Synthesis of Optically Active Fluoroadamantane Derivative Having Different Substituents on its *tert*-Carbons and its Use as a Non-racemizable Source for New Optically Active Admantane Derivatives

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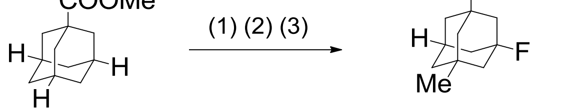
ABSTRACT: Enantiomerically pure methyl 3-fluoro-5-methyladamantane-1-carboxylate was obtained by the separation of its racemate which was prepared from methyl adamantane-1-carboxylate in three steps in 86% overall yield. From the resulting pure enantiomers, a new optically active adamantane compound was prepared by the substitution of a fluorine atom with a phenyl group. Both enantiomers of 3-amino-5-methyladamantane-1-carbooxylic acid were also prepared.

1. Introduction

Adamantane is a simple cage compound comprising six *sec*-carbons and four *tert*-carbons. Substitution of its all *tert*-carbons with different substituents results in derivatives with chirarity. However, there are few studies on the synthesis of optically active adamantanes having different substituent on the *tert*-carbons.[1] Recently, we reported selctive fluorination of the *tert*-carbon of adamantane by IF_5[2] or via an electrochemical method.[3] We also reported the selective introduction of the functional group on the *tert*-carbon of adamantane by the substitution with the fluorine atom.[4] In this study, we synthesized an adamantane derivative having four different substituents on its *tert*-carbons by using our methods, and separated both enantiomers from the resulting racemic adamantane derivative. We also synthesized new optically active adamantane derivatives from the separated enantiomers.

2. Results and discussion

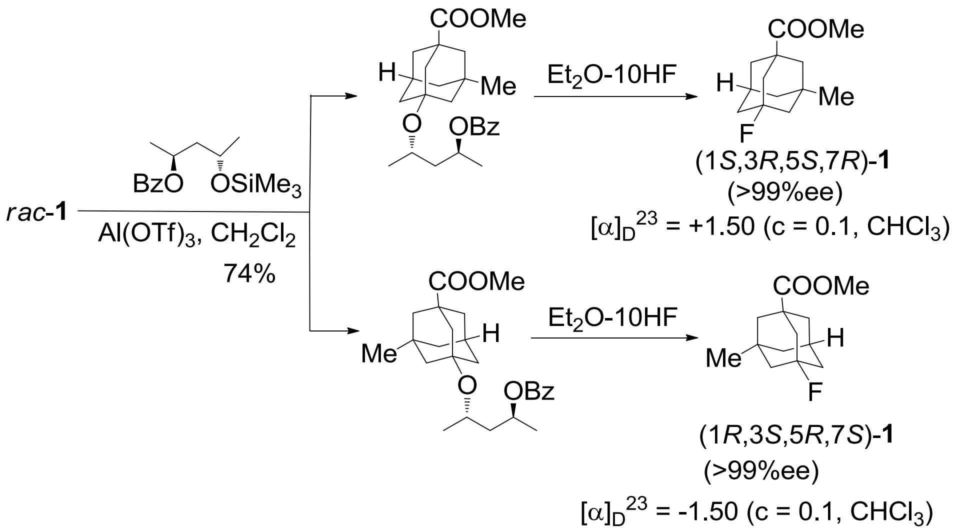
We synthesized *rac*-methyl 3-fluoro-5-methyladamantane-1-carboxylate (**1**) from methyl adamantane-1-carboxylate (**2**) in 86% overall yield as shown in scheme 1.



2 *rac*-**1**

Scheme 1. Synthesis of *rac*-methyl 3-fluoro-5-methyladamantane-1-carboxylate **1**. Reagents and conditions: (1) IF_5, CH_2Cl_2, 40 °C, 12h; (2) Me_3Al, CH_2Cl_2, rt, 30 min; (3) IF_5, CH_2Cl_2, 40 °C 12h, overall yield 86%.

Then, *rac*-**1** was converted to a mixture of diastereomers by attaching a chiral auxiliality to separate them by HLPC using a non-chiral column. We applied many chiral auxialities, and find that when a (2*S*,4*S*)-4-(benzoyloxy)pentan-2-yl)oxy group was introduced to the *tert*-carbon of **1** by the reaction with (2*S*,4*S*)-4-benzolyoxy-2-trimethylsiloxypentane,[4] each diastereomers could be separated by HLPC using a non-chiral column. After the separation, the chiral auxiliality was removed by the treatment with 10HF-Et_2O.[5] Although a cationic species was expected to be formed during the removal of the chiral auxiliality, racemization was not observed under the conditions, and both enantiomers could be obtained with high optical purity (>99%ee)[6] (Scheme 2).



Scheme 2. Separation of both enantiomers of **1**

To determine the absolute stereochemistry, an isomer with negative optical rotation value ((-)-**1**) was converted into the imide of (1*S*)-(-)-10,2-camphorsultam,[7] and from its X-ray crystallography,[8] absolute configuration of (-)-**1** was shown to be (1*R*,3*S*,5*R*,7*S*) (Fig 1).

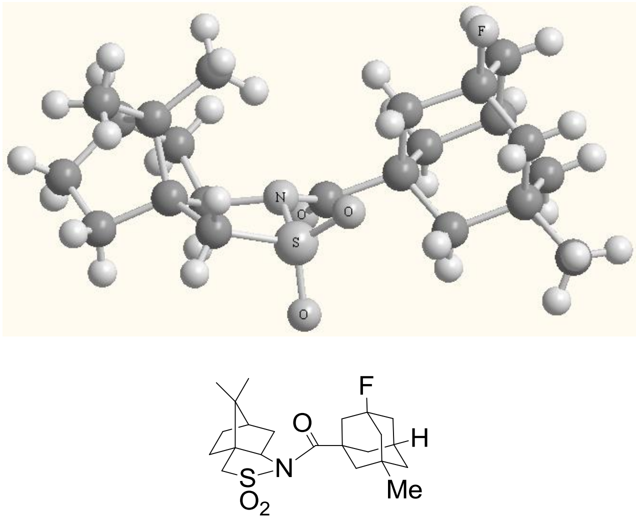


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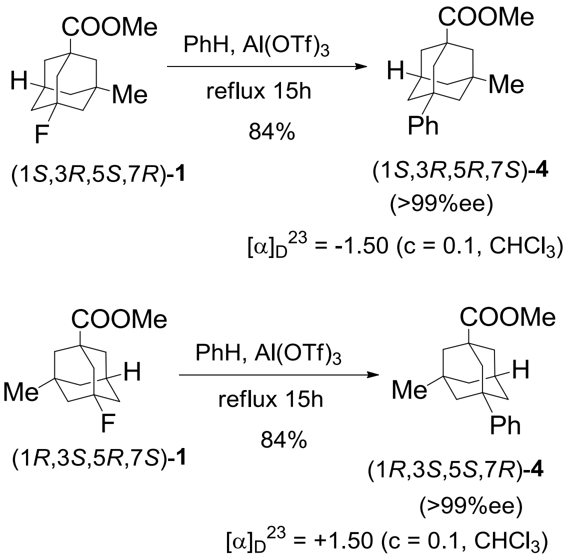
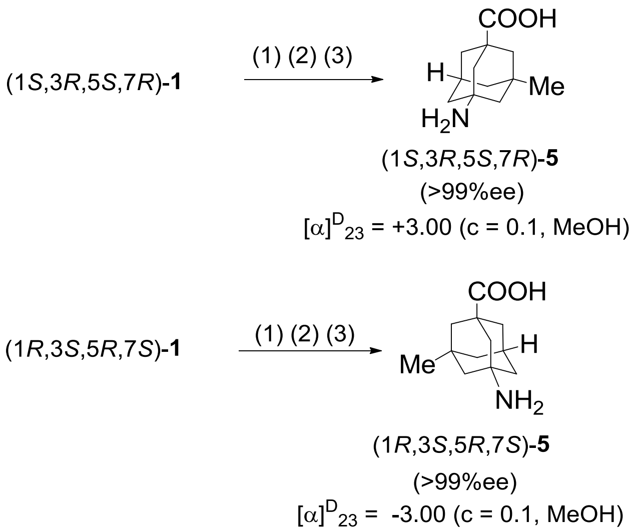
Figure 1. X-ray crystallography of (1*S*)-(-)-10,2-camphorsultam imide **3** prepared from (-)-**1**.

As functional groups can be introduced onto the *tert*-carbons of **1** by substitution with the fluorine atom without racemization,[4] new optically active adamantane derivatives could be prepared from **1**. For instance, a phenyl group was introduced to both enantiomers of **1** by Friedel-Crafts reaction and the both enantiomers of methyl 3-methyl-5-phenyl-1-adamantanecarboxylate **4** were obtained with high optical purities (Scheme 3).



Scheme 3. Introduction of a phenyl group on (1*S*,3*R*,5*S*,7*R*)- and (1*R*,3*S*,5*R*,7*S*)-**1** without racemization

There are several bioactive derivatives of aminoadamantane, among which 3-aminoadamnatane-1-carboxylic acid derivatives are attracting attention as rigid γ-amino butyric acid analogs.[9] Although synthesis of simple aminoadamantanecarboxylic acids have been reported,[9] the optically acitive ones have not yet been synthesized. We synthesized an optically active 3-amino-5-methyladamantane-1-carboxylic acid **5** from **1** by azidation, ester saponification, and reduction of the azido group, and both enantiomers of **5** were obtained in optically pure form (Scheme 4).



Scheme 4. Synthesis of optically active adamantaneamino acid **5**.
Reagents and conditions: (1) Me_3SiN_3, $Al(OTf)_3$;
(2) NaOH, MeOH; (3) H_2, Pd-C overall yield 94%.

3. Conclusion

Both enantiomers of methyl 3-fluoro-5-methyladamantane-1-carboxylate **1** were prepared and applied for the synthesis of new optically active adamantane derivatives. Although the introduction of functional groups into optically pure **1** was performed under acidic or basic conditions, racemization was not observed. Therefore, **1** can be used as a non-racemizable source for various optically active adamantane derivatives.

4. Experimental section

General Methods. The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) spectra, ^{19}F NMR (376 MHz) spectra, and ^{13}C NMR (100 MHz) were recorded on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. HPLC Jasco LC-2000 plus was used for HPLC analysis. Anhydrous HF in cylinder was purchased from Stella Chemifa. $Al(OTf)_3$ and $AlMe_3$ in hexane were purchased from Aldrich and Tokyo Kasei, respectively. (2*S*,4*S*)-4-((Trimethylsilyl)oxy)pentan-2-yl benzoate was prepared from commercial (*S*,*S*)-pentane-2,4-diol by monobenzoylation,[10] followed by trimethylsilation.[10] (-)-10,2-Camphorsultam was prepared from commercial (+)-(1*S*)-camphorsulfonic acid according to a literature.[11] Et_2O-10HF was prepared by the addition of dry ether to anhydrous HF at 0 °C in Teflon bottle acoording to a literature.[5] Caution: Anhydrous HF is an extremely corrosive low-boiling gas (19.5 °C) and, it should be handled in a well-ventilated hood with protective gloves. IF_5 was donated from Asahi Glass Co. Ltd. and used as a mixture with 5 eq of CH_2Cl_2 for easy handling. The reaction using IF_5 or HF was perfoemed in a Teflon ™ FEP centrifuge tube with a tight screw cap. X-ray crystallography was recorded using a Rigaku RAXIS-RAPID.

4. 1. Preparation of *rac*-methyl 3-fluoro-5-methyladamantane-1-carboxylate (*rac*-1).

4.1.1. Fluorination of methyl adamantane-1-carboxylate 2. Fluorination of **2** was carried out as reported before.[2]

4.1.2. Methylation of methyl 3-fluoroadamantane-1-carboxylate with Me_3Al. The crude methyl 3-fluoroadamantane-1-carboxylate obtained above was dissolved in CH_2Cl_2 (20 mL) and 1.4 M hexane solution of Me_3Al (19 mL, 27 mmol) was added at 0 °C. The mixture was stirred at room temperature for 30 min and quenched by the successive addition of MeOH (5 mL) and H_2O (10 mL) at 0 °C. After extraction with CH_2Cl_2 (30 mL X 3), combined organic phase was dried over $MgSO_4$. GC analysis showed the complete consumption of the starting material. The mixture was concentrated under reduced pressure and the resulting crude product of methyl 3-methyladamantane-1-carboxylate was used for the next step without purification.

4.1.3. Fluorination of methyl 3-methyladamantane-1-carboxylate. Fluorination of the crude methyl 3-methyladamantane-1-carboxylate was carried out using IF_5-$5CH_2Cl_2$ (48 g, 75 mmol) and CH_2Cl_2 (20 mL) as described before. Purification by column chromatography (silica gel/hexane:Et_2O = 6:1) gave *rac*-**1** (4.865 g) in 86 % yield from **2**. In a HPLC analysis of *rac*-**1** using CHIRAPAK AD-H column (DAICEL CHEMICAL INDUSTRIES Ltd.) (4.6 mm I.D. x 250 mm) (5 μm) (hexane:EtOH = 99:1, 0.5 mL/min); 20 °C, two peaks of same height appeared at 11.3 min and 13.2 min, respectively. *rac*-**1**: IR (neat) 2949, 1734, 1260, 1228, 1009 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.38-2.35 (m, 1H), 1.96 (brs, 2H), 1.81-1.79 (m, 2H), 1.72 (brs, 2H), 1.61 (d, *J* = 5.7 Hz, 2H), 1.56 (brs, 2H), 1.38 (brs, 2H), 0.95 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –135.38 (s, 1F). ^{13}C NMR (100MHz, $CDCl_3$) δ 176.2 (d, $^4J_{C-F}$ = 2.4 Hz), 92.9 (d, $^1J_{C-F}$ = 184.4 Hz), 51.9, 48.5 (d, $^2J_{C-F}$ = 16.8 Hz), 45.2 (d, $^3J_{C-F}$ = 10.5 Hz), 44.5 (d, $^4J_{C-F}$ = 1.9 Hz), 43.0 (d, $^2J_{C-F}$ = 20.1 Hz), 41.9 (d, $^4J_{C-F}$ = 2.2 Hz), 41.0 (d, $^2J_{C-F}$ = 17.5 Hz), 36.9 (d, $^4J_{C-F}$ = 1.9 Hz), 34.4 (d, $^3J_{C-F}$ = 10.1 Hz), 30.9 (d, $^3J_{C-F}$ = 10.1 Hz), 29.5 (d, $^4J_{C-F}$ = 1.2 Hz). HRMS (EI) calcd for $C_{13}H_{19}FO_2$ 226.1369, found 226.1366

4.2. Isolation of (1*S*,3*R*,5*S*,7*R*)-methyl 3-fluoro-5-methyladamantane-1-carboxylate ((1*S*,3*R*,5*S*,7*R*)-1) and (1*R*,3*S*,5*R*,7*S*)-methyl 3-fluoro-5-methyladamantane-1-carboxylate ((1*R*,3*S*,5*R*,7*S*)-1).

4.2.1. Introduction of a chiral auxiality to *rac*-1. Preparation of methyl 3-(((2*S*, 4*S*)-4-(benzoyloxy)pentan-2-yl)oxy)-5-methyladamantane-1-carboxylate. Under nitrogen atmosphere, a mixture of *rac*-**1** (226 mg, 1 mmol), (2*S*,4*S*)-4-((trimethylsilyl)oxy)pentan-2-yl benzoate (337 mg, 1.2 mmol), and $Al(OTf)_3$ (142 mg, 0.3 mmol) in dry CH_2Cl_2 (10 mL) was stirred under reflux for 12 h. The mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (20 mL X 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane:ether = 2:1) gave methyl 3-(((2S,4S)-4-(benzoyloxy)pentan-2-yl)oxy)-5-methyladamantane-1-carboxylate (307 mg) as a mixture of two diastereomers in 74% yield. IR (neat) 2944, 1715, 1281cm^{-1}. ^{1}H NMR δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.44 (dd, *J* = 7.8, 7.6 Hz, 2H), 5.20-5.16 (m, 1H), 3.95 (brs, 1H), 3.55 (s, 3H), 2.19-2.16 (m, 1H), 1.87-1.24 (m, 14H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.73 (s, 1.5H), 0.69 (s, 1.5H). ^{13}C NMR δ 176.8 (0.5C), 176.7 (0.5C), 166.0, 132.7 (0.5C), 132.9 (0.5C), 130.9 (0.5C), 130.9 (0.5C), 129.4, 129.38, 128.3 (2C), 73.6 (0.5C), 73.6 (0.5C), 62.4 (0.5C), 62.3 (0.5C), 51.6 (0.5C), 51.6 (0.5C), 48.5 (0.5C), 48.1 (0.5C), 45.2 (0.5C), 45.2 (0.5C), 44.6 (0.5C), 44.6 (0.5C), 44.2, 43.2 (0.5C), 43.0 (0.5C), 42.2 (0.5C), 42.1 (0.5C), 41.4, 40.84, 32.9 (0.5C), 32.9 (0.5C), 37.1, 30.2 (0.5C), 30.1 (0.5C), 29.7 (0.5C), 29.6 (0.5C), 24.5 (0.5C), 24.4 (0.5C), 20.5 (0.5C), 20.5 (0.5C). HRMS (EI) calcd for $C_{25}H_{35}O_5$ (M^++H) 415.2484, found 415.2480.

4.2.2. Separation of diastereomers of methyl 3-(((2S,4S)-4-(benzoyloxy)pentan-2-yl)oxy)-5-methyladamantane-1-carboxylate. Separation of the diastereomers prepared above was performed by HPLC using non-chiral column, Mightysil RP-18GP column (Kanto Chemical Co., INC) (20 mm I.D. x 250 mm) (5 μm) (MeOH:H_2O = 8:2, 5.0 mL/min); 20 °C. The peaks of two diasteromers appeared at 50.7 min and 52.6 min, respectively. As a single operation was not enough to obtain pure isomers, the collected fractions were subjected to the second separation and the pure isomers (>99%) were obtained.

4.2.3. Preparation of optically pure 1 by removal of the chiral auxiality. A pure diastereomer separated above (207 mg, 0.5 mmol) and Et_2O-10HF (4 mL) in a Teflon reactor was stirred at room temperature for 24h. Then, the mixture was diluted with water (10 mL) and poured into aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (20 mL X 3) and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane:Et_2O = 2:1) gave optically pure **1** (84 mg) in 74 % yield. HPLC analysis using chiral column showed both enantiomers of **1** were optically pure (>99%ee).

An enantiomer **1** derived from a diastereomer (appeared at 50.7 min in HPLC) showed the positive optical rotation ($[\alpha]^{23}_{D}$ = +1.50 (c = 0.1, $CHCl_3$)). The other enantimer (its precursor appeared at 52.6 min in HPLC) showed the negative optical rotation ($[\alpha]^{23}_{D}$ = -1.50 (c = 0.1, $CHCl_3$)).

4.3. Synthesis of *N*-[(-)-2,10-camphorsulfonyl]-(1*R*,3*S*,5*R*,7*S*)-3-fluoro-5-methyladamantane-1-carboxyamide 3 and its X-ray analysis. Saponification of an ester (-)-**1** was performed by 3M NaOH in a mixture of THF and MeOH (1:1) at room temperature for 9h. Then the mixture was extracted with ether and the separated aqueous layer was acidified with 3M HCl and extracted with ether. The crude acid was obtained by concentration of the ethereal extract and the resulting acid was converted to acid chloride by the reaction with 1.5 eq of oxalyl chloride in CH_2Cl_2 under reflux for 2h. After concentration, the crude acid chloride was used for the next step without further purification. To a suspension of NaH (60% paraffin 61mg, 1.5 mmol) in THF (10 mL) was added (-)-10,2-camphorsultam[11] (236 mg, 1.1 mmol) at 0°C and the mixture was stirred for 30 min. Then, the acid chloride (82 mg, 0.36 mmol) prepared above was added at 0°C, and the mixture was stirred under reflux for 5 h. 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:AcOEt = 3:1) gave **3** (66 mg) in 45% yield based on the acid chloride. Recrystallization from hexane/CH_2Cl_2 gave a white solid: mp 188-189 °C: IR (KBr): 2944, 1686 (C=O), 1323(S=O) cm^{-1}. ^{1}H NMR δ 4.02 (1H, dd, *J* = 7.5 Hz), 3.46 (2H, t, *J* = 14.8 Hz), 2.39 (1H, brs), 2.21-2.17 (1H, m), 2.11-1.98 (3H, m), 1.90-1.84 (5H, m), 1.78-1.71 (4H, m), 1.63-1.57 (2H, m), 1.48-1.26 (4H, m) 1.14 (3H, s), 0.96 (3H, s), 0.95 (3H, s). ^{19}F NMR δ –134.50 (s, 1F). ^{13}C NMR δ

177.3 (d, $^4J_{C\text{-}F}$ =1.9 Hz), 93.7 (d, $^1J_{C\text{-}F}$ =184 Hz), 67.1 53.72, 49.2 (d, $^3J_{C\text{-}F}$ =10.5 Hz), 48.3 (d, $^2J_{C\text{-}F}$ =16.8 Hz), 48.2, 47.8, 44.1, 43.4 (d, $^4J_{C\text{-}F}$ =1.9 Hz), 42.4 (d, $^2J_{C\text{-}F}$ =20.6 Hz), 41.7 (d, $^4J_{C\text{-}F}$ =1.9 Hz), 40.9 (d, $^2J_{C\text{-}F}$ =17.5 Hz), 38.8, 35.8 (d, $^4J_{C\text{-}F}$ =1.9 Hz), 34.5 (d, $^3J_{C\text{-}F}$ =10.1 Hz), 32.6, 31.0 (d, $^3J_{C\text{-}F}$ =10.5 Hz), 29.6 (d, $^4J_{C\text{-}F}$ =1.0 Hz), 26.6, 20.5, 19.9. HRMS(EI) Calcd for $C_{22}H_{33}FO_3S$ (EI) (M^++H) 410.2165, found 410.2159. From X-ray crystallography analysis, the absolute structure of (-)-**1** was found to be (1*R*,3*S*,5*R*,7*S*)-**1**.

4.4. (1*S*,3*R*,5*R*,7*S*)-Methyl 3-methyl-5-phenyladamantane-1-carboxylate ((1*S*,3*R*,5*R*,7*S*)-4).

A mixture of (1*S*,3*R*,5*S*,7*R*)-**1** (226 mg, 1 mmol) and $Al(OTf)_3$ (95 mg, 0.2 mmol) in dry benzene (10 mL) was stirred under reflux for 15 h. The mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL X 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography gave (1*S*,3*R*,5*R*,7*S*)-**4** (245 mg) in 86 % yield. Enantiomeric excess value of the product (>99%ee) was determined by HPLC analysis using CHIRAPAK AD-H column; hexane:EtOH = 99:1, 0.5 mL/min); 20 °C. (1*S*,3*R*,5*R*,7*S*)-**4**; t_R = 10.3min, $[\alpha]^{23}_D$ = -1.50 (c = 0.1, $CHCl_3$), {(1*R*,3*S*,5*S*,7*R*)-**4**; t_R = 9.1 min. $[\alpha]^{23}_D$ = +1.50 (c = 0.1, $CHCl_3$)}. IR (neat) 2900, 1729 (C=O), 1261cm^{-1}. ^{1}H NMR δ 7.38-7.17 (m, 5H), 3.67 (s, 3H), 2.29-2.27 (m, 1H), 2.01-1.93 (m, 2H), 1.83-1.77 (m, 4H), 1.68-1.57 (m, 4H), 1.48 (s, 2H), 0.93 (s, 3H). ^{13}C NMR δ 177.7, 149.6, 128.2 (2C), 125.8, 124.8 (2C), 51.6, 49.2, 44.8, 43.5, 42.6, 42.6, 41.3, 37.4, 37.3, 31.0, 30.5, 29.2. HRMS (EI) calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1767 .

4.5. (1*S*,3*R*,5*S*,7*R*)-3-Amino-5-methyladamantane-1-carboxylic acid ((1*S*,3*R*,5*S*,7*R*)-5).

4.5.1. Azidation of (1*S*,3*R*,5*S*,7*R*)-**1.** A mixture of (1*S*,3*R*,5*S*,7*R*)-**1** (226 mg, 1 mmol), $TMSN_3$ (230 mg, 2 mmol), and $Al(OTf)_3$ (190 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) was stirred under reflux for 12 h. The mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL X 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a colorless liquid. The crude product was used for the next step without further purification.

4.5.2. Saponification of methyl 3-azido-5-methyladamantane-1-carboxylate. The crude methyl 3-azido-5-methyladamantane-1-carboxylate obtained above was dissolved in a mixture of MeOH (4 mL), THF (4 mL), and 3M aq NaOH (2 mL) and the mixture was stirred at room temperature for 4 h. The mixture was poured into a mixture of 3M aq NaOH (20 mL) and CH_2Cl_2 (20 mL). The separated aqueous layer was acidified by 1M HCl to pH 1 and extracted with CH_2Cl_2 (20 mL X 3). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a white solid which was used for the next step without further purification.

4.5.3. Reduction of the azido group of 3-azido-5-methyladamantane-1-carboxylic acid. The crude 3-azido-5-methyladamantane-1-carboxylic acid obtained above, 5 % Pd-C (30 mg), and MeOH (10 mL) were introduced into a reaction vessel equipped with a balloon filled with H_2 gas. The atmosphere of the reaction vessel was replaced with H_2 completely and the reaction mixture was stirred at room temperature for 2 h. The catalyst was removed by filtration through a celite and the celite was washed with ether (20 mL X 2). The combined filtrate was concentrated under reduced pressure to give pure **5** (197 mg) in 94 % yield from **1**. **5**; White solid. mp 279-281 °C; IR (KBr) 3380, 2922, 1625, 1543, 1385 cm^{-1}. ^1H NMR (CD_3OH) δ 3.30-3.28 (m, 3H), 2.27-2.25 (m, 1H), 1.87-1.36 (m, 12H), 0.92 (s, 3H). ^{13}C NMR (CD_3OD) δ 182.4, 53.0, 46.3, 45.0, 44.3, 42.0, 41.5, 38.9, 37.3, 31.9, 29.7, 28.8. HRMS (ESI) calcd for $C_{12}H_{19}NO_2$ 209.1415, found 209.1416. (1*S*,3*R*,5*S*,7*R*)-**5** $[\alpha]^{23}_D$ = +3.0 (c = 0.1, MeOH) { (1*R*,3*S*,5*R*,7*S*)-**5** $[\alpha]^{23}_D$ = -3.0 (c = 0.1, MeOH)}. After protection of amino group with Cbz,[10] enantiomeric purity was determined by HPLC analysis using CHIRAPAK AD-H column; hexane:EtOH = 90:10, 0.8 mL/min); 20 °C. A Cbz derivative of (1*S*,3*R*,5*S*,7*R*)-**5**; t_R = 29.2min (>99%ee) {A Cbz derivative of (1*R*,3*S*,5*R*,7*S*)-**5**; t_R = 31.7min (>99%ee) }.

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Supplementary data

X-ray crystallography data of compound **3**.

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