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Carbocyclization reactions of terminally difluorinated alkenyl active methine compounds mediated by SnCl₄ and amine

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Dedicated to Professor Ronald Eric Banks on the occasion of his 70th birthday

Abstract

Carbocyclization of terminally difluorinated 3-butenyl active methine compounds 1a-1e proceeded through the 5-*endo* mode, upon treating with SnCl₄ and triethylamine to give fluorocyclopentene derivatives 3a-3e. Iodocarbocyclization of dimethyl 2-(4,4-difluorobut-3-enyl)-malonate (1a) mediated by I₂, SnCl₄ and amine provided 2,2-difluoro-3-iodocyclopentane-1,1-dicarboxylate 4a through the 5-*endo* mode, while in the case of 2-(5,5-difluoropent-4-enyl)malonate (1f) 5-*exo* mode cyclization reaction took place to give difluoroiodomethylcy-clopentane derivative **5f**.

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1. Introduction

Development of new synthetic methods for fluorine-containing carbocyclic compounds is an important subject, in particular related to efficient preparation of targeted fluorinemodified biologically active compounds. Electrophilic fluorination of an enolate or an equivalent such as a silyl enol ether derived from cyclic ketones is one of several general and important methods [1–3]. Nucleophilic fluorination of hydroxyl group and carbonyl group in the aliphatic ring compounds, for example, by means of (diethylamino)sulfur trifluoride (DAST) or related reagents, is also widely used [4–6]. Building block chemistry often provides highly reliable and efficient means for the preparation of densely functionalized compounds [7–11], and thus new reactions and new methods based on building block chemistry attract much attention. For example, on the basis of unique properties of 1,1-difluorovinylidene double bond ($CF_2=C$), Ichikawa et al. demonstrated that the 5-endo-trig cyclizations smoothly proceed for 1,1-difluoro-1-alkenes having a

variety of heteroatom as well as carbon nucleophiles through addition–elimination process to give a variety of fluorinated five-membered ring compounds [12–15].

We reported that carbocyclization (iodocarbocyclization [16–19] and intramolecular carbometalation [20–22]) of active methine compounds having an unactivated unsaturated carbon–carbon bond in the α -substituent can be effectively promoted by a Lewis acid such as TiCl₄ or SnCl₄ and amine or by Ti(OR)₄. Scheme 1 shows typical examples with 4-pentenylmalonate, which gave the iodocarbocyclization product and the carbostannylation product nearly quantitatively. The characteristic features of these intramolecular cyclization reactions are the mode of cyclization mode, it should be noted that only *exo* cyclizations are achieved; that is, 5-*exo*, 6-*exo* and 3-*exo* cyclizations regardless of the chain length do not effectively proceed.

As an extension of our carbocyclization reactions to terminally difluorinated alkenyl active methine compounds, we have focused our attention to examine the fluorine substituent effect on the cyclization mode with a hope to develop new synthetic methods for fluorinated carbocyclic systems.

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Scheme 1. Iodocarbocyclization and intramolecular carbometalation.

2. Results and discussion

The attempted cyclization of dimethyl 2-(4,4-difluorobut-3-enyl)malonate (1a) was conducted under various reaction conditions. While Ti(Oi-Pr)₄, TiCl₄-Et₃N, ZnCl₂-Et₃N, Et₂Zn did not work at all resulting in recovery of **1a**, SnCl₄ (1.8 eq.) and Et_3N (1.0 eq.) in CH_2Cl_2 at room temperature promoted the 5-endo cyclization to give 2-flurorocyclopent-2-ene-1,1-dicarboxylate **3a** in 88% yield (Table 1, entry 1). With the corresponding hydrocarbon substrate, dimethyl 3butenymalonate, such 5-endo cyclization was not observed upon treating with SnCl₄ and Et₃N. The reaction pathway possibly involves the formation of a Sn-enolate of the malonate moiety, which attacks the double bond activated by coordination to SnCl₄ to give the intramolecular carbostannylation intermediate **2a** followed by fluoride β -elimination. The fluoride β -elimination step should be an irreversible and crucial step for this 5-endo type cyclization to proceed. It is noted that, however, the cyclized product 3a did not form when lithium or sodium enolate of the malonate 1a was used (n-BuLi, THF, reflux or NaH, DMF, 100 °C).

Similar to the case of the malonate 1a, the SnCl₄–Et₃N system was also effective for the 5-*endo* cyclization of the

Table 1



F F	E ₁ E ₂	SnCl ₄ , Et ₃ N CH ₂ Cl ₂	$\left[\begin{array}{c} SnCl_{3} \\ F \\ F \\ E_{1} \\ E_{2} \end{array}\right]$,	
	E a CO b CO	₁ E₂ ₂MeCO₂Me ₂Bn CO₂Bn	c P(O)(OEt); d CN e COMe	₂ CO ₂ Et CO ₂ Me CO ₂ Me		
Entry	1	SnCl ₄ -Et ₃ N (eq.)	Temperature	Time (h)	3	Yield (%) ^a
1	1a	1.8/1.0	RT	6	3a	88
2	1b	1.8/1.0	RT	10	3b	34 ^b
3	1c	3.6/2.2	RT	8	3c	85
4	1d	15.0/2.0	Reflux	18	3d	43
5	1e	15.0/2.0	Reflux	18	3e	38 [°]

^a Isolated yield.

^b Recovery of **1b** was 27%.

^c Recovery of **1e** was 31%.

terminally *gem*-difluoro-3-butenyl derivatives of phosphonoacetate **1c**, cyanoacetate **1d** and acetoacetate **1e** giving rise to the corresponding fluorocyclopentene compounds **3b–3d**. The decrease in the pK_a value of these active methine compounds as compared with that of malonate **1a** resulted in lower reactivity as well as lower yields of the products, in particular in the cases of cyanoacetate **1d** and acetoacetate **1e**, requiring a large excess amount of SnCl₄ for the reaction to proceed (entries 4, 5).

With 2-(5,5-diffuoropent-4-enyl) malonate (1f) neither 6-endo nor 5-exo cyclization proceeded under the various reaction conditions using SnCl₄ and amine. This is a sharp contrast to the result with the hydrocarbon counterpart, 4-pentenylmalonate [22]. That is, reaction of dimethyl 4-pentenylmalonate with SnCl₄ and Et₃N proceeds easily at room temperature to afford the 5-exo cyclized product in quantitative yield. This organostannane compound having a six-membered coordination structure between stannane and carbonyl-oxygen is extremely stable (see Scheme 1). The present SnCl₄-Et₃N mediated reaction was applied to the ortho-substituted difluorinated styrene derivative 1g, which would have a conformational advantage for the cyclization reaction due to the presence of benzene ring as the tether. However, neither 6-endo nor 5-exo cyclization was observed under the Lewis acid mediated conditions. In the case of this styrene derivative 1g, a nucleophilic addition-elimination process via 6-endo-trig smoothly proceeded to give the dihydronaphtharene 3g in 65% yield when treating with NaH in DMF at room temperature for 3 h [15] (Scheme 2).



Next, we examined the iodocarbocyclization reactions of the difluorinated substrates. We found that iodocarbocyclization of the 2-(4,4-difluorobut-3-enyl)malonate (**1a**) proceeds when **1a** is treated with I₂ (2.2 eq.), SnCl₄ (2.7 eq.) and 2,6-dimethoxypyridine (DMP, 2.2 eq.) giving rise to 5-*endo* cyclization product **4a** in 70% yield along with the formation of the fluorocyclopentene **3a** in 5% yield (Scheme 3). In a similar manner, the dibenzyl malonate **1b** gave the iodocyclopentane compound **4b** in 73% yield. The product ratio varied with the amine used. For example, the use of Et₃N instead of DMP resulted in lower yield of the iodide **4a** (55%) with the increased yield of **3a** (30%). TiCl₄ was less effective than SnCl₄. Thus, treatment of **1a** with TiCl₄ (1.8 eq.), Et₃N (1.5 eq.) and I₂ (1.5 eq.) in refluxing CH₂Cl₂







Scheme 3. Iodocarbocyclization of 1a and 1b.



Scheme 4. Iodocarbocyclization of 1f and 1g.

for 18 h gave **4a** in only 30% yield. Contrary to the successful iodocarbocyclization reaction with the difluorinated 3-butenylmalonate **1a**, the corresponding hydrocarbon counterpart, dimethyl 3-butenylmalonate, did not give the iodocarbocycliation product regardless of the cyclization mode (5-*endo* or 4-*exo* manner). Under similar reaction conditions for **4a** from **1a**, iodocarbocyclization of 2-(5,5-difluoropent-4enyl)malonate (**1f**) or the styrene derivative **1g** proceeded in 5-*exo* mode to give (difluoroiodomethyl)cyclopentane derivative **5f** (58% yield) and indane derivative **5g** (80% yield), respectively (Scheme 4). The cyclization mode is the same as in the case of the analogous hydrocarbon derivative [19,22].

Two examples of functional conversion of the iodocarbocyclized products **4b** and **5f** are shown in Scheme 5. Conversion of the iodide **4b** to the hydroxyl compound **6** could be achieved in 80% yield (conversion yield) by oxygenative radical procedure [23] using benzotrifluoride (BTF) as a solvent. Dehydroiodination of **5f** proceeded by simply treating with DBU to give difluoromethylene compound **7** in 90% yield. Furthermore, with both **4b** and **5f**, reduction of iodo substituent to hydrogen can be easily accomplishes



under the radical conditions (Bu₃SnH or (TMS)₃SiH, cat. AIBN in toluene, 70 $^\circ\text{C}$).

In conclusion, carbocyclization (carbostannylation and iodocarbocyclization) of terminally difluorinated alkenyl active methine compounds can be effectively mediated by the SnCl₄-amine system to give the fluorinated carbocycles.

3. Experimental details

General: ¹H- and ¹³C-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer, and chemical shifts were reported in parts per million (ppm) using CHCl₃ (7.26 ppm) in CDCl₃ for ¹H-NMR, and CDCl₃ (77.01 ppm) for ¹³C-NMR as an internal standard, respectively. ¹⁹F-NMR spectra were taken on a Brucker AM400 spectrometer, and chemical shifts were reported in parts per million using benzotrifluoride as a standard. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or VG Auto Spec. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica–gel, 50 µm) with UV detector.

3.1. Preparation of dimethyl 2-(4,4-difluorobut-3enyl)malonate (**1a**): general procedure for the preparation of difluorinated alkenylactive methine compounds

Under an argon atmosphere, dimethyl malonate (3.90 mmol) was treated with NaH (60%, 2.32 mmol) in THF (10 ml) for 30 min and then 4,4-difluorobut-3-enyl mesylate (1.93 mmol), NaI (0.96 mmol) and DMF (3 ml) was added. After being stirred for 4 h at 80 °C, addition of NH₄Cl aq. followed by extractive work-up and purification of the extracts by silica–gel column chromatography (hexane and ethyl acetate, 4:1) gave **1a** in 92% yield.

Dimethyl 2-(4,4-difluorobut-3-enyl)malonate (**1a**): Colorless oil. IR (neat) ν (cm⁻¹): 2960, 1748, 1436. ¹H-NMR (400 MHz, CDCl₃) δ : 1.95–2.09 (4H, m), 3.38 (1H, t, J =7.0 Hz), 3.75 (6H, s), 4.12 (1H, dtd, J = 25.0, 7.5, 2.2 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 20.1 (d, J = 4.4 Hz), 23.4, 50.7, 52.5, 76.6 (dd, J = 22.8, 20.8 Hz), 156.6 (dd, J = 286.8, 286.8 Hz), 169.5. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : –27.6 (1F, dd, J = 45.0, 25.0 Hz), –25.0 (1F, d, J = 45.0 Hz). MS (EI) m/z: 223 ($M^+ + 1$), 202, 191. HRMS; Calcd. for C₉H₁₃F₂O₄ ($M^+ + 1$): 223.0773, Found: 223.0782.

Dibenzyl 2-(4,4-difluorobut-3-enyl)malonate (**1b**): Colorless oil. IR (neat) v (cm⁻¹): 1747. ¹H-NMR (400 MHz, CDCl₃) δ : 1.98–2.06 (4H, m), 3.46 (1H, t, J = 7.2 Hz), 4.10 (1H, dtd, J = 25.0, 7.8, 2.6 Hz), 5.13 (2H, d, J = 12.3 Hz), 5.17 (2H, d, J = 12.3 Hz), 7.26–7.35 (10H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 20.0 (d, J = 4.5 Hz), 28.3, 51.1, 67.2, 76.6 (dd, J = 22.8, 20.8 Hz), 128.2, 128.4, 128.5, 135.2, 156.5 (dd, J = 287.6, 286.5 Hz), 168.5. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -27.5 (1F, dd, J = 45.0, 25.0 Hz), -25.0 (1F, d, J = 45.0 Hz). MS (EI) m/z: 374 (M^+), 283. HRMS; Calcd. for $C_{14}H_{13}F_2O_4$ ($M^+ - C_7H_7$): 283.0782, Found: 283.0789.

Ethyl 2-(*diethoxyphosphoryl*)-6,6-*difluorohex-5-enoate* (*Ic*): Colorless oil. IR (neat) v (cm⁻¹): 1739, 1647, 1254, 1051, 1024, 969. ¹H-NMR (400 MHz, CDCl₃) δ : 1.28 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.2 Hz), 1.33 (3H, t, J = 7.3 Hz), 1.85–2.15 (4H, m), 2.93 (1H, ddd, J = 23.2, 10.6, 3.6 Hz), 4.10–4.24 (7H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 13.8, 16.0, 16.1, 20.8 (dd, J = 16.0, 4.4 Hz), 26.4, 44.6 (d, J = 131.7 Hz), 61.2, 62.5 (d, J = 7.7 Hz), 62.6 (d, J = 7.4 Hz), 76.4 (dd, J = 21.2, 21.2 Hz), 156.4 (dd, J = 287.3, 287.3 Hz), 168.6 (d, J = 4.9 Hz). ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -27.7 (1F, dd, J = 45.0, 25.0 Hz), -24.9 (1F, d, J = 45.0 Hz). MS (EI) *m/z*: 315 (*M*⁺ + 1). HRMS; Calcd. for C₁₂H₂₁F₂O₅P (*M*⁺): 314.1095, Found: 314.1088.

Methyl 2-*cyano*-6,6-*difluorohex*-5-*enoate* (1*d*): Colorless oil. IR (neat) v (cm⁻¹): 2318, 1750. ¹H-NMR (400 MHz, CDCl₃) δ : 2.04 (2H, td, J = 7.9, 7.0 Hz), 2.22 (2H, dt, J = 7.9, 7.9 Hz), 3.53 (2H, t, J = 7.0 Hz), 3.83 (3H, s), 4.16 (1H, dtd, J = 24.7, 7.9, 2.1 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 19.7 (d, J = 4.7 Hz), 29.4, 36.4, 53.6, 75.7 (dd, J = 23.9, 20.4 Hz), 115.9, 156.9 (dd, J = 288.8, 287.2 Hz), 166.2. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -26.2 (1F, dd, J = 42.2, 24.7 Hz), -23.8 (1F, d, J = 42.2 Hz). MS (EI) *m/z*: 189 (*M*⁺). HRMS; Calcd. for C₈H₉F₂NO₂ (*M*⁺): 189.0601, Found: 189.0593.

Methyl 2-acetyl-6,6-difluorohex-5-enoate (**1e**): Colorless oil. IR (neat) v (cm⁻¹): 1747, 1718. ¹H-NMR (400 MHz, CDCl₃) δ : 1.88–2.04 (4H, m), 2.22 (3H, s), 3.44 (1H, t, J = 7.0 Hz), 3.74 (3H, s), 4.11 (1H, dtd, J = 25.0, 7.8, 2.3 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 20.1 (d, J = 4.3 Hz), 27.6, 29.0, 52.5, 58.5, 76.7 (dd, J = 20.5, 20.5 Hz), 156.9 (dd, J = 288.8, 287.2 Hz), 169.9, 202.4. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : –27.7 (1F, dd, J = 46.0, 25.0 Hz), –25.1 (1F, d, J = 46.0 Hz). MS (EI) *m/z*: 206 (*M*⁺). HRMS; Calcd. for C₉H₁₂F₂O₃ (*M*⁺): 206.0755, Found: 206.0732.

Dimethyl 2-(5,5-difluoropent-4-enyl)malonate (**I**f): Colorless oil. IR (neat) ν (cm⁻¹): 3004, 2960, 1750. ¹H-NMR (400 MHz, CDCl₃) δ: 1.35–1.43 (2 H, m), 1.87–1.95 (2H, m), 2.01 (2H, qt J = 7.5, 1.7 Hz), 3.36 (1H, t, J = 7.5 Hz), 3.74 (6H, s), 4.12 (1 H, dtd, 25.3, 7.9, 2.5 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ: 21.8 (d, J = 4.1 Hz), 27.1, 28.0, 51.4, 52.5, 77.2 (t, J = 21.5 Hz), 156.4 (dd, J = 287.0, 287.0 Hz), 169.7. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ: -28.4 (1F, m), -26.1 (1F, ddm, 47, 17 Hz). MS (EI) *m/z*: 237 (M^+ + 1), 205. HRMS; Calcd. for C₁₀H₁₅F₂O₄ (M^+ + 1): 237.0938, Found: 237.0939.

Dimethyl 2-[2-(2,2-difluorovinyl)benzyl]malonate (**1g**): Colorless oil. IR (neat) v (cm⁻¹): 1747. ¹H-NMR (400 MHz, CDCl₃) δ : 3.46 (1H, t, J = 7.2 Hz), 3.76 (2H, d, J = 7.2 Hz), 3.78 (6H, s), 6.28 (1H, dd, J = 27.3, 4.2 Hz), 6.95–7.08 (1H, m), 7.13–7.24 (3H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 38.4, 53.4, 55.9, 109.1 (dd, J = 22.9, 20.3 Hz), 126.3, 126.4, 127.4, 129.1, 130.0, 131.6 (dd, J = 8.0, 8.0 Hz), 154.3 (dd, J = 291.2, 288.3 Hz), 168.6. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -27.4 (1F, dd, J = 33.6, 4.2 Hz), -26.8 (1F, dd, J = 33.6, 28.6 Hz). MS (EI) m/z: 237 (M^+ + 1), 205. HRMS; Calcd. for C₁₄H₁₄F₂O₄ (M^+): 283.0782, Found: 283.0786.

3.2. Preparation of dimethyl 2-fluorocyclopent-2-ene-1, 1-dicarboxylate (**3a**)

Under an argon atmosphere, a mixture of 1a (0.32 mmol), SnCl₄ (0.57 mmol) and Et₃N (0.32 mmol) in CH₂Cl₂ (1 ml) was stirred for 6 h at room temperature, and then to the reaction mixture was added 5% HCl. Extractive work-up and purification of the extracts by silica–gel column chromatography (hexane and ethyl acetate, 4:1) gave **3a** (0.28 mmol, 88% yield).

Dimethyl 2-fluorocyclopent-2-ene-1,1-dicarboxylate (**3a**): Colorless oil. IR (neat) v (cm⁻¹): 3028, 2960, 2864, 1740. ¹H-NMR (400 MHz, CDCl₃) δ: 2.28–2.35 (2H, m), 2.59 (2H, t, J = 7.1 Hz), 3.77 (6H, s), 5.32 (1H, t, J = 2.4 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ: 23.9 (d, J = 7.8 Hz), 31.8 (d, J = 3.6 Hz), 53.0, 62.4 (d, J = 19.1 Hz), 108.5 (d, J = 10.5 Hz), 155.6 (d, J = 283.4 Hz), 169.5 (d, J = 4.4 Hz). ¹⁹F-NMR (376.5 MHz, CDCl₃) δ: -63.8 (1F, t, J = 6.0 Hz). MS (EI) m/z: 202 (M^+), 170, 143. HRMS; Calcd. for C₉H₁₁FO₄ (M^+): 202.0634, Found: 202.0641.

Dibenzyl 2-fluorocyclopent-2-ene-1,1-dicarboxylate (**3b**): Colorless oil. IR (neat) v (cm⁻¹): 1737, 1680. ¹H-NMR (400 MHz, CDCl₃) δ : 2.29 (2H, tdd, J = 6.4, 6.4, 2.5 Hz), 2.58 (2H, t, J = 6.4 Hz), 5.15 (4H, s), 5.31 (1H, t, J = 2.5 Hz), 7.21–7.29 (10H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 24.0 (d, J = 7.7 Hz), 31.7 (d, J = 3.6 Hz), 62.8 (d, J = 18.9 Hz), 67.5, 108.8 (d, J = 15.3 Hz), 127.8, 128.2, 128.5, 135.2, 155.9 (d, J = 283.6 Hz), 168.8 (d, J = 4.2 Hz). ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -63.4 (1F, t, J = 6.4 Hz). MS (EI) m/z: 354 (M^+). HRMS; Calcd. for C₂₁H¹⁹FO₄ (M^+): 354.1267, Found: 354.1260.

Ethyl 1-diethoxyphosphoryl-2-fluorocyclopent-2-ene-1carboxylate (**3c**): Colorless oil. IR (neat) v (cm⁻¹): 1736, 1679, 1254, 1025. ¹H-NMR (400 MHz, CDCl₃) δ : 1.30 (3H, t, J = 7.1 Hz), 1.32 (6H, t, J = 7.1 Hz), 2.27–2.40 (2H, m), 2.52–2.70 (2H, m), 4.10–4.30 (6H, m), 5.30 (1H, dd, J = 5.4, 2.8 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 13.8, 16.2, 16.2, 24.2 (d, J = 7.7, 4.0 Hz), 30.4 (dd, J = 3.8, 3.8 Hz), 57.4 (dd, J = 143.8, 19.4 Hz), 61.9, 63.0 (d, J = 6.9 Hz), 63.2 (d, J = 7.1 Hz), 107.7 (dd, J = 10.6, 10.5 Hz), 155.9 (dd, J = 281.1, 12.0 Hz), 168.9 (d, J = 4.6 Hz). ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -60.6 (1F, dtd, J = 12.0, 6.0, 6.0 Hz). MS (EI) *m*/*z*: 295 (*M*⁺). HRMS; Calcd. for C₁₂H₂₁FO₅P (*M*⁺): 295.1111, Found: 295.1065.

Methyl 1-cyano-2-fluorocyclopent-2-ene-1,1-dicarboxylate (*3d*): Colorless oil. IR (neat) v (cm⁻¹): 2360, 1743. ¹H-NMR (400 MHz, CDCl₃) δ : 2.46–2.54 (2H, m), 2.59–2.75 (2H, m), 3.88 (3H, s), 5.48 (1H, t, J = 2.5 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 24.7 (d, J = 6.9 Hz), 34.5 (d, J = 3.2 Hz), 50.5 (d, J = 21.4 Hz), 54.2, 110.0 (d, J = 8.9 Hz), 116.6, 153.5 (d, J = 284.8 Hz), 166.8. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -62.9 (1F, t, J = 5.0 Hz). MS (EI) m/z: 169 (M^+). HRMS; Calcd. for C₈H₈FNO₃ (M^+): 169.0539, Found: 169.0531.

Methyl 1-acetyl-2-fluorocyclopent-2-ene-1-carboxylate (3e): Colorless oil. IR (neat) v (cm⁻¹): 1747, 1719. ¹H-NMR (400 MHz, CDCl₃) δ : 2.22–2.32 (2H, m), 2.27 (3H, s), 2.43–2.62 (2H, m), 3.79 (3H, s), 5.35 (1H, ddd, J = 2.5, 2.4, 0.7 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 23.9 (d, J = 8.1 Hz), 27.1, 30.3 (d, J = 4.2 Hz), 53.0, 68.5 (d, J = 18.8 Hz), 109.0 (d, J = 10.6 Hz), 156.5 (d, J = 282.3 Hz), 171.4, 202.5. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -62.9 (1F, br. s). MS (EI) *m*/*z*: 186 (*M*⁺). HRMS; Calcd. for C₉H₁₁FO₃ (*M*⁺): 186.0692, Found: 186.0681.

3.3. Preparation of dimethyl 2,2-difluoro-3iodocyclopentane-1,1-dicarboxylate (**4a**)

Under an argon atmosphere, a mixture of **1a** (0.32 mmol), I₂ (0.71 mmol), SnCl₄ (0.85 mmol) and 2,6-dimethoxypyridine (0.70 mmol) in CH₂Cl₂ (1 ml) was stirred for 26 h at room temperature, and then to the reaction mixture was added 5% HCl. Extractive work-up and purification of the extracts by silica–gel column chromatography (hexane and ethyl acetate, 4:1) gave **4a** (0.22 mmol, 70% yield) and **3a** (15.5 µmol, 5% yield).

Dimethyl 2,2-difluoro-3-iodocyclopentane-1,1-dicarboxylate (4a): Colorless oil. IR (neat) v (cm⁻¹): 2957, 1739, 1436, 1285. ¹H-NMR (400 MHz, CDCl₃) δ : 2.11–2.25 (2H, m), 2.39–2.51 (1H, m), 2.74–2.84 (1H, m), 3.78 (3H, s), 3.84 (3H, s), 4.66–4.86 (1H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 20.6 (dd, J = 24.2, 24.2 Hz), 30.8 (d, J = 5.9 Hz), 31.0 (d, J = 3.3 Hz), 53.4 (d, J = 18.1 Hz), 60.3 (dd J = 28.0, 19.7 Hz), 124.2 (dd, J = 271.1, 250.0 Hz), 165.8, 168.4 (d, J = 11.0 Hz). ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -51.5 (1F, dd, J = 232.3, 4.3 Hz), -33.7 (1F, dd, J = 232.3, 25.6 Hz). MS (EI) m/z: 328 (M^+ – HF), 317, 269. HRMS; Calcd. for C₉H₁₀FO₄I (M^+ – HF): 327.9607, Found: 327.9608.

Dibenzyl 2,2-difluoro-3-iodocyclopentane-1,1-dicarboxylate (**4b**): Colorless oil. IR (neat) v (cm⁻¹): 1737, 1680. ¹H-NMR (400 MHz, CDCl₃) δ : 2.12–2.24 (2H, m), 2.36–2.47 (1H, m), 2.76–2.87 (1H, m), 4.77 (1H, d, J = 25.6, 11.0, 9.4, 4.3 Hz), 5.20 (2H, d, J = 12.0 Hz), 5.25 (2H, d, J = 12.0 Hz), 7.20–7.23 (2H, m), 7.26–7.34 (8H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 20.6 (dd, J = 24.0, 24.0 Hz), 30.8 (d, J = 9.3 Hz), 30.8, 60.5 (dd J = 27.9, 19.5 Hz), 68.0, 68.8, 124.3 (dd, J = 271.0, 250.0 Hz), 127.9, 128.0, 128.3, 128.5, 128.6, 128.6, 134.5, 134.9, 165.0, 167.7 (d, J = 10.9 Hz). ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -51.1 (1F, dd, J = 232.0, 4.3 Hz), -33.7 (1F, dd, J = 232.0, 25.6 Hz). MS (EI) m/z: 409 ($M^+ - C_7H_7$). HRMS; Calcd. for C₁₄H₁₂F₂O₄I ($M^+ - C_7H_7$): 408.9748, Found: 408.9757. Dimethyl 2-(difluoroiodomethyl)cyclopentane-1, 1-dicarboxylate (5f): Colorless oil. IR (neat) v (cm⁻¹): 3024, 2960, 1740, 1734. ¹H-NMR (400 MHz, CDCl₃) δ : 1.49– 1.62 (1H, m), 1.88–2.02 (2H, m), 2.11–2.28 (2H, m), 2.59 (1H, dt, J = 13.6, 8.7 Hz), 3.70 (3H, s), 3.74 (3H, s), 3.86 (1H, dtd, J = 26.7, 8.0, 4.1 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 21.5, 30.1, 36.0, 52.9 (d, J = 33.9 Hz), 60.1 (t, J = 17.4 Hz), 61.0, 102.3 (t, J = 318.3 Hz), 169.4, 171.0. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : 17.8 (1F, dd, J = 170.0, 26.7 Hz), 28.3 (1F, d, J = 170.0 Hz). MS (EI) m/z: 363 ($M^+ + 1$), 331, 283, 235 ($M^+ - 1$), 187, 175. Anal. Calcd. for C₁₀H₁₃F₂O₄I: C, 33.17; H, 3.62, Found: C, 33.16; H, 3.54.

Dimethyl 1-(difluoroiodomethyl)indan-2,2-dicarboxylate (**5g**): Colorless solid. mp 80–82 °C IR (KBr) v (cm⁻¹): 1737. ¹H-NMR (400 MHz, CDCl₃) δ : 3.54 (1H, d, J = 16.7 Hz), 3.70 (3H, s), 3.79 (3H, s), 4.19 (1H, d, J = 16.7 Hz), 4.67 (1H, dd, J = 14.7, 10.0 Hz), 7.23–7.28 (2H, m), 7.34 (1H, dd, J = 7.8, 7.5 Hz), 7.51 (1H, d, J = 7.5 Hz). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 39.5, 53.1, 53.5, 62.9 (t, J = 4.6 Hz), 63.4 (t, J = 19.9 Hz), 101.9 (t, J = 317.3 Hz), 124.8, 127.0, 127.2, 129.4, 137.1, 140.9, 168.1, 170.5. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -28.6 (1F, dd, J = 185.6, 10.0 Hz), -22.3 (1F, dd, J = 185.6, 14.3 Hz). MS (EI) *m/z*: 283 (*M*⁺ – I). HRMS; Calcd. for C₁₄H₁₃F₂O₄ (*M*⁺ – I): 283.0782, Found: 283.0768.

3.4. Reaction of 1g with NaH

Under an argon atmosphere, a mixture of 1g (0.49 mmol) and NaH (60%, 0.64 mmol) in DMF (5 ml) was stirred for 3 h at room temperature, and then to the reaction mixture was added 5% HCl. Extractive work-up and purification of the extracts by silica–gel column chromatography (hexane and ethyl acetate, 4:1) gave 3g (0.32 mmol, 65% yield).

Dimethyl 3-fluoro-1H-naphthalene-2,2-dicarboxylate (3g): Colorless solid. mp 94–96 °C IR (KBr) v (cm⁻¹): 1750. ¹H-NMR (400 MHz, CDCl₃) δ : 3.63 (1H, d, J =12.0 Hz), 3.68 (1H, d, J = 12.0 Hz), 3.79 (6H, s), 6.28 (1H, d, J = 12.6 Hz), 7.04 (1H, d, J = 6.5 Hz), 7.12–7.20 (3H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 37.2 (d, J = 2.6 Hz), 53.4, 58.2 (d, J = 18.7 Hz), 108.2 (d, J =18.7 Hz), 126.3, 126.4, 127.4, 127.4, 129.1, 130.6 (d, J = 8.0 Hz), 156.2 (d, J = 272.2 Hz), 168.6. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -47.4 (1F, ddd, J = 12.6, 3.0, 3.0 Hz). MS (EI) m/z: 264 (M^+). HRMS; Calcd. for C₁₄H₁₃FO₄ (M^+): 264.0798, Found: 264.0781. Anal. Calcd. for C₁₄H₁₃FO₄: C, 63.63; H, 4.96, Found: C, 63.58; H, 5.14.

3.5. Dimethyl 2,2-difluoro-3-hydoxycyclopentane-1, 1-dicarboxylate (6)

Dioxygen was bubbled at 0 $^\circ C$ into a solution of 4b (0.10 mmol) and Bu₃SnH (32 μ mol) in BTF (2 ml) for

1 h, and then under O_2 atmosphere the solution was stirred for 10 days at 0 °C. Extractive work-up and purification of the extracts by silica–gel column chromatography (hexane and ethyl acetate, 3:1) gave **6** (38 µmol, 38% yield) and **4b** (53 µmol, 53% yield).

Dimethyl 2,2-difluoro-3-hydoxycyclopentane-1,1-dicarboxylate (6): Colorless oil. IR (neat) v (cm⁻¹): 2957, 1739, 1436, 1285. ¹H-NMR (400 MHz, CDCl₃) δ : 1.62– 1.75 (1H, m), 2.16–2.29 (2H, m), 2.44 (1H, ddd, J = 10.8, 9.9, 1.8 Hz), 2.87 (1H, d, J = 8.1 Hz), 4.28–4.39 (1H, m), 5.11 (2H, s), 5.12 (2H, s), 7.18–7.26 (10H, m). ¹³C-NMR (100.6 MHz, CDCl₃) δ : 27.6, 28.3 (d, J = 4.2 Hz), 63.1 (dd, J = 24.3, 22.1 Hz), 67.8, 68.0, 73.8 (dd J = 29.7, 19.6 Hz), 128.0, 128.0, 128.4, 128.5, 128.5, 134.6, 134.8, 166.3 (d, J = 3.8 Hz), 167.4 (d, J = 5.1 Hz). ¹⁹F-NMR (376.5 MHz, CDCl₃) δ : -56.6 (1F, dd, J = 244.9, 7.7 Hz), -47.3 (1F, dd, J = 244.9, 11.9 Hz). MS (EI) *m/z*: 390 (*M*⁺). HRMS; Calcd. for C₂₁H₂₀F₂O₅ (*M*⁺): 390.1279, Found: 390.1256.3.6.

Dimethyl 2-(2,2-difluoromethylene)cyclopentane-1,1dicarboxylate (7): Colorless oil. IR (neat) ν (cm⁻¹): 3032, 2964, 1760, 1742. ¹H-NMR (400 MHz, CDCl₃) δ: 1.74– 1.82 (2H, m), 2.35 (1H, t, J = 7.0 Hz), 2.36 (1H, t, J = 7.0 Hz), 2.43 (2H, ddd, J = 10.8, 7.0, 3.5 Hz), 3.76 (6H, s). ¹³C-NMR (100.6 MHz, CDCl₃) δ: 24.8, 26.9, 37.9, 53.0, 61.1, 91.5 (dd, J = 15.9, 28.9 Hz), 153.0 (dd, J = 291.2, 284.7 Hz), 170.4. ¹⁹F-NMR (376.5 MHz, CDCl₃) δ: -20.8 (1F, d, J = 43.4 Hz), -21.8 (1F, dt, J = 43.4, 3.5 Hz). MS (EI) m/z: 235 (M^+ + 1), 234 (M^+), 175. Anal. Calcd. for C₁₀H₁₂F₂O₄: C, 51.28; H, 5.16, Found: C, 51.33; H, 5.29.

References

- [1] G.S. Lal, G.P. Pez, R.G. Syvret, Chem. Rev. 96 (1996) 1737.
- [2] S. Rosen, Chem. Rev. 96 (1996) 1717.
- [3] T. Nakano, M. Makino, Y. Morizawa, Y. Matsumura, Angew. Chem. Int. Ed. Engl. 35 (1996) 1019.
- [4] M. Hudlicky, Org. React. 35 (1988) 513.
- [5] G.S. Lal, G.P. Pez, R.J. Pesaresi, F.M. Prozonic, H. Cheng, J. Org. Chem. 64 (1999) 7048.
- [6] R. Fernandez, S. Castillon, Tetrahedron 55 (1999) 8497.
- [7] J.M. Percy, Top. Curr. Chem. 193 (1997) 131.
- [8] J. Leroy, H. Molines, C. Wakselman, J. Org. Chem. 52 (1987) 290.
- [9] H. Amii, T. Kobayashi, H. Terasawa, K. Uneyama, Org. Lett. 3
- (2001) 3103.
- [10] Q. Shen, G.B. Hammond, J. Am. Chem. Soc. 124 (2002) 6534.
- [11] J.M. Percy, S. Pintat, Chem. Commun. (2000) 607.
- [12] J. Ichikawa, Y. Wada, T. Okauchi, T. Minami, Chem. Commun. (1997) 1537.
- [13] J. Ichikawa, M. Fujiwara, Y. Wada, T. Okauchi, T. Minami, Chem. Commun. (2000) 1887.
- [14] J. Ichikawa, K. Sakoda, Y. Wada, Chem. Lett. (2002) 282.
- [15] J. Ichikawa, Y. Wada, M. Fujiwara, K. Sakoda, Synthesis (2002) 1917.
- [16] O. Kitagawa, T. Inoue, T. Taguchi, Tetrahedron Lett. 33 (1992) 2167.
- [17] O. Kitagawa, T. Inoue, T. Taguchi, Rev. Heteroatom Chem. 15 (1996) 243.
- [18] O. Kitagawa, T. Taguchi, Synlett (1999) 1191.
- [19] O. Kitagawa, T. Suzuki, T. Inoue, Y. Watanabe, T. Taguchi, J. Org. Chem. 63 (1998) 9470.
- [20] O. Kitagawa, T. Suzuki, T. Inoue, T. Taguchi, Tetrahedron Lett. 39 (1998) 7357.
- [21] O. Kitagawa, T. Suzuki, H. Fujiwara, T. Taguchi, Tetrahedron Lett. 40 (1999) 2549.
- [22] O. Kitagawa, H. Fujiwara, T. Suzuki, T. Taguchi, M. Shiro, J. Org. Chem. 65 (2000) 6819.
- [23] E. Nakamura, T. Inubushi, S. Aoki, D. Machii, J. Am. Chem. Soc. 113 (1991) 8980.