Synthesis of New Optically Active Propargylic Fluorides and Application to the Enantioselective Synthesis of Monofluorinated Analogues of Fatty Acid Metabolites

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A new approach to obtain optically active unsaturated or polyunsaturated systems with a single fluorine atom in an allylic or propargylic position is reported. Central to this strategy is the high regio- and stereocontrol observed during the fluorination of propargylic alcohols allowing a short and efficient synthesis of **1**. Further, simple functional group transformations gave the enals **2** and **3**. These three key intermediates were used for the preparation of optically active monofluorinated analogues of fatty acid metabolites.

Introduction

The effects of fluorine on physical properties and chemical reactivity explain why fluorinated compounds were intensively studied and overwhelmingly used in areas as diverse as pharmaceuticals, agrochemicals, and polymers.[1] It is well-known that the introduction of fluorine atoms strongly modifies the biological and pharmacological activity in a molecule.[2] The isosteric and isoelectronic nature of the fluorine to the hydroxyl group renders the fluorinated analogues as useful pharmacological lead compounds.[3,4] Hence, it is important to control the regio- and stereoselectivity of the fluorination reaction. Particularly, the difficulties encountered during selective monofluorination in a position vicinal to unsaturated derivatives, especially allylic systems[5,6] are well-known and such compounds were not widespread. In addition, the importance of optical purity in bioactive compounds is well-established, underscoring the need to synthesize optically pure fluorinated analogues.[7] Only a few examples of optically active allylic and propargylic monofluorinated compounds have been reported to date.[5] Davis et al. reported an elegant approach using enantiomerically enriched α-fluoro carbonyls[8] as the precursor to a Horner−Wadsworth−Emmons olefination process.[9] However, they underline experimental difficulties concerning the slight loss of enantiomeric purity of the α-fluoro aldehydes during the Dess−Martin oxidation of the precursor α-fluoro alcohols.[10] Several years ago we started a program in this field and we have reported for the first time that transition metal complexes allow selective monofluorination.[11−14] A second strategy, via small chiral fluorinated building blocks, was also envisaged.[15,16] It is based on propargylic fluorides and takes advantage of the very high regio- and stereoselectivity observed during the dehydroxy-fluorination of propargylic alcohol with diethylamino sulfur trifluoride (DAST) at low temperature.[13,15] The later strategy can further lead to two approaches depending upon the post-treatment of the optically active propargylic monofluorinated key intermediate **A**. We have already demonstrated in the first approach that the intermediate **A** can be elaborated into a polyunsaturated system **B** with a fluorine in the allylic position by a sequential hydrometalation and palladium catalyzed coupling reactions (Figure 1). While the palladium coupling was stereospecific, the first step (hydrostannylation reaction) lead to a mixture of *Z* and *E* isomers which had to be separated by chromatography.[16] To avoid this lack of stereocontrol, herein we report an alternative approach by functionalizing the chiral synthon **A**. Formylation of **A** followed by partial hydro-

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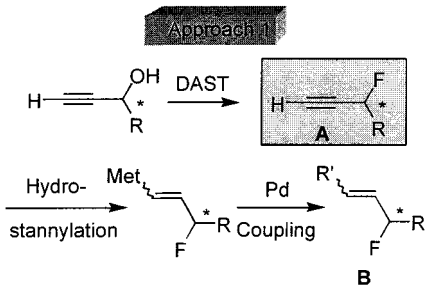


Figure 1. The propargylic pathway to allylic fluorides.

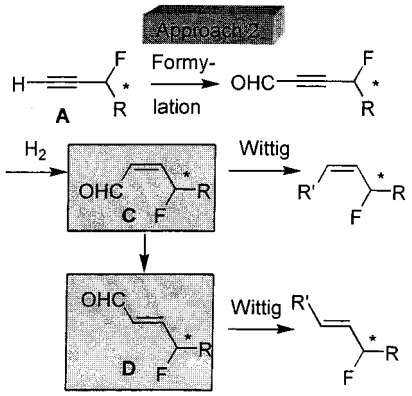


Figure 2. The propargylic pathway to allylic fluorides.

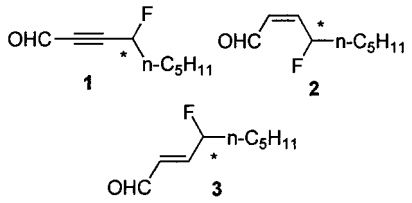


Figure 3. New chiral fluorinated key intermediates.

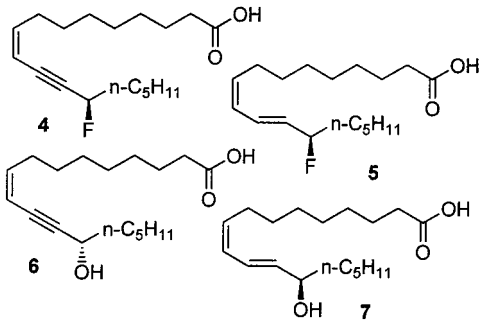
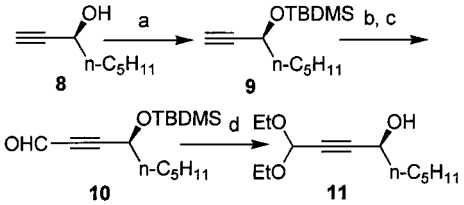


Figure 4. Natural products and their monofluorinated analogues.

genation would provide two new fluorinated key enal intermediates **C** and **D** (Figure 2). These fluorinated synthons should, in principle, be versatile intermediates for the preparation of a large number of enantiomerically pure compounds with a fluorine atom vicinal to unsaturated or polyunsaturated skeletons.

The purpose of this paper is to report the successful preparation of the key intermediates **1**, **2**, and **3** in optically active form (ee = 96%) (Figure 3) and their use for the preparation of enantiomerically enriched fluorinated analogues **4** and **5** of the polyunsaturated fatty acid metabolites **6** and **7** (Figure 4).

Scheme 1. Synthesis of Alcohol 11[a]



[a] Reagents and conditions: (a) TBDMSCl, NEt_3, DMAP, THF, rt (95%); (b) *n*-BuLi, HMPA, THF, −70 °C; (c) DMF, −65 °C to −35 °C (89%); (d) $HC(OEt)_3$, pTsOH, EtOH, rt (91%).

Results and Discussion

Preparation of Alcohol 11. The first stage of our synthesis was the preparation of the optically active alcohol **11** as a key compound to obtain the three new fluorinated intermediates **1**, **2**, and **3**. This could be accomplished in three steps and in 77% overall yield from the oct-1-yn-3-ol **8** (Scheme 1). The enantiomerically pure (*S*)-oct-1-yn-3-ol **8** was obtained either commercially[17] or by resolution of its racemic mixture.[18] The (*S*)-alcohol **8** was first protected to give *tert*-butyldimethylsilyl ether **9** and then treated with butyllithium to get acetylide which was directly formylated[19] using DMF. Finally, the TBDMS group in **10** was cleaved and the aldehyde function was protected as diethyl acetal in a one-pot reaction. At this stage the optical purity of **11** (ee ≥ 96%) was determined by ^{1}H NMR using $Eu(hfc)_3$ as the chiral shift reagent.

Stereoselective Dehydroxy-Fluorination of 11 and Synthesis of 1. To obtain the highest stereoselectivity in the dehydroxy-fluorination using DAST, previous studies[11,15] have established the importance of maintaining a low temperature. Furthermore, the amount of the byproduct formed by elimination of HF[16] during the dehydroxy-fluorination was minimized at −78 °C (less than 8%) and could be easily removed by chromatography.[20] Deacetalization of **12**, with a large excess of formic acid, furnished the fluorinated key intermediate **1** (53% overall yield from (*S*)-oct-1-yn-3-ol **8**). The aldehyde **1** was used directly in the next steps, due to its relative instability. Enantiomeric excess (ee) of the fluorinated compounds **12** and **1** was established by a fully decoupled ^{19}F NMR analyses in C_6D_6 of the imidazolidine **13** obtained by coupling **1** with chiral diamine (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenyl ethylenediamine[21,22] (Scheme 2). When ^{19}F NMR was recorded on a racemic mixture of **13**, two well separated peaks corresponding to the two diastereomers were obtained allowing an easy measurement of the diastereomeric excess (de). These NMR analysis gave a de of 96% for **13** and a 96% ee value for **1**.

Synthesis of 2 and 3. The two other fluorinated building blocks **2** and **3** were obtained from **12** in two

(17) (*S*)-oct-1-yn-3-ol was purchased from Aldrich Chemical Co.

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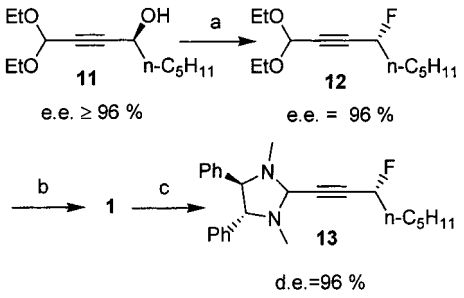
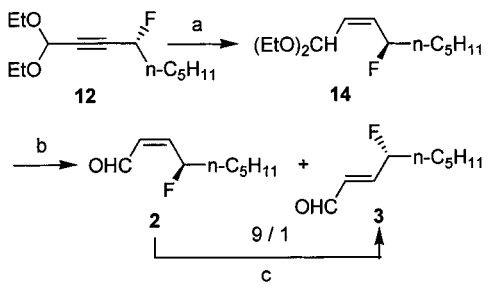
Scheme 2. Stereoselectivity of Fluorination[a]



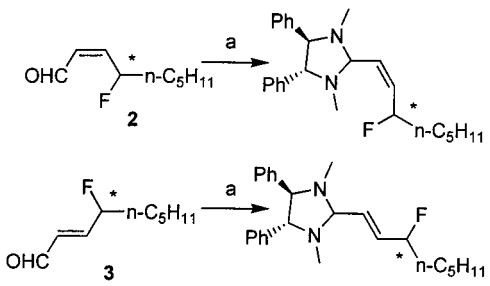
[a] Reagents and conditions: (a) DAST, CH_2Cl_2, −78 °C (85%); (b) HCOOH, CH_2Cl_2, rt (92%); (c) (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenyl ethylenediamine, 3 Å molecular sieves, CH_2Cl_2, rt (100%).

Scheme 3. Synthesis of Chiral Molecules 2 and 3[a]



[a] Reagents and conditions: (a) pyridine, Lindlar catalyst, H_2, *n*-pentane, rt (99%); (b) HCOOH, CH_2Cl_2, rt, (**2**, 87% and **3**, 8%); (c) DMSO, 80 °C (100%).

Scheme 4. ee Determination of 2 and 3[a]



[a] Reagents and conditions: (a) (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenyl ethylenediamine, 3 Å molecular sieves, CH_2Cl_2, rt (100%).

steps. A partial hydrogenation of **12** using 20 wt % Pd/$CaCO_3$ gave exclusively the corresponding *Z* alkene **14**.[23] A rapid deacetalization of **14** with a large excess of formic acid afforded the aldehydes **2** and **3** (46% overall yield from (*S*)-oct-1-yn-3-ol **8**, 9:1 (*Z*/*E*)) which were separated by flash chromatography. The *Z* aldehyde **2** was surprisingly stable since it was left unchanged after 7 days in benzene at 60 °C. However, it could be quantitatively isomerized to the *E* aldehyde **3** by heating in DMSO at 80 °C (Scheme 3).

Enantiomeric excess of the aldehydes **2** and **3** were controlled using the same method as the one previously described for the aldehyde **1** (Scheme 4) and similar results were obtained (ee = 96% for **2** and **3**, in each case). Similar sets of reactions were performed on (*R*)-oct-1-yn-3-ol to give the corresponding (*S*)-enantiomers of **1**, **2**, and **3** with 96% ee in each case.

(23) It is essential to remove all sulfur impurities from **12** in order to successfully perform the hydrogenation. For similar observations see: Graham, S. M.; Prestwich, G. D. *J. Org. Chem.* **1994**, *59*, 2956−2966.

It is important to notice that **3** is the monofluorinated analogue of (*E*)-4-hydroxy-2-nonenal (4-HNE).[24] The 4-HNE is formed in vivo as a breakdown product of oxidized polyunsaturated lipids resulting from a variety of physiological processes known as *oxidative stress*.[25] Recent studies of the 4-HNE highlight the biological importance of this molecule.[26] We have reported herein the first enantioselective synthesis of such a fluorinated analogue, which could be useful for biological studies on this type of metabolites.

Synthesis of the Analogues of Natural Products. The propargylic aldehyde **1** and the enal **3** could also be useful intermediates for the synthesis of monofluorinated analogues of natural products, and two of such examples were selected for our studies. The 13-(*S*)-hydroxy-octadec-9-(*Z*)-en-11-ynoic acid **6** (as well as its *E* isomer) is an inhibitor toward spore germination of rice blast fungus.[27] The 13-(*R*)-hydroxy-octadeca-9-(*Z*),11-(*E*)-dienoic acid **7** (13-HODE, also called coriolic acid) is a natural product[28] involved in tumor cell adhesion[29] and possesses anti-TXA_2 activity[30] among other biological activities. Its (*S*)-isomer is an inhibitor of RBL-1 (rat basophilic leukemia) 5-lipoxygenase.[31] It acts as a self-defense agent against rice blast disease,[32] displays unique calcium ionophoric properties,[33] and it is also present in sera of patients with familial mediterranean fever and may have a role in its pathogenesis.[34] Furthermore, it acts as a vessel wall chemorepellant,[35] it is an inhibitor of platelet agregation[30] and platelet adhesion in human endothelium cell cultures,[36] and it appears to be involved in tumor cell adhesion[37] and melatonin regulation of cancer growth.[38]

Since the (*S*)-enantiomer of **8** is the most easily accessible on a large scale by resolution, starting from (*S*)-oct-1-yn-3-ol **8,** the fluorinated (*R*)-series analogues of fatty acid metabolites have been prepared. The analogues of (+)-(13*R*)-13-hydroxy-octadec-9-en-11-ynoic acid methyl ester as a mixture of *Z*/*E* isomers, **15** and **16**, was obtained by a Wittig reaction between the aldehyde (+)-(4*R*)-**1** and (8-methoxycarbonyl-octyl)-triphenyl-phosphorane **17** in the ratio 7/3 (Scheme 5). The diastereomers **15** and **16** were separated by preparative TLC. Their stereochemistry was established by ^{1}H NMR using the $^3J_{HH}$ coupling constants, 10.8 Hz for the *Z* isomer and 15.9 Hz for the *E* isomer.

The (+)-(13*R*)-13-fluoro-octadeca-9-(*Z*),11-(*E*)-dienoic acid methyl ester **18** was obtained similarly after Wittig reaction between the aldehyde (−)-(4*R*)-(*E*)-**3** and (8-methoxycarbonyl-octyl)-triphenyl-phosphorane (Scheme 5).[24,39]

(24) For previous synthesis, but in racemic form, see: Grée, D.; Grée, R.; Boukerb, A.; Laabassi, M. *Tetrahedron Lett.* **1997**, 38, 6209−6212.

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(26) See for instance: Deng, Y.; Salomon, R. G. *J. Org. Chem.* **1998**, *63*, 3504−3507. Xu, G.; Liu, Y.; Sayre, L. M. *J. Org. Chem.* **1999**, *64*, 5732−5745 and references cited herein.

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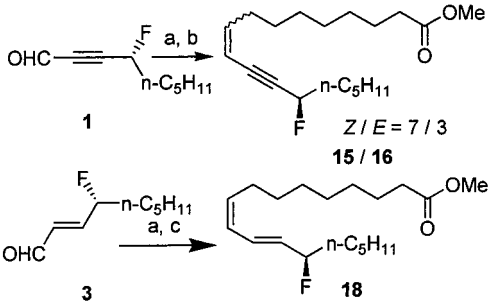
Scheme 5. Synthesis of the Optically Active Fluorinated Analogue of 6 and 7[a]



[a] Reagents and conditions: (a) Br-$^{+}$Ph$_3$P(CH$_2$)$_8$COOMe (**17**), LiHMDS, HMPA, THF, −20 °C to −45 °C; (b) **1**, −70 °C to −10 °C (**15**, 37% and **16**, 15%); (c) **3**, −78 °C to −10 °C (40%).

The overall yields, from (*S*)-oct-1-yn-3-ol **8**, were 20% (6 steps) for **15**, 8% (6 steps) for **16,** and 18% (8 steps) for **18**.

Conclusion

Results reported herein confirm the interest and usefulness of the propargylic pathway to allylic fluorides. This approach provides a short and efficient preparation of new optically active monofluorinated intermediates which have been used in the enantioselective synthesis of fluorinated analogues of unsaturated fatty acid metabolites. These chiral synthons have the potential to be used in the synthesis of a broad variety of optically active allylic fluorinated compounds.[40] Further applications of the present reactions will be reported in due course.

Experimental Section

General. All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen with magnetic stirring. Thin-layer chromatography (TLC) was done on Merck (Art. 1.05554) precoated silica gel 60 F_{254} aluminum sheets (layer thickness, 0.2 mm) and developed in the indicated eluent systems. Visualization was effected with a UV lamp (254 nm) and/or by staining with *p*-anisaldehyde/H_2SO_4 solution. Preparative thin-layer chromatographic separations were obtained using Merck (Art. 1.13895) silica gel 60 F_{254} preparative plates (layer thickness, 1 mm). Flash column chromatography was performed using silica gel 60 (Geduran, 40−63 μm, Merck). Solvents were purified as follows: Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl under N_2. Diethyl ether and dichloromethane were distilled from P_2O_5 and stored over 3 Å molecular sieves. Triethylamine and dimethylformamide were distilled from CaH_2. The petroleum ether used had a boiling range of 30−60 °C. NMR spectra were recorded on a 400 MHz spectrometer. All chemical shifts are reported in parts per million (δ). ^{1}H NMR (400 MHz) spectra were recorded at room temperature in $CDCl_3$ solution and referenced to residual $CHCl_3$ (7.27 ppm). Fully decoupled ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solution. The center peak of $CDCl_3$ (77.0 ppm) was used as the internal reference. ^{19}F NMR (376.5 MHz) spectra were recorded in $CDCl_3$ solution using $CFCl_3$ as internal reference. Elemental analyses were performed by the department of microanalyses (I.C.S.N.) in Gif-sur-Yvette (France). Mass spectra were carried out at the C.R.M.P.O. in Rennes (France). IR spectra were recorded on a FT-IR spectrophotometer using NaCl cells. Optical rotation was recorded at 589 nm.

(±)-3-(*O*-*tert*-Butyldimethylsilyl)-1-octyne (9). A solution of oct-1-yn-3-ol **8** (10.39 g, 79.0 mmol), Et_3N (22.4 mL, 158.1 mmol, 2.0 equiv), DMAP (0.98 g, 7.9 mmol, 0.1 equiv) and TBDMSCl (13.45 g, 87.5 mmol, 1.1 equiv) in 120 mL of THF was stirred at room temperature for 24 h. Saturated NaCl (20 mL) was added and the solution was extracted with Et_2O (3 × 20 mL). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give a yellow oil. Purification by flash chromatography (petroleum ether/Et_2O, 95/5) gave the title compound **9** (18.00 g, 95%) as a colorless oil: TLC *Rf* = 0.97 (petroleum ether/Et_2O, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (td, *J* = 6.4 Hz, *J* = 2.0 Hz, 1H), 2.38 (d, *J* = 2.0 Hz, 1H), 1.71−1.64 (m, 2H), 1.48−1.38 (m, 2H), 1.37−1.24 (m, 4H), 0.91 (s, 9H), 0.90 (t, *J* = 6.7 Hz, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.77, 71.82, 62.76, 38.52, 31.41, 25.76, 24.78, 22.56, 18.22, 14.00, −4.60, −5.09; MS (EI) 70 eV *m*/*z* (rel int) 239 (13.1, [M − ·H]$^+$), 75 (100.0, [EtO−CH=OH]$^+$); HRMS (EI) 70 eV calcd. for $C_{14}H_{27}O^{28}Si$ [M − ·H]$^+$, 239.1831; found, 239.182. Anal. Calcd. for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 69.47; H, 11.65. IR (neat) ν 3313, 2960, 2860, 1472, 1253, 1120, 1092, 839, 778 cm^{-1}; (+)-(3*R*)-**9** [α]$^{20}_D$ = +44.7 (*c* = 0.38; CH_2Cl_2); (−)-(3S)-**9** [α]$^{20}_D$ = −43.4 (*c* = 0.41; CH_2Cl_2).

(±)-4-(*O*-*tert*-Butyldimethylsilyl)-2-yne-non-1-al (10). A solution of silylated alcohol **9** (10.49 g, 43.6 mmol) in anhydrous THF (200 mL) was treated with *n*-butyllithium (30 mL of a 1.6 M solution in hexanes, 48.0 mmol, 1.1 equiv) under nitrogen at −70 °C. The solution was stirred for an additional 20 min and anhydrous HMPA (38.3 mL, 218.1 mmol, 5.0 equiv) was added. The temperature was raised to −40 °C in 140 min and then lowered again to −65 °C. Freshly distilled DMF (6.8 mL, 87.2 mmol, 2.0 equiv) was added. The reaction mixture was slowly allowed to warm to −35 °C in 140 min and quenched at this temperature by adding aqueous NH_4Cl. The crude product was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated at reduced pressure. The product was purified on silica gel (petroleum ether/Et_2O, 95/5) to give aldehyde **10** (10.42 g, 89%) as a pale yellow oil: TLC *Rf* = 0.76 (petroleum ether/Et_2O, 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 4.52 (t, *J* = 6.6 Hz, 1H), 1.78−1.69 (m, 2H), 1.49−1.39 (m, 2H), 1.37−1.25 (m, 4H), 0.91 (s, 9H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.71, 98.14, 83.48, 62.78, 37.67, 31.29, 25.67, 24.64, 22.48, 18.15, 13.96, −4.63, −5.12; MS (EI) 70 eV *m*/*z* (rel int) 253 (0.8, [M − ·Me]$^+$), 211 (12.3, [M − ·*t*Bu]$^+$), 75 (100.0, [EtO−CH=OH]$^+$); HRMS (EI) 70 eV calcd. for $C_{14}H_{25}O_228Si$ [M − ·Me]$^+$, 253.1624; found, 253.162 and calcd. for $C_{11}H_{19}O_228Si$ [M − ·*t*Bu]$^+$, 211.1154; found, 211.115; (+)-(4*R*)-**10** [α]$^{20}_D$ = +45.7 (*c* = 0.44; CH_2Cl_2); (−)-(4S)-**10** [α]$^{20}_D$ = −48.8 (*c* = 0.51; CH_2Cl_2).

(±)-1,1-Diethoxynon-2-yn-4-ol (11). A solution of aldehyde **10** (10.40 g, 38.7 mmol), anhydrous triethyl orthoformate (7.9 mL, 46.5 mmol, 1.2 equiv), and *p*-toluenesulfonic acid monohydrate (6.38 g, 38.7 mmol, 1 equiv) in 150 mL ethyl alcohol was stirred at room temperature for 3 h. The reaction mixture was neutralized with solid Na_2CO_3 and diluted with water and

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(39) Starting from the aldehyde **2**, the same Wittig reaction was not successful and only degradation products were observed.
(40) The stability of such fluorides is also of much interest with regards to their potential use in synthesis. From our experience the acetals corresponding to **1**, **2**, and **3** are very stable and are the best intermediates to be stored (several months at 0 °C). As pure compounds and under nitrogen atmosphere, the aldehydes **1**, **2**, and **3** are stable a few days at room temperature and for several weeks in a refrigerator. As expected, the polyunsaturated derivatives decompose relatively rapidly at room temperature but they can be stored for several weeks under an inert atmosphere in a refrigerator.

Et_2O. The phases were separated and the extraction was completed with Et_2O (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to give a yellow oil which was subjected to flash chromatography (petroleum ether/Et_2O, 8/2) to afford alcohol **11** (8.01 g, 91%) as a pale yellow oil: TLC $Rf = 0.57$ (petroleum ether/Et_2O, 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (d, $J = 1.3$ Hz, 1H), 4.42 (qd, $J = 5.6$ Hz, $J = 1.3$ Hz 1H), 3.74 (dqd, $J = 9.3$ Hz, $J = 5.0$ Hz, $J = 2.2$ Hz, 2H), 3.58 (dq, $J = 9.5$ Hz, $J = 7.1$ Hz, 2H), 2.08 (d, $J = 5.6$ Hz, 1H), 1.75−1.67 (m, 2H), 1.49−1.42 (m, 2H), 1.34−1.27 (m, 4H), 1.23 (t, $J = 7.1$ Hz, 6H), 0.89 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 91.21, 86.51, 79.96, 62.24, 60.86, 60.77, 37.38, 31.35, 24.73, 22.50, 15.01, 13.94; MS (EI) 70 eV *m*/*z* (rel int) 227 (3.4, $[M - \cdot H]^+$), 183 (100.0, $[M - \cdot OEt]^+$); HRMS (EI) 70 eV calcd. for $C_{13}H_{23}O_3$ $[M - \cdot H]^+$, 227.1647; found, 227.164. Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.09; H, 10.61. IR (neat) ν 3400, 2976, 2933, 2863, 1459, 1392, 1356, 1328, 1148, 1119, 1053, 1011 cm^{-1}; (+)-(4*R*)-**11** $[\alpha]^{20}_D = +0.9$ ($c = 0.44$; CH_2Cl_2); (−)-(4S)-**11** $[\alpha]^{20}_D = -0.8$ ($c = 0.26$; CH_2Cl_2).

(±)-1,1-Diethoxynon-2-yn-4-fluoro (12). To a solution of DAST (4.1 mL, 29.5 mmol, 1.2 equiv) in 90 mL of distilled CH_2Cl_2 at −78 °C was added under nitrogen a solution of alcohol **11** (5.61 g, 24.6 mmol) in 5.0 mL of distilled CH_2Cl_2 via cannula. The solution was stirred at −78 °C for an additional hour and quenched with saturated K_2CO_3. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were dried under $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (pentane/$CHCl_3$, 8/2) afforded the fluorinated compound **12** (4.80 g, 85%) as a pale yellow oil: TLC $Rf = 0.68$ (pentane/Et_2O, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dd, $J_{H-F} = 4.2$ Hz, $J = 1.0$ Hz, 1H), 5.14 (dtd, $J_{H-F} = 48.3$ Hz, $J = 6.1$ Hz, $J = 1.0$ Hz, 1H), 3.74 (dqd, $J = 9.8$ Hz, $J = 4.5$ Hz, $J = 2.6$ Hz, 2H), 3.60 (dq, $J = 9.2$ Hz, $J = 7.1$ Hz, 2H), 1.97−1.75 (m, 2H), 1.57−1.38 (m, 2H), 1.37−1.28 (m, 4H), 1.24 (t, $J = 7.0$ Hz, 6H), 0.90 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 91.06, 83.14 (d, $J = 10.3$ Hz), 82.36 (d, $J = 167.7$ Hz), 81.92 (d, $J = 26.1$ Hz), 60.97, 60.92, 35.59 (d, $J = 22.1$ Hz), 31.16, 24.06 (d, $J = 3.8$ Hz), 22.40, 14.98, 13.88; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −175.45 (dddd, $J = 48.3$ Hz, $J = 22.0$ Hz, $J = 19.4$ Hz, $J = 4.2$ Hz); MS (EI) 70 eV *m*/*z* (rel int) 229 (1.2, $[M - \cdot H]^+$), 185 (100.0, $[M - \cdot OEt]^+$); HRMS (EI) 70 eV calcd. for $C_{13}H_{22}O_2F$ $[M - \cdot H]^+$, 229.1604; found, 229.162. Anal. Calcd. for $C_{13}H_{23}FO_2$: C, 67.79; H, 10.07. Found: C, 68.04; H, 10.12. IR (neat) ν 2977, 2932, 2874, 2180, 1468, 1354, 1328, 1155, 1120, 1055, 1017, 905, 734 cm^{-1}; (−)-(4S)-**12** $[\alpha]^{20}_D = -4.8$ ($c = 0.37$; CH_2Cl_2); (+)-(4*R*)-**12** $[\alpha]^{20}_D = +4.7$ ($c = 0.49$; CH_2Cl_2).

(±)-4-Fluoro-2-yn-non-1-al (1). To a solution of acetal **12** (0.53 g, 2.3 mmol) in CH_2Cl_2 (20 mL) was added at room temperature formic acid (17.7 mL, 460.6 mmol, 200.0 equiv). After being stirred for 70 min the mixture was neutralized with solid Na_2CO_3 (24.4 g) and diluted with saturated Na_2CO_3 solution. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to give the aldehyde **1** (0.33 g, 92%) as a yellow oil. NMR analysis showed a clean crude product and the aldehyde was used directly for the next steps due to its relative instability. TLC $Rf = 0.60$ (pentane/Et_2O, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, $J_{H-F} = 2.8$ Hz, 1H), 5.26 (dt, $J_{H-F} = 48.0$ Hz, $J = 6.2$ Hz 1H), 2.02−1.80 (m, 2H), 1.56−1.43 (m, 2H), 1.40−1.27 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.90 (d, $J = 3.1$ Hz), 91.29 (d, $J = 26.7$ Hz), 86.08 (d, $J = 9.9$ Hz), 81.82 (d, $J = 172.4$ Hz), 34.94 (d, $J = 21.8$ Hz), 31.09, 23.95 (d, $J = 3.8$ Hz), 22.35, 13.86; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −178.56 (dddd, $J = 48.0$ Hz, $J = 22.0$ Hz, $J = 19.9$ Hz, $J = 2.8$ Hz); MS (EI) 70 eV *m*/*z* (rel int) 155 (0.3, $[M - \cdot H]^+$), 141 (1.4, $[M - \cdot Me]^+$), 136 (1.1, $[M - HF]^+$), 43 (100.0, $[C_3H_7]^+$); HRMS (EI) 70 eV calcd. for $C_9H_{12}FO$ $[M - \cdot H]^+$, 155.0872; found, 155.088; calcd. for $C_8H_{10}FO$ $[M - \cdot Me]^+$, 141.0716; found, 141.071; calcd. for $C_9H_{12}O$ $[M - HF]^+$, 136.0888; found, 136.090; (−)-(4S)-**1** $[\alpha]^{20}_D = -13.1$ ($c = 0.18$; CH_2Cl_2); (+)-(4*R*)-**1** $[\alpha]^{20}_D = +13.7$ ($c = 0.26$; CH_2Cl_2).

(±)-1,1-Diethoxynon-2-(*Z*)-en-4-fluoro (14). To a solution of acetal **12** (2.85 g, 12.4 mmol) and pyridine (1 mL, 12.4 mmol, 1.0 equiv) in 40 mL of pentane at room temperature was added Lindlar catalyst (0.57 g, 20% weight). The black suspension was stirred under a hydrogen atmosphere. When analysis of an aliquot by ^{19}F NMR showed no starting material, the reaction mixture was filtered through Celite and concentrated at reduced pressure. Purification by flash chromatography (pentane/Et_2O, 8/2) gave the title compound **14** (2.86 g, 99%) as a colorless oil: TLC $Rf = 0.68$ (pentane/Et_2O, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (dddd, $J_{H-F} = 11.9$ Hz, $J = 11.6$ Hz, $J = 8.1$ Hz, $J = 1.0$ Hz, 1H), 5.61 (dddd, $J = 11.6$ Hz, $J = 6.0$ Hz, $J_{H-F} = 2.0$ Hz, $J = 1.0$ Hz, 1H), 5.32 (dtd, $J_{H-F} = 49.3$ Hz, $J = 7.6$ Hz, $J = 4.7$ Hz, 1H), 5.21 (dd, $J = 5.0$ Hz, $J = 1.7$ Hz, 1H), 3.64 (dqd, $J = 9.4$ Hz, $J = 3.4$ Hz, $J = 3.7$ Hz, 2H), 3.51 (dqd, $J = 9.1$ Hz, $J = 7.1$ Hz, $J = 2.0$ Hz, 2H), 1.82−1.50 (m, 2H), 1.50−1.35 (m, 2H), 1.35−1.28 (m, 4H), 1.22 (t, $J = 7.0$ Hz, 3H), 1.20 (t, $J = 6.9$ Hz, 3H), 0.91 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.32 (d, $J = 22.1$ Hz), 130.47 (d, $J = 9.9$ Hz), 97.57, 89.32 (d, $J = 162.1$ Hz), 60.89, 60.33, 35.43 (d, $J = 22.5$ Hz), 31.54, 24.28 (d, $J = 4.2$ Hz), 22.50, 15.18, 13.94; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −174.00 (dddd, $J = 49.3$ Hz, $J = 28.5$ Hz, $J = 17.3$ Hz, $J = 11.9$ Hz); MS (EI) 70 eV *m*/*z* (rel int) 232 (1.2, $M^{+\cdot}$), 187 (100.0, $[M - \cdot OEt]^+$); HRMS (EI) 70 eV calcd. for $C_{13}H_{25}FO_2$ $M^{+\cdot}$, 232.1839; found, 232.184. Anal. Calcd. for $C_{13}H_{25}FO_2$: C, 67.20; H, 10.85. Found: C, 66.94; H, 10.63. IR (neat) ν 2975, 2931, 2873, 2360, 1459, 1392, 1333, 1122, 1055, 1002, 909 cm^{-1}; (−)-(4S)-**14** $[\alpha]^{20}_D = -33.1$ ($c = 0.24$; CH_2Cl_2); (+)-(4*R*)-**14** $[\alpha]^{20}_D = +37.7$ ($c = 0.57$; CH_2Cl_2).

(±)-4-Fluoro-2-(*Z*)-en-non-1-al (2) and (±)-4-Fluoro-2-(*E*)-en-non-1-al (3). A stirred solution of acetal **14** (0.31 g, 1.3 mmol) in CH_2Cl_2 (20 mL) was treated with formic acid (5.1 mL, 131.9 mmol, 100.0 equiv). After 5 min at room temperature, the reaction mixture was neutralized with solid Na_2CO_3 (7.0 g) and diluted with saturated Na_2CO_3 solution. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the crude product by flash chromatography on silica gel (pentane/Et_2O, 95/5) gave the two title isomers: *Z*-**2** (0.18 g, 87%) and *E*-**3** (0.02 g, 8%), each as a pale yellow oil.

Cis Isomer. TLC $Rf = 0.46$ (pentane/Et_2O, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (dd, $J = 7.0$ Hz, $J_{H-F} = 0.9$ Hz, 1H), 6.51 (ddd, $J_{H-F} = 21.2$ Hz, $J = 11.8$ Hz, $J = 6.5$ Hz, 1H), 6.04 (ddt, $J = 11.8$ Hz, $J = 7.0$ Hz, $J_{H-F} = J_{H-H} = 1.4$ Hz, 1H), 5.66 (ddddd, $J_{H-F} = 49.4$ Hz, $J = 7.9$ Hz, $J = 6.5$ Hz, $J = 4.9$ Hz, $J = 1.4$ Hz, 1H), 1.93−1.64 (m, 2H), 1.56−1.40 (m, 2H), 1.39−1.27 (m, 4H), 0.90 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.15 (d, $J = 4.2$ Hz), 147.28 (d, $J = 22.5$ Hz), 129.75 (d, $J = 5.0$ Hz), 90.06 (d, $J = 169.2$ Hz), 35.33 (d, $J = 21.9$ Hz), 31.35, 24.20 (d, $J = 4.0$ Hz), 22.44, 13.92; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −175.50 (ddt, $J = 49.4$ Hz, $J = 26.9$ Hz, $J = 21.2$ Hz); MS (EI) 70 eV *m*/*z* (rel int) 158 (17.3, $M^{+\cdot}$), 43 (100.0, $[C_3H_7]^+$); HRMS (EI) 70 eV calcd. for $C_9H_{15}FO$ $M^{+\cdot}$, 158.1107; found, 158.111. Anal. Calcd. for $C_9H_{15}FO$: C, 68.32; H, 9.56. Found: C, 67.75; H, 9.61; IR (neat) ν 2958, 2933, 2860, 2361, 1688, 1618, 1468, 1415, 1380, 1232, 1126, 1011, 989, 937, 911 cm^{-1}; (−)-(4S)-(*Z*)-**2** $[\alpha]^{20}_D = -43.0$ ($c = 0.10$; CH_2Cl_2); (+)-(4*R*)-(*Z*)-**2** $[\alpha]^{20}_D = +41.8$ ($c = 0.40$; CH_2Cl_2).

Trans Isomer. TLC $Rf = 0.32$ (pentane/Et_2O, 8/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (dd, $J = 7.8$ Hz, $J_{H-F} = 1.7$ Hz, 1H), 6.77 (ddd, $J_{H-F} = 20.0$ Hz, $J = 15.8$ Hz, $J = 4.0$ Hz, 1H), 6.32 (dddd, $J = 15.8$ Hz, $J = 7.8$ Hz, $J = 1.7$ Hz, $J_{H-F} = J_{H-H} = 1.0$ Hz, 1H), 5.21 (ddddd, $J_{H-F} = 48.3$ Hz, $J = 7.0$ Hz, $J = 5.6$ Hz, $J = 4.0$ Hz, $J = 1.7$ Hz, 1H), 1.83−1.69 (m, 2H), 1.56−1.40 (m, 2H), 1.39−1.29 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.81, 153.24 (d, $J = 19.8$ Hz), 130.97 (d, $J = 8.8$ Hz), 90.98 (d, $J = 174.3$ Hz), 34.46 (d, $J = 21.4$ Hz), 31.37, 24.18 (d, $J = 3.8$ Hz), 22.40, 13.90; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −184.76 (ddt, $J = 48.3$ Hz, $J = 25.8$ Hz, $J = 20.0$ Hz); MS (EI) 70 eV *m*/*z* (rel int) 158 (0.2, $M^{+\cdot}$), 43 (100.0, $[C_3H_7]^+$); HRMS (EI) 70 eV calcd. for $C_9H_{15}FO$ $M^{+\cdot}$, 158.1107; found, 158.111; IR (neat) ν 2957, 2933, 2853, 2731, 1695, 1647, 1468, 1380, 1348, 1131, 1067, 976, 906, 734 cm^{-1}; (+)-(4S)-

(*E*)-**3** $[\alpha]^{20}_D = +29.6$ ($c = 0.20$; CH_2Cl_2); (−)-(4*R*)-(*E*)-**3** $[\alpha]^{20}_D = -29.1$ ($c = 0.34$; CH_2Cl_2).

Note: isomerization of the cis isomer **2** by heating at 80 °C in DMSO for 34 h gave quantitatively the trans isomer **3**.

(+)-(13*R*)-13-Fluoro-octadec-9-(*Z*)-en-11-ynoic acid Methyl Ester (15) and (−)-(13*R*)-13-Fluoro-octadec-9-(*E*)-en-11-ynoic Acid Methyl Ester (16). After three successive azeotropic removals of the residual moisture (using toluene (6 mL) at 60 °C), (8-methoxycarbonyl-octyl)-triphenyl phosphonium bromide **17** (0.54 g, 1.0 mmol, 2.0 equiv) was dissolved in 20 mL of anhydrous THF. The solution was cooled to −20 °C and freshly prepared LiHMDS (202 mg, 1.2 mmol, 2.3 equiv) was added under N_2 atmosphere. The reaction mixture was stirred for 30 min and then cooled to −45 °C and HMPA (1.70 mL, 9.4 mmol, 18 equiv) was added. After 10 min at that temperature, the reaction mixture was lowered again to −70 °C followed by the addition of aldehyde **1** (81.8 mg, 0.5 mmol, 1.0 equiv). The reaction mixture was allowed to warm to −10 °C in 190 min and then quenched by adding aqueous NH_4Cl. The crude product was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The product was purified on silica gel (pentane/Et_2O, 8/2) to give a mixture of the two title compounds *Z*/*E* (84 mg, ratio: 7/3). A preparative TLC (pentane/Et_2O, 98/2 with 8 elutions) gave the two isomers: *Z*-**15** (59 mg, 37%) and *E*-**16** (25 mg, 15%), each as a colorless oil.

Cis Isomer. TLC *Rf* = 0.48 (pentane/Et_2O, 98/2 with 7 elutions); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (dtd, J = 10.8 Hz, J = 7.5 Hz, J_{H-F} = 1.3 Hz, 1H), 5.50 (ddd, J = 10.8 Hz, J_{H-F} = 5.0 Hz, J = 1.4 Hz, 1H), 5.24 (dtd, J_{H-F} = 48.5 Hz, J = 6.4 Hz, J = 1.4 Hz, 1H), 3.67 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.33−2.26 (m, 2H), 1.97−1.75 (m, 2H), 1.67−1.57 (m, 2H), 1.55−1.45 (m, 2H), 1.45−1.27 (m, 12H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.28, 145.61 (d, J = 4.0 Hz), 107.97 (d, J = 4.0 Hz), 89.71 (d, J = 24.9 Hz), 84.72 (d, J = 10.4 Hz), 83.23 (d, J = 166.2 Hz), 51.43, 36.02 (d, J = 22.5 Hz), 34.04, 31.26, 30.26, 29.02, 29.00, 28.90, 28.59, 24.87, 24.18 (d, J = 4.0 Hz), 22.47, 13.93; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −170.93 (dtd, J = 48.5 Hz, J = 19.9 Hz, J = 5.0 Hz); MS (EI) 70 eV *m*/*z* (rel int) 310 (0.9, $M^{+\cdot}$); 290 (16.0, $[M - HF]^{+\cdot}$), 91 (100.0); HRMS (EI) 70 eV calcd. for $C_{19}H_{31}FO_2$ $M^{+\cdot}$, 310.2308; found, 310.231; calcd. for $C_{19}H_{30}O_2$ $[M - HF]^{+\cdot}$, 290.2246; found, 290.225; (+)-(13*R*)-(*Z*)-**15** $[\alpha]^{20}_D = +6.7$ ($c = 0.25$; CH_2Cl_2).

Trans Isomer. TLC *Rf* = 0.43 (pentane/Et_2O, 98/2 with 7 elutions); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dtd, J = 15.9 Hz, J = 7.1 Hz, J_{H-F} = 1.6 Hz, 1H), 5.51 (ddq, J = 15.9 Hz, J_{H-F} = 4.8 Hz, J = 1.6 Hz, 1H), 5.19 (dtd, J_{H-F} = 48.8 Hz, J = 6.4 Hz, J = 1.6 Hz, 1H), 3.67 (s, 3H), 2.31 (t, J = 7.5 Hz, 2H), 2.11 (qdd, J = 7.1 Hz, J = 1.6 Hz, J_{H-F} = 1.5 Hz, 2H), 1.95−1.73 (m, 2H), 1.66−1.57 (m, 2H), 1.53−1.43 (m, 2H), 1.42−1.24 (m, 12H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.26, 146.56 (d, J = 7.8 Hz), 108.4 (d, J = 4.0 Hz), 86.71 (d, J = 10.4 Hz), 84.16 (d, J = 25.7 Hz), 83.26 (d, J = 166.2 Hz), 51.44, 36.02 (d, J = 22.5 Hz), 34.03, 33.02, 31.27, 29.00, 28.83, 28.44, 24.87, 24.19 (d, J = 3.2 Hz), 22.46, 13.93; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −170.99 (dtdd, J = 48.8 Hz, J = 19.7 Hz, J = 4.8 Hz, J = 1.5 Hz); MS (EI) 70 eV *m*/*z* (rel int) 290 (12.9, $[M - HF]^{+\cdot}$), 91 (100.0); HRMS (EI) 70 eV calcd. for $C_{19}H_{30}O_2$ $[M - HF]^{+\cdot}$, 290.2246; found, 290.225; (−)-(13*R*)-(*E*)-**16** $[\alpha]^{20}_D = -4.8$ ($c = 0.21$; CH_2Cl_2).

(+)-(13*R*)-13-Fluoro-octadeca-9-(*Z*),11-(*E*)-dienoic Acid Methyl Ester (18). After two successive azeotropic removals of the residual moisture (using toluene (5 mL) at 60 °C), (8-methoxycarbonyl-octyl)-triphenyl phosphonium bromide **17** (0.65 g, 1.3 mmol, 1.7 equiv) was dissolved in 20 mL of anhydrous THF. The solution was cooled to −15 °C and freshly prepared LiHMDS (315 mg, 1.9 mmol, 2.5 equiv) was added under N_2 atmosphere. The reaction mixture was stirred for 25 min and then cooled to −40 °C and HMPA (2.0 mL, 11.4 mmol, 15.1 equiv) was added. After 10 min at that temperature, the reaction mixture was lowered again to −78 °C followed by the addition of aldehyde **3** (119 mg, 0.8 mmol, 1.0 equiv). The reaction mixture was allowed to warm to −10 °C in 205 min and was then quenched by adding aqueous NH_4Cl. The crude product was extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The product was purified on silica gel (petroleum ether/Et_2O, 95/5 with 2% NEt_3) to give the title compound **18** (92.6 mg, 40%) as a colorless oil: TLC *Rf* = 0.68 (pentane/Et_2O, 8/2 + 2% NEt_3); note: TLC plates were preeluted with the solvent system; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (dddt, J = 15.3 Hz, J = 11.0 Hz, J_{H-F} = 4.2 Hz, J = 1.0 Hz, 1H), 5.98 (td, J = 11.0 Hz, J_{H-F} = 1.0 Hz, 1H), 5.67 (ddd, J = 15.3 Hz, J_{H-F} = 12.7 Hz, J = 6.9 Hz, 1H), 5.51 (dt, J = 11.0 Hz, J = 7.6 Hz, 1H), 4.93 (dtd, J_{H-F} = 48.7 Hz, J = 6.9 Hz, J = 5.7 Hz, 1H), 3.67 (s, 3H), 2.31 (t, J = 7.5 Hz, 2H), 2.18 (qt, J = 7.6 Hz, J = 1.3 Hz, 2H), 1.83−1.53 (m, 4H), 1.50−1.26 (m, 14H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.29, 134.22 (d, J = 3.2 Hz), 130.76 (d, J = 18.1 Hz), 127.96 (d, J = 12.1 Hz), 127.35 (d, J = 3.2 Hz), 93.76 (d, J = 165.0 Hz), 51.44, 35.51 (d, J = 22.9 Hz), 34.05, 31.56, 29.44, 29.07, 29.04, 28.98, 27.72, 24.89, 24.44 (d, J = 4.4 Hz), 22.51, 13.98; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −171.80; (+)-(13*R*)-(9*Z*)-(11*E*)-**18** $[\alpha]^{20}_D = +16.4$ ($c = 0.32$; CH_2Cl_2).

General Procedure for Determination the Enantiomeric Excess of Aldehydes 1, 2, and 3. A solution of the corresponding aldehyde (about 10 mg), (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenyl ethylenediamine[21,22] (1.2 equiv; ee, 100%) and activated 3 Å molecular sieves were stirred at room temperature in CH_2Cl_2 (2 mL) for 4 h. The reaction mixture was filtered and concentrated under reduced pressure. A fully decoupled ^{19}F NMR was recorded on the crude product. Two peaks corresponding to the two diastereomers were then obtained and the diastereomeric excess was calculated from the ratio between the integration of the peaks. This value can be directly extrapolated to the ee of the starting aldehydes since the reaction is rapid and quantitative.

^{19}F NMR analyses in C_6D_6 performed on the diastereomer (Scheme 2) were obtained from

(+)-(4*R*)-**1**: $\delta = -172.92$ ppm

(−)-(4S)-**1**: $\delta = -172.02$ ppm

^{19}F NMR analyses in $CDCl_3$ performed on the diastereomer (Scheme 4) obtained from

(+)-(4*R*)-(*Z*)-**2**: $\delta = -171.32$ ppm

(−)-(4S)-(*Z*)-**2**: $\delta = -169.87$ ppm

(+)-(4*R*)-(*E*)-**3**: $\delta = -174.47$ ppm

(−)-(4S)-(*E*)-**3**: $\delta = -175.00$ ppm

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**−**3**, **8**−**12**, **14**−**16**, and **18**. ^{19}F NMR spectra for **1**−**3**, **12**, **14**−**16**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org

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