SREBP 経路を介する脂質生合成を選択的に阻害するビタミン D 誘導体の合成研究

Synthesis of vitamin D analogs with selective inhibitory activity to lipid biosynthesis through SREBP pathway

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博士論文

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略語表

AF-2	activation function-2
CYP	cytochrome P450
IC_{50}	half maximal inhibitory concentration
INSIG	insulin inducing gene
LBD	ligand binding domain
DNA	deoxyribonucleic acid
RXR	retinoid X receptor
S1P	site 1 protease
S2P	site 2 protease
SCAP	SREBP cleavage-activating protein
SRE	sterol regulatory element
SREBP	sterol regulatory element-binding protein
SSD	sterol sensing domain
VDR	vitamin D receptor
VDRE	vitamin D response element

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第 1 章　序論

第 1 節　ビタミン D の代謝産物による SREBP 阻害について

ステロール調節エレメント結合タンパク質（sterol regulatory element-binding protein 以下、SREBP）は小胞体膜上に局在する 2 回膜貫通型タンパク質であり、脂質恒常性に関与する転写因子としてコレステロール、脂肪酸、トリグリセリド、リン脂質の生合成及び細胞内への取り込みなどを制御する遺伝子の発現を調整することによりすべての組織における脂質代謝の司令塔的役割を果たす[1-4]（Figure 1）。SREBP は、細胞質内側に配向した C 末端が、同様に細胞質側に配向した 8 回膜貫通型タンパク質（SREBP cleavage-activating protein 以下、SCAP）の C 末端と結合することで、小胞体膜上にて SCAP と二量体を形成している[5]。SCAP の細胞貫通領域には sterol sensing domain（以下、SSD）が存在しており[6]、小胞体膜中のコレステロール量が増加すると、SCAP の SSD にコレステロールが結合し、それにより SCAP は 6 回膜貫通型タンパク質 insulin inducing gene（以下、INSIG）に認識され、SREBP-SCAP-INSIG 三量体が形成されることが報告されている[7]。一方で、小胞体膜中におけるコレステロール量が減少すると、SCAP と INSIG の結合は抑制される方向に働き、SREBP-SCAP-INSIG 三量体が形成されにくくなり、SREBP-SCAP 二量体は小胞輸送を介して、ゴルジ体へと輸送される[8]。ゴルジ体で SREBP は、2 か所の切断を受けることで、活性型へと誘導される。最初に、site 1 protease（以下、S1P）の働きにより SREBP の 2 か所の膜貫通領域をつないでいるループ部位が切断を受けることで SREBP は、N 末端側と C 末端側の 2 つに分かれる[9]。続いてその N 末端側が、site 2 protease（S2P）によりさらに切断されることで SREBP は活性型となり、活性型 SREBP が細胞質内へと放出される[10]。遊離した活性型 SREBP は、ホモ二量体となり、細胞核へ移行し、DNA 上 sterol regulatory element（以下、SRE）配列に結合することで、コレステロールの取り込みや合成に関与する遺伝子群の発現が亢進される。コレステロール量が増加すると、小胞体膜上で再び SREBP-SCAP-INSIG 三

量体が形成されることで上述の SREBP プロセッシングが抑制され、その結果コレステロールの取り込みや合成に関与する遺伝子の発現が抑制される方向に働く。

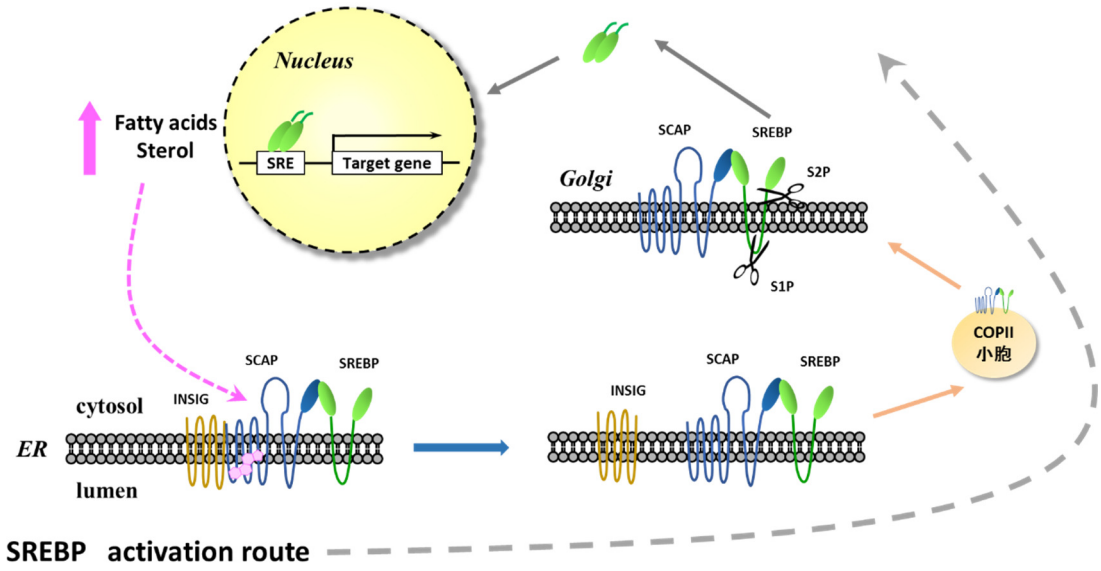


Figure 1. 細胞内での SREBP プロセシング機構

コレステロールと同様に SCAP と相互作用することで小胞体膜上での SREBP-SCAP 二量体の安定化をもたらし SREBP を阻害する活性をもつ分子として fatostatin や betulin が報告されている[11,12]（Figure 2）。2017 年に、京都大学の上杉らは、ビタミン D_3 の代謝産物の一つである 25-hydroxyvitamin D_3 [25(OH)D_3]（**1**）が、コレステロール、betulin 及び fatostatin と全く異なった作用機序で SREBP を阻害することを見出した（Figure 3）[13]。そのメカニズムとは、25(OH)D_3（**1**）が SREBP 及び SCAP 双方の分解を誘導するというものである（Figure 4）。すなわち、25(OH)D_3（**1**）が SCAP と相互作用し SSD に結合することにより、SCAP における C 末端側が構造変化を起こし、セリンプロテアーゼによって C 末端側が切断される。続いてユビキチン化を受け、プロテアソームの働きにより SCAP は分解される。結合パートナーであり安定化因子でもあった SCAP が失われることで SREBP もまた同様に不安定化し、分解されるというものである[13]。

上述のように、25(OH)D_3（**1**）は SCAP と SREBP を分解することで、SREBP 経路によるコレステロールの取り込みや合成を阻害することから、脂質の代謝異常や、脂質代謝の亢進が知られている肝がんの治療薬としての応用が期待されている（中川ら、未発表データ）。

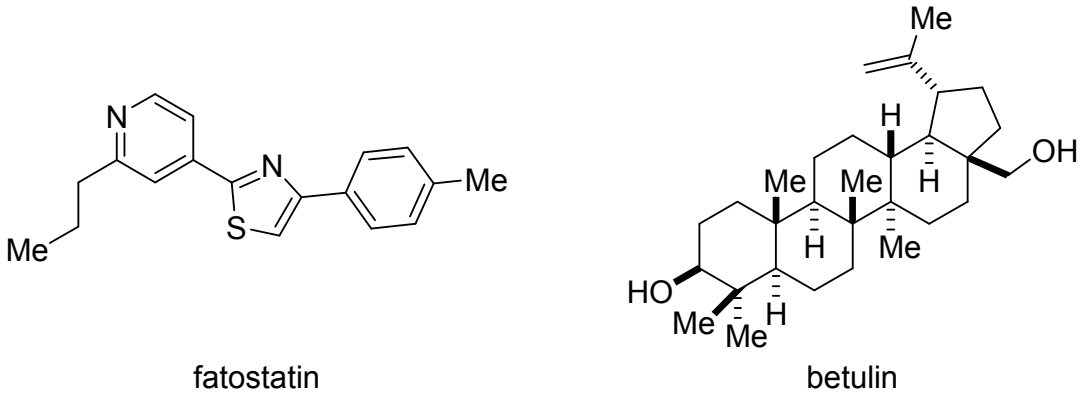
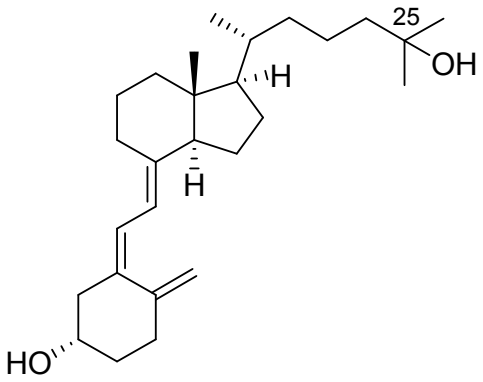


Figure 2. fatostatin 及び betulin の構造



25-hydroxyvitamin D_3 (**1**)

Figure 3. 25-hydroxyvitamin D_3 [25(OH)D_3]（**1**）の構造

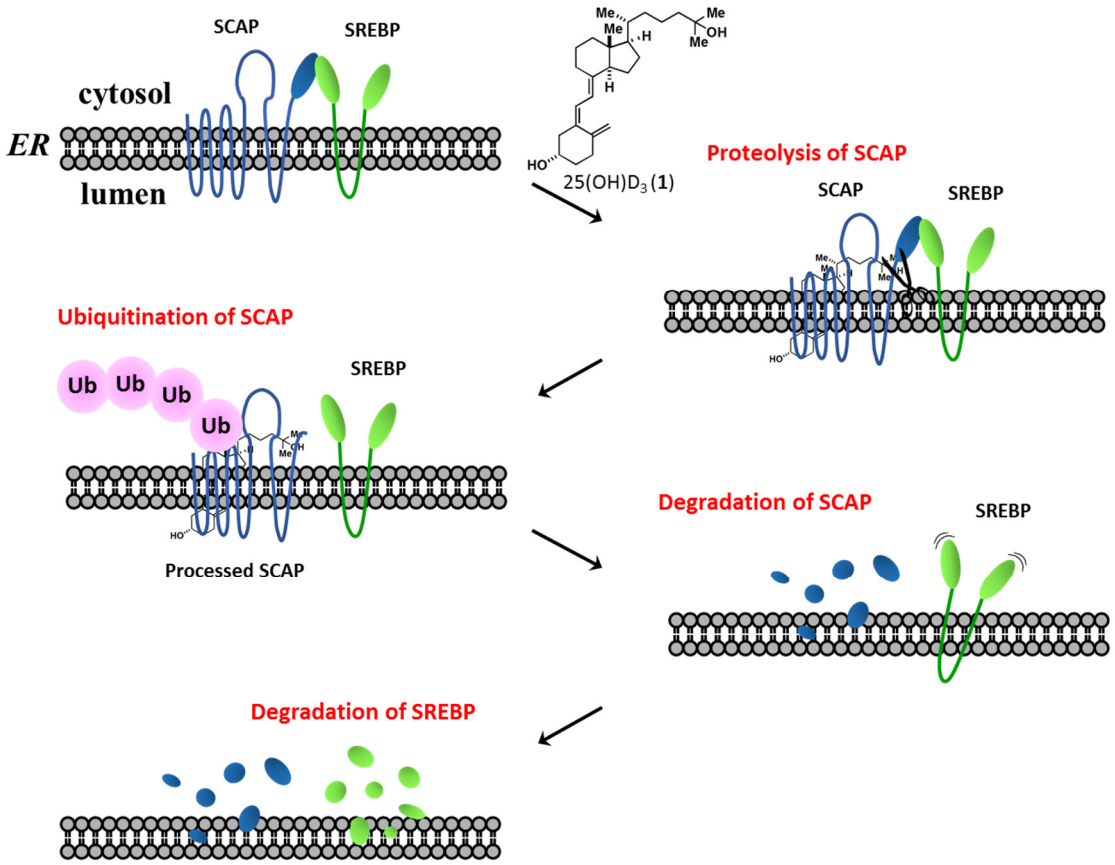


Figure 4. 25(OH)D_3（**1**）による SREBP 阻害機構 [13)]

第 2 節　SREBP 阻害薬設計におけるビタミン D_3 代謝産物の問題点

がんや脂質代謝異常などの疾患治療薬として 25(OH)D_3（**1**）そのものを臨床で実際に用いようとした場合には、以下に挙げる問題点が存在する。すなわち 25(OH)D_3（**1**）の 1α位が水酸化されて生じる活性型ビタミン D_3 [1α,25-dihydroxyvitamin D_3、1,25(OH)$_2D_3$（**2**）] が引き起こす高カルシウム血症などの副作用の問題である。

皮膚で紫外線照射により産生されるビタミン D_3、あるいは食物から摂取されるビタミン D_3 は、肝臓で CYP2R1 により 25 位が水酸化され、25(OH)D_3（**1**）となり、さらに腎臓で CYP27B1 により 1α位が水酸化され、活性型ビタミン D_3、1,25(OH)$_2D_3$（**2**）となる（Figure 5）[14-18)]。1,25(OH)$_2D_3$（**2**）がもつ生理作用は、核内受容体の一つであるビタミン D 受容体

vitamin D receptor （以下、VDR）を介する標的遺伝子の発現制御により引き起こされる。VDR を介する標的遺伝子の発現は、カルシウム代謝のみならず、骨形成、ホルモンの産生・分泌、細胞の分化・増殖、アポトーシス誘導、免疫調節、など様々な生命反応までに関与している[19-23]。これまでの研究から、生体内のほぼすべての組織・細胞に VDR が存在することが確認されている[24]。

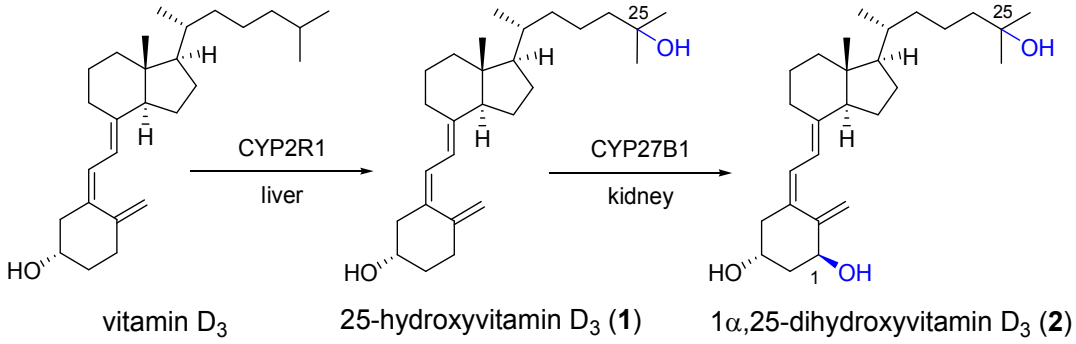


Figure 5. ビタミン D_3 の活性化代謝経路

VDR は核内受容体スーパーファミリーの一つであり、リガンド依存性の DNA 結合型転写因子である。VDR は他の核内ステロイドホルモン受容体と同様に、構造と機能から構造領域に分割することができる。すなわち VDR では N 末端側から、いくつかの構造と機能別に A 領域から E 領域に定義されており、それぞれの領域は異なる機能を有している[25]（Figure 6）。直接 DNA に結合する領域は、受容体タンパク質中央に位置する C 領域であり、2 個の亜鉛フィンガー構造を有している。リガンド結合領域（ligand binding domain、LBD）は C 末端側の E 領域に存在し、この領域がリガンド結合に依存的な転写促進領域（AF-2）である。$1,25(OH)_2D_3$（**2**）が LBD の中央部に存在する疎水性ポケットにはまりこむと[26]、C 末端側に位置する helix 12（H12）の立体構造が大きく変化する。H12 が立体的に構造変化することにより、VDR はレチノイド X 受容体（RXR）との VDR/RXR ヘテロ二量体を形成し、DNA 上のビタミン D 応答エンハンサー配列（vitamin D response element、VDRE）に結合する。そして、さらにそれがコアクチベーターと結合することにより転写を促進する[27,28]（Figure 7）。

上記のようなメカニズムで 1,25(OH)$_2$D$_3$（**2**）は様々な生理作用を引き起こすことから、がんや骨代謝疾患をはじめとする多様な疾患への治療薬（一般名、カルシトリオール）として応用が進められてきた。実際に、1,25(OH)$_2$D$_3$（**2**）は骨粗鬆症の治療薬として使用されている。しかしながら、1,25(OH)$_2$D$_3$（**2**）は、望まない作用として高カルシウム血症などを惹起することがあるため、がん治療薬などとして臨床応用するためには、これらの作用を分離したビタミン D$_3$ 誘導体の創製が必要不可欠であり、研究開発が進められている [29,30]。SREBP 阻害薬としてビタミン D$_3$ 誘導体を適用するためにも作用分離は避けて通れない課題であり、それに向けた誘導体合成研究が行われている [13,31]。

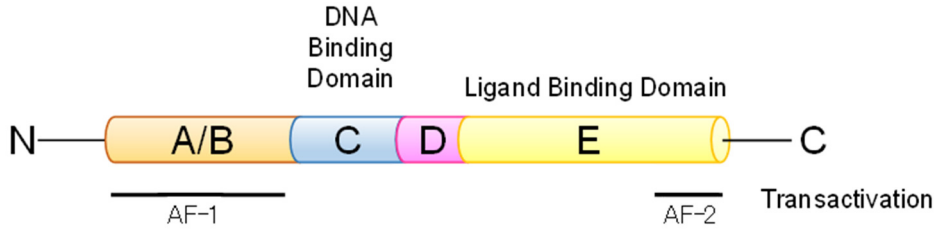


Figure 6. VDR の領域構造と領域機能

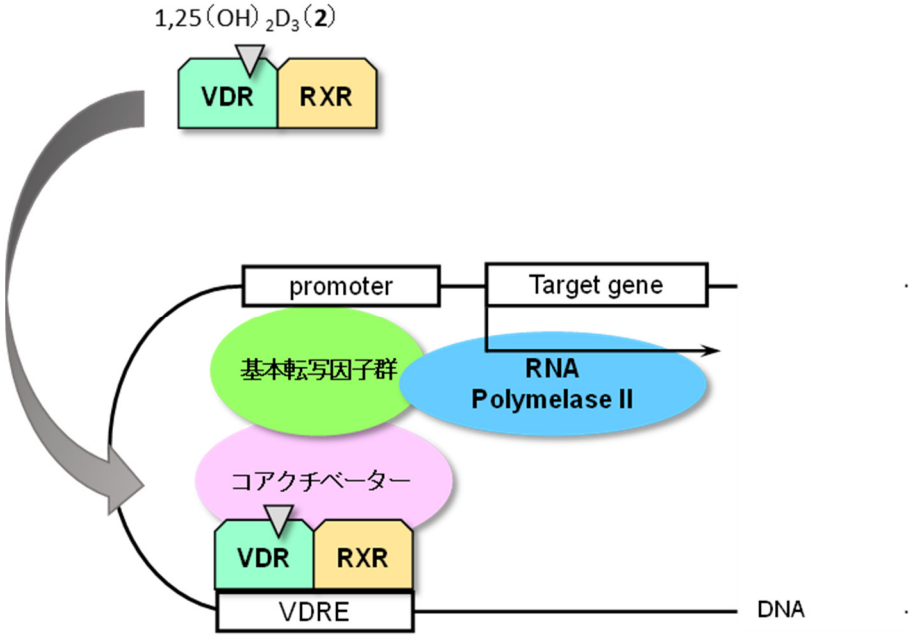


Figure 7. VDR による転写制御

第 3 節　研究目的

VDR を介する高カルシウム血症などの副作用を示さず SREBP のみを高選択的に阻害できる『脂質生合成を選択的に阻害する新規ビタミン D_3 誘導体の創製』を目的として、研究に着手した。25(OH)D_3（**1**）の A 環部は CYP27B1 の働きで 1 位 α 方向への水酸化を受けることにより VDR への結合親和性が劇的に向上する。これまでに合成された選択的 SREBP 阻害活性をもつビタミン D_3 誘導体は 1α 水酸化を防ぎ VDR 活性の発現を抑制する目的で、A 環 1 位に様々な置換基導入が施されている [31]。導入された置換基の影響でこれら誘導体群は VDR に対する結合親和性を著しく低く抑えられることが *in vitro* における評価で判明している。これらの知見から、VDR 活性を抑えながら、SREBP を不可逆的に分解する作用を維持したビタミン D_3 誘導体を設計する上で、A 環部の構造変化は有効であると考えた。ビタミン D_3 誘導体を SREBP 阻害薬として利用する際にはホルモン量ではない高濃度での使用が必要不可欠と考えられ、これまでに合成されたビタミン D_3 誘導体よりもさらに VDR 活性が低く高選択的 SREBP 阻害活性をもつビタミン D_3 誘導体の創製が求められる。これまでの合成研究では A 環構造として、シクロヘキサン環を基本骨格とする構造展開がおこなわれてきたが、本研究では、さらなる選択性の向上を期すためにシクロヘキサン環以外の A 環構造にも着目し構造展開を行う中で、最適構造を探索することとした（Figure 8）。

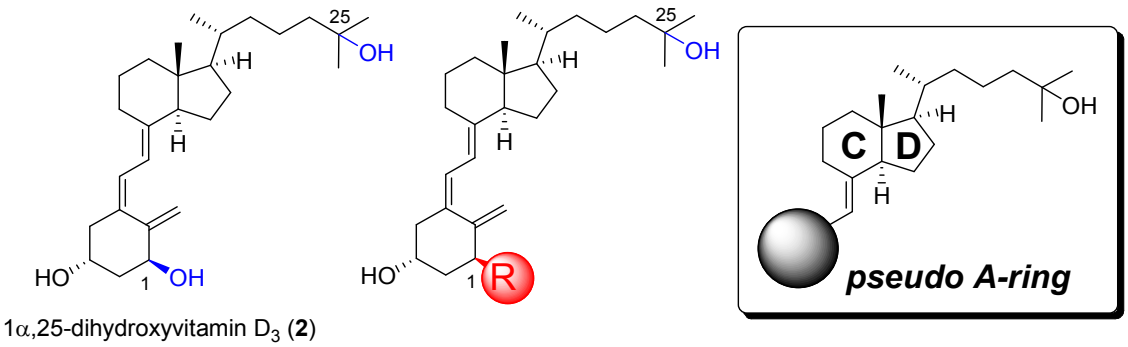
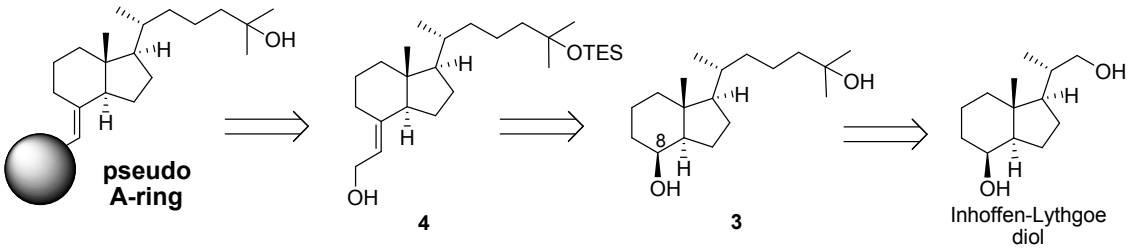


Figure 8. 1α,25-hydroxyvitamin D_3（**2**）と 1 位が置換された 25-hydroxyvitamin D_3 及び本研究で設計した誘導体の構造

第 2 章　擬似 A 環部が導入されたビタミン D_3 誘導体の合成及びその活性評価

第 1 節　合成計画

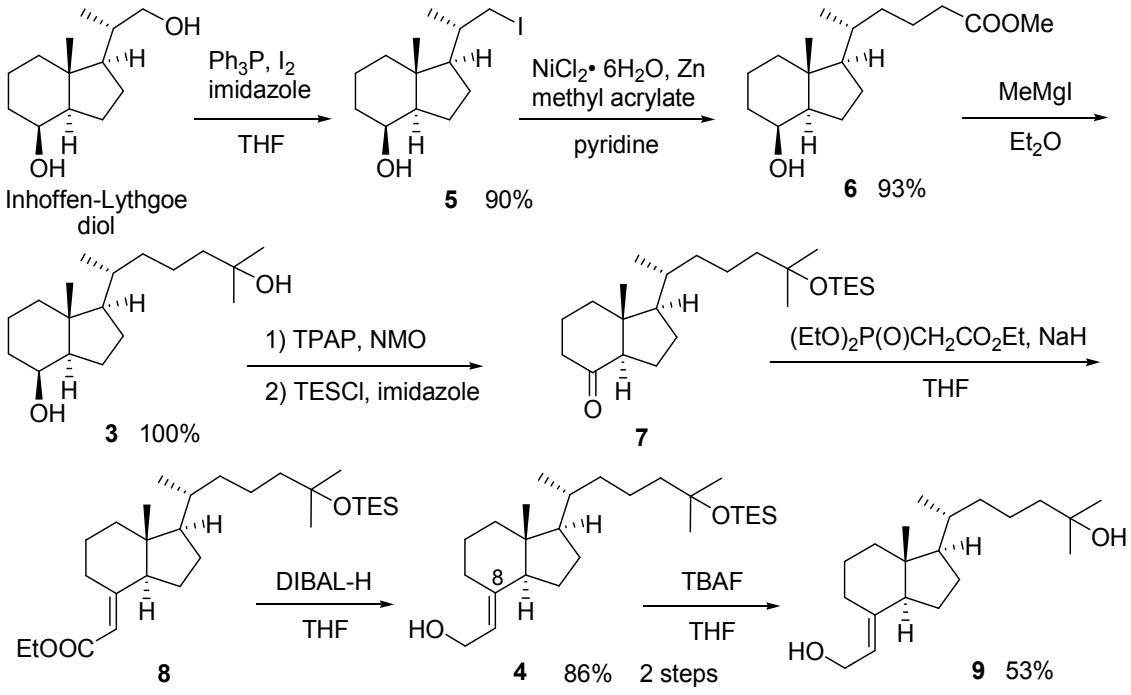
所属研究室ではこれまでに数百種の VDR リガンドを開発しており、その中には 14-*epi*-プレビタミン D_3 誘導体のように VDR 結合親和性のないビタミン D_3 誘導体群が合成されていた [32]。初期の SREBP 抑制 *in vitro* スクリーニングでは A 環と CD 環の相対配置が **1** とは異なる 14-*epi*-プレビタミン D_3 誘導体群にも良好な抑制活性が認められた（未発表データ）。そこで、SREBP 抑制活性は CD 環構造を保持すればある程度 A 環部を大きく構造変換しても再現できるとの仮説を立てた。そこでシクロヘキサン環を基本骨格とした A 環部の代替として様々な構造をもつ「擬似 A 環部」が導入されたビタミン D_3 誘導体群の新規合成ルートを開発すべく、Scheme 1 のように逆合成解析を行った。Inhoffen-Lythgoe diol[33]を出発原料として、Mouriño らの方法 [34]により側鎖を伸長しジオール体 **3** へと導くこととした。このジオール体に対し 8 位（ステロイドのナンバリングによる）へのエキソメチレン部位の導入や、所属研究室で開発した方法 [35]により 4 工程で 25 位のヒドロキシ基が TES 保護されたアリルアルコール体 **4** へと誘導することとした。擬似 A 環部の導入は光延反応やクリック反応を基本としながら行うこととし、導入する A 環部の構造は立体的嵩高さや極性の大小を鑑みながら可能な限り多様なものとすることとした。



Scheme 1. 擬似 A 環部が導入されたビタミン D_3 誘導体の逆合成解析

第 2 節　CD 環部へのアリルアルコール部位導入

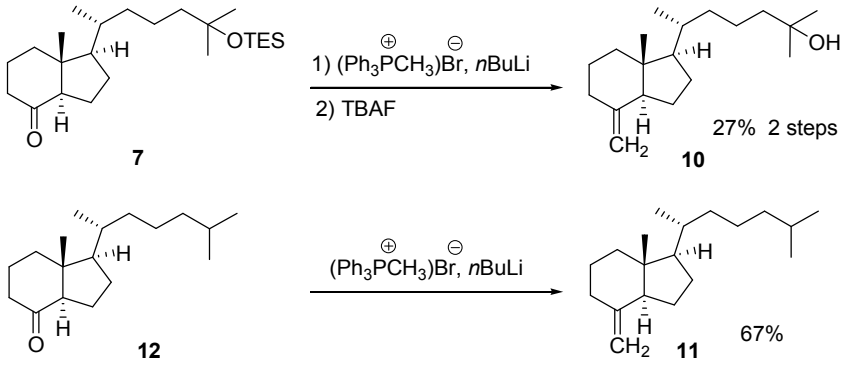
ビタミン D_2 のオゾン分解と還元反応により得られる Inhoffen-Lythgoe diol を出発物質とし、第一級アルコールのヒドロキシ基を Appel 反応の条件下でヨウ素化した。続いて塩化ニッケル（Ⅱ）六水和物及び活性化した亜鉛粉末を用いた側鎖部の伸長によりメチルエステルを導入後、methyl Grignard 試薬を過剰量反応させることでジメチル基の導入とともに 25 位ヒドロキシ基を構築することで **3** を得た。次に合成した **3** を用いて 8 位にアリルアルコール部位が導入された CD 環部 **4** を合成した（Scheme 2）。すなわち **3** に対し TPAP/NMO を用いた 8 位ヒドロキシ基の酸化 [36]と 25 位の第三級アルコールのヒドロキシ基を TES エーテルとして保護し、ケトン **7** とした。**7** に対して塩基存在下で ethyl diethylphosphonoacetate を作用させることで二炭素増炭したエチルエステル体 **8** とし、エチルエステル部位を DIBAL-H によってヒドリド還元することでアリルアルコール **4** を合成した [35]。その後、25 位ヒドロキシ基の脱シリル化によって **9** へと誘導した。



Scheme 2. CD 環部アリルアルコール体（**4**,**9**）の合成

第 3 節　8 位修飾型ビタミン D_3 誘導体の合成

CD 環部 8 位が修飾されたビタミン D_3 誘導体の合成を行った。A 環部の存在が SREBP 阻害活性に与える影響を測る目的で A 環部が欠損したビタミン D_3 誘導体 **10** と、25 位のヒドロキシ基が SREBP 阻害活性に及ぼす影響を評価する目的で 25 位にヒドロキシ基が存在しない誘導体 **11** をそれぞれ合成した。**10** の合成は、前節で合成した 8 位ケトン体 **7** を出発原料として Wittig 反応[37]でエキソメチレン部位を導入し、最後に 25 位ヒドロキシ基の脱シリル化経由で行った。また **11** の合成は、Grundmann's ketone **12**[38]を出発原料として行った。**12** に対し先ほどと同様に Wittig 反応でエキソメチレン基を導入した **11** へと誘導した（Scheme 3）。



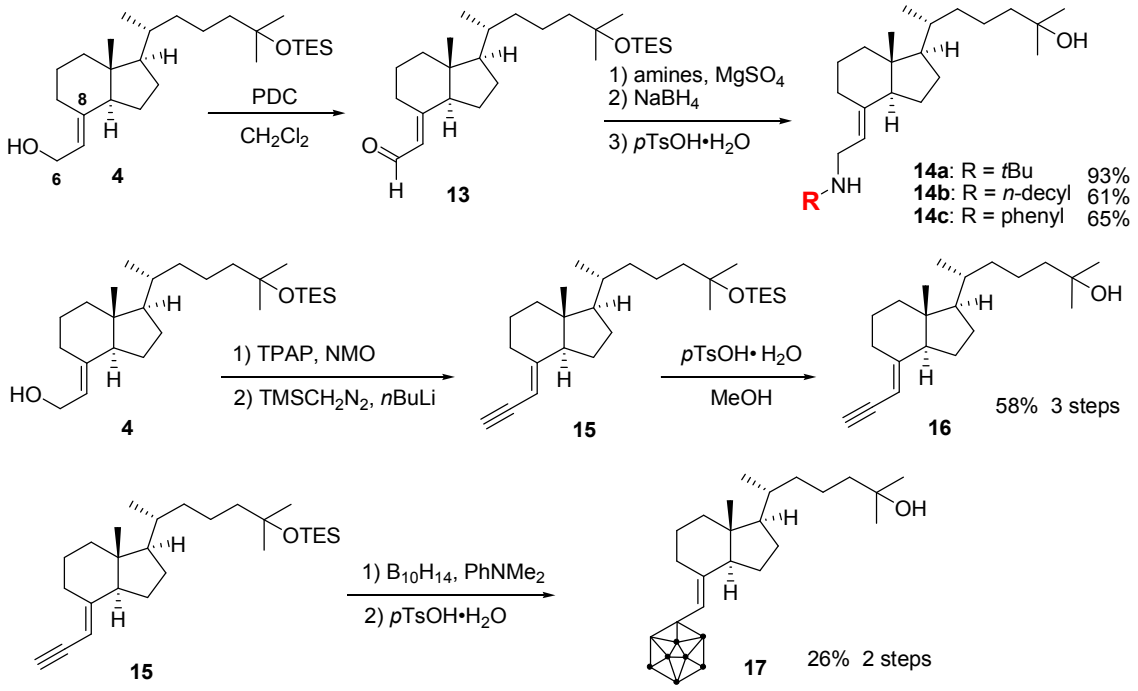
Scheme 3. 8 位修飾型ビタミン D_3 誘導体（**10**,**11**）の合成

次節からは CD 環部 **4** のアリルアルコール部位を足掛かりとした 6 位への擬似 A 環部導入についての詳細を示す。

第 4 節　CD 環部置換基 6 位への擬似 A 環部導入

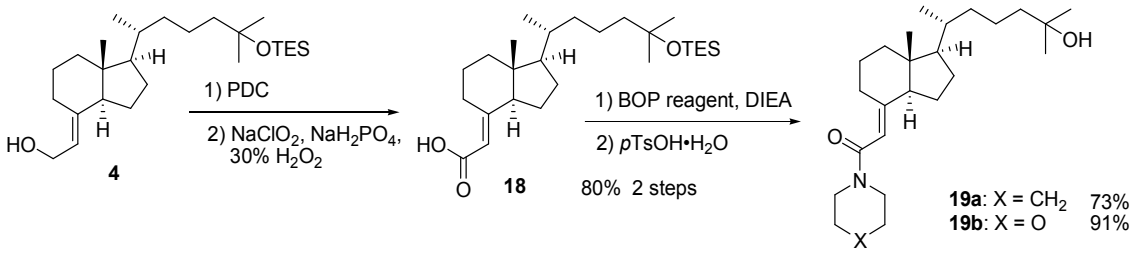
合成したアリルアルコール体 **4** を用いて CD 環部置換基 6 位への官能基導入を行った（Scheme 4）。アルデヒド体 **13** と一級アミンとを反応させることによって得られるイミン

をヒドリド還元することで、それぞれ *t*-ブチルアミン、デシルアミン、フェニルアミン構造を有する誘導体 3 種（**14a**, **14b**, **14c**）を得た[39]。また、アリルアルコール体 **4** を酸化しアルデヒド体へと変換後、塩基性条件下 TMS ジアゾメタンを用いるアルキン合成法[40,41]を利用することでアルキン体 **15** を合成した。さらに導入したアルキン部位に対してデカボランを加熱条件下で反応させることでオルトカルボラン構造を有する誘導体 **17** へと導いた[42]（Scheme 4）。



Scheme 4. 6 位修飾型ビタミン D_3 誘導体（**14a**,**14b**,**14c**,**16**,**17**）の合成

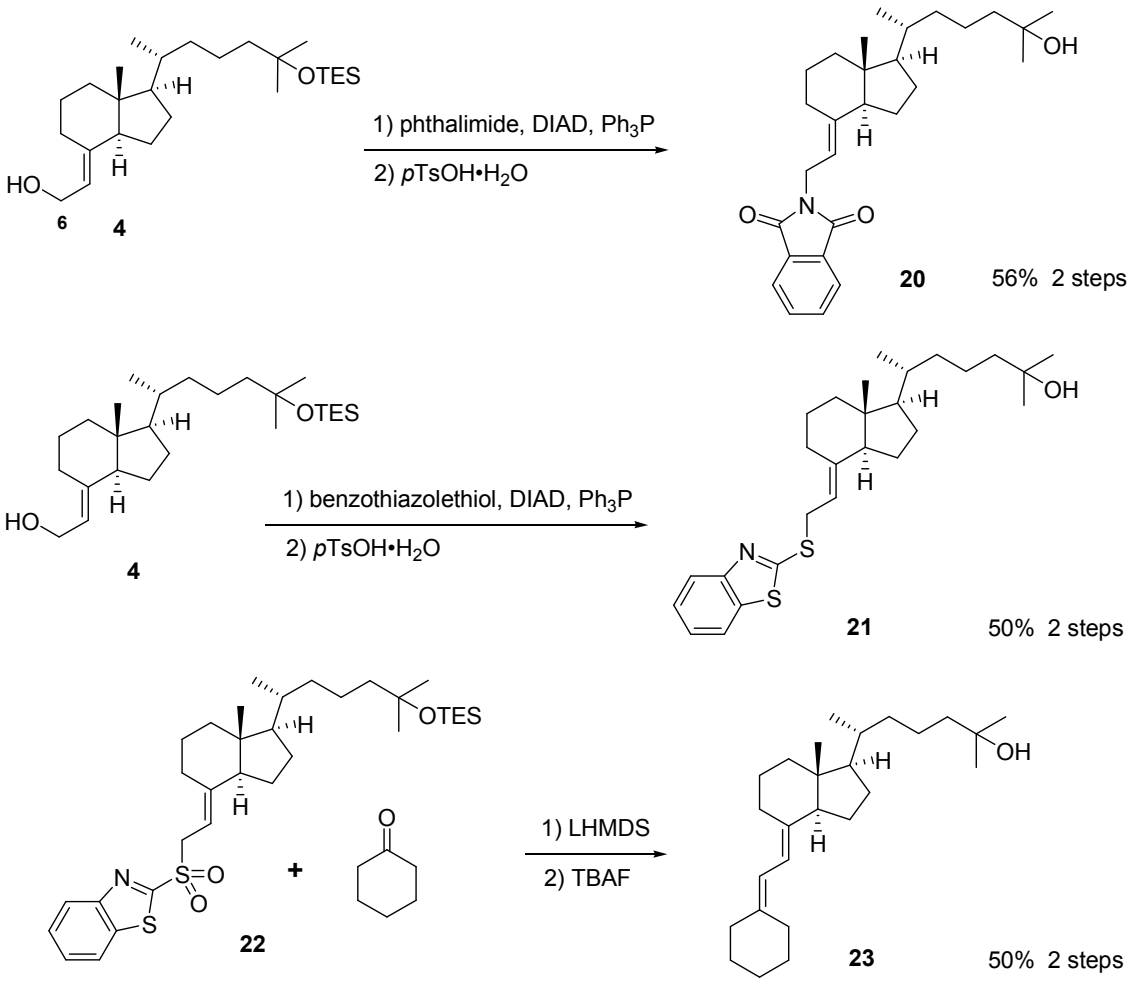
アリルアルコール体 **4** を PDC 酸化でアルデヒド体 **13** へと変換し、続いて Pinnick 酸化[43]でカルボン酸 **18** へと誘導後、環状第二級アミンと縮合させることで環状アミド体 2 種（**19a**,**19b**）を合成した（Scheme 5）。



Scheme 5. 6 位修飾型ビタミン D_3 誘導体（**19a**,**19b**）の合成

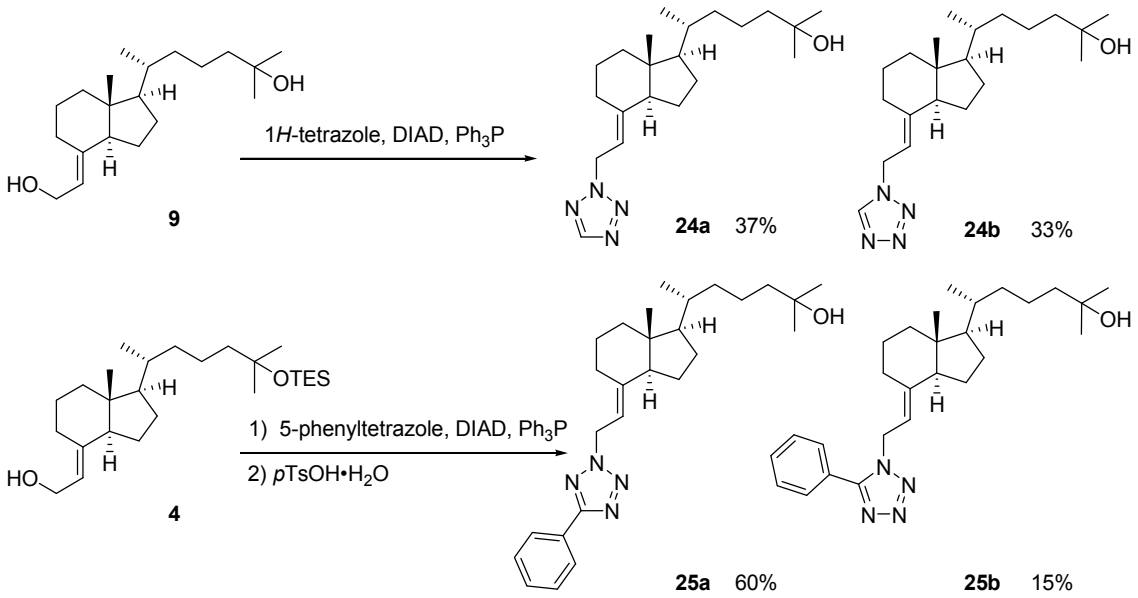
第 5 節　光延反応を利用した CD 環部置換基 6 位への擬似 A 環部導入

光延反応 [44,45]により CD 環部置換基 6 位へフタルイミド基やベンゾチアゾールスルファニル基をそれぞれ導入後、25 位ヒドロキシ基の脱シリル化によりフタルイミド体 **20** とベンゾチアゾールスルフィド体 **21** とを合成した。導入したベンゾチアゾールスルフィド部位を酸化しスルホン体 **22** に誘導後、Julia オレフィネーション [35]によりシクロヘキサノンとカップリングさせることでシクロヘキサン体 **23** を合成した（Scheme 6）。



Scheme 6. 6 位修飾型ビタミン D_3 誘導体（**20**,**21**,**23**）の合成

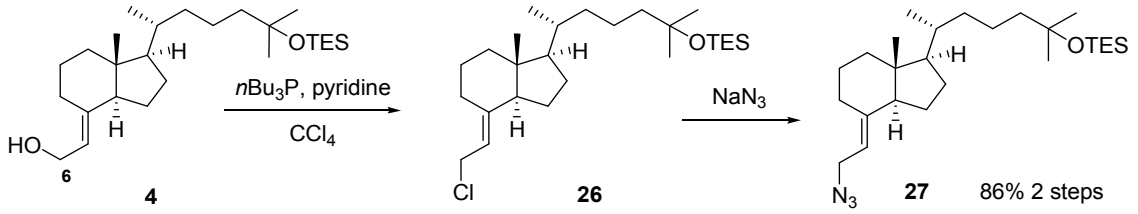
また同様の条件下で、CD 環部置換基 6 位へテトラゾール環を導入した。得られたテトラゾール 2 位置換体とテトラゾール 1 位置換体の混合物はシリカゲルカラムクロマトグラフィーで分離精製した（Scheme 7）。



Scheme 7. 6 位修飾型ビタミン D_3 誘導体（**24a**,**24b**,**25a**,**25b**）の合成

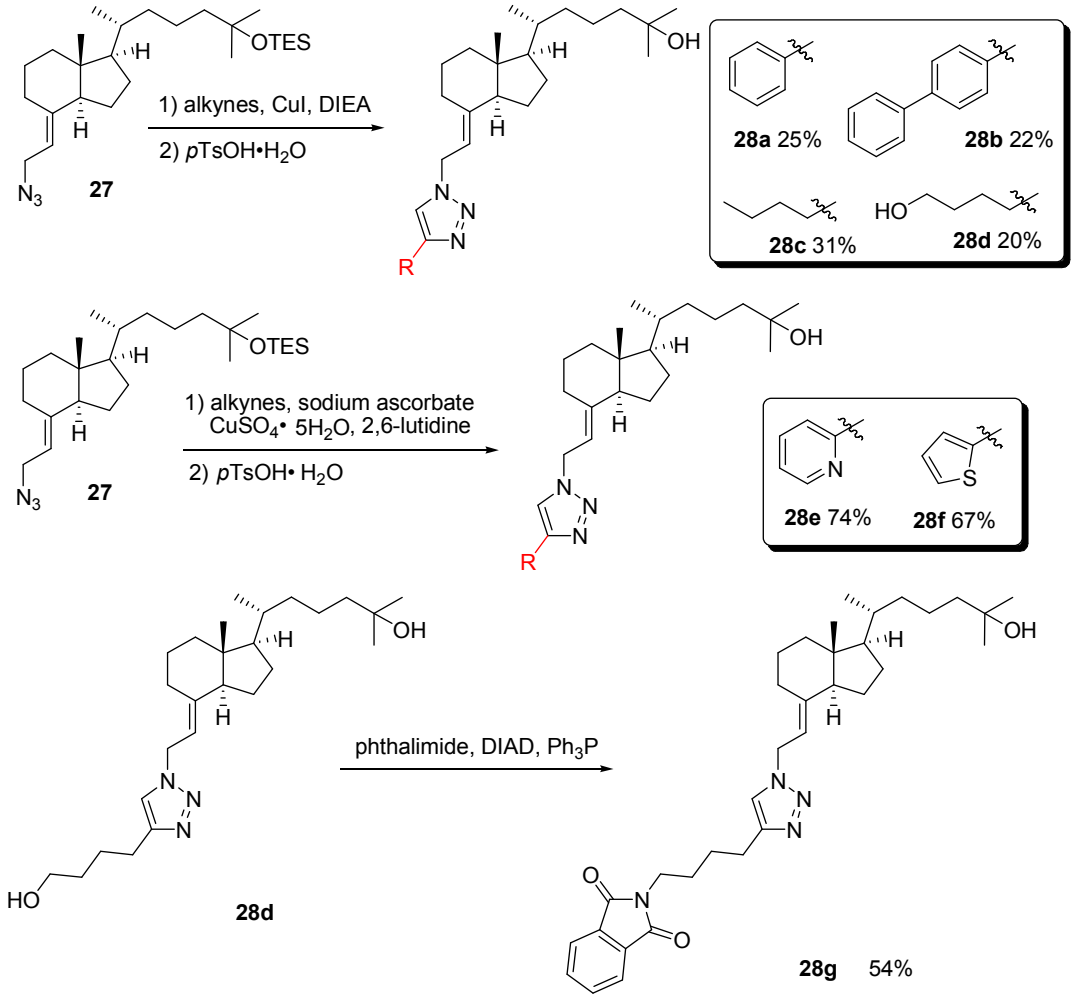
第 6 節　クリック反応を用いた CD 環部置換基 6 位へのトリアゾール骨格の導入

CD 環部置換基 6 位へのトリアゾール環の導入を目指し、その前駆体であるアジド体 **27** の合成を行った（Scheme 8）。アリルアルコール体 **4** に対し、CCl_4 溶媒中 tri-*n*-butylphosphine を反応させることで塩素化物 **26** に変換後 [46]、続いて NaN_3 を作用させることでアジド体 **27** へと導いた。



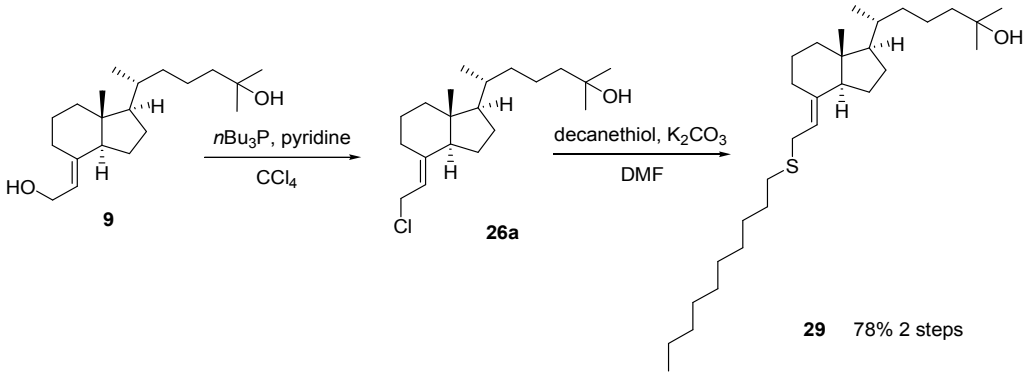
Scheme 8. アジド体 **27** の合成

次に、合成したアジド体 **27** と種々のアルキンとをカップリングさせることで [47]、擬似 A 環部としてトリアゾール環を基本骨格とする誘導体（**28a**～**28f**）を合成した。さらに、**28d** に対し光延反応でフタルイミド基が導入された **28g** も合成した（Scheme 9）。



Scheme 9. 6 位にトリアゾール部位が導入された誘導体（**28a**～**28g**）の合成

アジド体 **27** の合成中間体である塩化物 **26a** を利用して塩基性条件下、デカンチオールを反応させることで長炭素鎖を持つスルフィド体 **29** も合成した（Scheme 10）。

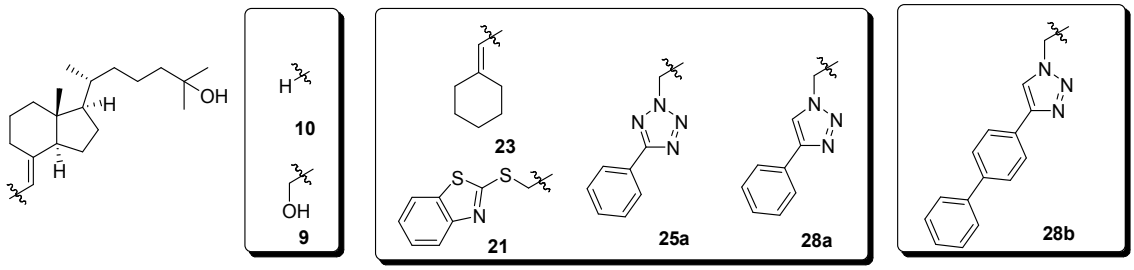


Scheme 10. スルフィド体 **29** の合成

第 7 節　擬似 A 環部が導入されたビタミン D_3 誘導体の活性評価

上述した手法により合成した擬似 A 環部が導入されたビタミン D_3 誘導体の *in vitro* での活性評価は、京都大学上杉研究室で実施した。

まず、合成したビタミン D_3 誘導体（**9**,**10**,**21**,**23**,**25a**,**28a**,**28b**）について、チャイニーズハムスター卵巣由来の CHO K1 細胞を用いたルシフェラーゼレポーターアッセイにより SREBP に対する阻害活性を評価した。コントロールデータとして 25(OH)D_3（**1**）を用いた。8 位に小さな置換基が導入された誘導体（**9**,**10**）は SREBP 阻害活性を示さなかった。一方で、より立体的に嵩高い環状の置換基を有する誘導体（**21**,**23**,**25a**,**28a**）は、SREBP 阻害活性を示したが、さらに嵩高い置換基が導入された誘導体（**28b**）では活性が消失するという結果となった（Figure 9）。



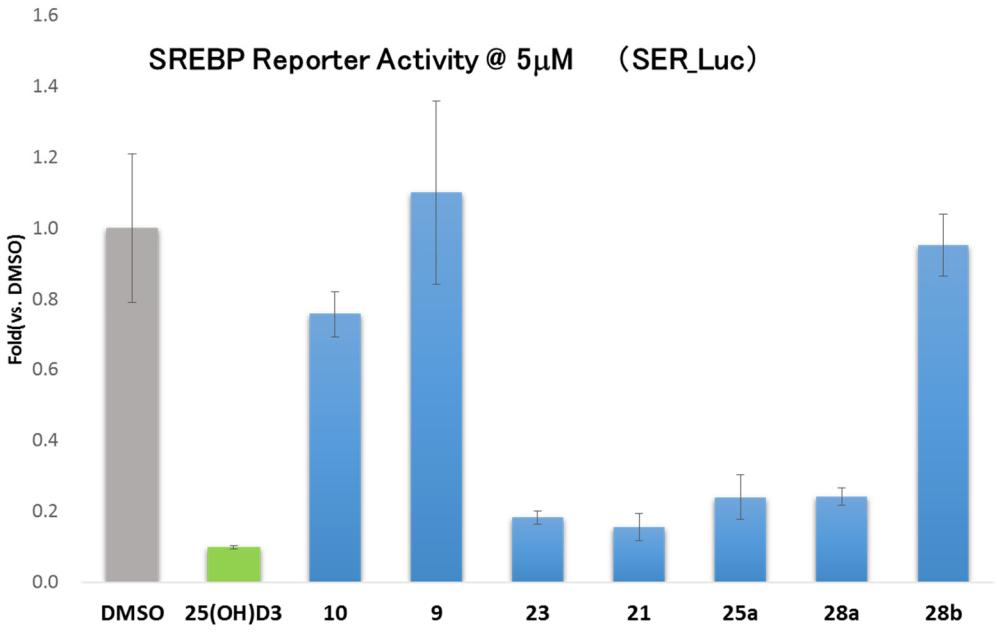


Figure 9. レポーターアッセイによる SREBP 阻害活性評価（上杉ら）

次にこれら合成した誘導体について、CHO K1 細胞を用いたルシフェラーゼレポーターアッセイによりその VDR 活性を評価した（Figure 10）。いずれの誘導体も導入されている A 環部がビタミン D の A 環部と比較して大幅に構造が変換されていることから、その VDR 活性は確認されなかった。

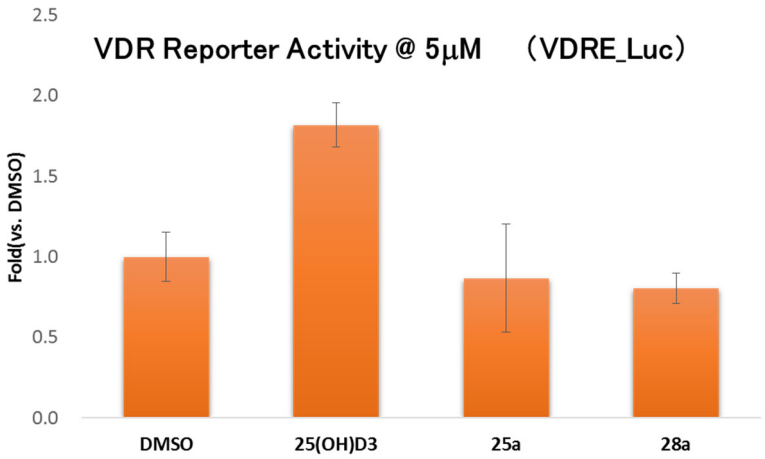


Figure 10. レポーターアッセイによる VDR 活性の評価（上杉ら）

上述したルシフェラーゼレポーターアッセイによる *in vitro* の結果が良好であった誘導体群を用いて *in vivo* による活性評価を行ったところ、予想に反して SREBP 阻害活性は発現しなかった（未発表データ）。その原因を考察したところ、ビタミン D の不活性化代謝酵素のである CYP24A1 の働きによりこれまで合成したビタミン D_3 誘導体が活性を発現する前に代謝不活化されたのではないかと考えた [48,49]。そこで、より代謝抵抗性の高いビタミン D_3 誘導体を合成することとした。

第 3 章　代謝抵抗性をもつビタミン D_3 誘導体前駆体の効率的合成法開発

第 1 節　CYP24A1 によるビタミン D_3 の代謝不活化経路

ビタミン D の側鎖 23 位および 24 位は CYP24A1 による水酸化を受け、23 位水酸化体はその後 3 段階の酸化過程を経ることにより側鎖にラクトン部位を有する代謝物へ、24 位水酸化体は続く 5 段階の酸化過程を経ることによりカルシトロン酸へと代謝不活化される[48,49]（Figure 11）。

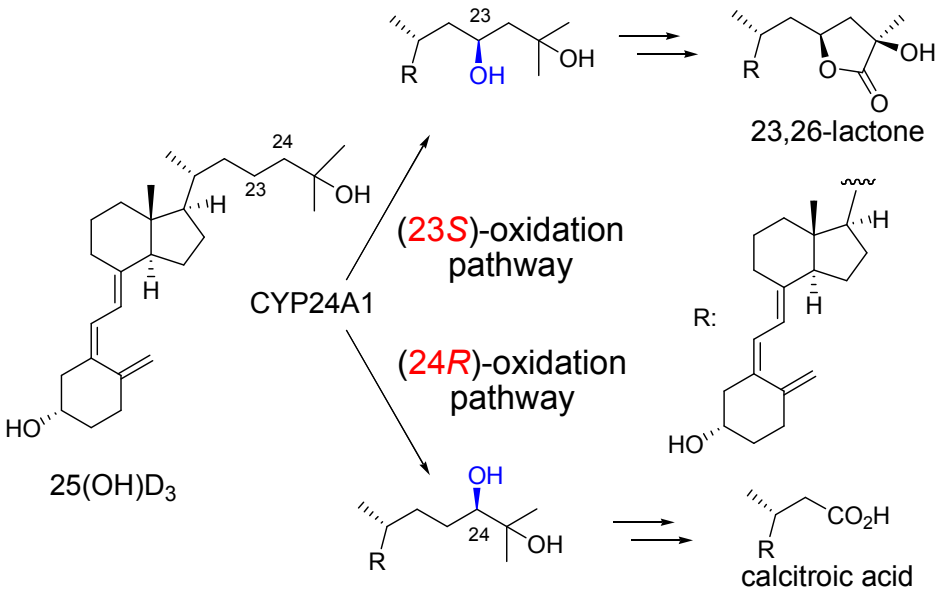


Figure 11. 25(OH)D_3 の主要不活性化代謝経路

第 2 章第 7 節で述べたとおり、合成した誘導体群は *in vitro* の評価で高い SREBP 阻害活性をもつが *in vivo* の評価では活性は発現しなかった（未発表データ）。その問題点を解決するため、ビタミン D 代謝不活化酵素である CYP24A1 による側鎖の水酸化を防ぐ目的で、側鎖の 23 位 24 位 26 位 27 位へフッ素原子が導入されたフッ素化ビタミン D_3 誘導体を設計し合成することとした（Figure 12）。本章では Figure 12 に示したフッ素化ビタミン D_3 誘導体の合成において、その重要な合成前駆体である側鎖がフッ素化された CD 環部 4 種の新規効率的合成法について詳述する。

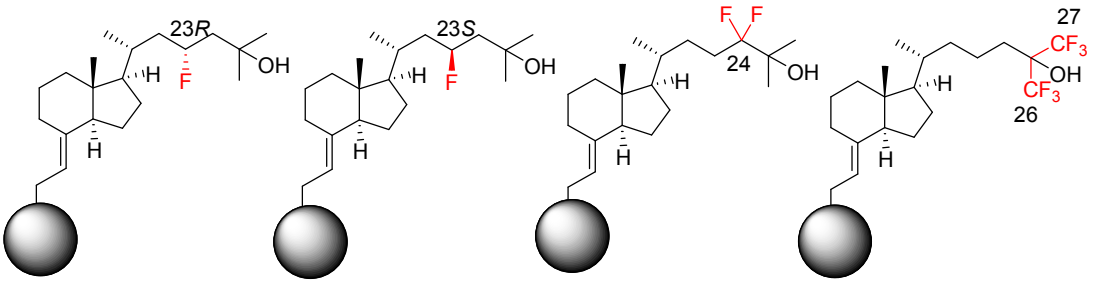


Figure 12. 4 種類の側鎖フッ素化ビタミン D_3 誘導体

第 2 節　医薬品候補化合物へのフッ素導入の意義

医薬品候補化合物上の水素原子をフッ素原子、もしくはフルオロアルキル基に置換することで、強固な C-F 結合の影響により代謝安定性が向上し、同時にフッ素原子の強い電気陰性度により化合物上の p*K*a 値や電子の局在性を変化させられる効果をもち、場合によっては脂溶性の向上や標的タンパク質への結合親和性向上につながることも知られている [50-54]。そのため、これらの効果を期待して医薬品候補化合物上へのフッ素原子導入が精力的に行われてきており、世界中で承認されている医薬品の 20%以上がその分子構造中にフッ素原子を有している [55,56]。

活性型ビタミン D_3 の側鎖上 C26 と C27 両メチル基をそれぞれトリフルオロメチル基に変換したファレカルシトリオール（**60**）はその一例であり、二次性副甲状腺機能亢進症やクル病、骨軟化症などの治療薬として臨床で用いられている。**60** は CD 環側鎖に導入されたヘキサフルオロイソプロパノール構造の影響で代謝が遅く [57-59]、医薬品の特徴として **60** の代謝物である 23 位水酸化体（**61**）にも強いビタミン D 活性が認められる [60,61]（Figure 13）。

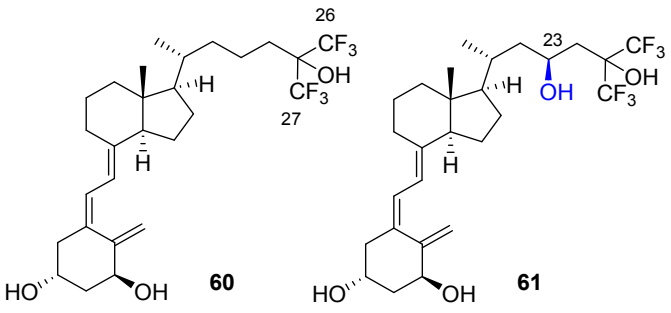
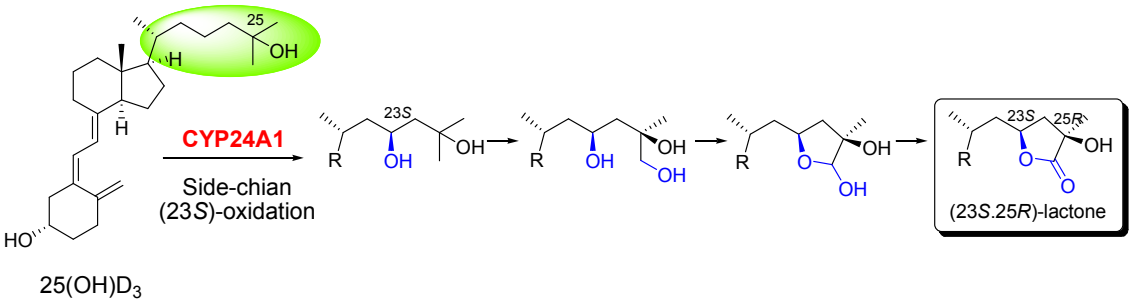


Figure 13. Falecalcitriol とその 23 位水酸化体

第 3 節　ビタミン D_3 側鎖 23 位への立体選択的フッ素導入

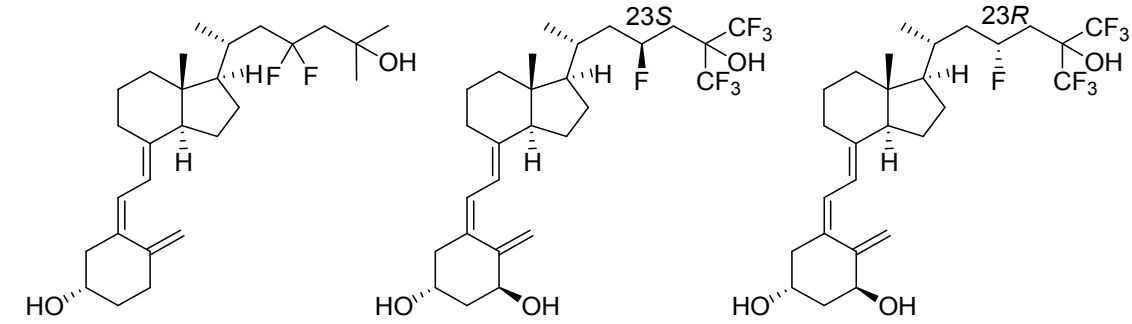
ビタミン D_3 側鎖 23 位はビタミン D の主要代謝酵素である CYP24A1 の働きにより 23*S*-水酸化を受けた後に、26 位の水酸化とアルデヒドへの酸化、ラクトール環の形成を経て（23*S*,25*R*）-ラクトン体へと代謝不活化される [62,63]（Figure 14）。



25(OH)D_3

Figure 14. CYP24A1 による 25(OH)D_3 の 23 位水酸化経路

側鎖 23 位は CYP24A1 による重要な代謝部位の 1 つであるが、23 位がフッ素化されたビタミン D_3 誘導体の合成はこれまでに報告されているだけで 3 例しか存在していない。小林らのグループが 1984 年に初めて 23,23-ジフルオロ-25-ヒドロキシビタミン D_3 [23,23-F_2-25(OH)D_3]（**62**）を報告し [64]、続いて 2000 年に池田らのグループが (23*S*)-23,26,26,26,27,27,27-ヘプタフルオロ-25-ヒドロキシビタミン D_3 [(23*S*)-23,26,26,26,27,27,27-F_7-25(OH)D_3]（**63**）とその 23*R* 体の [(23*R*)-23,26,26,26,27,27,27-F_7-25(OH)D_3]（**64**）2 種の合成を報告している [65]（Figure 15）。



23,23-F_2-25(OH)D_3 (**62**)　　(23*S*)-23,26,26,26,27,27,27-F_7-1α,25(OH)$_2$$D_3$ (**63**)　　(23*R*)-23,26,26,26,27,27,27-F_7-1α,25(OH)$_2$$D_3$ (**64**)

Figure 15. これまでに合成された側鎖 23 位がフッ素化されたビタミン D_3 誘導体

私は第 2 章の結果から代謝抵抗性を持つビタミン D_3 誘導体の合成に着手した。その中で CYP24A1 による代謝部位の 1 つである側鎖 23 位に着目し、その部位がフッ素化されたビタミン D_3 誘導体の合成前駆体である 23 位フッ素化 CD 環部 2 種 **52**,**53** の新規効率的合成法を開発することとした（Figure 16）。

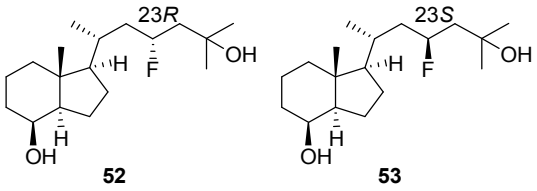


Figure 16. 側鎖 23 位がフッ素化された CD 環部 2 種

第 4 節　ビタミン D_3 側鎖 23 位への立体選択的フッ素導入　（逆合成解析）

前節で述べたとおり、CYP24A1 に対する代謝抵抗性を高める効果を期待して 23 位フッ素化 CD 環部 2 種（**52**,**53**）を設計し、それらの逆合成解析を Figure 17 に示した。23 位への立体選択的なフッ素導入は、その前駆体として合成する 23 位水酸化体[66-69]（**65**,**66**）に対する立体選択的脱酸素的フッ素化を鍵反応として行うこととした。23 位へのヒドロキシ基導入はアルデヒド体（**67**）への酢酸エチルの付加で行い、23 位のヒドロキシ基の立体は新 Mosher 法で決定することとした。

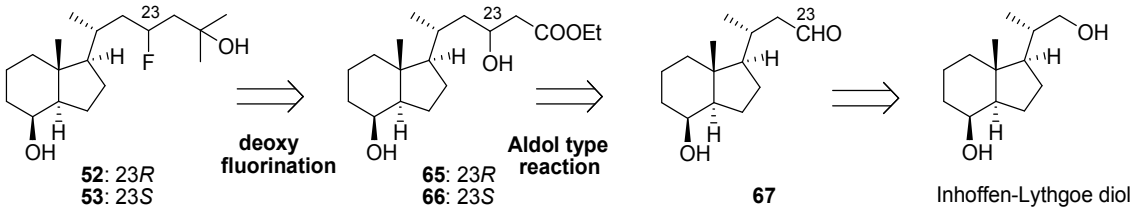
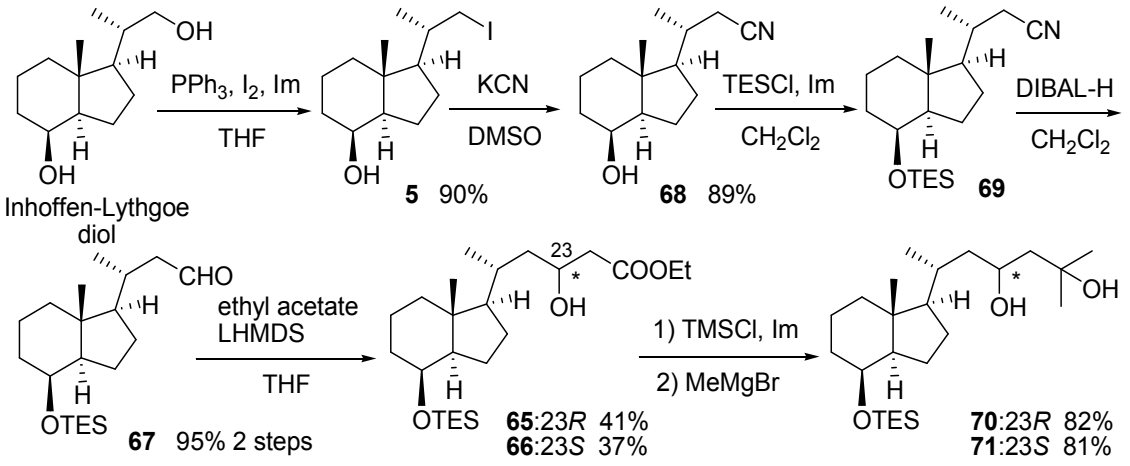


Figure 17. 側鎖 23 位がフッ素化された CD 環部 **52**,**53** の逆合成解析

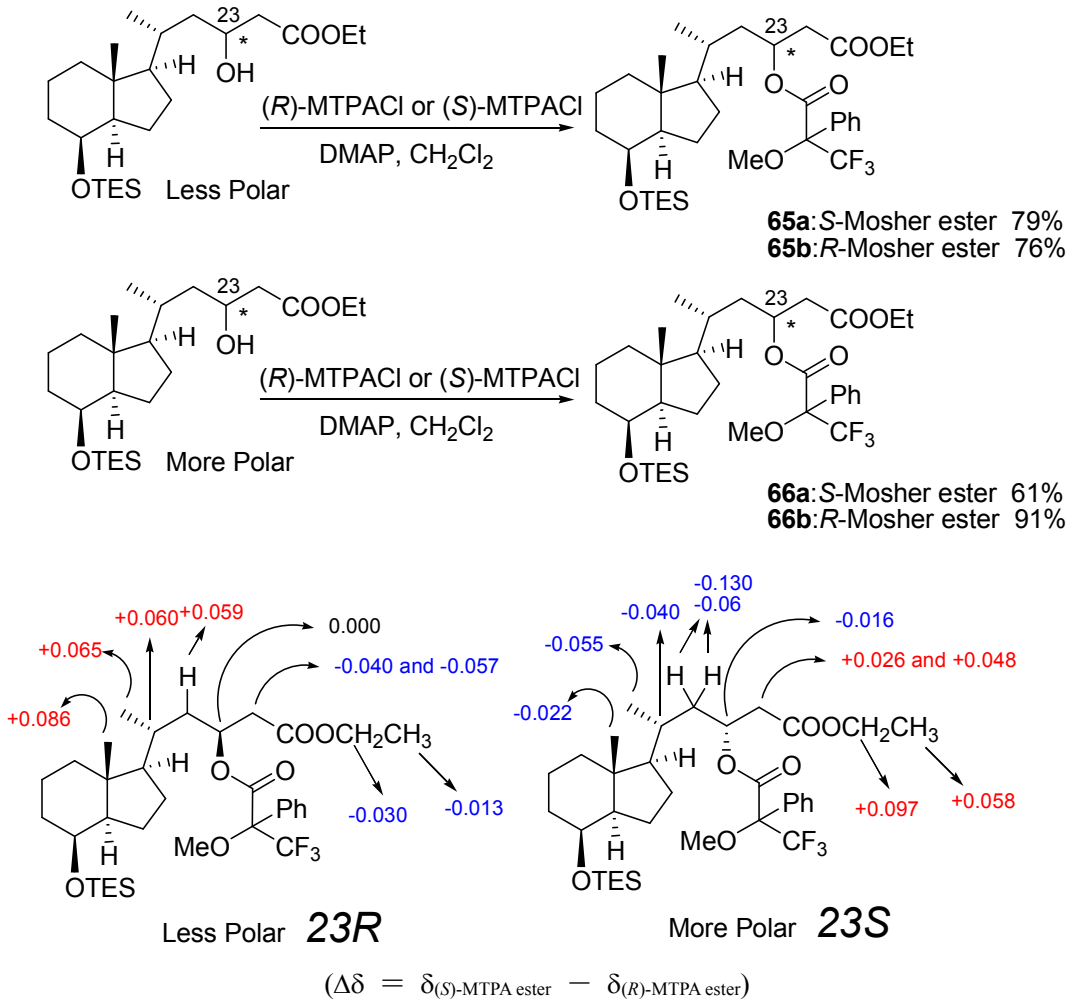
第 5 節

ビタミン D_3 側鎖 23 位への立体選択的フッ素導入　（23 位、25 位へのヒドロキシ基導入）

逆合成解析に基づき、まず Inhoffen-Lythgoe diol を出発原料として、22 位ヒドロキシ基のヨウ素化、シアノ化[70]、8 位ヒドロキシ基の TES 保護、DIBAL-H によるシアノ基の還元と続く加水分解によりアルデヒド体 **67**[71]へと誘導した。続いて酢酸エチルを LHMDS 存在下、アルデヒド基とカップリングさせることにより対応する 23-OH 体（**65**,**66**）をほぼ 1:1 のジアステレオマー混合物で得た。両ジアステレオマーをシリカゲルカラムクロマトグラフィーで分割後、次いで過剰量の MeMgBr で 25 位メチル化とともに 25 位ヒドロキシ基の導入を行った（Scheme 11）。23 位の立体化学は **65** と **66** を用いて新 Mosher 法で決定した[72-75]（Scheme 12）。



Scheme 11. 側鎖 23 位が水酸化された CD 環部の合成

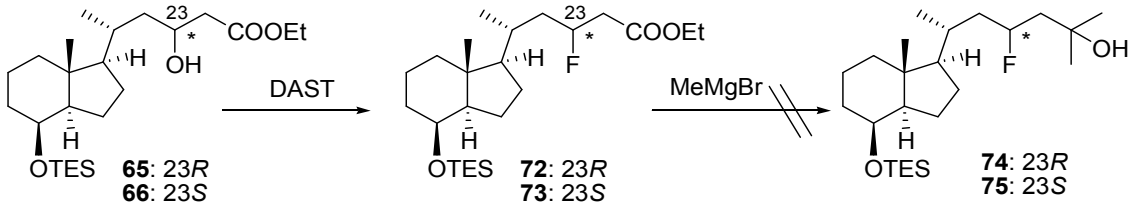


Scheme 12. 新 Mosher 法による側鎖 23 位ヒドロキシ基の立体化学決定

第 6 節

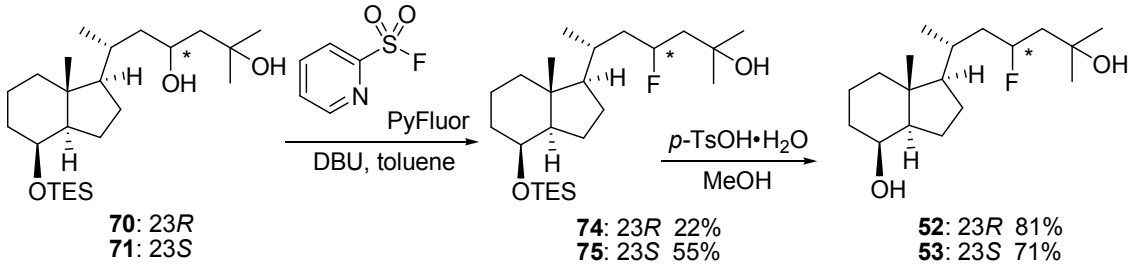
ビタミン D_3 側鎖 23 位への立体選択的フッ素導入（23 位へのフッ素導入と代謝抵抗性の評価）

次に得られた **65** と **66** を用いて、DAST[76]による立体選択的脱酸素的フッ素化反応を試みたところ狙い通り、23*R* の水酸化体 **65** からは立体反転した 23*S* 体のフッ素化体 **73** が、23*S* の水酸化体 **66** からは 23*R* 体のフッ素化体 **72** を得ることが出来た。しかしながら、それらを用いて MeMgBr による 25 位へのジメチル化兼ヒドロキシ基導入を行ったところ強塩基性条件下で HF の脱離が優先し、目的の化合物を得ることが出来なかった（Scheme 13）。



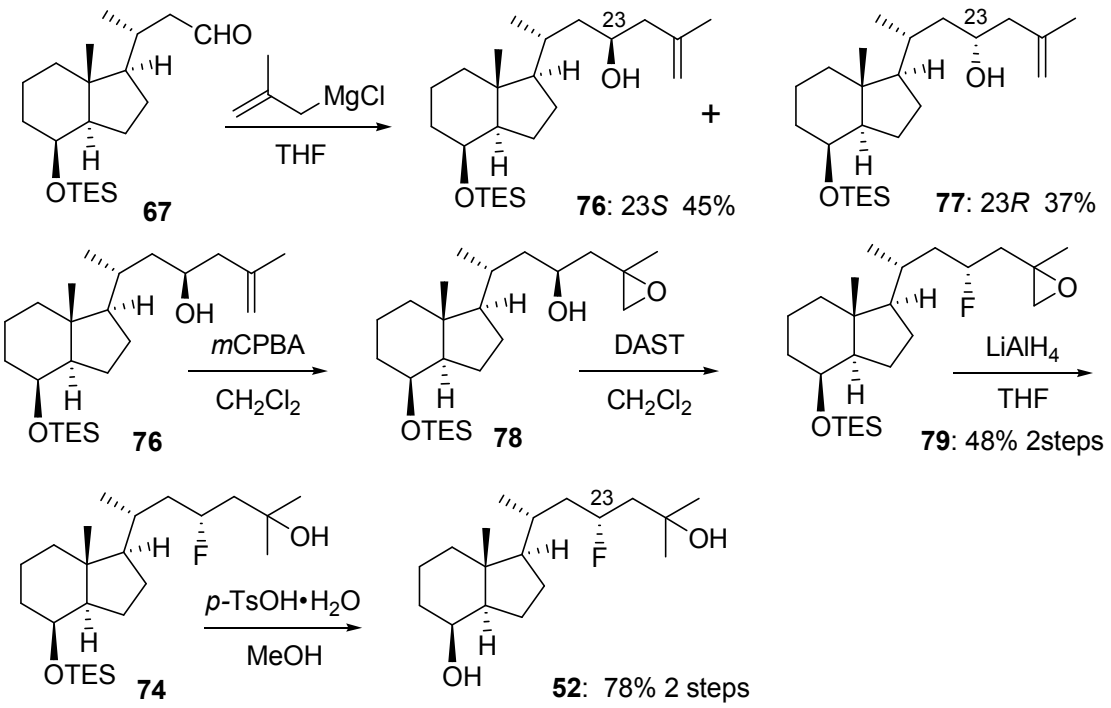
Scheme 13. 側鎖 23 位がフッ素化された CD 環部の合成

そこで、23 位 25 位水酸化体 **70**,**71** を用いて、フッ素化反応を試みた。DAST を用いた際には目的のフッ素化体 **74**,**75** は得られなかったが、より温和な条件下で立体反転を伴う脱酸素的フッ素化を行うことが出来る PyFluor を用いたところ [77]、23 位に導入されたヒドロキシ基の立体化学から立体反転した 23 位フッ素化体 2 種を中程度の収率で得ることが出来た（Scheme 14）。



Scheme 14. 側鎖 23 位がフッ素化された CD 環部の合成

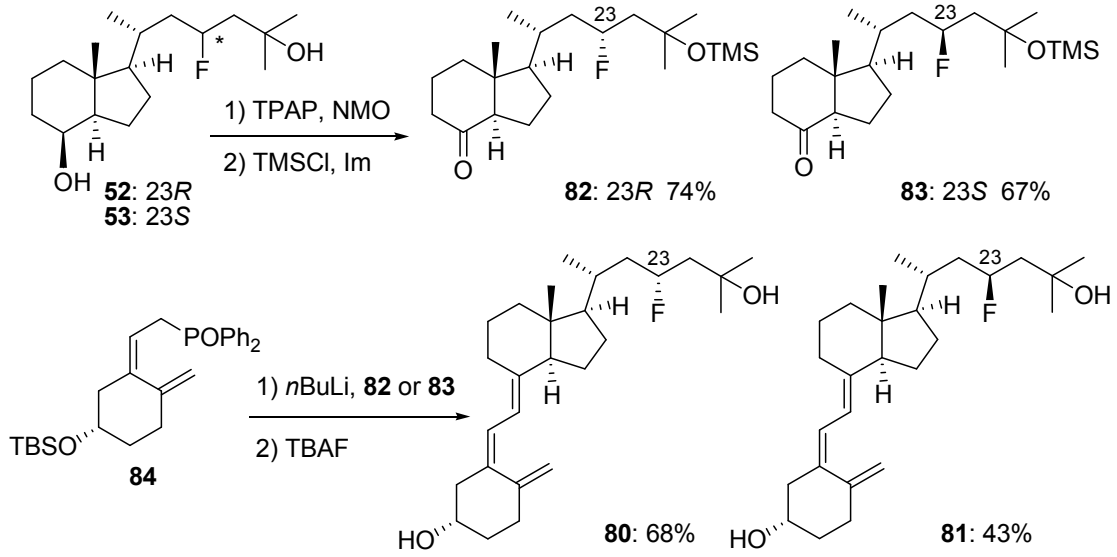
Scheme 14 の合成ルートでは脱酸素的フッ素化の工程で 23*R* 体 **74** が低収率にとどまってしまったため、別工程からの効率的合成法の開発を行った（Scheme 15）。アルデヒド体 **67** に対し、methylallylmagnesium chloride を作用させ、得られた 23*S* 体 **76** と 23*R* 体 **77** をカラムクロマトグラフィーで分離した。**76** の末端オレフィン部位を *m*CPBA でエポキシ化し、続いて DAST による脱酸素的フッ素化で 23*R* のフッ素化体 **79** とした。**79** のエポキシ部位を $LiAlH_4$ で開環し、8 位ヒドロキシ基の脱シリル化で目的の 23*R* フッ素化 CD 環部 **52** をより効率よく得ることが出来た。



Scheme 15. 側鎖 23 位がフッ素化された CD 環部の改良合成

合成した 23 位フッ素化体が、CYP24A1 に対して代謝抵抗性をもつかを試験するために、(23*R*)-フルオロ-25-ヒドロキシビタミン D_3 [(23*R*)-F-25(OH)D_3]（**80**）とその 23*S* 体 [(23*S*)-F-25(OH)D_3]（**81**）をそれぞれ合成し、25(OH)D_3 （**1**）と比較することとした。

(23*R*)-フッ素化体 **52** と(23*S*)-フッ素化体 **53** の 8 位を TPAP 酸化し、25 位を TMS 保護することで得られた 8-ケト体（**82**,**83**）を別途合成した A 環部ホスフィンオキシド（**84**）[78]とカップリングさせることで、23 位フッ素化ビタミン D_3 誘導体（**80**,**81**）を合成した（Scheme 16）。これら **80** と **81** の CYP24A1 に対する代謝抵抗性を評価したところ、25(OH)D_3（**1**）と比較して 23*R* 体 **80** は **1** と同等の効率で代謝されたが、23*S* 体 **81** は k_{cat}/K_m 値から 4 倍程度の高い代謝抵抗性をもつという興味深い知見を得た [79]（Table 1）。



Scheme 16. 側鎖 23 位がフッ素化されたビタミン D_3 誘導体の合成

Table 1. 25(OH)D_3（**1**）と **80**,**81** の代謝抵抗性評価

Substrate	k_{cat} (min^{-1})	K_m (μM)	k_{cat}/K_m
25(OH)D_3 (**1**)	15.3 ± 4.5	0.76 ± 0.21	20.1
(23*R*)-23-F-25(OH)D_3 (**80**)	7.8 ± 2.1	0.39 ± 0.13	20.0
(23*S*)-23-F-25(OH)D_3 (**81**)	2.1 ± 0.5	0.38 ± 0.13	5.5

第 7 節　ビタミン D_3 側鎖 24 位への効率的ジフルオロ基導入法の開発

ビタミン D_3 側鎖 24 位も同様に CYP24A1 の働きにより水酸化を受け、その後多段階の酸化工程を経てカルシトロン酸に代謝不活化される（Figure 18）。そのため、側鎖 24 位の水酸化を防ぐ目的で 24 位がジフルオロ化されたビタミン D_3 誘導体の合成は、高山らのグループ [80-83]や小林らのグループ [84]によって精力的に行われてきており、その主たる合成法ではコレステロール骨格が出発原料として利用された。著者は 24 位ジフルオロ化ビタミン D_3 誘導体の重要な合成前駆体である CD 環部 **30** に着目した。**30** はこれまでに DeLuca らによって 1 例合成例が報告されているが [85]、その手法は全収率の低さなどの問題点が内在しており、大スケールでの合成を鑑みた際には更なる改善が求められる（Scheme 17）。

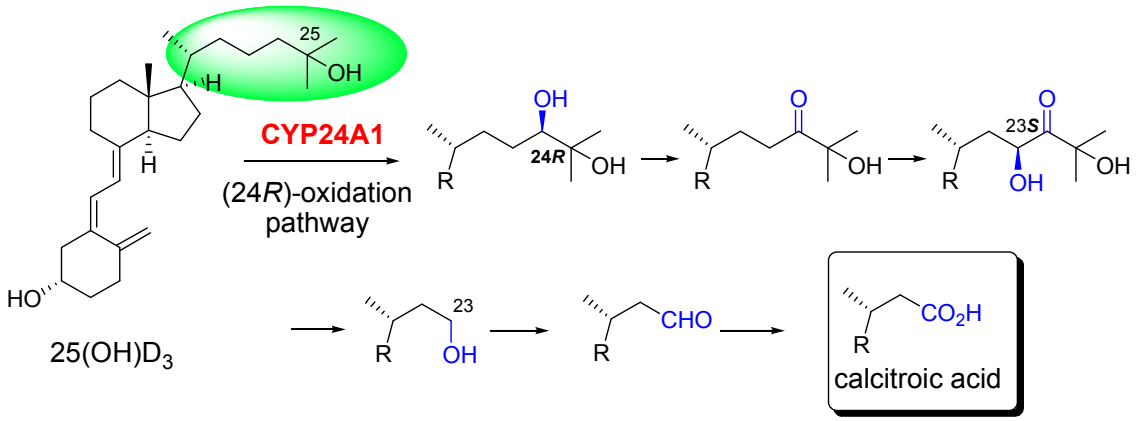
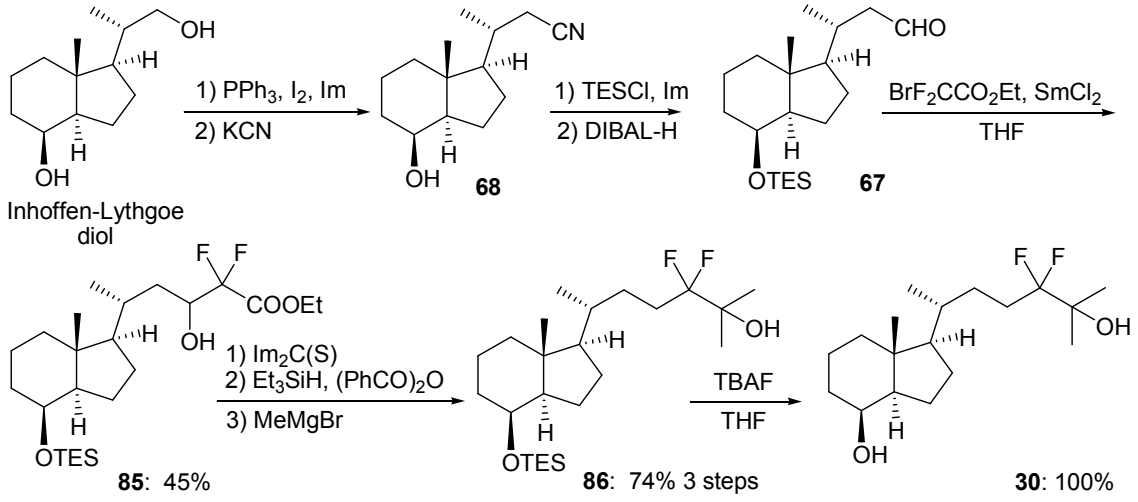


Figure 18. CYP24A1 による 25(OH)D_3 の 24 位水酸化経路

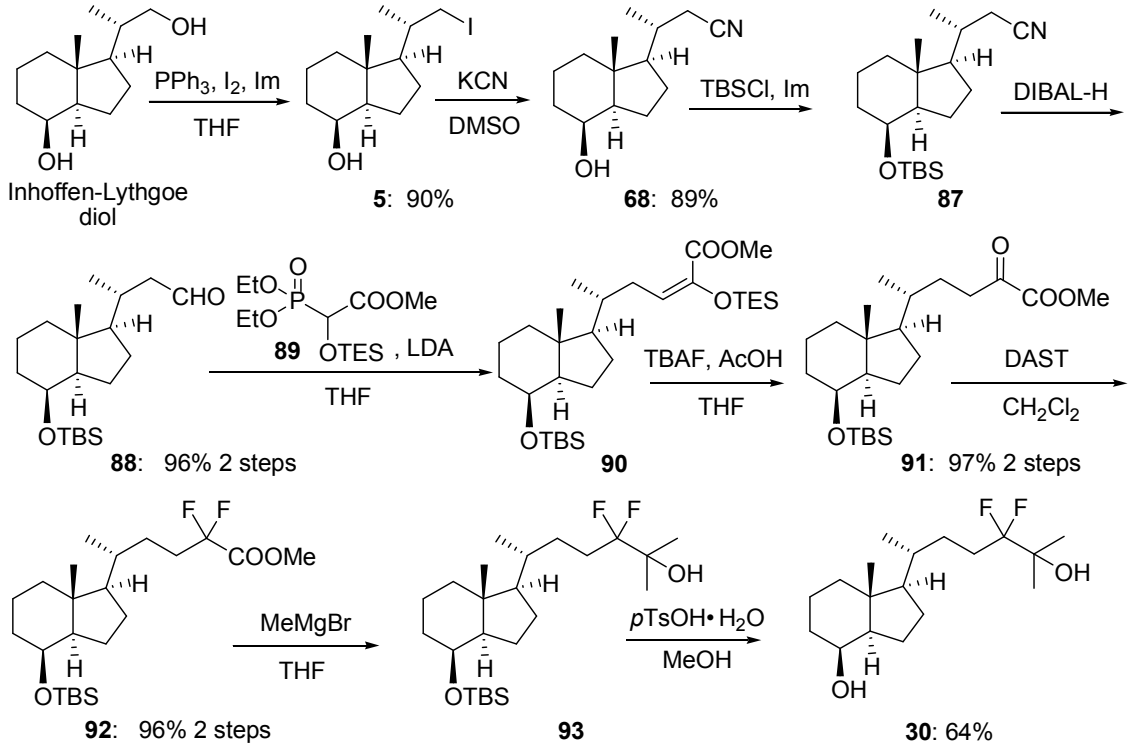


Scheme 17. 側鎖 24 位がフッ素化された CD 環部 **30** の合成（DeLuca ら）

そこでより簡便で効率的な合成法の探索研究を行い、本合成ステップの重要な鍵反応であるジフルオロ部位の導入を α-ケトエステルに対する DAST を用いるジフルオロ化反応を適用することとし合成検討を開始した。

合成法を Scheme 18 に示した。第 3 章第 2 節の合成と同様に Inhoffen-Lythgoe diol から第一級アルコールのヒドロキシ基をヨウ素化し、シアノ基へと変換した。8 位ヒドロキシ基の TBS 化を行った後に、DIBAL-H による還元と続く加水分解を経ることでアルデヒド **88** へと導いた。中村の手法 [86,87]を参考に合成した Horner-Emmons 試薬 **89** と **88** をカップリン

グさせ、得られたシリルエノールエーテル **90** に対して酢酸存在下 TBAF を作用させることで鍵化合物である α-ケトエステル **91** へと誘導した。酢酸は本反応を円滑に進行させるうえで必要不可欠であり、エノールエーテル分解時に発生する α-アニオンを速やかにプロトン化させるうえで、適度な酸性度を持つプロトンソースとしての役割を持っていると考えられる。α-ケトエステル **91** に対して DAST によるフッ素化を行い、ジフルオロメチレン部位を構築し、続いて methyl Grignard 試薬を作用させることで **93** へと導いた。最後に 8 位のヒドロキシ基の脱シリル化により目的の 24,24-difluoro CD 環部（**30**）をアルデヒド体 **88** から全収率 60%で合成することができ、DeLuca らの手法と比較して 2 倍以上の効率で合成可能であることを示した [88]。

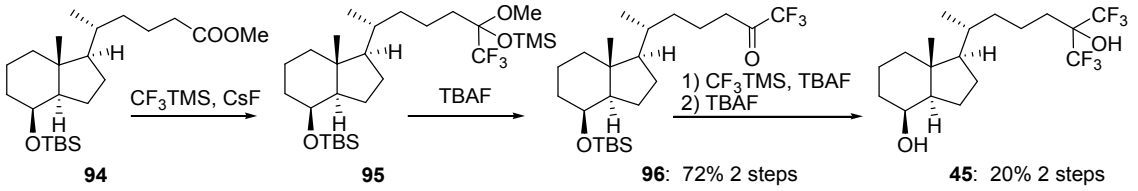


Scheme 18. 側鎖 24 位がフッ素化された CD 環部 **30** の合成

第 8 節　ビタミン D_3 側鎖へのヘキサフルオロイソプロパノール構造の導入

第 3 章第 2 節でも述べたように側鎖上 C26 と C27 両メチル基がそれぞれトリフルオロメチル基に変換されたヘキサフルオロイソプロパノール構造を有するビタミン D_3 誘導体も、導入されているフッ素原子の影響で CYP24A1 に対する高い代謝抵抗性を持つ[57-59]。それ故、代謝抵抗性を持つビタミン D 誘導体合成における有力な候補構造として、その前駆体である CD 環部 **45** の効率的合成法の開発を行った。一般的にヘキサフルオロイソプロパノール構造の構築はヘキサフルオロアセトンに対する求核付加反応で行われるが[89-97]、ヘキサフルオロアセトン三水和物の脱水や乾燥工程、反応で使用する際のヘキサフルオロアセトンガスの使用の煩雑さが本手法の問題点であるといえる。それらの問題点を回避する目的で、CF_3TMS[98]を用いたエステル構造に対する二段階トリフルオロメチル化反応を利用し、CD 環部側鎖にヘキサフルオロイソプロパノール構造の導入を行った。

側鎖にメチルエステルが導入された CD 環部 **94**[99]に対し、一段階目の CF_3 化は真空減圧で乾燥した CsF を触媒として用いることで、エステル部位への CF_3 化が進行した。生成したアセタール構造を TBAF で CF_3 ケトン構造へと導いたのちに、二段階目の CF_3 化を CF_3TMS/TBAF の系で行い、次いで 8 位ヒドロキシ基の脱シリル化を経ることで目的の CD 環部 **45** を合成することが出来た[100]（Scheme 19）。



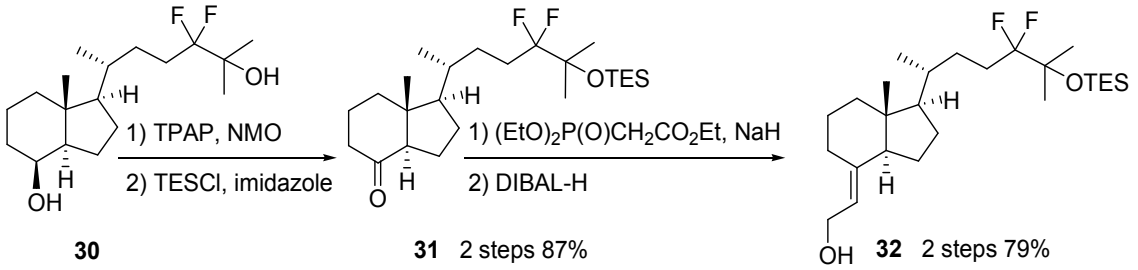
94　**95**　**96**: 72% 2 steps　**45**: 20% 2 steps

Scheme 19. 側鎖にヘキサフルオロイソプロパノール構造が導入された CD 環部の合成

第 4 章　代謝抵抗性をもつビタミン D_3 誘導体の合成及びその活性評価

第 1 節　側鎖 24 位がジフルオロ化されたビタミン D_3 誘導体の合成

第 3 章で合成した側鎖 24 位がジフルオロ化された CD 環部 **30** を出発原料として第 2 章第 2 節と同様の合成法でアリルアルコール **32** へと変換した（Scheme 20）。

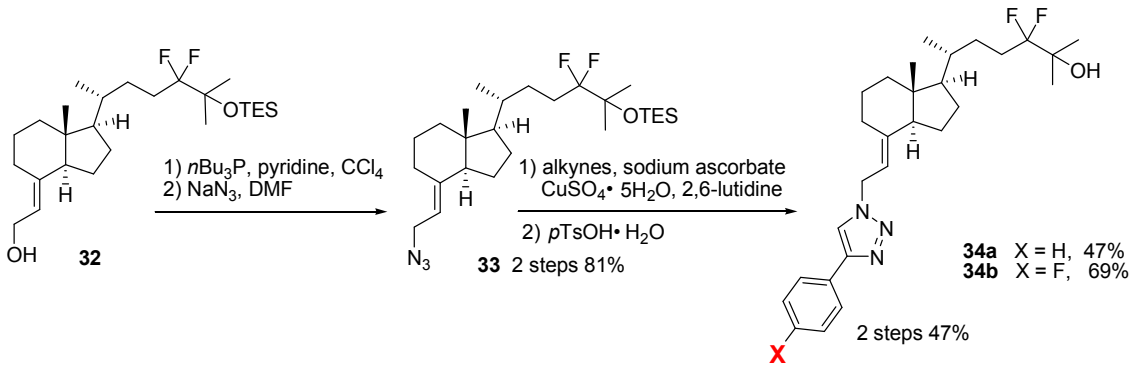


30　　**31**　2 steps 87%　　**32**　2 steps 79%

Scheme 20. 側鎖 24 位がジフルオロ化された CD 環部アリルアルコール体の合成

合成したアリルアルコール体に対し、擬似 A 環部の導入をおこなった。第 2 章第 7 節で *in vitro* における SREBP 阻害活性、VDR 無活性の双方の結果が良好であった 4-フェニルトリアゾール環と 5-フェニルテトラゾール環を基本骨格として合成した。

まずは、トリアゾール環の導入法を以下に示す（Scheme 21）。アリルアルコール部位を第 2 章第 6 節と同様の手法で塩素化し、続いてアジド体 **33** へと変換した。導入したアジド基とフェニルアセチレンおよび 4-フルオロフェニルアセチレンをそれぞれクリック反応でカップリングさせ、25 位の脱シリル化を経ることでトリアゾール環をもつ誘導体 **34a** と **34b** を合成した。



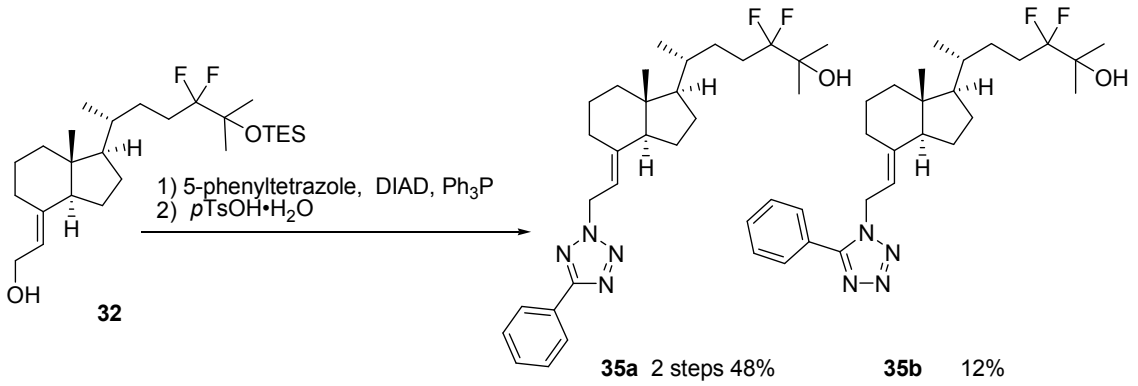
32　　**33**　2 steps 81%

34a　X = H,　47%
34b　X = F,　69%

2 steps 47%

Scheme 21. トリアゾール環を有する新規フッ素化ビタミン D_3 誘導体（**34a**,**34b**）の合成

続いてアリルアルコール体に対し、テトラゾール環の導入をおこなった。第 2 章第 5 節で行った手法を用いて 5-フェニルテトラゾール環を導入し、得られた 2 位置換体 **35a** と 1 位置換体 **35b** 双方をシリカゲルカラムクロマトグラフィーで精製単離した（Scheme 22）。



Scheme 22. テトラゾール環を有する新規フッ素化ビタミン D_3 誘導体（**35a**,**35b**）の合成

本手法を用いて合成した誘導体群を以下に示す。A 環部フェニル基上に置換基導入を行い、パラ置換体 **36a**～**39b**（Figure 19）、メタ置換体 **40a**～**42b**（Figure 20）、オルト置換体 **43a**～**44b**（Figure 21）を得ることができた。

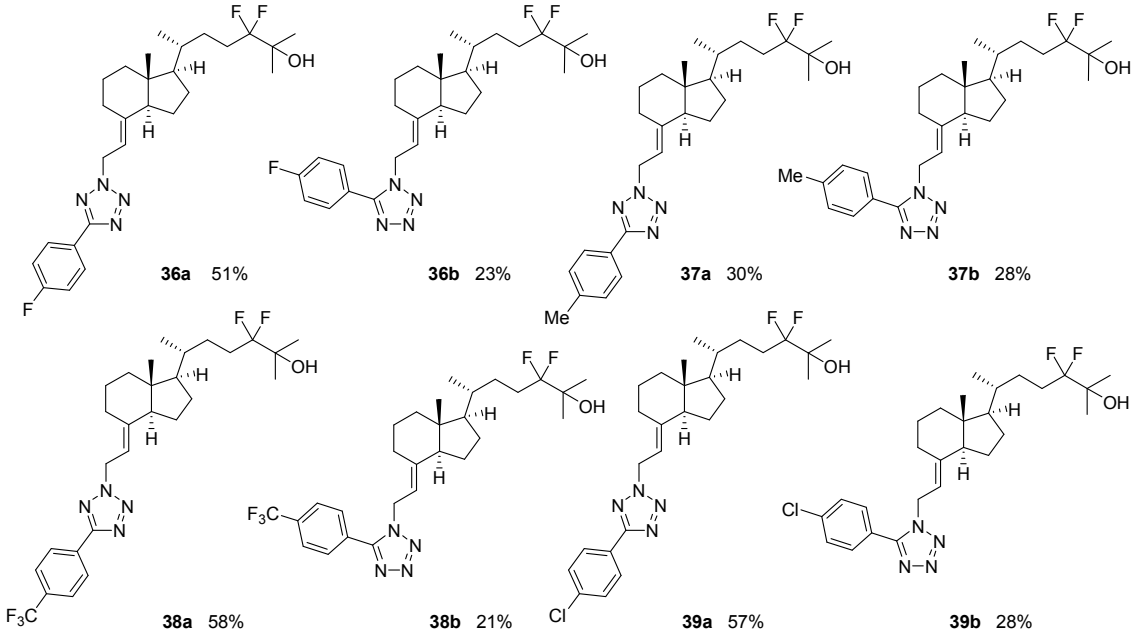


Figure 19. パラ置換フッ素化ビタミン D_3 誘導体

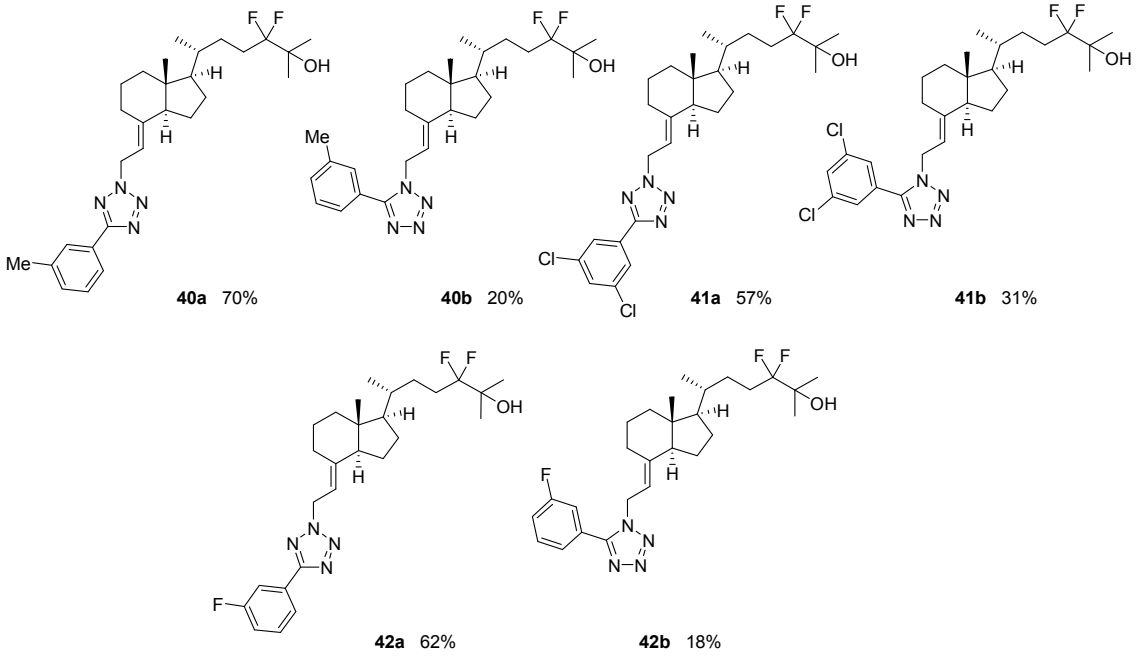


Figure 20. メタ置換フッ素化ビタミン D_3 誘導体

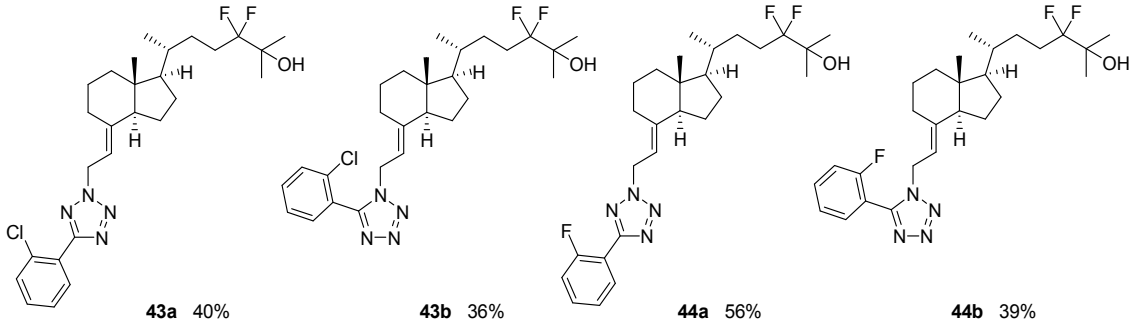
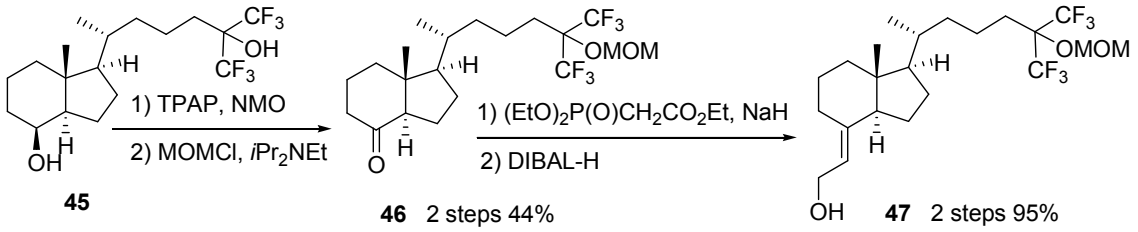


Figure 21. オルト置換フッ素化ビタミン D_3 誘導体

第 2 節

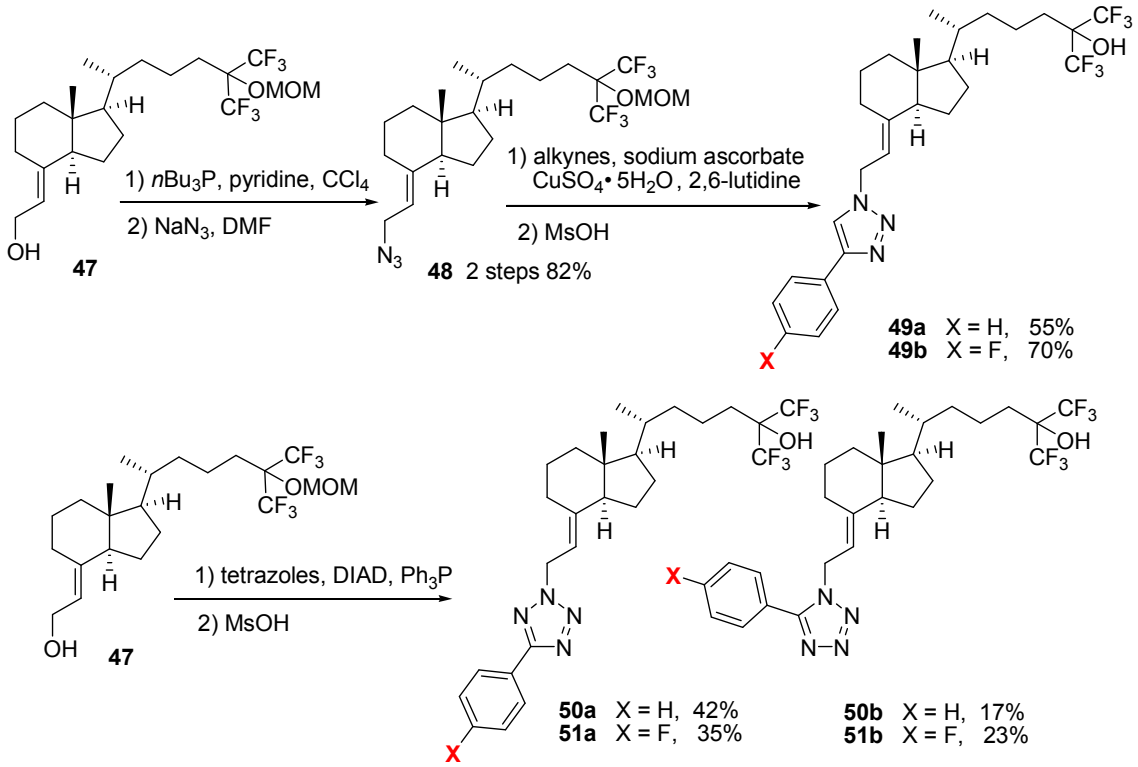
側鎖にヘキサフルオロイソプロパノール構造が導入されたビタミン D_3 誘導体の合成

側鎖にヘキサフルオロイソプロパノール構造が導入された CD 環部 **45** を出発原料として第 2 章第 2 節の手法を応用することで、4 段階でアリルアルコール **47** へと変換した（Scheme 23）。



Scheme 23. ヘキサフルオロイソプロパノール骨格を有する CD 環部アリルアルコール体 **47** の合成

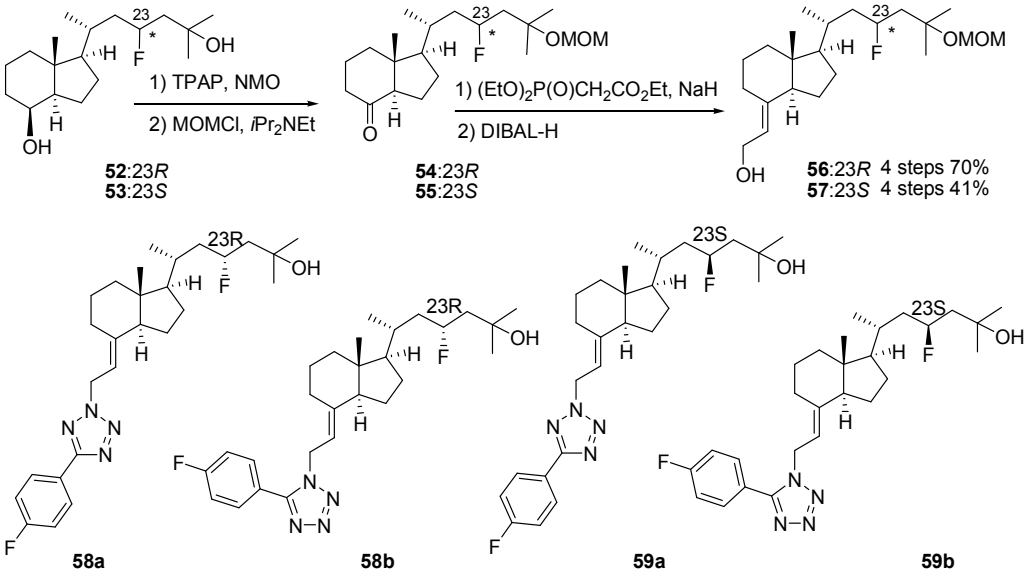
第 2 章第 6 節の手法によりアリルアルコール部位を塩素化し、次いでアジド化、続いてクリック反応によりトリアゾール環を導入した。また **47** に対し光延反応でテトラゾール環を導入した（Scheme 24）。



Scheme 24. ヘキサフルオロイソプロパノール骨格を有するビタミン D_3 誘導体の合成

第 3 節　側鎖 23 位がフッ素化されたビタミン D_3 誘導体の合成

側鎖 23 位モノフッ素化体 2 種、すなわち 23*R* 体 **52** と 23*S* 体 **53** をそれぞれ利用してビタミン D_3 誘導体合成を行った（Scheme 25）。同様の手法でフッ素化 CD 環部からアリルアルコール体（**56**,**57**）へと導き、光延反応により 4-フルオロフェニルテトラゾール環を導入することで 4 種類のビタミン D_3 誘導体（**58a**,**58b**,**59a**,**59b**）を合成した。

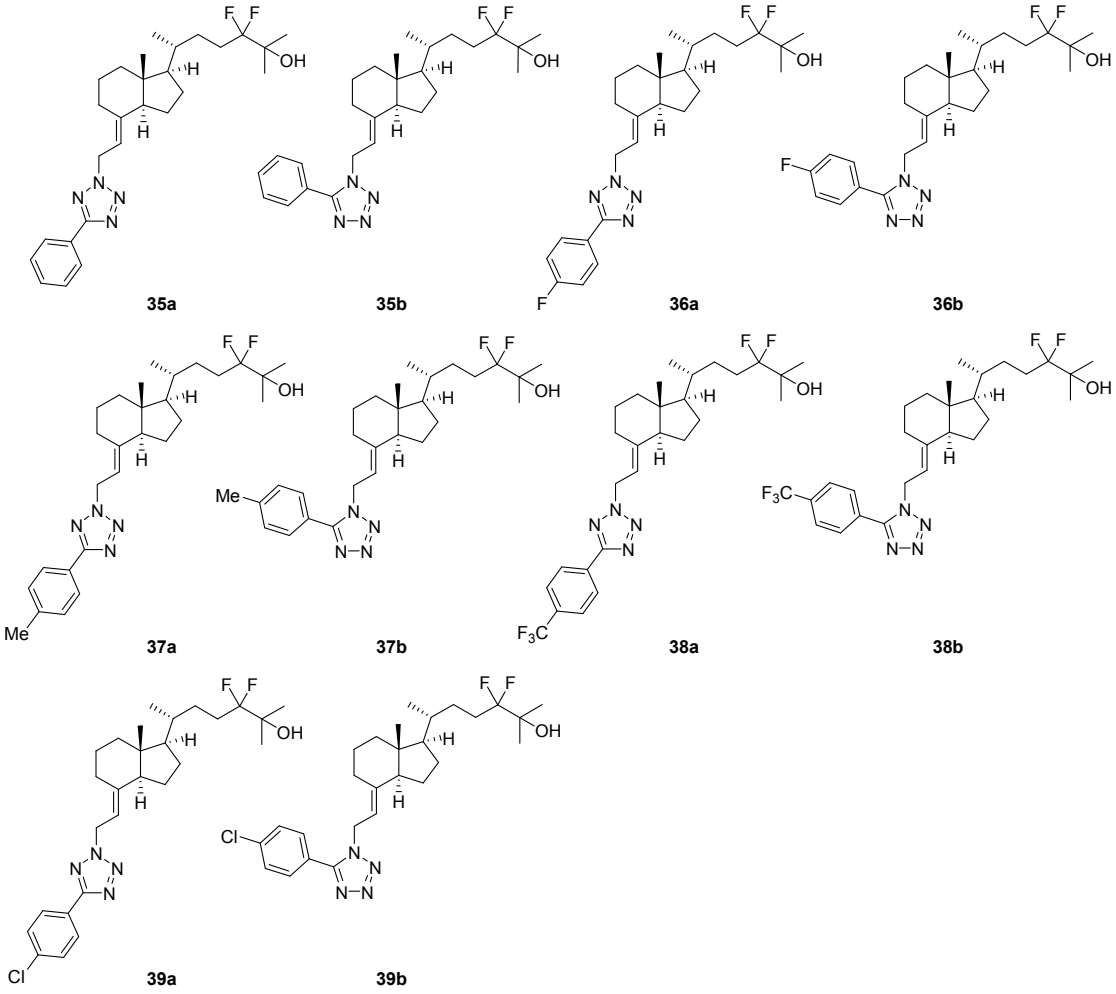


Scheme 25. 側鎖 23 位がフッ素化されたビタミン D_3 誘導体の合成

第 4 節　側鎖がフッ素化されたビタミン D_3 誘導体の活性評価

合成した側鎖がフッ素化されたビタミン D_3 誘導体の *in vitro* での評価について、京都大学上杉研究室で実施した。第 4 章第 1 節で合成した側鎖 24 位がジフルオロ化されたビタミン D_3 誘導体について、CHO K1 細胞を用いるルシフェラーゼレポーターアッセイによりその SREBP 阻害活性を評価した結果、多くの誘導体が 25(OH)D_3（**1**）と同程度の SREBP 阻害活性を示した（Figures 22,23）。芳香環上へのフッ素導入（**36a**,**36b**,**42a**,**42b**,**44a**,**44b**）は SREBP 阻害活性にほとんど影響を与えないことが分かった。その一方で、嵩高い置換基が導入され

た誘導体群（**38a**,**38b**,**41a**,**41b**）では、SREBP 阻害活性が低下傾向を示した。



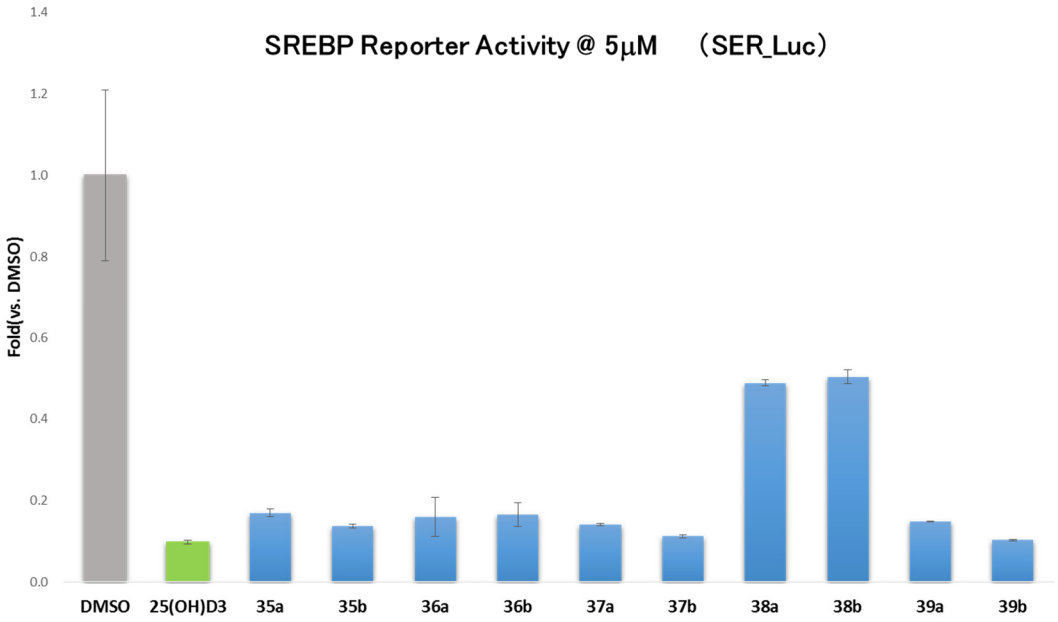
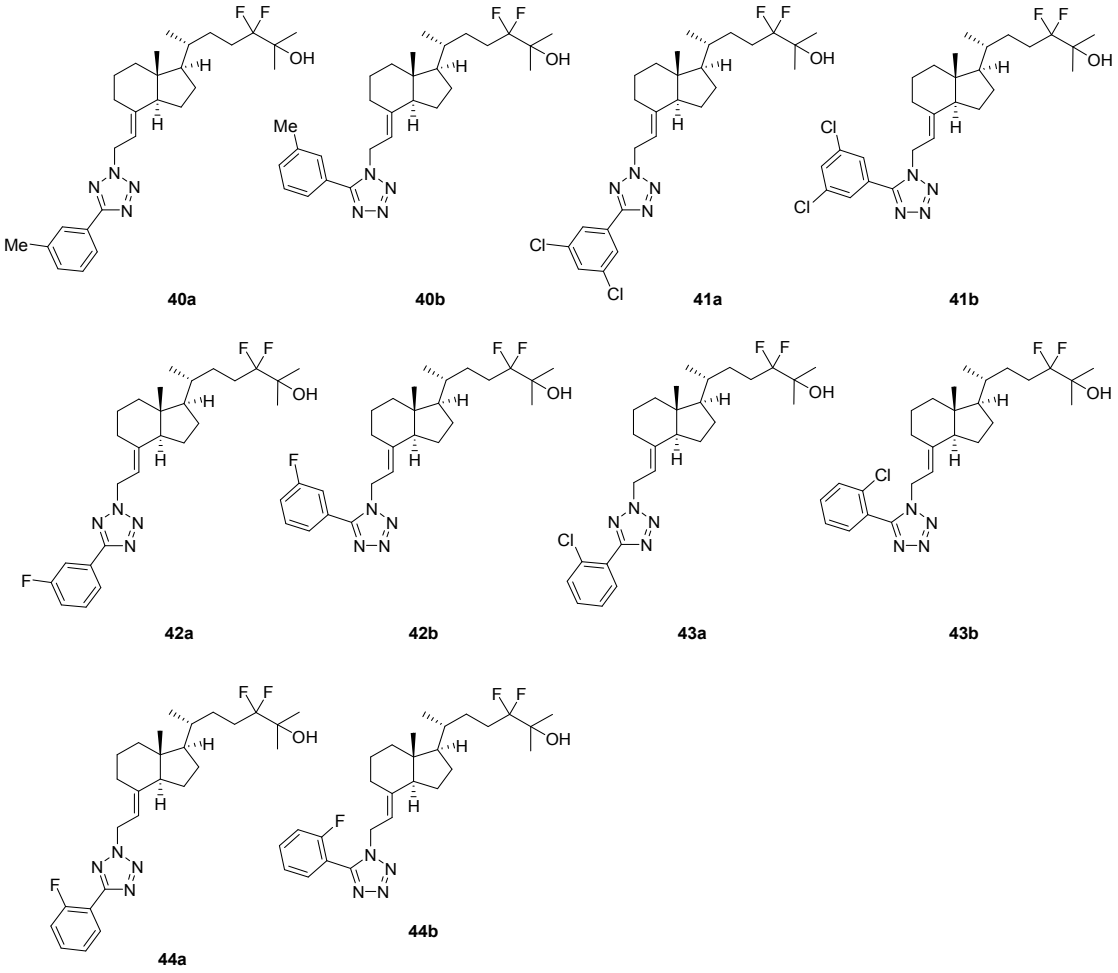


Figure 22. レポーターアッセイによる SREBP 阻害活性評価（上杉ら）



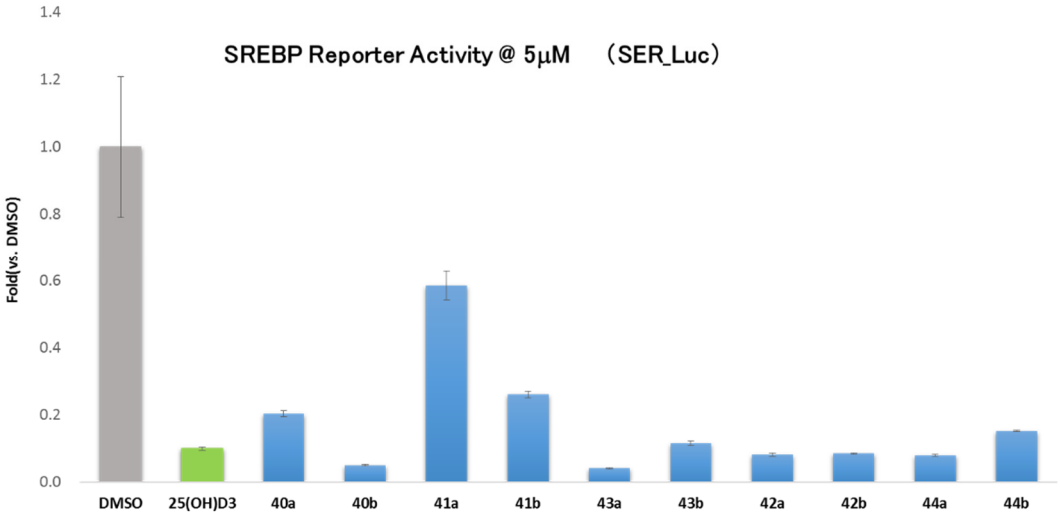


Figure 23. レポーターアッセイによる SREBP 阻害活性評価（上杉ら）

次に、上記の誘導体について、CHO K1 細胞を用いたルシフェラーゼレポーターアッセイによりその VDR 活性を評価した。その結果、ベンゼン環上パラ位に置換基導入されたもの（**36a**,**36b**,**37a**,**37b**,**38a**,**38b**,**39a**,**39b**）は、若干の VDR 活性が認められたが、どの誘導体でも 25(OH)D_3（**1**）と比較して VDR 活性は弱く、狙いの作用分離の観点からも良好な結果を与えることが分かった（Figures 24,25）。

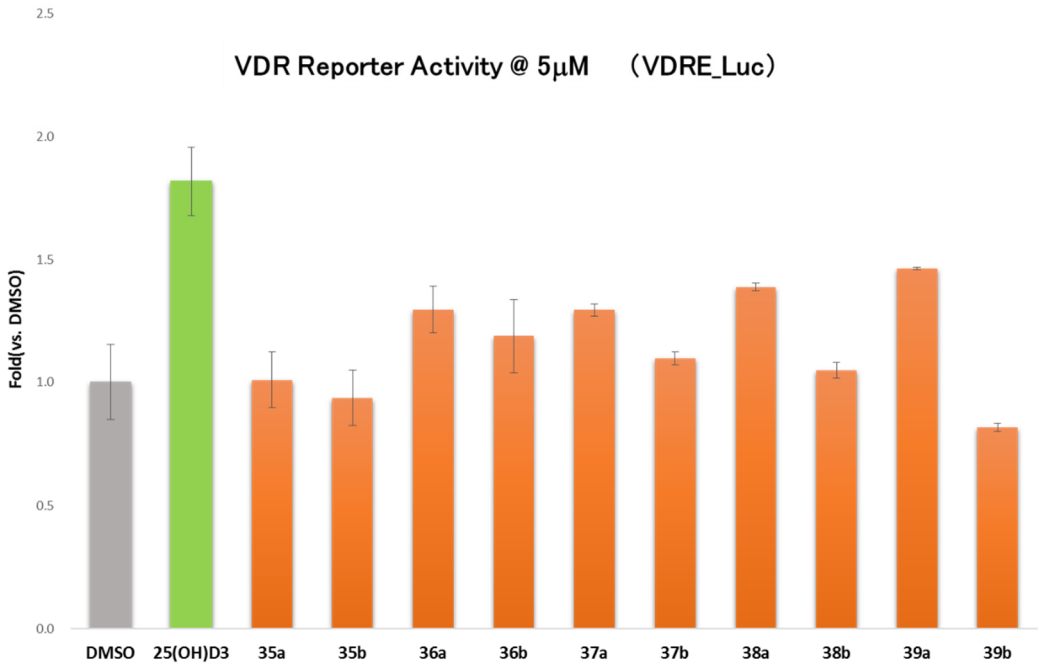


Figure 24. レポーターアッセイによる VDR 活性評価（上杉ら）

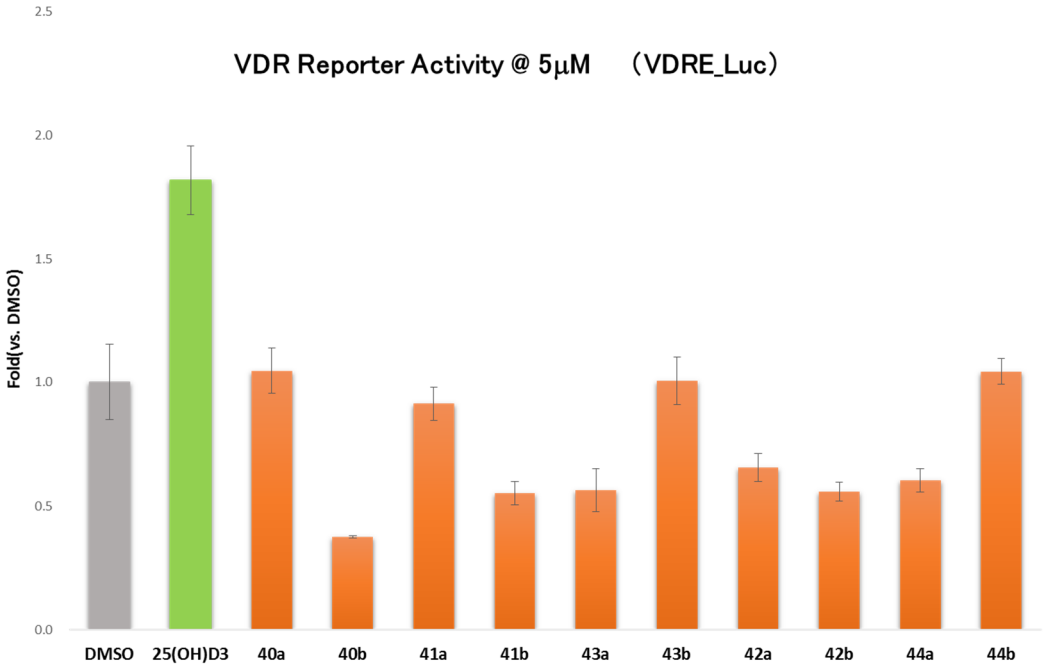


Figure 25. レポーターアッセイによる VDR 活性評価（上杉ら）

続いて合成した新規フッ素化ビタミン D_3 誘導体群の *in vivo* による評価について、東京大学医学部消化器内科中川勇人博士の所属グループで実施した。最初に *in vitro* の評価で結果の良かった誘導体 **35b** を用いてマウスによる短期での活性評価を行った。その評価方法を以下に示す。

3 種類の飼育条件のマウスを作製した（Figure 26）。1 つ目のグループはコントロールデータとして通常食を 96 時間与えた群、2 つ目のグループは 48 時間絶食後、48 時間低脂肪高炭水化物ビタミン D 欠乏食を与えた群、3 つ目のグループは 2 番目のグループと同様の条件で **35b** を 24 時間ごとに 10 mg/kg ずつ腹腔内投与した群であり、それぞれのマウスの 96 時間後の SREBP 標的遺伝子の発現量を比較することで **35b** の SREBP 阻害活性を評価した。コントロールマウスと比較して 2 番目のマウスの SREBP 下流遺伝子は高発現することが確認できた。そして **35b** 投与群は非投与群である 2 番目のマウスと比較し、SREBP 下流遺伝子の発現を抑制しており、**35b** の投与が SREBP 阻害している可能性を示す結果を得ること

が出来た（Figure 27）。同時に、**35b** 投与群では血清カルシウム濃度の上昇は確認されず、短期の試験では良好な結果を得ることが出来た（Figure 28）。

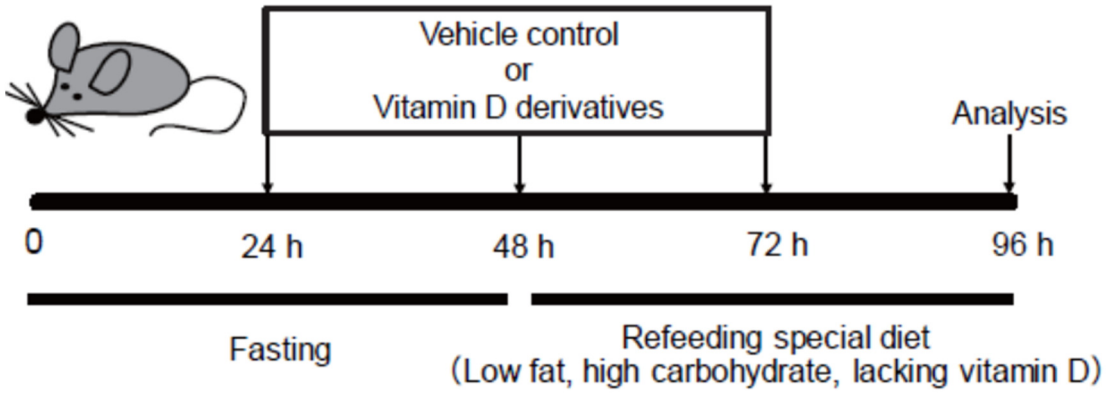


Figure 26. 短期試験用マウスの作成手順（中川ら）

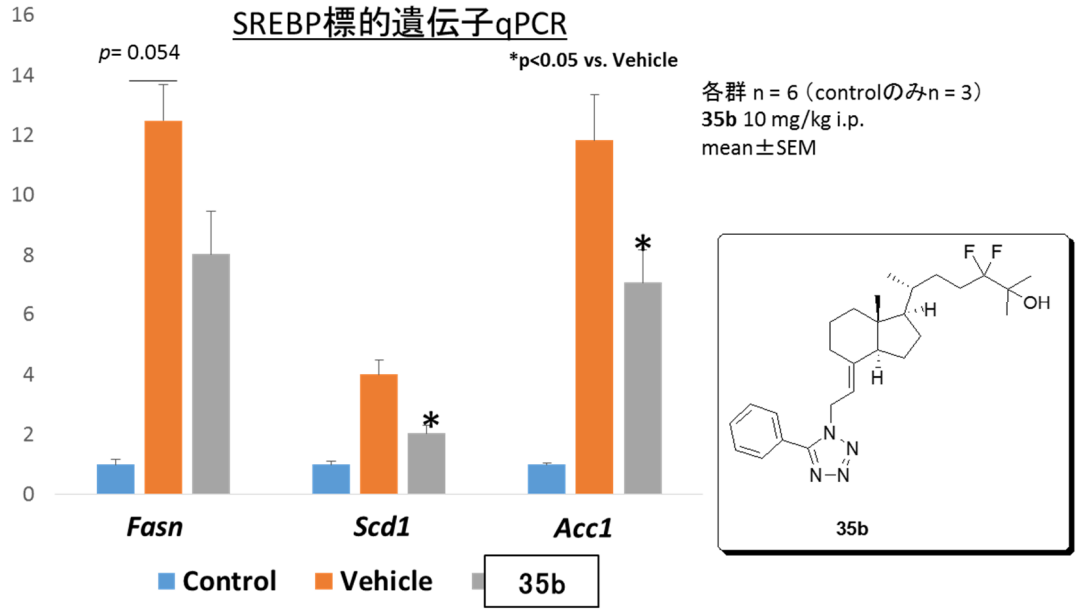


Figure 27. SREBP 下流遺伝子の発現量（中川ら）

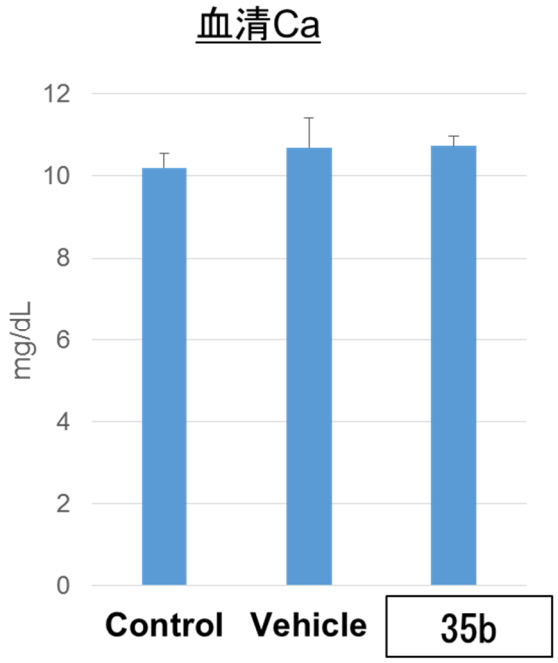


Figure 28. 血清中のカルシウム量（中川ら）

続いて **35b** を長期評価へと適用した。レプチンを欠損した ob/ob マウスに対し **35b** を週に 5 回 10 mg/kg ずつ腹腔内投与し、4 週間にわたって評価を行った（Figure 29）。4 週間後のマウスの体重変化量を比較したところ **35b** を投与しない群と比較して **35b** 投与群では体重の増加が減少することが確認できた。一方、25(OH)D_3 投与群は副作用である高カルシウム血症を発症し衰弱していくという結果となった（Figure 30）。**35b** 投与群では血清 ALT も減少しており、肝臓機能の低下を抑制するのと同時に血中のカルシウム濃度も上昇していないことから、高カルシウム血症という VDR を介する副作用を発症していないことも示すことができた（Figure 31）。肝臓の病理写真では脂肪の蓄積量が **35b** を投与していない群と比較して抑制されていることが判別できた（Figure 32）。

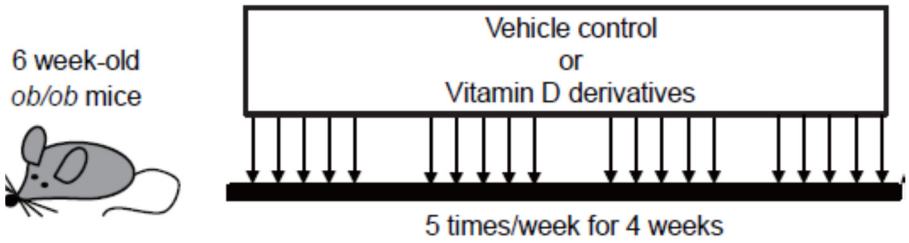


Figure 29. ob/ob マウスに対する長期試験（中川ら）

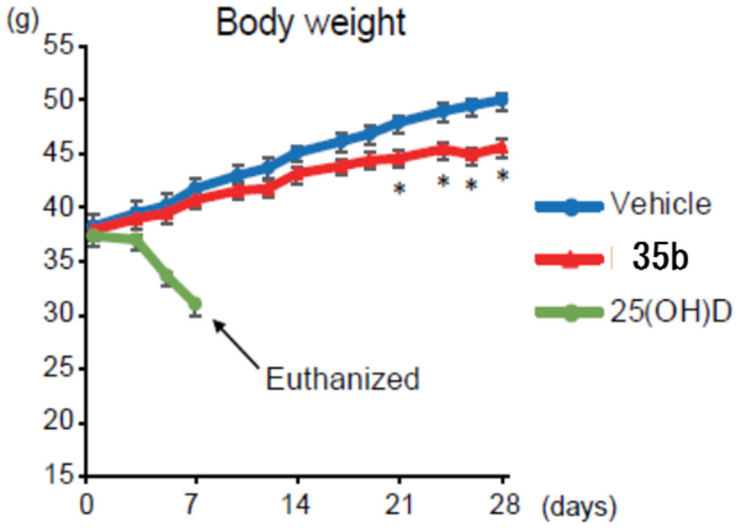


Figure 30. ob/ob マウスの 4 週間の体重変化（中川ら）

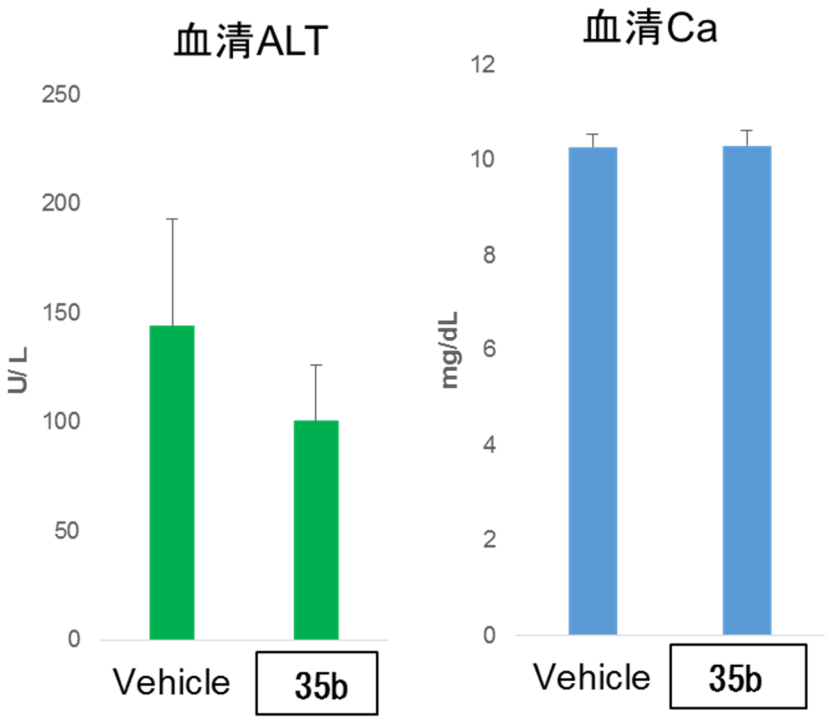


Figure 31. 4 週間後における ob/ob マウスの血液検査結果（中川ら）

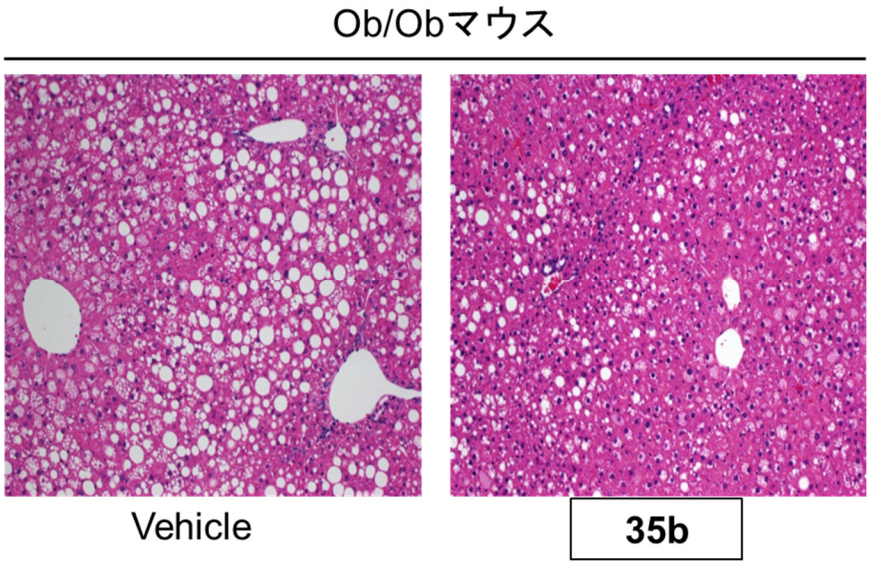


Figure 32. 4 週間後におけるマウスの肝臓病理写真（中川ら）

第 5 節　誘導体群の *in vivo* における体内動態の考察

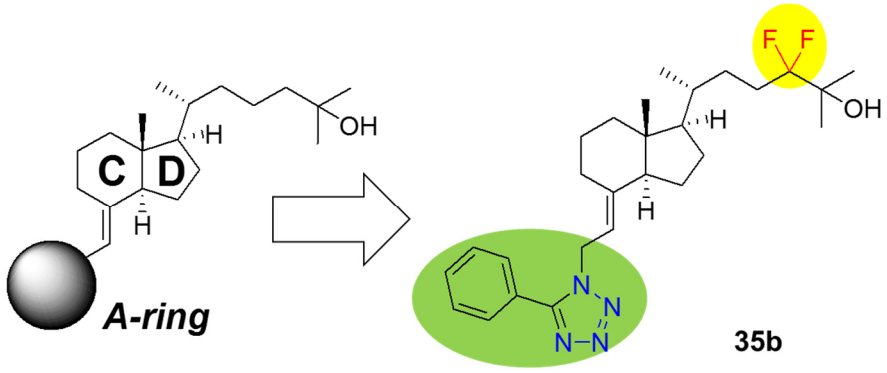
合成したこれら誘導体群の *in vivo* における体内動態は、過去に合成された他のビタミン D 誘導体と類似していると考えられる。第 2 章でも上述したように、ビタミン D_3 は肝臓で 25 位の水酸化を受けた後、腎臓で 1 位の水酸化を経て活性型ビタミン D_3 となり各組織に運ばれてその役割を果たす。それらの過程において、ビタミン D_3 が血中を輸送されるときにビタミン D 結合タンパク（DBP）と結合することが知られている。

しかしながら、所属研究室で開発した A 環部 2 位が置換基修飾されたビタミン D_3 誘導体は DBP との結合能が大幅に低下するものがあり、特に 2 位α方向にヒドロキシプロピル基を有する 19-ノルビタミン D_3 誘導体（MART-10）では活性型ビタミン D_3 の 4%程度に低下することが知られている [35,49]。本研究で合成した誘導体群も MART-10 と同様に、構造変化がなされた擬似 A 環部が導入されており、このことから血中では DBP と結合せずに存在していると考えられる。

誘導体群の細胞への取り込み機構は、類似の脂溶性と構造をもつという共通点から、活性型ビタミン D_3 と同様に進行していると考えられる。細胞中へと取り込まれた後は、その脂溶性から小胞体膜中の脂質二重層に侵入し、そこで膜タンパクとして存在する SCAP と相互作用することで活性が発現すると考察される。

第 5 章　結語

VDR を介する作用を示さず高選択的に SREBP を阻害する、『脂質生合成を選択的に阻害する新規ビタミン D_3 誘導体の創製』を目的として、新規誘導体群の合成を行った。ビタミン D_3 誘導体の新規化合物 87 種類を合成した。その結果、擬似 A 環部として立体的嵩高さの小さな置換基が導入された際には SREBP 阻害活性は発現しなかったが、中程度の立体的嵩高さの誘導体群では活性が発現した。そしてさらに嵩高い置換基が導入された際には活性が消失した。これらの知見から最適 A 環構造の探索と同時に CYP24A1 代謝抵抗性の向上を目指し、側鎖フッ素導入を行った結果、6 位に二環性の 5-フェニル-1*H*-テトラゾール構造を有し、24 位がジフルオロ化された新規ビタミン D_3 誘導体 **35b** が、VDR 活性が発現せず、SREBP を選択的に阻害することを見出した。また、誘導体の合成過程において、側鎖がフッ素化された CD 環部 4 種の新規効率的合成法を確立することに成功した。



CD 環部置換基 6 位に様々な擬似 A 環部構造を導入したビタミン D 誘導体合成を行った。立体的嵩高さの小さな置換基を導入した際には、極性の大小にも関わらず SREBP 阻害活性は発現しなかったが、より嵩高い環状の置換基を導入した際に SREBP 阻害活性が発現し、さらに嵩高い置換基や直鎖上の置換基を導入すると活性が消失するという知見を得た。合成した誘導体は導入されている A 環部の影響で VDR 活性を抑えることが出来た。しかしながら合成した誘導体群は *in vivo* の評価で SREBP 阻害活性は発現しなかった。これらの研究結果について第 2 章で述べた。

CYP24A1 に対する代謝抵抗性を高める目的で、側鎖部がフッ素化されたビタミン D 誘導体の合成前駆体であるフッ素化 CD 環部 4 種の新規効率的合成法の開発を行った。すなわち、

①23 位フッ素化 CD 環部 2 種の新規立体選択的合成法の開発：23 位水酸化体の立体化学は新 Mosher 法で決定し、続いて PyFluor を用いた立体選択的脱酸素的フッ素化反応によりフッ素導入を行った。

②24 位がジフルオロ化された CD 環部の効率的合成法の開発：ジフルオロ基の導入は α-ケトエステルに対する DAST を用いたジフルオロ化反応によって行った。

③ヘキサフルオロイソプロパノール構造の効率的導入法の開発：カルボニル基に対する二段階の CF_3 化反応によりヘキサフルオロイソプロパノール構造を導入した。

これらの研究成果について第 3 章で述べた。

第 3 章で合成法を確立した CD 環部を用いて、側鎖部がフッ素化されたビタミン D 誘導体の合成を行った。A 環部の構造は第 2 章で *in vitro* の評価結果が良かったトリアゾール環、テトラゾール環を基本骨格として導入した。その結果、側鎖 24 位へのジフルオロ部位と A 環部として 5-フェニル-1*H*-テトラゾール構造の導入により *in vitro*、*in vivo* 双方の評価系で VDR に作用せず高い SREBP 阻害活性を示すという良好な結果を得た。これらの研究結果について第 4 章で述べた。

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General procedure

^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-400 NMR (400 MHz) and ECP-600 NMR (600 MHz) spectrometers. ^{1}H NMR spectra were referenced with $(CH_3)_4Si$ (δ 0.0 ppm) as an internal standard. ^{13}C NMR spectra were referenced with deuterated solvent (δ 77.0 ppm for $CDCl_3$ and 49.3 ppm for CD_3OD). IR spectra were recorded on a JASCO FT-IR-800 Fourier transform infrared spectrophotometer. High resolution mass spectra were obtained on a SHIMADZU LCMS-IT-TOF mass spectrometer with a positive electrospray ionization (ESI) method. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Column chromatography was performed on silica gel 60N (Kanto Chemical Co., Inc., 40-50 μm) or silica gel 60 (Merck, 0.040-0.063 mm). Preparative thin-layer chromatography was performed on silica gel 60 F_{254} (Merck, 0.5 mm). All experiments were performed under anhydrous conditions in an atmosphere of argon, unless otherwise stated.

(6*R*)-2-Methyl-6-[(1*R*,3a*S*,7a*R*)-7a-methyl-4-methyleneoctahydro-1*H*-inden-1-yl]heptan-2-ol (**10**)

To the suspension of the methyltriphenylphosphonium bromide (90.5 mg, 0.253 mmol) in THF (2 mL) was added *n*-BuLi (146 μL, 1.65 M in hexane, 0.241 mmol) at -78°C and stirred at the same temperature for 15 min and 0°C for 20 min. To the mixture was added 8-keto CD ring (**7**) (50.0 mg, 0.127 mmol) in THF (2 mL) and stirred at the same temperature for 1 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at 0°C, the mixture was extracted with EtOAc twice, dried over Na_2SO_4, filtered, and concentrated. The obtained residue was used for the next reaction without further purification.
Tetrabutylammonium fluoride (381 μL, 1 M in THF, 0.381 mmol) was added to a solution of the above crude residue in THF (5 mL). The mixture was stirred at room temperature for 24 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain **10** (9.6 mg, 27%, 2 steps) as a colorless oil.

10: $[\alpha]_D^{27}$ +63.5 (c 0.754, $CHCl_3$); IR (neat) 3360, 1649, 1469, 1378, 1148, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 1.02-1.09 (m, 1H), 1.21-1.64 (m, 1H), 1.84-2.01 (m, 4H), 2.26 (dd, *J* = 4.1, 13.3 Hz, 1H), 4.46 (d, *J* = 1.8 Hz, 1H), 4.72 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 18.8, 20.8, 22.2, 23.7, 27.7, 29.2, 29.4, 35.4, 36.1, 36.4, 40.2, 44.4, 45.1, 55.3, 56.3, 71.1, 105.0, 149.6; HRMS (ESI^+) calcd for $C_{19}H_{33}$ $[M-OH]^+$ 261.2577, found 261.2577.

(1*R*,3a*S*,7a*R*)-7a-Methyl-4-methylene-1-[(2*R*)-6-methylheptan-2-yl] octahydro-1*H*-indene (**11**)

To the suspension of the methyltriphenylphosphonium bromide (80.7 mg, 0.226 mmol) in THF (2 mL) was added *n*-BuLi (131 μL, 1.65 M in hexane, 0.215 mmol) at -78°C and stirred at 0°C for 20 min. The mixture was added 8-keto CD ring (**12**) [38] (30.0 mg, 0.113 mmol) in THF (2 mL) and stirred at 60°C for 1 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl, the mixture was extracted with EtOAc twice, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane only) to obtain **11** (20.0 mg, 67%) as a colorless oil.

11: $[\alpha]_D^{27}$ +40.5 (c 1.28, $CHCl_3$); IR (neat) 1653, 1469, 1378, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.86 (d, *J* = 1.8 Hz, 3H), 0.88 (d, *J* = 1.8 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.98-1.64 (m, 1H), 1.82-2.01 (m, 4H), 2.24-2.28 (m, 1H), 4.45 (d, *J* = 1.8 Hz, 1H), 4.73 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 18.8, 22.3, 22.6, 22.8, 23.8, 23.9, 27.7, 28.0, 35.4, 36.1, 36.2, 39.5, 40.2, 45.1, 55.3, 56.4, 104.9, 149.7; HRMS (ESI^+) calcd for $C_{19}H_{35}$ $[M+H]^+$ 261.2577, found 261.2577.

(6*R*)-6-{(1*R*,3a*S*,7a*R*,*E*)-4-[2-(*tert*-Butylamino)ethylidene]-7a-methyl octahydro-1*H*-inden-1-yl}-2-methylheptan-2-ol (**14a**)

PDC (127.9 mg, 0.34 mmol) was added to the solution of **4** (99.5 mg, 0.225 mmol) in CH_2Cl_2 (4 mL) and DMF (0.5 mL) at room temperature, and the mixture was stirred at the same temperature under air for 2 h. The solution was diluted with Et_2O, filtered through a celite pad, and concentrated. To the solution of the obtained crude aldehyde **13** above and *tert*-butylamine (99.4 mg,

143 μL, 1.36 mmol) in CH_2Cl_2 (5 mL) was added anhydrous $MgSO_4$ (1g) at room temperature under air. The mixture was stirred for 70 min and refluxed overnight. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The obtained crude imine was used for the next reaction without further purification. To the solution of the above crude imine in MeOH (3 mL) was added $NaBH_4$ (5.1 mg, 0.136 mmol) at 0°C. The mixture was stirred at the same temperature under air for 1 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The obtained crude amine was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (129.3 mg, 0.68 mmol) was added to a solution of the above crude amine in MeOH (10 mL). The mixture was stirred at room temperature under air for 20 min. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was diluted with MeOH (3 mL) and 1 M aqueous NaOH (3 mL) and stirred for 10 min. To the mixture was added H_2O, and extracted with CH_2Cl_2 four times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc only 1% Et_3N) to obtain **14a** (76.2 mg, 93%, 4 steps) as a colorless oil.

14a: $[\alpha]_D^{27}$ +63.0 (c 0.44, $CHCl_3$); IR (neat) 3365, 1470, 1377, 1363, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.98-2.00 (m, 35H), 2.55-2.59 (m, 1H), 3.21-3.30 (m, 2H), 5.08 (t, *J* = 6.7 Hz, 1H) , 6.62-6.64 (m, 2H) , 6.69-6.72 (m, 1H), 7.15-7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.8, 20.8, 22.2, 23.4, 27.7, 28.7, 28.8, 29.2, 29.3, 36.1, 36.4, 39.4, 40.4, 44.4, 45.2, 50.8, 55.7, 56.5, 71.1, 118.6, 141.5; HRMS (ESI^+) calcd for $C_{24}H_{46}ON$ $[M+H]^+$ 364.3574, found 364.3603.

(6*R*)-6-{(1*R*,3a*S*,7a*R*,*E*)-4-[2-(Decylamino)ethylidene]-7a-methyloctahydro-1*H*-inden-1-yl}-2-methylheptan-2-ol (**14b**)

PDC (222.5 mg, 0.591 mmol) was added to the solution of **4** (100.0 mg, 0.237 mmol) in CH_2Cl_2 (4 mL) at room temperature, and the mixture was stirred at the same temperature under air for 4 h. The solution was diluted with Et_2O,

filtereted through a celite pad, and concentrated. To the solution of the obtained crude aldehyde **13** above and 1-aminodecane (184.6 mg, 233 μL, 1.19 mmol) in CH_2Cl_2 (5 mL) was added anhydrous $MgSO_4$ (1g) at room temperature under air. The mixture was stirred for 1 h and refluxed for 1 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The obtained crude imine was used for the next reaction without further purification. To the solution of the obtained crude imine above in MeOH (10 mL) was added $NaBH_4$ (26.9 mg, 0.711 mmol) at 0°C. The mixture was stirred at the same temperature under air for 45 min. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The obtained crude amine was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (225.4 mg, 1.19 mmol) was added to a solution of the above crude amine in MeOH (10 mL). The mixture was stirred at room temperature under air for 20 min. After the reaction was quenched with 3 M aqueous NaOH solution, and stirred for 15 min. The mixture was extracted with CH_2Cl_2 four times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc : MeOH = 7 : 1, 1% Et_3N) to obtain **14b** (64.5 mg, 61% 4 steps) as a colorless oil.

14b: $[\alpha]_D^{27}$ +54.0 (c 1.38, $CHCl_3$); IR (neat) 3358, 1467, 1215 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.06-1.65 (m, 39H), 1.80-1.98 (m, 3H), 2.53-2.61 (m, 3H), 3.23-3.29 (m, 2H), 5.02 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 14.1, 18.8, 20.8, 22.2, 22.6, 23.4, 27.4, 27.6, 28.7, 29.1, 29.3, 29.3, 29.5, 29.5, 29.9, 31.9, 36.1, 36.4, 40.4, 44.4, 45.1, 46.2, 49.3, 55.6, 56.5, 70.9, 118.4, 141.6; HRMS (ESI^+) calcd for $C_{30}H_{58}ON$ $[M+H]^+$ 448.4513, found 448.4550.

(6*R*)-2-Methyl-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(phenylamino) ethylidene]octahydro-1*H*-inden-1-yl}heptan-2-ol (**14c**)

PDC (333.8 mg, 0.887 mmol) was added to the solution of **4** (151.7 mg, 0.359 mmol) in CH_2Cl_2 (6 mL) at room temperature, and the mixture was stirred at the same temperature under air for 3 h. The solution was diluted with Et_2O, filtereted through a celite pad, and concentrated to obtain the crude aldehyde.

To the solution of the above crude aldehyde **13** and aniline (330.6 mg, 324 μL, 3.55 mmol) in CH_2Cl_2 (10 mL) was added anhydrous $MgSO_4$ (1g) at room temperature under air. The mixture was stirred for 90 min and refluxed for 40 min. After the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The obtained crude imine was used for the next reaction without further purification. To the solution of the above crude imine in MeOH (10 mL) was added $NaBH_4$ (40.2 mg, 1.07 mmol) at 0°C. The mixture was stirred at the same temperature under air for 30 min. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The obtained crude amine was used for the next reaction without further purification. *p*-Toluenesulfonic acid monohydrate (2.7 g, 14.2 mmol) was added to a solution of the above crude amine in MeOH (10 mL). The mixture was stirred at room temperature under air for 45 min. After the reaction was quenched with 1 M aqueous NaOH solution, and stirred for a further 10 min. The mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 10 : 1 – 3 : 1) to obtain **14c** (88.6 mg, 65% 4 steps) as a colorless oil.

14c: $[\alpha]_D^{27}$ +67.9 (c 1.89, $CHCl_3$); IR (neat) 3368, 1603, 1505, 1469, 1377, 1318, 1248, 1216, 1151, 755, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 1.03-1.10 (m, 1H), 1.18-1.72 (m, 22H), 1.84-2.06 (m, 3H), 2.65-2.69 (m, 1H), 3.71-3.81 (m, 2H), 5.01 (t, *J* = 6.6 Hz, 1H) , 6.62-6.64 (m, 2H) , 6.69-6.72 (m, 1H), 7.15-7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.8, 20.8, 22.2, 23.4, 27.6, 28.8, 29.2, 29.3, 36.1, 36.4, 40.3, 41.3, 45.2, 55.6, 56.5, 71.1, 113.0, 117.1, 117.3, 129.1, 143.0, 148.4; HRMS (ESI^+) calcd for $C_{26}H_{42}ON$ $[M+H]^+$ 384.3261, found 384.3258.

(6*R*)-2-Methyl-6-[(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-(prop-2-yn-1-ylidene) octahydro-1*H*-inden-1-yl]heptan-2-ol (**16**)

To the solution of **4** (522.4 mg, 1.24 mmol) in CH_2Cl_2 (10 mL) were added 4-methylmorpholine *N*-oxide (290.5 mg, 2.48 mmol) and 4Å molecular sieves (100 mg), cooled to 0°C. To the mixture was added TPAP (130.3 mg, 0.37 mmol) and stirred at 0°C for 1 h. The reaction was diluted with excess amount of Et_2O. The

mixture was filtered with celite and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 10 : 1) to obtain the crude aldehyde **13** (439.2 mg), and this was used for the next reaction without further purification. To the solution of the trimethylsilyl diazomethane (71 μL, 2.0 M in diethylether, 0.143 mmol) in THF (2 mL) was added *n*-BuLi (82 μL, 1.65 M in hexane, 0.135 mmol) at -78°C and stirred at the same temperature for 15 min. To the mixture was added the crude CD aldehyde above (30 mg) in THF (2 mL) and stirred at the same temperature for 30 min. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at -78°C, the mixture was extracted with EtOAc twice, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 50 : 1) to obtain the crude CD-alkyne **15** (22.2 mg). *p*-Toluenesulfonic acid monohydrate (27.0 mg, 0.142 mmol) was added to a solution of the crude CD-alkyne **15** (30.0 mg) in MeOH (3 mL). The mixture was stirred at room temperature under air for 10 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 4 : 1) to obtain **16** (19.7 mg, 58% 3 steps) as a colorless oil.

16: $[\alpha]_D^{27}$ +147.1 (c 1.52, $CHCl_3$); IR (neat) 3381, 3310, 2360, 2341, 1627, 1470, 1378, 1214, 1149, 911, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.93 (d, *J* = 6.0 Hz, 3H), 1.02-1.08 (m, 1H), 1.18-1.63 (m, 17H), 1.67-1.72 (m, 1H), 1.75-1.80 (m, 1H), 1.84-1.93 (m, 1H), 2.00-2.04 (m, 1H), 2.96-2.99 (m, 2H), 5.05-5.06 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.7, 20.8, 21.9, 23.3, 27.6, 29.2, 29.4, 31.4, 36.0, 36.3, 40.0, 44.4, 46.3, 55.7, 56.4, 71.1, 79.3, 81.6, 99.3, 157.9; HRMS (ESI^+) calcd for $C_{21}H_{32}$ $[M\text{-}OH]^+$ 285.2577, found 285.2571.

(6*R*)-6-[(1*R*,3a*S*,7a*R*,*E*)-4-(*orto*-Carboranylmethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**17**)

To a solution of *N*,*N*-dimethylaniline (93.2 mg, 97 μL, 0.769 mmol) and alkynyl-CD-ring **15** (51.1 mg, 0.123 mmol) in toluene (5 mL) was added $B_{10}H_{14}$ (43.3 mg, 0.356 mmol) at room temperature, and the mixture was stirred at

100°C for 15 min. The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (hexane only – hexane : EtOAc = 20 : 1) and followed by purification by flash column chromatography on silica gel (hexane : EtOAc = 100 : 1) to obtain the crude product (20.0 mg).

p-Toluenesulfonic acid monohydrate (14.1 mg, 0.074 mmol) was added to a solution of the above crude product in MeOH (3 mL). The mixture was stirred at room temperature for 10 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain **17** (13.1 mg, 26%, 2 steps) as a colorless oil.

17: $[\alpha]_D^{27}$ +117.4 (c 1.01, $CHCl_3$); IR (neat) 3463, 2602, 2565, 1467, 1440, 1376, 1208, 1128, 1072, 1020, 931, 721 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.50 (s, 3H), 0.55-0.62 (m, 1H), 0.92-2.82 (m, 38H), 3.20 (d, *J* = 13.2 Hz, 3H), 3.64 (brs, 1H), 5.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.7, 18.8, 20.7, 22.1, 23.4, 27.3, 29.0, 29.4, 35.9, 36.3, 40.0, 44.3, 46.8, 56.3, 56.6, 62.8, 71.0, 74.0, 114.9, 150.3; HRMS (ESI^-) calcd for $C_{21}H_{43}OB_{10}$ $[M-H]^-$ 421.4282, found 421.4321.

2-[(1*R*,3a*S*,7a*R*,*E*)-7a-Methyl-1-{(2*R*)-6-methyl-6-[(triethylsilyl)oxy] heptan-2-yl}octahydro-4*H*-inden-4-ylidene]acetic acid (**18**)

PDC (127.9 mg, 0.34 mmol) was added to the solution of **4** (103.9 mg, 0.246 mmol) in CH_2Cl_2 (4 mL) at room temperature, and the mixture was stirred at the same temperature under air for 3 h. The solution was diluted with Et_2O, filtereted with celite, and concentrated to obtain the crude aldehyde **13**.

To the mixture of the above crude aldehyde **13**, NaH_2PO_4 (74.3 mg, 0.476 mmol), 30% H_2O_2 (72 μL) in H_2O (1 mL) and *t*-BuOH (3 mL) was added $NaClO_2$ (24.6 mg, 0.272 mmol) at 0°C under air and stirred at the same temperature for 5 min and at room temperature for 4 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain **18** (82.5 mg, 80%, 2 steps) as a colorless oil.

18: $[\alpha]_D^{27}$ +93.9 (c 1.54, $CHCl_3$); IR (neat) 3048, 1686, 1638, 1459, 1416, 1268, 1212, 1045, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 3H), 0.56 (q, *J* = 7.8 Hz, 1H), 0.92-0.99 (m, 13H), 1.19-1.77 (m, 19H), 1.84-1.96 (m, 1H), 2.01-2.04 (m, 1H), 2.10-2.15 (m, 1H), 3.82-3.88 (m, 1H), 5.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 7.1, 12.0, 18.7, 20.8, 22.1, 24.0, 27.4, 29.8, 29.9, 30.0, 35.9, 36.3, 40.1, 45.5, 47.4, 56.8, 57.1, 73.4, 111.3, 166.6, 172.0; HRMS (ESI^+) calcd for $C_{28}H_{46}O_3SiNa$ $[M+Na]^+$ 481.3108, found 481.3065.

2-{(1*R*,3a*S*,7a*R*,*E*)-1-[(2*R*)-6-Hydroxy-6-methylheptan-2-yl]-7a-methyloctahydro-4*H*-inden-4-ylidene}-1-(piperidin-1-yl)ethan-1-one (**19a**)

To a solution of piperidine (24.1 mg, 28 μL, 0.283 mmol) and **18** (82.5 mg, 0.189 mmol) in DMF (3 mL) were added diisopropylethylamine (61.0 mg, 82 μL, 0.472 mmol) and BOP reagent (166.8 mg, 0.377 mmol) at 0°C, and the mixture was stirred at room temperature for 15 min. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated to obtain the crude amide.

p-Toluenesulfonic acid monohydrate (179.4 mg, 0.943 mmol) was added to a solution of the above crude amide in MeOH (5 mL). The mixture was stirred at room temperature for 10 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1 – 1 : 1) to obtain **19a** (57.3 mg, 73%, 2 steps) as a colorless oil.

19a: $[\alpha]_D^{27}$ +84.8 (c 0.96, $CHCl_3$); IR (neat) 3374, 1610, 1444, 1255, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.01-1.11 (m, 1H), 1.20-2.03 (m, 30H), 2.72-2.77 (m, 1H), 3.46-3.51 (m, 3H), 3.61 (brs, 1H), 5.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.7, 20.7, 22.1, 23.3, 24.6, 25.8, 26.4, 27.5, 29.2, 29.3, 30.5, 36.0, 36.3, 40.0, 42.2, 44.3, 46.1, 47.5, 55.6, 56.4, 71.0, 114.8, 149.8, 167.7; HRMS (ESI^+) calcd for $C_{25}H_{44}NO_2$ $[M+H]^+$ 390.3367, found 390.3391.

2-{(1*R*,3aS,7a*R*,*E*)-1-[(2*R*)-6-Hydroxy-6-methylheptan-2-yl]-7a-methyloctahydro-4*H*-inden-4-ylidene}-1-morpholinoethan-1-one (**19b**)

To a solution of morpholine (32.0 mg, 32 μL, 0.367 mmol) and **18** (80.2 mg, 0.184 mmol) in DMF (3 mL) were added diisopropylethylamine (80 μL, 0.46 mmol) and BOP reagent (162.4 mg, 0.367 mmol) at 0°C, and the mixture was stirred at room temperature for 21 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated to obtain the crude amide.

p-Toluenesulfonic acid monohydrate (175.0 mg, 0.92 mmol) was added to a solution of the above crude amide in MeOH (10 mL). The mixture was stirred at room temperature for 20 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain **19b** (65.4 mg, 91%, 2 steps) as a colorless oil.

19b: $[\alpha]_D^{27}$ +91.8 (c 1.14, $CHCl_3$); IR (neat) 3426, 1615, 1463, 1231, 1117, 851, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.59 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 1.03-1.11 (m, 1H), 1.21-1.62 (m, 19H), 1.69-1.71 (m, 1H), 1.76-1.81 (m, 1H), 1.88-1.92 (m, 1H), 2.01-2.06 (m, 2H), 2.83-2.85 (m, 1H), 3.52 (brs, 1H), 3.65-3.69 (m, 6H), 5.51 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.1, 18.7, 20.7, 22.1, 23.4, 27.4, 29.2, 29.4, 30.6, 36.0, 36.3, 39.9, 41.7, 44.3, 46.3, 46.9, 55.8, 56.4, 66.9, 71.0, 113.6, 152.3, 167.9; HRMS (ESI^+) calcd for $C_{24}H_{41}NO_3Na$ $[M+Na]^+$ 414.2979, found 414.2998.

2-(2-{(1*R*,3a*S*,7a*R*,*E*)-1-[(2*R*)-6-Hydroxy-6-methylheptan-2-yl]-7a-methyloctahydro-4*H*-inden-4-ylidene}ethyl)isoindoline-1,3-dione (**20**)

To a solution of phthalimide (69.6 mg, 0.473 mmol), Ph_3P (29.9 mg, 0.473 mmol), and **4** (100.0 mg, 0.237 mmol) in THF (5 mL) was added diisopropyl azodicarboxylate (249 μL, 1.9 M in toluene, 0.473 mmol) at 0°C, and the mixture was stirred at the room temperature for 10 min. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 6 : 1) to obtain the crude phthalimide product.

p-Toluenesulfonic acid monohydrate (113.1 mg, 0.595 mmol) was added to a

solution of the above crude phthalimide in MeOH (10 mL). The mixture was stirred at room temperature for 30 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc only) to obtain **20** (57.8 mg, 56% 2 steps) as a colorless oil.

20: $[\alpha]_D^{27}$ +44.7 (c 0.98, $CHCl_3$); IR (neat) 3394, 1715, 1394, 1088, 941, 724 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.49 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.99-1.05 (m, 1H), 1.17-1.64 (m, 19H), 1.66-1.71 (m, 2H), 1.80-1.86 (m, 1H), 1.92 (t, *J* = 9.6 Hz, 1H), 1.92 (dt, *J* = 3.0, 11.4 Hz, 1H), 2.91-2.95 (m, 1H), 4.27-4.37 (m, 2H), 5.20 (t, *J* = 7.2 Hz, 1H), 7.67-7.70 (m, H), 7.81-7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.8, 20.8, 22.1, 23.4, 27.6, 28.8, 29.2, 29.3, 35.1, 36.0, 36.3, 40.3, 44.4, 45.4, 55.6, 56.4, 71.1, 113.7, 123.1, 132.3, 133.7, 144.5, 168.1; HRMS (ESI^+) calcd for $C_{28}H_{39}NO_3Na$ $[M+Na]^+$ 460.2822, found 460.2850.

(6*R*)-6-{(1*R*,3a*S*,7a*R*,*E*)-4-[2-(Benzo[*d*]thiazol-2-ylthio)ethylidene]-7a-methyloctahydro-1*H*-inden-1-yl}-2-methylheptan-2-ol (**21**)

To a solution of 2-mercaptobenzothiazole (29.7 mg, 0.178 mmol), Ph_3P (29.9 mg, 0.114 mmol), and **4** (30.7 mg, 0.073 mmol) in CH_2Cl_2 (10 mL) was added diisopropyl azodicarboxylate (60 μL, 1.9 M in toluene, 0.114 mmol) at 0°C, and the mixture was stirred at the same temperature for 2 h. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 10 : 1) to obtain the crude sulfide.

Tetrabutylammonium fluoride (111 μL, 1 M in THF, 0.111 mmol) was added to a solution of the above crude sulfide in THF (5 mL). The mixture was stirred at room temperature for 21 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 5 : 1) to obtain **21** (16.1 mg, 50%, 2 steps) as a colorless oil.

21: $[\alpha]_D^{27}$ +77.3 (c 1.24, $CHCl_3$); IR (neat) 3390, 1457, 1427, 1377, 1238, 996, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.49 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.00-1.08 (m, 1H), 1.21-1.73 (m, 21H), 1.81-2.00 (m, 3H), 1.81-2.00 (m, 3H), 2.74-2.78 (m, 1H), 4.02 (dd, *J* = 7.1, 12.4 Hz, 1H), 4.13 (dd, *J* = 7.8, 12.8 Hz, 1H), 5.20 (t, *J* = 8.0 Hz, 1H), 7.28 (td, *J* = 1.4, 8.2 Hz, 1H), 7.41 (td, *J* = 1.4, 7.8 Hz, 1H), 7.75 (dd, *J* = 1.4, 7.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 18.8, 20.8, 22.1, 23.5, 27.6, 28.8, 29.2, 29.3, 31.3, 36.0, 36.3, 40.3, 44.4, 45.6, 55.7, 56.4, 71.1, 113.1, 120.9, 121.4, 124.1, 126.0, 135.2, 146.1, 153.3, 167.2; HRMS (ESI^+) calcd for $C_{27}H_{40}NOS_2$ $[M+H]^+$ 458.2546, found 458.2578.

3-Deoxy-25-hydroxy-19-*nor*vitamin D_3 (**23**)

LHMDS (332 μL, 1.0 M THF solution, 0.332 mmol) was added to the solution of CD-ring sulfone (**22**) [35] (99.1 mg, 0.164 mmol) in THF (2 mL) at -78℃. After stirring for 30 min, the solution of cyclohexanone (48.8 mg, 50 μL, 0.497 mmol) was added to the reaction mixture, and the mixture was stirred at -78℃ for 30 min. After the reaction was quenched with H_2O at the same temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane only) to obtain the crude coupling product (41.5 mg), and it was used for the next reaction without further purification. Tetrabutylammonium fluoride (497 μL, 1 M THF solution, 0.497 mmol) was added to the solution of the above crude coupling product (41.5 mg) in THF (5 mL), and the mixture was stirred at room temperature for 24 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain **23** (30.9 mg, 50%, 2 steps) as a colorless oil.

23: $[\alpha]_D^{27}$ +64.3 (c 2.06, $CHCl_3$); IR (neat) 3368, 1445, 1376, 1215, 1148, 863, 759 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 1.03-1.08 (m, 1H), 1.20-1.67 (m, 23H), 1.86-1.92 (m, 1H), 1.97-2.01 (m, 2H), 2.13-2.24 (m, 3H), 2.33-2.35 (m, 1H), 2.78-2.82 (m, 1H), 5.84 (d, *J* = 12.0 Hz, 1H), 6.06 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.1, 198.8, 20.8,

22.3, 23.4, 26.9, 27.6, 27.7, 28.6, 28.7, 28.9, 29.2, 29.3, 36.1, 36.4, 37.6, 40.6, 44.4, 45.6, 56.3, 56.5, 71.1, 115.7, 117.3, 140.4, 140.6; HRMS (ESI^-) calcd for $C_{26}H_{43}O$ $[M-H]^-$ 371.3308, found 371.3310.

(6*R*)-6-{(1*R*,3a*S*,7a*R*,*E*)-4-[2-(2*H*-Tetrazol-2-yl)ethylidene]-7a-methyl octahydro-1*H*-inden-1-yl}-2-methylheptan-2-ol (**24a**)

(6*R*)-6-{(1*R*,3a*S*,7a*R*,*E*)-4-[2-(1*H*-Tetrazol-1-yl)ethylidene]-7a-methyloctahydro-1*H*-inden-1-yl}-2-methylheptan-2-ol (**24b**)

To a solution of 1*H*-tetrazole (45.4 mg, 0.649 mmol), Ph_3P (206.4 mg, 9.72 mmol), and **9** (100 mg, 0.324 mmol) in THF (5 mL) was added diisopropyl azodicarboxylate (512 μL, 1.9 M in toluene, 9.72 mmol) at 0°C, and the mixture was stirred at room temperature for 1 h. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1 – EtOAc only) to obtain the less polar product **24a** (43.2 mg, 37%) and the more polar product **24b** (38.8 mg, 33%) each as a colorless oil.

24a: $[\alpha]_D^{27}$ +53.6 (c 1.31, $CHCl_3$); IR (neat) 3427, 1468, 1454, 1376, 1282, 1027, 911, 736 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.50 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.01-1.06 (m, 1H), 1.20-2.02 (m, 24H), 2.77-2.80 (m, 1H), 5.23-5.32 (m, 3H), 8.47 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.8, 20.8, 22.0, 23.3, 27.5, 28.0, 29.2, 29.4, 36.0, 36.3, 40.1, 44.3, 45.8, 50.1, 55.6, 56.4, 71.0, 111.4, 148.1, 152.8; HRMS (ESI^+) calcd for $C_{21}H_{36}N_4ONa$ $[M+Na]^+$ 383.2781, found 383.2793.

24b: $[\alpha]_D^{27}$ +64.5 (c 0.62, $CHCl_3$); IR (neat) 3400, 1468, 1445, 1376, 1162, 1101, 912, 734, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 1.01-1.09 (m, 1H), 1.20-1.61 (m, 18H), 1.72-1.82 (m, 2H), 1.86-1.94 (m, 1H), 2.01-2.08 (m, 3H), 2.65-2.70 (m, 1H), 5.03-5.12 (m, 1H), 5.23 (t, *J* = 7.3 Hz, 1H), 8.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.8, 20.8, 22.1, 23.3, 27.5, 28.9, 29.2, 29.4, 36.0, 36.3, 40.0, 44.3, 45.3, 45.8, 55.6, 56.4, 71.1, 110.9, 151.8, 149.4; HRMS (ESI^+) calcd for $C_{21}H_{36}N_4ONa$ $[M+Na]^+$ 383.2781, found 383.2789.

(6*R*)-2-Methyl-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(5-phenyl-2*H*-tetrazol-2-yl)ethylidene]octahydro-1*H*-inden-1-yl}heptan-2-ol (**25a**)

(6*R*)-2-Methyl-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(5-phenyl-1*H*-tetrazol-1-yl)ethylidene]octahydro-1*H*-inden-1-yl}heptan-2-ol (**25b**)

To a solution of 5-phenyl-1*H*-tetrazole (311.3 mg, 2.13 mmol), Ph_3P (372.5 mg, 1.42 mmol), and **4** (305.3 mg, 0.722 mmol) in THF (10 mL) was added diisopropyl azodicarboxylate (1.12 mL, 1.9 M in toluene, 2.13 mmol) at 0°C, and the mixture was stirred at the same temperature for 3 h. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain the crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (285.3 mg, 1.50 mmol) was added to a solution of the above less polar crude product in MeOH (10 mL). The mixture was stirred at room temperature for 40 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain **25a** (187.8 mg, 60%) as a colorless oil.

25a: $[\alpha]_D^{27}$ +41.2 (c 1.33, $CHCl_3$); IR (neat) 3419, 1467, 1450, 1378, 1216, 761, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 1.00-1.10 (m, 1H), 1.19-2.05 (m, 24H), 2.83-2.86 (m, 1H), 5.29-5.36 (m, 3H), 7.43-7.52 (m, 3H), 8.12-8.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.8, 20.8, 22.0, 23.4, 27.6, 29.1, 29.2, 29.4, 36.0, 36.3, 40.2, 44.4, 45.9, 50.2, 55.7, 56.5, 71.1, 111.6, 126.8, 127.6, 128.8, 130.1, 148.0, 165.0; HRMS (ESI^+) calcd for $C_{27}H_{40}N_4ONa$ $[M+Na]^+$ 459.3094, found 459.3079.

p-Toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol) was added to a solution of the above more polar crude product in MeOH (10 mL). The mixture was stirred at room temperature for 40 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the

mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **25b** (48.4 mg, 15%) as a colorless oil.

25b: $[\alpha]_D^{27}$ +67.2 (c 0.09, $CHCl_3$); IR (neat) 3425, 1471, 1377, 1219, 758, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.46 (s, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 1.00-1.07 (m, 1H), 1.21-1.72 (m, 21H), 1.82-2.01 (m, 3H), 2.51-2.56 (m, 1H), 5.07-5.17 (m, 3H), 7.52-7.60 (m, 3H), 7.68-7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.8, 20.8, 22.1, 23.1, 27.5, 28.9, 29.2, 29.4, 36.0, 36.3, 40.0, 44.3, 45.6, 45.7, 55.52, 56.4, 71.1, 112.9, 124.2, 128.8, 129.1, 131.1, 146.5, 154.1; HRMS (ESI^+) calcd for $C_{27}H_{40}N_4ONa$ $[M+Na]^+$ 459.3094, found 459.3093.

({(6*R*)-6-[(1*R*,3a*S*,7a*R*,*E*)-4-(2-Azidoethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-yl}oxy)triethylsilane (**27**)

To the solution of **4** (300.0 mg, 0.71 mmol) and pyridine (337.0 mg, 344 μL, 4.26 mmol) in CCl_4 (30 mL) was added tri-*n*-butylphosphine (574.6 mg, 700 μL, 2.84 mmol) at 0 °C, over 5 min, and the mixture was stirred at the same temperature for 15 min. After the reaction was diluted with hexane (50 mL), the mixture was filtered, and concentrated. The obtained crude allyl chloride (**26**) was used for the next reaction without further purification.

To the solution of the above crude allylchloride in DMF (15 mL) was added NaN_3 (138.5 mg, 2.13 mmol) at room temperature, and the mixture was stirred at the same temperature for 20 min. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc =30 : 1) to obtain **27** (273.1 mg, 86%, 2 steps) as a colorless oil.

27: $[\alpha]_D^{27}$ +36.6 (c 1.61, $CHCl_3$); IR (neat) 2095, 1380, 1235, 1045, 743 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.57 (q, *J* = 8.0 Hz, 1H), 0.59 (s, 1H), 0.93 (d, *J* = 6.6 Hz, 1H), 0.95 (t, *J* = 8.4 Hz, 1H), 0.99-1.06 (m, 1H), 1.19-1.55 (m, 20H), 1.67-1.71 (m, 2H), 1.86-1.94 (m, 1H), 2.00-2.05 (m, 2H), 2.60-2.62 (m, 1H), 3.73 (dd, *J* = 6.6, 13.2 Hz, 1H), 3.89 (dd, *J* = 7.8, 13.8 Hz, 1H), 5.13 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 6.9, 7.2, 11.9, 18.9, 20.9, 22.2, 23.9, 27.6, 28.9, 29.9, 30.1, 36.2, 36.5, 40.4, 45.2, 45.6, 47.5, 55.9, 56.7, 73.5, 112.7,

147.2;

(6*R*)-2-Methyl-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethylidene]octahydro-1*H*-inden-1-yl}heptan-2-ol (**28a**)

To a solution of phenylacetylene (56.9 mg, 24 μL, 0.557 mmol), diisopropylethylamine (719.9 mg, 0.97 mL, 5.57 mmol), and **27** (50.3 mg, 0.112 mmol) in THF (4 mL) was added CuI (21.2 mg, 0.557 mmol) at room temperature, and the mixture was stirred at the same temperature for 68 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The obtained crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (106.0 mg, 0.557 mmol) was added to a solution of the above crude triazole in MeOH (5 mL). The mixture was stirred at room temperature under air for 15 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain **28a** (12.1 mg, 25%, 2 steps) as a colorless oil.

28a: $[\alpha]_D^{27}$ +50.5 (c 0.29, $CHCl_3$); IR (neat) 3393, 1468, 1378, 1223, 766, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.58 (s, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 1.03-1.11 (m, 1H), 1.21-1.61 (m, 20H), 1.74-1.81 (m, 2H), 1.87-1.94 (m, 1H), 2.01-2.06 (m, 2H), 2.73-2.75 (m, 1H), 5.04-5.10 (m, 2H), 5.27 (t, *J* = 7.5 Hz, 1H), 7.31-7.33 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.70 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.8, 20.8, 22.1, 23.4, 27.5, 28.9, 29.2, 29.4, 36.0, 36.3, 40.1, 44.4, 45.7, 47.2, 55.7, 56.5, 71.1, 112.8, 118.9, 125.7, 128.0, 128.8, 130.8, 147.3, 147.8; HRMS (ESI^+) calcd for $C_{28}H_{41}N_3O$ $[M+H]^+$ 436.3322, found 436.3312.

(6*R*)-6-[(1*R*,3a*S*,7a*R*,*E*)-4-(2-{4-[(1,1'-Biphenyl)-4-yl]-1*H*-1,2,3-triazol-1-yl}ethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**28b**)

To a solution of 4-ethynylbiphenyl (99.3 mg, 0.557 mmol),

diisopropylethylamine (719.9 mg, 0.97 mL, 5.57 mmol), and **27** (50.3 mg, 0.112 mmol) in THF (8 mL) was added CuI (106.1 mg, 0.557 mmol) at room temperature, and the mixture was stirred at the same temperature for 112 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The obtained crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (106.0 mg, 0.557 mmol) was added to a solution of the above crude triazole in MeOH (10 mL). The mixture was stirred at room temperature under air for 20 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain **28b** (12.5 mg, 22%, 2 steps) as a colorless oil.

28b: $[\alpha]_D^{27}$ +41.8 (c 0.96, $CHCl_3$); IR (neat) 3350, 1443, 1376, 1215, 1148, 840, 767, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.59 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.04-1.11 (m, 1H), 1.22-1.61 (m, 20H), 1.75-1.83 (m, 2H), 1.88-1.95 (m, 1H), 2.03-2.07 (m, 2H), 2.74-2.77 (m, 1H), 5.06-5.13 (m, 2H), 5.29 (t, *J* = 7.2 Hz, 1H), 7.34-7.37 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 2H), 7.75 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.8, 20.8, 22.1, 23.4, 27.5, 28.9, 29.2, 29.4, 36.0, 36.3, 40.1, 44.3, 45.7, 47.3, 55.7, 56.5, 71.1, 112.8, 118.9, 126.0, 127.0, 127.4, 127.5, 128.8, 129.8, 140.6, 140.8, 147.4, 147.4; HRMS (ESI^+) calcd for $C_{34}H_{45}N_3ONa$ $[M+Na]^+$ 543.3455, found 534.3494.

(6*R*)-6-{(1*R*,3a*S*,7a*R*,*E*)-4-[2-(4-Butyl-1*H*-1,2,3-triazol-1-yl)ethylidene]-7a-methyloctahydro-1*H*-inden-1-yl}-2-methylheptan-2-ol (**28c**)

To a solution of 1-hexyne (9.9 mg, 13.8 μL, 0.12 mmol), diisopropylethylamine (719.9 mg, 0.97 mL, 5.57 mmol), and **27** (53.8 mg, 0.112 mmol) in THF (4 mL) was added CuI (106.1 mg, 0.557 mmol) at room temperature, and the mixture was stirred at the same temperature for 112 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and

concentrated. The obtained crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (106.0 mg, 0.557 mmol) was added to a solution of the above crude triazole in MeOH (5 mL). The mixture was stirred at room temperature under air for 20 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1 – 1 : 1) to obtain **28c** (15.6 mg, 31%, 2 steps) as a colorless oil.

28c: $[\alpha]_D^{27}$ +57.5 (c 1.20, $CHCl_3$); IR (neat) 3400, 1467, 1377, 1215, 1047, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.91-0.94 (m, 6H), 1.02-1.08 (m, 1H), 1.19-1.57 (m, 21H), 1.61-1.66 (m, 2H), 1.71-1.77 (m, 2H), 1.85-1.92 (m, 1H), 1.98-2.04 (m, 2H), 2.67-2.71 (m, 3H), 4.94-5.01 (m, 2H), 5.20 (t, *J* = 7.2 Hz, 1H), 7.20 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 13.8, 18.8, 20.8, 22.1, 22.3, 23.4, 25.4, 27.5, 28.8, 29.2, 29.4, 31.6, 36.0, 36.3, 40.1, 44.3, 45.6, 47.0, 55.6, 56.4, 71.0, 113.1, 119.8, 146.7, 148.4; HRMS (ESI^+) calcd for $C_{26}H_{45}N_3ONa$ $[M+Na]^+$ 438.3455, found 438.3473.

(6*R*)-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[4-(4-Hydroxybutyl)-1*H*-1,2,3-triazol-1-yl]ethylidene}-7a-methyloctahydro-1H-inden-1-yl]-2-methylheptan-2-ol (**28d**)

To a solution of 5-hexyn-1-ol (108.9 mg, 120 μL, 1.11 mmol), diisopropylethylamine (1.44 g, 1.94 mL, 11.14 mmol), and **27** (60 mg, 0.124 mmol) in THF (8 mL) was added CuI (212.2 mg, 1.11 mmol) at room temperature, and the mixture was stirred at the same temperature for 118 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The obtained crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (216.0 mg, 1.11 mmol) was added to a solution of the above crude triazole in MeOH (20 mL). The mixture was stirred at room temperature under air for 25 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc

only) to obtain **28d** (19.2 mg, 20%, 2 steps) as a colorless oil.

28d: $[\alpha]_D^{27}$ +40.0 (c 1.48, $CHCl_3$); IR (neat) 3363, 1468, 1378, 1216, 1052, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 1.02-1.08 (m, 1H), 1.21-1.92 (m, 26H), 1.98-2.04 (m, 2H), 2.66-2.70 (m, 1H), 2.74 (t, *J* = 7.5 Hz, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 4.94-5.01 (m, 2H), 5.20 (t, *J* = 7.2 Hz, 1H), 7.23 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.8, 20.8, 22.1, 23.4, 25.3, 25.6, 27.5, 28.8, 29.2, 29.4, 32.1, 36.0, 36.3, 40.1, 44.3, 45.6, 47.0, 55.6, 56.4, 62.4, 71.0, 113.0, 119.9, 146.8, 148.0; HRMS (ESI^+) calcd for $C_{26}H_{45}N_3O_2Na$ $[M+Na]^+$ 454.3394, found 438.3404.

(6*R*)-2-Methyl-6-[(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-{2-[4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]ethylidene}octahydro-1*H*-inden-1-yl]heptan-2-ol (**28e**)

To a mixture of 2-ethynylpyridine (38.6 mg, 38 μL, 0.374 mmol), sodium L-ascorbate (38.3 mg, 0.193 mmol), 2,6-lutidine (39.0 mg, 43 μL, 0.364 mmol), and **27** (83.8 mg, 0.187 mmol) in *t*-BuOH (3 mL) and H_2O (3 mL) was added $CuSO_4$-$5H_2O$ (5.2 mg, 0.021 mmol) at room temperature, and the mixture was stirred at the same temperature for 24 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The obtained crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (182.8 mg, 0.961 mmol) was added to a solution of the above crude triazole in MeOH (10 mL). The mixture was stirred at room temperature under air for 20 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain **28e** (60.3 mg, 74%, 2 steps) as a colorless oil.

28e: $[\alpha]_D^{27}$ +55.2 (c 1.08, $CHCl_3$); IR (neat) 3410, 1600, 1471, 1420, 1337, 1200, 1044, 782, 793 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.93 (d, *J* = 6.0 Hz, 3H), 1.02-1.10 (m, 1H), 1.20-1.60 (m, 19H), 1.71-1.80 (m, 2H), 1.85-1.92 (m, 1H), 1.99-2.46 (m, 2H), 2.71-2.74 (m, 1H), 5.04-5.10 (m, 2H), 5.26 (t, *J* = 7.5 Hz, 1H), 7.20-7.22 (m, 1H), 7.77 (td, *J* = 1.8, 7.8 Hz, 1H), 8.11 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 11.9, 18.8, 20.8, 22.1, 23.3, 27.5, 28.8, 29.2, 29.4, 36.0, 36.3, 40.1, 44.3, 45.6, 47.3, 55.6, 56.4, 71.0, 112.6, 120.2, 121.3, 122.7, 137.0, 147.5, 148.2, 149.2, 150.4; HRMS (ESI^+) calcd for $C_{27}H_{40}N_4ONa$ $[M+Na]^+$ 459.3094, found 459.3103.

(6*R*)-2-Methyl-6-[(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-{2-[4-(thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl]ethylidene}octahydro-1*H*-inden-1-yl]heptan-2-ol (**28f**)

To a mixture of 2-ethynylthiophene (39.4 mg, 36 μL, 0.364 mmol), sodium L-ascorbate (37.8 mg, 0.191 mmol), 2,6-lutidine (39.0 mg, 42 μL, 0.364 mmol), and **27** (81.6 mg, 0.182 mmol) in *t*-BuOH (3 mL) and H_2O (3 mL) was added $CuSO_4$-$5H_2O$ (4.2 mg, 0.017 mmol) at room temperature, and the mixture was stirred at the same temperature for 22 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The obtained crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (179.2 mg, 0.942 mmol) was added to a solution of the above crude triazole in MeOH (10 mL). The mixture was stirred at room temperature under air for 20 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain **28f** (53.5 mg, 67%, 2 steps) as a colorless oil.

28f: $[\alpha]_D^{27}$ +47.2 (c 1.35, EtOH); IR (neat) 3418, 1665, 1468, 1420, 1376, 1044, 761 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.57 (s, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 1.20-1.10 (m, 1H), 1.22-2.06 (m, 24H), 2.70-2.74 (m, 1H), 5.04-5.10 (m, 2H), 5.25 (t, *J* = 7.6 Hz, 1H), 7.07 (dd, *J* = 3.7, 4.9 Hz, 1H), 7.29 (dd, *J* = 1.4, 5.0 Hz, 1H), 7.37 (dd, *J* = 1.4, 3.7 Hz, 1H), 7.61 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.8, 20.8, 22.1, 23.4, 27.5, 28.9, 29.2, 29.4, 36.0, 36.3, 40.1, 44.3, 45.7, 47.3, 55.7, 56.5, 71.1, 112,7, 118.4, 124.0, 124.9, 127.6, 133.2, 142.8, 147.5; HRMS (ESI^+) calcd for $C_{26}H_{39}N_3OSNa$ $[M+Na]^+$ 464.2706, found 464.2731.

2-{4-[1-(2-{(1*R*,3a*S*,7a*R*,*E*)-1-[(2*R*)-6-Hydroxy-6-methylheptan-2-yl]-7a-methyloctahydro-4*H*-inden-4-ylidene}ethyl)-1*H*-1,2,3-triazol-4-yl] butyl}isoindoline-1,3-dione (**28g**)

To a solution of phthalimide (11.7 mg, 0.073 mmol), Ph_3P (26.0 mg, 0.10 mmol), and **28d** (17.1 mg, 0.0396 mmol) in THF (3 mL) was added diisopropyl azodicarboxylate (52 μL, 1.9 M in toluene, 0.10 mmol) at 0°C, and the mixture was stirred at room temperature for 30 min. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain **28g** (12.0 mg, 54%) as a colorless oil.

28g: $[\alpha]_D^{27}$ +32.8 (c 0.92, $CHCl_3$); IR (neat) 3404, 1714, 1468, 1398, 1216, 1037, 722 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.03-1.08 (m, 1H), 1.21-1.57 (m, 19H), 1.71-1.76 (m, 6H), 1.85-1.91 (m, 1H), 1.98-2.04 (m, 2H), 2.68-2.70 (m, 1H), 2.76 (t, *J* = 6.9 Hz, 2H), 3.71 (t, *J* = 6.6 Hz, 2H), 4.93-5.01 (m, 2H), 5.20 (t, *J* = 7.2 Hz, 1H), 7.25 (s, 1H), 7.69-7.72 (m, 2H), 7.81-7.84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.8, 20.8, 22.1, 23.4, 25.1, 26.7, 27.5, 28.1, 28.8, 29.2, 29.4, 36.0, 36.3, 37.6, 40.1, 44.4, 45.6, 47.1, 55.6, 56.4, 71.1, 113.0, 120.1, 123.2, 132.1, 133.9, 146.9, 147.5, 168.4; HRMS (ESI^+) calcd for $C_{34}H_{48}N_4O_3Na$ $[M+Na]^+$ 583.3619, found 583.3622.

(6*R*)-6-{(1*R*,3a*S*,7a*R*,*E*)-4-[2-(Decylthio)ethylidene]-7a-methylocta hydro-1*H*-inden-1-yl}-2-methylheptan-2-ol (**29**)

To the solution of **9** (96.5 mg, 0.312 mmol) and pyridine (153.5 mg, 157 μL, 1.94 mmol) in CCl_4 (15 mL) and CH_2Cl_2 (15 mL) was added tri-*n*-butylphosphine (263.0 mg, 320 μL, 1.30 mmol) at 0°C, and the mixture was stirred at the same temperature for 15 min. After the reaction was diluted with hexane, the mixture was filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain a crude chloride **26a**. The crude allylchloride **26a** was used for the next reaction without further purification. To the solution of the above crude allyl chloride **26a**, K_2CO_3 (61.6 mg, 0.446 mmol), and KI (37.0 mg, 0.223 mmol)

in DMF (4 mL) and CH_2Cl_2 (15 mL) was added decanethiol (388.8 mg, 423 μL, 2.23 mmol) at room temperature under air, and the mixture was stirred at the same temperature for 190 min. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain **29** (80.8 mg, 78%, 2 steps) as a colorless oil.

29: $[\alpha]_D^{27}$ +89.6 (c 2.19, $CHCl_3$); IR (neat) 3370, 1467, 1377, 1217, 1148 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 1.02-1.08 (m, 1H), 1.21-1.68 (m, 37H), 1.83-2.01 (m, 3H), 2.45 (t, *J* = 7.8 Hz, 3H), 2.57-2.61 (m, 1H), 3.15 (dd, *J* = 7.8, 13.2 Hz, 1H), 3.24 (dd, *J* = 8.4, 13.2 Hz, 1H), 5.02 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 14.1, 18.8, 20.8, 22.2, 22.7, 23.5, 27.6, 28.5, 28.6, 29.0, 29.2, 29.3, 29.3, 29.5, 29.5, 29.7, 31.0, 31.9, 36.1, 36.4, 40.4, 44.4, 45.1, 55.7, 56.5, 71.1, 116.4, 142.3; HRMS (ESI^+) calcd for $C_{30}H_{56}O_3SNa$ $[M+Na]^+$ 487.3944, found 487.3965.

2-(1*R*,3a*S*,7a*R*,*E*)-2-(1-{(2*R*)-5,5-Difluoro-6-methyl-6-[(triethylsilyl)oxy] heptan-2-yl}-7a-methyloctahydro-4*H*-inden-4-ylidene)ethan-1-ol (**32**)

To a suspension of NaH (315.1 mg, 60% in oil, 7.90 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (1.90 g, 1.7 mL, 8.46 mmol) at 0°C, and the mixture was stirred at 0°C for 30 min. Ketone (**31**) [88] (331.1 mg, 0.769 mmol) was dissolved in THF, and the solution was added to the mixture at the same temperature. After being stirred at room temerature for 72 h, the reaction mixture was quenched with H_2O and saturated aqueous NH_4Cl at room temperature. The mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 10 : 1) to obtain crude ethyl ester (343.7 mg) as a colorless oil.

To the solution of the above ethyl ester (343.7 mg) in THF (10 mL) was added DIBAL-H (4.1 mL, 1.0 M toluene solution, 4.1 mmol) at -78°C, and the mixture was stirred at room temperature for 40 min. After the reaction was quenched with H_2O and saturated aqueous potassium sodium tartrate at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash

column chromatography on silica gel (hexane : EtOAc = 7 : 1) to obtain alcohol **32** (278.8 mg, 79%, 2 steps) as a colorless oil.

32: $[\alpha]_D^{27}$ +42.6 (c 0.68, $CHCl_3$); IR (neat) 3330, 1458, 1384, 1198, 1162, 1054, 738 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.60 (q, *J* = 7.8 Hz, 6H), 0.93-0.96 (m, 12H), 1.24-2.05 (m, 23H), 2.61-2.64 (m, 1H), 4.17-4.23 (m, 2H), 5.22 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 6.6, 6.9, 11.8, 18.6, 22.1, 23.5, 24.3, 24.6, 26.8, 27.0 (t, *J* = 24.5 Hz), 27.4, 28.7, 35.7, 40.3, 45.3, 55.6, 56.3, 58.7, 75.6 (t, *J* = 28.7 Hz), 119.3, 125.3 (t, *J* = 247.1 Hz), 143.7; HRMS (ESI^+) calcd for $C_{26}H_{48}O_2F_2SiNa$ $[M+Na]^+$ 481.3284, found 481.3254.

({(6*R*)-6-[(1*R*,3a*S*,7a*R*,*E*)-4-(2-Azidoethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]-3,3-difluoro-2-methylheptan-2-yl}oxy)triethylsilane (**33**)

To the solution of the allyl alcohol **32** (133.0 mg, 0.29 mmol) and pyridine (70 μL, 0.87 mmol) in CCl_4 (10 mL) was added tri-*n*-butylphosphine (362 μL, 1.45 mmol) at 0°C, over 10 min, and the mixture was stirred at the same temperature for 10 min. After the reaction was diluted with hexane, the mixture was filtered, and concentrated. To the residue was added hexane, the mixture was filtered, and concentrated. The crude allyl chloride was used for the next reaction without further purification.

To the solution of the crude allyl chloride in DMF (15 mL) was added NaN_3 (57.2 mg, 0.88 mmol) at room temperature, and the mixture was stirred at the same temperature for 20 min. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 50 : 1) to obtain azide **33** (114.1 mg, 81%, 2 steps) as a colorless oil.

33: $[\alpha]_D^{27}$ +35.3 (c 2.43, $CHCl_3$); IR (neat) 2104, 1464, 1380, 1240, 1197, 1161, 1057, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.57-0.63 (m, 9H), 0.93 (m, 12H), 1.24-2.02 (m, 23H), 3.73 (dd, *J* = 7.3, 13.3 Hz, 1H), 3.90 (dd, *J* = 8.3, 13.3 Hz, 1H), 5.13 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.6, 6.9, 11.8, 22.1, 23.8, 24.3, 26.8, 27.0 (t, *J* = 24.8 Hz), 27.4, 28.8, 35.7, 40.2, 45.1, 47.4, 55.8, 56.3, 75.6 (t, *J* = 28.1 Hz), 112.7, 125.3 (t, *J* = 247.9 Hz), 147.1; HRMS (ESI^+) calcd for $C_{26}H_{48}N_3OF_2Si$ $[M+H]^+$ 484.3529, found 484.3518.

(6*R*)-3,3-Difluoro-2-methyl-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethylidene]octahydro-1*H*-inden-1-yl}heptan-2-ol (**34a**)

To a mixture of phenylacetylene (20 μL, 0.186 mmol), 2,6-lutidine (29 μL, 0.248 mmol), sodium ascorbate (33.1 mg, 0.167 mmol) and 24,24-difluoro-CD-ring **33** (60 mg, 0.124 mmol) in *t*BuOH (3 mL) and H_2O (3 mL) was added $CuSO_4$-$5H_2O$ (3.2 mg, 0.013 mmol) at room temperature, and the mixture was stirred at the same temperature for 22 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol) was added to a solution of the crude triazole product in MeOH (10 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **34a** (24.7 mg, 47% 2 steps) as a colorless oil.

34a: $[\alpha]_D^{27}$ +48.3 (c 0.45, $CHCl_3$); IR (neat) 3378, 1470, 1380, 1177, 1017, 767, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (s, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 1.25-2.07 (m, 23H), 2.72-2.77 (m, 1H), 5.03-5.12 (m, 2H), 5.28 (t, *J* = 7.3 Hz, 1H), 7.32 (tt, *J* = 0.9, 7.3 Hz, 1H), 7.40-7.44 (m, 2H), 7.70 (s, 1H), 7.81-7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.6, 22.0, 23.3, 23.5, 26.7, 27.3, 27.3 (t, *J* = 26.7 Hz), 28.8, 35.6, 40.0, 45.6, 47.2, 55.6, 56.1, 73.3 (t, *J* = 27.7 Hz), 112.9, 118.9, 125.5 (t, *J* = 246.0 Hz), 125.6, 128.0, 128.7, 130.7, 147.1, 147.7; HRMS (ESI^+) calcd for $C_{28}H_{39}N_3OF_2Na$ $[M+Na]^+$ 494.2953, found 494.2941.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**34b**)

To a solution of 4-fluorophenylacetylene (23.3 mg, 0.194 mmol), 2,6-lutidine (21 μL, 0.182 mmol), sodium ascorbate (30.5 mg, 0.154 mmol) and 24,24-difluoro-CD-ring **33** (44.0 mg, 0.091 mmol) in *t*BuOH (3 mL) and H_2O (2 mL)

was added $CuSO_4$-$5H_2O$ (4.5 mg, 0.018 mmol) at room temperature, and the mixture was stirred at the same temperature for 74 h 30 min. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude triazole product was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol) was added to a solution of the crude triazole product in MeOH (10 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **34b** (30.8 mg, 69% 2 steps) as a colorless oil.

34b: $[\alpha]_D^{27}$ +44.2 (c 2.37, $CHCl_3$); IR (neat) 3393, 1498, 1380, 1230, 1177, 1016, 843, 759 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.58 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.25-2.05 (m, 23H), 2.73-2.75 (m, 1H), 5.03-5.10 (m, 2H), 5.27 (t, *J* = 7.2 Hz, 1H), 7.08-7.12 (m, 2H), 7.66 (s, 1H), 7.77-7.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.6, 22.1, 23.4, 23.6, 26.8, 27.4, 27.4 (t, *J* = 27.3 Hz), 28.8, 35.6, 40.0, 45.7, 47.3, 55.6, 56.2, 73.3 (t, *J* = 27.2 Hz), 111.6, 115.8 (d, *J* = 21.6 Hz), 118.6, 125.5 (t, *J* = 246.9 Hz), 127.0, 127.4 (d, *J* = 7.2 Hz), 146.9, 147.3, 163.1 (d, *J* = 245.7 Hz); HRMS (ESI^+) calcd for $C_{28}H_{38}N_3OF_3Na$ $[M+Na]^+$ 512.2859, found 512.2880.

(6*R*)-3,3-Difluoro-2-methyl-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(5-phenyl-2*H*-tetrazol-2-yl)ethylidene]octahydro-1*H*-inden-1-yl}heptan-2-ol (**35a**)

(6*R*)-3,3-Difluoro-2-methyl-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(5-phenyl-1*H*-tetrazol-1-yl)ethylidene]octahydro-1*H*-inden-1-yl}heptan-2-ol (**35b**)

To a solution of 5-phenyl-1*H*-tetrazole (126.7 mg, 0.867 mmol), Ph_3P (152.3 mg, 0.581 mmol), and 24,24-difluoro-CD-ring **32** (132.0 mg, 0.288 mmol) in THF (5 mL) was added diisopropyl azodicarboxylate (454 μL, 1.9 M in toluene, 0.863 mmol) at 0°C, and the mixture was stirred at the same temperature for 45 min. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel

(hexane : EtOAc = 4 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol) was added to a solution of the above less polar crude product in MeOH (10 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain **35a** (65.4 mg, 48%) as a colorless oil.

35a: $[\alpha]_D^{27}$ +38.1 (c 0.54, $CHCl_3$); IR (neat) 3445, 1468, 1450, 1381, 1177, 1017, 736, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.27-2.04 (m, 23H), 2.84 (dd, *J* = 3.9, 15.9 Hz, 1H), 5.25-5.35 (m, 3H), 7.43-7.49 (m, 3H), 8.13-8.15 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.3, 23.5, 26.7, 27.4 (t, *J* = 25.1 Hz), 27.4, 29.0, 35.6, 40.1, 45.8, 50.1, 55.6, 56.1, 73.3 (t, *J* = 27.8 Hz), 111.7, 125.5 (t, *J* = 247.1 Hz), 126.8, 127.6, 128.8, 130.1, 147.8, 165.0; HRMS (ESI^+) calcd for $C_{27}H_{38}N_4OF_2Na$ $[M+Na]^+$ 495.2906, found 495.2891.

p-Toluenesulfonic acid monohydrate (190.8 mg, 1.0 mmol) was added to a solution of the above more polar crude product in MeOH (10 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **35b** (16.3 mg, 12%) as a colorless oil.

35b: $[\alpha]_D^{27}$ +46.6 (c 1.28, $CHCl_3$); IR (neat) 3408, 1471, 1381, 1177, 1017, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.46 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.26-2.08 (m, 23H), 2.53-2.57 (m, 1H), 5.04-5.17 (m, 3H), 7.52-7.60 (m, 3H), 7.68-7.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.1, 23.6, 26.7, 27.3, 27.3 (t, *J* = 24.8 Hz), 28.9, 35.6, 40.0, 45.6, 45.7, 55.5, 56.1, 73.3 (t, *J* = 26.7 Hz), 112.9, 124.2, 125.5 (t, *J* = 247.0 Hz), 128.8, 129.1, 131.1, 146.4, 154.1; HRMS (ESI^+) calcd for $C_{27}H_{38}N_4OF_2Na$ $[M+Na]^+$ 495.2906, found 495.2908.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**36a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**36b**)

To a solution of 5-(4-fluorophenyl)-1*H*-tetrazole (75.8 mg, 0.462 mmol), Ph_3P (79.4 mg, 0.303 mmol), and 24,24-difluoro-CD-ring **32** (69.4 mg, 0.151 mmol) in CH_2Cl_2 (3 mL) was added diisopropyl azodicarboxylate (239 μL, 1.9 M in toluene, 0.454 mmol) at 0°C, and the mixture was stirred at the same temperature for 2 h. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 4 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (96.9 mg, 0.509 mmol) was added to a solution of the above less polar crude product in MeOH (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 150 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 3 : 1) to obtain **36a** (37.9 mg, 51%) as a colorless oil.

36a: $[\alpha]_D^{27}$ +39.0 (c 2.92, $CHCl_3$); IR (neat) 3430, 1464, 1380, 1177, 1043, 848, 763 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.95 (d, *J* = 7.2 Hz, 3H), 1.26-2.04 (m, 23H), 2.84 (dd, *J* = 4.2, 13.2 Hz, 1H), 5.21-5.34 (m, 3H), 7.14-7.18 (m, 2H), 8.11-8.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.3, 23.6, 26.8, 27.4 (t, *J* = 24.5 Hz), 27.4, 29.0, 35.6, 40.1, 45.8, 50.2, 55.6, 56.1, 73.3 (t, *J* = 27.3 Hz), 111.6, 115.9 (d, *J* = 23.0 Hz), 123.9, 125.5 (t, *J* = 236.9 Hz), 128.8 (d, *J* = 8.6 Hz), 147.5, 163.9 (d, *J* = 248.4 Hz), 164.2; HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_3Na$ $[M+Na]^+$ 513.2812, found 513.2812.

p-Toluenesulfonic acid monohydrate (94.6 mg, 0.497 mmol) was added to a solution of the above more polar crude product in MeOH (5 mL). The mixture was stirred at room temperature for 120 min under air. After the reaction was

quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **36b** (16.9 mg, 23%) as a colorless oil.

36b: $[\alpha]_D^{27}$ +45.2 (c 1.30, $CHCl_3$); IR (neat) 3399, 1479, 1384, 1240, 1176, 1017, 851, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.47 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.24-2.01 (m, 23H), 2.54-2.57 (m, 1H), 5.05-5.15 (m, 3H), 7.23-7.25 (m, 2H), 7.69-7.72 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.1, 23.6, 26.7, 27.3, 27.4 (t, *J* = 24.5 Hz), 28.9, 35.6, 39.9, 45.6, 45.7, 55.5, 56.1, 73.3 (t, *J* = 26.6 Hz), 112.8, 116.5 (d, *J* = 21.6 Hz), 120.4 (d, *J* = 2.9 Hz), 125.5 (t, *J* = 245.7 Hz), 131.0 (d, *J* = 8.6 Hz), 146.6, 153.3, 164.4 (d, *J* = 251.4 Hz); HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_3Na$ $[M+Na]^+$ 513.2812, found 513.2816.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-methylphenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**37a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-methylphenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**37b**)

To a solution of 5-(4-methylphenyl)-1*H*-tetrazole (29.5 mg, 0.184 mmol), Ph_3P (52.7 mg, 0.201 mmol), and 24,24-difluoro-CD-ring **32** (42.4 mg, 0.092 mmol) in CH_2Cl_2 (3 mL) was added diisopropyl diazocarboxylate (88 μL, 1.9 M in toluene, 0.166 mmol) at 0°C, and the mixture was stirred at 0°C for 5 min and then at room temperature for 40 min. The mixture was evaporated in vacuo, and the residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1 – 3 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (109.6 mg, 0.576 mmol) was added to a solution of the above less polar crude product in MeOH (5 mL) and CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1 h under air. *p*-Toluenesulfonic acid monohydrate (109.6 mg, 0.576 mmol) was added to a mixture and stirred at the same temperature for further 30 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room

temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 3 : 1) to obtain **37a** (13.5 mg, 30%) as a colorless oil.

37a: $[\alpha]_D^{27}$ +35.9 (c 1.04, $CHCl_3$); IR (neat) 3442, 1464, 1380, 1176, 1041, 1017, 830, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.25-2.04 (m, 23H), 2.41 (s, 3H), 2.83-2.85 (m, 1H), 5.21-5.35 (m, 3H), 7.28 (d, *J* = 7.8 Hz, 2H), 8.02 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 21.5, 22.0, 23.3, 23.6, 26.8, 27.4 (t, *J* = 24.4 Hz), 27.4, 29.1, 35.6, 40.1, 45.8, 50.1, 55.6, 56.1, 73.3 (t, *J* = 26.6 Hz), 111.8, 124.8, 125.5 (t, *J* = 246.3 Hz), 126.7, 129.5, 140.3, 147.7, 165.1; HRMS (ESI^+) calcd for $C_{28}H_{40}N_4OF_2Na$ $[M+Na]^+$ 509.3062, found 509.3075.

p-Toluenesulfonic acid monohydrate (203.6 mg, 1.07 mmol) was added to a solution of the above more polar crude product in MeOH (5 mL) and CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 70 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **37b** (12.7 mg, 28%) as a colorless oil.

37b: $[\alpha]_D^{27}$ +41.3 (c 0.98, $CHCl_3$); IR (neat) 3418, 1479, 1380, 1176, 1013, 826, 759 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.48 (s, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 1.24-2.01 (m, 23H), 2.45 (s, 3H), 2.56-2.58 (m, 1H), 5.04-5.15 (m, 3H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 21.5, 22.1, 23.1, 23.6, 26.7, 27.3, 27.4 (t, *J* = 24.5 Hz), 28.9, 35.6, 40.0, 45.6, 45.6, 55.5, 56.1, 73.3 (t, *J* = 27.3 Hz), 113.1, 121.2, 125.4 (t, *J* = 245.6 Hz), 128.7, 129.8, 141.6, 146.2, 154.1; HRMS (ESI^+) calcd for $C_{28}H_{40}N_4OF_2Na$ $[M+Na]^+$ 509.3062, found 509.3079.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-trifluoromethylphenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**38a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-trifluoromethylphenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**38b**)

To a solution of 5-(4-trifluoromethylphenyl)-1*H*-tetrazole (61.5 mg, 0.287 mmol), Ph_3P (72.2 mg, 0.275 mmol), and 24,24-difluoro-CD-ring **32** (60.1 mg, 0.131 mmol) in CH_2Cl_2 (8 mL) was added diisopropyl azodicarboxylate (124 μL, 1.9 M in toluene, 0.235 mmol) at 0°C, and the mixture was stirred at 0°C for 70 min. The mixture was evaporated in vacuo, and the residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 4 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (386.8 mg, 2.03 mmol) was added to a solution of the above less polar crude product in MeOH (5 mL) and CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 35 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 3 : 1) to obtain **38a** (41.4 mg, 58%) as a white powder.

38a: $[\alpha]_D^{27}$ +35.2 (c 3.17, $CHCl_3$); IR (neat) 3431, 1471, 1324, 1173, 1133, 1066, 858 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 1.26-2.05 (m, 23H), 2.83-2.86 (m, 1H), 5.27-5.35 (m, 3H), 7.74 (d, *J* = 8.1 Hz, 2H), 8.26 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.4, 23.56, 26.8, 27.4, 27.4 (t, *J* = 24.4 Hz), 29.1, 35.6, 40.1, 45.9, 50.3, 55.6, 56.1, 73.3 (t, *J* = 27.2 Hz), 111.5, 123.9 (q, *J* = 270.0 Hz), 125.5 (t, *J* = 246.9 Hz), 125.8, 127.0, 131.0, 131.9 (q, *J* = 31.7 Hz), 148.3, 163.8; HRMS (ESI^-) calcd for $C_{28}H_{37}N_4OF_5Cl$ $[M+Cl]^-$ 575.2582, found 575.2577.

p-Toluenesulfonic acid monohydrate (411.7 mg, 2.05 mmol) was added to a solution of the above more polar crude product in MeOH (5 mL) and CH_2Cl_2 (6 mL). The mixture was stirred at room temperature for 60 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **38b** (15.1 mg, 21%) as

a white powder.

38b: $[\alpha]_D^{27}$ +40.8 (c 1.16, $CHCl_3$); IR (neat) 3522, 1459, 1328, 1173, 1129, 1073, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.45 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.22-2.10 (m, 23H), 2.53-2.57 (m, 1H), 5.04-5.20 (m, 3H), 7.82 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.4, 23.55, 26.7, 27.3, 27.3 (t, *J* = 24.8 Hz), 28.9, 35.6, 39.9, 45.6, 45.9, 55.5, 56.1, 73.3 (t, *J* = 27.2 Hz), 112.5, 123.5 (q, *J* = 271.7 Hz), 125.4 (t, *J* = 246.0 Hz), 126.1, 127.8, 129.3, 133.1 (q, *J* = 32.7 Hz), 146.9, 153.0; HRMS (ESI^-) calcd for $C_{28}H_{37}N_4OF_5Cl$ $[M+Cl]^-$ 575.2582, found 575.2590.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-chlorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**39a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-chlorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**39b**)

To a solution of 5-(4-chlorophenyl)-1*H*-tetrazole (44.7 mg, 0.248 mmol), Ph_3P (67.6 mg, 0.258 mmol), and 24,24-difluoro-CD-ring **32** (49.8 mg, 0.109 mmol) in CH_2Cl_2 (8 mL) was added diisopropyl azodicarboxylate (103 μL, 1.9 M in toluene, 0.196 mmol) at 0°C, and the mixture was stirred at the same temperature for 110 min. The mixture was evaporated in vacuo, and the residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (435.3 mg, 2.29 mmol) was added to a solution of the above less polar crude product in MeOH (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 3 : 1) to obtain **39a** (31.4 mg, 57%) as a colorless oil.

39a: $[\alpha]_D^{27}$ +41.4 (c 2.42, $CHCl_3$); IR (neat) 3414, 1456, 1326, 1175, 1093, 1017, 841, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 1.23-2.05 (m, 23H), 2.81-2.85 (m, 1H), 5.20-5.35 (m, 3H), 7.45

(dt, 2.3, 8.2 Hz, 2H), 8.07 (dt, 2.3, 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.3, 23.5, 26.7, 27.4 (t, *J* = 24.8 Hz), 29.0, 35.6, 40.1, 45.8, 50.2, 55.6, 56.1, 73.3 (t, *J* = 27.2 Hz), 111.6, 125.5 (t, *J* = 246.0 Hz), 126.1, 128.0, 129.1, 136.1, 148.0, 164.1; HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_2ClNa$ $[M+Na]^+$ 529.2516, found 529.2531.

p-Toluenesulfonic acid monohydrate (389.5 mg, 2.05 mmol) was added to a solution of the above more polar crude product in MeOH (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 85 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **39b** (15.3 mg, 28%) as a colorless oil.

39b: $[\alpha]_D^{27}$ +43.0 (c 1.18, $CHCl_3$); IR (neat) 3423, 1471, 1380, 1174, 1093, 1013, 838, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.47 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 1.24-2.05 (m, 23H), 2.54-2.58 (m, 1H), 5.03-5.18 (m, 3H), 7.53 (dt, *J* = 2.1, 8.2 Hz, 2H), 7.65 (dt, *J* = 2.1, 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.1, 23.5, 26.7, 27.3, 27.3 (t, *J* = 24.3 Hz), 28.9, 35.6, 39.9, 45.6, 45.8, 55.5, 56.1, 73.3 (t, *J* = 27.2 Hz), 112.8, 122.6, 125.4 (t, *J* = 246.0 Hz), 129.5, 130.1, 137.6, 146.7, 153.2; HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_2ClNa$ $[M+Na]^+$ 529.2516, found 529.2510.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(3-methylphenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**40a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(3-methylphenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**40b**)

To a solution of 5-(3-methylphenyl)-1*H*-tetrazole (28.6 mg, 0.179 mmol), Ph_3P (47.8 mg, 0.182 mmol), and 24,24-difluoro-CD-ring **32** (51.4 mg, 0.112 mmol) in CH_2Cl_2 (8 mL) was added diisopropyl azodicarboxylate (83 μL, 1.9 M in toluene, 0.157 mmol) at 0°C, and the mixture was stirred at 0°C for 5 min and then at room temperature for 20 min. To the mixture were added diisopropyl azodicarboxylate (83 μL, 1.9 M in toluene, 0.157 mmol) and Ph_3P (83.7 mg,

0.319 mmol) and stirred at room temperature for 40 min. The mixture was evaporated in vacuo, and the residue was roughly purified on a preparative silica gel TLC plate (hexane : EtOAc = 3 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (584.6 mg, 3.07 mmol) was added to a solution of the above less polar crude product in MeOH (10 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 90 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 2 : 1) to obtain **40a** (38.1 mg, 70%) as a colorless oil.

40a: $[\alpha]_D^{27}$ +23.1 (c 2.93, $CHCl_3$); IR (neat) 3423, 1471, 1380, 1180, 1017, 858, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 1.26-2.06 (m, 23H), 2.43 (s, 3H), 2.83-2.86 (m, 1H), 5.22-5.35 (m, 3H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 21.4, 22.0, 23.3, 23.6, 26.8, 27.4 (t, *J* = 24.4 Hz), 27.4, 29.0, 35.6, 40.1, 45.8, 50.2, 55.6, 56.1, 73.4 (t, *J* = 27.3 Hz), 111.8, 123.9, 125.5 (t, *J* = 246.3 Hz), 127.4, 127.5, 128.8, 130.9, 138.6, 147.8, 165.1; HRMS (ESI^+) calcd for $C_{28}H_{40}N_4OF_2Na$ $[M+Na]^+$ 509.3062, found 509.3068.

p-Toluenesulfonic acid monohydrate (376.1 mg, 1.98 mmol) was added to a solution of the above more polar crude product in MeOH (10 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 60 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 2) to obtain **40b** (11.0 mg, 20%) as a colorless oil.

40b: $[\alpha]_D^{27}$ +44.6 (c 0.85, $CHCl_3$); IR (neat) 3411, 1475, 1380, 1180, 1125, 1021, 918, 854, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.46 (s, 3H), 0.93 (d, *J* = 6.0 Hz, 3H), 1.24-1.99 (m, 23H), 2.43 (s, 3H), 2.53-2.56 (m, 1H), 5.04-5.16 (m, 3H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz,

1H), 7.51 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 21.4, 22.0, 23.1, 23.6, 26.7, 27.3, 27.3 (t, *J* = 24.5 Hz), 28.9, 35.6, 40.0, 45.5, 45.6, 55.5, 56.1, 73.3 (t, *J* = 27.2 Hz), 113.0, 124.1, 125.4 (t, *J* = 246.3 Hz), 128.9, 129.5, 139.2, 146.2, 154.2; HRMS (ESI$^+$) calcd for $C_{28}H_{40}N_4OF_2Na$ $[M+Na]^+$ 509.3062, found 509.3039.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(3,5-dichlorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**41a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(3,5-dichlorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**41b**)

To a solution of 5-(2,4-dichlorophenyl)-1*H*-tetrazole (40.8 mg, 0.190 mmol), Ph_3P (47.6 mg, 0.181 mmol), and 24,24-difluoro-CD-ring **32** (40.8 mg, 0.089 mmol) in CH_2Cl_2 (4 mL) was added diisopropyl azodicarboxylate (138 μL, 1.9 M in toluene, 0.262 mmol) at 0°C, and the mixture was stirred at 0°C for 35 min and then at room temperature for 25 min. The mixture was evaporated in vacuo, and the residue was roughly purified on a preparative silica gel TLC plate (hexane : EtOAc = 3 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (200.3 mg, 1.05 mmol) was added to a solution of the above less polar crude product in MeOH (10 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 2 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) and followed by purification on a preparative silica gel TLC plate (hexane : EtOAc = 2 : 1) to obtain **41a** (27.6 mg, 57%) as a colorless oil.

41a: $[\alpha]_D^{27}$ +33.8 (c 2.12, $CHCl_3$); IR (neat) 3439, 1571, 1515, 1444, 1399, 1173, 1017, 862, 735 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 1.24-2.05 (m, 23H), 2.81-2.84 (m, 1H), 5.25-5.34 (m, 3H), 7.45 (t, *J* = 2.4 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8,

18.6, 22.0, 23.3, 23.6, 26.8, 27.4 (t, *J* = 24.4 Hz), 27.4, 29.0, 35.6, 40.1, 45.9, 50.4, 55.6, 56.1, 73.4 (t, *J* = 27.3 Hz), 111.4, 125.1, 125.5 (t, *J* = 246.3 Hz), 130.0, 130.4, 135.6, 148.3, 162.9; HRMS (ESI$^-$) calcd for $C_{28}H_{37}N_4O_3F_2Cl_2$ [M+HCOO]$^-$ 585.2216, found 585.2215.

p-Toluenesulfonic acid monohydrate (580.1 mg, 3.05 mmol) was added to a solution of the above more polar crude product in MeOH (20 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) and followed by purification on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **41b** (15.0 mg, 31%) as a colorless oil.

41b: $[\alpha]_D^{27}$ +30.1 (c 1.15, $CHCl_3$) ; IR (neat) 3435, 1567, 1527, 1451, 1380, 1176, 1013, 905, 866, 727 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.95 (d, *J* = 6.0 Hz, 3H), 1.24-2.05 (m, 23H), 2.81-2.84 (m, 1H), 5.25-5.34 (m, 3H), 7.45 (t, *J* = 2.4 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.1, 23.7, 26.7, 27.3, 27.3 (t, *J* = 24.4 Hz), 28.9, 35.6, 39.9, 45.6, 46.1, 55.5, 56.1, 73.4 (t, *J* = 27.3 Hz), 112.4, 125.4 (t, *J* = 245.7 Hz), 127.0, 127.2, 131.2, 136.1, 147.1, 152.0; HRMS (ESI$^-$) calcd for $C_{28}H_{37}N_4O_3F_2Cl_2$ [M+HCOO]$^-$ 585.2216, found 585.2221.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(3-fluorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**42a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(3-fluorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**42b**)

To a solution of 5-(3-fluorophenyl)-1*H*-tetrazole (36.4 mg, 0.222 mmol), Ph_3P (58.9 mg, 0.225 mmol), and 24,24-difluoro-CD-ring **32** (52.9 mg, 0.115 mmol) in CH_2Cl_2 (8 mL) was added diisopropyl diazocarboxylate (103 μL, 1.9 M in toluene, 0.196 mmol) at 0°C, and the mixture was stirred at 0°C for 20 min. The mixture was evaporated in vacuo, and the residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1 – 2 : 1) to obtain

crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (123.3 mg, 0.65 mmol) was added to a solution of the above less polar crude product in MeOH (10 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 2 : 1) to obtain **42a** (34.8 mg, 62%) as a colorless oil.

42a: $[\alpha]_D^{27}$ +38.9 (c 2.68, $CHCl_3$); IR (neat) 3439, 1471, 1380, 1225, 1176, 1021, 763 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 1.24-2.04 (m, 23H), 2.83-2.85 (m, 1H), 5.28-5.37 (m, 3H), 7.22 (dd, *J* = 8.4, 10.2 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 3H), 7.24-7.46 (m, 1H), 8.12 (td, *J* = 1.8, 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.3, 23.5, 26.8, 27.3 (t, *J* = 24.5 Hz), 27.3, 29.0, 35.6, 40.1, 45.8, 50.2, 55.6, 56.1, 73.3 (t, *J* = 27.3 Hz), 111.5, 113.8 (d, *J* = 24.5 Hz), 117.0 (d, *J* = 21.5 Hz), 122.4 (d, *J* = 2.9 Hz), 125.5 (t, *J* = 246.3 Hz), 129.6 (d, *J* = 8.7 Hz), 130.5 (d, *J* = 8.6 Hz), 148.1, 163.0 (d, *J* = 244.2 Hz), 164.0 (d, *J* = 3.0 Hz); HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_3Na$ $[M+Na]^+$ 513.2812, found 513.2817.

p-Toluenesulfonic acid monohydrate (211.9 mg, 1.11 mmol) was added to a solution of the above more polar crude product in MeOH (10 mL). The mixture was stirred at room temperature for 40 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **42b** (10.2 mg, 18%) as a colorless oil.

42b: $[\alpha]_D^{27}$ +66.9 (c 0.79, $CHCl_3$); IR (neat) 3411, 1475, 1384, 1204, 1176, 1017, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 1.24-2.04 (m, 23H), 2.83-2.85 (m, 1H), 5.28-5.37 (m, 3H), 7.22 (dd, *J* = 8.4, 10.2 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 3H), 7.24-7.46 (m, 1H), 8.12 (td, *J* = 1.8, 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.0, 23.6, 26.7, 27.3, 27.3 (t, *J* = 24.5 Hz), 27.3, 28.9, 35.6, 39.9, 45.6, 45.9, 55.5, 56.1, 73.3

(t, J = 26.6 Hz), 112.7, 116.1 (d, J = 23.0 Hz), 118.3 (d, J = 21.6 Hz), 124.6 (d, J = 4.4 Hz), 125.4 (t, J = 245.6 Hz), 126.1 (d, J = 8.6 Hz), 131.0 (d, J = 8.6 Hz), 146.7, 153.0, 162.7 (d, J = 247.1 Hz); HRMS (ESI$^+$) calcd for $C_{27}H_{37}N_4OF_3Na$ $[M+Na]^+$ 513.2812, found 513.2821.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(2-chlorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**43a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(2-chlorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**43b**)

To a solution of 5-(2-chlorophenyl)-1*H*-tetrazole (39.9 mg, 0.221 mmol), Ph_3P (58.2 mg, 0.222 mmol), and 24,24-difluoro-CD-ring **32** (51.7 mg, 0.113 mmol) in CH_2Cl_2 (8 mL) was added diisopropyl diazocarboxylate (103 μL, 1.9 M in toluene, 0.196 mmol) at 0°C, and the mixture was stirred at 0°C for 35 min. The mixture was evaporated in vacuo, and the residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (573.2 mg, 3.01 mmol) was added to a solution of the above less polar crude product in MeOH (20 mL). The mixture was stirred at room temperature for 5 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 3 : 1) to obtain **43a** (22.7 mg, 40%) as a colorless oil.

43a: $[\alpha]_D^{27}$ +37.7 (c 1.75, $CHCl_3$); IR (neat) 3435, 1446, 1380, 1176, 1125, 1073, 1038, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, J = 6.4 Hz, 3H), 1.24-2.05 (m, 23H), 2.83-2.87 (m, 1H), 5.29-5.39 (m, 3H), 7.35-7.42 (m, 2H), 7.52-7.54 (m, 1H), 7.91-7.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.4, 23.6, 26.8, 27.4 (t, J = 24.8 Hz), 27.4, 29.0, 35.6, 40.1, 45.8, 50.3, 55.6, 56.1, 73.3 (t, J = 26.7 Hz), 111.6, 125.5 (t, J = 246.0 Hz), 126.8, 126.8, 130.8, 130.9, 131.3, 133.1, 148.1, 163.2; HRMS (ESI$^+$) calcd for $C_{27}H_{37}N_4OF_2ClNa$ $[M+Na]^+$ 529.2516, found 529.2519.

p-Toluenesulfonic acid monohydrate (580.7 mg, 3.05 mmol) was added to a solution of the above more polar crude product in MeOH (20 mL). The mixture was stirred at room temperature for 90 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **43b** (20.7 mg, 36%) as a colorless oil.

43b: $[\alpha]_D^{27}$ +29.4 (c 1.59, $CHCl_3$); IR (neat) 3407, 1459, 1380, 1176, 1125, 1073, 1020, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.40 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 1.18-2.02 (m, 23H), 2.36-2.40 (m, 1H), 4.91-5.06 (m, 3H), 7.40-7.45 (m, 2H), 7.51-7.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 18.6, 21.9, 23.1, 23.5, 26.7, 27.2, 27.3 (t, *J* = 24.8 Hz), 28.5, 35.6, 40.0, 45.4, 55.4, 56.0, 73.3 (t, *J* = 26.7 Hz), 112.0, 124.4, 125.4 (t, *J* = 246.0 Hz), 127.2, 130.1, 131.9, 132.5, 133.9, 147.1, 152.2; HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_2ClNa$ $[M+Na]^+$ 529.2516, found 529.2531.

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(2-fluorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**44a**)

(6*R*)-3,3-Difluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(2-fluorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**44b**)

To a solution of 5-(2-fluorophenyl)-1*H*-tetrazole (36.5 mg, 0.222 mmol), Ph_3P (59.2 mg, 0.226 mmol), and 24,24-difluoro-CD-ring **32** (51.4 mg, 0.112 mmol) in CH_2Cl_2 (8 mL) was added diisopropyl azodicarboxylate (103 μL, 1.9 M in toluene, 0.196 mmol) at 0°C, and the mixture was stirred at 0°C for 30 min. The mixture was evaporated in vacuo, and the residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1 – 2 : 1) to obtain crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (585.7 mg, 3.08 mmol) was added to a solution of the above less polar crude product in MeOH (20 mL). The mixture was stirred at room temperature for 105 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over

Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 2 : 1) to obtain **44a** (30.8 mg, 56%) as a colorless oil.

44a: $[\alpha]_D^{27}$ +36.7 (c 2.37, $CHCl_3$); IR (neat) 3435, 1479, 1376, 1228, 1180, 1037, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 1.24-2.04 (m, 23H), 2.83-2.85 (m, 1H), 5.28-5.37 (m, 3H), 7.22 (dd, *J* = 8.4, 10.2 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 3H), 7.24-7.46 (m, 1H), 8.12 (td, *J* = 1.8, 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.6, 22.0, 23.3, 23.6, 26.8, 27.3 (t, *J* = 24.5 Hz), 27.4, 29.1, 35.6, 40.1, 45.8, 50.3, 55.6, 56.1, 73.3 (t, *J* = 27.3 Hz), 111.6, 115.8 (d, *J* = 11.4 Hz), 116.6 (d, *J* = 20.1 Hz), 124.4 (d, *J* = 4.2 Hz), 125.5 (t, *J* = 246.3 Hz), 129.9, 131.1 (d, *J* = 8.7 Hz), 148.0, 160.1 (d, *J* = 254.3 Hz), 161.2 (d, *J* = 4.4 Hz); HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_3Na$ $[M+Na]^+$ 513.2812, found 513.2797.

p-Toluenesulfonic acid monohydrate (619.1 mg, 3.25 mmol) was added to a solution of the above more polar crude product in MeOH (20 mL). The mixture was stirred at room temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **44b** (21.6 mg, 39%) as a colorless oil.

44b: $[\alpha]_D^{27}$ +38.0 (c 1.66, $CHCl_3$); IR (neat) 3423, 1479, 1384, 1217, 1173, 1021, 774, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.36 (s, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 1.20-2.06 (m, 23H), 2.47-2.52 (m, 1H), 4.98-5.12 (m, 3H), 7.24-7.29 (m, 1H), 7.33 (td, *J* = 1.8, 7.4 Hz, 1H), 7.56-7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 18.6, 21.9, 23.1, 23.5, 26.7, 27.3, 27.3 (t, *J* = 24.3 Hz), 28.6, 35.6, 40.0, 45.5, 45.6, 45.7, 55.4, 56.0, 73.3 (t, *J* = 27.2 Hz), 112.1, 112.9 (d, *J* = 14.3 Hz), 116.3 (d, *J* = 21.0 Hz), 125.0 (d, *J* = 2.9 Hz), 125.4 (t, *J* = 246.0 Hz), 131.8, 133.5 (d, *J* = 7.6 Hz), 147.0, 150.1, 159.6 (d, *J* = 248.8 Hz); HRMS (ESI^+) calcd for $C_{27}H_{37}N_4OF_3Na$ $[M+Na]^+$ 513.2812, found 513.2825.

2-{(1*R*,3a*S*,7a*R*,*E*)-7a-Methyl-1-[(2*R*)-7,7,7-trifluoro-6-(methoxymethoxy)-6-(trifluoromethyl)heptan-2-yl]octahydro-4*H*-inden-4-ylidene}ethan-1-ol (**47**)

To a suspension of NaH (277.2 mg, 60% in oil, 6.93 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (1.75 g, 1.56 mL, 7.79 mmol) at 0°C, and the mixture was stirred at 0°C for 30 min. Ketone (**46**) [32,100] (374.6 mg, 0.866 mmol) was dissolved in THF (5 mL) and the solution was added to the mixture at the same temperature. After being stirred at room temerature for 64 h, the reaction mixture was quenched with H_2O and saturated aqueous NH_4Cl at room temperature. The mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 10 : 1) to obtain the crude ethyl ester (418.2 mg) as a colorless oil.

To the solution of the above crude ethyl ester (418.2 mg, 0.832 mmol) in THF (10 mL) was added DIBAL-H (2.5 mL, 1.00 M toluene solution, 2.5 mmol) at -78°C, and the mixture was stirred at room temperature for 20 min. After the reaction was quenched with H_2O and saturated aqueous potassium sodium tartrate at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain alcohol **47** (364.7 mg, 95%, 2 steps) as a colorless oil.

47: $[\alpha]_D^{27}$ +72.2 (c 1.37, $CHCl_3$); IR (neat) 3343, 1471, 1284, 1217, 1145, 1049, 937 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.03-1.11 (m, 1H), 1.25-1.67 (m, 20H), 1.83-2.04 (m, 5H), 2.11 (dd, *J* = 4.2, 11.4 Hz, 1H), 3.46 (s, 3H), 4.17-4.23 (m, 2H), 4.91 (dd, *J* = 6.9, 9.6 Hz, 2H), 5.22 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.7, 19.0, 22.2, 23.5, 27.6, 28.7, 28.8, 35.9, 36.4, 40.3, 45.3, 55.6, 56.4, 56.6, 58.7, 80.2 (sept, *J* = 28.7 Hz), 92.8, 119.3, 123.0 (q, *J* = 288.6 Hz), 143.6.

(1*R*,3a*S*,7a*R*,*E*)-4-(2-Azidoethylidene)-7a-methyl-1-[(2*R*)-7,7,7-trifluoro-6-(methoxymethoxy)-6-(trifluoromethyl)heptan-2-yl]octahydro-1*H*-indene (**48**)

To the solution of the CD-ring **47** (187.8 mg, 0.408 mmol) and pyridine (99 μL, 1.22 mmol) in CCl_4 (20 mL) was added tri-*n*-butylphosphine (509 μL, 2.04 mmol) at 0 °C, over 5 min, and the mixture was stirred at the same temperature for 10 min. After the reaction was diluted with hexane, the mixture was filtered, and concentrated. To the residue was added hexane, the mixture was filtered with celite, and concentrated. The crude allylchloride was used for the next

reaction without further purification.

To the solution of the above crude allylchloride in DMF (25 mL) was added NaN_3 (79.5 mg, 1.22 mmol) at room temperature, and the mixture was stirred at the same temperature for 20 min. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 50 : 1) to obtain azide **48** (162.3 mg, 82%, 2 steps) as a colorless oil.

48: $[\alpha]_D^{27}$ +36.3 (c 0.208, $CHCl_3$); IR (neat) 2100, 1468, 1284, 1217, 1161, 1049 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.59 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.05-1.11 (m, 1H), 1.26-1.71 (m, 10H), 1.85-2.04 (m, 5H), 2.60-2.64 (m, 1H), 3.46 (s, 3H), 3.73 (dd, *J* = 7.2, 13.8 Hz, 2H), 3.89 (dd, *J* = 8.4, 13.8 Hz, 2H), 4.90-4.93 (m, 2H), 5.13 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.7, 18.9, 22.1, 23.8, 27.5, 28.8, 35.9, 36.3, 40.2, 45.1, 47.4, 55.7, 56.4, 56.5, 80.20 (sept, *J* = 28.0 Hz), 92.8, 112.8, 123.0 (q, *J* = 288.6 Hz), 147.0; HRMS (ESI^+) calcd for $C_{22}H_{34}N_3O_2F_6$ $[M+H]^+$ 486.2550, found 486.2555.

(6*R*)-1,1,1-Trifluoro-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethylidene]octahydro-1*H*-inden-1-yl}-2-(trifluoromethyl)heptan-2-ol (**49a**)

To a solution of ethynylbenzene (20 μL, 0.186 mmol), 2,6-lutidine (29 μL, 0.248 mmol), sodium ascorbate (24.6 mg, 0.124 mmol) and CD-ring **48** (60.0 mg, 0.124 mmol) in *t*BuOH (3 mL) and H_2O (3 mL) was added $CuSO_4$-$5H_2O$ (3.1 mg, 0.012 mmol) at room temperature, and the mixture was stirred at the same temperature for 25 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude triazole product was used for the next reaction without further purification.

Methanesulfonic acid (0.4 mL) was added to a solution of the above crude product in MeOH (20 mL). The mixture was stirred at room temperature under air for 9 h. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 2 : 1) to obtain **49a** (37.1

mg, 55%) as a colorless oil.

49a: $[\alpha]_D^{27}$ +22.3 (c 0.24, $CHCl_3$); IR (neat) 3143, 1468, 1225, 763 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.04-1.11 (m, 1H), 1.21-2.04 (m, 17H), 2.72-2.75 (m, 1H), 4.21 (brs, 1H), 5.03-5.09 (m, 2H), 5.25 (t, *J* = 7.2 Hz, 1H), 7.32-7.34 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.70 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.9, 18.5, 18.7, 22.1, 23.4, 27.5, 28.8, 30.9, 35.8, 36.1, 40.0, 45.7, 47.3, 55.6, 56.3, 76.3 (sept, *J* = 28.8 Hz), 112.8, 119.0, 123.3 (q, *J* = 285.8 Hz), 125.7, 128.2, 128.8, 130.5, 147.3, 147.8; HRMS (ESI^+) calcd for $C_{28}H_{36}N_3OF_6$ $[M+H]^+$ 544.2757, found 544.2787.

(6*R*)-1,1,1-Trifluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-(trifluoromethyl)heptan-2-ol (**49b**)

To a solution of 1-ethynyl-4-fluorobenzene (17.1 mg, 0.142 mmol), 2,6-lutidine (16 μL, 0.142 mmol), sodium ascorbate (17.8 mg, 0.090 mmol) and CD-ring **47** (34.5 mg, 0.071 mmol) in *t*BuOH (3 mL) and H_2O (3 mL) was added $CuSO_4$-$5H_2O$ (3.3 mg, 0.013 mmol) at room temperature, and the mixture was stirred at the same temperature for 63 h. After the reaction was quenched with H_2O, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude triazole product was used for the next reaction without further purification.

Methanesulfonic acid (0.2 mL) was added to a solution of the above crude product in MeOH (10 mL). The mixture was stirred at room temperature under air for 20 h. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **49b** (27.8 mg, 70%) as a colorless oil.

49b: $[\alpha]_D^{27}$ +41.3 (c 2.14, $CHCl_3$); IR (neat) 3147, 1498, 1470, 1228, 843, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.04-1.11 (m, 1H), 1.22-2.04 (m, 17H), 2.71-2.74 (m, 1H), 5.01-5.09 (m, 2H), 5.24 (t, *J* = 7.5 Hz, 1H), 7.09-7.12 (m, 2H), 7.66 (s, 1H), 7.76-7.78 (m, 2H); ^{13}C NMR

(150 MHz, $CDCl_3$) δ 11.9, 18.5, 18.7, 22.1, 23.4, 27.5, 28.8, 31.0, 35.8, 36.1, 40.0, 45.7, 47.4, 55.6, 56.3, 76.3 (sept, *J* = 28.8 Hz), 112.8, 115.8 (d, *J* = 21.6 Hz), 118.8, 123.3 (q, *J* = 284.4 Hz), 126.7, 127.5 (d, *J* = 8.6 Hz), 146.9, 147.4, 162.7 (d, *J* = 245.6 Hz); HRMS (ESI^+) calcd for $C_{28}H_{34}N_3OF_7Na$ $[M+Na]^+$ 584.2482, found 584.2477.

(6*R*)-1,1,1-Trifluoro-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(5-phenyl-2*H*-tetrazol-2-yl)ethylidene]octahydro-1*H*-inden-1-yl}-2-(trifluoromethyl)heptan-2-ol (**50a**)

(6*R*)-1,1,1-Trifluoro-6-{(1*R*,3a*S*,7a*R*,*E*)-7a-methyl-4-[2-(5-phenyl-1*H*-tetrazol-1-yl)ethylidene]octahydro-1*H*-inden-1-yl}-2-(trifluoromethyl)heptan-2-ol (**50b**)

To a solution of 5-phenyl-1*H*-tetrazole (166.6 mg, 1.14 mmol), Ph_3P (199.3 mg, 0.76 mmol), and CD-ring **47** (175.0 mg, 0.38 mmol) in THF (5 mL) was added diisopropyl diazocarboxylate (600 μL, 1.9 M in toluene, 1.14 mmol) at 0°C, and the mixture was stirred for 1 h. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 4 : 1) to obtain the crude products (less polar and more polar products).

Methanesulfonic acid (0.4 mL) was added to a solution of the above less polar crude product in MeOH (20 mL). The mixture was stirred at room temperature under air for 6 h. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 10 : 1) to obtain **50a** (87.2 mg, 42%) as a colorless oil.

50a: $[\alpha]_D^{27}$ +33.8 (c 0.68, $CHCl_3$); IR (neat) 3205, 1471, 1452, 1228, 1176, 734 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.04-1.11 (m, 1H), 1.23-2.03 (m, 17H), 2.83-2.86 (m, 1H), 3.13 (brs, 1H), 5.28-5.45 (m, 3H), 7.44-7.50 (m, 3H), 8.13-8.15 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.5, 18.7, 22.0, 23.3, 27.5, 29.1, 30.8, 35.8, 36.1, 40.1, 45.9, 50.2, 55.6, 56.3, 76.2 (sept, *J* = 28.7 Hz), 111.7, 123.2 (q, *J* = 284.4 Hz), 126.8, 127.6,

128.8, 130.2, 147.9, 165.0; HRMS (ESI$^-$) calcd for $C_{28}H_{35}N_4O_3F_6$ [M+HCOO]$^-$ 589.2619, found 589.2594.

Methanesulfonic acid (0.4 mL) was added to a solution of the above more polar crude product in MeOH (20 mL). The mixture was stirred at room temperature under air for 8 h. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 2 : 1) to obtain **50b** (35.7 mg, 17%) as a colorless oil.

50b: $[\alpha]_D^{27}$ +40.5 (c 0.19, $CHCl_3$); IR (neat) 3227, 1475, 1225, 759 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.44 (s, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 1.03-1.10 (m, 1H), 1.20-1.99 (m, 17H), 2.51-2.55 (m, 1H), 3.85 (brs, 1H), 5.06-5.17 (m, 3H), 7.53-7.59 (m, 3H), 7.67-7.68 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.4, 18.6, 22.0, 23.1, 27.4, 28.9, 30.9, 35.8, 36.1, 40.0, 45.6, 45.7, 55.4, 56.2, 76.3 (sept, *J* = 28.8 Hz), 112.8, 123.3 (q, *J* = 284.4 Hz), 124.0, 128.8, 129.2, 131.2, 146.5, 154.1; HRMS (ESI$^-$) calcd for $C_{28}H_{35}N_4O_3F_6$ [M+HCOO]$^-$ 589.2619, found 589.2582.

(6*R*)-1,1,1-Trifluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-(trifluoromethyl)heptan-2-ol (**51a**)

(6*R*)-1,1,1-Trifluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-(trifluoromethyl)heptan-2-ol (**51b**)

To a solution of 5-(4-fluorophenyl)-1*H*-tetrazole (43.5 mg, 0.27 mmol), Ph_3P (46.4 mg, 0.18 mmol), and CD-ring **47** (40.7 mg, 0.088 mmol) in CH_2Cl_2 (5 mL) was added diisopropyl azodicarboxylate (140 μL, 1.9 M in toluene, 0.27 mmol) at 0°C, and the mixture was stirred for 1 h. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain the crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (625.0 mg, 3.29 mmol) was added to a solution of the above less polar crude product in MeOH (7.5 mL) and CH_2Cl_2 (7.5 mL). The mixture was stirred at room temperature for 17 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 4 : 1) to obtain **51a** (17.6 mg, 35%) as a colorless oil.

51a: $[\alpha]_D^{27}$ +34.7 (c 1.35, $CHCl_3$); IR (neat) 3291, 1468, 1225, 1157, 846 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 1.03-1.10 (m, 1H), 1.22-2.04 (m, 17H), 2.81-2.84 (m, 1H), 3.89 (brs, 1H), 5.27-5.33 (m, 3H), 7.14-7.18 (m, 2H), 8.10-8.13 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.5, 18.6, 22.0, 23.3, 27.5, 29.0, 30.9, 35.8, 36.1, 40.1, 45.8, 50.2, 55.6, 56.3, 76.2 (sept, *J* = 28.7 Hz), 111.5, 116.0 (d, *J* = 23.0 Hz), 123.3 (q, *J* = 284.4 Hz), 123.7, 128.8 (d, *J* = 7.2 Hz), 148.1, 164.0 (d, *J* = 248.6 Hz), 164.2; HRMS (ESI^-) calcd for $C_{27}H_{33}N_4OF_6Cl$ $[M+Cl]^-$ 597.2237, found 597.2245.

p-Toluenesulfonic acid monohydrate (201.1 mg, 1.06 mmol) was added to a solution of the above more polar crude product in MeOH (5 mL) and CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 26 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **51b** (11.4 mg, 23%) as a colorless oil.

51b: $[\alpha]_D^{27}$ +34.9 (c 0.88, $CHCl_3$); IR (neat) 3216, 1479, 1232, 846 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.45 (s, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 1.06-1.10 (m, 1H), 1.22-2.00 (m, 17H), 2.53-2.55 (m, 1H), 5.05-5.15 (m, 3H), 7.22-7.26 (m, 2H), 7.68-7.70 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.4, 18.6, 22.0, 23.1, 27.4, 28.9, 30.9, 35.8, 36.1, 39.9, 45.6, 45.8, 55.4, 56.2, 76.2 (sept, *J* = 28.7 Hz), 112.7, 116.5 (d, *J* = 21.6 Hz), 120.1, 123.3 (q, *J* = 285.8 Hz), 131.0 (d, *J* = 8.6 Hz), 146.7, 153.3, 164.4 (d, *J* = 251.4 Hz); HRMS (ESI^+) calcd for $C_{27}H_{33}N_4OF_6Na$ $[M+Na]^+$ 585.2435, found 585.2445.

2-{(1*R*,3a*S*,7a*R*,*E*)-1-[(2*R*,4*R*)-4-Fluoro-6-(methoxymethoxy)-6-methylheptan-2-yl]-7a-methyloctahydro-4*H*-inden-4-ylidene}ethan-1-ol (**56**)

4-Methylmorpholine *N*-oxide (50.7 mg, 0.43 mmol) was added to the solution of **52** (101.8 mg, 0.339 mmol) in CH_2Cl_2 (4 mL), and the mixture was cooled to 0°C. TPAP (61.7 mg, 0.176 mmol) was added to the mixture, and the mixture was stirred at 0°C for 90 min. The reaction was diluted with excess amount of Et_2O. The mixture was directly purified by flash column chromatography on silica gel (Et_2O only) to obtain the crude ketone, and this was used for the next reaction without further purification.

MOMCl (136.5 mg, 129.0 μL, 1.70 mmol) was added to the 0 °C cooled solution of the above crude ketone and diisopropylethylamine (262.9 mg, 354.0 μL, 2.03 mmol) in CH_2Cl_2 (4 mL), and the mixture was stirred at room temperature for 19 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at 0 °C, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain a crude MOM protected ketone **54**.

To a suspension of NaH (135.6 mg, 60% in oil, 3.39 mmol) in THF (1 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (836.2 mg, 747 μL, 3.73 mmol) at 0°C, and the mixture was stirred at 0°C for 30 min. The above crude ketone **54** was dissolved in THF (4 mL) and the solution was added to the mixture at the same temperature. After being stirred at room temperature for 120 h, the reaction mixture was quenched with H_2O and saturated aqueous NH_4Cl at room temperature. The mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain the crude ethyl ester (111.6 mg) as a colorless oil.

To the solution of the crude ethyl ester (111.6 mg) (111.6 mg) in toluene (10 mL) was added DIBAL-H (788 μL, 1.03 M hexane solution, 0.811 mmol) at -78°C, and the mixture was stirred at room temperature for 10 min. After the reaction was quenched with H_2O and saturated aqueous potassium sodium tartrate at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain alcohol **56** (88.2 mg, 70%, 4 steps) as a colorless oil.

56: $[\alpha]_D^{27}$ +65.8 (c 2.19, $CHCl_3$); IR (neat) 3423, 1464, 1384, 1148, 1038 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.57 (s, 3H), 0.99-1.12 (m, 4H), 1.24-2.03 (m, 22H), 3.36 (s, 3H), 4.15-4.23 (m, 2H), 4.71 (dd, *J* = 7.8, 33.6 Hz, 2H), 4.88 (dddt, *J* = 2.4, 8.4, 10.8, 51.6 Hz), 5.21 (t, *J* = 6.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.8, 22.2, 23.4, 25.9, 27.6, 28.7, 32.4, 40.4, 42.9 (d, *J* = 20.1 Hz), 45.4, 47.9 (d, *J* = 20.1 Hz), 55.2, 55.6, 56.9, 58.7, 75.3, 88.6 (d, *J* = 165.2 Hz), 91.0, 119.3, 143.5; HRMS (ESI^+) calcd for $C_{22}H_{39}O_3FNa$ $[M+Na]^+$ 393.2775, found 393.2789.

2-{(1*R*,3a*S*,7a*R*,*E*)-1-[(2*R*,4*S*)-4-Fluoro-6-(methoxymethoxy)-6-methylheptan-2-yl]-7a-methyloctahydro-4*H*-inden-4-ylidene}ethan-1-ol (**57**)

4-Methylmorpholine *N*-oxide (87.8 mg, 0.750 mmol) was added to the solution of **53** (111.1 mg, 0.370 mmol) in CH_2Cl_2 (4 mL), and the mixture was cooled to 0°C. TPAP (72.5 mg, 0.206 mmol) was added to the mixture, and the mixture was stirred at 0°C for 90 min. The reaction was diluted with excess amount of Et_2O. The mixture was directly purified by flash column chromatography on silica gel (Et_2O only) to obtain the crude ketone, and this was used for the next reaction without further purification.

MOMCl (107.2 mg, 101.1 μL, 1.33 mmol) was added to the 0 °C cooled solution of the above crude ketone and diisopropylethylamine (258.1 mg, 347.8 μL, 2.00 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at 0 °C for 25 min and at room temperature for 19 h. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at 0 °C, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain a crude MOM protected ketone **55**.

To a suspension of NaH (106.5 mg, 60% in oil, 2.66 mmol) in THF (2 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (671.3 mg, 599.4 μL, 3.00 mmol) at 0°C, and the mixture was stirred at 0°C for 15 min. The above crude ketone **55** was dissolved in THF (2 mL) and the solution was added to the mixture at the same temperature. After being stirred at room temperature for 93 h, the reaction mixture was quenched with H_2O and saturated aqueous NH_4Cl at room temperature. The mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain the crude ethyl

ester (64.3 mg) as a colorless oil.

To the solution of the above crude ethyl ester (64.3 mg) in toluene (5 mL) was added DIBAL-H (450 μL, 1.04 M hexane solution, 0.468 mmol) at -78°C, and the mixture was stirred at room temperature for 10 min. After the reaction was quenched with H_2O and saturated aqueous potassium sodium tartrate at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain alcohol **57** (50.3 mg, 41%) as a colorless oil.

57: $[\alpha]_D^{27}$ +51.7 (c 1.97, $CHCl_3$); IR (neat) 3411, 1468, 1384, 1145, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.00 (d, *J* = 6.0 Hz, 3H), 1.16-2.01 (m, 24H), 2.59-2.63 (m, 1H), 3.35 (s, 3H), 4.15-4.23 (m, 2H), 4.70 (dd, *J* = 7.3, 15.6 Hz, 2H), 5.20 (tt, *J* = 4.1, 18.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 19.5, 22.1, 23.4, 25.8, 27.5, 27.8, 28.6, 34.3 (d, *J* = 5.7 Hz), 40.3, 42.3 (d, *J* = 20.0 Hz), 45.3, 47.5 (d, *J* = 20.0 Hz), 55.1, 55.5, 56.8, 58.6, 75.3, 90.8 (d, *J* = 165.0 Hz), 90.9, 119.4, 143.4; HRMS (ESI^+) calcd for $C_{22}H_{39}O_3FNa$ $[M+Na]^+$ 393.2775, found 393.2789.

(4*R*,6*R*)-4-Fluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**58a**)

(4*R*,6*R*)-4-Fluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**58b**)

To a solution of 5-(4-fluorophenyl)-1*H*-tetrazole (26.5 mg, 0.16 mmol), Ph_3P (42.9 mg, 0.16 mmol), and CD-ring **56** (28.5 mg, 0.077 mmol) in CH_2Cl_2 (2 mL) was added diisopropyl azodicarboxylate (73 μL, 1.9 M in toluene, 0.14 mmol) at 0°C, and the mixture was stirred for 35 min. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with CH_2Cl_2 three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain the crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (200.2 mg, 1.05 mmol) was added to a solution of the above less polar crude product in MeOH (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 16 h under air. After the

reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **58a** (17.5 mg, 48%) as a colorless oil.

58a: $[\alpha]_D^{27}$ +47.5 (c 1.35, $CHCl_3$); IR (neat) 3427, 1464, 1236, 1152, 846 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.57 (s, 3H), 1.00-1.13 (m, 4H), 1.27-2.06 (m, 22H), 2.82-2.85 (m, 1H), 4.95 (dtt, *J* = 2.4, 10.8, 51.0 Hz, 1H), 5.26-5.34 (m, 3H), 7.15-7.18 (m, 2H), 8.11-8.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.8, 22.0, 23.3, 27.5, 29.0, 29.8, 32.3, 40.2, 42.7 (d, *J* = 2.5 Hz), 45.9, 48.7 (d, *J* = 18.6 Hz), 50.2, 55.7, 56.7, 70.2, 90.0 (d, *J* = 163.8 Hz), 111.7, 116.0 (d, *J* = 21.5 Hz), 123.9, 128.8 (d, *J* = 8.6 Hz), 147.9, 163.9 (d, *J* = 247.1 Hz), 164.8; HRMS (ESI^+) calcd for $C_{27}H_{38}N_4OF_2Na$ $[M+Na]^+$ 495.2906, found 495.2901.

p-Toluenesulfonic acid monohydrate (203.4 mg, 1.07 mmol) was added to a solution of the above more polar crude product in MeOH (5 mL) and CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 17 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 2) to obtain **58b** (8.2 mg, 23%) as a colorless oil.

58b: $[\alpha]_D^{27}$ +52.4 (c 0.631, $CHCl_3$); IR (neat) 3427, 1475, 1240, 1161, 851 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.49 (s, 3H), 0.99-1.12 (m, 4H), 1.25-2.04 (m, 22H), 2.54-2.57 (m, 1H), 4.94 (dtt, *J* = 2.4, 9.6, 51.6 Hz, 1H), 5.06-5.13 (m, 3H), 7.23-7.25 (m, 2H), 7.69-7.71 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 18.8, 22.1, 23.1, 27.4, 28.9, 29.8, 29.8, 32.2, 40.0, 42.6 (d, *J* = 20.1 Hz), 45.7 (d, *J* = 5.7 Hz), 48.6 (d, *J* = 18.8 Hz), 55.5, 56.6, 70.2, 89.9 (d, *J* = 163.8 Hz), 112.8, 116.5 (d, *J* = 21.6 Hz), 120.4, 131.0 (d, *J* = 8.6 Hz), 146.6, 153.3, 164.4 (d, *J* = 251.4 Hz); HRMS (ESI^+) calcd for $C_{27}H_{38}N_4OF_2Na$ $[M+Na]^+$ 495.2906, found 495.2918.

(4*S*,6*R*)-4-Fluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-2*H*-tetrazol-2-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**59a**)

(4*S*,6*R*)-4-Fluoro-6-[(1*R*,3a*S*,7a*R*,*E*)-4-{2-[5-(4-fluorophenyl)-1*H*-tetrazol-1-yl]ethylidene}-7a-methyloctahydro-1*H*-inden-1-yl]-2-methylheptan-2-ol (**59b**)

To a solution of 5-(4-fluorophenyl)-1*H*-tetrazole (23.8 mg, 0.14 mmol), Ph_3P (36.4 mg, 0.14 mmol), and CD-ring **57** (25.4 mg, 0.069 mmol) in CH_2Cl_2 (2 mL) was added diisopropyl azodicarboxylate (65 μL, 1.9 M in toluene, 0.27 mmol) at 0°C, and the mixture was stirred for 30 min. After the reaction was quenched with H_2O at 0°C, the mixture was extracted with CH_2Cl_2 three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain the crude products (less polar and more polar products).

p-Toluenesulfonic acid monohydrate (194.7 mg, 1.02 mmol) was added to a solution of the above less polar crude product in MeOH (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 19 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **59a** (16.0 mg, 49%) as a colorless oil.

59a: $[\alpha]_D^{27}$ +41.2 (c 1.23, $CHCl_3$); IR (neat) 3439, 1468, 1228, 1157, 846 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.01 (d, *J* = 6.0 Hz, 3H), 1.22-2.04 (m, 23H), 2.82-2.85 (m, 1H), 4.92 (ddtd, *J* = 1.8, 6.6, 10.2, 50.4 Hz, 1H), 5.26-5.34 (m, 3H), 7.14-7.18 (m, 2H), 8.11-8.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 19.4, 22.0, 23.3, 27.8, 29.0, 29.6, 34.2 (d, *J* = 5.7 Hz), 40.1, 42.1 (d, *J* = 18.6 Hz), 45.8, 48.0 (d, *J* = 18.6 Hz), 55.2, 55.6, 56.7, 70.2, 92.2 (d, *J* = 162.2 Hz), 111.7, 116.0 (d, *J* = 21.5 Hz), 123.9, 128.8 (d, *J* = 8.6 Hz), 147.8, 163.9 (d, *J* = 248.6 Hz), 164.2; HRMS (ESI^+) calcd for $C_{27}H_{38}N_4OF_2Na$ $[M+Na]^+$ 495.2906, found 495.2914.

p-Toluenesulfonic acid monohydrate (190.2 mg, 1.00 mmol) was added to a solution of the above more polar crude product in MeOH (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 19 h under air. After the

reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified on a preparative silica gel TLC plate (hexane : EtOAc = 1 : 1) to obtain **59b** (7.4 mg, 23%) as a colorless oil.

59b: $[\alpha]_D^{27}$ +37.8 (c 0.576, $CHCl_3$); IR (neat) 3418, 1475, 1236, 1161, 842 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.01 (d, *J* = 6.0 Hz, 3H), 1.22-2.04 (m, 23H), 2.82-2.85 (m, 1H), 4.92 (ddtd, *J* = 1.8, 6.6, 10.2, 50.4 Hz, 1H), 5.26-5.34 (m, 3H), 7.14-7.18 (m, 2H), 8.11-8.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.8, 19.4, 22.1, 23.2, 27.8, 29.0, 29.7, 30.0, 34.3 (d, *J* = 5.7 Hz), 40.0, 42.2 (d, *J* = 20.1 Hz), 45.7 (d, *J* = 18.6 Hz), 48.1 (d, *J* = 18.6 Hz), 55.5, 56.7, 70.3, 92.3 (d, *J* = 162.3 Hz), 113.0, 116.6 (d, *J* = 21.5 Hz), 120.4, 131.1 (d, *J* = 8.7 Hz), 146.6, 153.4, 164.5 (d, *J* = 251.3 Hz); HRMS (ESI^+) calcd for $C_{27}H_{38}N_4OF_2Na$ $[M+Na]^+$ 495.2906, found 495.2918.

Ethyl (3*R*,5*R*)-3-hydroxy-5-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl) oxy]octahydro-1*H*-inden-1-yl}lhexanoate (**65**)

Ethyl (3*S*,5*R*)-3-hydroxy-5-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl) oxy]octahydro-1*H*-inden-1-yl}hexanoate (**66**)

To the solution of ethyl acetate (595.8 mg, 0.58 mmol) in THF (6 mL) was added LHMDS (5.6 mL, 1 M THF solution, 5.6 mmol) at -78 ℃, the mixture was stirred at the same temperature for 15 min, and a solution of **67** (381.5 mg, 1.13 mmol) in THF (9 mL) was added. The reaction mixture was stirred at -78 ℃ for 10 min. After the reaction was quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 8 : 1) to obtain **65** (190.3 mg, 41%) (less polar) and **66** (179.1mg, 37%) (more polar) as colorless oils.

65: $[\alpha]_D^{27}$ +38.1 (c 0.46, $CHCl_3$); IR (neat) 3461, 1736, 1374, 1166, 1027, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (q, *J* = 7.8 Hz, 6H), 0.92-1.03 (m, 17H), 1.10 (td, *J* = 2.8, 12.8 Hz, 1H), 1.18-1.37 (m, 8H), 1.52-1.87 (m, 6H), 1.97 (dt,

J = 2.8, 12.4 Hz, 1H), 3.04 (brs, 1H, OH), 2.41-2.42 (m, 2H), 4.02 (dd, *J* = 2.9, 5.2 Hz, 1H), 4.08-4.12 (m, 1H), 4.16 (q, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9, 6.9, 13.5, 14.2, 17.7, 18.5, 23.0, 27.4, 31.8, 34.6, 40.8, 42.3, 42.4, 42.9, 53.1, 57.3, 60.6, 65.3, 69.4, 173.0; HRMS (ESI$^+$) calcd for $C_{24}H_{46}O_4SiNa$ $[M+Na]^+$ 449.3058, found 449.3070.

66: $[\alpha]_D^{27}$ +57.4 (c 0.48, $CHCl_3$); IR (neat) 3461, 1737, 1373, 1166, 1035, 745 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.54 (q, *J* = 7.8 Hz, 6H,), 0.89-0.96 (m, 15H), 1.00-1.37 (m, 12H), 1.50-1.67 (m, 3H), 1.74-1.87 (m, 2H), 1.93 (dt, *J* = 3.0, 12.8 Hz, 1H), 2.30 (dt, *J* = 9.2, 16.5 Hz, 1H), 2.55 (dt, *J* = 2.8, 16.5 Hz, 1H), 3.04 (brs, 1H), 4.01-4.11 (m, 2H), 4.16 (q, *J* = 6.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.9, 6.9, 13.5, 14.1, 17.6, 19.2, 23.0, 27.6, 33.2, 34.6, 40.7, 40.8, 42.2, 42.8, 53.0, 57.3, 60.6, 66.8, 69.3, 173.2; HRMS (ESI$^+$) calcd for $C_{24}H_{46}O_4SiNa$ $[M+Na]^+$ 449.3058, found 449.3064.

(4*R*,6*R*)-2-Methyl-6-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl) oxy]octahydro-1*H*-inden-1-yl}heptane-2,4-diol (**70**)

TMSCl (63.5 mg, 70 μL, 0.585 mmol) was added to the 0 ℃ cooled solution of **65** (221.4 mg, 0.519 mmol) and imidazole (142.7 mg, 2.10 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 15 min. After the reaction was quenched with H_2O at 0 ℃, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The crude residue was used for the next reaction without further purification.

MeMgBr (4.6 mL, 1.12 M THF solution, 5.19 mmol) was added to the solution of crude residue in THF (10 mL) at room temperature, and the mixture was refluxed for 20 min. After the reaction was quenched with H_2O and saturated aqueous NH_4Cl at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain **70** (175.6 mg, 82%, 2 steps) as a colorless oil.

70: $[\alpha]_D^{27}$ +36.7 (c 1.36, $CHCl_3$); IR (neat) 3357, 1467, 1376, 1166, 1084, 1020, 743 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.55 (q, *J* = 7.8 Hz, 6H), 0.93-1.03 (m, 16H), 1.20-1.46 (m, 13H), 1.54-1.68 (m, 5H), 1.77-1.86 (m, 2H), 1.97 (dt, *J* = 2.8, 12.4 Hz, 1H), 1.98 (dt, *J* = 3.6, 12.0 Hz, 1H), 2.53 (brs, 2H), 4.02 (dd, *J* =

2.4, 5.1 Hz, 1H), 4.02 (td, *J* = 2.4, 10.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.9, 6.9, 13.6, 17.7,18.7, 23.0, 27.5, 27.8, 31.7, 32.0, 34.6, 40.9, 42.3, 44.8, 49.0, 53.1, 57.5, 66.8, 69.4, 71.6; HRMS (ESI$^+$) calcd for $C_{24}H_{48}NaO_3SiNa$ $[M+Na]^+$ 435.3264, found 435.3265.

(4*S*,6*R*)-2-Methyl-6-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl)oxy] octahydro-1*H*-inden-1-yl}heptane-2,4-diol (**71**)

To the solution of **66** (97.6 mg, 0.229 mmol) and imidazole (47.8 mg, 0.702 mmol) in CH_2Cl_2 (5 mL) was added TMSCl (63.5 mg, 70 μL, 0.585 mmol), and the mixture was stirred at room temperature for 15 min. After the reaction was quenched with water at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated to give the crude residue.

To the solution of the above crude residue in THF (5 mL) was added MeMgBr (2.1 mL, 1.12 M THF solution, 2.34 mmol) at room temperature and refluxed for 20 min. After the reaction was quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain **71** (77.8 mg, 81%, 2 steps) as a colorless oil.

71: $[\alpha]_D^{27}$ +69.3 (c 1.39, $CHCl_3$); IR (neat) 3367, 1464, 1376, 1165, 1085, 1025, 739 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.55 (q, *J* = 7.8 Hz, 6H), 0.91 (s, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 1.04 (q, *J* = 9.6 Hz, 1H), 1.12 (td, *J* = 3.6, 13.2 Hz, 1H), 1.17-1.38 (m, 13H), 1.47-1.68 (m, 5H), 1.77-1.86 (m, 2H), 1.95 (dt, *J* = 3.0, 12.6 Hz, 1H), 2.67 (brs, 2H), 4.02 (dd, *J* = 3.0, 5.4 Hz, 1H), 4.07-4.11 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.9, 6.9, 13.6, 17.7, 19.1, 23.0, 27.6, 27.7, 32.2, 33.1, 34.6, 40.8, 42.2, 44.8, 47.3, 53.0, 57.5, 68.3, 68.4, 71.9; HRMS (ESI$^+$) calcd for $C_{24}H_{48}O_3SiNa$ $[M+Na]^+$ 435.3265, found 435.3280.

Ethyl (*3R*,5*R*)-5-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl}-3-{[(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy} hexanoate (**65a**)

To the solution of **65** (14.9 mg, 0.035 mmol) and *N*,*N*-dimethyl-4-

aminopyridine (5.5 mg, 0.045 mmol) in CH_2Cl_2 (0.5 mL) was added (*R*)-(-)-MTPACl (35.5 mg, 0.141 mmol) at room temperature, and the mixture was stirred for 1 h. To the mixture was added *N*,*N*-dimethyl-4-aminopyridine (20.3 mg, 0.166 mmol) and stirred at the same temperature for 10 min. The solution is directly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) and followed by purification on a preparative silica gel TLC plate (hexane : EtOAc = 4 : 1) to obtain **65a** (17.8 mg, 79%) as a colorless oil.

65a: $[\alpha]_D^{27}$ +22.2 (c 1.37, $CHCl_3$); IR (neat) 1750, 1269, 1184, 1031 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.56 (q, *J* = 8.4 Hz, 6H), 0.82 (s, 3H), 0.94-0.99 (m, 12H), 1.06-1.11 (m, 2H), 1.15-1.20 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.30-1.41 (m, 4H), 1.53 (qd, *J* = 6.0, 11.4 Hz, 1H), 1.58 (s, 1H), 1.65-1.67 (m, 1H), 1.73-1.81 (m, 2H), 1.84-1.88 (m, 1H), 1.93 (dt, *J* = 3.6, 12.6 Hz, 1H), 2.50 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.69 (dd, *J* = 6.0, 15.9 Hz, 1H), 3.52 (s, 3H), 4.01-4.02 (m, 1H), 4.05-4.14 (m, 2H), 5.54-5.59 (m, 1H), 7.38-7.40 (m, 3H), 7.54-7.55 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.0, 7.0, 13.5, 14.2, 17.7, 18.5, 23.1, 27.4, 32.3, 34.6, 40.0, 40.6, 40.8, 42.3, 53.1, 55.4, 57.1, 60.9, 69.4, 71.5, 84.7 (q, *J* = 27.3 Hz), 123.4 (q, *J* = 287.3 Hz), 127.6, 128.5, 129.6, 132.2, 166.1, 169.9; HRMS (ESI^+) calcd for $C_{34}H_{53}O_6F_3SiNa$ $[M+Na]^+$ 665.3456, found 665.3504.

Ethyl (3*R*,5*R*)-5-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl}-3-{[(2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy} hexanoate (**65b**)

To the solution of **65** (15.0 mg, 0.035 mmol) and *N*,*N*-dimethyl-4-aminopyridine (17.1 mg, 0.140 mmol) in CH_2Cl_2 (0.5 mL) was added (*S*)-(-)-MTPACl (35.5 mg, 0.141 mmol) at room temperature, and the mixture was stirred for 1 h. The solution was directly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) and followed by purification on a preparative silica gel TLC plate (hexane : EtOAc = 4 : 1) to obtain **65b** (17.1 mg, 76%) as a colorless oil.

65b: $[\alpha]_D^{27}$ +57.0 (c 1.31, $CHCl_3$); IR (neat) 1748, 1269, 1185, 1031 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (q, *J* = 7.8 Hz, 6H), 0.74 (s, 3H), 0.84-0.92 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 9H), 0.95 (t, *J* = 8.4 Hz, 3H), 1.05 (dt, *J* = 3.0, 12.6 Hz, 1H), 1.10-1.17 (m, 2H), 1.20-1.35 (m, 4H), 1.24 (t, *J* = 8.1 Hz, 3H), 1.42-

1.50 (m, 1H), 1.57 (s, 1H), 1.64-1.71 (m, 2H), 1.74-1.81 (m, 2H), 1.89 (dt, *J* = 3.0, 12.6 Hz, 1H), 2.55 (dd, *J* = 5.7, 15.3 Hz, 1H), 2.73 (dd, *J* = 5.7, 15.6 Hz, 1H), 3.56 (s, 3H), 3.99-4.00 (m, 1H), 4.08-4.15 (m, 2H), 5.55-5.59 (m, 1H), 7.36-7.39 (m, 3H), 7.53-7.56 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.0, 7.0, 13.5, 14.2, 17.7, 18.4, 23.0, 27.3, 32.1, 34.7, 40.3, 40.8, 40.8, 42.3, 53.1, 55.6, 57.0, 61.0, 69.4, 71.2, 84.4 (q, *J* = 28.8 Hz), 123.4 (q, *J* = 287.3 Hz), 127.2, 128.4, 129.6, 132.4, 166.1, 169.9; HRMS (ESI$^+$) calcd for $C_{34}H_{53}O_6F_3SiNa$ $[M+Na]^+$ 665.3456, found 665.3502.

Ethyl (3*S*,5*R*)-5-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl}-3-{[(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy} hexanoate (**66a**)

To the solution of **66** (15.2 mg, 0.036 mmol) and *N*,*N*-dimethyl-4-aminopyridine (19.7 mg, 0.161 mmol) in CH_2Cl_2 (0.5 mL) was added (*R*)-(-)-MTPACl (35.5 mg, 0.141 mmol) at room temperature, and the reaction mixture was stirred for 1 h. The solution was directly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) and followed by purification on a preparative silica gel TLC plate (hexane : EtOAc = 4 : 1) to obtain **66a** (14.0 mg, 61%) as a colorless oil.

66a: $[\alpha]_D^{27}$ +4.8 (c 0.37, $CHCl_3$); IR (neat) 1747, 1267, 1170, 1022 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.55 (q, *J* = 8.0 Hz, 6H), 0.88 (s, 3H), 0.92-1.18 (m, 16H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.29-1.38 (m, 3H), 1.41 (dd, *J* = 4.5, 10.2 Hz, 1H), 1.52-1.67 (m, 4H), 1.72-1.84 (m, 2H), 1.92 (dt, *J* = 3.0, 12.6 Hz, 1H), 2.58 (dd, *J* = 8.7, 16.8 Hz, 1H), 2.68 (dd, *J* = 3.9, 16.2 Hz, 1H), 3.54 (s, 3H), 4.00-4.01 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 5.52 (tt, *J* = 4.2, 8.7 Hz, 1H), 7.38-7.40 (m, 3H), 7.52-7.53 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.0, 7.0, 13.5, 14.2, 17.7, 19.0, 23.0, 27.6, 33.1, 34.6, 38.7, 39.7, 40.8, 42.3, 53.0, 55.5, 57.1, 61.0, 69.4, 72.9, 84.6 (q, *J* = 27.3 Hz), 123.3 (q, *J* = 287.3 Hz), 127.5, 128.4, 129.6, 132.4, 165.9, 170.3; HRMS (ESI$^+$) calcd for $C_{34}H_{53}O_6F_3SiNa$ $[M+Na]^+$ 665.3456, found 665.3486.

Ethyl (3*S*,5*R*)-5-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl)oxy]octahydro-1*H*-inden-1-yl}-3-{[(2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]oxy}

hexanoate (**66b**)

To the solution of **66** (15.0 mg, 0.035 mmol) and *N*,*N*-dimethyl-4-aminopyridine (17.1 mg, 0.140 mmol) in CH_2Cl_2 (0.5 mL) was added (*S*)-(-)-MTPACl (35.5 mg, 0.141 mmol) at room temperature, and the reaction mixture was stirred for 1 h. The solution was directly purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) and followed by purification on a preparative silica gel TLC plate (hexane : EtOAc = 4 : 1) to obtain **66b** (20.4 mg, 91%) as a colorless oil.

66b: $[\alpha]_D^{27}$ +49.1 (c 1.57, $CHCl_3$); IR (neat) 1748, 1271, 1170, 1021 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (q, *J* = 7.8 Hz, 6H), 0.90 (s, 3H), 0.94 (t, *J* = 8.1 Hz, 9H), 1.02 (d, *J* = 6.0 Hz, 3H), 1.04-1.13 (m, 2H), 1.16-1.23 (m, 5H), 1.32-1.37 (m, 4H), 1.47 (td, *J* = 5.4, 10.8 Hz, 1H), 1.54-1.62 (m, 2H), 1.66-1.68 (m, 1H), 1.72-1.76 (m, 1H), 1.78-1.83 (m, 2H), 1.95 (dt, *J* = 2.4, 12.0 Hz, 1H), 2.54 (dd, *J* = 9.0, 16.8 Hz, 1H), 2.65 (dd, *J* = 3.3, 16.8 Hz, 1H), 3.52 (s, 3H), 4.02 (s, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 5.54 (tt, *J* = 3.9, 8.4 Hz, 1H), 7.38-7.39 (m, 3H), 7.52-7.53 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.0, 7.0, 13.6, 14.1, 17.7, 18.9, 23.0, 27.6, 33.2, 34.6, 38.5, 39.9, 40.8, 42.3, 53.1, 55.4, 57.2, 60.8, 69.4, 73.1, 84.6 (q, *J* = 27.3 Hz), 123.4 (q, *J* = 285.9 Hz), 127.7, 128.4, 129.6, 132.3, 165.7, 170.1; HRMS (ESI^+) calcd for $C_{34}H_{53}O_6F_3SiNa$ $[M+Na]^+$ 665.3456, found 665.3472.

(4*R*,6*R*)-4-Fluoro-2-methyl-6-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl) oxy]octahydro-1*H*-inden-1-yl}heptan-2-ol (**74**)

PyFluor (16.1 mg, 0.10 mmol) was added to the solution of **71** (34.3 mg, 0.083 mmol) and DBU (25.3 mg, 25 μL, 0.17 mmol) in toluene (166 μL), and the mixture was stirred at room temperature for 90 h. After the reaction was quenched with water at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 6 : 1) to obtain **74** (7.6 mg, 22%) as a colorless oil.

74: $[\alpha]_D^{27}$ +41.2 (c 1.05, $CHCl_3$); IR (neat) 3410, 1459, 1376, 1166, 1085, 1025, 739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.55 (q, *J* = 7.2 Hz, 6H), 0.91 (s, 3H),

0.93-0.97 (m, 12H), 1.07-1.72 (m, 19H), 1.78-1.85 (m, 3H), 1.94 (dt, *J* = 3.6, 12.6 Hz, 1H), 4.03 (dd, *J* = 3.0, 4.5 Hz, 1H), 4.86-4.99 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.9, 6.9, 13.5, 17.7, 19.2, 23.0, 27.6, 29.5, 30.0, 33.5 (d, *J* = 5.7 Hz), 33.6, 40.8, 42.1 (d, *J* = 18.6 Hz), 42.2, 47.9 (d, *J* = 18.8 Hz), 53.0, 57.1, 69.3, 70.2, 92.5 (d, *J* = 160.8 Hz); HRMS (ESI$^+$) calcd for $C_{24}H_{47}FO_2SiNa$ $[M+Na]^+$ 437.3227, found 437.3234.

(4*S*,6*R*)-4-Fluoro-2-methyl-6-{(1*R*,3a*R*,4*S*,7a*R*)-7a-methyl-4-[(triethylsilyl) oxy]octahydro-1*H*-inden-1-yl}heptan-2-ol (**75**)

PyFluor (946.3 mg, 5.87 mmol) was added to the solution of **70** (1.84 g, 4.46 mmol) and DBU (1.36 g, 1.33 mL, 8.92 mmol) in toluene (10.4 mL), and the mixture was stirred at room temperature for 1 day. After the reaction was quenched with water at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : Et_2O = 2 : 1) and followed by repurification on flash column chromatography on silica gel (hexane : Et_2O = 3 : 1) to obtain **75** (1.02 g, 55%) as a colorless oil.

75: $[\alpha]_D^{27}$ +45.4 (c 0.81, $CHCl_3$); IR (neat) 3401, 1458, 1377, 1165, 1084, 1035, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55 (q, *J* = 8.3 Hz, 6H), 0.93-1.34 (m, 30H), 1.49-1.99 (m, 8H), 4.03 (dd, *J* = 2.3, 4.9 Hz, 1H), 4.86-5.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.9, 6.9, 13.5, 17.7, 18.7, 23.0, 27.3, 29.7, 29.9, 31.6 (d, *J* = 5.7 Hz), 34.6, 40.8, 42.3, 42.7 (d, *J* = 21.0 Hz), 48.7 (d, *J* = 18.2 Hz), 53.1, 57.1, 69.4, 70.2, 90.2 (d, *J* = 163.1 Hz); HRMS (ESI$^+$) calcd for $C_{24}H_{47}FO_2SiNa$ $[M+Na]^+$ 437.3227, found 437.3211.

(1*R*,3a*R*,4*S*,7a*R*)-1-[(2*R*,4*R*)-4-Fluoro-6-hydroxy-6-methylheptan-2-yl]-7a-methyloctahydro-1*H*-inden-4-ol (**52**)

Method A

p-Toluenesulfonic acid monohydrate (95.1 mg, 0.5 mmol) was added to the solution of **74** in MeOH (5 mL), and the mixture was stirred at room temperature for 15 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, and washed with brine, dried over Na_2SO_4, filtered, and

concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1) to obtain **52** (39.2 mg, 81%) as a colorless oil.

Method B

*m*CPBA (87.8 mg, 0.51 mmol) was added to the solution of **76** (103.2 mg, 0.26 mmol) and $NaHCO_3$ (642.4 mg, 7.65 mmol) in CH_2Cl_2 (3 mL) at 0°C, and the mixture was stirred at the same temperature for 1 h under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, and washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain the crude product **78**.

DAST (95.1 mg, 0.5 mmol) was added to the solution of the crude product **78** in CH_2Cl_2 (4 mL) at -78°C, and the mixture was stirred at the same temperature for 15 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with CH_2Cl_2 three times, and washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 10 : 1) to obtain the crude fluoro-epoxide **79**.

$LiAlH_4$ (14.0 mg, 0.37 mmol) was added to the solution of the crude **79** in THF (3 mL) at 0°C, and the mixture was stirred at the same temperature for 1 h. After the reaction was quenched with MeOH, water and saturated aqueous potassium sodium tartrate were added. The mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used for the next reaction without further purification.

p-Toluenesulfonic acid monohydrate (100.6 mg, 0.53 mmol) was added to the solution of the crude residue **74** in MeOH (5 mL), and the mixture was stirred at room temperature for 15 min under air. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, and washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain **52** (30.0 mg, 37%, 4 steps) as a colorless oil.

52: $[\alpha]_D^{27}$ +27.7 (c 0.50, $CHCl_3$); IR (neat) 3364, 1470, 1381, 1166, 1147, 981,

871 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (s, 3H), 0.98 (d, *J* = 6.0 Hz, 3H), 0.99-1.11 (m, 2H), 1.14-1.20 (m, 1H), 1.25-1.36 (m, 2H), 1.28 (s, 3H), 1.31 (s, 3H), 1.42-1.73 (m, 8H), 1.80-1.95 (m, 5H), 2.01-2.03 (m, 1H), 4.07-4.08 (m, 1H), 4.89-5.02 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.5, 17.4, 18.6, 22.5, 27.2, 29.8 (d, *J* = 12.9 Hz), 31.6, 33.6, 40.4, 42.0, 42.6 (d, *J* = 21.6 Hz), 48.7 (d, *J* = 18.6 Hz), 52.6, 56.9, 69.3, 70.2, 90.1 (d, *J* = 163.7 Hz); HRMS (ESI^+) calcd for $C_{18}H_{33}O_2FNa$ $[M+Na]^+$ 323.2357, found 323.2361.

(1*R*,3a*R*,4*S*,7a*R*)-1-[(2*R*,4*S*)-4-Fluoro-6-hydroxy-6-methylheptan-2-yl]-7a-methyloctahydro-1*H*-inden-4-ol (**53**)

p-Toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol) was added to the solution of **75** in MeOH (10 mL), and the mixture was stirred at room temperature for 1 h under air. *p*-Toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol) was added to the mixture, and the mixture was stirred at the same temperature for further 70 min. After the reaction was quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1 – 1 : 1) to obtain **53** (73.5 mg, 71%) as a white powder.

53: $[\alpha]_D^{27}$ +38.2 (c 0.69, $CHCl_3$); IR (neat) 3405, 1470, 1379, 1163, 992, 942 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.11-1.69 (m, 20H), 1.79-1.91 (m, 4H), 1.98-2.00 (m, 1H), 4.06-4.07 (m, 1H), 4.86-4.98 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.4, 17.4, 19.1, 22.5, 27.4, 29.6, 29.9, 33.5 (d, *J* = 5.7 Hz), 33.5, 40.3, 41.9, 42.0 (d, *J* = 18.6 Hz), 47.9 (d, *J* = 20.1 Hz), 52.5, 56.9, 69.3, 70.2, 92.3 (d, *J* = 162.3 Hz); HRMS (ESI^+) calcd for $C_{18}H_{33}O_2FNa$ $[M+Na]^+$ 323.2357, found 323.2361.

(1*R*,3a*R*,7a*R*)-1-{(2*R*,4*R*)-4-Fluoro-6-methyl-6-[(trimethylsilyl)oxy]heptan-2-yl}-7a-methyloctahydro-4*H*-inden-4-one (**82**)

4-Methylmorpholine *N*-oxide (33.8 mg, 0.29 mmol) was added to the solution of **52** (39.2 mg, 0.13 mmol) in CH_2Cl_2 (2 mL), and the mixture was cooled to 0°C. TPAP (22.9 mg, 0.065 mmol) was added to the mixture, and the mixture

was stirred at 0°C for 90 min. The reaction was diluted with excess amount of Et_2O. The mixture was directly purified by flash column chromatography on silica gel (Et_2O only) to obtain the crude ketone, and this was used for the next reaction without further purification.

TMSCl (35.3 mg, 41 μL, 0.33 mmol) was added to the 0 °C cooled solution of crude ketone and imidazole (35.4 mg, 0.52 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 15 min. After the reaction was quenched with H_2O at 0 °C, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain **82** (35.5 mg, 74%, 2 steps) as a colorless oil.

82: $[\alpha]_D^{27}$ -6.6 (c 0.35, $CHCl_3$); IR (neat) 1715, 1468, 1382, 1250, 1040, 842 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.11 (s, 9H), 0.66 (s, 3H), 1.11 (dddd, *J* = 1.2, 10.2, 13.8, 40.2 Hz, 1H), 1.26 (s, 3H), 1.30 (s, 3H), 1.31-1.38 (m, 1H), 1.43 (q, *J* = 9.6 Hz, 1H), 1.50-1.63 (m, 4H), 1.66-1.83 (m, 4H), 1.87-1.95 (m, 2H), 2.00-2.04 (m, 1H), 2.13-2.16 (m, 1H), 2.20-2.25 (m, 1H), 2.27-2.31 (m, 1H), 2.45 (dd, *J* = 7.2, 11.4 Hz, 1H), 4.82-4.94 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 2.6, 12.5, 18.7, 19.1, 24.0, 27.4, 29.2, 31.7, 31.9, 39.0, 41.0, 42.8 (d, *J* = 20.1 Hz), 50.0, 50.5 (d, *J* = 20.1 Hz), 57.0, 62.0, 73.0, 89.1 (d, *J* = 165.1 Hz), 211.9; HRMS (ESI^+) calcd for $C_{21}H_{39}O_2FSiNa$ $[M+Na]^+$ 393.2601, found 393.2583.

(1*R*,3a*R*,7a*R*)-1-{(2*R*,4*S*)-4-Fluoro-6-methyl-6-[(trimethylsilyl)oxy]heptan-2-yl}-7a-methyloctahydro-4*H*-inden-4-one (**83**)

4-Methylmorpholine *N*-oxide (23.6 mg, 0.20 mmol) was added to the solution of **53** (34.6 mg, 0.12 mmol) in CH_2Cl_2 (2 mL), and the mixture was cooled to 0°C. TPAP (23.9 mg, 0.068 mmol) was added to the mixture, and the mixture was stirred at 0°C for 2 h. The reaction was diluted with excess amount of Et_2O. The mixture was directly purified by flash column chromatography on silica gel (Et_2O only) to obtain the crude ketone, and this was used for the next reaction without further purification.

TMSCl (31.3 mg, 36 μL, 0.29 mmol) was added to the 0 °C cooled solution of crude ketone and imidazole (32.8 mg, 0.48 mmol) in CH_2Cl_2 (4 mL), and the mixture was stirred for 15 min. TMSCl (31.3 mg, 36 μL, 0.29 mmol) was added to the mixture, and the mixture was stirred for 10 min. After the reaction was

quenched with H_2O at 0 °C, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 5 : 1) to obtain **83** (28.7 mg, 67%, 2 steps) as a colorless oil.

83: $[\alpha]_D^{27}$ +10.3 (c 2.21, $CHCl_3$); IR (neat) 1715, 1461, 1382, 1250, 1043, 843 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.10 (s, 9H), 0.65 (s, 3H), 1.03 (d, *J* = 6.0 Hz, 3H), 1.26-1.34 (m, 7H), 1.43-1.77 (m, 9H), 1.85-2.03 (m, 3H), 2.11-2.13 (m, 1H), 2.19-2.29 (m, 2H), 2.45 (dd, *J* = 7.8, 12.0 Hz, 3H), 4.79-4.91 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 2.5, 13.4, 17.4, 19.1, 22.5, 27.4, 29.6, 29.9, 33.9 (d, *J* = 5.7 Hz), 33.5, 40.3, 41.9, 42.0 (d, *J* = 18.6 Hz), 47.9 (d, *J* = 20.1 Hz), 52.5, 56.9, 69.3, 70.2, 92.3 (d, *J* = 162.3 Hz), 211.9; HRMS (ESI^+) calcd for $C_{21}H_{39}O_2FSiNa$ $[M+Na]^+$ 393.2601, found 393.2593.

(23*R*)-23-Fluoro-25-hydroxyvitamin D_3 (**80**)

*n*BuLi (120 μL, 1.6 M hexane solution, 0.19 mmol) was added to the solution of A-ring phosphine oxide **84** (88.2 mg, 0.19 mmol) in THF (2 mL) at -78°C. After stirring for 30 min, the solution of ketone **82** (35.5 mg, 0.096 mmol) in THF (2 mL) was added to the reaction mixture, and the mixture was stirred at -78°C for 15 min, 0°C for 15 min, and then, at room temperature for 10 min. After the reaction was quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 50 : 1 – 1 : 1) to obtain the crude coupling product (45.4 mg), and it was used for the next reaction without further purification.

Tetrabutylammonium fluoride (450 μL, 1 M THF solution, 0.45 mmol) was added to the solution of the crude coupling product (45.4 mg) in THF (3 mL), and the mixture was stirred at room temperature for 4 h. After the reaction was quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain **80** (27.1 mg, 68%, 2 steps) as a white powder.

80: $[\alpha]_D^{27}$ +75.3 (c 2.08, EtOH); UV(EtOH) λ_{max} 212.8, 264.2 nm; IR (neat)

3366, 1438, 1380, 1160, 1049, 893 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.62 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.27-2.26 (m, 26H), 2.45 (dt, *J* = 5.0, 13.8 Hz, 1H), 2.58 (dd, *J* = 3.7, 12.8 Hz, 1H), 2.89-2.93 (m, 1H), 3.77-3.83 (m, 1H), 4.79 (d, *J* = 1.8 Hz, 1H), 4.83-5.02 (m, 1H), 5.08 (brs, 1H), 6.08 (d, *J* = 11.5 Hz, 1H), 6.26 (d, *J* = 11.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 12.7, 19.6, 23.58, 24.8, 29.0, 30.2, 31.3, 33,9, 34.1, 36.9, 42.2, 44.5 (d, *J* = 21.0 Hz), 47.3 (d, *J* = 3.8 Hz), 50.6 (d, *J* = 19.1 Hz), 57.8, 58.5, 70.9, 90.2 (d, *J* = 165.0 Hz), 112.9, 119.4, 122.9, 137.7, 142.7, 137.7, 142.7, 147.3; HRMS (ESI^+) calcd for $C_{27}H_{43}O_2FNa$ $[M+Na]^+$ 441.3139, found 441.3134.

(23*S*)-23-Fluoro-25-hydroxyvitamin D_3 (**81**)

*n*BuLi (97 μL, 1.6 M hexane solution, 0.15 mmol) was added to the solution of A-ring phosphine oxide **84** (72.3 mg, 0.16 mmol) in THF (2 mL) at -78°C. After stirring for 30 min, the solution of ketone **83** (28.7 mg, 0.077 mmol) in THF (2 mL) was added to the reaction mixture, and the mixture was stirred at -78°C for 15 min, 0°C for 15 min, and then, at room temperature for 10 min. After the reaction was quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 50 : 1) to obtain the crude coupling product (42.8 mg), and it was used for the next reaction without further purification.

Tetrabutylammonium fluoride (424 μL, 1 M THF solution, 0.424 mmol) was added to the solution of the crude coupling product (42.8 mg) in THF (3 mL), and the mixture was stirred at room temperature for 5 h. After the reaction was quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 1 : 1) to obtain **81** (13.9 mg, 43%, 2 steps) as a white powder.

81: $[\alpha]_D^{27}$ +55.6 (c 0.54, EtOH); UV(EtOH) λ_{max} 212.6, 264.6 nm; IR (neat) 3377, 1440, 1379, 1265, 1159, 1052, 740 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.62 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.27-1.84 (m, 22H), 1.94-2.26 (m, 6H), 2.45 (dt, *J* = 5.0, 13.8 Hz, 1H), 2.58 (dd, *J* = 3.6, 12.4 Hz, 1H), 2.90 (dd, *J* = 4.1, 12.4 Hz, 1H), 3.80 (ddd, *J* = 3.7, 8.7, 12.8 Hz, 1H), 4.78-4.96 (m, 2H), 5.08

(brs, 1H), 6.08 (d, J = 11.5 Hz, 1H), 6.26 (d, J = 11.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 12.6, 20.4, 23.6, 24.8, 29.0, 29.2, 30.2, 31.3, 33,9, 35.9 (d, J = 5.7 Hz), 36.9, 42.2, 44.0 (d, J = 20.0 Hz), 47.3 (d, J = 10.5 Hz), 50.1 (d, J = 19.7 Hz), 57.8, 58.6, 70.9, 92.3 (d, J = 164.9 Hz), 113.0, 119.4, 122.9, 137.7, 142.7, 147.3; HRMS (ESI$^+$) calcd for $C_{27}H_{43}O_2FNa$ $[M+Na]^+$ 441.3139, found 441.3141.

Methyl 2-(diethoxyphosphoryl)-2-[(triethylsilyl)oxy]acetate (**89**). [87]

89: IR (neat) 1754, 1268, 1133, 1025, 969, 810, 750 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.64 (q, J = 7.8 Hz, 6H), 0.96 (t, J = 7.8 Hz, 9H), 1.33 (q, J = 6.6 Hz, 6H), 3.79 (s, 3H), 4.12-4.26 (m, 4H), 4.16 (d, J = 17.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.4, 6.5, 16.4 (d, J = 5.7 Hz), 52.5, 63.6 (d, J = 7.2 Hz), 70.5 (t, J = 24.8 Hz), 169.1; HRMS (ESI$^+$) calcd for $C_{13}H_{30}O_6SiP$ $[M+H]^+$ 341.1544, found 341.1556.

Methyl 5-{4-[(*tert*-butyldimethylsilyl)oxy]-7a-methyloctahydro-1*H*-inden-1-yl}-2-oxohexanoate (**91**).

To the solution of Horner-Emmons reagent **89** (7.34 g, 21.6 mmol) in THF (20 mL) was added LDA (lithium diisopropylamide) (10.9 mL, 2 M THF/heptane/ethylbenzene solution, 21.8 mmol) at -40℃, the mixture was stirred at the same temperature for 20 min, and a solution of **88** (6.65 g, 19.6 mmol) in THF (15 mL) was added. The reaction mixture was stirred at 0 ℃ for 5 min. After the reaction had been quenched with H_2O and saturated aqueous NH_4Cl at 0 ℃, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The crude residue of **90** was used for the next reaction without further purification. To the crude residue of **90** in CH_2Cl_2 (40 mL) were added AcOH (6 mL) and tetrabutylammonium fluoride (27.4 mL, 1 M THF solution, 27.4 mmol) at 0℃, and the mixture was stirred at room temperature for 30 min. After the reaction had been quenched with H_2O at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 7 : 1) to obtain **91** (7.77 g, 97%) as a colorless oil [83].

1-(5,5-Difluoro-6-hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (**30**)

To the solution of **91** (8.08 g, 19.7 mmol) in CH_2Cl_2 (30 mL) was slowly added *N*,*N*-diethylaminosulfur trifluoride (DAST) (6.5 mL, 7.3 g, 49.2 mmol) at 0°C, and the mixture was stirred at room temperature for 17 h. The mixture was cooled to -78°C and MeOH and H_2O were slowly added. The mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 20 : 1) to obtain a crude residue of **92**.

To the solution of the crude residue of **92** in THF (30 mL) was added MeMgCl (16.7 mL, 3.0 M THF solution, 50.0 mmol) at 0°C, and the mixture was stirred for 15 min. After the reaction had been quenched with H_2O and HCl (1.0 M in H_2O), the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The crude residue of **93** was used for the next reaction without further purification.

To the crude residue of **93** in MeOH (30 mL) was added *p*-toluenesulfonic acid monohydrate (6.12 g, 32.2 mmol), and the mixture was stirred at room temperature for 19 h under air. After the reaction had been quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain **30** (4.0 g, 64%, 3 steps) as a white powder [85].

Cell Culture

CHO-K1 cells were maintained in medium A (1:1 mixture of Ham's F-12 medium and DMEM, supplemented with 100 units/mL penicillin, 100 μg/mL streptomycin sulfate, and 5% [v/v] fetal bovine serum) at 37°C in a humidified 5% CO_2 incubator.

Luciferase Reporter Assay

CHO-K1 cells were seeded into 96-well plates at 8×10^3 cells per well in medium A and incubated for 24 h. For SREBP reporter assay, cells were co-transfected with an SRE-1-driven luciferase reporter plasmid (pSRE-Luc) and an actin promoter-driven β-galactosidase expression plasmid (pAc-β-gal) at a 20:1 ratio, using FuGENE HD Transfection Reagent (Promega) according to the manufacturer's protocol. For VDR reporter assay, Cignal Vitamin D Receptor Reporter (QIAGEN) was transfected instead of pSRE-Luc. After 20 h, the medium was changed to medium B (1:1 mixture of Ham's F-12 medium and DMEM, supplemented with 100 units/mL penicillin, 100 μg/mL streptomycin sulfate, 5% [v/v] lipid-depleted serum, 50 μM compactin (Tokyo Chemical Industry), and 50 μM lithium mevalonate (Sigma-Aldrich) containing the specific test compounds. After 24h incubation, the cells in each well were lysed with 100 μL of 1x Reporter Lysis Buffer (Promega), and 50 μL of aliquots were used to measure luciferase and β-gal activities. Luciferase activity was measured using the Steady-Glo Luciferase Assay System (Promega), and β-gal activity was measured using the β-Galactosidase Enzyme Assay System (Promega). Luciferase activity was normalized to β-gal activity.

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