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Synthesis of γ-Monofluorinated Goniothalamin Analogues via Regio- and Stereoselective Ring-Opening Hydrofluorination of Epoxide

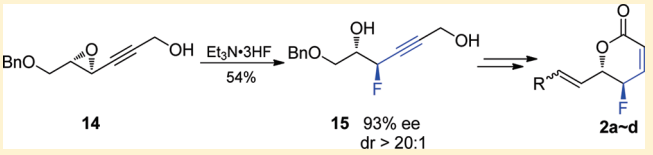
Jun-Ling Chen,[†] Feng Zheng,[‡] Yangen Huang,[†] and Feng-Ling Qing*[,†,‡]

[†]College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

[‡]Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 345 Lingling Lu, Shanghai 200032, China

Supporting Information

ABSTRACT: A stereoselective synthesis of the biologically interesting γ-monofluorinated goniothalamin analogue **2a** was described. The features of the synthesis included regioselective reduction of the unprotected hydroxypropynyl moiety of compound **10** by Red-Al, asymmetric Sharpless epoxidation of allyl alcohol **11**, and regio- and stereoselective ring-opening hydrofluorination of the hydroxypropynyl epoxide **14** with $Et_3N \cdot 3HF$ in high ee and dr. The chiral hydroxypropynyl fluorohydrin **15** was used as a valuable building block for preparation of a range of γ-monofluorinated α,β-unsaturated δ-lactones.



INTRODUCTION

Natural products possessing an α,β-unsaturated δ-lactone moiety usually display interesting biological activities, such as insect growth inhibition, antitumor, antibacterial, antifungal, and immunosuppressive properties.[1] The α,β-unsaturated δ-lactone unit is presumed to serve as the pharmacophore and be responsible for biological activities as a result of its ability to act as a Michael acceptor.[1d,f,h,2] In pharmaceutical research, fluorine has been considered as a suitable bioisostere for hydrogen on steric grounds.[3] Quite often, fluorine is introduced to improve metabolic stability[4] and modulate physicochemical properties, such as lipophilicity or basicity,[3,5] because of its electronegative properties and the chemical inertness of the C−F bond. With a long-term interest in development of efficient methodologies for introduction of the fluorine atom into organic molecules and synthesis of fluorinated biologically interesting compounds, we intended to introduce the fluorine atom(s) into the γ-position of α,β-unsaturated δ-lactone. Such modification could make the double bond more electron deficient and lead to a better Michael acceptor with minimum steric change. Recently, an efficient and general strategy to construct γ-difluoromethylenated α,β-unsaturated δ-lactones from various aldehydes has been developed in our group, which was successfully applied to the synthesis of two enantiomers of *gem*-difluoromethylenated goniothalamin.[6] To study the effect of fluorine substituents on bioactivities of α,β-unsaturated δ-lactone containing compounds, besides γ-difluorinated derivatives, the γ-monofluorinated counterparts are another important class to be evaluated (Figure 1). Herein, we report a novel route for the enantio- and diastereoselective synthesis of hydroxypropynyl fluorohydrin, from which a range of chiral γ-monofluorinated α,β-unsaturated δ-lactones was prepared. It should be noteworthy that synthetic approaches to

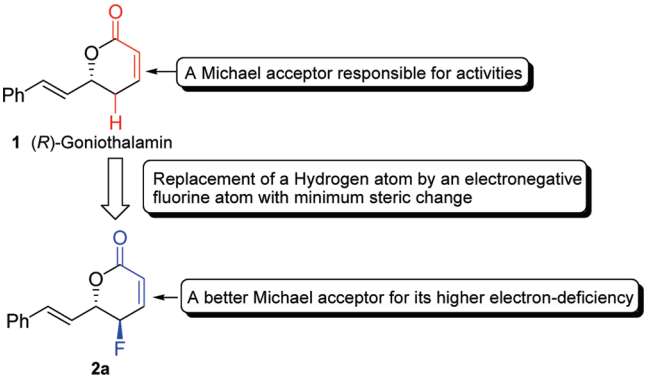


Figure 1. Rationale for the design of the target molecule **2a**.

chiral γ-monofluorinated α,β-unsaturated δ-lactone are rather scarce, although the synthesis of propargylic fluorides from the dehydroxyfluorination reactions of propargylic alcohols with diethylaminosulfur trifluoride (DAST) has been thoroughly investigated by René Grée and co-workers.[7,8] Furthermore, the hydroxypropenyl fluorohydrin and its precursor, hydroxypropynyl fluorohydrin, are valuable building blocks, by which a wide library of chiral fluorinated compounds could be accessed via simple functional group manipulations.[9]

RESULTS AND DISCUSSION

Our synthetic strategy for the synthesis of γ-monofluorinated goniothalamin **2a** was outlined in Scheme 1. We envisioned that the

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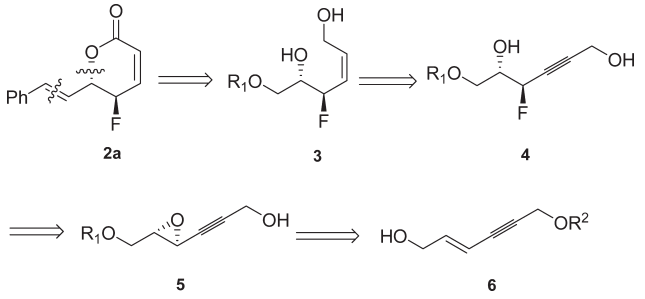
Scheme 1



styryl moiety would be installed via a Horner−Wadsworth−Emmons (HWE) reaction, and the key lactone could be constructed by oxidative ring closure of monofluorodiol **3** which in turn would be obtained from propargyl alcohol **4** through partial hydrogenation. The two stereocenters of compound **4** could be established via regio- and stereoselective ring-opening hydrofluorination of enantiopure epoxide **5**. The enantiopure expoxide **5** could be prepared by Sharpless asymmetric epoxidation of allyl alcohol **6**.

Silyl ether **8** and 3-iodoprop-2-yn-1-ol **9** were straightforwardly prepared from commercially available propargyl alcohol **7** via TBS protection and iodination,[10] respectively (Scheme 2). The Sonogashira cross-coupling of compounds **8** and **9** afforded intermediate **10** in 69% yield. Regioselective reduction of the unprotected hydroxypropynyl moiety of **10** by Red-Al provided allyl alcohol **11** in 88% yield, which was then subjected to the Sharpless asymmetric epoxidation to afford the corresponding epoxide **12** in 84% yield. The primary hydroxyl group of **12** was then protected with the benzyl group to afford silyl ether **13** in 90% yield. Treatment of compound **13** with tetrabutylammonium fluoride (TBAF) gave the precursor of ring-opening hydrofluorination **14** in 96% yield with 92% ee.

With epoxide **14** in hand, we then turned our attention to the key step for the construction of fluorohydrin **15** via ring-opening hydrofluorination of **14** with different nucleophilic fluorinating reagents.[11,12] The optimization of the reaction of epoxide **14** with fluoride sources was summarized in Table 1. Reaction **14** with bifluoride (KHF_2) in the presence of 18-crown-6 in DMF failed to generate any of the desired fluoride adduct (Table 1, entry 1). With Olah's reagent Py·HF as the fluorine source, only trace of product **15** was detected by ^{19}F NMR (entry 2). Treatment of **14** with $BF_3 \cdot Et_2O$ resulted in complex reaction (entry 3). The fluorohydrin **15** was obtained in 30% yield when n-$Bu_4NF \cdot 2HF$ was used as the fluorine source (entry 4). To our delight, the ring-opening hydrofluorination of **14** with more nucleophlic $Et_3N \cdot 3$ HF gave fluorohydrin **15** in 54% yield as a single product (entry 5). This complete regio- and stereocontrol reaction was consistent with a mechanism involving a stereoselective S_N2-type epoxide ring-opening process. The fluoride attacked the epoxide **14** at the C4 carbon with the inversion of the stereochemistry to give 4-fluoro-2-ol regioselectively owing to the higher density of positive charge at C4 carbon caused by the electron-withdrawing property of the adjacent hydroxypropynyl group.

Partial hydrogenation of the fluorohydrin **15** with Pd/$BaSO_4$ proceeded smoothly to afford (*Z*)-1,5-diol **16** in 80% yield (Scheme 3). Oxidative cyclization of **16** with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and bisacetoxyiodobenzene (BAIB)[13] gave the desired lactone **17** in 97% yield.

Scheme 2

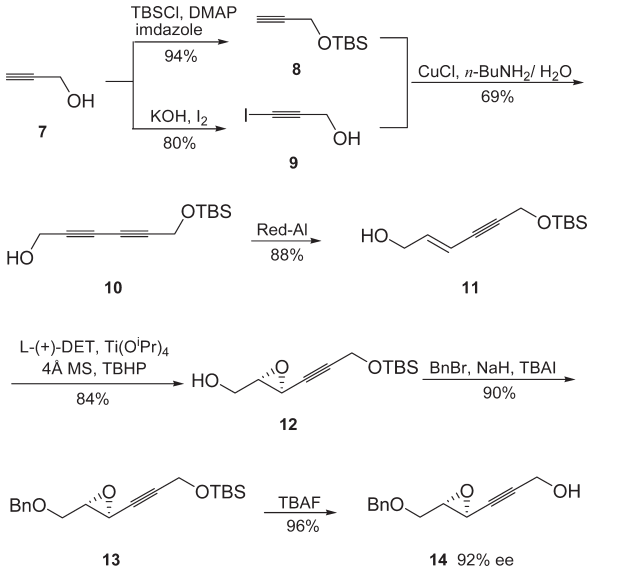


Table 1. Preparation of the Hydroxypropynyl Fluorohydrin 15 via Ring-Opening Hydrofluorination of 14

entry	reaction conditions	solvent	yield (%)
1	KHF_2, 18-Crown-6, 100 °C	DMF	—[a]
2	HF·Py, 0 °C	CH_2Cl_2	trace[a]
3	$BF_3 \cdot Et_2O$, −35 °C	CH_2Cl_2	—[a]
4	n-$Bu_4NF \cdot 2HF$, 95 °C	---	30%[b]
5	$Et_3N \cdot 3HF$, 70 °C	---	54%[b]

[a] Determined by ^{19}F NMR. [b] Isolated yield.

Unfortunately, cleavage of the benzyl ether protecting group in lactone **17** using DDQ, BCl_3, or $TiCl_4$ failed to give alcohol **18**, probably due to the decomposition of the unsaturated lactone structure under these reaction conditions.

It was decided to introduce the styryl moiety prior to the construction of the lactone ring. Protection of diol **15** with TBSOTf afforded silyl diether **19** which was subjected to partial hydrogenation, giving (*Z*)-silyl diether **20** in 95% yield (Scheme 4). However, as shown in Table 2, the debenzylation reactions of **20** with different deprotecting reagents resulted in complex reaction or low yield of alcohol **21** due to the desilylation of the primary silyl ether and the subsequent side reactions under these reaction conditions.

As the TBDPS-ether was much more stable than the TBS-ether, protection of the primary hydroxyl of compound **15** as TBDPS-ether and followed by silylation of the secondary hydroxyl group with TBSOTf afforded compound **22** in 89% yield (Scheme 5). Fortunately, removal of the benzyl group in **22** with DDQ delivered the desired alcohol **23** in 83% yield. Oxidation of alcohol **23** with $SO_3 \cdot Py$[14] gave aldehyde **24** in 90% yield. The HWE reaction of **24** with diethylbenzylphosphonate gave the

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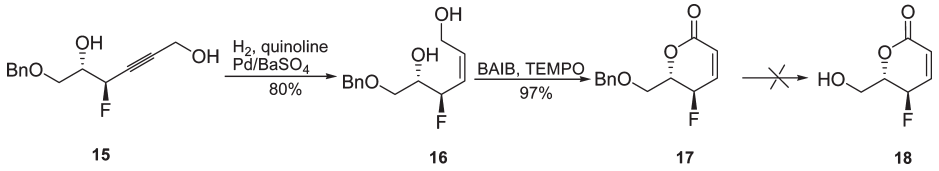
Scheme 3



Scheme 4

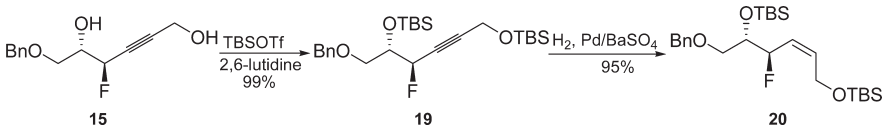
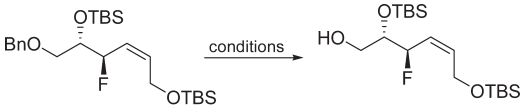


Table 2. Attempts at Removal of the Benzyl Group of 21



entry	reagent	temp. (°C)	solvent	results
1	$TiCl_4$	0	DCM	complex
2	BCl_3	−78	DCM	complex
3	DDQ	40	DCM/H_2O	40%[a]
4	Li, naphthaline	−78	THF	complex
5	$HCOONH_4$, Pd/C	65	MeOH	complex
6	1-methyl-1,4-cyclohexadiene, Pd/C	55	EtOH	complex

[a] Isolated yield of alcohol **21**.

(2*Z*,6*E*)-diene **25a** as the major product (C6, *E*:*Z* = 98:2). Treatment of diene **25a** with TBAF gave diol **26a**. Finally, oxidation of **26a** with TEMPO and BAIB afforded the γ-monofluorinated goniothalamin analogue **2a**.

The relative configuration of product **2a** was determined by single-crystal X-ray diffraction analysis (Figure 2), which

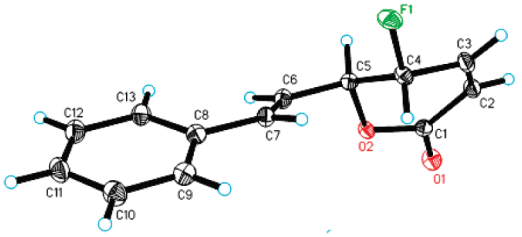


Figure 2. ORTEP drawing of the X-ray crystallographic structure of **2a**.

unambiguously confirmed the relative *anti*-configuration of the fluorine atom and the hydroxyl group of compound **15**. The absolute configuration was established by the known enantioselectivity of the Sharpless epoxidation.

The utility of the fluorinated building block **24** was demonstrated by the further synthesis of a range of γ-monofluorinated α,β-unsaturated δ-lactones. Carbon extension of the molecular skeleton of aldehyde **24** via HWE olefination with diethyl (4-methoxyphenyl)- and (4-fluorophenyl)-methylphosphonate gave (2*Z*,6*E*)-diene **25b** and **25c** in high stereoselectivity, respectively. Removal of the silyl groups followed by oxidative ring closure afforded the corresponding *p*-substituted phenyl

Scheme 5

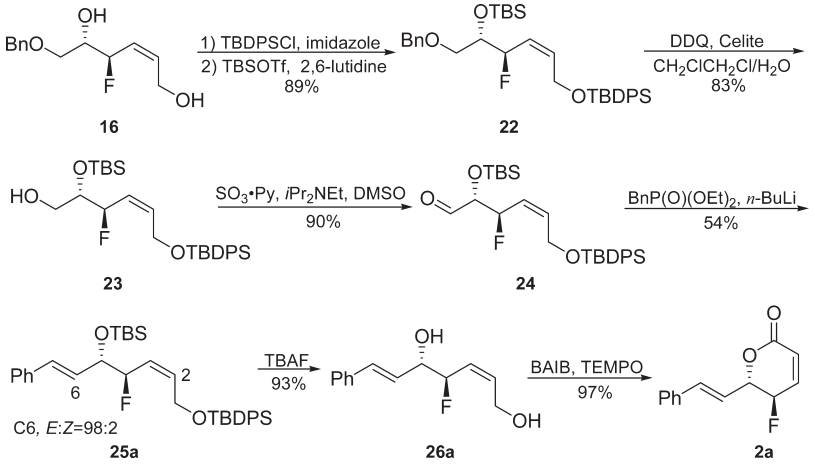


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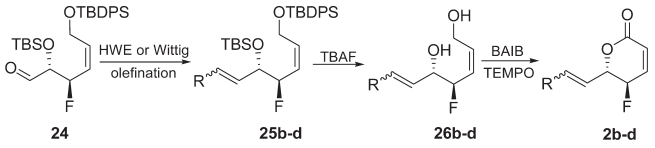
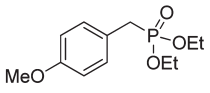
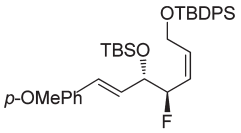
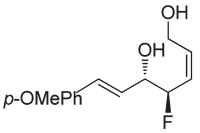
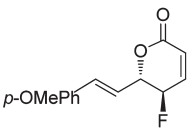
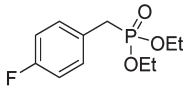
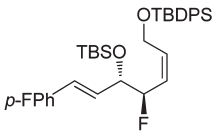
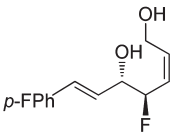
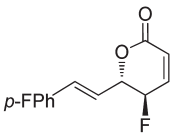
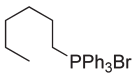
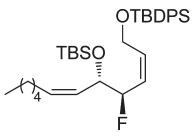
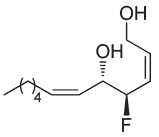
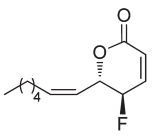
Table 3. Syntheses of γ-Monofluorinated α,β-Unsaturated δ-Lactones 2b−d



Entry	Phosphonate or phosphonium salt	25b-d	26b-d	2b-d
1		 **25b** 20%, *E*:*Z*=95:5	 **26b** 99%	 **2b** 96%
2		 **25c** 52%, *E*:*Z*=96:4	 **26c** 93%	 **2c** 96%
3		 **25d** 92%, *Z*:*E*=92:8	 **26d** 99%	 **2d** 81%

γ-monofluorinated goniothalamin analogues **2b** and **2c** (Table 3), respectively. Moreover, γ-monofluorinated (6*Z*,2*Z*)-lactone **2d**, an analogue of natural product (−)-argentilactone that exhibited both antiprotozoal[15] and cytotoxic activity,[16] was also prepared through a similar process as described above. The *Z* geometry of the double bond in the heptenyl moiety of **2d** was readily constructed via the Wittig olefination (*Z*:*E* = 92:8).

CONCLUSION

In conclusion, we have designed and synthesized a new range of γ-monofluorinated α,β-unsaturated δ-lactones, including the analogues of naturally occurring goniothalamin and argentilactone. Our synthesis is highlighted by the construction of the chiral hydroxypropynyl fluorohydrin in high efficiency via asymmetric Sharpless epoxidation and regio- and stereoselective ring-opening hydrofluorination of the derived epoxy.

EXPERIMENTAL SECTION

6-(*tert*-Butyldimethylsilyloxy)hexa-2,4-diyn-1-ol (10).[17] CuCl (2.47 g, 25.0 mmol) was dissolved in a mixture of 233 mL of H_2O and 100 mL of *n*-butylamine. Then, *tert*-butyldimethyl(prop-2-ynyloxy)silane **8** (21.25 g, 125.0 mmol) was added at 0 °C, followed by the dropwise addition of 3-iodoprop-2-yn-1-ol **9** (15.17 g, 83.4 mmol). Whenever the reaction mixture turned to green, a few crystals of $NH_2OH\cdot HCl$ were added. After stirring for 20 min at 0 °C and for another 30 min at room temperature, the reaction mixture was filtered through a pad of silica gel. After aqueous workup, the crude product was purified by column chromatography (petroleum ether:ethyl acetate = 15:1) to give **10** (12.88 g, 69%) as a red liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (s, 2H), 4.34 (s, 2H), 1.75 (br, 1H), 0.90 (s, 9H), 0.12 (s, 6H).

(*E*)-6-(*tert*-Butyldimethylsilyloxy)hex-2-en-4-yn-1-ol (11).[17] To 6-(*tert*-butyldimethylsilyl)oxy-2,4-hexadiyn-1-ol **10** (19.80 g, 88.39 mmol) in THF (250 mL) was slowly added Red-Al (3.4 M in toluene, 39 mL, 132.60 mmol) at −78 °C over 30 min. The temperature was slowly warmed to 0 °C, and the mixture was stirred for another 1.5 h. The reaction was quenched at 0 °C with H_2O (133 mL). Then 10% (m/V) NaOH in water (133 mL) was added, and the mixture was stirred vigorously and then filtered. The layers were separated, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to give alcohol **11** (17.60 g, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 16.0, 5.2 Hz, 1H), 5.77 (d, *J* = 15.9 Hz, 1H), 4.43 (s, 2H), 4.22 (d, *J* = 5.1 Hz, 2H), 1.59 (br, 1H), 0.91 (s, 9H), 0.13 (s, 6H).

((2*S*,3*S*)-3-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)oxiran-2-yl)methanol (12). To anhydrous CH_2Cl_2 (200 mL) were added sequentially powdered 4 Å molecular sieves (8 g), L-(+)-diethyl tartrate (3.90 g, 18.53 mmol), and $Ti(O^iPr)_4$ (4.66 mL, 15.44 mmol) at −20 °C. The resultant mixture was stirred for 20 min at −20 °C, and a solution of **11** (17.45 g, 77.21 mmol) in CH_2Cl_2 (60 mL) was added over a period of 15 min. The reaction mixture was allowed to stir at −20 °C for another 30 min before addition of *tert*-butylhydroperoxide (35 mL, 4.5 M). The resultant reaction mixture was stirred at −20 °C for an additional 18 h, and then a solution of L-tartaric acid (8.8 g, 60.0 mmol) and $FeSO_4\cdot 7H_2O$ (23.0 g, 82.7 mmol) in H_2O (400 mL) was added. The resultant mixture was stirred vigorously at room temperature for 1 h. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (silica gel,

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petroleum ether:ethyl acetate = 7:1) afforded the epoxy **12** (15.70 g, 84%) as a pale yellow oil: $[\alpha]_D^{26.7}$ +25.3 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, *J* = 1.4 Hz, 2H), 3.94 (dd, *J* = 13.0, 1.7 Hz, 1H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.47 (d, *J* = 1.6 Hz, 1H), 3.31−3.28 (m, 1H), 1.88 (s, 1H), 0.89 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 83.1, 80.6, 60.2, 59.8, 51.7, 42.6, 25.8, 18.3, −5.2; IR (thin film) ν_{max} 3446, 2940, 2860, 2239, 1640, 1256, 1086, 840 cm^{-1}; MS (ESI) *m*/*z* 260.1 $[M + NH_4]^+$. Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15. Found: C, 59.31, H, 9.35.

(3-((2*S*,3*S*)-3-((Benzyloxy)methyl)oxiran-2-yl)prop-2-ynyloxy)(*tert*-butyl)dimethyl-silane (13). To a suspension of sodium hydride (80% in oil, 2.55 g, 85.00 mmol) in anhydrous THF (150 mL) was added a solution of **12** (13.69 g, 56.57 mmol) in THF (150 mL) for 20 min at −40 °C. Benzyl bromide (10.0 mL, 84.21 mmol) and tetrabutylammonium iodide (1.08 g, 2.87 mmol) were then added sequentially, and the resulting mixture was stirred at 25 °C under nitrogen for another 2 h. Water (100 mL) was added, and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 60:1) to afford **13** (16.94 g, 90%) as a colorless liquid: $[\alpha]_D^{26.7}$ −30.2 (*c* 3.53, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.26 (m, 5H), 4.56 (s, 2H), 4.33 (d, *J* = 1.5 Hz, 2H), 3.73 (ABd, *J* = 11.7, 3.0 Hz, 1H), 3.54 (ABd, *J* = 11.8, 4.7 Hz, 1H), 3.37 (dd, *J* = 3.4, 1.4 Hz, 1H), 3.33 (ddd, *J* = 5.1, 3.0, 2.2 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.6, 128.4, 127.8, 127.7, 82.8, 80.8, 73.4, 68.7, 58.6, 51.6, 42.8, 25.8, 18.2, −5.2; IR (thin film) ν_{max} 3450, 3068, 3023, 2939, 2859, 1640, 1461, 1368, 1255, 1091 cm^{-1}; MS (ESI) *m*/*z* 350.1 $[M + NH_4]^+$. HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{28}NaO_3Si$, 355.1706; found, 355.1710.

3-((2*S*,3*S*)-3-((Benzyloxy)methyl)oxiran-2-yl)prop-2-yn-1-ol (14). A solution of TBAF in THF (1 M, 55.0 mL) was added to a solution of **13** (16.90 g, 50.90 mmol) in THF (250 mL) at −5 °C. After stirring for 20 min, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were concentrated and purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 5:2) to afford **4** (10.65 g, 96%, 92% ee) as a colorless oil: Chiral HPLC (Phenomenex Lux 5 μ Cellulose−2,2-propanol:hexane = 1:9, 250 × 4.6 mm, 214 nm, 0.7 mL/min), t_R = 39.78 min (minor), t_R = 42.83 min (major); $[\alpha]_D^{28}$ −64.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.53 (s, 2H), 4.22 (s, 2H), 3.71 (ABd, *J* = 11.7, 2.9 Hz, 1H), 3.50 (ABd, *J* = 11.8, 4.7 Hz, 1H), 3.37 (dd, *J* = 3.5, 1.5 Hz, 1H), 3.36−3.32 (m, 1H), 2.93 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.8, 130.9, 130.3, 130.2, 85.1, 83.7, 75.8, 70.9, 61.1, 53.1, 53.0, 45.3; IR (thin film) ν_{max} 3432, 3060, 3029, 2940, 2863, 1637, 1448, 1363, 1233, 1094 cm^{-1}; MS (ESI) *m*/*z* 236.1 $[M + NH_4]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{14}NaO_3$, 241.0841; found, 241.0846.

(4*R*,5*S*)-6-(Benzyloxy)-4-fluorohex-2-yne-1,5-diol (15). A mixture of **14** (9.83 g, 45.1 mmol) and $Et_3N \cdot 3HF$ (50 mL, 304 mmol) was stirred at 70 °C overnight under a nitrogen atmosphere. Water (200 mL) was added, and the mixture was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (3 × 150 mL) and then water (150 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 16:9) to afford **15** (16.94 g, 54%, 93% ee) as a yellowish syrup: Chiral HPLC (Phenomenex Lux 5 μ Cellulose−2,2-propanol:hexane = 3:7, 250 × 4.6 mm, 214 nm, 0.5 mL/min), t_R = 12.48 min (minor), t_R = 13.48 min (major); $[\alpha]_D^{28.3}$ +116 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.20 (ddt, *J* = 47.6, 5.0, 1.5 Hz, 1H), 4.54 (d, *J* = 1.2 Hz, 2H), 4.26 (dd, *J* = 6.9, 1.4 Hz, 2H), 4.05 (td, *J* = 10.6, 5.0 Hz, 1H), 3.64 (ABdd, *J* = 9.9, 4.8, 0.8 Hz, 1H), 3.60 (ABdd, *J* = 11.7, 5.7, 1.8 Hz, 1H), 3.35 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.4, 128.4, 127.8, 127.7, 88.7 (d, *J* = 10.2 Hz), 82.8 (d, *J* = 171.6 Hz), 79.1 (d, *J* = 25.9 Hz), 73.4, 71.4 (d, *J* = 23.8 Hz), 69.4, 50.3; ^{19}F NMR (400 MHz, $CDCl_3$) δ −183.4 to −183.5 (m, 1F); IR (thin film) ν_{max} 3399, 3060, 3031, 2922, 2868, 2230, 1636, 1450, 1362, 1216, 1106 cm^{-1}; MS (ESI) *m*/*z* 256.0 $[M + NH_4]^+$, 261.0 $[M + Na]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}FNaO_3$, 261.0903; found, 261.0908.

(*Z*,4*R*,5*S*)-6-(Benzyloxy)-4-fluorohex-2-ene-1,5-diol (16). To a solution of diol **15** (940 mg, 3.95 mmol) in *n*-hexane (24 mL) and acetone (16 mL) were added quinoline (332 mg) and $Pd/BaSO_4$ (166 mg) and stirred under a hydrogen atmosphere at room temperature for 1 h. The reaction mixture was filtered, evaporated, and purified by column chromatography (petroleum ether:ethyl acetate = 16:9) to afford **16** (758 mg) in 80% yield as a pale yellow syrup: $[\alpha]_D^{25.2}$ −57.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 5.99 (dtdd, *J* = 7.9, 6.6, 2.2, 1.1 Hz, 1H), 5.72−5.63 (m, 1H), 5.30 (dt, *J* = 46.6, 7.2 Hz, 1H), 4.57 (s, 2H), 4.17 (dd, *J* = 11.9, 8.1 Hz, 2H), 3.91−3.84 (m, 1H), 3.67 (ABdd, *J* = 9.8, 3.9, 2.1 Hz, 1H), 3.59 (ABdd, *J* = 9.8, 6.3, 1.9 Hz, 1H), 2.74 (s, 1H), 2.16 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.6, 135.0 (d, *J* = 10.3 Hz), 128.5, 127.9, 127.8, 126.8 (d, *J* = 21.6 Hz), 88.1 (d, *J* = 166 Hz), 73.6, 71.1 (d, *J* = 26.4 Hz), 70.3 (d, *J* = 4.5 Hz), 58.4; ^{19}F NMR (400 MHz, $CDCl_3$) δ −184.5 to −184.7 (m, 1F); IR (thin film) ν_{max} 3401, 3041, 3027, 2919, 2869, 1629, 1453, 1415, 1365, 1210, 1026 cm^{-1}; MS (ESI) *m*/*z* 258.1 $[M + NH_4]^+$, 263.2 $[M + Na]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{17}FNaO_3$, 263.1060; found, 263.1053.

(5*R*,6*S*)-6-((Benzyloxy)methyl)-5-fluoro-5,6-dihydropyran-2-one (17). To a solution of **16** (160 mg, 0.67 mmol) in CH_2Cl_2 (6 mL) was added bisacetoxyiodobenzene (657 mg, 2.0 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (21 mg, 20 mol %) at room temperature. After stirring for 2 h, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ (30 mL) and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with saturated solutions of $NaHCO_3$ (30 mL), NH_4Cl (30 mL), and brine (30 mL) in turn, 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 **17** (152 mg, 97%) as a yellow oil: $[\alpha]_D^{21.9}$ −37.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 6.89 (td, *J* = 9.9, 2.9 Hz, 1H), 6.10 (dt, *J* = 10.0, 1.7 Hz, 1H), 5.41 (dddd, *J* = 47.7, 7.4, 2.9, 1.4 Hz, 1H), 4.66−4.59 (m, 1H), 4.62 and 4.57 (AB, J_{AB} = 12 Hz, 2H), 3.79 (ABdd, *J* = 11.1, 3.6, 1.4 Hz, 1H), 3.75 (ABdd, *J* = 11.1, 3.5, 1.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.7 (d, *J* = 3.2 Hz), 144.4 (d, *J* = 20.8 Hz), 139.6, 130.9, 130.3, 130.0, 125.1 (d, *J* = 8.3 Hz), 83.4 (d, *J* = 172 Hz), 81.3 (d, *J* = 25.6 Hz), 76.1, 70.2 (d, *J* = 3.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −188.63 (dt, *J* = 47.8, 10.8 Hz, 1F); ν_{max} 3070, 3032, 2923, 2867, 1740, 1637, 1596, 1456, 1380, 1234, 1118 cm^{-1}; MS (ESI) *m*/*z* 259.1 $[M + Na]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{13}FNaO_3$, 259.0747; found, 259.0740.

(8*R*,9*S*)-9-(Benzyloxymethyl)-8-fluoro-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridec-6-yne (19). To a solution of **15** (1.13 g, 4.75 mmol) in CH_2Cl_2 (80 mL) was added 2,6-lutidine (1.66 mL, 14.25 mmol), and the mixture was cooled to −40 °C. Then TBSOTf (4.36 mL, 19.0 mmol) was added slowly, and the mixture was stirred for another 4 h at room temperature. The mixture was quenched with brine (100 mL) and was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were concentrated and purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 100: 1) to afford **19** (2.19 g, 99%) as a colorless oil: $[\alpha]_D^{20.0}$ −50.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 5.35−5.13 (dt, *J* = 47.4, 1.6 Hz, 1H), 4.55 (s, 2H), 4.39 (dd, *J* = 6.7, 1.4 Hz, 2H), 4.12 (ddd, *J* = 8.6, 4.8, 2.9 Hz, 1H), 3.65−3.60 (m, 1H), 3.56−3.52 (m, 1H), 0.94 (s, 9H), 0.93 (s, 9H), 0.15 (s, 6H), 0.09 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0, 127.3, 126.6, 126.6, 87.3, 82.9 (d, *J* = 173 Hz), 77.9 (d, *J* = 7.0 Hz), 72.5, 71.8 (d, *J* = 23.1 Hz), 70.0 (d, *J* = 6.0 Hz), 50.6 (d, *J* = 3.2 Hz), 24.8, 24.7, 17.2, 17.1, −5.8, −5.8, −6.2, −6.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −183.15 to −183.32 (m, 1F); IR

(thin film) ν_{max} 3060, 3041, 2941, 2863, 1590, 1464, 1265, 1106 cm^{-1}; MS (ESI) m/z 489.3 $[M + Na]^+$; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{43}FNaO_3Si_2$, 489.2633; found, 489.2632.

(8*R*,9*S*,*Z*)-9-(Benzyloxymethyl)-8-fluoro-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridec-6-ene (20). To a solution of **19** (2.00 g, 4.29 mmol) in *n*-hexane (80 mL) was added $Pd/BaSO_4$ (180 mg) and stirred under hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered, evaporated, and purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 100:1) to afford **20** (1.91 g, 95%): $[\alpha]_D^{23.0}$ −219 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 5.92−5.87 (m, 1H), 5.72−5.63 (m, 1H), 5.37−5.22 (m, 1H), 4.52 (s, 2H), 4.39−4.33 (m, 1H), 4.26−4.20 (m, 1H), 4.14 (ddd, *J* = 8.8, 5.9, 3.6 Hz, 1H), 3.47−3.41 (m, 1H), 3.41−3.35 (m, 1H), 0.94 (s, 9H), 0.88 (s, 9H), 0.11 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 138.9 (d, *J* = 10.1 Hz), 130.7, 130.0, 129.9, 126.0 (d, *J* = 20.7 Hz), 90.9 (d, *J* = 166 Hz), 75.8, 75.1 (d, *J* = 23.4 Hz), 73.6 (d, *J* = 7.3 Hz), 62.0, 28.3, 28.1, 20.6, 20.5, 3.4, −2.4, −2.5, −2.8, −2.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −179.54 to −179.70 (m, 1F); IR (thin film) ν_{max} 3462, 30720 2954, 2930, 2859, 1582, 1467, 1255, 1110 cm^{-1}; MS (ESI) m/z 491.3 $[M + Na]^+$; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{45}FNaO_3Si_2$, 491.2789; found, 491.2784.

(2*S*,3*R*,*Z*)-2,6-Bis(*tert*-butyldimethylsilyloxy)-3-fluorohex-4-en-1-ol (21). To a solution of compound **20** (920 mg, 1.96 mmol) in CH_2Cl_2 (24.8 mL) and water (1.2 mL) was added DDQ (1.84 g, 7.86 mmol). The reaction mixture was stirred vigorously for 20 h at 40 °C and then filtered. The filtrate was washed with saturated solution of $NaHCO_3$ (30 mL). The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 50:1) to give alcohol **21** (297 mg, 40%) as a pale yellow oil: $[\alpha]_D^{23.7}$ −209 (*c* 0.79, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.83−5.76 (m, 1H), 5.59 (q, *J* = 11.0 Hz, 1H), 5.33 (ddd, *J* = 47.0, 9.0, 4.5 Hz, 1H), 4.26 (ddd, *J* = 6.1, 3.7, 1.3 Hz, 2H), 3.97 (td, *J* = 10.8, 4.9 Hz, 1H), 3.59 (ABdd, *J* = 11.5, 4.9, 1.6 Hz, 1H), 3.51 (ABd, *J* = 11.5, 6.1 Hz, 1H), 2.40 (s, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (d, *J* = 10.2 Hz), 125.7 (d, *J* = 20.9 Hz), 87.8 (d, *J* = 165.7 Hz), 73.7 (d, *J* = 23.9 Hz), 62.9 (d, *J* = 6.2 Hz), 59.5 (d, *J* = 1.3 Hz), 25.9, 25.8, 18.3, 18.1, −4.6, −4.8, −5.1, −5.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −181.42 to −181.58 (m, 1F); IR (thin film) ν_{max} 3465, 3070, 2933, 2855, 1562, 1470, 1257, 1109 cm^{-1}; MS (ESI): m/z 401.2 $[M + Na]^+$; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{39}FNaO_3Si_2$, 401.2320; found, 401.2314.

(8*R*,9*S*,*Z*)-9-(Benzyloxymethyl)-8-fluoro-2,2,11,11,12,12-hexamethyl-3,3-diphenyl-4,10-dioxa-3,11-disilatridec-6-ene (22). To a solution of compound **16** (1.40 g, 5.83 mmol) in CH_2Cl_2 (60 mL) were added imidazole (595 mg, 8.75 mmol) and TBDPSCl (1.92 g, 7.00 mmol), and the mixture was stirred for 0.5 h at room temperature before the mixture was quenched with brine (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was redissolved in CH_2Cl_2 (60 mL) and cooled to −40 °C, and then 2,6-lutidine (1.35 mL, 11.60 mmol) was added. Then TBSOTf (1.85 g, 7.00 mmol) was added slowly. After stirring for 12 h at room temperature, the mixture was quenched with brine (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were concentrated and purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 100:1) to afford **22** (3.06 g, 89% for two steps) as a colorless liquid. $[\alpha]_D^{20.0}$ −205 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4H), 7.45−7.35 (m, 6H), 7.29−7.19 (m, 5H), 5.98−5.91 (m, 1H), 5.70−5.61 (m, 1H), 5.08 (dddd, *J* = 47.0, 8.9, 3.5, 0.9 Hz, 1H), 4.40−4.33 (m, 1H), 4.37 (s, 2H), 4.27−4.21 (m, 1H), 4.07−4.00 (m, 1H), 3.34 (ddd, *J* = 9.5, 5.6, 2.6 Hz, 1H), 3.27 (dd, *J* = 9.7, 6.6 Hz, 1H), 1.06 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.9, 134.8 (d, *J* = 10.2 Hz), 134.5, 134.5, 132.5, 132.4, 128.7, 128.6, 127.3, 126.7, 126.7, 126.5, 126.5, 123.0 (d, *J* = 21.1 Hz), 87.5 (s, *J* = 156 Hz), 86.70, 72.3, 71.7 (d, *J* = 23.2 Hz), 70.1 (d, *J* = 7.2 Hz), 59.4 (d, *J* = 1.4 Hz), 25.7, 24.7, 18.1, 17.1, −5.8, −5.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −179.59 (dt, *J* = 47.1, 11.9 Hz, 1F); IR (thin film) ν_{max} 3061, 3039, 2941, 2860, 1591, 1464, 1421, 1255, 1106 cm^{-1}; MS (ESI) m/z 615.3 $[M + Na]^+$; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{35}H_{49}FNaO_3Si_2$, 615.3102; found, 615.3097.

(2*S*,3*R*,*Z*)-2-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-3-fluorohex-4-en-1-ol (23). To a solution of compound **22** (1.41 g, 2.38 mmol) in 1,2-dichloroethane (40 mL) and water (1.6 mL) were added DDQ (2.20 g, 6.2 mmol) and Celite (1.10 g). The reaction mixture was stirred vigorously for 8 h at 50 °C and then filtered. The filtrate was washed with saturated solutions of $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (80 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 50:1) to give alcohol **23** (988 mg, 83%) as a colorless liquid: $[\alpha]_D^{20.0}$ −116 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 6.5 Hz, 4H), 7.47−7.39 (m, 6H), 5.95 (dtd, *J* = 9.0, 6.2, 2.8 Hz, 1H), 5.65 (q, *J* = 11.0 Hz, 1H), 5.12 (ddd, *J* = 47.2, 8.9, 4.8 Hz, 1H), 4.36−4.26 (m, 2H), 3.88 (dq, *J* = 10.2, 5.0 Hz, 1H), 3.57 (ABd, *J* = 10.8, 4.2 Hz, 1H), 3.51 (ABd, *J* = 11.3, 5.2 Hz, 1H), 1.97 (s, 1H), 1.08 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.6, 135.5, 135.4, 133.3 (d, *J* = 10.3 Hz), 129.8, 129.8, 127.8, 125.2 (d, *J* = 20.8 Hz), 87.8 (d, *J* = 167 Hz), 73.8 (d, *J* = 24.7 Hz), 63.0 (d, *J* = 6.0 Hz), 60.4, 26.8, 25.8, 19.1, 18.1, −4.6, −4.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −180.51 (dt, *J* = 47.1, 11.1 Hz, 1F); IR (thin film) ν_{max} 3463, 3072, 2955, 2932, 2858, 1582, 1468, 1426, 1255, 1111 cm^{-1}; MS (ESI) m/z 525.3 $[M + Na]^+$; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{28}H_{43}FNaO_3Si_2$, 525.2633; found, 525.2621.

(2*S*,3*R*,*Z*)-2-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-3-fluorohex-4-enal (24). To a solution of alcohol **23** (1.49 g, 3.53 mmol) in CH_2Cl_2 (30.0 mL) at −30 °C was added $(i\text{-}Pr)_2NEt$ (1.80 mL, 1.04 mmol). After stirring for 5 min, a solution of SO_3·Pyridine (1.44 g, 8.89 mmol) in DMSO (3.8 mL) was added. The reaction mixture was stirred for 30 min at −30 °C, then quenched by the slow addition of a saturated solution of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 80:1) to give aldehyde **24** (1.33 g, 90%): $[\alpha]_D^{22.8}$ −136 (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.71−7.69 (m, 4H), 7.48−7.40 (m, 6H), 6.00−5.93 (m, 1H), 5.67 (tdt, *J* = 10.7, 8.8, 1.7 Hz, 1H), 5.26 (dddd, *J* = 46.9, 8.8, 4.1, 1.0 Hz, 1H), 4.34 (dddd, *J* = 14.1, 6.5, 4.0, 1.7 Hz, 1H), 4.24 (ABdd, *J* = 9.9, 5.0, 1.7 Hz, 1H), 4.19 (ABdd, *J* = 13.1, 4.1, 1.2 Hz, 1H), 1.08 (s, 9H), 0.93 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.1 (d, *J* = 7.4 Hz), 136.4 (d, *J* = 10.1 Hz), 135.5, 133.3, 133.2, 129.8, 127.8, 122.9 (d, *J* = 21.2 Hz), 87.6 (d, *J* = 172 Hz), 79.2 (d, *J* = 24.7 Hz), 60.5 (d, *J* = 1.6 Hz), 26.7, 25.6, 19.1, 18.2, −4.9, −5.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −180.8 to −181.2 (m, 1F); IR (thin film) ν_{max} 3071, 3049, 2972, 2959, 2893, 2859, 2247, 1740, 1576, 1468, 1428, 1257, 1110 cm^{-1}; MS (MALDI) m/z 523.2 $[M + Na]^+$; HRMS (MALDI) m/z $[M + Na]^+$ calcd for $C_{28}H_{41}FNaO_3Si_2$, 523.2476; found, 523.2483.

(8*R*,9*S*,2*Z*,6*E*)-8-Fluoro-2,2,11,11,12,12-hexamethyl-3,3-diphenyl-9-styryl-4,10-dioxa-3,11-disilatridec-6-ene (25a). To a solution of diethyl benzylphosphonate (359 mg, 1.56 mmol) in THF (5 mL) at −78 °C under nitrogen atmosphere was added *n*-BuLi (0.62 mL, 2.5 M in hexanes, 1.56 mmol). After stirring for 20 min, the mixture was warmed to −30 °C, left to stand for 30 min, and recooled to −78 °C, and a solution of **24** (520 mg, 1.04 mmol) in THF (5 mL) was then added dropwise. The mixture was stirred for 3 h at room

temperature and then diluted with brine (10 mL) and extracted with ethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel (petroleum ether:ethyl acetate = 100:1) of the residue yielded **25a** (325 mg, 54%) as colorless oil: $[\alpha]_D^{22.6}$ −194 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 4H), 7.47−7.37 (m, 6H), 7.37−7.23 (m, 5H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.06 (dd, *J* = 15.9, 6.4 Hz, 1H), 6.00−5.93 (m, 1H), 5.74−5.63 (m, 1H), 4.96 (ddd, *J* = 47.6, 8.4, 4.1 Hz, 1H), 4.47−4.41 (m, 1H), 4.39−4.33 (m, 1H), 4.27 (dt, *J* = 9.8, 4.2 Hz, 1H), 1.08 (s, 9H), 0.94 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.6, 135.6, 135.5, 135.4 (d, *J* = 9.7 Hz), 133.5, 133.4, 132.0, 129.7, 129.7, 128.6, 127.7, 127.6, 126.5, 124.6 (d, *J* = 21.5 Hz), 90.3 (d, *J* = 171 Hz), 75.1 (d, *J* = 24.9 Hz), 60.7, 26.8, 25.8, 19.1, 18.3, −4.5, −4.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −176.3 to −176.5 (m, 1F); IR (thin film) ν_{max} 3068, 3023, 2956, 2933, 2891, 2858, 1581, 1576, 1468, 1424, 1362, 1256, 1108 cm^{-1}; MS (ESI) *m*/*z* 597.3 $[M + Na]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{47}FNaO_2Si_2$, 597.2997; found, 597.3001.

(2*Z*,4*R*,5*S*,6*E*)-4-Fluoro-7-phenylhepta-2,6-diene-1,5-diol (26a). A solution of TBAF in THF (1 M, 1.3 mL) was added to a solution of **25a** (300 mg, 0.52 mmol) in THF (8 mL) at room temperature. After stirring for 2 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were concentrated and purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 16:9) to afford **26a** (108 mg, 93%) as a colorless oil: $[\alpha]_D^{24.0}$ −183 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.23 (m, 5H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.21 (dd, *J* = 16.0, 6.6 Hz, 1H), 6.00−5.93 (m, 1H), 5.74−5.65 (m, 1H), 5.25 (dddd, *J* = 47.7, 8.1, 5.2, 1.1 Hz, 1H), 4.42−4.35 (m, 1H), 4.26−4.15 (m, 2H), 3.18 (s, 1H), 2.71 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.2, 134.8 (d, *J* = 10.0 Hz), 133.4, 128.7, 128.1, 126.7, 126.6 (d, *J* = 17.5 Hz), 126.1 (d, *J* = 4.6 Hz), 90.1 (d, *J* = 169 Hz), 73.7 (d, *J* = 25.5 Hz), 58.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −181.27 to −182.02 (m, 1F); IR (thin film) ν_{max} 3555, 3411, 3027, 2925, 2855, 1652, 1599, 1494, 1415, 1424, 1301, 1011 cm^{-1}; MS (ESI) *m*/*z* 245.1 $[M + Na]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}FNaO_2$, 245.0954; found, 245.0952.

(5*R*,6*S*)-5-Fluoro-5,6-dihydro-6-styrylpyran-2-one (2a). To a solution of **26a** (100 mg, 0.45 mmol) in CH_2Cl_2 (6 mL) was added bisacetoxyiodobenzene (444 mg, 1.35 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (15 mg, 20 mol %) at room temperature. After stirring for 2 h, the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ (30 mL) and extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed in turn with saturated solutions of $NaHCO_3$ (30 mL), NH_4Cl (30 mL), and brine (30 mL), 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 **2a** (95 mg, 97%) as a white solid: mp 43−45 °C; $[\alpha]_D^{23.5}$ +145 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (m, 5H), 6.93 (tdd, *J* = 8.7, 5.7, 3.0 Hz, 1H), 6.82 (dd, *J* = 15.9, 5.6 Hz, 1H), 6.20 (dd, *J* = 15.8, 6.3 Hz, 1H), 6.20−6.16 (m, 1H), 5.23−5.16 (m, 1H), 5.09 (dddd, *J* = 46.8, 7.1, 3.0, 1.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.3 (d, *J* = 2.9 Hz), 141.7 (d, *J* = 21.0 Hz), 135.4 (d, *J* = 8.9 Hz), 128.8, 126.9, 123.5, 123.4, 121.8, 121.8, 84.0 (d, *J* = 176 Hz), 80.2 (d, *J* = 24.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −186.4 to −186.7 (m, 1F); IR (thin film) ν_{max} 3060, 3027, 2924, 2856, 1739, 1626, 1576, 1438, 1382, 1232, 1012 cm^{-1}; MS (ESI) *m*/*z* 241.1 $[M + Na]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{11}FNaO_2$, 241.0641; found, 241.0641.

(8*R*,9*S*,*Z*)-8-Fluoro-9-(4-methoxystyryl)-2,2,11,11,12,12-hexamethyl-3,3-diphenyl-4,10-dioxa-3,11-disilatridec-6-ene (25b). Compound **25b** (130 mg, 20%) was prepared from compound **24** (540 mg, 1.08 mmol) using the same process as described for compound **25a**. Colorless oil: $[\alpha]_D^{21.4}$ −206 (*c* 0.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 4H), 7.49−7.37 (m, 6H), 7.30−7.27 (m, 2H), 6.88−6.85 (m, 2H), 6.53 (d, *J* = 15.8 Hz, 1H), 5.99−5.93 (m, 1H), 5.90 (dd, *J* = 15.9, 6.6 Hz, 1H), 4.93 (ddd, *J* = 47.7, 8.4, 4.1 Hz, 1H), 4.44−4.36 (m, 1H), 4.36−4.32 (m, 1H), 4.29−4.22 (m, 1H), 3.85 (s, 3H), 1.10 (s, 9H), 0.93 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.7, 137.9, 137.9, 137.7, 135.8 (d, *J* = 10.2 Hz), 133.8, 132.0, 131.9, 130.0, 127.8, 127.7, 127.3 (d, *J* = 21.2 Hz), 116.3, 92.7 (d, *J* = 171 Hz), 77.6 (d, *J* = 24.8 Hz), 63.0, 57.7, 29.1, 28.2, 21.4, 20.6, −2.12, −2.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ −176.12 to −176.62 (m, 1F); IR (thin film) ν_{max} 3040, 2939, 2895, 2859, 1605, 1511, 1465, 1424, 1253, 1104 cm^{-1}; MS (ESI) *m*/*z* 627.3 $[M + Na]^+$; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{49}FNaO_3Si_2$, 627.3102; found, 627.3091.

(2*Z*,4*R*,5*S*,6*E*)-4-Fluoro-7-(4-methoxyphenyl)hepta-2,6-diene-1,5-diol (26b). Compound **26b** (50 mg, 99%) was prepared from compound **25b** (120 mg, 4.53 mmol) using the same process as described for compound **26a**. Colorless oil: $[\alpha]_D^{21.3}$ −131 (*c* 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 2H), 6.88−6.84 (m, 2H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.07 (dd, *J* = 15.9, 6.9 Hz, 1H), 6.00 (dddd, *J* = 12.9, 7.5, 6.5, 1.2 Hz, 1H), 5.79−5.65 (m, 1H), 5.28 (ddd, *J* = 47.6, 8.1, 5.0 Hz, 1H), 4.43−4.37 (m, 1H), 4.29−4.18 (m, 2H), 3.81 (s, 3H), 2.04 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.7, 134.9 (d, *J* = 10.0 Hz), 133.2, 128.9, 127.9, 126.5 (d, *J* = 22.0 Hz), 123.6, 123.5, 114.0, 114.0, 90.6 (d, *J* = 168.8 Hz), 74.0 (d, *J* = 25.0 Hz), 58.9, 55.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −181.70 to −182.10 (m, 1F); IR (thin film) ν_{max} 3318, 3032, 2925, 2895, 2852, 1605, 1511, 1468, 1250, 1029 cm^{-1}; MS (EI) *m*/*z* 252.1 M^+; HRMS (EI) *m*/*z* M^+ calcd for $C_{14}H_{17}FO_3$, 252.1162; found, 252.1161.

(5*R*,6*S*)-6-(4-Methoxystyryl)-5-fluoro-5,6-dihydropyran-2-one (2b). Compound **2b** (47 mg, 96%) was prepared from compound **26b** (50 mg, 0.20 mmol) using the same process as described for compound **2a**. White solid: mp 108−110 °C; $[\alpha]_D^{22.6}$ +135 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.32 (m, 2H), 6.94 (td, *J* = 9.2, 3.0 Hz, 1H), 6.89−6.86 (m, 2H), 6.76 (d, *J* = 15.9 Hz, 1H), 6.18 (ddd, *J* = 10.0, 1.8, 1.3 Hz, 1H), 6.05 (dd, *J* = 15.9, 6.4 Hz, 1H), 5.16 (dddd, *J* = 48.3, 7.0, 3.0, 1.2 Hz, 1H), 5.14 (dddd, *J* = 13.5, 9.8, 6.8, 1.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.1, 141.7 (d, *J* = 20.9 Hz), 135.2, 128.2, 128.0, 123.5 (d, *J* = 8.1 Hz), 119.4, 119.4, 114.1, 84.0 (d, *J* = 176 Hz), 80.5 (d, *J* = 25.5 Hz), 55.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −186.15 to −186.40 (m, 1F); IR (thin film) ν_{max} 2923, 2849, 1730, 1642, 1597, 1508, 1238, 1009 cm^{-1}; MS (EI) *m*/*z* 248.1 M^+; HRMS (EI) *m*/*z* M^+ calcd for $C_{14}H_{13}FO_3$, 248.0849; found, 248.0853.

(8*R*,9*S*,*Z*)-8-Fluoro-9-(4-fluorostyryl)-2,2,11,11,12,12-hexamethyl-3,3-diphenyl-4,10-dioxa-3,11-disilatridec-6-ene (25c). Compound **25c** (186 mg, 52%) was prepared from compound **24** (300 mg, 0.60 mmol) using the same process as described for compound **25a**. Colorless oil: $[\alpha]_D^{21.9}$ −153 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 8.1, 1.5 Hz, 4H), 7.45−7.34 (m, 6H), 7.29−7.24 (m, 2H), 7.00−6.95 (m, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 5.94 (dd, *J* = 16.0, 4.0 Hz, 1H), 5.94−5.90 (m, 1H), 5.64 (ddd, *J* = 11.7, 10.2, 8.5 Hz, 1H), 4.93 (ddd, *J* = 47.5, 8.4, 4.1 Hz, 1H), 4.43−4.37 (m, 1H), 4.36−4.28 (m, 1H), 4.25−4.18 (m, 1H), 1.05 (s, 9H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.4 (d, *J* = 247 Hz), 135.5, 135.4, 135.3 (d, *J* = 10.0 Hz), 133.4 (d, *J* = 8.2 Hz), 132.7, 130.7, 129.7 (d, *J* = 3.5 Hz), 128.0, 128.0, 127.7, 127.7, 127.4, 124.5 (d, *J* = 21.3 Hz), 115.5 (d, *J* = 21.2 Hz), 90.3 (d, *J* = 171 Hz), 74.9 (d, *J* = 24.9 Hz), 60.7, 26.7, 25.8, 19.1, 18.2, −4.5, −4.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.06 to −114.29 (m, 1F), −176.30 to −176.61 (m, 1F); IR (thin film) ν_{max} 3043, 2943, 2860, 1592, 1509, 1418, 1242, 1005 cm^{-1}; MS (MALDI) *m*/*z* 615.3 $[M + Na]^+$; HRMS (MALDI) *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{46}F_2NaO_2Si_2$, 615.2902; found, 615.2906.

(2*Z*,4*R*,5*S*,6*E*)-4-Fluoro-7-(4-fluorophenyl)hepta-2,6-diene-1,5-diol (26c). Compound **26c** (60 mg, 93%) was prepared from compound **25c** (160 mg, 0.27 mmol) using the same process as described for compound **26a**. White solid: mp = 92−93 °C; $[\alpha]_D^{21.7}$ −144 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H), 7.09−7.03

(m, 2H), 6.72 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 16.0, 6.6 Hz, 1H), 6.08−6.01 (m, 1H), 5.81−5.72 (m, 1H), 5.33 (dddd, J = 47.6, 8.1, 5.1, 1.2 Hz, 1H), 4.49−4.42 (m, 1H), 4.35−4.24 (m, 2H), 2.19 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.6 (d, J = 248 Hz), 134.9 (d, J = 10.0 Hz), 132.2, 128.3, 128.2, 126.5 (d, J = 22.1 Hz), 125.7, 115.6 (d, J = 21.5 Hz), 90.5 (d, J = 169 Hz), 73.6 (d, J = 25.4 Hz), 58.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.10 to −113.55 (m, 1F), −181.79 to −182.06 (m, 1F); IR (thin film) ν_{max} 3405, 3043, 2926, 2870, 1584, 1508, 1415, 1229, 1013 cm^{-1}; MS (EI) m/z 240.1 M$^+$; HRMS (EI) m/z M$^+$ calcd for $C_{13}H_{14}F_2O_2$, 240.0962; found, 240.0966.

(5*R*,6*S*)-6-(4-Fluorostyryl)-5-fluoro-5,6-dihydropyran-2-one (2c). Compound **2c** (34 mg, 96%) was prepared from compound **26c** (36 mg, 0.15 mmol) using the same process as described for compound **2a**. White solid: mp 93−94 °C. $[\alpha]_D^{21.0}$ +226 (c 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 2H), 7.07−7.01 (m, 2H), 6.94 (td, J = 9.7, 2.8 Hz, 1H), 6.79 (d, J = 15.9 Hz, 1H), 6.18 (dt, J = 10.0, 1.4 Hz, 1H), 6.13 (dd, J = 16.0, 6.1 Hz, 1H), 5.16 (dddd, J = 47.6, 7.3, 2.8, 1.3 Hz, 1H), 5.19−5.12 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.0 (d, J = 248 Hz), 161.3, 141.9 (d, J = 20.9 Hz), 134.3, 131.5 (d, J = 3.6 Hz), 128.5 (d, J = 8.2 Hz), 123.3 (d, J = 8.1 Hz), 121.6, 115.8 (d, J = 21.8 Hz), 84.1 (d, J = 176 Hz), 80.0 (d, J = 25.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.35 to −112.44 (m, 1F), −187.34 (dt, J = 49.4, 9.1 Hz, 1F); IR (thin film) ν_{max} 3065, 2921, 2851, 1731, 1633, 1594, 1510, 1415, 1378, 1232, 1014 cm^{-1}; MS (EI) m/z 236.1 M$^+$; HRMS (EI) m/z M$^+$ calcd for $C_{13}H_{10}F_2O_2$, 236.0649; found, 236.0648.

(8*R*,9*S*,*Z*)-8-Fluoro-9-((*Z*)-hept-1-enyl)-2,2,11,11,12,12-hexamethyl-3,3-diphenyl-4,10-dioxa-3,11-disilatridec-6-ene (25d). To a solution of $CH_3(CH_2)_5P^+Ph_3Br^-$ (380 mg, 0.89 mmol) in THF (5 mL) was added NaHMDS (0.44 mL, 0.89 mmol) at −78 °C under nitrogen atmosphere. After stirring for 20 min, the mixture was warmed to −30 °C, left to stand for 30 min, and recooled to −78 °C, and a solution of **24** (200 mg, 0.40 mmol) in THF (5 mL) was then added dropwise. The mixture was stirred for 3 h at room temperature and then diluted with brine (10 mL) and extracted with ethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether: ethyl acetate = 100:1) to give **25d** (209 mg, 92%) as a colorless oil: $[\alpha]_D^{21.3}$ −105 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.69 (m, 4H), 7.46−7.37 (m, 6H), 5.95−5.89 (m, 1H), 5.67−5.59 (m, 1H), 5.43−5.37 (m, 1H), 5.15 (t, J = 9.7 Hz, 1H), 4.74 (ddd, J = 48.4, 8.4, 4.0 Hz, 1H), 4.57−4.51 (m, 1H), 4.34−4.25 (m, 1H), 4.25−4.19 (m, 1H), 2.05−1.88 (m, 2H), 1.32 (q, J = 6.8 Hz, 2H), 1.31−1.19 (m, 4H), 1.06 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.5, 135.1, 135.0, 133.5 (d, J = 11.0 Hz), 132.7, 129.7, 129.7, 128.5, 128.4, 127.7, 124.8 (d, J = 21.6 Hz), 90.1 (d, J = 171 Hz), 70.3 (d, J = 24.9 Hz), 60.6, 31.5, 29.1, 28.0, 26.8, 25.7, 22.5, 19.1, 18.1, 14.0, −4.6, −4.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −176.10 (dt, J = 47.5, 11.5 Hz, 1F); IR (thin film) ν_{max} 3059, 3017, 2934, 2860, 1581, 1466, 1256, 1105 cm^{-1}; MS (MALDI) m/z 591.3 [M + Na]$^+$; HRMS (MALDI) m/z [M + Na]$^+$ calcd for $C_{34}H_{53}FNaO_2Si_2$, 591.3466; found, 591.3467.

(2*Z*,4*R*,5*S*,6*Z*)-4-Fluorododeca-2,6-diene-1,5-diol (26d). Compound **26d** (75 mg, 99%) was prepared from compound **25d** (200 mg, 0.35 mmol) using the same process as described for compound **26a**. Colorless oil: $[\alpha]_D^{20.0}$ −12.3 (c 0.79, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (dddd, J = 13.9, 6.6, 2.2, 1.1 Hz, 1H), 5.69 (dd, J = 10.0, 5.4 Hz, 1H), 5.71−5.61 (m, 1H), 5.39−5.34 (m, 1H), 5.15 (dddd, J = 47.8, 8.2, 4.9, 0.9 Hz, 1H), 4.54 (ddd, J = 13.1, 7.2, 4.9 Hz, 1H), 4.25−4.14 (m, 2H), 2.82 (s, 2H), 2.17−2.02 (m, 2H), 1.45−1.34 (q, J = 7.4 Hz, 2H), 1.35−1.24 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.0, 134.9 (d, J = 10.1 Hz), 126.5, 126.4 (d, J = 22.5 Hz), 126.3, 91.4 (d, J = 169 Hz), 68.7 (d, J = 25.7 Hz), 58.6, 31.5, 29.2, 28.0, 22.5, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −181.93 (dt, J = 47.8, 13.3 Hz, 1F); IR (thin film) ν_{max} 3391, 3020, 2927, 2862, 1575, 1418, 1020 cm^{-1}; MS (EI) m/z 198.1 [M$^+$ − H_2O]; HRMS (EI) m/z [M$^+$ − H_2O] calcd for $C_{12}H_{19}FO$, 198.1420; found, 198.1422.

(5*R*,6*S*)-5-Fluoro-6-((*Z*)-hept-1-enyl)-5,6-dihydropyran-2-one (2d). Compound **2d** (55 mg, 81%) was prepared from compound **26d** (70 mg, 0.32 mmol) using the same process as described for compound **2a**. Colorless oil: $[\alpha]_D^{22.1}$ −392 (c 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (td, J = 9.8, 2.8 Hz, 1H), 6.18 (d, J = 9.6 Hz, 1H), 5.87 (dt, J = 10.5, 7.6 Hz, 1H), 5.42 (t, J = 9.8 Hz, 1H), 5.35−5.28 (m, 1H), 5.03 (ddd, J = 47.6, 6.3, 2.5 Hz, 1H), 2.23−2.08 (m, 2H), 1.51−1.38 (q, J = 6.8 Hz, 2H), 1.38−1.26 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.6 (d, J = 3.1 Hz), 141.6 (d, J = 20.3 Hz), 139.2, 123.7 (d, J = 8.2 Hz), 122.7 (d, J = 3.1 Hz), 83.9 (d, J = 176 Hz), 76.1 (d, J = 25.6 Hz), 31.4, 28.9, 28.0, 22.4, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −185.24 (dt, J = 47.5, 9.6 Hz, 1F); IR (thin film) ν_{max} 3021, 2930, 2860, 1741, 1635, 1462, 1379, 1229, 1019 cm^{-1}; MS (EI) m/z 212.0 M$^+$; HRMS (EI) m/z M$^+$ calcd for $C_{12}H_{17}FO_2$, 212.1213; found, 212.1212.

■ ASSOCIATED CONTENT

Supporting Information. Chiral HPLC analytical spectra of compounds **14** and **15**, copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds, and crystallographic data for compound **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: flq@mail.sioc.ac.cn.

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