



Synthesis of functionalized adamantanes from fluoroadamantanes

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ARTICLE INFO

Article history:

Received 3 February 2009

Received in revised form 24 February 2009

Accepted 24 February 2009

Available online 3 March 2009

Keywords:

Fluoroadamantane

Functionalization

Substitution

Fluoromemantine

ABSTRACT

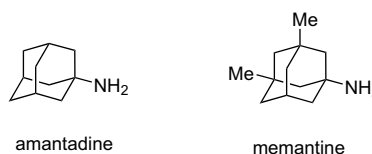
Selective introduction of functional groups on the *tert*-carbon of adamantane was performed by substitution with fluorides. A methyl, phenacyl, aryl, cyclohexyl, alkoxy, or azido group was introduced into the adamantane skeleton without influencing the other functional groups present. Various functionalized adamantanes were synthesized using this scheme. A fluorinated analog of memantine (3-fluoro-5,7-dimethyl-1-adamantylammonium acetate **25**) was synthesized from methyl 3,5-dimethyladamantane-1-carboxylate **6**.

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1. Introduction

Adamantane consists of four *tert*-carbons and six *sec*-carbons bonded together to form a simple cage compound. Adamantane derivatives, such as aminoadamantanes, are known to have interesting biological properties, 1-aminoadamantane (amantadine) and 3,5-dimethyl-1-aminoadamantane (memantine) are used medically to treat influenza, Parkinson disease, and Alzheimer disease.¹ Furthermore, because incorporation of an adamantane unit into polymers can enhance their thermal stability and improve their physical properties,² adamantane compounds are attracting a great deal of attention as functional materials. Functional groups can be introduced on the *tert*-carbons of adamantanes by several methods, including oxidation reactions,³ radical reactions,⁴ Friedel–Crafts reactions,⁵ and cross-coupling reactions.⁶ However, most of these reactions have been applied to the unsubstituted substrates, and few have been used for the synthesis of *poly*-functionalized adamantanes.^{3f,3d,5} Recently, we reported a selective introduction of fluorine atoms on the *tert*-carbons of adamantanes by an electrochemical method⁷ or by reaction with IF₅.⁸ One to four fluorine atoms can be introduced selectively on substituted adamantanes without influencing other functional groups such as the ester and the cyano group. Recently, alkyl fluorides have been used as substrates for alkylation or introduction of functional groups by substitution of a fluorine atom.⁹ Therefore, we planned to develop

an effective method for the synthesis of functionalized adamantanes using the fluoroadamantanes as a starting material.



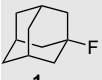
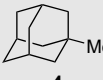
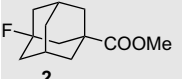
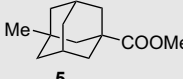
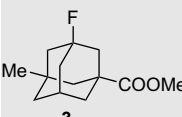
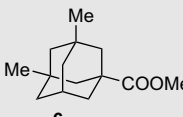
2. Results and discussion

We used Me₃Al for the methylation of 1-fluoroadamantane (**1**)^{7,8} analogous to the method for the methylation of *tert*-alkyl fluorides by Me₃Al reported by Maruoka et al.^{9a} We found that the reaction proceeds under mild conditions to give 1-methyladamantane (**4**) in high yield (Table 1). The reaction of methyl 3-fluoroadamantane-1-carboxylate (**2**)^{7,8} with Me₃Al proceeded without affecting the ester group to give methyl 3-methyladamantane-1-carboxylate (**5**) in high yield. However, the reaction of methyl 3,5-difluoroadamantane-1-carboxylate with Me₃Al was sluggish, and methyl 3,5-dimethyladamantane-1-carboxylate (**6**) was obtained only in poor yield. On the other hand, **6** can be prepared in high yield from methyl 3-fluoro-5-methyladamantane-1-carboxylate (**3**) by reaction with Me₃Al.¹⁰ Attempts to use other alkylaluminum reagents, such as Et₃Al or *i*-Bu₃Al, for reaction with **1** were unsuccessful. During the reaction, fluoride reduction occurred competitively, and significant amount of unsubstituted adamantane as well as the expected 1-alkyladamantanes was formed.^{9a}

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Table 1
Methylation of fluoroadamantanes with Me₃Al^a

Substrate	Product	Yield ^b (%)
		94
		98
		92

^a 1.1 equiv of Me₃Al to substrate was used.^b Isolated yield based on substrate.

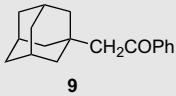
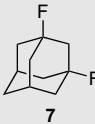
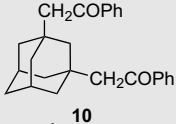
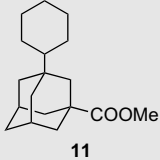
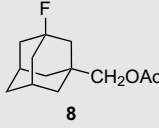
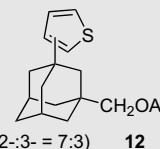
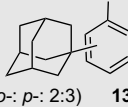
Next, we examined the Friedel–Crafts-type reactions for alkylation of the adamantanes. Maruoka also reported that *tert*-alkyl groups can be introduced into an α -position of the esters by the Me₃Al-catalyzed reaction of ketene silyl acetals with *tert*-alkyl fluorides.^{9a} The reaction of **1** with an α -(trimethylsiloxy)styrene proceeded smoothly in the presence of a Lewis acid to give 1-phenacyladamantane (**9**) in high yield (entry 1 in Table 2). BF₃ etherate or Al(OTf)₃,¹² used as Lewis acid, is effective for this reaction, and AlCl₃ or TiCl₄ is not suitable because they cause the undesired competitive chlorination of the adamantanes. The reaction of α -(trimethylsiloxy)styrene with difluoroadamantane (**7**) was sluggish, and required higher temperature. Under a high temperature condition, 1,3-diphenacyladamantane (**10**) was obtained in moderate yield (entry 2).¹³ The Lewis acid-catalyzed reaction of **2** with cyclohexene proceeded slowly without

influencing the ester group giving an isomeric mixture of methyl 3-(cyclohexen-1-yl)adamantane-1-carboxylate and methyl 3-(cyclohexen-3-yl)adamantane-1-carboxylate. Their double bonds in these compounds were hydrogenated without purification, and methyl 3-cyclohexyladamantane-1-carboxylate (**11**) was isolated in high yield (entry 3). Friedel–Crafts reaction of thiophene with **8** or that of anisole with **1** gave isomeric mixtures of thienyladamantanes (**12**) or (methoxyphenyl)adamantanes (**13**), respectively¹⁷ (entries 4 and 5).

An ethoxy group¹⁸ or an azido group²² can be introduced into the adamantane **1** by reaction with ethoxytrimethylsilane or azido-trimethylsilane in the presence of a Lewis acid, giving high yields of 1-ethoxyadamantane (**15**) or 1-azidoadamantane (**16**) (entries 1 and 2 in Table 3). The functional groups, such as an acetoxy group (entry 3) and an ester group (entries 4, 5, and 7), can tolerate the reaction conditions and the corresponding functionalized ethers (**17**, **18**, and **20**) and an azide (**19**) were obtained in high yields. An electron-withdrawing substituents on adamantane decreases the reactivity toward the electrophiles, and a higher temperature was required for introduction of an ethoxy group to the substrate having two ester groups (**14**) (entry 4). The reaction of ethoxytrimethylsilane with 1,3-difluoroadamantane **7** also required a higher temperature to obtain 1,3-diethoxyadamantane (**20**) (entry 6). Introduction of a (1*R*)-menthoxy group is possible by using a (1*R*)-menthoxytrimethylsilane, and the corresponding (1*R*)-menthyl ether (**21**) was obtained in high yield (entry 7).

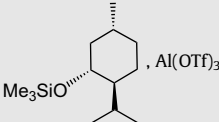
Introduction of a fluorine atom into bioactive compounds can enhance or modify their activity, and therefore the fluorinated analogs of bioactive compounds have attracted much attention.²³ Memantine, 1-amino-3,5-dimethyladamantane, is used to treat Parkinson disease and Alzheimer disease, and therefore its fluorinated analog should be evaluated. We attempted to synthesize 1-amino-3-fluoro-5,7-dimethyladamantane, a fluorinated analog

Table 2
Friedel–Crafts-type alkylation of adamantanes

Entry	Substrate	Reagent	Reaction conditions	vProduct	Yield ^a (%)
1		Me ₃ SiO-C(=O)-Ph, BF ₃ ·Et ₂ O	rt, 4 h		97
2		Me ₃ SiO-C(=O)-Ph, Al(OTf) ₃	40 °C, 15 h		60
3		Cyclohexene, Al(OTf) ₃	83 °C, 20 h		91 ^b
4		Thiophene, Al(OTf) ₃	40 °C, 15 h	 (2:3- = 7:3)	75
5		Anisole, Al(OTf) ₃	rt, 12 h	 (o-: p-: 2:3)	94

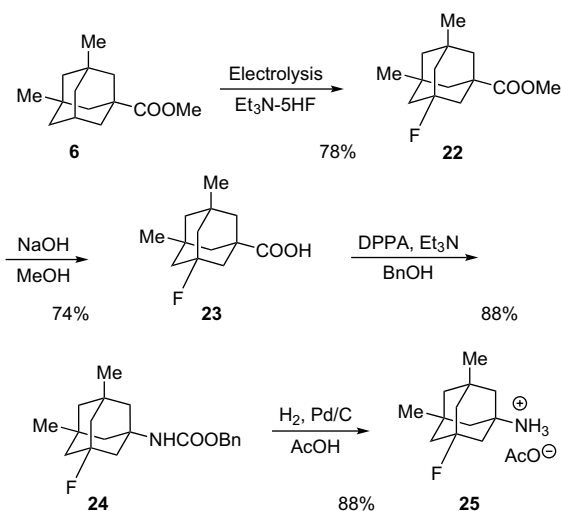
^a Isolation yield based on substrate used.^b Product was isolated after hydrogenation.

Table 3
Alkoxylation and azidation of adamantanes

Entry	Substrate	Reagent	Reaction conditions	Product	Yield ^a (%)
1	1	EtOSiMe ₃ , BF ₃ ·Et ₂ O	rt, 24 h	15	97
2	1	N ₃ SiMe ₃ , BF ₃ ·Et ₂ O	rt, 5 h	16	97
3	8	EtOSiMe ₃ , Al(OTf) ₃	rt, 20 h	17	80
4	14	EtOSiMe ₃ , Al(OTf) ₃	84 °C, 8 h	18	98
5	3	N ₃ SiMe ₃ , Al(OTf) ₃	rt, 24 h	19	95
6	7	EtOSiMe ₃ , Al(OTf) ₃	30 °C, 8 h	20	82
7	3	 , Al(OTf) ₃	40 °C, 24 h	21	96

^a Isolation yield based on substrate used.

of memantine, from methyl 3,5-dimethyladamantane-1-carboxylate **6**.²⁴ Fluorine atom was electrochemically introduced on a *tert*-carbon of **6** to give methyl 7-fluoro-3,5-dimethyladamantane-1-carboxylate (**22**) in 78% yield.⁷ Conversion of the ester group of **6** to amine was performed using a published procedure.²⁴



Scheme 1. Fluoromemantine synthesis.

After the hydrolysis of ester group, the resulting 3-fluoro-5,7-dimethyladamantane-1-carboxylic acid (**23**) was treated with diphenylphosphoryl azide (DPPA) to give the *N*-benzylcarbonate of the 1-amino-3-fluoro-5,7-dimethyladamantane (**24**). Deprotection of the amino group in acetic acid gave 3-fluoro-5,7-dimethyl-1-adamantylammonium acetate (**25**) (Scheme 1).

3. Conclusion

Selective alkylation or introduction of functional groups on the *tert*-carbon of adamantane was performed by substitution with fluorides. The reaction proceeds under mild conditions, and various functionalized adamantanes were synthesized. We also performed the synthesis of 3-fluoro-5,7-dimethyl-1-adamantylammonium acetate **25**, which is a fluorinated analog of memantine.

4. Experimental

4.1. General

The IR spectra were recorded using a JASCO FT/IR-410. The ¹H NMR (400 MHz), ¹⁹F NMR (376 MHz), and ¹³C NMR (100 MHz) spectra were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, δ , were referred to TMS (¹H, ¹³C) and CFCl₃ (¹⁹F), respectively. The EI low- and high-resolution mass spectra were

measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Me₃Al in hexane and Et₃N-5HF were purchased from Tokyo Kasei Co., Ltd. Al(OTf)₃ was purchased from Aldrich and used after drying under reduced pressure. Fluoroadamantanes **1**, **2**, **3**, **7**, **8**, **14** were prepared by the previously reported methods.^{7,8}

4.2. 1-Methyladamantane (4)

To a CH₂Cl₂ solution (8 mL) of 1-fluoroadamantane **1**^{7,8} (77 mg, 0.5 mmol) was added at room temperature under N₂ atmosphere, a 1.4 M hexane solution of Me₃Al (0.4 mL, 0.55 mmol), and the mixture was stirred for 30 min. Then, the mixture was poured into water (30 mL) and extracted with CH₂Cl₂ (20 mL×3). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane/ether=10:1) gave **4** (71 mg) in 94% yield; white solid: mp 101 °C (lit.^{11c} 100–101 °C). IR (KBr): 2900, 1454 cm⁻¹. ¹H NMR δ 1.92 (3H, br s), 1.75–1.54 (6H, m), 1.44 (6H, br s), 0.76 (3H, s). ¹³C NMR δ 44.61 (3C), 36.91 (3C), 31.44 (3C), 29.79, 28.85.

4.3. Methyl 3-methyladamantane-1-carboxylate (5)

The reaction was carried out as described above using methyl 3-fluoroadamantane-1-carboxylate **2**^{7,8} (106 mg, 0.5 mmol). Purification by column chromatography (silica gel, hexane/ether=5:1) gave **5** (101 mg) in 98% yield; clear oil. IR (neat): 2903, 1730 (C=O), 1233 cm⁻¹. ¹H NMR δ 3.65 (3H, s), 2.06 (2H, br s), 1.84–1.75 (4H, m), 1.62–1.56 (4H, m), 1.43 (4H, br s), 0.83 (3H, s). ¹³C NMR δ 178.11, 51.53, 45.51, 43.43 (2C), 41.59, 38.14 (2C), 35.66, 30.78, 30.01, 28.49 (2C). HRMS (EI) calcd for C₁₃H₂₀O₂ 208.14633, found 208.14615.

4.4. Methyl 3,5-dimethyladamantane-1-carboxylate (6)

The reaction was carried out as described above using **3**⁸ (113 mg, 0.5 mmol). Purification by column chromatography (silica gel, hexane/ether=10:1) gave **6** (102 mg) in 92% yield; clear oil. IR (neat): 2900, 1732 (C=O), 1455, 1263 cm⁻¹. ¹H NMR δ 3.65 (3H, s), 2.11–2.09 (1H, m), 1.71 (2H, br s), 1.56–1.47 (4H, m), 1.38–1.30 (4H, m), 1.15 (2H, br s), 0.84 (6H, s). ¹³C NMR δ 178.07, 51.58, 50.61, 44.93 (2C), 42.72 (2C), 42.52, 37.51, 30.85 (2C), 30.41 (2C), 29.12. HRMS (EI) calcd for C₁₄H₂₂O₂ 222.1620, found 222.1616.

4.5. 2-(1-Adamantyl)-1-phenylethanone (9)

A mixture of **1**^{7,8} (77 mg, 0.5 mmol), α-(trimethylsiloxy)styrene (192 mg, 1.0 mmol), and BF₃ etherate (10 mg, 0.07 mmol) in CH₂Cl₂ (8 mL) was stirred at room temperature for 4 h. Then, the mixture was poured to water (30 mL) and extracted with CH₂Cl₂ (20 mL×3). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane/ether=5:1) gave **9** (123 mg) in 97% yield; white solid: mp 66–67 °C (lit.²⁵ mp 64–65 °C). IR (KBr): 2907, 1665 (C=O), 1257 cm⁻¹. ¹H NMR δ 7.96–7.94 (2H, m), 7.57–7.53 (1H, m), 7.47–7.43 (2H, m), 2.72 (2H, s), 1.94 (3H, br s), 1.70–1.61 (12H, m). ¹³C NMR δ 200.27, 138.81, 132.67, 128.40 (2C), 128.34 (2C), 51.16, 42.92 (3C), 36.69 (3C), 33.89, 28.64 (3C).

4.6. 1,3-Diphenacyladamantane (10)

The reaction was carried out as described above using **7**^{7,8} (88 mg, 0.5 mmol), α-(trimethylsiloxy)styrene (288 mg, 1.5 mmol), and Al(OTf)₃ (237 mg, 0.5 mmol) in CH₂Cl₂ (8 mL) under reflux for 15 h. Purification by column chromatography (silica gel, hexane/ether=5:1) gave **10** (108 mg) in 60% yield; pale yellow oil. IR (neat): 2894, 1672 (C=O), 1254 cm⁻¹. ¹H NMR δ 7.93–7.90 (4H, m), 7.56–7.52 (2H, m), 7.49–7.41 (4H, m), 2.75 (4H, s), 2.02 (2H, br s), 1.65–1.56

(12H, m). ¹³C NMR δ 199.99 (2C), 138.64 (2C), 132.77 (2C), 128.46 (4C), 128.29 (4C), 50.59 (2C), 48.36, 41.89 (4C), 35.75, 34.59 (2C), 28.56 (2C). HRMS (EI) calcd for C₂₆H₂₈O₂ 372.2089, found 372.2089.

4.7. Methyl 3-cyclohexyladamantane-1-carboxylate (11)

A mixture of **2**^{7,8} (106 mg, 0.5 mmol) and Al(OTf)₃ (47 mg, 0.1 mmol) in cyclohexene (20 mL) was stirred under reflux for 20 h. Then, the mixture was poured to water (30 mL) and extracted with CH₂Cl₂ (20 mL×3). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane/AcOEt=20:1) gave **11** (116 mg) in 91% yield; clear oil. IR (neat): 2926, 1731 (C=O), 1241 cm⁻¹. ¹H NMR δ 3.65 (3H, s), 1.84–1.74 (8H, m), 1.65–1.57 (6H, m), 1.51–1.43 (4H, m), 1.25–1.06 (4H, m), 0.98–0.83 (3H, m). ¹³C NMR δ 178.37, 51.53, 48.30, 41.57, 41.03, 38.67 (2C), 38.59 (2C), 36.28, 34.73, 28.48 (2C), 27.15 (2C), 26.82, 26.05 (2C). HRMS (EI) calcd for C₁₈H₂₈O₂ 276.2089, found 276.2095.

4.8. 1-Acetoxyethyl-3-thienyladamantane (12)

The reaction was carried out as described above using **8**^{7,8} (113 mg, 0.5 mmol) and Al(OTf)₃ (24 mg, 0.05 mmol) in thiophene (2 mL) at 40 °C under N₂ atmosphere for 15 h. Purification by column chromatography (silica gel, hexane/ether=5:1) gave **12** (109 mg) in 75% yield as a mixture of isomers (thien-2-yl/thien-3-yl=7:3); pale yellow oil. IR (neat): 2905, 1742 (C=O), 1245 cm⁻¹. ¹H NMR δ 7.28–7.26 (0.3H, m), 7.14 (0.7H, dd, *J*=5.0, 1.3 Hz), 7.09 (0.3H, dd, *J*=5.0, 1.3 Hz), 6.96–6.93 (1H, m), 6.83 (0.7 Hz, dd, *J*=3.6, 1.3 Hz), 3.75 (2H, s), 2.18 (2H, br s), 2.07 (3H, s), 1.98–1.82 (4H, m), 1.75–1.68 (4H, m), 1.57 (4H, br s). ¹³C NMR (thien-2-yl isomer): δ 171.29, 157.12, 126.31, 122.08, 120.38, 73.43, 46.54, 44.25 (2C), 38.28 (2C), 36.34, 35.87, 34.21, 28.60 (2C), 20.85; (thien-3-yl isomer): δ 171.27, 152.73, 125.35, 125.07, 117.59, 73.61, 45.13, 42.84 (2C), 38.43 (2C), 36.03, 35.49, 34.01, 28.50 (2C), 20.85. HRMS (EI) calcd for C₁₇H₂₂O₂S 290.13405, found 290.13436.

4.9. 1-Methoxyphenyladamantane (13)

The reaction was carried out as described above using **1**^{7,8} (77 mg, 0.5 mmol) and Al(OTf)₃ (47 mg, 0.1 mmol) in anisole (2 mL) at room temperature under N₂ atmosphere for 12 h. Purification by column chromatography (silica gel, hexane/AcOEt=20:1) gave 1-(*o*-methoxyphenyl)adamantane (46 mg) and 1-(*p*-methoxyphenyl)adamantane (68 mg) in 94% total yield. *o*-Isomer: white solid: mp 100–102 °C (lit.²⁶ mp 100–102 °C). ¹H NMR δ 7.26–7.16 (2H, m), 6.94–6.87 (2H, m), 3.83 (3H, s), 2.10–2.06 (9H, m), 1.77 (6H, br s). ¹³C NMR δ 158.78, 138.46, 126.75, 126.42, 120.43, 111.62, 54.89, 40.51 (3C), 37.12 (3C), 36.92, 29.08 (3C). *p*-Isomer: white solid, mp 79–80 °C (lit.²⁶ mp 80–83 °C). ¹H NMR δ 7.28 (2H, d, *J*=8.9 Hz), 6.84 (2H, d, *J*=8.9 Hz), 3.79 (3H, s), 2.08 (3H, br s), 1.89 (6H, br s), 1.80–1.71 (6H, m). ¹³C NMR δ 157.28, 143.65, 125.74 (2C), 113.33 (2C), 55.13, 43.34 (3C), 36.76 (3C), 35.48, 28.95 (3C).

4.10. 1-Ethoxyadamantane (15)²⁷

The reaction was carried out as described above using **1**^{7,8} (77 mg, 0.5 mmol), Me₃SiOEt (118 mg, 1.0 mmol), and BF₃ etherate (10 mg, 0.07 mmol) in CH₂Cl₂ (8 mL) at room temperature for 24 h. Purification by column chromatography (silica gel, hexane/ether=5:1) gave **15** (87 mg) in 97% yield; clear oil. IR (neat): 2907, 1117 cm⁻¹. ¹H NMR δ 3.47 (2H, q, *J*=6.9 Hz), 2.91 (3H, br s), 1.75 (6H, s), 1.66–1.58 (6H, m), 1.16 (3H, t, *J*=7.0 Hz). ¹³C NMR δ 71.78, 54.87, 41.58 (3C), 36.48 (3C), 30.46 (3C), 16.35.

4.11. 1-Azidoadamantane (16)²⁸

The reaction was carried out as described above using **1**^{7,8} (77 mg, 0.5 mmol), Me₃SiN₃ (115 mg, 1.0 mmol), and BF₃ etherate (10 mg, 0.07 mmol) in CH₂Cl₂ (8 mL) at room temperature for 5 h. Purification by column chromatography (silica gel, hexane/ether=10:1) gave **16** (86 mg) in 97% yield; clear oil. IR (neat): 2917, 2086 (N₃), 1253 cm⁻¹. ¹H NMR δ 2.15 (3H, br s), 1.81 (6H, s), 1.71–1.62 (6H, m). ¹³C NMR δ 59.00, 41.49 (3C), 35.88 (3C), 29.77 (3C).

4.12. 1-Acetoxyethyl-3-ethoxyadamantane (17)

The reaction was carried out as described above using **8**^{7,8} (113 mg, 0.5 mmol), Me₃SiOEt (118 mg, 1 mmol), and Al(OTf)₃ (119 mg, 0.25 mmol) in CH₂Cl₂ (2 mL) at room temperature under N₂ atmosphere for 20 h. Purification by column chromatography (silica gel, hexane/ether=2:1) gave **17** (101 mg) in 80% yield; yellow oil. IR (neat): 2907, 1744 (C=O), 1243 cm⁻¹. ¹H NMR δ 3.74 (2H, s), 3.47 (2H, q, *J*=7.0 Hz), 2.24–2.22 (2H, m), 2.06 (3H, s), 1.77–1.68 (4H, m), 1.58–1.55 (4H, m), 1.45 (4H, br s), 1.16 (3H, t, *J*=7.0 Hz). ¹³C NMR δ 171.16, 73.00, 72.10, 55.10, 43.15, 40.84 (2C), 38.23 (2C), 36.35, 35.75, 29.87 (2C), 20.78, 16.19. HRMS (EI) calcd for C₁₅H₂₄O₃ 252.17255, found 252.17273.

4.13. Dimethyl 5-ethoxyadamantane-1,3-dicarboxylate (18)

The reaction was carried out as described above using **14**⁷ (135 mg, 0.5 mmol), Me₃SiOEt (118 mg, 1 mmol), and Al(OTf)₃ (119 mg, 0.25 mmol) in CH₂Cl₂ (2 mL) under reflux for 8 h. Purification by column chromatography (silica gel, hexane/AcOEt=2:1) gave **18** (145 mg) in 98% yield; pale yellow oil. IR (neat): 2949, 1731 (C=O), 1223 cm⁻¹. ¹H NMR δ 3.68 (6H, s), 3.49 (2H, q, *J*=7.0 Hz), 2.39–2.37 (1H, m), 1.96 (2H, br s), 1.88 (4H, br s), 1.77 (4H, br s), 1.73 (2H, br s), 1.16 (3H, t, *J*=7.0 Hz). ¹³C NMR δ 175.88 (2C), 71.70 (2C), 55.17, 51.51 (2C), 43.26, 41.58 (2C), 39.61, 38.89, 36.81 (2C), 29.30, 15.74. HRMS (EI) calcd for C₁₆H₂₄O₅ 296.16238, found 296.16173.

4.14. Methyl 3-azido-5-methyladamantane-1-carboxylate (19)

The reaction was carried out as described above using **3**⁸ (113 mg, 0.5 mmol), Me₃SiN₃ (104 mg, 0.9 mmol), and Al(OTf)₃ (95 mg, 0.2 mmol) in CH₂Cl₂ (2 mL) at room temperature for 24 h. Purification by column chromatography (silica gel, hexane/ether=8:1) gave **19** (118 mg) in 95% yield; clear oil. IR (neat): 2924, 2360, 2090 (N₃), 1731 (C=O), 1261 cm⁻¹. ¹H NMR δ 3.68 (3H, s), 2.31–2.29 (1H, m), 1.93–1.83 (2H, m), 1.78–1.69 (4H, m), 1.66–1.47 (4H, m), 1.41 (2H, br s), 0.94 (3H, s). ¹³C NMR δ 176.35, 59.46, 51.56, 47.22, 44.35, 43.60, 41.95, 41.90, 39.82, 36.86, 32.59, 29.69, 29.67. HRMS (EI) calcd for C₁₃H₁₉O₂N₃ 249.1477, found 249.1476.

4.15. 1,3-Diethoxyadamantane (20)

The reaction was carried out as described above using **7**^{7,8} (88 mg, 0.5 mmol), Me₃SiOEt (173 mg, 1.5 mmol), and Al(OTf)₃ (237 mg, 0.5 mmol) in CH₂Cl₂ (8 mL) at 30 °C for 8 h. Purification by column chromatography (silica gel, hexane/ether=3:1) gave **20** (92 mg) in 82% yield; clear oil. IR (neat): 2927, 1079 cm⁻¹. ¹H NMR δ 3.47 (4H, q, *J*=7.0 Hz), 2.30 (2H, br s), 1.78 (2H, s), 1.71–1.65 (8H, m), 1.17 (6H, t, *J*=7.0 Hz). ¹³C NMR δ 74.16 (2C), 55.48 (2C), 45.45, 40.69 (4C), 35.45, 30.76 (2C), 16.27 (2C). HRMS (EI) calcd for C₁₄H₂₄O₂ 224.1776, found 224.1770.

4.16. Methyl 3-(1*R*)-menthoxy-5-methyladamantane-1-carboxylate (21)

The reaction was carried out as described above using **3**⁸ (113 mg, 0.5 mmol), (1*R*)-MenOSiMe₃ (148 mg, 0.65 mmol), and Al(OTf)₃ (119 mg, 0.25 mmol) in CH₂Cl₂ (10 mL) at room temperature for 24 h. Purification by column chromatography (silica gel, hexane/AcOEt=10:1) gave **21** (174 mg) in 96% yield; clear oil. IR (neat): 2949, 1730, 1455 cm⁻¹. ¹H NMR δ 3.66 (3H, s), 3.37–3.31 (1H, dt, *J*=4.3, 10.4 Hz), 2.28–2.21 (2H, m), 1.93–1.35 (16H, m), 1.13–0.80 (13H, m), 0.72 (3H, d, *J*=6.9 Hz). ¹³C NMR δ 177.09, 73.34, 70.10, 51.74, 49.33 (0.5), 49.30 (0.5), 49.06, 45.72, 44.75 (0.5), 44.72 (0.5), 44.38 (0.5), 44.35 (0.5), 43.66 (0.5), 43.63 (0.5), 42.39, 41.57 (0.5), 41.50 (0.5), 37.29 (0.5), 37.24 (0.5), 34.48, 33.18 (0.5), 33.15 (0.5), 31.77, 30.36, 30.06, 24.66, 23.17, 22.43, 21.61, 16.14.²⁹ HRMS (EI) calcd for C₂₃H₃₈O₃ 362.28210, found 362.28225.

4.17. Methyl 3-fluoro-5,7-dimethyladamantane-1-carboxylate (22)

Electrochemical fluorination was performed as reported before.⁷ A Et₃N-5HF solution (12 mL) of **6** (223 mg, 1 mmol) was introduced into an undivided cell made of Teflon PFA. The electrolysis was carried out at room temperature using two smooth Pt sheets (20 mm×20 mm) for the anode and cathode at 2.55 V (vs Ag/Ag⁺) until 3.0 F/mol of electricity had passed. Then, the reaction mixture was poured into water and extracted with CH₂Cl₂ (20 mL×3). The combined organic layers was washed with aqueous NaHCO₃ and dried over MgSO₄. Purification by column chromatography (silica gel, hexane/AcOEt=10:1) gave **22** (187 mg) in 78% yield; clear oil. IR (neat): 2951, 1732, 1269 cm⁻¹. ¹H NMR δ 3.68 (3H, s), 1.91 (2H, d, *J*=5.3 Hz), 1.60–1.38 (8H, m), 1.16–1.12 (2H, m), 0.96 (6H, s). ¹⁹F NMR δ –137.62 (s, 1F). ¹³C NMR δ 176.16 (d, *J*=2.4 Hz), 93.49 (d, *J*=184.0 Hz), 51.90, 49.32 (d, *J*=1.9 Hz), 47.76 (2C, d, *J*=16.8 Hz), 45.48 (d, *J*=10.8 Hz), 43.90 (2C), 42.38 (d, *J*=20.1 Hz), 34.63 (2C, d, *J*=11.1 Hz), 29.18 (2C). HRMS (EI) calcd for C₁₄H₂₁O₂F 240.1526, found 240.1526.

4.18. 3-Fluoro-5,7-dimethyladamantane-1-carboxylic acid (23)

A mixture of **22** (390 mg, 1.6 mmol), 1 M aqueous NaOH (3.2 mL), MeOH (1.2 mL), and THF (0.8 mL) was stirred at room temperature for 15 h. The mixture was extracted with CH₂Cl₂ (20 mL) and organic layer was washed with 1 M aqueous NaOH (10 mL). The combined aqueous layer was acidified with 1 M HCl and extracted with CH₂Cl₂ (20 mL×3). The combined organic layer was dried over MgSO₄ and concentrated under reduced pressure to give **23** (268 mg) in 74% yield; white solid: mp 118–120 °C. IR (KBr): 3403, 2926, 1697 cm⁻¹. ¹H NMR δ 11.50 (1H, s), 1.93 (2H, d, *J*=5.5 Hz), 1.58–1.43 (8H, m), 1.21–1.13 (2H, m), 0.97 (6H, s). ¹⁹F NMR δ –137.89 (s, 1F). ¹³C NMR δ 182.28 (d, *J*=2.2 Hz), 93.36 (d, *J*=184.0 Hz), 49.26 (d, *J*=1.9 Hz), 47.70 (2C, d, *J*=16.8 Hz), 45.33 (d, *J*=11.0 Hz), 43.60 (2C, d, *J*=1.9 Hz), 42.05 (d, *J*=20.6 Hz), 34.63 (2C, d, *J*=10.1 Hz), 29.16 (2C, d, *J*=1.4 Hz). HRMS (EI) calcd for C₁₃H₁₉O₂F 226.13691, found 226.13676.

4.19. 1-(Benzyloxycarbonylamino)-3-fluoro-5,7-dimethyladamantane (24)

A mixture of **23** (280 mg, 1.2 mmol), Et₃N (170 mg, 1.7 mmol), diphenylphosphoryl azide (413 mg, 1.5 mmol) in benzene (10 mL) was stirred under reflux for 45 min. After cooling to room temperature, benzyl alcohol (260 mg, 2.4 mmol) was added and the mixture was stirred under reflux for 3 days. After cooling to room temperature, a volatile part was removed under reduced pressure. Purification by column chromatography (silica gel, hexane/AcOEt=4:1) gave

24 (350 mg) in 88% yield; clear oil. IR (neat): 3328, 2950, 2137, 1714, 1523, 1215 cm^{-1} . ^1H NMR δ 7.39–7.32 (5H, m), 5.04 (2H, s), 4.72 (1H, br s), 2.00 (2H, d, $J=5.6$ Hz), 1.64–1.52 (8H, m), 1.13 (2H, s), 0.96 (s, 6H). ^{19}F NMR δ –138.16 (s, 1F). ^{13}C NMR δ 154.26, 136.46, 128.52 (3C), 128.10 (2C), 93.36 (d, $J=184.4$ Hz), 66.14, 54.40 (d, $J=12.9$ Hz), 49.20 (d, $J=1.9$ Hz), 47.62 (2C, d, $J=16.8$ Hz), 46.53 (2C), 45.23 (d, $J=19.0$ Hz), 34.61 (2C, d, $J=10.3$ Hz), 28.86 (2C, d, $J=1.4$ Hz). HRMS (EI) calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_2\text{F}$ 331.19475, found 331.19439.

4.20. 3-Fluoro-5,7-dimethyl-1-adamantylammonium acetate (**25**)

A hydrogenolysis operation was performed in an autoclave. A mixture of acetic acid (2 mL), 10% Pd–C (0.2 g), and **24** (166 mg, 0.5 mmol) was stirred at room temperature under H_2 atmosphere (4 atm) for 24 h. The catalyst was removed by filtration and washed with ether. The filtrate was concentrated under reduced pressure to give a solid material. Recrystallization from hexane/ CH_2Cl_2 gave a pure **25** (106 mg) in 88% yield; a white solid: mp 132–133 °C. IR (KBr): 3430, 2951, 1559 cm^{-1} . ^1H NMR δ 6.15 (3H, br s), 2.01 (3H, s), 1.82 (2H, d, $J=5.3$ Hz), 1.59–1.35 (8H, m), 1.26–1.17 (2H, m), 0.98 (6H, s). ^{19}F NMR δ –138.98 (s, 1F). ^{13}C NMR δ 178.23, 92.78 (d, $J=185.9$ Hz), 53.56 (d, $J=12.0$ Hz), 48.81, 47.24 (2C, d, $J=17.0$ Hz), 46.36 (2C), 45.22 (d, $J=20.1$ Hz), 34.74 (2C, d, $J=10.3$ Hz), 28.69 (2C), 24.92. HRMS (EI) calcd for $\text{C}_{12}\text{H}_{20}\text{NF}$ (free amine) 197.1580, found 197.1582.

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