Highly enantioselective trifluoropyruvate-ene reactions with steroidal side chains catalyzed by dicationic palladium Lewis acid complex for late-stage fluoromethyl-functionalization: Remarkable high agonist and antagonist activities of the ene products even in low VDR binding affinity

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Chiral Pd-catalyzed trifluoropyruvate-ene reactions with steroidal side chains for late-stage fluoromethyl-functionalization: Remarkably high agonist activities of ene products even in low VDR binding affinity^{†,§}

[†]Dedicated to Professor Jiro Tsuji in the honor of his Tetrahedron Prize

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ABSTRACT

The highly enantioselective trifluoropyruvate-ene reactions of chiral steroid side chain olefins were achieved by dicationic palladium complexes as chiral Lewis acid catalysts to give steroidal ene-products in high diastereoselectivity. The ene products exhibited remarkably high agonist activities for human osteocalcin even in low **vitamin D receptor** binding affinity for human vitamin D hormone receptor.

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1. Introduction

In modern organic synthesis, palladium complexes have been widely employed as effective catalysts for carbon-carbon bond formation¹ as highlighted in the Nobel prize in Chemistry 2010 on the “Palladium-Catalyzed Cross-Coupling Reactions” primarily based on their stable oxidation states (Pd(0) and Pd(II)) via 1) Pd(0) to/from Pd(II) redox catalytic cycles, 2) Pd(II) to Pd(II) catalytic cycles, and 3) Pd(II) to/from comparatively unstable Pd(IV) catalytic cycles. The Pd(II) to Pd(II) catalytic cycles are further classified into 2-1) Pd(II) Lewis acid catalysis particularly with coordinatively unsaturated sixteen-electron dicationic Pd(II) complexes in preference to the neutral Pd(II) complexes and 2-2) Pd(II) to Pd(II) catalysis involving simultaneous oxidation process of the Pd(0) intermediary state; We have already reported the first example of asymmetric catalytic intermolecular C-H bond activation/C-C bond formation, namely Fujiwara-Moritani reaction² via simultaneous oxidation with perbenzoic acid³ (Scheme 1)⁴ and the Claisen rearrangement⁵ (Scheme 2)⁶ catalyzed by the chiral neutral Pd(II) catalysts, Pd(II)-OxNTf and Pd(II)-DABNTf catalysts, respectively; In contrast to the generally observed *E* → *syn* diastereoselectivity through the widely accepted six-membered chair-like Claisen transition state, an intriguing *E* → *anti* diastereoselectivity was found via the rarely precedented boat-like transition state (A) along with high enantioselectivity (up to

83% ee) by the carbophilic Lewis acid Pd(II)-DABNTf catalyst (Scheme 2). As chiral cationic Pd(II) catalysts, we have also developed dicationic biphenylphosphine (BIPHEP)- and BINAP-Pd(II) complexes with strongly anionic ligands such as hexafluoroantimonate (SbF₆⁻) as effective chiral Lewis acid catalysts for the carbonyl-ene⁷ and Friedel-Crafts⁸ reactions with 1,2-dicarbonyl chelate substrates such as glyoxylate and trifluoropyruvate.

Scheme 1.

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Scheme 2.

Why are these Pd(II) complexes so effective as Lewis acidic catalysts? Mellor and Maley orders of stability of the first and second transition series of divalent metals with bidentate chelate substrates such as salicylaldehyde, glycine, 8-hydroxyquinoline, and ethylenediamine are⁹ (Values in parenthesis () are Allred-Rochow electronegativity scale. Values in parenthesis [] are tetrahedral or square planar Pauling covalent radii.): Pd (1.35) [1.32] > Cu (1.75) [1.32] > Ni (1.75) [1.39] > Co (1.70) [1.32] > Zn (1.66) [1.31] > Fe (1.64) > Mn (1.60) > Mg (1.23) [1.40]. Pd(II) complexes are therefore the most stable and more Lewis acidic complexes than Cu(II) complexes, with bidentate chelate substrates positioning neighbouring functionalities. Although Lewis acidities of metal complexes are dependent on ligands associated therewith.

Organofluorine compounds have attracted current attention in the fields of pharmaceuticals, agrochemicals, and organic materials by virtue of their unique chemical, biological, and physical properties.¹⁰ In drug design, trifluoromethyl-functionalities are logically employed, because trifluoromethyl groups can render higher stability of C-F bond and neighboring chemical bonds against oxidative metabolism, and can simultaneously increase lipophilicity and polarity in drug candidates.¹¹ Therefore, a variety of synthetic methods to introduce trifluoromethyl-functionalities into organic molecules have been reported to afford the trifluoromethyl-substituted analogues, even in optically active forms. Particularly, α -trifluoromethyl-substituted tertiary alcohols synthesized via the catalytic asymmetric carbon-carbon bond formation have attracted current interest due to the unique biological activities of drug candidates such as **trifluoromethylated** glucocorticoid receptor agonists.¹²

Fluorinated steroids,¹³ vitamin D analogues,¹⁴ in particular have attracted much attention in their synthesis, biochemistry and biological activities. **25-Bis(trifluoromethyl) vitamin D** analogue is now in market as “Hornel”, falecalcitriol, namely 26,26,26,27,27,27-hexafluoro analogue of the active form of 1,25-dihydroxy vitamin D against further oxidative metabolism at 26 and/or 27, **and with increased lipophilicity**.¹⁵ Therefore, synthetic methods to introduce single trifluoromethyl functionality into biologically active metabolites of 1,25-dihydroxy vitamin D in asymmetric manner have been required in order to further examine their biological activities. Trifluoromethyl analogues of active metabolites as tertiary 25-alcohol derivatives, such as 26,23S-lactone and its’ intermediates¹⁶ bearing the quaternary carbon centers¹⁷ can be synthesized via the catalytic asymmetric carbonyl-ene reactions with trifluoropyruvate (“trifluoropyruvate-ene reactions”).^{7d,e} Herein, we report the highly enantioselective trifluoropyruvate-ene reactions as one of the most atom economical¹⁸ and catalytic asymmetric carbon-carbon bond formations, catalyzed by dicationic palladium complexes as the most effective chiral Lewis acid catalysts to provide trifluoromethyl analogues of 26,23S-lactone and synthetic intermediates.

2. Results and discussion

Initially, we evaluated the transition-metal complexes, which can be utilized efficiently as a Lewis acid catalyst, in trifluoropyruvate-ene reaction with isobutene (Table 1).^{19, Sb} Encouraged by the excellent enantioselectivities, we investigated the dicationic Pd complexes **1a-d** (5 mol%) prepared *in situ* from the corresponding dichloride complex and two equivalents of AgSbF₆ (Table 1). As chiral ligands in the dicationic palladium catalysts, (S)-BINAP, (S)-MeO-BIPHEP, (S)-tol-BINAP, and (S)-SEGPPOS exhibited the excellent yields and enantioselectivities (entries 1-4). These reactions proceeded smoothly even under solvent-free conditions to provide the corresponding trifluoropyruvate-ene products **3** within 10 minutes (entries 1-4). When the cationic box-copper catalysts, one of the most efficient Lewis acids,²⁰ were employed, the solvent-free conditions were not appropriate regardless of the counter anions widely screened (entries 5-6). Although the copper catalysis (0.01 mol%) was facilitated in Et₂O and led to the excellent results (99% yield, 99% *ee*), the catalytic activity was extremely lower even in 0.1 mol% catalyst loading (14-24 h) than that of the palladium catalysts (entries 8 vs. 1-4: 10 min, 0.01 mol%). Unfortunately, the iron catalyst decreased both in the catalytic activity and enantioselectivity (entry 9). As a result, we concluded that the Pd catalyst **1a** in entry 1 was the best catalyst in trifluoropyruvate-ene reaction, due to higher performance of catalytic activity and lower-cost of the chiral ligands.¹⁹

Table 1.

entry	cat*	X	conditions	conv (%) ^b	ee (%) ^c
1	1a	0.01	neat, -20 °C, 10 min	94	96
2	1b	0.01	neat, -20 °C, 10 min	98	98
3	1c	0.01	neat, -20 °C, 10 min	96	91
4	1d	0.01	neat, -20 °C, 10 min	90	96
5	1e	0.01	neat, -20 °C, 24 h	74	14
6	1f	0.01	neat, -20 °C, 24 h	69	41
7	1f	0.01	Et ₂ O, -20 °C, 14 h	64	72
8	1f	0.1	Et ₂ O, -20 °C, 14 h	99	99
9	1g	10	CH ₂ Cl ₂ , -20 °C, 20 h	65	12

^aIsolated yield. ^bEnantiopurity was determined by chiral HPLC analysis.

We applied the highly enantioselective trifluoropyruvate-ene reactions catalyzed by the dicationic Pd complexes **1a** to steroidal olefins for *late-stage trifluoromethyl-functionalization* (Scheme 3). The steroidal olefin **4** could be employed for the ene reactions in the catalysis of the Pd complexes, (R)-**1a** and (S)-**1a** to afford (25S)-**5** and (25R)-**5** as single diastereomers in 81% and 76% yields, respectively, although the relatively high catalyst loading (10 mol%) was employed for smooth reactions; **The absolute stereochemistry for vitamin D analogs follows the general rule: (R)- and (S)-1a afford (S)- and (R)-ene products.**

Scheme 3.

Next, we investigated as to whether the direct lactonization of steroidal ene products proceeds or not under the dicationic palladium catalysis (Scheme 4). In view of the sequential ene and lactonization reactions by the dicationic Pd catalysts, the direct lactonization of the ene-product **3** obtained from isobutene was first examined to provide the corresponding lactone **6** in 45% isolated yield (Eq. 1). Furthermore, examination of tandem trifluoropyruvate-ene and lactonization sequence starting from isobutene gave the lactone product **6** in 38% isolated yield (Eq. 2). Unfortunately however, the steroidal ene product (25*S*)-**5** was not able to transform to lactone **7** by (S)-**1a** under various reaction conditions (Eq. 3).

Scheme 4.

Scheme 5.

Therefore, iodolactone (22*S*,23*R*,25*S*)-**9** was synthesized via the hydrolysis of ester (25*S*)-**5** followed by the iodolactonization with I₂ and 2,4,6-colidine.²¹ The trifluoromethyl analogue **9** of natural-type lactone was obtained in 86% yield as virtually single diastereomeric form (>99%) via the favorable six-membered transition state (**B**) with the sterically demanding trifluoromethyl group in equatorial orientation, by decreasing the amount of colidine up to 1.5 equivalent in dichloromethane rather than acetonitrile at -30 °C (Scheme 5). The reduction of (22*S*,23*R*,25*S*)-**9** using *n*Bu₃SnH and AIBN led to the lactone (23*S*,25*S*)-**7** in 89% yield. The desilylation and oxidation of the silyl ether **7** gave ketone (23*S*,25*S*)-**10** in 92% yield, then bromo-olefin (23*S*,25*S*)-**11** was obtained by the Wittig **olefination** reaction with lithium hexamethyldisilazide. Finally, the steroidal C,D-ring with bromo-olefin **11** underwent the Pd-catalyzed Trost A-ring attachment²² with the chiral A-ring portion of enyne to afford the trifluoromethyl analogue **12** of natural-type calcitriol lactone in 56% isolated yield.

Significantly, steroid olefin **13** even with labile B-ring triene portion could be employed for our trifluoropyruvate-ene reaction in the presence of (R)-**1a** under solvent-free conditions, providing the desired product (25*S*)-**14** in 43% isolated yield as a single diastereomer (Scheme 6, Eq. 1). The result clearly indicates that our Pd-catalyzed trifluoropyruvate-ene reaction is efficiently applicable for *late-stage fluoromethyl-functionalization*. As expected, (S)-**1a** under the same reaction conditions gave the opposite single diastereomer (25*R*)-**14** (Eq. 2).

Scheme 6.

The steroidal trifluoropyruvate-ene products along with the further transformed trifluoromethyl analogues of **carcitrilol** lactone were subjected to the biological tests generally executed for vitamin D analogues such as agonist activities for human osteocalcin and VDR (vitamin D receptor) binding affinity for human vitamin D hormone receptor. VDR Binding affinity and agonist (EC_{50} (nM)) activity thus obtained are tabularized in Table 2.²³ Interestingly, the steroidal ene products themselves, namely the unsaturated trifluoromethyl analogues of not only (25S)-methyl ester but also (25R)-methyl ester show significantly high agonist activity (ten times and two hundred ten times active, respectively) even with only half level of binding affinity with VDR (1/1.8 and 1/1.6, respectively). Particularly, the (25R)- $\Delta_{22(23)}$ -methyl ester show remarkable high agonist activity (EC_{50} 0.003 nM) with two order of magnitude than the parent 1,25-dihydroxy vitamin D₃ (EC_{50} 0.638 nM).

Table 2.

	VDR Binding Affinity	agonist EC_{50} (nM) ²⁶
1,25-(OH) ₂ D ₃	1	0.638 - 0.836
(23S,25S)- 12	1 / 29	702
(25S)- 14'	1 / 1.8	0.066
(25R)- 14'	1 / 1.6	0.003

3. Conclusions

In summary, we have succeeded in the highly enantioselective trifluoropyruvate-ene reactions with steroid side chain olefins by virtue of the most stable and Lewis acidic Pd²⁺ catalysts amongst the first and second transition series of divalent metals with bidentate chelate substrates such as trifluoropyruvate. The

remarkably high agonist activities of the ene products than the modified trifluoromethyl analogue of *e.g.* **carcitrilol** lactone. Development of novel and practical reactions to provide optically active α -fluoromethyl-substituted tertiary alcohol drugs and their analogues with quaternary carbon centers in this context of *late-stage fluoromethyl-functionalization* is on-going in our laboratory.

4. Experimental

4.1. General

¹H, ¹³C, and ¹⁹F NMR spectra were measured on Bruker AV300M (300 MHz) spectrometers. Chemical shifts of ¹H NMR were expressed in parts per million relative to the singlet (δ = 7.26) for CDCl₃. Chemical shifts of ¹³C NMR were expressed in parts per million relative to the central line of the triplet (δ = 77.0) for CDCl₃. Chemical shifts of ¹⁹F NMR were expressed in parts per million relative to the singlet (δ = -63.24) for benzotrifluoride (BTF) as an internal standard. Optical rotations were measured on a JASCO P-1020. Mass spectra were measured on a JEOL JMS-T100CS (Accu-TOF) spectrometer. IR spectra were measured on a JASCO FT/IR-4200 spectrometer. High performance liquid chromatography (HPLC) was conducted on JASCO PU-980, LG-980-02, DG-980-50, MD-2010, and CO-966 instrument equipped with model UV-975 spectrometers as an ultra violet light. Dichloromethane, toluene, and diethyl ether were purchased from Kanto Chemical Co., Inc. Ethyl trifluoropyruvate was provided from Central Glass Co., Ltd. Silver hexafluoroantimonate was purchased from Aldrich. PdCl₂[(S)-BINAP] was synthesized according to the reported procedure.

4.2. General Procedure for Catalytic Asymmetric Ene Reaction with Trifluoropyruvate (Table 1, entry 1)

To a solution of PdCl₂[(S)-BINAP] (3.2 mg, 0.004 mmol) and ethyl trifluoropyruvate **2a** (5.3 mL, 40 mmol) was added AgSbF₆ (3.0 mg, 0.0088 mmol) at room temperature under argon atmosphere. After stirring for 30 min, isobutene (ca. 0.2 mmol) was added at -78 °C. The reaction mixture was stirred at -20 °C for 10 min, and then directly loaded onto a short silica-gel column (hexane/AcOEt = 1/1) to remove the catalyst. Purification by silica-gel chromatography (hexane/AcOEt = 9/1) gave alcohol product **3**.²⁴ The enantiomeric excess was determined by chiral HPLC analysis.

4.3.1. 4-Methyl-2-hydroxy-2-trifluoromethylpentano-4-lactone 6

To a solution of PdCl₂[(S)-BINAP] (32 mg, 0.04 mmol) in CH₂Cl₂ (4 mL) was added AgSbF₆ (30.2 mg, 0.088 mmol) at room temperature. After stirring for 30 min, ethyl trifluoropyruvate **2a** (68 mg, 0.4 mmol) and isobutene (112 mg, 2.0 mmol) were added to the mixture at -30 °C. After the reaction mixture was stirred at -15 °C for 4 h, warmed up to 80 °C, and stirred for 24 h to give 38 % of **6** after silica-gel chromatography. ¹H NMR (CDCl₃, 300 MHz) δ 1.54 (s, 3H), 1.59 (s, 3H), 2.38 (d, J = 17.7 Hz, 1H), 2.51 (d, J = 5.0 Hz, 1H), 3.75 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 28.7, 29.2, 42.4, 77.1, 83.6, 122.9 (q, ¹ J_{C-F} = 285.3 Hz), 171.1; ¹⁹F NMR (CDCl₃, 282 MHz) δ -80.5 (s); HRMS (APCI) Calcd for C₇H₈F₃O₃ [M-H]⁻ 197.0426, Found: 197.0427.

4.3.2. (22E,8S,25S)-Des-A,B-8-(*tert*-Butyldimethylsiloxy)-25-hydroxy-27,27,27-trifluoro-26-ethoxycarbonyl-22-cholestene (25S)-5

To a solution of (R)-BINAP-PdCl₂ (8.0 mg, 0.01 mmol) in CH₂Cl₂ (1 mL) was added AgSbF₆ (7.6 mg, 0.022 mmol) at room

temperature. After stirring for 30 min, ethyl trifluoropyruvate **2a** (34 mg, 0.2 mmol) and **4** (33.7 mg, 0.1 mmol) were added to the mixture at -20 °C. After the reaction mixture was stirred at that temperature for 3 h, triethylamine (25 μ L) was added at that temperature. The solution was then quenched with sat. NaHCO₃ and extracted three times with Et₂O. The combined organic layer was washed with brine, dried over MgSO₄ and evaporated under reduced pressure. The resultant residue was purified by silica-gel chromatography (hexane/Et₂O = 20/1, after hexane only) gave 41 mg (81 %) of (25S)-**5**.

¹H NMR (CDCl₃, 300 MHz) δ -0.008 (s, 3H), -0.006 (s, 3H), 0.89 (s, 9H), 0.91 (s, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.04~2.08 (m, 16H), 2.58 (t, J = 7.2 Hz, 2H), 3.75 (s, 1H), 3.99 (d, J = 2.1 Hz, 1H), 4.31 (t, J = 7.2 Hz, 2H), 5.20 (td, J = 7.2, 15.3 Hz, 1H), 5.43 (dd, J = 8.7, 15.3 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ -5.2, -4.9, 13.9, 17.6, 18.0, 20.4, 23.0, 25.8, 27.6, 34.4, 35.0, 39.8, 40.6, 42.1, 53.1, 56.1, 63.5, 69.4, 77.8 (q, ² J_{C-F} = 28.5 Hz), 117.6, 123.4 (q, ¹ J_{C-F} = 284.3 Hz), 143.7, 169.4; ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.4 (s); IR (neat, cm⁻¹) 3505, 2949, 2861, 1741, 1307, 1242, 1186, 1019, 836; HRMS (ESI-TOF) Calcd for C₂₆H₄₅F₃O₄Na₁Si₁ [M+Na]⁺ 529.2937, Found: 529.2932; [α]_D²⁶ +31.8 (c = 0.12 in CHCl₃).

4.3.3. (22E,8S,25S)-Des-A,B-8-(*tert*-Butyldimethylsiloxy)-25-hydroxy-27,27,27-trifluoro-26-cholestenoic acid (25S)-**8**

To a solution of (25S)-**5** (152 mg, 0.3 mmol) in a MeOH/H₂O (7:3) mixture (2.5 ml), 0.5N KOH (1.81 ml, 0.91 mmol) was added. The reaction mixture was stirred at 65 °C for 7 h, and MeOH was removed *in vacuo*. 1N HCl was added until pH 1~2 was reached, and the reaction mixture was extract with EtOAc (3 $\times$ 20 ml), dried over Na₂SO₄, and evaporated under reduced pressure to give 136 mg (95%) of (25R)-**8**.

¹H NMR (CDCl₃, 300 MHz) δ -0.003 (s, 3H), -0.012 (s, 3H), 0.89 (s, 9H), 0.92 (s, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.06~2.10 (m, 15H), 2.64 (m, 2H), 4.00 (s, 1H), 5.24 (td, J = 7.2, 15.3 Hz, 1H), 5.51 (dd, J = 8.7, 15.3 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ -5.2, -4.9, 13.9, 17.6, 18.0, 20.3, 23.0, 25.8, 27.7, 34.4, 35.2, 39.9, 40.6, 42.1, 53.1, 56.0, 69.4, 77.9 (q, ² J_{C-F} = 28.5 Hz), 116.9, 123.1 (q, ¹ J_{C-F} = 284.5 Hz), 144.9, 173.4; ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.1 (s); IR (neat, cm⁻¹) 3412, 2938, 2855, 1727, 1248, 1181. HRMS (APCI) Calcd for C₂₄H₄₁F₃O₄Na₁Si₁ [M+Na]⁺ 501.2624, Found: 501.2615; [α]_D²⁷ +28.6 (c = 0.21 in CHCl₃).

4.3.4. (8S,22S,23S,25S)-Des-A,B-8-(*tert*-Butyldimethylsiloxy)-22-iodo-25-hydroxy-25-trifluoromethylcholestane-26,23-lactone (22S,23R,25S)-**9**

A solution of (25S)-**8** (23.9 mg, 0.05 mmol) and 2,4,6-collidine (9.9 μ L, 0.075 mmol) in Et₂O (3.6 ml) was stirred at room temperature for 30 min, the mixture was cooled to -30 °C, and then I₂ (38.1 mg, 0.15 mmol) was added. After 24 h, the mixture was diluted with CHCl₃, washed with aq. Na₂S₂O₃ and brine, dried over Na₂SO₄, and evaporated under reduced pressure. The resultant residue was purified by silica-gel chromatography to give 26.0 mg (86 %) of (22S,23S,25S)-**9**.

¹H NMR (CDCl₃, 300 MHz) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.94 (d, J = 6.0 Hz, 3H), 1.01 (s, 3H), 1.12~1.95 (m, 14H), 2.28 (dd, J = 9.0, 14.4 Hz, 1H), 3.18 (dd, J = 6.0, 14.4 Hz, 1H), 4.01 (d, J = 2.4 Hz, 1H), 4.10 (dd, J = 1.5, 10.5 Hz, 1H), 4.75 (ddd, J = 6.0, 9.0, 10.5 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ -5.2, -4.9, 1.0, 15.0, 16.1, 17.6, 18.0, 22.8, 25.8, 26.3, 34.3, 36.6, 39.3, 40.7, 42.2, 48.9, 52.9, 56.3, 69.3, 76.2 (q, ² J_{C-F} = 31.8 Hz), 123.0 (q, ¹ J_{C-F} = 283.4 Hz), 170.9; ¹⁹F NMR (CDCl₃, 282 MHz) δ -80.2 (s); IR (neat, cm⁻¹) 3416, 2949, 2855, 1770, 1460, 1212. HRMS (APCI) Calcd for C₂₄H₄₁F₃I₁O₄Si₁ [M+H]⁺ 605.1771, Found: 605.1756; [α]_D²⁷ -0.89 (c = 0.11 in CHCl₃).

4.3.5. (8S,23S,25S)-Des-A,B-8-(*tert*-Butyldimethylsiloxy)-25-hydroxy-25-trifluoromethylcholestane-26,23-lactone (22S,25S)-**7**

To a solution of (22S,23S,25S)-**9** (125 mg, 0.21 mmol) in benzene (7.9 ml) was added *n*-BuSnH (110 μ L, 0.42 mmol) and AIBN (6.9 mg, 0.042 mmol). The reaction mixture was stirred for 3 min at 65 °C, and diluted with Et₂O. The reaction mixture was washed with brine, and dried over MgSO₄ and evaporated under reduced pressure. The resultant residue was purified by silica-gel chromatography to give 100 mg (89%) of (23S,25S)-**7**.

¹H NMR (CDCl₃, 300 MHz) δ -0.002 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.94 (s, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.13~1.89 (m, 14H), 1.97 (td, J = 2.7, 12.3 Hz, 1H), 2.12 (dd, J = 9.3, 14.4 Hz, 1H), 2.86 (dd, J = 6.0, 14.4 Hz, 1H), 3.43 (s, 1H), 4.00 (d, J = 2.4 Hz, 1H), 4.60~4.69 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ -5.2, -4.9, 13.7, 17.6, 18.0, 18.5, 23.0, 25.8(2C), 27.3, 32.5, 34.4, 37.7, 40.7, 42.3, 42.8, 53.1, 69.3, 76.1 (q, ² J_{C-F} = 31.5 Hz), 123.3 (q, ¹ J_{C-F} = 283.4 Hz), 171.5; ¹⁹F NMR (CDCl₃, 282 MHz) δ -80.2 (s); IR (neat, cm⁻¹) 3438, 2943, 2861, 1787, 1466, 1202, 1162, 834; HRMS (APCI) Calcd for C₂₄H₄₀F₃O₄Si₁ [M-H]⁻ 477.2645, Found: 477.2656; [α]_D²⁶ +24.6 (c = 0.18 in CHCl₃).

4.3.6. (8S,23S,25S)-Des-A,B-8,25-Dihydroxy-25-trifluoromethylcholestane-26,23-lactone (23S,25S)-**10'**

To a solution of (23S,25S)-**7** (100 mg, 0.21 mmol) in MeOH (4.2 ml) was added *p*-TsOH (47.0 mg, 0.27 mmol) and the resulting mixture was stirred for 12 h at 65 °C. The reaction mixture was diluted with AcOEt and sat. NaHCO₃ was added. The resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The resultant residue was purified by silica-gel chromatography to give 76.5 mg (92%) of (23S,25S)-**10'**.

¹H NMR (CDCl₃, 300 MHz) δ 0.94 (s, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.05~1.90 (m, 15H), 2.00 (d, J = 12.9 Hz, 1H), 2.11 (dd, J = 9.3, 14.1 Hz, 1H), 2.85 (dd, J = 6.3, 14.1 Hz, 1H), 4.08 (s, 1H), 4.47 (bs, 1H), 4.63 (d, J = 8.1 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 13.5, 17.3, 18.4, 22.4, 27.2, 32.5, 33.4, 37.7, 40.4, 42.0, 42.8, 52.5, 56.8, 69.3, 75.8, 76.0 (q, ² J_{C-F} = 31.5 Hz), 123.3 (q, ¹ J_{C-F} = 283.4 Hz), 171.6; ¹⁹F NMR (CDCl₃, 282 MHz) δ -80.1 (s). IR (neat, cm⁻¹) 3450, 2932, 1782, 1457, 1193; HRMS (APCI) Calcd for C₁₈H₂₆F₃O₄ [M-H]⁻ 363.1783, Found: 367.1776; [α]_D²⁵ +35.5 (c = 0.11 in CHCl₃).

4.3.7. (23S,25S)-Des-A,B-25-Hydroxy-25-trifluoromethylcholestane-8-one-26,23-lactone (23S,25S)-**10**

To a solution of (23S,25S)-**10'** (76.5 mg, 0.21 mmol) in CH₂Cl₂ (4.2 ml) was added tetra-*n*-propylammonium perruthenate (7.4 mg, 0.021 mmol), 4-methylmorpholine *N*-oxide (98.4 mg, 0.84 mmol) and powdered molecular sieves 4A at 0 °C. The mixture was stirred for 2 h at the temperature and loaded on silica-gel chromatography to give 65.4 mg (86 %) of (23S,25S)-**10**.

¹H NMR (CDCl₃, 300 MHz) δ 0.64 (s, 3H), 1.03 (d, J = 6.3 Hz, 3H), 1.24~2.32 (m, 15H), 2.44 (dd, J = 7.5, 11.4 Hz, 1H), 2.86 (dd, J = 6.3, 14.4 Hz, 1H), 4.29 (s, 1H), 4.59~4.67 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 12.5, 18.5, 19.1, 23.9, 27.4, 32.6, 37.7, 38.9, 40.8, 42.7, 49.9, 56.7, 61.8, 75.5, 75.9 (q, ² J_{C-F} = 31.6 Hz), 123.1 (q, ¹ J_{C-F} = 288.8 Hz), 171.2, 212.3; ¹⁹F NMR (CDCl₃, 282 MHz) δ -80.1 (s); IR (neat, cm⁻¹) 3439, 2945, 2850, 1778, 1694, 1406, 1150; HRMS (APCI) Calcd for C₁₈H₂₄F₃O₄ [M-H]⁻ 361.1627, Found: 361.1313; [α]_D²⁶ +11.9 (c = 0.17 in CHCl₃).

4.3.8. (23S,25S)-Des-A,B-8-Bromomethylidene-25-hydroxy-25-trifluoromethylcholestane-26,23-lactone (23S,25S)-**11**

To a solution of bromomethyltriphenylphosphonium bromide (393 mg, 0.9 mmol) in toluene (2.4 ml) was added lithium

hexamethyldisilazane (151 mg, 0.9 mmol) at -78 °C, and the mixture was warmed up to 0 °C and stirred for 10 min. After cooling to -78 °C, to the resulting solution was added (23*S*,25*S*)-**10** (65.4 mg, 0.18 mmol) in toluene (1.2 ml) dropwise, and the mixture was stirred at -30 °C for 2 h. To the reaction mixture was added sat. NH₄Cl. The resulting mixture was warmed up to room temperature and extracted with AcOEt. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The resultant residue was purified by silica-gel chromatography to give 6.8 mg (0.016 mmol, 18%) of (23*S*,25*S*)-**11**.

¹H NMR (CDCl₃, 300 MHz) δ 0.60 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.19~2.05 (m, 15H), 2.13 (ddd, *J* = 1.2, 9.3, 14.4 Hz, 1H), 2.88 (dd, *J* = 6.3, 14.4 Hz, 1H), 4.60~4.69 (m, 1H), 5.66 (s, 1H), 5.95 (s, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ -80.2 (s); IR (neat, cm⁻¹) 3433, 3087, 2938, 2860, 1782, 1718, 1172; HRMS (APCI) Calcd for C₁₉H₂₅BrF₃O₃ [M-H]⁻ 439.0919, Found: 439.0939; [α]_D²⁵ +74.3 (c = 0.11 in CHCl₃).

4.3.9. 25-Trifluoromethyl-1α,25-dihydroxy-26,23-carcitriol lactone (23*S*,25*S*)-**12**

To a solution of A-ring precursor enyne (4.0 mg, 0.01 mmol) and (23*S*,25*S*)-**11** (3.2 mg, 0.0073 mmol) in toluene/NEt₃ (730 μl, toluene/NEt₃ = 1 : 3) were added Pd(PPh₃)₄ (2.5 mg, 0.002 mmol), and the mixture was stirred at 110 °C for 4 h, according to the reported procedure.²⁰ The mixture was filtered through a silica-gel pad, and concentrated. The residue was subjected to silica-gel preparative TLC to give crude mixture of the protected derivative (3.0 mg, 56 %). To the crude mixture dissolved in THF (273 μl), was added HF/Py (70 %, 116 μl) at 0 °C, and stirred for 2 h. To the mixture was added sat. NH₄Cl. The resulting mixture was warmed up to room temperature and extracted with AcOEt, dried over MgSO₄, filtered and concentrated under reduced pressure. The resultant residue was purified by silica-gel chromatography to give 0.7 mg (34 %) of (23*S*,25*S*)-**12**.

¹H NMR (CDCl₃, 300 MHz) δ 0.58 (s, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.23~1.75 + 1.83~2.10 (m, 22H), 2.28~2.35 (m, 1H), 2.60 (dd, *J* = 0.9, 11.1 Hz, 1H), 2.83~2.86 (m, 1H), 4.22~4.24 (m, 1H), 4.43~4.44 (m, 1H), 5.00 (s, 1H), 5.34 (s, 1H), 6.00 (d, *J* = 11.4 Hz, 1H), 6.37 (d, *J* = 11.7 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ -80.2 (s); HRMS (APCI) Calcd for C₂₇H₃₆F₃O₅ [M-H]⁻ 497.2515, Found: 497.2535; [α]_D²⁵ +26.5 (c = 0.04 in CHCl₃).

4.3.10. Steroid olefin **13**

To a solution of methyltriphenylphosphonium bromide (61mg, 0.17 mmol) in THF (0.9 ml) was added *n*-BuLi (0.11 ml of a 1.35 M solution in hexane, 0.15 mmol) at 0 °C. After the mixture was stirred for 1 h, a solution of calcitric aldehyde (29.4 mg, 0.05 mmol) in THF (0.2 ml) was added slowly. The resulting mixture was stirred at 0 °C for 30 min and quenched by sat. NH₄Cl. The mixture was extracted with Et₂O, washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. The resultant residue was purified by silica-gel chromatography to give 25.2 mg (86 %) of **13**.

¹H NMR (CDCl₃, 300 MHz) δ 0.060~0.064 (m, 12 H), 0.54 (s, 3H), 0.85~0.88 (m, 18H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.26~2.27 (m, 17H), 2.46 (dd, *J* = 3.9, 13.2Hz, 1H), 2.82 (d, *J* = 10.5 Hz, 1H), 4.15~4.23 (m, 1H), 4.36~4.39 (m, 1H), 4.86 (d, *J* = 2.4Hz, 1H), 4.97 (s, 1H), 5.01 (d, *J* = 3.3 Hz, 1H), 5.18 (d, *J* = 1.5 Hz, 1H), 5.71~5.85 (m, 1H), 6.02 (d, *J* = 11.4 Hz, 1H), 6.24 (d, *J* = 11.1 Hz, 1H); HRMS (APCI) Calcd for C₃₆H₆₅O₂Si₂ [M+H]⁺ 585.4523, Found: 585.4544.

4.3.11. (25*S*)-Trifluoromethyl-1α,3β-bis(*tert*-butyldimethylsilyloxy)-22-dehydrocarcitril methyl ester (25*S*)-**14**

To a solution of (*R*)-BINAP-PdCl₂ (9.6 mg, 0.012 mmol) in CH₂Cl₂ (1 mL) was added AgSbF₆ (8.2 mg, 0.024 mmol) at room temperature. After stirring for 30 min, the solution was added to a mixture of methyl trifluoropyruvate **2b** (337μl, 3 mmol) and **13** (17.6 mg, 0.03 mmol) at -40 °C for 2.5 h. The solution was quenched by sat. NaHCO₃ and extracted three times with Et₂O. The combined organic layer was washed with brine, dried over MgSO₄ and evaporated under reduced pressure. The resultant residue was purified by silica-gel chromatography to give 5.1 mg (43 %) of (25*S*)-**14**.

¹H NMR (CDCl₃, 300 MHz) δ 0.04~0.06 (m, 12H), 0.53 (s, 3H), 0.87~0.88 (m, 18H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.23~1.33+1.41~2.05 (m, 13H), 2.17~2.27 (m, 2H), 2.45 (dd, *J* = 3.6, 9.9 Hz, 1H), 2.57~2.62 (m, 2H), 2.83 (d, *J* = 10.8Hz, 1H), 3.73 (s, 1H), 3.88 (s, 3H), 4.17~4.22 (m, 1H), 4.36~4.39 (m, 1H), 4.86 (d, *J* = 2.1 Hz, 1H), 5.18 (d, *J* = 1.5Hz, 1H), 5.21~5.28 (m, 1H), 5.46 (dd, *J* = 8.7, 15.3 Hz, 1H), 6.01 (d, *J* = 11.1 Hz, 1H), 6.22 (d, *J* = 11.4 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.3 (s); HRMS (APCI) Calcd for C₄₀H₆₈F₃O₅Si₂[M+H]⁺ 741.4558, Found: 741.4558.

4.3.12. (25*R*)-Trifluoromethyl-1α,3β-bis(*tert*-butyldimethylsilyloxy)-22-dehydrocarcitril methyl ester (25*R*)-**14**

(25*R*)-**14** was synthesized in 23% yield according to a similar manner to that of (25*S*)-**14**.

¹H NMR (CDCl₃, 300 MHz) δ 0.02~0.04 (m, 12H), 0.60 (s, 3H), 0.80~0.89 (m, 18H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.15~1.34 and 1.45~1.67 (m, 13H), 2.06~2.25 (m, 2H), 2.45 (dd, *J* = 1.2, 9.9 Hz, 1H), 2.59~2.63 (m, 2H), 2.83 (d, *J* = 13.5 Hz, 1H), 3.74 (s, 1H), 3.88 (s, 3H), 4.18~4.21 (m, 1H), 4.34~4.47 (m, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 5.17 (s, 1H), 5.20~5.30 (m, 1H), 5.42~5.47 (m, 1H), 6.01 (d, *J* = 11.4 Hz, 1H), 6.22 (d, *J* = 10.8 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.4 (s).

4.3.13. (25*S*)-Trifluoromethyl-22-dehydrocarcitril (25*S*)-**14'**

To a solution of (25*S*)-**14** (3.2 mg, 0.0043 mmol) in THF (0.3 ml) was added HF/Py (0.13ml) at 0 °C, and stirred for 4 h. To the mixture was added sat. NaHCO₃, washed with brine, extracted by AcOEt, dried over MgSO₄ and concentrated. The residue was purified by silica-gel chromatography to give (25*S*)-**14'** (1.4 mg, 62 %).

¹H NMR (CDCl₃, 300 MHz) δ 0.58 (s, 3H), 0.83~0.90 (m, 4H), 0.99 (d, *J* = 6.3Hz, 3H), 1.25~2.07 (m, 13H), 2.27~2.34 (m, 3H), 3.05 (d, *J* = 7.5 Hz, 1H), 3.76 (s, 1H), 3.86 (s, 3H), 4.20~4.23 (m, 1H), 4.40~4.42 (m, 1H), 5.00 (s, 1H), 5.21~5.28 (m, 1H), 5.32 (s, 1H), 5.45 (dd, *J* = 8.7, 15.6 Hz, 1H), 6.01 (d, *J* = 10.8 Hz, 1H), 6.37 (d, *J* = 11.4 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.3 (s).

4.3.14. (25*R*)-Trifluoromethyl--22-dehydrocarcitril (25*R*)-**14'**

(25*R*)-**14'** was synthesized in 56 % yield according to a similar manner to that of (25*S*)-**14'**.

¹H NMR (CDCl₃, 300 MHz) δ 0.54 (s, 3H), 0.83~0.88 (m, 4H), 1.00 (d, *J* = 6.0 Hz, 3H), 1.23~2.06 (m, 13H), 2.27~2.34 (m, 1H), 2.58~2.63 (m, 2H), 2.83 (d, *J* = 15.3Hz, 1H), 3.74 (s, 1H), 3.88 (s, 3H), 4.20~4.22 (m, 1H), 4.40~4.43 (m, 1H), 4.99 (s, 1H), 5.23 (dd, *J* = 7.8, 15.9 Hz, 1H), 5.32 (s, 1H), 5.46 (dd, *J* = 8.7, 15.6 Hz, 1H), 6.01 (d, *J* = 11.4 Hz, 1H), 6.37 (d, *J* = 11.1 Hz, 1H); ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.4 (s).

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