 29.7 Hz), 51.3 (t, *J* = 2.1 Hz), 25.7, 18.2, 17.9, −5.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −94.9 to −95.9 (m, 1F), −96.0 to −97.0 (m, 1F); IR (thin film) $\upsilon_{max}$ 3426, 3039, 2933, 2860, 2259, 1677, 1473, 1257, 1103 cm$^{-1}$; MS (ESI): *m*/*z* = 308.1 $[M + NH_4]^+$, 329.0 $[M + K]^+$; HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{24}F_2NaO_2Si$: 313.1406; found: 313.1404.

**1-(*tert*-Butyldimethylsilyloxy)-4,4-difluorodec-2-yn-5-ol (11d).** Colorless oil (670 mg, 77%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.40 (t, *J* = 4.4 Hz, 2H), 3.74−3.84 (m, 1H). 1.90 (s, 1H), 1.25−1.78 (m, 8H), 0.88−0.94 (m, 3H), 0.91 (s, 9H), 0.13 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 114.4 (t, *J* = 236.7 Hz), 87.8 (t, *J* = 6.4 Hz), 75.8 (t, *J* = 39.6 Hz), 74.2 (t, *J* = 28.0 Hz), 51.3 (t, *J* = 2.0 Hz), 31.5, 30.2 (t, *J* = 1.5 Hz), 25.7, 25.0, 22.5, 18.2, 14.0, −5.2; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −95.3 to −96.3 (m, 1F), −96.4 to −97.4 (m, 1F); IR (thin film) $\upsilon_{max}$ 3443, 2958, 2933, 2862, 2258, 1472, 1364, 1257, 1106 cm$^{-1}$; MS (ESI): *m*/*z* = 321.2 $[M + H]^+$, 338.4 $[M + NH_4]^+$, 343.3 $[M + Na]^+$; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{30}F_2NaO_2Si$: 343.1875; found: 343.1879.

**General Procedure for the Preparation of Compounds 12a−d.** To a solution of **11a** (145 mg, 0.44 mmol) in hexane (7 mL) was added Lindlar catalyst (19 mg) at room temperature. After stirring under hydrogen atmosphere for 21 h, the reaction mixture was filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to afford **12a** (146 mg, 100% yield).

**(*Z*)-5-(*tert*-Butyldimethylsilyloxy)-2,2-difluoro-1-phenylpent-3-en-1-ol (12a).** Colorless oil (146 mg, quantitive yield). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40−7.44 (m, 2H). 7.33−7.38 (m, 3H), 5.85−5.95 (m, 1H), 5.32−5.48 (m, 1H), 4.89 (td, *J* = 9.6, 3.6 Hz, 1H), 4.06−4.26 (m, 2H), 2.79 (br s, 1H), 0.87 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 140.8 (t, *J* = 4.8 Hz), 136.0 (t, *J* = 2.3 Hz), 128.8, 128.2, 127.6, 120.8 (t, *J* = 245.1 Hz), 119.8 (t, *J* = 26.8 Hz), 76.1 (t, *J* = 29.0 Hz), 59.7 (t, *J* = 3.9 Hz), 25.9, 18.2, −5.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −101.7 to −102.7 (m, 1F). −102.9 to −103.9 (m, 1F); IR (thin film) $\upsilon_{max}$ 3409, 3068, 3037, 2957, 2931, 2859, 1668, 1497, 1473, 1456, 1257, 1060 cm$^{-1}$; MS (ESI): *m*/*z* = 329.1 $[M + H]^+$; HRMS (MALDI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{26}F_2NaO_2Si$: 351.1562; found: 351.1568.

**(*Z*)-5-(*tert*-Butyldimethylsilyloxy)-1-(2,6-dichlorophenyl)-2,2-difluoropent-3-en-1-ol (12b).** Colorless oil (354 mg, quantitive yield). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.30 (t, *J* = 9.0 Hz, 2H), 7.15−7.21 (m, 1H), 5.86−5.95 (m, 1H), 5.46−5.68 (m, 2H), 4.17−4.45 (m, 2H), 3.94 (br s, 1H), 0.84 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 140.8 (t, *J* = 4.8 Hz), 136.9, 134.4, 130.9, 130.5, 130.1, 129.0, 120.9 (t, *J* = 247.9 Hz), 120.6 (t, *J* = 26.0 Hz), 74.2 (t, *J* = 30.1 Hz), 59.9 (t, *J* = 4.1 Hz), 25.9 (t, *J* = 19.6 Hz), 18.3, −5.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −100.5 to −100.7 (m, 2F); IR (thin film) $\upsilon_{max}$ 3450, 2957, 2931, 2859, 1564, 1438, 1256, 1097 cm$^{-1}$; MS (ESI): *m*/*z* = 397.1 $[M + H]^+$, 419.1 $[M + Na]^+$; HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{24}Cl_2F_2NaO_2Si$: 419.0783; found: 419.0782.

**(2*E*,6*Z*)-8-(*tert*-Butyldimethylsilyloxy)-5,5-difluorooocta-2,6-dien-4-ol (12c).** Colorless oil (246 mg, 96%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.84−6.02 (m, 2H), 5.41−5.57 (m, 2H), 4.40−4.45 (m, 2H), 4.19−4.28 (m, 1H), 2.24 (br s, 1H), 1.74−1.77 (m, 3H), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 140.5 (t, *J* = 4.7 Hz), 132.1, 125.3 (dd, *J* = 4.0, 2.4 Hz), 120.5 (t, *J* = 244.5 Hz), 120.2 (t, *J* = 25.9 Hz), 74.7 (dd, *J* = 30.7, 29.0 Hz), 60.1 (t, *J* = 3.9 Hz), 25.9, 18.3, 17.9, −5.3; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −102.8 to −103.8 (m, 1F), −104.3 to −105.3 (m, 1F); IR (thin film) $\upsilon_{max}$ 3418, 3039, 2958, 2932, 2860, 1668, 1475, 1464, 1257, 1095 cm$^{-1}$; MS (ESI): *m*/*z* = 293.2 $[M + H]^+$, 315.1 $[M + Na]^+$; HRMS (EI): *m*/*z* $[M^+ - CH_3C{\equiv}CH]$ calcd for $C_{11}H_{22}F_2O_2Si$: 252.1357; found: 252.1361.

**(*Z*)-1-(*tert*-Butyldimethylsilyloxy)-4,4-difluorodec-2-en-5-ol (12d).** Colorless oil (185 mg, 92%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.94−6.03 (m, 1H), 5.42−5.59 (m, 1H), 4.41−4.46 (m, 2H), 3.69−3.79 (m, 1H), 1.78 (br s, 1H), 1.26−1.59 (m, 8H), 0.88−0.92 (m, 3H), 0.90 (s, 9H), 0.08 (s, 6H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 140.4 (t, *J* = 4.9 Hz), 121.5 (t, *J* = 243.9 Hz), 120.3 (t,

$J$ = 26.7 Hz), 73.9 (t, $J$ = 29.2 Hz), 60.0 (t, $J$ = 3.9 Hz), 31.6, 29.9 (t, $J$ = 2.8 Hz), 25.9, 25.2, 22.5, 18.3, 14.0, −5.2; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −102.5 to −103.5 (m, 1F), −104.9 to −105.8 (m, 1F); IR (thin film) $\upsilon_{max}$ 3424, 2938, 2922, 2860, 1668, 1472, 1465, 1410, 1257, 1099 cm$^{-1}$; MS (ESI): $m/z$ = 323.2 $[M + H]^+$; HRMS (EI): $m/z$ $[M - H]^+$ calcd for $C_{16}H_{31}F_2O_2Si$: 321.2061; found: 321.2051.

Compounds **13a**−**d** were prepared from **12a**−**d** using the same procedure of preparation of compound (*S*)-**9**.

**(*Z*)-4,4-Difluoro-5-phenylpent-2-ene-1,5-diol (13a).** Colorless oil (88 mg, 94%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32−7.43 (m, 5H), 5.88−5.99 (m, 1H), 5.36−5.52 (m, 1H), 4.88 (t, $J$ = 9.3 Hz, 1H), 4.09−4.18 (m, 1H), 3.96−4.05 (m, 1H), 3.70 (br s, 1H), 2.18 (br s, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 138.4 (t, $J$ = 5.2 Hz), 136.1 (dd, $J$ = 4.5, 1.4 Hz), 128.8, 128.2, 127.7, 122.0 (t, $J$ = 26.7 Hz), 120.8 (t, $J$ = 245.8 Hz), 75.7 (t, $J$ = 30.0 Hz), 58.7 (t, $J$ = 3.4 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −99.8 to −100.8 (m, 1F), −101.2 to −102.2 (m, 1F); IR (thin film) $\upsilon_{max}$ 3367, 3039, 2918, 2854, 1668, 1497, 1455, 1029 cm$^{-1}$; MS (ESI): $m/z$ = 232.1 $[M + NH_4]^+$, 237.0 $[M + Na]^+$; HRMS (ESI): $m/z$ $[M + Na]^+$ calcd for $C_{11}H_{12}F_2NaO_2$: 237.0698; found: 237.0698.

**(*Z*)-5-(2,6-Dichlorophenyl)-4,4-difluoropent-2-ene-1,5-diol (13b).** White solid (40 mg, 95%); Mp = 67−69 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.35 (t, $J$ = 7.4 Hz, 2H), 7.20−7.27 (m, 1H). 5.97−6.06 (m, 1H), 5.60−5.74 (m, 2H), 4.24−4.43 (m, 3H), 2.12 (br s, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 138.8 (t, $J$ = 5.1 Hz), 136.9, 134.5, 130.7, 130.5, 130.2, 129.0, 122.7 (dd, $J$ = 27.4, 25.8 Hz), 120.9 (dd, $J$ = 248.7, 247.3 Hz), 74.0 (dd, $J$ = 31.9, 28.8 Hz), 59.0 (t, $J$ = 4.1 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −99.4 (ddd, $J$ = 252.1, 13.6, 10.0 Hz, 1F), −101.1 (dt, $J$ = 253.3, 15.9 Hz, 1F); IR (KBr) $\upsilon_{max}$ 3365, 2929, 1581, 1564, 1438, 1035 cm$^{-1}$; MS (ESI): $m/z$ = 305.1 $[M + Na]^+$; HRMS (ESI): $m/z$ $[M + Na]^+$ calcd for $C_{11}H_{10}Cl_2F_2NaO_2$: 304.9918; found: 304.9920.

**(2*Z*,6*E*)-4,4-Difluoroocta-2,6-diene-1,5-diol (13c).** Yellow oil (78 mg, 90%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.00−6.10 (m, 1H), 5.85−5.96 (m, 1H), 5.46−5.64 (m, 2H), 4.32−4.43 (m, 2H), 4.25 (dd, $J$ = 16.4, 9.5 Hz, 1H), 2.76 (br s, 1H), 2.20 (br s, 1H), 1.76 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 138.5 (t, $J$ = 5.3 Hz), 132.2, 125.3 (dd, $J$ = 4.1, 2.6 Hz), 122.4 (t, $J$ = 26.4 Hz), 120.5 (t, $J$ = 244.5 Hz), 74.5 (t, $J$ = 30.2 Hz), 59.0 (t, $J$ = 3.4 Hz), 17.9; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −101.0 to −102.0 (m, 1F), −103.3 to −104.3 (m, 1F); IR (thin film) $\upsilon_{max}$ 3350, 2922, 1672, 1450, 1413, 1026 cm$^{-1}$; MS (ESI): $m/z$ = 196.1 $[M + NH_4]^+$, 201.1 $[M + Na]^+$; HRMS (EI): $m/z$ $M^+$ calcd for $C_8H_{12}F_2O_2$: 178.0805; found: 178.0807.

**(*Z*)-4,4-Difluorodec-2-ene-1,5-diol (13d).** Colorless oil (81 mg, 88%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.00−6.06 (m, 1H), 5.47−5.61 (m, 1H), 4.22−4.41 (m, 2H). 3.65−3.76 (m, 1H), 3.54 (s, 1H), 3.47 (s, 1H), 1.20−1.65 (m, 8H), 0.86−0.90 (m, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 138.2 (t, $J$ = 5.2 Hz), 122.5 (dd, $J$ = 27.4, 26.0 Hz), 121.4 (t, $J$ = 244.4 Hz), 73.6 (dd, $J$ = 30.9, 28.8 Hz), 58.8 (t, $J$ = 3.5 Hz), 31.6, 29.9 (dd, $J$ = 7.3, 1.3 Hz), 25.3, 22.5, 14.0; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −101.0 (dt, $J$ = 254.4, 6.8 Hz, 1F), −104.7 (dt, $J$ = 254.4, 13.0 Hz, 1F); IR (thin film) $\upsilon_{max}$ 3344, 2958, 2932, 2863, 1668, 1464, 1413, 1033 cm$^{-1}$; MS (ESI): $m/z$ = 226.1 $[M + NH_4]^+$; HRMS (EI): $m/z$ $[M^+ - OH]$ calcd for $C_{10}H_{17}F_2O$: 191.1247; found: 191.1239.

Compounds **14a**−**d** were prepared from **13a**−**d** using the same procedure of preparation of compound (*S*)-**1**.

**5,5-Difluoro-6-phenyl-5,6-dihydropyran-2-one (14a).** White solid (28 mg, 92%). Mp = 95−97 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.42−7.50 (m, 5H), 6.91 (ddd, $J$ = 10.0, 8.3, 1.6 Hz, 1H), 6.40 (dt, $J$ = 10.0, 1.2 Hz, 1H), 5.57 (dd, $J$ = 20.3, 5.0 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 160.7, 138.3 (dd, $J$ = 34.6, 25.0 Hz), 130.0, 129.9, 128.5, 128.1, 126.4 (t, $J$ = 9.0 Hz), 111.8 (dd, $J$ = 247.9, 236.5 Hz), 80.7 (dd, $J$ = 32.4, 27.1 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −105.2 (dd, $J$ = 289.0, 20.2 Hz, 1F), −110.2 (dt, $J$ = 288.3, 6.5 Hz, 1F); IR (KBr) $\upsilon_{max}$ 3077, 2955, 2925, 2854, 1742, 1638, 1501, 1459, 1276 cm$^{-1}$; MS (ESI): $m/z$ = 228.1 $[M + NH_4]^+$, 233.0 $[M + Na]^+$; HRMS (EI): $m/z$ $M^+$ calcd for $C_{11}H_8F_2O_2$: 210.0499; found: 210.0492.

**6-(2,6-Dichlorophenyl)-5,5-difluoro-5,6-dihydropyran-2-one (14b).** Colorless oil (18 mg, 96%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.39−7.44 (m, 2H), 7.26−7.34 (m, 1H), 6.92 (ddd, $J$ = 10.2, 8.4, 1.8 Hz, 1H), 6.56 (dd, $J$ = 22.5, 8.1 Hz, 1H), 6.45−6.49 (m, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 159.5, 137.4 (dd, $J$ = 32.1, 25.6 Hz), 137.3, 136.5, 131.4, 130.9, 128.5, 126.7 (dd, $J$ = 9.7, 8.0 Hz), 126.0, 112.2 (dd, $J$ = 251.8, 236.0 Hz), 77.9 (dd, $J$ = 36.6, 25.8 Hz); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −94.3 (dd, $J$ = 288.3, 22.1 Hz, 1F), −103.4 (dt, $J$ = 288.5, 8.2 Hz, 1F); IR (thin film) $\upsilon_{max}$ 3082, 2926, 2854, 1748, 1649, 1582, 1565, 1439, 1114 cm$^{-1}$; MS (ESI): $m/z$ = 279.0 $[M + H]^+$, 296.0 $[M + NH_4]^+$; HRMS (EI): $m/z$ $M^+$ calcd for $C_{11}H_6Cl_2F_2O_2$: 277.9713; found: 277.9718.

**(*E*)-5,5-Difluoro-6-(prop-1-enyl)-5,6-dihydropyran-2-one (14c).** Colorless oil (16 mg, 82%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.78−6.86 (m, 1H), 6.31 (d, $J$ = 10.2 Hz, 1H), 6.02−6.13 (m, 1H), 5.63 (qd, $J$ = 7.7, 1.4 Hz, 1H), 4.93 (td, $J$ = 11.6, 7.8 Hz, 1H). 1.83 (dd, $J$ = 6.8, 1.1 Hz, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 160.5 (t, $J$ = 2.0 Hz), 137.9 (dd, $J$ = 29.7, 28.8 Hz), 136.3, 126.6 (t, $J$ = 8.9 Hz), 119.8 (dd, $J$ = 3.6, 2.0 Hz), 112.1 (dd, $J$ = 242.1, 240.4 Hz), 80.3 (dd, $J$ = 31.1, 29.8 Hz), 18.1; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −108.5 (dd, $J$ = 11.4, 4.4 Hz, 2F); IR (thin film) $\upsilon_{max}$ 3076, 2925, 2861, 1751, 1677, 1643, 1383, 1285, 1069 cm$^{-1}$; MS (EI): $m/z$ (%) = 174 (1) $M^+$, 104 (100), 76 (48); HRMS (EI): $m/z$ $M^+$ calcd for $C_8H_8F_2O_2$: 174.0492; found: 174.0497.

**5,5-Difluoro-6-pentyl-5,6-dihydropyran-2-one (14d).** Yellowish oil (40 mg, 85%). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.80 (ddd, $J$ = 10.2, 7.4, 2.9 Hz, 1H), 6.30 (d, $J$ = 10.2 Hz, 1H), 4.47 (ddd, $J$ = 17.3, 13.3, 7.3 Hz, 1H), 1.86 (dd, $J$ = 14.6, 7.4 Hz, 2H), 1.26−1.76 (m, 6H), 0.89−0.94 (m, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −109.5 (dd, $J$ = 288.3, 16.8 Hz), −110.5 (dt, $J$ = 287.9, 7.2 Hz).

**Acknowledgment.** We thank the National Natural Science Foundation of China, Ministry of Education of China, and Shanghai Municipal Scientific Committee for funding this work.

**Supporting Information Available:** Copies of $^1$H NMR and $^{13}$C NMR spectra of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061012R