Tetrahedron 65 (2009) 3682–3687

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of functionalized adamantanes from fluoroadamantanes

Motoshi Aoyama, Shoji Hara *

Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

ARTICLE INFO

Article history:
Received 3 February 2009
Received in revised form 24 February 2009
Accepted 24 February 2009
Available online 3 March 2009

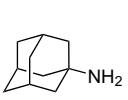
Keywords:
Fluoroadamantane
Functionalization
Substitution
Fluoromemantine

ABSTRACT

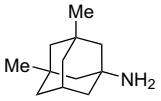
Selective introduction of functional groups on the *tert*-carbon of adamantane was performed by substitution with fluorides. A methyl, phenacyl, aryl, cyclohexyl, alkoxy, or azido group was introduced into the adamantane skeleton without influencing the other functional groups present. Various functionalized 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**.

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 method[7] or by reaction with IF_5.[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.



amantadine



memantine

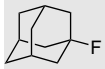
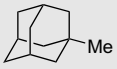
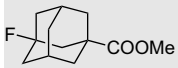
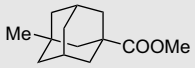
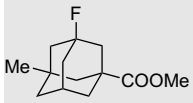
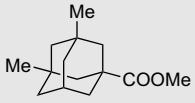
2. Results and discussion

We used Me_3Al for the methylation of 1-fluoroadamantane (**1**)[7,8] analogous to the method for the methylation of *tert*-alkyl fluorides by Me_3Al 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 Me_3Al 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 Me_3Al 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 Me_3Al.[10] Attempts to use other alkylaluminium reagents, such as Et_3Al or *i*-Bu_3Al, 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]

* Corresponding author. Tel./fax: +81 11 706 6556.
E-mail address: shara@eng.hokudai.ac.jp (S. Hara).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.02.059

Table 1
Methylation of fluoroadamantanes with Me_3Al[a]

Substrate	Product	Yield[b] (%)
 **1**	 **4**	94
 **2**	 **5**	98
 **3**	 **6**	92

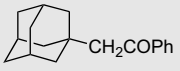
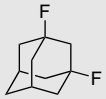
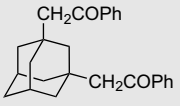
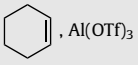
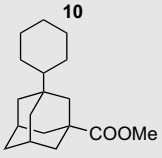
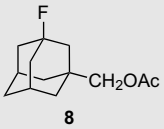
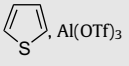
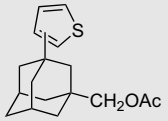
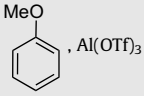
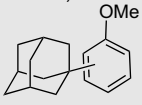
[a] 1.1 equiv of Me_3Al to substrate was used.
[b] Isolated yield based on substrate.

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 Me_3Al-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). BF_3 etherate or $Al(OTf)_3$,[12] used as Lewis acid, is effective for this reaction, and $AlCl_3$ or $TiCl_4$ 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**[16] gave isomeric mixtures of thienyladamantanes (**12**) or (methoxyphenyl)adamantanes (**13**), respectively[17] (entries 4 and 5).

An ethoxy group[18] or an azido group[22] can be introduced into the adamantane **1** by reaction with ethoxytrimethylsilane or azidotrimethylsilane 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).

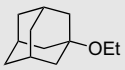
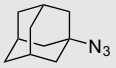
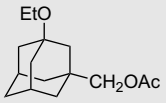
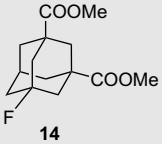
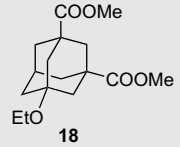
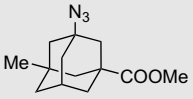
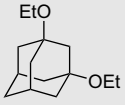
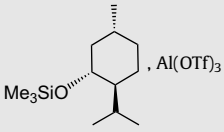
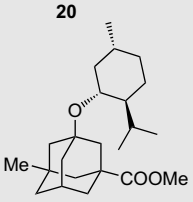
Introduction of a fluorine atom into bioactive compounds can enhance or modify their activity, and therefore the fluorinated analogs of bioactive compounds have attracted much attention.[23] Memantine, 1-amino-3,5-dimethyladamantane, is used to treat Parkinson disease and Alzheimer disease, and therefore 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	**1**		rt, 4 h	 **9**	97
2	 **7**		40 °C, 15 h	 **10**	60
3	**2**		83 °C, 20 h	 **11**	91[b]
4	 **8**		40 °C, 15 h	 (2-:3- = 7:3) **12**	75
5	**1**		rt, 12 h	 (*o*-: *p*-: 2:3) **13**	94

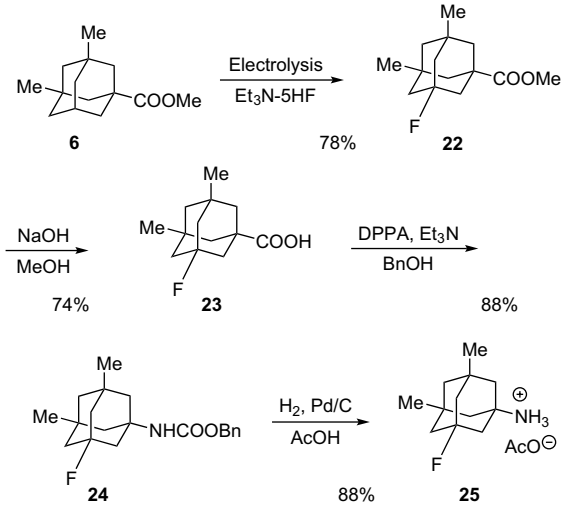
[a] Isolation yield based on substrate used.
[b] Product was isolated after hydrogenation.

Table 3
Alkoxylation and azidation of adamantanes

Entry	Substrate	Reagent	Reaction conditions	Product	Yield[a] (%)
1	**1**	$EtOSiMe_3$, $BF_3 \cdot Et_2O$	rt, 24 h	 **15**	97
2	**1**	N_3SiMe_3, $BF_3 \cdot Et_2O$	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_3SiMe_3, $Al(OTf)_3$	rt, 24 h	 **19**	95
6	**7**	$EtOSiMe_3$, $Al(OTf)_3$	30 °C, 8 h	 **20**	82
7	**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), ^{19}F NMR (376 MHz), and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, were referred to TMS (^1H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI low- and high-resolution mass spectra were

measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. Me_3Al in hexane and Et_3N-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 CH_2Cl_2 solution (8 mL) of 1-fluoroadamantane **1**[7,8] (77 mg, 0.5 mmol) was added at room temperature under N_2 atmosphere, a 1.4 M hexane solution of Me_3Al (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 CH_2Cl_2 (20 mL×3). The combined organic layer was dried over $MgSO_4$ 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). ^{13}C 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). ^{13}C 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 $C_{13}H_{20}O_2$ 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). ^{13}C 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 $C_{14}H_{22}O_2$ 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 BF_3 etherate (10 mg, 0.07 mmol) in CH_2Cl_2 (8 mL) was stirred at room temperature for 4 h. Then, the mixture was poured to water (30 mL) and extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was dried over $MgSO_4$ 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). ^{13}C 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 CH_2Cl_2 (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). ^{13}C 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 $C_{26}H_{28}O_2$ 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 CH_2Cl_2 (20 mL×3). The combined organic layer was dried over $MgSO_4$ 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). ^{13}C 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 $C_{18}H_{28}O_2$ 276.2089, found 276.2095.

4.8. 1-Acetoxymethyl-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 N_2 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). ^{13}C 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 $C_{17}H_{22}O_2S$ 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 N_2 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). ^{13}C 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). ^{13}C 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), Me_3SiOEt (118 mg, 1.0 mmol), and BF_3 etherate (10 mg, 0.07 mmol) in CH_2Cl_2 (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). ^{13}C 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), Me_3SiN_3 (115 mg, 1.0 mmol), and BF_3 etherate (10 mg, 0.07 mmol) in CH_2Cl_2 (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 (N_3), 1253 cm^{-1}. ^1H NMR δ 2.15 (3H, br s), 1.81 (6H, s), 1.71–1.62 (6H, m). ^{13}C NMR δ 59.00, 41.49 (3C), 35.88 (3C), 29.77 (3C).

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

The reaction was carried out as described above using **8**[7,8] (113 mg, 0.5 mmol), Me_3SiOEt (118 mg, 1 mmol), and $Al(OTf)_3$ (119 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2 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). ^{13}C 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 $C_{15}H_{24}O_3$ 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), Me_3SiOEt (118 mg, 1 mmol), and $Al(OTf)_3$ (119 mg, 0.25 mmol) in CH_2Cl_2 (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). ^{13}C 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 $C_{16}H_{24}O_5$ 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), Me_3SiN_3 (104 mg, 0.9 mmol), and $Al(OTf)_3$ (95 mg, 0.2 mmol) in CH_2Cl_2 (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 (N_3), 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). ^{13}C 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 $C_{13}H_{19}O_2N_3$ 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), Me_3SiOEt (173 mg, 1.5 mmol), and $Al(OTf)_3$ (237 mg, 0.5 mmol) in CH_2Cl_2 (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). ^{13}C 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 $C_{14}H_{24}O_2$ 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*)-MenOSiMe$_3$ (148 mg, 0.65 mmol), and $Al(OTf)_3$ (119 mg, 0.25 mmol) in CH_2Cl_2 (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). ^{13}C 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 $C_{23}H_{38}O_3$ 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 Et_3N-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 CH_2Cl_2 (20 mL×3). The combined organic layers was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. 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). ^{19}F NMR δ −137.62 (s, 1F). ^{13}C 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 $C_{14}H_{21}O_2F$ 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 CH_2Cl_2 (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 CH_2Cl_2 (20 mL×3). The combined organic layer was dried over $MgSO_4$ 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). ^{19}F NMR δ −137.89 (s, 1F). ^{13}C 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 $C_{13}H_{19}O_2F$ 226.13691, found 226.13676.

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

A mixture of **23** (280 mg, 1.2 mmol), Et_3N (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 $C_{20}H_{26}NO_2F$ 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 $C_{12}H_{20}NF$ (free amine) 197.1580, found 197.1582.

References and notes

1. (a) Wishnok, J. S. *J. Chem. Educ.* **1973**, *50*, 780; (b) Spasov, A. A.; Khamidova, T. V.; Bugaeva, L. I.; Morozov, I. S. *Pharm. Chem. J.* **2000**, *34*, 1; (c) Sonkusare, S. K.; Kaul, C. L.; Ramarao, K. P. *Pharmacol. Res.* **2005**, *51*, 1.
2. (a) Ohfuji, T.; Ogawa, T.; Kuhara, K.; Sasago, M. *J. Vac. Sci. Technol., B* **1996**, *14*, 4203; (b) Su, X.; Jing, X. *J. Appl. Polym. Sci.* **2007**, *106*, 737 and the references are cited therein.
3. (a) Olah, G. A.; Gupta, B. G. B. *J. Org. Chem.* **1980**, *45*, 3532; (b) Olah, G. A.; Wang, Q. *Synthesis* **1992**, 1090; (c) Krasutsky, A. P.; Kuehl, C. J.; Zhdankin, V. V. *Synlett* **1995**, 1081; (d) Olah, G. A.; Ramaiah, P.; Rao, C. B.; Sandford, G.; Golam, R.; Trivedi, N. J.; Olah, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 7246; (e) Sorochinsky, A. E.; Petrenko, A. A.; Soloshonok, V. A.; Resnati, G. *Tetrahedron* **1997**, *53*, 5995; (f) Oshita, M.; Chatani, N. *Org. Lett.* **2004**, *6*, 4323; (g) Wanka, L.; Cabrele, C.; Vanejews, M.; Schreiner, P. R. *Eur. J. Org. Chem.* **2007**, 1474.
4. (a) Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285; (b) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Gunchenko, P. A.; Kolomitsin, I. V.; Wittkopp, A.; Feder, G.; Fokin, A. A. *Chem.—Eur. J.* **2001**, *7*, 4997.
5. Sasaki, T.; Nakanishi, A.; Ohno, M. *Chem. Pharm. Bull.* **1982**, *30*, 2051.
6. Bräse, S.; Waegell, B.; Meijere, A. *Synthesis* **1998**, 148.
7. Aoyama, M.; Fukuhara, T.; Hara, S. *J. Org. Chem.* **2008**, *73*, 4186.
8. Hara, S.; Aoyama, M. *Synthesis* **2008**, 2510.
9. (a) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679; (b) Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555; (c) Begum, S. A.; Terao, J.; Kambe, N. *Chem. Lett.* **2007**, 196; (d) Terao, J.; Begum, S. A.; Shinohara, Y.; Tomita, M.; Naitoh, Y.; Kambe, N. *Chem. Commun.* **2007**, 855; (e) Terao, J.; Todo, H.; Watabe, H.; Ikumi, A.; Shinohara, Y.; Kambe, N. *Pure Appl. Chem.* **2008**, *80*, 941.
10. Methylation at *tert*-carbon of the adamantane was previously performed by the reaction of MeMgX with Cl-, Br-, or I-adamantane at higher temperature (40–85 °C).[11] But methylation of the adamantanes having functional group was not reported.
11. (a) Osawa, E.; Majerski, Z.; Schleyer, P. R. *J. Org. Chem.* **1971**, *36*, 205; (b) Molle, G.; Dubois, J. E.; Bauer, P. *Can. J. Chem.* **1987**, *65*, 2428; (c) Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 729; (d) Kira, M.; Akiyama, M.; Ichinose, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 8256.
12. Olah, G. A.; Farooq, O.; Morteza, S.; Farnia, F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560.
13. Compound **5** was previously prepared by photochemical reaction of acetophenone enolate with 1-iodoadamantane in moderate yield.[14] However, application of that method for the synthesis of **10** was unsuccessful.[15]
14. Borosky, G. L.; Pierini, A. B.; Rossi, R. A. *J. Org. Chem.* **1990**, *55*, 3705.
15. Lee, G. S.; Bashara, J. N.; Sabih, G.; Oganesyan, A.; Godjoian, G.; Duong, H. M.; Marinez, E. R.; Gutiérrez, C. G. *Org. Lett.* **2004**, *6*, 1705.
16. Friedel–Crafts adamantylation of aromatic compounds using 1-fluoroadamantane was previously studied by Olah et al., see: Olah, G. A.; Farooq, O.; Morteza, S.; Farnia, F.; Wu, A. *J. Org. Chem.* **1990**, *55*, 1516.
17. As for the Friedel–Crafts adamantylation of arenes using bromo- or chloroadamantanes, see: (a) Perkins, R.; Bennett, S.; Bowering, E.; Burke, J.; Reid, K.; Wall, D. *Chem. Ind.* **1980**, 790; (b) Handa, I.; Bauer, L. *J. Chem. Eng. Data* **1984**, *29*, 223; (c) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2053.
18. 1-Alkoxyadamantanes were previously prepared by oxidation–solvation of 1-iodoadamantane,[19] solvolysis of 1-adamantanyl chloroformate,[20] or photo-induced substitution reaction of haloadamantane.[21] However, those methods are not practical for the synthesis of alkoxyadamantanes because significant amount of by-products was formed[19,20] or chemical yields of the products were not shown.[21]
19. Davidson, R. I.; Kropp, P. J. *J. Org. Chem.* **1982**, *47*, 1904.
20. Moss, R. A.; Tian, J.; Sauers, R. R. *Org. Lett.* **2004**, *6*, 4293.
21. Miller, J. B.; Salvador, J. R. *J. Org. Chem.* **2002**, *67*, 435.
22. (a) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192; (b) Papeo, G.; Posteri, H.; Vianello, P.; Varasi, M. *Synthesis* **2004**, 2886; (c) Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi, N. *Tetrahedron Lett.* **2004**, *45*, 3291; (d) Rad, M. N. S.; Behrouz, S.; Khalafi-Nezhad, A. *Tetrahedron Lett.* **2007**, *48*, 3445.
23. (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, NY, 1991; (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.
24. Fluorinated analogs of amantadine were previously prepared, see: Jasys, V. J.; Lombardo, F.; Appleton, T. A.; Bordner, J.; Ziliox, M.; Volkmann, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 466.
25. Lewis, F. D.; Johnson, R. W.; Kory, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 6100.
26. Ng, S. *Aust. J. Chem.* **1973**, *26*, 2303.
27. Meyer, W. P.; Martin, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 1231.
28. Nyfeler, E.; Renaud, P. *Org. Lett.* **2008**, *10*, 985.
29. As four *tert*-carbons of the adamantane skeleton were substituted by different atoms, the compounds **3** is optically active (racemic)**24** and compounds **21** is a mixture of two diastereomers.[30] Therefore, in ^{13}C NMR of **21**, the signals of two diastereomers appeared separately.
30. (a) Applequist, J.; Rivers, P.; Applequist, D. E. *J. Am. Chem. Soc.* **1969**, *91*, 5705; (b) Schreiner, P. R.; Fokin, A. A.; Lauenstein, O.; Okamoto, Y.; Wakita, T.; Rinderspacher, C.; Robinson, G. H.; Vohs, J. K.; Campana, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 13348.