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# Direct conversion of epoxides to *vic*-difluorides

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## Abstract

*vic*-Difluoro compounds can be directly prepared from epoxides by reaction with Et<sub>3</sub>N-3HF and DFMBBA under microwave irradiation conditions.

*Keywords:* Microwave-irradiation, Epoxide, Fluorination, *vic*-Difluoride

## 1. Introduction

*vic*-Difluorides have been prepared from alkenes using F<sub>2</sub> [1-7], XeF<sub>2</sub> [8-10], *p*-TolIF<sub>2</sub> [11], or an electrochemical method [12]. Among them, F<sub>2</sub> has been most frequently used for the synthesis of natural product analogs having *vic*-difluoro function [1,3-7]. However, due to inaccessibility and violent reactivity, the use of F<sub>2</sub> have been restricted. *vic*-Difluoro compounds can be also prepared from epoxides directly or in two steps. The epoxides can be converted to *vic*-difluorides directly by the reaction with *N,N*-diethylaminosulfur trifluoride (DAST) [13]. However, under the reaction conditions, the rearrangement takes place to give a mixture of *vic*- and *gem*-difluoro products. On the other hand, *vic*-difluorides can be selectively prepared from the epoxides in two steps [14,15]. Initially, the epoxides are converted to fluorohydrines by amine-HF, and deoxyfluorination of the fluorohydrines by DAST gives

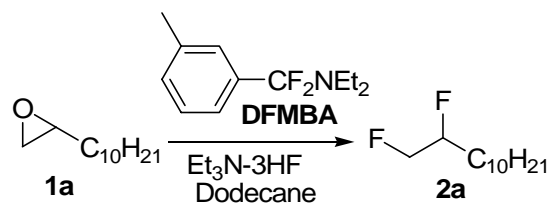
*vic*-difluorides. The reaction proceeds regio- and stereoselectively, and *threo* and *erythro* isomers of *vic*-difluorides can be prepared specifically from *trans*- and *cis*-epoxides, respectively. However, this method involves a tedious two-step procedure and overall yields are not high. Recently, we found that both ring-opening fluorination of epoxides by Et<sub>3</sub>N-3HF [16] and deoxyfluorination of alcohols by *N,N*-diethyl- $\alpha,\alpha$ -difluoro-(*m*-methylbenzyl)amine (DFMBA) [17,18] can be effectively carried out under microwave irradiation. During our continuous study of the fluorination reaction using microwave irradiation, we found that both ring-opening fluorination of the epoxides and deoxyfluorination of the resulting fluorohydrines can be carried out in one pot by the microwave irradiation of epoxides with Et<sub>3</sub>N-3HF and DFMBA, and *vic*-difluoro compounds can be directly prepared.

## 2. Result and discussion

The reaction of 1-dodecene oxide (**1a**) with DFMBA in the presence or absence of Et<sub>3</sub>N-3HF was examined (Table 1). The irradiation of microwave was carried out for 30 min using a modified household microwave oven, and dodecane (bp 216 °C) was used as solvent. When 1.2 eq of DFMBA was used for the reaction with **1a** in the absence, or presence of 0.1 eq of Et<sub>3</sub>N-3HF, 1,2-difluorododecane (**2a**) was obtained in low yield (Entries 1 and 2). The yield of **2a** could be improved by using 0.5 eq of Et<sub>3</sub>N-3HF (Entry 3). This result is consistent with the previous result where more than 0.5 eq of Et<sub>3</sub>N-3HF was necessary to completely convert the epoxides to the fluorohydrine [16]. Consequently, the best result was obtained by using 0.5 eq of Et<sub>3</sub>N-3HF and 1.5 eq of DFMBA to **1a** (Entry 5). When the reaction was carried out under the conditions of Entry 5 using conventional oil-bath heating instead of microwave irradiation, the yield of **2a** decreased to 42 %. Therefore, the microwave irradiation was found to be more effective than the conventional oil-bath heating in this

*vic*-difluorination reaction [19].

Table 1. Reaction of dodecene oxide with DFMBA and Et<sub>3</sub>N-3HF<sup>a</sup>



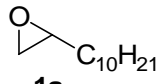

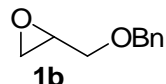
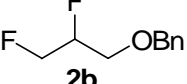
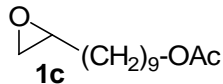
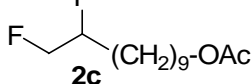
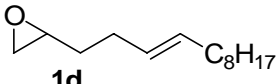
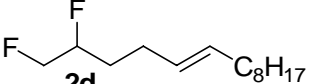
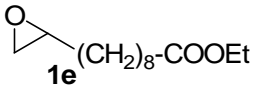
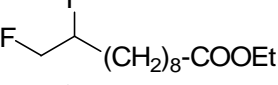
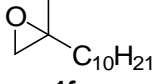
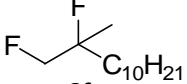
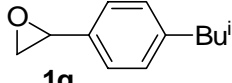
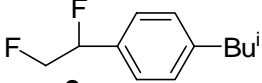
Entry	Et <sub>3</sub> N-3HF	DFMBA	Yield, % <sup>b</sup>
	<b>1a</b>	<b>1a</b>	
1	0	1.2	6
2	0.1	1.2	21
3	0.5	1.2	67
4	1.0	1.2	64
5	0.5	1.5	72
6	0.5	2.0	72

<sup>a</sup> The reaction was carried out for 30 min.

<sup>b</sup> Isolated yield based on **1a**.

Under the conditions, various epoxides (**1a-f**) could be directly converted to *vic*-difluorides (**2a-f**) as shown in Table 2. The functional groups such as ether (**1b**), ester (**1c**, **e**) and double bond (**1d**) can tolerate the reaction conditions and the corresponding *vic*-difluorides (**2b**, **c**, **d**, **e**) could be obtained in good yield. In the reaction of a styrene oxide derivative (**1g**), the microwave irradiation condition is too harsh, and conventional oil-bath heating gave better result.

Table 2. Direct conversion of epoxides to *vic*-difluorides<sup>a</sup>

Epoxide	Product	Yield, % <sup>b</sup>
 <b>1a</b>	 <b>2a</b>	72
 <b>1b</b>	 <b>2b</b>	71
 <b>1c</b>	 <b>2c</b>	70
 <b>1d</b>	 <b>2d</b>	71
 <b>1e</b>	 <b>2e</b>	67
 <b>1f</b>	 <b>2f</b>	64 <sup>c</sup>
 <b>1g</b>	 <b>2g</b>	61 <sup>d</sup>

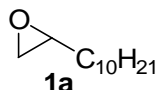
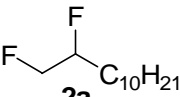
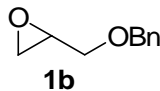
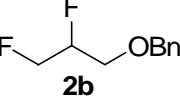
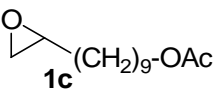
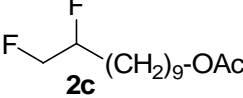
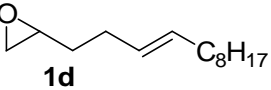
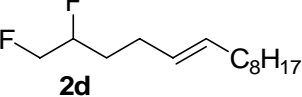
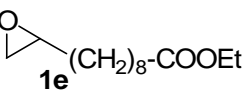
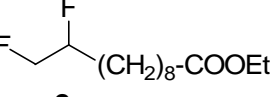
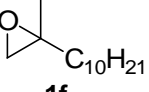
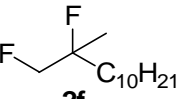
<sup>a</sup> If otherwise not mentioned, the reaction was carried out under microwave irradiation using 1.5 eq of DFMBFA and 0.5 eq of Et<sub>3</sub>N-3HF to **1**. <sup>b</sup> Isolated yield based on **1**.

<sup>c</sup> Microwave was irradiated for 5 min. <sup>d</sup> The reaction was carried out using oil bath at 100 °C for 20 h.

When a household microwave oven is used, the presence of a hydrocarbon solvent is critical. Both DFMBFA and Et<sub>3</sub>N-3HF absorb microwave very well, and vigorous reflux of the solvent starts by the microwave irradiation. When the reaction is carried out in a polar solvent or without a solvent, the reaction mixture reaches high temperature and undesired side reaction also takes place. A hydrocarbon solvent such as dodecane is necessary to control the reaction temperature. On the other hand, when a microwave oven for organic synthesis, which can keep the temperature in the oven constant during the reaction by controlling the power, is used, the reaction can be carried out without a solvent. When the reaction of **1a-f** was carried out at constant

temperature under microwave irradiation, the corresponding *vic*-difluorides (**2a-f**) could be obtained in comparable yields without a solvent (Table 3).

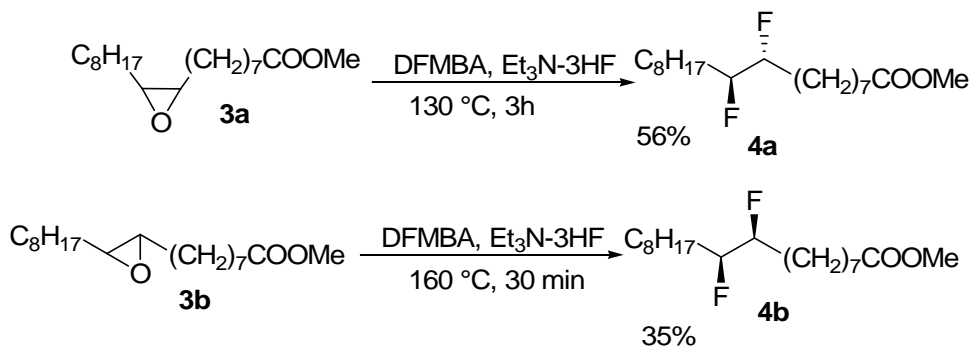
Table 3. Direct conversion of epoxides to *vic*-difluorides by microwave irradiation under temperature control<sup>a</sup>

Epoxide	Reaction conditions	Product	Yield, % <sup>b</sup>
 <b>1a</b>	216 °C, 5 min	 <b>2a</b>	75
 <b>1b</b>	180 °C, 30 min	 <b>2b</b>	68
 <b>1c</b>	180 °C, 5 min	 <b>2c</b>	71
 <b>1d</b>	216 °C, 30 min	 <b>2d</b>	67
 <b>1e</b>	180 °C, 30 min	 <b>2e</b>	78
 <b>1f</b>	180 °C, 30 min	 <b>2f</b>	71

<sup>a</sup> The reaction was carried out under microwave irradiation using 1.5 eq of DF MBA and 0.5 eq of Et<sub>3</sub>N·3HF to **1**. <sup>b</sup> Isolated yield based on **1**.

Recently, O'Hagan *et al.* synthesized both a *threo*-9,10-difluorostearic acid ester (**4a**) and an *erythro*-isomer (**4b**) from a (*E*)-9,10-epoxystearic acid ester (**3a**) and (*Z*)-isomer (**3b**) in two steps [15]. Thus, treatment of epoxides (**3a**, **b**) with pyridine-HF gave the corresponding fluorohydrines, which were then converted to **4a** and **4b** by DAST. The reaction stereospecifically proceeded and both **4a** and **4b** could be selectively obtained from **3a** and **3b**, respectively. However, overall yields of **4a** and **4b** from **3a** and **3b** are 16.5 % and 28.9 %, respectively. Furthermore, during the deoxyfluorination of fluorohydrines by DAST, an elimination reaction competitively

took place to give a significant amount of olefinic by-products (50%). Therefore, before isolation of **4a** and **4b**, ozone-oxidation was carried out to separate them from the olefinic by-products. On the other hand, **4a** and **4b** could be directly obtained from **3a** and **3b** in 56% and 35 % yield, respectively, by the reaction with DFMBBA and Et<sub>3</sub>N-3HF under temperature-controlled microwave irradiation conditions. Formation of olefinic by-products was not a serious problem, and **4a** and **4b** could be obtained by simple column chromatography after the reaction (Scheme 1).



**Scheme 1**

### 3. Experimental

#### 3.1. General methods

The IR spectra were recorded using a JASCO FT/IR-410. The <sup>1</sup>H NMR (400MHz), <sup>13</sup>C NMR (100 MHz), and <sup>19</sup>F NMR (376MHz) spectra were recorded in CDCl<sub>3</sub> on a JEOL JNM-A400II FT NMR and the chemical shift,  $\delta$ , are referred to TMS (<sup>1</sup>H, <sup>13</sup>C) and CFCl<sub>3</sub> (<sup>19</sup>F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Silica gel 60 F<sub>254</sub> was used for tlc analysis. Microwave irradiation was carried out using a GoldStar microwave oven (500W,

MW-JIK96H5) or an IDX microwave oven for organic synthesis (0–300 W, IMCR-25003) having temperature control. A GoldStar microwave oven was modified to accept a port for connecting a reactor to a reflux condenser located outside the oven. A hole of 10 mm diameter was drilled in the oven top and an 80-mm length of Teflon™ PFA tube was snugly fitted into the hole. A reflux condenser located outside was connected to the port tightly and another side of the port in the oven was used to connect to a reactor which is a Teflon™ PFA tube with a diameter of 10 mm and a length of 80 mm sealed at one end. DFMBBA was obtained from Mitubishi Gas Chemical Company Inc. and used without further purification. Though handling DFMBBA with glassware is possible, it is recommended to use equipment made of Teflon™. As DFMBBA is slightly moisture-sensitive, it should be handled as quickly as possible in air and kept in a Teflon™ bottle with a tight screw cap. Epoxides **1a-c**, **e**, **3a**, **b** were prepared by the epoxydation of olefines with m-CPBA. Epoxides **1d**, **f** were prepared by the reaction of aldehydes with trimethyloxosulfonium ylide [20]. (*E*)- and (*Z*)-9-Octadecenoic acid were purchased from Aldrich Chemical Co. Et<sub>3</sub>N-3HF was purchased from Aldrich Chemical Co. and distilled before use.

### *3.2. General procedure using household microwave oven*

Into a reactor consisting of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end, were introduced dodecane (1 ml), **1** (1 mmol), DFMBBA (320 mg, 1.5 mmol), and Et<sub>3</sub>N-3HF (82 mg, 0.5 mmol). The open end of the reactor was connected to a port in a household microwave oven and the port was connected to a reflux condenser located outside the oven. Then, the reaction mixture was submitted to microwave irradiation for 30 min. During the irradiation, the reaction mixture was refluxed vigorously. After the reaction, the reaction mixture was poured into aq NaHCO<sub>3</sub> and extracted with ether three times. The combined ethereal layers were dried over MgSO<sub>4</sub>,

concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane–Et<sub>2</sub>O) gave **2**.

### 3.3. General procedure using microwave oven under temperature control

Into a reactor consisting of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end, were introduced **1** (1 mmol), DFMBBA (320 mg, 1.5 mmol), and Et<sub>3</sub>N–3HF (82 mg, 0.5 mmol). The open end of the reactor was connected to a reflux condenser. Then, the reaction mixture was submitted to microwave irradiation and during the irradiation, the temperature was kept constant. After cooling, the reaction mixture was poured into an aqueous NaHCO<sub>3</sub> solution. The product was extracted with ether three times and the combined ethereal layers were dried over MgSO<sub>4</sub>. Purification by column chromatography (silica gel/hexane-ether) gave **2**.

#### 3.3.1. 1,2-Difluorododecane (**2a**)

$R_f = 0.28$  (hexane); IR: (neat)  $\nu$  2926, 2855, 1467 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$  0.88 (t,  $J_{HH} = 6.8$  Hz, 3H, CH<sub>3</sub>), 1.21–1.74 (m, 18H, CH<sub>2</sub>), 4.34–4.79 (m, 3H, CFH–CFH<sub>2</sub>). <sup>13</sup>C NMR  $\delta$  14.08 (CH<sub>3</sub>), 22.67 (CH<sub>2</sub>), 24.73 (CH<sub>2</sub>), 24.77 (CH<sub>2</sub>), 29.32 (2C, CH<sub>2</sub>), 29.40 (CH<sub>2</sub>), 29.54 (d,  $J_{CF} = 5.8$  Hz, CH<sub>2</sub>–CH<sub>2</sub>CHF), 30.01 (dd,  $J_{CF} = 19.7$ ,  $J_{CF} = 5.7$  Hz, CH<sub>2</sub>–CF), 31.89 (CH<sub>2</sub>), 84.26 (dd,  $J_{CF} = 171.9$ ,  $J_{CF} = 22.2$  Hz, CH<sub>2</sub>F), 91.95 (dd,  $J_{CF} = 171.9$ ,  $J_{CF} = 18.9$  Hz, CHF). <sup>19</sup>F NMR  $\delta$  –230.35 (ddt,  $J_{FF} = 20.8$ ,  $J_{FHvic} = 13.4$ ,  $J_{FHgem} = 47.6$  Hz, 1F, CFH<sub>2</sub>), –189.60 – –189.18 (m, 1F, CFH). HRMS calc for C<sub>12</sub>H<sub>24</sub>F<sub>2</sub> 206.1846, found 206.1847.

#### 3.3.2. 1-Benzyloxy-2,3-difluoropropane (**2b**)

$R_f = 0.29$  (hexane:ether = 10:1); IR: (neat)  $\nu$  2926, 2869, 1454, 1108, 1030 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$  3.69 (ddd,  $J_{HF} = 20.0$ ,  $J_{HH} = 4.8$ ,  $J_{HF} = 1.0$  Hz, 2H, CFH–CH<sub>2</sub>O), 4.50–4.89

(m, 3H, CFH-CFH<sub>2</sub>), 4.55 (s, 2H, OCH<sub>2</sub>Ph), 7.27–7.36 (m, 5H, Ar). <sup>13</sup>C NMR δ 67.74 (dd, J<sub>CF</sub> = 23.9, J<sub>CF</sub> = 8.2 Hz, CFH-CH<sub>2</sub>O), 73.55 (PhCH<sub>2</sub>O), 82.12 (dd, J<sub>CF</sub> = 171.1, J<sub>CF</sub> = 23.0 Hz, CH<sub>2</sub>F), 90.33 (dd, J<sub>CF</sub> = 174.4, J<sub>CF</sub> = 19.8 Hz, CHF), 127.65 (2C, Ar), 127.85 (Ar), 128.43 (2C, Ar), 137.40 (Ar). <sup>19</sup>F NMR δ -230.35 (ddt, J<sub>FF</sub> = 21.4, J<sub>FHvic</sub> = 13.5, J<sub>FHgem</sub> = 47.8 Hz, 1F, CFH<sub>2</sub>), -196.84 – -196.54 (m, 1F, CFH). HRMS calc for C<sub>10</sub>H<sub>12</sub>OF<sub>2</sub> 186.0856, found 186.0863.

### 3.3.3. 1-Acetoxy-10,11-difluoroundecane (2c)

R<sub>f</sub> = 0.27 (hexane:ether = 7:1); IR: (neat) ν 2930, 2857, 1739, 1242 cm<sup>-1</sup>. <sup>1</sup>H NMR δ 1.30–1.77 (m, 16H, CH<sub>2</sub>), 2.05 (s, 3H, OCOCH<sub>3</sub>) 4.05 (t, J<sub>HH</sub> = 7.4 Hz, 2H, CH<sub>2</sub>OAc), 4.34–4.79 (m, 3H, CFH-CFH<sub>2</sub>). <sup>13</sup>C NMR δ 20.89 (CH<sub>3</sub>), 24.68 (d, J<sub>CF</sub> = 3.9 Hz, CH<sub>2</sub>-CH<sub>2</sub>CF), 25.83 (CH<sub>2</sub>), 28.53 (CH<sub>2</sub>), 29.13 (CH<sub>2</sub>), 29.24 (2C, CH<sub>2</sub>), 29.30 (CH<sub>2</sub>), 29.95 (dd, J<sub>CF</sub> = 20.0, J<sub>CF</sub> = 6.6 Hz, CH<sub>2</sub>-CF), 64.56 (CH<sub>2</sub>OAc), 84.12 (dd, J<sub>CF</sub> = 172.7, J<sub>CF</sub> = 22.5 Hz, CH<sub>2</sub>F), 91.80 (dd, J<sub>CF</sub> = 171.9, J<sub>CF</sub> = 18.9 Hz, CHF), 171.23 (C=O). <sup>19</sup>F NMR δ -230.42 (ddt, J<sub>FF</sub> = 20.7, J<sub>FHvic</sub> = 13.9, J<sub>FHgem</sub> = 47.8 Hz, 1F, CFH<sub>2</sub>), -189.69 – -189.26 (m, 1F, CFH). HRMS calc for C<sub>13</sub>H<sub>25</sub>O<sub>2</sub>F<sub>2</sub> (M<sup>+</sup>+H) 251.1822, found 251.1818.

### 3.3.4. 1,2-Difluoro-5-tetradecene (2d)

R<sub>f</sub> = 0.29 (hexane); IR:(neat) ν 2925, 2854, 1456 cm<sup>-1</sup>. <sup>1</sup>H NMR δ 0.88 (t, J<sub>HH</sub> = 6.8 Hz, 3H, CH<sub>3</sub>), 1.27–1.35 (m, 12H, CH<sub>2</sub>), 1.53–1.87 (m, 2H, CH<sub>2</sub>-CF), 1.96–2.00 (m, 2H, CH<sub>2</sub>-CH=), 2.07–2.23 (m, 2H, =CH-CH<sub>2</sub>), 4.34–4.80 (m, 3H, CFH-CFH<sub>2</sub>), 5.36–5.41 (m, 1H, CH=CH), 5.44–5.52 (m, 1H, CH=CH). <sup>13</sup>C NMR δ 14.08 (CH<sub>3</sub>), 22.66 (CH<sub>2</sub>), 27.65 (d, J<sub>CF</sub> = 4.1 Hz, CH<sub>2</sub>-CH<sub>2</sub>CF), 29.16(CH<sub>2</sub>), 29.29(CH<sub>2</sub>), 29.46 (2C, CH<sub>2</sub>), 29.85 (dd, J<sub>CF</sub> = 5.8, J<sub>CF</sub> = 20.6 Hz, CH<sub>2</sub>-CF), 31.88(CH<sub>2</sub>), 32.52(CH<sub>2</sub>), 84.09 (dd, J<sub>CF</sub> = 172.8, J<sub>CF</sub> = 22.3 Hz, CH<sub>2</sub>F), 91.10 (dd, J<sub>CF</sub> = 172.0, J<sub>CF</sub> = 19.0 Hz, CHF), 128.03 (CH=CH), 132.21 (CH=CH). <sup>19</sup>F NMR δ -230.49 (ddt, J<sub>FHgem</sub> = 47.4, J<sub>FF</sub> = 21.1, J<sub>FHvic</sub>

= 13.2 Hz, 1F, CFH<sub>2</sub>), -190.77 – -190.35 (m, 1F, CFH). HRMS calc for C<sub>14</sub>H<sub>26</sub>F<sub>2</sub> 232.2003, found 232.2005.

### 3.3.5. Ethyl 10,11-difluoroundecanoate (2e)

$R_f$  = 0.27 (hexane:ether = 7:1); IR: (neat)  $\nu$  2932, 2858, 1735, 1465, 1183 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$  1.26 (t,  $J_{HH}$  = 7.1 Hz, 3H, CH<sub>3</sub>), 1.31–1.76 (m, 14H, CH<sub>2</sub>), 2.29 (t,  $J_{HH}$  = 7.6 Hz, 2H, CH<sub>2</sub>-COOEt), 4.12 (q,  $J_{HH}$  = 7.3 Hz, 2H, CH<sub>3</sub>-CH<sub>2</sub>O), 4.34–4.78 (m, 3H, CFH-CFH<sub>2</sub>). <sup>13</sup>C NMR  $\delta$  14.11 (CH<sub>3</sub>), 24.60 (d,  $J_{CF}$  = 4.1 Hz, CH<sub>2</sub>-CH<sub>2</sub>CF), 24.80 (CH<sub>2</sub>), 28.94 (CH<sub>2</sub>), 29.00 (CH<sub>2</sub>), 29.07 (CH<sub>2</sub>), 29.12 (CH<sub>2</sub>), 29.86 (dd,  $J_{CF}$  = 20.5,  $J_{CF}$  = 6.6 Hz, CH<sub>2</sub>-CF), 34.19 (CH<sub>2</sub>), 60.01 (-OCH<sub>2</sub>), 84.03 (dd,  $J_{CF}$  = 172.8,  $J_{CF}$  = 23.0 Hz, CH<sub>2</sub>F), 91.71 (dd,  $J_{CF}$  = 171.9,  $J_{CF}$  = 18.9 Hz, CHF), 173.68 (C=O). <sup>19</sup>F NMR  $\delta$  -230.41 (ddt,  $J_{FHgem}$  = 47.0,  $J_{FF}$  = 20.3,  $J_{FHvic}$  = 13.5 Hz, 1F, CFH<sub>2</sub>), -189.67 – -189.25 (m, 1F, CFH). HRMS calc for C<sub>13</sub>H<sub>24</sub>O<sub>2</sub>F<sub>2</sub> 250.1744, found 250.1741.

### 3.3.6. 1,2-Difluoro-2-methyldodecane (2f)

$R_f$  = 0.33 (hexane); IR: (neat)  $\nu$  2926, 2855, 1467 cm<sup>-1</sup>. <sup>1</sup>H NMR  $\delta$  0.88 (t,  $J_{HH}$  = 6.8 Hz, 3H, CH<sub>3</sub>), 1.26–1.43 (m, 16H, CH<sub>2</sub>), 1.36 (dd,  $J_{HF}$  = 21.4,  $J_{HF}$  = 2.2 Hz, 3H, CF-CH<sub>3</sub>), 1.53–1.74 (m, 2H, CH<sub>2</sub>-CF), 4.30 (dd,  $J_{HFgem}$  = 47.6,  $J_{HFvic}$  = 3.4 Hz, 1H, CF-CFH<sub>2</sub>), 4.33 (dd,  $J_{HFgem}$  = 47.6,  $J_{HFvic}$  = 2.9 Hz, 1H, CF-CFH<sub>2</sub>). <sup>13</sup>C NMR  $\delta$  14.10 (CH<sub>3</sub>), 20.23 (dd,  $J_{CF}$  = 24.7,  $J_{CF}$  = 5.8 Hz, CF-CH<sub>3</sub>), 22.68 (CH<sub>2</sub>), 23.09 (d,  $J_{CF}$  = 5.8 Hz, CH<sub>2</sub>-CH<sub>2</sub>CF), 29.32 (CH<sub>2</sub>), 29.46 (CH<sub>2</sub>), 29.53 (CH<sub>2</sub>), 29.58 (CH<sub>2</sub>), 29.90 (CH<sub>2</sub>), 31.89 (CH<sub>2</sub>), 35.69 (dd,  $J_{CF}$  = 22.2,  $J_{CF}$  = 3.3 Hz, CH<sub>2</sub>-CF), 86.38 (dd,  $J_{CF}$  = 176.1,  $J_{CF}$  = 27.2 Hz, CH<sub>2</sub>F), 95.30 (dd,  $J_{CF}$  = 169.5,  $J_{CF}$  = 17.3 Hz, CHF). <sup>19</sup>F NMR  $\delta$  -229.83 (dtq,  $J_{FF}$  = 12.8,  $J_{FHgem}$  = 47.0,  $J_{FH}$  = 1.0 Hz, 1F, CH<sub>2</sub>F), -162.30 – -154.97 (m, 1F, CFCH<sub>3</sub>). HRMS calc for C<sub>13</sub>H<sub>25</sub>F (M-HF) 200.1958, found 200.1936.

### 3.3.7. 1,2-Difluoro-1-(p-isobutylphenyl)ethane (2g)

$R_f = 0.23$  (hexane); IR: (neat)  $\nu$  2956, 1466, 1021  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$  0.88 (d,  $J_{\text{HH}} = 6.6$  Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 1.81-1.91 (m, 1H,  $\text{CHMe}_2$ ), 2.48 (d,  $J_{\text{HH}} = 7.1$  Hz, 2H,  $\text{PhCH}_2$ ), 4.44-4.76 (m, 1H,  $\text{PhCHF-CFH}_2$ ), 5.68 (dm,  $J_{\text{HFgem}} = 51.2$  Hz, 1H,  $\text{PhCFH-CFH}_2$ ), 7.18 (d,  $J_{\text{HH}} = 8.1$  Hz, 2H, *Ar*), 7.25-7.27 (m, 2H, *Ar*).  $^{13}\text{C}$  NMR  $\delta$  22.29 (2C,  $(\text{CH}_3)_2$ ), 30.17 ( $\text{CHMe}_2$ ), 45.08 ( $\text{CH}_2\text{-Ph}$ ), 84.79 (dd,  $J_{\text{CF}} = 177.7$ ,  $J_{\text{CF}} = 25.5$  Hz,  $\text{CH}_2\text{F}$ ), 92.27 (dd,  $J_{\text{CF}} = 174.0$ ,  $J_{\text{CF}} = 19.7$  Hz,  $\text{CHF}$ ), 125.80 (d,  $J_{\text{CF}} = 6.6$  Hz, 2C, *Ar*), 129.43 (2C, *Ar*), 131.77 (dd,  $J_{\text{CF}} = 20.6$ ,  $J_{\text{CF}} = 8.2$  Hz, *Ar*), 142.97 (*Ar*).  $^{19}\text{F}$  NMR  $\delta$  -222.94 (ddt,  $J_{\text{FHvic}} = 4.2$ ,  $J_{\text{FF}} = 4.2$ ,  $J_{\text{FHgem}} = 45.1$  Hz, 1F,  $\text{CFH}_2$ ), -185.31 - -185.01 (m, 1F,  $\text{CFH}$ ). IR (neat): 2956, 1466, 1021  $\text{cm}^{-1}$ . HRMS calc for  $\text{C}_{12}\text{H}_{16}\text{F}_2$  198.1220, found 198.1222.

### 3.3.8. erythro-Methyl 9, 10-difluorooctadecanoate (**4a**)

$R_f = 0.49$  (hexane:ether = 5:1); IR: (neat)  $\nu$  2921, 1743, 1469, 1174, 1071  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$  0.88 (d,  $J_{\text{HH}} = 6.6$  Hz, 3H,  $\text{CH}_3$ ), 1.28-1.71 (m, 26H,  $\text{CH}_2$ ), 2.31 (t,  $J_{\text{HH}} = 7.6$  Hz, 2H,  $\text{CH}_2\text{-COOMe}$ ), 3.67 (s, 3H,  $\text{OCH}_3$ ), 4.37-4.56 (m, 2H,  $\text{CHF-CHF}$ ).  $^{13}\text{C}$  NMR  $\delta$  14.05 ( $\text{CH}_3$ ), 22.62 ( $\text{CH}_2$ ), 24.84 ( $\text{CH}_2$ ), 24.92 (d,  $J_{\text{CF}} = 2.5$  Hz,  $\text{CH}_2\text{-CH}_2\text{CFH}$ ), 25.00 (d,  $J_{\text{CF}} = 2.9$  Hz,  $\text{CH}_2\text{-CH}_2\text{CFH}$ ), 28.97 ( $\text{CH}_2$ ), 29.02 ( $\text{CH}_2$ ), 29.13 ( $\text{CH}_2$ ), 29.18 ( $\text{CH}_2$ ), 29.35 ( $\text{CH}_2$ ), 29.37 ( $\text{CH}_2$ ), 30.00 (dd,  $J_{\text{CF}} = 9.1$ ,  $J_{\text{CF}} = 5.0$  Hz,  $\text{CH}_2\text{-CHF}$ ), 30.22 (dd,  $J_{\text{CF}} = 9.1$ ,  $J_{\text{CF}} = 5.0$  Hz,  $\text{CH}_2\text{-CHF}$ ), 31.81 ( $\text{CH}_2$ ), 34.01 ( $\text{CH}_2$ ), 51.41 ( $\text{OCH}_3$ ), 93.75 (dd,  $J_{\text{CF}} = 174.4$ ,  $J_{\text{CF}} = 26.3$  Hz, 2C,  $\text{CHF}$ ), 174.21 ( $\text{C=O}$ ).  $^{19}\text{F}$  NMR  $\delta$  -193.54 - -193.06 (m, 2F,  $\text{CFH-CFH}$ ) [15].

### 3.3.9. threo-Methyl 9, 10-difluorooctadecanoate (**4b**)

$R_f = 0.47$  (hexane:ether = 5:1); IR: (neat)  $\nu$  2918, 1743, 1473, 1216, 1177  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR  $\delta$  0.88 (d,  $J_{\text{HH}} = 6.6$  Hz, 3H,  $\text{CH}_3$ ), 1.28-1.81 (m, 26H,  $\text{CH}_2$ ), 2.31 (t,  $J_{\text{HH}} = 7.6$  Hz, 2H,  $\text{CH}_2\text{-COOMe}$ ), 3.67 (s, 3H,  $\text{OCH}_3$ ), 4.30-4.51 (m, 2H,  $\text{CHF-CHF}$ ).  $^{13}\text{C}$  NMR  $\delta$  14.11 ( $\text{CH}_3$ ), 22.67 ( $\text{CH}_2$ ), 24.89 ( $\text{CH}_2$ ), 24.98 (d,  $J_{\text{CF}} = 2.5$  Hz,  $\text{CH}_2\text{-CH}_2\text{CFH}$ ), 25.05

(d,  $J_{CF} = 2.5$  Hz,  $\text{CH}_2\text{-CH}_2\text{CFH}$ ), 29.02 ( $\text{CH}_2$ ), 29.08 ( $\text{CH}_2$ ), 29.17 ( $\text{CH}_2$ ), 29.23 ( $\text{CH}_2$ ), 29.40 ( $\text{CH}_2$ ), 29.43 ( $\text{CH}_2$ ), 30.06 (dd,  $J_{CF} = 8.3$ ,  $J_{CF} = 5.0$  Hz,  $\text{CH}_2\text{-CHF}$ ), 30.27 (dd,  $J_{CF} = 8.2$ ,  $J_{CF} = 4.9$  Hz,  $\text{CH}_2\text{-CHF}$ ), 31.86 ( $\text{CH}_2$ ), 34.06 ( $\text{CH}_2$ ), 51.47 ( $\text{OCH}_3$ ), 93.80 (dd,  $J_{CF} = 172.7$ ,  $J_{CF} = 23.0$  Hz, 2C, CHF), 174.28 ( $\text{C=O}$ ).  $^{19}\text{F}$  NMR  $\delta$  -197.13 – -196.69 (m, 2F,  $\text{CFH-CFH}$ ) [15].

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