Journal of Fluorine Chemistry 133 (2012) 38–51

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Preparation of (*Z*)-1-fluoro-1-alkenyl carboxylates, carbonates and carbamates through chromium mediated transformation of dibromofluoromethylcarbinyl esters and the reactivity as double acyl group donors

Akio Saito [a,1], Manabu Tojo [a], Hikaru Yanai [a,*], Fukiko Wada [a], Muga Nakagawa [a], Midori Okada [b], Azusa Sato [b], Rieko Okatani [b], Takeo Taguchi [a,*]

[a] School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan
[b] Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

ARTICLE INFO

Article history:
Received 11 July 2011
Accepted 19 July 2011
Available online 26 July 2011

This paper is dedicated to Professor Wei-Yuan Huang on the occasion of his 90th birthday.

Keywords:
Fluoroalkenyl ester
Chromous chloride
Dibromofluoromethyl
Fluorocarbene
2,3-Sigmatropic rearrangement
Enzyme inhibitor
Acylation
Acyl donor

ABSTRACT

$CrCl_2$/Mn-mediated transformation of various dibromofluoromethylcarbinyl esters including carboxylates, carbonates and carbamates provided 1-fluoro-1-alkenyl esters via [2,3]-sigmatropic rearrangement of ester group. Reaction proceeded by using $CrCl_2$/Mn system under mild conditions (in THF at room temperature) to give 1-fluoro-1-alkenyl esters in good yield with an excellent *Z* selective manner. 1-Fluoro-1-alkenyl ester thus obtained acts as a double acyl donor in the reaction with necleophiles such as amine, thiol, alcohol as well as bifunctional necleophiles such as ethylene diamine derivative.

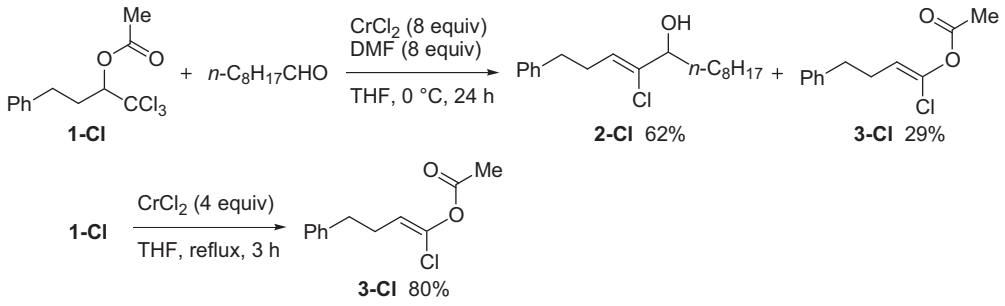
1. Introduction

Development of new and efficient synthetic methods for fluorinated olefins has been extensively investigated, since fluorinated olefins are an important class of compounds in both synthetic chemistry, as well as in medicinal chemistry and material sciences [1,2]. Our research group has been also engaging in this field, in which our recent development of stereoselective construction of functionalized fluorinated olefins directed to the fluoroalkene dipeptide isosteres is one of the representative achievements [3]. We have also developed new methods for fluoroalkene synthesis utilizing chromium chemistry. This involves the Cr(II)-mediated stereospecific fluoroalkenylation reaction of aldehyde using 1-bromo-1-fluoroalkenes (kinetic separation) [4] and the stereoselective synthesis of (*Z*)-2-fluoro-1-alkenyl ether derivatives from dibromofluoromethylcarbinyl alkyl ethers and silyl ethers [5]. Concerning these chromium chemistries, similar study to the former one was also reported by Pannecouk group [6] and the related study to the latter was reported by Falck and Mioskowski group [7]. Cr(II)-Mediated Reformatsky type reaction of bromofluoroacetates was also reported by Falck and Mioskowski group [8].

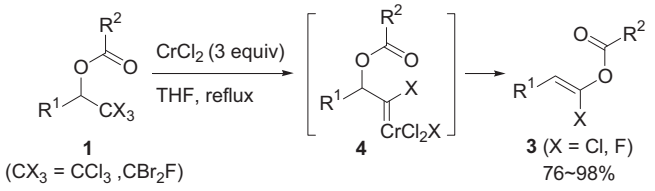
Cr(II)-mediated chloroalkenylation reaction using trichloromethyl substrates were investigated by several groups and a variety of synthetic reactions have been explored [9–11]. In 2001, Takai reported the *Z*-selective chloroalkenylation of aldehydes with putative chloroalkenyl chromium species *in situ* generated via *gem*-dichromium intermediate by treating trichloromethylcarbinyl acetate **1-Cl** with $CrCl_2$ in the presence of DMF to give the allyl alcohol **2-Cl**. In this paper it was pointed out that 1-chloroalkenyl acetate **3-Cl** was also detected as a side product (Scheme 1) [12]. We found that its formation could be realized when the starting ester **1-Cl** was simply react with $CrCl_2$ in THF under reflux conditions. However, detail on the chemistry of 1-chloroalkenyl ester such as mechanistic aspects, scope and limitations of the substrates and the utility of the products had not been examined.

* Corresponding authors. Tel.: +81 426 76 3257; fax: +81 426 76 3257.
E-mail addresses: yanai@toyaku.ac.jp (H. Yanai), taguchi@toyaku.ac.jp (T. Taguchi).
[1] Present address: Showa Pharmaceutical University, 3-3165 Higashi Tamagawagakuen, Machida, Tokyo 194-8543, Japan.

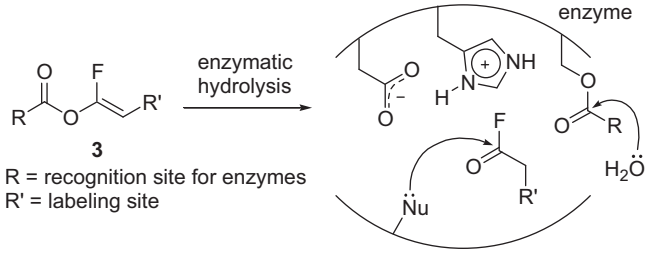
0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.07.022



Scheme 1.



Scheme 2.



Scheme 3.

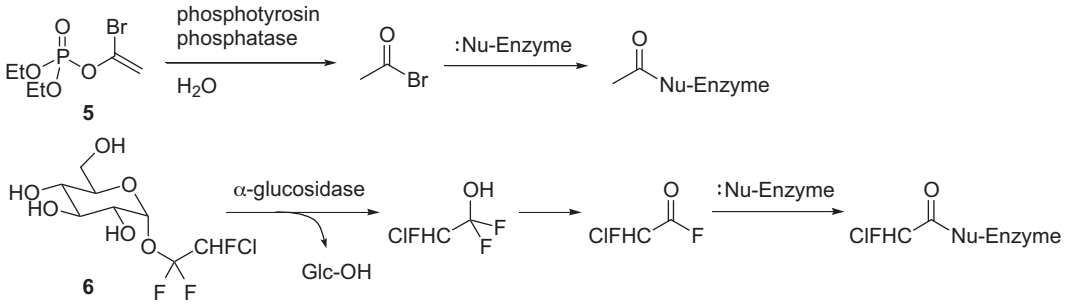
Later, in 2005 Falck and Mioskowski reported this ester group rearrangement reaction of trihalomethylcarbinol esters **1** leading to highly *Z*-selective and high yield synthesis of 1-chloro or 1-fluoro-1-alkenyl esters **3** (Scheme 2) [7]. Generally, for these reactions, 3.0 equiv. of $CrCl_2$ in THF under reflux conditions was employed. Mechanistic discussion indicating the intramolecular nucleophilic attack of the nonbonded electrons of carbonyl oxygen atom to the Fischer chromium halocarbene intermediate **4** to induce [2,3]-sigmatropic rearrangement was also provided. For the synthesis of fluorinated derivatives **3** (X = F), dibromofluoromethyl substrates were subjected to the Cr(II)-mediated reaction as we had also reported [13]. In 2009, as an extension of this chromium chemistry, the same group reported a highly stereoselective synthesis of (1*Z*,3*E*)-1-halo-1,3-dienol esters [14].

As will be mentioned below, we were interested in 1-fluoro-1-alkenyl ester structure from the view point of a molecular design of hydrolytic enzyme inhibitors and the synthetic utility as unique double acyl group donors to nucleophiles.

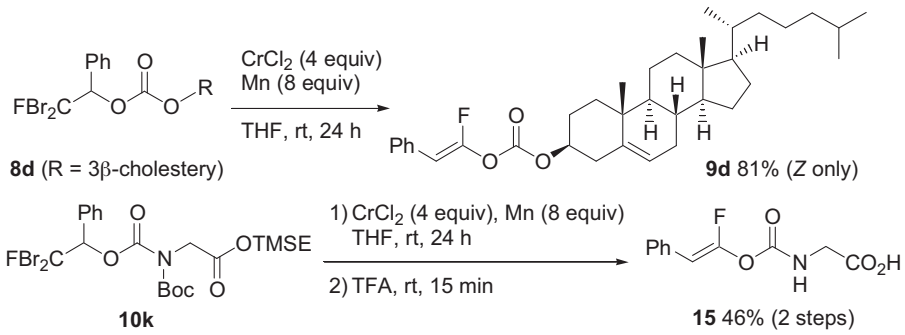
As a general consideration, synthetic methods for 1-halo-1-alkenyl esters are quite limited. Windlanski reported the synthesis of 1-bromovinyl esters by the addition of bromine to vinyl esters followed by dehydrobromination of the dibromide with strong base such as LiHMDS at low temperature [15]. This method was also demonstrated to be applicable to the synthesis of 1-bromovinyl phosphate **5** (in Scheme 4), which was shown to act as an inhibitor of phosphotyrosine phosphatase [15,16]. For the synthesis of 1-fluoro-1-alkeny ester by adapting the similar protocol, we have to develop an efficient conditions for both halofluorination of alkenyl esters and the subsequent selective dehydrohalogenation reaction. There have been no reports dealing with such reactions and these remain as the future subjects. Ram reported the preparation of 1-chloro-1-alkenyl esters via radical acyloxy group rearragement (Surzur–Tanner reaction) of trichloromethylcarbinyl esters promoted by CuCl/bipyridine complex [17]. We applied this reaction to dibromofluoromethyl derivatives for the synthesis of fluoroalkeny ester, but the reaction proceeded very slowly and the yield of the fluoroalkeny ester was very low [18].

It is expected that reaction of 1-fluoro-1-alkenyl ester **3** with a nucleophile (Nu–H) including enzymatic hydrolysis will deliver the acylated compound (RCONu) and the acyl fluoride ($R'CH_2COF$) converted from the liberated fluoroenol, which can act as the second acyl transfer reagent to the nucleophilic center to give the acylated compound ($R'CH_2CONu$). Schematic enzymatic hydrolysis leading to the second acylation step by acyl fluoride is illustrated in Scheme 3. The idea is similar to those of Windlanski's bromovinyl phosphate **5** as phosphatase inhibitor [15,16] or Halazy's α-1,1-difluoroethyl glycoside **6** as α-glucosidase inhibitor [19] (Scheme 4). In both cases, enzymatic reactions provided reactive acylating reagents, which caused the irreversible inhibition by trapping nucleophic centers in the enzyme.

In this paper, we report a stereoselective synthesis of various (*Z*)-1-fluoro-1-alkenyl esters through Cr(II)-mediated [2,3]-rearrangement of a variety type of dibromofluoromethylcarbinyl esters



Scheme 4.



Scheme 5.

including carbonates **8** and carbamates **10** leading to the compounds of biological interest such as **9d** and **15** (Scheme 5). By employing $CrCl_2$/Mn system reaction proceeded smoothly at room temperature. Furthermore, we demonstrate that 1-fuoro-1-alkenyl ester **3** thus obtained can serve as a double acyl group donor in the reaction with necleophiles such as amine, thiol, alcohol as well as bifunctional necleophiles such as 1,2-diamine derivatives (Scheme 6).

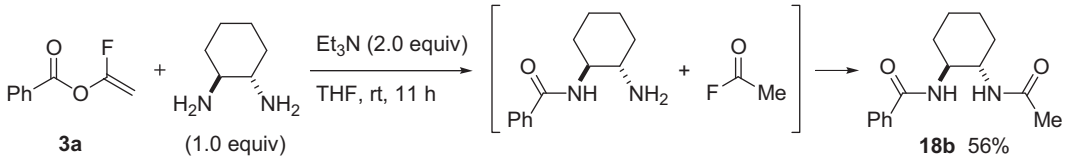
2. Results and discussion

2.1. Preparation of 1-fluoro-1-alkenyl esters

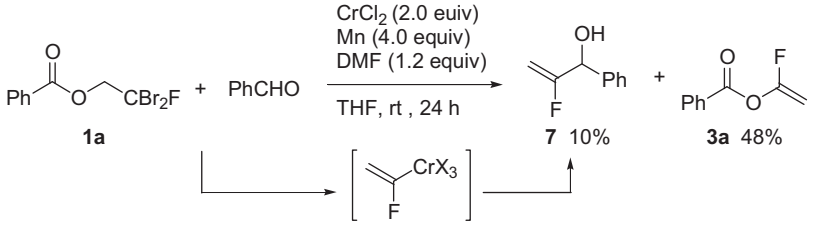
During our early stage to explore fluoroalkenylation reaction of aldehydes with fluoroalkenyl chromium species, we conducted the Barbier type reaction of 2,2-dibromo-2-fluoroethyl benzoate **1a** with benzaldehyde in the presence of $CrCl_2$ pretreated with DMF according to Takai's chloroalkenylation reaction as described in Scheme 1 [12]. Even under our optimized conditions for the fluoroalkenylation, the desired fluoroallyl alcohol **7** was obtained only in 10% yield, but, in stead, 1-fluorovinyl benzoate **3a** was a major product isolated in 48% yield and at the same time **1a** was recovered in 16% (Scheme 7).

Since the product, 1-fluoro-1-alkenyl ester **3a**, attracted our attention as described above, we examined in detail to establish the optimized reaction conditions together with the scope and limitations of the substrates, in particular toward molecular design of inhibitors for some hydrolytic enzymes.

Selected results of the survey of reaction conditions for the ester group rearrangement are summarized in Table 1. As the substrates we chose carboxylate of dibromofluoroethanol (primary alcohol) **1a** and those of two dibromofluoromethylcarbinols (secondary alcohol) **1b–c**, as well as ethyl carbonates **8a–b** and *N,N*-dimethyl carbamates **10a–b**. In the case of dibromofluoroethyl benzoate **1a**, reaction proceeded slowly when treating with 4 equiv. of $CrCl_2$ in THF at room temperature and after 13 h we obtained 1-fluorovinyl benzoate **3a** in 55% isolated yield (entry 1). Addition of Mn powder was found to be effective to enhance the reaction rate and to reduce the amount of expensive $CrCl_2$ [20]. That is, as shown in entry 2, a combined use of 1.5 equiv. of $CrCl_2$ and 4.0 equiv. of Mn in THF at room temperature resulted in the consumption of **1a** within 5 h to give **3a** in 65% yield. Effect of Mn powder as an additive on the efficiency of the reaction was much more significant in the reaction of less reactive esters of secondary alcohols. For example, while the reaction of **1b** and **8a** did not proceed at room temperature by the single use of $CrCl_2$ (4 equiv., entries 4 and 7 vs. entry 1), a combined use of 2.0 equiv. of $CrCl_2$ and 8.0 equiv. of Mn in THF at room temperature for 16 h promoted the reaction to give the desired products **3b** and **9a** in excellent yields in both cases (entries 5 and 8). Under the same conditions, not only these benzylic substrates **1b** and **8a**, aliphatic substrates **1c** and **8b** also provided the corresponding fluoroalkenyl esters **3c** and **9b** in excellent yields (entries 6 and 9). It should be noted that the reactions proceeded in completely stereoselective manner to give *Z*-configurated products [7]. Similar transformation was found to be applicable to carbamates **10a** and **10b** to give the products **11a** and **11b** in 61% and 65%, respectively under the same conditions. Thus, $CrCl_2$/Mn system works nicely for the transformation of dibromofluoromethylcarbinol esters into 1-fluoro-1-alkeny esters under mild conditions such as in THF at room temperature.

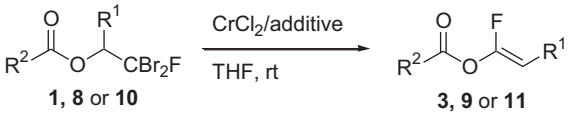


Scheme 6.



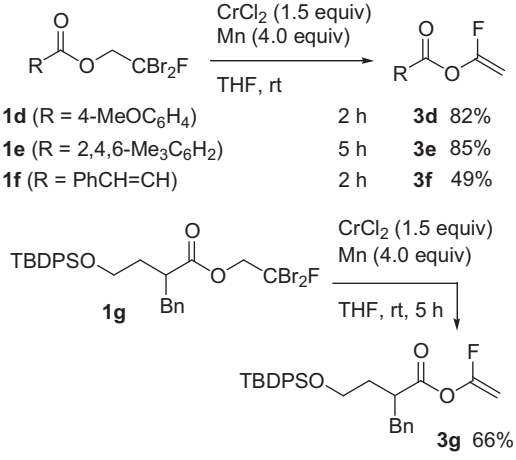
Scheme 7.

Table 1
Survey of reaction conditions for ester rearrangement.



Entry	Substrate	R^1	R^2	$CrCl_2$ (equiv.)	Additive (equiv.)	Time (h)	Product	Yield[a] (%)
1	**1a**	H	Ph	4.0	None	13	**3a**	55
2	**1a**	H	Ph	1.5	Mn (4.0)	5	**3a**	65
3	**1a**	H	Ph	3.0	Mn (2.0)/$(Ph_3P)_2NiCl_2$ (0.1)	6	**3a**	55
4	**1b**	Ph	Me	4.0	None	20	**3b**	0[b]
5	**1b**	Ph	Me	2.0	Mn (8.0)	15	**3b**	98[c]
6	**1c**	$PhCH_2CH_2$	Me	2.0	Mn (8.0)	16	**3c**	95[c]
7	**8a**	Ph	EtO	4.0	None	20	**9a**	0[b]
8	**8a**	Ph	EtO	2.0	Mn (8.0)	16	**9a**	88[c]
9	**8b**	$PhCH_2CH_2$	EtO	2.0	Mn (8.0)	16	**9b**	98[c]
10	**10a**	Ph	Me_2N	2.0	Mn (8.0)	23	**11a**	61[d]
11	**10b**	$PhCH_2CH_2$	Me_2N	2.0	Mn (8.0)	15	**11b**	65[c]

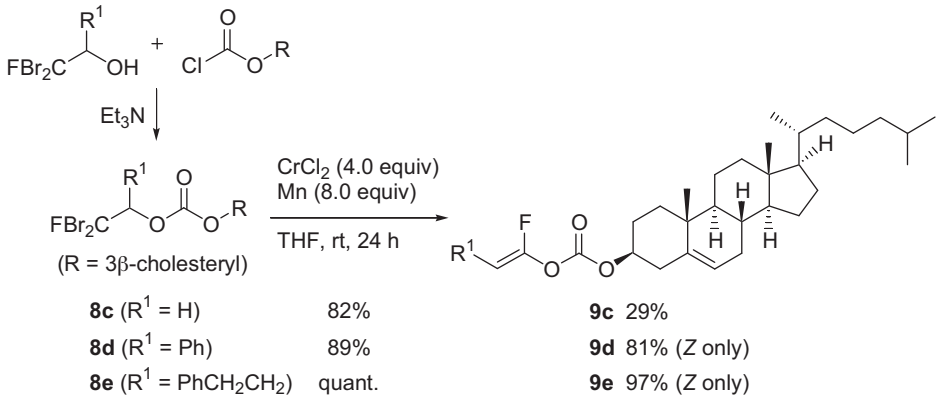
[a] Isolated yield.
[b] No reaction.
[c] (*Z*)-isomer only.
[d] *Z*/*E* = 11:1.



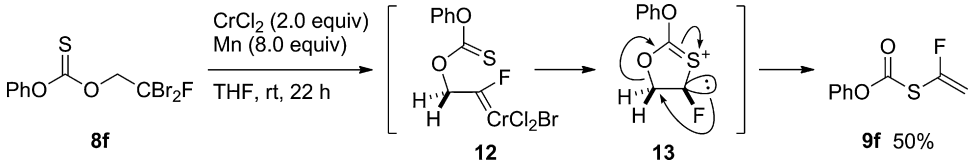
Scheme 8.

Followings are additional examples of the transformation of dibromofluoroethyl carboxylates using $CrCl_2$/Mn system (Scheme 8). Reaction of 2,4,6-trimethylbenzoate **1e**, a sterically bulky substrate, also proceeded smoothly to give the expected product **3e** in high (85%) yield. Under the same conditions, cinnamate **1f**, α,β-unsaturated ester, afforded the fluorovinyl ester **3f** in moderate (49%) yield. Silyl ether moiety (TBDPS ether) was not affected under the present transformation reaction as shown in the reaction of γ-silyloxybutylate **1g** giving rise to the product **3g** in 66% yield.

Since carbonate derivatives can be used as the substrate (Table 1, entries 7–9), we designed 3β-cholesteryl fluoroalkenyl carbonate **9** as a model structure of inhibitor for cholesterol esterase (CEase) [21]. Cholesterol esterase (CEase) catalyzes hydrolysis of sterol esters into cholesterol and fatty acid resulting in the elevation of cholestrol level [22,23]. Inhibitor of cholesterol esterase (CEase) is expected to lower cholesterol level by the different mechanism from that of the inhibitor of HMG-CoA reductase, which is responsible for the rate determining step of cholesterol biosynthesis [21]. Several *O*-3β-cholesteryl *N*-aryl carbamates were reported as a inhibitor of CEase [24]. The starting substrates **8c–e** were prepared in good yields by esterification of dibromofluoromethylcarbinols with commercially available cholesteryl chloroformate. Transformation into fluoroalkenyl carbonates **9c–e** proceeded rather slowly with these substrates **8c–e** and thus, reactions were completed by using 4.0 equiv. of $CrCl_2$ and 8.0 equiv. of Mn powder in THF at room temperature for 24 h to give **9c** in 29%, **9d** in 81% and **9e** in 97% yield, respectively. Similarly to other examples, reaction proceeded in *Z*-selective manner for **9d** and **9e** (Scheme 9).



Scheme 9.

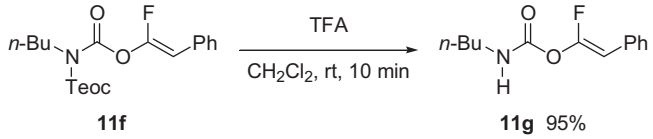


Scheme 10.

We found that thiocarbonate is also used in this transformation. Thus, when the thiocarbonate **8f** was reacted under the similar conditions applied to the carbonate **8a–b** (Table 1), the rearranged 1-fluorothiovinyl derivative **9f** was obtained in 50% yield. This result indicated that the reaction possibly proceeded via five membered sulfonium yield intermediate **13** formed by the attack of sulfur atom on the fluorocarbenoid species **12** (Scheme 10) [7,14].

Next, attempts were made toward chemical modification of amino acids by introducing *N*-fluoroalkenyloxycarbonyl group. As shown before (Table 1) *N*,*N*-dimethyl carbamates **10a** or **10b**, which does not have a hydrogen atom on the nitrogen atom performed as a nice substrate providing the desired fluoroalkenyl carbamates **11a** or **11b** in moderate yields. However, as shown in Table 2, it was found that $CrCl_2$/Mn-mediated transformation of N-H substrates such as **10c** or **10d** gave a somewhat sluggish mixture and the expected fluoroalkenyl products **11c** and **11d** were isolated only in 12% and 39% yield, respectively (Table 2, entries 2, 3). To overcome such low yield with N–H substrates, we examined *N*-protection. *N*-Boc group should be the first choice for this purpose due to the accumulated data as the most common *N*-protective group concerning its introduction, reactivity and deprotection. As expected, reaction of *N*-Boc *N*-isopropyl derivative **10e** under the standard conditions proceeded much more cleanly to give the rearranged product **11e** in 51% yield (entry 4). Likewise, the use of *N*-2-(trimethylsilyl)ethyloxycarbonyl (Teoc) was also effective. That is, *N*-Teoc *N*-butyl derivative **10f** was converted to the fluoroalkenyl carbamate **11f** in 65% yield (entry 5).

Deprotection of these Boc and Teoc group can be performed by treating with trifluoroacetic acid (TFA) without a remarkable affect on fluoroalkenyl ester moiety. For example, treatment of the *N*-Teoc derivative **11f** with TFA (6 equiv.) in CH_2Cl_2 at room temperature for 10 min gave the deprotected N–H compound **11g** in 95% yield (Scheme 11) [25]. Deprotection of *N*-Boc group was also achieved by the conventional conditions such as TAF treatment at room temperature as shown in the case of glycine derivative (see Scheme 13).

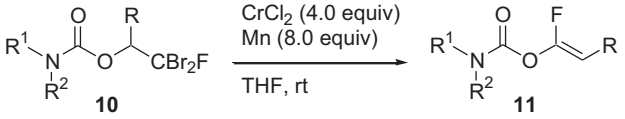


Scheme 11.

As the structurally simplest amino acid, sarcosine (*N*-methylglycine) methyl ester was selected. Three dibromofluoromethylcarbinyl carbamates **10h–j** were prepared by esterification reaction with *N*-chloroformyl intermediate generated by treating sarcosine methyl ester with triphosgene (see Section 4). $CrCl_2$/Mn-mediated transformation proceeded smoothly to give the products **11h–j** in good yields with *Z* selective manner for **11i** and **11j** (Scheme 12). Unfortunately, selective conversion of methyl ester to free acid form was difficult under both basic and acidic conditions.

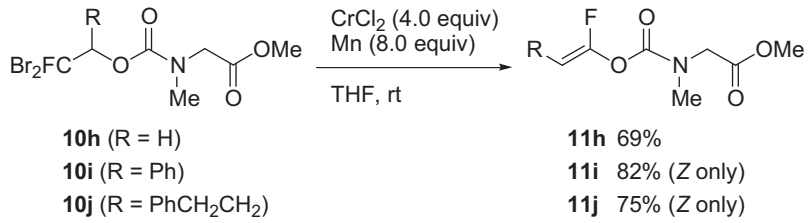
Above results suggested that for the preparation of *N*-1-fluoro-1-alkenyloxycarbonyl α-amino acids as its N-H and free acid form such as glycine derivative **15**, protection of both amino group and carboxyl group is required at the Cr(II)-mediated transformation step. On the basis of successful deprotection of 2-(trimethylsilyl)ethyl ester (TMSE ester) by TFA within a short period (Scheme 11), we examine the use of *N*-Boc glycine TMSE ester **10k** as a model substrate. Scheme 13 illustrates the whole reaction steps. Esterification of *N*-Boc-glycine with 2-(trimethylsilyl)ethanol in the presence of EDC·HCl (96% yield) followed by chloroformylation with triphosgene and pyridine gave the crude carbamoyl chloride **14**, which in turn was reacted with dibromofluoromethylphenylcarbinol to give **10k** in 82% yield. Reaction of **10k** with $CrCl_2$/Mn system proceeded smoothly to give the rearranged product **11k** in 65% yield. Deprotection of both *N*-Boc group and TMSE ester was effected by TFA treatment for 15 min without the use of solvent and the desired final product **15** was isolated in 70% yield (Scheme 13). When the TFA treatment was carried out in CH_2Cl_2, *N*-Boc group was deprotected prior to TMSE ester moiety.

Table 2
Preparation of 1-fluoro-1-alkenyl carbamates.

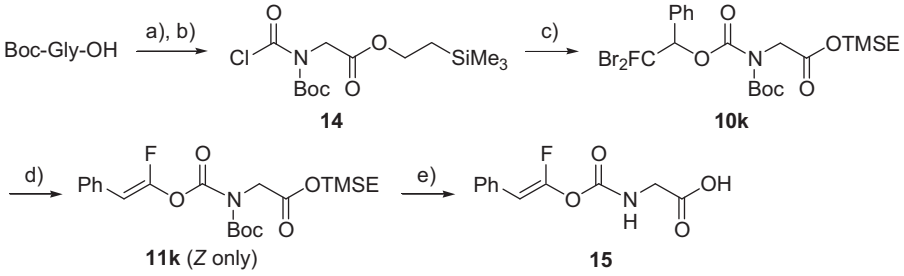


Entry	**10**	R	R^1	R^2	Time (h)	**11**	Yield[a] (%)
1[b]	**10a**	Ph	Me	Me	23	**11a**	61[c]
2	**10c**	H	*n*-Pr	H	16	**11c**	12
3	**10d**	Ph	*n*-Pr	H	18	**11d**	39[d]
4	**10e**	H	*i*-Pr	Boc[e]	24	**11e**	51
5	**10f**	Ph	*n*-Bu	Teoc[f]	20	**11f**	65[d]

[a] Isolated yield.
[b] Table 1, entry 10.
[c] *Z*/*E* = 11:1.
[d] (*Z*)-isomer only.
[e] *tert*-Butyloxycarbonyl.
[f] 2-(Trimethylsilyl)ethyloxycarbonyl.



Scheme 12.



Scheme 13. *Reagents and conditions:* a) 2-(trimethylsilyl)ethanol, EDC·HCl, CH_2Cl_2, rt, 3 h, 96%); b) triphosgene, pyridine, CH_2Cl_2, −30 °C to rt, 24 h; c) $CBr_2FCH(Ph)OH$, Et_3N, DMAP, THF, rt, 24 h, 81% (2 steps); d) $CrCl_2$ (2.0 equiv.), Mn (8.0 equiv.), THF, rt, 24 h, 65%; e) TFA, rt, 15 min, 70%.

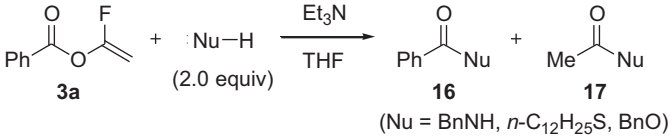
As described above, we have developed a facile synthetic procedure for a variety type of 1-fluoro-1-alkenyl esters through the Cr(II)-mediated ester rearrangement of dibromofluoromethylcarbinyl esters. In particular, a successful synthesis of cholesterol and amino acid derivatives would attract much interests in the field of bioorganic and medicinal chemistry.

2.2. Reaction of 1-fluoro-1-alkenyl ester with nucleophiles

As mentioned before (Scheme 3), it is expected that nucleophilic cleavage of 1-fluoro-1-alkenyl ester such as by aminolysis or alcoholysis would provide the corresponding acyl fluoride, which further acts as a reactive acylating reagent. If such a reaction can be performed by a certain hydrolytic enzymes (esterase and peptidase e.g.), irreversible inhibition of the enzyme by the acylation of the nucleophilic center in the enzyme can be possibly realized. To confirm chemically that 1-fluoro-1-alkenyl ester can serve as a double acylating reagent, we conducted the reaction of 1-fluorovinyl benzoate **3a** with a primary amine, thiol and alcohol under neutral or slightly basic conditions.Reaction of 1-fluorovinyl benzoate **3a** with benzylamine (2 equiv.) in the presence of triethylamine as HF scavenger proceeded at room temperature to give the benzamide **16a** and acetoamide **17a** in 92% and 91% yield, respectively. Similar results were obtained on using a thiol (dodecane-1-thiol) and a primary alcohol (benzyl alcohol). In the presence of triethylamine (2 equiv.), reaction of the fluorovinyl benzoate **3a** with dodecane-1-thiol (2 equiv.) in THF at room temperature for 14 h provided the benzoly **16b** and acetyl thiol ester **17b** in 87% and 83% yield, respectively. In the case of benzyl alcohol (2 equiv. in the presence of 1.2 equiv. of Et_3N), while the reaction did not proceed at room temperature, at 40 °C for 21 h in THF the reaction completed giving rise to the benzoate **16c** in 82% and the acetate **17c** in 60% yield, respectively. These examples clearly indicated that 1-fluoro-1-alkenyl ester **3a** shows a similar reactivity to that of methyl or ethyl benzoate. Furthermore, nearly equal production of benzoyl and acetyl derivatives (**16** and **17**) in the reaction with these nucleophiles (2 equiv.) indicated that the fluoroalkenyl moiety also acts as a highly reactive acetyl donor (Table 3).

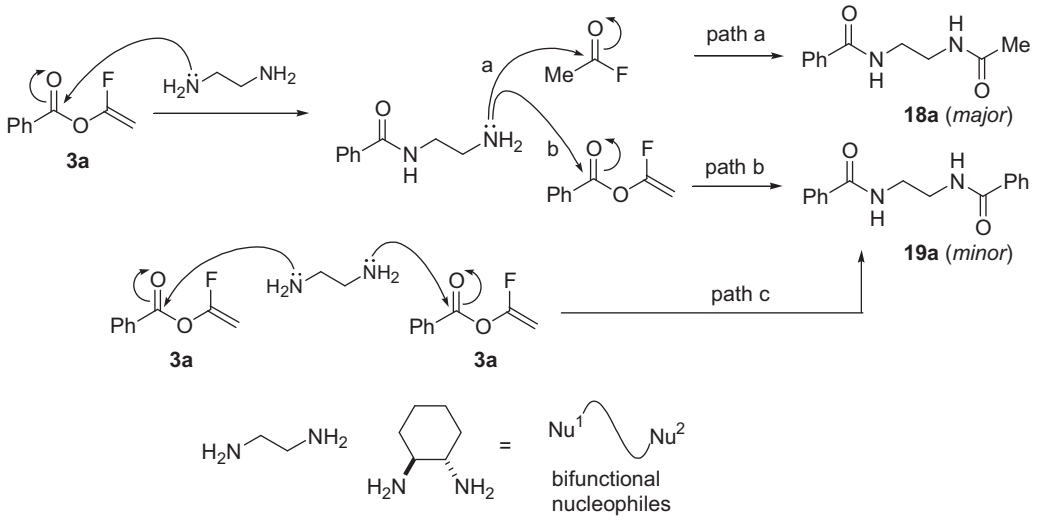
The results mentioned above clearly indicated that 1-fluoro-1-alkenyl ester **3** can act as a double acylating reagent via stepwise reactions. Thereby, if the acyl transfer reaction of 1-fluoro-1-alkenyl ester with a bifunctional nucleophile proceeds selectively at one of the two nucleophilic centers for the first step, subsequent acylation of the other nucleophilic center by the acyl fluoride generated *in situ* would result in the unsymmetrical diacylation of the bifunctional substrate. Path a in Scheme 14 shows an example using ethylene diamine as a model nucleophile. In Scheme 14, path

Table 3
Reaction of 1-fluorovinyl benzoate **3a** with nucleophiles.



Entry	Nu–H	Et_3N (equiv.)	Temp. (°C)	Time (h)	Yield[a] (%)			
					16		**17**	
1	$BnNH_2$	1.0	rt	19	**16a**	92	**17a**	91
2	n-$C_{12}H_{25}SH$	2.0	rt	14	**16b**	87	**17b**	83
3	BnOH	1.2	40	21	**16c**	82	**17c**	60

[a] Isolated yield.



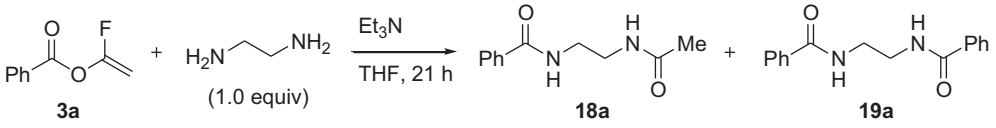
Scheme 14.

b and path c would be possible competitive reactions leading to the symmetrically diacylated product **19a**, where path b shows a stepwise reaction and path c shows that both nucleophilic centers react almost at the same time. For the ease of analysis of the products, we chose symmetrical bifunctional nucleophiles such as ethylene diamine and *trans*-cyclohexane 1,2-diamine as the model substrates.

Reaction of **3a** with ethylene diamine (1.0 equiv.) in the presence of triethylamine (1.2 equiv.) in THF (0.125 M of **3a**) at room temperature for 21 h led to the isolation of unsymmetrically diacylated amide **18a** in 46% yield accompanying the dibenzoylated amide **19a** in 15% yield, thus the ratio of **18a** and **19a** was 3.1:1 (entry 1, Table 4). Similar results were obtained by changing the concentration of the substrate (0.5 M of **3a**, rt, 21 h; **18a** (46%): **19a** (18%) = 2.6:1, entry 2) or by lowering the reaction temperature (Et_3N 2.0 equiv., 0 °C, 21 h; **18a** (40%): **19a** (15%) = 2.6:1, entry 4). It is obvious that low selectivity of unsymmetrical diacylation is due to the competitive benzoylation of both amino groups at the same time rather than the ideal stepwise reaction, since ethylene diamine is a sterically unhindered bifunctional nucleophile resulting in the facile approach of both amino groups to the ester carbonyl group of **3a** (path c in Scheme 14).

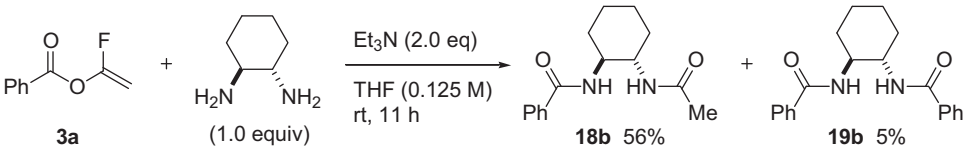
To achieve a higher selectivity, we examined *trans*-cyclohexane 1,2-diamine as a conformationally more rigid and sterically more crowded nucleophile. As expected, reaction of **3a** with *trans*-cyclohexane 1,2-diamine (1.0 equiv.) in the presence of Et_3N (2.0 equiv.) in THF (0.125 M of **3a**) at room temperature for 11 h gave the unsymmetrically diacylated amide **18b** (56% yield) and dibenzoylated amide **19b** (5% yield) in a ratio 11: 1 (Scheme 15).Although more data are required to see the insight of the present double acylation reaction of bifunctional nucleophiles, structure design of nucleophile is one of the important factors to realize a stepwise acyl transfer reaction. As an alternative design of the 1-fluoro-1-alkenyl ester compound, we examined *O*-protected

Table 4
Survey of reaction conditions for desymmetrization of ethylene diamine with **3a**.

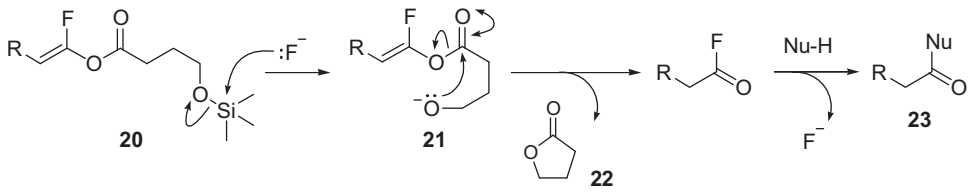


Entry	Concentration of **3a** (mol L^{-1})	Et_3N (equiv.)	Temp. (°C)	Yield[a] (%)		**18a**/**19a**[b]
				18a	**19a**	
1	0.125	1.2	rt	46	15	3.1:1
2	0.5	1.2	rt	46	18	2.6:1
3	0.25	1.2	rt	42	19	2.2:1
4	0.25	2.0	0	40	15	2.6:1

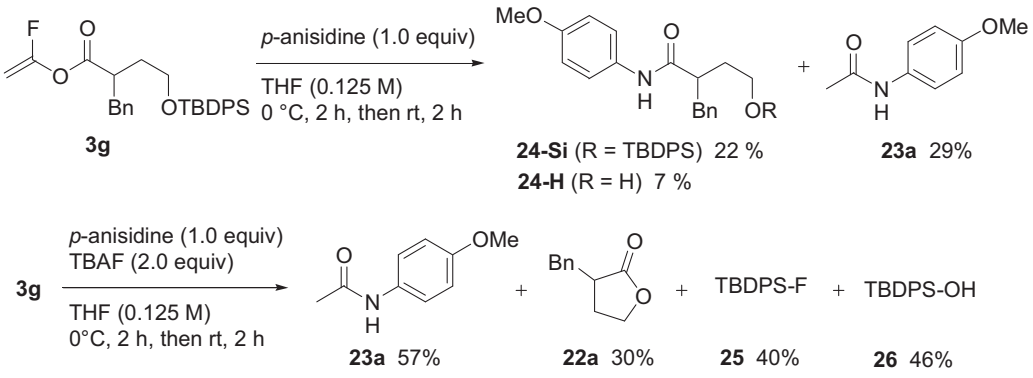
[a] Isolated yield.
[b] Based on isolated yield.



Scheme 15.



Scheme 16.



Scheme 17.

4-hydroxybutanoyl derivative **20** (Scheme 16). With such a substrate selective *O*-deprotection to generate an alkoxide form **21** would initiate the intramolecular lactonization to give γ-butyrolactone **22** accompanying the *in situ* generation of acyl fluoride, which in turn reacts with a co-existing nucleophile giving rise to the product **23**. Reaction of silyl ether with fluoride (tetrabutylammonium fluoride: TBAF) would be expected to realize a selective cleavage of *O*-protection to generate the alkoxide form as shown in Scheme 16.

For the ease of handling of the products benzyl group was introduced at α position of the model ester substrate **3g** (Scheme 17). As a control experiment we checked a suitable nucleophile for this substrate. We found that reaction of 1-fluorovinyl ester **3g** having *tert*-butyldiphenylsilyl (TBDPS) ether moiety with *p*-anisidine proceeded fairly slowly as compared to that with primary alkylamine such as benzylamine. That is, treatment of **3g** with *p*-anisidine (1 equiv.) in THF at 0 °C for 2 h, then at room temperature for 2 h gave the three amides **24-Si**, **24-H** and **23a** in 22%, 7% and 29% yield, respectively accompanying the recovery of **3 g** (ca 60%). The isolated amides **24-Si** and **24-H** were derived by nucleophilic attack of *p*-anisidine on ester carbonyl group of **3g** and the acetyl derivative **23a** was formed by the reaction of *p*-anisidine with *in situ* generated acetyl fluoride. The ratio of **24-Si**/**24-H** and **23a** was 1:1 indicating that an almost single reaction course (aminolysis of **3g** and the subsequent acetylation by acetyl fluoride) was involved in this case. Next, fluoride-promoted *O*-desilylation reaction in the presence of *p*-anisidine was conducted. Thus, on using TBAF (2 equiv., 1 M THF solution) complete consumption of **3g** was observed and the expected lactone compound **22a** and the acetoanilide derivative **23a** were isolated in 30% and 57% yield, respectively. TBDPS-F **25** and TBDPS-OH **26** were also isolated in 40% and 46% yield, indicating the complete cleavage of silyl ether bond. In this case, direct aminolysis of **3g** by *p*-anisidine was possibly excluded due the absence of the anilide **24-Si** and/or **24-H** in the reaction mixture. As a consequence, the main reaction course involved the stepwise *O*-desilylation by TBAF followed by the intramolecular lactonization and the liberation of acetyl fluoride, which finally reacted with the co-existing nucleophile *p*-anisidine (Scheme 17).

3. Conclusion

We have developed an efficient procedure for the stereoselective synthesis of (*Z*)-1-fluoro-1-alkenyl esters through the $CrCl_2$/Mn-mediated reaction of dibromofluoromethylcarbinyl esters including carboxylates, carbonates and carbamates. Furthermore, we demonstrated that nucleophilic acyl substitution of 1-fluoro-1-alkenyl ester with amines and alcohols delivers acyl fluoride which act as the second acylating reagent in the same reaction system. These results and a successful synthesis of cholesterol and amino acid derivatives would provide important informations toward to the molecular design of inhibitors for hydrolytic enzymes.

4. Experimental

4.1. General

All reactions were carried out under argon atmosphere. ^1H and ^{13}C NMR spectra were taken on a Bruker dpx400 spectrometer or Varian Mercury 300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^1H NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C NMR as an internal standard, respectively. ^{19}F NMR spectra were taken on a Bruker dpx400 spectrometer, and chemical shifts were reported in parts per million using benzotrifluoride as a standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-620 infrared spectrophotometer. Mass spectra (MS) were obtained on a VG Auto Spec (EI) and a Micromass LCT (ESI-TOF). Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV or RI detector. Anhydrous $CrCl_2$ was purchased from Aldrich. 2,2-Dibromo-2-fluoroethanol was prepared by $LiBH_4$ reduction of ethyl dibromofluoroacetate in the presence of $(MeO)_3B$ [5]. 2,2-Dibromo-2-fluoro-1-phenylethanol

and 1,1-dibromo-1-fluoro-4-phenylbutan-2-ol were prepared according to the reported procedure [26,27].

4.2. General procedure for the preparation of dibromofluoromethylcarbinyl esters (1, 8 and 10)

A mixture of the dibromofluoroalcohol (1.0 equiv.), acid chloride (1.1–1.5 equiv.) and triethylamine (2.2–3.0 equiv.) in THF was stirred for 1 h at 0 °C, then for additional appropriate period (usually 2–3 h) at room temperature. As in the cases of **1e**, **1f**, **8c–e** catalytic amount of 4-dimethylaminopyridine was also added. Usual workup (addition of water, extraction with diethyl ether or ethyl acetate, dried over $MgSO_4$) followed by purification by silica gel column chromatography (mixture of hexane and EtOAc as eluent) gave the corresponding ester.

4.2.1. 2,2-Dibromo-2-fluoroethyl benzoate (1a) [7]

96% yield; colorless semi-solid; Mp. 27.0–28.0 °C; IR (neat) ν 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (2H, d, J_{H-F} = 15.4 Hz), 7.46–7.51 (2H, m), 7.60–7.64 (1H, m), 8.11–8.13 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.7 (d, J_{C-F} = 22.6 Hz), 91.2 (d, J_{C-F} = 320.9 Hz), 128.6, 128.7, 130.1, 133.8, 164.7. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.2 (1F, t, J_{F-H} = 15.4 Hz). HRMS (EI) calcd for $C_9H_7Br_2FO_2$ $[M]^+$, 323.8797; found, 323.8799; Anal. calcd for $C_9H_7Br_2FO_2$: C, 33.16; H, 2.16. Found: C, 33.20; H, 2.30.

4.2.2. 2,2-Dibromo-2-fluoro-1-phenylethyl acetate (1b)

82% yield; colorless oil; IR (neat) ν 3037, 2937, 2849, 1761, 1217, 1201, 1061, 781, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s), 6.31 (1H, d, J_{H-F} = 12.8 Hz), 7.37–7.55 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 81.3 (d, J_{C-F} = 22.5 Hz), 96.6 (d, J_{C-F} = 322.9 Hz), 128.2, 129.2, 129.7, 132.9, 168.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ–0.3 (1F, d, J_{F-H} = 12.8 Hz); MS (EI) m/z 338 $[M]^+$, 340 $[M+2]^+$, 342 $[M+4]^+$; Anal. calcd for $C_{10}H_9Br_2FO_2$: C, 35.33; H, 2.67. Found: C, 35.54; H, 2.88.

4.2.3. 2,2-Dibromo-2-fluoroethyl 4-methoxybenzoate (1d)

70% yield; colorless solid; Mp. 50.0–51.2 °C; IR (neat) ν 2972, 1721, 1606, 1262, 1064, 1023, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 4.96 (2H, d, J_{H-F} = 15.5 Hz), 6.96 (2H, d, J = 9.0 Hz), 8.08 (2H, d, J = 9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 72.6 (d, J_{C-F} = 22.8 Hz), 91.5 (d, J_{C-F} = 320.8 Hz), 113.9, 121.1, 132.2, 164.1, 164.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.3 (1F, t, J_{F-H} = 15.5 Hz); MS (EI) m/z 354 $[M]^+$, 356 $[M+2]^+$, 358 $[M+4]^+$; Anal. calcd for $C_{10}H_9Br_2FO_3$: C, 33.74; H, 2.55. Found: C, 33.77; H, 2.65.

4.2.4. 2,2-Dibromo-2-fluoroethyl 2,4,6-trimethylbenzoate (1e)

79% yield; colorless oil; IR (neat) ν 2956, 2924, 1740, 1246, 1165, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 2.36 (6H, s), 4.99 (2H, d, J_{H-F} = 15.6 Hz), 6.89 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.1, 72.8 (d, J_{C-F} = 22.5 Hz), 90.7 (d, J_{C-F} = 321.1 Hz), 128.7, 129.1, 136.0, 140.2, 168.0; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.1 (1F, t, J_{F-H} = 15.6 Hz); MS (EI) m/z 366 $[M]^+$, 368 $[M+2]^+$, 370 $[M+4]^+$; Anal. calcd for $C_{12}H_{13}Br_2FO_2$: C, 39.16; H, 3.56. Found: C, 39.28; H, 3.69.

4.2.5. 2,2-Dibromo-2-fluoroethyl cinnamate (1f)

78% yield; colorless oil; IR (neat) ν 1725, 1635, 1148, 921, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (2H, d, J_{H-F} = 15.7 Hz), 6.52 (1H, d, J = 16.0 Hz), 7.40–7.43 (3H, m), 7.56–7.58 (2H, m), 7.82 (1H, d, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.3 (d, J_{C-F} = 22.3 Hz), 91.3 (d, J_{C-F} = 320.9 Hz), 116.2, 128.4, 129.0, 130.8, 133.9, 147.1, 165.0; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.3 (1F, t, J_{F-H} = 15.7 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_{10}Br_2FO_2$ $[M+H]^+$, 350.9032; found, 350.9060; Anal. calcd for $C_{11}H_9Br_2FO_2$: C, 37.53; H, 2.58. Found: C, 37.83; H, 2.76.

4.2.6. 2,2-Dibromo-2-fluoroethyl-2-benzyl-4-(tert-butyldiphenylsilyloxy)butanoate (1g)

60% yield; colorless oil; IR (neat) ν 2931, 2854, 1752, 1146, 1109, 741, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.78–1.82 (1H, m), 1.98–2.05 (1H, m), 2.83 (1H, dd, J = 13.5, 6.9 Hz), 3.03 (1H, dd, J = 13.5, 7.9 Hz), 3.06–3.17 (1H, m), 3.71 (2H, t, J = 6.1 Hz), 4.53–4.68 (2H, m), 7.16–7.24 (3H, m), 7.26–7.31 (2H, m), 7.36–7.41 (6H, m), 7.60–7.64 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.8, 34.2, 38.1, 43.8, 61.5, 72.1 (d, J_{C-F} = 22.4 Hz), 91.0 (d, J_{C-F} = 321.1 Hz), 126.5, 127.7, 128.5, 129.0, 129.64 and 129.66, 133.56 and 133.64, 135.53 and 135.57, 138.6, 173.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.3 (1F, t, J_{F-H} = 15.7 Hz); HRMS (ESI-TOF) calcd for $C_{29}H_{34}Br_2FO_3Si$ $[M+H]^+$, 635.0628; found, 635.0619; Anal. calcd for $C_{29}H_{33}Br_2FO_3Si$: C, 54.73; H, 25.23. Found: C, 54.90; H, 5.36.

4.2.7. 2,2-Dibromo-2-fluoro-1-phenylethyl ethyl carbonate (8a)

92% yield; colorless oil; IR (neat) ν 2984, 1757, 1456, 1253, 1092, 1006, 786, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, J = 7.1 Hz), 4.21–4.31 (2H, m), 6.12 (1H, d, J_{H-F} = 11.9 Hz), 7.38–7.58 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 65.3, 84.6 (d, J_{C-F} = 2.9 Hz), 96.1 (d, J_{C-F} = 322.5 Hz), 128.3, 129.1, 129.9, 132.4, 153.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-0.7 (1F, d, J_{F-H} = 11.9 Hz); MS (EI) m/z 368 $[M]^+$, 370 $[M+2]^+$, 372 $[M+4]^+$; Anal. calcd for $C_{11}H_{11}Br_2FO_3$: C, 35.71; H, 3.00. Found: C, 36.09; H, 3.21.

4.2.8. 1-[Dibromo(fluoro)methyl]-3-phenylpropyl ethyl carbonate (8b)

71% yield; colorless oil; IR (neat) ν 3028, 2983, 2937, 2865, 1756, 1496, 1456, 1247, 1123, 1028, 783, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (3H, t, J = 7.1 Hz), 2.16–2.24 (1H, m), 2.33–2.39 (1H, m), 2.69–2.86 (2H, m), 4.29 (2H, q, J = 7.1 Hz), 5.22 (1H, ddd, J_{H-H} = 9.2, 1.5 Hz, J_{H-F} = 8.3 Hz), 7.21–7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 31.3, 32.5, 65.2, 82.6 (d, J_{C-F} = 21.9 Hz), 97.1 (d, J_{C-F} = 321.5 Hz), 126.4, 128.4, 128.6, 140.0, 154.1; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 2.2 (1F, d, J_{F-H} = 8.3 Hz); HRMS (EI) calcd for $C_{13}H_{15}Br_2FO_3$ $[M]^+$, 395.9372; found, 395.9366.

4.2.9. 2,2-Dibromo-2-fluoroethyl (3S,10R,13R,17R)-17-[(1R)-1,5-dimethylhexyl]-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl carbonate (8c)

82% yield; colorless amorphous solid; $[\alpha]_D^{25}$–23.1 (c = 1.0, $CHCl_3$); Mp. 110–111 °C; IR (KBr) ν 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (3H, s), 0.86 (3H, d, J = 6.6 Hz), 0.87 (3H, d. J = 6.6 Hz), 0.91 (3H, d, J = 6.5 Hz), 0.94–2.04 (29H, m), 2.42 (2H, brd, J = 7.8 Hz), 4.49–4.58 (1H, m), 4.77 (2H, d, J_{H-F} = 15.5 Hz), 5.41 (1H, brd, J = 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.7, 19.3, 21.0, 22.6, 22.8, 23.8, 24.3, 27.5, 28.0, 28.2, 31.8, 31.9, 35.8, 36.2, 36.5, 36.8, 37.8, 39.5, 39.7, 42.3, 50.0, 56.1, 56.7, 74.9 (d, J_{C-F} = 22.4 Hz),79.4, 90.6 (d, J_{C-F} = 321.2 Hz), 123.3, 139.0, 153.1; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 2.2 (1F, t, J_{F-H} = 15.5 Hz); MS (EI) m/z 396 $[M-C_3H_2Br_2FO_3]^+$; Anal. calcd for $C_{30}H_{47}Br_2FO_3$: C, 56.79; H, 7.47. Found: C, 56.79; H, 7.26.

4.2.10. 2,2-Dibromo-2-fluoro-1-phenylethyl (3S,10R,13R,17R)-17-[(1R)-1,5-dimethylhexyl]-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl carbonate (8d)

89% yield (a mixture of diastereomers in a ratio of 1:1); colorless amorphous solid; Mp. 126–127 °C; IR (KBr) ν 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (3H, s), 0.86 (3H, d, J = 6.6 Hz), 0.87 (3H, d. J = 6.6 Hz), 0.92 (3H, d, J = 6.5 Hz), 0.95–2.05 (29H, m), 2.34–2.49 (2H, m), 4.47–4.55 (1H, m), 5.38 (1H, dd, J = 24.0, 0.5 Hz), 6.13 (1H, d, J_{H-F} = 12.0 Hz), 7.39–7.58 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.7, 19.3, 21.0, 22.6, 22.8, 23.8, 24.3, 27.5, 27.6, 28.0, 28.2, 31.8, 31.9, 35.8, 36.2, 36.5, 36.8, 37.8, 39.5, 39.7, 42.3, 50.0, 56.1,

56.7, 79.4, 84.4 (d, J_{C-F} = 23.3 Hz), 84.5 (d, J_{C-F} = 22.6 Hz), 96.2 (d, J_{C-F} = 323.0 Hz), 96.2 (d, J_{C-F} = 322.5 Hz), 123.2, 123.2, 128.3, 129.1, 129.9, 132.4, 139.1, 152.8; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-0.6 (0.5F, d, J = 12.0 Hz),–0.7 (0.5F, d, J = 12.0 Hz).

4.2.11. 1-[Dibromo(fluoro)methyl]-3-phenylpropyl (3S,10R,13R,17R)-17-[(1R)-1,5-dimethylhexyl]-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl carbonate (8e)

98% yield (a mixture of diastereomers in a ratio of 1:1); colorless solid; Mp. 88–90 °C; IR (KBr) ν 1753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (3H, s), 0.87 (3H, d, J = 6.6 Hz), 0.88 (3H, d. J = 6.6 Hz), 0.93 (3H, d, J = 6.5 Hz), 0.95–2.04 (29H, m), 2.12–2.41 (4H, m), 2.66–2.86 (2H, m), 4.52–4.59 (1H, m), 5.22 (1H, ddd, J_{H-F} = 9.2 Hz, J_{H-H} = 9.2, 2.0 Hz), 5.43 (1H, brs), 7.21–7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.7, 19.3, 21.1, 22.6, 22.8, 23.8, 24.3, 27.5, 28.0, 28.2, 31.3, 31.8, 31.9, 32.5, 35.8, 36,2, 36.5, 36.8, 36.8, 37.8, 39.5, 39.7, 42.3, 50.0, 56.2, 56.7, 79.2, 82.5 (d, J_{C-F} = 22.3 Hz), 97.2 (d, J_{C-F} = 321.8 Hz), 123.2, 126.4, 128.4, 128.6, 139.0, 139.1, 140.0, 153.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 2.1 (0.5F, d, J_{H-F} = 9.2 Hz), 2.1 (0.5F, d, J_{H-F} = 9.2 Hz); Anal. calcd for $C_{38}H_{55}Br_2FO_3$: C, 61.79; H, 7.51. Found: C, 61.94; H, 7.32.

4.2.12. O-(2,2-Dibromo-2-fluoroethyl) O-phenyl carbonothioate (8f)

98% yield; pale yellow oil; IR (neat) ν 1289 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, d, J_{H-F} = 15.0 Hz), 7.15–7.47 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.8 (d, J_{C-F} = 22.5 Hz), 89.0 (d, J_{C-F} = 321.4 Hz), 121.6, 126.9, 129.7, 153.4, 193.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 2.7 (1F, t, J_{F-H} = 15.0 Hz); MS (EI) m/z 203 $[M-C_2H_2Br_2F]^+$.

4.2.13. 2,2-Dibromo-2-fluoro-1-phenylethyl dimethylcarbamate (10a)

84% yield; colorless oil; IR (neat) ν 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (3H, s), 3.10 (3H, s), 6.23 (1H, d, J_{H-F} = 11.3 Hz), 7.35–7.56 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0, 36.8, 82.4 (d, J_{C-F} = 23.0 Hz), 97.7 (d, J_{C-F} = 322.5 Hz), 128.1, 129.0, 129.5, 133.4, 153.9; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 0.8 (1F, d, J_{F-H} = 11.3 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_{13}Br_2FNO_2$ $[M+H]^+$, 367.9297; found, 367.9288.

4.2.14. 1-[Dibromo(fluoro)methyl]-3-phenylpropyl dimethylcarbamate (10b)

67% yield; colorless oil; IR (neat) ν 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06–2.42 (2H, m), 2.77 (2H, t, J = 7.9 Hz), 2.95 (3H, s), 2.98 (3H, s), 5.35 (1H, ddd, J_{H-H} = 10.1, 2.4 Hz, J_{H-F} = 7.7 Hz), 7.18–7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 32.8, 35.9, 36.8, 80.4 (d, J_{C-F} = 21.9 Hz), 98.8 (d, J_{C-F} = 322.0 Hz), 126.2, 128.4, 128.5, 140.7, 154.8; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.3 (1F, d, J_{F-H} = 7.7 Hz); HRMS (ESI-TOF) calcd for $C_{13}H_{17}Br_2FNO_2$ $[M+H]^+$, 395.9610; found, 395.9632.

4.2.15. 2,2-Dibromo-2-fluoro-1-phenylethyl propylcarbamate (10c)

A mixture of 2,2-dibromo-2-fluoroethanol (220 mg, 1.0 mmol), triethylamine (0.42 mL, 3.0 mmol) and *n*-propylisocyanate (0.25 mL, 2.50 mmol) was stirred for 10 h at room temperature. Usual work up (addition of water, extraction with ether, dried over $MgSO_4$) followed by purification by silica gel column chromatography (hexane/EtOAc = 10:1) gave **10c** (293 mg, 96% yield). Colorless oil; IR (neat) ν 3342, 1720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.50–1.60 (2H, m), 3.19 (2H, dt, J = 6.8 Hz, 6.8 Hz), 4.72 (2H, d, J_{H-F} = 15.8 Hz), 4.98 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 23.0, 43.0, 72.7 (d, J_{C-F} = 22.1 Hz), 92.2 (d, J_{C-F} = 321.2 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.0 (1F, t, J_{F-H} = 15.8 Hz). HRMS (ESI-TOF) calcd for $C_6H_{11}Br_2FNO_2$ $[M+H]^+$, 305.9141; found, 305.9164.

4.2.16. 2,2-Dibromo-2-fluoro-1-phenylethyl propylcarbamate (10d)

Similar to **10c**, this compound was prepared from 2,2-dibromo-2-fluoro-1-phenylethanol, *n*-propylisocyanate and triethylamine. Colorless oil; IR (neat) ν 3422, 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.4 Hz), 1.49–1.58 (2H, m), 3.12–3.23 (2H, m), 5.07 (1H, br.s), 6.23 (1H, d, J_{H-F} = 12.2 Hz), 7.37–7.54 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 23.0, 43.0, 81.8 (d, J_{C-F} = 22.7 Hz), 97.5 (d, J_{C-F} = 322.7 Hz), 128.1, 129.0, 129.5, 133.3, 153.9; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 0.4 (1F, d, J_{F-H} = 12.2 Hz); HRMS (ESI-TOF) calcd for $C_{12}H_{15}Br_2FNO_2$ $[M+H]^+$, 381.9454; found, 381.9475.

4.2.17. tert-Butyl 2,2-dibromo-2-fluoroethyl isopropyldicarbonimidoate (10e)

A mixture of **10d** (2.0 mmol), di-*tert*-butyldicarbonate (5.0 mmol) and DMAP (5 mg) in THF was stirred for 24 h at room temperature and the following purification by silica gel column chromatography (hexane/EtOAc = 50:1) gave **10e** (1.75 mmol, 87% yield). Colorless oil; IR (neat) ν 1750, 1712 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (6H, d, J = 6.8 Hz), 1.52 (9H, s), 4.48 (1H, septet, J = 6.8 Hz), 4.82 (1H, d, J_{H-F} = 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 27.9, 49.9, 73.8 (d, J_{C-F} = 22.0 Hz), 83.5, 90.7 (d, J_{C-F} = 321.2 Hz), 152.1, 152.2; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 3.1 (1F, t, J_{F-H} = 15.8 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_{18}Br_2FNNaO_2$ $[M+Na]^+$, 427.9498; found, 427.9521; Anal. calcd for $C_{11}H_{18}Br_2FNO_4$: C, 32.46; H, 4.46; N, 3.44. Found: C, 32.66; H, 4.57; N, 3.35.

4.2.18. 2,2-Dibromo-2-fluoro-1-phenylethyl 2-(trimethylsilyl)ethyl butyldicarbonimidoate (10f)

Under argon atmosphere at −30 °C, to triphosgene (1.0 M solution in CH_2Cl_2, 1.0 mL, 1.0 mmol) was added a mixture of 2-(trimethylsilanyl)ethyl butylcarbamate (217 mg, 1.0 mmol) and pyridine (0.25 mL, 3.0 mmol) in CH_2Cl_2 (2 mL) and then, the reaction mixture was stirred for 21 h, during these period temperature raised slowly to room temperature. Extractive work up (addition of iced water, Et_2O for extraction, dried over $MgSO_4$) followed by concentration under reduced pressure gave the crude carbamoyl chloride. A mixture of the crude carbamoyl chloride, 2,2-dibromo-2-fluoro-1-phenylethanol (300 mg, 1.0 mmol), triethylamine (0.28 mL, 2.0 mmol) and DMAP (5 mg) in THF (2 mL) and CH_2Cl_2 (1 mL) was stirred for 24 h at room temperature. Extractive work up (addition of iced water, Et_2O for extraction, dried over $MgSO_4$) followed by purification by silica gel column chromatography (hexane/EtOAc = 50: 1) gave **10f** (387 mg, 72% yield). Colorless oil; IR (neat) ν 1758, 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ-0.09 (9H, s), 0.81 (3H, t, J = 7.4 Hz), 0.96–1.01 (2H, m), 1.20–1.26 (2H, m), 1.48–1.56 (2H, m), 3.63–3.67 (2H, m), 4.19–4.23 (2H, m), 6.18 (1H, d, J = 11.2 Hz), 7.22–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ-1.7, 13.7, 17.5, 19.8, 30.9, 46.7, 65.8, 83.3 (d, J_{C-F} = 23.2 Hz), 96.2 (d, J_{C-F} = 322.2 Hz), 128.1, 129.0, 129.7, 132.4, 151.1, 153.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 0.1 (1F, d, J_{F-H} = 11.2 Hz); Anal. calcd for $C_{19}H_{28}Br_2FNO_4Si$: C, 42.16; H, 5.21; N, 2.59. Found: C, 42.16; H, 5.16; N, 2.45.

4.2.19. Methyl 2-[{[dibromo(fluoro)methoxy]carbonyl}(methyl)amino]acetate (10h)

Similar to **10f**, this compound was prepared in 70% yield via *N*-chloroformylation of sarcosine methyl ester hydrochloride by triphosgene treatment. Colorless oil; IR (neat) ν 1747, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (1.5H, s) and 3.04 (1.5H, s), 3.73 (3H, s), 4.03 (1H, s), 4.04 (1H, s), 4.71 (1H, d, J_{H-F} = 15.4 Hz), 4.75 (1H, d, J = 15.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 36.3, 50.3, 50.7, 52.1, 52.2, 73.4 (d, J_{C-F} = 22.4 Hz), 73.5 (d, J = 22.4 Hz), 91.6 (d, J_{C-F} = 321.0 Hz), 91.8 (d, J_{C-F} = 321.0 Hz), 153.9, 154.7, 169.3, 169.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ 2.6 (0.5F, d, J_{F-H} = 15.4 Hz) and 2.9

(0.5F, d, J_{F-H} = 15.4 Hz); HRMS (ESI-TOF) calcd for $C_7H_{11}Br_2FNO_4$; 349.9039 $[M+H]^+$, found: 349.9063.

4.2.20. Methyl 2-[[(2,2-dibromo-2-fluoro-1-phenylethoxy)carbonyl](methyl)amino]acetate (10i)

64% yield; colorless oil; IR (neat) ν 1754, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (1.5H, s) and 3.17 (1.5H, s), 3.72 (1.5H, s) and 3.76 (1.5H, s), 4.05 (1H, s), 4.10 (0.5H, d, J = 17.9 Hz) and 4.18 (0.5H, d, J = 17.9 Hz), 6.20 (0.5H, d, J_{H-F} = 10.5 Hz) and 6.23 (0.5H, d, J_{H-F} = 10.5 Hz), 7.35–7.55 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9, 36.9, 50.6, 50.8, 52.2, 52.3, 82.7 (d, J_{C-F} = 23.5 Hz), 82.8 (d, J_{C-F} = 23.1 Hz), 97.1 (d, J_{C-F} = 322.0 Hz), 97.3 (d, J_{C-F} = 322.5 Hz), 128.1, 128.2, 128.9, 129.6, 133.0, 153.5, 154.4, 169.4, 169.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 0.4 (0.5F, d, J_{F-H} = 10.5 Hz) and 0.7 (0.5F, d, J_{F-H} = 10.5 Hz); HRMS (ESI-TOF) calcd for $C_{13}H_{14}Br_2FNO_4Na$ $[M+Na]^+$, 447.9171; found: 447.9198.

4.2.21. Methyl 2-[({1-[dibromo(fluoro)methyl]-3-phenylpropoxy}carbonyl)(methyl)amino] acetate (10j)

55% yield; colorless oil; IR (neat) ν 1752, 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05–2.22 (1H, m), 2.35–2.43 (1H, m), 2.74–2.85 (2H, m), 3.09 (1.5H, s) and 3.09 (1.5H, s), 3.79 (1.5H, s) and 3.80 (1.5H, s), 3.94 (0.5H, d, J = 18.0 Hz) and 4.05 (0.5H, d, J = 17.7 Hz), 4.15 (0.5H, d, J = 18.0 Hz) and 4.18 (0.5H, d, J = 17.7 Hz),5.38 (1H, dt, J_{H-F} = 8.2 Hz, J_{H-H} = 2.2 Hz), 7.22–7.35 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.0, 31.1, 32.7, 32.8, 35.8, 36.9, 50.3, 50.8, 52.1, 52.2, 80.4 (d, J_{C-F} = 21.9 Hz), 80.7 (d, J_{C-F} = 22.2 Hz), 98.1 (d, J_{C-F} = 321.8 Hz), 98.2 (d, J_{C-F} = 321.8 Hz), 126.7, 128.8, 128.8, 128.9, 140.4, 140.5, 154.2, 155.5, 169.3, 169.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ 2.7 (0.5F, d, J_{F-H} = 8.2 Hz) and 3.4 (0.5F, d, J_{F-H} = 8.2 Hz); HRMS (ESI-TOF) calcd for $C_{15}H_{19}Br_2FNO_4$ $[M+H]^+$, 453.9665; found, 453.9641; Anal. calcd for $C_{15}H_{18}Br_2FNO_4$: C, 39.59; H, 3.99; N, 3.08. Found: C, 39.43; H, 4.04; N, 2.81.

4.2.22. 2-(Trimethylsilyl)ethyl 2-{(tert-butoxycarbonyl)[(2,2-dibromo-2-fluoro-1-phenyl-ethoxy)carbonyl]amino}acetate (10k)

81% yield; colorless oil; IR (neat) ν 1773, 1742, 1705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (9H, s), 0.93–0.98 (2H, m), 1.55 (9H, s), 4.20–4.24 (2H, m), 4.46 (2H, s), 6.29 (1H, d, J_{H-F} = 12.6 Hz), 7.38–7.54 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5, 15.3, 28.0, 47.7, 63.9, 83.8 (d, J_{C-F} = 22.5 Hz), 84.5, 95.9 (d, J_{C-F} = 322.8 Hz), 128.2, 129.2, 129.9, 132.2, 150.9, 151.1, 168.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −0.6 (1F, d, J_{F-H} = 12.6 Hz); HRMS (ESI-TOF) calcd for $C_{21}H_{31}Br_2FNO_6Si$ $[M+H]^+$, 598.0271; found, 598.0253.

4.3. General procedure for $CrCl_2$/Mn mediated transformation of dibromofluoromethylcarbinyl esters

Under argon atmosphere, after a mixture of $CrCl_2$ (740 mg, 6.0 mmol) and Mn powder (880 mg, 16 mmol) suspended in THF (8.0 mL) was sonicated by ultrasound for 10 min, was added dibromofluoro ester **1e** (1.50 g, 4.0 mmol) and the reaction mixture was stirred for 5 h at room temperature. Extractive work up (addition of water, Et_2O for extraction, dried over $MgSO_4$) followed by purification by silica gel column chromatography (hexane/EtOAc = 20:1) gave **3e** (708 mg, 82% yield).

4.3.1. 1-Fluoroethenyl benzoate (3a) [7]

65% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (1H, dd, J_{H-F} = 37.4 Hz, J_{H-H} = 4.0 Hz), 4.49 (1H, dd, J_{H-H} = 4.0 Hz, J_{H-F} = 3.7 Hz), 7.48–7.52 (2H, m), 7.63–7.68 (1H, m), 8.09–8.12 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.6 (d, J_{C-F} = 27.0 Hz), 127.6, 128.8, 130.5, 134.4, 155.4 (d, J_{C-F} = 281.5 Hz), 162.6; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −15.3 (1F, dd, J_{F-H} = 37.4, 3.7 Hz); Anal. calcd for $C_9H_7FO_2$: C, 65.05; H, 4.25. Found: C, 64.94; H, 4.65.

4.3.2. (Z)-1-Fluoro-2-phenylethenyl acetate (3b)

98% yield; colorless oil; IR (neat) ν 3033, 2926, 1742, 1374, 1231, 1177, 1052, 721, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 5.48 (1H, d, J_{H-F} = 28.3 Hz), 7.35–7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 95.3 (d, J_{C-F} = 15.8 Hz), 127.3, 128.1 (d, J_{C-F} = 3.1 Hz), 128.5, 131.2 (d, J_{C-F} = 6.0 Hz), 150.3 (d, J_{C-F} = 291.1 Hz), 167.2; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −17.6 (1F, d, J_{F-H} = 28.3 Hz); HRMS (EI) calcd for $C_{10}H_9FO_2$ $[M]^+$, 180.0587; found, 180.0599.

4.3.3. (Z)-1-Fluoro-4-phenyl-1-butenyl acetate (3c) [7]

95% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (3H, s), 2.42 (2H, dtd, J = 7.6, 7.6, 2.0 Hz), 2.73 (2H, t, J = 7.6 Hz), 4.44 (1H, dt, J_{H-F} = 27.3 Hz, J_{H-H} = 7.6 Hz), 7.19–7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 24.9, 35.4, 92.3 (d, J_{C-F} = 22.7 Hz), 126.0, 128.4, 128.4, 141.1, 150.2 (d, J_{C-F} = 280.4 Hz), 167.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −26.4 (1F, d, J_{F-H} = 27.3 Hz); Anal. calcd for $C_{12}H_{13}FO_2$: C, 69.22; H, 6.29. Found: C, 69.26; H, 6.43.

4.3.4. 1-Fluorovinyl 4-methoxybenzoate (3d)

82% yield; colorless oil; IR (neat) ν 1755, 1606, 1214, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (3H, s), 4.21 (1H, dd, J_{H-F} = 37.5 Hz, J_{H-H} = 3.9 Hz), 4.40 (1H, t, J_{H-F} = 3.9 Hz, J_{H-H} = 3.9 Hz), 6.90 (2H, d, J = 8.9 Hz), 7.98 (2H, d, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 77.4 (d, J_{C-F} = 27.7 Hz), 114.1, 119.7, 132.7, 155.5 (d, J_{C-F} = 281.1 Hz), 162.2 (d, J_{C-F} = 2.6 Hz), 164.6; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-14.7 (1F, dd, J_{F-H} = 37.5, 3.9 Hz); MS (EI) m/z 135 $[M-C_2H_2FO]^+$, 107 $[M-C_3H_2FO_2]^+$; Anal. calcd for $C_{10}H_9FO_3$: C, 61.22; H, 4.62. Found: C, 61.34; H, 4.74.

4.3.5. 1-Fluorovinyl 2,4,6-trimethylbenzoate (3e)

85% yield; colorless oil; IR (neat) ν 2927, 1767, 1709, 1211, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 2.38 (6H, s), 4.28 (1H, dd, J_{H-F} = 37.2 Hz, J_{H-H} = 3.8 Hz), 4.48 (1H, t, J_{H-F} = 3.8 Hz, J_{H-H} = 3.8 Hz), 6.90 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.2, 77.5 (d, J_{C-F} = 26.8 Hz), 127.7, 128.8, 136.4, 140.9, 155.2 (d, J_{C-F} = 282.4 Hz), 165.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-15.2 (1F, dd, J_{F-H} = 37.2, 3.8 Hz); MS (EI) m/z 147 $[M-C_2H_2FO]^+$, 119 $[M-C_3H_2FO_2]^+$; Anal. calcd for $C_{12}H_{13}FO_2$: C, 69.22; H, 6.29. Found: C, 69.19; H, 6.42.

4.3.6. 1-Fluorovinyl cinnamate (3f)

49% yield; colorless oil. IR (neat) ν 1758, 1633, 1177, 1109, 983, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (1H, dd, J_{H-F} = 37.6 Hz, J_{H-H} = 4.0 Hz), 4.43 (1H, t, J = 4.0 Hz), 6.31 (1H, d, J = 16.0 Hz), 7.40–7.45 (3H, m), 7.55–7.57 (2H, m), 7.86 (1H, d, J = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.3 (d, J_{C-F} = 27.3 Hz), 115.1, 128.5, 129.1, 131.3, 133.6, 148.7, 155.3 (d, J_{C-F} = 280.5 Hz), 162.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −15.1 (1F, dd, J = 37.6, 3.1 Hz); MS (EI) m/z 131 $[M-C_2H_2FO]^+$, 103 $[M-C_3H_2FO_2]^+$, 77 $[C_6H_5]^+$; Anal. calcd for $C_{11}H_9FO_2$: C, 68.74; H, 4.72. Found: C, 68.93; H, 4.97.

4.3.7. 1-Fluorovinyl-2-benzyl-4-(tert-butyldiphenylsilyloxy)butanoate (3g)

66% yield; colorless solid; Mp. 37.1–39.5 °C; IR (neat) ν 3069, 2932, 2857, 2361, 1783, 1709, 1110, 1082, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.79–1.88 (1H, m), 1.95–2.07 (1H, m), 2.88 (1H, dd, J = 13.7, 6.9 Hz), 3.02 (1H, dd, J = 13.7, 8.0 Hz), 3.10–3.20 (1H, m), 3.72 (2H, t, J = 5.6 Hz), 3.92 (1H, dd, J_{H-F} = 37.7 Hz, J_{H-H} = 3.7 Hz), 4.28 (1H, dd, J_{H-H} = 3.7 Hz, J_{H-F} = 3.0 Hz), 7.18 (2H, brd, J = 7.0 Hz), 7.21–7.33 (3H, m), 7.34–7.46 (6H, m), 7.61–7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 26.9, 34.1, 38.0, 43.6, 61.3, 77.0 (d, J_{C-F} = 26.7 Hz), 126.7, 127.7, 128.6, 129.0, 129.7, 133.5 and 133.6, 135.54 and 135.56, 138.2, 155.2 (d, J_{C-F} = 281.7 Hz), 171.3 (d, J_{C-F} = 3.0 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-15.3 (1F, dd, J_{F-H} = 37.7, 3.0 Hz); MS (ESI-TOF) m/z 477 $[M + H]^+$;

Anal. calcd for $C_{29}H_{33}FO_3Si$: C, 73.07; H, 6.98. Found: C, 73.09; H, 7.19.

*4.3.8. Ethyl (Z)-1-fluoro-2-phenylethenyl carbonate (**9a**)*

88% yield; colorless oil; IR (neat) ν 3030, 2987, 2916, 1783, 1715, 1262, 1218, 1153, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, t, J = 7.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 5.55 (1H, d, J_{H-F} = 27.5 Hz), 7.24–7.28 (1H, m), 7.33–7.37 (2H, m), 7.42–7.44 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 66.1, 95.0 (d, J_{C-F} = 16.0 Hz), 127.5 (d, J_{C-F} = 1.6 Hz), 128.2 (d, J_{C-F} = 6.9 Hz), 128.6, 131.0 (d, J_{C-F} = 6.3 Hz), 150.4 (d, J_{C-F} = 292.7 Hz), 151.4 (d, J_{C-F} = 3.8 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ–19.7 (1F, d, J_{F-H} = 27.5 Hz); Anal. calcd for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.27. Found: C, 62.99; H, 5.29.

*4.3.9. Ethyl (Z)-1-fluoro-4-phenyl-1-butenyl carbonate (**9b**)*

98% yield; colorless oil; IR (neat) ν 3028, 2917, 2849, 1782, 1731, 1267, 1191, 1162, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, J = 7.1 Hz), 2.41 (2H, dt, J = 7.7, 7.7 Hz), 2.73 (2H, t, J = 7.7 Hz), 4.30 (2H, q, J = 7.1 Hz), 4.53 (dt, 1H, J_{H-F} = 26.5 Hz, J_{H-H} = 7.7 Hz), 7.17–7.23 (3H, m), 7.26–7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 24.9, 35.3, 65.7, 92.0 (d, J_{C-F} = 22.8 Hz), 126.1, 128.4, 128.4, 149.1, 150.5 (d, J_{C-F} = 281.2 Hz), 151.6; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-28.0 (1F, d, J_{F-H} = 26.5 Hz); Anal. calcd for $C_{13}H_{15}FO_3$: C, 65.53; H, 6.35. Found: C, 65.88; H, 6.22.

*4.3.10. (2S,4aR,6aR,7R)-7-[(1R)-1,5-Dimethylhexyl]-4a,6a-dimethyl-1,2,3,4,4a,4b,5,6,6a,7,8,9, 10,10a,10b,11-hexadecahydro-2-chrysenyl 1-fluorovinyl carbonate (**9c**)*

29% yield; colorless solid; Mp. 69.0–70.5 °C; $[\alpha]_D^{25}$ − 30.0 (c = 1.0, $CHCl_3$); IR (KBr) ν 1782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (3H, s), 0.88 (3H, d, J = 6.6 Hz), 0.88 (3H, d. J = 6.6 Hz), 0.92 (3H, d, J = 6.5 Hz), 0.95–2.65 (29H, m), 2.26–2.42 (2H, m), 4.23 (1H, dd, J_{H-F} = 36.5 Hz, J_{H-H} = 4.0 Hz), 4.35 (1H, dd, J = 4.0, 2.9 Hz), 4.53–4.60 (1H, m) 5.42 (1H, d, J = 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.7, 19.3, 21.1, 22.6, 22.8, 23.8, 24.3, 27.4, 28.0, 28.2, 31.8, 31.9, 35.8, 36,2, 36.5, 36.8, 37.7, 39.5, 39.7, 42.3, 50.0, 56.2, 56.7, 76.9 (d, J_{C-F} = 30.2 Hz), 80.2, 123.5, 138.8, 150.2 (d, J_{C-F} = 2.3 Hz), 155.3 (d, J_{C-F} = 282.4 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-17.1 (1F, brd, J_{F-H} = 36.5 Hz); MS (EI) m/z 369 $[M-C_3H_3FO_3]^+$; Anal. calcd for $C_{30}H_{47}FO_3$: C, 75.91; H, 9.98. Found: C, 75.74; H, 9.85.

*4.3.11. (2S,4aR,6aR,7R)-7-[(1R)-1,5-Dimethylhexyl]-4a,6a-dimethyl-1,2,3,4,4a,4b,5,6,6a,7,8,9, 10,10a,10b,11-hexadecahydro-2-chrysenyl (Z)-1-fluoro-2-phenylethenyl carbonate (**9d**)*

81% yield; colorless solid; Mp. 107–108 °C; $[\alpha]_D^{25}$ − 27.7 (c = 1.0, $CHCl_3$); IR (KBr) ν 1691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (3H, s), 0.87 (3H, d, J = 6.6 Hz), 0.87 (3H, d. J = 6.6 Hz), 0.91 (3H, d, J = 6.5 Hz), 0.91–2.05 (29H, m), 2.42–2.53 (2H, m), 4.55–4.65 (1H, m), 5.43 (1H, brd), 5.45 (1H, d, J_{H-F} = 27.5 Hz), 7.23–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.7, 19.3, 21.1, 22.6, 22.8, 23.8, 24.3, 27.5, 28.0, 28.2, 31.9, 35.8, 36,2, 36.5, 36.8, 37.7, 39.5, 39.7, 42.3, 50.0, 56.2, 56.7, 80.4, 95.0 (d, J_{C-F} = 16.1 Hz), 123.6, 127.4, 128.2 (d, J_{C-F} = 6.0 Hz), 128.6, 131.1 (d, J_{C-F} = 6.4 Hz), 138.8, 150.5 (d, J_{C-F} = 292.6 Hz), 150.7 (d, J_{C-F} = 3.2 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −19.6 (1F, d, J_{F-H} = 27.5 Hz); MS (EI) m/z 369 $[M-C_9H_7FO_3]^+$; Anal. calcd for $C_{36}H_{51}FO_3$: C, 78.50; H, 9.33. Found: C, 78.35; H, 9.20.

*4.3.12. (2S,4aR,6aR,7R)-7-[(1R)-1,5-Dimethylhexyl]-4a,6a-dimethyl-1,2,3,4,4a,4b,5,6,6a,7,8,9, 10,10a,10b,11-hexadecahydro-2-chrysenyl (Z)-1-fluoro-4-phenyl-1-butenyl carbonate (**9e**)*

97% yield; colorless solid; Mp. 94–95 °C; $[\alpha]_D^{25}$ − 26.9 (c = 1.0, $CHCl_3$); IR (KBr) ν 1768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (3H, s), 0.93 (3H, d, J = 6.6 Hz), 0.93 (3H, d. J = 6.6 Hz), 0.98 (3H, d, J = 6.5 Hz), 1.05–2.06 (29H, m), 2.45–2.50 (4H, m), 2.78 (2H, t, J = 7.6 Hz), 4.52–4.64 (1H, m) 4.58 (1H, dt, J_{H-F} = 26.5 Hz, J_{H-H} = 7.6 Hz), 5.47 (1H, d, J = 2.6 Hz), 7.24–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.7, 19.2, 21.1, 22.6, 22.8, 23.8, 24.3, 25.0, 27.4, 28.0, 28.2, 31.8, 31.9, 35.3, 35.8, 36,2, 36.5, 36.7, 37.7, 39.5, 39.7, 42.3, 50.0, 56.2, 56.7, 79.9, 92.0 (d, J_{C-F} = 23.0 Hz), 123.4, 126.1, 128.4, 128.4, 138.8, 141.0, 150.6 (d, J_{C-F} = 281.8 Hz), 151.0 (d, J_{C-F} = 3.6 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-27.7 (1F, brd, J_{F-H} = 26.5 Hz); MS (EI) m/z 369 $[M-C_{11}H_{11}FO_3]^+$; Anal. calcd for $C_{38}H_{55}FO_3$: C, 78.85; H, 9.58. Found: C, 78.84; H, 9.26.

*4.3.13. S-(1-Fluorovinyl) O-phenyl carbonothioate (**9f**)*

98% yield; colorless oil; IR (neat) ν 1752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, dd, J_{H-F} = 40.5 Hz, J_{H-H} = 3.3 Hz), 5.44 (1H, dd, J_{H-F} = 9.4 Hz, J_{H-H} = 3.3 Hz), 7.19–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.2 (d, J_{C-F} = 21.2 Hz), 121.0, 126.6, 129.6, 151.1, 153.3 (d, J_{C-F} = 302.0 Hz), 164.8 (d, J_{C-F} = 4.6 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ–15.1 (1F, dd, J_{F-H} = 40.5, 9.4 Hz); MS (EI) m/z 198 $[M]^+$.

*4.3.14. (Z)- and (E)-1-Fluoro-2-phenylethenyl dimethylcarbamate (**Z-11a** and **E-11a**)*

Z-11a 57% yield; colorless solid; Mp. 44.0–45.1 °C; IR (KBr) ν 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (3H, s), 3.07 (3H, s), 5.45 (1H, d, J_{H-F} = 27.7 Hz), 7.20–7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.5, 36.9, 95.1 (d, J_{C-F} = 17.9 Hz), 127.0, 128.0 (d, J_{C-F} = 6.9 Hz), 128.4, 131.7 (d, J_{C-F} = 6.3 Hz), 150.9 (d, J_{C-F} = 290.9 Hz), 152.2 (d, J_{C-F} = 3.7 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-15.8 (1F, d, J_{F-H} = 27.7 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_{13}FNO_2$ $[M+H]^+$, 210.0930; found, 210.0910; Anal. calcd for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.21; H, 5.71; N, 6.65.

E-11a 5% yield; colorless oil; IR (neat) ν 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.05 (3H, s), 3.10 (3H, s), 5.79 (1H, d, J_{H-F} = 5.9 Hz), 7.20–7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 37.0, 94.9 (d, J_{C-F} = 35.5 Hz), 127.0, 127.6 (d, J_{C-F} = 3.2 Hz), 128.5, 131.8 (d, J_{C-F} = 7.9 Hz), 151.2 (d, J_{C-F} = 6.0 Hz), 151.2 (d, J_{C-F} = 281.1 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −15.5 (1F, d, J_{F-H} = 5.9 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_{13}FNO_2$ $[M+H]^+$, 210.0930; found, 210.0919; Anal. calcd for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.09; H, 5.90; N, 6.37.

*4.3.15. (Z)-1-Fluoro-4-phenyl-1-butenyl dimethylcarbamate (**11b**)*

65% yield; colorless oil; IR (neat) ν 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (2H, dt, J = 7.7, 7.7 Hz), 2.72 (2H, t, J = 7.7 Hz), 2.97 (3H, s), 2.97 (3H, s), 4.43 (1H, dt, J_{H-F} = 26.7 Hz, J_{H-H} = 7.7 Hz), 7.19–7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 35.5, 36.4, 36.8, 92.0 (d, J_{C-F} = 25.0 Hz), 126.0, 128.4, 128.4, 141.3, 150.9 (d, J_{C-F} = 280.1 Hz), 152.5 (d, J_{C-F} = 4.0 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −24.4 (1F, d, J_{F-H} = 26.7 Hz); HRMS (ESI-TOF) calcd for $C_{13}H_{17}FNO_2$ $[M+H]^+$, 238.1243; found, 238.1250.

*4.3.16. 1-Fluorovinyl propylcarbamate (**11c**)*

12% yield; colorless oil; IR (neat) ν 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.4 Hz), 1.52–1.62 (2H, m), 3.19 (2H, dt, J = 6.8, 6.7 Hz),.13 (1H, dd, J_{H-F} = 37.1 Hz, J_{H-H} = 3.6 Hz), 4.31 (1H, dd, J_{H-H} = 3.6 Hz, J_{H-F} = 2.9 Hz), 5.04 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 22.8, 43.1, 76.8 (d, J_{C-F} = 29.4 Hz), 151.4, 155.4 (d, J_{C-F} = 280.4 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −14.5 (1F, brd, J_{F-H} = 37.1 Hz); MS (ESI-TOF) m/z 171 $[M+H+Na]^+$.

*4.3.17. (Z)-1-Fluoro-2-phenylethenyl propylcarbamate (**11d**)*

39% yield; colorless oil; IR (neat) ν 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.4 Hz), 1.56–1.65 (2H, m), 3.21–3.26 (2H, m), 5.03 (1H, brs), 5.45 (1H, d, J_{H-F} = 27.8 Hz), 7.20–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 22.9, 43.2, 95.0 (d, J_{C-F} = 17.9 Hz), 127.1, 128.1 (d, J_{C-F} = 6.8 Hz), 128.5, 131.6 (d, J_{C-F} = 6.3 Hz), 150.7 (d, J_{C-F} = 290.9 Hz), 151.8 (d, J_{C-F} = 3.6 Hz); ^{19}F

NMR (376.5 MHz, $CDCl_3$) δ −16.4 (1F, d, J_{F-H} = 27.8 Hz); HRMS (ESI-TOF) calcd for $C_{12}H_{15}FNO_2$ $[M+H]^+$, 224.1087; found, 224.1077.

*4.3.18. tert-Butyl 1-fluorovinyl isopropyldicarbonimidoate (**11e**)*

51% yield; colorless oil; IR (neat) ν 1773, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (6H, d, J = 6.8 Hz), 1.52 (9H, s), 4.21 (1H, dd, J_{H-F} = 36.8 Hz, J_{H-H} = 4.0 Hz), 4.37 (1H, dd, J_{H-H} = 4.0 Hz, J_{H-F} = 2.9 Hz), 4.46 (1H, septet, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 27.8, 50.3, 77.2 (d, J_{C-F} = 28.0 Hz), 83.9, 149.7 (d, J_{C-F} = 3.2 Hz), 151.6, 155.1 (d, J_{C-F} = 282.0 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −16.0 (1F, dd, J_{F-H} = 36.8, 2.9 Hz); HRMS (ESI-TOF) calcd for $C_{11}H_{18}FNO_4Na$ $[M+Na]^+$; 270.1118, found: 270.1118.

*4.3.19. (Z)-1-Fluoro-2-phenylethenyl 2-(trimethylsilyl)ethyl butyldicarbonimidoate (**11f**)*

65% yield; colorless oil; IR (neat) ν 1729, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (9H, s), 0.96 (3H, t, J = 7.3 Hz), 1.10–1.14 (2H, m), 1.32–1.43 (2H, m), 1.60–1.68 (2H, m), 3.76 (2H, t, J = 7.5 Hz), 4.33–4.38 (2H, m), 5.54 (1H, d, J_{H-F} = 27.6 Hz), 7.22–7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6, 13.7, 17.5, 19.8, 30.8, 47.1, 66.4, 95.8 (d, J_{C-F} = 15.8 Hz), 127.4 (d, J_{C-F} = 1.5 Hz), 128.1 (d, J_{C-F} = 6.9 Hz), 128.5, 131.1 (d, J_{C-F} = 6.2 Hz), 150.0 (d, J_{C-F} = 292.7 Hz), 150.1 (d, J_{C-F} = 3.8 Hz), 153.0; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −18.4 (1F, d, J_{F-H} = 27.6 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{28}FNNaO_4Si$ $[M+Na]^+$; 404.1669, found: 404.1650; Anal. calcd for $C_{19}H_{28}FNO_4Si$: C, 59.82; H, 7.40; N, 3.67. Found: C, 59.98; H, 7.49; N, 3.41.

*4.3.20. (Z)-1-Fluoro-2-phenylethenyl butylcarbamate (**11g**)*

95% yield; colorless oil; IR (neat) ν 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.3 Hz), 1.34–1.43 (2H, m), 1.52–1.59 (2H, m), 3.26 (2H, dt, J = 6.7, 6.7 Hz), 5.02 (1H, brs), 5.45 (1H, d, J_{H-F} = 27.8 Hz), 7.21–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.8, 31.6, 41.2, 95.1 (d, J_{C-F} = 18.0 Hz), 127.1 (d, J_{C-F} = 1.5 Hz), 128.1 (d, J_{C-F} = 7.0 Hz), 128.5, 131.7 (d, J_{C-F} = 6.1 Hz), 150.7 (d, J_{C-F} = 290.4 Hz), 151.8; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −16.2 (1F, d, J_{F-H} = 27.8 Hz); HRMS (ESI-TOF) calcd for $C_{13}H_{17}FNO_2$ $[M+H]^+$, 238.1243; found, 238.1242.

*4.3.21. Methyl 2-[{[(1-fluorovinyl)oxy]carbonyl}(methyl)amino]acetate (**11h**)*

69% yield; colorless oil; IR (neat) ν 1748, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (1.5H, s) and 3.05 (1.5H, s), 3.76 (1H, s), 3.77 (1H, s), 4.02 (1H, s), 4.05 (1H, s), 4.12 (0.5H, dd, J_{H-F} = 34.3 Hz, J_{H-H} = 3.3 Hz), 4.17 (0.5H, dd, J_{H-F} = 34.3 Hz, J_{H-H} = 3.3 Hz), 4.30–4.34 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.8, 36.3, 50.7, 52.2, 52.3, 77.0 (d, J_{C-F} = 28.2 Hz), 77.1 (d, J_{C-F} = 29.2 Hz), 155.4 (d, J_{C-F} = 293.7 Hz), 168.9 (d, J_{C-F} = 5.9 Hz), 171.0; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −14.8 (0.5F, dd, J_{F-H} = 34.3, 3.3 Hz) and −14.9 (0.5F, dd, J_{F-H} = 34.3, 3.3 Hz); HRMS (ESI-TOF) calcd for $C_7H_{11}FNO_4$ $[M+H]^+$, 192.0672; found, 192.0678; Anal. calcd for $C_7H_{10}FNO_4$: C, 43.98; H, 5.27; N, 7.33. Found: C,44.01; H, 5.51; N, 6.93.

*4.3.22. Methyl 2-[({[(Z)-1-fluoro-2-phenylethenyl]oxy}carbonyl)(methyl)amino]acetate (**11i**)*

82% yield; colorless oil; IR (neat) ν 1747, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.05 (1.5H, s) and 3.09 (1.5H, s), 3.77 (1.5H, s) and 3.79 (1.5H, s), 4.06 (1H, s), 4.07 (1H, s), 5.44 (0.5H, d, J_{H-F} = 25.8 Hz) and 5.50 (0.5H, d, J_{H-F} = 25.8 Hz), 7.20–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.8, 36.3, 50.8, 52.1, 52.2, 95.1 (d, J_{C-F} = 17.4 Hz), 95.2 (d, J_{C-F} = 17.4 Hz), 127.5, 128.1 (d, J_{C-F} = 6.9 Hz), 128.8, 131.6 (d, J_{C-F} = 5.6 Hz), 150.6 (d, J_{C-F} = 291.3 Hz) 150.7 (d, J_{C-F} = 290.4 Hz), 151.8 (d, J_{C-F} = 3.1 Hz), 152.6 (d, J_{C-F} = 3.4 Hz), 168.9. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −16.9 (0.5F, d, J_{F-H} = 25.8 Hz) and −17.0 (0.5F, d, J_{F-H} = 25.8 Hz); HRMS (ESI-TOF) calcd for $C_{13}H_{15}FNO_4$ $[M+H]^+$, 268.0985; found, 268.0995.

*4.3.23. Methyl 2-[({[(Z)-1-fluoro-4-phenyl-1-butenyl]oxy}carbonyl)(methyl)amino]acetate (**11j**)*

75% yield; colorless oil; IR (neat) ν 1746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43–2.50 (2H, m), 2.74–2.79 (2H, m), 3.07 (1.5H, s) and 3.08 (1.5H, s), 3.81 (1.5H, s) and 3.81 (1.5H, s), 4.07 (1H, s), 4.10 (1H, s), 4.48 (0.5H, dt, J_{H-F} = 26.5 Hz, J_{H-H} = 7.6 Hz) and 4.54 (0.5H, dt, J_{H-F} = 26.5 Hz, J_{H-H} = 7.6 Hz), 7.23–7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 35.4, 35.8, 36.2, 50.6, 52.2, 52.3, 92.2 (d, J_{C-F} = 24.2 Hz), 92.3 (d, J_{C-F} = 24.1 Hz), 125.9, 128.3, 128.4, 141.2, 150.4 (d, J_{C-F} = 281.0 Hz), 150.5 (d, J_{C-F} = 280.2 Hz), 152.1 (d, J_{C-F} = 3.7 Hz), 152.9 (d, J_{C-F} = 4.0 Hz), 169.0, 169.0. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ-25.4 (1F, d, J_{F-H} = 26.5 Hz); HRMS (ESI-TOF) calcd for $C_{15}H_{18}FNNaO_4$ $[M+Na]^+$, 318.1118; found, 318.1120; Anal. calcd for $C_{15}H_{18}FNO_4$: C, 61.01; H, 6.14; N, 4.74. Found: C, 60.93; H, 6.24; N, 4.47.

*4.3.24. 2-(Trimethylsilyl)ethyl 2-[(tert-butoxycarbonyl)({[(Z)-1-fluoro-2-phenylethenyl]oxy}-carbonyl)amino]acetate (**11k**)*

65% yield; colorless oil; IR (neat) ν 1746, 1729, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (9H, s), 1.03 (2H, t, J = 8.6 Hz), 1.54 (9H, s), 4.29 (2H, t, J = 8.6 Hz), 4.44 (2H, s), 5.55 (1H, d, J_{H-F} = 27.5 Hz), 7.24–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ-1.6, 17.4, 27.8, 47.7, 64.1, 84.9, 95.8 (d, J_{C-F} = 15.4 Hz), 127.4 (d, J_{C-F} = 1.3 Hz), 128.2 (d, J_{C-F} = 6.9 Hz), 128.5, 130.9 (d, J_{C-F} = 6.3 Hz), 149.8 (d, J_{C-F} = 292.9 Hz), 149.9 (d, J_{C-F} = 3.8 Hz), 150.5, 168.2; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −18.8 (1F, d, J_{F-H} = 27.5 Hz); HRMS (ESI-TOF) calcd for $C_{21}H_{30}FNNaO_6Si$ $[M+Na]^+$, 462.1724; found, 462.1692.

*4.3.25. 2-[[({(Z)-1-Fluoro-2-phenylethenyl}oxy)carbonyl]amino]acetic acid (**15**)*

70% yield; colorless solid; Mp. 198–200 °C (dec.); IR (KBr) ν 3294, 1733, 1717 cm^{-1}; ^1H NMR (400 MHz, CD_3COOD) δ 4.08 (2H, s), 5.56 (1H, d, J_{H-F} = 28.0 Hz), 7.27–7.43 (5H, m); ^{13}C NMR (100 MHz, CD_3COOD) δ 43.2, 96.3 (d, J_{C-F} = 17.4 Hz), 128.2, 129.0 (d, J_{C-F} = 7.1 Hz), 129.5, 132.6 (d, J_{C-F} = 7.2 Hz), 151.6 (d, J_{C-F} = 289.2 Hz), 174.7, 178.1; ^{19}F NMR (376.5 MHz, CD_3COOD) δ −17.4 (1F, d, J_{F-H} = 28.0 Hz).

4.4. Reaction of 1-fluorovinyl benzoate 3a with trans-cyclohexane 1,2-diamine

A mixture of 1-fluorovinyl benzoate **3a** (83.0 mg, 0.5 mmol), *trans*-cyclohexane 1,2-diamine (60 μL, 0.5 mmol) and triethylamine (140 μL, 1.0 mmol) in THF (4.0 mL) was stirred for 11 h at room temperature. Addition of water (10 mL), extraction with EtOAc (15 mL × 3) and the subsequent purification by silica gel column chromatography (eluted by ethyl acetate) gave *N*-(2-acetylaminocyclohexyl)benzamide **18b** (72.6 mg, 56% yield) and *N*,*N*′-1,2-cyclohexanediylbisbenzamide **19b** (8.2 mg, 5.0% yield). Structures of products were determined by comparing NMR data with those of authentic samples [28].

4.5. Reaction of 1-fluorovinyl 4-silyloxybutanoate 3g with TBAF in the presence of p-anisidine

A mixture of fluorovinyl ester **3g** (143 mg, 0.30 mmol), *p*-anisidine (37 mg, 0.30 mmol) and TBAF (0.6 mL, 0.6 mmol) in THF (2.4 mL) was stirred for 2 h at 0 °C, then for additional 2 h at room temperature. Addition of water (10 mL), extraction with ethyl acetate (15 mL × 3) and the subsequent purification by silica gel column chromatography (hexane/EtOAc = 100:1 ∼ 5:1) gave, in the order of elution, TBDPS-F **25** (30 mg, 40% yield), TBDPS-OH **26** (32 mg, 46% yield), butyrolactone **22a** (16 mg, 30% yield) and 4-methoxyacetoanilide **23a** (28 mg, 57% yield), respectively. These products were unambiguously determined by comparison of spectra data with those of authentic samples [29].

References

[1] (a) T. Hiyama, Organofluorine Compounds: Chemistry and Applications, Springer, Berlin, 2000;
(b) R.D. Chambers (Ed.), Organofluorine chemistry: fluorinated alkenes and reactive intermediates, Top. Current Chem., vol. 192, Springer-Verlag, Berlin, 1997;
(c) T. Allemendinger, E. Felder, E. Hungerbuhler, Selective fluorination in organic and bioorganic chemistry, in: J.T. Welch (Ed.), ACS Symposium Series, vol. 456, ACS, Washington, DC, 1991, pp. 186–195;
(d) J.T. Welch, J. Lin, L.G. Boros, B. DeCorte, K. Bergmann, R. Gimi, Biomedical frontiers of fluorine chemistry, in: I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), ACS Symposium Series, vol. 639, ACS, Washington, DC, 1996, pp. 129–142;
(e) D.J. Burton, Z.-Y. Yang, W. Qiu, Chem. Rev. 96 (1996) 1641–1715.

[2] Recent reviews:
(a) T. Taguchi, H. Yanai, in: Ojima (Ed.), Fluorine in Medicinal Chemistry and Chemical Biology, Wiley-Blackwell, Chchester, 2009, pp. 257–290;
(b) S. Couve-Bonnaire, D. Cahard, X. Pannecoucke, Org. Biomol. Chem. 5 (2007) 1151–1157;
(c) G. Landelle, M. Bergeron, M. Turcotte-Savard, J. Paquin, Chem. Soc. Rev. 40 (2011) 2867–2908;
(d) H. Yanai, T. Taguchi, Eur. J. Org. Chem. (2011), doi:10.1002/ejoc.201100495.

[3] (a) M. Okada, Y. Nakamura, A. Sato, H. Horikawa, A. Saito, T. Taguchi, Chem. Lett. (2002) 28–29;
(b) M. Okada, Y. Nakamura, A. Saito, A. Sato, H. Horikawa, T. Taguchi, Tetrahedron Lett. 43 (2002) 5845–5847;
(c) Y. Nakamura, M. Okada, A. Sato, H. Horikawa, M. Koura, A. Saito, T. Taguchi, Tetrahedron 61 (2005) 5741–5753;
(d) Y. Nakamura, M. Okada, M. Koura, M. Tojo, A. Saito, A. Sato, T. Taguchi, J. Fluorine Chem. 127 (2006) 627–636;
(e) H. Yanai, H. Okada, A. Sato, M. Okada, T. Taguchi, Tetrahedron Lett. 52 (2011) 2997–3000;
(f) D. Watanabe, M. Koura, A. Saito, H. Yanai, Y. Nakamura, M. Okada, A. Sato, T. Taguchi, J. Fluorine Chem. 132 (2011) 327–338.

[4] A. Saito, M. Nakagawa, T. Taguchi, J. Fluorine Chem. 126 (2005) 1166–1173.

[5] M. Nakagawa, A. Saito, A. Soga, N. Yamamoto, T. Taguchi, Tetrahedron Lett. 46 (2005) 5257–5261.

[6] (a) G. Dutheuil, X. Lei, X. Pannecoucke, J.-C. Quirion, J. Org. Chem. 70 (2005) 1911–1914;
(b) G. Dutheuil, C. Paturel, X. Lei, S. Couve-Bonnaire, X. Pannecoucke, J. Org. Chem. 71 (2006) 4316–4319.

[7] R. Bejot, S. Tisserand, L.M. Reddy, D.K. Barma, R. Baati, J.R. Falck, C. Mioskowski, Angew. Chem. Int. Ed. 44 (2005) 2008–2011.

[8] D.K. Barma, A. Kundeu, H. Zhang, C. Mioskowski, J.R. Falk, J. Am. Chem. Soc. 125 (2003) 3218–3219.

[9] (a) A. Fürstner, Chem. Rev. 99 (1999) 991–1045;
(b) L.A. Wessjohann, G. Scheid, Synthesis (1999) 1–36.

[10] (a) J.R. Falck, D.K. Barma, C. Mioskowski, T. Schlama, Tetrahedron Lett. 40 (1999) 2091–2904;
(b) R. Baati, D.K. Barma, J.R. Falck, C. Mioskowski, J. Am. Chem. Soc. 123 (2001) 9196–9198;
(c) R. Baati, D.K. Barma, U.M. Krishna, C. Mioskowski, J.R. Falck, Tetrahedron Lett. 43 (2002) 959–961;
(d) R. Bejot, S. Tisserand, D.R. Li, J.R. Falck, C. Mioskowski, Tetrahedron Lett. 48 (2007) 3855–3858.

[11] J.R. Falck, D.K. Barma, R. Baati, C. Mioskowski, Angew. Chem., Int. Ed. 40 (2001) 1281–1283.

[12] K. Takai, R. Kokumai, T. Nobunaka, Chem. Commun. 112 (2001) 8–1129.

[13] Preliminary results of this paper had been firstly reported at the 123rd Annual Meeting of Pharmaceutical Society of Japan, March 2003, Nagasaki, Japan; Abstract 2, p. 78 and then at the 226th ACS National Meeting, September 2003, New York, NY, USA. Abstract: Division of Fluorine Chemistry, No. 11.

[14] D. Kashinath, C. Mioskowski, J.R. Falck, M. Goli, L. Meunier, R. Baati, A. Wagner, Org. Biomol. Chem. 7 (2009) 1771–1774.

[15] J.K. Stowell, T.S. Widlanski, J. Am. Chem. Soc. 116 (1994) 789–790.

[16] T.S. Widlanski, WO 9521847 (1995).

[17] (a) R.N. Ram, N.K. Meher, Org. Lett. 5 (2003) 145–147;
(b) R.N. Ram, T.P. Manoj, Org. Lett. 10 (2008) 2243–2246.

[18] For example, reaction of **1b** (1 equiv.) with by CuCl/bipyridine complex (4 equiv.) in 1,2-dichloroethane under reflux for 8 h resulted in the isolation of the fluoroalkenyl ester **3b** in 23% yield (Z/E = 6.7:1) along with the recovery of **1b** (42%).

[19] S. Halazy, C. Danzin, A. Ehrhard, F. Gerhart, J. Am. Chem. Soc. 111 (1989) 3484–3485.

[20] (a) A. Fürstner, N. Shi, J. Am. Chem. Soc. 118 (1996) 2533–2534;
(b) A. Fürstner, N. Shi, J. Am. Chem. Soc. 118 (1996) 12349–12357.

[21] S.R. Feaster, D.M. Quinn, Methods Enzymol. 286 (1997) 231–252.

[22] (a) S.G. Bhat, H.L. Brockman, Biochem. Biophys. Res. Commun. 109 (1982) 486–492;
(b) L.L. Gallo, S.B. Clark, S. Myers, G.V.J. Vohouny, J. Lipid Res. 25 (1984) 604–612.

[23] J. Brodt-Eppkey, P. White, S. Jenkins, D.Y. Hui, Biochem. Biophys. Acta 1272 (1995) 69–72.

[24] (a) G. Lin, C.-Y. Lai, Tetrahedron Lett. 36 (1995) 6117–6120;
(b) S.R. Feaster, K. Lee, N. Baker, D.M. Quinn, Biochemistry 35 (1996) 16723–16734.

[25] K.K. Hansen, B. Grosch, S. Greiveldinger-Poenaru, P.A. Bartlett, J. Org. Chem. 68 (2003) 8465–8470.

[26] T. Hara, M. Shimizu, T. Hiyama, Synlett (1996) 831–832.

[27] M. Kuroboshi, N. Yamada, Y. Takede, T. Hiyama, Synlett (1995) 987–988.

[28] Y. Wakabayashi, S. Imamura, JP50946 (1986).

[29] (a) For **22a**, see: M. Yato, K. Homma, A. Ishida, Tetrahedron, 57 (2001) 5353–5359;
(b) For TBDPS-F, see: R. Damrauer, R.A. Simon, B. Kanner, Organometallics, 7 (1988) 1161–1164;
(c) For TBDPS-OH **26**, see: S. Imazeki, H. Sugawara, A. Sano, T. Akiyama, Bull. Chem. Soc. Jpn. 81 (2008) 623–629.