小員環の特性を活用した生物活性分子の合成及び新規反応の開発

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博士論文

小員環の特性を活用した生物活性分子の合成及び新規反応の開発

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第 1 章　序論

第 1 節　飽和炭素環式化合物

シクロアルカンはメチレン基 n 個から成る飽和炭素環式化合物であり、その環の大きさによって、小員環（n = 3, 4）、普通環（n = 5, 6, 7）、中員環（n = 8–11）、大員環（n ≧ 12）に分類される。理想的には sp^3 炭素の結合角は 109.5 °であるが、シクロアルカンでは結合角は環の員数に依存し、結合角が理想的な 109.5 °からずれると、結合角歪み（Baeyer strain）が生じる。シクロプロパン及びシクロブタンの結合角はそれぞれ 60 °と 90 °であり、109.5 °からの差が大きいため、結合角歪みは小員環で顕著である（Figure 1）。二面角（dihedral angle）が最安定配座からずれることによって生じる歪みをねじれ歪み（Pitzer 歪み）と呼ぶ。シクロプロパンはシクロアルカンの中で唯一平面構造をとり、二面角が 0°で C–H 結合が全て重なるように強いられているため、ねじれ歪みを生じる。一方シクロブタンでは、このねじれ歪みを最小にするよう翼型（wing-shaped）と呼ばれる折れ曲がった配座をとっている。シクロヘキサンのいす型配座（chair）では結合角が理想的であり、且つ二面角も 60°と理想的で C–H 結合の重なりがないため、シクロヘキサンには歪みが存在しない。

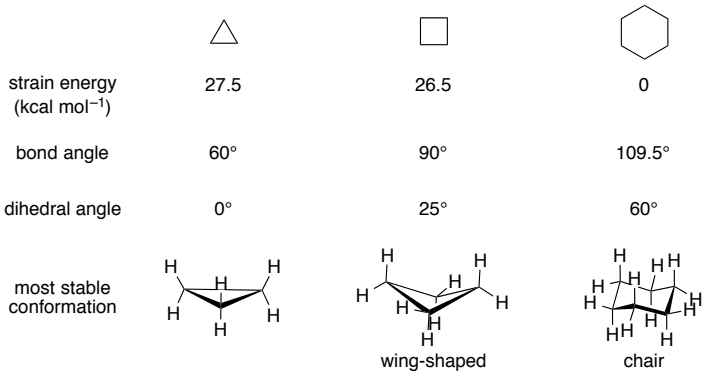


Figure 1. Comparison of Strain Energy and Conformations of Cycloalkanes[1]

第 2 節　小員環炭化水素の合成法

小員環炭化水素は天然物にも多く見られる重要な骨格である。例えばシクロブタン環を有するものとして、α-ピネンのような単純なテルペンから、高度に酸化された海産テルペノイド providencin[2]、オキシインドールが bicyclo[4.2.0]octane にスピロ縮環した独特な構造を持つ welwitindolinone A[3] などが挙げられる（Figure 2）。シクロプロパンを有するものとしては、ワラビに含まれる発ガン性物質 ptaquiloside[4]、5 つのシクロプロパン環を有する抗生物質 FR-900848[5] などがある。バレイショの水耕栽培液から単離されたシストセンチュウ孵化

促進物質 solanoeclepin A のように、三員環と四員環の両方を有する天然物も知られている[6]。小員環は環歪みが大きいため、歪みの小さい環を構築するよりも困難ではあるが、これまでにいくつかの有用な小員環合成法が確立されてきた。

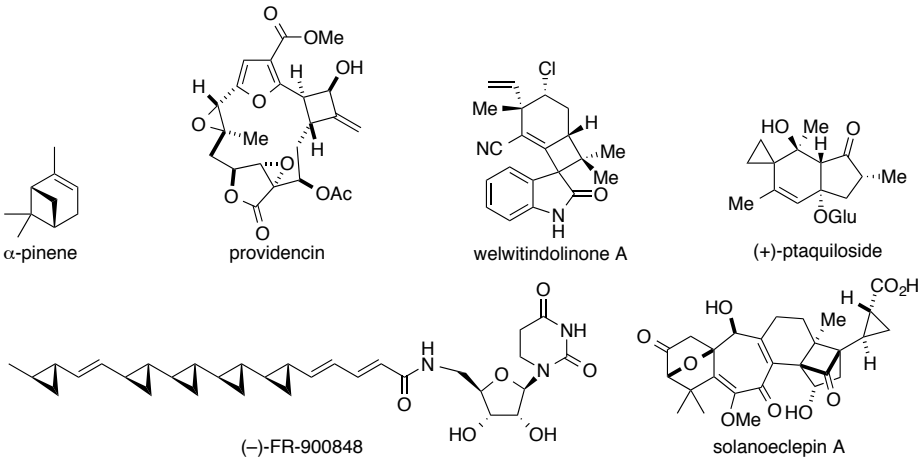
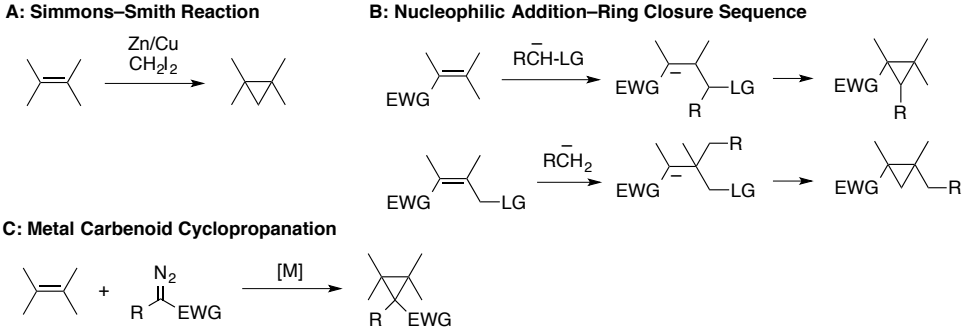


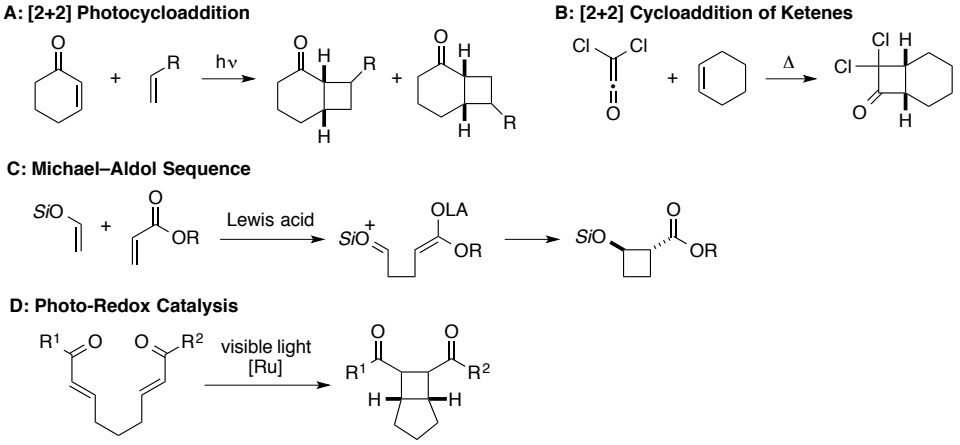
Figure 2. Some Small Ring-Based Natural Products

シクロプロパンの一般的合成法として、古くから Simmons–Smith 反応が利用されてきた（Scheme 1A）[7]。この反応は温和な条件で進行し、官能基選択性が高いだけでなく、反応点近傍にヘテロ原子が置換した不斉中心が存在すると、そこへの配位を介して高い立体選択性を発現させることもできる。また電子不足オレフィンへの Michael 付加と生じたエノラートによる閉環反応によって、シクロプロパン環を構築することができる（Scheme 1B）[7a,7g]。この反応で非環状オレフィンを用いると、通常反応は非立体特異的に進行し、*trans*-オレフィンからも *cis*-オレフィンからも *trans*-シクロプロパンを与える。これらの反応機構に基づいたエナンチオ選択的反応の報告例も多数存在するが、概してそのエナンチオ選択性は高くはない。現在では不斉シクロプロパン化には、適切な不斉配位子を持つ金属カルベノイドがよく用いられている（Scheme 1C）[7a,7g]。



Scheme 1. General Strategies for the Synthesis of Cyclopropanes

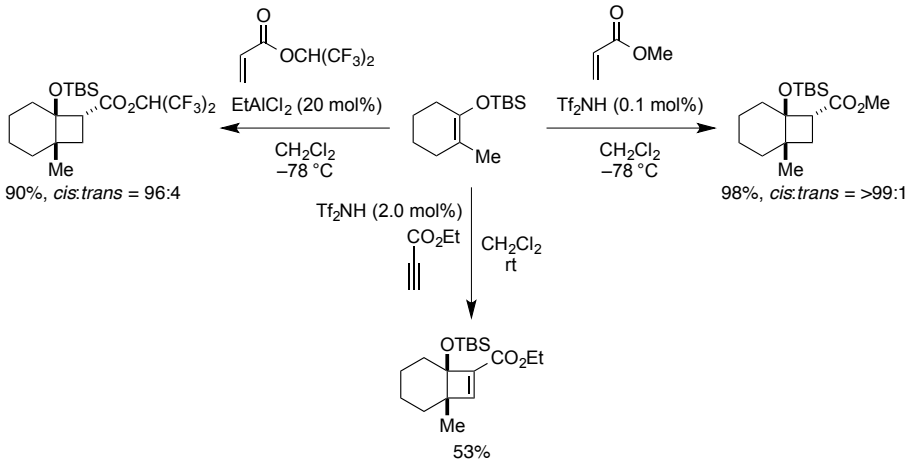
次にシクロブタンの代表的な合成法を紹介する（Scheme 2）。まず古典的な方法として、光[2+2]環化付加反応やケテンの[2+2]環化付加反応が挙げられる（Scheme 2A and B）[8]。[$\pi 2_s+\pi 2_s$]型の環化付加は熱禁制であるので、通常光条件が用いられる。しかしながら、光[2+2]環化付加では立体選択性や位置選択性の制御及び *cis–trans* 異性化の問題があり、分子間反応や非環状の基質への適用は難しい。また特殊な反応装置が必要であるというデメリットもある。一方ケテンの[2+2]環化付加は熱的条件で容易に進行するが、不安定なケテンの調製が煩雑であるなどの問題もある。



Scheme 2. General Strategies for the Synthesis of Cyclobutanes

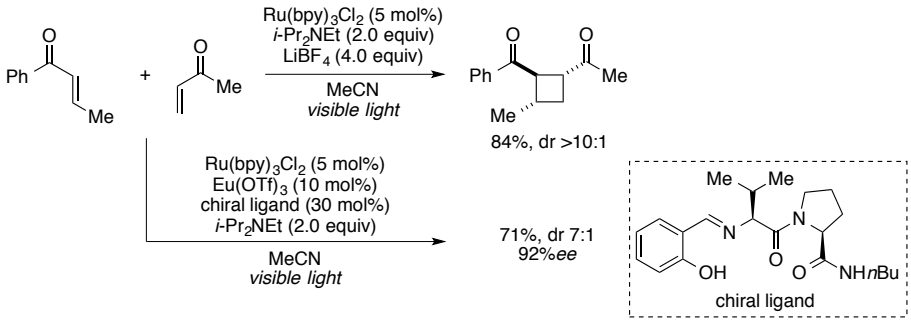
エノラートとα,β-不飽和カルボニル化合物間での、連続的な Michael 付加とアルドール反応から成る段階的[2+2]環化付加反応によって、四員環を立体選択的に合成する手法も知られている（Scheme 2C）[9]。この反応は当研究グループでも精力的に研究してきており、二塩化エチルアルミニウム（$EtAlCl_2$）や、トリフリックイミド（Tf_2NH）といった酸触媒が効果的であることを見出している（Scheme 3）[10]。$EtAlCl_2$ の系では、アクリル酸ヘキサフルオロイソプロピルを用いた場合、高い収率及び立体選択性が確認されたが、20 mol%と多量な触媒が必要であることや、厳密な無水条件が必要であることに課題が残った。一方 Tf_2NH を用いる系では、真の触媒は Tf_2NH とシリルエノールエーテルから系中で発生するシリルトリフリックイミドであることが明らかになっており、この活性種は多少の湿気が存在しても、シリルエノールエーテルが存在する限り再生可能であることから、高い触媒回転率を達成できた。グラムスケールの反応でも、収率や選択性を損なわないことを実証しており、不飽和エステルとしてプロピオール酸エステルを用いることで、縮環シクロブテンを合成することも可能である。山本らは、非常に嵩高い tris(trimethylsilyl)silyl (TTMSS)基を用いることで、これまで困難であったアルデヒド由来のシリルエノールエーテルの[2+2]環化付加

反応を達成している[9g]。また Corey らは、光学活性オキサザボロリジン–$AlBr_3$ 複合体を用いた触媒的不斉[2+2]環化付加を報告している[9h]。



Scheme 3. Catalytic [2+2] Cycloaddition between Silyl Enol Ethers and Unsaturated Esters

近年研究が盛んな可視光酸化還元触媒を用いた[2+2]環化付加反応も報告されてきている（Scheme 2D）[11]。先駆的な例として Yoon らは 2008 年に、可視光と $Ru(bipy)_3Cl_2$ を用いたエノンの分子内[2+2]環化付加を報告している[11a]。最近ではこの反応は、分子間の交差[2+2]環化付加及び[11b,d]、キラル配位子を併用した不斉[2+2]環化付加にまで進化を遂げている（Scheme 4）[11g]。

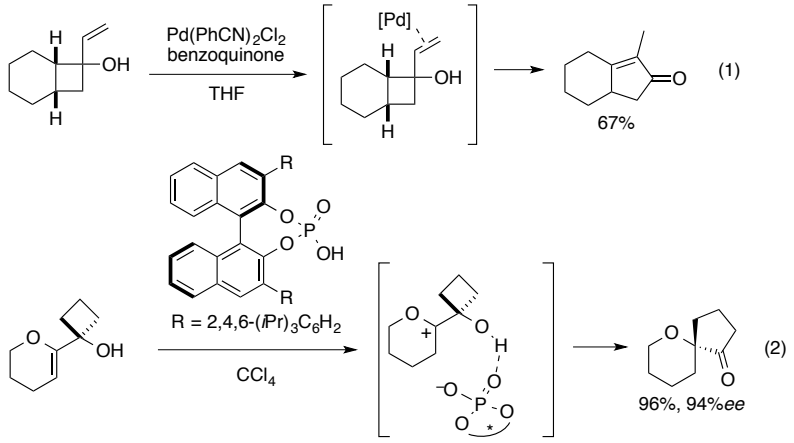


Scheme 4. [2+2] Photocycloaddition Using Visible Light

第 3 節　小員環の炭素–炭素結合の開裂

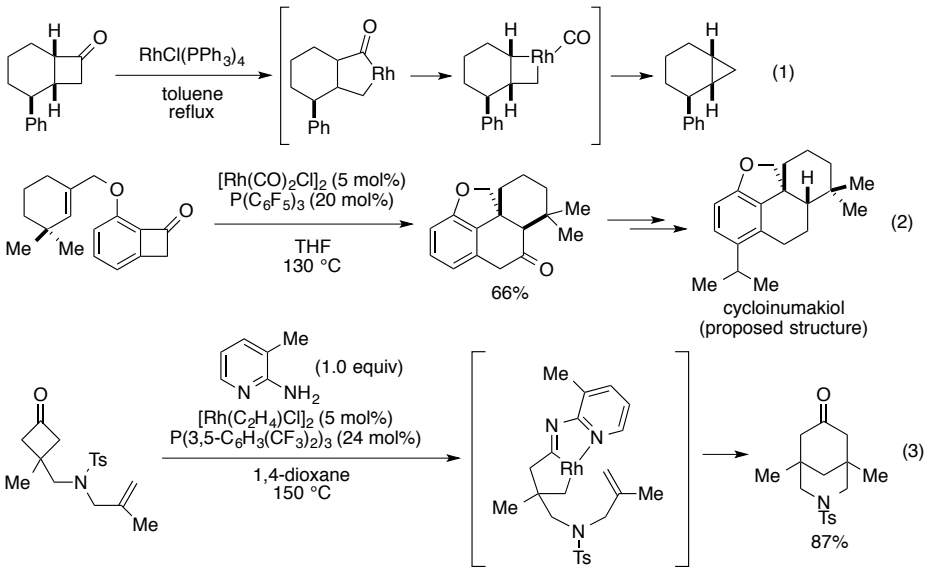
環歪みの解消を駆動力として、小員環の炭素–炭素結合の開裂を伴う反応がこれまでに多く開発されてきた[12]。四員環化合物に焦点を当てると、遷移金属や有機触媒など手法は様々ではあるが、その炭素–炭素結合は Wagner–Meerwein 転位やセミピナコール転位のような 1,2-転位の機構で開裂させる報告例がほとんどであった。例えば Clark らは、1-ビニルシク

ロブタノールに対してパラジウム(II)触媒でオレフィンを活性化すると、Wagner–Meerwein 転位が進行し、続くβ-水素脱離とオレフィンの異性化を経由して、環拡大反応が進行することを報告している（Scheme 5, eq. 1）[13]。また有機触媒を用いた例として、Tu らはキラルリン酸触媒を用いたエナンチオ選択的なシクロブタノールのスピロエーテルへの転位反応を報告している（eq. 2)。キラルリン酸触媒がエノールエーテルを活性化し、キラルイオン対遷移状態を経由して、不斉 1,2-転位が高いエナンチオ選択性で進行する [14]。



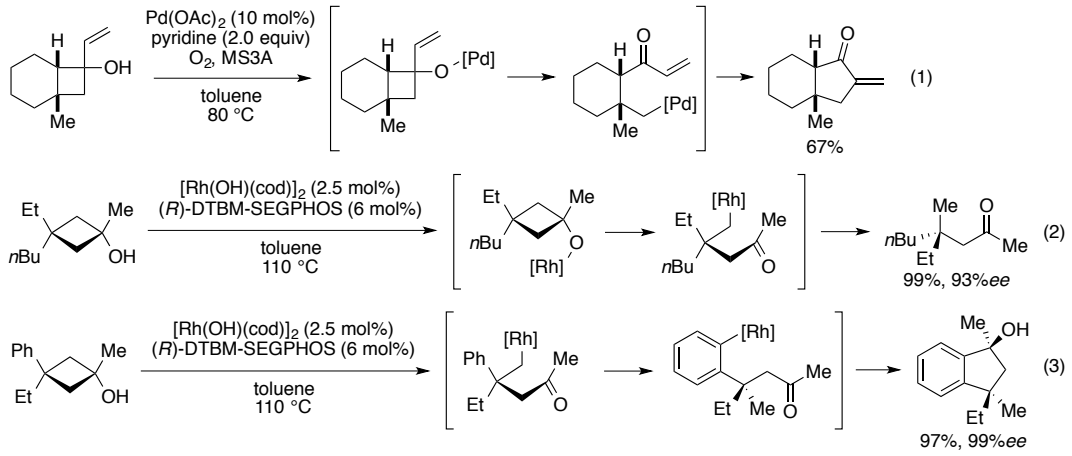
Scheme 5. Carbon–Carbon Bond Cleavage through 1,2-Shift

このような状況下、村上・伊藤らは 1994 年にロジウム錯体がシクロブタノンのカルボニル炭素とそのα位炭素との間の結合に直接的に挿入することを世界で初めて示した（Scheme 6, eq. 1）[15]。この発見が契機となり、酸化的付加による炭素–炭素結合の開裂を経由する反応開発が、現在も国内外で精力的に行われている [16]。最近の例では Dong らが cycloinumakiol（提出構造）の四環性骨格の構築に、酸化的付加による炭素–炭素結合活性化を経由する三置換アルケンのカルボアシル化反応を利用し、初の全合成を達成している(eq. 2)[17]。また彼らは、シクロブタノンから二環性架橋構造を構築できることも報告している（eq. 3）[18]。この反応では、まず基質のシクロブタノンと 2-アミノ-3-メチルピリジンからイミンが生成し、そのピリジン環の窒素にロジウムが配位することにより、近傍の炭素–炭素結合への酸化的付加が促進される。生成したローダサイクルへのオレフィン挿入と還元的脱離の後、イミンが加水分解されることで生成物が得られる。複雑な分子骨格の構築に炭素–炭素結合活性化の化学が有効であることを実証している点が意義深い。



Scheme 6. Carbon–Carbon Bond Cleavage through Oxidative Addition

遷移金属触媒による炭素–炭素結合のもう一つの切断様式は、β-炭素脱離と呼ばれる過程である [19]。β-炭素脱離による炭素–炭素結合の切断は、酸化的付加による切断よりも穏和な条件で進行することが多い。植村らは、シクロブタノールに酢酸パラジウム及びピリジンを作用させると、生じたパラジウムアルコラートからβ-炭素脱離が立体障害の少ない側で進行した後、Heck 反応が起こることを報告している（Scheme 7, eq. 1）[20]。同様の基質から使用するパラジウム触媒によって、炭素–炭素結合の切断様式が変化している点が興味深い（Scheme 5, eq. 1）。また、対称なシクロブタノールのエナンチオ選択的なβ-炭素脱離による非対称化によって、不斉炭素を構築する反応が開発されている。例えば Cramer らは、エナンチオ選択的なプロトン化により不斉第四級炭素を有するケトンを得ている（eq. 2）[21]。またシクブタノールの 3 位にフェニル基を有する基質では、β-炭素脱離によって生じたアルキ



Scheme 7. Carbon–Carbon Bond Cleavage through β-Carbon Elimination

ルロジウム種が C–H 活性化を起こし、生成したアリールロジウム錯体がケトンへ求核攻撃することで、多置換インダノンを高収率かつ高立体選択的に合成できる（eq. 3）[22]。

第 4 節　面性不斉分子

キラリティーとは右手と左手のように、ある化合物がその鏡像と重ね合わさることができない構造として存在することを言う。最も一般的なキラリティーは、4 つの置換基が全て異なる炭素原子に代表される中心性不斉である。しかし不斉中心を持たなくとも、キラリティーが生じる場合がある。3 つの炭素原子間に 2 つの連続する二重結合を持つアレンは、両端の炭素原子がそれぞれ異なる置換基を持つときに軸性不斉を示す（Figure 3A）[23]。さらにはアレンのように結合軸が全く回転できない場合でなくても、回転が抑制されてさえいれば軸性不斉を生じる場合がある。例えば、遷移金属触媒反応の不斉配位子として用いられる BINAP は、嵩高いジフェニルホスフィノ基とナフチル基のペリ位水素によって結合回転が制限されているために、エナンチオマーが生じる（Figure 3B）。このような不斉を特にアトロプ異性と呼ぶ。6 個のベンゼン環が縮環した[6]ヘリセンは、末端のベンゼン環同士の立体反発により平面構造を取れず、右巻きと左巻きのらせん不斉を生じる（Figure 3C）[24]。

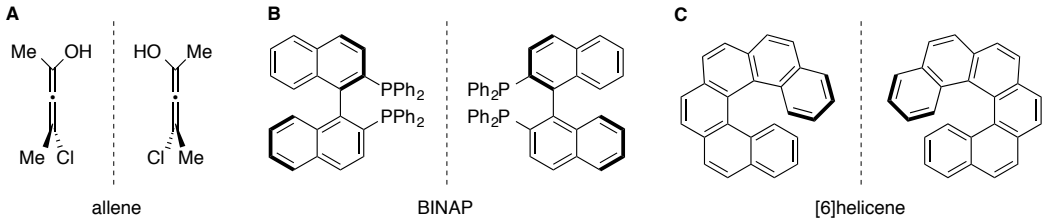


Figure 3. Compounds with Axial Chirality or Helical Chirality

次に面性不斉を有する化合物を挙げる（Figure 4）。フェロセンに代表されるような、2 つのシクロペンタジエニルを配位子として持つメタロセンは、少なくとも 2 つの置換基を一つのシクロペンタジエニル上に有する場合に面性不斉を示す（Figure 4A）。Fu らは、フェロセン骨格に DMAP を縮合させた化合物を設計し、それを不斉求核触媒として用いたケテンとイミンの触媒的不斉[2+2]環化付加をはじめ[25]、様々な不斉反応を報告している（Scheme 8）[26]。

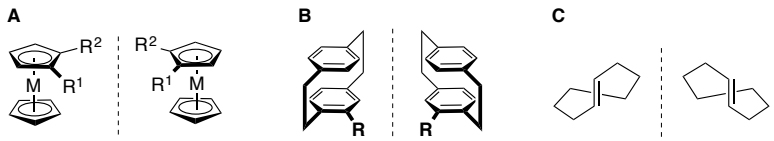
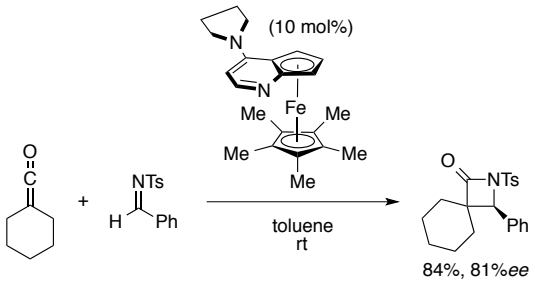
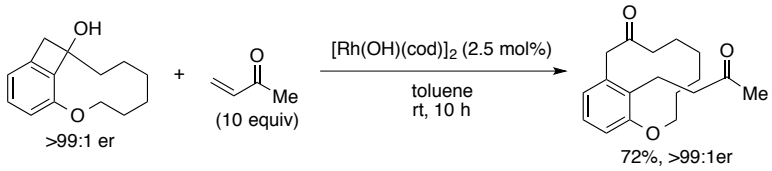


Figure 4. Planar Chiral Molecules (A) Metallocenes (B) Cyclophanes (C) *trans*-Cyclooctene



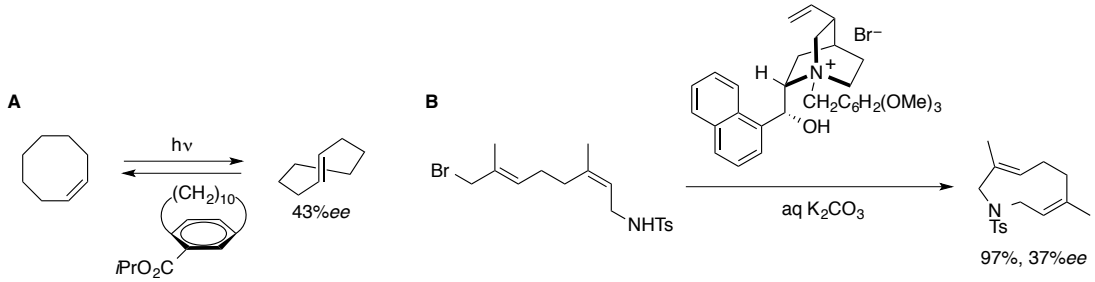
Scheme 8. Asymmetric Synthesis of β-Lactams by a Planar Chiral Catalyst

芳香環の回転が制限されているシクロファン誘導体は面性不斉を示し（Figure 4B）、様々な立体選択的な反応の不斉源として利用されている[27]。村上らは最近、光反応で合成可能な中心性不斉を有するベンゾシクロブテノールから、不斉転写を伴う炭素–炭素結合の活性化を用いた独自のアプローチで、面性不斉を有するメタシクロファンを立体選択的に合成することに成功した（Scheme 9）[28]。



Scheme 9. Cyclophanes with Planar Chirality

Trans-アルケンを有する環状化合物は、環反転が制限されており、面性不斉を示す場合がある。例えば *trans*-シクロオクテンは室温で安定に存在する最小の *trans*-シクロアルケンであり、メチレン鎖が短く環反転が困難であるため、十分安定な面性不斉を示し、そのラセミ化半減期は 30 °C で 10^5 年とされている（Figure 4C）[29]。1962 年に Cope らが初めて、*trans*-シクロオクテンの光学分割に成功した[30]。環の員数が大きくなると環反転が容易になるため、*trans*-シクロノネン（$t_{1/2}$ = 6 s at 30 °C）や *trans*-シクロデセン（$t_{1/2} = 10^{-4}$ s at 30 °C）は、室温では光学活性体として単離することが困難である[29]。鹿又・井上らは、面性不斉シクロファ

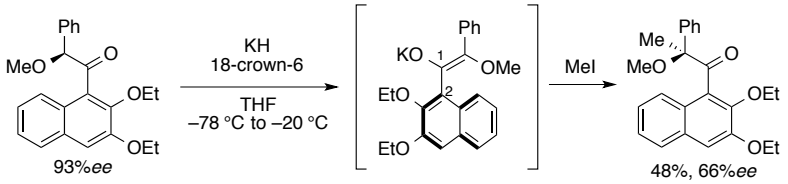


Scheme 10. Synthesis of Planar Chiral *trans*-Cycloalkenes

ンを光学活性な光増感剤として用いた *cis*-シクロオクテンの光異性化反応を見出し、*trans*-シクロオクテンの不斉合成を達成した（Scheme 10A）[31]。また友岡らは動的面性不斉を有するヘテロ中員環化合物を精力的に研究しており [32]、キラルプロモーターを用いた窒素原子を有する面性不斉九員環化合物のエナンチオ選択的な合成を達成している（Scheme 10B）[32d]。

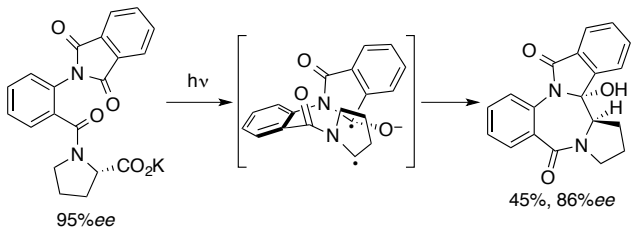
第 5 節　不斉記憶型反応

不斉記憶（Memory of chirality）とは、本来は反応の進行と共に失われるべき原料系の不斉情報が、反応中間体に一定時間内保存される現象のことである [33]。軸性不斉エノラートを経由する不斉記憶型反応は、冨士・川端らによって精力的に研究されてきており、先駆的な例として独自に設計したキラルな 1-ナフチルケトンの不斉アルキル化を報告している（Scheme 11）[34]。このケトンの塩基処理によってエノラートが生じると中心性不斉を失うが、生じるエノラートは C(1)–C(2)結合の回転が制限されているために軸性不斉を持ち、そのラセミ化半減期は–20 °C で 24 日と概算されている。この中間体の軸性不斉を経由して、不斉情報が生成物の中心性不斉へと転写される。この先行研究を皮切りに、アミノ酸誘導体から生成する C–N 軸性不斉を持つエノラートや [35]、ラセミ化半減期が極めて短い C–O 軸性不斉エノラートを経由する不斉誘導も達成された [36]。



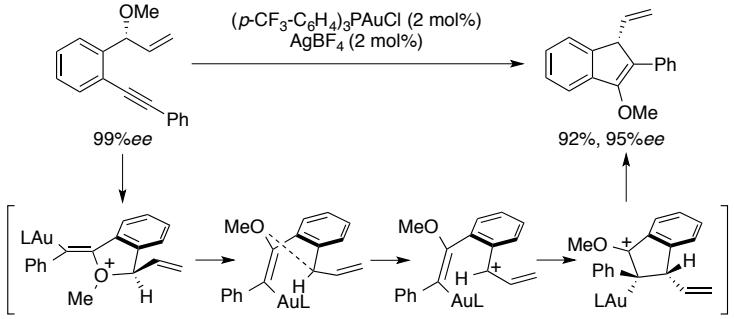
Scheme 11. Asymmetric Alkylation of a Naphthyl Ketone

不斉記憶は軸性不斉エノラートの化学を中心として発展してきたが、軸性不斉を有するラジカル中間体やカチオン中間体を経由する報告例も見られる。例えば Griesbeck らは、軸性不斉ビラジカル中間体を経由する不斉光環化反応を報告している（Scheme 12）[37]。この



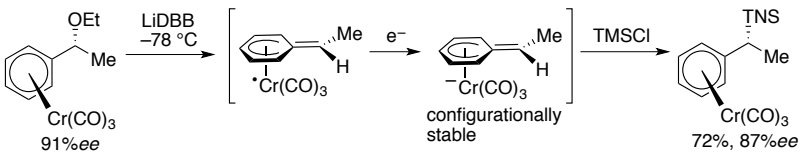
Scheme 12. Asymmetric Decarboxylative Photocyclization through Axially Chiral Intermediates

反応では、まず光照射によるカルボキシラートからイミドのカルボニル基への電子移動が起こり、脱炭酸が進行する。生じたビラジカル中間体のアミド部位とイミド部位の回転障壁が高いために、その軸性不斉に原料のキラリティーが保存され、ビラジカルの再結合により光学活性な七員環を与える。また Toste らは、金触媒を用いたベンジルエーテルの環化異性化反応において、原料の中心性不斉が、生成物であるインデンの中心性不斉に転写されることを見出している（Scheme 13）[38]。金触媒によって活性化されたアルキンに対して、酸素原子の求核攻撃が進行した後、ビニル基とエノールエーテル部位の立体反発を避けながら、生じるカチオンと芳香環の軌道の重なりが最大になるような遷移状態を経て、軸性不斉を有するベンジルカチオンが生じる。次いでカチオンへの求核攻撃と金の脱離を経て、光学活性なインデンが生成する。



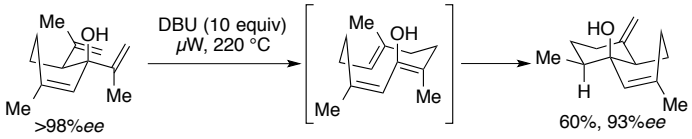
Scheme 13. Intramolecular Carboalkoxylation of Alkynes through Axially Chiral Cationic Intermediates

以上のような軸性不斉中間体を経由する不斉記憶型反応と比較すると、中間体の面性不斉を介する不斉記憶型反応の例は限定的である。そのような状況下 Schmalz らは、面性不斉ラジカル中間体を経由するアレーン–クロム錯体の立体特異的極性転換反応を報告している（Scheme 14）[39]。光学活性クロム錯体の一電子還元によって生成するラジカル種は、ベンジル位の結合の回転障壁を持つために面性不斉を有する。DFT 計算により、このラジカル種のラセミ化障壁は 13.2 kcal/mol と推定されており、これは–78 °C で約 1 分のラセミ化半減期に相当する。この面性不斉ラジカル中間体を即座に還元して、立体化学的に安定なアニオン中間体を生じさせ、クロロトリメチルシランで捕捉することで光学活性な生成物が得られる。



Scheme 14. Enantioselective Alkylation of Chrominium Complexes through Planar Chiral Intermediates.

また Barriault らは、1,2-ジビニルシクロヘキセノールのタンデムオキシ Cope 転位–エン反応において、*trans,cis*-共役ジエノールともう一つの *trans*-二重結合を持つ面性不斉中間体を介した不斉転写を確認しており、光学活性なデカリン骨格を得ている（Scheme 15）[40]。

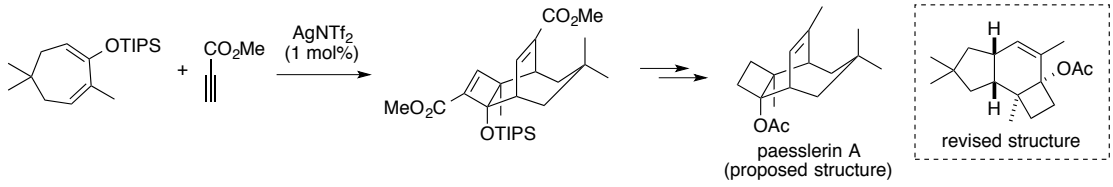


Scheme 15. Tandem Oxy-Cope/Ene Reaction through Planar Chiral Intermediates

第 6 節　触媒的[2+2]環化付加の応用

小員環化合物はその歪みに由来して、他の員数の環状化合物にはない独特な性質を持つ。しかしながら小員環化合物の実用的合成法は限られていることもあり、その有用性はこれまで十分には開拓されていなかった。そこで当研究室では、四員環化合物の新規合成法の開発に取り組み、シリルエノールエーテルと不飽和エステルの触媒的[2+2]環化付加反応を報告した（Scheme 3）[10]。この方法を用いれば、シクロブタン及びシクロブテン類を簡便且つ大スケールで合成できる。この反応を応用して、当研究室ではこれまで様々な研究を展開してきた。

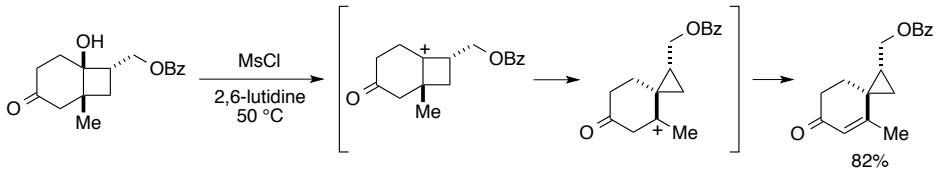
例えば、[2+2]環化付加を複雑な分子構造の簡便な構築に利用することを目指して、上記反応を基盤とした多成分連結反応を企画し、三環性セスキテルペン paesslerin A の全合成を達成した（Scheme 16）[41]。しかしながら合成品のスペクトルデータは、天然物とは異なり、提出構造が誤りであることが明らかとなった。最近、修正構造の提出を目指した全合成も達成し、paesslerin A の真の化学構造を明らかにした [42]。



Scheme 16. Total Synthesis of Paeesslerin A

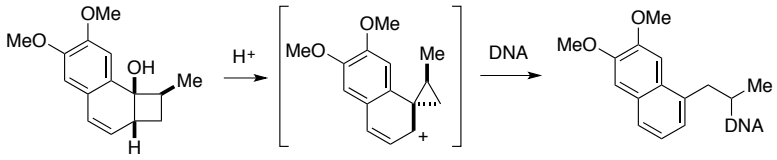
[2+2]環化付加によって得られる縮環シクロブタンの独特な反応性を利用して、セスキテルペンである illudine 類の生合成を模倣した縮環シクロブタノールのスピロシクロプロパンへの環縮小転位反応を開発した（Scheme 17）[43]。縮環シクロブタノールの第三級ヒドロキ

シ基をメシル化して脱離基として活性化すると、歪みの解消を駆動力とした環縮小転位が立体特異的に進行する。



Scheme 17. Ring-Contraction Rearrangement

また上記の環縮小転位反応をケミカルバイオロジー研究へと展開した。腫瘍細胞のミトコンドリア内は pH が低いという特徴的な性質を認識する腫瘍細胞に選択的な DNA アルキル化剤の創製を目指して、酸性条件下でのみ DNA を切断する三環性シクロブタノールの設計及び合成を行った（Scheme 18）[44]。この化合物を酸性条件に付すと、ヒドロキシ基がプロトン化されることで活性化され、環縮小転位が起こる。続いてスピロシクロプロパンが DNA からの求核攻撃を受けて DNA との共有結合を形成することで、この化合物が DNA アルキル化剤として働く。実際にプラスミド DNA を用いた活性評価試験により、狙い通り酸性条件下でのみ、DNA 切断活性を示すことを確認している。



Scheme 18. Ring-Contraction Rearrangement and Ring-Opening under Aqueous Acidic Condition

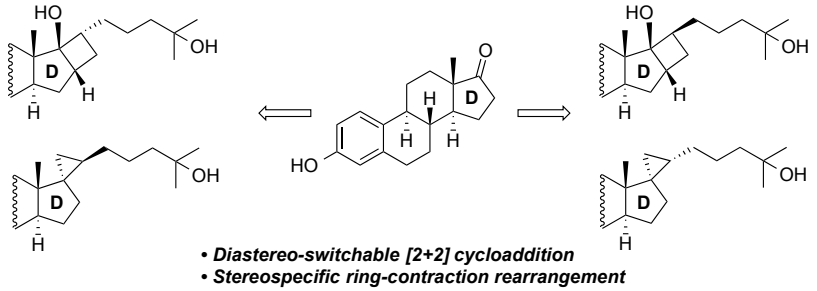
第 7 節　本論文の概要

前節で概説したように当研究グループではこれまで、小員環の潜在的有用性を拡張すべく、様々な研究を展開してきた。筆者は、小員環化合物の更なる可能性や知見の発掘を目指した研究に取り組んできた。以下にその概略を示す。

[2+2]環化付加及び環縮小転位を利用した小員環を有するステロイド誘導体の合成と活性評価（第 2 章）

創薬研究において活性の増強や副作用の乖離を狙い、生物活性物質に不飽和結合や環構造を導入して、その配座を固定化する戦略は広く用いられる。本研究ではステロイドをモデル化合物とし、その配座固定化に独特で剛直な小員環を利用することを考えた。当研究

グループで開発した[2+2]環化付加[10]及びシクロブタノールの環縮小転位[43]を利用して、四員環及び三員環をそれぞれD環に導入した（Scheme 19）。この[2+2]環化付加では、反応温度によってシクロブタンの *cis* 体と *trans* 体の生成比が完全に逆転することを見出し、両ジアステレオマーを作り分けた。加えて環縮小転位は立体特異的に進行するため、スピロシクロプロパンの両ジアステレオマーも得られた。以上のように本合成戦略を用いると、小員環を有するステロイド誘導体の各ジアステレオマーを立体分岐的に合成できる。合成した小員環を有するステロイド誘導体の核内受容体の転写活性化能を評価したところ、小員環を持たない誘導体と比較して、より高いビタミンD受容体転写活性化能のefficacyを持つ化合物が見つかった。



Scheme 19. Steroidal Derivatives Bearing a Small Ring

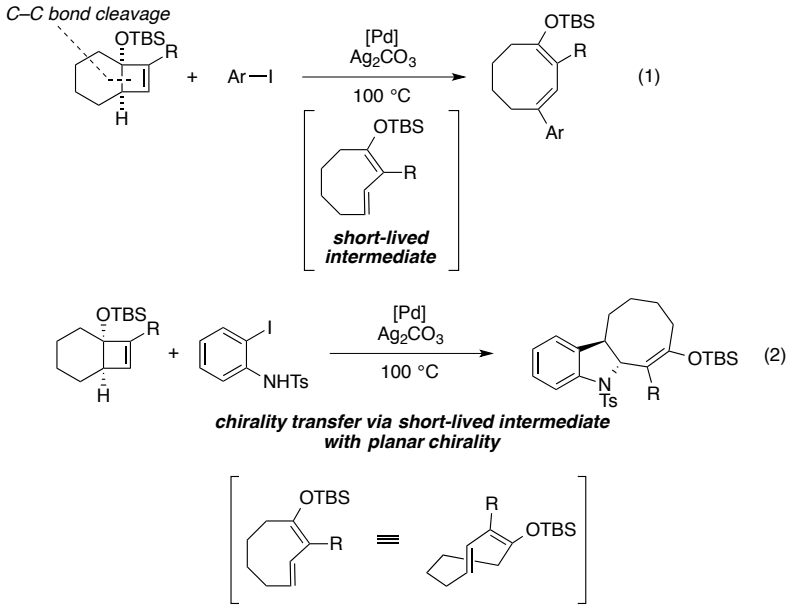
面性不斉短寿命中間体を経由する縮環シクロブテンの環拡大反応（第3章）

近年、小員環化合物の炭素-炭素結合を切断する過程を積極的に取り入れたアプローチで分子骨格を形成する反応の開発が、国内外で精力的に行われている。しかしながら、当研究室の方法で容易に合成できる縮環シクロブテンを基質とした反応は、ほとんど報告例がなく、その合成素子としての可能性に興味を持った[45]。その中で、縮環シクロブテンの核間位炭素–炭素結合の切断を組み込んだ反応を開発できれば、一般的に分子内閉環反応での合成が困難な中員環骨格を効率的に形成できる手法となるのではないかと考えた

種々検討の結果、縮環シクロブテンとヨウ化アリールをパラジウム触媒及び炭酸銀存在下で100 °Cに加熱したところ、アリール化を伴った環拡大反応が進行することがわかった（Scheme 20, eq. 1）。反応機構を詳細に調べたところ、本反応は縮環シクロブテンの熱的4π電子環状反応により生じる *cis,trans*-シロキシジエンを経由していることが明らかになった。この *cis,trans*-シロキシジエンは中員環内に *trans*-二重結合を有しており、高度に歪んでいるため、縮環シクロブテンを再生する逆反応が非常に速い短寿命中間体である。この短寿命中間体をパラジウム触媒で捕捉するアプローチで中員環合成に利用した点が、本反応の特徴である。

次に、*cis,trans*-シロキシジエン短寿命中間体の面性不斉に注目した。ある種の *trans*-シク

ロアルケンは、面性不斉を有することが知られており、*trans*-オレフィンを有する短寿命中間体も面性不斉を持つと考えた。そこで、縮環シクロブテンの中心性不斉が短寿命中間体の面性不斉を介して、生成物のキラリティーへと転写されることを期待し、新たな反応系を設計した。検討の結果、縮環シクロブテンと *o*-ヨードアニリン誘導体をパラジウム触媒存在下で加熱すると、中員環縮環型 *trans*-インドリンが得られた（Scheme 20, eq. 2)。さらにこの反応で光学活性な縮環シクロブテンを用いた場合、その熱的 4π電子環状反応によって不斉中心が全て消失するにも関わらず、短寿命中間体の面性不斉を介して光学活性な生成物が得られる興味深い現象を確認した。



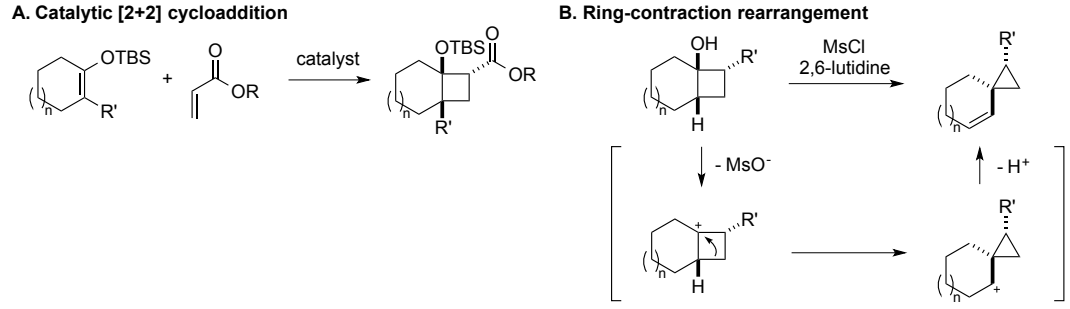
Scheme 20. Ring Expanding Reactions of Fused Cyclobutenes via Short-Lived Intermediates with Planar Chirality

第 2 章　[2+2]環化付加及び環縮小転位を利用した小員環を有するステロイド誘導体の合成と活性評価

第 1 節　背景

近年 X 線結晶構造解析を利用した合理的な医薬品設計が、必要不可欠になりつつある。受容体や酵素の結合部位の構造が決定されれば、ドッキングスタディなどのコンピュータシミュレーションによって、ヒット化合物の発見にかかる期間を短縮化できる。また X 線結晶構造解析は、後期のリード化合物の構造最適化の際にも役立ち、結合部位の結晶構造に適合するように官能基の三次元配置をサブオングストロームの分解能でチューニングすることができる。ターゲットタンパク質と最適な位置で相互作用させることで活性の増強や副作用の乖離を狙い、リード化合物の配座を固定化することは医薬開発においてよく用いられる戦略である。アルケンやアルキン、芳香環、アミドなどのような剛直な構造を導入すると、結合回転できる側鎖の動きを抑えることができる。シクロプロパンやシクロブタンのような小員環炭化水素も剛直な構造を持つため、これらもまた医薬品の配座固定に利用されるが、その数は限られている[46]。その主な原因は、実用的な小員環合成法が不足していることにある。

当研究グループではこれまでに、官能基化されたシクロブタン環やスピロシクロプロパン環を構築する手法を開発してきた。酸触媒として二塩化エチルアルミニウム（$EtAlCl_2$）やトリフリックイミド（Tf_2NH）を用いたシリルエノールエーテルと不飽和エステルの[2+2]環化付加によって、シクロブタン環が高立体選択的に構築できる（Scheme 21A）[10]。またスピロシクロプロパンを与える縮環シクロブタノールの立体特異的な環縮小転位も報告している（Scheme 21B）[43]。この転位反応は、三級カルボカチオンを経由し、続いて歪みの解消を駆動力として隣接する炭素–炭素結合が転位することで進行している。



Scheme 21. Our Methods for Constructing Small Rings

これらの合成法の応用として、配座固定化のためにシクロブタン環やスピロシクロプロパン環を導入した医薬品誘導体の立体選択的な合成を考え、ステロイドをモデル化合物と

して設定した。ステロイド化合物は独特な縮環構造から成る生物活性物質で、広く医薬品として利用されている。しかしながら多様な生物活性を持つために、時に重篤な副作用が問題となる。例えば、活性型ビタミン D（カルシトリオール）は、核内受容体の一種であるビタミン D 受容体（VDR）との結合を引き金に、骨恒常性や免疫、細胞成長、分化などの幅広い生物学的機能に関与する[47]。カルシトリオール誘導体は骨粗鬆症や乾癬に有効であることが知られているが[48]、高カルシウム血症などの重篤な副作用のために医薬品としての使用は限られている[47c]。これまで、目的の活性を保持しつつも副作用が低減された医薬候補化合物の創出に向けて、多くのカルシトリオール誘導体が合成されてきた[47c,49]。例えば Mouriño は、不飽和結合や環構造を導入して側鎖の配座を固定化したカルシトリオール誘導体の合成を行っており[50]、ヒト結腸癌細胞のビタミン D 受容体の転写活性化能を有する誘導体も報告している[50c]。本章では、触媒的[2+2]環化付加と環縮小転位を利用した小員環を有するステロイド誘導体の立体分岐的な合成とその活性評価について述べる。

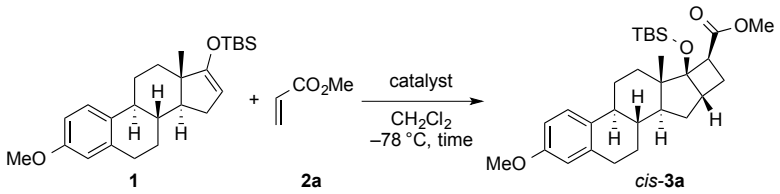
第 2 節　触媒的[2+2]環化付加によるシクロブタン環の立体選択的な構築

始めに、エストロン 3-メチルエーテルから誘導したシリルエノールエーテル **1** とアクリル酸メチル（**2a**）の[2+2]環化付加反応を検討した（Table 1）。シリルエノールエーテル **1** を 1.0 mol%の Tf_2NH 存在下、–78 °C で 1.3 当量の **2a** と反応させると、シクロブタン *cis*-**3a** が 5%収率で得られた（entry 1）。Tf_2NH やアクリル酸メチルの当量を増やしても、収率は減少或いは微増するに留まった（entries 2–4）。触媒として 1,1,3,3-tetrakis(triflyl)propane（$Tf_2CHCH_2CHTf_2$）を用いても収率の向上は見られなかったが（entry 5）[51]、$EtAlCl_2$ を用いると *cis*-**3** の収率が 77%まで向上した（entry 6）。

興味深いことに、**2a** の代わりにアクリル酸ヘキサフルオロイソプロピル（HFIP）（**2b**）を用いると、反応条件に応じてジアステレオ選択性が切り替わることがわかった（Table 2）。$EtAlCl_2$ 存在下でシリルエノールエーテル **1** を **2b** と–78 °C で反応させると、*trans*-**3b** が高立体選択的に 85%収率で得られた（entry 1）。反応時間に依らず、*trans* 選択性はほぼ一定であった（entries 1 and 2）。一方で反応温度を–60 °C まで上げると **3b** の *trans* 選択性は減少し（entry 3）、–40 °C では選択性が逆転して *cis* 体が選択的に得られた（entry 4）。さらに反応温度を室温まで上げると、*trans* 体は全く得られず、Michael 付加体 **4**（12%）とともに *cis*-**3b**（74%）が選択的に得られた（entry 5）。反応を–78 °C で 10 分間行った後、室温でさらに 10 分間反応させた場合も、*trans* 体は全く得られず、*cis*-**3b** と **4** が得られた（entry 6）。これらの結果は *trans*-**3b** が速度論支配の生成物であり、*cis*-**3b** が熱力学支配の生成物であることを

示唆している。アクリル酸メチル（**2a**）との反応では、室温でも–78 °C でも *cis*-**3a** のみが得られた（entry 8 and Table 1 entry 6）。反応温度を–90 °C まで下げても、*trans*-**3a** はマイナージアステレオマーとしてしか得られなかった（entry 7）。以上の結果より、*trans*-**3** から *cis*-**3** への異性化の活性化エネルギーは、エステルの置換基に依存していると言える。

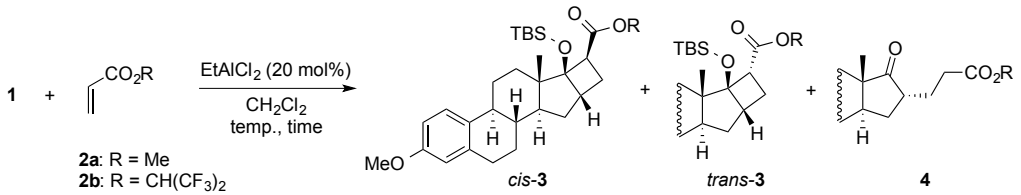
Table 1. Catalyst Screening for the [2+2] Cycloaddition of **1** with **2a**



entry	catalyst (mol%)	**2a** (equiv)	time (h)	yield of *cis*-**3a** (%)[a]
1	Tf_2NH (1.0)	1.3	2.5	5
2	Tf_2NH (5.0)	1.3	2.5	4
3	Tf_2NH (5.0)	2.5	1.0	33
4	Tf_2NH (20)	2.5	2.0	10
5	$Tf_2CHCH_2CHTf_2$ (20)	2.5	2.0	17
6	$EtAlCl_2$ (20)	2.0	2.0	77

[a] Isolated yields.

Table 2. Effect of Acrylate and Reaction Temperature in the [2+2] Cycloaddition

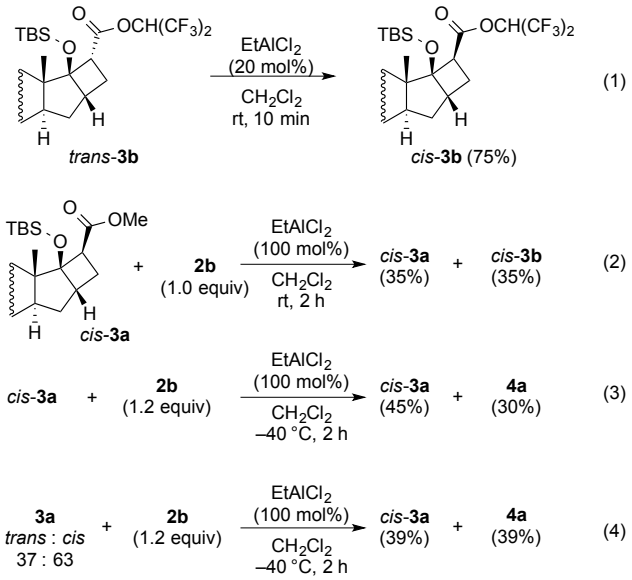


entry	acrylate **2**	temp. (°C)	time (min)	yield of **3** (%)[a]	*trans*:*cis*
1	**2b**	−78	10	85	95:5
2	**2b**	−78	120	89	94:6
3	**2b**	−60	10	86	64:36
4	**2b**	−40	10	89	5:95
5	**2b**	rt	120	74[b]	0:100
6	**2b**	−78 then rt	10 then 10	70[b]	0:100
7	**2a**	−90	10	77	35:65
8	**2a**	rt	120	72	0:100

[a] Isolated yields. [b] Michael adduct **4** was obtained in 5–12 % yield.

第 3 節　[2+2]環化付加におけるジアステレオ選択性の温度依存性の考察

ジアステレオ選択性についての知見を得るため、クロスオーバー実験を行った。シクロブタン *trans*-**3b** に対し室温で $EtAlCl_2$ を作用させると *cis*-**3b** へ完全に異性化した一方（Scheme 22, eq. 1)、$EtAlCl_2$ を加えない場合では反応は全く起こらなかった。シクロブタン *cis*-**3b** に対して室温で同触媒を用いても、*trans*-**3b** への異性化は進行しなかった。メチルエステル *cis*-**3a** と 1 当量のアクリル酸 HFIP（**2b**）の混合物に室温で $EtAlCl_2$ を作用させると、35%の原料 *cis*-**3a** の回収とともにクロスオーバー付加体 *cis*-**3b** が 35%収率で単一のジアステレオマーとして得られた（eq. 2)。これらの結果は、$EtAlCl_2$ がシリルエノールエーテル **1** とアクリル酸エステル **2** を再生する逆[2+2]環化付加を促進していることを示唆している。再生したシリルエノールエーテル **1** の[2+2]環化付加では、**2b** と系中で発生した **2a** とが競合した結果、*cis*-**3a** と *cis*-**3b** の混合物が得られた。対照的にメチルエステル *cis*-**3a** の反応を–40 °C で行ってもクロスオーバー付加体は得られず、開環体 **4a** が収率 30%で得られた（eq. 3)。*Trans*/*cis* 混合物の **3a** を–40 °C で $EtAlCl_2$ と反応させると、**4a** の生成とともに *trans*-**3a** から *cis*-**3a** へのエピメリ化が観測されるのみで、クロスオーバー付加体は得られなかった（eq. 4)。



Scheme 22. Mechanistic Insights into the $EtAlCl_2$–Catalyzed [2+2] Cycloaddition

以上の結果に基づいて、$EtAlCl_2$ を用いた **1** の触媒的[2+2]環化付加の反応機構を Figure 5 に示す。シリルエノールエーテル **1** のアクリル酸エステル **2** への Michael 付加は立体的に空いているα面から進行し、両性イオン中間体 **5** を生じる。低温では **5** の分子内アルドール型の付加反応はより有利な遷移状態 **TS-1** を経て、速度論支配の生成物である *trans*-**3** を与える。一方、嵩高いシリルオキシ基とケテンアセタール部位との立体障害のためにより不利

な遷移状態 **TS-II** からは、*cis*-**3** が得られる。C14 位のアキシアル水素とエステル部位との立体障害のために、*trans*-**3** は *cis*-**3** より不安定であると考えられる。実際にこれは、*trans*-**3b** と *cis*-**3b** の DFT 計算の結果により支持される（$\Delta G°_{cis-trans} = -12.6$ kJ/mol）[52]。エピメリ化の機構は幾分複雑である。室温では、*trans*-**3** と *cis*-**3** はシリルエノールエーテル **1** を経由する逆[2+2]環化付加によって平衡にあり、熱力学的により安定な *cis*-**3** を与える。一方、–40 °C では逆[2+2]環化付加は進行しなかった。これは、*cis*-**3** へのエピメリ化はシロキソニウムイオン **5** を経た逆アルドール反応によって進行していることを示唆している。加えてケトン **4** は、後処理中にケテンシリルアセタール **6** の脱シリル化が起こることで生じたと考えられる。なお、[2+2]環化付加で合成できるエステルを有するシクロブタンのエノール化はほとんど進行しないことが、これまでの当研究グループの知見として得られており、*trans*-**3** のエノール化を経る *cis*-**3** へのエピメリ化の可能性は低いと思われるが、完全には否定できない。

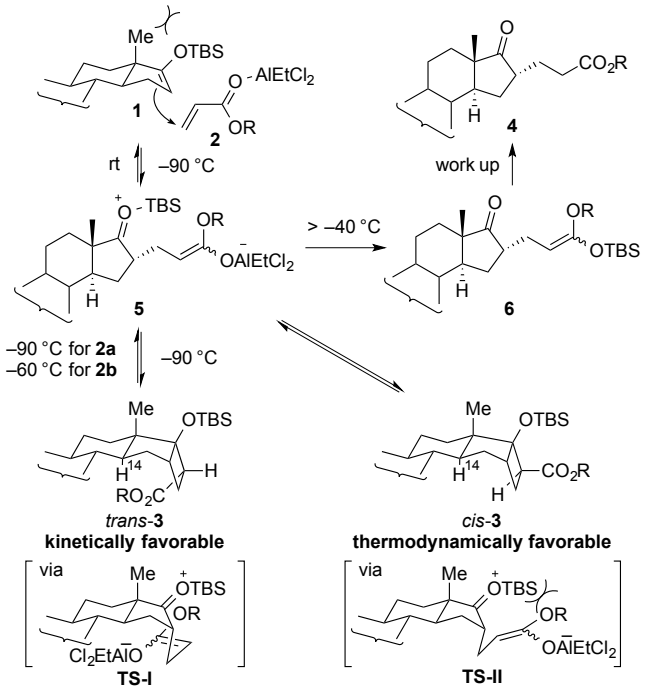
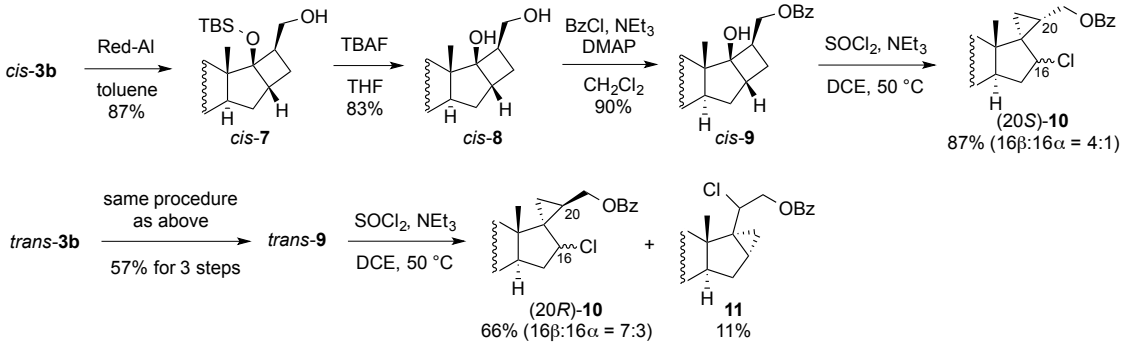


Figure 5. Possible Mechanism for the $EtAlCl_2$–Catalyzed [2+2] Cycloaddition under Kinetic and Thermodynamic Conditions

第 4 節　スピロシクロプロパン環の構築及び D 環側鎖の導入

シクロブタン環が構築できたので、次にスピロシクロプロパンを与えるシクロブタノールの環縮小転位を検討した（Scheme 23）。環縮小転位の基質を得るため、*cis*-**3b** のエステル

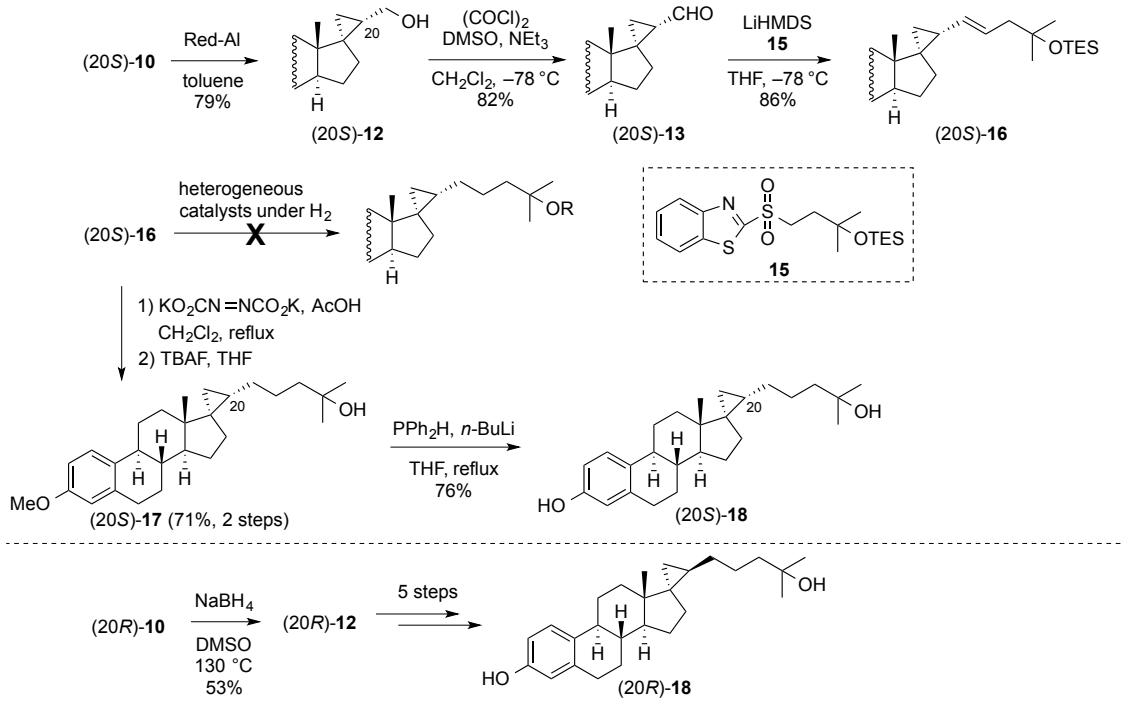
を Red–Al で還元し、TBS 基の除去と続く第 1 級ヒドロキシ基のベンゾイル保護を経て、*cis*-**9** を合成した。なお、*trans*-**9** も同様な方法で *trans*-**3b** から合成した。環縮小転位の基質が合成できたので、まず過去の報告に従って [43]、*cis*-**9** を 2,6-ルチジン溶媒中で塩化メタンスルホニルと反応させたが、約 40%の原料回収とともにメシル化体が約 30%収率で得られるのみであった。塩化オキサリルやトリフルオロメタンスルホン酸無水物を用いて、第 3 級ヒドロキシ基を脱離基に変換することを試したが、スピロシクロプロパンは全く得られなかった。一方で塩化チオニルを用いた場合に、(20*S*)-**10** が高収率で得られることがわかった（87%, 16β:16α = 4:1）。なお、(20*S*)-**10** の立体配置は NOE によって決定した。同条件は *trans*-**9** の環縮小転位にも適用可能で、収率の低下が見られたものの、(20*R*)-**10** が立体特異的に得られた（66%, 16β:16α = 7:3）。これらの環縮小転位では、カルボカチオン中間体は塩化物イオンの求核攻撃を受け、(20*S*)-**10** 及び(20*R*)-**10** を生成したが、カチオン中間体が脱離を起こした生成物は観測されなかった。(20*S*)-**10** と(20*R*)-**10** の収率の差異は、副生物 **11** の生成に起因する。この副生物が *trans*-**9** の環縮小転位でのみ得られた原因は完全には解明できていないが、シクロブタンの X 線結晶構造解析により、核間位 C–O 結合と転位する炭素–炭素結合との二面角が *cis* と *trans* で異なることが明らかになっており、その二面角の差が転位に影響を与えていると考えられる。



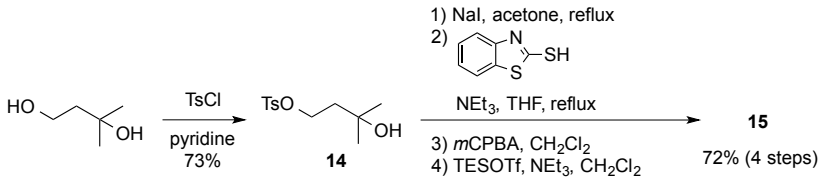
Scheme 23. Construction of a Spirocyclopropane Ring by Ring-Contraction Rearrangement

小員環を導入できたので、次にコレスタン側鎖の導入を検討した（Scheme 24）。まず、Red–Al で(20*S*)-**10** のベンゾイル基の除去及び脱塩素化をワンポットで行い、続いて Swern 酸化を行うことでアルデヒド(20*S*)-**13** を得た。炭素鎖の伸長は(20*S*)-**13** に対するベンゾチアゾリルスルホン **15** を用いたワンポットの Julia オレフィン化で行った。なお **15** は、3-メチル-1,3-ブタンジオールから 5 工程で合成した（Scheme 25）。このオレフィン化において、スルホン **15** の水酸基を TES 基で保護していない場合、原料のアルデヒドの残存が多く見られた。得られたオレフィンの還元を酢酸エチル中で Pd/C を用いた接触還元で行ったが、シクロプロパン環の開環が併発した。そこで他の不均一系触媒による接触還元を検討した。Pd/Fib や Pd/C(en)の場合、二重結合は還元されず三員環の開環が選択的に進行した。メタノ

ール中 Pd/MS5A[53] や Pd/BN[54] を用いた場合、反応は全く進行しなかった。酢酸エチル中 Rh/alumina を用いると、三員環の開環を伴わず二重結合を還元できたが、A 環もシクロヘキサン環へと還元されてしまうことがわかった。不均一系触媒を用いた接触還元を断念し、次にジイミド還元を行ったところ [55]、二重結合を選択的に還元することができ、続いて TBAF で TES 基の除去を行い、(20*S*)-**17** を得た。おそらくシクロプロパン環の不安定さのために、最後の A 環部メチル基の除去も困難であった。スピロシクロプロパン(20*S*)-**17** に対し、BBr_3 や TMSI, NaSEt, $AlMe_3$/NaI[56] などの条件で脱保護を試みたが、いずれも複雑な混合物を与えるのみであった。種々検討の結果、*n*-BuLi/PPh_2H を用いると(20*S*)-**18** を 76%収率で得ることができた [57]。同様な方法で(20*R*)-**10** から(20*R*)-**18** の合成も達成したが、(20*R*)-**10** の還元において Red–Al を用いると、副生物が多く見られた。代わりに DMSO 中 130 °C で水素化ホウ素ナトリウムを使用すると、副生物の生成を抑えることができ、(20*R*)-**12** を 53%収率で得た [58]。

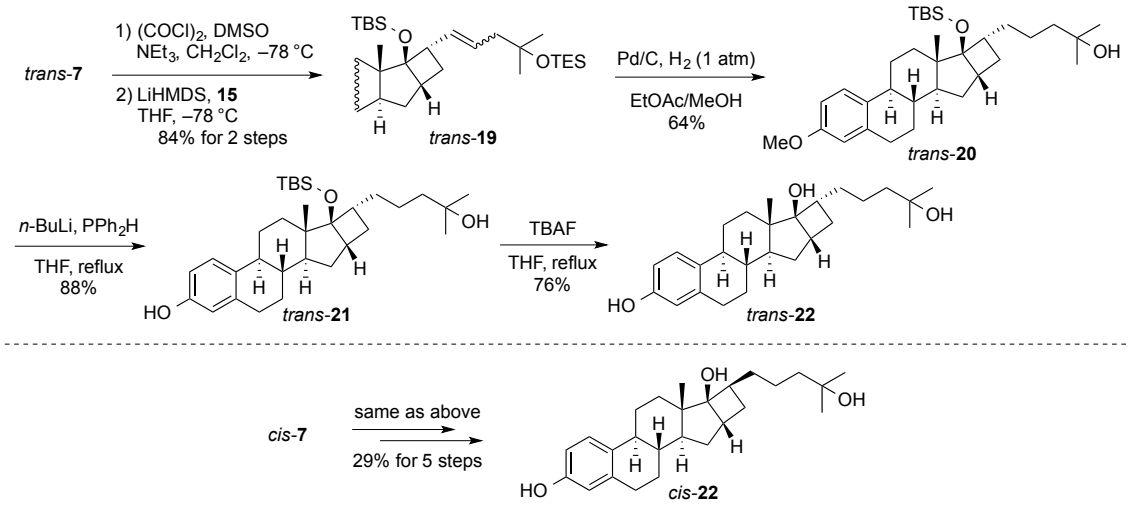


Scheme 24. Installation of a Side Chain and Completion of the Synthesis of (20*S*)- and (20*R*)-**18**



Scheme 25. Preparation of Benzothiazolyl Sulfone **15**

シクロブタン環への側鎖の導入も同様な戦略で行った（Scheme 26）。シクロブタノール *trans*-**7** 及び *cis*-**7** の Swern 酸化と続くワンポット Julia オレフィン化により、*trans*-**19** 及び *cis*-**19** をそれぞれ得た。生成したオレフィンの還元と TES 基の除去を Pd/C を用いた接触還元によってワンポットで行った。最後にメチル基と TBS 基を除去し、*trans*-**22** 及び *cis*-**22** の合成を完了した。またこれらの構造が正しいことを X 線結晶構造解析によって証明した。



Scheme 26. Installation of a Side Chain and Completion of the Synthesis of *trans*- and *cis*-**22**

第 5 節　小員環を有する 3-ケトリトコール酸誘導体の合成

リトコール酸（LCA）やその代謝産物である 3-ケトリトコール酸（3-ketoLCA）は、ビタミン D3 骨格を持たないにも関わらず、ビタミン D 受容体（VDR）アゴニストとして働く胆汁酸である（Figure 6）[59]。さらに LCA の 3 位ヒドロキシ基がホルミル化やアセチル化された誘導体は、それぞれ 3 倍、30 倍の VDR アゴニスト活性を持つことが明らかになっている [59b]。LCA 誘導体はビタミン D3 骨格を持たないために、副作用の高カルシウム血症を誘発せず [59c]、ガンや白血病などの治療薬として期待されている。最近、LCA 誘導体による VDR のアゴニスト作用機構の解明を目指して、LCA 誘導体と VDR の複合体の結晶構造が解かれた [60]。その結果 LCA 誘導体は、VDR が結合するのと同じリガンド結合部位に結合するものの、その向きが逆転していることが明らかになった（Figure 7）。以上のように LCA 誘導体は、ビタミン D3 骨格を持たないにも関わらず、VDR アゴニスト活性を持つ興味深い化合物である。筆者はこれまでに確立した合成戦略を用いて、D 環に小員環を導入した新規 3-ketoLCA 誘導体の合成を行い、その活性評価を行うことで、小員環導入による側鎖固定化の医薬化学における有用性を評価することとした。

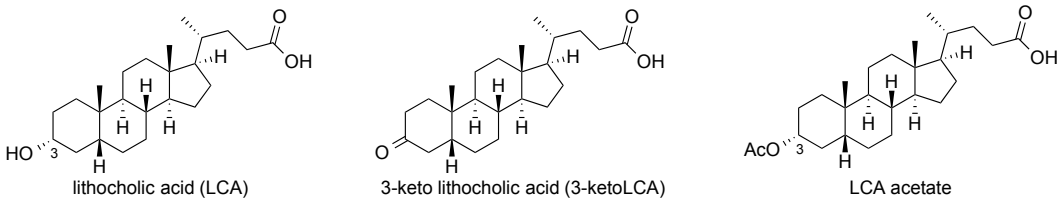


Figure 6. Bile acids as ligands for Vitamin D Receptor

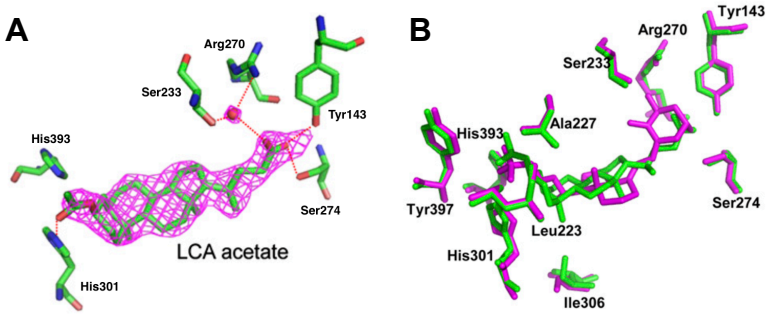
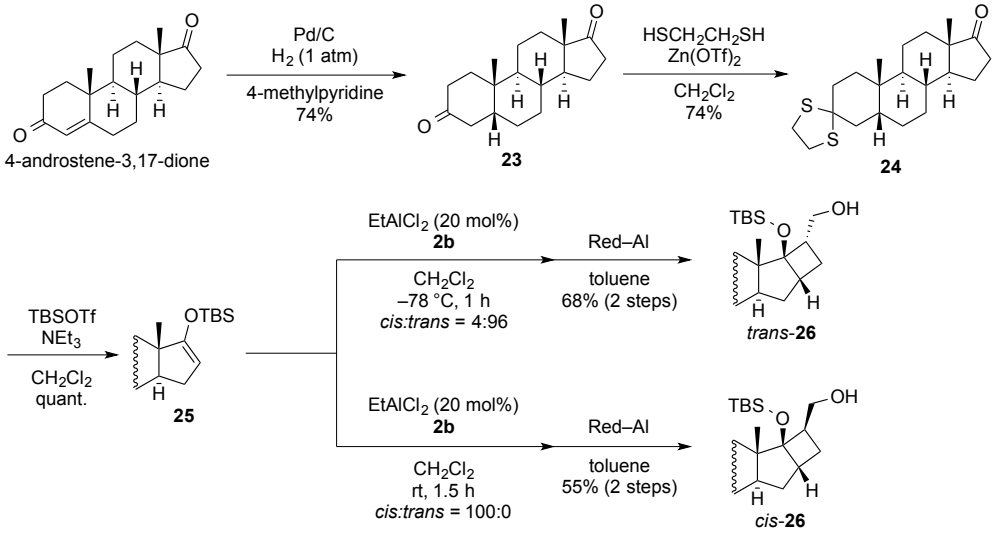


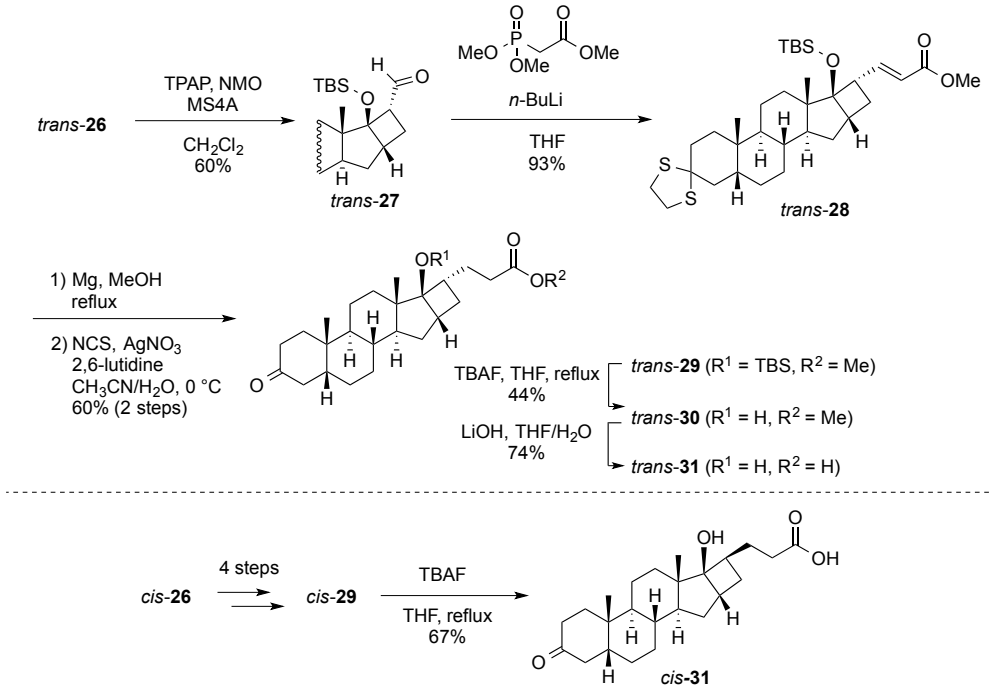
Figure 7. (A) Hydrogen-Bonding Network between VDR and LCA Acetate (B) Superposition of LCA Acetate (green) and Calcitriol (magenta) in VDR Complexes[60]

入手容易な 4-androstene-3,17-dione を原料に、まず D 環へのシクロブタン環の導入を目指した（Scheme 27）。A 環部の二重結合を接触水素化によって還元し[61]、A 環部ケトンをチオアセタールで保護した後、シリルエノールエーテル **25** へと誘導した。続いて温度制御下での **25** の[2+2]環化付加及びエステルの還元によって、シクロブタノール *trans*-, *cis*-**26** を立体選択的に作り分けた。



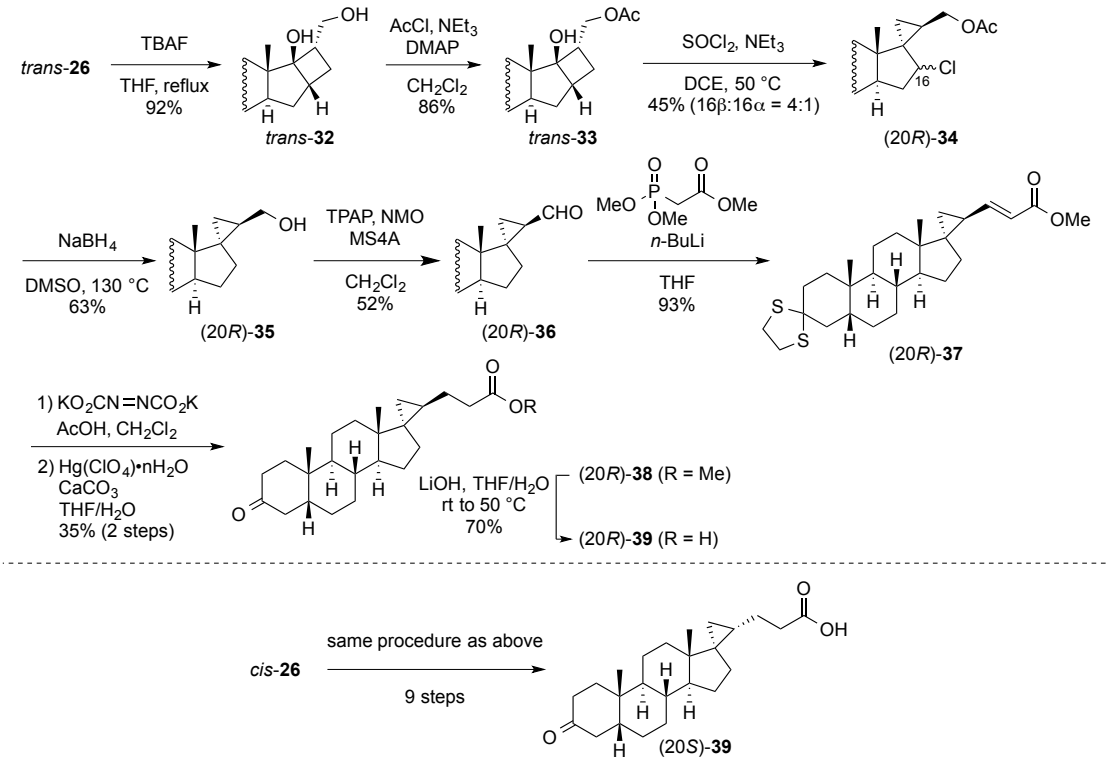
Scheme 27. Construction of a Cyclobutane Ring by Diastereo-Switchable [2+2] Cycloaddition

続いてシクロブタン環への炭素鎖の導入を目指した（Scheme 28）。シクロブタノール *trans*-**26** を TPAP でアルデヒド *trans*-**27** へと酸化した後、Horner–Wadsworth–Emmons 反応によって不飽和エステル *trans*-**28** を得た。生じた不飽和エステルを Mg/MeOH を用いて 1,4-還元し[62]、続いて NCS でチオアセタールの除去を行うことで *trans*-**29** を得た[63]。最後に TBS 基の除去とエステルの加水分解を行って、所望の *trans*-**31** を合成した。同様な方法でシクロブタノール *cis*-**26** から *cis*-**31** も合成したが、*cis*-**29** に対して TBAF を作用させると、TBS の除去とメチルエステルの加水分解が一挙に進行した。



Scheme 28. Completion of the Synthesis of *trans*-, and *cis*-**31**

次にスピロシクロプロパンを有する誘導体の合成を目指した（Scheme 29）。まずシクロブタノール *trans*-**26** の TBS 基の除去と第 1 級ヒドロキシ基のアセチル化、塩化チオニルを用いた環縮小転位によって(20*R*)-**34** を得た。続いて(20*R*)-**34** を DMSO 中 130 °C で水素化ホウ素ナトリウムを用いて還元し、TPAP 酸化と Horner–Wadsworth–Emmons 反応を経て不飽和エステル(20*R*)-**37** を合成した。生成した炭素–炭素二重結合の還元は、Mg/MeOH の条件では三員環の開環が起こるため、ジイミド還元で行った[55]。最後にチオアセタールの除去とエステルの加水分解を経て、(20*R*)-**39** を合成した。同様な方法で *cis*-**26** から(20*S*)-**39** の合成も達成した。



Scheme 29. Completion of the Synthesis of (20*R*)-, and (20*S*)-**39**

第 6 節　生物活性評価

合成した小員環を有する 3-ketoLCA 誘導体及びエストロン誘導体のビタミン D 受容体転写活性化能とエストロゲン受容体α及びβの転写活性化能を、ルシフェラーゼレポーターアッセイによって評価した。その結果 *trans*-**22**, *cis*-**22**, (20*R*)-**18**, (20*S*)-**18** は、ナチュラルリガンドであるカルシトリオールよりは弱いものの、ビタミン D 受容体転写活性化能を有することがわかった（Figure 8A）。また *trans*-**22** 及び *cis*-**22** はエストロゲン受容体α転写活性化能を示し（Figure 8B）、さらに *trans*-**22** はエストロゲン受容体β転写活性化能も有することがわかった（Figure 8C）。ケトリトコール酸誘導体 *trans*-**31**, *cis*-**31** 及び(20*R*)-**39**, (20*S*)-**39** は、どの受容体に対してもほとんど活性を示さなかった。(20*R*)-**18** 及び(20*S*)-**18** はビタミン D 受容体アゴニストとして働く一方で、エストロゲン受容体α及びβの転写活性化能を抑制していることから、エストロゲン受容体α及びβのインバースアゴニストとして働くことが示唆された。

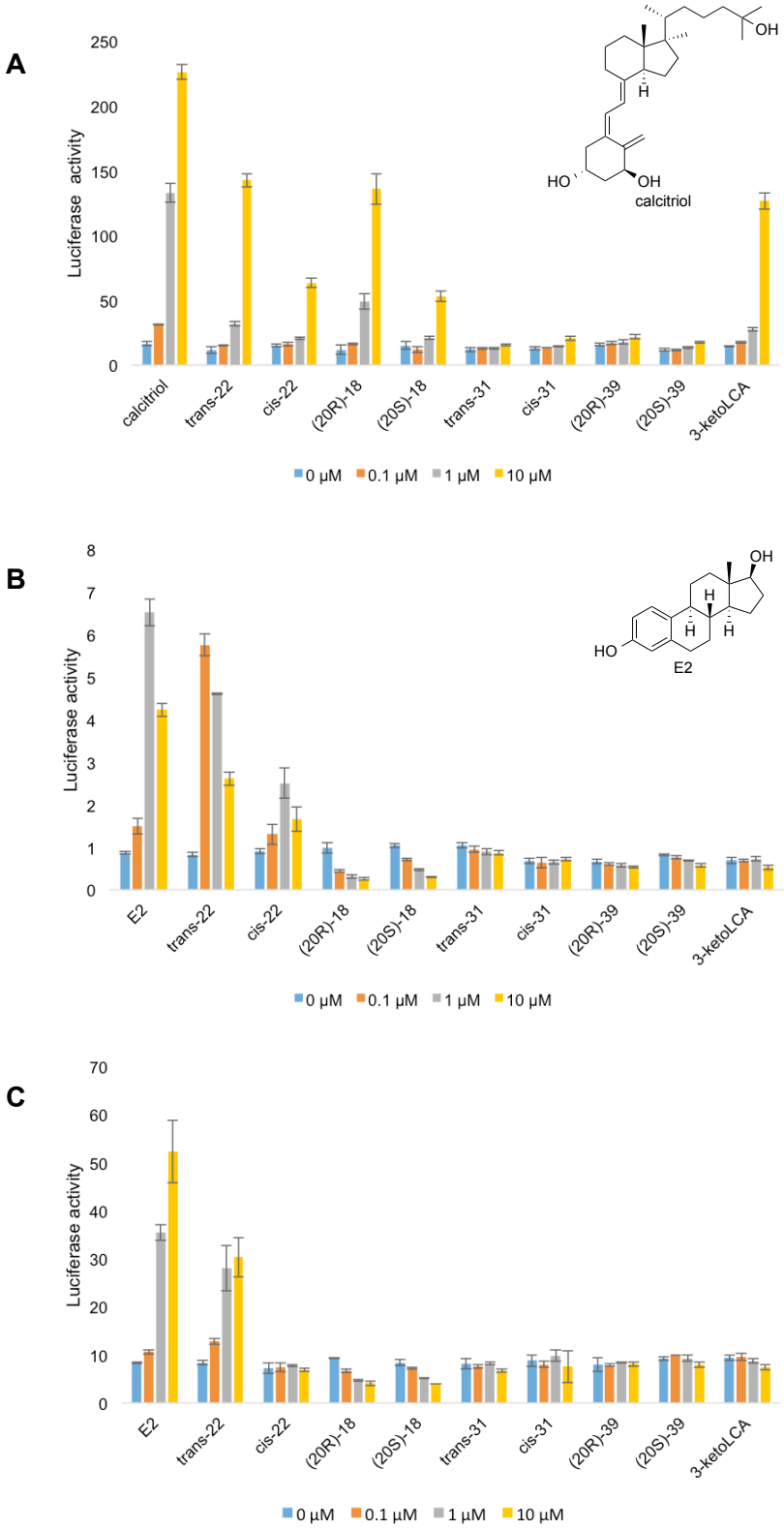
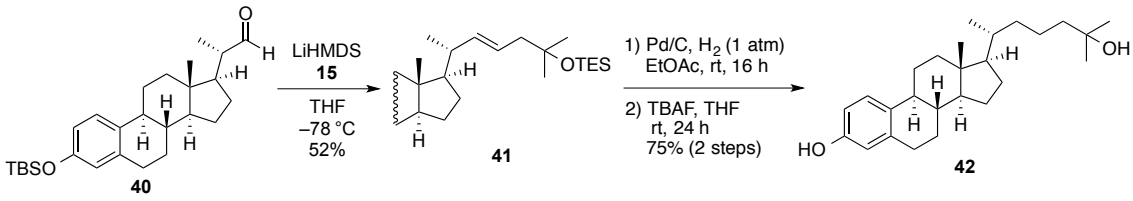


Figure 8. Transcriptional Activation of Nuclear Receptors (A) Vitamin D Receptor (B) Estrogen Receptor α (C) Estrogen Receptor β. E2; 17β-estradiol. Calcitriol and E2 were used at the concentrations of 0, 0.01, 0.1, 1 nM.

次に小員環導入によるビタミン D 受容体転写活性化能への影響を調べるため、小員環を排除したエストロン誘導体 **42** を既知化合物であるアルデヒド **40** から合成し（Scheme 30）[64]、小員環の有無によるビタミン D 受容体転写活性化能の差異を評価した（Figure 9）。その結果、小員環を持たない **42** は、小員環を有する誘導体 *trans*-**22** や(20*R*)-**18** より高い potency を持ち、*trans*-**22** と(20*R*)-**18** の EC_{50} がそれぞれ 4.1 μM と 35 μM である一方、**42** の EC_{50} は 0.85 μM と見積もられた。しかしながら、小員環を有する *trans*-**22** と(20*R*)-**18** は、**42** より高い最大活性化能を持つことがわかった。この結果は、*trans*-**22** や(20*R*)-**18** が SRC-1 などの VDR の coactivator の結合を促進、あるいは N-CoR などの corepressor の解離を促進することで高い efficacy を示した可能性を示唆する [65]。



Scheme 30. Synthesis of **42**

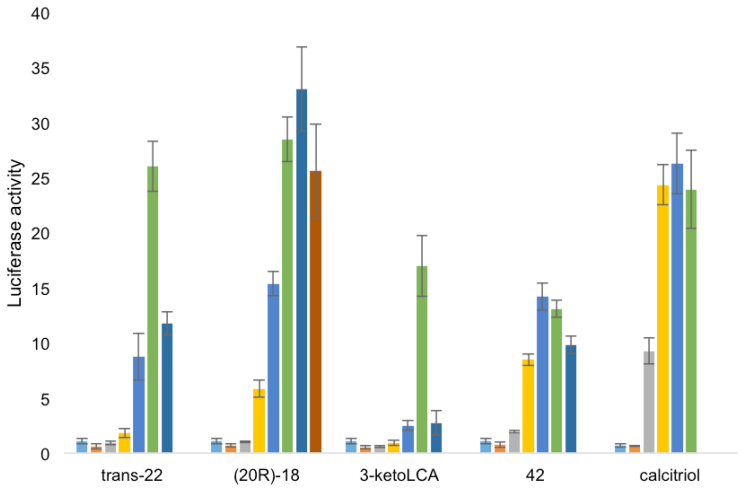
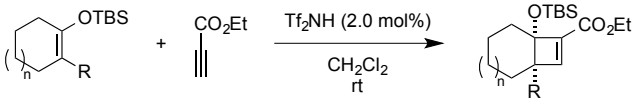


Figure 9. Transcriptional Activation of Vitamin D Receptor. *Trans*-**22** and **42** were used at the concentrations of 0, 0.1, 0.3, 1, 3, 10, 30 μM (left to right). (20*R*)-**18** was used at the concentrations of 0, 0.1, 0.3, 1, 3, 10, 30, 100, 180 μM (left to right). 3-KetoLCA was used at the concentrations of 0, 0.1, 0.3, 1, 3, 10, 30, 100 μM (left to right). Calcitriol was used at the concentrations of 0, 0.01, 0.1, 1, 10, 100 nM (left to right).

第 3 章　面性不斉短寿命中間体を経由する縮環シクロブテンの環拡大反応

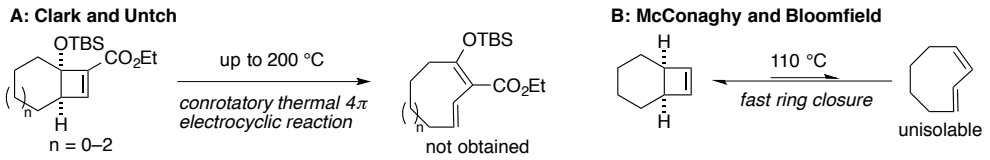
第 1 節　背景

シクロブテンはその大きな歪みに由来した高い反応性を持つため、様々な分子変換の可能性を持った魅力的な化合物である。当研究室では以前に、トリフリックイミド（Tf_2NH）を酸触媒として用いたシリルエノールエーテルとプロピオール酸エステルの[2+2]環化付加反応を報告している（Scheme 31）[10c,10d]。シクロブテンの実用的合成法は未だに限られている現状の中、この反応を用いれば、縮環シクロブテンが簡便かつ大スケールで合成できる。近年、小員環化合物の炭素–炭素結合を切断する過程を取り入れた手法で、分子骨格を作る研究が国内外で精力的に行われているが、これまで縮環シクロブテンを基質とした反応はほとんど報告例がなかった[45]。そこで筆者は、縮環シクロブテンの合成素子としての可能性に興味を持った。



Scheme 31. Catalytic [2+2] Cycloaddition to Afford Fused Cyclobutenes

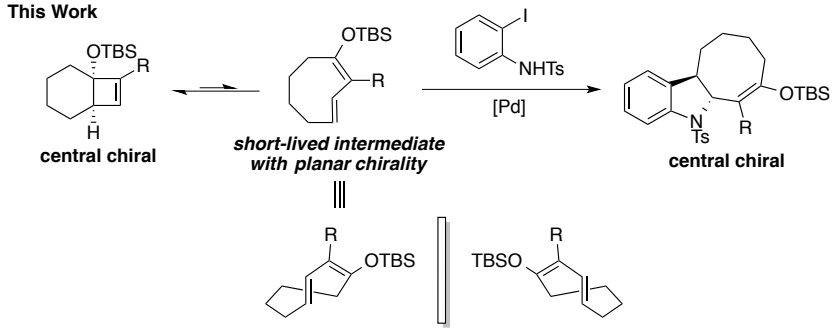
過去に Clark と Untch は、単環性シクロブテンの熱的 4π電子環状反応は速やかに進行する一方で、縮環シクロブテンは 200 °C まで加熱しても所望の開環は進行しないことを報告していた（Scheme 32A）[9a]。この縮環シクロブテンの開環が進行しないのは、熱的電子環状反応が Woodward-Hofmann 則に従って同旋的に進行すると、生成物である *cis*,*trans*-シロキシジエンの中員環内に *trans*-二重結合を生成することになり、その歪みが非常に大きいためであると考察されている。一方で McConaghy と Bloomfield は、bicyclo[4.2.0]octene の熱的電子環状反応は 110 °C 程度の温度でも進行するものの、原料を再生する速い逆反応のために開環体を単離できないことを報告していた（Scheme 32B）[66]。この McConaghy らの報告から、Clark らの縮環シクロブテンでも同様に開環体 *cis*,*trans*-シロキシジエンが一時的には生成している可能性があり、この短寿命な中間体を中員環合成へ利用できるのではないかと考えた。



Scheme 32. Previous Reports on Thermal Ring Opening of Fused Cyclobutenes

中員環は天然物や医薬品等の生物活性物質にも広く存在する基本骨格であるにも関わらず、その効率的構築法の開発は未だ現代有機化学の重要な課題の一つである。一般的に鎖状分子の分子内閉環反応による中員環の構築は、エントロピー及びエンタルピー的に不利であるために困難である [67]。別の中員環合成の戦略として、Grob/Wharton 開裂に代表されるような縮環化合物の環拡大反応が挙げられ [68]、この反応はこれまでに多くの天然物合成にも利用されてきた。環拡大反応では、環化反応での中員環合成において分子間反応を抑制する目的で用いられる高希釈条件が不要であるという利点がある。環拡大による中員環の構築は生合成経路においても利用されていることから [69]、合理的な手法と言える。

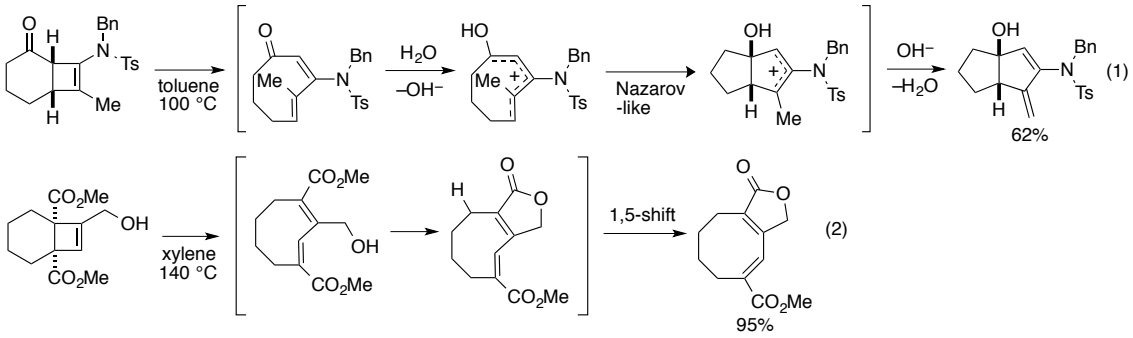
さらに筆者は、*cis*,*trans*-シロキシジエン短寿命中間体の面性不斉に着目した。ある種の *trans*-シクロアルケンは面性不斉を持ち、環の大きさがその立体化学的安定性に大きく影響することが知られている。例えば、*trans*-シクロオクテンは室温で立体化学的に安定である一方 ($t_{1/2}$ = 10^5 years at 30 °C)、より環の員数が大きい *trans*-シクロノネン ($t_{1/2}$ = 6 s at 30 °C) や *trans*-シクロデセン ($t_{1/2}$ = 10^{-4} s at 30 °C) は容易に環反転できるため、室温では光学活性体として単離することが困難である [29]。筆者は、*cis*,*trans*-シロキシジエン短寿命中間体の面性不斉を介した不斉転写を伴う中員環合成法の開発に興味を持ち、短寿命中間体の *trans*-二重結合をパラジウム触媒で捕捉するアプローチでの中員環縮環型インドリンの合成を着想した (Scheme 33)。すなわち、この反応で光学活性な縮環シクロブテンを用いた場合に、電子環状反応によってその不斉点が完全に消滅しても、短寿命中間体の面性不斉を介して、光学活性な生成物が得られるのではないかと期待した。



Scheme 33. Palladium-Catalyzed Ring Expanding Reaction of Fused Cyclobutenes via Short-Lived Intermediates with Planar Chirality

ごく最近になって、本研究で志向したような *cis*,*trans*-シクロアルカジエン短寿命中間体を経由する反応が報告され始めた (Scheme 34)。Krenske/Houk/Hsung らは、*cis*,*trans*-シクロオクタジエノン中間体に対し、系中に微量存在する水分子が酸触媒として働き、ナザロフ型の反応が進行した後、脱プロトン化によって二環性第三級アルコールが得られることを

報告した（eq. 1）[70]。また Milburn らの報告では、*cis*,*trans*-シクロオクタジエン中間体において、ヒドロキシ基が分子内のエステルに求核攻撃し、続く 1,5-ヒドリドシフトによるオレフィンの異性化を経て、中員環縮環型ラクトンを得ている（eq. 2）[71]。しかしながらこれらはいずれも、不安定中間体を分子内反応で捕捉した例であり、またその面性不斉への着目は見られない。本研究のように分子間反応での短寿命中間体の捕捉は、より挑戦的な課題である。且つ、本研究は短寿命中間体の面性不斉を介した不斉中員環合成も志向しており、有機合成化学だけでなくモレキュラーキラリティーの観点からも意義深いと言える。

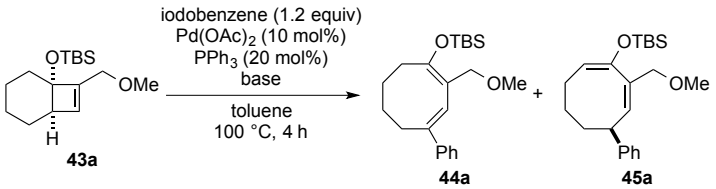


Scheme 34. Recently Reported Reactions via Short–Lived *cis*,*trans*-Cycloalkadienes

第 2 節　パラジウム触媒を用いたアリール化を伴う環拡大反応の最適化

まず *cis*,*trans*-シロキシジエン短寿命中間体の *trans*-二重結合をパラジウム触媒で捕捉することが可能であるかを検証するため、Heck 反応の条件による縮環シクロブテンのアリール化を伴う環拡大反応を試みた（Table 3）。縮環シクロブテン **43a** とヨードベンゼンを酢酸パラジウム及びトリフェニルホスフィン、*N*,*N*-ジイソプロピルエチルアミン（DIPEA）存在下、トルエン中 100 °C で 4 h 撹拌したところ、*cis*,*cis*-シロキシジエン **44a** が 34%収率で得られた（entry 1）。炭酸カリウムや炭酸セシウムなどの無機塩基を用いた場合、**44a** の収率は低下し、位置異性体である **45a** が副生物として得られた（entries 2 and 3）。塩基として銀塩を試したところ、**44a** の収率の向上が見られ、炭酸銀を用いた場合に最も高い収率で **44a** が得られた（entries 4–6）。また炭酸銀を 2.0 当量から 1.0 当量まで減らしても、同様な結果であった（entries 6 and 7）。

Table 3. A Screen of Bases for Arylative Ring Expansion[a]

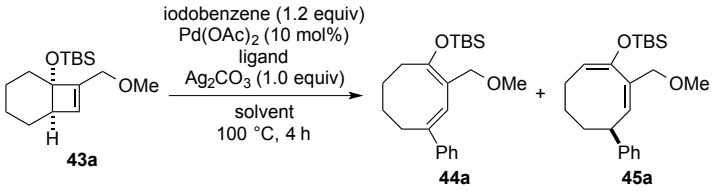


entry	base (equiv)	yield **44a** (%)[b]	yield **45a** (%)[b]
1	DIPEA (2.0)	34	0
2	K_2CO_3(2.0)	8	3
3	Cs_2CO_3 (2.0)	27	3
4	Ag_3PO_4 (2.0)	45	4
5	AgOAc (2.0)	74	9
6	Ag_2CO_3 (2.0)	79	5
7	Ag_2CO_3 (1.0)	84	6

[a]Reactions performed on a 0.2 mmol scale in toluene (2.0 mL). [b]Isolated yields.

次に配位子及び溶媒の検討を行った（Table 4）。しかしながら、トリフェニルホスフィンに代えて単座ホスフィン配位子（entries 2–4）や二座ホスフィン配位子（entries 5–9）を用いても、**44a** の収率及び選択性の向上は見られなかった。DMF や DMSO、CH_3CN などの配位性溶媒を用いると、シロキシジエン **44a** 及び **45a** はほとんど得られず、**44a** 或いは **45a** が脱シリル化されて生成したと考えられるα,β-不飽和ケトンが 40%程度の収率で得られるのみであった（entries 10–12）。ジクロロエタンや 1,4-ジオキサンの場合、**44a** の収率は 65%程度に留まり（entries 13, 14）、THF の場合では多くの原料が回収され、**44a** が低収率で得られるのみであった(entry 15)。以上の結果より、塩基として 1.0 当量の炭酸銀を用い、配位子にトリフェニルホスフィン、溶媒にトルエンを用いる条件を、アリール化を伴う環拡大反応の最適条件とした。

Table 4. Screens of Ligands and Solvents for Arylative Ring Expansion[a]



entry	ligand (equiv)	solvent	yield **44a** (%)[b]	yield **45a** (%)[b]
1	PPh_3 (0.2)	toluene	84	6
2	P(*o*-tol)$_3$ (0.2)	toluene	7	3
3	P(2-furyl)$_3$ (0.2)	toluene	31	19
4	PCy_3 (0.2)	toluene	19	45
5	dppf (0.1)	toluene	66	14
6	dppe (0.1)	toluene	27	8
7	dppp (0.1)	toluene	38	32
8	dppb (0.1)	toluene	31	30
9	Xantphos (0.1)	toluene	8	10
10	PPh_3 (0.2)	DMF	trace	0
11	PPh_3 (0.2)	DMSO	0	0
12	PPh_3 (0.2)	CH_3CN	trace	0
13	PPh_3 (0.2)	dichloroethane	66	7
14	PPh_3 (0.2)	1,4-dioxane	65	8
15	PPh_3 (0.2)	THF	17	0

[a]Reactions performed on a 0.2 mmol scale in solvent (2.0 mL). [b]Isolated yields.

第 3 節　基質一般性の検討

アリール化を伴う環拡大反応の最適条件を用いて、本反応の基質適用範囲を調べた（Figure 10）。シクロブテン上の置換基がメチル基やエトキシカルボニル基でも反応は円滑に進行した（**44b** and **44c**）。電子求引性置換基であるホルミル基や電子供与性置換基のメトキシ基を有するヨウ化アリールも適用可能であった（**44d** and **44e**）。2-ヨードチオフェンや3-ヨードピリジンなどの複素環を用いた場合でも、反応速度の低下は見られたが、**44f**（64%）及び **44g**（42%）が得られた。本反応は、七員環が縮環したシクロブテンにも適用可能で、対応する九員環が良好な収率で得られた（**44h** and **44i**）。なお **44i** は X 線結晶構造解析によって、その構造が正しいことを確認している。

次に反応が全く進行せず、原料回収に終わった基質を示す。五員環が縮環したシクロブテン **43b** や、ベンゼン環がさらに縮環した三環性シクロブテン **43c** の場合、それぞれ環の員数の減少と sp^2 炭素数の増加に起因して、*cis,trans*-シロキシジエン中間体の歪みが大きすぎるために反応が進行しなかったものと考えられる。四置換オレフィンを有する **43d** や核間位にメチル基を有する **43e** では、中間体の *trans*-オレフィンが三置換オレフィンとなり、その立体障害の増大のため、アリールパラジウム種への挿入が難しくなっていると考えられる。

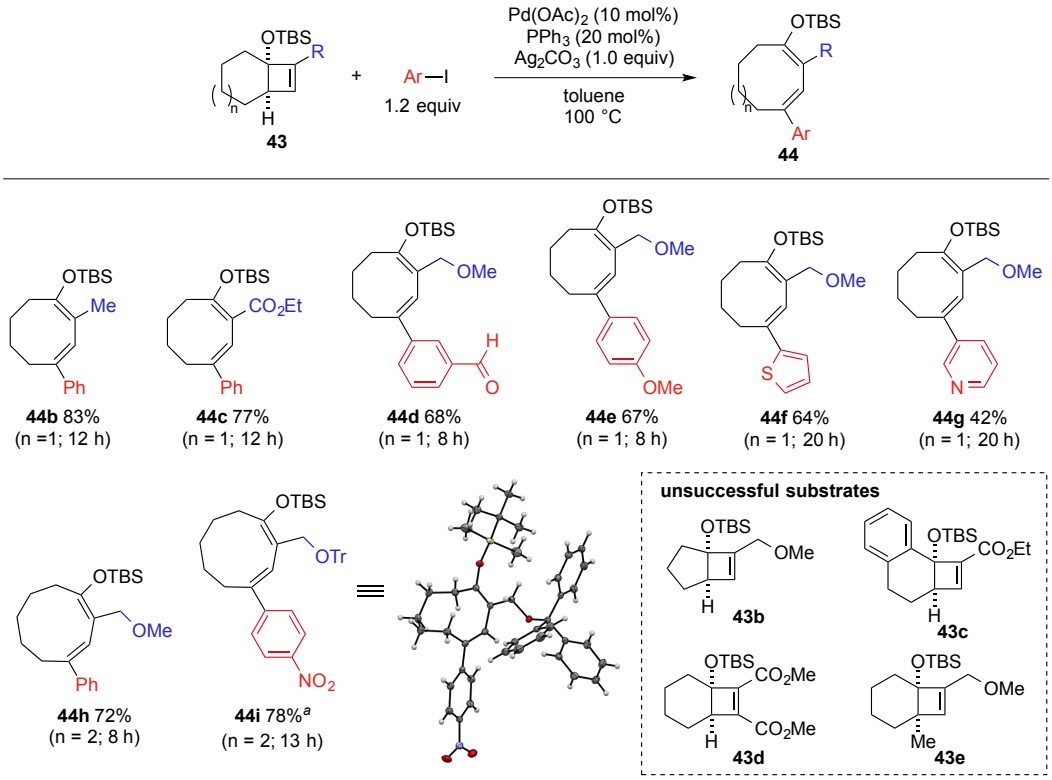
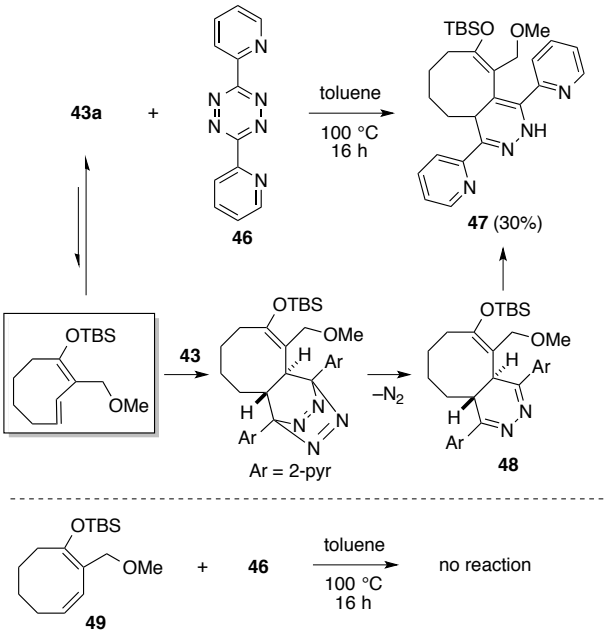


Figure 10. Substrate Scope of Arylative Ring Expansion. Reactions were performed on a 0.2 mmol scale in toluene (2.0 mL). Yields are those of isolated products. [a]1.2 mmol scale.

第 4 節　反応機構

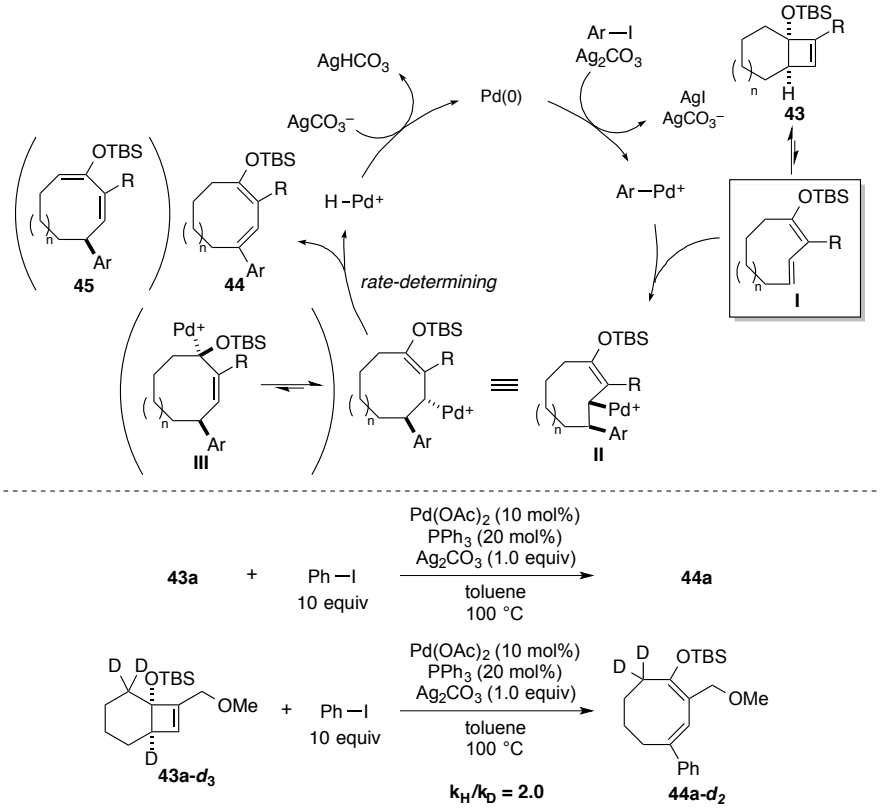
本反応が *cis,trans*-シロキシジエン短寿命中間体を経由していることを証明するため、*trans*-シクロオクテン誘導体との Diels–Alder 反応において、非常に高い反応性を示すことが知られているテトラジンを使った *cis,trans*-シロキシジエンの捕捉を試みた[72]。シクロブテン **43a** とテトラジン **46** を、パラジウム触媒の反応と同条件であるトルエン中 100 °C に加熱すると、原料 **43a** の回収とともに、*cis,trans*-シロキシジエンと **46** の逆電子要請型 Diels–Alder 反応と続く窒素の脱離を駆動力とした逆 Diels–Alder 反応を経て生成したと考えられる **47**

を単離することに成功した（Scheme 35）。しかしながら、**48** から **47** への速い互変異性化のために、**48** が *trans* に縮環していることを確認することはできなかった。一方で、別途合成した *cis*,*cis*-シロキシジエン **49** とテトラジン **46** との反応を同条件で行ったが、反応は全く進行しなかったことから、**47** が *cis*,*cis*-シロキシジエンを経由して生成している可能性は否定できる。以上の結果から、本反応条件で *cis*,*trans*-シロキシジエンが系中で生成していることを確認した。



Scheme 35. Trapping of the Short-Lived *cis*,*trans*-Siloxydiene by Diels–Alder Reaction

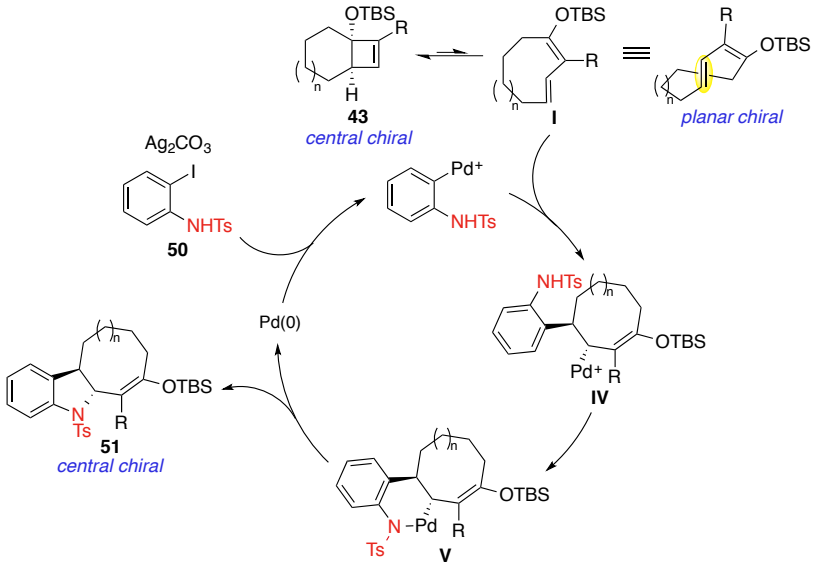
これまでの結果を踏まえて、反応機構を次のように提案する（Scheme 36）。まず、0 価パラジウムのヨウ化アリールへの酸化的付加と炭酸銀によるヨウ化物イオンの引き抜きにより、カチオン性アリールパラジウム種が生成する。このパラジウム種が、縮環シクロブテンの可逆な熱的電子環状反応によって一時的に生成する *cis*,*trans*-シロキシジエン **I** の *trans*-オレフィンに *syn* 付加し、アルキルパラジウム錯体 **II** が生成し、その炭素–炭素結合が回転すると、パラジウムとアリール基が *trans* に位置するようになる。続いてβ-水素脱離により生成物 **44** とともにパラジウムヒドリド種が生じるが、これは塩基による脱プロトン化を受けて、0 価パラジウムが再生する。位置異性体 **45** の生成は、**II** から **III** へのσ-π-σ相互変換と続くβ水素脱離によって説明できる。また速度論的同位体効果（KIE）の測定を行ったところ、シクロブテン **43a** とその重水素化体 **43a-*d*$_3$** を独立な系で反応させた場合に、KIE 値 2.0 が観測された [73]。この結果は、C–H 結合の切断が関与する β-水素脱離が本反応の律速段階にあることを示唆している。



Scheme 36. Proposed Catalytic Cycle for Arylative Ring Expansion and Kinetic Isotope Effect

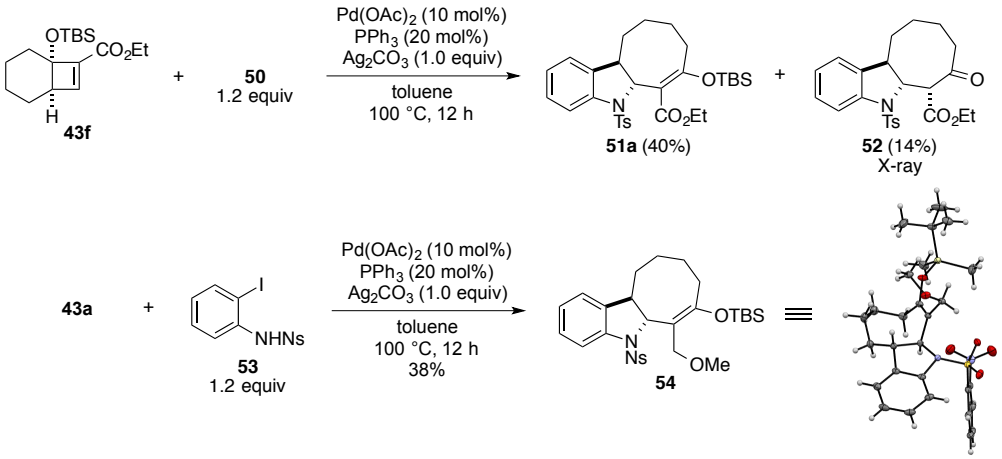
第 5 節　中員環縮環型インドリンの合成

短寿命である *cis*,*trans*-シロキシジエンを中員環合成に利用することに成功したので、続いて短寿命中間体の面性不斉に目を向けた。原料であるシクロブテンの中心性不斉が、短寿命中間体の面性不斉を介して、生成物のキラリティーに転写されるような反応が可能であるかを検証するため、キラルな生成物を与える反応系を設計した（Scheme 37）。すなわち、ヨウ化アリールとして *o*-ヨードアニリン誘導体 **50** を用いれば、アルキルパラジウム中間体 **IV** においてβ-水素脱離が進行するよりも速く六員環パラダサイクル **V** を形成し、続く還元的脱離によってキラルな中員環縮環型 *trans*-インドリン **51** が得られるのではないかと考えた。



Scheme 37. Working Hypothesis for Synthesis of *trans*-Indolines with Chirality Transfer

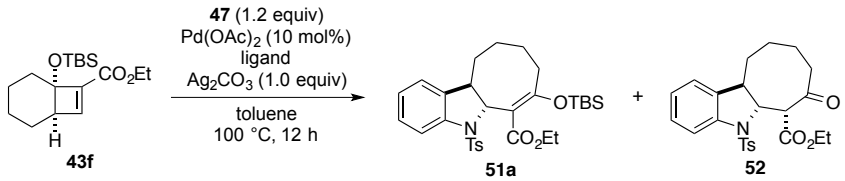
縮環シクロブテン **43f** とトシル基で保護された *o*-ヨードアニリン **50** を酢酸パラジウム及びトリフェニルホスフィン、炭酸銀存在下、トルエン中 100 °C で 12 h 撹拌したところ、*trans*-インドリン **51a**（40%, single diastereomer）とケトン **52**（14%）が得られた（Scheme 38）。なおケトン **52** の立体化学は、X 線結晶構造解析によって決定した。またシクロブテン **43a** とノシル基で保護された *o*-ヨードアニリン **53** から得られたインドリン **54** は、その X 線結晶構造解析から *trans* に縮環していることを証明しており、その類比から *trans*-インドリン **51a** の相対立体配置も決定した。



Scheme 38. Synthesis of Medium Ring Fused *trans*-Indolines

収率の向上を目指して、配位子のスクリーニングを行った（Table 5）。その結果、トリ 2-フリルホスフィンを用いた場合に、最も良い収率で **51a** が得られることがわかった（entry 3）。この最適条件を用いて、基質一般性を調べた（Table 6）。七員環が縮環したシクロブテン **43g** の反応では、良好な収率で九員環が縮環したインドリン **51b** を与えた。ベンゼン環がさらに縮環したシクロブテン **43h** では、インドリン **51c** が高収率で得られた（dr 9:1）。シクロブテン **43a** の反応では、配位子にトリフェニルホスフィンを用いた場合とは異なり（Scheme 38）、メトキシ基の脱離を伴ってエキソオレフィン **51d** が得られた。一方、窒素官能基を有するシクロブテン **43i** や **43j** では脱離は起こらず、インドリン **51e** 及び **51f** がそれぞれ得られた。

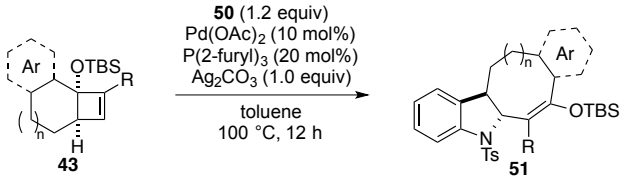
Table 5. A Screen of Ligands for Synthesis of *trans*-Indolines[a]

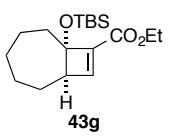
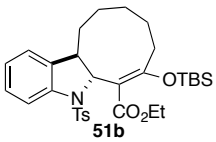
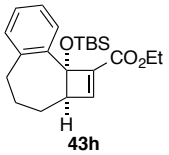
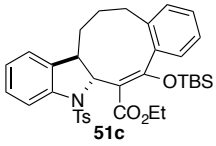
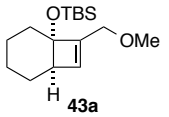
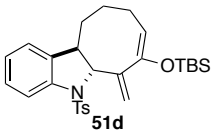
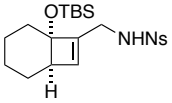
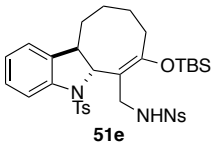
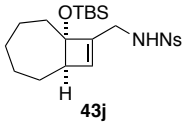
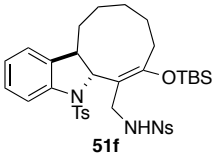


entry	ligand (equiv)	yield **51a** (%)[b]	yield **52** (%)[b]
1	PPh_3 (0.2)	40	14
2	P(*o*-tol)$_3$ (0.2)	24	19
3	P(2-furyl)$_3$ (0.2)	65	7
4	PCy_3 (0.2)	31	7
5	dppf (0.1)	30	8
6	dppe (0.1)	31	14
7	dppp (0.1)	26	25
8	dppb (0.1)	31	15
9	Xantphos (0.1)	18	37

[a]Reactions performed on a 0.2 mmol scale in toluene (2.0 mL). [b]Isolated yields.

Table 6. Substrate Scope for Synthesis of Medium Ring Fused *trans*-Indolines[a]



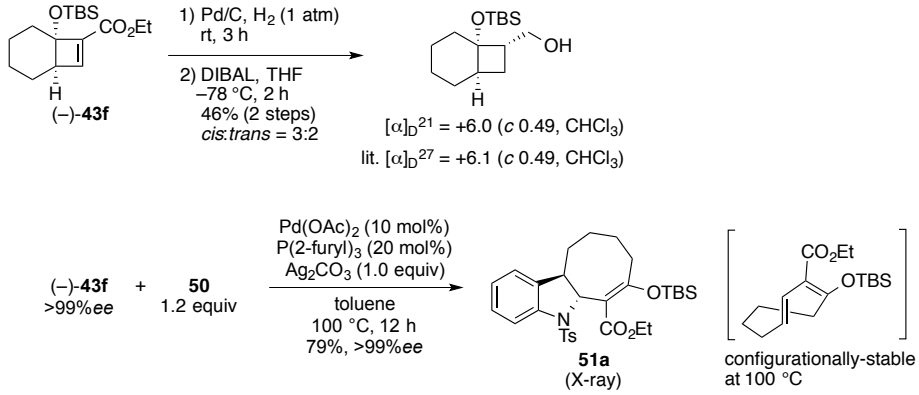
entry	substrate	product	yield (%)[b]
1			73
2			82 (dr 9:1)
3			54
4			53
5			63

[a]Reactions performed on a 0.2 mmol scale in toluene (2.0 mL). [b]Isolated yields.

第 6 節　不斉転写を利用した中員環縮環型インドリンの不斉合成

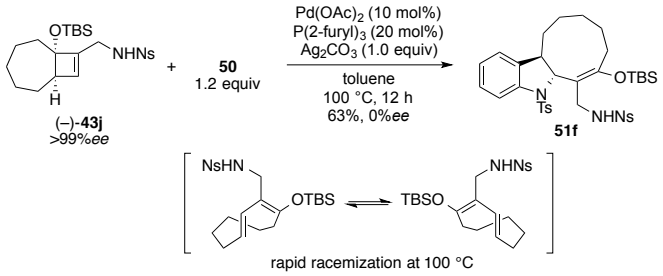
次に光学純粋な基質を用いて、生成物にキラリティーが転写されるかどうか調べた。光学純粋な基質は、キラル HPLC を用いた光学分割によって調製し、得られた(–)-**43f** を既知化合物へと誘導して旋光度の比較を行うことで、その絶対配置を決定した（Scheme 39）[10b]。光学純粋な(–)-**43f** を最適化した反応条件に付すと、不斉純度を全く損なうことなく光学活性なインドリン **51a** が得られた。なお生成物 **51a** の絶対立体配置は、X 線結晶構造解析によって決定している。光学純粋な(–)-**43f** のみをトルエン中 100 °C で 12 h 攪拌しても、不斉

純度の低下が全く見られなかったことから、**43f** の電子環状反応で生じる *cis,trans*-シロキシオクタジエン中間体は 100 °C でもラセミ化しない程の立体化学的安定性を有していることが示唆された。



Scheme 39. Determination of Absolute Configuration and Chirality Transfer Reaction of (–)-**43f**

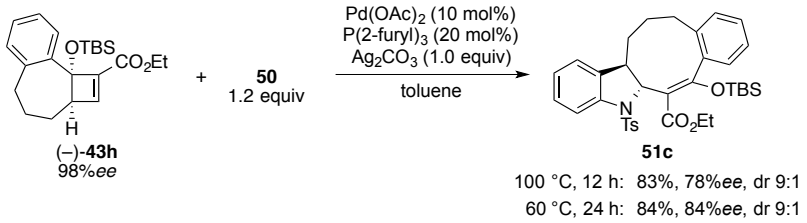
次に七員環が縮環したシクロブテンでも不斉が転写されるかを検証した（Scheme 40）。しかしながら光学純粋な(–)-**43j** を用いた反応では、キラリティーは全く保持されず、生成物 **51f** がラセミ体として得られた。光学純粋な(–)-**43j** のみをトルエン中 100 °C で 12 h 撹拌すると、完全にラセミ化したことから、**43j** の電子環状反応で生じる *cis,trans*-シロキシノナジエン中間体は立体化学的に不安定であることが示唆された。この結果は、*trans*-シクロアルケンの立体化学的安定性が環の員数に強く影響されることに一致する。



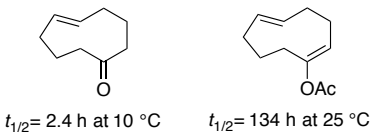
Scheme 40. Chirality Transfer Reaction of (–)-**43j**

一方で七員環が縮環したシクロブテンでも、ベンゼン環がさらに縮環した三環性シクロブテン(–)-**43h** では、20%程度のラセミ化を伴うものの、光学活性な **51c** (78%*ee*)が得られることがわかった（Scheme 41）。また反応温度を 60 °C まで低下させた場合、生成物 **51c** の鏡像体過剰率は 84%*ee* まで向上した。光学活性な(–)-**43h** (98%*ee*)のみをトルエン中 100 °C で 12 h 撹拌すると、鏡像体過剰率は 69%*ee* まで低下したことから、**43h** から生じる *cis,trans*-シロキシノナジエン中間体は 100 °C で動的な面性不斉を有していることが確認された。ベ

ンゼン環が縮環した(–)-**43h** の反応では、生成物に不斉が保持されるという結果を解釈するにあたり、友岡らは(*E*)-5-cyclononen-1-one よりも対応するエノラートの方が、ラセミ化半減期が長く、sp^2 炭素数の増加が立体化学的安定性を向上させることを報告している（Scheme 42）[32e]。よって(–)-**43h** は、ベンゼン環を導入したことによる sp^2 炭素数の増加に起因して、*cis*,*trans*-シロキシノナジエン中間体が立体化学的により安定となり、完全にはラセミ化せず不斉転写が進行したと考えられる。



Scheme 41. Chirality Transfer Reaction of (–)-**43h**



Scheme 42. Dynamic Chirality of (*E*)-5-Cyclononen-1-one and its Enolate

第 4 章　結論

以上のように筆者は、当研究グループで開発した触媒的[2+2]環化付加反応の応用として、メディシナルケミストリーと新規反応開発の観点から小員環の有用性の拡張を目指した研究を展開した。

小員環の特性である剛直な配座を生物活性分子の側鎖固定化に利用することを考え、ステロイドをモデル化合物と設定し、小員環を導入した誘導体を合成した。興味深いことに、ステロイド D 環部の[2+2]環化付加は反応温度を制御することで、シクロブタンの両ジアステレオマーを作り分けることが可能であった。また立体特異的なシクロブタノールの環縮小転位を利用することで、スピロシクロプロパンの 2 種類のジアステレオマーも合成できる。すなわち[2+2]環化付加及び環縮小転位を用いる本合成戦略では、4 種類の小員環を有するステロイドを立体分岐的に合成できる。合成した誘導体の核内受容体の転写活性化能を測定した結果、小員環を有するいくつかの誘導体が、小員環を持たない誘導体と比較して、より高いビタミン D 受容体転写活性化能を有することがわかった。この結果は、生物活性分子の活性の増大に、小員環導入による側鎖固定化が有効である可能性を示唆する。

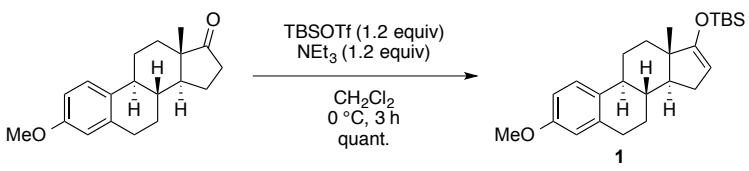
[2+2]環化付加によって簡便且つ大スケールで合成できる縮環シクロブテンの合成素子としての有用性の開拓を目指し、パラジウム触媒を用いた環拡大反応を開発した。反応機構を詳細に調べたところ、縮環シクロブテンの熱的電子環状反応によって、*cis,trans*-シロキシジエンが中間体として短寿命ながら生成していることが明らかになった。その短寿命中間体を外部反応剤で捕捉するアプローチで、一般的に分子内閉環反応での合成が困難な中員環を良好な収率で構築することができ、シクロブテンの合成素子としての有用性を示すことができた。さらに筆者は、*cis,trans*-シロキシジエン短寿命中間体の面性不斉に着目し、シクロブテンの中心性不斉が、短寿命中間体の面性不斉を介して生成物の中心性不斉に転写されるという興味深い現象を確認した。このような中間体の面性不斉を介する不斉記憶型反応の報告例は極めて限定的であり、有機合成だけでなく不斉研究の観点からも本研究成果は意義深いと自負している。本研究を一つの契機として、小員環化合物や *trans*-シクロアルケンをはじめとする歪んだ化合物の更なる有用性の発掘や多角的な応用を期待したい。

実験項

General Remarks

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware. Dehydrated solvents were purchased for the reactions and used without further desiccation. Reagents were purchased and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck TLC silica gel 60 F_{254}. Column chromatography was performed using Fuji Silysia BW-200 silica gel. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA 500 instrument. The ^{1}H chemical shifts were calibrated with internal tetramethylsilane (TMS, 0 ppm) in deuterated organic solvents. The ^{13}C chemical shifts are reported relative to $CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm), acetone-d_6 (206.7 and 30.4 ppm), MeOH-d_4 (49.0 ppm) or THF-d_8 (67.4 and 25.3 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Low-resolution mass spectra (LRMS) were recorded on a SHIMADZU GCMS-QP2010 SE spectrometer (EI) or a JEOL MS700 spectrometer (FAB). High-resolution mass spectra (HRMS) were recorded on a JEOL MS700 spectrometer (FAB) or a SHIMADZU LCMS-IT-TOF fitted with an ESI. IR experiments were recorded on a SHIMADZU IRAffinity-1 spectrometer. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. All melting points were determined using a Yamato MP-21 melting point apparatus and are uncorrected. Optical rotations were obtained on a JASCO P-1030 polarimeter. X-ray diffraction data were recorded on a RIGAKU R-AXIS RAPID system. High performance liquid chromatography (HPLC) analyses were performed on a SHIMADZU analytical system equipped with two LC-20AT pumps and a SPD-20A UV/Vis detector using YMC CHIRAL Amylose-SA column (250 × 4.6 mm). Preparative HPLC was performed on a YMC LC-forte/R using YMC CHIRAL Amylose-SA column (250 × 20 mm). Compounds **40**,[64] **S1**,[45a] **S2**,[45a] **S4**,[10d] **S5**,[10c] **S8**,[45a] dipotassium azodicarboxylate,[74] and cyclohexanone-d_4[75] were prepared according to previous procedures.

Compound 1



To a solution of estrone 3-methyl ether (20.1 g, 70.6 mmol) in CH_2Cl_2 (176 mL) were added triethylamine (12 mL, 84 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.6 mL, 29 mmol) at 0 °C. The mixture was stirred for 3 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give **1** (31.0 g, quant.) as a white solid, which was used in the next step without further purification. Analytical sample was obtained by column chromatography (hexane/ethyl acetate 20:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.5 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 4.47 (dd, *J* = 2.9, 1.2 Hz, 1H), 3.77 (s, 3H), 2.93-2.83 (m, 2H), 2.32 (m, 1H), 2.25 (m, 1H), 2.10 (ddd, *J* = 13.7, 5.7, 2.9 Hz, 1H), 1.93–1.87 (m, 2H), 1.80 (m, 1H), 1.62-1.35 (m, 5H), 0.94 (s, 9H), 0.86 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 157.4, 138.1, 133.1, 126.0, 113.8, 111.3, 98.4, 55.2, 54.0, 44.8, 44.6, 37.2, 33.6, 29.7, 28.1, 27.1, 26.3, 25.7, 18.1, 15.4, –4.6, –5.0 ppm.

LRMS (FAB) *m*/*z* 398 (M).

Anal. Calcd for $C_{25}H_{38}O_2Si$: C, 75.32; H, 9.61. Found: C, 75.19; H, 9.45.

IR ($CHCl_3$) ν = 2927, 2855, 1616, 1252 cm^{-1}.

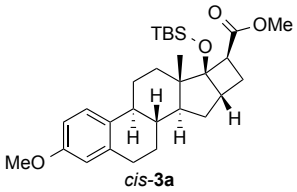
mp 123–126 °C.

$[\alpha]_D^{23}$ +82.0 (*c* 1.6, $CHCl_3$).

General Procedure for the [2+2] Cycloaddition

A Schlenk tube equipped with a magnetic stirrer bar was charged with silyl enol ether (0.2 mmol) and α,β-unsaturated ester (0.4 mmol) in dichloromethane (0.8 mL). At the appropriate temperature, a 1.0 M solution of ethylaluminum dichloride in hexane (0.04 mL, 0.04 mmol) was dropwise added to the resulting solution. After being stirred for the appropriate time, the resulting mixture was quenched with triethylamine at the same temperature. To the mixture, saturated aqueous Rochelle salt was added and stirred vigorously for 30 min. The aqueous layer was extracted with $CHCl_3$ twice, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford desired cyclobutanes.

Compound *cis*-3a



cis-**3a**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.32 (dd, *J* = 9.2, 8.6 Hz, 1H), 2.90–2.80 (m, 3H), 2.64 (dd, *J* = 7.2, 7.2 Hz, 1H), 2.40–2.35 (m, 1H), 2.26 (ddd, *J* = 11.5, 10.9, 4.3 Hz, 1H), 1.95–1.89 (m, 1H), 1.67 (ddd, *J* = 12.9, 12.9, 4.0 Hz, 1H), 1.65–1.43 (m, 6H), 1.40 (ddd, *J* = 11.5, 11.2, 7.2 Hz, 1H), 1.32 (ddd, *J* = 12.3, 9.2, 2.6 Hz, 1H), 0.86 (s, 9H), 0.71 (s, 3H), 0.25 (s, 3H), 0.10 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 157.5, 137.9, 132.7, 126.4, 113.8, 111.5, 91.0, 55.2, 51.4, 48.4, 46.9, 44.3, 42.9, 40.5, 38.6, 31.7, 30.1, 29.8, 27.7, 26.1, 26.0, 23.2, 18.2, 14.2, –1.4, –2.9 ppm.

LRMS (FAB) *m*/*z* 484 (M).

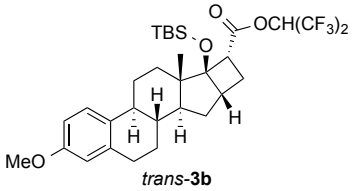
Anal. Calcd for $C_{29}H_{44}O_4Si$: C, 71.85; H, 9.15. Found: C, 71.67; H, 8.99.

IR ($CHCl_3$) ν = 2930, 2857, 1737, 1609 cm^{-1}.

mp 179–181 °C.

$[\alpha]_D^{24}$ +66.0 (*c* 1.3, $CHCl_3$).

Compound *trans*-3b



trans-**3b**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J*= 8.6, 2.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 5.76 (sep, $^3J_{(H,F)}$ = 6.0 Hz, 1H), 3.77 (s, 3H), 3.46 (dd, *J* = 10.9, 9.2 Hz, 1H), 2.88–2.84 (m, 2H), 2.68–2.62 (m, 1H), 2.29 (ddd, *J* = 13.8, 10.9, 10.6 Hz, 1H), 2.24–2.14 (m, 2H), 1.99–1.89 (m, 2H), 1.72 (ddd, *J* = 13.8, 9.2, 5.5 Hz, 1H), 1.70–1.64 (m, 1H), 1.58–1.30 (m, 6H), 0.92 (s, 9H), 0.74 (s, 3H), 0.26 (s, 3H), 0.16 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 157.4, 137.9, 132.6, 126.3, 120.6 (q, $^1J_{(C,F)}$ = 276.4 Hz), 113.7, 111.4, 92.6, 66.7 (sep, $^2J_{(C,F)}$ = 34.9 Hz), 55.2, 48.7, 48.5, 46.4, 43.3, 43.0, 38.7, 33.0, 30.6, 29.8, 27.7, 26.2, 25.5, 21.5, 18.1, 16.5, –3.0, –3.5 ppm.

LRMS (FAB) *m*/*z* 620 (M).

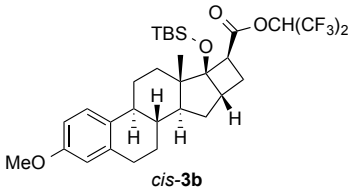
Anal. Calcd for $C_{31}H_{42}F_6O_4Si$: C, 59.98; H, 6.82. Found: C, 59.95; H, 6.56.

IR ($CHCl_3$) ν = 2932, 2859, 1769, 1610 cm^{-1}.

mp 139–140 °C.

$[\alpha]_D^{29}$ –4.2 (*c* 1.0, $CHCl_3$).

Compound *cis*-3b



cis-**3b**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 5.63 (sep, $^3J_{(H,F)}$ = 6.0 Hz, 1H), 3.78 (s, 3H), 3.54 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.90–2.86 (m, 2H), 2.82 (ddd, *J* = 12.6, 10.0, 9.8 Hz, 1H), 2.74–2.70 (m, 1H), 2.42–2.37 (m, 1H), 2.30 (ddd, *J* = 11.5, 10.6, 4.6 Hz, 1H), 1.95–1.89 (m, 1H), 1.69–1.57 (m, 4H), 1.54–1.37 (m, 5H), 0.84 (s, 9H), 0.73 (s, 3H), 0.32 (s, 3H), 0.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 157.5, 137.8, 132.5, 126.4, 120.6 (q, $^1J_{(C,F)}$ = 280.0 Hz), 113.8, 111.5, 92.1, 66.9 (sep, $^2J_{(C,F)}$ = 34.9 Hz), 55.2, 48.8, 47.2, 44.2, 42.2, 40.5, 38.5, 31.3, 29.8, 29.4, 27.7, 26.0, 25.7, 23.3, 18.2, 14.1, –1.0, –2.7 ppm.

LRMS (FAB) *m*/*z* 620 (M).

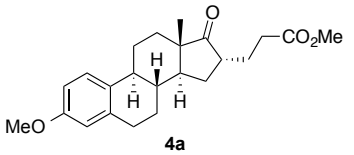
Anal. Calcd for $C_{31}H_{42}F_6O_4Si$: C, 59.98; H, 6.82. Found: C, 59.91; H, 6.95.

IR ($CHCl_3$) ν = 2932, 2860, 1782, 1610 cm^{-1}.

mp 147–150 °C.

$[\alpha]_D^{31}$ +54.0 (*c* 2.2, $CHCl_3$).

Compound 4a



4a

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 2.89 (br t, *J* = 4.8 Hz, 2H), 2.47–2.37 (m, 4H), 2.30–1.88 (m, 5H), 1.74–1.45 (m, 8H), 0.94 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 221.1, 173.6, 157.6, 137.7, 132.0, 126.3, 113.9, 111.6, 55.2, 51.6, 48.8, 48.2, 44.0, 43.8, 38.3, 32.5, 31.7, 39.6, 27.6, 26.50, 26.47, 25.8, 14.5 ppm.

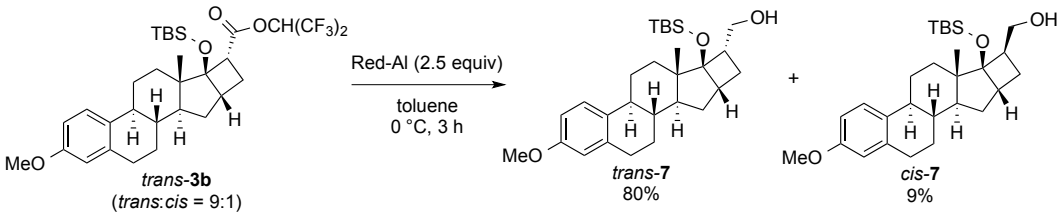
LRMS (FAB) *m*/*z* 370 (M).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{20}H_{30}O_4Na$ 393.2042; Found 393.2028.

IR (KBr) ν = 2947, 1747, 1732, 1608, 1501 cm^{-1}.

$[\alpha]_D^{24}$ +58.0 (*c* 0.3, $CHCl_3$).

Compound *trans*-7



To a solution of a mixture of *trans*- and *cis*-**3b** (21.0 g, 33.8 mmol, 9:1) in toluene (135 mL) was added a 3.6 M solution of Red-Al in toluene (24 mL, 86 mmol) at 0 °C. After being stirred for 3 h, the reaction mixture was quenched with saturated aqueous Rochell salt, and stirred vigorously for 30 min. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a white solid, which was purified by column chromatography (hexane/ethyl acetate 9:1) to afford *trans*-**7** (12.4 g, 80%) as a white solid along with *cis*-**7** (1.39 g, 9%). Analytical sample was obtained by recrystallization from hexane/ethyl acetate as white blocks.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 4.01 (ddd, *J* = 10.0, 10.0, 6.0 Hz, 1H), 3.86 (ddd, *J* = 9.7, 9.7, 5.8 Hz, 1H), 3.78 (s, 3H), 2.89–2.77 (m, 3H), 2.58–2.51 (m, 1H), 2.36 (ddd, *J* = 12.0, 12.0, 9.8 Hz, 1H), 2.30–2.22 (m, 2H), 1.98–1.89 (m, 1H), 1.81–1.71 (m, 2H), 1.62–1.34 (m, 6H), 1.22 (br s, 1H), 0.97 (ddd, *J* = 12.9, 8.6, 4.9 Hz, 1H), 0.90 (s, 9H), 0.74 (s, 3H), 0.22 (s, 3H), 0.13 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 138.0, 132.6, 126.4, 113.8, 111.5, 90.4, 62.7, 55.2, 50.6, 48.3, 47.5, 43.9, 41.6, 38.9, 33.2, 31.9, 29.9, 27.9, 26.5, 25.8, 24.6, 18.2, 17.2, –2.7, –3.1 ppm.

LRMS (EI) *m*/*z* 456 (M), 441 (M–Me).

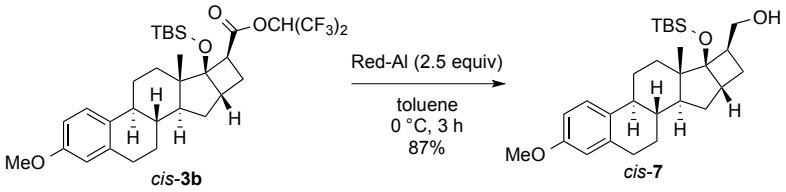
Anal. Calcd for $C_{28}H_{44}O_3Si$: C, 73.63; H, 9.71. Found: C, 73.38; H, 9.93.

IR ($CHCl_3$) ν = 3494 (br), 2949, 2855, 1250 cm^{-1}.

mp 189–191 °C.

$[\alpha]_D^{20}$ +14.2 (*c* 1.00, $CHCl_3$).

Compound *cis*-7



To a solution of *cis*-**3b** (8.04 g, 13.0 mmol) in toluene (65 mL) was added 3.6 M Red-Al in toluene (9.0 mL, 32 mmol) at 0 °C. After being stirred for 3 h, the reaction mixture was quenched with saturated aqueous Rochell salt, and stirred vigorously for 30 min. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a white solid, which was purified by column chromatography (hexane/ethyl acetate 9:1) to afford *cis*-**7** (5.17g, 87%) as a white solid. Analytical sample was obtained by recrystallization from hexane/acetate as white blocks.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 3.83 (ddd, *J* = 10.9, 10.9, 2.3 Hz, 1H), 3.78 (s, 3H), 3.49 (ddd, *J* = 10.9, 10.9, 5.8 Hz, 1H), 2.89–2.86 (m, 2H), 2.78–2.67 (m, 1H), 2.66–2.59 (m, 1H), 2.41–2.31 (m, 1H), 2.25 (ddd, *J* = 10.9, 10.9, 3.4 Hz, 1H), 1.94–1.83 (m, 2H), 1.81 (dd, *J* = 10.9, 1.7 Hz, 1H), 1.71–1.59 (m, 3H), 1.53–1.40 (m, 5H), 1.29 (ddd, *J* = 12.4, 9.2, 2.9 Hz, 1H), 0.94 (s, 9H), 0.73 (s, 3H), 0.30 (s, 3H), 0.16 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) d 157.4, 137.9, 132.7, 126.4, 113.8, 111.4, 90.7, 63.8, 55.2, 47.9, 46.4, 44.1, 39.3, 38.9, 38.4, 31.9, 29.8, 29.7, 27.7, 26.1, 26.0, 24.2, 18.4, 14.5, –1.2, –2.3 ppm.

LRMS (FAB) *m*/*z* 457 (M+H).

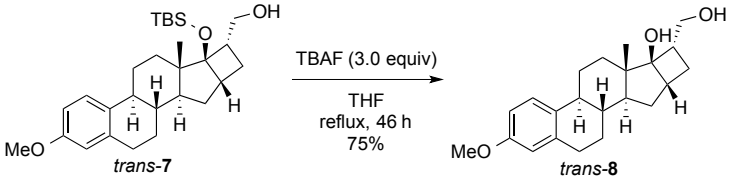
Anal. Calcd for $C_{28}H_{44}O_3Si$: C, 73.63; H, 9.71. Found: C, 73.36; H, 9.91.

IR ($CHCl_3$) ν = 3500 (br), 2929, 2856, 1253 cm^{-1}.

mp 204–205 °C.

$[\alpha]_D^{20}$ +29.2 (*c* 1.00, $CHCl_3$).

Compound *trans*-8



A mixture of *trans*-**7** (7.74 g, 16.9 mmol) and a 1.0 M solution of TBAF in THF (51 mL, 51 mmol) was heated under reflux for 46 h. After cooling to room temperature, the resulting mixture was

diluted with $CHCl_3$, and washed with water. The aqueous layer was extracted with $CHCl_3$, dried over Na_2SO_4. Concentration *in vacuo* and purification by column chromatography (ethyl acetate) gave *trans*-**8** (4.30 g, 75%) as a pale yellow solid. Analytical sample was obtained by recrystallization from ethyl acetate as white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.9 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 4.04 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.84 (dd, *J* = 8.6, 8.6 Hz, 1H), 3.78 (s, 3H), 2.89–2.76 (m, 3H), 2.42–2.25 (m, 4H), 1.96–1.91 (m, 2H), 1.88 (ddd, *J* = 11.5, 11.5, 5.7 Hz, 1H), 1.79 (ddd, *J* = 12.0, 3.6, 3.3 Hz, 1H), 1.72 (ddd, *J* = 12.7, 12.7, 3.9 Hz, 1H), 1.57–1.36 (m, 6H), 1.03–0.95 (m, 1H), 0.84 (s, 3H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ 157.0, 137.5, 132.2, 126.2, 113.4, 111.5, 87.2, 60.9, 54.8, 50.2, 47.9, 46.7, 43.4, 41.1, 38.6, 32.7, 31.6, 29.4, 27.4, 26.2, 25.0, 16.4 ppm.

LRMS (EI) *m*/*z* 342 (M), 324 (M–H_2O), 309 (M–H_2O–Me).

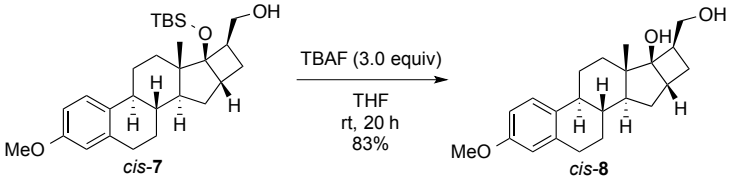
Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 76.88; H, 9.00.

IR ($CHCl_3$) ν = 3287 (br), 2974, 2924, 2859, 1709, 1636, 1501, 1350, 1254, 1184 cm^{-1}.

mp 199–201 °C.

$[\alpha]_D^{20}$ +25.2 (*c* 1.00, THF).

Compound *cis*-8



A mixture of *cis*-**7** (34.4 g, 75.4 mmol) and a 1.0 M solution of TBAF in THF (226 mL, 226 mmol) was stirred at room temperature for 20 h. The resulting mixture was diluted with $CHCl_3$, and washed with water. The aqueous layer was extracted with $CHCl_3$, dried over Na_2SO_4. Concentration *in vacuo* and purification by column chromatography (hexane/ethyl acetate 3:2) gave *cis*-**8** (15.0 g, 83%) as a white solid. Analytical sample was obtained by recrystallization from ethyl acetate as white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 1H), 6.73 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 3.85–3.74 (m, 2H), 3.78 (s, 3H), 2.93–2.82 (m, 2H), 2.62–2.55 (m, 1H), 2.50 (s, 1H), 2.41–2.32 (m, 2H), 2.28–2.20 (m, 2H), 2.17–2.09 (m, 1H), 1.97–1.89 (m, 1H), 1.69 (ddd, *J* = 11.2, 11.2, 5.5 Hz, 1H), 1.56–1.36 (m, 7H), 1.27 (ddd, *J* = 12.6, 9.5, 3.5 Hz, 1H), 0.80 (s, 3H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ 157.0, 137.4, 132.3, 126.2, 113.4, 111.4, 86.6, 62.3, 54.9, 48.6,

45.4, 43.6, 40.4, 38.3, 37.9, 31.5, 29.4, 29.3, 27.3, 25.8, 24.9, 13.9 ppm.

LRMS (EI) *m*/*z* 342 (M), 324 (M–H_2O).

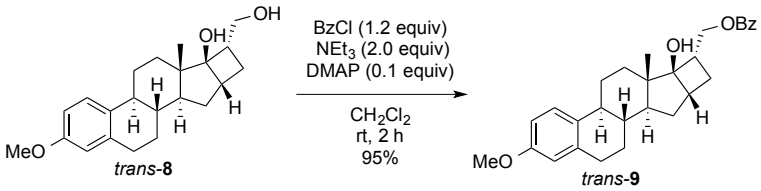
Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.43; H, 8.89.

IR (KBr) ν = 3264 (br), 2932, 2920, 2859, 1609, 1499, 1236 cm^{-1}.

mp 203–205 °C (dec.).

$[\alpha]_D^{20}$ +36.5 (*c* 1.00, $CHCl_3$).

Compound *trans*-9



To a suspension of *trans*-**8** (3.10 g, 9.05 mmol) and DMAP (112 mg, 0.917 mmol) in CH_2Cl_2 (36 mL) were added triethylamine (2.5 mL, 18 mmol) and benzoyl chloride (1.3 mL, 11 mmol). After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid. The residue was purified by column chromatography (hexane/ethyl acetate 4:1 to 1:1) to yield *trans*-**9** (3.85 g, 95%) as a white solid. Analytical sample was obtained by recrystallization from hexane/ethyl acetate as white crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.44 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 4.63 (dd, *J* = 11.2, 7.7 Hz, 1H), 4.58 (dd, *J* = 10.9, 8.9 Hz, 1H), 3.78 (s, 3H), 3.10–3.03 (m, 1H), 2.93–2.83 (m, 2H), 2.49–2.41 (m, 2H), 2.33–2.27 (m, 2H), 1.96–1.91 (m, 2H), 1.85–1.80 (m, 1H), 1.71 (ddd, *J* = 12.4, 12.4, 2.3 Hz, 1H), 1.62–1.56 (m, 2H), 1.52–1.38 (m, 3H), 1.18–1.10 (m, 1H), 0.86 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 157.4, 137.8, 132.9, 132.4, 130.2, 129.5, 128.3, 126.3, 113.7, 111.4, 88.5, 64.4, 55.1, 48.7, 47.2, 45.7, 43.6, 42.2, 38.9, 32.7, 31.6, 29.8, 27.7, 26.3, 24.1, 16.1 ppm.

LRMS (EI) *m*/*z* 446 (M), 428 (M–H_2O).

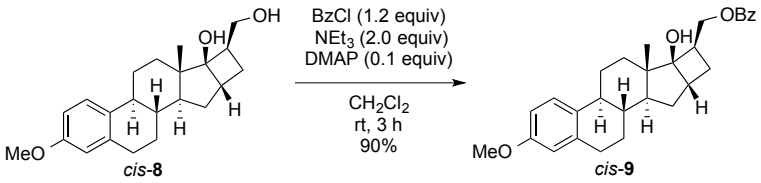
Anal. Calcd for $C_{29}H_{34}O_4$: C, 78.00; H, 7.67. Found C, 77.84; H, 7.67.

IR ($CHCl_3$) ν = 3491 (br), 2936, 2866, 1713, 1609, 1501, 1450, 1273, 1219 cm^{-1}.

mp 168–169 °C.

$[\alpha]_D^{20}$ +23.3 (*c* 1.00, $CHCl_3$).

Compound *cis*-9



To a suspension of *cis*-**8** (5.32 g, 15.5 mmol) and DMAP (191 mg, 1.56 mmol) in CH_2Cl_2 (62 mL) were added triethylamine (4.3 mL, 31 mmol) and benzoyl chloride (2.2 mL, 19 mmol). After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid. The residue was purified by column chromatography (hexane/ethyl acetate 4:1) to yield *cis*-**9** (6.25 g, 90%) as a white solid. Analytical sample was obtained by recrystallization from hexane/ethyl acetate as white crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.58 (tt, *J* = 7.5, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 1H), 6.68 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.63 (d, *J* = 2.9 Hz, 1H), 4.75 (dd, *J* = 11.5, 9.8 Hz, 1H), 4.24 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.76 (s, 3H), 2.92–2.77 (m, 3H), 2.43–2.38 (m, 1H), 2.26–2.16 (m, 2H), 2.10–2.02 (m, 1H), 1.95–1.88 (m, 1H), 1.75–1.67 (m, 1H), 1.60 (ddd, *J* = 12.3, 12.3, 8.3 Hz, 1H), 1.55–1.34 (m, 7H), 0.80 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 157.4, 137.9, 133.0, 132.5, 130.1, 129.5, 128.4, 126.2, 113.7, 111.3, 87.1, 65.2, 55.1, 49.7, 46.0, 44.0, 40.0, 38.6, 35.3, 31.4, 29.8, 29.6, 27.6, 26.0, 24.4, 13.8 ppm.

LRMS (EI) *m*/*z* 446 (M).

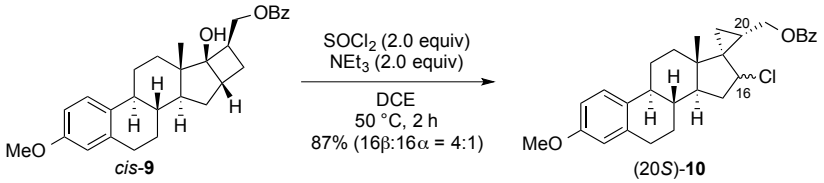
Anal. Calcd for $C_{29}H_{34}O_4$: C, 78.00; H, 7.67. Found C, 77.91; H, 7.81.

IR ($CHCl_3$) ν = 3464 (br), 2932, 2862, 1713, 1605, 1501, 1450, 1277 cm^{-1}.

mp 126–128 °C.

$[\alpha]_D^{20}$ +38.6 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-10



To a solution of *cis*-**9** (6.15 g, 13.8 mmol) in dichloroethane (69 mL) were added triethylamine (3.8 mL, 28 mmol) and thionyl chloride (2.0 mL, 28 mmol). After being stirred at 50 °C for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to afford (20*S*)-**10** (5.60 g, 87%, dr 4:1) as a white solid. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample. The following data are for the major diastereomer of (20*S*)-**10**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.45 (dd, *J* = 8.1, 8.1 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 4.74 (dd, *J* = 11.7, 6.0 Hz, 1H), 4.44 (dd, *J* = 11.5, 8.6 Hz, 1H), 4.32 (dd, *J* = 8.3, 5.2 Hz, 1H), 3.78 (s, 3H), 2.94–2.82 (m, 2H), 2.78 (ddd, *J* = 13.5, 8.0, 8.0 Hz, 1H), 2.34–2.26 (m, 1H), 2.25–2.17 (m, 1H), 2.00 (ddd, *J* = 13.5, 13.5, 5.4 Hz, 1H), 1.93–1.85 (m, 1H), 1.58–1.35 (m, 5H), 1.31–1.22 (m, 2H), 1.17 (s, 3H), 1.08 (ddd, *J* = 12.9, 12.9, 4.1 Hz, 1H), 0.49 (dd, *J* = 5.7, 5.7 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 157.5, 137.8, 132.8, 132.2, 130.6, 129.6, 128.3, 126.2, 113.8, 111.6, 67.0, 66.8, 55.2, 52.5, 43.8, 43.7, 42.4, 39.6, 39.0, 32.8, 29.7, 27.6, 25.7, 19.3, 18.9, 17.7 ppm.

LRMS (EI) *m*/*z* 464 (M), 429 (M–Cl), 342 (M–BzOH), 307 (M–Cl–BzOH).

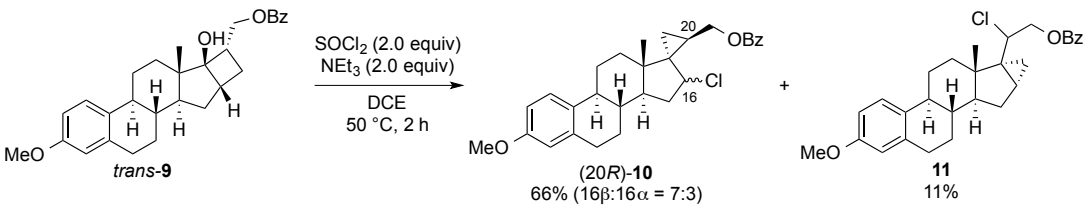
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{29}H_{33}ClO_3Na$ 487.2010; Found 487.2018.

IR ($CHCl_3$) ν = 2932, 2859, 1717, 1609, 1501, 1450, 1258, 1177, 1111 cm^{-1}.

mp 177–179 °C.

$[\alpha]_D^{20}$ +54.7 (*c* 1.00, $CHCl_3$).

Compounds (20*R*)-10 and 11



To a solution of *trans*-**9** (1.51 g, 3.38 mmol) in dichloroethane (17 mL) were added triethylamine (0.93 mL, 6.7 mmol) and thionyl chloride (0.49 mL, 6.8 mmol). After being stirred at 50 °C for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to afford (20*R*)-**10** (1.03 g, 66%, dr 7:3) as a white solid and **11** (173 mg, 11%) as a pale yellow oil. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample.

Data for the major diasteromer of (20*R*)-**10**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 6.9 Hz, 1H), 7.46 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 4.51 (dd, *J* = 11.2, 8.3 Hz, 1H), 4.40 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.96 (dd, *J* = 8.0, 6.3 Hz, 1H), 3.78 (s, 3H), 2.94–2.82 (m, 2H), 2.70–2.63 (m, 1H), 2.34–2.21 (m, 2H), 1.98–1.82 (m, 3H), 1.65 (ddd, *J* = 11.8, 3.2, 3.2 Hz, 1H), 1.58–1.36 (m, 5H), 1.17 (s, 3H), 1.13 (dd, *J* = 5.2, 5.2 Hz, 1H), 0.79 (dd, *J* = 9.5, 4.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 157.5, 137.7, 132.9, 132.1, 130.3, 129.6, 128.3, 126.2, 113.7, 111.5, 69.5, 64.8, 55.2, 53.3, 43.6, 43.3, 41.9, 38.5, 38.3, 36.7, 29.6, 27.5, 25.9, 22.7, 19.2, 17.5 ppm.

LRMS (EI) *m*/*z* 464 (M), 429 (M–Cl), 342 (M–BzOH), 307 (M–Cl–BzOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{29}H_{33}ClO_3Na$ 487.2010; Found 487.2011.

IR ($CHCl_3$) ν = 2936, 1717, 1609, 1501, 1450, 1273, 1111 cm^{-1}.

mp 60–63 °C.

$[\alpha]_D^{20}$ +29.3 (*c* 1.00, $CHCl_3$).

Data for compound **11**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 4.93 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.29 (dd, *J* = 11.5, 7.8 Hz, 1H), 4.23 (dd, *J* = 11.5, 6.1 Hz, 1H), 3.77 (s, 3H), 2.91–2.80 (m, 2H), 2.36–2.29 (m, 1H), 2.21–2.08 (m, 2H), 1.87–1.80 (m, 1H), 1.72–1.64 (m, 2H), 1.55–1.48 (m, 3H), 1.41 (ddd, *J* = 11.8, 11.8, 4.0 Hz, 1H), 1.37–1.30 (m, 1H), 1.14 (d, *J* = 6.3, 4.0 Hz, 1H), 1.10–1.04 (m, 1H), 1.01 (s, 3H), 0.68 (dd, *J* = 8.3, 6.9 Hz, 1H) ppm.

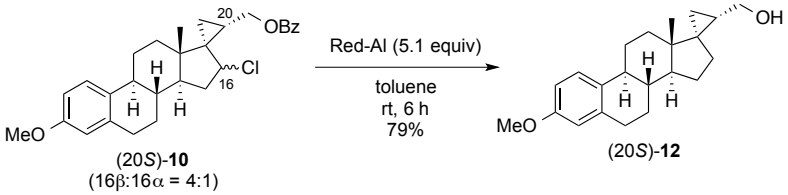
^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 157.5, 137.8, 133.3, 132.7, 129.72, 129.68, 128.5, 126.1, 113.8, 111.4, 66.2, 60.4, 55.2, 45.9, 44.3, 42.9, 39.0, 37.4, 35.0, 29.7, 27.9, 26.6, 26.3, 24.6, 17.7,

10.5 ppm.

LRMS (FAB) *m*/*z* 464 (M), 429 (M–Cl), 307 (M–Cl–BzOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{29}H_{33}ClO_3Na$ 487.2010; Found 487.2021.

Compound (20*S*)-12



To a solution of compound (20*S*)-**10** (2.09 g, 4.50 mmol, dr 4:1) in toluene (23 mL) was added a 3.6 M Red-Al solution in toluene (6.3 mL, 23 mmol) under argon at 0 °C. After being stirred at room temperature for 6 h, the reaction was quenched with saturated aqueous Rochell salt. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. The crude material was purified by column chromatography (hexane/diethyl ether 7:3) to afford (20*S*)-**12** (1.17 g, 79%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 3.64 (br m, 1H), 3.53 (br m, 1H), 2.91–2.82 (m, 2H), 2.28–2.18 (m, 2H), 2.10–2.03 (m, 1H), 1.94–1.87 (m, 2H), 1.50–1.39 (m, 6H), 1.25–1.18 (m, 2H), 1.11 (ddd, *J* = 12.6, 12.6, 4.0 Hz, 1H), 0.99–0.92 (m, 2H), 0.81 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 138.0, 132.8, 126.2, 113.7, 111.4, 65.1, 55.1, 53.3, 43.9, 41.4, 39.5, 36.3, 33.2, 29.9, 29.0, 27.8, 26.1, 24.6, 19.8, 17.2, 16.2 ppm.

LRMS (EI) *m*/*z* 326 (M), 308 (M–H_2O).

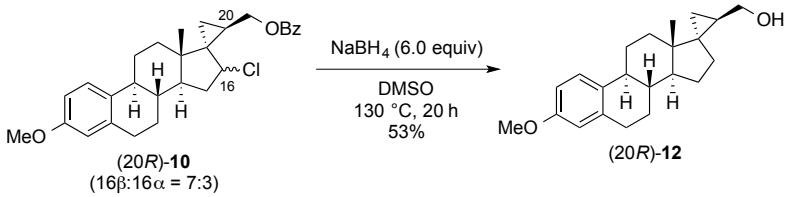
Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found C, 80.68; H, 9.54.

IR ($CHCl_3$) ν = 3410 (br), 3009, 2932, 2866, 1609, 1501, 1450, 1219 cm^{-1}.

mp 112–113 °C.

$[\alpha]_D^{20}$ +27.1 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-12



A mixture of (20*R*)-**10** (1.59 g, 3.42 mmol), $NaBH_4$ (776 mg, 20.5 mmol) and DMSO (14 mL) was stirred for 20 h at 130 °C. After cooling to room temperature, water was added to the mixture. The aqueous layer was extracted with hexane/ethyl acetate (4:1), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was partially purified by column chromatography (hexane/diethyl ether 1:1) to give (20*R*)-**12** (584 mg, 53%) as a white gum.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 3.87 (dd, *J* = 10.9, 6.3 Hz, 1H), 3.77 (s, 3H), 3.54 (dd, *J* = 10.9, 10.9 Hz, 1H), 2.93–2.78 (m, 2H), 2.31–2.17 (m, 2H), 2.14–2.03 (m, 1H), 1.97–1.89 (m, 1H), 1.88–1.78 (m, 1H), 1.58–1.30 (m, 8H), 1.17–1.11 (m, 1H), 0.89 (s, 3H), 0.67 (dd, *J* = 4.6, 4.6 Hz, 1H), 0.42 (dd, *J* = 8.3, 4.3 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 137.9, 132.6, 126.2, 113.7, 111.4, 63.1, 55.1, 54.5, 43.5, 41.4, 39.1, 36.6, 35.8, 29.8, 27.6, 26.4, 25.0, 24.6, 17.1 ppm (two signals missing).

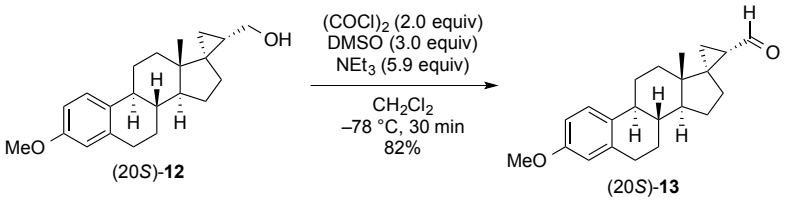
LRMS (EI) *m*/*z* 326 (M).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{22}H_{30}O_2Na$ 349.2138; Found 349.2145.

IR ($CHCl_3$) ν = 3383 (br), 2928, 2862, 1609, 1574, 1501, 1454, 1281, 1018 cm^{-1}.

$[\alpha]_D^{20}$ +19.6 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-13



To a solution of oxalyl chloride (0.32 mL, 3.7 mmol) in CH_2Cl_2 (4.0 mL) was dropwise added a solution of DMSO (0.40 mL, 5.6 mmol) in CH_2Cl_2 (5.0 mL) at –78 °C. After being stirred for 5 min, a solution of (20*S*)-**12** (601 mg, 1.84 mmol) in CH_2Cl_2 (9.0 mL) was dropwise added. After being stirred for 10 min at –78 °C, triethylamine (1.5 mL, 10.8 mmol) was added. After being stirred for 20 min, the resulting mixture was allowed to warm to ambient temperature, diluted with $CHCl_3$, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane/ethyl acetate 10:1) to afford (20*S*)-**13** (490 mg, 82%) as a white solid. Analytical sample was obtained by recrystallization from hexane/ethyl acetate as a white needle.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (d, *J* = 6.3 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 3.77 (s, 3H), 2.97–2.83 (m, 2H), 2.33–2.17 (m, 3H), 2.00–1.93 (m, 2H), 1.79–1.70 (m, 2H), 1.52–1.39 (m, 6H), 1.26 (ddd, *J* = 12.1, 3.4, 3.4 Hz, 1H), 1.18–1.15 (m, 2H), 0.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 157.5, 137.9, 132.3, 126.2, 113.8, 111.4, 55.1, 52.4, 43.80, 43.78, 42.6, 39.3, 32.9, 31.0, 29.8, 29.5, 27.7, 25.9, 24.7, 21.0, 17.1 ppm. LRMS (EI) *m*/*z* 324 (M), 309 (M–Me), 291 (M–Me–H_2O).

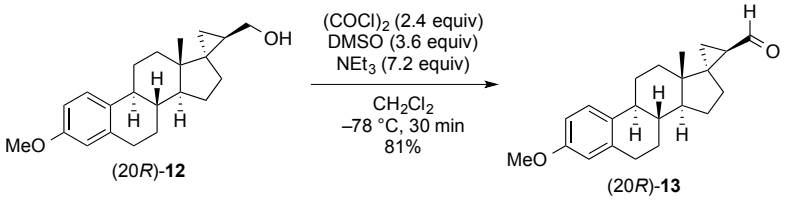
Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found C, 81.17; H, 8.55.

IR ($CHCl_3$) ν = 2932, 2913, 2866, 1701, 1609, 1501, 1238, 1172, 1042 cm^{-1}.

mp 148–149 °C (dec.).

$[\alpha]_D^{20}$ +47.7 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-13



To a solution of oxalyl chloride (0.37 mL, 4.3 mmol) in CH_2Cl_2 (5.0 mL) was dropwise added a solution of DMSO (0.46 ml, 6.5 mmol) in CH_2Cl_2 (5.0 mL) at –78 °C. After being stirred for 5 min, a solution of (20*R*)-**12** (584 mg, 1.80 mmol) in CH_2Cl_2 (12 mL) was dropwise added. After being stirred for 20 min at –78 °C, triethylamine (1.8 mL, 13 mmol) was added. After being stirred for 10 min, the resulting mixture was allowed to warm to ambient temperature, diluted with $CHCl_3$, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane/ethyl acetate 10:1) to afford (20*R*)-**13** (471 mg, 81%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H), 3.78 (s, 3H), 2.93–2.83 (m, 2H), 2.37–2.15 (m, 3H), 1.95–1.85 (m, 3H), 1.75 (dd, *J* = 5.2, 5.2 Hz, 1H), 1.62–1.37 (m, 8H), 1.10 (dd, *J* = 7.9, 5.0 Hz, 1H), 0.89 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 157.5, 137.8, 132.2, 126.2, 113.8, 111.5, 55.2, 54.4, 44.9, 43.4, 42.0, 39.2, 36.3, 36.2, 35.4, 29.8, 27.5, 26.3, 24.4, 21.9, 18.0 ppm.

LRMS (EI) *m*/*z* 324 (M), 309 (M–Me), 291 (M–Me–H_2O).

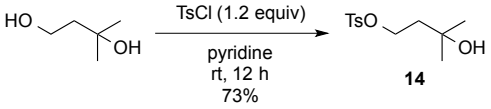
Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found C, 81.50; H, 8.92.

IR ($CHCl_3$) ν = 2932, 2866, 1694, 1609, 1501, 1161, 1038 cm^{-1}.

mp 128–129 °C.

$[\alpha]_D^{20}$ +42.7 (*c* 1.00, $CHCl_3$).

Compound 14



To a stirred solution of 3-methyl-1,3-butanediol (4.19 g, 40.2 mmol) in pyridine (100 mL) was added tosyl chloride (9.15 g, 48.0 mmol) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated *in vacuo*, and azeotroped with toluene. The resulting pale yellow oil was purified by column chromatography (hexane/ethyl acetate 3:2 to 1:1) to afford **14** (7.62 g, 73%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.21 (t, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 1.86 (t, *J* = 6.9 Hz, 2H), 1.22 (s, 6H) ppm.

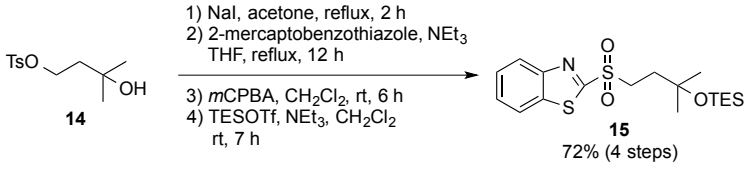
^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 132.7, 129.7, 127.7, 69.3, 67.5, 41.5, 29.4, 21.4 ppm.

LRMS (FAB) *m*/*z* 259 (M+H), 241 (M–OH).

HRMS (FAB) *m*/*z*: $[M+H]^+$ Calcd for $C_{12}H_{19}O_4S$ 259.0999; Found 259.0975.

IR (neat) ν = 3518 (br), 2970, 1597, 1465, 1354, 1172 cm^{-1}.

Compound 15



To a solution of **14** (7.62 g, 29.5 mmol) in acetone (98 mL) was added NaI (11.2 g, 74.7 mmol). The mixture was heated under reflux for 2 h. The resulting mixture was allowed to cool to room temperature, and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a brown oil

(5.79 g). To a solution of the brown oil (5.79 g) in THF (90 mL) were added triethylamine (5.6 mL, 41 mmol) and 2-mercaptobenzothiazole (5.67 g, 33.9 mmol). After being heated under reflux for 12 h, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and washed with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a yellow oil (6.87 g). To a solution of the yellow oil (6.87 g) in CH_2Cl_2 (135 mL) was added *m*CPBA (75%, 18.8 g, 81.7 mmol) at 0 °C. After being stirred for 6 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$, and passed through a short pad of silica gel with hexane/ethyl acetate (1:1) to give a white solid (7.67 g). To a solution of the white solid (7.67 g) in CH_2Cl_2 (67 mL) were added triethylamine (7.5 mL, 54 mmol) and triethylsilyl trifluoromethanesulfonate (7.3 mL, 32 mmol) at 0 °C under argon. After being stirred for 7 h at room temperature, the reaction mixture was quenched with water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a brown solid. The residue was purified by column chromatography (hexane/ethyl acetate 10:1) to afford **15** (8.49 g, 72%, four steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.02 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.65 (ddd, *J* = 8.2, 7.0, 1.4 Hz, 1H), 7.60 (ddd, *J* = 7.8, 6.6, 1.5 Hz, 1H), 3.65–3.62 (m, 2H), 1.95–1.92 (m, 2H), 1.23 (s, 6H), 0.87 (t, *J* = 8.0 Hz, 9H), 0.51 (q, *J* = 8.0 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 152.7, 136.7, 127.9, 127.5, 125.4, 122.2, 71.8, 51.2, 36.9, 29.7, 6.9, 6.5 ppm.

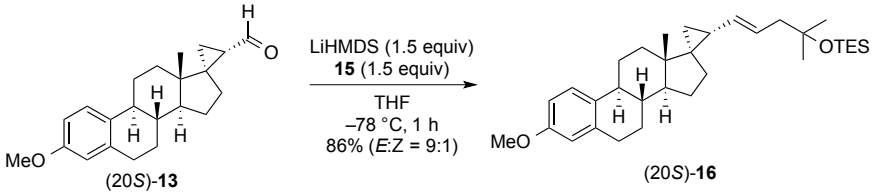
LRMS (FAB) *m*/*z* 400 (M+H), 370 (M–Et), 268 (M–TES).

Anal. Calcd for $C_{18}H_{29}NO_3S_2Si$: C, 54.10; H, 7.31; N, 3.50. Found: C, 53.90; H, 7.31; N, 3.47.

IR (neat) ν = 2951, 2873, 1470, 1327, 1304, 1146 cm^{-1}.

mp 57–59 °C.

Compound (20*S*)-16



To a solution of **15** (648 mg, 1.62 mmol) in THF (6.0 mL) was added a 1.0 M solution of LiHMDS in toluene (1.6 mL, 1.6 mmol) at –78 °C. After being stirred for 30 min, a solution of (20*S*)-**13** (352

mg, 1.08 mmol) in THF (10 mL) was added, and stirred for 1 h. The reaction mixture was diluted with ethyl acetate, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to afford an inseparable *E*/*Z* mixture of (20*S*)-**16** (470 mg, 86%, *E*/*Z* 9:1) as a colorless oil. The following data were collected as a 9:1 *E*/*Z* mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H), 5.52 (dt, *J* = 15.2, 7.5 Hz, 0.9H), 5.50 (dt, *J* = 10.9, 3.7 Hz, 0.1H), 5.08 (dd, *J* = 15.2, 8.9 Hz, 0.9H), 5.01 (dd, *J* = 10.3, 10.3 Hz, 0.1H), 3.77 (s, 3H), 2.95–2.75 (m, 2H), 2.34–2.02 (m, 5H), 1.97–1.84 (m, 2H), 1.50–1.28 (m, 7H), 1.27–1.18 (m, 1.6H), 1.18 (s, 2.7H), 1.17 (s, 2.7H), 1.15–1.05 (m, 2H), 0.95 (t, *J* = 8.1 Hz, 9H), 0.78 (s, 3H), 0.57 (q, *J* = 8.0 Hz, 6H), 0.15 (dd, *J* = 5.5, 5.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 138.1, 134.3, 132.9, 126.3, 125.5, 113.8, 111.4, 73.5, 55.2, 53.5, 48.4, 43.9, 41.9, 39.4, 38.0, 33.4, 29.9, 29.7, 29.6, 27.8, 26.1, 24.7, 20.9, 19.2, 16.7, 7.1, 6.8 ppm (Signals of the minor isomer were not observed).

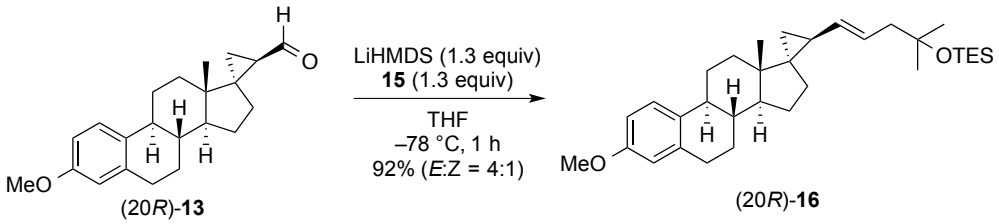
LRMS (EI) *m*/*z* 508 (M), 493 (M–Me), 479 (M–Et), 450 (M–2Et). 376 (M–TESOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{33}H_{52}O_2SiNa$ 531.3629; Found 531.3631.

IR (neat) ν = 2954, 2909, 2874, 1609, 1501, 1238, 1042, 1018 cm^{-1}.

$[\alpha]_D^{20}$ +23.3 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-16



To a solution of **15** (747 mg, 1.87 mmol) in THF (5 mL) was added a 1.0 M solution of LiHMDS in toluene (1.9 mL, 1.9 mmol) at –78 °C. After being stirred for 30 min, a solution of (20*R*)-**13** (463 mg, 1.43 mmol) in THF (10 mL) was added, and stirred for 1 h. The reaction mixture was diluted with ethyl acetate, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to afford an inseparable *E*/*Z* mixture of (20*R*)-**16** (667

mg, 92%, *E*/*Z* 4:1) as a colorless oil. The following data were collected as a 4:1 *E*/*Z* mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 5.54 (dt, *J* = 15.2, 7.2 Hz, 0.8H), 5.43 (dt, *J* = 10.4, 7.8 Hz, 0.2H), 5.29–5.18 (m, 1H), 3.77 (s, 3H), 2.92–2.79 (m, 2H), 2.33–2.05 (m, 5H), 1.95–1.78 (m, 2H), 1.60–1.26 (m, 9H), 1.22 (s, 1.2H), 1.18 (s, 4.8H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 2.4H), 0.87 (s, 0.6H), 0.83–0.78 (m, 1H), 0.57 (q, *J* = 8.0 Hz, 6H), 0.54–0.51 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 138.0, 133.3, 132.9, 126.3, 125.5, 113.7, 111.4, 73.7, 55.2, 54.6, 48.6, 43.6, 41.7, 39.1, 37.9, 36.2, 35.7, 29.9, 29.8, 29.5, 27.7, 26.4, 25.7, 24.8, 20.3, 16.0, 7.1, 6.8 ppm (Signals of the minor isomer were not observed).

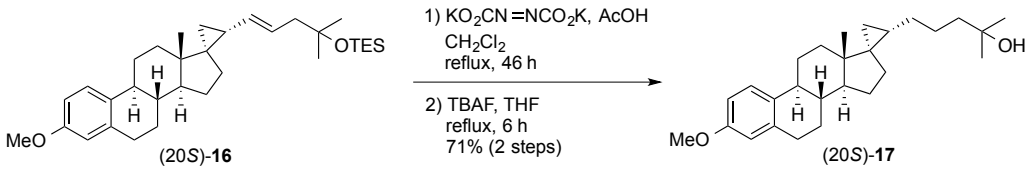
LRMS (EI) *m*/*z* 508 (M), 493 (M–Me), 479 (M–Et), 450 (M–2Et). 376 (M–TESOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{33}H_{52}O_2SiNa$ 531.3629; Found 531.3619.

IR ($CHCl_3$) ν = 2932, 2913, 2874, 1609, 1501, 1458, 1234, 1153, 1038, 1015 cm^{-1}.

$[\alpha]_D^{20}$ +28.6 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-17



To a suspension of (20*S*)-**16** (166 mg, 0.326 mmol, *E*/*Z* 9:1) and dipotassium azodicarboxylate (317 mg, 1.63 mmol) in CH_2Cl_2 (1.0 mL) was added a 1 M solution of acetic acid in CH_2Cl_2 (3.3 mL, 3.3 mmol) dropwise at reflux. Additional dipotassium azodicarboxylate (317 mg, 1.63 mmol) and a 1.0 M solution of acetic acid (3.3 mL, 3.3 mmol) were added after 3, 6, 22, 25, 28, 31, 34, 43 h, respectively. The reaction mixture was stirred under reflux for a total 46 h, and the resulting mixture was filtered through Celite. The eluent was concentrated under reduced pressure to give the spirocyclopropane (166 mg) as a pale yellow oil. To a solution of the spirocyclopropane (166 mg) in THF (2 mL) was added a 1.0 M solution of TBAF (1.7 mL, 1.7 mmol), and the solution was heated under reflux for 6 h. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate, and washed with water. The aqueous layer was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/ethyl acetate 4:1) to give (20*S*)-**17** (92.3 mg, 71% for two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.63 (d, *J* =

2.0 Hz, 1H), 3.77 (s, 3H), 2.92–2.82 (m, 2H), 2.27–2.18 (m, 2H), 2.04–2.01 (m, 1H), 1.95–1.87 (m, 2H), 1.54–1.16 (m, 20H), 1.10 (ddd, J = 13.2, 13.2, 4.0 Hz, 1H), 0.85 (dd, J = 8.9, 4.3 Hz, 1H), 0.77 (s, 3H), 0.58–0.52 (m, 1H), –0.26 (dd, J = 4.9, 4.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 138.0, 132.9, 126.2, 113.7, 111.3, 70.9, 55.1, 53.6, 43.9, 43.8, 41.3, 39.4, 36.0, 33.3, 31.6, 29.9, 29.2, 29.1, 29.0, 27.8, 26.1, 24.9, 24.6, 17.4, 17.1, 17.0 ppm.

LRMS (EI) *m*/*z* 396 (M), 378 (M–H_2O), 363 (M–H_2O–Me).

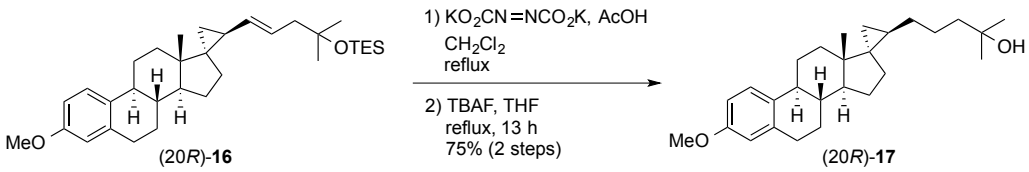
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{27}H_{41}O_2$ 397.3101; Found 397.3096.

IR ($CHCl_3$) ν = 3333 (br), 2970, 2924, 2901, 1501, 1454, 1381, 1084, 1049 cm^{-1}.

mp 107–109 °C.

$[\alpha]_D^{20}$ +21.1 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-17



To a suspension of (20*R*)-**16** (483 mg, 0.949 mmol, *E*/*Z* 4:1) and dipotassium azodicarboxylate (922 mg, 4.75 mmol) in CH_2Cl_2 (5.0 mL) was added a 1.0 M solution of acetic acid in CH_2Cl_2 (9.4 mL, 9.4 mmol) dropwise at reflux. Additional dipotassium azodicarboxylate (922 mg, 4.75 mmol) and a 1.0 M solution of acetic acid in CH_2Cl_2 (9.4 mL, 9.4 mmol) were added after 3, 17, 29, 42, 47, 53, 67, 70, 74, 77 h, respectively. The reaction mixture was stirred under reflux for a total 89 h, and the resulting mixture was filtered through Celite. The eluent was concentrated under reduced pressure to give a pale yellow oil (402 mg, only about 50% conversion by ^{1}H NMR). Again, to a suspension of the pale yellow oil (402 mg) and dipotassium azodicarboxylate (768 mg, 3.95 mmol) in CH_2Cl_2 (4.0 mL) was added a 1.0 M solution of acetic acid in CH_2Cl_2 (8.0 mL, 8.0 mmol) dropwise at reflux. Additional dipotassium carboxylate (770 mg, 3.96 mmol) and a 1.0 M solution of acetic acid in CH_2Cl_2 (8.0 mL, 8.0 mmol) were added after 5, 9, 12, 32, 36, 49, 58 h, respectively. The reaction mixture was stirred under reflux for a total 72 h, and the resulting white suspension was allowed to cool to room temperature, and diluted with water. The aqueous layer was extracted with $CHCl_3$, and washed with brine, dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow oil (390 mg). To a solution of the pale yellow oil (390 mg, 0.763 mmol) in THF (5.0 mL) was added a 1.0 M solution of TBAF in THF (2.3 mL, 2.3 mmol). After being refluxed for 13 h, the resulting mixture was allowed to cool to room temperature, and diluted with water. The aqueous layer was

extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (hexane/ethyl acetate 5:1) to afford (20*R*)-**17** (284 mg, 75% for two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.63 (d, *J* = 2.6 Hz, 1H), 3.77 (s, 3H), 2.92–2.80 (m, 2H), 2.29–2.16 (m, 2H), 2.04–1.98 (m, 1H), 1.94–1.89 (m, 1H), 1.84–1.73 (m, 2H), 1.56–1.24 (m, 13H), 1.22 (s, 6H), 1.13–1.05 (m, 1H), 0.91 (s, 3H), 0.72 (m, 1H), 0.42 (dd, *J* = 4.9, 4.9, Hz, 1H), 0.27 (dd, *J* = 8.6, 4.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 138.1, 132.9, 126.2, 113.7, 111.4, 71.1, 55.2, 54.7, 43.9, 43.7, 41.6, 39.1, 36.7, 36.2, 35.6, 29.92, 29.90, 29.3, 29.2, 27.7, 26.5, 25.4, 24.8, 22.6, 18.4, 16.2 ppm.

LRMS (EI) *m*/*z* 396 (M), 378 (M–H_2O), 363 (M–H_2O–Me), 348 (M–H_2O–2Me).

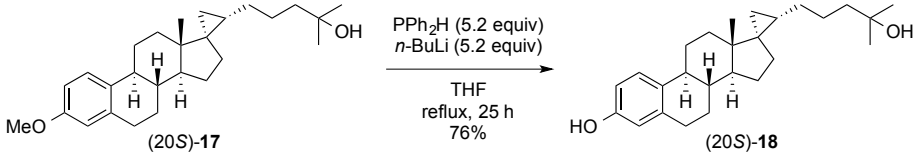
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{27}H_{41}O_2$ 397.3101; Found 397.3115.

IR ($CHCl_3$) ν = 3333 (br), 2970, 2924, 2901, 1501, 1454, 1381, 1084, 1049 cm^{-1}.

mp 95–96 °C.

$[\alpha]_D^{20}$ +13.0 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-18



(20*S*)-**17** (20*S*)-**18**

To a solution of diphenylphosphine (0.12 mL, 0.69 mmol) in THF (1.0 mL) were added a 2.5 M solution of *n*-BuLi in hexane (0.27 mL, 0.68 mmol) and a solution of (20*S*)-**17** (52.0 mg, 0.132 mmol) in THF (1.0 mL). After the red solution was heated under reflux for 25 h, the resulting mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate 7:3) to give (20*S*)-**18** (38.2 mg, 76%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.6 Hz, 1H), 6.62 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 4.71 (br s, 1H), 2.90–2.77 (m, 2H), 2.30–2.13 (m, 2H), 2.09–1.99 (m, 1H), 1.97–1.83 (m, 2H), 1.55–1.21 (m, 19H), 1.16 (ddd, *J* = 12.3, 2.9, 2.9 Hz, 1H), 1.08 (ddd, *J* = 12.6, 12.6, 4.0 Hz, 1H), 0.85 (dd, *J* = 9.2, 4.3 Hz, 1H), 0.76 (s, 3H), 0.58–0.51 (m, 1H), –0.26 (dd, *J* = 4.9, 4.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 138.4, 132.9, 126.4, 115.2, 112.6, 71.5, 53.7, 44.0, 43.8, 41.4,

39.5, 36.0, 33.3, 31.6, 29.7, 29.2, 29.1, 29.0, 27.8, 26.2, 24.9, 24.6, 17.5, 17.11, 17.07 ppm.

LRMS (EI) *m*/*z* 382 (M), 364 (M–H_2O), 349 (M–H_2O–Me).

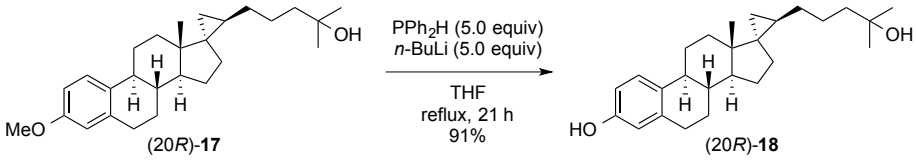
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{26}H_{39}O_2$ 383.2945; Found 383.2931.

IR (KBr) ν = 3717 (br), 3292 (br), 2968, 2932, 2864, 1611, 1585, 1501, 1452, 1375, 1287, 1240 cm^{-1}.

mp 80–83 °C.

$[\alpha]_D^{20}$ +9.85 (*c* 0.50, $CHCl_3$).

Compound (20*R*)-18



To a solution of diphenylphosphine (0.33 mL, 1.90 mmol) in THF (1.0 mL) were added a 2.5 M solution of *n*-BuLi in hexane (0.76 mL, 1.90 mmol) and a solution of (20*R*)-**17** (151 mg, 0.381 mmol) in THF (3.0 mL). After the red solution was heated under reflux for 21 h, the resulting mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate 4:1 to 7:3) to give (20*R*)-**18** (133 mg, 91%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.3 Hz, 1H), 6.62 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 2.88–2.78 (m, 2H), 2.26–2.15 (m, 2H), 2.05–1.98 (m, 1H), 1.93–1.87 (m, 1H), 1.84–1.73 (m, 2H), 1.56–1.29 (m, 14H), 1.23 (s, 6H), 1.10–1.05 (m, 1H), 0.91 (s, 3H), 0.72 (m, 1H), 0.42 (dd, *J* = 4.3, 4.3, Hz, 1H), 0.27 (dd, *J* = 8.6, 4.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, acetone-d_6) δ 156.5, 139.0, 132.7, 127.5, 116.5, 114.1, 70.7, 56.2, 45.4, 45.2, 43.0, 40.9, 38.2, 37.5, 37.0, 31.5, 31.0, 30.4, 29.1, 27.9, 26.8, 26.0, 24.1, 19.5, 17.3 ppm.

LRMS (EI) *m*/*z* 382 (M), 364 (M–H_2O), 349 (M–H_2O–Me).

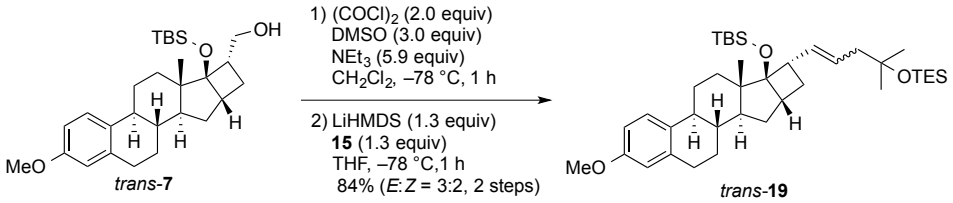
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{26}H_{38}O_2Na$ 405.2764; Found 405.2772.

IR (KBr) ν = 3319 (br), 2968, 2857, 2816, 1614, 1585, 1504, 1440, 1375, 1283, 1213, 1148, 895 cm^{-1}.

mp 192–193 °C.

$[\alpha]_D^{20}$ +14.1 (*c* 1.00, THF).

Compound *trans*-19



To a solution of oxalyl chloride (0.38 mL, 4.4 mmol) in CH_2Cl_2 (5.0 mL) was dropwise added a solution of DMSO (0.47 mL, 6.6 mmol) in CH_2Cl_2 (6.0 mL) at –78 °C. After being stirred for 5 min, *trans*-**7** (1.00 g, 2.19 mmol) in CH_2Cl_2 (11 mL) was dropwise added. After being stirred for 40 min at –78 °C, triethylamine (1.8 mL, 13 mmol) was added. After being stirred for 20 min, the resulting mixture was allowed to warm to ambient temperature, diluted with $CHCl_3$, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and passed through a short pad of silica gel with hexane/diethyl ether (10:1) to obtain a crude aldehyde (936 mg) as a white solid, which was used directly in the next step without further purification. To a solution of **15** (1.07 g, 2.69 mmol) in THF (7 mL) was added a 1.0 M solution of LiHMDS in toluene (2.7 mL, 2.7 mmol) at –78 °C under argon. After being stirred for 30 min, a solution of the above crude aldehyde (936 mg, 2.06 mmol) in THF (13 mL) was added, and stirred for 1 h. The reaction mixture was diluted with ethyl acetate, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow solid. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to afford an inseparable *E*/*Z* mixture of *trans*-**19** (1.18 g, 84% for two steps, *E*/*Z* 3:2) as a colorless oil. The following data were collected as a 3:2 *E*/*Z* mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 0.4H), 7.21 (d, *J* = 8.6 Hz, 0.6H), 6.71 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.63 (d, *J* = 2.9 Hz, 1H), 5.86–5.77 (m, 1H), 5.49 (ddt, *J* = 10.9, 7.5, 0.9 Hz, 0.4H), 5.43 (ddt, *J* = 15.5, 7.2, 1.4 Hz, 0.6H), 3.77 (s, 3H), 3.44–3.36 (m, 0.4H), 3.26–3.18 (m, 0.6H), 2.93–2.81 (m, 2H), 2.60–2.54 (m, 0.4H), 2.51–2.42 (m, 1H), 2.38–2.28 (m, 1H), 2.27–2.13 (m, 4H), 2.06 (ddd, *J* = 3.8, 3.8, 3.2 Hz, 0.6H), 1.97–1.90 (m, 1H), 1.89–1.78 (m, 1H), 1.60–1.33 (m, 6H), 1.20 (s, 1.2H), 1.18 (s, 1.2H), 1.17 (s, 3.6H), 1.08–0.89 (m, 19H), 0.70 (s, 1.8H), 0.69 (s, 1.2H), 0.57 (q, *J* = 8.1 Hz, 2.4H), 0.56 (q, *J* = 8.0 Hz, 3.6H), 0.27 (s, 1.2H), 0.21 (s, 1.8H), 0.133 (s, 1.8H), 0.127 (s, 1.2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 157.3, 138.1, 138.0, 133.02, 133.0, 132.7, 132.6, 127.0, 126.5, 126.4, 125.6, 113.7, 111.41, 111.38, 92.0, 91.7, 73.6, 73.4, 55.2, 50.5, 48.47, 48.45, 48.3, 47.1, 47.0,

45.8, 44.0, 43.8, 43.3, 41.5, 41.0, 38.87, 38.85, 33.7, 33.6, 31.2, 30.0, 29.94, 29.91, 29.85, 29.7, 28.7, 27.89, 27.85, 26.42, 26.37, 26.0, 25.9, 25.8, 18.3, 17.01, 16.95, 7.1, 6.8, –2.4, –2.7, –3.1, –3.3 ppm (some signals missing).

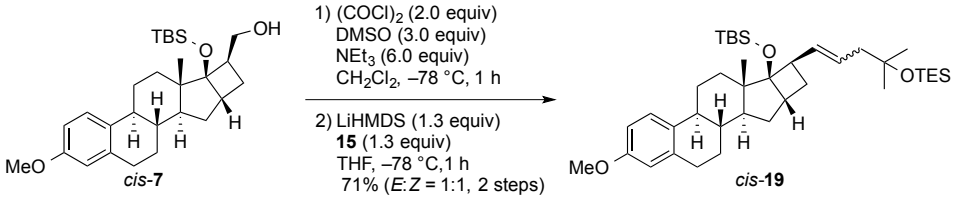
LRMS (EI) *m*/*z* 638 (M), 623 (M–Me), 609 (M–Et), 581 (M–*t*Bu), 506 (M–TESOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{39}H_{66}O_3Si_2Na$ 661.4442; Found 661.4428.

IR ($CHCl_3$) ν = 2955, 2928, 1501, 1458, 1254, 1238, 1045 cm^{-1}.

$[\alpha]_D^{20}$ +11.5 (*c* 1.00, $CHCl_3$).

Compound *cis*-19



To a solution of oxalyl chloride (0.49 mL, 5.7 mmol) in CH_2Cl_2 (7.0 mL) was dropwise added a solution of DMSO (0.61 mL, 8.6 mmol) in CH_2Cl_2 (6.0 mL) at –78 °C. After being stirred for 5 min, a solution of *cis*-**7** (1.30 g, 2.85 mmol) in CH_2Cl_2 (15 mL) was dropwise added. After being stirred for 40 min at –78 °C, triethylamine (2.4 mL, 17 mmol) was added. After being stirred for 20 min, the resulting mixture was allowed to warm to ambient temperature, diluted with $CHCl_3$, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and passed through a short pad of silica gel with hexane/ethyl acetate (20:1) to obtain a crude aldehyde (1.21 g) as a white solid, which was used directly in the next step without further purification. To a solution of **15** (1.39 g, 3.48 mmol) in THF (8.0 mL) was added a 1.0 M solution of LiHMDS in toluene (3.5 mL, 3.5 mmol) at –78 °C under argon. After being stirred for 30 min, a solution of the above crude aldehyde (1.21 g, 2.66 mmol) in THF (19 mL) was added, and stirred for 1 h. The reaction mixture was diluted with ethyl acetate, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/ethyl acetate 50:1) to afford an inseparable *E*/*Z* mixture of *cis*-**19** (1.29 g, 71% for two steps, *E*/*Z* 1:1) as a colorless oil. The following data were collected as a 1:1 *E*/*Z* mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.9 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H), 5.74 (dt, *J* = 10.0, 7.9 Hz, 0.5H), 5.43 (dd, *J* = 15.5, 6.1 Hz, 0.5H), 5.45–5.32 (m, 1H),

3.78 (s, 3H), 3.27–3.21 (m, 0.5H), 3.11–3.04 (m, 0.5H), 2.96–2.82 (m, 2H), 2.60 (dd, *J* = 7.5, 7.5 Hz, 0.5H), 2.54 (dd, *J* = 8.0, 8.0 Hz, 0.5H), 2.35–2.05 (m, 5H), 1.99–1.90 (m, 1H), 1.74–1.64 (m, 1H), 1.62–1.38 (m, 8H), 1.20 (s, 1.5H), 1.19 (s, 1.5H), 1.18 (s, 1.5H), 1.16 (s, 1.5H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.92 (s, 4.5H), 0.90 (s, 4.5H), 0.70 (s, 1.5H), 0.69 (s, 1.5H), 0.574 (q, *J* = 7.7 Hz, 3H), 0.569 (q, *J* = 8.1 Hz, 3H), 0.26 (s, 1.5H), 0.22 (s, 1.5H), 0.10 (s, 1.5H), 0.08 (s, 1.5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 137.9,134.1, 132.90, 132.87, 132.8, 126.3, 126.1, 125.3, 113.8, 111.4, 90.7, 90.5, 73.6, 73.5, 55.1, 48.4, 48.34, 48.32, 47.0, 46.9, 44.31, 44.27, 43.4, 40.8, 40.5, 40.3, 38.7, 38.6, 35.9, 32.1, 31.9, 30.4, 30.0, 29.9, 29.80, 29.76, 29.6, 29.5, 29.3, 28.3, 27.8, 26.14, 26.10, 18.64, 18.56, 14.6, 14.5, 7.11, 6.8, –1.46, –1.51, –2.4 ppm (some signals missing).

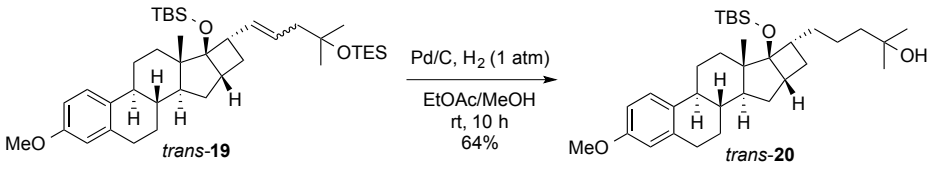
LRMS (EI) *m*/*z* 638 (M), 609 (M–Et), 581 (M–*t*Bu), 506 (M–TESOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{39}H_{66}O_3Si_2Na$ 661.4442; Found 661.4439.

IR ($CHCl_3$) ν = 2951, 2928, 2878, 2855, 1501, 1462, 1234, 1153, 1099, 1045, 1018 cm^{-1}.

$[\alpha]_D^{20}$ +4.95 (*c* 1.00, $CHCl_3$).

Compound *trans*-20



A mixture of *trans*-**19** (1.18 g, 1.85 mmol, *E*/*Z* 3:2), 10% Pd/C (200 mg) and ethyl acetate/MeOH (1:1, 18 mL) was stirred under H_2 (1 atm) at room temperature for 10 h. The reaction mixture was filtered through Celite, and concentrated under reduced pressure to give a pale yellow oil, which was purified by column chromatography (hexane/diethyl ether 3:2) to afford *trans*-**20** (626 mg, 64%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 3.78 (s, 3H), 2.90–2.82 (m, 2H), 2.59 (dddd, *J* = 12.6, 12.6, 8.0, 5.5 Hz, 1H), 2.48–2.44 (m, 1H), 2.36–2.22 (m, 3H), 1.95–1.88 (m, 2H), 1.84–1.72 (m, 2H), 1.68–1.64 (m, 2H), 1.56–1.38 (m, 7H), 1.36–1.28 (m, 1H), 1.21 (s, 6H), 1.16–1.09 (m, 1H), 0.89 (s, 9H), 0.82 (ddd, *J* = 12.9, 8.6, 4.9 Hz, 1H), 0.72 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 138.1, 132.9, 126.4, 113.7, 111.4, 90.4, 71.0, 55.2, 48.8, 48.6, 47.5, 44.0, 43.9, 41.5, 39.0, 33.3, 31.9, 31.4, 30.0, 29.3, 29.2, 27.9, 27.4, 26.5, 25.9, 23.1, 18.3, 17.5, –2.7, –3.0 ppm.

LRMS (EI) *m*/*z* 526 (M), 511 (M–Me), 411 (M–TBS).

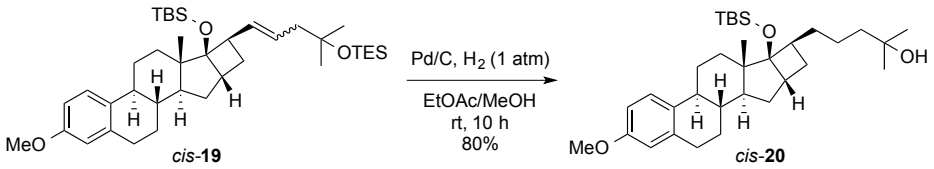
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{33}H_{54}O_3SiNa$ 549.3734; Found 549.3752.

IR ($CHCl_3$) ν = 3422 (br), 2940, 2862, 1612, 1485, 1454, 1238, 1211, 1103 cm^{-1}.

mp 52–55 °C.

$[\alpha]^{20}_D$ +9.64 (*c* 1.00, $CHCl_3$).

Compound *cis*-20



A mixture of *cis*-**19** (1.29 g, 2.02 mmol, *E*/*Z* 1:1), 10% Pd/C (215 mg) and ethyl acetate/MeOH (1:1, 20 mL) was stirred under H_2 (1 atm) at room temperature for 10 h. The reaction mixture was filtered through Celite, and concentrated under reduced pressure to give a white gum, which was purified by column chromatography (hexane/diethyl ether 3:2) to afford *cis*-**20** (847 mg, 80%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 3.78 (s, 3H), 2.89–2.83 (m, 2H), 2.54 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.38–2.30 (m, 2H), 2.23 (dd, *J* = 9.9, 9.9 Hz, 1H), 1.93–1.83 (m, 2H), 1.68–1.21 (m, 15H), 1.20 (s, 6H), 0.91 (s, 9H), 0.69 (s, 3H), 0.24 (s, 3H), 0.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 138.0, 132.9, 126.4, 113.8, 111.4, 90.2, 71.1, 55.2, 48.3, 46.6, 44.4, 44.3, 40.0, 38.6, 38.1, 32.0, 31.9, 29.9, 29.7, 29.5, 29.2, 29.0, 27.8, 26.2, 23.0, 18.6, 14.6, –1.2, –2.3 ppm.

LRMS (EI) *m*/*z* 526 (M), 511 (M–Me), 411 (M–TBS).

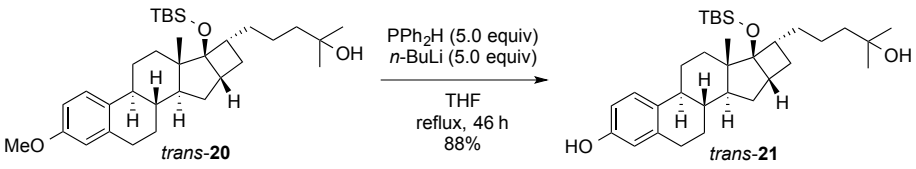
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{33}H_{54}O_3SiNa$ 549.3734; Found 549.3737.

IR (neat) ν = 3325 (br), 2970, 2928, 1612, 1500, 1254, 1092, 1045 cm^{-1}.

mp 63–66 °C.

$[\alpha]_D^{20}$ +19.0 (*c* 1.00, $CHCl_3$).

Compound *trans*-21



To a solution of diphenylphosphine (0.53 mL, 3.1 mmol) in THF (4.0 mL) were added a 2.5 M

solution of *n*-BuLi in hexane (1.2 mL, 3.0 mmol) and a solution of *trans*-**20** (533 mg, 1.01 mmol) in THF (6.0 mL). The red solution was heated under reflux for 27 h, and the diphenyl phosphine (0.35 mL, 2.0 mmol) and a 2.5 M solution of *n*-BuLi in hexane (0.81 mL, 2.0 mmol) were added again to the mixture. After being stirred for additional 19 h under reflux, the resulting mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate 3:1) to give *trans*-**21** (458 mg, 88%) as a white solid. Analytical sample was obtained by recrystallization from ethyl acetate as a white powder.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.57 (d, *J* = 2.6 Hz, 1H), 2.88–2.79 (m, 2H), 2.62–2.54 (m, 1H), 2.48–2.44 (m, 1H), 2.32 (ddd, *J* = 12.0, 12.0, 9.5 Hz, 1H), 2.26–2.20 (m, 2H), 1.94–1.88 (m, 2H), 1.84–1.72 (m, 2H), 1.67–1.60 (m, 2H), 1.57–1.25 (m, 9H), 1.21 (s, 6H), 1.16–1.09 (m, 1H), 0.89 (s, 9H), 0.82 (ddd, *J* = 12.2, 8.5, 5.2 Hz, 1H), 0.72 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 138.3, 132.7, 126.6, 115.2, 112.6, 90.4, 71.4, 48.8, 48.6, 47.5, 43.9, 41.5, 38.9, 33.3, 31.9, 31.4, 29.8, 29.2, 29.1, 27.8, 27.3, 26.5, 25.9, 23.1, 18.3, 17.5, 18.3, 17.5, –2.7, –3.0 ppm.

LRMS (EI) *m*/*z* 512 (M), 453 (M–2Me–OH), 397 (M–TBS).

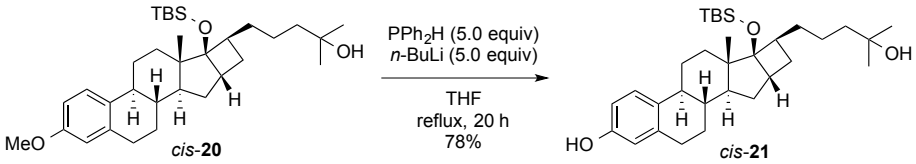
Anal. Calcd for $C_{32}H_{52}O_3Si$: C, 74.94; H, 10.22. Found: C, 74.70; H, 10.29.

IR (neat) ν = 3329 (br), 2974, 2928, 2893, 1454, 1088, 1049 cm^{-1}.

mp 178–179 °C.

$[\alpha]_D^{20}$ +5.35 (*c* 1.00, $CHCl_3$).

Compound *cis*-21



To a solution of diphenylphosphine (0.99 mL, 5.7 mmol) in THF (4.0 mL) were added a 2.5 M solution of *n*-BuLi in hexane (2.3 mL, 5.8 mmol) and a solution of *cis*-**20** (603 mg, 1.14 mmol) in THF (7.0 mL). After the red solution was heated under reflux for 20 h, the resulting mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate, washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration under reduced

pressure gave a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate 3:1) to give *cis*-**21** (455 mg, 78%) as a white solid. Analytical sample was obtained by recrystallization from ethyl acetate as a white powder.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.3 Hz, 1H), 6.64 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 4.56 (s, 1H), 2.85–2.82 (m, 2H), 2.54 (ddd, *J* = 8.4, 8.4, 1.6 Hz, 1H), 2.35–2.28 (m, 2H), 2.23–2.19 (m, 1H), 1.92–1.83 (m, 2H), 1.67–1.24 (m, 16H), 1.21 (s, 3H), 1.20 (s, 3H), 0.91 (s, 9H), 0.69 (s, 3H), 0.24 (s, 3H), 0.10 (s, 3H) ppm.

^{13}C NMR (125 MHz, THF-d_8) δ 156.4, 138.1, 131.6, 126.7, 115.9, 113.6, 91.4, 69.7, 49.3, 47.6, 45.5, 45.4, 41.0, 40.0, 39.2, 33.3, 32.7, 30.7, 30.6, 30.1, 29.4, 28.9, 27.2, 26.7, 23.8, 19.4, 15.3, –1.0, –2.0 ppm.

LRMS (EI) *m*/*z* 512 (M).

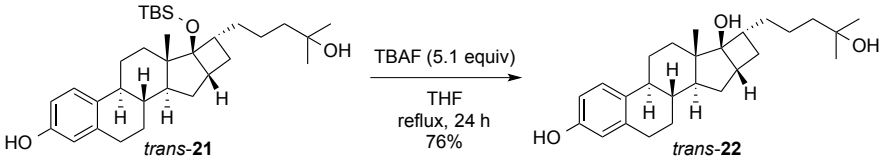
Anal. Calcd for $C_{32}H_{52}O_3Si$: C, 74.94; H, 10.22. Found: C, 74.79; H, 10.44.

IR (neat) ν = 3314 (br), 2974, 2882, 1088, 1045 cm^{-1}.

mp 205–206 °C.

$[\alpha]_D^{20}$ +21.5 (*c* 1.00, THF).

Compound *trans*-22



To a solution of *trans*-**21** (120 mg, 0.234 mmol) in THF (1.0 mL) was added a 1.0 M solution of TBAF in THF (1.2 mL, 1.2 mmol), and the solution was heated under reflux for 24 h. The resulting mixture was allowed to cool to room temperature, and purified by column chromatography (hexane/ethyl acetate 2:3) to give *trans*-**22** (71 mg, 76%) as a white solid.

^{1}H NMR (500 MHz, MeOH-d_4) δ 7.09 (d, *J* = 8.6 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.48 (d, *J* = 1.7 Hz, 1H), 2.81–2.76 (m, 2H), 2.62–2.55 (m, 1H), 2.42–2.23 (m, 3H), 2.21 (ddd, *J* = 11.1, 11.1, 3.0 Hz, 1H), 2.02–1.91 (m, 3H), 1.80–1.65 (m, 3H), 1.56–1.33 (m, 9H), 1.161 (s, 3H), 1.158 (s, 3H), 0.86 (m, 1H), 0.80 (s, 3H) ppm.

^{13}C NMR (125 MHz, MeOH-d_4) δ 155.9, 138.8, 132.6, 127.3, 116.0, 113.7, 89.2, 71.4, 50.0, 49.6, 48.9, 45.3, 44.8, 42.4, 40.6, 33.9, 33.4, 32.6, 30.8, 29.3, 29.1, 29.0, 28.3, 27.7, 24.1, 17.3 ppm.

LRMS (EI) *m*/*z* 398 (M), 380 (M–H_2O).

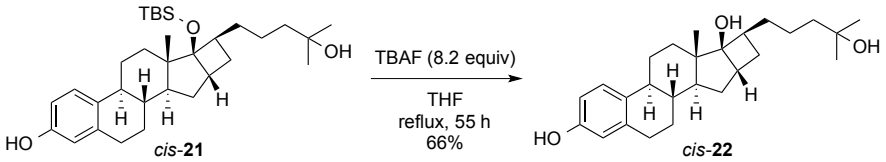
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{26}H_{38}O_3Na$ 421.2713; Found 421.2720.

IR (THF) ν = 3348 (br), 1454, 1361, 1288, 1222, 1080 cm^{-1}.

mp 197–198 °C.

$[\alpha]_D^{20}$ +12.8 (*c* 1.00, THF).

Compound *cis*-22



To a solution of *cis*-**21** (138 mg, 0.269 mmol) in THF (1.0 mL) was added a 1.0 M solution of TBAF in THF (2.2 mL, 2.2 mmol), and the solution was heated under reflux for 55 h. After cooling to room temperature, the resulting mixture was diluted with ethyl acetate, and washed with water. The aqueous layer was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (hexane/ethyl acetate 1:1 to 2:3) to give *cis*-**22** (70.0 mg, 66%) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.50 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 4.46 (s, 1H), 4.02 (s, 1H), 2.78–2.65 (m, 2H), 2.29–2.09 (m, 4H), 1.85–1.61 (m, 3H), 1.50–1.13 (m, 14H), 1.04 (s, 6H), 0.67 (s, 3H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ 154.9, 137.2, 130.6, 126.0, 114.9, 112.7, 86.3, 68.9, 48.8, 45.5, 44.2, 43.6, 40.2, 38.5, 36.4, 31.9, 31.5, 29.5, 29.4, 29.2, 28.8, 27.4, 25.9, 22.1, 14.1 ppm.

LRMS (EI) *m*/*z* 398 (M), 380 (M–H_2O), 365 (M–H_2O–Me).

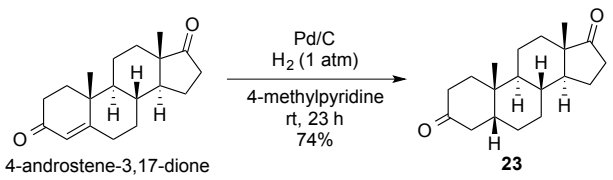
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{26}H_{39}O_3$ 399.2899; Found 399.2882.

IR (THF) ν = 3298 (br), 2932, 1616, 1582, 1454, 1369, 1069 cm^{-1}.

mp 222–223 °C (dec.).

$[\alpha]_D^{20}$ +66.9 (*c* 1.00, THF).

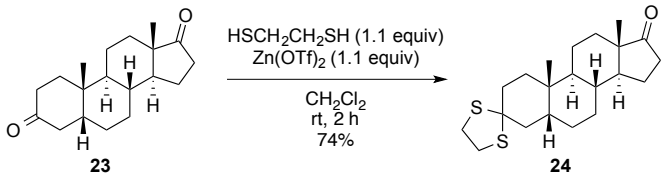
Compound 23



A mixture of 4-androstene-3,17-dione (21.4 g, 74.5 mmol), 10% Pd/C (2.14 g) and 4-methylpyridine (250 mL) was stirred under H_2 (1 atm) at room temperature for 23 h. The reaction mixture was

filtered through Celite, diluted with ethyl acetate, washed with 10% HCl and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a pale purple solid. The residue was dissolved in chloroform and passed through a short pad of silica gel with hexane/ethyl acetate (7:3) to give a white solid, which was recrystallized from hexane/acetone to afford **23** (16.0 g, 74%) as white needles. The spectral data were identical to those reported.[61]

Compound 24



23 **24**

To a mixture of ketone **23** (15.9 g, 55.1 mmol), zinc trifluoromethanesulfonate (22.0 g, 60.5 mmol) and CH_2Cl_2 (184 mL) was added 1,2-ethanedithiol (5.1 mL, 61.2 mmol). After being stirred for 2 h at room temperature, the reaction mixture was quenched with water. The aqueous layer was extracted with $CHCl_3$ twice, and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a white solid, which was purified by recrystallization from ethyl acetate to afford **24** (14.9 g, 74%) as white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32–3.26 (m, 4H), 2.47–2.37 (m, 2H), 2.12–2.05 (m, 1H), 1.99–1.80 (m, 6H), 1.74 (ddd, *J* = 13.8, 2.6, 2.6 Hz, 1H), 1.68–1.46 (m, 5H), 1.45–1.24 (m, 6H), 1.13 (dddd, *J* = 13.2, 13.2, 13.2, 4.0 Hz, 1H), 0.99 (s, 3H), 0.85 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 221.1, 69.4, 51.3, 47.7, 43.2, 43.1, 40.5, 38.7, 37.7, 37.6, 36.6, 35.8, 35.2, 34.5, 31.6, 26.6, 25.4, 23.3, 21.7, 20.2, 13.7 ppm.

LRMS (EI) *m*/*z* 364 (M), 336 (M–CO), 303 (M–CO–Me–H_2O).

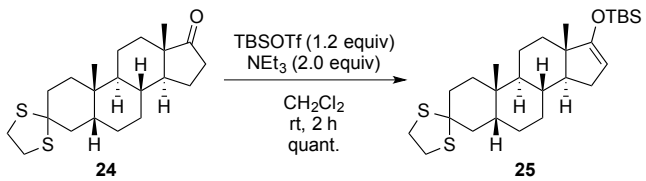
Anal. Calcd for $C_{21}H_{32}OS_2$: C, 69.18; H, 8.85. Found: C, 69.24; H, 9.00.

IR ($CHCl_3$) ν = 2920, 2855, 1732, 1450, 1215, 1049 cm^{-1}.

mp 222–224 °C.

$[\alpha]_D^{20}$ +100 (*c* 1.00, $CHCl_3$).

Compound 25



24 **25**

To a solution of ketone **24** (8.80 g, 24.1 mmol) in CH_2Cl_2 (96 mL) were added triethylamine (6.6 mL, 48 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.6 mL, 29 mmol). The mixture was stirred at room temperature for 2 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and passed through a short pad of silica gel with hexane/diethyl ether (10:1) to give **25** (11.6 g, quant.) as a white solid, which was used in the next step without further purification. Analytical sample was obtained by column chromatography (hexane/diethyl ether 50:1 to 20:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (s, 1H), 3.35–3.23 (m, 4H), 2.43 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.01–1.69 (m, 7H), 1.67–1.60 (m, 2H), 1.59–1.52 (m, 1H), 1.49–1.37 (m, 4H), 1.34–1.22 (m, 4H), 1.08 (dddd, *J* = 13.5, 13.5, 12.6, 4.0 Hz, 1H), 0.98 (s, 3H), 0.92 (s, 9H), 0.81 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 98.6, 69.7, 54.7, 44.6, 43.5, 43.3, 41.0, 38.7, 37.8, 37.6, 36.6, 34.7, 34.1, 33.6, 28.2, 26.8, 25.9, 23.4, 20.6, 18.1, 15.3, –4.7, –4.9 ppm.

LRMS (EI) *m*/*z* 478 (M), 463 (M–Me).

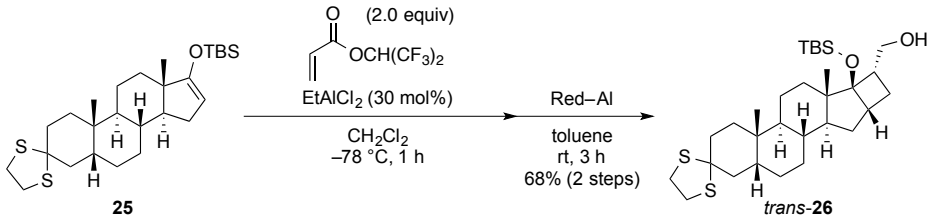
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{27}H_{47}OS_2Si$ 479.2838; Found 479.2841.

IR ($CHCl_3$) ν = 2928, 2855, 1617, 1447, 1250, 1227, 1107 cm^{-1}.

mp 118–120 °C.

$[\alpha]_D^{20}$ +43.2 (*c* 1.00, $CHCl_3$).

Compound *trans*-26



To a solution of **25** (7.99 g, 16.7 mmol) in CH_2Cl_2 (84 mL) were added 1,1,1,3,3,3-hexafluoroisopropyl acrylate (5.0 mL, 34 mmol) and a 1.0 M solution of ethylaluminum dichloride in hexane (5.0 mL, 5.0 mmol) at –78 °C. After being stirred for 1 h, the resulting mixture was quenched with triethylamine (25 mL). To the mixture, saturated aqueous Rochelle salt was added and stirred vigorously for 30 min. The aqueous layer was extracted with $CHCl_3$ twice, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give an orange oil. The residue was passed

through a short pad of silica gel with hexane/diethyl ether (20:1) to give a white solid (9.18 g, *cis*:*trans* = 4:96 by ^{1}H NMR), which was used directly in the next step without further purification. To a solution of the white solid (9.18 g) in toluene (66 mL) was added a 3.6 M solution of Red-Al in toluene (9.1 mL, 33 mmol) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous Rochell salt, and stirred vigorously for 30 min. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow solid, which was purified by column chromatography (hexane/ethyl acetate 20:1 to 4:1) to afford *trans*-**26** (6.08 g, 68% for two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02–3.96 (m, 1H), 3.87 (ddd, *J* = 9.7, 9.7, 5.2 Hz, 1H), 3.34–3.25 (m, 4H), 2.82–2.73 (m, 1H), 2.51–2.40 (m, 2H), 2.36–2.28 (m, 1H), 2.00 (ddd, *J* = 13.8, 13.8, 3.2 Hz, 1H), 1.92–1.79 (m, 3H), 1.73 (ddd, *J* = 13.8, 3.4, 3.4 Hz, 1H), 1.65–1.54 (m, 4H), 1.52–1.18 (m, 10H), 1.10–1.01 (m, 1H), 0.96 (s, 3H), 0.94–0.86 (m, 10H), 0.68 (s, 3H), 0.19 (s, 3H), 0.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 90.4, 69.8, 62.8, 50.4, 48.5, 48.3, 43.4, 43.3, 41.6, 40.4, 38.7, 37.8, 37.7, 36.7, 35.8, 34.6, 33.5, 32.0, 26.9, 26.8, 25.8, 24.6, 23.5, 20.8, 18.2, 17.3, –2.7, –3.1 ppm.

LRMS (EI) *m*/*z* 536 (M), 521 (M–Me).

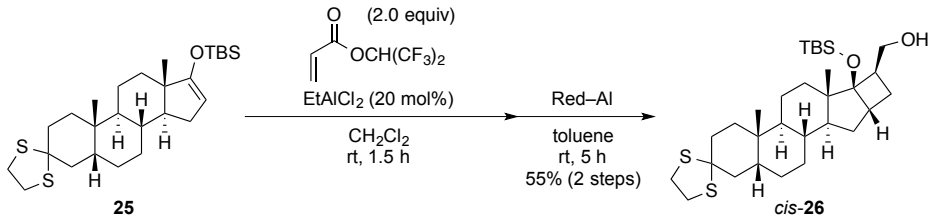
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{30}H_{53}O_2S_2Si$ 537.3256; Found 537.3244.

IR (KBr) ν = 3433 (br), 2953, 2928, 2859, 1447, 1385, 1377, 1256, 1252, 1120, 1009 cm^{-1}.

mp 84–86 °C.

$[\alpha]_D^{20}$ +9.6 (*c* 1.00, $CHCl_3$).

Compound *cis*-26



To a solution of **25** (7.86 g, 16.4 mmol) in CH_2Cl_2 (55 mL) were added 1,1,1,3,3,3-hexafluoroisopropyl acrylate (4.8 mL, 33 mmol) and a 1.0 M solution of ethylaluminum dichloride in hexane (3.3 mL, 3.3 mmol). After being stirred for 1.5 h at room temperature, the resulting mixture was quenched with triethylamine (25 mL). To the mixture, saturated aqueous Rochelle salt was added and stirred vigorously for 30 min. The aqueous layer was extracted with

$CHCl_3$ twice, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. The residue was passed through a short pad of silica gel with hexane/diethyl ether (20:1) to give a white solid (9.26 g, *cis*:*trans* = 100:0 by ^{1}H NMR), which was used directly in the next step without further purification. To a solution of the white solid (9.26 g) in toluene (65 mL) was added a 3.6 M solution of Red-Al in toluene (9.2 mL, 33 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction mixture was quenched with saturated aqueous Rochell salt, and stirred vigorously for 30 min. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate 20:1 to 9:1) to afford *cis*-**26** (4.84 g, 55% for two steps) as a white solid. Analytical sample was obtained by recrystallization from hexane/ethyl acetate as white blocks.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (ddd, *J* = 10.9, 10.9, 2.3 Hz, 1H), 3.48 (ddd, *J* = 11.2, 11.2, 5.7 Hz, 1H), 3.33–3.26 (m, 4H), 2.74–2.67 (m, 1H), 2.59–2.53 (m, 1H), 2.45 (dd, *J* = 13.5, 13.5 Hz, 1H), 1.98 (ddd, *J* = 14.1, 14.1, 3.2 Hz, 1H), 1.92–1.71 (m, 6H), 1.65–1.59 (m, 1H), 1.53–1.43 (m, 6H), 1.42–1.36 (m, 1H), 1.34–1.20 (m, 6H), 1.14–1.05 (m, 1H), 0.97 (s, 3H), 0.92 (s, 9H), 0.67 (s, 3H), 0.27 (s, 3H), 0.14 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 90.8, 69.7, 63.8, 48.8, 46.2, 43.4, 43.3, 40.6, 39.3, 38.8, 38.7, 37.8, 37.7, 36.7, 35.3, 34.5, 32.2, 29.7, 26.8, 26.6, 26.1, 24.2, 23.4, 20.3, 18.4, 14.6, –1.2, –2.3 ppm.

LRMS (EI) *m*/*z* 536 (M), 521 (M–Me).

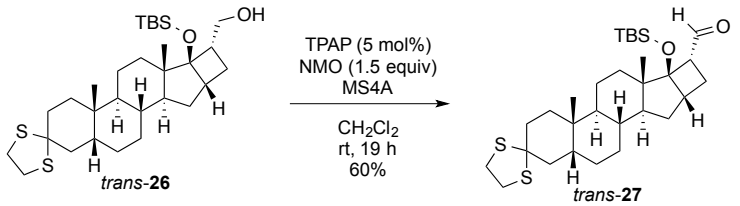
Anal. Calcd for $C_{30}H_{52}O_2S_2Si$: C, 67.11; H, 9.76. Found: C, 67.13; H, 9.95.

IR (KBr) ν = 3447 (br), 2953, 2928, 2857, 1447, 1387, 1377, 1254, 1080, 1065 cm^{-1}.

mp 172–173 °C.

$[\alpha]_D^{20}$ +25.6 (*c* 1.00, $CHCl_3$).

Compound *trans*-27



To a solution of *trans*-**26** (800 mg, 1.49 mmol) in CH_2Cl_2 (15 mL) were added MS4A (3.21 g), NMO (265 mg, 2.26 mmol) and TPAP (26.0 mg, 74.0 μmol), and the reaction mixture was stirred for 19 h at room temperature, The resulting mixture was filtered though Celite, and concentrated in

vacuo. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to give *trans*-**27** (480 mg, 60%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.1 (d, *J* = 1.4 Hz, 1H), 3.35 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.32–3.23 (m, 4H), 2.60–2.55 (m, 1H), 2.40 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.09–2.02 (m, 1H), 1.96 (ddd, *J* = 14.0, 14.0, 2.9 Hz, 1H), 1.88–1.76 (m, 4H), 1.72–1.67 (m, 2H), 1.64–1.58 (m, 1H), 1.47–1.38 (m, 5H), 1.33–1.17 (m, 5H), 1.13–1.03 (m, 2H), 0.94 (s, 3H), 0.92 (s, 9H), 0.68 (s, 3H), 0.24 (s, 3H), 0.16 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 95.6, 69.8, 59.9, 48.6, 47.6, 43.4, 43.3, 42.3, 40.0, 38.7, 37.9, 37.6, 36.7, 35.9, 34.6, 34.5, 33.4, 27.0, 26.7, 25.7, 23.5, 21.0, 18.7, 18.2, 16.2, –2.8, –3.3 ppm.

LRMS (EI) *m*/*z* 534 (M), 519 (M–Me), 477 (M–*t*Bu).

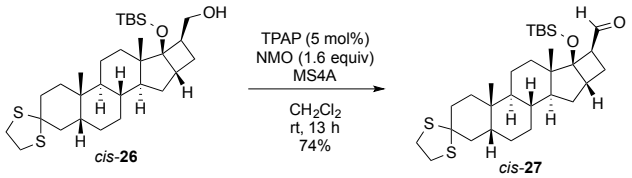
Anal. Calcd for $C_{30}H_{50}O_2S_2Si$: C, 67.36; H, 9.42. Found: C, 67.27; H, 9.42.

IR (KBr) ν = 2928, 2857, 1709, 1472, 1447, 1260, 895, 835, 773 cm^{-1}.

mp 71–73 °C.

$[\alpha]_D^{20}$ –37.8 (*c* 1.00, $CHCl_3$).

Compound *cis*-27



To a solution of *cis*-**26** (766 mg, 1.43 mmol) in CH_2Cl_2 (14 mL) were added MS4A (3.00 g), NMO (268 mg, 2.29 mmol) and TPAP (26.1 mg, 74.3 μmol), and the reaction mixture was stirred for 13 h at room temperature, The resulting mixture was filtered though Celite, and concentrated in vacuo. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to give *cis*-**27** (568 mg, 74%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (s, 1H), 3.35–3.24 (m, 5H), 2.85 (ddd, *J* = 12.3, 9.5, 9.5 Hz, 1H), 2.58 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.44 (dd, *J* = 13.5, 13.5 Hz, 1H), 2.01 (ddd, *J* = 13.8, 13.8, 3.2 Hz, 1H), 1.95–1.81 (m, 3H), 1.74 (ddd, *J* = 13.8, 3.2, 3.2 Hz, 1H), 1.67–1.25 (m, 13H), 1.19 (ddd, *J* = 12.6, 8.9, 2.9 Hz, 1H), (ddd, *J* = 13.5, 13.5, 3.8 Hz, 1H), 0.99 (s, 3H), 0.84 (s, 9H), 0.68 (s, 3H), 0.13 (s, 3H), 0.07 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 92.9, 69.6, 49.7, 49.0, 46.5, 43.3, 41.1, 40.6, 38.8, 37.8, 37.7, 36.7, 35.4, 34.6, 32.3, 30.3, 26.8, 26.5, 25.9, 23.4, 20.9, 20.3, 18.4, 14.1, –1.6, –2.9 ppm.

LRMS (EI) *m*/*z* 534 (M), 519 (M–Me), 477 (M–*t*Bu).

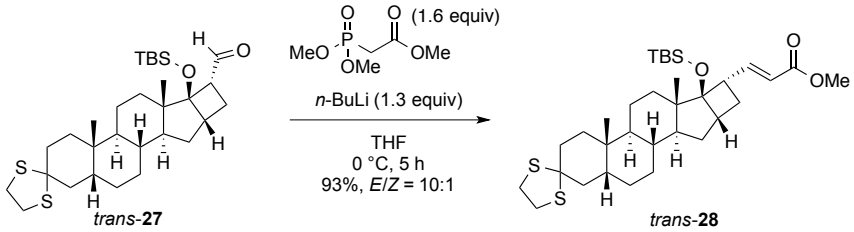
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{30}H_{50}O_2S_2SiNa$ 557.2913; Found 557.2925.

IR ($CHCl_3$) ν = 2928, 2859, 1721, 1447, 1250, 1007, 837, 760 cm^{-1}.

mp 109–111 °C.

$[\alpha]_D^{20}$ +58.8 (*c* 1.00, $CHCl_3$).

Compound *trans*-28



To a solution of trimethyl phosphonoacetate (0.20 mL, 1.3 mmol) in THF (3 mL) was added a 2.5 M solution of *n*-BuLi in hexane (0.44 mL, 1.1 mmol) at – 78 °C. After the mixture was stirred for 30 min at 0 °C, a solution of *trans*-**27** (446 mg, 0.834 mmol) in THF (5.3 mL) was added at –78 °C. The reaction mixture was stirred for 5 h at 0 °C and quenched with water. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a white solid. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to afford *trans*-**28** (460 mg, 93%, *E*:*Z* = 10:1) as a white solid. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample. The following data are for the (*E*)-isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 15.8, 7.2 Hz, 1H), 5.74 (ddd, *J* = 15.8, 1.7, 1.7 Hz, 1H), 3.81 (s, 3H), 3.34–3.24 (m, 5H), 2.56–2.50 (m, 1H), 2.41 (dd, *J* = 13.2, 13.2, Hz, 1H), 2.37–2.29 (m, 1H), 1.96–1.77 (m, 4H), 1.75–1.69 (m, 1H), 1.57–1.22 (m, 13H), 1.18 (ddd, *J* = 12.6, 12.6, 4.3 Hz, 1H), 1.13–1.04 (m, 1H), 0.93 (s, 3H), 0.89 (s, 9H), 0.66 (s, 3H), 0.20 (s, 3H), 0.12 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 149.1, 118.7, 92.8, 69.8, 51.7, 50.1, 48.6, 48.4, 43.33, 43.28, 41.9, 40.5, 38.7, 37.73, 37.67, 36.7, 35.7, 34.4, 33.5, 32.2, 26.9, 26.7, 25.7, 24.6, 23.5, 20.9, 18.2, 16.9, –2.7, –3.1 ppm.

LRMS (EI) *m*/*z* 590 (M), 575 (M–Me), 559 (M–OMe), 533 (M–*t*Bu).

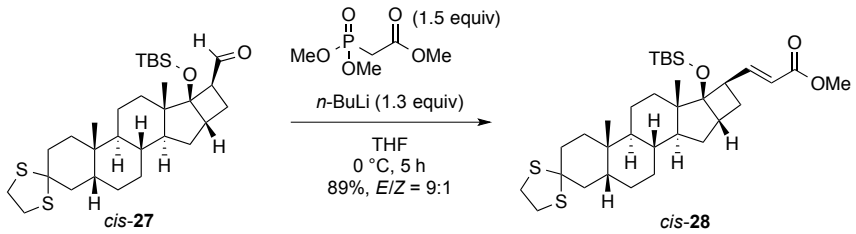
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{33}H_{54}O_3S_2Si$ 591.3357; Found 591.3371.

IR (KBr) ν = 2953, 2930, 2859, 1726, 1445, 1260 cm^{-1}.

mp 154–157 °C.

$[\alpha]_D^{20}$ +45.8 (*c* 1.00, $CHCl_3$).

Compound *cis*-28



To a solution of trimethyl phosphonoacetate (0.33 mL, 2.1 mmol) in THF (4 mL) was added a 2.5 M solution of *n*-BuLi in hexane (0.71 mL, 1.8 mmol) at – 78 °C. After the mixture was stirred for 30 min at 0 °C, a solution of *cis*-**27** (730 mg, 1.36 mmol) in THF (10 mL) was added at –78 °C. The reaction mixture was stirred for 5 h at 0 °C and quenched with water. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a white solid. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to afford *cis*-**28** (714 mg, 89%, *E*:*Z* = 9:1) as a white solid. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample. The following data are for the (*E*)-isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 15.8, 6.0 Hz, 1H), 5.73 (ddd, *J* = 15.8, 1.8, 1.8 Hz, 1H), 3.71 (s, 3H), 3.33–3.21 (m, 5H), 2.60–2.55 (m, 1H), 2.45 (dd, *J* = 13.2, 13.2, Hz, 1H), 2.34–2.26 (m, 1H), 2.00 (ddd, *J* =13.8, 13.8, 2.6 Hz, 1H), 1.93–1.80 (m, 3H), 1.74 (ddd, *J* = 13.8, 2.9, 2.9 Hz, 1H), 1.66–1.60 (m, 1H), 1.51–1.45 (m, 5H), 1.44–1.37 (m, 2H), 1.36–1.22 (m, 6H), 1.15–1.05 (m, 1H), 0.98 (s, 3H), 0.86 (s, 9H), 0.66 (s, 3H), 0.18 (s, 3H), 0.07 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 151.6, 120.1, 91.5, 69.7, 51.2, 49.2, 46.8, 43.4, 43.3, 40.7, 40.6, 40.3, 38.8, 37.8, 37.7, 36.7, 35.5, 34.6, 32.2, 29.5, 27.5, 26.9, 26.6, 25.9, 23.5, 20.3, 18.4, 14.4, –1.6, –2.5 ppm.

LRMS (EI) *m*/*z* 590 (M), 575 (M–Me), 559 (M–OMe), 533 (M–*t*Bu).

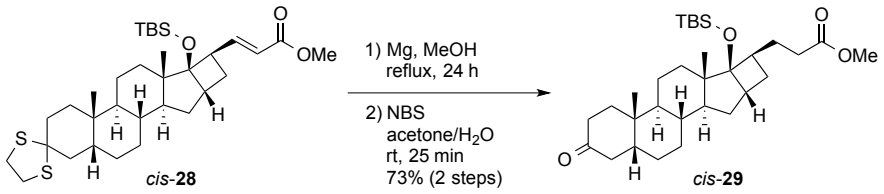
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{33}H_{54}O_3S_2Si$ 613.3176; Found 613.3181.

IR (KBr) ν = 2930, 2857, 1724, 1653, 1472, 1447, 1258, 1163 cm^{-1}.

mp 108–110 °C.

$[\alpha]_D^{20}$ +64.8 (*c* 1.00, $CHCl_3$).

Compound *cis*-29



A mixture of *cis*-**28** (323 mg, 0.547 mmol) and magnesium turnings (163 mg, 6.71 mmol) in MeOH (11 mL) was stirred under reflux for 24 h. After the resulting mixture was allowed to cool to room temperature and diluted with diethyl ether, 1.0 M HCl was added carefully until excess magnesium was dissolved, and the aqueous layer was extracted with diethyl ether twice. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow solid (349 mg). To a solution of the pale yellow solid (349 mg) in acetone/H_2O (20:1, 10 mL) was added NBS (632 mg, 3.55 mmol). The reaction mixture was stirred for 25 min at room temperature, and quenched with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a pale yellow oil. The residue was purified by column chromatography (hexane/ethyl acetate 8:1) to give *cis*-**29** (220 mg, 73% for two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.74 (dd, *J* = 14.4, 14.4 Hz, 1H), 2.57–2.50 (m, 1H), 2.38–2.26 (m, 3H), 2.23–2.12 (m, 2H), 2.08–2.02 (m, 1H), 1.94–1.77 (m, 4H), 1.66–1.47 (m, 7H), 1.44–1.24 (m, 8H), 1.17 (ddd, *J* = 13.8, 13.8, 3.8 Hz, 1H), 1.04 (s, 3H), 0.90 (s, 9H), 0.69 (s, 3H), 0.25 (s, 3H), 0.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 174.3, 90.1, 51.3, 49.1, 46.4, 44.4, 42.4, 41.1, 39.9, 37.2, 37.1, 37.0, 35.3, 35.1, 32.6, 32.1, 29.8, 28.7, 26.6, 26.3, 26.0, 25.9, 22.7, 20.6, 18.6, 14.6, –1.3, –2.4 ppm.

LRMS (EI) *m*/*z* 516 (M), 501 (M–Me), 459 (M–*t*Bu).

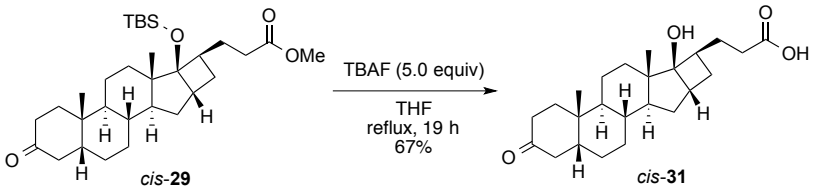
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{31}H_{53}O_4Si$ 517.3713; Found 517.3724.

IR (KBr) ν = 2951, 2930, 2859, 1742, 1713, 1472, 1437, 1252, 1175, 1120, 1082 cm^{-1}.

mp 120–122 °C.

$[\alpha]_D^{20}$ +32.8 (*c* 1.00, $CHCl_3$).

Compound *cis*-31



To a solution of *cis*-**29** (155 mg, 0.300 mmol) in THF (1.0 mL) was added 1.0 M TBAF solution in THF (1.5 mL, 1.5 mmol), and the reaction mixture was heated under reflux for 19 h. The resulting mixture was allowed to cool to room temperature, washed with water, and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a light brown solid. The residue was purified by column chromatography (hexane/ethyl acetate 3:2 to 1:1) to afford *cis*-**31** (80.9 mg, 67%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75 (dd, J = 14.1, 14.1, Hz, 1H), 2.40–2.25 (m, 5H), 2.19 (d, J = 14.6 Hz, 1H), 2.10–2.02 (m, 2H), 1.96–1.82 (m, 4H), 1.71–1.63 (m, 1H), 1.60–1.25 (m, 15H), 1.22–1.13 (m, 1H), 1.04 (s, 3H), 0.76 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8, 179.3, 87.5, 50.3, 45.6, 44.2, 42.3, 41.0, 40.8, 37.1, 37.0, 35.7, 35.4, 35.0, 32.4, 31.7, 29.8, 28.5, 26.5, 25.9, 25.7, 22.6, 20.5, 13.9 ppm.

LRMS (EI) *m*/*z* 388 (M), 370 (M–H_2O), 355 (M–H_2O–Me).

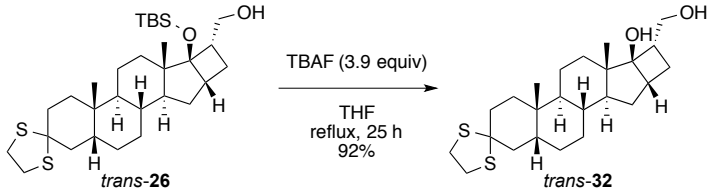
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{24}H_{36}O_4Na$ 411.2506; Found 411.2503.

IR (KBr) ν = 3431 (br), 2934, 2862, 1734, 1713, 1452, 1381, 1339, 1263, 1184 cm^{-1}.

mp 82–84 °C.

$[\alpha]_D^{20}$ +50.0 (*c* 1.00, $CHCl_3$).

Compound *trans*-32



A mixture of *trans*-**26** (4.87 g, 9.07 mmol) and a 1.0 M solution of TBAF in THF (35 mL, 35 mmol) was heated under reflux for 25 h. The resulting mixture was allowed to cool to room temperature, washed with water, and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a brown solid. The residue was purified by column chromatography (hexane/ethyl acetate 2:3) to give *trans*-**32** (3.54 g, 92%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (ddd, *J* = 10.9, 10.9, 4.0 Hz, 1H), 3.84 (ddd, *J* = 11.7, 11.7, 3.7 Hz, 1H), 3.36–3.24 (m, 4H), 2.83–2.72 (m, 1H), 2.44 (dd, *J* = 13.5, 13.5 Hz, 1H), 2.39–2.29 (m, 2H), 2.01 (ddd, *J* = 13.8, 13.8, 2.6 Hz, 1H), 1.94–1.79 (m, 4H), 1.77–1.55 (m, 5H), 1.54–1.20 (m, 10H), 1.08 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1H), 0.97 (s, 3H), 0.93 (dd, *J* = 8.3, 8.3 Hz, 1H), 0.78 (s, 3H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ 87.2, 69.6, 61.0, 50.1, 48.7, 46.7, 43.1, 42.7, 41.1, 38.2, 37.3, 37.2, 36.5, 35.4, 34.2, 33.0, 31.7, 26.5, 26.4, 25.0, 23.5, 20.4, 16.5 ppm (one signal missing).

LRMS (EI) *m*/*z* 422 (M), 404 (M–H_2O).

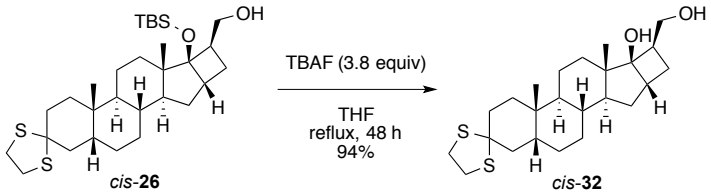
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{24}H_{38}O_2S_2Na$ 445.2105; Found 445.2108.

IR (KBr) ν = 3480, 3395, 3186, 2963, 2924, 2853, 1445, 1377, 1279, 1007, 995 cm^{-1}.

mp 140–143 °C.

$[\alpha]_D^{20}$ +22.9 (*c* 1.00, $CHCl_3$).

Compound *cis*-32



A mixture of *cis*-**26** (4.07 g, 7.59 mmol) and a 1.0 M solution of TBAF in THF (29 mL, 29 mmol) was heated under reflux for 48 h. The resulting mixture was allowed to cool to room temperature, washed with water, and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a brown solid. The residue was purified by column chromatography (hexane/ethyl acetate 7:3) to give *cis*-**32** (3.01 g, 94%) as a white solid. Analytical sample was obtained by recrystallization from hexane/ethyl acetate as white needles.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85–3.70 (m, 2H), 3.38–3.22 (m, 4H), 2.63–2.53 (m, 1H), 2.49 (s, 1H), 2.45 (dd, *J* = 13.5, 13.5 Hz, 1H), 2.34–2.26 (m, 1H), 2.18 (dd, *J* = 5.7, 5.7 Hz, 1H), 2.15–2.06 (m, 1H), 1.99 (ddd, *J* = 13.8, 13.8, 2.9 Hz, 1H), 1.94–1.79 (m, 3H), 1.74 (ddd, *J* = 13.8, 2.6, 2.6 Hz, 1H), 1.67–1.60 (m, 1H), 1.55–1.18 (m, 13H), 1.16–1.03 (m, 1H), 0.98 (s, 3H), 0.74 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 88.4, 69.7, 63.5, 49.8, 45.4, 43.30, 43.25, 41.4, 40.6, 38.7, 37.8, 37.02, 36.69, 35.4,34.5, 32.1, 29.8, 26.8, 26.5, 23.4, 23.1, 20.3, 13.7 ppm.

LRMS (EI) *m*/*z* 422 (M), 404 (M–H_2O).

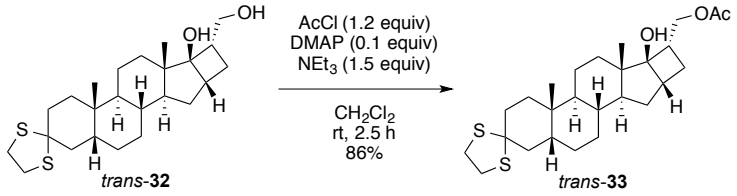
Anal. Calcd for $C_{24}H_{38}O_2S_2$: C, 68.20; H, 9.01. Found: C, 68.20; H, 9.06.

IR ($CHCl_3$) ν = 3387 (br), 2928, 2859, 2361, 1447, 1381, 756 cm^{-1}.

mp 168–169 °C.

$[\alpha]_D^{20}$ +33.6 (*c* 1.00, $CHCl_3$).

Compound *trans*-33



To a mixture of *trans*-**32** (3.00 g, 7.10 mmol) and DMAP (86.7 mg, 0.709 mmol) in CH_2Cl_2 (36 mL) were added triethylamine (1.5 mL, 10.8 mmol) and acetyl chloride (0.60 mL, 8.5 mmol). The reaction mixture was stirred for 2.5 h at room temperature, and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a white solid. The residue was purified by column chromatography (hexane/ethyl acetate 4:1) to afford *trans*-**33** (2.83 g, 86%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (dd, *J* = 11.2, 7.2 Hz, 1H), 4.26 (dd, *J* = 10.9, 8.3 Hz 1H), 3.34–3.24 (m, 4H), 2.89–2.80 (m, 1H), 2.42 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.39–2.27 (m, 2H), 2.08 (s, 3H), 2.01 (ddd, *J* = 13.8, 13.8, 2.9 Hz, 1H), 1.93–1.80 (m, 4H), 1.77–1.55 (m, 5H), 1.51–1.22 (m, 9H), 1.12–0.98 (m, 2H), 0.98 (s, 3H), 0.78 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 88.6, 69.7, 64.0, 49.4, 47.0, 45.7, 43.4, 43.2, 42.3, 40.2, 38.7, 37.8, 37.6, 36.7, 35.9, 34.6, 33.0, 31.6, 26.9, 26.8, 23.9, 23.5, 21.1, 20.7, 16.2 ppm.

LRMS (EI) *m*/*z* 464 (M), 431 (M–Me–H_2O), 404 (M–AcOH), 386 (M–H_2O–AcOH).

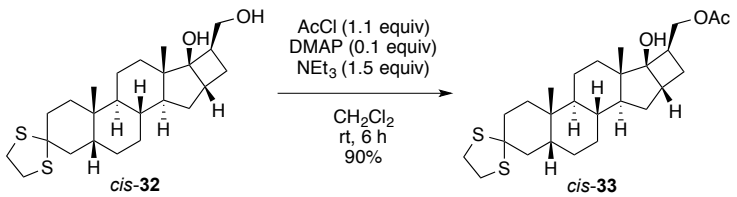
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{26}H_{40}O_3S_2Na$ 487.2311; Found 487.2306.

IR ($CHCl_3$) ν = 3410 (br), 2928, 2862, 1728, 1447, 1369, 1238, 1215, 1026 cm^{-1}.

mp 83–85 °C.

$[\alpha]_D^{20}$ +24.4 (*c* 1.00, $CHCl_3$).

Compound *cis*-33



To a mixture of *cis*-**32** (1.80 g, 4.26 mmol) and DMAP (51.3 mg, 0.420 mmol) in CH_2Cl_2 (21 mL)

were added triethylamine (0.89 mL, 6.4 mmol) and acetyl chloride (0.36 mL, 4.7 mmol). The reaction mixture was stirred for 6 h at room temperature, and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a white solid. The residue was purified by column chromatography (hexane/ethyl acetate 4:1) to afford *cis*-**33** (1.79 g, 90%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 9.8, 9.8, Hz, 1H), 4.00 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.35–3.24 (m, 4H), 2.71 (s, 1H), 2.68–2.59 (m, 1H), 2.44 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.32–2.24 (m, 1H), 2.04 (s, 3H), 2.03–1.78 (m, 5H), 1.74 (d, *J* = 13.5 Hz, 1H), 1.66–1.60 (m, 1H), 1.54–1.04 (m, 14H), 0.97 (s, 3H), 0.73 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 87.1, 69.7, 64.7, 50.7, 45.7, 43.33, 43.31, 40.6, 39.9, 38.8, 37.9, 37.7, 36.7, 35.6, 35.1, 34.6, 31.6, 29.6, 26.8, 26.6, 24.3, 23.4, 21.1, 20.4, 13.8 ppm.

LRMS (EI) *m*/*z* 464 (M), 449 (M–Me), 404 (M–AcOH).

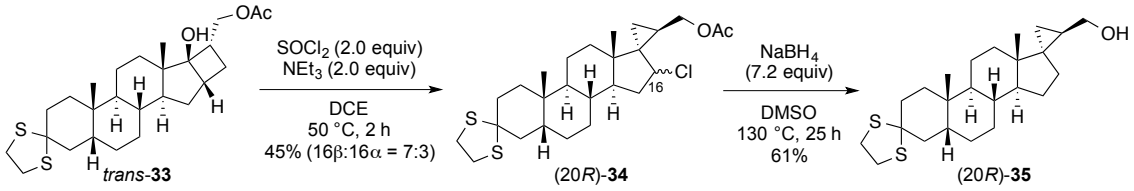
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{26}H_{40}O_3S_2Na$ 487.2311; Found 487.2314.

IR ($CHCl_3$) ν = 3441 (br), 2928, 2859, 1717, 1447, 1366, 1250, 1034 cm^{-1}.

mp 69–71 °C.

$[\alpha]_D^{20}$ +60.0 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-35



To a solution of *trans*-**33** (2.19 g, 4.71 mmol) in dichloroethane (24 mL) were added triethylamine (1.3 mL, 9.4 mmol) and thionyl chloride (0.69 mL, 9.5 mmol) under argon. After being stirred at 50 °C for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 10:1) to afford (20*R*)-**34** (1.12 g, 49%, dr 7:3) as a pale yellow solid. The inseparable mixture was used in the next step without separation. The mixture of (20*R*)-**34** (1.12 g, 2.32 mmol), $NaBH_4$ (634 mg, 16.8 mmol) and DMSO (7.5 mL) was stirred for 25 h at 130 °C. After cooling to room temperature, water was added to the mixture. The aqueous layer was extracted with hexane/ethyl acetate (4:1) three times, and the combined organic layers were

washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was partially purified by column chromatography (hexane/ethyl acetate 4:1) to give (20*R*)-**35** (578 mg, 61%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (ddd, *J* = 11.5, 5.8, 5.8, Hz, 1H), 3.49 (ddd, *J* = 10.1, 10.1, 3.7 Hz, 1H), 3.33–3.24 (m, 4H), 2.42 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.04–1.93 (m, 2H), 1.92–1.65 (m, 6H), 1.61–1.01 (m, 15H), 0.96 (s, 3H), 0.83 (s, 3H), 0.61 (dd, *J* = 5.2, 5.2 Hz, 1H), 0.39 (dd, *J* = 8.3, 4.3 Hz, 1H) ppm.

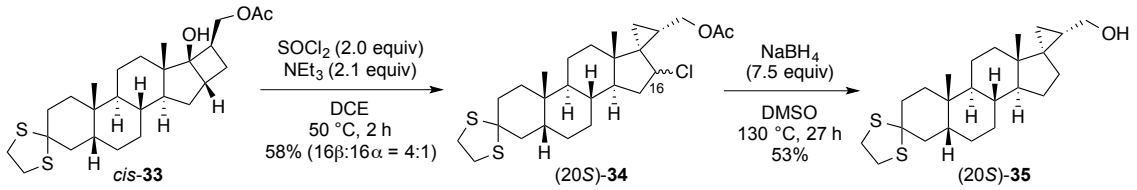
^{13}C NMR (125 MHz, $CDCl_3$) δ 69.7, 63.2, 55.6, 43.22, 43.20, 41.3, 40.2, 38.7, 37.8, 37.7, 36.8, 36.59, 36.56, 36.0, 35.8, 34.3, 26.9, 26.4, 25.0, 24.9, 23.4, 20.7, 17.1, 17.0 ppm.

LRMS (EI) *m*/*z* 406 (M), 388 (M–H_2O), 373 (M–H_2O–Me).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{24}H_{38}OS_2Na$ 407.2442; Found 407.2456.

$[\alpha]_D^{20}$ +33.2 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-35



To a solution of *cis*-**33** (2.09 g, 4.50 mmol) in dichloroethane (23 mL) were added triethylamine (1.3 mL, 9.4 mmol) and thionyl chloride (0.66 mL, 9.1 mmol) under argon. After being stirred at 50 °C for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/diethyl ether 9:1) to afford (20*S*)-**34** (1.26 g, 58%, dr 4:1) as a pale yellow solid. The inseparable mixture was used in the next step without separation. The mixture of (20*S*)-**34** (1.08 g, 2.24 mmol), $NaBH_4$ (633 mg, 16.7 mmol) and DMSO (7.5 mL) was stirred for 27 h at 130 °C. After cooling to room temperature, water was added to the mixture. The aqueous layer was extracted with hexane/ethyl acetate (4:1) three times, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 4:1) to give (20*S*)-**35** (485 mg, 53%) as a white amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68–3.57 (m, 1H), 3.54–3.44 (m, 1H), 3.35–3.23 (m, 4H), 2.42 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.09–1.68 (m, 6H), 1.65–1.57 (m, 1H), 1.49 (dd, *J* = 13.5, 2.9 Hz, 1H), 1.45–

1.15 (m, 10H), 1.14–1.00 (m, 2H), 0.96 (s, 3H), 0.95–0.85 (m, 3H), 0.75 (s, 3H), –0.03 (s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 69.7, 65.2, 54.4, 43.4, 43.3, 41.2, 40.5, 38.7, 37.8, 37.7, 36.7, 36.4, 36.3, 34.5, 33.3, 29.0, 26.9, 26.7, 24.9, 23.4, 20.5, 19.7, 17.2, 16.2 ppm.

LRMS (EI) *m*/*z* 406 (M), 391 (M–Me).

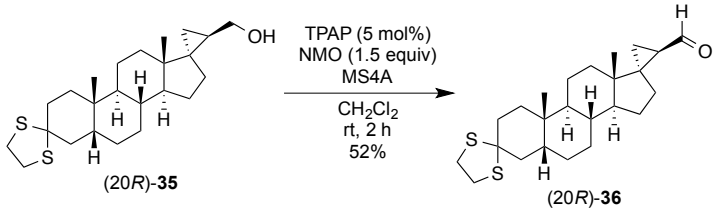
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{24}H_{39}OS_2$ 407.2442; Found 407.2428.

IR ($CHCl_3$) ν = 3356 (br), 2924, 2859, 1443, 1377, 1273, 1215, 1107, 1015 cm^{-1}.

mp 69–71 °C.

$[\alpha]_D^{20}$ +30.2 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-36



To a solution of (20*R*)-**35** (513 mg, 1.26 mmol) in CH_2Cl_2 (13 mL) were added MS4A (630 mg), NMO (226 mg, 1.93 mmol) and TPAP (22.5 mg, 64.0 μmol), and the reaction mixture was stirred for 2 h at room temperature, The resulting mixture was filtered though Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 20:1 to 10:1) to give (20*R*)-**36** (265 mg, 52%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.09 (d, *J* = 7.5 Hz, 1H), 3.34–3.25 (m, 4H), 2.41 (dd, *J* = 13.2, 13.2 Hz, 1H), 2.17–2.08 (m, 1H), 1.98 (ddd, *J* = 13.5, 13.5, 2.9 Hz, 1H), 1.91–1.67 (m, 7H), 1.65–1.59 (m, 1H), 1.52–1.25 (m, 12H), 1.13–1.04 (m, 2H), 0.96 (s, 3H), 0.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 69.6, 55.5, 44.9, 43.2, 43.1, 41.8, 40.1, 38.7, 37.8, 37.7, 36.6, 36.4, 36.2, 35.4, 34.4, 26.8, 26.3, 24.7, 23.3, 21.9, 20.7, 18.0 ppm.

LRMS (EI) *m*/*z* 404 (M), 389 (M–Me), 376 (M–CO).

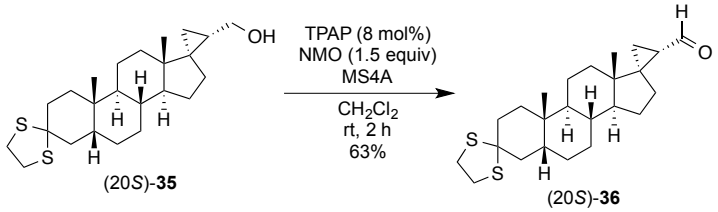
Anal. Calcd for $C_{24}H_{36}OS_2$: C, 71.23; H, 8.97. Found: C, 71.19; H, 9.08.

IR (KBr) ν = 2970, 2934, 2918, 2857, 2830, 1690, 1445, 1429, 1383, 1279, 1177 cm^{-1}.

mp 218–219 °C.

$[\alpha]_D^{20}$ +73.4 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-36



To a solution of (20*S*)-**35** (361 mg, 0.888 mmol) in CH_2Cl_2 (8.8 mL) were added MS4A (450 mg), NMO (158 mg, 1.35 mmol) and TPAP (26.1 mg, 74.3 μmol), and the reaction mixture was stirred for 2 h at room temperature, The resulting mixture was filtered though Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 10:1) to give (20*S*)-**36** (226 mg, 63%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (d, *J* = 6.3 Hz, 1H), 3.35–3.24 (m, 4H), 2.41 (dd, *J*= 13.5, 13.5 Hz, 1H), 2.19–2.10 (m, 1H), 2.02–1.77 (m, 5H), 1.76–1.57 (m, 4H), 1.54–1.20 (m, 10H), 1.17–1.05 (m, 3H), 1.01–0.92 (m, 4H), 0.78 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 69.6, 53.4, 43.7, 43.2, 42.5, 40.4, 38.8, 37.8, 37.7, 36.7, 36.3, 34.5, 33.1, 31.0, 29.5, 26.8, 26.5, 25.0, 23.4, 21.0, 20.4, 17.1 ppm.

LRMS (EI) *m*/*z* 404 (M), 389 (M–Me), 376 (M–CO).

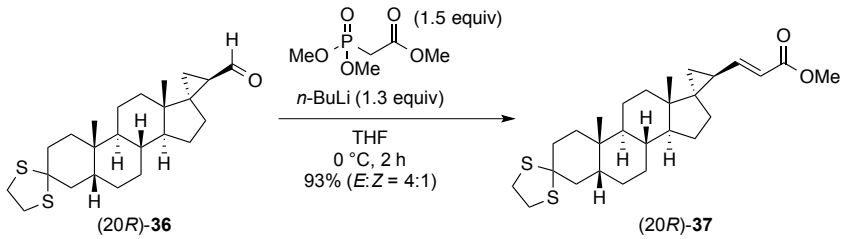
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{24}H_{36}OS_2Na$ 427.2105; Found 427.2115.

IR (KBr) ν = 2926, 2886, 2857, 1703, 1445, 1379, 1274, 1169, 1098, 1022 cm^{-1}.

mp 74–76 °C.

$[\alpha]_D^{20}$ +54.2 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-37



To a solution of trimethyl phosphonoacetate (0.14 mL, 0.87 mmol) in THF (2.0 mL) was added a 2.5 M solution of *n*-BuLi in hexane (0.30 mL, 0.75 mmol) at – 78 °C. After the mixture was stirred for 30 min at 0 °C, a solution of (20*R*)-**36** (232 mg, 0.573 mmol) in THF (4.0 mL) was added at –78 °C. The reaction mixture was stirred for 2 h at 0 °C and quenched with water. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a white solid. The residue was

purified by column chromatography (hexane/diethyl ether 10:1) to afford (20*R*)-**37** (246 mg, 93%, *E*:*Z* = 4:1) as a white solid. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample. The following data are for (*E*)-isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (dd, *J* = 15.2, 4.1 Hz, 1H), 5.87 (d, *J* = 15.2 Hz, 1H), 3.70 (s, 3H), 3.35–3.20 (m, 4H), 2.41 (dd, *J* = 13.8, 13.8 Hz, 1H), 2.11–1.93 (m, 2H), 1.92–1.78 (m, 3H), 1.77–1.69 (m, 2H), 1.68–1.58 (m, 2H), 1.52–1.22 (m, 12H), 1.15–1.01 (m, 2H), 0.95 (s, 3H), 0.85 (dd, *J* = 8.0, 4.6 Hz, 1H), 0.79 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 152.2, 118.1, 69.7, 55.5, 51.2, 43.2, 42.1, 41.8, 40.1, 38.7, 37.8, 37.7, 36.6, 36.3, 36.0, 35.5, 34.4, 26.9, 26.5, 26.4, 24.9, 23.5, 23.4, 20.7, 16.7 ppm.

LRMS (EI) *m*/*z* 460 (M), 445 (M–Me), 429 (M–OMe).

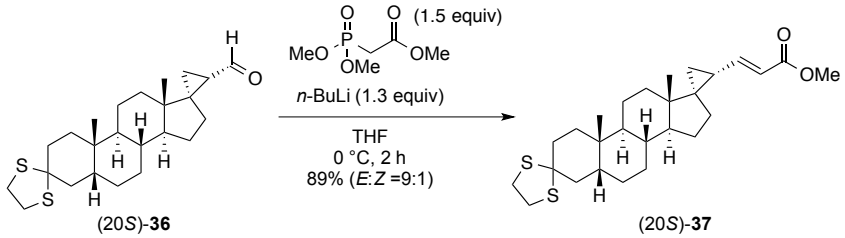
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{27}H_{40}O_2S_2Na$ 483.2362; Found 483.2372.

IR ($CHCl_3$) ν = 2926, 2859, 1719, 1638, 1437, 1383, 1271, 1148, 1045 cm^{-1}.

mp 93–96 °C.

$[\alpha]_D^{20}$ +82.8 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-37



To a solution of trimethyl phosphonoacetate (0.13 mL, 0.81 mmol) in THF (1.0 mL) was added a 2.5 M solution of *n*-BuLi in hexane (0.28 mL, 0.70 mmol) at – 78 °C. After the mixture was stirred for 30 min at 0 °C, a solution of (20*S*)-**36** (220 mg, 0.544 mmol) in THF (4.5 mL) was added at –78 °C. The reaction mixture was stirred for 2 h at 0 °C and quenched with water. The aqueous layer was extracted with ethyl acetate twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a white solid. The residue was purified by column chromatography (hexane/diethyl ether 10:1) to afford (20*S*)-**37** (224 mg, 89%, *E*:*Z* = 9:1) as a white solid. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample. The following data are for the (*E*)-isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 15.5, 10.3 Hz, 1H), 5.86 (d, *J* = 15.2 Hz, 1H), 3.71 (s, 3H), 3.34–3.24 (m, 4H), 2.41 (dd, *J* = 13.5, 13.5 Hz, 1H), 2.10–2.02 (m, 1H), 1.97 (ddd, *J* = 13.8, 13.8, 2.6 Hz, 1H), 1.92–1.76 (m, 4H), 1.75–1.68 (m, 1H), 1.65–1.57 (m, 1H), 1.51–1.18 (m, 12H),

1.14–1.04 (m, 2H), 1.01–0.92 (m, 1H), 0.96 (s, 3H), 0.72 (s, 3H), 0.51 (dd, J = 4.9 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$) δ 167.1, 153.1, 118.2, 69.7, 54.2, 51.2, 43.31, 43.27, 42.3, 41.7, 40.4, 38.8, 37.8, 37.7, 36.7, 36.3, 34.5, 33.4, 29.8, 26.9, 26.6, 24.9, 23.4, 22.3, 21.9, 20.4, 16.7 ppm.

LRMS (EI) *m*/*z* 460 (M), 445 (M–Me), 429 (M–OMe).

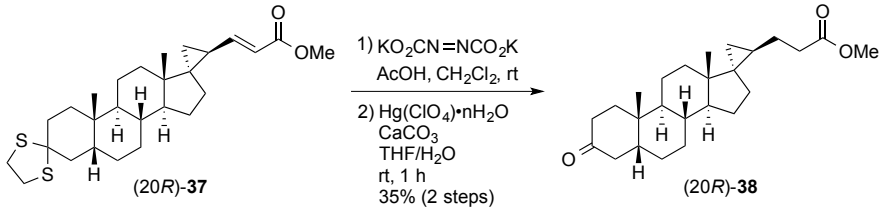
HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{27}H_{40}O_2S_2Na$ 483.2362; Found 483.2359.

IR ($CHCl_3$) ν = 2924, 2862, 1717, 1643, 1435, 1377, 1269, 1246, 1146 cm^{-1}.

mp 86–88 °C.

$[\alpha]_D^{20}$ +150 (*c* 0.20, $CHCl_3$).

Compound (20*R*)-38



To a suspension of (20*R*)-**37** (218 mg, 0.473 mmol, *E*/*Z* 4:1) and dipotassium azodicarboxylate (460 mg, 2.37 mmol) in CH_2Cl_2 (0.5 mL) was added a 1.0 M solution of acetic acid in CH_2Cl_2 (4.7 mL, 4.7 mmol) dropwise. Additional dipotassium azodicarboxylate (460 mg, 2.37 mmol) and a 1.0 M solution of acetic acid in CH_2Cl_2 (4.7 mL, 4.7 mmol) were added after 3, 6, 19, 22, 25, 28, 43, 46, 50, 55 h, respectively. The reaction mixture was stirred at room temperature for a total 67 h, and the resulting mixture was diluted with water. The aqueous layer was extracted with with $CHCl_3$ twice, wahed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a colorless oil (231 mg, about 80% conversion by ^{1}H NMR). Again, to a suspension of the colorless oil (231 mg) and dipotassium azodicarboxylate (460 mg, 2.37 mmol) in CH_2Cl_2 (0.5 mL) was added a 1.0 M solution of acetic acid in CH_2Cl_2 (4.7 mL, 4.7 mmol) dropwise at room temperature. Additional dipotassium carboxylate (460 mg, 2.37 mmol) and a 1.0 M solution of acetic acid in CH_2Cl_2 (0.5 mL, 0.5 mmol) were added after 6, 10, 22, 25, 28, 32, 44, 47, 50 h, respectively. The reaction mixture was stirred at room temperature for a total 70 h, and the resulting white suspension was diluted with water. The aqueous layer was extracted with $CHCl_3$, and washed with brine, dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow oil (214 mg). To a solution of the pale yellow oil (214 mg) in THF/H_2O (20:1, 5.0 mL) were added calcium carbonate (464 mg, 4.64 mmol) and mercury perchlorate *n*-hydrate (406 mg). After being stirred at rrom temperature for 1 h, the resulting mixture was filtered through Celite eluting with diethyl ether. The eluent was concentrated under reduced pressure to give a pale yellow oil, which was purified by column chromatography

(hexane/ethyl acetate 9:1 to 4:1) to afford (20*R*)-**38** (64.3 mg, 35% for two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.70 (dd, *J* = 14.2, 14.2 Hz, 1H), 2.39 (ddd, *J* = 8.4, 8.4, 1.8 Hz, 2H), 2.34 (ddd, *J* = 14.9, 14.9, 5.7 Hz, 1H), 2.20–2.14 (m, 1H), 2.13–1.95 (m, 4H), 1.94–1.78 (m, 2H), 1.77–1.67 (m, 1H), 1.55–1.08 (m, 14H), 1.02 (s, 3H), 0.90 (s, 3H), 0.75–0.67 (m, 1H), 0.39 (dd, *J* = 4.9, 4.9 Hz, 1H), 0.26 (dd, *J* = 8.3, 4.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 174.2, 55.8, 51.4, 44.3, 42.3, 41.5, 40.7, 37.2, 37.0, 36.9, 36.0, 35.9, 35.8, 35.0, 34.9, 26.6, 25.7, 25.02, 24.97, 22.6, 22.0, 20.9, 17.9, 16.3 ppm.

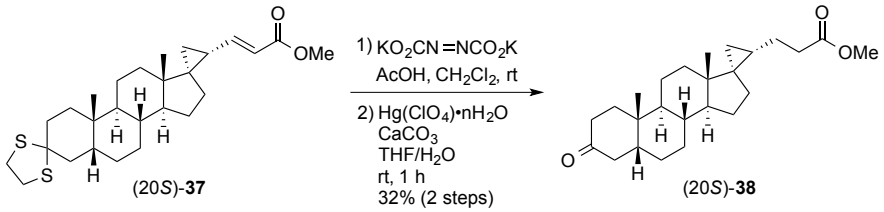
LRMS (EI) *m*/*z* 386 (M), 371 (M–Me), 354 (M–MeOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{25}H_{38}O_3Na$ 409.2713; Found 409.2706.

IR ($CHCl_3$) ν = 2936, 2862, 1736, 1713, 1447, 1219, 1169 cm^{-1}.

$[\alpha]_D^{20}$ +11.6 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-38



To a suspension of (20*S*)-**37** (165 mg, 0.358 mmol, *E*/*Z* 9:1) and dipotassium azodicarboxylate (348 mg, 1.79 mmol) in CH_2Cl_2 (0.5 mL) was added a 1.0 M solution of acetic acid in CH_2Cl_2 (3.6 mL, 3.6 mmol) dropwise. Additional dipotassium azodicarboxylate (348 mg, 1.79 mmol) and a 1.0 M solution of acetic acid in CH_2Cl_2 (3.6 mL, 3.6 mmol) were added after 5, 11, 25, 28, 31, 34 h, respectively. The reaction mixture was stirred at room temperature for a total 50 h, and the resulting mixture was diluted with water. The aqueous layer was extracted with with $CHCl_3$ twice, wahed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a colorless oil (86.9 mg). To a solution of the colorless oil (86.9 mg) in THF/H_2O (20:1, 2.0 mL) were added calcium carbonate (191 mg, 1.91 mmol) and mercury perchlorate *n*-hydrate (163 mg). After being stirred at rrom temperature for 1 h, the resulting mixture was filtered through Celite eluting with diethyl ether. The eluent was concentrated under reduced pressure to give a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate 9:1) to afford (20*S*)-**38** (44.3 mg, 32% for two steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 14.3, 14.3 Hz, 1H), 2.40 (ddd, *J* = 7.8 6.6, 6.6 Hz, 2H), 2.33 (ddd, *J* = 14.6, 14.6, 5.5 Hz, 1H), 2.16 (dd, *J* = 14.1, 1.7 Hz, 1H), 2.08–1.97 (m, 3H), 1.89 (dddd, *J* = 14.1, 14.1, 4.6, 4.6 Hz, 1H), 1.85–1.76 (m, 2H), 1.67–1.55 (m, 5H), 1.53–1.44 (m, 3H),

1.43–1.24 (m, 7H), 1.15 (dddd, *J* = 13.5, 13.5, 9.7, 3.8 Hz, 1H), 1.07 (d, *J* = 12.3 Hz, 1H), 1.02 (s, 3H), 0.93 (ddd, *J* = 12.6, 12.6, 3.8 Hz, 1H), 0.82 (dd, *J* = 8.9, 4.3 Hz, 1H), 0.74 (s, 3H), 0.52 (ddt, *J* = 6.9, 6.9, 6.9 Hz, 1H), –0.24 (dd, *J* = 4.9, 4.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 174.1, 54.7, 51.4, 44.4, 42.3, 41.3, 41.0, 37.18, 37.06, 36.2, 36.1, 35.0, 34.6, 33.4, 28.9, 26.6, 25.9, 24.8, 22.6, 20.7, 17.2, 17.0, 16.6, 13.7 ppm.

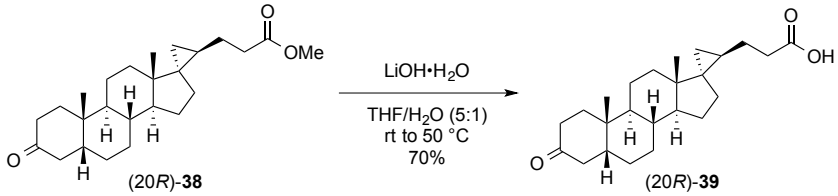
LRMS (EI) *m*/*z* 386 (M), 371 (M–Me), 354 (M–MeOH).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{25}H_{38}O_3Na$ 409.2713; Found 409.2709.

IR ($CHCl_3$) ν = 2938, 2864, 2136, 1717, 1449, 1439, 1377, 1171 cm^{-1}.

$[\alpha]_D^{20}$ +31.2 (*c* 1.00, $CHCl_3$).

Compound (20*R*)-39



To a solution of (20*R*)-**38** (34.9 mg, 90.3 μmol) in THF/H_2O (5:1, 1 mL) was added lithium hydroxide monohydrate (21.1 mg, 0.502 mmol). After being stirred at room temperature for 24 h, the reaction mixture was stirred at 50 °C for 19 h. The resulting mixture was allowed to ccol to room temperature, and acidified with 1.0 M HCl. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 3:1) to give (20*R*)-**39** (23.6 mg, 70%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (t, *J* = 14.6, 14.6 Hz, 1H), 2.46–2.40 (m, 2H), 2.34 (ddd, *J* = 14.6, 14.6, 5.2 Hz, 1H), 2.21–1.96 (m, 5H), 1.89 (dddd, *J* = 14.0, 14.0, 4.6, 4.6 Hz, 1H), 1.85–1.78 (m, 1H), 1.77–1.68 (m, 1H), 1.59–1.32 (m, 9H), 1.30–1.10 (m, 5H), 1.02 (s, 3H), 0.91 (s, 3H), 0.75 (ddt, *J* = 7.8, 5.4, 5.4 Hz, 1H), 0.42 (dd, *J* = 4.6, 4.6 Hz, 1H), 0.28 (dd, *J* = 8.6, 4.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 179.5, 55.7, 53.7, 44.3, 42.3, 41.5, 40.7, 37.2, 37.0, 36.9, 35.9, 35.8, 34.9, 29.2, 26.6, 25.7, 25.0, 24.7, 22.6, 21.9, 20.9, 17.9, 16.4 ppm.

LRMS (EI) *m*/*z* 372 (M), 354 (M–H_2O), 339 (M–H_2O–Me).

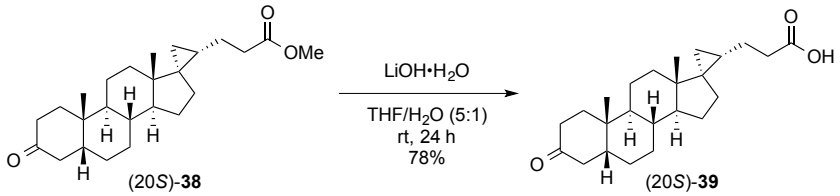
HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{24}H_{37}O_3$ 372.2743; Found 372.2713.

IR (KBr) ν = 3435 (br), 3048, 2938, 2866, 1742, 1713, 1449, 1379, 1269, 1165 cm^{-1}.

mp 141–143 °C.

$[\alpha]_D^{20}$ +10.4 (*c* 1.00, $CHCl_3$).

Compound (20*S*)-39



To a solution of (20*S*)-**38** (28.6 mg, 74.0 μmol) in THF/H_2O (5:1, 1 mL) was added lithium hydroxide monohydrate (17.9 mg, 0.426 mmol). After being stirred at room temperature for 24 h, the resulting mixture was acidified with 1.0 M HCl, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a colorless oil. The residue was purified by column chromatography (hexane/ethyl acetate 4:1 to 3:1) to give (20*S*)-**39** (21.6 mg, 78%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 14.4, 14.4 Hz, 1H), 2.50–2.39 (m, 2H), 2.33 (ddd, *J* = 15.2, 15.2, 5.5 Hz, 1H), 2.16 (d, *J* = 14.4 Hz, 1H), 2.08–1.97 (m, 3H), 1.95–1.76 (m, 3H), 1.67–1.55 (m, 3H), 1.53–1.43 (m, 3H), 1.42–1.23 (m, 6H), 1.21–1.11 (m, 1H), 1.07 (d, *J* = 12.1 Hz, 1H), 1.02 (s, 3H), 0.93 (ddd, *J* = 12.9, 12.9, 2.3 Hz, 1H), 0.83 (dd, *J* = 9.2, 4.6 Hz, 1H), 0.75 (s, 3H), 0.55 (ddt, *J* = 7.2, 7.2, 7.2 Hz, 1H), –0.22 (dd, *J* = 4.6, 4.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 179.3, 54.7, 44.4, 42.3, 41.3, 41.0, 37.2, 37.0, 36.20, 36.18, 35.0, 34.5, 33.4, 28.9, 26.6, 26.3, 25.9, 24.8, 22.6, 20.7, 17.2, 17.0, 16.5 ppm.

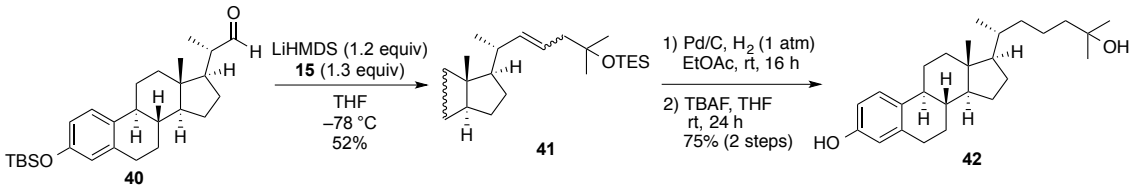
LRMS (EI) *m*/*z* 372 (M), 354 (M–H_2O), 339 (M–H_2O–Me).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{24}H_{36}O_3Na$ 395.2556; Found 395.2561.

IR (KBr) ν = 3468 (br), 3057, 2940, 2860, 1719, 1435, 1377, 1298, 1211 cm^{-1}.

$[\alpha]_D^{20}$ +26.8 (*c* 1.00, $CHCl_3$).

Compound 42



To a solution of **15** (300 mg, 0.751 mmol) in THF (2.0 mL) was added a 1.0 M solution of LiHMDS in toluene (0.7 mL, 0.7 mmol) at –78 °C under argon. After being stirred for 30 min, a solution of **40** (245 mg, 0.574 mmol) in THF (3.0 mL) was added, and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether twice,

and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to afford an inseparable *E*/*Z* mixture of **41** (183 mg, 52%) as a white solid. The *E*/*Z* mixture was used in the next step without separation. A mixture of **41** (133 mg, 0.218 mmol), 10% Pd/C (13.3 mg) and ethyl acetate (2.0 mL) was stirred under H_2 (1 atm) at room temperature for 16 h. The reaction mixture was filtered through Celite, and concentrated under reduced pressure to give a colorless oil (133 mg). To a solution of the colorless oil (133 mg) in THF (1.0 mL) was added a 1.0 M solution of TBAF (1.0 mL, 1.0 mmol), and the solution was stirred at room temperature for 24 h. The resulting mixture was diluted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a yellow oil, which was purified by column chromatography ($CHCl_3$/MeOH 50:1) to give **42** (63.0 mg, 75% for two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 8.3, 3.5 Hz, 1H), 6.62 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.56 (d, *J* = 2.6 Hz, 1H), 4.81 (br, 1H), 2.88–2.75 (m, 2H), 2.25–2.05 (m, 3H), 1.91–1.81 (m, 2H), 1.71–1.04 (m, 23H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.69 (s, 3H) ppm.

^{13}C NMR (125 MHz, THF-d_8) δ 156.4, 138.0, 131.7, 126.7, 115.8, 113.5, 69.6, 57.5, 56.5, 45.5, 44.9, 43.7, 41.1, 40.2, 37.7, 36.9, 30.6, 29.9, 29.7, 29.2, 28.9, 27.8, 24.8, 21.6, 19.2, 12.4 ppm.

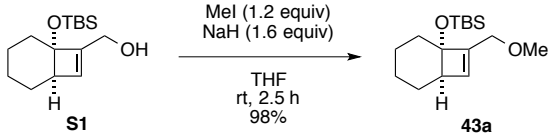
LRMS (EI) *m*/*z* 384 (M), 366 (M–H_2O).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{26}H_{40}O_2Na$ 407.2920; Found 407.2909.

IR (KBr) ν = 3392, 3142, 2934, 2866, 1611, 1506, 1458, 1236 cm^{-1}.

$[\alpha]_D^{22}$ +69.7 (*c* 0.20, $CHCl_3$).

Compound 43a



To a solution of **S1** (1.25 g, 4.42 mmol) in THF (11 mL) at 0 °C were added NaH (60%, 280 mg, 7.00 mmol) and MeI (0.33 mL, 5.3 mmol). After stirring at room temperature for 2.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether twice, and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a yellow oil, which was purified by column chromatography (hexane/diethyl ether 50:1) to afford **43a** (1.22 g, 98%) as a colorless oil.

TLC R_f = 0.43 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 3.90 (s, 2H), 3.39 (s, 3H), 2.68 (m, 1H), 1.75–1.67 (m, 3H), 1.55–1.40 (m, 5H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm.

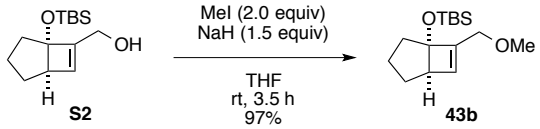
^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 131.4, 78.4, 67.6, 58.7, 49.3, 32.3, 25.7, 23.2, 18.0, 17.8, 17.6, –2.8, –3.1 ppm.

LRMS (EI) *m/z* 282 (M), 267 (M–Me), 251 (M–OMe), 225 (M–*t*Bu), 193 (M–*t*Bu–MeOH).

Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 67.78; H, 10.96.

IR (neat) ν = 2928, 2855, 1462, 1250, 1103, 833, 772 cm^{-1}.

Compound 43b



To a solution of **S2** (1.30 g, 5.11 mmol) in THF (10 mL) at 0 °C were added NaH (60%, 309 mg, 7.73 mmol) and MeI (0.64 mL, 10.3 mmol). After stirring at room temperature for 3.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether twice, and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a pale yellow oil, which was purified by column chromatography (hexane/diethyl ether 50:1) to afford **43b** (1.33 g, 97%) as a colorless oil.

TLC R_f = 0.36 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (s, 1H), 3.90 (s, 2H), 3.37 (s, 3H), 2.83 (s, 1H), 1.85 (dd, *J* = 12.3, 4.9 Hz, 1H), 1.73–1.65 (m, 1H), 1.53–1.39 (m, 3H), 1.38–1.29 (m, 1H), 0.87 (s, 9H), 0.084 (s, 3H), 0.076 (s, 3H) ppm.

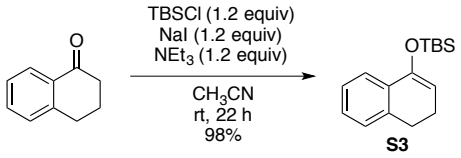
^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 128.6, 87.7, 67.2, 58.6, 52.5, 33.8, 25.7, 25.6, 23.5, 18.0, –3.1, –3.3 ppm.

LRMS (EI) *m/z* 268 (M), 253 (M–Me), 237 (M–OMe), 211 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{28}O_2SiNa$ 291.1751; Found 291.1755.

IR (neat) ν = 2931, 2855, 1250, 1173, 1099, 887, 833, 772 cm^{-1}.

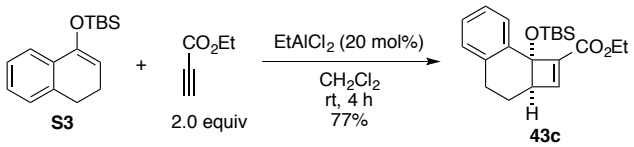
Compound S3



To a stirred solution of α–tetralone (2.93 g, 20.0 mmol) in acetonitrile (25 mL) were added

triethylamine (3.3 mL, 23.8 mmol), *tert*-butyldimethylchlorosilane (3.67 g, 24.4 mmol) and sodium iodide (3.61 g, mmol). After being stirred for 22 h at room temperature, the resulting mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a brown oil. The residue was passed through a short pad of silica gel with hexane/diethyl ether (50:1) to afford **S3** (5.09 g, 98%) as a yellow oil, which was used in the next step without further purification. The spectral data were identical to those reported.[76]

Compound 43c



To a solution of **S3** (269 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) were added ethyl propiolate (0.21 mL, 2.1 mmol) and a 1.0 M solution of ethylaluminum dichloride (0.2 mL, 0.2 mmol). After being stirred for 4 h at room temperature, the resulting mixture was quenched with saturated aqueous Rochelle salt and stirred vigorously for 30 min. The aqueous layer was extracted with $CHCl_3$ twice, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (hexane/diethyl ether 50:1) to give **43c** (284 mg, 77%) as a pale yellow oil.

TLC R_f = 0.57 (hexane/diethyl ether 4:1; UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.27 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.17 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 4.12–4.03 (m, 2H), 3.25–3.20 (m, 1H), 2.73 (d, *J* = 15.2 Hz, 1H), 2.36 (ddd, *J* = 14.3, 14.3, 4.3 Hz, 1H), 2.05–1.96 (m, 1H), 1.64 (dddd, *J* = 13.8, 13.8, 3.7, 3.7 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H) ppm.

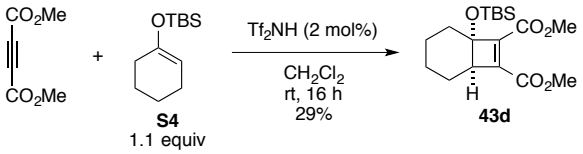
^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 146.4, 142.3, 138.6, 135.5, 128.5, 127.6, 126.5, 126.0, 76.0, 59.9, 51.6, 27.3, 25.8, 23.6, 18.3, 14.0, –2.8, –3.1 ppm.

LRMS (EI) *m/z* 358 (M), 343 (M–Me), 301 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{30}O_3SiNa$ 381.1856; Found 381.1861.

IR ($CHCl_3$) ν = 2932, 2855, 1717, 1308, 1254, 1096 cm^{-1}.

Compound 43d



To a solution of **S4** (1.91 g, 8.99 mmol) were added dimethyl acetylenedicarboxylate (0.98 mL, 8.0 mmol) and a 80 mM solution of triflic imide in toluene (2.0 mL, 0.16 mmol). After being stirred at room temperature for 16 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a brown oil, which was purified by column chromatography (hexane/diethyl ether 20:1 to 10:1) to give **43d** (823 mg, 29%) as a colorless oil.

TLC R_f = 0.47 (hexane/diethyl ether 3:1; UV, phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.79 (s, 3H), 2.90 (dd, J = 4.9, 4.9 Hz, 1H), 2.02 (ddd, J = 13.5, 4.9, 4.9 Hz, 1H), 1.92–1.74 (m, 3H), 1.65–1.55 (m, 1H). 1.54–1.36 (m, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm.

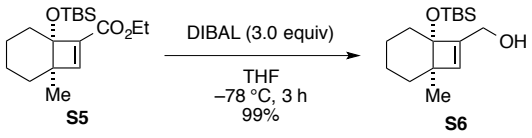
^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 161.3, 146.6, 143.2, 76.9, 51.9, 51.6, 50.7, 31.7, 25.5, 21.7, 17.9, 17.3, 17.2, –3.1, –3.2 ppm.

LRMS (EI) *m/z* 354 (M), 297 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{30}O_5SiNa$ 377.1755; Found 377.1749.

IR (neat) ν = 2932, 2859, 1721, 1435, 1250 cm^{-1}.

Compound S6



To a solution of compound **S5** (3.26 g, 10.0 mmol) in THF (25 mL) at –78 °C was added dropwise 1.0 M DIBAL solution in hexane (30 mL, 30 mmol), and the resulting solution was stirred for 3 h. The reaction mixture was added into saturated aqueous Rochelle salt, stirred vigorously for 30 min, and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a colorless oil. The residue was purified by column chromatography (hexane/diethyl ether 4:1) to afford compound **S6** (2.80 g, 99%) as a colorless oil.

TLC R_f = 0.18 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (m, 1H), 4.20 (dd, J = 14.9, 3.2 Hz, 1H), 4.11 (dd, J = 14.9, 6.0 Hz, 1H), 1.84–1.78 (m, 2H), 1.55–1.40 (m, 6H), 1.07 (s, 3H), 0.88(s, 9H), 0.10 (s, 6H) ppm.

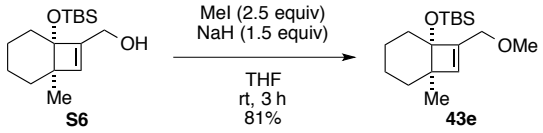
^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 136.3, 80.6, 59.2, 50.1, 31.5, 30.2, 25.9, 22.5, 18.3, 17.6, 17.2, –2.4 ppm.

LRMS (EI) *m/z* 282 (M), 265 (M–OH), 207 (M–*t*Bu–H_2O).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{30}O_2SiNa$ 305.1907; Found 305.1925.

IR (neat) ν = 3333 (br), 2934, 2857, 1472, 1454, 1256, 1144, 1111, 887, 835, 773 cm^{-1}.

Compound 43e



To a solution of **S6** (1.45 g, 5.13 mmol) in THF (10 mL) at 0 °C were added NaH (60%, 314 mg, 7.85 mmol) and MeI (0.80 mL, 13 mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether twice, and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a brown oil, which was purified by column chromatography (hexane/ether 50:1 to 20:1) to afford **43e** (1.23 g, 81%) as a colorless oil.

TLC R_f = 0.62 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (dd, *J* = 1.8, 1.4 Hz, 1H), 3.91 (dd, *J* = 14.1, 1.5 Hz, 1H), 3.86 (dd, *J* = 14.1, 1.7 Hz, 1H), 3.38 (s, 3H), 1.80–1.71 (m, 2H), 1.55–1.40 (m, 6H), 1.05 (s, 3H), 0.87 (s, 9H), 0.08 (s, 6H) ppm.

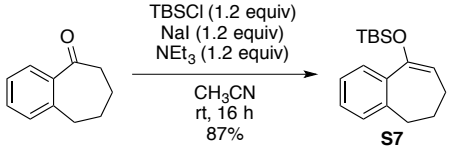
^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 137.8, 80.4, 68.2, 58.7, 50.1, 31.6, 30.3, 25.84, 25.78, 22.4, 18.4, 17.4, 17.2, –2.4, –2.6 ppm.

LRMS (EI) *m/z* 296 (M), 281 (M–Me), 265 (M–OMe), 239 (M–*t*Bu), 207 (M–*t*Bu–MeOH).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{37}O_2SiNa$ 319.2064; Found 397.2043.

IR (neat) ν = 2928, 2855, 1462, 1254, 1107, 883, 833, 772 cm^{-1}.

Compound S7



To a stirred solution of 1-benzosuberone (3.21 g, 20.0 mmol) in acetonitrile (25 mL) were added triethylamine (3.3 mL, 23.8 mmol), *tert*-butyldimethylchlorosilane (3.67 g, 24.4 mmol) and sodium iodide (3.61 g, mmol). After being stirred for 16 h at room temperature, the resulting mixture was

quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with hexane twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a brown oil. The residue was passed through a short pad of silica gel with hexane/diethyl ether (50:1) to afford **S7** (4.79 g, 87%) as a pale yellow oil, which was used in the next step without further purification.

TLC R_f = 0.77 (hexane/diethyl ether 10:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.24 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 1H), 7.19 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.16 (dd, *J* = 7.2, 1.4 Hz, 1H), 5.42 (dd, *J* = 6.9, 6.9 Hz, 1H), 2.64 (dd, *J* = 6.6, 6.6 Hz, 2H), 2.04 (ddd, *J* = 7.0, 7.0, 7.0 Hz, 1H), 2.03 (ddd, *J* = 6.9, 6.9, 6.9 Hz, 1H), 1.88 (ddd, *J* = 7.2, 6.9, 6.9 Hz, 2H), 0.95 (s, 9H), 0.08 (s, 6H) ppm.

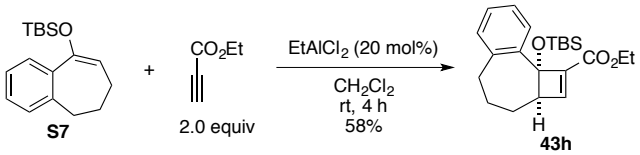
^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 140.8, 138.4, 128.6, 127.4, 126.8, 125.7, 109.2, 33.4, 33.2, 25.8, 23.6, 18.2, –4.6 ppm.

LRMS (EI) *m/z* 274 (M), 259 (M–Me), 217 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{27}OSi$ 275.1826; Found 275.1821.

IR (neat) ν = 2928, 2893, 2855, 1632, 1470, 1354, 1331, 1231, 1180, 1134, 1072 cm^{-1}.

Compound 43h



To a solution of **S7** (1.37 g, 4.99 mmol) in CH_2Cl_2 (33 mL) were added ethyl propiolate (1.0 mL, 9.8 mmol) and a 1.0 M solution of ethylaluminum dichloride (1.0 mL, 1.0 mmol). After being stirred for 4 h at room temperature, the resulting mixture was quenched with saturated aqueous Rochelle salt and stirred vigorously for 30 min. The aqueous layer was extracted with $CHCl_3$ twice, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (hexane/diethyl ether 50:1) to give **43h** (1.07 g, 58%) as a pale yellow oil.

TLC R_f = 0.31 (hexane/diethyl ether 10:1; UV, $KMnO_4$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.22 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.15 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.07 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.04 (d, *J* = 1.2 Hz, 1H), 4.36 (dq, *J* = 10.6, 7.2 Hz, 1H), 4.26 (dq, *J* = 10.9, 7.2 Hz, 1H), 3.28 (ddd, *J* = 12.9, 12.9, 6.9 Hz, 1H), 2.76 (ddd, *J* = 13.5, 2.9, 1.1 Hz, 1H), 2.54 (dd, *J* = 13.2, 6.3 Hz, 1H), 1.75 (dddd, *J* = 12.9, 12.9, 6.0, 6.0 Hz, 1H), 1.67 (ddd, *J* = 14.3, 6.0, 2.9 Hz, 1H), 1.57 (dddd, *J* = 12.9, 12.9, 6.6, 6.6 Hz, 1H), 1.37 (t, *J*

= 6.9 Hz, 3H), 0.88–0.81 (m, 1H), 0.81 (s, 9H), –0.01 (s, 3H), –0.28 (s, 3H) ppm.

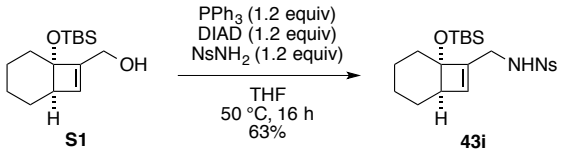
^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 152.0, 141.4, 139.0, 138.9, 129.2, 128.6, 128.2, 125.9, 84.9, 60.3, 55.2, 30.3, 25.7, 25.6, 24.2, 18.2, 14.3, –3.3, –3.9 ppm.

LRMS (EI) *m/z* 372 (M), 357 (M–Me), 315 (M–*t*Bu), 299 (M–CO_2Et).

Anal. Calcd for $C_{21}H_{30}O_3Si$: C, 70.35; H, 8.43. Found: C, 70.36; H, 8.60.

IR ($CHCl_3$) ν = 2928, 2901, 2855, 1717, 1308, 1250, 1227, 1173, 1096, 1066 cm^{-1}.

Compound 43i



To a solution of **S1** (1.07 g, 3.99 mmol), triphenyl phosphine (1.26 g, 4.80 mmol) and 2-nitrobenzenesulfonamide (0.97 g, mmol) in THF (20 mL) was added a 1.9 M solution of diisopropyl azodicarboxylate in toluene (2.5 mL, 4.8 mmol). After being stirred at 50 °C for 16 h, the resulting mixture was concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (hexane/ethyl acetate 10:1 to 4:1) to give **43i** (1.14 g, 63%) as a white solid.

TLC R_f = 0.36 (hexane/ethyl acetate 4:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.08 (m, 1H), 7.80–7.83 (m, 1H), 7.76–7.68 (m, 2H), 5.87 (s, 1H), 5.57 (t, *J* = 5.2 Hz, 1H), 3.75–3.67 (m, 2H), 2.61 (br s, 1H), 1.74–1.60 (m, 3H), 1.52–1.36 (m, 3H), 1.35 (m, 2H), 0.83 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 147.0, 133.54, 133.50, 132.7, 132.1, 131.1, 125.3, 78.4, 49.0, 40.6, 31.8, 25.6, 22.8, 17.9, 17.7, 17.2, –2.8, –3.1 ppm.

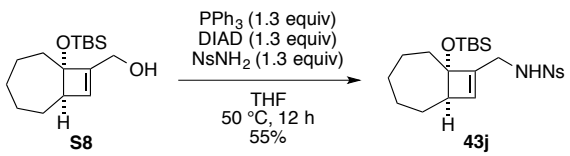
LRMS (EI) *m/z* 452 (M), 395 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{32}N_2O_5SSiNa$ 475.1693; Found 475.1700.

IR ($CHCl_3$) ν = 2928, 2905, 2855, 1539, 1412, 1358, 1254, 1169, 1126, 1065 cm^{-1}.

mp 94–95 °C.

Compound 43j



To a solution of **S8** (453 mg, 1.60 mmol), triphenyl phosphine (534 mg, 2.04 mmol) and

2-nitrobenzenesulfonamide (412 mg, 2.04 mmol) in THF (9.0 mL) was added a 1.9 M solution of diisopropyl azodicarboxylate in toluene (1.1 mL, 2.1 mmol). After being stirred at 50 °C for 12 h, the resulting mixture was concentrated under reduced pressure to give a yellow oil. The residue was purified by column chromatography (hexane/ethyl acetate 10:1 to 4:1) to give **43j** (433 mg, 55%) as a white solid.

TLC R_f = 0.31 (hexane/ethyl acetate 4:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17–8.12 (m, 1H), 7.90–7.85 (m, 1H), 7.76–7.69 (m, 2H), 5.87 (s, 1H), 5.48 (br, 1H), 3.75–3.66 (m, 2H), 2.69 (br, 1H), 1.78–1.47 (m, 6H), 1.42–1.18 (m, 4H), 0.82 (s, 9H), 0.07 (s, 3H), –0.03 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 147.2, 133.6, 133.5, 132.7, 131.1, 125.3, 83.2, 55.2, 40.3, 36.4, 32.1, 30.1, 26.8, 25.6, 23.8, 18.1, –2.7, –3.3 ppm (one signal missing).

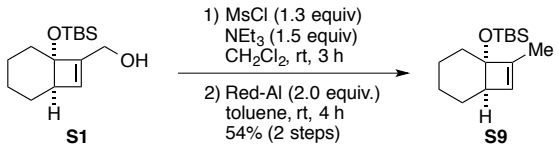
LRMS (EI) *m/z* 466 (M), 451 (M–Me), 409 (M–*t*Bu).

Anal. Calcd for $C_{22}H_{34}N_2O_2SSi$: C, 56.62; H, 7.34; N, 6.00. Found: C, 56.69; H, 7.40; N, 5.96.

IR (KBr) ν = 3321, 2953, 2928, 2853, 1541, 1369, 1339, 1256, 1167, 1072 cm^{-1}.

mp 99–101 °C.

Compound S9



To a solution of **S1** (339 mg, 1.26 mmol) in CH_2Cl_2 (4.2 mL) at 0 °C were added triethylamine (0.27 mL, 2.0 mmol) and mesyl chloride (0.13 mL, 1.7 mmol), and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was quenched with water, and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. The residue was dissolved in $CHCl_3$, and passed through a short pad of silica gel with hexane/ether (4:1) to give a yellow oil (356 mg). This compound is unstable, so used directly in the next step without further purification. To a solution of the pale yellow oil (356 mg) in toluene (5.2 mL) was added 3.5 M Red-Al (0.59 mL, 2.1 mmol), and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was added into saturated aqueous Rochelle salt, stirred vigorously for 30 min, and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/diethyl ether 50:1) to afford **S9** (173 mg, 54% for two steps) as a colorless oil.

TLC R_f = 0.64 (hexane; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 1H), 2.63 (s, 1H), 1.71–1.62 (m, 3H), 1.59 (m, 3H), 1.53–1.32 (m, 5H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H) ppm.

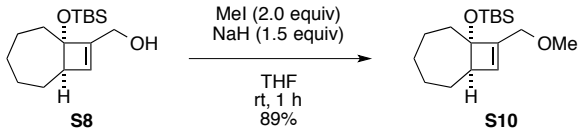
^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 129.9, 78.6, 49.1, 31.8, 25.8, 23.2, 18.1, 17.9, 17.7, 11.5, –2.7 ppm.

LRMS (EI) *m/z* 252 (M), 237 (M–Me), 195 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{31}OSi$ 253.1982; Found 253.1995.

IR (neat) ν = 2932, 2855, 1254, 1126, 1103, 980, 833, 772 cm^{-1}.

Compound S10



To a solution of **S8** (1.41 g, 4.99 mmol) in THF (10 mL) at 0 °C were added NaH (60%, 301 mg, 7.53 mmol) and MeI (0.62 mL, 10 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with diethyl ether twice, and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a yellow oil, which was purified by column chromatography (hexane/diethyl ether 50:1) to afford **S10** (1.55 g, 89%) as a colorless oil.

TLC R_f = 0.33 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (s, 1H), 3.88 (s, 2H), 3.37 (s, 3H), 2.80–2.70 (m, 1H), 1.86–1.75 (m, 2H), 1.54–1.44 (m, 1H), 1.42–1.24 (m, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H) ppm.

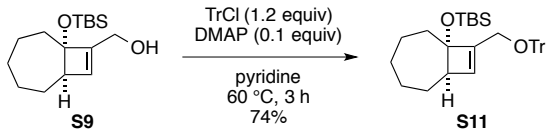
^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 132.4, 83.3, 67.5, 58.7, 55.8, 36.7, 32.2, 30.7, 27.2, 25.7, 23.9, 18.2, –2.7, –3.2 ppm.

LRMS (EI) *m/z* 296 (M), 281 (M–Me), 239 (M–*t*Bu).

Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 68.78; H, 11.05.

IR (neat) ν = 2924, 2851, 1458, 1250, 1192, 1103, 1069, 833, 772 cm^{-1}.

Compound S11



To a solution of compound **S9** (681 mg, 2.41 mmol) in pyridine (6.0 mL) were added trityl chloride

(808 mg, 2.90 mmol) and DMAP (36.3 mg, 0.297 mmol). After stirring at 60 °C for 3 h, the resulting mixture was allowed to cool to room temperature, extracted with diethyl ether, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a yellow oil, which was purified by column chromatography (hexane/diethyl ether 50:1) to afford compound **S11** (933 mg, 74%) as a colorless oil. Analytical sample was obtained by trituration with hexane as a white solid.

TLC R_f = 0.53 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.44 (m, 6H), 7.32–7.27 (m, 6H), 7.25–7.20 (m, 3H), 6.15 (s, 1H), 3.58–3.48 (m, 2H), 2.79–2.73 (m, 1H), 1.84–1.74 (m, 2H), 1.70–1.57 (m, 4H), 1.52–1.26 (m, 4H), 0.77 (s, 9H), 0.04 (s, 3H), –0.12 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 144.1, 131.7, 128.7, 128.6, 127.8, 127.7, 126.9, 86.5, 83.4, 59.5, 55.9, 36.9, 32.3, 30.7, 27.2, 25.7, 24.0, 18.2, –2.8, –3.3 ppm.

LRMS (EI) *m/z* 524 (M), 467 (M–*t*Bu), 281 (M–Tr), 243 (Tr).

Anal. Calcd for $C_{35}H_{44}O_2Si$: C, 80.10; H, 8.45. Found: C, 79.94; H, 8.66.

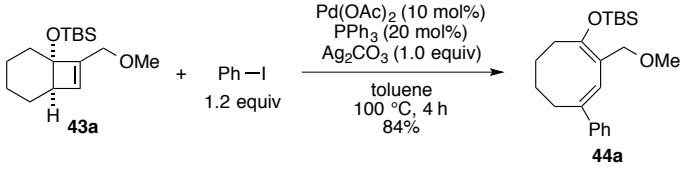
IR (KBr) ν = 2955, 2926, 2851, 1491, 1462, 1449, 1250, 1194, 1107, 1074, 1051, 988, 835, 770, 702 cm^{-1}.

mp 112–113 °C.

General Procedure for the synthesis of *cis*,*cis*-siloxydienes 44

To a solution of cyclobutene **43** (0.2 mmol) in toluene (2.0 mL) were added aryl iodide (0.24 mmol), Ag_2CO_3 (55 mg, 0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 20 μmol) and triphenylphosphine (10.5 mg, 40.0 μmol). The reaction mixture was stirred at 100 °C for indicated time. The resulting mixture was allowed to cool to room temperature, filtered through Celite eluting with diethyl ether, and concentrated under reduced pressure. The residue was purified by column chromatography to afford **44**.

Compound 44a



The general procedure was used with cyclobutene **43a** (57.2 mg, 0.202 mmol) and iodobenzene (27 μL, 0.242 mmol). The reaction mixture was stirred at 100 °C for 4 h. The crude material was

purified by column chromatography (hexane/diethyl ether 20:1) to give **44a** (60.8 mg, 84%) as a colorless oil.

TLC R_f = 0.38 (hexane/diethyl ether 10:1; UV, phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.47 (dd, *J* = 6.9, 1.4 Hz, 2H), 7.29 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.24–7.19 (m, 1H), 6.33 (s, 1H), 4.10 (s, 2H), 3.28 (s, 3H), 2.61 (br, 1H), 2.29 (dd, *J* = 3.8, 3.8 Hz, 2H), 1.57 (br, 4H), 0.99 (s, 9H), 0.22 (s, 6H) ppm.

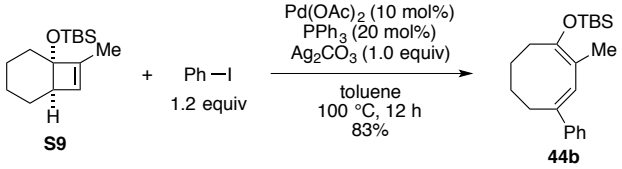
^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 142.6, 139.7, 128.1, 126.7, 126.4, 125.9, 115.2, 70.0, 57.7, 33.9, 30.3, 25.9, 23.8, 22.6, 18.4, –3.7 ppm.

LRMS (EI) *m/z* 358 (M), 343 (M–Me), 327 (M–OMe), 301 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{30}O_2SiNa$ 381.2220; Found 381.2216.

IR (neat) ν = 2928, 2855, 1639, 1447, 1254, 1231, 1177, 1080, 868, 833, 779, 760 cm^{-1}.

Compound 44b



The general procedure was used with cyclobutene **S9** (53.1 mg, 0.210 mmol) and iodobenzene (28 μL, 0.251 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 50:1) to give **44b** (57.3 mg, 83%) as a colorless oil.

TLC R_f = 0.19 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.45 (dd, *J* = 7.2, 1.1 Hz, 2H), 7.30 (dd, *J* = 7.5 Hz, 2H), 7.21 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.17 (s, 1H), 2.56 (br, 2H), 2.28–2.19 (m, 2H), 1.71 (s, 3H), 1.60–1.40 (br, 4H), 0.99 (s, 9H), 0.20 (s, 6H) ppm.

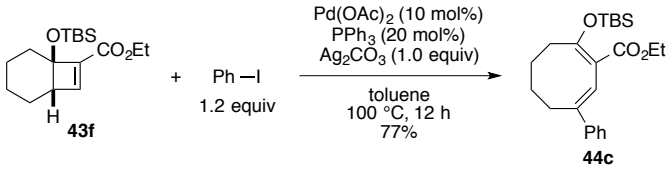
^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 142.8, 138.1, 128.5, 128.2, 126.6, 126.4, 113.1, 33.8, 30.2, 26.0, 24.0, 22.7, 18.5, 16.2, –3.6 ppm.

LRMS (EI) *m/z* 328 (M), 313 (M–Me), 271 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{32}OSiNa$ 351.2114; Found 351.2121.

IR (neat) ν = 2928, 2855, 1647, 1254, 1215, 1180, 1150 cm^{-1}.

Compound 44c



The general procedure was used with cyclobutene **43f** (64.0 mg, 0.206 mmol) and iodobenzene (28 μL, 0.251 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 10:1) to give **44c** (61.0 mg, 77%) as a colorless oil.

TLC R_f = 0.39 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.47 (dd, *J* = 8.6, 1.4 Hz, 2H), 7.32 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.25 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.50 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.59 (br, 2H), 2.33 (dd, *J* = 6.9, 4.3 Hz, 2H), 1.70–1.39 (br, 4H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.98 (s, 9H), 0.26 (s, 6H) ppm.

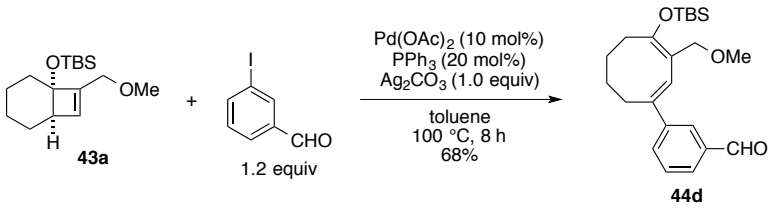
^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 160.6, 142.2, 140.7, 128.2, 127.1, 126.6, 123.1, 111.6, 59.8, 35.0, 30.0, 25.9, 23.3, 22.9, 18.6, 14.4, –3.5 ppm.

LRMS (EI) *m/z* 386 (M), 371 (M–Me), 341 (M–OEt), 329 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{34}O_3SiNa$ 409.2169; Found 409.2175.

IR (neat) ν = 2932, 2859, 1717, 1593, 1250, 1196, 1053, 837, 756 cm^{-1}.

Compound 44d



The general procedure was used with cyclobutene **43a** (58.6 mg, 0.207 mmol) and 3-iodobenzaldehyde (58.1 mg, 0.250 mmol). The reaction mixture was stirred at 100 °C for 8 h. The crude material was purified by column chromatography (hexane/diethyl ether 10:1) to give **44d** (54.3 mg, 68%) as a colorless oil.

TLC R_f = 0.38 (hexane/diethyl ether 4:1; UV, phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 10.0 (s, 1H), 7.97 (s, 1H), 7.78–7.70 (m, 2H), 7.46 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.41 (s, 1H), 4.11 (s, 2H), 3.29 (s, 3H), 2.64 (br, 2H), 2.35–2.24 (m, 2H), 1.58 (br, 4H), 1.00 (s, 9H), 0.23 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 151.9, 143.5, 138.4, 136.4, 132.4, 128.8, 128.1, 127.6, 127.4,

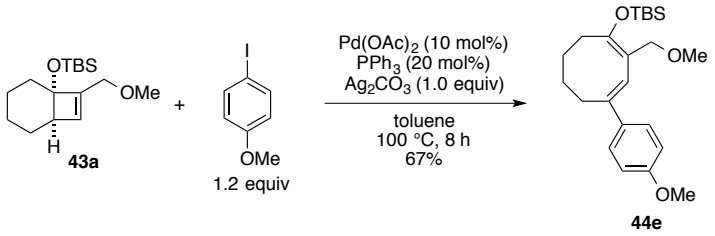
115.0, 69.9, 57.7, 33.8, 30.2, 25.9, 23.6, 22.4, 18.4, –3.7 ppm.

LRMS (EI) *m/z* 386 (M), 355 (M–OMe), 329 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{34}O_3SiNa$ 409.2169; Found 409.2174.

IR (neat) ν = 2928, 2889, 2855, 1701, 1636, 1447, 1362, 1238, 1177, 1142, 1080 cm^{-1}.

Compound 44e



The general procedure was used with cyclobutene **43a** (59.1 mg, 0.209 mmol) and 4-iodoanisole (59.7 mg, 0.255 mmol). The reaction mixture was stirred at 100 °C for 8 h. The crude material was purified by column chromatography (hexane/diethyl ether 20:1 to 10:1) to give **44e** (53.9 mg, 67%) as a colorless oil.

TLC R_f = 0.30 (hexane/diethyl ether 10:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.41 (d, *J* = 8.9, Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.25 (s, 1H), 4.09 (s, 2H), 3.80 (s, 3H), 3.28 (s, 3H), 2.58 (br 2H), 2.31–2.23 (m, 2H), 1.56 (br, 4H), 0.99 (s, 9H), 0.21 (s, 6H) ppm.

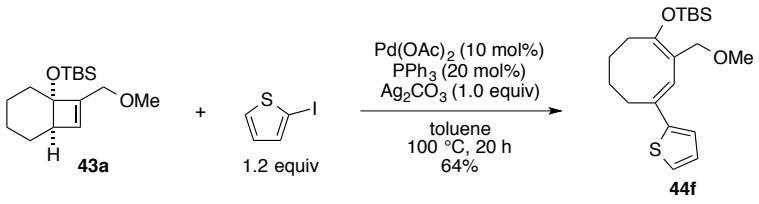
^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 151.1, 139.2, 135.0, 127.5, 124.3, 115.3, 113.5, 70.0, 57.7, 55.2, 33.8, 30.2, 25.9, 23.7, 22.7, 18.4, –3.7 ppm.

LRMS (EI) *m/z* 388 (M), 357 (M–OMe), 331 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{36}O_3SiNa$ 411.2326; Found 411.2326.

IR (neat) ν = 2928, 2855, 1636, 1607, 1512, 1447, 1288, 1246, 1215, 1177, 1146, 1107, 1080, 1038 cm^{-1}.

Compound 44f



The general procedure was used with cyclobutene **43a** (56.7 mg, 0.201 mmol) and 2-iodothiophene (25 μL, 0.24 mmol). The reaction mixture was stirred at 100 °C for 20 h. The crude material was

purified by column chromatography (hexane/diethyl ether 20:1) to give **44f** (47.2mg, 64%) as a yellow oil.

TLC R_f = 0.32 (hexane/ether 10:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.11 (d, *J* = 5.2 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.96 (dd, *J* = 4.9, 3.5 Hz, 1H), 6.48 (s, 1H), 4.09 (s, 2H), 3.28 (s, 3H), 2.58 (br, 2H), 2.25 (br, 2H), 1.57 (br 4H), 0.98 (s, 9H), 0.21 (s, 6H) ppm.

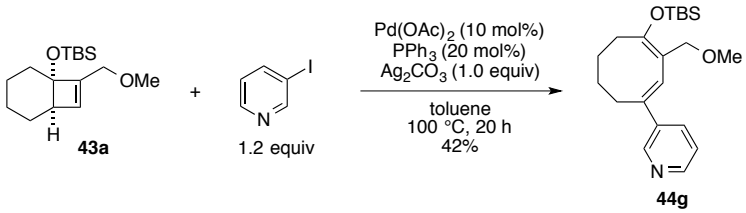
^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 147.1, 133.6, 127.3, 124.4, 123.4, 122.5, 114.8, 69.8, 57.7, 33.7, 30.8, 25.9, 23.6, 23.0, 18.4, –3.7 ppm.

LRMS (EI) *m/z* 364 (M), 349 (M–Me), 333 (M–OMe), 307 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{32}O_2SSiNa$ 387.1784; Found 387.1788

IR (neat) ν = 2928, 2889, 2855, 2816, 1632, 1447, 1362, 1281, 1254, 1215, 1177, 1080 cm^{-1}.

Compound 44g



The general procedure was used with cyclobutene **43a** (56.6 mg, 0.200 mmol) and 3-iodopyridine (50.6 mg, 0.247 mmol). The reaction mixture was stirred at 100 °C for 20 h. The crude material was purified by column chromatography (hexane/diethyl ether 4:1 to 1:1) to give **44g** (30.2 mg, 42%) as a colorless oil.

TLC R_f = 0.23 (hexane/diethyl ether 1:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 8.71 (d, *J* = 2.0 Hz, 1H), 8.45 (dd, *J* = 4.6, 1.5 Hz, 1H), 7.74 (ddd, *J* = 8.1, 1.5, 1.5 Hz, 1H), 7.21 (dd, *J* = 8.1, 4.9 Hz, 1H), 6.36 (s, 1H), 4.11 (s, 2H), 3.29 (s, 3H), 2.61 (br, 2H), 2.35–2.22 (m, 2H), 1.65–1.43 (br m, 4H), 0.99 (s, 9H), 0.22 (s, 6H) ppm.

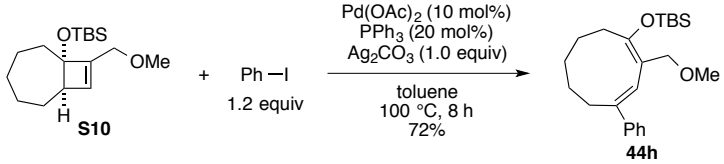
^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 148.0, 147.8, 137.9, 136.7, 133.5, 127.6, 123.0, 114.9, 69.9, 57.8, 33.8, 30.1, 25.9, 23.5, 22.4, 18.4, –3.7 ppm.

LRMS (EI) *m/z* 359 (M), 328 (M–OMe), 302 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{33}NO_2SiNa$ 382.2173; Found 382.2178.

IR (neat) ν = 2928, 2889, 2859, 2816, 1636, 1470, 1447, 1362, 1288, 1254, 1234, 1080 cm^{-1}.

Compound 44h



The general procedure was used with cyclobutene **S10** (64.3 mg, 0.217 mmol) and iodobenzene (29 μL, 0.260 mmol). The reaction mixture was stirred at 100 °C for 8 h. The crude material was purified by column chromatography (hexane/diethyl ether 10:1) to give **44h** (58.1 mg, 72%) as a colorless oil.

TLC R_f = 0.66 (hexane/diethyl ether 4:1; UV, phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.32 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.23 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.29 (s, 1H), 4.06 (s, 2H), 3.31 (s, 3H), 2.73–2.67 (m, 2H), 2.34–2.27 (m, 2H), 1.58–1.48 (m, 6H), 0.99 (s, 9H), 0.19 (s, 6H) ppm.

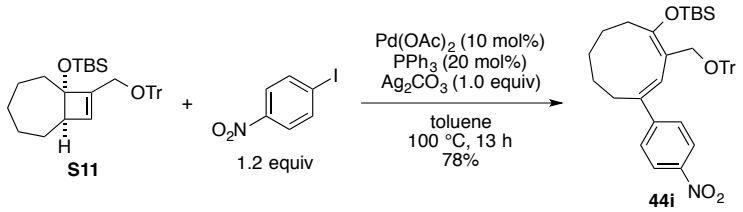
^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 144.0, 141.5, 128.1, 127.1, 126.9, 126.4, 115.6, 69.8, 58.1, 35.3, 30.4, 29.8, 26.4, 25.9, 24.6, 18.4, –3.8 ppm.

LRMS (EI) *m/z* 372 (M), 357 (M–Me), 341 (M–OMe), 327 (M–CH_2OMe), 315 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{36}O_2SiNa$ 395.2377; Found 395.2369.

IR (neat) ν = 2924, 2855, 1647, 1454, 1254, 1196, 1080, 934, 837, 764 cm^{-1}.

Compound 44i



To a solution of cyclobutene **S11** (642 mg, 1.22 mmol) in toluene (12 mL) were added 1-iodo-4-nitrobenzene (367 mg, 1.47 mmol), Ag_2CO_3 (673 mg, 2.44 mmol), $Pd(OAc)_2$ (27.3 mg, 0.122 mmol) and triphenylphosphine (67.4 mg, 0.257 mmol). The reaction mixture was stirred at 100 °C for 13 h. The resulting mixture was allowed to cool to room temperature, filtered through Celite with ether, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/diethyl ether 50:1) to give **44i** (617 mg, 78%) as a yellow amorphous solid. Analytical sample was obtained by recrystallization from toluene as yellow blocks.

TLC R_f = 0.34 (hexane/diethyl ether 10:1; UV, phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.44–7.38 (m, 6H),

7.24–7.16 (m, 9H), 6.55 (s, 1H), 3.79 (s, 2H), 2.90 (m, 2H), 2.25 (br, 2H), 1.66–1.55 (br, 6H), 0.74 (s, 9H), –0.04 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 148.8, 146.6, 144.3, 142.5, 138.6, 131.6, 128.8, 127.6, 126.8, 123.7, 115.4, 86.4, 61.5, 34.9, 31.1, 29.7, 26.3, 25.7, 24.9, 18.2, –4.0 ppm.

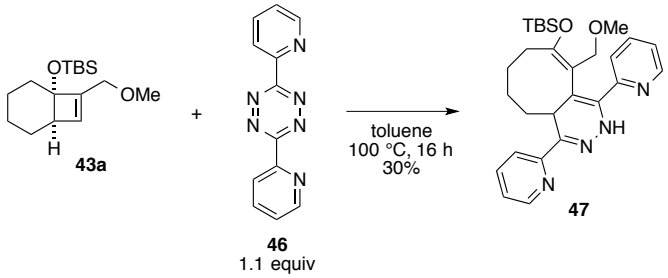
LRMS (EI) *m/z* 645 (M), 402 (M–Tr), 243 (Tr).

Anal. Calcd for $C_{41}H_{47}NO_4Si$: C, 76.24; H, 7.33; N, 2.17. Found: C, 75.99; H, 7.42; N, 2.14.

IR (KBr) ν = 2953, 2926, 2853, 1647, 1593, 1516, 1342, 1259, 1202, 839 cm^{-1}.

mp 159–160 °C.

Compound 47



A solution of cyclobutene **43a** (57.1 mg, 0.202 mmol) and tetrazine **46** (52.3 mg, 0.221 mmol) in toluene (2.0 mL) was stirred at 100 °C for 16 h. The resulting mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 4:1) to give **47** (30.2 mg, 30%) as a yellow oil.

TLC R_f = 0.34 (chloroform/methanol 10:1; UV, phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H, NH), 8.59–8.54 (m, 2H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.65 (ddd, *J* = 8.0, 8.0, 1.8 Hz, 1H), 7.59 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 1H), 7.17 (dd, *J* = 4.9, 4.9, 1H), 7.16 (dd, *J* = 5.8, 5.8 Hz, 1H), 4.14 (d, *J* = 10.4 Hz, 1H), 4.04 (dd, *J* = 10.6, 2.6 Hz, 1H), 4.03 (d, *J* = 10.3 Hz, 1H), 3.19 (s, 3H), 2.67 (ddd, *J* = 12.6, 12.6, 5.2 Hz, 1H), 1.96–1.71 (m, 4H), 1.67–1.43 (m, 3H), 0.97 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H) ppm.

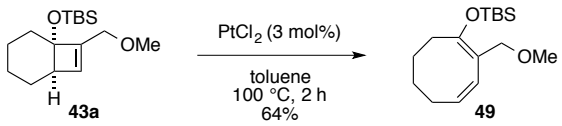
^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 152.3, 151.4, 148.6, 148.2, 143.1, 135.8, 135.7, 132.3, 122.9, 122.3, 122.2, 120.6, 115.9, 113.1, 69.4, 58.4, 40.1, 31.7, 29.6, 26.5, 26.0, 25.7, 18.2, –3.5, –3.9 ppm.

LRMS (EI) *m/z* 490 (M), 458 (M–MeOH), 445 (M–CH_2OMe), 401 (M–MeOH–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{38}N_4O_2SiNa$ 513.2656; Found 513.2663.

IR (neat) ν = 3368, 2951, 2928, 2855, 1636, 1566, 1466, 1431, 1254, 1177, 1042 cm^{-1}.

Compound 49



To a solution of compound **43a** (305 mg, 1.08 mmol) in toluene (7.0 mL) were added $PtCl_2$ (8.6 mg, 32 μmol). After stirring at 100 °C for 2 h, the resulting mixture was allowed to cool to room temperature, filtered through Celite with ether, and concentrated *in vacuo*. The crude material was purified by column chromatography (hexane/diethyl ether 20:1) to give compound **49** (247 mg, 64%) as a colorless oil.

TLC R_f = 0.56 (hexane/diethyl ether 20:1; UV, phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (d, J = 11.2 Hz, 1H), 5.64 (dt, J = 11.2, 7.2 Hz, 1H), 4.04 (s, 2H), 3.28 (s, 3H), 2.26 (br, 2H), 2.15 (br, 1H), 1.51 (br, 4H), 0.96 (s, 9H), 0.18 (s, 6H) ppm.

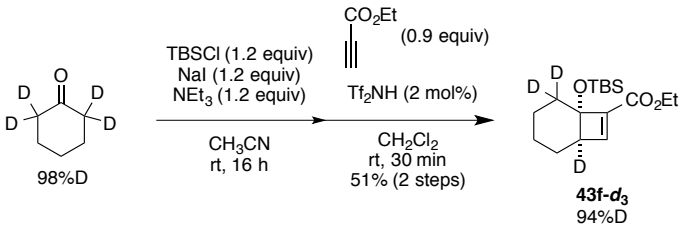
^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 130.1, 127.8, 114.0, 69.6, 57.6, 32.9, 28.8, 25.9, 23.2, 23.0, 18.4, –3.7 ppm.

LRMS (EI) *m/z* 282 (M), 267 (M–Me), 251 (M–OMe), 225 (M–*t*Bu), 193 (M–*t*Bu–MeOH).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{30}O_2SiNa$ 305.1907; Found 305.1885.

IR (neat) ν = 2928, 2859, 1647, 1447, 1238, 1146, 1084, 829, 775 cm^{-1}.

Compound 43f-*d*$_3$



To a solution of cyclohexanone-d_4 (2.06 g, 20.2 mmol) in CH_3CN (25 mL) were added triethylamine (3.4 mL, 25 mmol), TBSCl (3.65 g, 24.2 mmol) and NaI (3.63 g, 24.2 mmol). After stirring at room temperature for 16 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with hexane, washed with brine, and dried over Na_2SO_4. Concentration under reduced pressure gave a brown oil, which was passed through a short pad of silica gel with hexane to afford a colorless oil (3.75 g). To a solution of the colorless oil (3.75 g) in CH_2Cl_2 (39 mL) were added ethyl propiolate (1.6 mL, 16 mmol) and a 80 mM solution of triflic imide in toluene (3.9 mL, 0.31 mmol). After being stirred at room temperature for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with $CHCl_3$, washed with brine, and dried over Na_2SO_4. Concentration

under reduced pressure gave a red oil, which was purified by column chromatography (hexane/diethyl ether 50:1) to afford compound **43f-*d*$_3$** (3.25 g, 51% for two steps) as a colorless oil.

TLC R_f = 0.36 (hexane/diethyl ether 10:1; UV, $KMnO_4$ stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 4.20 (m, 2H), 1.78 (ddd, *J* = 15.5, 9.5, 6.0 Hz, 1H), 1.58–1.50 (m, 2H), 1.48–1.35 (m, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm.

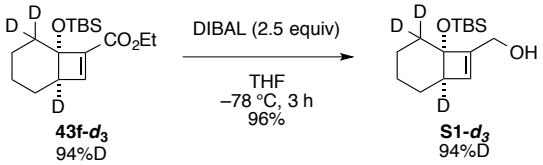
^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 148.8, 143.8, 77.8, 59.8, 49.8 (t), 31.4 (quin), 25.6, 22.7, 17.9, 17.8, 17.2, 14.2, –3.1, –3.2 ppm.

LRMS (EI) *m/z* 313 (M), 267 (M–EtOH).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{27}D_3O_3SiNa$ 336.2045; Found 308.2023.

IR (neat) ν = 2932, 1721, 1246, 1215, 1123, 941, 837, 772 cm^{-1}.

Compound S1-*d*$_3$



43f-*d*$_3$ 94%D **S1-*d*$_3$** 94%D

To a solution of compound **43f-*d*$_3$** (1.69 g, 5.39 mmol) in THF (13 mL) at –78 °C was added dropwise a 1.0 M DIBAL solution in hexane (14 mL, 14 mmol), and the resulting solution was stirred for 3 h. The reaction mixture was added into saturated aqueous Rochelle salt, stirred vigorously for 30 min, and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a colorless oil. The residue was purified by column chromatography (hexane/diethyl ether 4:1) to afford compound **S1-*d*$_3$** (1.40 g, 96%) as a colorless oil.

TLC R_f = 0.15 (hexane/diethyl ether 4:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 4.22 (dd, *J* = 14.3, 4.3 Hz, 1H), 4.14 (dd, *J* = 14.6, 6.3 Hz, 1H), 1.88–1.83 (m, 1H), 1.72 (dt, *J* = 13.8, 8.3 Hz, 1H), 1.57–1.50 (m, 2H), 1.48–1.38 (m, 3H), 0.86 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H) ppm.

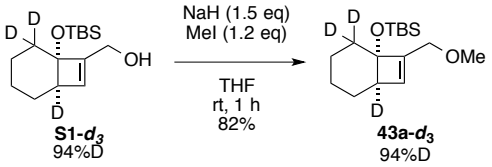
^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 129.7, 78.4, 58.3, 48.2 (t), 31.3 (quin), 25.5, 22.9, 17.8, 17.5, 17.2, –3.0, –3.3 ppm.

LRMS (EI) *m/z* 271 (M), 214 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{25}D_3O_2SiNa$ 294.1939; Found 294.1931.

IR (neat) ν = 3325 (br), 2928, 2855, 1462, 1254, 1049, 941, 833, 760 cm^{-1}.

Compound 43a-d_3



To a solution of **S1-d_3** (0.600 g, 2.21 mmol) in THF (7 mL) at 0 °C were added NaH (60%, 134 mg, 3.35 mmol) and MeI (0.17 mL, 2.7 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether twice, and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave a yellow oil, which was purified by column chromatography (hexane/diethyl ether 50:1 to 20:1) to afford **43a-d_3** (516 mg, 82%) as a colorless oil.

TLC R_f = 0.43 (hexane/diethyl ether 10:1; phosphomolybdic acid stain).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 3.90 (s, 2H), 3.39 (s, 3H), 1.74–1.65 (m, 1H), 1.52–1.40 (m, 5H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm.

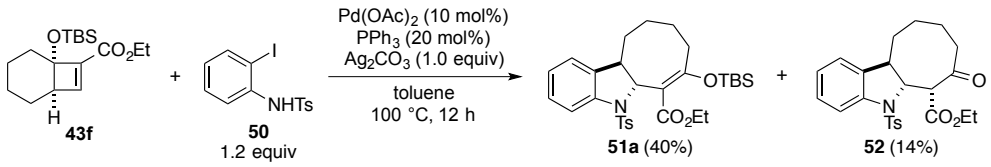
^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 131.3, 78.2, 67.6, 58.7, 48.7 (t), 31.6 (quin), 25.7, 23.1, 18.0, 17.6, 17.5, –2.9, –3.1 ppm.

LRMS (EI) *m/z* 285 (M), 228 (M–*t*Bu).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{27}D_3O_2SiNa$ 308.2095; Found 308.2073.

IR (neat) ν = 2928, 2855, 2820, 1462, 1254, 1107, 941, 833, 772 cm^{-1}.

Compounds 51a and 52



To a solution of cyclobutene **43f** (63.8 mg, 0.205 mmol) in toluene (2.0 mL) were added aryl iodide **50** (92.8 mg, 0.263 mmol), Ag_2CO_3 (58.9 mg, 0.214 mmol), $Pd(OAc)_2$ (4.8 mg, 21 μmol) and triphenylphosphine (11.9 mg, 45.4 μmol). The reaction mixture was stirred at 100 °C for 12 h. The resulting mixture was allowed to cool to room temperature, filtered through Celite eluting with diethyl ether, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/diethyl ether 10:1 to 1:1) to give **51a** (45.8 mg, 40%) as a colorless oil along with **52** (12.7 mg, 14%) as a brown solid. Analytical sample of **52** was obtained by

recrystallization from ether as white crystals.

Data for compound **51a**:

TLC R_f = 0.23 (hexane/diethyl ether 4:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.18 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.02–6.94 (m, 2H), 4.25–4.11 (m, 2H), 4.15 (d, 10.9 Hz, 1H), 3.52 (ddd, *J* = 10.6, 10.6, 1.5 Hz, 1H), 2.51 (ddd, *J* = 13.2, 13.2, 6.6 Hz, 1H), 2.37 (s, 3H), 2.32 (ddd, *J* = 13.5, 9.8, 2.3 Hz, 1H), 2.20 (ddd, *J* = 14.3, 6.0, 2.0 Hz, 1H), 2.02–1.84 (m, 2H), 1.67–1.57 (m, 1H), 1.55–1.45 (m, 1H), 1.16 (t, *J* = 6.9 Hz, 3H), 1.04–0.94 (m, 1H), 1.00 (s, 9H), 0.32 (s, 3H), 0.30 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 156.2, 144.0, 142.3, 133.4, 132.8, 129.4, 127.8, 127.7, 123.4, 123.0, 115.1, 114.3, 69.7, 59.7, 50.3, 31.2, 31.0, 27.6, 26.0, 24.4, 21.5, 18.6, 14.2, –3.3, –4.0 ppm.

LRMS (EI) *m/z* 555 (M), 540 (M–Me), 498 (M–*t*Bu), 400 (M–Ts), 343 (M–*t*Bu–Ts).

Anal. Calcd for $C_{30}H_{41}NO_5SSi$: C, 64.83; H, 7.44; N, 2.52. Found: C, 64.62; H, 7.64; N, 2.46.

IR ($CHCl_3$) ν = 2928, 2859, 1724, 1701, 1597, 1458, 1362, 1173 cm^{-1}.

mp 52–54 °C.

Data for compound **52**:

TLC R_f = 0.24 (hexane/diethyl ether 1:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.23–7.18 (m, 3H), 7.03 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 4.53 (d, *J* = 5.8 Hz, 1H), 4.42 (dd, *J* = 5.6, 5.6 Hz, 1H), 4.09–3.97 (m, 2H), 3.31 (ddd, *J* = 12.3, 4.9, 4.9 Hz, 1H), 2.68–2.58 (m, 2H), 2.36 (s, 3H), 1.97–1.87 (m, 1H), 1.84–1.70 (m, 2H), 1.68–1.60 (m, 1H), 1.57–1.47 (m, 1H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.49 (dddd, *J* = 13.2, 13.2, 4.9, 4.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 167.3, 144.6, 141.2, 136.5, 132.9, 129.6, 127.8, 127.4, 124.7, 123.7, 116.3, 65.7, 62.1, 60.9, 42.9, 42.8, 33.8, 25.6, 24.4, 21.6, 13.5 ppm.

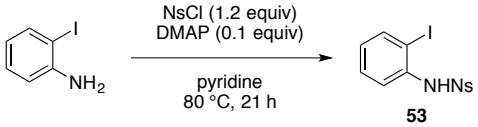
LRMS (FAB) *m/z* 442 (M+H).

Anal. Calcd for $C_{24}H_{27}NO_5S$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.17; H, 6.35; N, 3.18.

IR (KBr) ν = 2986, 2965, 2930, 2909, 1751, 1734, 1699, 1481, 1460, 1352, 1171 cm^{-1}.

mp 170–171 °C.

Compound 53



To a solution of 2-iodoaniline (1.33 g, 6.07 mmol) and DMAP (78.9 mg, 0.646 mmol) in pyridine (20 mL) was added 2-nitrobenzenesulfonyl chloride (1.62 g, 7.31 mmol). After being stirred at 80 °C for 21 h, the resulting mixture was allowed to cool to room temperature, diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 4:1 to 3:2) and recrystallization from hexane/ethyl acetate to give **53** (927 mg, 38%) as yellow crystals.

TLC R_f = 0.31 (hexane/ethyl acetate 3:2; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.78–7.71 (m, 2H), 7.69–7.63 (m, 3H), 7.37 (ddd, *J* = 8.0, 1.2, 1.2 Hz, 1H), 6.93 (ddd, *J* = 7.6, 1.7, 1.7 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 139.5, 137.2, 134.1, 133.4, 132.9, 130.8, 129.4, 127.9, 125.6, 125.1, 92.6 ppm.

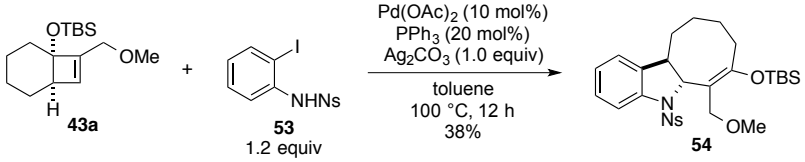
LRMS (FAB) *m/z* 405 (M+H).

Anal. Calcd for $C_{12}H_9IN_2O_4S$: C, 35.66; H, 2.24; N, 6.93; O, 15.83; S, 7.93; I, 31.40. Found: C, 35.45; H, 2.29; N, 6.75.

IR ($CHCl_3$) ν = 3649, 3291, 2986, 2970, 2901, 1539, 1470, 1393, 1346, 1173, 1065 cm^{-1}.

mp 144–145 °C.

Compound 54



To a solution of cyclobutene **43a** (60.2 mg, 0.213 mmol) in toluene (2.0 mL) were added aryl iodide **53** (104 mg, 0.257 mmol), Ag_2CO_3 (61.3 mg, 0.222 mmol), $Pd(OAc)_2$ (5.4 mg, 24 μmol) and triphenylphosphine (10.5 mg, 40.0 μmol). The reaction mixture was stirred at 100 °C for 12 h. The resulting mixture was allowed to cool to room temperature, filtered through Celite with diethyl ether, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/diethyl ether 4:1) to give **54** (45.1 mg, 38%) as a yellow solid. Analytical

sample was obtained by recrystallization form diethyl ether.

TLC R_f = 0.40 (hexane/diethyl ether 4:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.66 (ddd, *J* = 87.8, 7.8, 1.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.52 (ddd, *J* = 8.0, 8.0, 1.4 Hz, 1H), 7.24–7.19 (m, 1H), 7.12–7.03 (m, 2H), 4.66 (d, *J* = 10.3 Hz, 1H), 4.35 (d, *J* = 10.6 Hz, 1H), 4.15 (d, *J* = 10.9 Hz, 1H), 3.36 (dd, *J* = 10.9, 10.9 Hz, 1H), 3.19 (s, 3H), 2.66 (ddd, *J* = 11.5, 11.5, 2.3 Hz, 1H), 2.40–2.30 (m, 1H), 2.13 (dd, *J* = 14.9, 4.9 Hz, 1H), 2.02–1.86 (m, 2H), 1.70–1.59 (m, 2H), 1.28–1.15 (m, 1H), 0.98 (s, 3H), 0.22 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 149.2, 141.8, 133.94, 133.86, 131.0, 130.6, 130.1, 127.8, 124.1, 124.0, 123.3, 115.6, 115.5, 71.4, 67.2, 58.2, 51.2, 30.5, 30.2, 27.4, 25.8, 25.1, 18.3, –3.8, –4.1 ppm.

LRMS (EI) *m/z* 558 (M), 527 (M–OMe), 501 (M–*t*Bu).

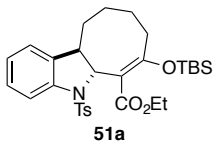
IR ($CHCl_3$) ν = 2928, 2859, 1651, 1547, 1458, 1373, 1258, 1173 cm^{-1}.

mp 149–150 °C (dec).

General procedure for the synthesis of *trans*-indolines 51

To a solution of cyclobutene **43** (0.2 mmol) in toluene (2.0 mL) were added aryl iodide **50** (0.24 mmol, 90 mg), Ag_2CO_3 (55 mg, 0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 20 μmol) and tri(2-furyl)phosphine (9.3 mg, 40 μmol). The reaction mixture was stirred at 100 °C for indicated time. The resulting mixture was allowed to cool to room temperature, filtered through Celite eluting with chloroform, and concentrated under reduced pressure. The residue was purified by column chromatography to afford *trans*-indoline **51**.

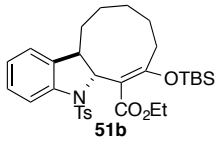
Compound 51a



51a

The general procedure was used with cyclobutene **43f** (62.8 mg, 0.202 mmol) and aryl iodide **50** (91.2 mg, 0.244 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 10:1 to 4:1) to give **51a** (72.6 mg, 65%) as a white amorphous solid.

Compound 51b



51b

The general procedure was used with cyclobutene **43g** (65.7 mg, 0.202 mmol) and aryl iodide **50** (90.8 mg, 0.243 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 10:1 to 4:1) to give **51b** (83.7 mg, 73%) as a white amorphous solid. Analytical sample was obtained by recrystallization from hexane/diethyl ether as white crystals.

TLC R_f = 0.26 (hexane/diethyl ether 4:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.55 (m, 3H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 4.74 (d, *J* = 4.6 Hz, 1H), 3.85 (dq, *J* = 10.9, 7.2 Hz, 1H), 3.76 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.61 (ddd, *J* = 11.8, 5.5, 5.5 Hz, 1H), 2.92 (ddd, *J* = 14.3, 14.3, 3.2 Hz, 1H), 2.35 (s, 3H), 2.21 (ddd, *J* = 14.3, 3.5, 3.5 Hz, 1H), 1.90–1.80 (m, 1H), 1.75–1.67 (m, 1H), 1.56–1.51 (m, 2H), 1.47–1.32 (m, 2H), 1.31–1.18 (m, 1H), 0.96 (s, 9H), 0.67–0.60 (m, 1H), 0.59 (t, *J* = 7.2 Hz, 3H), 0.28 (s, 3H), 0.27 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 156.6, 143.8, 142.1, 137.5, 134.3, 129.3, 127.2, 127.1, 124.0, 123.3, 117.4, 115.9, 63.3, 59.5, 46.5, 33.0, 30.3, 26.1, 24.2, 21.5, 21.0, 19.2, 18.6, 13.0, –3.5, –4.1 ppm.

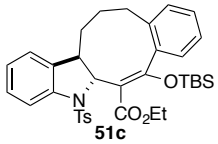
LRMS (EI) *m/z* 569 (M), 554 (M–Me), 414 (M–Ts), 357 (M–Ts–*t*Bu).

Anal. Calcd for $C_{31}H_{43}NO_5SSi$: C, 65.34; H, 7.61; N, 2.46. Found: C, 65.18; H, 7.86; N, 2.40.

IR (KBr) ν = 2953, 2928, 2855, 1719, 1618, 1474, 1460, 1360, 1167 cm^{-1}.

mp 138–139 °C.

Compound 51c



51c

The general procedure was used with cyclobutene **43h** (75.1 mg, 0.202 mmol) and aryl iodide **50** (90.2 mg, 0.242 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 4:1) to give **51c** (103 mg, 82%, dr 9:1) as a white amorphous solid. Analytical sample was obtained by recrystallization from hexane/diethyl ether as white crystals. The following data are for the major diastereomer.

TLC R_f = 0.32 (hexane/diethyl ether 3:2; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.50 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.4, 7.4, 1.4 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.14 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.97 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.82 (s, 4H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.91 (d, *J* = 4.6 Hz, 1H), 3.25 (dd, *J* = 9.8, 4.9 Hz, 1H), 2.91 (ddd, *J* = 12.9, 12.9, 5.2 Hz, 1H), 2.75 (ddd, *J* = 14.4, 3.7, 3.7 Hz, 1H), 2.23 (s, 3H), 2.03–1.88 (m, 2H), 1.58 (ddd, *J* = 14.6, 14.6, 4.9 Hz, 1H), 0.91 (s, 9H), 0.77 (3H), 0.39–0.28 (m, 1H), –0.09 (s, 3H), –0.13 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 157.7, 143.2, 142.1, 139.9, 137.7, 137.2, 132.5, 129.8, 129.2, 128.8, 128.1, 127.3, 127.2, 126.1, 124.01, 123.95, 116.2, 113.8, 70.9, 59.5, 46.7, 37.2, 30.2, 28.8, 25.4, 21.4, 18.2, 13.3, –3.8, –4.4 ppm.

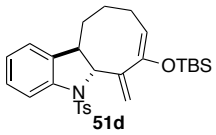
LRMS (EI) *m/z* 617 (M), 602 (M–Me), 560 (M–*t*Bu), 462 (M–Ts), 405 (M–*t*Bu–Ts).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{35}H_{43}NO_5SSiNa$ 640.2523; Found 640.2522.

IR ($CHCl_3$) ν = 2970, 2928, 2901, 2859, 1717, 1362, 1246, 1169, 1134, 1092 cm^{-1}.

mp 213–214 °C.

Compound 51d



51d

The general procedure was used with cyclobutene **43a** (55.1 mg, 0.195 mmol) and aryl iodide **50** (89.1 mg, 0.239 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 4:1) to give **51d** (51.9 mg, 54%) as a white amorphous solid. Analytical sample was obtained by recrystallization from diethyl ether as colorless plates.

TLC R_f = 0.31 (hexane/diethyl ether 4:1; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.23 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.05 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.70 (s, 1H), 5.63 (s, 1H), 5.20 (dd, *J* = 9.8, 9.8 Hz, 1H), 5.00 (s, 1H), 2.98 (d, *J* = 11.5 Hz, 1H), 2.35 (s, 3H), 2.33–2.26 (m, 1H), 2.25–2.16 (m, 1H), 1.84–1.75 (m, 1H), 1.69–1.61 (m, 1H), 1.46 (dddd, *J* = 13.5, 13.5, 4.9, 4.9 Hz, 1H), 0.36 (dddd, *J* = 12.9, 12.9, 4.6, 4.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 144.1, 143.6, 141.0, 136.1, 133.8, 129.4, 127.9, 127.6, 124.8, 124.5, 117.1, 113.1, 11.3, 68.0, 48.5, 36.0, 28.1, 15.9, 24.2, 21.5, 18.2, –4.2, –4.5 ppm.

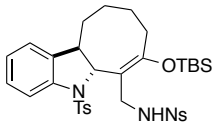
LRMS (EI) *m/z* 495 (M), 438 (M–*t*Bu), 340 (M–Ts).

Anal. Calcd for $C_{28}H_{37}NO_3SSi$: C, 67.84; H, 7.52; N, 2.83; O, 9.68; S, 6.47; Si, 5.67. Found: C, 67.62; H, 2.88; N, 7.53.

IR (KBr) ν = 2951, 2930, 1593, 1481, 1458, 1354, 1250, 1172, 1155, 1136, 1041 cm^{-1}.

mp 209–210 °C (dec.).

Compound 51e



51e

The general procedure was used with cyclobutene **43i** (92.7 mg, 0.205 mmol) and aryl iodide **50** (92.1 mg, 0.247 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/ethyl acetate 4:1) to give **51e** (72.3 mg, 53%) as a white solid.

TLC R_f = 0.51 (hexane/ethyl acetate 3:2; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 6.0, 3.5 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.76 (dd, *J* = 6.0, 3.4 Hz, 1H), 7.60 (dd, *J* = 6.0, 3.4 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.23–7.17 (m, 3H), 6.99 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.86 (dd, *J* = 9.5, 2.3 Hz, 1H), 4.28 (dd, *J* = 13.8, 9.5 Hz, 1H), 4.02 (dd, *J* = 13.8, 2.6 Hz, 1H), 3.93 (d, *J* = 11.5 Hz, 1H), 3.05 (dd, *J* = 10.9, 10.9 Hz, 1H), 2.44–2.31 (m, 4H), 2.26 (ddd, *J* = 9.5, 9.5, 2.3 Hz, 1H), 2.08 (dd, *J* = 14.6, 6.0 Hz, 1H), 1.97–1.76 (m, 2H), 1.55–1.44 (m, 2H), 0.97–0.87 (m, 1H), 0.95 (s, 9H), 0.22 (s, 3H), 0.14 (s, 3H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ 149.5, 147.8, 144.8, 141.7, 134.0, 133.2, 132.6, 132.3, 130.5, 129.9, 129.4, 127.8, 127.6, 124.7, 124.0, 123.4, 115.0, 113.6, 71.0, 48.9, 29.7, 29.0, 27.1, 25.5, 23.1, 21.0, 17.8, –4.1, –4.2 ppm (one signal missing).

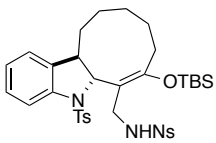
LRMS (EI) *m/z* 697 (M), 695 (M–2H), 640 (M–*t*Bu), 542 (M–Ts), 485 (M–*t*Bu–Ts).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{34}H_{43}N_3O_7S_2SiNa$ 720.2204; Found 720.2203.

IR (KBr) ν = 3335, 2959, 2930, 2857, 1659, 1599, 1537, 1458, 1398, 1360, 1173, 930 cm^{-1}.

mp 220–222 °C (dec.).

Compound 51f



51f

The general procedure was used with cyclobutene **43j** (94.7 mg, 0.203 mmol) and aryl iodide **50** (92.8 mg, 0.249 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/ethyl acetate 3:1) to give **51f** (91.3 mg, 63%) as a white solid.

TLC R_f = 0.49 (hexane/ethyl acetate 3:2; UV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.66 (ddd, *J* = 7.7, 7.7, 1.5 Hz, 1H), 7.58 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.13 (dd, *J* = 8.1 Hz, 1H), 6.98 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 5.64 (d, *J* = 8.3 Hz, 1H), 4.52 (d, *J* = 5.2 Hz, 1H), 3.87 (dd, *J* = 11.8, 7.8 Hz, 1H), 3.61 (d, *J* = 12.4 Hz, 1H), 3.27 (ddd, *J* = 11.2, 5.2, 5.2 Hz, 1H), 2.76 (ddd, *J* = 13.8, 13.8, 3.8 Hz, 1H), 2.34 (s, 3H), 2.12 (d, *J* = 14.6 Hz, 1H), 1.78 (dddd, *J* = 12.6, 12.6, 6.3, 6.3 Hz, 1H), 1.66 (ddd, *J* = 13.2, 13.2, 2.0 Hz, 1H), 1.52–1.44 (m, 2H), 1.37 (ddd, *J* = 12.9, 12.9, 1.2 Hz, 1H), 1.30–1.11 (m, 2H), 0.92 (s, 9H), 0.58–0.46 (m, 1H), 0.22 (s, 3H), 0.16 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 147.9, 144.2, 141.2, 135.8, 133.6, 133.2, 133.0, 132.5, 130.9, 129.4, 127.7, 127.1, 125.2, 124.5, 123.9, 116.4, 116.0, 64.8, 45.4, 39.8, 33.4, 28.8, 25.7, 24.1, 21.5, 21.3, 19.5, 18.3, –3.91, –3.94 ppm.

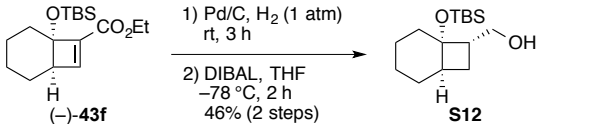
LRMS (EI) *m/z* 711 (M), 654 (M–*t*Bu), 556 (M–Ts), 499 (M–*t*Bu–Ts).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{35}H_{45}N_3O_7S_2SiNa$ 734.2360; Found 734.2374.

IR (KBr) ν = 3333, 2957, 2930, 2857, 1657, 1599, 1537, 1460, 1400, 1362, 1173 cm^{-1}.

mp 171–172 °C.

Preparation of compound (–)-43f and determination of its absolute configuration



$[\alpha]_D^{21}$ = +6.0 (*c* 0.49, $CHCl_3$)

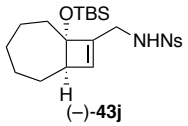
lit. $[\alpha]_D^{27}$ = +6.1 (*c* 0.49, $CHCl_3$)

Racemic mixture of **43f** was separated by preparative chiral HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/methyl *t*-butyl ether = 97/3, flow rate: 18 mL/min, detection: UV 254 nm). Analytical HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/methyl *t*-butyl ether = 97/3, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 25 °C) major 13.8 min, minor 14.4 min. $[\alpha]_D^{20}$ –82.2 (*c* 1.00, $CHCl_3$, >99%*ee*).

The absolute configuration of (–)-**43f** was determined by the direct conversion to the known alcohol **S12** according to the following procedure. A mixture of (–)-**43f** (59.0 mg, 0.190 mmol), 10% Pd/C

(89.0 mg) and ethyl acetate (2.0 mL) was stirred under H_2 (1 atm) at room temperature for 3 h. The resulting mixture was filtered through Celite, and concentrated under reduced pressure to give colorless oil. To a solution of the oil in THF (2.0 mL) was added dropwise a 1.0 M solution of DIBAL in hexane (0.57 mL, 0.57 mmol) at –78 °C, and the resulting solution was stirred for 2 h. The reaction mixture was added into saturated aqueous Rochelle salt, stirred vigorously for 30 min, and extracted with diethyl ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a colorless oil. The residue was purified by column chromatography (hexane/diethyl ether 4:1) to afford compound **S12** (23.4 mg, 46% for two steps, *cis*:*trans* = 3:2) as a colorless oil. The diastereomers were partially separated upon careful column chromatography to obtain an analytical sample, and the spectral data and specific rotation were identical to those reported.[10b] For *cis*-isomer: $[\alpha]_D^{21}$ +6.0 (*c* 0.49, $CHCl_3$); lit. $[\alpha]_D^{27}$ +6.1 (*c* 0.49, $CHCl_3$).

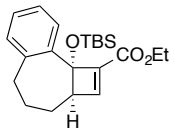
Preparation of compound (–)-43j



(–)-**43j**

Racemic mixture of **43j** was separated by preparative chiral HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/*i*-PrOH = 95/5, flow rate: 18 mL/min, detection: UV 254 nm). Analytical HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/*i*-PrOH = 95/5, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 25 °C) major 26.2 min, minor 27.8 min. $[\alpha]_D^{20}$ –10.8 (*c* 1.00, $CHCl_3$, >99%*ee*). The absolute configuration was tentatively assigned by analogy to (–)-**43f**.

Preparation of compound (–)-43h



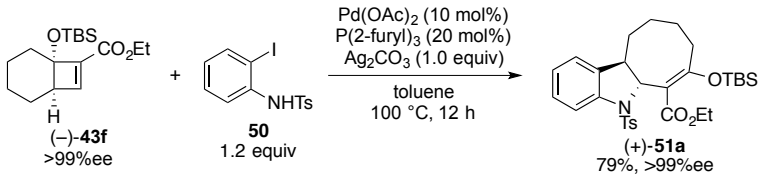
(–)-**43h**

Racemic mixture of (±)-**43h** was separated by preparative chiral HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/methyl *t*-butyl ether = 97/3, flow rate: 18 mL/min, detection: UV 254 nm). $[\alpha]_D^{20}$ –181 (*c* 1.08, $CHCl_3$, >99%*ee*). Analytical HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/methyl *t*-butyl ether = 97/3, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 25 °C) major 12.5 min, minor 14.1 min. The absolute configuration was tentatively

assigned by analogy to (–)-**43f**.

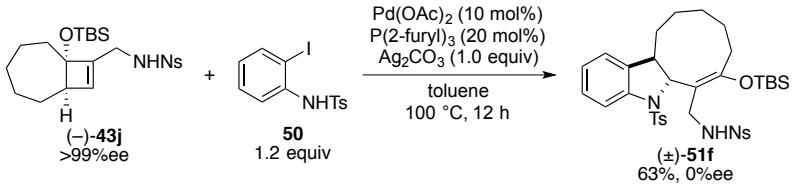
Synthesis of *trans*-indolines using enantiopure starting materials

Reaction of (–)-43f



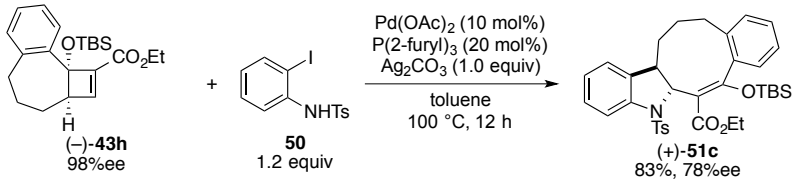
The general procedure was used with cyclobutene (–)-**43f** (31.7 mg, 0.102 mmol, >99%*ee*) and aryl iodide **50** (46.5 mg, 0.125 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 10:1 to 4:1) to give (+)-**51b** (44.7 mg, 79%, >99%*ee*) as a white solid. Analytical HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/*i*-PrOH = 95/5, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 25 °C) major 33.6 min, minor 35.3 min. $[\alpha]_D^{20}$ +33.0 (*c* 1.00, $CHCl_3$, >99%*ee*). Single crystals were obtained by recrystallization from toluene, and the absolute configuration was determined by X-ray crystallographic analysis.

Reaction of (–)-43j



The general procedure was used with cyclobutene (–)-**43j** (47.3 mg, 0.101 mmol, >99%*ee*) and aryl iodide **50** (46.5 mg, 0.125 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/ethyl acetate 3:1) to give (±)-**51f** (45.6 mg, 63%, 0%*ee*) as a white amorphous solid. Analytical HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/*i*-PrOH = 90/10, flow rate: 1.0 mL/min, detection: UV 254 nm, temperature: 25 °C) 19.7 min, 26.4 min.

Reaction of (–)-43h



The general procedure was used with cyclobutene (–)-**43h** (37.4 mg, 0.100 mmol, 98%*ee*) and aryl iodide **50** (45.1 mg, 0.121 mmol). The reaction mixture was stirred at 100 °C for 12 h. The crude material was purified by column chromatography (hexane/diethyl ether 4:1) to give (+)-**51c** (51.3 mg, 83%, dr 9:1, 78%*ee*) as a white solid. Analytical HPLC (column: YMC CHIRAL Amylose-SA, eluent: hexane/*i*-PrOH = 95/5, flow rate: 1.0 mL/min, detection: UV 254 nm, temperature: 25 °C) major 11.4 min, minor 15.1 min. $[\alpha]_D^{22}$ +47.1 (*c* 0.50, $CHCl_3$, 78%*ee*). The absolute configuration was tentatively assigned by analogy to (+)-**51a**.

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