

(+)-*trans*-Dihydronarciclasine と Paesslerin A
の全合成

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第 1 章 序論

第 1 節 天然物の合成研究の意義

自然は人間の想像を超えて多様な構造や生理活性を持った化合物を供給してくれる。その中には優れた医薬品として期待される化合物も数多く見出されている。しかしながら、魅力ある生理活性物質は天然から極微量しか得られないことが多い。医薬品として安定的に供給するには、天然から得られる化合物のみでは不足することがほとんどであり、化学合成等によって供給することが求められる。この合成経路の開発は天然物化学の重要な研究課題の一つである。また、全合成研究の過程で新規反応を見出すこともあり、有機合成化学の発展にも貢献している。さらに、立体化学が予めわかっているものを原料とすることで天然物の構造を最終的に確定することができ、絶対立体化学を含めた天然物の構造情報を確実なものとするができる。

確立した合成経路を基に様々な類縁体を合成することが可能となり、構造活性相関研究による医薬品としての構造最適化を行うことで、もとの天然物より活性が増強されたり、副作用が軽減された化合物の発見に結びつくこともある。また、全合成の過程で得られた数多くの合成中間体のスクリーニングを行うことで思わぬ活性を持つ化合物が見出される可能性もある。さらに、標的タンパク質探索等の分子生物学的研究のためのプローブ合成へと展開することも可能である。このように天然物の合成研究は化学、医学、薬学、分子生物学などの分野の発展に大きく貢献している。

天然物の合成研究が医薬品の開発へ発展した例として、ハーバード大学の岸義人らとエーザイの共同研究がある。彼らは海洋天然物 **halichondrin B** の右半分だけでも強力な活性を維持できることを見出した。プロセス開発を経て、2011 年、米国において抗悪性腫瘍剤 (**HARAVEN[®]**) として上市された (Figure 1)。天然物よりもはるかに構造を単純化させることに成功したが、それでも 19 個の不斉点、分子量 826 の複雑な化合物を 60 工程を超える完全化学合成で供給しているのだから驚異的である。誰もが工業化は不可能と思うことに果敢に挑み実現した研究者たちに深く感銘を受けた。現在、天然からの創薬は細菌の培養による発酵法が主流であるが、**HARAVEN[®]** の成功例は、天然物の合成研究の意義について今一度見つめ直すきっかけを与えてくれた。今後、複雑な構造故にこれまで表舞台にあることのなかった優れた生理活性物質が医薬品として供給されることを願ってやまない。

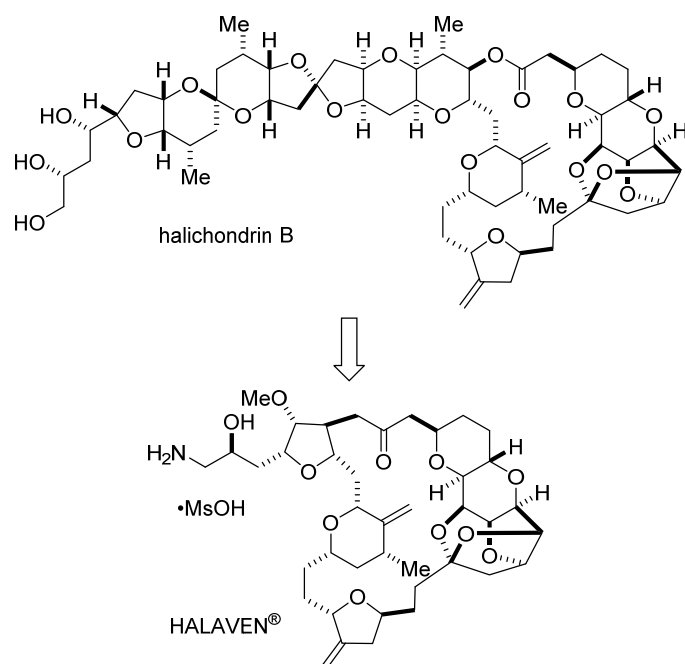
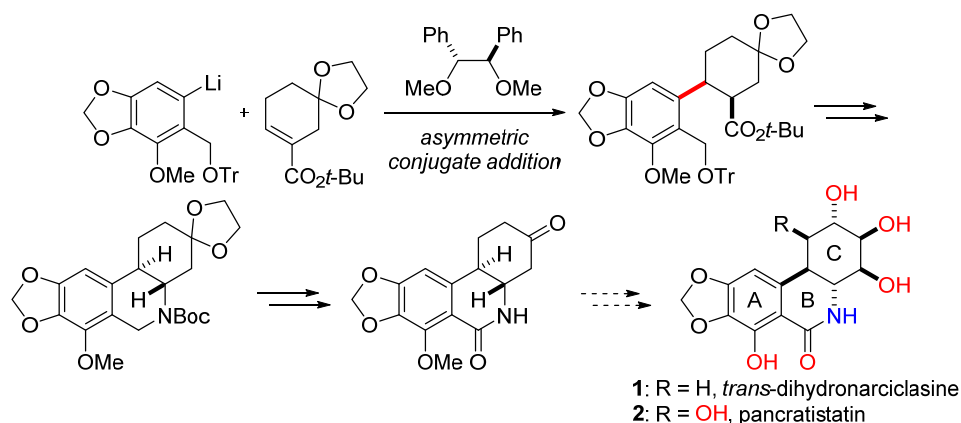


Figure 1. Halichondrin B and HALAVEN®

第 2 節 本論文の概要

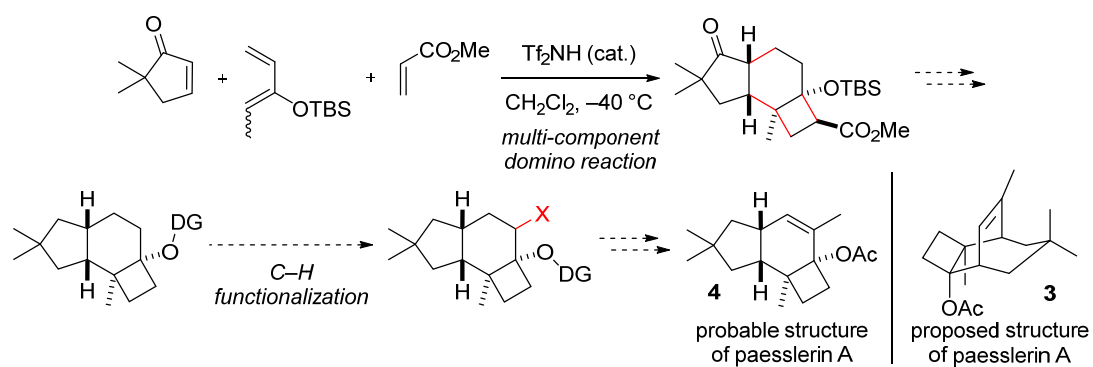
著者はこれまで一貫して天然物の合成研究に取り組んできた。第 2 章以降では、抗腫瘍活性を有するヒガンバナアルカロイドおよびプロトイルダンテルペノイドの全合成について記述する。「不斉共役付加反応」および「多成分連続反応」という 2 つの反応が全合成を達成する上で重要な役割を果たした。

医薬品の中にはキラルな化合物が多く含まれており、それらのエナンチオマーは異なる薬効や毒性を示す。よって、望みの立体化学を有する光学活性体を得ることは必要不可欠であり、一般性の高い素反応を不斉反応へ展開することは重要な課題である。中でも、有機化合物の基本骨格を構築する炭素-炭素結合形成反応は現在最も盛んに研究されている分野である。当研究室では、外部キラル配位子制御による不斉共役付加反応を報告してきた。その応用研究として、ヒガンバナアルカロイド(+)-*trans*-dihydronarciclasine (**1**) や pancratistatin (**2**) の合成研究を計画した。当研究室の Mohamed らはキラルジエーテル配位子存在下、高い収率およびエナンチオ選択性でアリールリチウムの α,β -不飽和エステルへの不斉共役付加反応に成功した (Scheme 1)。引き続き、ラセミ体を用いた合成研究を行い、穏和な条件でベンジル位を酸化し B 環の構築を報告している。著者は、構築した不斉点を足掛かりに C 環への立体選択的な酸素官能基の導入を検討し、(+)-*trans*-dihydronarciclasine (**1**) の不斉全合成を達成した。これらの詳細については第 2 章第 3 節および第 4 節で述べる。



Scheme 1. Synthetic study of pancratistatin-class alkaloids

有機合成化学の発展とともに何を作るかではなく、如何に作るかが大変重要視されるようになった。複雑な分子であっても安く、早く、簡単に合成できる方法論の開発が求められている。中でも、一挙に数工程の反応を行う連続反応や多成分反応が効率的な反応として注目を集め、盛んに研究されている。当然のことながら、単段階の反応を組み合わせた手法と比べ反応および精製工程を短縮化することができる。さらに、単純な化合物を出発原料とすれば基質に多様性を持たせることも可能であり類縁体合成にも適用できる。当研究室でも抗腫瘍活性を示す **paesslerin A** の合成研究において多成分連続反応を利用している (Scheme 2)。当研究グループの稲永らによる **paesslerin A** の提出構造 (3) の全合成の結果、構造訂正が必要なことが明らかになった。詳細な NMR 解析の結果、**paesslerin A** の真の構造はプロトイルダン骨格を有する 4 であると推測した。稲永らは TiF_2NH を触媒とする多成分連続反応を利用することで単純な原料から 4 の骨格を一挙に構築することにも成功している。得られた三環性化合物から 4 へ導くためにはシクロヘキサン環への置換基導入が大きな課題となった。そこで、著者は分子内に存在する官能基を足掛かりとする戦略を考案した。主に核間位ヒドロキシ基を足掛かりとする戦略を検討し、シクロヘキサン環上の C-H 結合を官能基化することに成功した。さらに、**paesslerin A** の予想構造 (4) の全合成を達成し真の構造を明らかにした。これらの詳細については第 3 章節 2 節および第 3 節で述べる。



Scheme 2. Synthetic study of paesslerin A

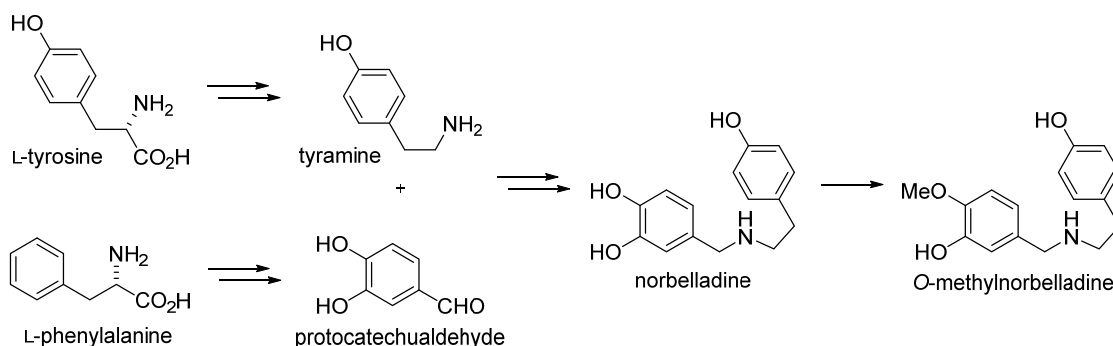
第2章 不斉共役付加反応を利用する(+)-*trans*-Dihydronariclasine の全合成

第1節 研究背景

第1項 ヒガンバナアルカロイドについて

ヒポクラテスがラッパズイセン *Narciclasus poeticus* L.の抽出液を子宮癌の治療に用いた紀元前4世紀以来、ヒガンバナ科植物の抽出成分に薬理効果があることは長い間認識されてきた¹。ヒガンバナ科に属する約1000種の植物のうち、少なくとも30種は癌治療のための民間療法として利用されてきた。このようにヒガンバナアルカロイドは古くから抗腫瘍活性や抗ウイルス活性、抗マラリア活性などの有用な活性を持つことが知られており、近年も100種類以上の構造的に多様なアルカロイドがヒガンバナ科植物から単離されている²。

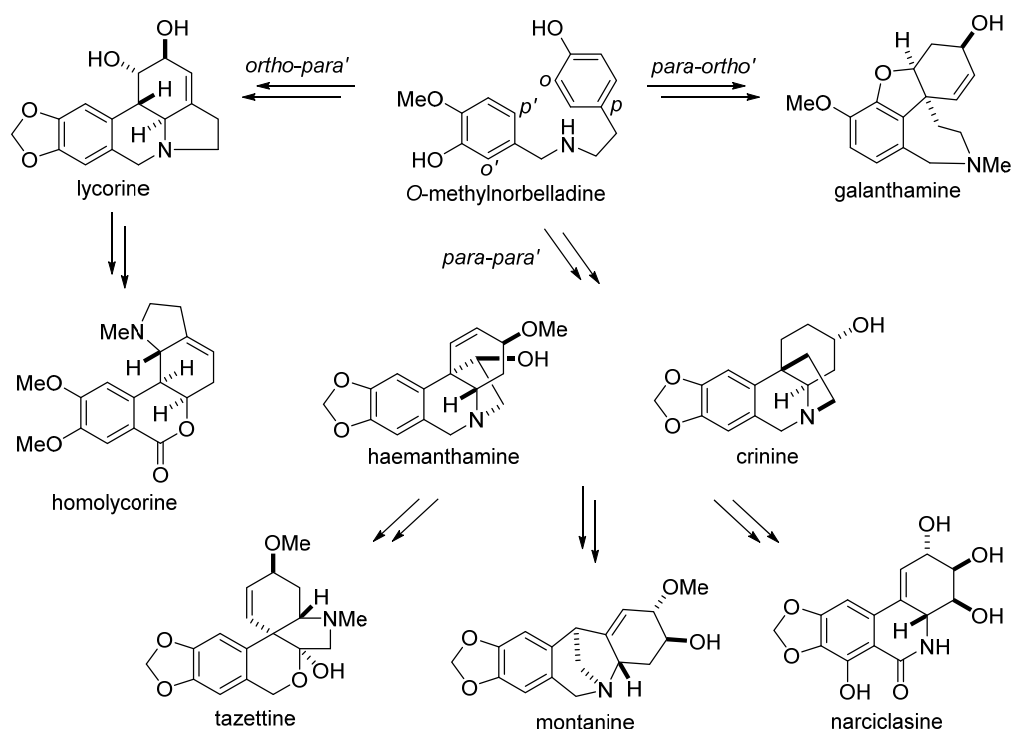
ヒガンバナアルカロイドの生合成は次のように考えられている³。まず、植物中で L-tyrosine から生じた tyramine と、L-phenylalanine から生じた protocatechualdehyde との縮合および還元によって norbelladine が生じる (Scheme 3)。さらに norbelladine から O-methylnorbelladine が生合成される。



Scheme 3. Biosynthesis of *O*-methylnorbelladine

O-methylnorbelladine が分子内フェノール酸化的カップリングによって閉環することで様々なヒガンバナアルカロイドが生合成され则认为されている (Scheme 4)。即ち、*O*-methylnorbelladine の *ortho-para'*カップリングにより lycorine や homolycorine を、*para-para'*カップリングにより haemanthamine や crinine、tazettine、montanine、narciclasine を、*para-ortho'*カップリングにより galanthamine がそれぞれ生合成され则认为されている。ヒガンバナアルカロイドの中でも特に代表的なものは lycorine と galanthamine である。Lycorine は 1877 年に初めて単離されたヒガンバナアルカロイドであり、抗腫瘍活性や抗ウイルス活性を有している⁴。Galanthamine はアセチルコリンエステラーゼ阻害作用を有し⁵、欧米ではアル

ツハイマー型認知症治療薬（Reminyl[®]）として用いられている。Reminyl[®]は 2011 年に日本でも承認されている。



Scheme 4. Biosynthetic pathways of the *Amaryllidaceae* alkaloids

一方、ヒガンバナアルカロイドの中でも特に有望な抗腫瘍活性を有するものが、*trans*-dihydronarciclasine (**1**) や pancratistatin (**2**) である (Figure 2)。Pancratistatin (**2**) は 1984 年に Pettit らによって、ハワイのヒガンバナ科植物 *Hymenocallis littoralis* から単離され、*in vitro* で強い抗腫瘍活性を示すことが報告された⁶。しかしながら、天然からの供給量が極めて少ないため、前臨床試験は滞ったままである。興味深い構造と魅力的な生理活性を持つため、1989 年に Danishefsky らによる初のラセミ全合成⁷が達成されて以来、Trost らによる不斉全合成⁸など、これまでに 10 を超える研究グループが全合成を報告している⁹。*trans*-Dihydronarciclasine (**1**) は元々、天然に存在する narciclasine から接触水素化によって化学合成された (Figure 3)¹⁰。その後、1990 年に Pettit らによって中国の薬用植物 *Zephyranthes candida* から単離され、特定のヒトの癌細胞株に対して、**2** よりもはるかに強い抗腫瘍活性を示す¹¹。さらに、最近の研究によって **1** は抗白血病活性を示すことも明らかとなった¹²。

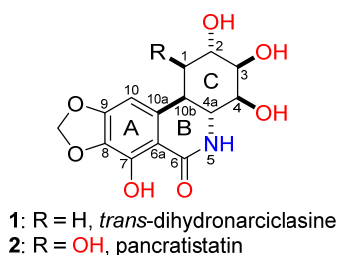


Figure 2. Structures of synthetic targets

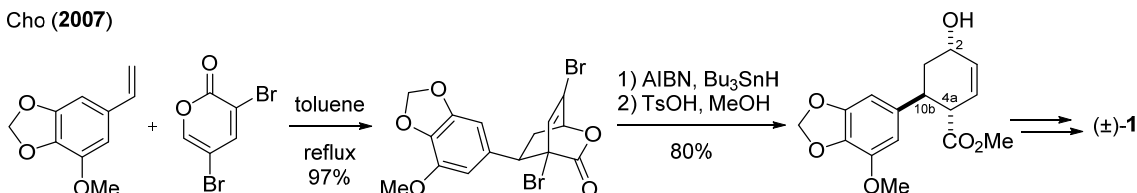


Figure 3. *Zephyranthes candida*

(<http://www.de.wikipedia.org> より引用)

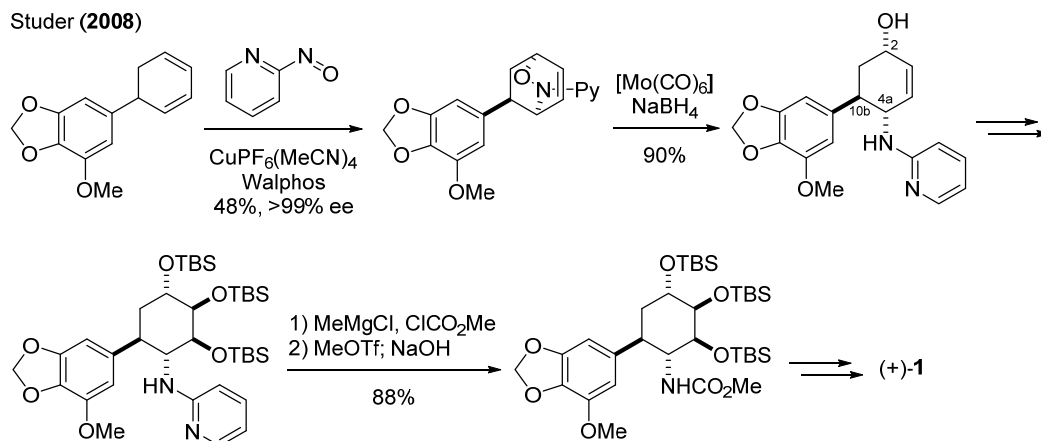
trans-Dihydronarciclasine (**1**) や pancratistatin (**2**) は低分子であるものの分子全体に複雑性を有しており、ヒガンバナアルカロイドの中でも特に合成的にチャレンジングな天然物である。具体的には、酸化度の高い多置換芳香環 (A 環) や 5~6 連続不斉点を有している (C 環)。また、C 環と *trans* 縮環しているラクタム環 (B 環) は、 sp^2 混成の 4 つの原子 (N5、C6、C6a、C10a) による平面性が損なわれるため高度に歪んでいる。よって、全合成を達成するためには徹底的に設計された合成計画が必要となる。*trans*-Dihydronarciclasine (**1**) の初のラセミ全合成が 2007 年に Cho らによって達成された^{13a}。鍵工程にスチレンと 3,5-ジブロモ-2-ピロンの Diels-Alder 反応を用いて、エンド付加体を高い選択性で得ることに成功した (Scheme 5)。続いて、ブロモ基の還元的除去とラクタムの開環を経て 3 つの不斉炭素有する双環性化合物に誘導し、その不斉源を基に 2 つのヒドロキシ基を立体選択的に導入し天然物へと導いた。

Cho (2007)



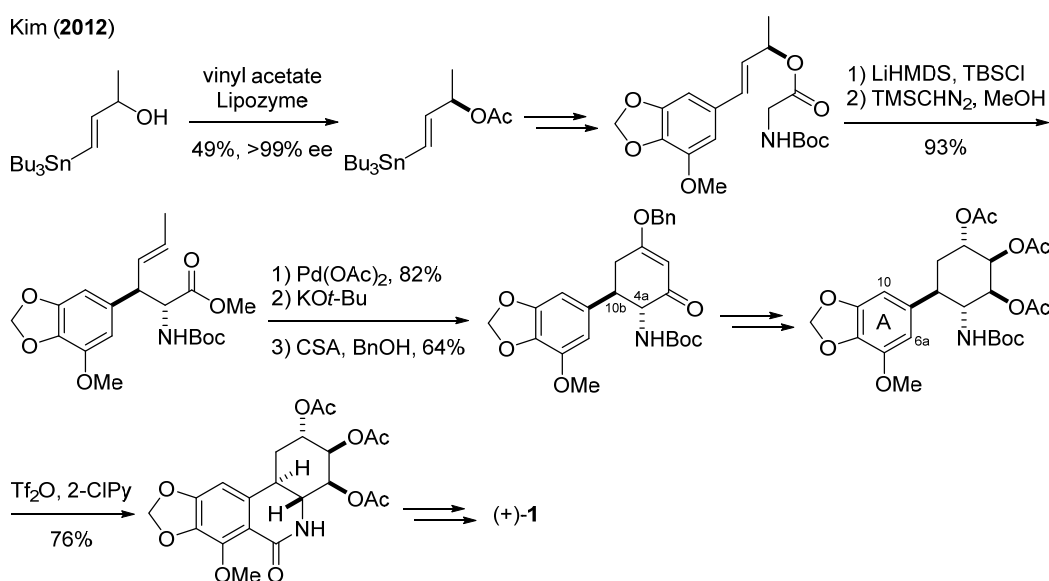
Scheme 5. First total synthesis of (±)-**1**

trans-Dihydronarciclasine (**1**) の初となる不斉全合成は 2008 年に Studer らによって達成された¹⁴。ラセミ体のシクロヘキサジエンに対し、キラル銅触媒を用いたエナンチオ選択的ニトロソ Diels-Alder 反応による速度論的光学分割を行い、高い不斉収率 (>99% ee) で付加体を得た (Scheme 6)。続いて、還元的に N-O 結合を開裂した後、Cho と同様に 3 つの不斉源を基に 2 つのヒドロキシ基を導入した。その後、MeOTf によるアンモニウム塩の形成と続く塩基性加水分解によりピリジニル基を除去して(+)-**1** へと導いた。



Scheme 6. First total synthesis of (+)-1

2012 年に 2 番目の不斉全合成が Kim らによって達成された¹⁵。まず、ラセミ体の γ -ヒドロキシビニルスタナンを酵素を用いた光学分割によって光学純品なアセチルエステルに変換した (Scheme 7)。数工程を経て合成したアリルエステルに対して Ireland–Claisen 転位を行うと、嵩高い Boc 基の影響により単一のジアステレオマーが得られた。続いて、位置選択的な Wacker 酸化、Dieckmann 縮合を経てビニロガスエステルへ変換した。B 環の形成には Friedel–Crafts 型の環化反応を用いた。Pancratistatin (2) の合成例も含めると B 環構築にはメチルカルバメートを基質として Bischler–Napieralski 反応を行う場合が多い。A 環上には反応点が 2 つあるため (6a 位および 10 位)、これまで位置選択性 (最高 3.6:1) は低かった。Kim らは *tert*-ブチルカルバメートを用いることでイソシアナートを経由して反応が進行していることを見出し、高い位置選択性 (12.5:1) でラクタムを構築することに成功した。



Scheme 7. Second total synthesis of (+)-1

いずれも B 環の構築には Bischler–Napieralski 反応を利用している。Kim らによって位置選択性が大幅に改善されるまでは不要な位置異性体が生成する問題があった。一方、当研究室では 6a 位に側鎖を持たせ、発生させたベンジルカチオンに窒素原子が付加するという方法をとっているため当然のことながら位置選択性の問題は生じない(第 1 節第 2 項参照)。不斉誘導の方法としては Studer や Kim らはラセミ体の光学分割を利用している。その場合理論的な最大収率は 50%に留まる。これに対して当研究室で開発した不斉共役付加反応は高収率、高立体選択的に進行する。光学的に純粋なキラルジエーテル配位子を大量かつ簡単に合成でき、回収して不斉収率を損なうことなく再利用することも可能である(第 1 節第 2 項および第 2 節参照)。C 環へのヒドロキシ基の導入では 2 位および 4a 位、10b 位の不斉源を足掛かりにヒドロキシ基を導入する方法が多い。著者も最終的には Cho や Studer と同様にオレフィンのヒドロキシ化を行う方法を採用した(第 3 節参照)。

第 2 項 外部キラル配位子制御による不斉共役付加反応について

当研究室では、これまで一貫して C_2 対称な外部キラル配位子制御による有機リチウム試薬の不斉共役付加反応を様々開発してきた¹⁶。その不斉誘起のコンセプトはリチウムと酸素原子のキレーションによる不斉空間の構築に基づく (Figure 4)。即ち、キラルジエーテル配位子と有機リチウム試薬が 5 員環キレート錯体を形成し、酸素原子上のメチル基は、隣接する炭素原子上のフェニル基との立体反発を避けるように 5 員環キレート面の上下に固定される。このように本来キラルではないエーテル酸素が、あたかもキラルな原子として機能することで、反応点近傍に高度な不斉空間が構築され高い立体選択性が発現される。

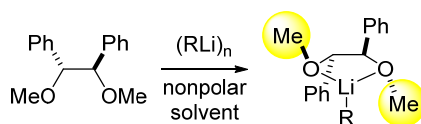
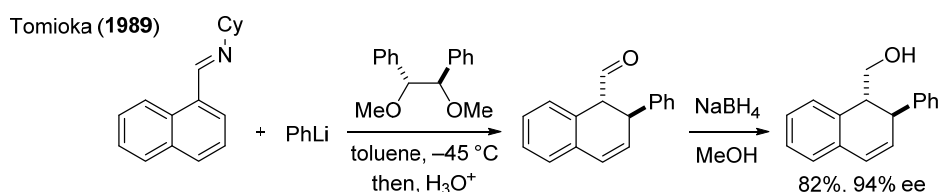


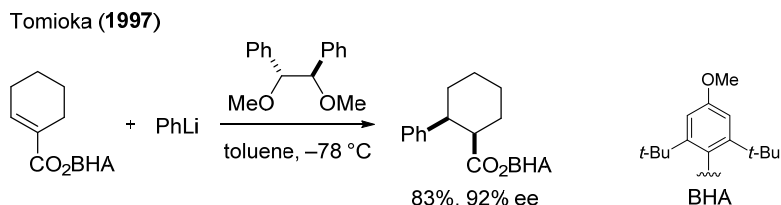
Figure 4. Our concept of the ligand design

1989 年には、キラルジエーテル配位子存在下、 α,β -不飽和アルジミンへのフェニルリチウムの付加に続いて酸加水分解と還元処理を行うと、94% ee と高い不斉収率で *trans*-アルコールが得られることを報告している (Scheme 8)¹⁷。



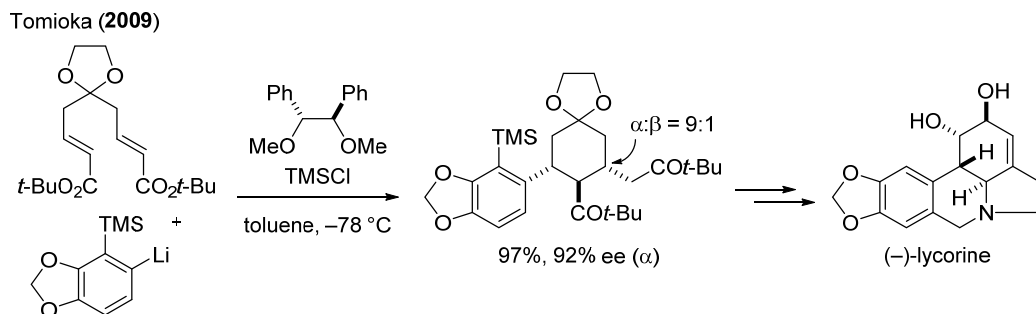
Scheme 8. Asymmetric conjugate addition to α,β -unsaturated aldimine

1997 年には、キラルジエーテル配位子存在下、 α,β -不飽和 BHA エステルへのフェニルリチウムの不斉共役付加を高いエナンチオ選択性で達成した (Scheme 9) ¹⁸。



Scheme 9. Asymmetric conjugate addition to α,β -unsaturated BHA ester

さらに、開発した不斉共役付加反応の天然物合成への応用も行っており、2009 年には、ヒガンバナアルカロイド(-)-lycorine の不斉全合成を達成した ¹⁹。分子内に 2 つの α,β -不飽和エステルを有する鎖状分子に、キラル配位子存在下、アリールリチウムを共役付加させると、生じたりチウムエステルエノラートが、引き続き分子内の不飽和エステルにマイケル付加し、3 連続不斉点および 2 つの炭素-炭素結合を一挙に構築して、付加成績体が高エナンチオ選択的に得られた (Scheme 10)。このタンデム閉環反応を鍵工程として(-)-lycorine に導いた。

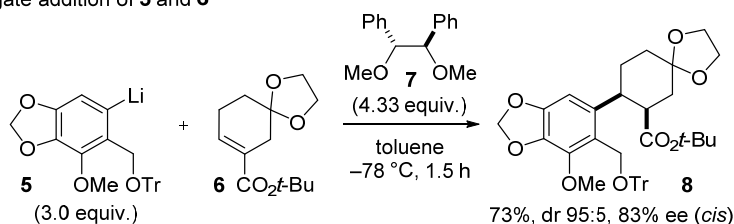


Scheme 10. Total synthesis of (-)-lycorine

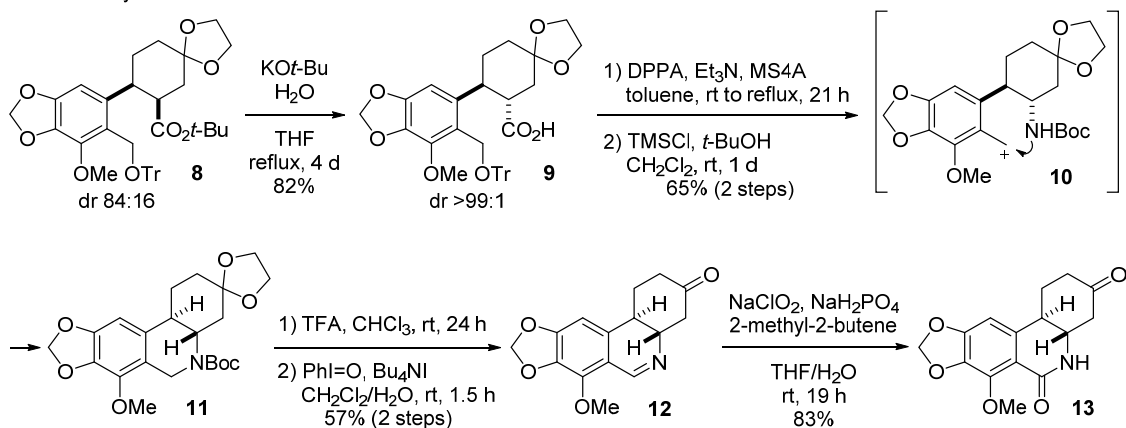
当研究室の Mohamed らはキラルジエーテル配位子 **7** 存在下、アリールリチウム **5** の不飽和エステル **6** への不斉共役付加反応を行い、付加体 **8** を 73% 収率、*cis*-体を 83% ee で得ることに成功した (Scheme 11) ²⁰。さらに、ラセミ体を用いた *trans*-dihydronarciclasine (**1**) および pancratistatin (**2**) の合成研究を行い、ラクタム **13** を最前線の化合物として得た。まず、KO*t*-Bu と水から系中で発生させた KOH²¹ と *cis*-エステル **8** を反応させると、エステル α -位のエピマー化とエステルの加水分解が進行し *trans*-カルボン酸 **9** が得られた。次に、DPPA²²を用いる Curtius 転位によりイソシアナートへ変換した後に、TMSClを加えて*t*-BuOH と加熱還流下反応させると、環化が進行した **11** が得られた。本反応は、系中発生した塩酸²³によってトリチルエーテルがプロトン化されると、トリチル基と酸素の結合ではなく電子

豊富なベンジル位の C–O 結合が選択的に切断されベンジルカチオンが生じる。これにカルバメートの窒素原子が付加することで **11** が生成する。続いて、TFA でアセタール部位の加水分解および Boc 基の除去を行ってアミンを得た。これに対してベンジル位の酸化を様々な検討したが、電子豊富な芳香環を有するため複雑な混合物を与えるのみだった。そこで、一旦ヨードソベンゼンでイミン **12** へ酸化²⁴ した後に当研究室で開発した亜塩素酸ナトリウムを用いる穏和な条件²⁵ で酸化すると、高収率でラクタム **13** に変換することに成功した。

1. Asymmetric conjugate addition of **5** and **6**



2. Racemic synthesis of amide **13**



Scheme 11. Asymmetric conjugate addition and racemic synthesis of amide **13**

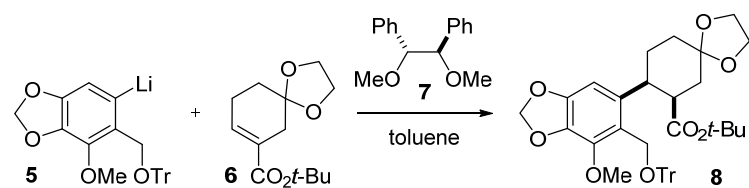
by Dr. Mohamed (2008)

第 2 節 不斉共役付加反応の最適化

前節で述べたように Mohamed らは本研究の鍵工程である不斉共役付加反応に成功したが、アリールリチウム **5** やキラルジエーテル配位子 **7** の当量、反応時間などの最適化が行われていなかった。そこで、まず著者は不斉共役付加反応の条件検討を行い最適化を試みることにした。アリールリチウム **5** を 3 当量、キラルジエーテル配位子 **7** を 3.3 当量用いた時に 92% 収率、96:4 のジアステレオ比で *cis* 体を主生成物とする付加体 **8** が得られた (Table 1, entry 3)。この時、*cis* 体を 92% ee で得ることに成功した。**5** を 2.0 当量、**7** を 2.3 当量に減らしても **8** は 91% 収率、*cis* 体は 89% ee で得られた (entry 2)。さらに **5** を 1.1 当量、**7** を 1.3 当量に減らしたところ、**8** の収率は 70% まで低下するものの、*cis* 体は 88% ee と高い不斉収

率を維持した (entry 1)。7 を触媒量に減らすと反応が著しく遅くなったため、昇温して反応を行うとブチルリチウムとの付加体が副生し、8 の収率の低下を招いた (entry 4)。以上の結果より、entry 3 の条件を最適条件とした。なお、当量以上用いているキラルジエーテル配位子 7 は、シリカゲルカラムクロマトグラフィーによって回収後、不斉収率を損なうことなく再利用することが可能であった。

Table 1. Asymmetric conjugate addition of **5** and **6**



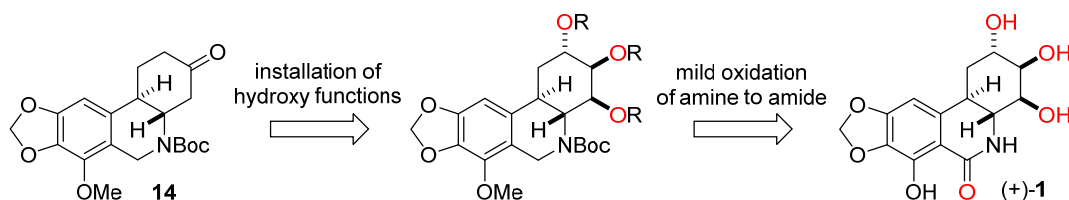
entry	5 ^a (equiv.)	7 (equiv.)	temperature & time	yield	dr (<i>cis:trans</i>)	ee (<i>cis</i>)
1	1.1	1.3	−78 °C, 26 h	70% ^b	95:5	88%
2	2.0	2.3	−95 °C, 1.5 h	91%	97:3	89%
3	3.0	3.3	−78 °C, 1.5 h	92%	96:4	92%
4	3.0	0.30	−60 °C, 1 d	9%	93:7	66%

^aAryllithium **5** was prepared from the corresponding aryl bromide and equimolar amount of butyl lithium in the presence of chiral ligand **7**.

^bEnoate **6** was recovered in 21% yield.

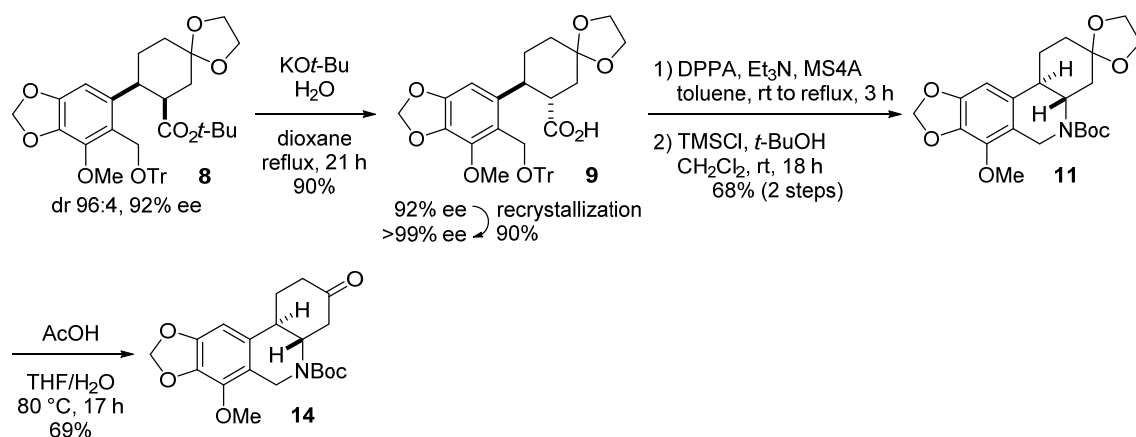
第3節 ケトンα-位の酸化の検討

不斉共役付加反応の最適条件を確立したので、次に Mohamed らが合成したラクタム **13** のシクロヘキサノン環の酸化を検討することとした。しかし、**13** の溶解性は著しく悪く CHCl₃ など限られた溶媒にしか溶解しないため続く変換が困難であった。そこで、**11** のアセタール部位を加水分解して得られるケトン **14** に対し、位置および立体選択的なヒドロキシ基の導入を行い、ラクタムへの酸化は合成の最終段階で行うこととした (Scheme 12)。



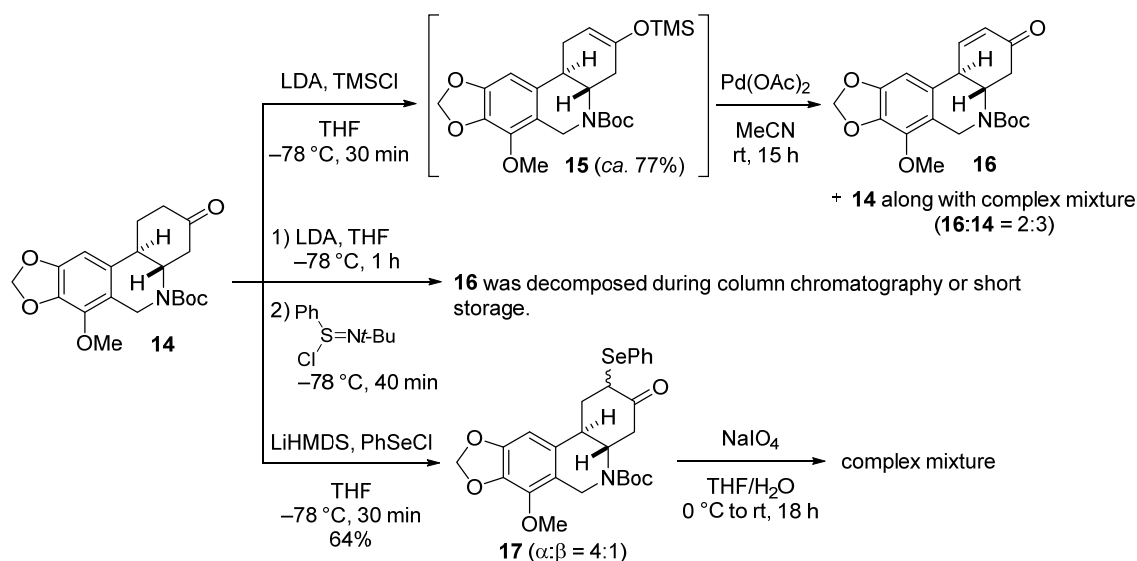
Scheme 12. Synthetic strategy of (+)-**1**

まず、当研究室の Mohamed らによって確立された経路で **11** まで不斉合成を行った。即ち、*cis*-エステル **8** を系中発生させた KOH を用いて、エステル α -位の異性化とエステルの加水分解を行い、*trans*-カルボン酸 **9** を得た。この時、溶媒を THF からジオキサンに変更することで、大幅に反応時間を短縮できた。得られた **9** をヘキサン-酢酸エチル混合溶媒から再結晶を行うとラセミ体が優先して晶出し、母液から光学的に純粋なカルボン酸を得ることに成功した (Scheme 13)。続いて、ベンジルカチオンを経由する環化反応により **11** へ変換した。最後に含水 THF 中、酢酸を用いてアセタールを加水分解し、ケトン **14** を合成した。



Scheme 13. Synthesis of ketone **14**

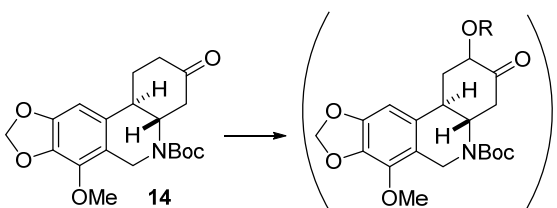
先に示した合成戦略に従って、**14** の C 環の酸化を検討した。ケトン **14** に対し LDA、TMSCl を用いたところ、原料はわずかに残ったもののシリルエノールエーテル **15** が位置選択的に得られることがわかった (Scheme 14)。得られた **15** を用いて伊藤-三枝酸化²⁶を行ったところ、目的物のエノン **16** とケトン **14** を約 2:3 の比で混合物として得た。しかし、低収率だけでなくカラムクロマトグラフィーで両者を分離するのも難しかった。また、ケトン **14** に対し、向山らの開発した *N*-*tert*-ブチルベンゼンスルフィンイミドイルクロリド²⁷ を用いてエノンへの酸化を試みたところ、反応終了時点の ¹H NMR ではエノン **16** と試薬由来の化合物が主として確認できた。しかし、シリカゲルカラムクロマトグラフィーによる精製後、あるいは短時間の冷凍保存後、目的物が減少したり分解物を与えたりした。さらに、 α 体を優先してセレニド **17** を得ることに成功したものの、続くセレノキシドの *syn*-脱離でも複雑な混合物を与えたため、エノン **16** を経由する合成は困難であると判断した。



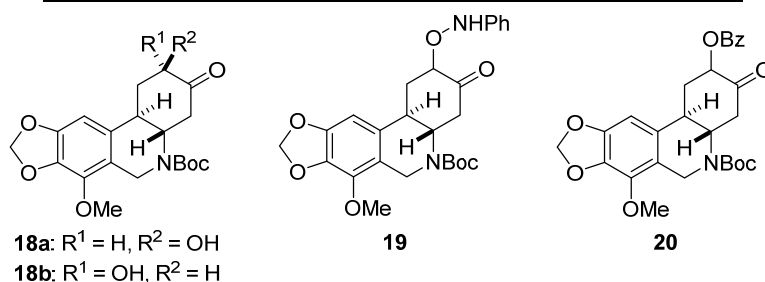
Scheme 14. Attempted synthesis of enone **16**

ケトン **14** に対し、位置および立体選択的な α -位の酸化を検討した (Table 2)。Davis のオキサジリジンを用いて酸化反応²⁸を行ったが、目的物は得られなかった (entry 1)。発生させたエノラートは MoO_5 -pyridine-HMPA (MoOPH)²⁹ やニトロソベンゼン³⁰ と反応させても目的物を与えなかった (entries 2 and 3)。また、石原らの報告した酸化条件³¹においても α -位が酸化された化合物は得られなかった (entry 4)。一方、シリルエノールエーテルを用いる Rubottom 酸化³²を行ったところ、望みの立体化学を持つ α -ヒドロキシケトン **18b** は得られなかったものの、逆の立体化学を持つ **18a** が低収率ながら得られた (entry 5)。

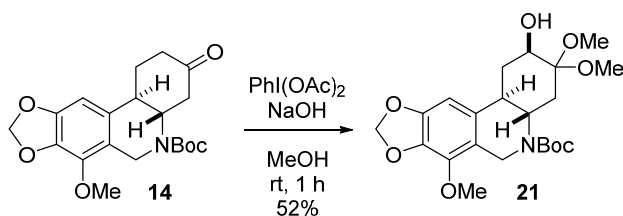
Table 2. α -oxidation of ketone **14**



entry	reagents and conditions	% yield
1	LiHMDS, THF, -78°C , 1 h; PhO ₂ S-N ₂ -Ph -78°C to rt, 1 h	0 (18)
2	LiHMDS, -78°C , 1 h; MoOPH, -78°C to rt, 1 h	0 (18)
3	(i) LiHMDS, TMSCl, Et ₃ N, THF, -78°C , 30 min (ii) PhN=O, TESOTf, 1,2-dichloropropane, 0°C , 1 h	0 (19)
4	PhCO ₂ H, TBHP, Bu ₄ NI, EtOAc, 75°C , 22 h	0 (20)
5	(i) LiHMDS, TMSCl, Et ₃ N, THF, -78°C , 20 min (ii) <i>m</i> CPBA, NaHCO ₃ , CH ₂ Cl ₂ , -20°C , 30 min (iii) TBAF, THF, 0°C , 30 min	15 (18a)



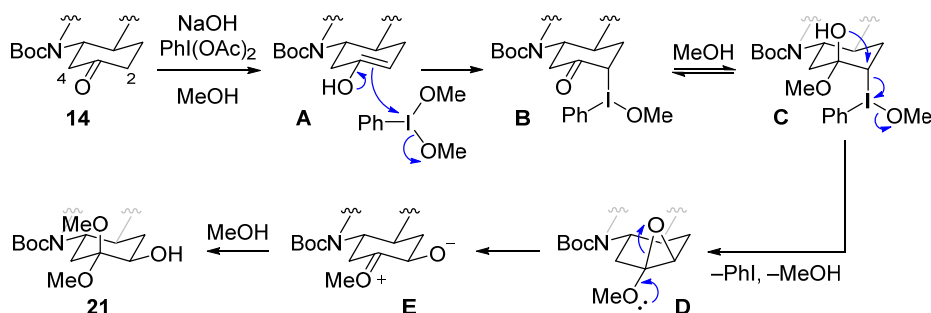
さらに検討を行った結果、Moriarty らの条件³³に従い水酸化ナトリウム存在下ヨードベンゼンジアセテートを用いて酸化したところ、位置および立体選択的にヒドロキシ基が導入されたジメチルアセタール **21** を 52%収率で得ることに成功した (Scheme 15)。



Scheme 15. Oxidation of ketone **14** under Moriarty's condition

ジメチルアセタール **21** が位置および立体選択的に得られた理由は次のように考えている。まず、ケトン **14** の C2 位および C4 位で可逆的に生じるエノラートのうち立体障害の少ない

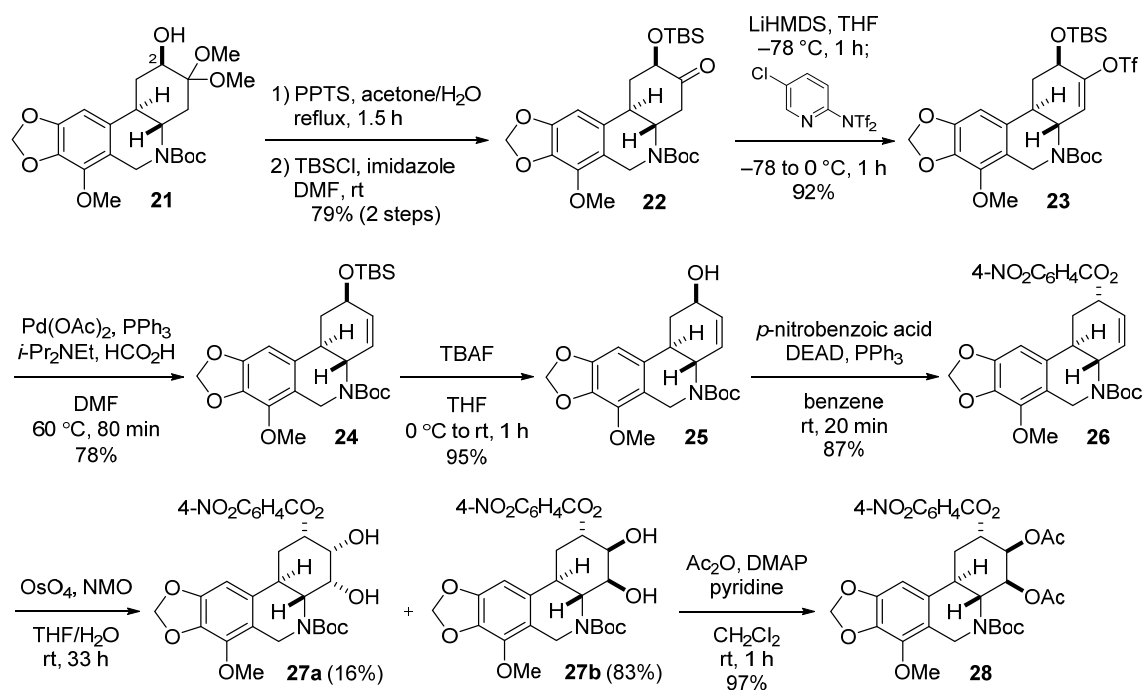
C2 位で生じたエノラート **A** が系中発生したヨウ素試薬と優先的に反応する (Scheme 16)。この時、ねじれ舟形の配座を避けるようにエノラートの面に対して下側からヨウ素試薬と反応して α -ヨードケトン **B** を与える。続いて、カルボニル炭素へメタノールが付加してヘミアセタール **C** が生じる。**C** は分子内 S_N2 反応によってエポキシド **D** となる。次いで、メトキシ基の孤立電子対から電子の押し出しが起こると、エポキシドが開環してオキソニウムカチオン **E** が生じる。これにメタノールが付加するとジメチルアセタール **21** が得られる。



Scheme 16. Rationale for the stereoselective formation of **21**

第 3 節 (+)-*trans*-Dihydronariclasine の全合成

前節ではケトン **14** の C 環に位置および立体選択的にヒドロキシ基を導入することに成功したが、天然物とは逆の立体化学であったため、C2 位の立体反転を行ってからその不斉源を基に残るヒドロキシ基を導入することとした。PPTS を触媒として **21** のアセタール部位を加水分解した後第二級ヒドロキシ基を TBS 基で保護し **22** とした (Scheme 17)。さらに、LiHMDS で脱プロトン化を行い、発生させたリチウムエノラートを Comins 試薬³⁴と反応させてエノールトリフラート **23** へ変換した。次に、触媒量のパラジウムを用いてトリフラートを還元的に除去³⁵し **24** を得た後に、TBAF を用いて TBS 基を除去しアリルアルコール **25** を得た。続く光延反応³⁶によって C2 位の立体反転を行い *p*-ニトロ安息香酸エステル **26** へ変換した。さらにオレフィン部位を四酸化オスミウムを用いてジアステレオ選択的に酸化してジオール **27b** を合成した。この時、ジオール **27a** も得られた。ジオール **27b** をアセチル基で保護しジアセテート **28** とした。



Scheme 17. Synthesis of diacetate **28**

ジオール **27a** および **27b** の立体化学は NOE 測定によって決定した (Figure 5)。

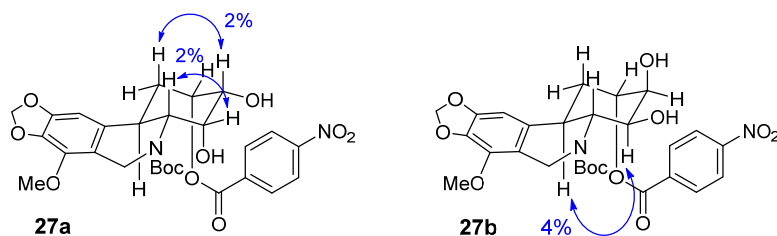
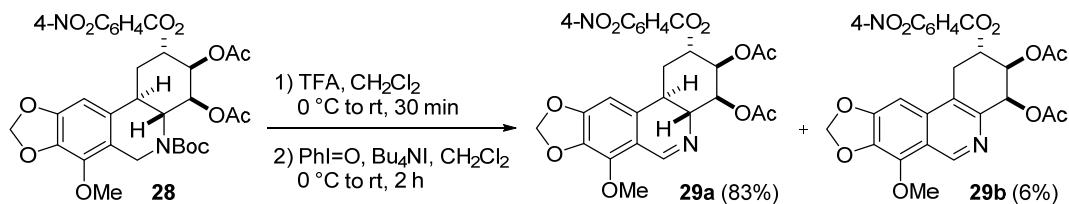


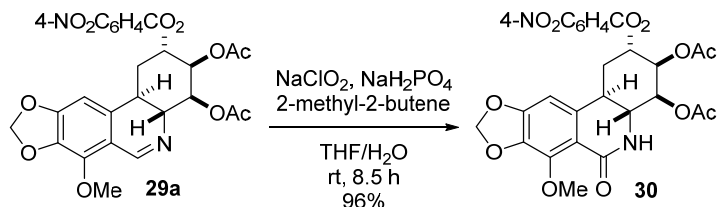
Figure 5. NOE correlations of diols **27a** and **27b**

ジアセテート **28** の Boc 基を TFA で除去した後に、ヨードソベンゼンでイミン **29a** に酸化²⁴した (Scheme 18)。この時、イミン **29a** がヨードソベンゼンとさらに反応することでイソキノリン **29b** が僅かに副生した。



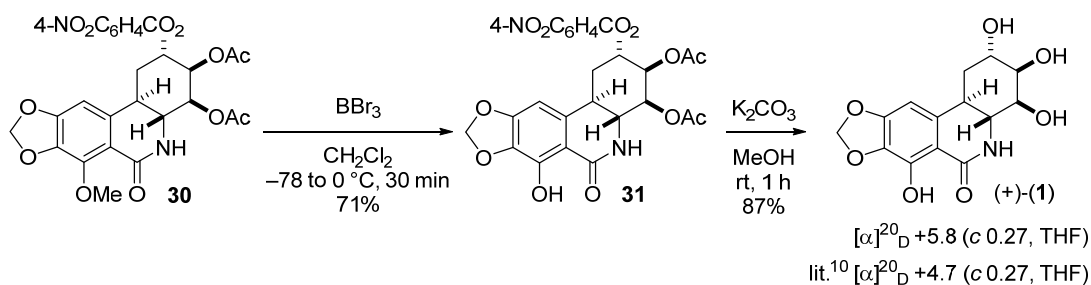
Scheme 18. Oxidation to imine **29a**

得られたイミン **29a** を亜塩素酸ナトリウムで酸化²⁵ したところ、高度に官能基化された複雑な基質であるにもかかわらず、高収率でラクタム **30** を得ることに成功した (Scheme 19)。



Scheme 19. Mild oxidation to imine **29a** to amide **30**

続いて、 BBr_3 を用いてメチル基を除去しフェノール **31** とした (Scheme 20)。最後にエステル部分の加溶媒分解を行い 22 工程、総収率 2.8% で (+)-*trans*-dihydronarciclasine (**1**) の全合成を達成した³⁷。旋光度 ($[\alpha]_D^{20} +5.8$ (c 0.27, THF)) を文献値¹⁰ ($[\alpha]_D^{20} +4.7$ (c 0.27, THF)) と比較して絶対配置の確認を行った。また、 ^1H および ^{13}C NMR、IR、MS のデータは全て文献値^{10,13-15} と一致した。



Scheme 20. Completion of the total synthesis of (+)-**1**

第3章 多成分連続反応を利用する Paesslerin A の全合成

第1節 研究背景

第1項 Paesslerin A の提出構造の全合成

当研究グループでは触媒量の Ti_2NH 存在下、シリルエノールエーテルとアクリル酸エステルあるいはプロピオール酸エステルを反応させると、[2+2]環化付加反応が高収率かつ高立体選択的に進行し、多置換シクロブタンを構築できることを見出している³⁸。2004年には Ti_2NH による[2+2]環化付加反応を多成分連続反応へと展開し、paesslerin A の提出構造 (3) の全合成を達成している³⁹。Paesslerin A は2001年に Palermo らによって亜南極に生息する軟珊瑚 *Alcyonium paessleri* より単離・構造決定されたセスキテルペノイドであり、人の癌細胞に対して細胞毒性を示すことが報告されている (Figures 6 and 7)⁴⁰。また、新奇なトリシクロ[4.3.2.0^{2,5}]ウンデセン骨格を有することから、合成化学上興味深い天然物である。

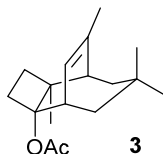


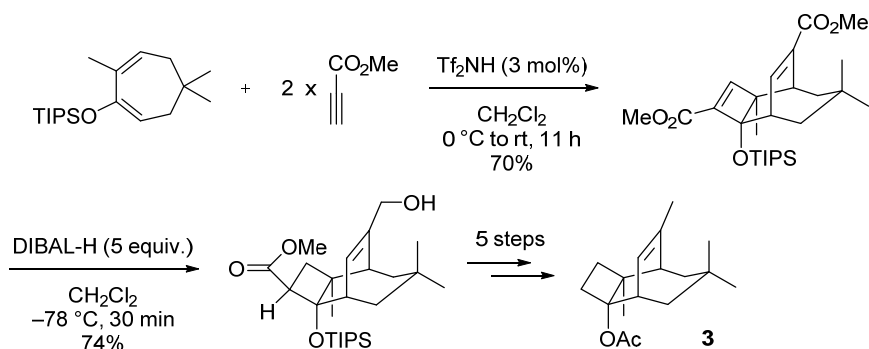
Figure 6. Proposed structure of paesslerin A



Figure 7. *Alcyonium paessleri*

(<http://www.reefthailand.com> より引用)

当研究室の稲永らは Ti_2NH 存在下、シロキシシクロヘプタジエンと2当量のプロピオール酸メチルを用いて Diels–Alder 反応と[2+2]環化付加反応の連続反応を行い、3の基本骨格を一挙に構築した (Scheme 21)。その後、分子内に2つ存在する α,β -不飽和エステル部の位置選択的な還元を経て paesslerin A の提出構造 (3) に導いた。しかしながら、合成品の¹Hおよび¹³C NMR スペクトルが天然物と一致しないことが判明した。アセチル基を加水分解により除去した後、*p*-ブロモベンゾイル化して X 線結晶構造解析を行った結果、合成した化合物の構造は3の三環性骨格を有することが確認されたため、Palermo らによって提出された paesslerin A の構造 (3) は誤りであることが明らかとなった³⁹。



Scheme 21. Total synthesis of **3**

そこで、Palermo らの論文に記載されている NMR データを詳細に解析した結果、paesslerin A の真の分子構造は、野副らによって *Fomitopsis insularis* の菌子体より単離・構造決定された protoilludenol (**32**)⁴¹ のアセチル化体 (**4**) に相当するのではないかと推定した (Figure 8)。両者は ¹H NMR スペクトルにおいて非常に良い類似が見られる。また、paesslerin A の提出構造で見られる二次元 NMR 相関は予想構造にも適合可能である。以上のような背景のもと、paesslerin A の予想構造 (**4**) を合成することで、真の構造を明らかにしようと考えた。

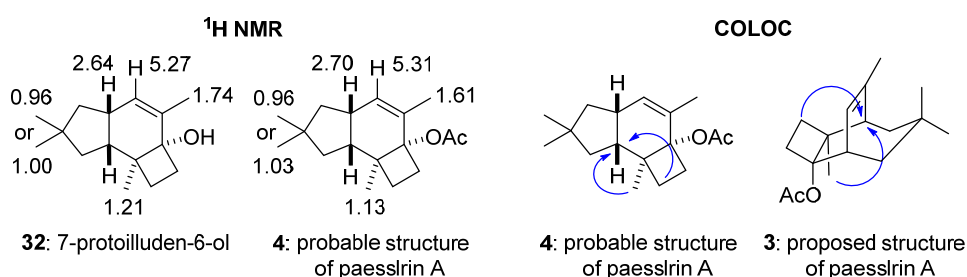


Figure 8. Comparison of NMR spectra

第2項 プロトイルダン類について

7-Protoilluden-6-ol (**32**) や paesslerin A の予想構造 (**4**) に見られる 5-6-4 員環が折れ曲がって縮環した特徴的な骨格はプロトイルダン骨格と呼ばれる。プロトイルダン骨格を有するセスキテルペノイドは 1967 年に McMorris らによってカヤタケ属のキノコである *Clitocybe illudens* から illudol が初めて単離・構造決定された (Figure 9)⁴²。以来、数多くのプロトイルダン類が単離されており、薬理活性を示すものも報告されている⁴³。最近では、2000 年に melleolide K が担子菌の *Armillariella mellea* の培地より単離・構造決定され、グラム陽性菌や酵母、真菌類に対して抗菌活性を有することが報告された⁴⁴。また、2002 年には *Lactarius atlanticus* の子実体より atlanticone D が単離・構造決定された⁴⁵。

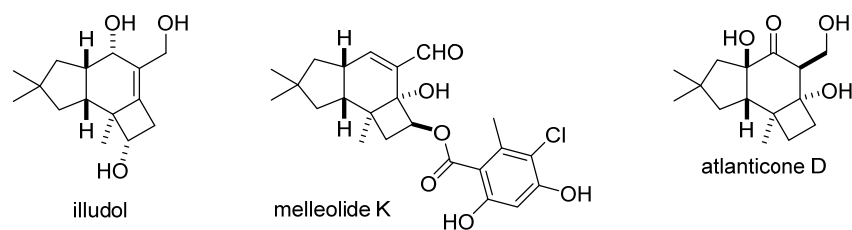
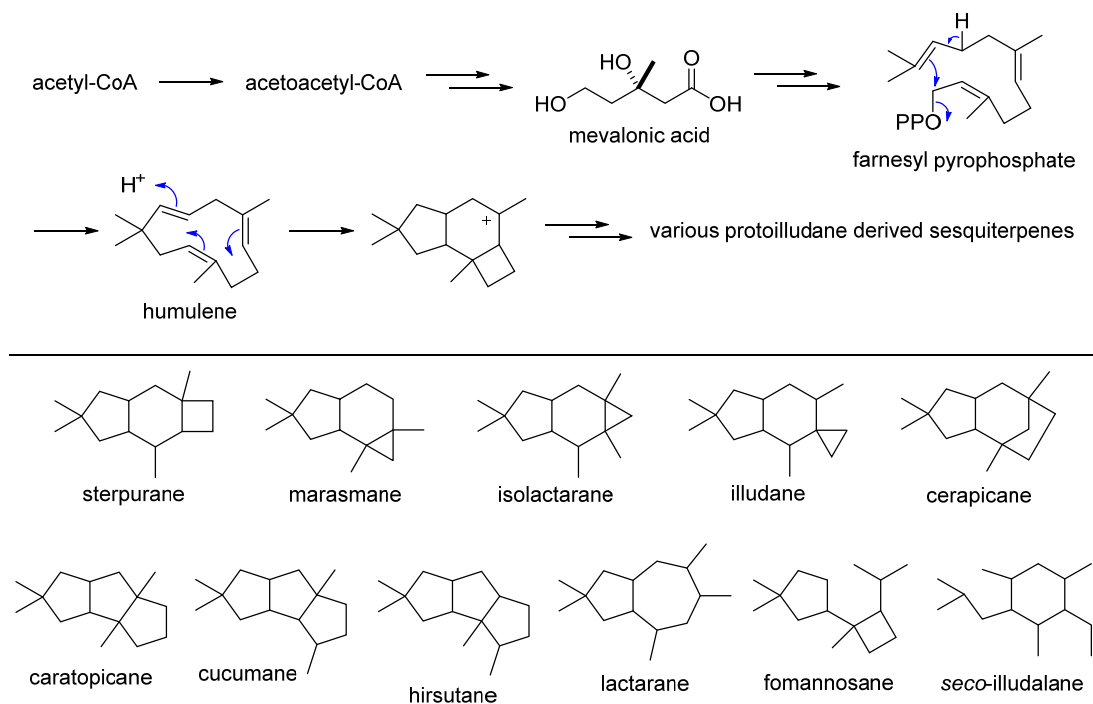


Figure 9. Representative protoilludane sesquiterpenoids

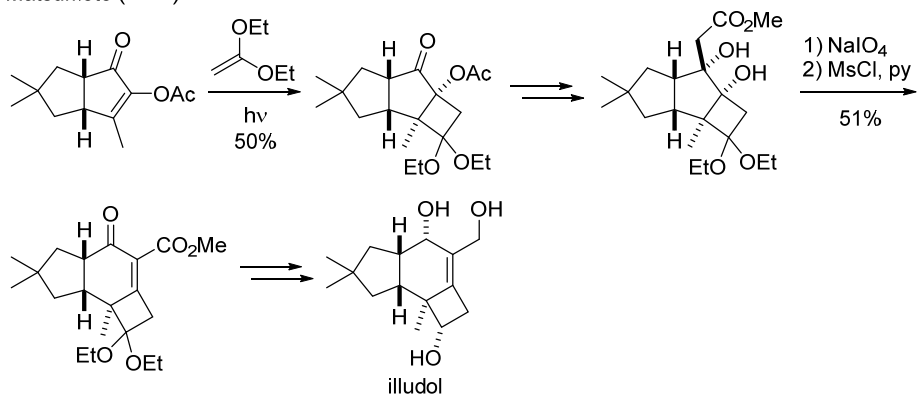
プロトイルダン類は担子菌類によって **humulene** から生合成されると考えられている⁴⁶。まず、メバロン酸から変換されたファルネシル二リン酸が酵素による環化を受けて **humulene** を与える。ここからカチオン環化が起こることによってプロトイルダン骨格が生じる。プロトイルダン骨格は縮環シクロブタンの歪みを解消するために更なる変換を受けやすく、Wagner–Meerwein 転位反応によって **sterpurane** や **illudane**、**hirsutane** などの多様な構造を持つセスキテルペンを生じる (Scheme 22)。



Scheme 22. Biosynthesis of protoilludanes and protoilludane-derived sesquiterpene families

プロトイルダン類の全合成例として 1971 年に松本らが初となる **illudol** のラセミ全合成を発表した⁴⁷。松本らは [2 + 2] 光環化付加反応によるシクロブタン環の構築と、ジオールの酸化的開裂および続くアルドール反応によるプロトイルダン骨格の形成を鍵工程として **illudol** へ導いた (Scheme 23)。

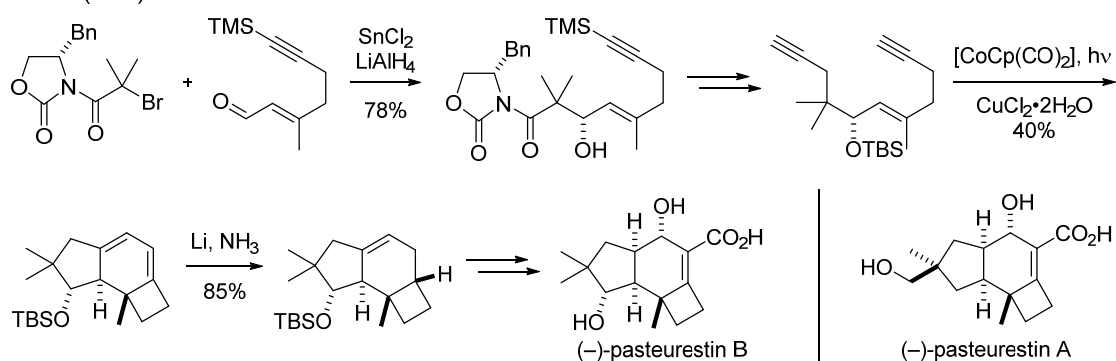
Matsumoto (1971)



Scheme 23. First total synthesis of illudol

また、2007年には Mulzer らが(-)-pasteurestin A および B の全合成を報告している (Scheme 24)⁴⁸。両天然物は 2002 年に微生物化学研究所の竹内らによって、*Agrocybe aegeritta* の発酵によって単離され、ウシの呼吸器疾患の病原菌である *Mannheimia haemolytica* に対して強い活性を示すことが知られている⁴⁹。Mulzer らはまず、キラルなプロモアシロキサゾリジノンとアルデヒドとの Reformatsky 反応を経由してエンジインを得た後、Vollhardt[2 + 2]光環化付加反応を行って三環性骨格を構築した。続いて、位置選択的な Birch 還元およびシクロヘキサン環の官能基化を経て、(-)-pasteurestin B へ導いた。同様の方法によって、(-)-pasteurestin A の全合成も達成した。

Mulzer (2007)

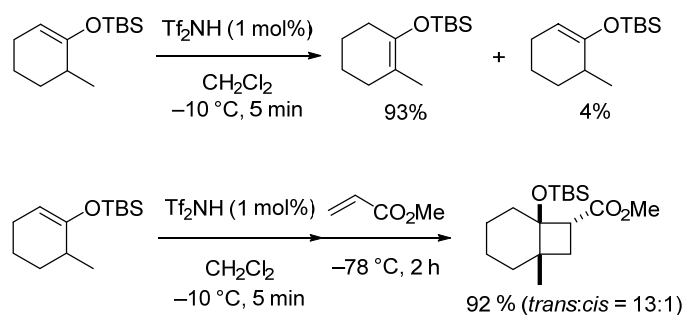


Scheme 24. Total synthesis of (-)-pasteurestins A and B

第3項 [4 + 2]-シリルエノールエーテルの異性化-[2 + 2]連続反応について

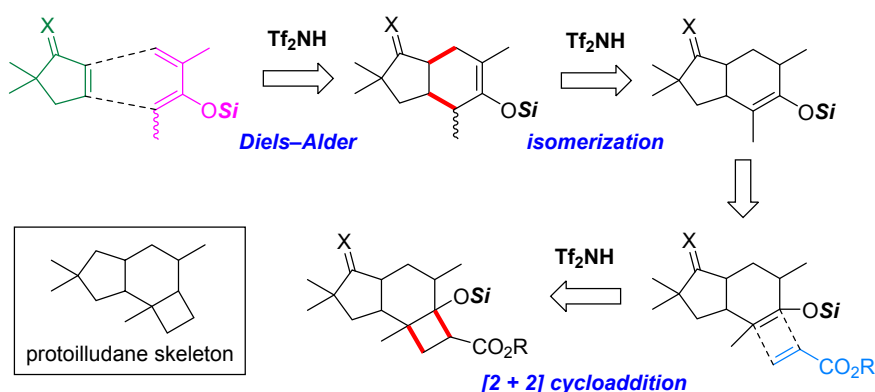
この項では、paesslerin A の予想構造 (4) の骨格構築に重要な役割を果たした多成分連続反応の背景について述べる。当研究グループでは Ti_2NH が環化付加反応ばかりでなく、速度論的に安定なシリルエノールエーテルから熱力学的に安定なシリルエノールエーテルへ

の異性化を促進することを見出している (Scheme 25)⁵⁰。さらに、シリルエノールエーテルの異性化と[2+2]環化付加反応をワンポットで行い、多置換ビスクロ[4.2.0]オクタンを高収率、高立体選択的に得ることにも成功している。



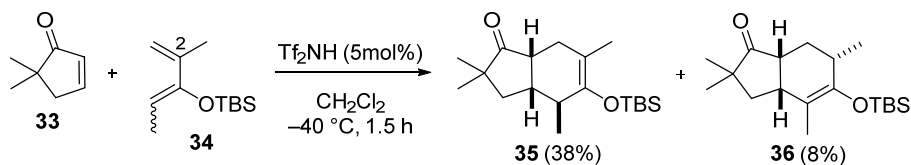
Scheme 25. Isomerization of silyl enol ether and its application

そこで、 Tf_2NH が異なる 3 つの反応、即ち Diels–Alder 反応とシリルエノールエーテルの異性化、[2+2]環化付加反応を触媒的に促進するならば、プロトイルダン骨格を一挙に構築できるものと期待した (Scheme 26)。



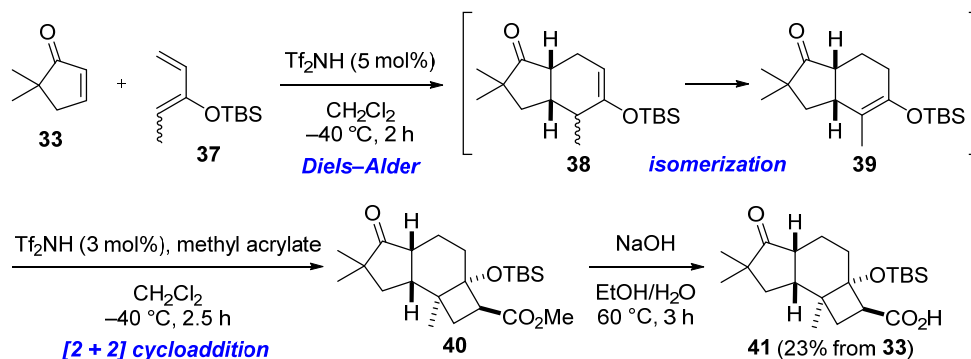
Scheme 26. Synthetic strategy of protoilludane skeleton

まず、2 位にメチル基を有するシロキシペンタジエン **34** を用いて Tf_2NH 存在下、シクロペンテノン **33** との Diels–Alder 反応を行うと、2 つのシリルエノールエーテル **35** および **36** の熱力学的安定性にあまり差がないため、異性化が十分に進行しないことがわかった (Scheme 27)⁵¹。従って、paesslerin A の予想構造 (**4**) の骨格を連続反応によって合成するためには、2 位が水素原子で置換されたシロキシペンタジエンが適していることがわかった。



Scheme 27. Isomerization experiment with 2-methylsilyloxypentadiene

すでに当研究グループでは *paesslerin* A の予想構造 (4) の骨格を一挙に構築することに成功した⁵²。 TiF_2NH 存在下、シクロペンテノン 33 と 2 位が水素原子で置換されたシロキシペンタジエン 37 を -40°C で反応させると、生じた付加体 38 の異性化が円滑に進行し、39 を与えた (Scheme 28)。続いてワンポットでアクリル酸メチルを加えると、三環性化合物 40 が得られた。エステル部位を加水分解したのちに結晶化させると、カルボン酸 41 を単一のジアステレオマーとして単離することができた。本反応では、単一の触媒である TiF_2NH が Diels–Alder 反応とシリルエノールエーテルの異性化、[2 + 2]環化付加という反応機構の異なる 3 つの反応を促進している (Scheme 28)⁵³。また、単回操作で 4 つの炭素–炭素結合と 5 つの連続不斉点を構築しており、非常に高度な分子変換として位置付けることができる。さらに、グラムスケールでも再現性良く反応を行うことができ、最高で 10 グラム程度のカルボン酸 41 を得ることが可能である。



Scheme 28. Multi-component domino reaction

カルボン酸 41 の立体化学および分子骨格は X 線結晶構造解析によって決定している (Figure 10)。

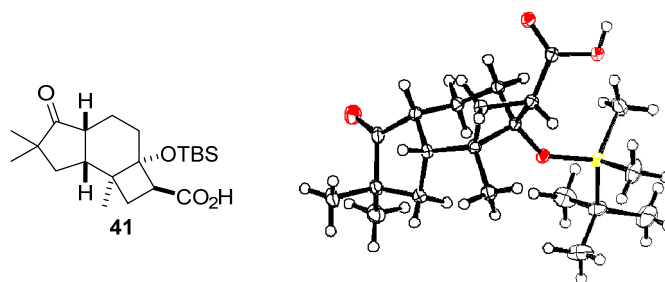
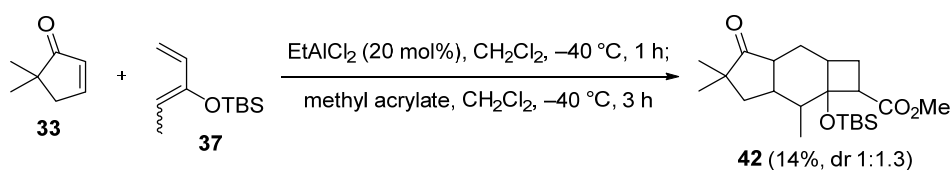


Figure 10. X-ray structure of carboxylic acid **41**

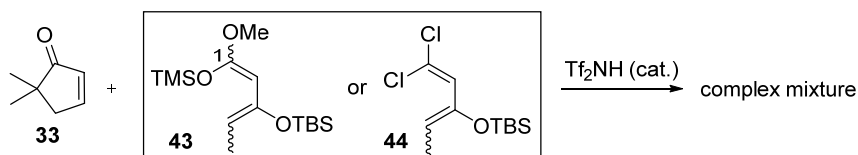
一方、著者は触媒として EtAlCl_2 を用いて上記の多成分連続反応を行うと、シリルエノールエーテルの異性化が進行しないため、直線型の三環性化合物 **42** が得られることを確認した (Scheme 29)。この結果は、同じ基質を用いても異なる骨格の連続反応成績体が触媒制御で合成し分けられることを示しており、医薬探索における多様性合成に応用できることが期待される。



Scheme 29. EtAlCl_2 -catalyzed cycloaddition cascade

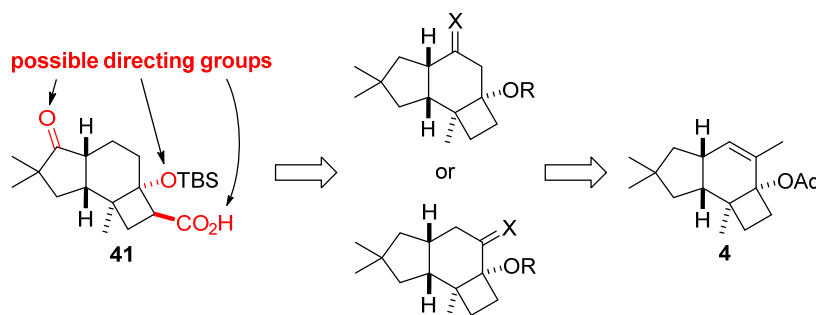
第2節 核間位ヒドロキシ基を足掛かりとする合成戦略

多成分連続反応によって得られたカルボン酸 **41** から paesslerin A の予想構造 (**4**) に導くために、シクロヘキサン環への置換基導入を検討することとした。当研究グループの石井らは1位に予め官能基を持つシロキシペンタジエン **43** や **44** を合成し、 Tf_2NH を触媒としてシクロペンテノン **33** との Diels–Alder 反応を行った (Scheme 30)⁵¹。しかしながら、複雑な混合物を与え目的の付加体を得ることはできなかった。



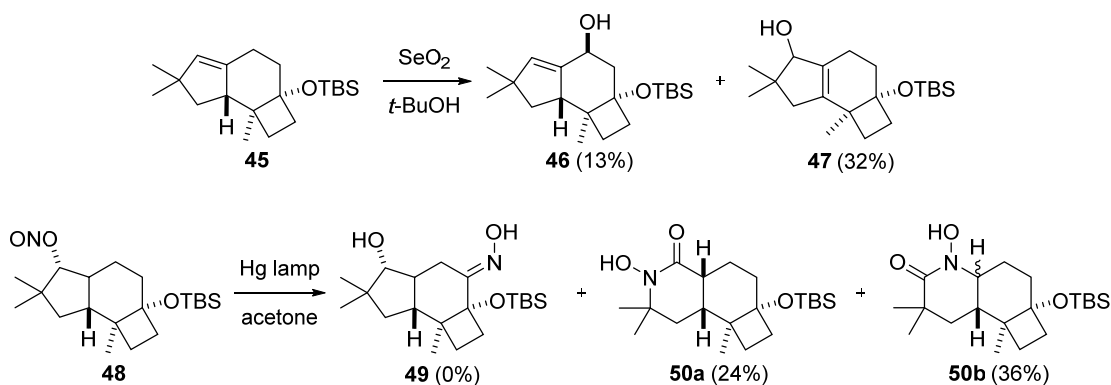
Scheme 30. Attempts using 1-substituted siloxypentadiene

そこで、著者はカルボン酸 **41** の分子内に存在する配向基を足掛かりとする戦略を立案した (Scheme 31)。この中間体は C-H 官能基化の足掛かりとして、5 員環カルボニル基、6 員環と 4 員環の核間位にあるヒドロキシ基、4 員環カルボキシル基を有している。



Scheme 31. C-H functionalization strategies toward **4**

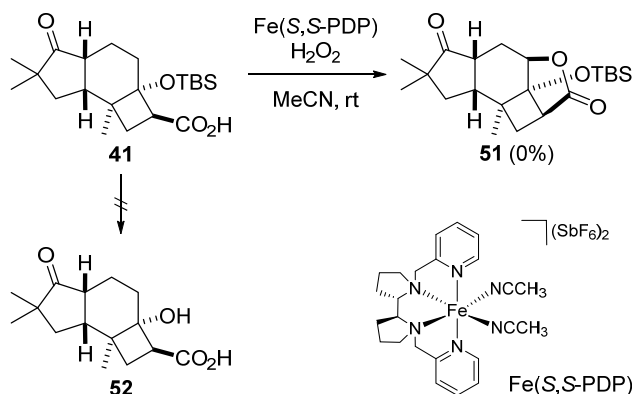
5 員環カルボニル基を足掛かりとする戦略は、当研究グループの石井らによって Barton 転位反応やアリル位の酸化反応などが鋭意検討されたが、いずれも満足のいく結果には至らなかった⁵¹。アルケン **45** に対して様々な条件でアリル位の酸化反応を検討した結果、唯一、二酸化セレンを用いた時に 13%収率でアリルアルコール **46** を得ることに成功した (Scheme 32)。しかしながら、主生成物としてアリルアルコール **47** が生じた。また、ニトロソエステル **48** に対して Barton 転位反応を行うと、ヒドロキサム酸の位置異性体 **50a** および **50b** がそれぞれ 24%、36%収率で生じ目的物 **49** を得ることはできなかった。



Scheme 32. Keto-carbonyl functions as a directing group

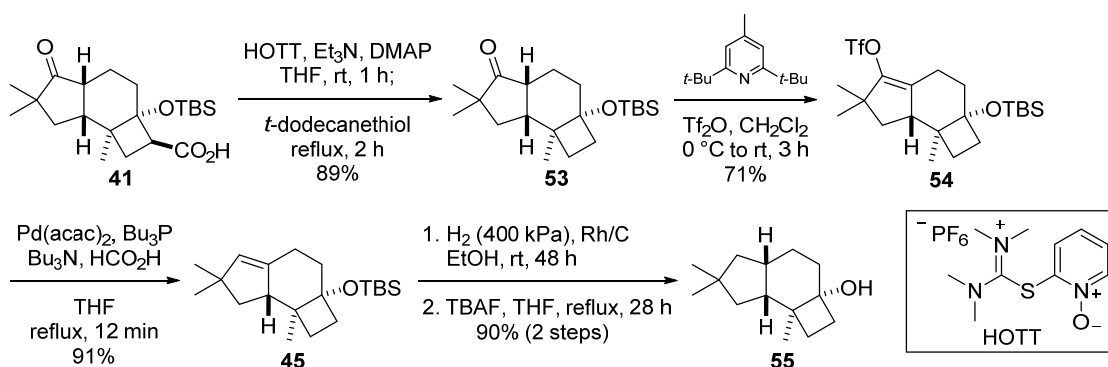
著者は、4 員環カルボキシル基を足掛かりとする戦略として White の鉄触媒 Fe(*S,S*-PDP)を用いる C-H 酸化反応⁵⁴を検討した。しかしながら、カルボン酸 **41** に対し Fe(*S,S*-PDP)と過酸化水素を作用させてもラクトン **51** は得られず原料の分解を招くのみであった (Scheme 33)。嵩高い TBS 基の影響で反応点近傍が立体的に混んでいると考え、様々な条件で TBS

基の除去を試みたがレトロアルドール反応が起こるためアルコール **52** を得ることはできなかった。



Scheme 33. Carboxyl function as a directing group

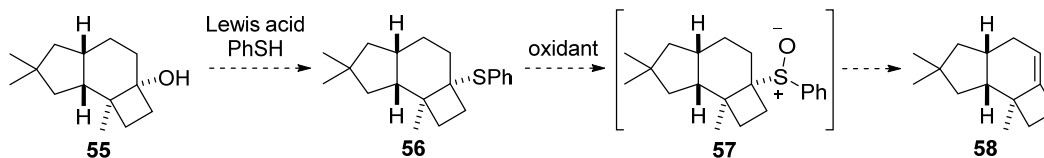
以上の結果を踏まえて、著者は核間位ヒドロキシ基を足掛かりとする戦略を中心に検討を行うこととした。まず、カルボン酸 **41** の 5 員環カルボニル基と 4 員環カルボキシル基を除去してアルコール **55** を合成した (Scheme 34)。**41** に対し改良 Barton 試薬である HOTT⁵⁵ を作用させて Barton エステルを調製したのち、ラジカル的に脱カルボキシル化を行って化合物 **53** を得た。これをビニルトリフラート **54** に変換し、触媒量のパラジウムを用いてトリフラートを還元的に除去⁵⁶ してアルケン **45** を得た。続いて、水素雰囲気下、加圧下でロジウム触媒を用いる接触還元を行うと、convex 面から立体選択的にアルケンの還元が進行した。さらに、TBAF を用いて TBS 基を除去してアルコール **55** を合成した。



Scheme 34. Synthesis of alcohol **55**

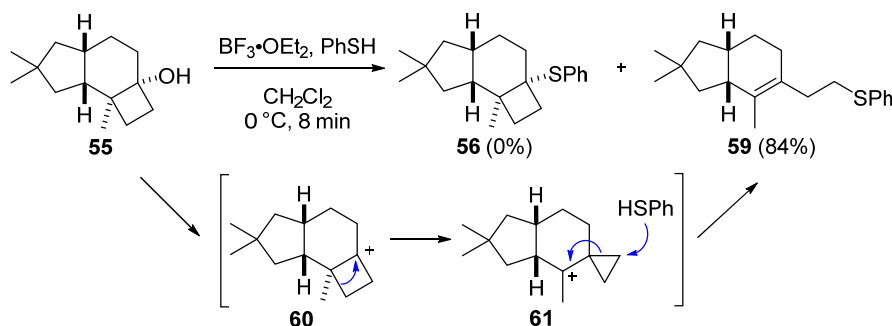
第 1 項 S_N1 反応を利用する合成検討

まず、アルコール **55** を S_N1 反応によってスルフィド **56** に変換し、これをスルホキシド **57** に酸化すれば *syn*-脱離によってアルケン **58** が得られると考えた (Scheme 35)。



Scheme 35. Synthetic strategy using S_N1 reaction

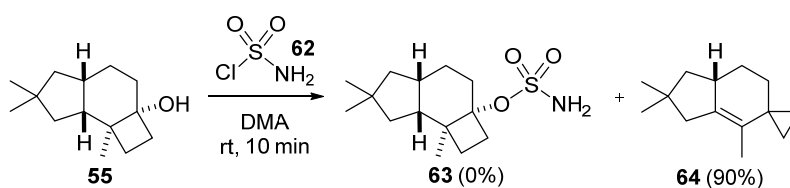
アルコール **55** とチオフェノールの混合物中に 0°C で $\text{BF}_3\cdot\text{OEt}_2$ を加えたところ、反応が速やかに進行し、オレフィン **59** が 84% 収率で生じた (Scheme 36)。反応機構は次のように考えられる。まず、核間位ヒドロキシ基が Lewis 酸によって活性化されて脱離し、第三級カルボカチオン **60** が生成する。続いて、縮環シクロブタンの歪みを解消するように 4 員環の炭素-炭素結合が転位⁵⁷して **61** となる。さらに、チオフェノールが立体的に接近しやすい三員環上の炭素を攻撃することで **59** が得られたと考えられる。



Scheme 36. Attempted S_N1 reaction

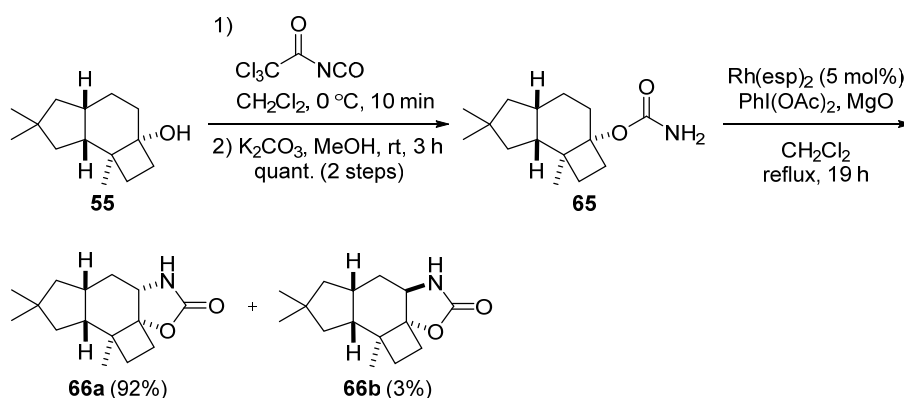
第 2 項 C-H アミノ化反応を利用する合成検討

次に、近接位の C-H 官能基化を利用することとした。その代表例として良く知られている Du Bois らのナイトレノイドの C-H アミノ化反応⁵⁸を検討した。まず、市販のクロソルホニルイソシアナートとギ酸からスルファモイルクロリド **62**^{58a} を調製した (Scheme 37)。これをアルコール **55** と反応させてスルファメート **63** を得ようとしたが、スピロシクロプロパン **64** が 90% 収率で生じた。これは **63** の脱離能が高いために環縮小転位⁵⁷が進行して第三級カルボカチオン **61** を生じ、次いで脱プロトン化が進行したものと考えられる。



Scheme 37. Ring contraction rearrangement

そこで、ナイトレノイド前駆体として脱離能の低いカルバメートを用いることとした。アルコール **55** を市販のトリクロロアセチルイソシアナートと反応させた後、メタノール中、炭酸カリウムで処理するとカルバメート **65** が高収率で得られた (Scheme 38)。続いて、5 mol% の $\text{Rh}(\text{esp})_2$ を用いて C-H アミノ化反応を行うと、望みの 6 員環上の C-H 結合で反応が進行したオキサゾリジノン **66a** および **66b** をそれぞれ 92%、3% 収率で得ることに成功した。4 員環上にも C-H アミノ化に適した C-H 結合が存在するが、6 員環と 4 員環の核間位に存在するメチル基との立体障害により 6 員環上の C-H 結合で優先的に反応が進行したと考えられる。



Scheme 38. C-H amination of carbamate **65**

オキサゾリジノン **66a** および **66b** の立体化学は NOESY 測定によって決定した (Figure 11)。

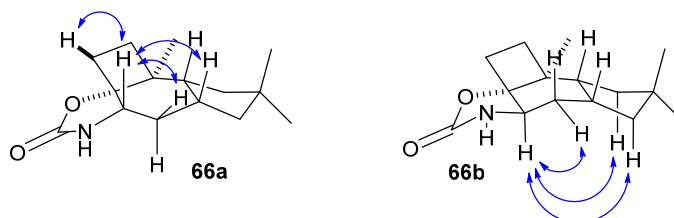


Figure 11. NOESY correlations of oxazolidinones **66a** and **66b**

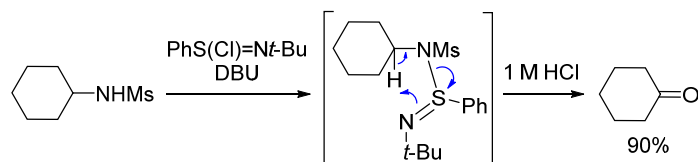
得られたオキサゾリジノン **66a** をアミノアルコールへ変換し、アミノ基をケトカルボニル基に変換することができれば **4** へ誘導し易くなると考えた (Scheme 39)。以下、アミノ基のケトカルボニル基への変換について検討を行った。



Scheme 39. Synthetic strategy of **4**

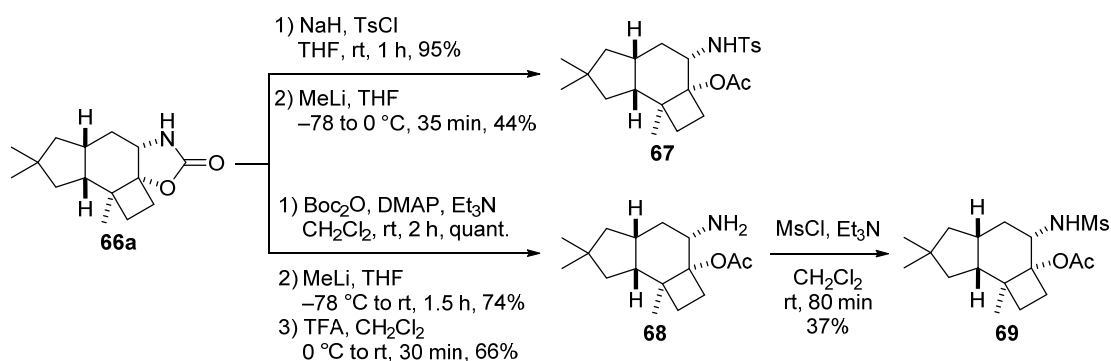
松尾、向山らは第一級アミンをカルボニル化合物へ変換する反応を報告している⁵⁹。第一級アミンをメシルアミドに変換してから *N*-*tert*-ブチルベンゼンスルフィニミドイルクロリドおよび DBU と反応させるとイミンを生じ、これが加水分解されるとケトンが得られる (Scheme 40)。報告されているアミンの酸化反応は、多くの場合、安定な共役イミンを与えるベンジルアミンやアリルアミンを基質としたものに限られる⁶⁰。これに対して脂肪族アミンの酸化は非共役イミンを与えるため、その報告例は極めて少ない。スルフィニミドイル試薬を用いるこの反応は、高収率で脂肪族アミンの酸化に成功した数少ない例である。

Matsuo & Mukaiyama (2001)



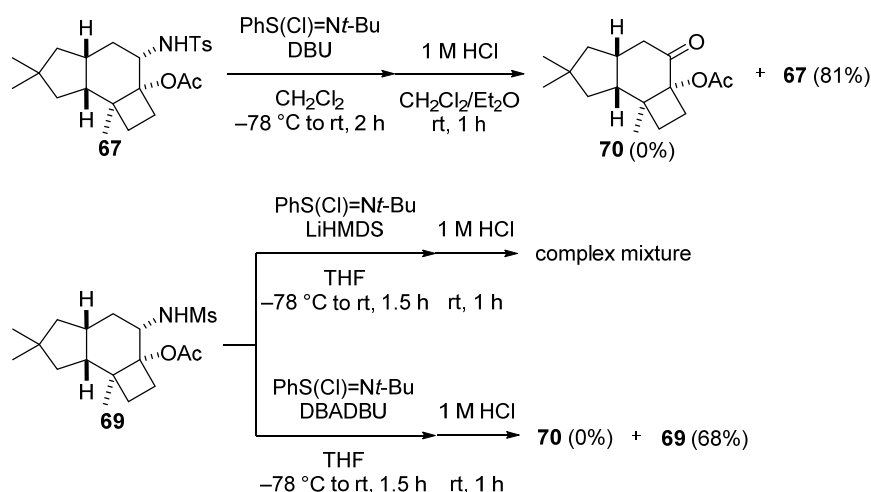
Scheme 40. Synthesis of ketone from mesylamide

まず、基質 **67** および **69** の合成を行った。オキサゾリジノン **66a** の窒素原子をトシル化したのちに MeLi と反応させて、トシルアミド **67** を合成した (Scheme 41)。続いて、**66a** の窒素原子を Boc 化したのちに MeLi と反応させて、生じたカルバメートを TFA で処理してアミン **68** を合成した。さらに、**68** を MsCl とトリエチルアミンと反応させて、メシルアミド **69** を合成した。



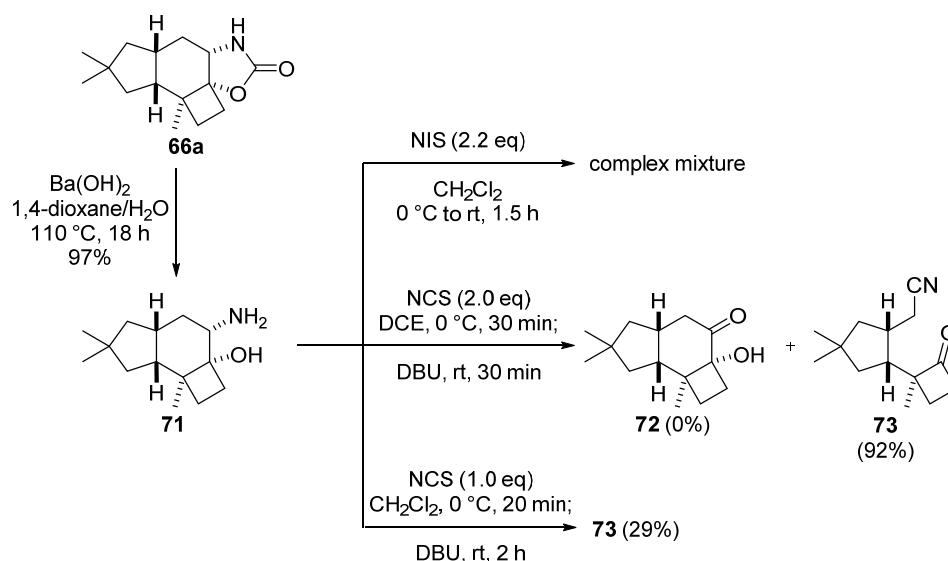
Scheme 41. Synthesis of tosylamide **67** and mesylamide **69**

合成したトシルアミド **67** と *N-tert*-ブチルベンゼンスルフィンイミドイルクロリドを反応させてもケトン **70** は得られず原料が回収された (Scheme 42)。向山らの報告で、トシルアミドよりも反応性の高いことが明らかとなったメシルアミド **69** や DBU よりも塩基性の強い DBADBU⁶¹ を用いても目的物は得られなかった。



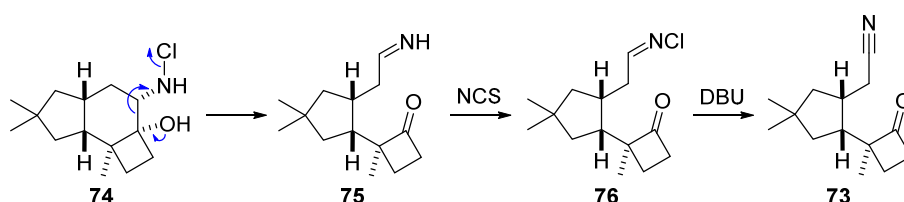
Scheme 42. Attempted synthesis of ketone using PhS(Cl)=N*t*-Bu

次に、*N*-ハロゲン化と続く塩基処理でイミンを生じさせ、それを加水分解することでケトンが得られるか検討した⁶²。オキサゾリジノン **66a** を Ba(OH)₂ を用いて加水分解し、アミノアルコール **31** へ変換した (scheme 43)。まず、**71** を NIS と反応させたところ複雑な混合物を与えた。続いて、2 当量の NCS を用いると反応が円滑に進行し、これを DBU で処理すると目的物ケトン **72** は得られず、ニトリル **73** が 92%収率で生じた。また、1 当量の NCS を用いた場合でも **73** が 29%収率で生じた。



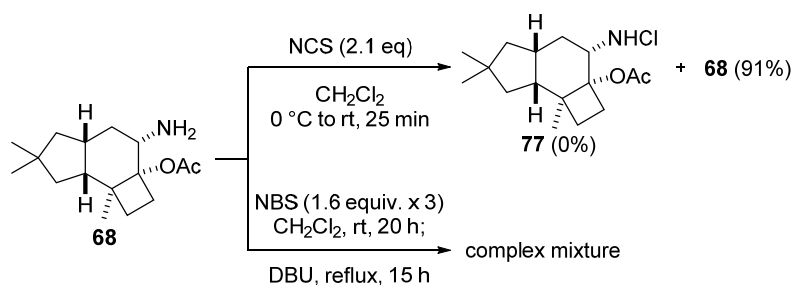
Scheme 43. Unexpected C–C bond cleavage

ニトリル **73** の生成機構は次のように考えられる。1 当量目の NCS との反応で生じた *N*-クロロアミン **74** から炭素–炭素結合の開裂が起きてイミン **75** を生じる (Scheme 44)。これが 2 当量目の NCS でクロロ化されて **76** となり、塩基によってニトリル **73** に変換される。ところで、このような反応は岡山大学の鳥居らによって既に報告例がある⁶³。彼らは電解質に飽和食塩水を用いて電気化学的に発生させた Cl^+ 種を 2-アミノ-1-シクロアルカノール類と反応させて、50~62%の収率で対応するケトニトリルを合成している。



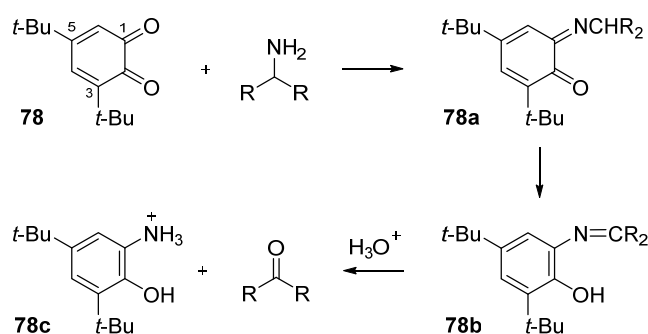
Scheme 44. Proposed reaction mechanism for the formation of **73**

酸素原子を保護することによって炭素–炭素結合の開裂を防げるのではないかと考え、アミン **68** に対して *N*-ハロゲン化を試みた (Scheme 45)。NCS を用いた場合は反応が進行せず *N*-クロロアミン **77** は得られなかった。NBS を用いた場合、試薬を随時追加していくことで、原料は消失したが、DBU を加えて加熱還流しても複雑な混合物を与えるのみだった。これはアセチル基を導入することで、窒素原子の周囲の立体障害が増加し反応性が低くなったためと考えられる。



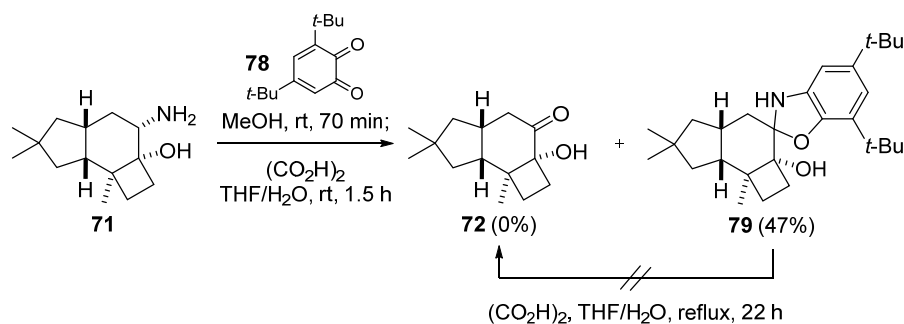
Scheme 45. Attempted transformation of amine **68** into ketone

続いて、Corey、阿知波によって開発されたアミノ基転位反応⁶⁴を検討した (Scheme 46)。ここで用いられる 3,5-ジ-*tert*-ブチル-1,2-ベンゾキノン (**78**) は、アミンの 1,4-付加を抑制するために嵩高い *tert*-ブチル基を 3 位と 5 位に有している。また、3 位に *tert*-ブチル基を有するためアミンは立体障害の小さい 1 位カルボニル基で選択的にアミンと反応するように設計されている。この反応ではまず、**78** とアミンとの反応によりイミン **78a** を生じる。続いて、芳香族化を駆動力とするプロトン移動が起こり新たなイミン **78b** が生じる。これを酸で加水分解するとケトンを得ることができる。生じたアンモニウムイオン **78c** は水溶性が高く、分液操作で容易に取り除くことが可能である。



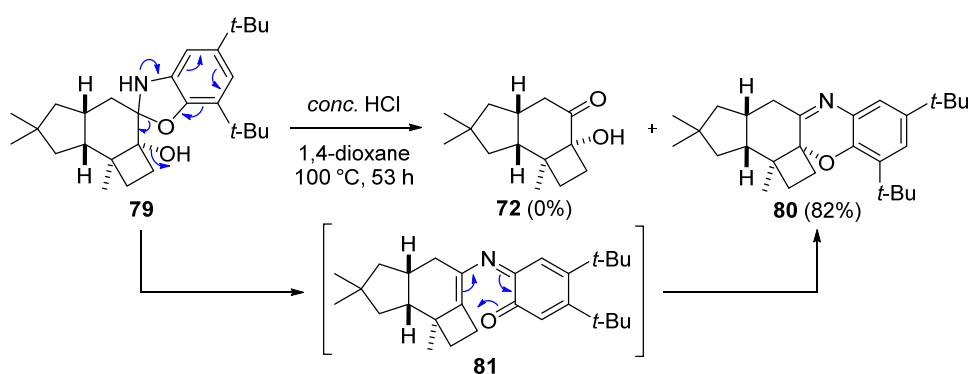
Scheme 46. Transamination

アミノアルコール **71** をアミノ基転位反応の条件に付すと、目的のケトン **72** は得られず、ヘミアミナール **79** が生じた (Scheme 47)。このようにヘミアミナールが得られた理由は、イミンの周囲が立体的に込み合っているため水分子が付加するよりも、分子内反応が優先したためと推測している。単離した **79** のシュウ酸による加水分解は反応温度を上げてでも進行しなかった。



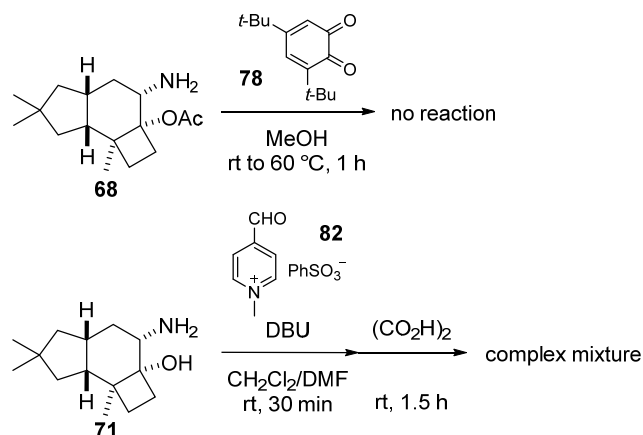
Scheme 47. Hemiaminal formation and attempted acid hydrolysis

そこで、濃塩酸を用いてジオキサン中 100 °C で加熱し⁶⁵、ヘミアミナル **79** の加水分解を行ったところ、予期せぬことに五環性化合物 **80** が生じた (Scheme 48)。これは窒素原子からの電子の押し出しで脱水反応が起きて **81** を生じ、続く電子環状反応によって得られたと考えられる。得られた **80** に対し、水酸化ナトリウムを用いた塩基性条件でのヘミアミナルの加水分解も検討したがケトンに変換することはできなかった。



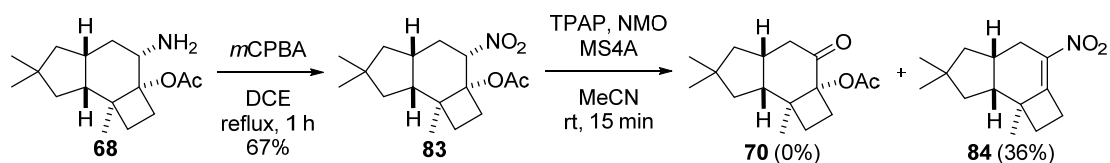
Scheme 48. Unexpected formation of pentacyclic compound **80**

この脱水反応を防ぐために核間位ヒドロキシ基をアセチル基で保護した基質 **68** では、立体障害のためかオルトベンゾキノン **78** との反応は全く進行しなかった (Scheme 49)。さらに、アミノアルコール **71** を反応性のより高いピリジニウム塩 **82**⁶⁶ と反応させても複雑な混合物を与えるのみだった。



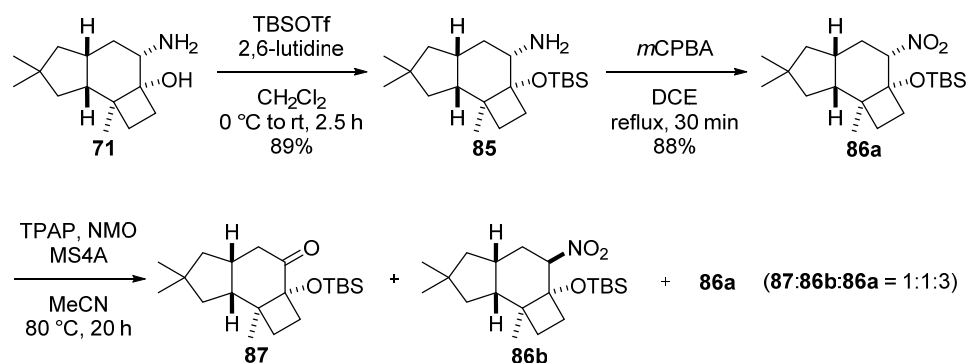
Scheme 49. Attempted transamination of **68** and **71**

以上の結果からアミノ基をケトカルボニル基に変換することは困難であることがわかった。そこでニトロ基をケトカルボニル基へ変換する Nef 反応⁶⁷について種々検討することとした。まず、井原、福本らによって報告された TPAP 酸化の条件⁶⁸を試した (Scheme 50)。アミン **68** を *m*CPBA で酸化してニトロアルカン **83** を得た。これを TPAP 酸化に付したところ、ケトン **70** は得られずニトロオレフィン **84** が 36%収率で得られた。このように、アセテートの脱離が優先して起こることが明らかとなった。



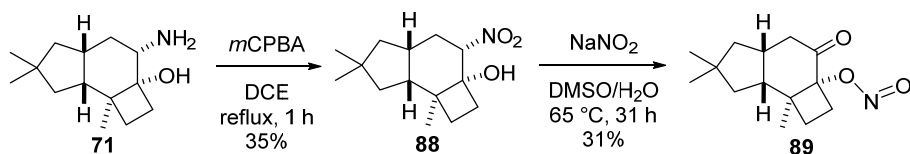
Scheme 50. Unexpected nitroolefin formation under TPAP oxidation condition

そこで、アセチル基を TBS 基に変更すれば脱離が抑制できると期待してニトロアルカン **86a** の合成を行った。アミノアルコール **71** を TBSOTf および 2,6-lutidine と反応させ、ヒドロキシ基を TBS 基で保護し **85** を合成した (Scheme 51)。得られた **85** のアミノ基を *m*CPBA で酸化してニトロアルカン **86a** を得た。これを TPAP 酸化の条件に付したところ、ケトン **87** と **86a** のエピマーと考えられる **86b** および原料が約 1:1:3 の比で生成した。



Scheme 51. Transformation of nitroalkane **86a** into ketone under TPAP oxidation condition

続いて、先程と同様に *m*CPBA を用いてアミノアルコール **71** をニトロアルコール **88** に酸化した (Scheme 52)。収率が 35%と低いのは炭素-炭素結合の開裂を伴った副生成物が生じたためである。得られたニトロアルコールを過剰量の亜硝酸ナトリウムと反応させると、望みのカルボニル化合物に変換された **89** が 31%収率で得られた。しかしながら、系中に存在する NO^+ 種がフリーのヒドロキシ基と反応したために亜硝酸エステルとして得られた。ここで、 NO^+ 種として考えられる化学種としては系中で発生する HNO_2 や N_2O_3 であると考えられる。



Scheme 52. Nef reaction of nitroalkane **88**

引き続き、ニトロ基のケトカルボニル基への変換を目指して条件を種々検討した (Table 3)。ヒドロキシ基を保護した基質を用いることで、 NO^+ 種と反応することを抑制できると期待して亜硝酸ナトリウムを用いる条件を再度検討した。アセチル基で保護した基質 **83** を用いたところ、ケトン **70** は得られず亜硝酸エステル **89** が生成した (entry 1)。TBS 基で保護した基質 **86a** では望みのケトン **87** が 15%収率で得られたが、カルボン酸 **90** が主生成物として得られた (entry 2)。また、水の代わりに酢酸を添加した場合には **90** のみが得られた (entry 3)。一方、水酸化カリウムと過マンガン酸カリウムを用いる条件において最も良い収率でケトンを得ることができた。しかしながら再現性に問題があった (entry 4)。以上のように、Nef 反応を利用することで望みのケトンを得ることに成功したが、いずれも低収率であり多段階の変換を要したため、他の合成経路を検討することとした。これまでに得られた知見では、分子全体が歪んでいるために核間位のヒドロキシ基は酸素原子から電子を押し出す場合もあれば、脱離基として働くこともあり非常に取り扱いにくい性質を持つ

ことがわかった。この特異な反応性を如何に制御できるかが **paesslerin A** の予想構造 (**4**) の全合成を達成する上で重要となる。

Table 3. Nef reactions of **83** and **86a**

83 R = Ac
86a R = TBS

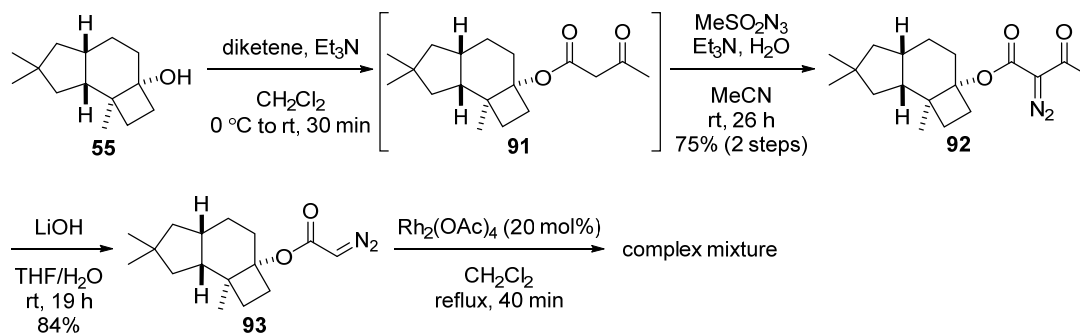
70 R = Ac
87 R = TBS
89 R = NO

90

entry	substrate	condition	result
1	83	NaNO ₂ (30 eq) DMSO/H ₂ O (7:1), 65 to 80 °C, 17 h	15% (89)
2	86a	NaNO ₂ (5.0 eq) DMSO/H ₂ O (7:1), 90 °C, 19 h	15% (87), 25% (90)
3	86a	NaNO ₂ (10 eq), AcOH (10 eq) DMSO, 65 to 90 °C, 8 h	46% (90)
4	86a	KOH (5.0 eq), MeOH, rt, 1h; KMnO ₄ (6.9 eq), MgSO ₄ (6.0 eq) 0 °C to rt, 1 h	43% (87) low reproducibility

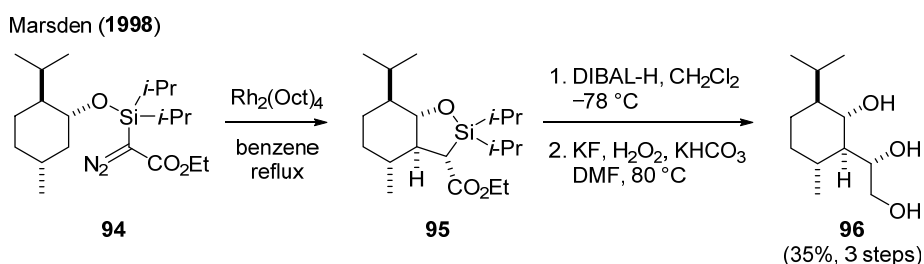
第3項 C-H 挿入反応を利用する合成検討 (1) : C2 単位の増炭による合成

前術したようにナイトレノイドの C-H 挿入反応により導入したアミノ基からの変換は困難を伴った。そこで、カルベノイドの C-H 挿入反応⁶⁹を行うことでシクロヘキサン環に直接炭素原子を導入できるか検討することとした。初めにジアゾアセテートの C-H 挿入反応を検討した。アルコール **55** をジケテンと反応させてケトエステル **91** とした後、ジアゾ化により **92** を得た (Scheme 53)。さらに、**92** を水酸化リチウムと反応させてジアゾアセテート **93** を合成した。これに対し Rh₂(OAc)₄ を用いてジクロロメタン中、加熱還流すると複雑な混合物を与えた。



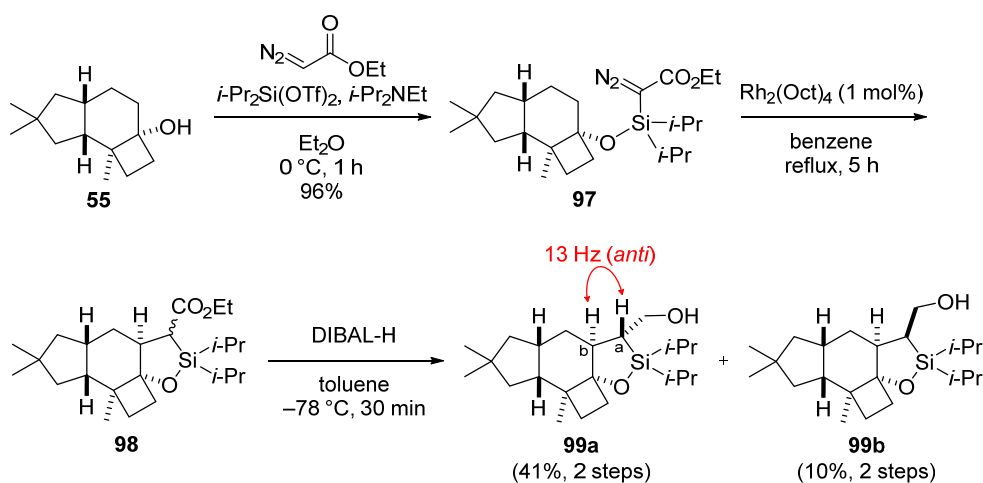
Scheme 53. Attempted C-H insertion reaction of diazoacetate **93**

Marsden らはケイ素原子で繋がれたジアゾアセテートを配向基とする基質 **94** に対して Rh 触媒 C-H 挿入反応を行うと、シロキサン **95** が得られることを報告している (Scheme 54)^{70a}。配向基に含まれるケイ素原子はテザーとしての役割だけでなく、マスクされたヒドロキシ基としてののちの官能基変換に利用することができる。Marsden らは得られた **95** を DIBAL-H 還元と Fleming-玉尾酸化⁷¹ に付すことでトリオール **96** に変換している。以下、この方法を検討することとした。



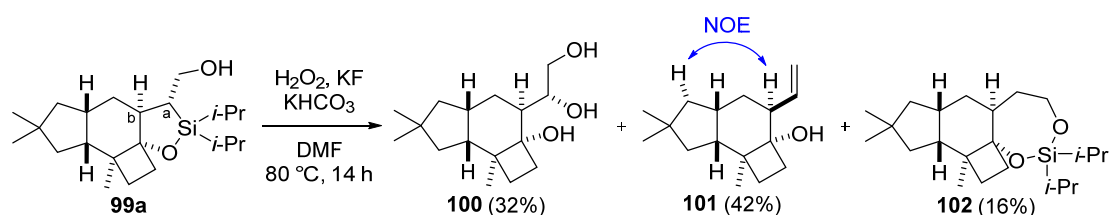
Scheme 54. C-H insertion reaction of silicon tethered diazoacetate

アルコール **55** を別途調製したエチルジアゾアセテート⁷² と市販の $i\text{-Pr}_2\text{Si}(\text{OTf})_2$ と反応させると、C-H 挿入反応前駆体である **97** が得られた (Scheme 55)。文献に従い、 $\text{Rh}_2(\text{Oct})_4$ を触媒としてベンゼン中、加熱還流すると核間位メチル基との立体反発を避けるように位置選択的にシロキサン **98** を得ることに成功した。**98** は分離困難なジアステレオマー混合物として得られたが、続く DIBAL-H 還元を行うとアルコール **99a** および **99b** をそれぞれ 41%、10% 収率で単離することに成功した。この時、**99a** の a 位および b 位の立体化学はカップリング定数 (13 Hz) から *anti* であると決定したが、最終的には Scheme 58 に示した NOE 相関と合わせて決定した。また、この時点で **99b** の立体化学は不明であった。



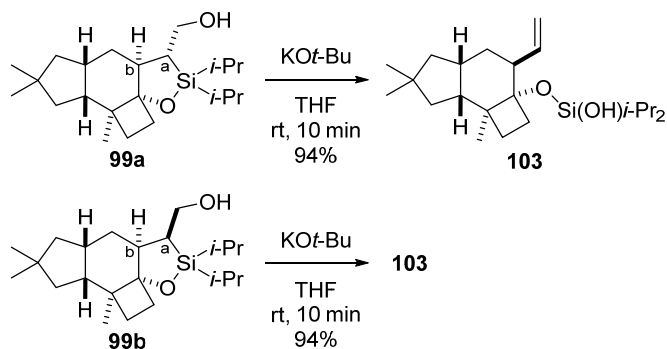
Scheme 55. C-H insertion reaction of silicon tethered diazoacetate **97**

合成したアルコール **99a** を用いて引き続き Marsden らの報告を参考に Fleming–玉尾酸化を行うと、トリオール **100** とオレフィン **101**、シリレンアセタール **102** がそれぞれ 32%、42%、16% 収率で生じた (Scheme 56)。Marsden らは Peterson 型の反応によりオレフィンが生成するためにトリオールの収率が低下するという報告をしていたため、ある程度この選択性は予測していたが **102** のようなシリレンアセタールも生じる興味深い結果となった。なお、**99a** の b 位の立体化学はオレフィン **101** の NOE 相関によって決定した。



Scheme 56. Fleming–Tamao oxidation of **99a**

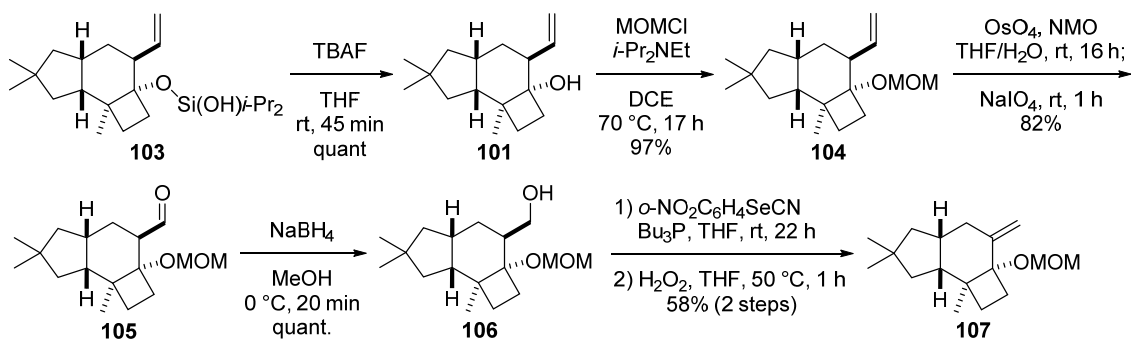
そこで、求核性が低く嵩高い塩基を用いれば、選択的に Peterson 型の反応が進行すると考えた。Clive らの報告⁷³を参考に **99a** をカリウム-*tert*-ブトキシドと反応させると、期待通りシラノール **103** を高収率で得ることに成功した (scheme 57)。また、立体化学が不明であったアルコール **99b** を同様の反応条件に付すと **103** が得られた。これより、**99b** は **99a** の a 位に関するエピマーであると決定した。



Scheme 57. Peterson type olefination of **99a** and **99b**

シラノール **103** を減炭してエキソオレフィンに変換し、これをエンドオレフィンに異性化させれば 7-protoilluden-6-ol (**32**) や paesslerin A の予想構造 (**4**) に導くことができる。まず、官能基変換にあたって立体障害となりうる嵩高いシリル基を TBAF を用いて除去し、得られたアルコール **101** をより立体障害の小さい MOM 基で保護して **104** とした (Scheme 58)。続いて、四酸化オスミウムを用いてオレフィンのジヒドロキシ化を行い、生じたジオールを過ヨウ素酸ナトリウムで酸化的に開裂しアルデヒド **105** を得た。得られた **105** を

水素化ホウ素ナトリウムで還元してアルコール **106** とした。さらに、西沢–Grieco 法⁷⁴を用いてエキソオレフィン **107** へ変換した。



Scheme 58. Synthesis of *exo*-olefin **107**

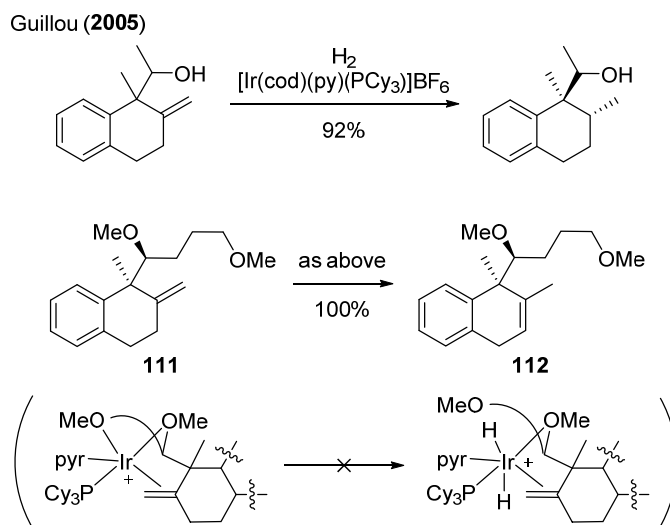
まず、合成した **107** に対して TsOH やヨウ素を用いたエキソオレフィンの異性化を検討したが、原料は消失するものの核間位ヒドロキシ基が脱離した生成物が得られるのみであった (Table 4, entries 1 and 2)。そこで遷移金属を用いる条件⁷⁵を検討することとした。遷移金属として Rh^I or ^{III}、Pd⁰ or ^{II}、Ru^{II} or ^{III}、Fe^{III}を用いる条件を種々検討した結果、唯一、水素雰囲気下で Pd/BaSO₄を用いた時のみエンドオレフィン **108** が確認できた (entry 8)。しかしながら、還元体 **109** を主生成物として与えた。その他の条件ではエンドオレフィン **108** を得ることはできなかった。なお、MOM 基の外れた **110** が得られた理由は系中で塩酸が生じたためと考えられる (entries 3, 11 and 12)。

Table 4. Attempted isomerization of *exo*-olefin **107**

entry	condition	result
1	TsOH, toluene, 50 °C	not observed
2	I ₂ , benzene, 50 °C	not observed
3	RhCl ₃ , EtOH, reflux, 15 h	107 + 110 (1.5:1)
4	(PPh ₃) ₃ RhCl, EtOH, reflux, 15 h	no reaction
5	[HRhCO(PPh ₃) ₃], benzen, 150 °C, 60 h	no reaction
6	H ₂ , Pd/C, EtOAc, rt, 5 min	109 (4:1)
7	H ₂ , Pd/CaCO ₃ , PPh ₃ , EtOAc, 60 °C, 14 h	no reaction
8	H ₂ , Pd/BaSO ₄ , EtOH, rt, 27 h	107 + 108 + 109 (1:1.5:3.3)
9	PdCl ₂ , Et ₃ SiH, rt, 22 h	no reaction
10	[(allyl)PdCl] ₂ , (<i>o</i> -tol) ₃ P, AgOTf, CH ₂ Cl ₂ , rt, 20 h	no reaction
11	RuCl ₃ , EtOH, 80 °C, 20 min	107 + 110 (1:2)
12	RuCl ₂ (PPh ₃) ₃ , EtOH, reflux, 14 h	107 + 110 (4:1)
13	Grubbs II, vinyloxytrimethylsilane, reflux, 17 h	no reaction
14	[Fe ₃ (CO) ₁₂], KOH, diglym, 100 °C, 16 h	no reaction

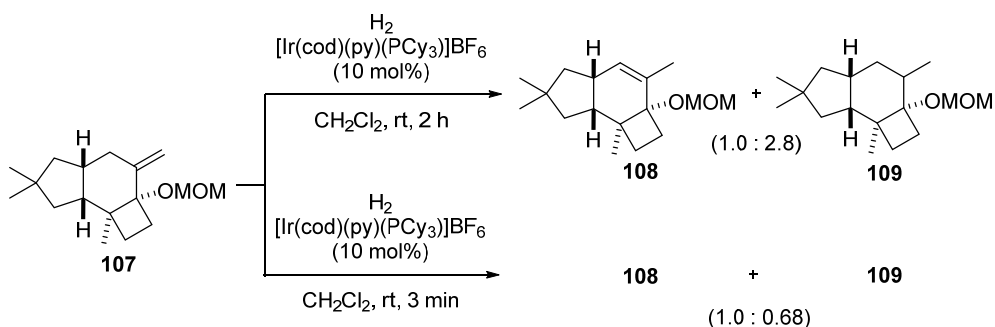
上記検討でエキソオレフィンの異性化がほとんど進行しなかったのは、基質との立体障害により金属中心が炭素-炭素二重結合に接近しにくいためと推測できる。ところで、一般に Crabtree 触媒などのカチオン性錯体は近傍に配位性官能基が存在すると、触媒配向により立体選択的な還元を起こすことが知られている (Scheme 59)⁷⁶。一方、興味深いことに Guillou らは水素雰囲気下、Crabtree 触媒を用いてエキソオレフィン **111** を還元することなく、エンドオレフィン **112** に異性化させることに成功している⁷⁷。その理由として Guillou らは、基質に存在する炭素原子で繋がれた 2 つのヘテロ原子がイリジウムに配位することで、その立体障害によりイリジウムの水素分子への酸化的付加が抑制されたためと推測している。また、Scheidt らも同様に Crabtree 触媒を用いたエキソオレフィンの異性化を報告している

⁷⁸。



Scheme 59. Isomerization of *exo*-olefin **111** using Crabtree's catalyst

そこで、エキソオレフィン **107** が分子内に配位性官能基を有していることに着目し、Crabtree 触媒を用いた異性化を検討した (Scheme 60)。まず、水素雰囲気下、**107** を Crabtree 触媒と反応させ 2 時間で反応を止めると、還元体 **109** との混合物ではあるものの異性化の進行した **108** が得られることがわかった。そこで、還元体の生成を抑えるために反応を 3 分で止めたところ、**108** を主生成物として得ることに成功した。しかしながら、再現性が低く還元体 **109** との分離も困難であった。



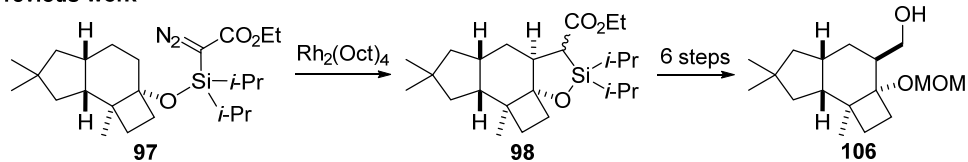
Scheme 60. Isomerization of *exo*-olefine **107** using Crabtree's catalyst

第 4 項 C-H 挿入反応を利用する合成検討 (2) : C1 単位の増炭による合成

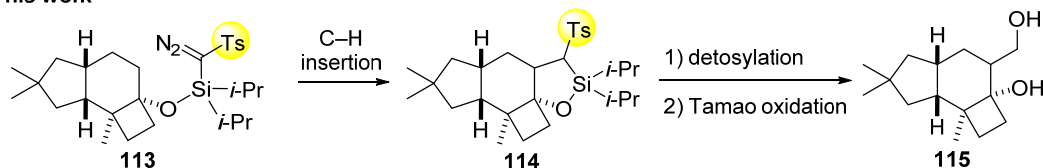
以上のように、ケイ素原子で繋がれたジアゾアセテート **97** の位置選択的な C-H 挿入反応を経てエキソメチレン **107** まで合成することに成功した。しかしながら、ジアゾアセテートを配向基とする場合、C2 単位を導入することになりアルコール **106** まで合成するのに 6 工程を要した (Scheme 61)。そこで、C1 単位を導入するために新たにエステル基ではなく、トシル基を配向基に含む基質 **113** の C-H 挿入反応を計画した。得られる C-H 挿入体 **114** に

対して、トシル基の除去と玉尾酸化を行えば、2 工程でジオール **115** の合成が可能になり、大幅な工程数の削減が期待できる。

Previous work

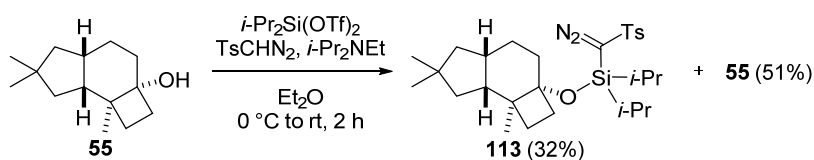


This work



Scheme 61. New directing group to enable one carbon insertion

ジアゾアセテート **97** の合成と同様の条件でアルコール **55** に新しい配向基を導入した (Scheme 62)。今回、市販のビストリフレート $i\text{-Pr}_2\text{Si}(\text{OTf})_2$ を用いると再現性が得られない問題が生じたため、Corey の方法⁷⁹により調製したものをを用いた。また、トシルジアゾメタンは文献⁸⁰を参考に 3 工程で合成した。嵩高いトシル基の立体障害のためか、目的のジアゾトシレート **113** の収率は 32%と低い、原料を 51%収率で回収できたためこの条件を採用した。



Scheme 62. Installation of silicon tethered diazotosylate

続いて、C-H 挿入反応の触媒を検討した (Table 5)。ジアゾアセテート **97** の C-H 挿入反応で用いた $\text{Rh}_2(\text{Oct})_4$ では、ベンゼンおよびトルエン中、加熱還流しても反応は進行しなかった (entries 1 and 4)。より沸点の高いキシレンを溶媒に用いた場合、痕跡量の **114** の生成を確認したが、基質の分解を伴った (entry 5)。その他のロジウムを中心金属とする触媒である $\text{Rh}_2(\text{OAc})_4$ 、 $\text{Rh}_2(\text{esp})_2$ 、 $\text{Rh}_2(\text{pfb})_4$ や $\text{Ni}(\text{acac})_2$ では原料を回収するのみであった (entries 2, 3, 6 and 7)。一方、 $\text{Cu}(\text{acac})_2$ を用いた場合、C-H 挿入反応が進行し、約 3:1 のジアステレオマー混合物として 51%収率で **114** を得ることに成功した (entry 8)。反応スケールを 1 mmol 以上にして行くと、触媒量を 10 mol%に低減することができ 84%収率まで向上させることができた (entry 9)。なお、C-H 挿入反応で得られたジステレオマーのうちメジャー体の構造

は、a 位および b 位のプロトンのカップリング定数（13 Hz）と Figure 13 に示した誘導体の X 線結晶構造解析により **114a** と決定した。

Table 5. Screening of C–H insertion catalyst

113 (16~30 μ mol) $\xrightarrow{\text{conditions}}$ **114** (major diastereomer **114a**)

13 Hz (*anti*)

entry	condition	result
1	Rh ₂ (Oct) ₄ (0.1 eq), benzene, reflux, 6 h	no reaction
2	Rh ₂ (OAc) ₄ (0.2 eq), benzene, reflux, 7 h	no reaction
3	Rh ₂ (esp) ₂ (0.1 eq), benzene, reflux, 12 h	no reaction
4	Rh ₂ (Oct) ₄ (0.1 eq), toluene, reflux, 18 h	no reaction
5	Rh ₂ (Oct) ₄ (0.2 eq), xylene, reflux, 19 h	114 (trace)
6	Rh ₂ (pfb) ₄ (0.1 eq), toluene, reflux, 17 h	no reaction
7	Ni(acac) ₂ (0.5 eq x 2), toluene, reflux, 17 h	no reaction
8	Cu(acac) ₂ (0.5 eq), toluene, reflux, 17 h	114 (51%, dr 3:1)
9*	Cu(acac) ₂ (10 mol%), toluene, reflux, 30 min	114 (84%, dr 4:1)

* The reaction was conducted under 1.17 mmol scale of **113**.

ジアゾトシレートの C–H 挿入反応において、*trans*-縮環のシロキサン **114a** が主生成物として得られる理由は次のように考察している（Figure 12）。エカトリアル位の C–H 結合で反応が進行した場合、環とトシル基との立体反発が生じる。一方、アキシアル位の C–H 結合の場合は、そのような立体反発が生じないためこちらの遷移状態から優先的に反応が進行したと考えられる。

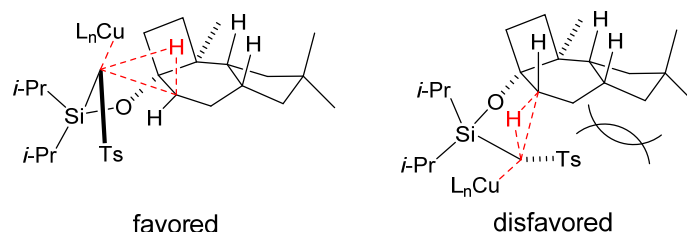
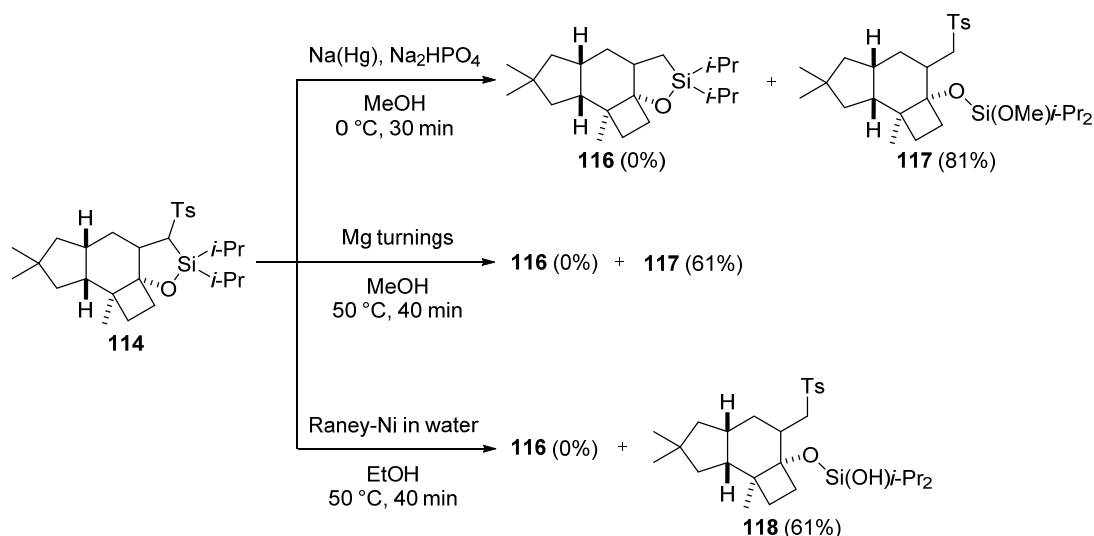


Figure 12. Rational for the stereoselectivity of C–H insertion reaction

C-H 挿入反応により得られた **114** に対してトシル基の除去を検討した (Scheme 63)。まず、メタノール中、ナトリウムアマルガムを用いる一電子還元を行うと、目的のシロキサン **116** は得られずスルホン **117** が 81%収率で生じた。同様にマグネシウムやラネーニッケルを用いる条件でも **116** は得られず、それぞれスルホン **117** および **118** が生じた。これらが生じた理由は次のように説明できる。即ち、**114** は電子吸引性のトシル基を持つため、系中で生じたメトキシドイオンあるいはヒドロキシドイオンがケイ素に付加して、炭素-ケイ素結合の開裂が生じたと考えられる。



Scheme 63. Attempted detosylation of **114**

そこで、求核剤となり得るアルコール系溶媒を用いない一電子還元の状態を検討した (Table 6)。リチウムとナフタレンからリチウムナフタレニドを発生させて、**114** と反応させると 68%収率でシロキサン **116a** を得ることに成功した (entry 1)。ナフタレンの代わりに 4,4'-ジ-*tert*-ブチルビフェニルを用いても同程度の収率で **116a** が得られた (entry 2)。ヨウ化サマリウムや AIBN/ Bu_3SnH ⁸¹ を用いる条件では反応が進行しなかった (entries 3 and 4)。また、リチウムやカルシウムを用いる Birch 条件では中程度の収率で **116a** を得ることができたが、副生成物との分離が困難であった (entries 5 and 6)。

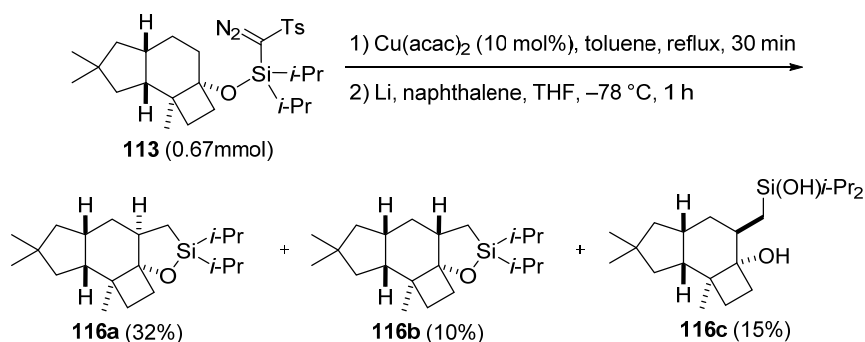
Table 6. Detosylation of siloxane **114**

114 (dr 4:1, 8~16 μ mol) **116a**

entry	condition	result
1	Li, naphthalene, THF, -78°C , 1.5 h	68%
2	Li, 4,4'-di- <i>tert</i> -butylbiphenyl, THF, -78°C , 1 h	62%
3	Sml_2 , DMPU, THF*, rt to 50°C , 2 h	no reaction
4	AIBN, Bu_3SnH , toluene, reflux, 21 h	0%
5	Li, liq. NH_3 , THF, -78°C , 1 h	ca. 50%
6	Ca, liq. NH_3 , Et_2O , -78°C , 1 h	ca. 60%

*refluxed with benzophenone ketyl before use

上記で確立したリチウムナフタレニドを用いる条件を反応スケールを上げて行くと、シロキサン **116a** および **116b**、シラノール **116c** がそれぞれ 2 工程で 32%、10%、15%収率で生じた (Scheme 64)。シラノール **116c** は主にシリカゲルカラムクロマトグラフィーによる精製の過程でシロキサン **116a** から生じた。シロキサン **116b** は小スケールでは確認できなかったマイナージアステレオマー由来の生成物である。



Scheme 64. Detosylation using lithium naphthalenide

なお、シラノール **116c** の立体化学は X 線結晶構造解析によって決定した (Figure 13)。

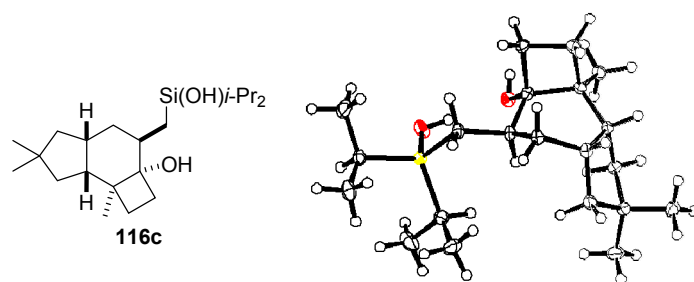
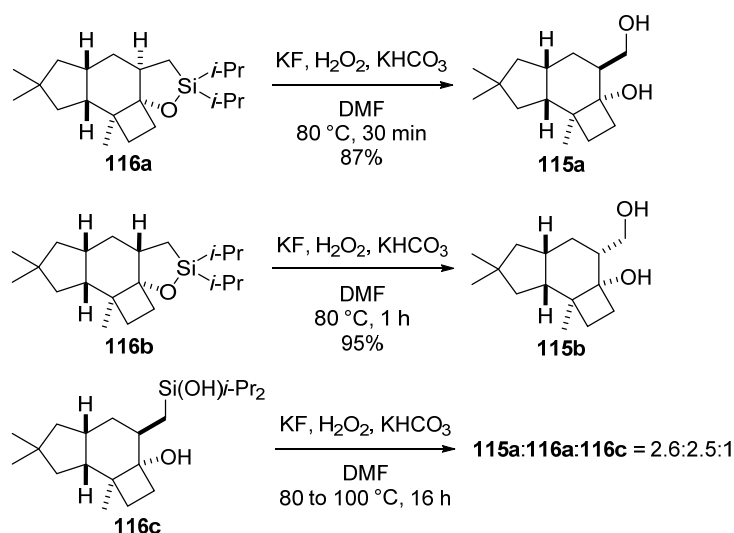


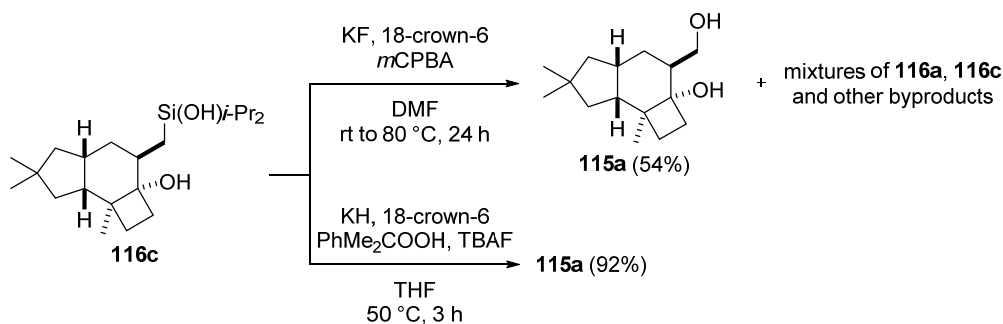
Figure 13. X-ray structure of silanol **116c**

得られた **116a**、**116b** および **116c** に対してそれぞれ Fleming–玉尾酸化を行った (Scheme 65)。 **116a** および **116b** は高収率でそれぞれジオール **115a** および **115b** に変換することができた。一方、**116c** は反応温度を 100 °C まで昇温して反応時間を延ばしても消失せず、16 時間後に反応を止めると、**115a** と **116a**、**116c** が 2.6 : 2.5 : 1 の比であった。



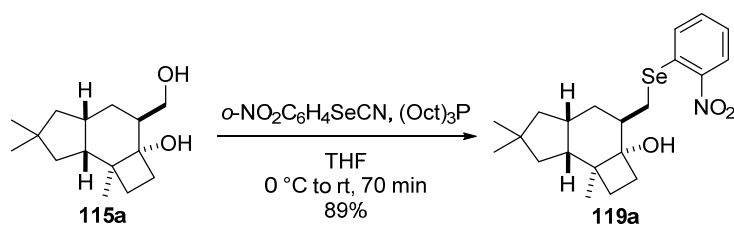
Scheme 65. Fleming–Tamao oxidation of **116**

そこで、**116c** に対して改良 Fleming–玉尾酸化を試みた (Scheme 66)。まず、KF と 18-crown-6、*m*CPBA を用いる条件⁸²では 54%収率でジオール **115a** を得ることができた。しかし、依然として **116a** と **116c** が残存しており、さらにその他の副生成物の存在も確認した。一方、KH とクメンヒドロペルオキシドを用いる Woerpel らの条件⁸³では、高収率で **115a** に変換することに成功した。求核性の増したクメンヒドロペルオキシドを用いたことが反応を円滑に進行させることに繋がったと考えている。



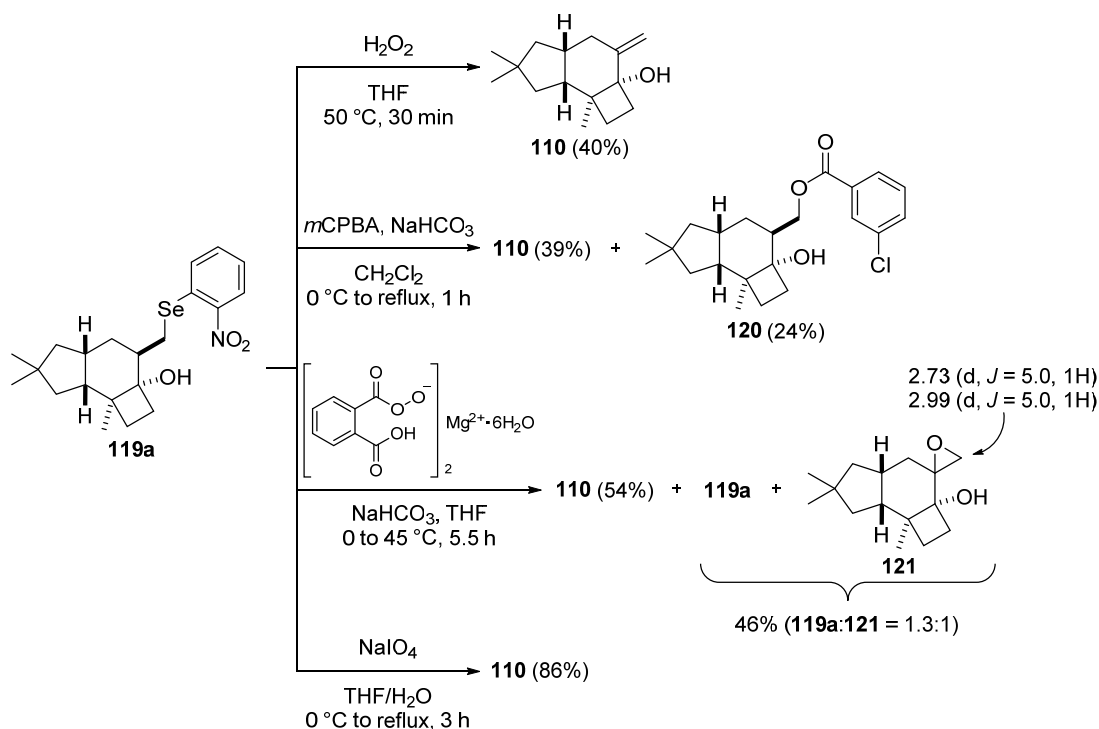
Scheme 66. Modified Fleming–Tamao oxidation of **116c**

得られたジオール **115a** を西沢–Grieco 法によりセレニド **119a** へ変換した (Scheme 67)。



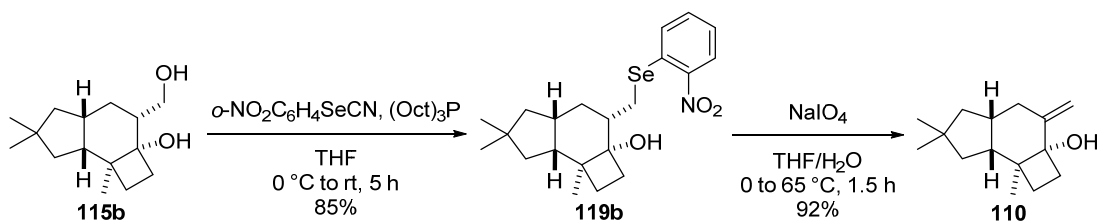
Scheme 67. Synthesis of selenide **119a**

続いて、酸化剤を変えてセレノキシドの *syn*-脱離を検討した (Scheme 68)。過酸化水素を用いた場合、反応が汚くなりエキソオレフィン **110** を 40% の低収率で得た。次に、*m*CPBA を用いた場合、**110** が 39% 収率で得られたが予期せぬことにカルボン酸が置換した **120** が 24% 収率で副生した。より穏和な酸化剤である magnesium monoperoxyphthalate (MMPP)⁸⁴ を用いた場合、**110** の収率は 54% まで向上したが、残りは **119a** とエポキシド **121** が 1.3 : 1 の比で生じていることを ¹H NMR および MS スペクトルより確認した。検討の結果、過ヨウ素酸ナトリウムを用いた場合に、最も高い収率で **110** を得ることに成功した。



Scheme 68. *syn*-Elimination of selenoxide

ジオール **115b** も **115a** と同様に西沢–Grieco 法を用いてエキソオレフィン **110** へ変換した (Scheme 69)。よって、C–H 挿入反応とトシル基の除去で得られた 3 つの化合物 **116a** と **116b**、**116c** は全て全合成に利用できることを示した。

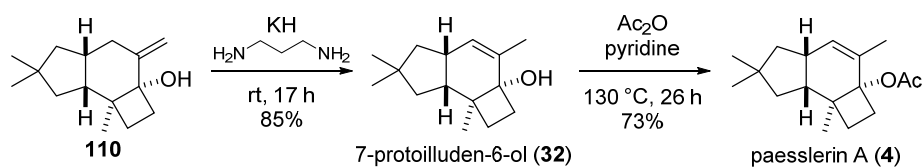


Scheme 69. Nishizawa–Grieco dehydration of **115b**

第 3 節 Paesslerin A の予想構造の全合成と構造訂正

エキソオレフィン **110** が得られたため paesslerin A の予想構造 (**4**) に導くための残る課題は、エキソオレフィン **110** のエンドオレフィンへの異性化および核間位ヒドロキシ基のアセチル化である。まず、エキソオレフィンの異性化について検討した結果、KH と 1,3-ジアミノプロパンから調製したカリウムアミドを用いる条件を見出した (Scheme 70)⁸⁵。ここでも再現性に問題が生じたが、吸湿性の高い 1,3-ジアミノプロパンを使用前に CaH_2 で予備

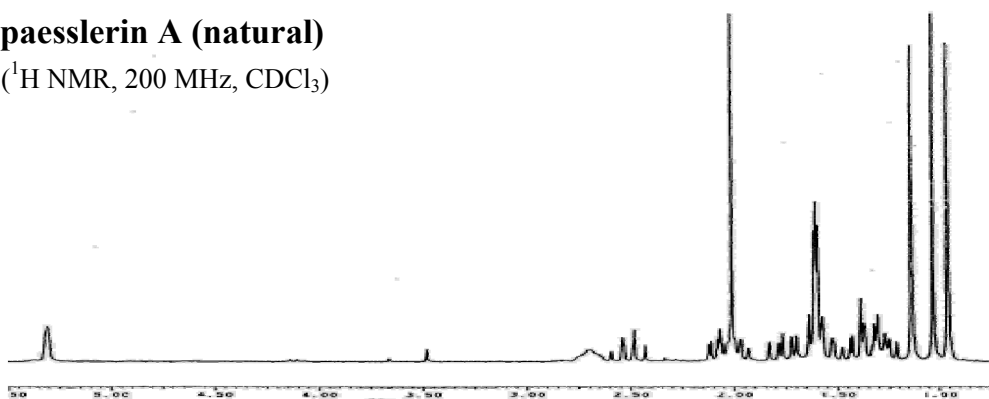
乾燥してから減圧蒸留したものを用いることで解決した。この条件で異性化を行うと、7-protoilluden-6-ol (**32**) を 85% 収率で得ることに成功した。この異性化の駆動力は次のように考察している。即ち、生じたアリルアニオンのカウンターカチオンであるカリウムカチオンにアルコキシドが配位することでアリルアニオンが安定化されると考えている。合成した **32** の ^1H NMR および MS スペクトルは野副らの単離文献⁴¹ のものと一致した。さらに、**32** をピリジン存在下、無水酢酸を溶媒としてアセチル化を行い 15 工程、総収率 1.0% で paesslerin A の予想構造 (**4**) の全合成を達成した⁸⁶。合成品の ^1H および ^{13}C NMR、MS スペクトルは Palermo らの単離文献⁴⁰ のものと一致した。よって、paesslerin A の真の構造は予想通り **4** であることを明らかにした。



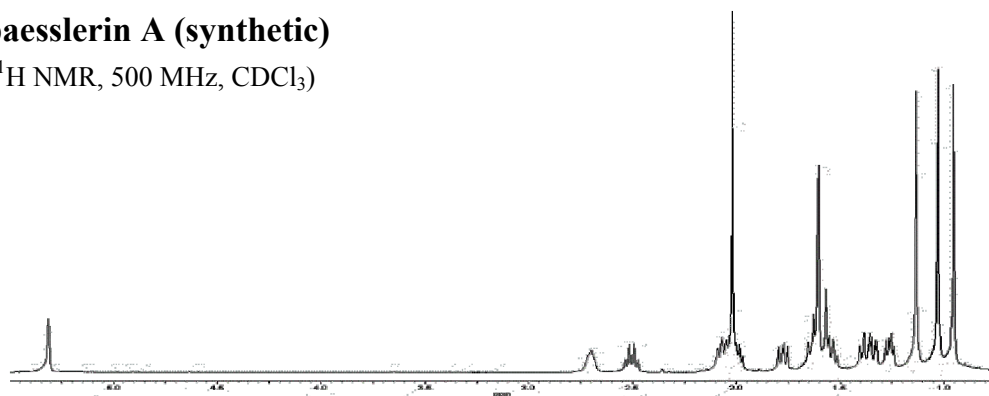
Scheme 70. Total synthesis and structural revision of paesslerin A

合成した paesslerin A の ^1H および ^{13}C NMR スペクトルはいずれも天然物と良い一致を示した (Figure 14)。

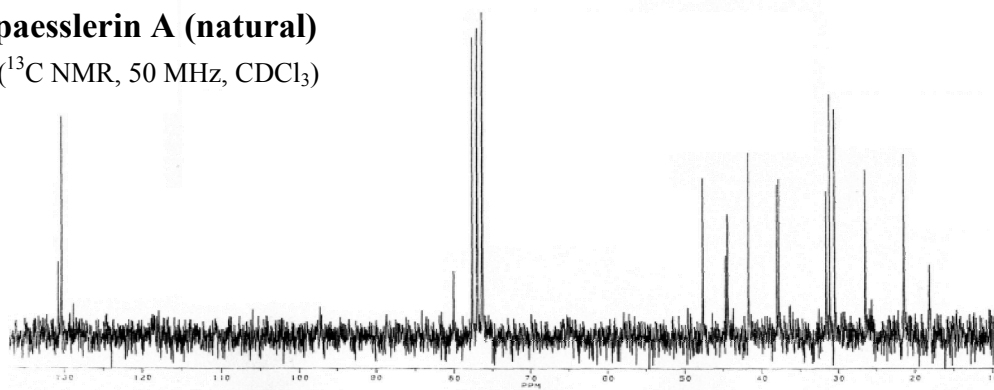
paesslerin A (natural)
 ^1H NMR, 200 MHz, CDCl_3)



paesslerin A (synthetic)
 ^1H NMR, 500 MHz, CDCl_3)



paesslerin A (natural)
 ^{13}C NMR, 50 MHz, CDCl_3)



paesslerin A (synthetic)
 ^{13}C NMR, 125 MHz, CDCl_3)

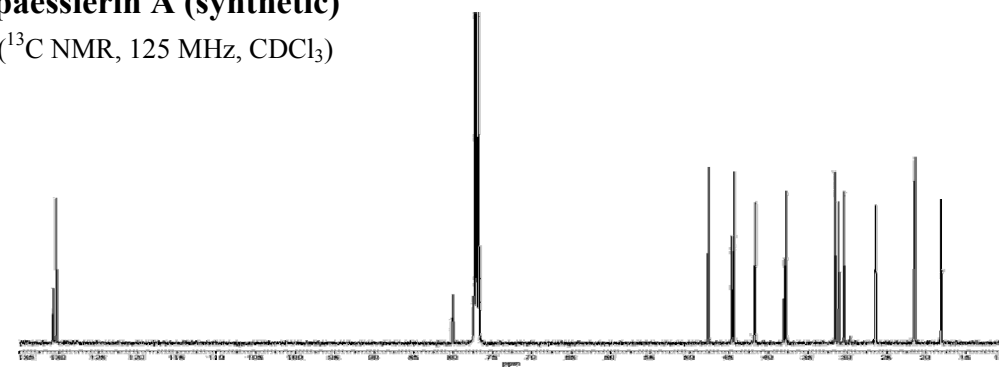
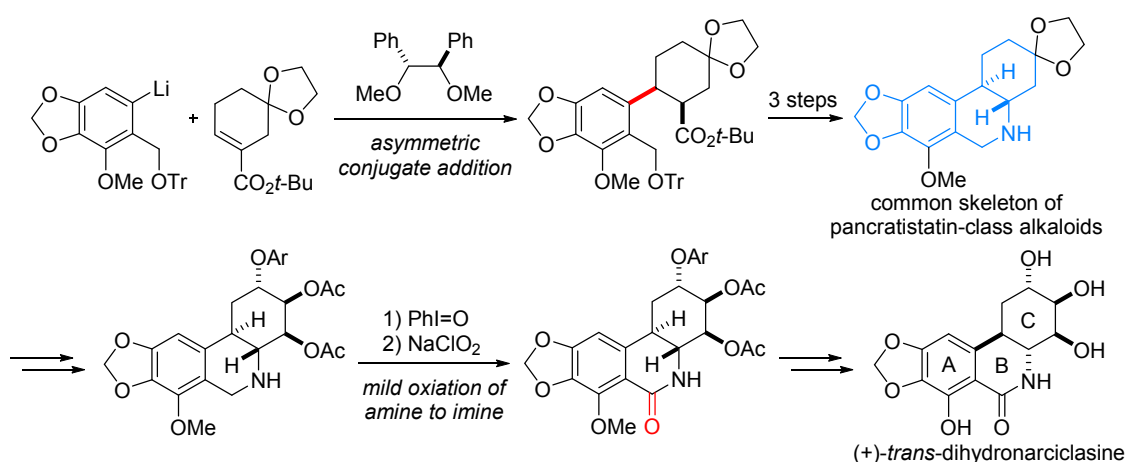


Figure 14. Comparison of ^1H and ^{13}C NMR spectra of natural and synthetic paesslerin A

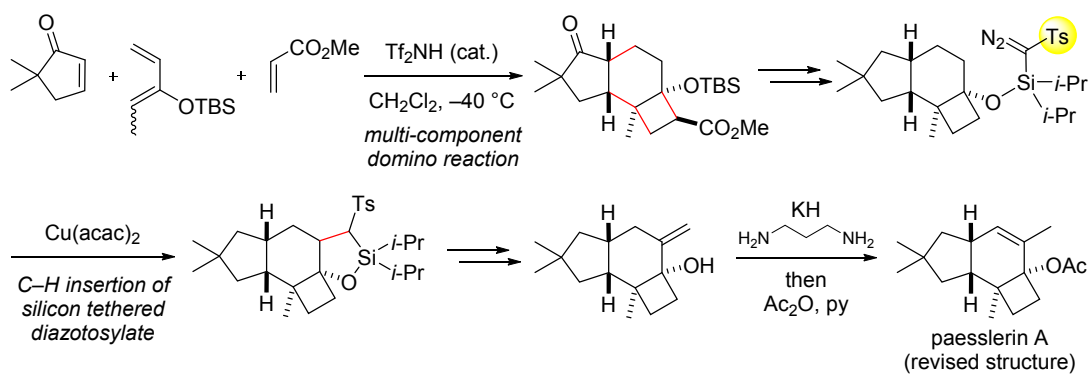
第 4 章 結論

著者はキラルジエーテル配位子制御によるアリールリチウムの α , β -不飽和エステルへの不斉共役付加反応の最適化を行い、高い不斉収率で付加体を得た (Scheme 71)。続く 3 工程で **pancratistatin** 型のアルカロイドに共通する骨格を構築した。この中間体から様々な類縁体を合成することが可能である。得られた 2 つの不斉源を足掛かりに C 環に 3 つのヒドロキシ基を立体選択的に導入した。最後に穏和な条件下、アミンからアミドへの酸化を行い 22 工程、総収率 2.8% で (+)-*trans*-dihydronarciclasine の 3 例目となる不斉全合成を達成した。



Scheme 71. Total synthesis of (+)-*trans*-dihydronarciclasine

また、当研究グループで開発された Ti_2NH を触媒とする多成分連続反応により **paesslerin A** の三環性骨格を一挙に構築した (Scheme 72)。著者はケイ素原子で繋がれたジアゾシレート配向基とする C-H 挿入反応を新規に開発し、シクロヘキサン環上に C1 単位を導入することに成功した。これにより、報告されたジアゾアセテートを配向基とする場合に比べて大幅に工程数を削減することができた。カリウムアミドを用いるエキソオレフィンのエンドオレフィンへの異性化を経て 15 工程、総収率 1.0% で **paesslerin A** の世界初となる全合成を達成し、予想構造が真の構造であることを明らかにした。本研究を通して核間位ヒドロキシ基の特異な反応性が様々な場面で問題となったが、シクロヘキサン環上に直接炭素原子を導入して官能基変換を簡略化することで解決に導いた。確立した合成法を利用すれば、より酸化度の高い **melleolide K** や **atlanticone D** のようなプロトイルダンセススキテルペノイドの全合成へ応用が可能である。



Scheme 72. Total synthesis of paesslerin A

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私のことを絶えず励まし支えてくれた筑波大学同期の山崎康介氏に深く感謝致します。

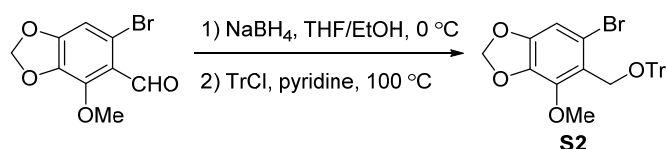
私の意見を尊重し、大学院進学を快く認め、研究生活を支えてくれた父・恒雄、母・記代子に心から深く感謝致します。

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2015 年 3 月

実験項

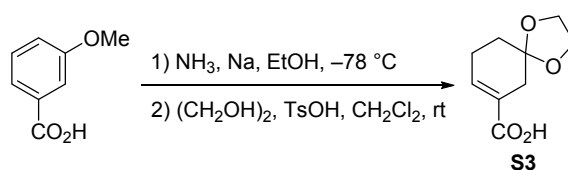
General. Silica gel was used for column chromatography. Thin layer chromatography (TLC) was visualized using a combination of UV and phosphomolybdic acid, anisaldehyde, ninhydrin, and potassium permanganate staining. NMR (500 MHz for ^1H and 125 MHz for ^{13}C) was measured in CDCl_3 unless otherwise mentioned. Chemical shifts and coupling constants are presented in ppm δ relative to tetramethylsilane and Hz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C peak multiplicity assignments were made based on DEPT data. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1} . All reagents were purchased from chemical companies and used as received. Dehydrated solvents were purchased for the reactions and used without further desiccation unless otherwise mentioned.



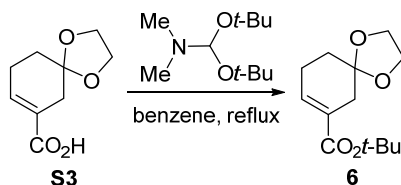
6-Bromo-4-methoxybenzo[d][1,3]dioxole-5-methanol (S1): To a solution of 6-bromo-4-methoxybenzo[d][1,3]dioxole-5-carbaldehyde⁸⁷ (8.30 g, 32.0 mmol) in THF (140 mL), cooled in an ice-water bath, were added NaBH_4 (1.84 g, 48.7 mmol) and EtOH (47 mL). The cooling bath was removed, the mixture was stirred for 30 min, and the reaction was quenched with saturated aqueous NH_4Cl (25 mL). The whole was extracted with EtOAc (500 mL), and the organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give the title compound as pale yellow solids (8.31 g), which was used directly in the next step without further purification. An analytical sample was obtained by recrystallization from hexane/EtOAc (2:1) as white blocks of mp $75\text{--}76\text{ }^\circ\text{C}$: R_f 0.29 (hexane/EtOAc 3:1). ^1H NMR: 2.12 (t, $J = 6.5$, 1H), 4.05 (s, 3H), 4.76 (d, $J = 6.5$, 2H), 5.95 (s, 2H), 6.77 (s, 1H). ^{13}C NMR: 60.1 (CH_2), 60.2 (CH_3), 101.6 (CH_2), 107.3 (CH), 115.8 (C), 125.4 (C), 136.2 (C), 142.6 (C), 149.6 (C). IR (KBr): 3340, 2955, 2893, 1620, 1466, 1412, 1358, 1258, 1227, 1089, 1057, 1011. EIMS m/z : 262 ($\text{M}+2$), 260 (M^+), 245 ($\text{M}+2\text{--OH}$), 243 (M--OH), 181 (M--Br). Anal. calcd. for $\text{C}_9\text{H}_9\text{BrO}_4$: C, 41.41; H, 3.47. found: C, 41.34; H, 3.46.

6-Bromo-4-methoxy-5-(trityloxymethyl)benzo[d][1,3]dioxole (S2): To a stirred solution of S1 (8.31 g) in dry pyridine (166 mL) was added TrCl (17.8 g, 63.9 mmol) at $100\text{ }^\circ\text{C}$. After 7 h, the reaction mixture was extracted with EtOAc (3 x 400 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4 . Concentration and recrystallization from EtOH/ CHCl_3 (4:1) gave the title compound (13.3 g, 83%) as off-white needles of mp $173\text{--}174\text{ }^\circ\text{C}$: R_f 0.62 (hexane/EtOAc 4:1 x 2). ^1H NMR: 3.90 (s, 3H), 4.19 (s, 2H), 5.95 (s, 2H), 6.77 (s, 1H), 7.22–7.25

(m, 3H), 7.29–7.32 (m, 6H), 7.55–7.57 (m, 6H). ^{13}C NMR: 59.9 (CH_3), 60.3 (CH_2), 86.6 (C), 101.5 (CH_2), 107.6 (CH), 117.4 (C), 123.8 (C), 126.9 (CH), 127.6 (CH), 129.2 (CH), 136.5 (C), 143.3 (C), 144.2 (C), 149.5 (C). IR (KBr): 3055, 3017, 2947, 2885, 1620, 1466, 1420, 1350, 1265, 1219, 1157, 1088, 1049. EIMS m/z : 261 ($\text{M}+2\text{-CPh}_3$), 259 (M-CPh_3), 243 (CPh_3), 228, 215, 200, 180, 165 (M-Br-OCPh_3), 77. FABMS m/z : 506 ($\text{M}+2\text{+H}$), 504 (M+H). Anal. calcd. for $\text{C}_{28}\text{H}_{23}\text{BrO}_4$: C, 66.81; H, 4.61. found: C, 66.56; H, 4.71.

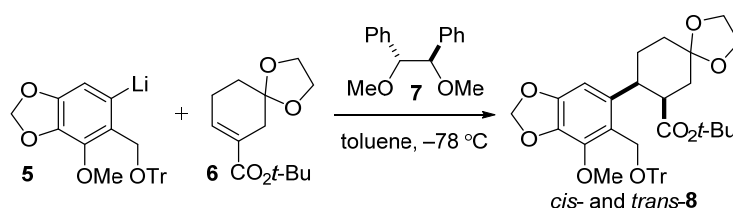


5,5-Ethylenedioxcyclohex-1-enecarboxylic Acid (S3):⁸⁸ To liquid ammonia (400 mL) was added a slurry of *m*-anisic acid (25.0 g, 164 mmol) in EtOH (90 mL) at $-78\text{ }^\circ\text{C}$. To the stirred mixture was added sodium (15 g, 0.65 mol) in small pieces over 1 h. After 1 h, the reaction mixture was allowed to warm up to rt and stirred for additional 3.5 h. After ice-water (600 mL) was added, the mixture, cooled in an ice bath, was acidified with 10% HCl to pH 4. The resulting precipitates were collected by filtration, washed with water, and dried *in vacuo* to give white solids (18.3 g) of mp $85\text{--}88\text{ }^\circ\text{C}$. To a stirred solution of the solids in CH_2Cl_2 (120 mL) were added ethylene glycol (17.7 g, 285 mmol) and *p*-TsOH $\cdot\text{H}_2\text{O}$ (1.14 g, 6.00 mmol) at rt. After 2 h, water (200 mL) was added, and the aqueous layer was extracted with EtO $_2$ (2 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give pale yellow solids (20.9 g), which was recrystallized from benzene to give the title compound (13.5 g, 45%) as pale yellow blocks of mp $70\text{--}72\text{ }^\circ\text{C}$: R_f 0.35 (hexane/EtOAc 1:1 x 2). ^1H NMR: 1.77 (t, $J = 6.5$, 1H), 2.46–2.51 (m, 4H), 3.98–4.04 (m, 4H), 7.14 (m, 1H). ^{13}C NMR: 25.1 (CH_2), 30.1 (CH_2), 34.2 (CH_2), 64.5 (CH_2), 107.5 (C), 127.8 (C), 141.4 (CH), 171.8 (C). IR (KBr): 1682, 1636, 1427, 1366, 1281, 1150, 1065. EIMS m/z : 184 (M^+), 169, 152, 139, 125, 109, 95. Anal. calcd. for $\text{C}_9\text{H}_{12}\text{O}_4$: C, 58.69; H, 6.57. found: C, 58.50; H, 6.40.



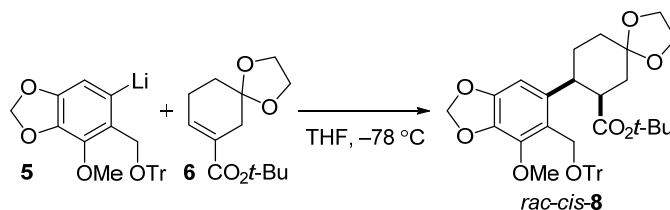
tert-Butyl 5,5-Ethylenedioxcyclohex-1-enecarboxylate (6): To a refluxing solution of α,β -unsaturated carboxylic acid **S3** (1.84 g, 10.0 mmol) in dry benzene (15 mL) was added $(t\text{-BuO})_2\text{CHNMe}_2$ ⁸⁹ (19.2 mL, 80.3 mmol) over 40 min. After 3 h, the reaction mixture was cooled to rt; washed with water (20 mL), saturated NaHCO_3 (2 x 20 mL), and brine; dried over Na_2SO_4 , and

concentrated *in vacuo*. The residue was recrystallized from hexane to give the title compound (2.12 g, 88%) as pale yellow blocks of mp 60–61 °C: R_f 0.60 (hexane/EtOAc 4:1 x 2). ^1H NMR: 1.47 (s, 9H), 1.74 (t, J = 6.5, 2H), 2.39–2.47 (m, 4H), 3.97–4.04 (m, 4H), 6.91 (m, 1H). ^{13}C NMR: 24.7 (CH₂), 28.0 (CH₃), 30.2 (CH₂), 34.7 (CH₂), 64.5 (CH₂), 80.2 (C), 107.8 (C), 129.8 (C), 137.3 (CH), 166.0 (C). IR (KBr): 2986, 2939, 2885, 1697, 1651, 1366, 1281, 1165, 1057. EIMS m/z : 240 (M^+), 184, 167, 154, 139, 57 (*t*-Bu). Anal. calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_4$: C, 64.98; H, 8.39. found: C, 64.72; H, 8.31.

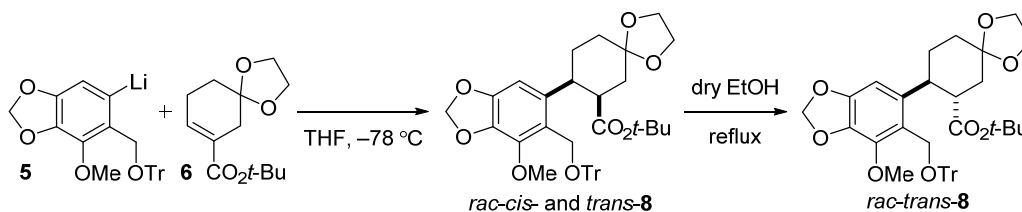


***tert*-Butyl (1*R*,2*S*)- and (1*S*,2*S*)-5,5-Ethylenedioxy-2-(7-methoxy-6-(trityloxymethyl)benzo [*d*][1,3]dioxol-5-yl)cyclohexanecarboxylate (*cis*- and *trans*-8):** To a solution of chiral ligand **7**⁹⁰ (800 mg, 3.30 mmol) and aryl bromide **S2** (1.51 g, 3.00 mmol) in dry toluene (40 mL) was added a 1.59 N hexane solution of BuLi (1.90 mL, 3.02 mmol) over 5 min at −78 °C, and the mixture was stirred for 1.5 h. A solution of α,β -unsaturated ester **6** (241 mg, 1.00 mmol) in dry toluene (9 mL + 1 mL washing) was added over 30 min, and the mixture was stirred for another 1.5 h. The reaction was quenched by the addition of dry MeOH (1.5 mL), and saturated aqueous NH_4Cl (25 mL) was subsequently added. The whole was extracted with EtOAc (50 mL + 2 x 25 mL), 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/EtOAc 6:1) to afford a 96:4 mixture of the title compounds with 92% ee (611 mg, 92% combined yield) as colorless amorphous of mp 122–125 °C: $[\alpha]_D^{25} -1.44$ (c 2.14, CHCl_3). ^1H and ^{13}C NMR, IR, MS were in agreement with those of the racemic samples (*vide infra*).

The diastereomeric ratio was determined based on the integration area of the ^1H NMR singlet signals at 1.18 and 0.97 ppm ($(\text{CH}_3)_3\text{C}$ of the major and minor isomers, respectively). The ee of the major isomer was determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 100/1, 1 mL/min, 254 nm, minor 35.3 min and major 39.3 min). The relative configuration was confirmed by epimerization of *rac-cis*-**8** to *rac-trans*-**8** under basic condition (*vide infra*). The absolute configuration was determined by the conversion into *trans*-dihydronarciclasine (**1**). The chiral ligand **7** was recovered quantitatively.

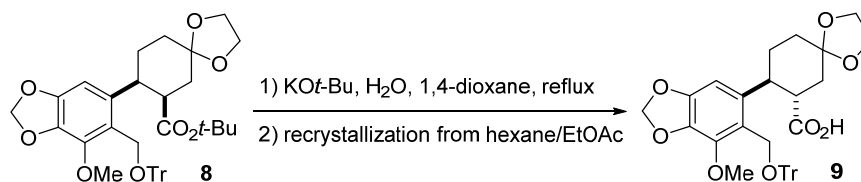


tert-Butyl (1*RS*,2*SR*)-5,5-Ethylenedioxy-2-{7-methoxy-6-(trityloxymethyl)benzo[*d*][1,3]dioxol-5-yl}cyclohexanecarboxylate (*rac-cis*-8): To a solution of aryl bromide **S2** (11.1 g, 22.1 mmol) in dry THF (80 mL) was added a 1.65 N hexane solution of BuLi (13.3 mL, 21.9 mmol) over 10 min at -78°C . After 2.5 h, a solution of α,β -unsaturated ester **6** (4.80 g, 20.0 mmol) in dry THF (40 mL) was added over 20 min, and the mixture was stirred for another 20 min. The reaction was quenched by the addition of dry MeOH (24 mL), and saturated aqueous NH_4Cl (200 mL) was subsequently added. The whole was extracted with EtOAc (3 x 400 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting pale yellow solids was reprecipitated from EtOAc/EtOH (1:2) to afford the title compound (11.4 g, 86%) as white solids of mp $203\text{--}204^{\circ}\text{C}$: R_f 0.25 (hexane/EtOAc 4:1). ^1H NMR: 1.18 (s, 9H), 1.45–1.51 (m, 2H), 1.69 (m, 1H), 1.82 (m, 1H), 2.01 (dd, $J = 6.5, 14.0$, 1H), 2.33 (m, 1H), 2.60 (ddd, $J = 6.0, 6.0, 6.5$, 1H), 2.80 (m, 1H), 3.89–3.94 (m, 5H), 4.00 (s, 3H), 4.33 (d, $J = 9.5$, 1H), 5.91 (s, 2H), 6.83 (s, 1H), 7.24 (t, $J = 7.5$, 3H), 7.31 (t, $J = 7.5$, 6H), 7.53 (d, $J = 7.5$, 6H). ^{13}C NMR: 27.1 (CH_2), 27.8 (CH_3), 33.5 (CH_2), 36.1 (CH_2), 37.0 (CH), 44.6 (CH), 56.7 (CH_2), 59.6 (CH_3), 64.1 (CH_2), 64.3 (CH_2), 79.6 (C), 86.6 (C), 100.8 (CH_2), 104.2 (CH), 108.2 (C), 121.4 (C), 126.9 (CH), 127.6 (CH), 128.9 (CH), 134.6 (C), 138.6 (C), 142.3 (C), 144.1 (C), 148.3 (C), 172.2 (C). IR (KBr): 3063, 2970, 2939, 2885, 2777, 1728, 1620, 1481, 1443, 1373, 1219, 1150, 1042. FABMS m/z : 687 (M+Na). EIMS m/z : 365, 347, 319, 303, 275, 257, 243 (CPh_3), 228, 215, 203, 181, 165, 152, 143, 133, 115, 99, 84, 77, 57 (*t*-Bu). HRMS-FAB m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{41}\text{H}_{44}\text{O}_8\text{Na}$, 687.2934; found, 687.2944. Anal. calcd. for $\text{C}_{41}\text{H}_{44}\text{O}_8$: C, 74.08; H, 6.67. found: C, 73.84; H, 6.67.



tert-Butyl (1*RS*,2*RS*)-5,5-Ethylenedioxy-2-{7-methoxy-6-(trityloxymethyl)benzo[*d*][1,3]dioxol-5-yl}cyclohexanecarboxylate (*rac-trans*-8): To a solution of aryl bromide **S2** (4.53 g, 9.00 mmol) in dry THF (30 mL) was added a 1.51 N hexane solution of BuLi (5.90 mL, 8.91 mmol) over 10 min at -78°C . After 2 h, a solution of α,β -unsaturated ester **6** (1.08 g, 4.49 mmol) in dry THF (10 mL) was added over 10 min, and the mixture was stirred for another 2 h. To the reaction mixture

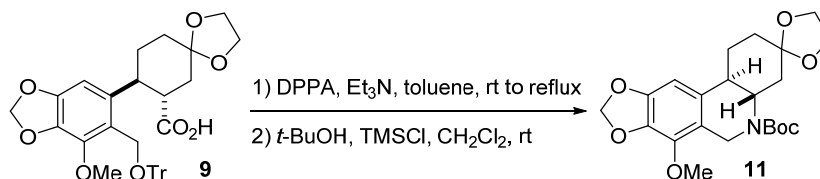
was added dry EtOH (5.9 mL) and the resulting mixture was heated under reflux for 7 days. After cooling to rt, brine was added, and the organic solvents were removed under reduced pressure. The remaining aqueous layer was extracted with EtOAc (2 x 100 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 4:1) to afford a 98:2 mixture of the title compound and *rac-cis-7* (2.78 g, 93% combined yield) as pale yellow solids. Recrystallization from EtOAc/EtOH (2:1) gave a diastereomerically pure sample (2.22 g, 80%) as pale yellow blocks of mp 193–194 °C: *R*_f 0.25 (hexane/EtOAc 4:1). ¹H NMR: 0.97 (s, 9H), 1.38–1.50 (m, 2H), 1.55–1.65 (m, 2H), 1.82–1.92 (m, 2H), 2.51 (ddd, *J* = 3.0, 11.5, 12.0, 1H), 2.65 (ddd, *J* = 3.0, 11.5, 12.5, 1H), 3.88 (d, *J* = 9.5, 1H), 3.92–3.95 (m, 4H), 3.96 (s, 3H), 4.45 (t, *J* = 9.5, 1H), 5.90 (d, *J* = 1.5, 1H), 5.92 (d, *J* = 1.5, 1H), 6.54 (s, 1H), 7.23–7.25 (m, 3H), 7.29–7.32 (m, 6H), 7.53–7.55 (m, 6H). ¹³C NMR: 27.6 (CH₃), 32.5 (CH₂), 34.8 (CH₂), 37.8 (CH₂), 40.5 (CH), 48.3 (CH), 56.5 (CH₂), 59.7 (CH₃), 64.3 (CH₂), 64.4 (CH₂), 79.6 (C), 86.6 (C), 100.8 (CH₂), 101.6 (CH), 108.1 (C), 121.5 (C), 127.0 (CH), 127.7 (CH), 129.0 (CH), 134.8 (C), 139.3 (C), 142.2 (C), 144.3 (C), 149.0 (C), 172.7 (C). IR (KBr): 3063, 2970, 2885, 1720, 1620, 1481, 1443, 1366, 1280, 1250, 1211, 1150, 1042. EIMS *m/z*: 421 (M–CPh₃), 365, 347, 319, 257, 243 (CPh₃), 215, 203, 165, 143, 77, 57 (*t*-Bu). FABMS *m/z*: 687 (M+Na). Anal. calcd. for C₄₁H₄₄O₈: C, 74.08; H, 6.67. found: C, 74.08; H, 6.62.



(1*S*,2*S*)-5,5-Ethylenedioxy-2-{7-methoxy-6-(trityloxymethyl)benzo[d][1,3]dioxol-5-yl}cy-

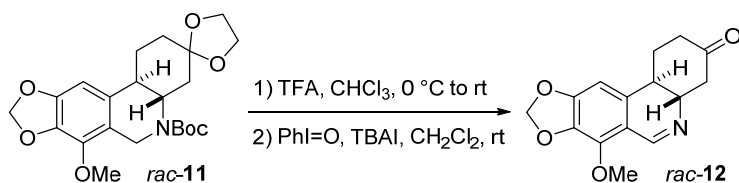
clohexanecarboxylic Acid (9): To a solution of *cis-8* (1.10 g, 1.65 mmol) in 1,4-dioxane (33 mL) were added H₂O (0.45 mL, 25 mmol) and a 1 M THF solution of KO*t*-Bu (25 mL, 25 mmol), and the mixture was heated under reflux for 21 h. After cooling to rt, saturated aqueous NH₄Cl (10 mL) and brine (50 mL) were added. The mixture was extracted with EtOAc (2 x 100 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 1:1) to afford the title compound (901 mg, 90%) as white amorphous. Recrystallization from hexane/EtOAc (1:1) gave a racemic compound (93.4 mg, 10%) as white solids of mp 223–224 °C. Concentration of the mother liquor provided the title compound (814 mg, 90%) with >99% ee as colorless amorphous of mp 142–145 °C: *R*_f 0.29 (hexane/EtOAc 1:1). [α]_D²⁵ +10.6 (*c* 1.49, THF). ¹H NMR (DMSO-*d*₆): 1.24 (m, 1H), 1.33 (dd, *J* = 12.0, 13.0, 1H), 1.49 (m, 1H), 1.57 (m, 1H), 1.66 (m, 1H), 1.81 (br d, *J* = 12.0, 1H), 2.50–2.63 (m, 2H), 3.86 (s, 4H), 3.91 (s, 3H), 3.95 (d, *J* = 9.0, 1H), 4.22 (d, *J* = 9.0, 1H), 5.98 (s, 2H), 6.45 (s, 1H), 7.26–7.29 (m, 3H), 7.33–7.36 (m, 6H), 7.45–7.46 (m, 6H), 11.7 (s, 1H). ¹³C NMR (DMSO-*d*₆): 32.0 (CH₂), 34.3

(CH₂), 37.9 (CH₂), 39.5 (CH), 46.5 (CH), 55.8 (CH₂), 59.5 (CH₃), 63.8 (CH₂), 63.9 (CH₂), 86.0 (C), 100.6 (CH), 101.0 (CH₂), 106.9 (C), 120.9 (C), 127.0 (CH), 127.8 (CH), 128.5 (CH), 134.5 (C), 139.3 (C), 141.8 (C), 143.8 (C), 148.8 (C), 174.4 (C). IR (KBr): 3449, 3055, 2947, 2893, 2677, 1705, 1620, 1481, 1381, 1281, 1219, 1126, 1042. FABMS *m/z*: 609 (M+H), 608 (M⁺), 349 (M-OCPh₃), 307, 289, 243 (CPh₃), 154. Anal. calcd. for C₃₇H₃₆O₈: C, 73.01; H, 5.96. found: C, 72.96; H, 5.99. The ee was determined in the next step.



(4a*S*,11b*R*)-5-*tert*-Butoxycarbonyl-3,3-ethylenedioxy-7-methoxy-1,2,3,4,4a,5,6,11b-octahydro[1,3]dioxolo[4,5-*j*]phenanthridine (11):

To a stirred solution of carboxylic acid **9** (1.60 g, 2.63 mmol) and Et₃N (0.80 mL, 5.8 mmol) in dry toluene (50 mL) were added powdered molecular sieves 4A (1.6 g) and (PhO)₂P(=O)N₃ (0.59 mL, 2.7 mmol), and the mixture was stirred for 1 h at rt and heated under reflux for 2 h. The mixture was cooled to rt, and insoluble materials were removed by filtration through a sintered glass funnel and washed with CHCl₃. The combined filtrate and washings were concentrated *in vacuo*, and the residue was dissolved in dry CH₂Cl₂ (50 mL). To the solution were added *t*-BuOH (13 mL) and TMSCl (1.7 mL, 14.0 mmol), and the mixture was stirred for 18 h at rt. To the mixture was added saturated aqueous NaHCO₃ (50 mL), and the organic layer was separated. The aqueous layer was extracted with CHCl₃ (100 mL, 2 x 50 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 6:1) to afford the title compound (751 mg, 68%) with >99% ee as colorless amorphous of mp 152–154 °C: R_f 0.33 (hexane/EtOAc 3:1). [α]_D²⁵ +31.6 (*c* 1.08, CHCl₃). ¹H NMR: 1.44 (s, 9H), 1.62 (dd, *J* = 12.0, 12.0, 1H), 1.73–1.76 (m, 2H), 1.94 (m, 1H), 2.27 (m, 1H), 2.40 (ddd, *J* = 3.0, 10.0, 11.0, 1H), 2.53 (br d, *J* = 12.0, 1H), 3.30 (ddd, *J* = 3.0, 11.0, 12.0, 1H), 3.58 (d, *J* = 15.0, 1H), 3.97–3.99 (m, 7H), 5.37 (d, *J* = 15.0, 1H), 5.90 (s, 1H), 5.91 (s, 1H), 6.48 (s, 1H). ¹³C NMR: 24.5 (CH₂), 28.5 (CH₃), 34.9 (CH₂), 37.6 (CH₂), 40.2 (CH₂), 41.0 (CH), 55.9 (CH), 60.1 (CH₃), 64.4 (CH₂), 64.5 (CH₂), 79.5 (C), 99.0 (CH), 100.7 (CH₂), 108.7 (C), 122.5 (C), 133.6 (C), 134.8 (C), 139.2 (C), 148.2 (C), 155.2 (C). IR (KBr): 2978, 2893, 1682, 1620, 1481, 1396, 1288, 1227, 1165, 1080, 1049. FABMS *m/z*: 442 (M+Na), 418, 362 (M-*t*-Bu), 318 (M-Boc), 218, 154, 136, 57 (*t*-Bu). HRMS-FAB *m/z*: [M+Na]⁺ calcd. for C₂₂H₂₉NNaO₇, 442.1842; found, 442.1857. Anal. calcd. for C₂₂H₂₉O₇: C, 62.99; H, 6.97; N, 3.34. found: C, 62.99; H, 6.70; N, 3.37. The ee was determined by HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 20/1, 1 mL/min, 254 nm, minor 15.3 min and major 19.7 min).

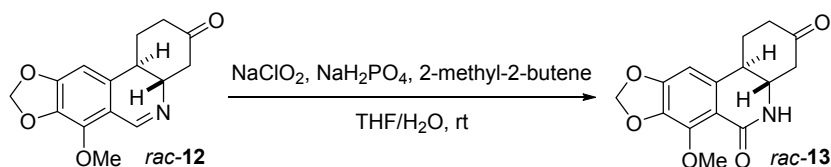


(4aSR,11bRS)-7-Methoxy-1,4,4a,5,6,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridin-3(2H)-one

(S4): To a stirred solution of *rac*-**11** (1.22 g, 2.91 mmol) in CHCl_3 (30 mL) was added TFA (15 mL) at 0 °C, and the mixture was stirred at rt for 18 h. The TFA was azeotropically removed with toluene, and the residue was dissolved in CHCl_3 (100 mL). The solution was washed with water (50 mL) and saturated aqueous NaHCO_3 (50 mL), dried over Na_2SO_4 , and concentrated *in vacuo* to afford the title compound (720 mg) as pale yellow solids, which was used directly in the next step without further purification. An analytical sample was obtained by reprecipitation of the pale yellow solids from hexane/EtOAc (1:1) as golden red solids of mp >150 °C (dec): R_f 0.31 (EtOAc/MeOH 9:1). ^1H NMR: 1.50 (m, 1H), 2.40–2.79 (m, 7H), 3.89 (dd, $J = 2.0, 16.5$, 1H), 4.00 (s, 3H), 4.13 (d, $J = 16.5$, 1H), 5.89 (m, 2H), 6.54 (s, 1H). ^{13}C NMR: 27.6 (CH_2), 41.1 (CH_2), 42.3 (CH), 44.4 (CH_2), 48.4 (CH_2), 58.0 (CH), 59.2 (CH_3), 99.9 (CH), 100.6 (CH_2), 120.4 (C), 130.4 (C), 133.9 (C), 139.7 (C), 148.0 (C), 208.7 (C). IR (KBr): 2924, 2885, 1712, 1620, 1481, 1319, 1304, 1273, 1218, 1134, 1057. FABMS m/z : 276 (M+H), 275 (M^+), 274 (M–H), 218, 154, 136. HRMS–FAB (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{18}\text{NO}_4$, 276.1236; found, 276.1236.

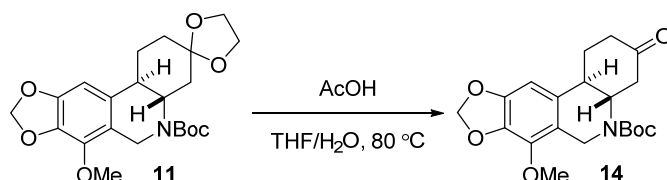
(4aSR,11bRS)-7-Methoxy-1,4,4a,11b-tetrahydro[1,3]dioxolo[4,5-j]phenanthridin-3(2H)one

(rac-12): To a stirred suspension of $\text{PhI}=\text{O}$ (1.61 g, 7.32 mmol) and Bu_4NI (193 mg, 0.523 mmol) in CH_2Cl_2 (60 mL) was added water (0.60 mL), and the mixture was stirred at rt for 15 min. To this suspension, **S4** (720 mg) in CH_2Cl_2 (75 mL + 5 mL washing) was added over 5 min. After 2 h, the reaction was quenched with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (150 mL), and the whole was extracted with CHCl_3 (2 x 100 mL). The combined organic layers were washed with water (200 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography ($\text{CHCl}_3/\text{EtOAc}$ 1:1) to afford the title compound (524 mg, 66%) as pale brown solids of mp 167–168 °C: R_f 0.27 ($\text{CHCl}_3/\text{EtOAc}$ 1:1). ^1H NMR: 1.63 (dddd, $J = 5.0, 12.0, 13.0, 14.0$, 1H), 2.45 (ddd, $J = 6.0, 14.0, 14.5$, 1H), 2.55–2.75 (m, 4H), 3.07 (ddd, $J = 2.0, 5.0, 14.5$, 1H), 3.22 (m, 1H), 4.09 (s, 3H), 5.97 (d, $J = 1.0$, 1H), 5.98 (d, $J = 1.0$, 1H), 6.54 (s, 1H), 8.56 (d, $J = 3.0$, 1H). ^{13}C NMR: 25.8 (CH_2), 37.4 (CH), 40.1 (CH_2), 49.0 (CH_2), 59.9 (CH_3), 60.3 (CH), 98.7 (CH), 101.4 (CH_2), 114.8 (C), 134.4 (C), 135.3 (C), 141.9 (C), 152.1 (C), 155.5 (CH), 209.8 (C). IR (neat): 2955, 2885, 1712, 1620, 1597, 1481, 1427, 1365, 1326, 1303, 1234, 1134, 1042. FABMS m/z : 274 (M+H), 154, 136. HRMS–FAB (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{16}\text{NO}_4$, 274.1079; found, 274.1078.



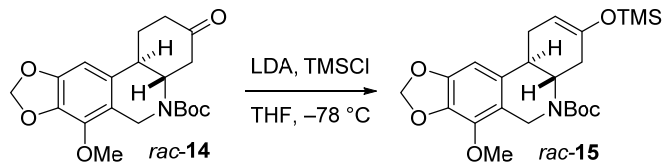
(4aSR,11bRS)-7-Methoxy-1,4a,5,11b-tetrahydro[1,3]dioxolo[4,5-j]phenanthridine-3,6(2H,

4H)-dione (rac-13): To a solution of imine *rac*-12 (258 mg, 0.944 mmol) in THF (30 mL) were added 2-methyl-2-butene (1.9 mL, 18 mmol), water (19 mL), NaH₂PO₄•2H₂O (1.45 g, 9.29 mmol), and NaClO₂ (844 mg, 9.33 mmol) at 0 °C. The mixture was stirred at rt for 19 h. Then, water (30 mL) was added, and the whole was extracted with CHCl₃ (100 + 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (acetone/hexane 1:1) to afford the title compound (226 mg, 83%) as off-white solids of mp >240 °C (dec): R_f 0.21 (hexane/acetone 1:1). ¹H NMR: 1.68 (m, 1H), 2.48–2.70 (m, 5H), 2.99 (ddd, *J* = 3.5, 11.5, 12.0, 1H), 3.51 (ddd, *J* = 5.0, 12.0, 12.5, 1H), 4.08 (s, 3H), 5.65 (br s, 1H), 6.01 (d, *J* = 1.5, 1H), 6.03 (d, *J* = 1.5, 1H), 6.52 (s, 1H). ¹³C NMR: 25.7 (CH₂), 40.0 (CH₂), 41.4 (CH), 45.8 (CH₂), 53.8 (CH), 60.8 (CH₃), 99.4 (CH), 101.7 (CH₂), 115.7 (C), 137.3 (C), 137.4 (C), 145.0 (C), 152.2 (C), 163.8 (C), 206.3 (C). IR (KBr): 1720, 1674, 1612, 1474, 1335. EIMS *m/z*: 289 (M⁺), 261, 243, 219, 204, 186. HRMS–EI (*m/z*): [M]⁺ calcd. for C₁₅H₁₅NO₅, 289.0950; found, 289.0952.



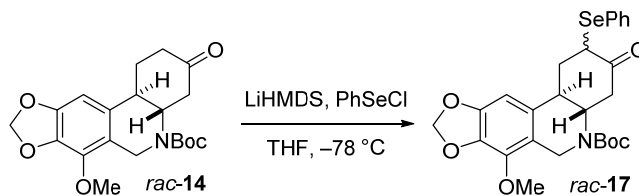
(4aS,11bR)-5-tert-Butoxycarbonyl-7-methoxy-1,4,4a,5,6,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridine-3(2H)-one (14): A solution of **11** (246 mg, 0.586 mmol) in AcOH/THF/ water (2:1:1, 8 mL) was heated at 80 °C for 17 h. Then, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (20 mL), and the whole was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford the title compound (151 mg, 69%) as colorless amorphous of mp 73–75 °C: R_f 0.21 (hexane/EtOAc 3:1). [α]_D²⁵ +46.1 (*c* 1.35, CHCl₃). ¹H NMR: 1.43 (s, 9H), 1.80 (dddd, *J* = 4.5, 11.5, 12.0, 13.0, 1H), 2.44–2.52 (m, 2H), 2.56–2.65 (m, 2H), 2.80 (ddd, *J* = 2.5, 11.5, 12.0, 1H), 3.15 (br d, *J* = 14.0, 1H), 3.36 (ddd, *J* = 3.5, 11.0, 11.5, 1H), 3.65 (d, *J* = 15.0, 1H), 4.00 (s, 3H), 5.41 (d, *J* = 15.0, 1H), 5.91 (d, *J* = 1.0, 1H), 5.93 (d, *J* = 1.0, 1H), 6.49 (s, 1H). ¹³C NMR: 25.0 (CH₂), 28.2 (CH₃), 37.3 (CH₂), 40.2 (CH₂), 40.2 (CH), 47.1 (CH₂), 56.7 (CH), 59.9 (CH₃), 80.1 (C), 98.9 (CH), 100.8 (CH₂), 122.3 (C), 132.1 (C), 134.9 (C), 139.1 (C), 148.3 (C), 154.6 (C), 208.2 (C). IR (KBr): 2924, 1690, 1620, 1481, 1396, 1304,

1250, 1157, 1072. FABMS m/z : 398 ($M+Na$), 342, 323, 274 ($M-Boc$), 199, 173. HRMS–FAB (m/z): $[M+Na]^+$ calcd. for $C_{20}H_{25}NNaO_6$, 398.1580; found, 398.1569.



(4aSR,11bRS)

-5-*tert*-Butoxycarbonyl-7-methoxy-3-((trimethylsilyl)oxy)-4,4a,6,11b-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (*rac*-15): To a stirred solution of diisopropylamine (0.080 mL, 0.57 mmol) in dry THF (0.4 mL) at 0 °C was added a 1.63 N hexane solution of BuLi (0.33 mL, 0.54 mmol). The mixture was stirred for 40 min at the same temperature. After cooling to –78 °C, *rac*-14 (100 mg, 0.266 mmol) in dry THF (4 mL + 2 x 0.5 mL washing) was added to the mixture. The mixture was stirred for 1 h. Then, dry TMSCl (0.17 mL, 1.35 mmol) was added. After additional 30 min, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (2 mL), and the whole was extracted with Et₂O (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to afford the title compound (112 mg, *ca.* 77%) as yellow oil: R_f 0.67 (hexane/EtOAc 3:1). ¹H NMR: 0.21 (s, 9H), 1.44 (s, 9H), 2.22–2.33 (m, 2H), 2.51–2.61 (m, 2H), 2.73 (dd, J = 5.0, 16.5, 1H), 3.42 (ddd, J = 5.0, 10.5, 10.5, 1H), 3.52 (d, J = 15.0, 1H), 3.99 (s, 3H), 4.97 (d, J = 5.5, 1H), 5.40 (d, J = 15.0, 1H), 5.90 (d, J = 1.5, 1H), 5.91 (d, J = 1.5, 1H), 6.47 (s, 1H).



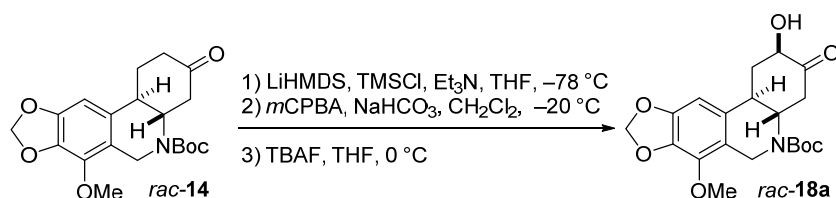
(4aSR,11bRS)-5-*tert*-Butoxycarbonyl-7-methoxy-3-oxo-2-(phenylselenanyl)-2,3,4,4a,6,11b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-3(2H)-one (*rac*-17): To a solution of *rac*-14 (50.8 mg, 0.135 mmol) in dry THF (2 mL) at –78 °C was added a 1.0 M THF solution of LiHMDS (0.20 mL, 0.20 mmol). The reaction mixture was stirred for 1 h at the same temperature, and a solution of PhSeCl (84.3 mg, 0.440 mmol) in dry THF (2 mL) was added. The mixture was stirred for 30 min at –78 °C. The reaction was quenched by the addition of saturated aqueous NH₄Cl (5 mL), and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting residue was purified by column

chromatography (hexane/EtOAc, 9:1) to afford the title compound (46.0 mg, 64%, α : β = 4:1) as brown oil.

α -isomer: R_f 0.44 (hexane/EtOAc 3:1). ^1H NMR: 1.43 (s, 9H), 2.33 (ddd, J = 5.0, 13.5, 13.5, 1H), 2.80 (br d, J = 14.0, 1H), 3.04–3.13 (m, 2H), 3.25 (dd, J = 13.0, 13.0, 1H), 3.36 (m, 1H), 3.71 (d, J = 15.0, 1H), 4.01 (s, 3H), 4.02 (m, 1H), 5.42 (d, J = 15.0, 1H), 5.92 (s, 1H), 5.94 (s, 1H), 6.43 (s, 1H), 7.30–7.32 (m, 3H), 7.56–7.57 (m, 2H).

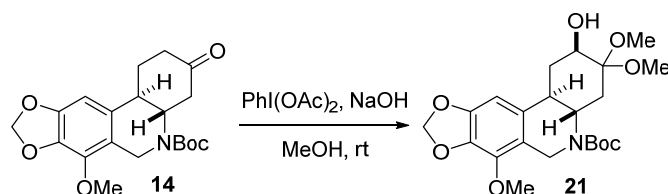
β -isomer: R_f 0.44 (hexane/EtOAc 3:1). ^1H NMR: 1.43 (s, 9H), 1.99 (q, J = 12.5, 1H), 2.54 (m, 1H), 2.60 (dd, J = 12.5, 12.5, 1H), 2.77 (m, 1H), 3.08 (m, 1H), 3.41 (m, 1H), 3.61 (d, J = 15.0, 1H), 3.89 (d, J = 15.0, 1H), 3.98 (s, 3H), 4.21 (dd, J = 6.5, 12.5, 1H), 5.90–5.92 (m, 2H), 6.32 (s, 1H), 7.29–7.35 (m, 3H), 7.62–7.64 (m, 2H).

The diastereomeric ratio was determined based on the integration area of the ^1H NMR singlet signals at 6.43 and 6.32 ppm (ArH of the α - and β -isomers, respectively).



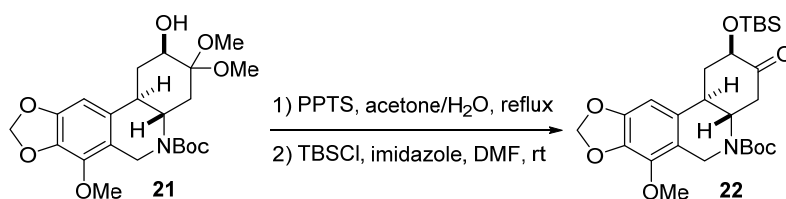
(2*RS*,4*aSR*,11*bRS*)-5-*tert*-Butoxycarbonyl-2-hydroxy-7-methoxy-1,2,4*a*,5,6,11*b*-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine-3(2*H*)-one (rac-18a): To a solution of *rac*-14 (51.2 mg, 0.136 mmol) in dry THF (2.5 mL) at $-78\text{ }^\circ\text{C}$ was added a 1.0 M THF solution of LiHMDS (0.18 mL, 0.18 mmol). The reaction mixture was stirred for 1 h at the same temperature, and TMSCl (0.030 mL, 0.24 mmol) and Et_3N (0.040 mL, 0.29 mmol) were added. After 20 min, the reaction mixture was diluted with Et_2O (10 mL) and washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue (58.0 mg) was used in the next step without further purification. To a solution of the crude product (58.0 mg) in dry CH_2Cl_2 (2 mL) was added *m*CPBA (47.9 mg, 0.21 mmol) at $-20\text{ }^\circ\text{C}$. After 30 min, the reaction was quenched by the addition of 10 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (1 mL) and brine (3 mL), and the whole was extracted with CHCl_3 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue (75.4 mg) was used in the next step without further purification. The crude product (75.4 mg) in THF was added 1.0 M THF solution of TBAF (0.26 mL, 0.26 mmol) at $0\text{ }^\circ\text{C}$. After 30 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL), and the whole was extracted with EtOAc (4 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (hexane/EtOAc, 7:1) to afford the title compound (8.2 mg, 15%) as pale yellow oil: R_f 0.31 (hexane/EtOAc 2:1 x 2). ^1H NMR: 1.45 (s, 9H), 1.68 (ddd, J = 12.0, 12.5, 13.0, 1H), 2.60 (dd, J = 12.5, 12.5, 1H), 2.94–2.99 (m, 2H),

3.31–3.35 (m, 2H), 3.66–3.69 (m, 2H), 4.01 (s, 3H), 4.32 (dd, $J = 7.0, 12.0$, 1H), 5.42 (d, $J = 15.5$, 1H), 5.92 (s, 1H), 5.94 (s, 1H), 6.49 (s, 1H). ^{13}C NMR: 28.2 (CH_3), 34.3 (CH_2), 37.6 (CH_2), 38.6 (CH), 44.2 (CH_2), 57.5 (CH), 59.9 (CH_3), 74.4 (CH), 80.3 (C), 98.9 (CH), 100.8 (CH_2), 122.0 (C), 131.3 (C), 135.0 (C), 139.1 (C), 148.3 (C), 154.6 (C), 207.5 (C). IR (neat): 3425, 3017, 1720, 1690, 1620, 1481, 1396, 1304, 1219, 1157, 1111, 1049. FABMS m/z : 392 ($\text{M}+\text{H}$), 391 (M^+), 390 ($\text{M}-\text{H}$), 334 ($\text{M}-t\text{-Bu}$), 318 ($\text{M}-Ot\text{-Bu}$), 290 ($\text{M}-\text{Boc}$), 218, 154, 136, 57 ($t\text{-Bu}$). HRMS–FAB (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{26}\text{NO}_7$, 392.1709; found, 392.1712.



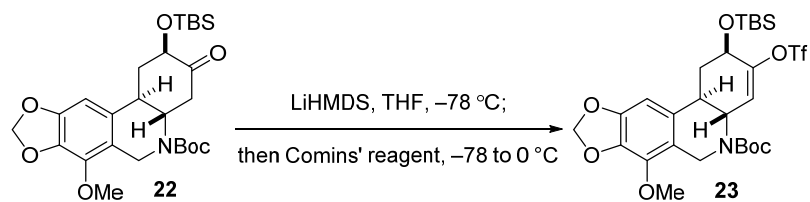
(2*R*,4*aS*,11*bR*)-5-*tert*-Butoxycarbonyl-2-hydroxy-3,3,7-trimethoxy-1,2,3,4,4*a*,5,6,11*b*-octa-

hydro[1,3]dioxolo[4,5-*j*]phenanthridine (21): To a solution of ketone **14** (270 mg, 0.719 mmol) in MeOH (6 mL), were added a 2.5 M methanol solution of NaOH (3.7 mL, 9.3 mmol) and PhI(OAc)₂ (463 mg, 1.44 mmol) at 0 °C. The mixture was warmed to rt and stirred for 2.5 h. Then, the reaction was quenched by the addition of saturated aqueous Na₂S₂O₃ (5 mL), and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 7:2) to afford the title compound (165 mg, 52%) as pale yellow amorphous of mp 71–74 °C: R_f 0.25 (hexane/EtOAc 3:1 x 2). $[\alpha]_D^{25} +14.0$ (c 1.36, CHCl_3). ^1H NMR: 1.42 (dd, $J = 11.0, 14.0$, 1H), 1.45 (s, 9H), 1.71 (ddd, $J = 11.5, 12.5, 13.0$, 1H), 2.41 (d, $J = 9.0$, 1H), 2.43–2.48 (m, 2H), 2.82 (dd, $J = 3.0, 14.0$, 1H), 3.11 (ddd, $J = 3.0, 11.0, 12.0$, 1H), 3.42 (s, 3H), 3.44 (s, 3H), 3.56 (d, $J = 15.0$, 1H), 3.87 (ddd, $J = 4.5, 9.0, 11.5$, 1H), 3.97 (s, 3H), 5.36 (d, $J = 15.0$, 1H), 5.90 (d, $J = 1.5$, 1H), 5.91 (d, $J = 1.5$, 1H), 6.46 (s, 1H). ^{13}C NMR: 28.4 (CH_3), 33.6 (CH_2), 36.0 (CH_2), 37.8 (CH_2), 39.4 (CH), 49.1 (CH_3), 50.8 (CH_3), 54.1 (CH), 59.9 (CH_3), 74.9 (CH), 79.7 (C), 98.9 (C), 99.0 (CH), 100.7 (CH_2), 122.1 (C), 132.9 (C), 134.8 (C), 139.0 (C), 148.1 (C), 155.0 (C). IR (KBr): 3495, 2978, 2939, 1690, 1620, 1481, 1396, 1304, 1215, 1165, 1049. EIMS m/z : 437 (M^+), 405 ($\text{M}-\text{MeOH}$), 380 ($\text{M}-t\text{-Bu}$), 348, 336 ($\text{M}-\text{Boc}$), 332, 304, 286, 249, 217, 57 ($t\text{-Bu}$). FABMS m/z : 460 ($\text{M}+\text{Na}$). HRMS–FAB (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{31}\text{NNaO}_8$, 460.1947; found, 460.1929.

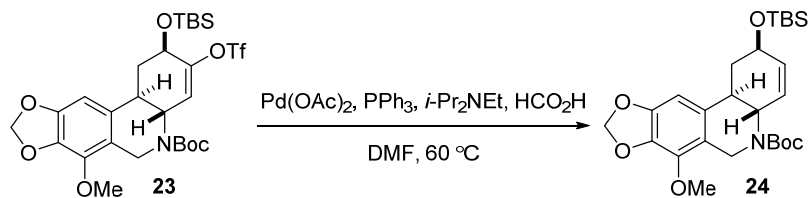


(2R,4aS,11bR)-5-tert-Butoxycarbonyl-2-hydroxy-7-methoxy-1,2,4a,5,6,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridine-3(2H)-one (18a): To a solution of dimethyl acetal **21** (75.5 mg, 0.173 mmol) in acetone/water (10:1, 3.3 mL) was added PPTS (8.7 mg, 0.035 mmol) at rt. The mixture was heated for 1.5 h under reflux. The reaction was quenched by the addition of saturated aqueous NaHCO₃ (5 mL), and the whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the title compound (82.1 mg), which was used directly in the next step without further purification. An analytical sample was obtained by column chromatography (hexane/EtOAc 3:1) as pale yellow solids of mp 166–169 °C: $[\alpha]_D^{25} +22.1$ (*c* 1.23, CHCl₃). ¹H and ¹³C NMR, IR, MS were in agreement with those of the racemic sample (*vide supra*).

(2R,4aS,11bR)-5-tert-Butoxycarbonyl-2-(tert-butyldimethylsiloxy)-7-methoxy-1,2,4a,5,6,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridine-3(2H)-one (22): To a solution of **18a** (82.1 mg) in dry DMF (1 mL) were added TBSCl (33.7 mg, 0.224 mmol) and imidazole (30.6 mg, 0.450 mmol) at rt. The mixture was stirred for 4.5 h. Then, TBSCl (32.2 mg, 0.214 mmol) and imidazole (30.3 mg, 0.445 mmol) were added again to the mixture. After additional 1 h, the reaction was quenched by the addition of water (5 mL), and the whole was extracted with EtOAc (10 mL + 2 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 15:1) to afford the title compound (69.1 mg, 79%) as colorless amorphous of mp 81–84 °C: *R*_f 0.67 (hexane/EtOAc 2:1). $[\alpha]_D^{25} +29.7$ (*c* 1.49, CHCl₃). ¹H NMR: 0.07 (s, 3H), 0.18 (s, 3H), 0.94 (s, 9H), 1.43 (s, 9H), 1.86 (ddd, *J* = 12.0, 12.0, 12.5, 1H), 2.52 (dd, *J* = 12.5, 12.5, 1H), 2.74 (ddd, *J* = 3.0, 7.0, 12.5, 1H), 2.93 (ddd, *J* = 3.0, 11.5, 12.0, 1H), 3.18 (dd, *J* = 3.5, 12.5, 1H), 3.30 (ddd, *J* = 3.5, 11.5, 12.5, 1H), 3.64 (d, *J* = 15.0, 1H), 4.00 (s, 3H), 4.36 (dd, *J* = 7.0, 12.0, 1H), 5.42 (d, *J* = 15.0, 1H), 5.92 (s, 1H), 5.94 (s, 1H), 6.50 (s, 1H). ¹³C NMR: –5.7 (CH₃), –4.7 (CH₃), 18.3 (C), 25.6 (CH₃), 28.1 (CH₃), 35.1 (CH₂), 37.3 (CH₂), 39.1 (CH), 45.2 (CH₂), 57.0 (CH), 59.8 (CH₃), 76.1 (CH), 80.0 (C), 98.7 (CH), 100.7 (CH₂), 122.0 (C), 131.5 (C), 134.9 (C), 139.1 (C), 148.3 (C), 154.5 (C), 205.3 (C). IR (KBr): 2932, 2862, 1728, 1690, 1620, 1481, 1396, 1250, 1150, 1072, 1042. EIMS *m/z*: 448 (M–*t*-Bu), 432 (M–*O**t*-Bu), 404 (M–Boc), 392, 348, 262, 218, 204, 57 (*t*-Bu). FABMS *m/z*: 506 (M+H), 505 (M⁺). HRMS–FAB (*m/z*): [M+H]⁺ calcd. for C₂₆H₄₀NO₇Si, 506.2574; found, 506.2569.

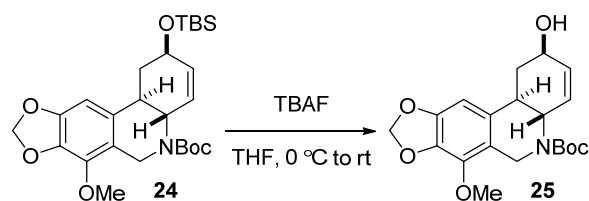


(2*R*,4*aR*,11*bR*)-5-*tert*-Butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)-7-methoxy-3-(trifluoromethanesulfonyloxy)-1,2,4*a*,5,6,11*b*-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine (23): To a solution of ketone **22** (389 mg, 0.769 mmol) in dry THF (8 mL) at -78°C was added a 1.0 M THF solution of LiHMDS (1.6 mL, 1.6 mmol). The mixture was stirred for 1 h, and a solution of *N*-(5-chloropyrid-2-yl)bis(trifluoromethanesulfonyl)imide (605 mg, 1.54 mmol) in dry THF (2 mL) was added. The mixture was stirred for 30 min at -78°C and for 30 min at 0°C . The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL), and the whole was extracted with EtOAc (3 x 30 mL). 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/EtOAc 20:1) to afford the title compound (452 mg, 92%) as pale yellow amorphous of mp $65\text{--}68^{\circ}\text{C}$: R_f 0.52 (hexane/EtOAc 5:1). $[\alpha]_D^{25} +20.9$ (c 2.02, CHCl_3). ^1H NMR: 0.18 (s, 6H), 0.95 (s, 9H), 1.45 (s, 9H), 1.85 (ddd, $J = 9.0, 12.5, 13.0$, 1H), 2.74 (ddd, $J = 2.5, 7.0, 12.5$, 1H), 2.80 (m, 1H), 3.77 (d, $J = 15.0$, 1H), 3.85 (ddd, $J = 1.5, 3.0, 11.0$, 1H), 4.01 (s, 3H), 4.64 (m, 1H), 5.28 (br s, 1H), 5.92 (d, $J = 1.5$, 1H), 5.94 (d, $J = 1.5$, 1H), 6.22 (s, 1H), 6.43 (s, 1H). ^{13}C NMR: -5.0 (CH_3), -4.6 (CH_3), 17.9 (C), 25.7 (CH_3), 28.2 (CH_3), 34.5 (CH_2), 37.6 (CH), 38.7 (CH_2), 55.6 (CH), 59.8 (CH_3), 67.7 (CH), 80.7 (C), 98.2 (CH), 100.9 (CH_2), 118.4 (q, $J_{\text{CF}} = 320$, C), 121.4 (C), 123.2 (CH), 131.0 (C), 134.9 (C), 139.5 (C), 148.5 (C), 155.0 (C). IR (naet): 3017, 2932, 2862, 1690, 1620, 1481, 1396, 1250, 1211, 1150, 1077, 1042. EIMS m/z : 580 ($\text{M}-t\text{-Bu}$), 524, 480, 448, 387, 316, 300, 272, 256, 204, 57 ($t\text{-Bu}$). FABMS m/z : 660 ($\text{M}+\text{Na}$). HRMS–FAB (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{27}\text{H}_{38}\text{F}_3\text{NNaO}_9\text{SSi}$, 660.1886; found, 660.1885.

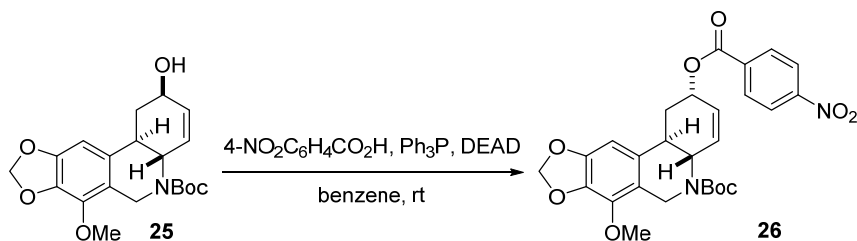


(2*R*,4*aS*,11*bR*)-5-*tert*-Butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)-2-(*tert*-butyldimethylsiloxy)-7-methoxy-1,2,4*a*,5,6,11*b*-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine (24): To a suspension of enol triflate **23** (219 mg, 0.343 mmol), $i\text{-PrNEt}_2$ (0.180 mL, 1.03 mmol), $\text{Pd}(\text{OAc})_2$ (11.4 mg, 0.0508 mmol), and PPh_3 (27.0 mg, 0.103 mmol) in dry DMF (3.5 mL) was added 99% formic acid (29.0 μL , 0.769 mmol). The resulting pale brown suspension was stirred for 80 min at

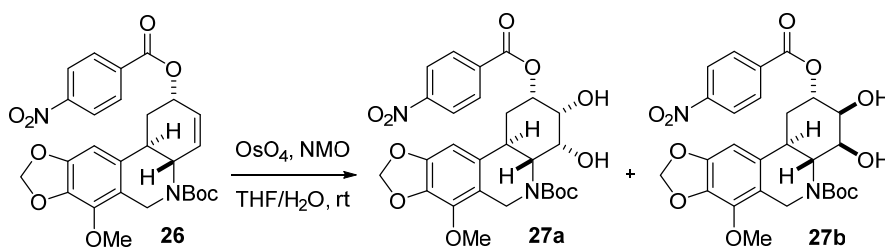
60 °C. Then, the mixture was diluted with EtOAc (20 mL), washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 20:1) to afford the title compound (131 mg, 78%) as colorless amorphous of mp 54–57 °C: R_f 0.58 (hexane/EtOAc 5:1). $[\alpha]_D^{25} +26.0$ (*c* 2.09, CHCl₃). ¹H NMR: 0.13 (s, 6H), 0.93 (s, 9H), 1.44 (s, 9 H), 1.69 (ddd, *J* = 10.0, 12.0, 12.5, 1H), 2.58 (dd, *J* = 6.5, 12.5, 1H), 2.77 (dd, *J* = 11.5, 12.0, 1H), 3.69 (d, *J* = 11.5, 1H), 3.89 (br s, 1H), 3.99 (s, 3H), 4.57 (m, 1H), 5.13 (br s, 1H), 5.60 (d, *J* = 10.0, 1H), 5.90 (d, *J* = 0.5, 1H), 5.91 (d, *J* = 0.5, 1H), 6.05 (d, *J* = 10.0, 1H), 6.50 (s, 1H). ¹³C NMR: –4.6 (CH₃), –4.5 (CH₃), 18.2 (C), 25.9 (CH₃), 28.4 (CH₃), 35.0 (CH₂), 38.1 (CH), 39.7 (CH₂), 56.9 (CH), 59.8 (CH₃), 68.9 (CH), 80.0 (C), 98.6 (CH), 100.7 (CH₂), 121.5 (C), 130.5 (CH), 131.4 (CH), 132.8 (C), 134.6 (C), 139.4 (C), 148.3 (C), 155.5 (C). IR (naet): 3009, 2932, 2862, 1690, 1620, 1481, 1389, 1250, 1219, 1165, 1072. EIMS *m/z*: 432 (M–*t*-Bu), 388 (M–Boc), 376, 357, 332, 301 (M–*t*-Bu–OTBS), 256, 240, 57 (*t*-Bu). FABMS *m/z*: 490 (M+H), 489 (M⁺). HRMS–FAB (*m/z*): [M+H]⁺ calcd. for C₂₆H₄₀NO₆Si, 490.2625; found, 490.2625.



(2*R*,4*aS*,11*bR*)-5-*tert*-Butoxycarbonyl-2-hydroxy-7-methoxy-1,2,4*a*,5,6,11*b*-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine (25): To a solution of TBS ether **24** (228 mg, 0.466 mmol) in dry THF (4.0 mL) was added a 1.0 M THF solution of TBAF (0.93 mL, 0.93 mmol) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (10 mL), and the whole was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford the title compound (167 mg, 95%) as colorless amorphous of mp 77–80 °C: R_f 0.25 (hexane/EtOAc 2:1). $[\alpha]_D^{25} +32.3$ (*c* 1.53, CHCl₃). ¹H NMR: 1.44 (s, 9 H), 1.60 (ddd, *J* = 9.5, 12.5, 13.0, 1H), 1.74 (m, 1H), 2.76–2.81 (m, 2H), 3.68 (d, *J* = 10.5, 1H), 3.90 (d, *J* = 15.0, 1H), 3.99 (s, 3H), 4.56 (br s, 1H), 5.13 (d, *J* = 15.0, 1H), 5.70 (d, *J* = 10.0, 1H), 5.91 (d, *J* = 0.5, 1H), 5.92 (d, *J* = 0.5, 1H), 6.13 (d, *J* = 10.0, 1H), 6.49 (s, 1H). ¹³C NMR: 28.4 (CH₃), 34.7 (CH₂), 38.1 (CH), 39.6 (CH₂), 57.0 (CH), 59.8 (CH₃), 68.0 (CH), 80.1 (C), 98.6 (CH), 100.7 (CH₂), 121.4 (C), 129.9 (CH), 132.0 (CH), 132.6 (C), 134.6 (C), 139.3 (C), 148.3 (C), 155.5 (C). IR (KBr): 3479, 2978, 2932, 2878, 1666, 1620, 1481, 1396, 1327, 1219, 1165, 1049. EIMS *m/z*: 375 (M⁺), 318 (M–*t*-Bu), 301, 274 (M–Boc), 256, 239, 57 (*t*-Bu). FABMS *m/z*: 376 (M+H), 375 (M⁺), 374 (M–H). HRMS–FAB (*m/z*): [M+H]⁺ calcd. for C₂₀H₂₆NO₆, 376.1760; found, 376.1756.



(2*S*,4*aS*,11*bR*)-5-*tert*-Butoxycarbonyl-7-methoxy-2-(4-nitrobenzoyloxy)-1,2,4*a*,5,6,11*b*-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine (26): To a solution of allylic alcohol **25** (78.8 mg, 0.210 mmol), 4-nitrobenzoic acid (70.5 mg, 0.422 mmol), and Ph₃P (110 mg, 0.419 mmol) in dry benzene (4.0 mL), was added a 40% solution of DEAD in toluene (0.19 mL, 0.42 mmol) at rt. After 20 min, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (8 mL), and the whole was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 10:1) to afford the title compound (95.3 mg, 87%) as yellow solids of mp 94–97 °C: R_f 0.60 (hexane/EtOAc 2:1). [α]_D²⁵ –59.7 (*c* 1.75, CHCl₃). ¹H NMR: 1.46 (s, 9H), 2.07 (ddd, *J* = 4.5, 13.0, 14.0, 1H), 2.67 (br d, *J* = 14.0, 1H), 3.00 (ddd, *J* = 2.0, 12.0, 13.0, 1H), 3.63 (d, *J* = 12.0, 1H), 3.96 (d, *J* = 15.5, 1H), 4.01 (s, 3H), 5.21 (d, *J* = 15.5, 1H), 5.71 (m, 1H), 5.88 (m, 1H), 5.91 (s, 2H), 6.45 (d, *J* = 9.5, 1H), 6.47 (s, 1H), 8.21 (d, *J* = 9.0, 2H), 8.27 (d, *J* = 9.0, 2H). ¹³C NMR: 28.4 (CH₃), 30.8 (CH₂), 33.8 (CH), 39.7 (CH₂), 56.8 (CH), 59.8 (CH₃), 68.1 (CH), 80.2 (C), 98.6 (CH), 100.8 (CH₂), 121.6 (C), 122.5 (CH), 123.4 (CH), 130.7 (CH), 132.4 (C), 134.7 (C), 135.6 (C), 137.6 (CH), 139.5 (C), 148.4 (C), 150.4 (C), 155.3 (C), 164.0 (C). IR (KBr): 2978, 1720, 1690, 1612, 1528, 1478, 1396, 1373, 1342, 1273, 1173, 1103. EIMS *m/z*: 467 (M–*t*-Bu), 301 (M–*t*-Bu–4-NO₂C₆H₄CO₂), 256, 241, 57 (*t*-Bu). FABMS *m/z*: 547 (M+Na). HRMS–FAB (*m/z*): [M+Na]⁺ calcd. for C₂₇H₂₈N₂NaO₉, 547.1693; found, 547.1679.

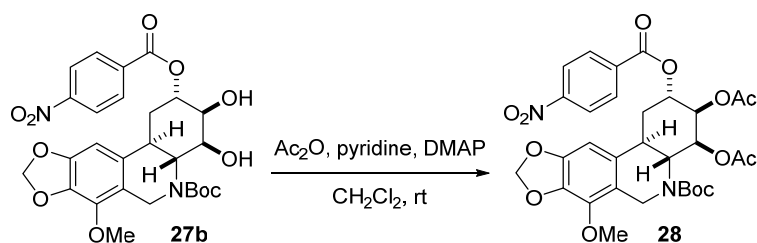


(2*S*,3*R*,4*R*,4*aR*,11*bR*)- and (2*S*,3*S*,4*S*,4*aR*,11*bR*)-5-*tert*-Butoxycarbonyl-3,4-dihydroxy-7-methoxy-2-(4-nitrobenzoyloxy)-1,2,3,4,4*a*,5,6,11*b*-octahydro[1,3]dioxolo[4,5-*j*]phenanthridine (27*a* and 27*b*): To a solution of **26** (72.6 mg, 0.138 mmol) in THF/water (6:1, 3.0 mL), were added NMO (32.3 mg, 0.276 mmol) and a 4% water solution of OsO₄ (0.42 mL, 0.069 mmol) at rt. After 33 h, the reaction was quenched with saturated aqueous Na₂S₂O₃ (5 mL), and the whole was

extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 3:1) to afford the title compounds (12.7 mg and 63.5 mg, 16% and 83%, respectively).

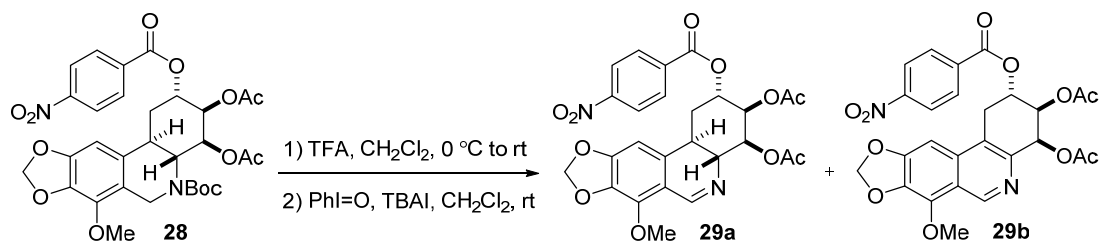
27a: Yellow solids of 145–147 °C. *R*_f 0.36 (hexane/EtOAc 1:1). $[\alpha]_D^{25} +17.8$ (*c* 0.50, CHCl₃). ¹H NMR: 1.47 (s, 9H), 1.82 (ddd, *J* = 2.5, 12.0, 14.5, 1H), 2.53 (br s, 1H), 2.69 (ddd, *J* = 3.0, 3.0, 14.5, 1H), 2.87 (br d, *J* = 9.0, 1H), 3.24 (br d, *J* = 11.5, 1H), 3.35 (ddd, *J* = 3.0, 11.5, 12.0, 1H), 3.72 (d, *J* = 13.5, 1H), 3.88 (m, 1H), 3.99 (s, 3H), 4.71 (br s, 1H), 5.43 (br s, 1H), 5.66 (m, 1H), 5.90 (d, *J* = 1.5, 1H), 5.91 (d, *J* = 1.5, 1H), 6.43 (s, 1H), 8.28 (s, 4H). ¹³C NMR: 28.3 (CH), 28.4 (CH₃), 30.0 (CH₂), 39.6 (CH₂), 60.1 (CH₃), 60.2 (CH), 69.4 (CH), 71.2 (CH), 72.7 (CH), 80.6 (C), 99.3 (CH), 100.9 (CH₂), 122.0 (C), 123.6 (CH), 131.0 (CH), 132.2 (C), 134.9 (C), 135.5 (C), 139.2 (C), 148.5 (C), 150.6 (C), 155.3 (C), 164.4 (C). EIMS *m/z*: 558 (M⁺), 502, 457 (M–Boc), 335 (M–*t*-Bu–4-NO₂C₆H₄CO₂), 290, 272, 218, 204, 150 (4-NO₂C₆H₄CO), 57 (*t*-Bu). FABMS *m/z*: 559 (M+H). 558 (M⁺), 557 (M–H). HRMS–FAB (*m/z*): [M+H]⁺ calcd. for C₂₇H₃₁N₂O₁₁, 559.1928; found, 559.1932.

27b: Yellow solids of mp 205–207. *R*_f 0.58 (hexane/EtOAc 1:1). $[\alpha]_D^{25} +1.40$ (*c* 3.04, CHCl₃). ¹H NMR: 1.49 (s, 9H), 2.30 (ddd, *J* = 2.5, 13.0, 14.0, 1H), 2.50 (br d, *J* = 14.0, 1H), 2.80 (ddd, *J* = 2.5, 11.0, 13.0, 1H), 3.01 (br s, 1H), 3.66 (d, *J* = 15.0, 1H), 3.70 (dd, *J* = 11.0, 11.0, 1H), 4.01 (s, 3H), 4.12 (m, 1H), 4.19 (br s, 1H), 5.35 (d, *J* = 15.0, 1H), 5.61 (m, 1H), 5.92 (s, 1H), 5.93 (s, 1H), 6.12 (br s, 1H), 6.48 (s, 1H), 8.16 (d, *J* = 9.0, 2H), 8.28 (d, *J* = 9.0, 2H). ¹³C NMR: 27.3 (CH₂), 28.3 (CH₃), 34.6 (CH), 38.6 (CH₂), 57.9 (CH), 60.0 (CH₃), 70.8 (CH), 72.2 (CH), 73.8 (CH), 81.9 (C), 99.3 (CH), 100.9 (CH₂), 121.9 (C), 123.6 (CH), 130.7 (CH), 131.9 (C), 134.9 (C), 135.2 (C), 139.1 (C), 148.6 (C), 150.6 (C), 159.6 (C), 163.3 (C). IR (neat): 3425, 3024, 2932, 1720, 1643, 1528, 1489, 1412, 1342, 1273, 1219, 1157, 1103, 1072. FABMS *m/z*: 559 (M+H), 557 (M–H), 503, 459, 457 (M–Boc), 274, 204, 154, 136, 57 (*t*-Bu). HRMS–FAB (*m/z*): [M+H]⁺ calcd. for C₂₇H₃₁N₂O₁₁, 559.1928; found, 559.1924.



(2*S*,3*R*,4*S*,4*aR*,11*bR*)-3,4-Diacetoxy-5-(*tert*-butoxycarbonyl)-7-methoxy-2-(4-nitrobenzoyloxy)-1,2,3,4,4*a*,5,6,11*b*-octahydro[1,3]dioxolo[4,5-*j*]phenanthridine (28): To a solution of diol **27b** (63.3 mg, 0.113 mmol) in dry CH₂Cl₂ (2 mL) were added pyridine (0.91 mL, 11 mmol), DMAP

(7.1 mg, 0.058 mmol), and Ac₂O (0.53 mL, 5.6 mmol) at rt. After 1 h, the mixture was diluted with EtOAc (20 mL), washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 3:1) to afford the title compound (70.4 mg, 97%) as pale yellow solids of mp 133–135 °C: R_f 0.29 (toluene/acetone 19:1 x 3). [α]_D²⁵ +40.4 (*c* 1.19, CHCl₃). ¹H NMR (60 °C): 1.44 (s, 9H), 2.04 (s, 3H), 2.08 (m, 1H), 2.14 (s, 3H), 2.61 (br d, *J* = 14.5, 1H), 3.05 (m, 1H), 3.82 (dd, *J* = 11.0, 11.0, 1H), 4.01 (s, 3H), 4.22 (br s, 1H), 4.78 (br s, 1H), 5.41 (br s, 1H), 5.61 (br s, 1H), 5.80 (m, 1H), 5.88 (s, 1H), 5.89 (s, 1H), 6.43 (s, 1H), 8.24 (d, *J* = 9.0, 2H), 8.30 (d, *J* = 9.0, 2H). ¹³C NMR (60 °C): 20.8 (CH₃), 20.8 (CH₃), 28.3 (CH₃), 29.5 (CH₂), 34.9 (CH), 42.1 (CH₂), 56.4 (CH), 59.7 (CH₃), 69.6 (CH), 70.9 (CH), 71.0 (CH), 80.2 (C), 99.6 (CH), 100.9 (CH₂), 122.3 (C), 123.7 (CH), 131.0 (CH), 131.2 (C), 134.8 (C), 135.0 (C), 139.8 (C), 148.6 (C), 151.1 (C), 155.7 (C), 163.3 (C), 169.2 (C), 170.1 (C). IR (neat): 2974, 2920, 1748, 1732, 1694, 1616, 1528, 1481, 1458, 1439, 1366, 1350, 1319, 1265, 1234, 1223, 1157, 1099, 1061, 1042. EIMS *m/z*: 642 (M⁺), 586, 541 (M–Boc), 527, 499, 466, 423, 359, 316, 299, 272, 256, 218, 204, 150 (4-NO₂C₆H₄CO), 57 (*t*-Bu). FABMS *m/z*: 643 (M+H), 642 (M⁺). HRMS–FAB (*m/z*): [M+H]⁺ calcd. for C₃₁H₃₅N₂O₁₃, 643.2139; found, 643.2131.



(2*S*,3*R*,4*S*,4*aR*,11*bR*)-3,4-Diacetoxy-7-methoxy-2-(4-nitrobenzoyloxy)-1,2,3,4,4*a*,11*b*-octa-

hydro[1,3]dioxolo[4,5-*j*]phenanthridine (S6): To a solution of **28** (65.4 mg, 0.102 mmol) in CH₂Cl₂ (1.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was warmed to rt and stirred for 30 min. The TFA was azeotropically removed with toluene, and the remaining residue was dissolved in CHCl₃ (20 mL), washed with saturated aqueous NaHCO₃ (2 x 5 mL) and brine, dried over Na₂SO₄, and concentrated *in vacuo* to give the title compound (63.8 mg), which was used directly in the next step without further purification. An analytical sample was obtained by column chromatography (NH silica, hexane/EtOAc 3:1) as yellow solids of mp 125–128 °C: R_f 0.41 (hexane/EtOAc 1:1 x 3). [α]_D²⁵ +49.3 (*c* 1.08, CHCl₃). ¹H NMR: 1.90 (ddd, *J* = 2.5, 13.0, 14.5, 1H), 1.95 (br s, 1H), 2.09 (s, 3H), 2.12 (s, 3H), 2.54 (dt, *J* = 14.5, 2.5, 1H), 2.98 (m, 1H), 3.05 (dd, *J* = 10.5, 10.5, 1H), 3.91 (dd, *J* = 1.5, 16.5, 1H), 3.99 (s, 3H), 4.13 (d, *J* = 16.5, 1H), 5.21 (dd, *J* = 3.0, 10.5, 1H), 5.42 (ddd, *J* = 2.5, 3.0, 3.0, 1H), 5.55 (dd, *J* = 3.0, 3.0, 1H), 5.86 (d, *J* = 1.5, 1H), 5.87 (d, *J* = 1.5, 1H), 6.43 (s, 1H), 8.23 (d, *J* = 9.0, 2H), 8.29 (d, *J* = 9.0, 2H). ¹³C NMR: 20.8 (CH₃), 20.9 (CH₃), 28.9 (CH₂), 36.3 (CH), 43.9 (CH₂), 55.3 (CH), 59.3 (CH₃), 67.9 (CH), 71.0 (CH), 72.7 (CH), 99.3 (CH), 100.7 (CH₂), 120.2

(C), 123.7 (CH), 129.6 (C), 130.9 (CH), 134.0 (C), 134.7 (C), 139.7 (C), 148.0 (C), 150.7 (C), 163.2 (C), 169.4 (C), 170.4 (C). IR (KBr): 3464, 2955, 2893, 1751, 1620, 1528, 1481, 1420, 1373, 1273, 1242, 1103, 1057. EIMS m/z : 542 (M^+), 541 ($M-H$), 499 ($M-Ac$), 423, 374, 316, 272, 256, 218, 204, 150 ($4-NO_2C_6H_4CO$). FABMS m/z : 543 ($M+H$). HRMS-FAB (m/z): $[M+H]^+$ calcd. for $C_{26}H_{27}N_2O_{11}$, 543.1615; found, 543.1619.

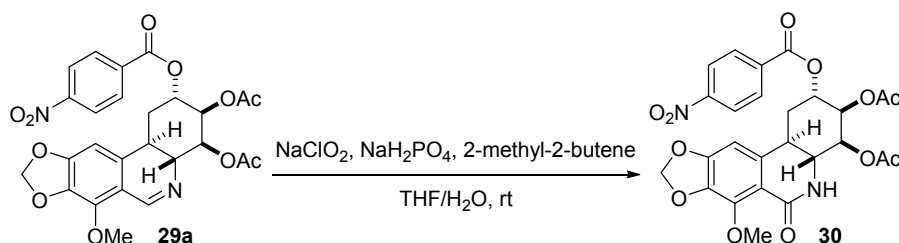
(2*S*,3*R*,4*S*,4*aR*,11*bR*)-3,4-Diacetoxy-7-methoxy-2-(4-nitrobenzoyloxy)-1,2,3,4,4*a*,11*b*-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine (29a) and

(2*S*,3*R*,4*S*)-3,4-diacetoxy-7-Methoxy-2-(4-nitrobenzoyloxy)-1,2,3,4-tetrahydro-[1,3]dioxolo[4,5-*j*]phenanthridine (29b): To a suspension of $PhI=O$ (44.8 mg, 0.204 mmol) in dry CH_2Cl_2 (2 mL), was added Bu_4NI (7.6 mg, 0.021 mmol) at rt. After 10 min, amine **S6** (63.8 mg) in dry CH_2Cl_2 (2 mL + 0.5 mL washing x 2) was added at 0 °C over 5 min, and the mixture was warmed to rt. After 1.5 h, another portion of $PhI=O$ (22.4 mg, 0.102 mmol) was added to the mixture. After additional 30 min, the reaction was quenched by the addition of 10% $Na_2S_2O_3$ (10 mL), and the whole was extracted with EtOAc (3 x 15 mL). 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/EtOAc 1:1) to afford the title compounds (45.9 mg and 3.4 mg, 83% and 6%, respectively).

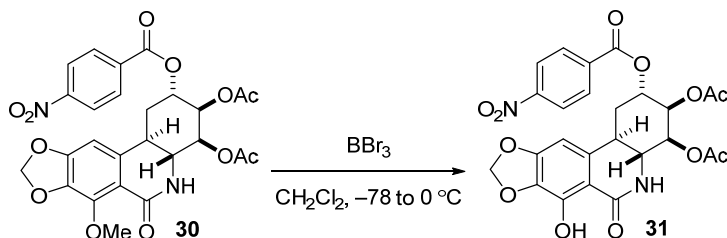
29a: Yellow solids of mp 126–128 °C. R_f 0.50 ($CHCl_3$ /EtOAc 1:1). $[\alpha]_D^{25} -6.85$ (c 1.05, $CHCl_3$). 1H NMR: 2.06 (ddd, $J = 3.0, 13.0, 14.5$, 1H), 2.11 (s, 3H), 2.14 (s, 3H), 2.60 (ddd, $J = 3.0, 3.0, 14.5$, 1H), 2.81 (m, 1H), 3.39 (m, 1H), 4.07 (s, 3H), 5.46 (ddd, $J = 3.0, 3.0, 3.0$, 1H), 5.50 (dd, $J = 3.0, 11.0$, 1H), 5.63 (dd, $J = 3.0, 3.0$, 1H), 5.96 (d, $J = 1.5$, 1H), 5.98 (d, $J = 1.5$, 1H), 6.47 (s, 1H), 8.21 (d, $J = 9.0$, 2H), 8.30 (d, $J = 9.0$, 2H), 8.64 (d, $J = 2.5$, 1H). ^{13}C NMR: 20.8 (CH_3), 21.1 (CH_3), 27.2 (CH_2), 32.0 (CH), 57.7 (CH), 60.0 (CH_3), 68.6 (CH), 70.4 (CH), 71.8 (CH), 98.5 (CH), 101.4 (CH_2), 114.8 (C), 123.7 (CH), 131.0 (CH), 134.5 (C), 134.6 (C), 134.9 (C), 141.9 (C), 150.8 (C), 152.1 (C), 156.3 (CH), 163.3 (C), 169.3 (C), 170.7 (C). IR (neat): 3024, 2955, 1744, 1628, 1597, 1528, 1481, 1435, 1373, 1273, 1234, 1103, 1049. EIMS m/z : 497 ($M-Ac$), 421, 374 ($M-4-NO_2C_6H_4CO_2$), 330, 314, 272, 253, 217, 150 ($4-NO_2C_6H_4CO$). FABMS m/z : 541 ($M+H$). HRMS-FAB (m/z): $[M+H]^+$ calcd. for $C_{26}H_{25}N_2O_{11}$, 541.1458; found, 541.1459.

29b: Pale yellow oil. R_f 0.60 ($CHCl_3$ /EtOAc 1:1). $[\alpha]_D^{16} +63.2$ (c 0.50, $CHCl_3$). 1H NMR: 2.20 (s, 3H), 2.16 (s, 3H), 3.08 (dd, $J = 8.5, 16.5$, 1H), 3.88 (dd, $J = 6.5, 16.5$, 1H), 4.23 (s, 3H), 5.72 (dd, $J = 4.0, 10.5$, 1H), 5.87 (ddd, $J = 6.5, 8.5, 10.5$, 1H), 6.09 (s, 1H), 6.10 (s, 1H), 6.59 (d, $J = 4.0$, 1H), 6.85 (s, 1H), 8.23 (d, $J = 8.5$, 2H), 8.32 (d, $J = 8.5$, 2H), 9.34 (s, 1H). ^{13}C NMR: 20.8 (CH_3), 21.0 (CH_3), 29.9 (CH_2), 60.1 (CH_3), 69.2 (CH), 70.3 (CH), 70.9 (CH), 93.4 (CH), 101.8 (CH_2), 120.0 (C), 122.0 (C), 123.8 (CH), 130.9 (CH), 132.8 (C), 134.3 (C), 134.9 (C), 137.8 (C), 143.0 (C), 146.3 (CH), 150.8 (C), 153.4 (C), 164.2 (C), 170.0 (C), 170.1 (C). IR (neat): 2924, 2855, 1744, 1643, 1612, 1528, 1458, 1373, 1273, 1234, 1096, 1049. EIMS m/z : 539 (M^++H), 538 (M^+), 495, 479, 453, 419,

371, 346, 328, 312, 286, 270, 255. HRMS–ESI (m/z): $[M+H]^+$ calcd. for $C_{26}H_{23}N_2O_{11}$, 539.1302; found, 539.1304.

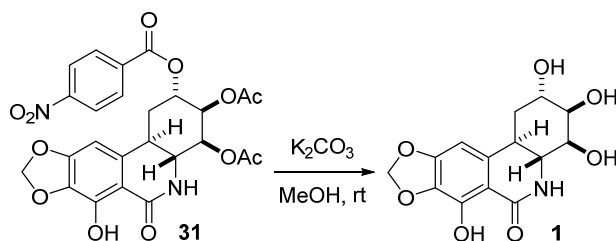


3,4-*O*-Diacetyl-7-*O*-methyl-2-*O*-(4-nitrobenzoyl)-*trans*-dihydronarciclasine (30): To a suspension of $NaClO_2$ (36.5 mg, 0.404 mmol) in THF (1.5 mL) were added a 2.0 M THF solution of 2-methyl-2-butene (0.40 mL, 0.80 mmol), a 1.0 M aqueous solution of NaH_2PO_4 (0.40 mL, 0.40 mmol), and then a solution of imine **29a** (43.7 mg, 0.0809 mmol) in THF (1.5 mL + 0.50 mL washing x 2) at rt. After 8.5 h, the mixture was diluted with EtOAc (20 mL) and washed with water, 10% $Na_2S_2O_3$, and brine (5 mL each). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 1:2) to afford the title compound (43.4 mg, 96%) as pale yellow solids of mp 167–169 °C: R_f 0.38 (hexane/acetone 1:1). $[\alpha]_D^{25} +61.8$ (c 1.00, $CHCl_3$). 1H NMR: 2.04 (m, 1H), 2.09 (s, 3H), 2.12 (s, 3H), 2.58 (m, 1H), 3.16 (ddd, $J = 3.5, 12.0, 13.0$, 1H), 3.76 (dd, $J = 11.0, 12.0$, 1H), 4.07 (s, 3H), 5.28 (dd, $J = 3.0, 11.0$, 1H), 5.47 (ddd, $J = 2.5, 2.5, 3.5$, 1H), 5.59 (dd, $J = 3.0, 3.5$, 1H), 6.00 (s, 1H), 6.02 (s, 1H), 6.31 (br s, 1H), 6.48 (s, 1H), 8.22 (d, $J = 9.0$, 2H), 8.32 (d, $J = 9.0$, 2H). ^{13}C NMR: 20.7 (CH_3), 20.8 (CH_3), 27.0 (CH_2), 36.2 (CH), 52.0 (CH), 60.8 (CH_3), 67.1 (CH), 70.2 (CH), 71.6 (CH), 98.9 (CH), 101.8 (CH_2), 115.4 (C), 123.8 (CH), 131.0 (CH), 134.4 (C), 136.9 (C), 137.2 (C), 145.1 (C), 150.9 (C), 152.1 (C), 163.2 (C), 163.7 (C), 169.1 (C), 170.4 (C). IR (KBr): 3433, 2924, 1751, 1666, 1612, 1528, 1481, 1443, 1340, 1273, 1234, 1096, 1057. EIMS m/z : 556 (M^+), 497 ($M-OAc$), 470 ($M-2Ac$), 437, 390 ($M-4-NO_2C_6H_4CO_2$), 346, 330, 304 ($M-4-NO_2C_6H_4CO_2-2Ac$), 241, 150 ($4-NO_2C_6H_4CO$). FABMS m/z : 557 ($M+H$). HRMS–FAB (m/z): $[M+H]^+$ calcd. for $C_{26}H_{25}N_2O_{12}$, 557.1407; found, 557.1398.



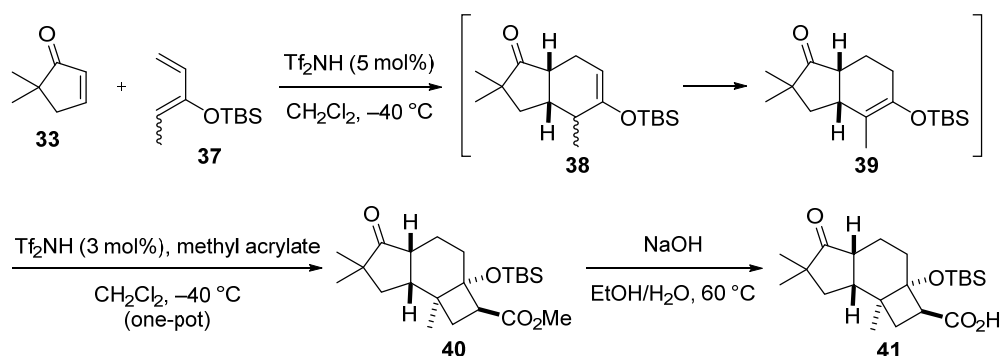
3,4-*O*-Diacetyl-2-*O*-(4-nitrobenzoyl)-*trans*-dihydronarciclasine (31): To a solution of methyl ether **30** (40.4 mg, 0.0726 mmol) in dry CH_2Cl_2 (4 mL) was added a 1 M CH_2Cl_2 solution of BBr_3

(94 μ L, 0.094 mmol) at -78 $^{\circ}$ C. The mixture was warmed to 0 $^{\circ}$ C and stirred for 30 min. Then, 28% NH_4OH (5 mL) was added at 0 $^{\circ}$ C. After 30 min, the mixture was extracted with EtOAc (15 mL, 2 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (CHCl_3 /hexane 5:1) to afford the title compound (27.9 mg, 71%) as pale yellow solids of mp 168 – 170 $^{\circ}$ C: R_f 0.56 (hexane/EtOAc 1:1). $[\alpha]_D^{25} +38.9$ (c 1.55, CHCl_3). ^1H NMR: 2.08 (m, 1H), 2.12 (s, 3H), 2.14 (s, 3H), 2.63 (m, 1H), 3.22 (ddd, $J = 3.5, 12.5, 13.0$, 1H), 3.89 (dd, $J = 11.5, 12.5$, 1H), 5.29 (dd, $J = 3.0, 11.5$, 1H), 5.48 (m, 1H), 5.62 (dd, $J = 3.0, 3.0$, 1H), 5.96 (s, 1H), 6.05 (s, 2H), 6.35 (s, 1H), 8.21 (d, $J = 8.5$, 2H), 8.32 (d, $J = 8.5$, 2H), 12.3 (s, 1H). ^{13}C NMR: 20.7 (CH_3), 20.8 (CH_3), 26.8 (CH_2), 34.9 (CH), 52.6 (CH), 67.1 (CH), 70.1 (CH), 71.7 (CH), 96.7 (CH), 102.4 (CH_2), 107.0 (C), 123.8 (CH), 131.0 (CH), 133.3 (C), 134.3 (C), 135.3 (C), 146.6 (C), 151.0 (C), 153.0 (C), 163.1 (C), 169.1 (C), 170.1 (C), 170.2 (C). IR (KBr): 3449, 3225, 2932, 1744, 1674, 1628, 1528, 1466, 1342, 1273, 1242, 1080, 1034. FABMS m/z : 543 ($\text{M}+\text{H}$), 542 (M^+), 420, 392 ($\text{M}-4\text{-NO}_2\text{C}_6\text{H}_4\text{CO}$), 350, 307, 289, 221, 207, 154, 136. HRMS–FAB (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_{12}$, 543.1251; found, 543.1241.



(+)-*trans*-Dihydronarciclasine (1): To a suspension of triester **31** (24.9 mg, 45.9 μ mol) in MeOH (3 mL), was added K_2CO_3 (38.0 mg, 0.275 mmol) at rt. After 1 h, saturated aqueous NH_4Cl (3 mL) was added to the reaction mixture, and the whole was extracted with EtOAc (6 x 6 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/MeOH 10:1) to afford the title compound (12.4 mg, 87%) as white solids of mp 273 – 275 $^{\circ}$ C, (lit.¹⁰ 290 – 291 $^{\circ}$ C): R_f 0.58 (EtOAc/MeOH 10:1). $[\alpha]_D^{20} +5.8$ (c 0.27, THF), (lit.¹⁰ $[\alpha]_D^{20} +4.7$ (c 0.27, THF)). ^1H NMR (CD_3OD): 1.83 (ddd, $J = 2.5, 13.0, 13.5$, 1H), 2.23 (ddd, $J = 3.0, 3.5, 13.5$, 1H), 3.00 (ddd, $J = 3.5, 12.5, 13.0$, 1H), 3.46 (dd, $J = 10.0, 12.5$, 1H), 3.86 (dd, $J = 3.0, 10.0$, 1H), 3.91 (dd, $J = 3.0, 3.0$, 1H), 4.08 (m, 1H), 6.00 (d, $J = 1.0$, 1H), 6.01 (d, $J = 1.0$, 1H), 6.45 (d, $J = 1.0$, 1H). ^{13}C NMR (CD_3OD): 29.6 (CH_2), 35.2 (CH), 56.3 (CH), 70.5 (CH), 71.5 (CH), 73.3 (CH), 97.7 (CH), 103.4 (CH_2), 108.2 (C), 133.9 (C), 139.7 (C), 147.3 (C), 154.3 (C), 171.9 (C). IR (KBr): 3402, 2924, 1666, 1628, 1466, 1342, 1288, 1234, 1080, 1034. FABMS m/z : 310 ($\text{M}+\text{H}$), 309 (M^+), 197, 149, 135. HRMS–FAB (m/z): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{NO}_7$, 310.0927; found, 310.0919.

^1H NMR, ^{13}C NMR, MS, and IR spectral data were identical to those reported.^{10, 13–15}

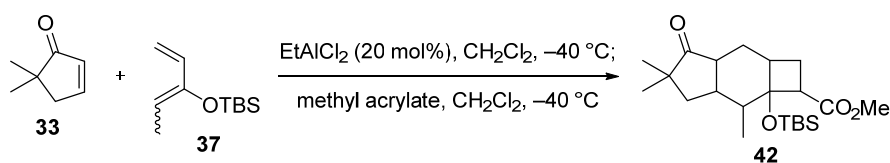


Methyl

(2*SR*,2*aRS*,4*aRS*,7*aRS*,7*bSR*)-2*a*-{(tert-Butyldimethylsilyl)oxy}-6,6,7*b*-trimethyl-5-oxodecahydro-1*H*-cyclobuta[*e*]indene-2-carboxylate (40**):** To a stirred solution of cyclopentenone **33**⁹¹ (14.5 g, 132 mmol) and siloxydiene **37**⁹² (29.3 g, 148 mmol, *Z:E* = 2.2:1) in dry CH_2Cl_2 (415 mL) at -40°C , was added a solution of Ti_2NH (1.88 g, 6.69 mmol) in dry toluene (83 mL) over 15 min. After 2 h, methyl acrylate (36.0 mL, 401 mmol) was added and then, a solution of Ti_2NH (1.14 g, 4.05 mmol) in dry toluene (50 mL) was added again over 5 min. The mixture was stirred for 1 h. Then, methyl acrylate (36.0 mL, 401 mmol) was added again to the mixture. After additional 1.5 h, the reaction was quenched by the addition of Et_3N (18 mL). Removal of the solvent under reduced pressure, followed by column chromatography of the residue (hexane/ EtOAc 95:5 to 9:1) to afford the title compound as a mixture with side products (26.4 g), which was used directly in the next step without further purification. An analytical sample was obtained by repeating column chromatography (hexane/ EtOAc 97:3) as colorless oil: R_f 0.46 (hexane/ EtOAc 5:1). ^1H NMR: 0.08 (s, 3H), 0.15 (s, 3H), 0.87 (s, 9H), 1.00 (s, 3H), 1.07 (s, 3H), 1.16 (s, 3H), 1.52–1.62 (m, 4H), 1.67 (m, 1H), 1.77–1.83 (m, 2H), 1.86 (dd, $J = 7.0, 12.5$, 1H), 2.17 (ddd, $J = 7.0, 7.0, 12.5$, 1H), 2.42 (m, 1H), 3.23 (dd, $J = 9.5, 9.5$, 1H), 3.70 (s, 3H). ^{13}C NMR: -3.4 (CH_3), -2.9 (CH_3), 18.2 (C), 19.9 (CH_2), 21.3 (CH_3), 24.3 (CH_3), 24.5 (CH_3), 25.7 (CH_3), 29.3 (CH_2), 31.8 (CH_2), 38.6 (CH), 40.9 (CH_2), 42.0 (C), 45.3 (C), 46.0 (CH), 47.7 (CH), 51.2 (CH_3), 77.1 (C), 173.1 (C), 225.1 (C). IR (neat): 2955, 2930, 2859, 1739, 1732, 1458, 1362, 1250, 1204, 1130, 1107. EIMS m/z : 394 (M^+), 379 ($\text{M}-\text{Me}$), 337 ($\text{M}-t\text{-Bu}$), 308 ($\text{M}-\text{CH}_2\text{CHCO}_2\text{Me}$), 251 ($\text{M}-t\text{-Bu}-\text{CH}_2\text{CHCO}_2\text{Me}$), 225, 185, 173, 159, 129. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{38}\text{NaO}_4\text{Si}$, 417.2437; found, 417.2440.

(2*SR*,2*aRS*,4*aRS*,7*aRS*,7*bSR*)-2*a*-{(tert-Butyldimethylsilyl)oxy}-6,6,7*b*-trimethyl-5-oxodecahydro-1*H*-cyclobuta[*e*]indene-2-carboxylic Acid (41**):** The mixture (26.4 g) was then dissolved in EtOH (360 mL) and H_2O (180 mL). NaOH (10.8 g, 270 mmol) was added to the stirred mixture. The reaction mixture was heated at 60°C for 3 h. After cooling to rt, the mixture was acidified by the addition of 3 N HCl (200 mL). The whole was extracted with EtOAc (600 mL + 2 x 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was dissolved in hexane (100 mL) and filtered. The solid was washed thoroughly with

hexane to afford the title compound (11.4 g, 23% from **33**) as white solids: Crystals suitable for X-ray diffraction studies were obtained by vapor diffusion. Colorless solids of mp 196–198 °C (EtOAc/hexane). R_f 0.31 (hexane/EtOAc 2:1). ^1H NMR: 0.10 (s, 3H), 0.16 (s, 3H), 0.87 (s, 9H), 1.01 (s, 3H), 1.08 (s, 3H), 1.17 (s, 3H), 1.55 (dd, $J = 12.5, 12.5$, 1H), 1.59–1.64 (m, 3H), 1.70 (m, 1H), 1.78 (dd, $J = 10.0, 10.5$, 1H), 1.85–1.92 (m, 2H), 2.19 (ddd, $J = 7.5, 7.5, 12.5$, 1H), 2.44 (m, 1H), 3.28 (dd, $J = 9.5, 10.0$, 1H). ^{13}C NMR (DMSO- d_6): –3.5 (CH₃), –2.8 (CH₃), 18.0 (C), 19.8 (CH₂), 21.1 (CH₃), 23.8 (CH₃), 24.2 (CH₃), 25.7 (CH₃), 29.1 (CH₂), 31.4 (CH₂), 37.9 (CH), 40.6 (CH₂), 41.3 (C), 44.7 (C), 44.8 (CH), 47.1 (CH), 76.5 (C), 173.7 (C), 224.0 (C). IR (KBr): 2959, 2930, 2859, 1738, 1697, 1458, 1420, 1252, 1196, 1136. EIMS m/z : 365 (M–Me), 323 (M–*t*-Bu), 308 (M–CH₂CHCO₂H), 279, 251 (M–*t*-Bu–CH₂CHCO₂H), 171, 159, 147, 129. HRMS–ESI (m/z): [M+Na]⁺ calcd. for C₂₁H₃₆NaO₄Si, 403.2281; found, 403.2286. Anal. calcd. for C₂₁H₃₆O₄Si: C, 66.27; H, 9.53. found: C, 66.17; H, 9.40.



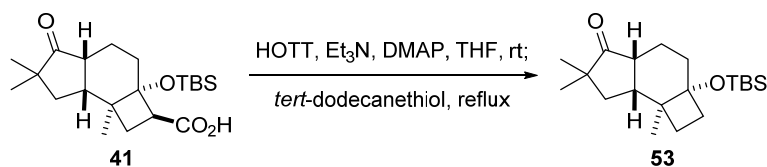
Methyl

7a-[(*tert*-Butyldimethylsilyl)oxy]-5,5,7-trimethyl-4-oxodecahydro-1*H*-cyclobuta[*f*]indene-1-carboxylate (42**):** To a stirred solution of cyclopentenone **33**⁹¹ (360 mg, 3.27 mmol) and siloxydiene **37**⁹² (779 mg, 3.93 mmol, $Z:E = 2.3:1$) in dry CH₂Cl₂ (11 mL) at –40 °C, was added a 1.0 M hexane solution of EtAlCl₂ (0.64 mL, 0.64 mmol) over 5 min. After 1 h, methyl acrylate (0.86 mL, 9.6 mmol) was added. The mixture was stirred for 2 h. Then, methyl acrylate (0.43 mL, 4.8 mmol) was added again to the mixture. After additional 1 h, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (10 mL). The whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2 to 9:1) to afford a 1:1.3 mixture of the title compound (176 mg, 14%).

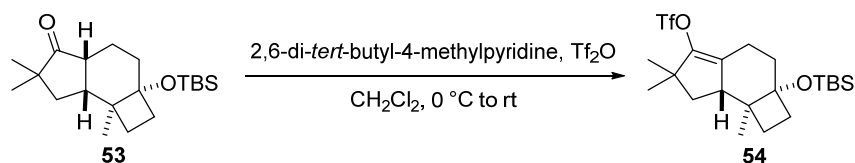
Major isomer: colorless oil. R_f 0.38 (toluene/EtOAc 19:1). ^1H NMR: 0.18 (s, 3H), 0.23 (s, 3H), 0.86 (d, $J = 7.0$, 3H), 0.90 (s, 9H), 1.02 (s, 3H), 1.14 (s, 3H), 1.42 (m, 1H), 1.54 (m, 1H), 1.63–1.81 (m, 3H), 1.88 (dd, $J = 13.0, 13.0$, 1H), 2.14 (m, 1H), 2.31 (m, 1H), 2.39–2.47 (m, 2H), 3.02 (dd, $J = 8.0, 10.0$, 1H), 3.68 (s, 3H). ^{13}C NMR: –2.8 (CH₃), –2.3 (CH₃), 12.9 (CH₃), 18.2 (C), 19.2 (CH₂), 19.5 (CH₂), 25.0 (CH₃), 25.6 (CH₃), 26.6 (CH₃), 29.9 (CH), 36.4 (CH), 36.5 (CH₂), 40.6 (CH), 45.3 (C), 45.4 (CH), 50.1 (CH), 51.4 (CH₃), 77.2 (C), 172.4 (C), 224.2 (C). IR (neat): 2955, 2859, 1736, 1462, 1254, 1196, 1165, 1115. EIMS m/z : 394 (M⁺), 379 (M–Me), 363 (M–OMe), 337 (M–*t*-Bu),

308 (M-CH₂CHCO₂Me), 305, 251 (M-*t*-Bu-CH₂CHCO₂Me), 159, 129. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₂H₃₈NaO₄Si, 417.2437; found, 417.2434.

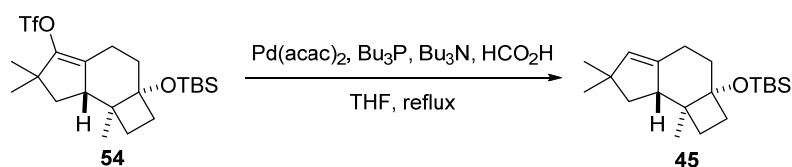
Minor isomer: colorless oil. R_f 0.63 (toluene/EtOAc 19:1). ¹H NMR: 0.19 (s, 3H), 0.22 (s, 3H), 0.80 (d, *J* = 6.5, 3H), 0.88 (s, 9H), 1.02 (s, 3H), 1.05 (m, 1H), 1.07 (s, 3H), 1.43 (dd, *J* = 11.0, 11.5, 1H), 1.60–1.68 (m, 2H), 1.97 (ddd, *J* = 5.0, 8.0, 13.0, 1H), 2.03–2.14 (m, 4H), 2.34 (m, 1H), 3.21 (dd, *J* = 9.5, 10.0, 1H), 3.67 (s, 3H). ¹³C NMR: -2.9 (CH₃), -2.3 (CH₃), 12.3 (CH₃), 18.2 (C), 22.8 (CH₂), 23.3 (CH₃), 24.8 (CH₃), 25.7 (CH₃), 26.5 (CH₂), 35.4 (CH), 36.1 (CH), 42.0 (CH), 43.2 (CH), 43.2 (CH₂), 46.3 (C), 48.8 (CH), 51.5 (CH₃), 80.8 (C), 172.9 (C), 224.7 (C). IR (neat): 2955, 2859, 1736, 1462, 1254, 1196, 1169, 1096. EIMS *m/z*: 394 (M⁺), 379 (M-Me), 363 (M-Me), 337 (M-*t*-Bu), 308 (M-CH₂CHCO₂Me), 251 (M-*t*-Bu-CH₂CHCO₂Me), 225, 185, 173, 159, 129. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₂H₃₈NaO₄Si, 417.2437; found, 417.2444.



(2a*RS*,4a*RS*,7a*RS*,7b*SR*)-2a-*tert*-butyldimethylsilyloxy-6,6,7b-trimethyldecahydro-5*H*-cyclobuta[*e*]inden-5-one (53): To a stirred solution of carboxylic acid **41** (3.53 g, 9.28 mmol) in dry THF (94 mL) were added HOTT⁵⁵ (*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouonium hexafluorophosphate; 4.50 g, 12.1 mmol), DMAP (114 mg, 0.933 mmol), and Et₃N (3.9 mL, 28 mmol) at rt. After 1 h, *tert*-dodecanethiol (6.5 mL, 28 mmol) was added to the mixture. The resulting mixture was heated under reflux for 2 h. After cooling to rt, the reaction was quenched by the addition of 1 N HCl (50 mL). The whole was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 1:0 to 95:5) to afford the crude product. Then, the residue was purified again by column chromatography (DIOL silica, hexane) to afford the title compound (2.78 g, 89%) as colorless oil: R_f 0.29 (hexane/EtOAc 95:5). ¹H NMR: 0.00 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.00 (s, 3H), 1.07 (s, 3H), 1.13 (s, 3H), 1.39 (ddd, *J* = 2.0, 9.5, 10.0, 1H), 1.45 (ddd, *J* = 9.5, 9.5, 10.0, 1H), 1.54 (dd, *J* = 12.5, 13.0, 1H), 1.61–1.69 (m, 4H), 1.79–1.83 (m, 2H), 2.10 (ddd, *J* = 7.5, 7.5, 13.0, 1H), 2.15 (ddd, *J* = 10.0, 10.0, 10.5, 1H), 2.44 (m, 1H). ¹³C NMR: -2.9 (CH₃), -2.7 (CH₃), 17.9 (C), 20.5 (CH₂), 21.0 (CH₃), 24.4 (CH₃), 24.5 (CH₃), 25.7 (CH₃), 26.9 (CH₂), 33.2 (CH₂), 36.5 (CH₂), 39.1 (CH), 40.8 (CH₂), 44.2 (C), 45.3 (C), 46.4 (CH), 73.9 (C), 225.9 (C). IR (neat): 2955, 2928, 2859, 1740, 1458, 1294, 1256, 1188, 1130, 1101, 1070, 1047, 1030. EIMS *m/z*: 336 (M⁺), 321 (M-Me), 308, 279 (M-*t*-Bu), 251, 223, 187, 159, 145, 133, 115 (TBS). HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₀H₃₆NaO₂Si, 359.2382; found, 359.2385.

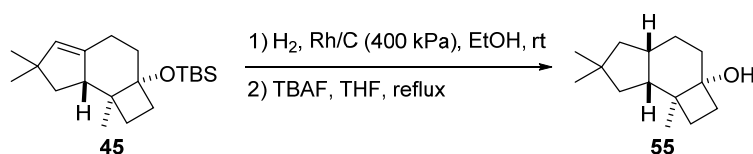


(2aRS,7aRS,7bSR)-2a-[(*tert*-Butyldimethylsilyl)oxy]-6,6,7b-trimethyl-2,2a,3,4,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]inden-5-yl Trifluoromethanesulfonate (54**):** To a stirred solution of ketone **53** (2.17 g, 6.45 mmol) in dry CH₂Cl₂ (65 mL) were added 2,6-di-*tert*-butyl-4-methylpyridine (5.31 g, 25.9 mmol) and trifluoromethanesulfonic anhydride (3.2 mL, 20 mmol) at 0 °C. The mixture was warmed to rt and stirred for 3 h. Then, the mixture was poured into pentane (130 mL) and filtered through a pad of Celite. Saturated aqueous NaHCO₃ (65 mL) was added to the filtrate. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane) to afford the title compound (2.14 g, 71%) as colorless oil: R_f 0.40 (hexane). ¹H NMR: 0.04 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.95 (s, 3H), 1.12 (s, 6H), 1.47 (m, 1H), 1.65–1.82 (m, 5H), 2.04 (ddd, *J* = 4.5, 9.0, 12.0, 1H), 2.19 (m, 1H), 2.28–2.41 (m, 2H), 2.77 (dd, *J* = 8.0, 8.0, 1H). ¹³C NMR: –2.9 (CH₃), 17.5 (CH₃), 18.2 (C), 18.4 (CH₂), 25.7 (CH₃), 26.0 (CH₃), 26.7 (CH₃), 31.3 (CH₂), 32.1 (CH₂), 33.9 (CH₂), 38.2 (CH₂), 43.1 (C), 45.1 (C), 45.3 (CH), 76.5 (C), 118.6 (q, *J*_{CF} = 315, C), 129.0 (C), 146.5 (C). IR (neat): 2959, 2934, 2859, 1458, 1410, 1258, 1211, 1142, 1107, 1059, 1034, 1001. EIMS *m/z*: 468 (M⁺), 453 (M–Me), 440, 411 (M–*t*-Bu), 355, 335 (M–SO₂CF₃), 307, 265, 203, 187, 175, 159, 145, 131, 119, 105. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₂₁H₃₅F₃NaO₄SSi, 491.1875; found, 491.1873.



***tert*-Butyldimethyl[(2aRS,7aRS,7bSR)-6,6,7b-trimethyl-1,2,3,4,6,7,7a,7b-octahydro-2a*H*-cyclobuta[*e*]inden-2a-yl]oxy]silane (**45**):** To a stirred solution of enol triflate **54** (3.00 g, 6.02 mmol) in dry THF (60 mL) were added Bu₃N (14.3 mL, 60.2 mmol), Bu₃P (0.59 mL, 2.4 mmol), Pd(acac)₂ (367 mg, 1.20 mmol), and formic acid (1.7 mL, 45 mmol). The reaction mixture was heated under reflux for 12 min. After cooling to rt, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (30 mL). The whole was extracted with EtOAc (60 mL + 2 x 30 mL). The combined organic layers were washed with 1 N HCl and brine (30 mL each), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane) to afford the title compound (1.76 g, 91%) as colorless oil: R_f 0.83 (hexane). ¹H NMR: 0.03 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.90 (s, 3H), 0.98 (s, 3H), 1.04 (s, 3H), 1.43 (dd, *J* = 8.5, 12.5, 1H), 1.47 (ddd, *J* = 7.5,

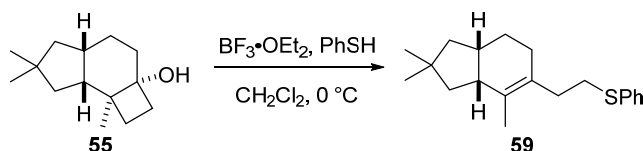
9.0, 11.0, 1H), 1.56–1.62 (m, 2H), 1.70 (ddd, $J = 5.0, 10.5, 11.0$, 1H), 1.80 (ddd, $J = 6.0, 12.0, 13.5$, 1H), 2.04 (ddd, $J = 5.0, 9.0, 12.0$, 1H), 2.13 (ddd, $J = 7.5, 10.5, 12.0$, 1H), 2.20–2.30 (m, 2H), 2.85 (m, 1H), 5.05 (m, 1H). ^{13}C NMR: -2.8 (CH_3), -2.7 (CH_3), 17.6 (CH_3), 18.2 (C), 20.8 (CH_2), 25.8 (CH_3), 28.4 (CH_3), 30.0 (CH_3), 31.6 (CH_2), 33.9 (CH_2), 34.0 (CH_2), 40.1 (CH_2), 44.4 (C), 45.5 (C), 51.4 (CH), 77.4 (C), 132.2 (CH), 139.8 (C). IR (neat): 2955, 2932, 2859, 1460, 1258, 1200, 1180, 1107, 1032, 1016. EIMS m/z : 320 (M^+), 305 ($\text{M}-\text{Me}$), 292, 277, 263 ($\text{M}-t\text{-Bu}$), 235, 189, 173, 160, 145, 133, 119, 105. Anal. calcd. for $\text{C}_{20}\text{H}_{36}\text{OSi}$: C, 74.93; H, 11.32. found: C, 75.07; H, 11.58.



***tert*-Butyldimethyl[*[(2aRS,4aSR,7aRS,7bSR)-6,6,7b-trimethyldecahydro-1H-cyclobuta[e]inden-2a-yl*]oxy]silane (S7):** A mixture of olefin **45** (726 mg, 2.26 mmol) and 5% Rh/C (461 mg, 0.25 mmol) in EtOH (7.5 mL) was stirred under hydrogen pressure (400 kPa) at rt. After 48 h, the reaction mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated *in vacuo* to afford the title compound (716 mg) as pale yellow oil, which was used directly in the next step without further purification. An analytical sample was obtained by column chromatography (hexane) as colorless oil: R_f 0.85 (hexane). ^1H NMR: 0.02 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 0.90 (s, 3H), 1.03 (s, 3H), 1.04 (s, 3H), 1.20–1.36 (m, 5H), 1.43–1.53 (m, 2H), 1.59 (ddd, $J = 3.0, 9.0, 12.0$, 1H), 1.65 (m, 1H), 1.74 (dd, $J = 3.0, 9.0$, 1H), 1.78 (ddd, $J = 2.0, 8.5, 10.0$, 1H), 1.88 (ddd, $J = 7.0, 8.0, 15.0$, 1H), 2.09 (q, $J = 10.0$, 1H), 2.16 (m, 1H). ^{13}C NMR: -2.8 (CH_3), -2.6 (CH_3), 18.0 (C), 22.6 (CH_3), 25.3 (CH_2), 25.8 (CH_3), 26.9 (CH_2), 29.4 (CH_3), 31.0 (CH_3), 33.2 (CH_2), 35.9 (CH_2), 36.1 (CH), 36.6 (C), 44.4 (CH_2), 45.1 (C), 45.7 (CH), 48.2 (CH_2), 74.6 (C). IR (neat): 2951, 2928, 2901, 2859, 1462, 1385, 1362, 1342, 1312, 1250, 1184, 1130, 1103, 1049, 1007. EIMS m/z : 322 (M^+), 307, 294, 279, 265 ($\text{M}-t\text{-Bu}$), 237, 189, 161, 115, 75, 41. FABMS m/z : 323 ($\text{M}+\text{H}$), 321, 294, 265 ($\text{M}-t\text{-Bu}$), 237, 189. Anal. calcd. for $\text{C}_{20}\text{H}_{38}\text{OSi}$: C, 74.46; H, 11.87. found: C, 74.33; H, 11.94.

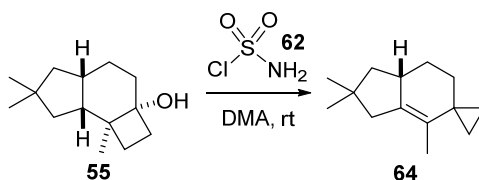
(2aRS,4aSR,7aRS,7bSR)-6,6,7b-Trimethyldecahydro-1H-cyclobuta[e]inden-2a-ol (55): A solution of **S7c** (716 mg) and 1 M THF solution of TBAF (11 mL, 11 mmol) was heated under reflux for 28 h. After cooling to rt, the reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL). The whole was extracted with EtOAc (3 x 10 mL). 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/EtOAc 95:5) to afford the title compound (424 mg, 90%) as colorless oil: R_f 0.38 (hexane/EtOAc 5:1). ^1H NMR: 0.91 (s, 3H), 1.04 (s, 3H), 1.12 (s, 3H), 1.19–1.40 (m, 5H), 1.50 (q, $J = 10.0$, 1H), 1.61–1.78 (m, 5H), 1.89–2.02 (m, 3H), 2.26 (m, 1H). ^{13}C

NMR: 21.4 (CH₃), 25.3 (CH₂), 26.1 (CH₂), 28.7 (CH₃), 30.4 (CH₃), 33.0 (CH₂), 33.8 (CH₂), 35.3 (CH), 36.9 (C), 44.4 (C), 44.7 (CH₂), 45.4 (CH), 48.1 (CH₂), 73.3 (C). IR (neat): 3406, 2928, 2866, 1460, 1447, 1381, 1370, 1246, 1185, 1123, 1092, 1026. EIMS *m/z*: 208 (M⁺), 193, 180, 162, 147, 135, 123, 109, 95, 81, 67, 55, 41. HRMS–ESI (*m/z*): [M+H]⁺ calcd. for C₁₄H₂₅O, 209.1905; found, 209.1892.



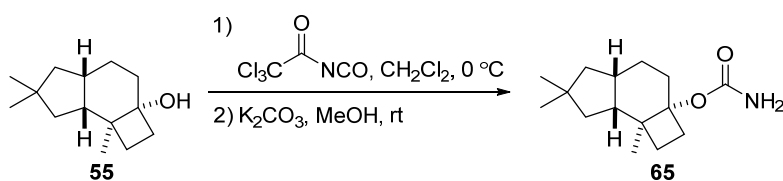
Phenyl[2-{(3*aRS*,7*a**SR*)-2,2,4-trimethyl-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-inden-5-yl}ethyl]sulfane**

(59): To a solution of alcohol **55** (31.7 mg, 0.152 mmol) and PhSH (155 μ L, 1.52 mmol) in dry CH₂Cl₂ (2 mL) was added BF₃·OEt₂ (21 μ L, 0.167 mmol) at 0 °C. After 8 min, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (5 mL). The whole was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane) to afford the title compound (38.1 mg, 84%) as pale yellow oil: R_f 0.68 (hexane/EtOAc 5:1). ¹H NMR: 0.98 (s, 3H), 1.04 (s, 3H), 1.15–1.22 (m, 2H), 1.33 (m, 1H), 1.53 (qd, *J* = 5.0, 13.0, 1H), 1.58 (s, 3H), 1.65 (dd, *J* = 8.0, 13.0, 1H), 1.72 (dd, *J* = 7.0, 12.0, 1H), 1.86–1.96 (m, 2H), 2.12 (m, 1H), 2.31–2.35 (m, 2H), 2.40 (m, 1H), 2.91–2.94 (m, 2H), 7.15 (dd, *J* = 7.0, 7.5, 1H), 7.25–7.28 (m, 2H), 7.33 (d, *J* = 7.0, 2H). ¹³C NMR: 17.8 (CH₃), 28.1 (CH₂), 28.7 (CH₂), 29.8 (CH₃), 31.0 (CH₃), 32.1 (CH₂), 33.4 (CH₂), 36.9 (CH), 37.6 (C), 44.5 (CH), 47.0 (CH₂), 47.2 (CH₂), 125.6 (CH), 127.8 (C), 128.8 (CH), 128.8 (CH), 131.4 (C), 137.0 (C). IR (neat): 2951, 2924, 2859, 1713, 1585, 1477, 1462, 1439, 1381, 1366. EIMS *m/z*: 300 (M⁺), 190 (M–PhSH), 175, 161, 135, 121, 107. HRMS–ESI (*m/z*): [M+H]⁺ calcd. for C₂₀H₂₉S, 301.1990; found, 301.1973.



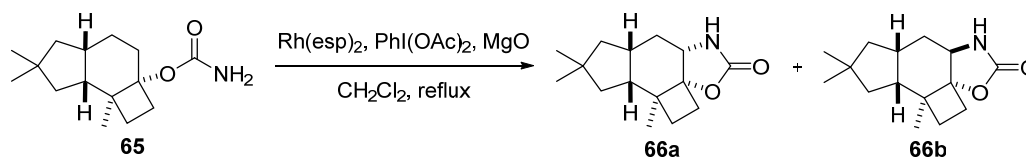
(*SR*)-2',2',4'-Trimethyl-1',2',3',6',7',7*a*'-hexahydrospiro[cyclopropane-1,5'-indene] (64): To a stirred solution of alcohol **55** (5.5 mg 26 μ mol) in dry DMA (0.5 mL) was added sulfamoyl chloride **62**^{58a} (15.8 mg 0.137 mmol). The reaction mixture was stirred at rt for 10 min. Then, the reaction was quenched by the addition of water (2 mL). The whole was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to afford the title compound (4.5 mg, 90%) as pale yellow oil: R_f 0.67 (hexane). ¹H NMR:

0.27 (m, 1H), 0.38 (m, 1H), 0.68 (m, 1H), 0.81 (m, 1H), 1.02 (s, 3H), 1.05–1.10 (m, 2H), 1.07 (s, 3H), 1.22 (s, 3H), 1.24 (m, 1H), 1.61 (dd, $J = 6.5, 11.5$, 1H), 1.86 (m, 1H), 2.01 (m, 1H), 2.09 (br s, 2H), 2.57 (m, 1H). ^{13}C NMR: 10.5 (CH₂), 12.3 (CH₃), 13.5 (CH₂), 20.7 (C), 28.8 (CH₂), 29.3 (CH₃), 30.4 (CH₃), 36.5 (CH₂), 37.2 (C), 41.5 (CH), 45.2 (CH₂), 48.3 (CH₂), 125.2 (C), 139.2 (C). IR (neat): 3075, 3001, 2951, 2924, 2851, 1458, 1450, 1381, 1366, 1072, 1038, 1011. EIMS m/z : 190 (M^+), 175 ($\text{M}-\text{Me}$), 161, 147, 134, 121, 119, 105. HRMS–ESI (m/z): $[\text{M}+\text{K}]^+$ calcd. for $\text{C}_{14}\text{H}_{22}\text{K}$, 229.1359; found, 229.1339.



(2aRS,4aSR,7aRS,7bSR)-6,6,7b-Trimethyldecahydro-1H-cyclobuta[e]inden-2a-yl Carbamate

(65): To a solution of alcohol **55** (279 mg, 1.34 mmol) in dry CH_2Cl_2 (8 mL) was added trichloroacetyl isocyanate (175 μL , 1.48 mmol) at 0 °C. After 10 min, the reaction mixture was concentrated *in vacuo*. To the resulting residue were added MeOH (8 mL) and K_2CO_3 (126 mg, 6.70 mmol) at rt. After 3 h, water (10 mL) was added, and the whole was extracted with EtOAc (20 mL + 2 x 10 mL). 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/EtOAc 5:2) to afford the title compound (340 mg, quant.) as colorless amorphous of mp 143–146 °C: R_f 0.42 (hexane/EtOAc 5:1). ^1H NMR: 0.92 (s, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.19–1.25 (m, 2H), 1.32 (m, 1H), 1.36–1.43 (m, 2H), 1.57–1.64 (m, 2H), 1.69 (dd, $J = 8.5, 13.0$, 1H), 1.93 (m, 1H), 1.97–2.05 (m, 2H), 2.19–2.28 (m, 2H), 2.39 (ddd, $J = 10.0, 10.5, 12.0$, 1H), 4.51 (br s, 2H). ^{13}C NMR: 22.3 (CH₃), 24.9 (CH₂), 28.0 (CH₂), 28.8 (CH₃), 30.4 (CH₂), 30.6 (CH₃), 31.3 (CH₂), 35.1 (CH), 36.8 (C), 43.4 (C), 44.7 (CH₂), 45.2 (CH), 48.0 (CH₂), 80.2 (C), 156.1 (C). IR (KBr): 3287, 2959, 2928, 2862, 1755, 1717, 1454, 1377, 1273, 1231, 1088, 1034. EIMS m/z : 223, 190, 180, 162, 147, 135, 123, 107. HRMS–ESI (m/z): $[\text{M}-\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{24}\text{NO}_2$, 250.1807; found, 250.1803.



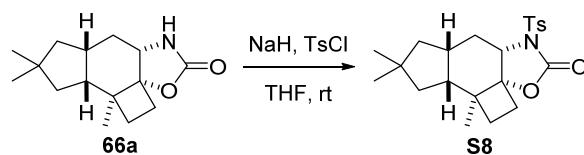
(2aRS,5aSR,6aRS,9aRS,9bSR)-8,8,9b-Trimethyldecahydrocyclobuta[6,7]indeno[5,6-*d*]oxazol-4(2H)-one **(66a)** **and**

(2aRS,5aRS,6aRS,9aRS,9bSR)-8,8,9b-Trimethyldecahydrocyclobuta[6,7]indeno[5,6-*d*]oxazol-4(2H)-one (66b): To a solution of carbamate **65** (246 mg, 0.979 mmol) in dry CH_2Cl_2 (6 mL) were

added successively MgO (91.8 mg, 2.28 mmol), PhI(OAc)₂ (442 mg, 1.37 mmol), and Rh₂(esp)₂ (18.6 mg, 24.5 μmol). The mixture was heated for 12.5 h under reflux. Then, Rh₂(esp)₂ (18.6 mg, 24.5 μmol) was added again to the reaction mixture. After additional 6.5 h, the mixture was filtered through a pad of Celite. The filter cake was rinsed with EtOAc. The combined filtrates were concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford the title compounds (225 mg and 6.2 mg, 92% and 3%, respectively).

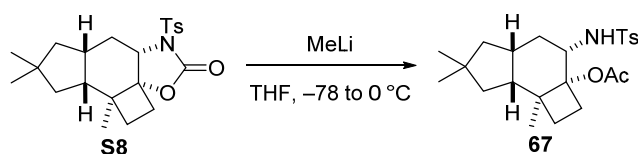
66a: White solids of mp 152–154 °C. R_f 0.25 (hexane/EtOAc 3:1 x 2). ¹H NMR: 0.97 (s, 3H), 1.06 (s, 3H), 1.26 (s, 3H), 1.28 (m, 1H), 1.35 (ddd, *J* = 12.0, 13.0, 13.0, 1H), 1.42 (d, *J* = 10.0, 1H), 1.47–1.50 (m, 2H), 1.54 (ddd, *J* = 4.5, 5.0, 13.0, 1H), 1.72 (dd, *J* = 7.5, 13.5, 1H), 1.87 (dt, *J* = 6.0, 10.0, 1H), 2.00 (ddd, *J* = 3.5, 7.0, 10.5, 1H), 2.05 (m, 1H), 2.37 (ddd, *J* = 10.5, 10.5, 11.0, 1H), 3.54 (dd, *J* = 5.0, 12.0, 1H), 5.25 (br s, 1H). ¹³C NMR: 21.0 (CH₃), 25.0 (CH₂), 31.5 (CH₂), 32.1 (CH₃), 32.4 (CH₃), 33.2 (CH₂), 34.9 (CH), 36.0 (C), 41.9 (CH₂), 44.6 (C), 45.7 (CH), 47.1 (CH₂), 58.4 (CH), 81.8 (C), 158.8 (C). IR (KBr): 3287, 2959, 2928, 2862, 1755, 1721, 1454, 1427, 1381, 1273, 1231, 1089, 1034. EIMS *m/z*: 249 (M⁺), 221, 207, 190, 177, 163, 152, 137, 123, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₅H₂₃NNaO₂, 272.1626; found, 272.1617.

66b: White solids of mp 151–155 °C. R_f 0.42 (hexane/EtOAc 3:1 x 2). ¹H NMR: 0.92 (s, 3H), 1.07 (s, 3H), 1.23 (s, 3H), 1.24–1.27 (m, 2H), 1.49–1.56 (m, 2H), 1.62 (ddd, *J* = 1.0, 3.5, 13.0, 1H), 1.77 (ddd, *J* = 5.0, 12.0, 12.0, 1H), 1.92 (ddd, *J* = 1.5, 8.5, 13.0, 1H), 2.04–2.12 (m, 2H), 2.17 (ddd, *J* = 7.0, 9.5, 16.5, 1H), 2.50 (ddd, *J* = 5.0, 10.0, 14.5, 1H), 2.70 (m, 1H), 3.83 (dd, *J* = 3.5, 13.5, 1H), 4.77 (br s, 1H). ¹³C NMR: 19.9 (CH₃), 23.7 (CH₂), 27.4 (CH₃), 28.4 (CH₂), 29.2 (CH₂), 29.9 (CH₃), 33.8 (CH), 37.6 (C), 43.3 (C), 46.8 (CH₂), 48.7 (CH), 50.6 (CH₂), 54.7 (CH), 88.0 (C), 160.6 (C). IR (KBr): 3248, 2951, 2932, 2862, 1759, 1458, 1447, 1366, 1315, 1288, 1080, 1045. EIMS *m/z*: 249 (M⁺), 221, 206, 190, 177, 163, 145, 137, 123, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₅H₂₃NNaO₂, 272.1626; found, 272.1617.

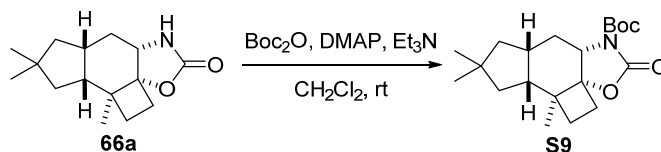


(2aRS,5aSR,6aRS,9aRS,9bSR)-8,8,9b-Trimethyl-5-tosyldecahydrocyclobuta[6,7]indeno[5,6-*d*]oxazol-4(2H)-one (S8): To a solution of oxazolidinone **66a** (21.0 mg, 84.2 μmol) and TsCl (19.3 mg, 0.101 mmol) in dry THF (2 mL) was added a 60% oil suspension of NaH (3.9 mg, 0.16 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (3 mL). The whole was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 8:1) to afford the title

compound (32.3 mg, 95%) as white solids of mp 154–156 °C: R_f 0.67 (hexane/EtOAc 2:1). ^1H NMR: 0.96 (s, 3H), 1.00 (s, 3H), 1.20 (s, 3H), 1.25–1.34 (m, 3H), 1.39 (dd, J = 7.0, 12.5, 1H), 1.48–1.52 (m, 2H), 1.75 (dd, J = 7.5, 13.5, 1H), 1.85 (ddd, J = 6.5, 7.0, 13.0, 1H), 1.92 (ddd, J = 3.5, 7.0, 11.5, 1H), 2.02 (ddd, J = 4.5, 5.0, 13.0, 1H), 2.11 (m, 1H), 2.29 (ddd, J = 10.5, 10.5, 11.5, 1H), 2.45 (s, 3H), 4.23 (dd, J = 5.0, 12.0, 1H), 7.34 (d, J = 8.0, 2H), 7.95 (d, J = 8.0, 2H). ^{13}C NMR: 20.9 (CH₃), 21.7 (CH₃), 24.7 (CH₂), 31.2 (CH₂), 31.4 (CH₂), 32.0 (CH₃), 32.3 (CH₃), 35.2 (CH), 35.9 (C), 41.7 (CH₂), 44.7 (C), 45.0 (CH), 46.8 (CH₂), 63.7 (CH), 80.6 (C), 128.3 (CH), 129.7 (CH), 135.4 (C), 145.3 (C), 151.0 (C). IR (KBr): 2951, 2866, 1778, 1763, 1597, 1458, 1369, 1265, 1169, 1142, 1096, 1034. EIMS m/z : 403 (M^+), 375, 255, 220, 204, 187, 176, 155, 135, 119, 107. HRMS–ESI (m/z): $[M+Na]^+$ calcd. for C₂₂H₃₀NO₄S, 404.1896; found, 404.1896.

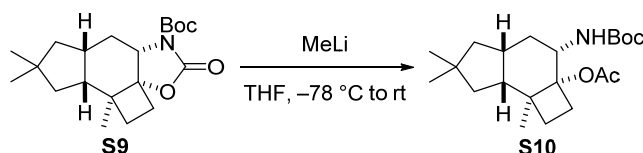


(2aRS,3SR,4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-(4-methylphenylsulfonamido)decahydro-1H-cyclobuta[e]inden-2a-yl Acetate (67): To a solution of *N*-tosyloxazolidinone **S8** (14.7 mg, 36.4 μmol) in dry THF (1.5 mL) at -78°C was added a 1.07 M ether solution of MeLi (0.070 mL, 0.075 mmol). The mixture was stirred at -78°C for 20 min and at 0°C for 15 min. The reaction was quenched by the addition of saturated aqueous NH₄Cl (3 mL). The whole was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 8:1) to afford the title compound (6.8 mg, 44%) as colorless oil: R_f 0.38 (hexane/EtOAc 3:1). ^1H NMR: 0.92 (s, 3H), 1.04 (s, 3H), 1.05 (s, 3H), 1.25–1.45 (m, 5H), 1.47 (ddd, J = 2.5, 7.0, 12.0, 1H), 1.54 (m, 1H), 1.66–1.77 (m, 3H), 2.07 (s, 3H), 2.11 (m, 1H), 2.20 (m, 1H), 2.43 (s, 3H), 3.24 (ddd, J = 4.0, 4.0, 12.5, 1H), 5.44 (d, J = 4.0, 1H), 7.31 (d, J = 8.0, 2H), 7.79 (d, J = 8.0, 2H). ^{13}C NMR: 21.5 (CH₃), 21.6 (CH₃), 21.8 (CH₃), 27.9 (CH₂), 30.4 (CH₂), 31.5 (CH₃), 31.7 (CH₂), 32.0 (CH₃), 35.8 (C), 38.1 (CH), 43.2 (CH₂), 44.5 (CH), 46.1 (C), 46.9 (CH₂), 58.6 (CH), 82.1 (C), 127.3 (CH), 129.6 (CH), 136.7 (C), 143.4 (C), 172.3 (C). IR (neat): 3433, 3291, 2927, 2866, 1744, 1462, 1319, 1234, 1157, 1088. EIMS m/z : 419 (M^+), 376 (M -Ac), 359, 319, 264 (M -SO₂Tol), 236, 222, 204, 187, 178, 155(SO₂Tol), 149, 121, 107, 91. HRMS–ESI (m/z): $[M+Na]^+$ calcd. for C₂₃H₃₃NNaO₄S, 442.2028; found, 442.2020.



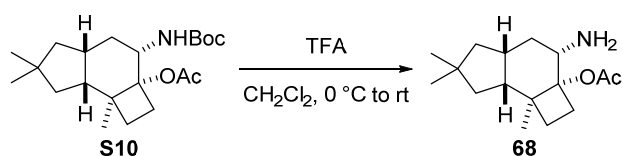
tert-Butyl

(2a*RS*,5a*SR*,6a*RS*,9a*RS*,9b*SR*)-8,8,9b-trimethyl-4-oxodecahydrocyclobuta[6,7]indeno[5,6-*d*]oxazole-5(2*H*)-carboxylate (S9): To a solution of oxazolidinone **66a** (142 mg, 0.569 mmol) in dry CH₂Cl₂ (4 mL) were added successively DMAP (7.3 mg, 60 μmol), Et₃N (158 μL, 1.14 mmol), and Boc₂O (196 μL, 0.853 mmol) at rt. After 2 h, the reaction was quenched by the addition of saturated aqueous NH₄Cl (5 mL). The whole was extracted with EtOAc (10 mL + 2 x 5 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford the title compound (200 mg, quant.) as colorless amorphous of mp 118–120 °C: *R*_f 0.29 (hexane/EtOAc 5:1). ¹H NMR: 0.97 (s, 3H), 1.06 (s, 3H), 1.25 (s, 3H), 1.25–1.32 (m, 2H), 1.35–1.44 (m, 2H), 1.49–1.55 (m, 2H), 1.55 (s, 9H), 1.74 (dd, *J* = 7.5, 13.5, 1H), 1.85–1.91 (m, 2H), 1.99 (m, 1H), 2.08 (m, 1H), 2.35 (ddd, *J* = 10.0, 10.5, 10.5, 1H), 3.99 (dd, *J* = 4.5, 12.0, 1H). ¹³C NMR: 20.9 (CH₃), 24.8 (CH₂), 28.0 (CH₃), 30.0 (CH₂), 31.5 (CH₂), 32.1 (CH₃), 32.4 (CH₃), 35.2 (CH), 35.9 (C), 41.8 (CH₂), 44.5 (C), 45.3 (CH), 46.9 (CH₂), 61.3 (CH), 78.9 (C), 83.6 (C), 149.6 (C), 151.4 (C). IR (neat): 2955, 2866, 1805, 1717, 1458, 1369, 1327, 1304, 1261, 1157, 1099, 1061, 1034. EIMS *m/z*: 249, 234, 221, 206, 190, 177, 162, 152, 137, 123, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₂₀H₃₁NNaO₄, 372.2151; found, 372.2150.

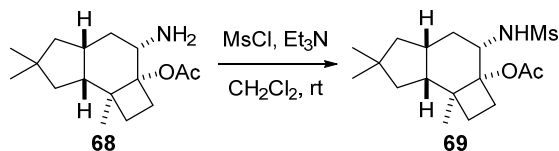


(2a*RS*,3*SR*,4a*RS*,7a*RS*,7b*SR*)-3-{(tert-Butoxycarbonyl)amino}-6,6,7b-trimethyldecahydro-1*H*-cyclobuta[*e*]inden-2a-yl Acetate (S10): To a solution of *N*-Bocoxazolidinone **S9** (122 mg, 0.349 mmol) in THF (1.5 mL) at –78 °C was added a 1.07 M Et₂O solution of MeLi (0.36 mL, 0.39 mmol). The mixture was stirred at –78 °C for 30 min, at 0 °C for 30 min, and at rt for 30 min. The reaction was quenched by the addition of saturated aqueous NH₄Cl (3 mL). The whole was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 93:7) to afford the title compound (94.3 mg, 74%) as colorless oil: *R*_f 0.33 (toluene/EtOAc 19:1). ¹H NMR: 0.94 (s, 3H), 1.06 (s, 3H), 1.11 (s, 3H), 1.27 (d, *J* = 13.5, 1H), 1.35–1.49 (m, 5 H), 1.44 (s, 9H), 1.67 (m, 1H), 1.71 (dd, *J* = 8.0, 13.5, 1H), 1.82 (ddd, *J* = 6.5, 6.5, 13.0, 1H), 2.07 (s, 3H), 2.22 (m, 1H),

2.39 (m, 1H), 2.56 (ddd, $J = 10.0, 10.0, 11.5$, 1H), 3.86 (m, 1H), 4.80 (br s, 1H). ^{13}C NMR: 21.6 (CH₃), 21.8 (CH₃), 27.7 (CH₂), 28.3 (CH₃), 30.9 (CH₂), 31.2 (CH₂), 31.5 (CH₃), 32.1 (CH₃), 35.8 (C), 38.0 (CH), 43.1 (CH₂), 45.0 (CH), 46.2 (C), 47.1 (CH₂), 54.8 (CH), 79.1 (C), 82.3 (C), 155.9 (C), 170.5 (C). IR (KBr): 3352, 2951, 2932, 2862, 1732, 1713, 1528, 1458, 1366, 1265, 1238, 1177, 1018. EIMS m/z : 365 (M^+), 309, 267, 249, 239, 221, 178, 162, 137, 110, 95. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{21}\text{H}_{35}\text{NNaO}_4$, 388.2464; found, 388.2461.

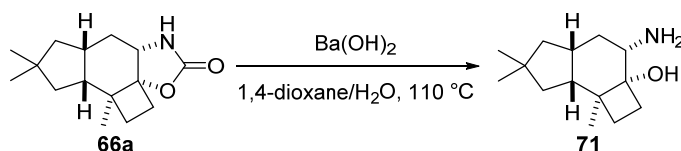


(2aRS,3SR,4aRS,7aRS,7bSR)-3-Amino-6,6,7b-trimethyldecahydro-1H-cyclobuta[e]inden-2a-yl Acetate (68): To a solution of *N*-Boc-*O*-acetylaminoalcohol **S10** (72.4 mg, 0.198 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.40 mL) at 0 °C. The mixture was warmed to rt and stirred for 30 min. The TFA was azeotropically removed with toluene, and the remaining residue was dissolved in EtOAc (5 mL), washed with saturated aqueous NaHCO_3 (2 x 5 mL) and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 2:1) to afford the title compound (34.3 mg, 66%) as pale yellow oil: R_f 0.54 (hexane/EtOAc 1:1). ^1H NMR: 0.94 (ddd, $J = 12.0, 13.0, 13.0$, 1H), 0.97 (s, 3H), 1.05 (s, 3H), 1.24 (s, 3H), 1.26–1.50 (m, 5H), 1.65–1.71 (m, 2H), 1.83–1.90 (m, 2H), 1.95 (s, 3H), 2.06 (m, 1H), 2.19 (ddd, $J = 10.0, 10.5, 10.5$, 1H), 3.73 (dd, $J = 5.0, 12.0$, 1H). ^{13}C NMR: 14.6 (CH₃), 21.4 (CH₃), 25.4 (CH₂), 32.1 (CH₂), 32.1 (CH₃), 32.3 (CH₃), 33.0 (CH₂), 35.5 (CH), 36.0 (C), 41.8 (CH₂), 44.4 (C), 46.2 (CH), 47.3 (CH₂), 70.4 (CH), 84.7 (C), 163.8 (C). IR (neat): 3372, 2951, 2936, 2862, 1667, 1458, 1439, 1381, 1366, 1285, 1254, 1231, 1034. EIMS m/z : 247, 232, 219, 204, 188, 178, 163, 139, 123, 107, 95. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{16}\text{H}_{27}\text{NNaO}_2$, 288.1939; found, 288.1930.

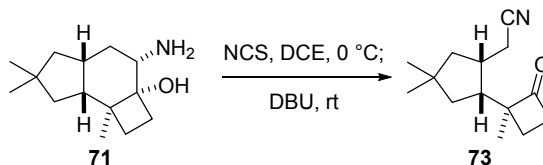


(2aRS,3SR,4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-(methylsulfonamido)decahydro-1H-cyclobuta[e]inden-2a-yl Acetate (69): To a solution of *O*-acetylaminoalcohol **68** (4.9 mg, 18 μmol) in dry CH_2Cl_2 (1 mL) were added Et_3N (8.2 μL , 59 μmol) and MsCl (4.2 μL , 54 μmol) at rt. The mixture was stirred for 30 min. Then, Et_3N (8.2 μL , 59 μmol) and MsCl (4.2 μL , 54 μmol) were added again to the mixture. After additional 50 min, the reaction was quenched by the addition of saturated aqueous NaHCO_3 (2 mL). The whole was extracted with EtOAc (3 x 5 mL), and the combined

organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford the title compound (2.3 mg, 37%) as white solids of mp 178–180 °C: R_f 0.38 (hexane/EtOAc 2:1). ¹H NMR: 0.95 (s, 3H), 1.08 (s, 3H), 1.13 (s, 3H), 1.31 (d, *J* = 13.5, 1H), 1.40 (br d, *J* = 10.0, 2H), 1.50 (m, 1H), 1.57–1.61 (m, 2H), 1.66 (m, 1H), 1.73 (dd, *J* = 8.0, 13.5, 1H), 1.83 (m, 1H), 2.08 (s, 3H), 2.19–2.28 (m, 2H), 2.60 (m, 1H), 3.01 (s, 3H), 3.69 (ddd, *J* = 6.0, 6.0, 11.0, 1H), 4.77 (d, *J* = 6.0, 1H). ¹³C NMR: 21.7 (CH₃), 21.9 (CH₃), 27.6 (CH₂), 31.3 (CH₂), 31.6 (CH₃), 32.2 (CH₃), 32.7 (CH₂), 35.9 (C), 37.9 (CH), 42.1 (CH₃), 43.0 (CH₂), 44.7 (CH), 46.3 (C), 47.0 (CH₂), 58.4 (CH), 81.9 (C), 171.3 (C). IR (KBr): 3248, 2951, 2866, 1732, 1462, 1366, 1319, 1231, 1146. EIMS *m/z*: 343 (M⁺), 301, 273, 264 (M–SO₂Me), 236, 222 (M–SO₂Me–Ac), 204, 187, 161, 137, 121, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₇H₂₉NNaO₄S, 366.1715; found, 366.1709.

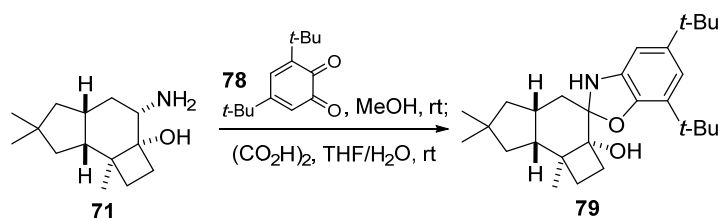


(2aRS,3SR,4aRS,7aRS,7bSR)-3-Amino-6,6,7b-trimethyldecahydro-1H-cyclobuta[e]inden-2a-ol (71): To a suspension of *N*-Bocaminoalcohol **66a** (249 mg, 0.999 mmol) in 1,4-dioxane/water (1:1, 10 mL) was added Ba(OH)₂ (1.71 g, 9.98 mmol). The mixture was heated at 110 °C for 18 h. After cooling to rt, the mixture was filtered through a glass filter and the filter cake was washed with MeOH. The filtrate and washings were combined and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/MeOH 10:1) to afford the title compound (216 mg, 97%) as white solids of mp 73–75 °C: R_f 0.10 (MeOH). ¹H NMR: 0.94 (s, 3H), 1.04 (s, 3H), 1.09 (ddd, *J* = 3.0, 3.5, 12.5, 1H), 1.20 (s, 3H), 1.23–1.47 (m, 6H), 1.67–1.71 (m, 2H), 1.81 (ddd, *J* = 6.5, 6.5, 13.0, 1H), 2.01 (ddd, *J* = 9.5, 10.0, 10.5, 1H), 2.13 (m, 1H), 3.01 (dd, *J* = 3.0, 12.5, 1H). ¹³C NMR: 21.4 (CH₃), 25.3 (CH₂), 31.9 (CH₃), 32.3 (CH₃), 32.5 (CH₂), 33.6 (CH₂), 35.7 (C), 38.3 (CH), 43.0 (CH₂), 45.5 (C), 46.0 (CH), 47.4 (CH₂), 55.3 (CH), 72.3 (C). IR (KBr): 3260, 2951, 2862, 1458, 1366, 1269, 1242, 1177, 1092, 1023. EIMS *m/z*: 223 (M⁺), 195, 178, 165, 149, 137, 121, 105. HRMS–ESI (*m/z*): [M+H]⁺ calcd. for C₁₄H₂₆NO, 224.2014; found, 224.2020.

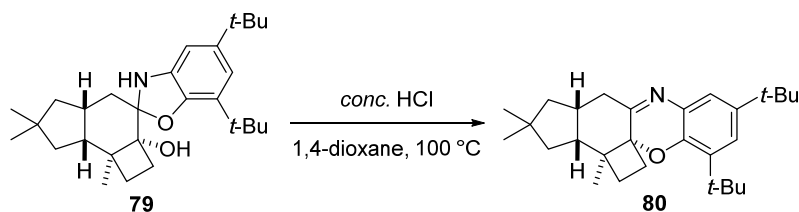


2-[(1RS,2RS)-4,4-Dimethyl-2-[(SR)-1-methyl-2-oxocyclobutyl]cyclopentyl]acetonitrile (73): To a solution of aminoalcohol **71** (5.4 mg, 24 μmol) in dry 1,2-dichloroethane (1 mL) was added NCS

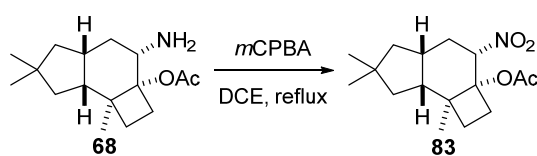
(6.4 mg, 48 μ mol) at 0 °C. The mixture was stirred for 30 min, and DBU (18 μ L, 0.12 mmol) was added. The mixture was warmed to rt and stirred for 30 min. The reaction mixture was diluted with EtOAc (10 mL), washed with 1 N HCl (2 x 2 mL) and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 9:1) to afford the title compound (4.8 mg, 92%) as colorless oil: R_f 0.44 (hexane/EtOAc 5:1). ¹H NMR: 1.03 (s, 3H), 1.15 (s, 3H), 1.30 (s, 3H), 1.40–1.48 (m, 2H), 1.56 (m, 1H), 1.75 (ddd, *J* = 6.0, 10.5, 11.0, 1H), 1.83 (dd, *J* = 8.0, 14.0, 1H), 2.09 (ddd, *J* = 7.0, 10.5, 11.0, 1H), 2.22 (dd, *J* = 11.0, 16.5, 1H), 2.31 (m, 1H), 2.36 (dd, *J* = 4.0, 16.5, 1H), 2.47 (m, 1H), 2.91 (ddd, *J* = 6.0, 10.5, 18.0, 1H), 3.16 (ddd, *J* = 7.0, 10.5, 18.0, 1H). ¹³C NMR: 20.0 (CH₂), 21.6 (CH₃), 22.2 (CH₂), 31.3 (CH₃), 32.0 (CH₃), 37.0 (C), 38.1 (CH), 40.8 (CH₂), 43.6 (CH₂), 45.4 (CH), 45.9 (CH₂), 64.6 (C), 119.6 (C), 214.2 (C). IR (KBr): 2959, 2934, 2868, 2243, 1767, 1458, 1072. EIMS *m/z*: 219 (M⁺), 204 (M–Me), 191, 176, 162, 148, 134, 120, 109. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₄H₂₁NNaO₃, 274.1419; found, 274.1420.



(2a'*RS*,4a'*RS*,7a'*RS*,7b'*SR*)-5,7-Di-*tert*-butyl-6',6',7b'-trimethyl-1',2',2a',4',4a',5',6',7',7a',7b'-decahydro-3*H*-spiro[benzo[*d*]oxazole-2,3'-cyclobuta[*e*]inden]-2a'-ol (79): To a solution of aminoalcohol **71** (16.8 mg, 75.2 μ mol) in dry MeOH (1 mL) was added 3,5-di-*tert*-butyl-1,2-benzoquinone **78** (18.6 mg, 84.4 μ mol). The mixture was stirred at rt for 70 min. Then, THF (1.5 mL), water (0.5 mL), and (CO₂H)₂ (20 mg) were added to the mixture. After 1.5 h, water (5 mL) was added, and the whole was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford the title compound (15.1 mg, 47%) as green solids of mp 120–125 °C: R_f 0.52 (hexane/EtOAc 5:1). ¹H NMR: 0.89 (s, 3H), 0.95 (s, 3H), 1.16 (s, 3H), 1.21 (dd, *J* = 8.5, 15.0, 1H), 1.26 (s, 9H), 1.37 (m, 1H), 1.38 (s, 9H), 1.44–1.46 (m, 2H), 1.52 (m, 1H), 1.75 (dd, *J* = 8.0, 14.0, 1H), 1.80 (m, 1H), 1.97 (m, 1H), 2.15 (m, 1H), 2.35 (m, 1H), 2.46 (m, 1H), 2.67 (br s, 1H), 2.74 (dd, *J* = 10.0, 15.0, 1H), 3.55 (br s, 1H), 6.47 (s, 1H), 6.62 (s, 1H). ¹³C NMR: 21.6 (CH₃), 29.9 (CH₃), 30.0 (CH₃), 31.6 (CH₃), 31.8 (CH₃), 34.0 (CH₂), 34.3 (C), 34.8 (C), 37.2 (CH₂), 40.2 (C), 40.9 (CH), 44.4 (CH₂), 47.9 (CH₂), 48.4 (CH₂), 52.0 (C), 59.9 (CH), 72.0 (C), 101.4 (C), 108.6 (CH), 112.4 (CH), 131.8 (C), 135.2 (C), 137.9 (C), 143.6 (C). IR (KBr): 3379, 2951, 2866, 1597, 1439, 1389, 1362, 1323, 1238, 1200, 1165, 1119, 1076. EIMS *m/z*: 425 (M⁺), 397, 382, 369, 312, 286, 272, 258, 246, 164, 107. HRMS–ESI (*m/z*): [M+H]⁺ calcd. for C₂₈H₄₄NO₂, 426.3372; found, 426.3372.

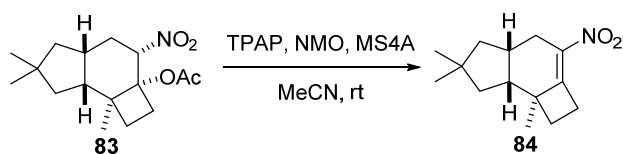


(2aSR,2bRS,5aRS,12aRS)-9,11-Di-*tert*-butyl-2a,4,4-trimethyl-2,2a,2b,3,4,5,5a,6-octahydro-1H-cyclobuta[*d*]cyclopenta[*b*]phenoxazine (80): To a solution of hemiaminal **79** (15.8 mg, 37.1 μ mol) in 1,4-dioxane (0.5 mL) was added *conc.* HCl (0.050 mL). The mixture was stirred for 53 h at 100 °C. After cooling to rt, the reaction was quenched by the addition of saturated NaHCO₃ (3 mL). The whole was extracted with EtOAc (3 x 3 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (12.4 mg, 82%) as green oil: *R*_f 0.54 (hexane/EtOAc 95:5 x 2). ¹H NMR: 0.96 (s, 3H), 1.03 (s, 3H), 1.18 (m, 1H), 1.20 (s, 3H), 1.31 (s, 9H), 1.35 (s, 9H), 1.38–1.45 (m, 2H), 1.70 (dd, *J* = 8.5, 13.5, 1H), 1.73 (ddd, *J* = 5.5, 13.0, 13.0, 1H), 1.84 (dd, *J* = 7.0, 12.0, 1H), 1.87 (m, 1H), 2.04 (dd, *J* = 12.0, 12.5, 1H), 2.12 (m, 1H), 2.23–2.30 (m, 2H), 2.46 (m, 1H), 7.12 (d, *J* = 2.0, 1H), 7.26 (d, *J* = 2.0, 1H). ¹³C NMR: 19.2 (CH₃), 29.7 (CH₃), 31.6 (CH₃), 32.0 (CH₃), 32.3 (CH₃), 32.5 (CH₂), 32.6 (CH₂), 34.4 (C), 34.9 (C), 35.7 (CH), 38.7 (C), 41.5 (CH₂), 43.1 (CH₂), 45.5 (C), 46.1 (CH₂), 56.9 (CH), 78.1 (C), 122.7 (CH), 123.2 (CH), 130.2 (C), 135.6 (C), 140.8 (C), 142.7 (C), 176.1 (C). IR (neat): 2955, 2870, 1678, 1466, 1408, 1362, 1296, 1261, 1234. EIMS *m/z*: 407 (M⁺), 392 (M–Me), 379, 364, 350 (M–*t*-Bu), 336, 322, 311, 282, 258, 245, 95, 57 (*t*-Bu). HRMS-ESI (*m/z*): HRMS–ESI (*m/z*): [M+H]⁺ calcd. for C₂₈H₄₂NO, 408.3266; found, 408.3272.

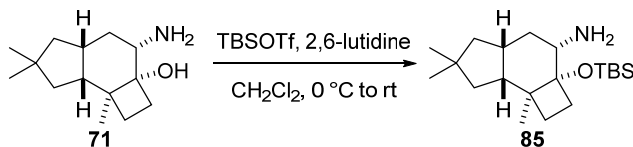


(2aRS,3SR,4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-nitrodecahydro-1H-cyclobuta[*e*]inden-2a-yl Acetate (83): To a solution of *O*-acetylaminoalcohol **68** (6.4 mg, 24 μ mol) in dry 1,2-dichloroethane (1.5 mL) was added *m*CPBA (21.5 mg, 0.125 mmol). The mixture was heated under reflux for 1 h. After cooling to rt, the reaction mixture was diluted with EtOAc (10 mL), washed with saturated aqueous NaHCO₃ (3 x 3 mL) and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 97:3) to afford the title compound (4.8 mg, 67%) as colorless oil: *R*_f 0.33 (hexane/EtOAc 5:1). ¹H NMR: 0.97 (s, 3H), 1.12 (s, 3H), 1.18 (s, 3H), 1.35 (dd, *J* = 1.0, 14.0, 1H), 1.45 (dd, *J* = 6.5, 12.5, 1H), 1.51–1.69 (m, 4H), 1.78 (dd, *J* = 8.0, 14.0, 1H), 1.86 (ddd, *J* = 6.5, 6.5, 13.0, 1H), 2.01 (s, 3H), 2.09 (ddd, *J* = 12.5, 13.0, 13.0, 1H), 2.16 (m,

1H), 2.71 (ddd, $J = 9.5, 10.0, 12.5$, 1H), 2.80 (ddd, $J = 2.0, 8.0, 12.5$, 1H), 4.77 (dd, $J = 3.0, 13.0$, 1H). ^{13}C NMR: 21.1 (CH₃), 21.6 (CH₃), 27.9 (CH₂), 28.8 (CH₂), 30.6 (CH₂), 31.5 (CH₃), 32.0 (CH₃), 35.8 (C), 37.2 (CH), 43.0 (CH₂), 44.8 (CH), 46.8 (CH₂), 47.1 (C), 79.7 (C), 88.8 (CH), 169.5 (C). IR (KBr): 2951, 2864, 1744, 1549, 1458, 1369, 1246, 1233. EIMS m/z : 249 (M–NO₂), 220, 207, 189, 179, 161, 147, 135, 121. HRMS–ESI (m/z): [M+Na]⁺ calcd. for C₁₆H₂₅NNaO₄, 318.1681; found, 318.1676.

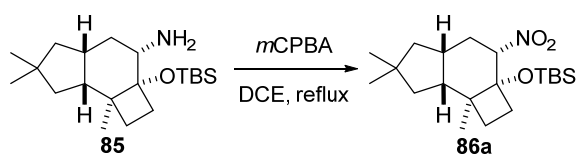


(4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-nitro-2,4,4a,5,6,7,7a,7b-octahydro-1H-cyclobuta[e]indene (84): To a solution of *O*-acetylnitroalcohol **83** (7.8 mg, 26 μmol) in dry MeCN (1 mL) was added successively powdered MS4A (14.3 mg), NMO (9.4 mg, 80 μmol), and TPAP (4.6 mg, 13 μmol) at rt. After 15 min, the mixture was filtered through a short pad of silica gel and rinsed with EtOAc. The combined filtrates were concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (2.2 mg, 36%) as colorless oil: R_f 0.67 (hexane/EtOAc 5:1). R_f 0.25 (EtOAc). ^1H NMR: 0.97 (s, 3H), 1.07 (m, 1H), 1.09 (s, 3H), 1.20 (s, 3H), 1.34 (dd, $J = 11.0, 12.5$, 1H), 1.45 (ddd, $J = 1.5, 8.0, 12.5$, 1H), 1.68 (ddd, $J = 1.5, 7.5, 12.5$, 1H), 1.84 (m, 1H), 2.00 (m, 1H), 2.07 (ddd, $J = 4.5, 11.0, 11.0$, 1H), 2.29 (ddd, $J = 8.0, 11.0, 11.0$, 1H), 2.57 (m, 1H), 3.15 (dd, $J = 7.0, 15.5$, 1H), 3.19–3.33 (m, 2H). ^{13}C NMR: 20.0 (CH₃), 27.2 (CH₂), 27.3 (CH₃), 29.6 (CH₂), 29.6 (CH₃), 36.5 (CH₂), 39.9 (C), 40.5 (CH₂), 41.2 (CH), 45.8 (CH), 47.9 (C), 47.9 (CH₂), 140.7 (C), 164.2 (C). IR (neat): 2955, 2936, 2866, 1508, 1462, 1335. EIMS m/z : 235 (M⁺), 218, 205, 189 (M–NO₂), 176, 159, 145, 133, 119, 105. HRMS–ESI (m/z): [M+Na]⁺ calcd. for C₁₄H₂₁NNaO₂, 258.1470; found, 258.1474.

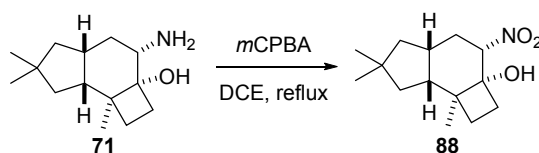


(2aRS,3SR,4aRS,7aRS,7bSR)-2a-[(*tert*-Butyldimethylsilyl)oxy]-6,6,7b-trimethyldecahydro-1H-cyclobuta[e]inden-3-amine (85): To a solution of aminoalcohol **71** (422 mg, 1.89 mmol) in dry CH₂Cl₂ (13 mL) were added 2,6-lutidine (1.1 mL, 9.5 mmol) and TBSOTf (1.3 mL, 5.7 mmol) at 0 °C. After 1.5 h, the mixture was warmed to rt and stirred for 1 h. The reaction was quenched by the addition of water (20 mL). The whole was extracted with EtOAc (30 mL + 2 x 15 mL), and the combined organic layers were washed with saturated aqueous NaHCO₃ and brine (15 mL each),

dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford the title compound (572 mg, 89%) as pale yellow oil: ¹H NMR: 0.07 (s, 3H), 0.19 (s, 3H), 0.90 (s, 9H), 0.92 (s, 3H), 1.04 (s, 3H), 1.09 (s, 3H), 1.18 (ddd, *J* = 3.0, 3.0, 12.5, 1H), 1.24 (d, *J* = 13.5, 1H), 1.28–1.39 (m, 4H), 1.49 (m, 1H), 1.67 (dd, *J* = 8.0, 13.5, 1H), 1.76 (ddd, *J* = 6.5, 7.0, 13.0, 1H), 1.83 (m, 1H), 2.09 (ddd, *J* = 9.5, 9.5, 10.0, 1H), 2.11 (m, 1H), 2.68 (dd, *J* = 3.0, 12.5, 1H). ¹³C NMR (C₆D₆): –2.0 (CH₃), –1.3 (CH₃), 18.8 (C), 23.4 (CH₃), 26.3 (CH₃), 27.3 (CH₂), 31.6 (CH₂), 32.1 (CH₃), 32.6 (CH₃), 35.8 (C), 36.1 (CH₂), 39.7 (CH), 43.8 (CH₂), 46.3 (CH), 47.0 (C), 47.9 (CH₂), 57.0 (CH), 77.4 (C). IR (neat): 3375, 2951, 2932, 2859, 1462, 1362, 1254, 1180, 1107, 1042. EIMS *m/z*: 337 (M⁺), 280 (M–*t*-Bu), 263, 252, 243, 235, 197, 186, 170, 165, 147, 128, 121, 108. HRMS–ESI (*m/z*): [M+H]⁺ calcd. for C₂₀H₃₀NOSi, 338.2879; found, 338.2878.

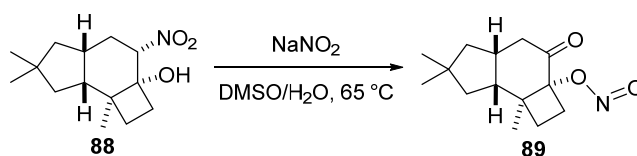


***tert*-Butyldimethyl[[(2*aRS*,3*SR*,4*aRS*,7*aRS*,7*bSR*)-6,6,7*b*-trimethyl-3-nitrodecahydro-1*H*-cyclobuta[*e*]inden-2*a*-yl]oxy]silane (86a):** To a solution of *O*-TBSaminoalcohol **85** (557 mg, 1.65 mmol) in dry 1,2-dichloroethane (10 mL) was added *m*CPBA (1.42 g, 8.23 mmol). The mixture was heated under reflux for 30 min. After cooling to rt, the reaction mixture was diluted with EtOAc (30 mL), washed with saturated aqueous NaHCO₃ (3 x 10 mL) and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (537 mg, 88%) as colorless oil: R_f 0.71 (hexane/EtOAc 5:1). ¹H NMR: –0.08 (s, 3H), 0.16 (s, 3H), 0.85 (s, 9H), 0.95 (s, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.36 (d, *J* = 13.5, 1H), 1.40–1.46 (m, 3H), 1.51 (m, 1H), 1.67 (ddd, *J* = 3.0, 3.0, 12.0, 1H), 1.74 (dd, *J* = 7.5, 13.5, 1H), 1.82 (ddd, *J* = 7.0, 7.5, 13.0, 1H), 2.03 (ddd, *J* = 12.0, 12.5, 12.5, 1H), 2.10 (m, 1H), 2.29 (ddd, *J* = 9.5, 10.0, 11.0, 1H), 2.65 (ddd, *J* = 1.5, 7.5, 11.0, 1H), 4.56 (dd, *J* = 3.0, 12.5, 1H). ¹³C NMR: –3.5 (CH₃), –1.6 (CH₃), 18.2 (C), 22.7 (CH₃), 25.9 (CH₃), 26.1 (CH₂), 27.8 (CH₂), 30.8 (CH₂), 31.8 (CH₃), 32.3 (CH₃), 35.7 (C), 37.7 (CH), 43.2 (CH₂), 45.4 (CH), 47.1 (CH₂), 48.6 (C), 77.6 (C), 90.0 (CH). IR (neat): 2951, 2932, 2862, 1551, 1462, 1373, 1312, 1258, 1177, 1126, 1099, 1045, 1029. EIMS *m/z*: 321, 310 (M–*t*-Bu), 293, 280, 265, 252, 238, 223, 184, 162, 147, 133, 121, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₂₀H₃₇NNaO₃Si, 390.2440; found, 390.2436.



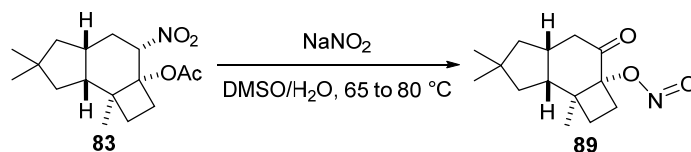
(2aRS,3SR,4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-nitrodecahydro-1H-cyclobuta[e]inden-2a-ol

(88): To a solution of aminoalcohol **71** (33.1 mg, 0.148 mmol) in dry 1,2-dichloroethane (2 mL) was added *m*CPBA (128 mg, 0.742 mmol). The mixture was heated under reflux for 1 h. After cooling to rt, the reaction mixture was diluted with EtOAc (10 mL), washed with saturated aqueous NaHCO₃ (3 x 3 mL) and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 97:3) to afford the title compound (13.0 mg, 35%) as colorless oil: R_f 0.33 (hexane/EtOAc 5:1). ¹H NMR: 0.96 (s, 3H), 1.10 (s, 3H), 1.20 (s, 3H), 1.38 (d, *J* = 13.5, 1H), 1.44–1.48 (m, 3H), 1.54 (m, 1H), 1.78 (dd, *J* = 7.5, 13.5, 1H), 1.81 (ddd, *J* = 3.5, 3.5, 12.5, 1H), 1.88 (m, 1H), 1.96 (ddd, *J* = 12.5, 13.0, 13.0, 1H), 2.12–2.18 (m, 3H), 2.53 (ddd, *J* = 1.5, 8.0, 11.5, 1H), 4.61 (dd, *J* = 3.5, 13.0, 1H). ¹³C NMR: 20.9 (CH₃), 25.3 (CH₂), 27.9 (CH₂), 31.7 (CH₃), 32.1 (CH₃), 32.4 (CH₂), 35.9 (C), 37.5 (CH), 42.9 (CH₂), 45.1 (CH), 47.0 (CH₂), 47.2 (C), 74.6 (C), 89.6 (CH). IR (KBr): 3566, 2967, 2949, 2868, 1545, 1458, 1364, 1234, 1161, 1088, 1040. EIMS *m/z*: 225, 207 (M–NO₂), 179, 161, 147, 135, 121, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₄H₂₃NNaO₃, 276.1576; found, 276.1570.

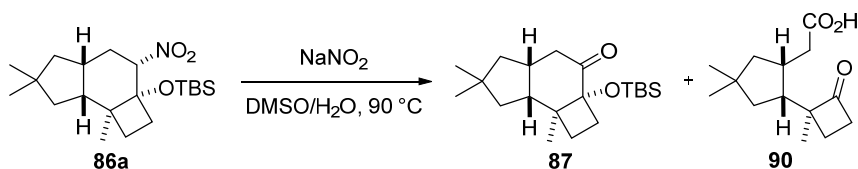


(2aRS,4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-oxodecahydro-1H-cyclobuta[e]inden-2a-yl Nitrite

(89): To a solution of nitroalcohol **88** (3.2 mg, 13 μmol) in DMSO/water (7:1, 1 mL) was added NaNO₂ (9.4 mg, 0.14 mmol). The mixture was stirred at 65 °C for 9 h. Then, NaNO₂ (27.1 mg, 0.393 mmol) was added again to the mixture. After additional 22 h, water (3 mL) was added, and the whole was extracted with Et₂O (3 x 3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 9:1) to afford the title compound (1.0 mg, 31%) as colorless oil: R_f 0.44 (hexane/EtOAc 5:1). ¹H NMR: 0.91 (s, 3H), 1.10 (s, 3H), 1.10 (s, 3H), 1.38–1.45 (m, 3H), 1.77 (m, 1H), 1.86 (ddd, *J* = 7.0, 8.5, 15.5, 1H), 2.04 (ddd, *J* = 6.5, 9.5, 15.5, 1H), 2.43–2.55 (m, 5H), 2.75 (ddd, *J* = 7.0, 9.5, 16.0, 1H). ¹³C NMR: 19.6 (CH₃), 27.5 (CH₃), 29.4 (CH₃), 34.5 (CH₂), 36.2 (CH₂), 38.4 (CH₂), 39.8 (CH), 42.2 (CH₂), 42.3 (C), 47.7 (CH₂), 54.5 (CH), 54.6 (C), 104.5 (C), 208.7 (C). IR (neat): 2955, 2866, 1755, 1539, 1462, 1385, 1354. EIMS *m/z*: 221 (M–NO), 189, 179, 161, 147, 133, 123, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₄H₂₁NNaO₃, 274.1419; found, 274.1420.



(2aRS,4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-oxodecahydro-1H-cyclobuta[e]inden-2a-yl Nitrite (89): To a solution of *O*-acetylnitroalcohol **83** (3.9 mg, 13 μ mol) in DMSO/water (7:1, 1 mL) was added NaNO₂ (9.6 mg, 0.14 mmol). The mixture was stirred at 65 °C for 6 h. Then, NaNO₂ (18.9 mg, 0.274 mmol) was added again to the mixture. The mixture was stirred at 80 °C for 10.5 h. Then, water (3 mL) was added, and the whole was extracted with Et₂O (3 x 3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 96:4) to afford the title compound (0.5 mg, 15%) as colorless oil.

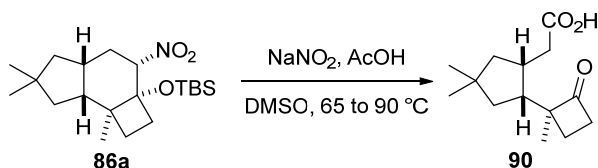


(2aRS,4aRS,7aRS,7bSR)-2a-((tert-Butyldimethylsilyl)oxy)-6,6,7b-trimethyloctahydro-1H-cyclobuta[e]inden-3(7bH)-one (87) and 2-[(1RS,2RS)-4,4-Dimethyl-2-((SR)-1-methyl-2-oxocyclobutyl)cyclopentyl]acetic Acid (90): To a solution of *O*-TBSnitroalcohol **86a** (16.7 mg, 45.4 μ mol) in DMSO/water (7:1, 0.5 mL) was added NaNO₂ (15.8 mg, 0.229 mmol). The mixture was stirred at 90 °C for 19 h. After cooling to rt, water (3 mL) was added, and the whole was extracted with Et₂O (3 x 3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compounds (2.3 mg and 2.7 mg, 15% and 25%, respectively).

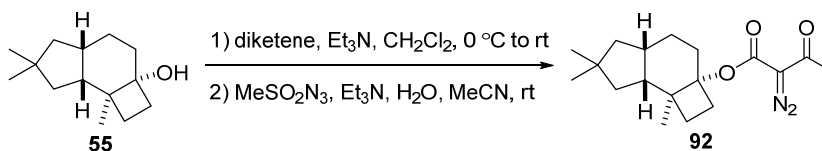
87: Colorless oil. R_f 0.46 (toluene/hexane 1:2). ¹H NMR: 0.02 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 0.91 (s, 3H), 1.01 (s, 3H), 1.13 (m, 1H), 1.16–1.20 (m, 4H), 1.41 (dd, *J* = 7.0, 12.5, 1H), 1.59 (ddd, *J* = 2.5, 11.0, 11.5, 1H), 1.70–1.79 (m, 2H), 2.07–2.13 (m, 2H), 2.24–2.29 (m, 2H), 2.71–2.81 (m, 2H). ¹³C NMR: –3.5 (CH₃), –1.0 (CH₃), 18.6 (C), 22.7 (CH₃), 25.9 (CH₃), 26.9 (CH₂), 28.3 (CH₃), 29.0 (CH₂), 30.2 (CH₃), 37.1 (C), 38.5 (CH), 41.0 (CH₂), 43.5 (CH₂), 45.6 (CH), 48.7 (CH₂), 50.7 (C), 79.9 (C), 212.3 (C). IR (neat): 2955, 2930, 2857, 1717, 1458, 1260, 1098, 1028. EIMS *m/z*: 321 (M–Me), 279 (M–*t*-Bu), 251, 221, 187, 169, 155, 107. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₂₀H₃₆NaO₂Si, 359.2382; found, 359.2389.

90: Colorless oil. R_f 0.42 (hexane/EtOAc 1:1). ¹H NMR: 1.01 (s, 3 H), 1.13 (s, 3H), 1.30 (s, 3H), 1.35–1.47 (m, 3H), 1.70–1.75 (m, 2H), 2.14 (ddd, *J* = 7.0, 10.0, 11.0, 1H), 2.24 (dd, *J* = 13.0, 15.0,

1H), 2.29 (ddd, $J = 7.0, 7.0, 13.0$, 1H), 2.35 (dd, $J = 3.0, 15.0$, 1H), 2.57 (m, 1H), 2.88 (ddd, $J = 6.0, 10.0, 17.5$, 1H), 3.12 (ddd, $J = 7.0, 10.5, 17.5$, 1H). ^{13}C NMR: 21.7 (CH₃), 22.1 (CH₂), 31.4 (CH₃), 32.2 (CH₃), 35.8 (CH₂), 37.0 (C), 37.4 (CH), 41.4 (CH₂), 43.5 (CH₂), 45.3 (CH), 46.0 (CH₂), 65.1 (C), 177.8 (C), 215.3 (C). IR (neat): 3412, 2955, 2932, 2868, 1773, 1707, 1385, 1069. EIMS m/z : 210, 195, 181, 167, 153, 139, 121, 107. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for C₁₄H₂₂NaO₃, 261.1467; found, 261.1463.



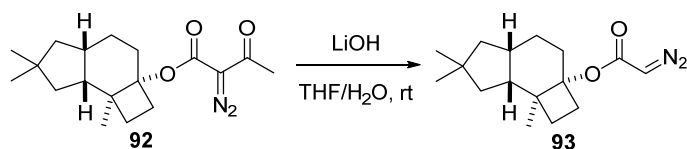
2-[(1*RS*,2*RS*)-4,4-Dimethyl-2-[(*SR*)-1-methyl-2-oxocyclobutyl]cyclopentyl]acetic Acid (90): To a solution of *O*-TBSnitroalcohol **86a** (3.4 mg, 9.2 μmol) in DMSO (0.5 mL) were added NaNO₂ (6.5 mg, 94 μmol) and acetic acid (5.3 μL , 93 μmol). The mixture was stirred at 65 °C for 4 h and 90 °C for 4 h. After cooling to rt, water (3 mL) was added, and the whole was extracted with Et₂O (3 x 3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 3:1) to afford the title compounds (1.0 mg, 46%) as colorless oil.



(2*aRS*,4*aSR*,7*aRS*,7*bSR*)-6,6,7*b*-Trimethyldecahydro-1*H*-cyclobuta[e]inden-2*a*-yl

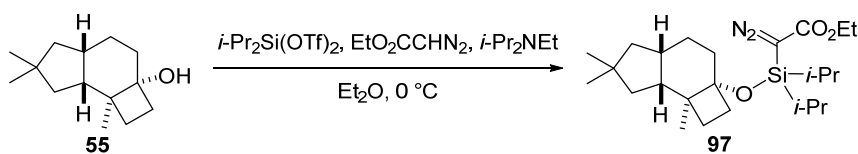
2-Diazo-3-oxobutanoate (92): To a solution of alcohol **55** (10.5 mg, 50.4 μmol) and Et₃N (0.035 mL, 0.25 mmol) in dry CH₂Cl₂ (1 mL) was added diketene (33 μL , 0.43 mmol) at 0 °C. After 10 min, the reaction mixture was warmed to rt and stirred for 20 min. Then, the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in MeCN (1 mL) and treated with Et₃N (0.035 mL, 0.25 mmol), water (4.5 μL , 0.25 mmol), and methanesulfonyl azide (37 μL , 0.43 mmol) at rt. After 26 h, water (3 mL) was added, and the whole was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 97:3) to afford the title compound (12.0 mg, 75%) as colorless oil: R_f 0.52 (hexane/EtOAc 5:1). ^1H NMR (C₆D₆): 0.87 (s, 3H), 0.95 (s, 3H), 1.04 (s, 3H), 1.09–1.32 (m, 5 H), 1.36–1.46 (m, 2H), 1.58 (dd, $d = 8.5, 13.0$, 1H), 1.74 (ddd, $J = 7.0, 7.0, 13.0$, 1H), 1.93–2.06 (m, 3H), 2.31 (s, 3H), 2.31–2.37 (m, 2H). ^{13}C NMR (C₆D₆): 22.4 (CH₃), 25.0 (CH₂), 28.0 (CH₃), 28.3 (CH₂), 28.7 (CH₃), 30.6 (CH₂), 30.6 (CH₃), 31.8

(CH₂), 35.1 (CH), 36.9 (C), 44.0 (C), 45.0 (CH₂), 45.2 (CH), 48.2 (CH₂), 82.3 (C), 159.8 (C), 188.8 (C). IR (neat): 2951, 2932, 2866, 2137, 1717, 1659, 1462, 1366, 1323, 1250, 1153, 1064. FABMS *m/z*: 341 (M+Na), 191, 176, 151. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₈H₂₆N₂NaO₃, 341.1841; found, 341.1842.



(2a*RS*,4a*SR*,7a*RS*,7b*SR*)-6,6,7b-Trimethyldecahydro-1*H*-cyclobuta[*e*]inden-2a-yl

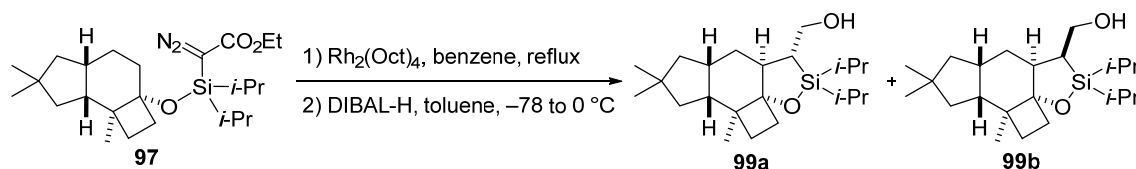
2-Diazoacetate (93): To a solution of diazoacetate **92** (9.8 mg, 31 μmol) in THF/water (2:1, 1.5 mL) was added LiOH·H₂O (12.8 mg, 0.305 mmol) at rt. After 19 h, water (2.5 mL) was added, and the whole was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (7.3 mg, 84%) as pale yellow oil: *R*_f 0.42 (toluene). ¹H NMR: 0.91 (s, 3H), 1.05 (s, 3H), 1.10 (s, 3H), 1.16–1.24 (m, 2H), 1.32 (m, 1H), 1.39 (ddd, *J* = 1.0, 7.0, 12.0, 1H), 1.43 (m, 1H), 1.59–1.66 (m, 2H), 1.69 (ddd, *J* = 1.0, 8.0, 13.0, 1H), 1.91–1.99 (m, 2H), 2.05 (ddd, *J* = 3.5, 8.0, 14.0, 1H), 2.24–2.30 (m, 2H), 2.38 (ddd, *J* = 10.0, 10.5, 12.0, 1H), 4.65 (br s, 1H). ¹³C NMR: 22.2 (CH₃), 24.9 (CH₂), 28.2 (CH₂), 28.7 (CH₃), 30.4 (CH₂), 30.5 (CH₃), 31.5 (CH₂), 34.9 (CH), 36.9 (C), 43.8 (C), 44.8 (CH₂), 45.1 (CH), 46.5 (CH), 48.0 (CH₂), 81.7 (C). IR (neat): 2947, 2932, 2866, 2110, 1686, 1462, 1377, 1342, 1234, 1200, 1061. HRMS–ESI (*m/z*): [M+Na]⁺ calcd. for C₁₆H₂₄N₂NaO₂, 299.1735; found, 299.1732.



Ethyl

2-Diazo-2-(diisopropyl){(2a*RS*,4a*SR*,7a*RS*,7b*SR*)-6,6,7b-trimethyldecahydro-1*H*-cyclobuta[*e*]inden-2a-yl}oxy)silyl)acetate (97): To a solution of diisopropylsilyl bis(trifluoromethanesulfonate) (2.26 g, 5.48 mmol) in dry Et₂O (6 mL) at 0 °C was added a mixture of ethyl diazoacetate⁷² (634 mg, 5.56 mmol) and *i*-Pr₂NEt (0.95 mL, 5.5 mmol) in dry Et₂O (3 mL). The resulting white suspension was stirred at 0 °C for 30 min and at rt for 1 h. After recooling to 0 °C, a solution of alcohol **55** (763 mg, 3.66 mmol) and *i*-Pr₂NEt (0.95 mL, 5.5 mmol) in dry Et₂O (3 mL + 1 mL washing) was added to the mixture. After 1 h, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (20 mL). The whole was extracted with EtOAc (3 x 10 mL), and the combined organic layers were

washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (1.53 g, 96%) as pale yellow oil: R_f 0.42 (hexane/EtOAc 95:5). ¹H NMR: 0.90 (s, 3H), 1.03 (s, 3H), 1.07–1.10 (m, 15H), 1.19–1.39 (m, 7H), 1.27 (t, *J* = 7.0, 3H), 1.46 (m, 1H), 1.60 (m, 1H), 1.64–1.70 (m, 2H), 1.81 (ddd, *J* = 2.5, 10.5, 13.0, 1H), 1.86–1.95 (m, 2H), 2.14 (m, 1H), 2.22 (m, 1H), 4.19 (q, *J* = 7.0, 2H). ¹³C NMR: 13.9 (CH), 14.1 (CH), 14.4 (CH₃), 17.3 (CH₃), 17.3 (CH₃), 17.4 (CH₃), 17.4 (CH₃), 22.8 (CH₃), 25.4 (CH₂), 26.7 (CH₂), 28.8 (CH₃), 30.5 (CH₃), 33.2 (CH₂), 34.6 (CH₂), 35.2 (CH), 36.8 (C), 44.3 (C), 44.7 (CH₂), 45.3 (C), 45.6 (CH), 48.2 (CH₂), 60.5 (CH₂), 76.0 (C), 169.2 (C). IR (neat): 2947, 2932, 2866, 2091, 1694, 1462, 1385, 1366, 1261, 1204, 1184, 1126, 1103, 1069, 1045, 1015. EIMS *m/z*: 406, 391, 363, 349, 335, 305, 267, 254, 239, 227, 211, 201, 187, 159, 133, 105, 91. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₄H₄₂N₂NaO₃Si, 457.2862; found, 457.2866.



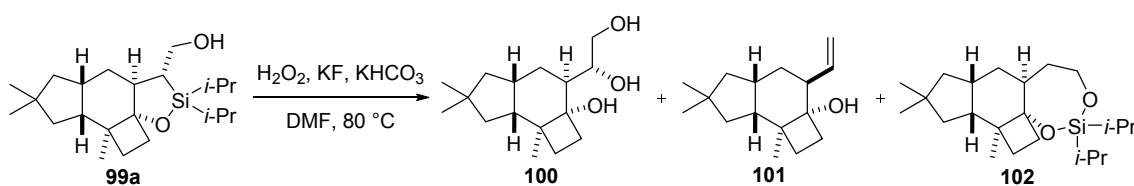
{(2aSR,5SR,5aRS,6aSR,9aRS,9bSR)-4,4-Diisopropyl-8,8,9b-trimethyldodecahydrocyclobuta[6,7]indeno[5,6-d][1,2]oxasilol-5-yl}methanol (99a) and

{(2aSR,5SR,5aRS,6aSR,9aRS,9bSR)-4,4-Diisopropyl-8,8,9b-trimethyldodecahydrocyclobuta[6,7]indeno[5,6-d][1,2]oxasilol-5-yl}methanol (99b): To a solution of diazoacetate **97** (1.53 g, 3.52 mmol) in dry benzene (15 mL) was added Rh₂(Oct)₄ (27.4 mg, 35.2 μmol). The mixture was stirred for 5 h under reflux. After cooling to rt, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford crude products. Then, the mixture was dissolved in toluene (10 mL). After cooling to -78 °C, 1.0 M toluene solution of DIBAL-H (9.3 mL, 9.3 mmol) was added to the mixture. The mixture was stirred for 30 min at -78 °C and for 15 min at 0 °C. The reaction was quenched by the addition of saturated aqueous Rochelle salt (40 mL). The mixture was stirred for 40 min at rt. Then, the whole was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2 to 94:6) to afford the title compounds (517 mg and 125 mg, 41% and 10%, respectively).

99a: Colorless oil. R_f 0.58 (hexane/EtOAc 5:1). ¹H NMR: 0.89 (s, 3H), 1.01 (s, 3H), 1.02–1.07 (s, 14H), 1.11–1.17 (m, 2H), 1.15 (s, 3H), 1.33 (ddd, *J* = 8.0, 8.0, 13.0, 1H), 1.37–1.43 (m, 3H), 1.54 (m, 1H), 1.73 (ddd, *J* = 6.5, 13.0, 13.0, 1H), 1.79 (ddd, *J* = 2.0, 8.5, 12.5, 1H), 1.85–1.93 (m, 2H), 2.00–2.10 (m, 2H), 2.55 (m, 1H), 3.84 (dd, *J* = 8.0, 10.0, 1H), 3.94 (dd, *J* = 8.0, 10.0, 1H), 5.30 (s, 1H). ¹³C NMR: 12.5 (CH), 12.6 (CH), 17.5 (CH₃), 17.7 (CH₃), 17.9 (CH₃), 18.0 (CH₃), 21.6 (CH₃), 26.8 (CH₃), 27.3 (CH₂), 28.2 (CH₂), 29.2 (CH), 29.6 (CH₃), 31.1 (CH₂), 34.4 (CH), 37.7 (C), 42.5

(CH), 44.8 (C), 46.5 (CH₂), 46.9 (CH), 50.2 (CH₂), 63.2 (CH₂), 83.2 (C). IR (neat): 3387, 2947, 2928, 2866, 1462, 1381, 1365, 1246, 1119, 1084, 1026. EIMS m/z : 364 (M⁺), 349 (M-Me), 336, 321 (M-*i*-Pr), 307, 293, 282, 239, 211, 171, 131, 105. HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₂₂H₄₀NaO₂Si, 387.2695; found, 387.2698.

99b: White solids of mp 119–121 °C. R_f 0.33 (hexane/EtOAc 5:1). ¹H NMR: 0.88 (s, 3H), 1.03 (s, 3H), 1.07–1.15 (m, 18H), 1.27 (dd, J = 10.5, 13.0, 1H), 1.32 (ddd, J = 3.0, 11.5, 11.5, 1H), 1.40 (m, 2H), 1.49 (m, 1H), 1.72 (m, 1H), 1.86 (m, 1H), 1.95–2.11 (m, 3H), 2.44 (ddd, J = 2.5, 9.5, 12.5, 1H), 2.54 (m, 1H), 3.52 (s, 1H), 3.86–3.91 (m, 2H). ¹³C NMR: 10.8 (CH), 11.2 (CH), 19.2 (CH₃), 19.5 (CH₃), 19.6 (CH₃), 20.7 (CH₃), 22.3 (CH₃), 26.4 (CH₃), 27.1 (CH₂), 27.9 (CH), 29.0 (CH₂), 29.2 (CH₃), 30.6 (CH₂), 33.6 (CH), 37.7 (C), 37.9 (CH), 45.0 (CH), 45.7 (C), 46.6 (CH₂), 48.8 (CH₂), 62.7 (CH₂), 78.4 (C). IR (KBr): 3300, 2943, 2926, 2866, 1458, 1382, 1364, 1310, 1254, 1171, 1128, 1101, 1072, 1034, 1003. EIMS m/z : 364 (M⁺), 349 (M-Me), 336, 321 (M-*i*-Pr), 307, 293, 282, 239, 211, 171, 131, 105. HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₂₂H₄₀NaO₂Si, 387.2695; found, 387.2697.



(*RS*)-1-[(2*aSR*,3*SR*,4*aSR*,7*aSR*,7*bSR*)-2*a*-Hydroxy-6,6,7*b*-trimethyldecahydro-1*H*-cyclobuta[*e*]inden-3-yl]ethane-1,2-diol (100) and

(2*aSR*,3*SR*,4*aSR*,7*aSR*,7*bSR*)-6,6,7*b*-Trimethyl-3-vinyldecahydro-1*H*-cyclobuta[*e*]inden-2*a*-ol (101) and

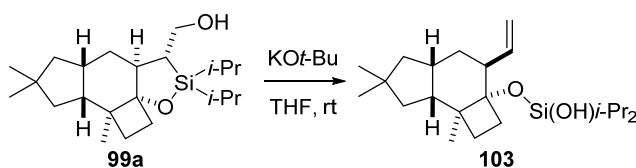
(2*aSR*,7*aSR*,8*aSR*,11*aSR*,11*bSR*)-4,4-Diisopropyl-10,10,11*b*-trimethyldodecahydrocyclobuta[4,5]indeno[5,6-*d*][1,3,2]dioxasilepine (102): To a solution of alcohol 99a (66.2 mg, 0.182 mmol) in dry DMF (1 mL) were added KHCO₃ (55.8 mg, 0.557 mmol), KF (32.0 mg, 0.551 mmol) and 30% H₂O₂ (186 μL, 1.8 mmol). The mixture was stirred at 80 °C for 14 h. After cooling to rt, the reaction was quenched by the addition of saturated aqueous Na₂S₂O₃ (3 mL). The whole was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1 to 1:1) to afford the title compounds (15.8 mg, 18.1 mg and 10.9 mg, 32%, 42% and 16%, respectively).

100: Colorless oil. R_f 0.25 (hexane/EtOAc 1:1). ¹H NMR: 0.88 (s, 3H), 1.04 (s, 3H), 1.13–1.19 (m, 1H), 1.14 (s, 3H), 1.21–1.28 (m, 2H), 1.36–1.43 (m, 2H), 1.52 (m, 1H), 1.63–1.74 (m, 2H), 1.91 (m, 1H), 1.98–2.08 (m, 2H), 2.34 (ddd, J = 3.0, 9.5, 12.5, 1H), 2.51 (m, 1H), 3.54 (m, 1H), 3.75–3.77 (m, 2H). ¹³C NMR: 22.0 (CH₃), 26.3 (CH₃), 27.3 (CH₂), 28.0 (CH₂), 28.4 (CH₂), 29.0 (CH₃), 32.6 (CH),

37.8 (C), 38.4 (CH), 44.5 (CH), 45.2 (C), 46.1 (CH₂), 48.7 (CH₂), 65.1 (CH₂), 73.2 (CH), 77.8 (C). IR (neat): 3366, 2951, 2928, 2868, 1447, 1437, 1383, 1366, 1339, 1260, 1132, 1092, 1028. EIMS *m/z*: 250 (M–H₂O), 240, 237, 222, 191, 178, 161, 150, 135, 121, 107. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₆H₂₈NaO₃, 291.1936; found, 291.1933.

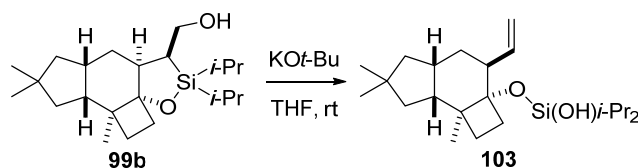
101: Colorless oil. R_f 0.54 (hexane/EtOAc 5:1). ¹H NMR: 0.89 (s, 3H), 1.04 (s, 3H), 1.11–1.16 (m, 4H), 1.26 (m, 1H), 1.32–1.38 (m, 2H), 1.42 (m, 1H), 1.48 (m, 1H), 1.72–1.76 (m, 2H), 1.83 (m, 1H), 1.91 (ddd, *J* = 7.0, 13.5, 13.5, 1H), 2.07 (m, 1H), 2.16 (m, 1H), 2.36 (m, 1H), 2.53 (m, 1H), 5.11–5.14 (m, 2H), 5.92 (m, 1H). ¹³C NMR: 22.3 (CH₃), 26.3 (CH₃), 27.4 (CH₂), 27.6 (CH₂), 29.1 (CH₃), 31.2 (CH₂), 32.8 (CH), 37.7 (C), 42.9 (CH), 44.8 (C), 45.2 (CH), 46.3 (CH₂), 49.1 (CH₂), 75.7 (C), 115.9 (CH₂), 139.0 (CH). IR (neat): 3462, 2951, 2926, 2866, 1458, 1447, 1366, 1261, 1123, 1098, 1078, 1032. EIMS *m/z*: 234 (M⁺), 219 (M–Me), 206, 188, 177, 163, 150, 137, 121, 109. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₆H₂₆NaO, 257.1881; found, 257.1880.

102: Colorless oil. R_f 0.67 (hexane/EtOAc 5:1). ¹H NMR: 0.88 (s, 3H), 0.89–1.12 (m, 18H), 1.13 (s, 3H), 1.17 (dd, *J* = 12.5, 12.5, 1H), 1.25 (dd, *J* = 9.0, 12.5, 1H), 1.33 (ddd, *J* = 3.5, 11.0, 11.0, 1H), 1.38–1.45 (m, 2H), 1.70 (ddd, *J* = 2.5, 9.0, 12.5, 1H), 1.73–1.90 (m, 3H), 1.97–2.05 (m, 2H), 2.16 (ddd, *J* = 3.5, 9.5, 12.5, 1H), 2.46 (m, 1H), 3.82 (ddd, *J* = 2.5, 9.5, 11.5, 1H), 3.90 (ddd, *J* = 3.0, 5.5, 11.5, 1H). ¹³C NMR: 13.0 (CH), 13.8 (CH), 17.4 (CH₃), 17.7 (CH₃), 17.7 (CH₃), 18.1 (CH₃), 23.4 (CH₃), 26.4 (CH₃), 27.2 (CH₂), 27.7 (CH₂), 29.3 (CH₃), 33.3 (CH), 35.0 (CH₂), 36.2 (CH₂), 37.7 (C), 39.5 (CH), 45.2 (CH), 45.9 (C), 46.3 (CH₂), 49.1 (CH₂), 64.1 (CH₂), 79.3 (C). IR (neat): 2945, 2926, 2866, 1458, 1383, 1252, 1140, 1115, 1086, 1063, 1001. EIMS *m/z*: 364 (M⁺), 349 (M–Me), 336, 321 (M–*i*-Pr), 293, 279, 265, 239, 214, 187, 171, 160, 145, 131, 105. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₂H₄₀NaO₂Si, 387.2695; found, 387.2722.

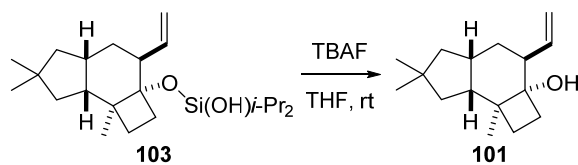


Diisopropyl[[(2a*SR*,3*SR*,4a*SR*,7a*RS*,7b*SR*)-6,6,7b-trimethyl-3-vinyldecahydro-1*H*-cyclobuta-*e*]inden-2a-yl]oxy]silanol (103): To a solution of alcohol **99a** (11.3 mg, 31.0 μmol) in dry THF (1 mL) was added KO*t*-Bu (6.5 mg, 58 μmol). The mixture was stirred at rt for 10 min. Then, the reaction was quenched by the addition of saturated aqueous NH₄Cl (3 mL). The whole was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (10.6 mg, 94%) as colorless oil: R_f 0.67 (hexane/EtOAc 1:1). ¹H NMR: 0.89 (s, 3H), 0.92–1.07 (m, 17H), 1.13 (s, 3H), 1.15–1.50 (m, 6H), 1.72 (m, 1H), 1.91 (ddd, *J* = 7.0, 13.5, 13.5, 1H), 2.02–2.24 (m, 3H), 2.43–2.51 (m, 2H), 5.12–5.15 (m, 2H), 6.06 (ddd, *J* = 8.5,

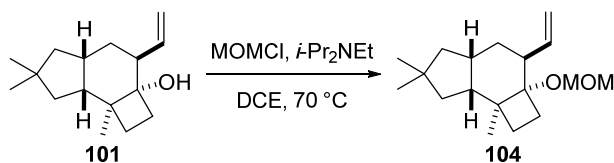
8.5, 17.5, 1H). ^{13}C NMR: 13.4 (CH), 13.9 (CH), 17.5 (CH₃), 17.6 (CH₃), 17.7 (CH₃), 17.7 (CH₃), 24.0 (CH₃), 26.4 (CH₃), 27.6 (CH₂), 27.7 (CH₂), 29.3 (CH₃), 32.5 (CH₂), 32.8 (CH), 37.7 (C), 44.7 (CH), 45.3 (CH), 46.0 (C), 46.2 (CH₂), 49.1 (CH₂), 78.7 (C), 115.8 (CH₂), 141.4 (CH). IR (neat): 3503, 2947, 2926, 2866, 1464, 1447, 1383, 1366, 1248, 1173, 1142, 1055, 1001. EIMS m/z : 364 (M^+), 349 ($\text{M}-\text{Me}$), 336, 321 ($\text{M}-i\text{-Pr}$), 307, 293, 282, 239, 227, 211, 188, 171, 159, 131, 105. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{22}\text{H}_{40}\text{NaO}_2\text{Si}$, 387.2695; found, 387.2696.



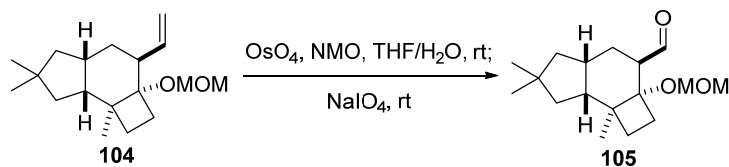
Diisopropyl[$\{(2aSR,3SR,4aSR,7aRS,7bSR)-6,6,7b\text{-trimethyl-3-vinyldecahydro-1H-cyclobuta}[e]\text{inden-2a-yl}\}$ oxy]silanol (103**):** To a solution of alcohol **99b** (10.2 mg, 28.0 μmol) in dry THF (1 mL) was added KOt-Bu (4.7 mg, 42 μmol). The mixture was stirred at rt for 10 min. Then, the reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The whole was extracted with EtOAc (3 x 3 mL). 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/EtOAc 99:1) to afford the title compound (9.6 mg, 94%) as colorless oil.



($2aSR,3SR,4aSR,7aRS,7bSR$)-6,6,7b-Trimethyl-3-vinyldecahydro-1H-cyclobuta[e]inden-2a-ol (101**):** To a solution of silanol **103** (529 mg, 1.45 mmol) in dry THF (3 mL) was added a 1 M THF solution of TBAF (4.4 mL, 4.4 mmol). The mixture was stirred at rt for 45 min. Then, the reaction was quenched by the addition of 1 N HCl (5 mL). The whole was extracted with EtOAc (10 mL + 2 x 5 mL), and the combined organic layers were washed with 1 N HCl and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (391 mg, quant.) as colorless oil.

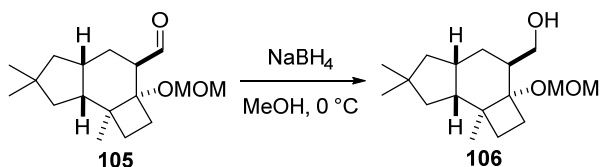


(2aSR,3SR,4aSR,7aRS,7bSR)-2a-(Methoxymethoxy)-6,6,7b-trimethyl-3-vinyldecahydro-1H-cyclobuta[e]indene (104): To a solution of olefin **101** (191 mg, 0.815 mmol) in dry 1,2-dichloroethane (2.5 mL) were added *i*-Pr₂NEt (0.56 mL, 3.2 mmol) and MOMCl (0.12 mL, 1.6 mmol). The mixture was stirred at 70 °C for 16.5 h. After cooling to rt, the reaction was quenched by the addition of saturated aqueous NH₄Cl (4 mL). The whole was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (220 mg, 97%) as colorless oil: R_f 0.54 (hexane/EtOAc 9:1). ¹H NMR: 0.89 (s, 3H), 1.05 (s, 3H), 1.06 (s, 3H), 1.10–1.15 (m, 4H), 1.23–1.31 (m, 2H), 1.37 (ddd, *J* = 3.0, 11.5, 11.5, 1H), 1.44 (ddd, *J* = 2.0, 7.0, 12.0, 1H), 1.51 (m, 1H), 1.71 (ddd, *J* = 2.0, 10.0, 10.5, 1H), 1.90 (ddd, *J* = 7.0, 13.5, 13.5, 1H), 1.98–2.07 (m, 2H), 2.31 (m, 1H), 2.49–2.54 (m, 2H), 3.40 (s, 3H), 4.58 (d, *J* = 7.0, 1H), 4.67 (d, *J* = 7.0, 1H), 5.06–5.10 (m, 2H), 5.89 (ddd, *J* = 7.0, 10.5, 17.5, 1H). ¹³C NMR: 22.0 (CH₂), 23.3 (CH₃), 26.3 (CH₃), 27.5 (CH₂), 29.1 (CH₃), 31.2 (CH₂), 32.7 (CH), 37.8 (C), 42.2 (CH), 45.1 (C), 45.2 (CH), 46.5 (CH₂), 48.9 (CH₂), 55.6 (CH₃), 82.9 (C), 93.3 (CH₂), 115.4 (CH₂), 139.2 (CH). IR (neat): 2951, 2928, 2870, 1636, 1462, 1447, 1385, 1366, 1250, 1211, 1150, 1092, 1038. EIMS *m/z*: 251, 239, 223, 209, 195, 181, 167, 153, 137, 123, 107, 45 (CH₂OCH₃). HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₈H₃₀NaO₂, 301.2143; found, 301.2141.

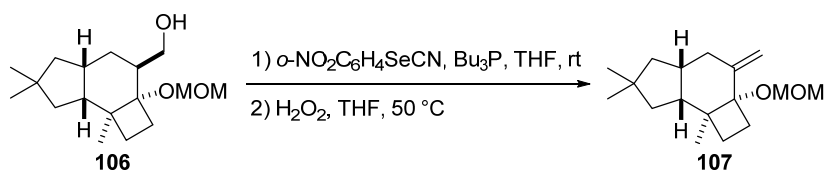


(2aSR,3RS,4aSR,7aRS,7bSR)-2a-(Methoxymethoxy)-6,6,7b-trimethyldecahydro-1H-cyclobuta[e]indene-3-carbaldehyde (105): To a solution of olefin **104** (185 mg, 0.664 mmol) in THF/water (5:1, 6 mL) were added NMO (233 mg, 1.99 mmol) and a 4% water solution of OsO₄ (0.12 mL, 0.020 mmol) at rt. After 16 h, NaIO₄ (285 mg, 1.33 mmol) in water (1.5 mL) was added to the mixture. After additional 1 h, the reaction was quenched by the addition of saturated aqueous Na₂S₂O₃ (5 mL). The whole was extracted with EtOAc (10 mL + 2 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2) to afford the title compound (153 mg, 82%) as colorless oil: R_f 0.29 (hexane/EtOAc 9:1). ¹H NMR: 0.90 (s, 3H), 1.03 (m, 1H), 1.05 (s, 3H), 1.09 (s, 3H), 1.21 (dd, *J* = 10.0, 12.0, 1H), 1.39–1.48 (m, 2H), 1.54–1.60 (m, 2H), 1.96 (ddd, *J* = 7.0, 13.5, 13.5, 1H), 2.09 (m, 1H), 2.17 (ddd, *J* = 3.0, 9.5, 9.5, 1H), 2.39 (m, 1H), 2.58 (m, 1H), 2.79 (m, 1H), 3.36 (s, 3H), 4.74 (d, *J* = 7.5, 1H), 4.78 (d, *J* = 7.5, 1H), 9.84 (s, 1H). ¹³C NMR: 22.8 (CH₃), 23.8 (CH₂), 26.0 (CH₃), 26.2 (CH₂), 27.4 (CH₂), 29.0 (CH₃), 32.0 (CH), 37.6 (C), 44.8 (CH), 45.8 (C), 46.3 (CH₂), 48.4 (CH₂), 49.8 (CH), 55.5 (CH₃), 80.5 (C), 92.9 (CH₂), 205.1 (CH). IR (neat):

2951, 2928, 2870, 1721, 1462, 1447, 1385, 1366, 1254, 1211, 1150, 1072, 1038. EIMS m/z : 252, 235 (M-CH₂OCH₃), 220, 207, 175, 135, 149, 107, 45 (CH₂OCH₃). HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₁₇H₂₈NaO₃, 303.1936; found, 303.1937.



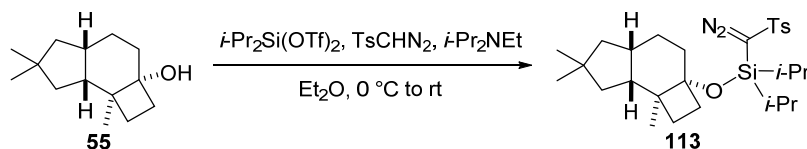
((2aSR,3SR,4aSR,7aRS,7bSR)-2a-(Methoxymethoxy)-6,6,7b-trimethyldecahydro-1H-cyclobuta [e]inden-3-yl)methanol (106): To a solution of aldehyde **105** (153 mg, 0.546 mmol) in MeOH (2 mL) was added NaBH₄ (30.5 mg, 0.806 mmol) at 0 °C. After 20 min, the reaction was quenched by the addition of saturated aqueous NH₄Cl (3 mL). The whole was extracted with EtOAc (10 mL + 2 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 5:1) to afford the title compound (167 mg, quant.) as colorless oil: R_f 0.38 (hexane/EtOAc 2:1). ¹H NMR: 0.90 (s, 3H), 1.00–1.07 (m, 7H), 1.27 (dd, *J* = 9.5, 12.5, 1H), 1.37 (ddd, *J* = 3.5, 11.5, 11.5, 1H), 1.41–1.46 (m, 2H), 1.51 (m, 1H), 1.68–1.77 (m, 2H), 2.00–2.08 (m, 3H), 2.17 (m, 1H), 2.51 (m, 1H), 3.36 (dd, *J* = 6.0, 11.0, 1H), 3.41 (s, 3H), 3.80 (dd, *J* = 5.5, 11.0, 1H), 4.70 (d, *J* = 7.0, 1H), 4.77 (d, *J* = 7.0, 1H). ¹³C NMR: 22.9 (CH₂), 23.0 (CH₃), 26.1 (CH₃), 27.4 (CH₂), 29.1 (CH₃), 29.5 (CH₂), 32.5 (CH), 37.8 (C), 39.0 (CH), 45.2 (CH), 45.9 (C), 46.6 (CH₂), 48.5 (CH₂), 55.6 (CH₃), 64.0 (CH₂), 83.3 (C), 93.1 (CH₂). IR (neat): 3449, 2951, 2928, 2870, 1462, 1447, 1385, 1366, 1146, 1076, 1038. EIMS m/z : 254, 222, 205, 177, 161, 150, 136, 121, 107, 45 (CH₂OCH₃). HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₁₇H₃₀NaO₃, 305.2093; found, 305.2092.



[{(2aSR,3RS,4aSR,7aRS,7bSR)-2a-(Methoxymethoxy)-6,6,7b-trimethyldecahydro-1H-cyclobuta [e]inden-3-yl)methyl}(2-nitrophenyl)selane (S11): To a solution of alcohol **106** (201 mg, 0.712 mmol) in dry THF (5 mL) were added *o*-NO₂C₆H₄SeCN (297 mg, 1.07 mmol) and Bu₃P (260 μL, 1.05 mmol) at rt. After 9 h, *o*-NO₂C₆H₄SeCN (58.9 mg, 0.213 mmol) and Bu₃P (53 μL, 0.21 mmol) were added again to the mixture. After additional 13 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 95:5) to afford the title compound (278 mg) as brown oil, which was used directly in the next step without further purification. An analytical sample was obtained by PTLC (hexane/EtOAc 7:1 x 2) as yellow oil: R_f 0.58

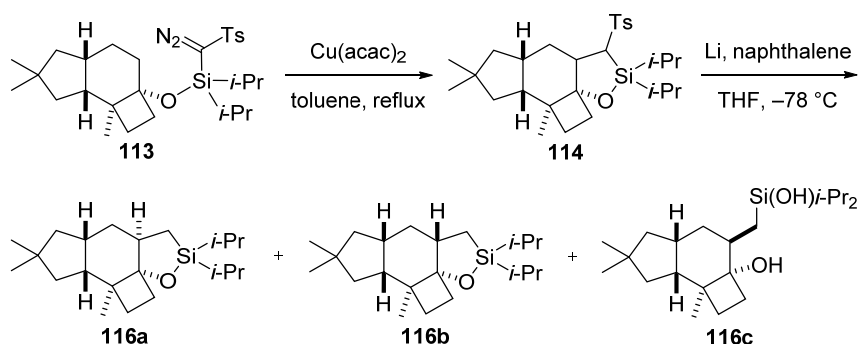
(hexane/EtOAc 3:1). ^1H NMR: 0.87 (s, 3H), 0.97 (s, 3H), 1.00 (m, 1H), 1.09 (s, 3H), 1.11 (dd, $J = 10.0, 12.5$, 1H), 1.40–1.44 (m, 2H), 1.57 (m, 1H), 1.66–1.73 (m, 2H), 1.80 (ddd, $J = 6.5, 13.5, 13.5$, 1H), 2.02–2.11 (m, 2H), 2.15 (m, 1H), 2.28 (m, 1H), 2.51 (m, 1H), 2.56 (dd, $J = 11.0, 11.0$, 1H), 3.23 (dd, $J = 2.0, 11.0$, 1H), 3.40 (s, 3H), 4.76 (d, $J = 7.0$, 1H), 4.78 (d, $J = 7.0$, 1H), 7.29 (dd, $J = 8.0, 8.0$, 1H), 7.51 (dd, $J = 8.0, 8.0$, 1H), 7.66 (d, $J = 8.0$, 1H), 8.27 (d, $J = 8.0$, 1H). ^{13}C NMR: 22.1 (CH₂), 23.2 (CH₃), 26.2 (CH₃), 27.4 (CH₂), 27.5 (CH₂), 29.1 (CH₃), 31.6 (CH₂), 32.9 (CH), 36.3 (CH), 37.8 (C), 45.4 (CH), 46.1 (C), 46.7 (CH₂), 48.5 (CH₂), 55.8 (CH₃), 83.8 (C), 93.2 (CH₂), 125.1 (CH), 126.3 (CH), 129.5 (CH), 133.4 (CH), 134.5 (C), 146.9 (C). IR (neat): 2951, 2928, 2866, 1589, 1566, 1512, 1462, 1450, 1335, 1304, 1254, 1146, 1096, 1072, 1038. EIMS m/z : 265 (M-*o*-NO₂C₆H₄Se), 247, 233, 215, 202, 186, 173, 159, 149, 135, 121, 95. HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₂₃H₃₃NNaO₄Se, 490.1473; found, 490.1472.

(2aSR,4aRS,7aRS,7bSR)-2a-(Methoxymethoxy)-6,6,7b-trimethyl-3-methylenedecahydro-1H-cyclobuta[e]indene (107): To a solution of **S11** (278 mg) in THF (4 mL) was added 30% H₂O₂ (0.36 mL, 3.52 mmol). The mixture was stirred at 50 °C for 1 h. After cooling to rt, the reaction was quenched by the addition of saturated aqueous Na₂S₂O₃ (2 mL). The whole was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2) to afford the title compound (110 mg, 58%) as pale yellow oil: R_f 0.33 (hexane/EtOAc 9:1). ^1H NMR: 0.93 (s, 3H), 1.04 (s, 3H), 1.21 (s, 3H), 1.25 (dd, $J = 3.5, 13.0$, 1H), 1.34 (ddd, $J = 2.0, 10.0, 10.5$, 1H), 1.37–1.39 (m, 2H), 1.53 (m, 1H), 1.65 (dd, $J = 8.0, 13.0$, 1H), 1.89 (ddd, $J = 8.0, 8.0, 11.5$, 1H), 2.02 (dd, $J = 11.0, 13.0$, 1H), 2.12 (m, 1H), 2.14 (ddd, $J = 2.0, 8.0, 11.5$, 1H), 2.22 (m, 1H), 2.37 (m, 1H), 3.41 (s, 3H), 4.50 (d, $J = 7.0$, 1H), 4.73 (d, $J = 7.0$, 1H), 5.00 (d, $J = 1.5$, 1H), 5.03 (d, $J = 1.5$, 1H). ^{13}C NMR: 21.8 (CH₃), 26.9 (CH₂), 27.6 (CH₂), 30.5 (CH₃), 31.4 (CH₃), 35.6 (CH₂), 36.4 (C), 39.1 (CH), 43.3 (CH₂), 46.3 (C), 46.4 (CH), 47.6 (CH₂), 55.5 (CH₃), 79.5 (C), 91.9 (CH₂), 111.4 (CH₂), 148.1 (C). IR (neat): 2951, 2932, 2866, 1643, 1462, 1396, 1261, 1234, 1153, 1107, 1045, 1007. EIMS m/z : 264 (M⁺) 249 (M-Me), 236, 219 (M-CH₂OCH₃), 201, 179, 161, 147, 107, 45 (CH₂OCH₃). HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₁₇H₂₈NaO₂, 287.1987; found, 287.1987.



(Diazo(tosyl)methyl)diisopropyl[[(2aRS,4aSR,7aRS,7bSR)-6,6,7b-trimethyldecahydro-2aH-cyclobuta[e]inden-2a-yl]oxy]silane (113): To a solution of diisopropylsilyl bis(trifluoromethanesulfonate)⁷⁹ (1.02 g, 2.47 mmol) in dry Et₂O (3 mL) at 0 °C was added a mixture of tosyl diazomethane⁸⁰ (489 mg, 2.49 mmol) and *i*-Pr₂NEt (0.43 mL, 2.5 mmol) in dry Et₂O

(1.5 mL) pre-cooled at 0 °C. The resulting pale yellow suspension was stirred at 0 °C for 30 min and at rt for 1 h. After recooling to 0 °C, a solution of alcohol **55** (344 mg, 1.65 mmol) and *i*-Pr₂NEt (0.43 mL, 2.5 mmol) in dry Et₂O (1.5 mL + 0.5 mL washing) was added to the mixture. The reaction mixture was stirred at 0 °C for 30 min and at rt for 1.5 h. Then, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (10 mL). The whole was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 97:3 to 9:1) to afford the title compound (276 mg, 32%, 66% brsm) as pale yellow oil: R_f 0.58 (hexane/EtOAc 5:1). ¹H NMR: 0.89 (s, 3H), 1.01–1.06 (m, 18H), 1.14–1.36 (m, 7H), 1.45 (ddd, *J* = 9.0, 10.5, 10.5, 1H), 1.58–1.71 (m, 3H), 1.79 (ddd, *J* = 3.0, 10.0, 13.0, 1H), 1.88–1.95 (m, 2H), 2.12 (ddd, *J* = 10.5, 10.5, 10.5, 1H), 2.22 (m, 1H), 2.44 (s, 3H), 7.32 (d, *J* = 8.5, 2H), 7.74 (d, *J* = 8.5, 2H). ¹³C NMR: 14.2 (CH), 14.4 (CH), 17.0 (CH₃), 17.1 (CH₃), 17.2 (CH₃), 17.3 (CH₃), 21.5 (CH₃), 22.8 (CH₃), 25.3 (CH₂), 26.5 (CH₂), 28.6 (CH₃), 30.4 (CH₃), 33.3 (CH₂), 34.5 (CH₂), 34.9 (CH), 36.8 (C), 44.6 (CH₂), 45.4 (CH), 48.0 (CH₂), 56.8 (C), 76.5 (C), 126.4 (CH), 129.6 (CH), 141.5 (C), 143.6 (C). IR (neat): 2947, 2928, 2866, 2075, 1462, 1327, 1204, 1184, 1146, 1103, 1084, 1049. EIMS *m/z*: 488, 473 (M-*i*-Pr), 445, 350, 333, 309, 293, 283, 163, 151, 135, 119. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₈H₄₄N₂NaO₃SSi, 539.2740; found, 539.2741.



**(2aSR,5aRS,6aSR,9aRS,9bSR)-4,4-Diisopropyl-8,8,9b-trimethyldodecahydrocyclobuta[6,7]inden-
no[5,6-*d*][1,2]oxasilole (116a) and**

**(2aSR,5aSR,6aSR,9aRS,9bSR)-4,4-Diisopropyl-8,8,9b-trimethyldodecahydrocyclobuta[6,7]inden-
no[5,6-*d*][1,2]oxasilole (116b) and**

**[{(2aSR,3RS,4aSR,7aRS,7bSR)-2a-Hydroxy-6,6,7b-trimethyldecahydro-1H-cyclobuta[*e*]inden-
3-yl)methyl]diisopropylsilanol (116c):** To a solution of diazo tosylate **113** (348 mg, 0.673 mmol) in dry toluene (6.7 mL) was added Cu(acac)₂ (17.7 mg, 67.6 μmol). The mixture was heated under reflux for 30 min. After cooling to rt, the solvent was removed *in vacuo*. The residue was purified by column chromatography (toluene) to afford an inseparable diastereomeric mixture of **114** (313 mg) as pale yellow oil, which was used directly in the next step without further purification. The THF

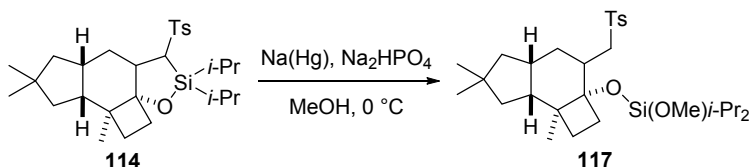
used in the next reaction was degassed by refluxing with benzophenone ketyl radical before use. A suspension of lithium (14.8 mg, 2.13 mmol) and naphthalene (247 mg, 1.93 mmol) in dry THF (1.5 mL) was sonicated for 1 h. The resulting dark green-colored suspension was cooled to $-78\text{ }^{\circ}\text{C}$ and a solution of the above product (313 mg) in dry THF (1.5 mL + 0.5 mL washing) pre-cooled at $-78\text{ }^{\circ}\text{C}$ was added over 5 min. After 1 h, the reaction was quenched by the addition of 1.0 M Et₂O solution of HCl (1 mL). Then, saturated aqueous NaHCO₃ (4 mL) was added to the mixture. The whole was extracted with EtOAc (10 mL + 2 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 1:0 to 9:1) to afford the title compounds (71.0 mg, 22.8 mg and 36.6 mg, 32%, 10% and 15%, respectively).

116a: Colorless oil. *R*_f 0.36 (hexane/EtOAc 95:5). ¹H NMR: 0.54 (dd, *J* = 13.5, 13.5, 1H), 0.59 (dd, *J* = 5.5, 13.5, 1H), 0.88–1.07 (m, 20H), 1.13 (m, 1H), 1.15 (s, 3H), 1.19 (dd, *J* = 9.0, 13.0, 1H), 1.34–1.42 (m, 4H), 1.76–1.86 (m, 3H), 1.91 (dddd, *J* = 2.0, 5.5, 13.5, 13.5, 1H), 1.98 (ddd, *J* = 4.0, 9.0, 13.0, 1H), 2.05 (m, 1H), 2.53 (m, 1H). ¹³C NMR: 9.8 (CH₂), 12.2 (CH), 12.8 (CH), 17.6 (CH₃), 17.7 (CH₃), 17.7 (CH₃), 17.9 (CH₃), 21.7 (CH₃), 26.8 (CH₃), 27.2 (CH₂), 27.5 (CH₂), 29.6 (CH₃), 33.7 (CH₂), 34.7 (CH), 37.7 (C), 37.9 (CH), 44.9 (C), 46.6 (CH₂), 47.3 (CH), 50.2 (CH₂), 83.6 (C). IR (neat): 2940, 2924, 2862, 1466, 1385, 1366, 1246, 1138, 1123, 1030. EIMS *m/z*: 334 (M⁺), 306, 291 (M-*i*-Pr), 263, 249, 235, 209, 198, 184, 142, 103. HRMS-ESI (*m/z*): [M+H]⁺ calcd. for C₂₁H₃₉OSi, 335.2770; found, 335.2769.

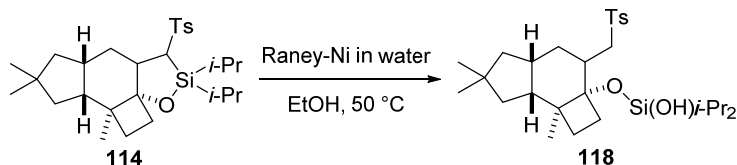
116b: Colorless oil. *R*_f 0.52 (hexane/EtOAc 95:5). ¹H NMR: 0.46 (d, *J* = 15.0, 1H), 0.94–1.04 (m, 20H), 1.11 (dd, *J* = 9.0, 15.0, 1H), 1.15 (s, 3H), 1.20–1.30 (m, 4H), 1.36 (d, *J* = 10.0, 2H), 1.42 (m, 1H), 1.59 (m, 1H), 1.64 (dd, *J* = 7.5, 13.0, 1H), 1.78 (m, 1H), 1.95 (ddd, *J* = 10.0, 10.0, 10.0, 1H), 2.03 (m, 1H), 2.16 (ddd, *J* = 4.0, 9.0, 13.0, 1H). ¹³C NMR: 10.9 (CH₂), 12.5 (CH), 13.2 (CH), 17.5 (CH₃), 17.6 (CH₃), 17.9 (CH₃), 18.2 (CH₃), 22.0 (CH₃), 25.6 (CH₂), 32.4 (CH₃), 32.6 (CH₃), 34.0 (CH₂), 34.8 (CH₂), 35.8 (C), 39.1 (CH), 42.6 (CH), 42.8 (CH₂), 45.8 (C), 46.5 (CH), 47.7 (CH₂), 82.5 (C). IR (neat): 2940, 2889, 2862, 1462, 1381, 1366, 1238, 1072, 1045. EIMS *m/z*: 334 (M⁺), 306, 291 (M-*i*-Pr), 263, 249, 209, 184, 142, 103. HRMS-ESI (*m/z*): [M+H]⁺ calcd. for C₂₁H₃₉OSi, 335.2770; found, 335.2775.

116c: Crystals suitable for X-ray diffraction studies were obtained by vapor diffusion. Colorless solids of mp 123–125 °C (CHCl₃/hexane). *R*_f 0.32 (hexane/EtOAc 5:1). ¹H NMR: 0.24 (dd, *J* = 2.0, 15.5, 1H), 0.83 (dd, *J* = 9.0, 15.5, 1H), 0.87 (s, 3H), 0.91 (m, 1H), 0.97–1.06 (m, 16H), 1.11 (m, 1H), 1.12 (s, 3H), 1.20 (br d, *J* = 14.0, 1H), 1.25 (dd, *J* = 10.0, 11.5, 1H), 1.33 (ddd, *J* = 2.0, 10.5, 11.0, 1H), 1.39 (dd, *J* = 7.0, 12.0, 1H), 1.45 (ddd, *J* = 10.5, 10.5, 10.5, 1H), 1.71–1.79 (m, 2H), 1.85 (ddd, *J* = 7.0, 14.0, 14.0, 1H), 2.00–2.07 (m, 2H), 2.27 (m, 1H), 2.45 (m, 1H), 3.34 (br s, 1H). ¹³C NMR (C₆D₆): 13.5 (CH₂), 13.6 (CH), 13.9 (CH), 17.8 (CH₃), 17.9 (CH₃), 18.0 (CH₃), 18.1 (CH₃), 22.6 (CH₃), 26.6 (CH₃), 27.4 (CH₂), 27.5 (CH₂), 29.5 (CH₃), 32.6 (CH), 34.0 (CH), 37.8 (C), 38.1 (CH₂),

45.5 (C), 45.7 (CH), 46.7 (CH₂), 49.5 (CH₂), 78.5 (C). IR (KBr): 3387, 3229, 2951, 2924, 2866, 1458, 1381, 1150, 1088. EIMS *m/z*: 334, 306, 291, 249, 235, 209, 163, 131, 105. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₁H₄₀NaO₂Si, 375.2695; found, 375.2695.

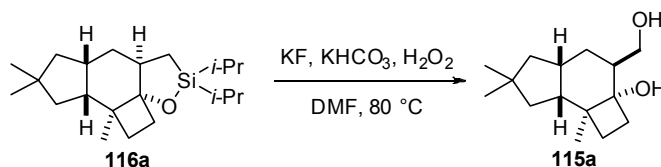


Diisopropyl(methoxy)[{(2a*SR*,4a*SR*,7a*RS*,7b*SR*)-6,6,7b-trimethyl-3-(tosylmethyl)decahydro-2a*H*-cyclobuta[*e*]inden-2a-yl}oxy]silane (117): To a solution of tosyl siloxane **114** (5.0 mg, 10 μmol) in MeOH were added Na₂HPO₄ (15.0 mg, 0.106 mmol) and Na(Hg) (5% Na, 22.8 mg, 50 μmol) at 0 °C. After 30 min, the reaction was quenched by the addition of saturated aqueous NH₄Cl (2 mL). The whole was extracted with EtOAc (6 mL + 2 x 3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2) to afford the title compound (4.2 mg, 81%) as colorless oil: ¹H NMR: 0.87 (s, 3H), 0.92–1.10 (m, 17 H), 1.09 (s, 3H), 1.25–1.49 (m, 5H), 1.70–1.78 (m, 2H), 1.93–2.09 (m, 4H), 2.27 (m, 1H), 2.43 (s, 3H), 2.91 (dd, *J* = 11.0, 14.0, 1H), 3.48 (s, 3H), 3.63 (dd, *J* = 2.0, 14.0, 1H), 7.32 (d, *J* = 8.5, 2H), 7.80 (d, *J* = 8.5, 2H). EIMS *m/z*: 477 (M–*i*-Pr), 449, 411, 365 (M–Ts), 336, 257, 215, 203, 193, 165, 145, 117.

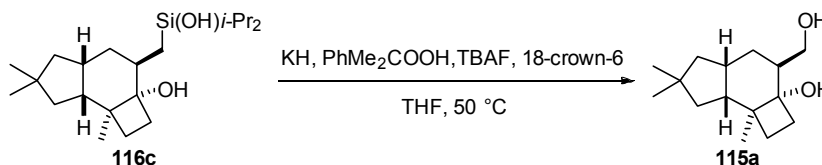


Diisopropyl[{(2a*SR*,3*RS*,4a*SR*,7a*RS*,7b*SR*)-6,6,7b-trimethyl-3-(tosylmethyl)decahydro-2a*H*-cyclobuta[*e*]inden-2a-yl}oxy]silanol (118): To a solution of tosyl siloxane **114** (4.4 mg, 9.0 μmol) in EtOH was added 50% Raney-Ni in water (110 mg). The mixture was stirred at 50 °C for 45 min. After cooling to rt, the reaction mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 98:2 to 94:6) to afford the title compound (2.8 mg, 61%) as colorless oil: *R*_f 0.17 (hexane/EtOAc 9:1). ¹H NMR: 0.87 (s, 3H), 0.89–0.96 (m, 2H), 1.00–1.05 (m, 15H), 1.12 (s, 3H), 1.13 (m, 1H), 1.28–1.35 (m, 2H), 1.39–1.48 (m, 2H), 1.65–1.90 (m, 4H), 1.99–2.10 (m, 2H), 2.41–2.44 (m, 2H), 2.45 (s, 3H), 2.82 (dd, *J* = 10.0, 13.5, 1H), 3.60 (d, *J* = 13.5, 1H), 7.35 (d, *J* = 8.5, 2H), 7.82 (d, *J* = 8.5, 2H). ¹³C NMR: 13.4 (CH), 13.5 (CH), 17.4 (CH₃), 17.5 (CH₃), 17.5 (CH₃), 17.7 (CH₃), 21.6 (CH₃), 24.1 (CH₃), 26.3 (CH₃), 27.2 (CH₂), 27.9 (CH₂), 29.1 (CH₃), 32.5 (CH₂), 32.8 (CH), 35.2 (CH), 37.6 (C), 44.6 (CH), 46.0

(CH₂), 46.6 (C), 48.1 (CH₂), 57.8 (CH₂), 78.9 (C), 128.0 (CH), 130.0 (CH), 137.2 (C), 144.6 (C). IR (neat): 3449, 2947, 2928, 2864, 1464, 1300, 1288, 1261, 1146, 1088, 1057. EIMS *m/z*: 491 (M–Me), 463 (M–*i*-Pr), 435, 411, 379, 351 (M–Ts), 322, 243, 203, 179, 161, 135, 119, 103. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₂₈H₄₆NaO₄SSi, 529.2784; found, 529.2789.

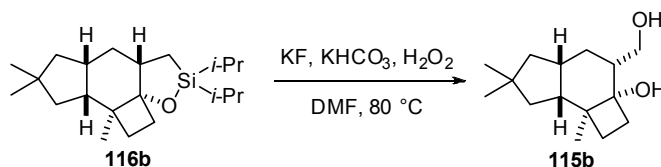


(2aSR,3SR,4aSR,7aRS,7bSR)-3-(Hydroxymethyl)-6,6,7b-trimethyldecahydro-2aH-cyclobuta[e]inden-2a-ol (115a): To a solution of siloxane **116a** (28.3 mg, 84.6 μmol) in DMF (1 mL) were added KF (20.9 mg, 0.360 mmol), KHCO₃ (33.8 mg, 0.338 mmol) and 30% H₂O₂ (69 μL, 0.68 mmol). The mixture was stirred at 80 °C for 30 min. After cooling to rt, the reaction was quenched by the addition of saturated aqueous Na₂S₂O₃ (2 mL). The whole was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 5:1 to 3:1) to afford the title compound (17.5 mg, 87%) as colorless solids of mp 138–140 °C (CHCl₃): R_f 0.30 (hexane/EtOAc 2:1). ¹H NMR: 0.89 (s, 3H), 1.04 (s, 3H), 1.07 (m, 1H), 1.13 (s, 3H), 1.15 (m, 1H), 1.26 (dd, *J* = 9.5, 12.5, 1H), 1.34–1.49 (m, 3H), 1.60 (ddd, *J* = 7.0, 13.5, 13.5, 1H), 1.74 (dd, *J* = 9.0, 12.5, 1H), 1.94 (ddd, *J* = 11.0, 11.0, 11.0, 1H), 2.02–2.09 (m, 2H), 2.27 (ddd, *J* = 3.0, 9.5, 12.5, 1H), 2.51 (m, 1H), 2.74 (br s, 1H), 2.90 (br s, 1H), 3.52 (dd, *J* = 3.5, 10.5, 1H), 3.80 (dd, *J* = 10.0, 10.5, 1H). ¹³C NMR: 21.7 (CH₃), 26.3 (CH₃), 27.0 (CH₂), 27.2 (CH₂), 28.5 (CH₂), 29.1 (CH₃), 32.7 (CH), 37.7 (C), 38.6 (CH), 45.1 (CH), 45.2 (C), 46.2 (CH₂), 48.9 (CH₂), 65.1 (CH₂), 78.1 (C). IR (KBr): 3383, 3356, 2955, 2932, 2893, 1474, 1462, 1447, 1420, 1369, 1265, 1157, 1045, 1026. EIMS *m/z*: 220 (M–H₂O), 210, 180, 161, 150, 136, 121, 107, 95. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₅H₂₆NaO₂, 261.1830; found, 261.1834.

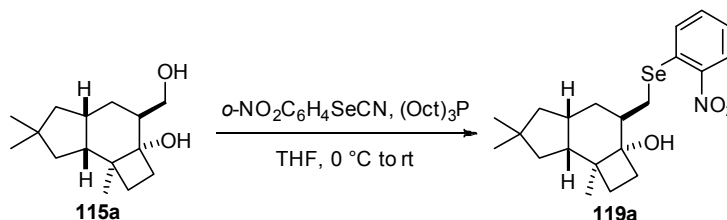


(2aSR,3SR,4aSR,7aRS,7bSR)-3-(Hydroxymethyl)-6,6,7b-trimethyldecahydro-2aH-cyclobuta[e]inden-2a-ol (115a): To dry potassium hydride powder (5.3 mg, 0.13 mmol) in THF (0.2 mL) was added 18-crown-6 (34.4 mg, 0.130 mmol), and the slurry was cooled to 0 °C. Then, 80% cumene hydroperoxide (24 μL, 0.13 mmol) was added, and the mixture was allowed to warm to rt. Silanol **116c** (4.6 mg, 13 μmol) in THF (0.5 mL + 0.3 mL washing) was added, followed by a 1 M THF

solution of TBAF (130 μ L, 0.13 mmol). The mixture was heated at 50 $^{\circ}$ C for 3 h. After cooling to rt, the reaction was quenched by the addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL). The whole was extracted with EtOAc (3 x 3 mL). 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/EtOAc 5:1 to 3:1) to afford the title compound (2.9 mg, 92%) as colorless solids.

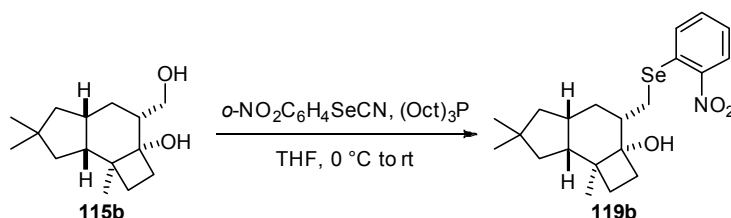


(2aSR,3RS,4aSR,7aRS,7bSR)-3-(Hydroxymethyl)-6,6,7b-trimethyldecahydro-2aH-cyclobuta[e]inden-2a-ol (115b): To a solution of siloxane **116b** (22.8 mg, 68.1 μ mol) in DMF (1 mL) were added KF (21.8 mg, 0.375 mmol), KHCO_3 (35.0 mg, 0.350 mmol) and 30% H_2O_2 (70 μ L, 0.69 mmol). The mixture was stirred at 80 $^{\circ}$ C for 1 h. After cooling to rt, the reaction was quenched by the addition of saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL). The whole was extracted with EtOAc (3 x 5 mL). 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/EtOAc 5:1 to 2:1) to afford the title compound (15.5 mg, 95%) as white solids of mp 59–62 $^{\circ}$ C: R_f 0.32 (hexane/EtOAc 2:1). ^1H NMR: 0.95 (s, 3H), 1.06 (s, 3H), 1.13 (s, 3H), 1.17 (m, 1H), 1.26–1.31 (m, 2H), 1.35–1.52 (m, 4H), 1.69–1.73 (m, 2H), 1.85 (ddd, J = 6.0, 6.0, 12.5, 1H), 1.90–1.99 (m, 2H), 2.09 (m, 1H), 2.26 (br s, 1H), 2.54 (br s, 1H), 3.70 (m, 1H), 3.97 (dd, J = 3.0, 11.0, 1H). ^{13}C NMR: 20.4 (CH_3), 25.4 (CH_2), 27.8 (CH_2), 32.0 (CH_3), 32.3 (CH_3), 34.2 (CH_2), 35.8 (C), 39.2 (CH), 43.0 (CH_2), 45.0 (CH), 45.7 (CH), 46.2 (C), 47.5 (CH_2), 64.5 (CH_2), 76.0 (C). IR (KBr): 3267, 2932, 2893, 2862, 1458, 1396, 1385, 1265, 1242, 1184, 1169, 1115, 1096, 1076, 1018. EIMS m/z : 210, 195, 177, 161, 153, 135, 121, 107, 95. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{26}\text{NaO}_2$, 261.1830; found, 261.1833.



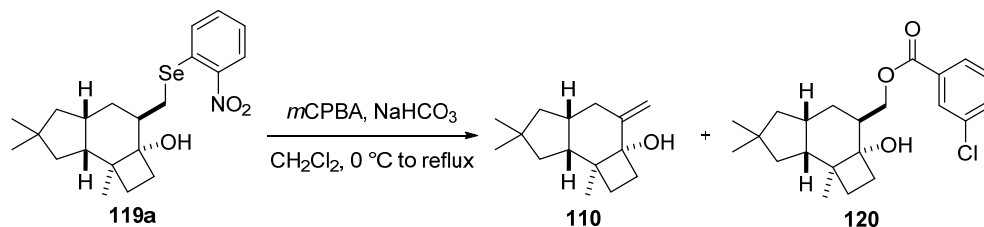
(2aSR,3RS,4aSR,7aRS,7bSR)-6,6,7b-Trimethyl-3-[(2-nitrophenyl)selanyl]methyl]decahydro-2aH-cyclobuta[e]inden-2a-ol (119a): The THF used in the reaction was degassed by refluxing with benzophenone ketyl radical before use. To a stirred solution of diol **115a** (98.5 mg, 0.413 mmol) in dry THF (4.1 mL) was added $o\text{-NO}_2\text{C}_6\text{H}_4\text{SeCN}$ (195 mg, 0.704 mmol). Then, the mixture was cooled to 0 $^{\circ}$ C and $(\text{Oct})_3\text{P}$ (>85%, 0.54 mL, 1.0 mmol) was added dropwise. The mixture was

stirred at rt for 70 min. Then, the solvent was removed *in vacuo*. The residue was purified by column chromatography (toluene/EtOAc 1:0 to 95:1) to afford the title compound (155 mg, 89%) as yellow oil: R_f 0.21 (toluene). ^1H NMR: 0.85 (s, 3H), 0.92 (s, 3H), 0.99 (dd, $J = 12.5, 12.5$, 1H), 1.08 (dd, $J = 9.5, 12.5$, 1H), 1.15 (s, 3H), 1.36–1.42 (m, 2H), 1.52–1.72 (m, 3H), 1.77 (ddd, $J = 7.5, 13.5, 13.5$, 1H), 1.81 (br s, 1H), 1.88 (m, 1H), 2.00–2.10 (m, 2H), 2.29 (ddd, $J = 3.0, 9.5, 12.5$, 1H), 2.52 (m, 1H), 2.57 (dd, $J = 11.0, 11.5$, 1H), 3.37 (dd, $J = 3.0, 11.5$, 1H), 7.29 (t, $J = 8.0$, 1H), 7.52 (t, $J = 8.0$, 1H), 7.74 (d, $J = 8.0$, 1H), 8.27 (d, $J = 8.0$, 1H). ^{13}C NMR (C_6D_6): 22.2 (CH_3), 26.4 (CH_3), 27.3 (CH_2), 27.5 (CH_2), 27.7 (CH_2), 29.2 (CH_3), 32.0 (CH_2), 33.4 (CH), 37.7 (C), 38.0 (CH), 45.4 (CH), 45.8 (C), 46.6 (CH_2), 48.9 (CH_2), 77.1 (C), 125.0 (CH), 126.3 (CH), 128.0 (CH), 133.2 (CH), 134.2 (C), 147.5 (C). IR (neat): 3447, 2951, 2926, 2866, 1591, 1566, 1512, 1449, 1333, 1304, 1252, 1126, 1096, 1038. EIMS m/z : 395, 221 ($\text{M}-o\text{-NO}_2\text{C}_6\text{H}_4\text{Se}$), 203, 189, 161, 147, 135, 119, 109, 95. HRMS-ESI (m/z): $[\text{M}+\text{K}]^+$ calcd. for $\text{C}_{21}\text{H}_{29}\text{KNO}_3\text{Se}$, 462.0950; found, 462.0951.



(2aSR,3SR,4aSR,7aRS,7bSR)-6,6,7b-Trimethyl-3-[(2-nitrophenyl)selanyl]methyl]decahydro-2aH-cyclobuta[e]inden-2a-ol (119b): The THF used in the reaction was degassed by refluxing with benzophenone ketyl radical before use. To a stirred solution of diol **115b** (7.9 mg, 33 μmol) in THF (0.7 mL) was added $o\text{-NO}_2\text{C}_6\text{H}_4\text{SeCN}$ (15.4 mg, 55.6 μmol). The mixture was cooled to 0 °C and $(\text{Oct})_3\text{P}$ (>85%, 44 μL , 84 μmol) was added dropwise. The mixture was stirred at rt for 1 h. Then, $o\text{-NO}_2\text{C}_6\text{H}_4\text{SeCN}$ (15.4 mg, 55.6 μmol) and $(\text{Oct})_3\text{P}$ (>85%, 44 μL , 84 μmol) were added again to the mixture. After 1 h, $o\text{-NO}_2\text{C}_6\text{H}_4\text{SeCN}$ (15.6 mg, 56.3 μmol) and $(\text{Oct})_3\text{P}$ (>85%, 44 μL , 84 μmol) were added again to the mixture. After 1 h, $o\text{-NO}_2\text{C}_6\text{H}_4\text{SeCN}$ (15.6 mg, 56.3 μmol) and $(\text{Oct})_3\text{P}$ (>85%, 44 μL , 84 μmol) were added again to the mixture. After additional 2 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (toluene/EtOAc 1:0 to 97:3) to afford crude products. Then, the mixture was purified by PTLC (toluene x 6) to afford the title compound (11.9 mg, 85%) as yellow solids of mp 154–157 °C: R_f 0.38 (toluene x 3). ^1H NMR: 0.95 (s, 3H), 1.05 (s, 3H), 1.17 (s, 3H), 1.25–1.35 (m, 3H), 1.39 (d, $J = 10.0$, 2H), 1.48–1.56 (m, 2H), 1.70 (dd, $J = 8.0, 13.5$, 1H), 1.74 (br s, 1H), 1.87 (m, 1H), 1.90–2.00 (m, 3H), 2.07 (m, 1H), 2.92 (dd, $J = 10.0, 11.0$, 1H), 3.20 (dd, $J = 4.5, 11.0$, 1H), 7.30 (dd, $J = 7.0, 8.5$, 1H), 7.51 (dd, $J = 7.0, 8.0$, 1H), 7.62 (d, $J = 8.0$, 1H), 8.28 (d, $J = 8.5$, 1H). ^{13}C NMR: 20.8 (CH_3), 25.7 (CH_2), 28.2 (CH_2), 31.1 (CH_2), 31.8 (CH_3), 32.3 (CH_3), 33.8 (CH_2), 35.8 (C), 39.4 (CH), 43.2 (CH_2), 43.3 (CH), 45.6 (CH), 46.1 (C), 47.4 (CH_2), 74.9 (C), 125.2 (CH), 126.4 (CH), 129.2 (CH), 133.5 (CH), 134.5 (C), 146.9

(C). IR (neat): 3537, 2928, 2862, 1589, 1562, 1508, 1458, 1327, 1304, 1234, 1088. FABMS m/z : 446 (M+Na). HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₂₁H₂₉NNaO₃Se, 446.1210; found, 446.1209.



(2aSR,4aRS,7aRS,7bSR)-6,6,7b-Trimethyl-3-methylenedecahydro-1H-cyclobuta[e]inden-2a-ol (110) and

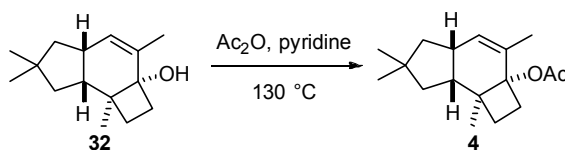
{(2aSR,3SR,4aSR,7aRS,7bSR)-2a-Hydroxy-6,6,7b-trimethyldecahydro-1H-cyclobuta[e]inden-3-yl}methyl 3-chlorobenzoate (120): To a solution of selenide **119a** (8.9 mg, 21 μ mol) in dry CH₂Cl₂ (1.5 mL) at 0 °C were added NaHCO₃ (7.1 mg, 85 μ mol) and *m*CPBA (7.2 mg, 42 μ mol). The mixture was stirred at rt for 30 min and heated under reflux for 1 h. After cooling to rt, the reaction was quenched by the addition of saturated aqueous Na₂S₂O₃ (3 mL). The whole was extracted with EtOAc (5 mL + 2 x 3 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1 to 95:5) to afford the title compounds (1.8 mg and 1.9 mg, 39% and 24%, respectively).

110: Colorless oil. R_f 0.24 (toluene). ¹H NMR: 0.88 (s, 3H), 0.95 (m, 1H), 0.98 (s, 3H), 1.14 (s, 3H), 1.22 (dd, *J* = 7.5, 12.5, 1H), 1.31 (ddd, *J* = 2.0, 7.0, 12.0, 1H), 1.44 (ddd, *J* = 3.5, 11.5, 11.5, 1H), 1.64 (ddd, *J* = 2.0, 8.5, 12.5, 1H), 1.66–1.74 (m, 2H), 1.97 (dd, *J* = 2.5, 13.5, 1H), 2.08 (m, 1H), 2.11–2.21 (m, 2H), 2.53 (m, 1H), 2.69 (dd, *J* = 7.0, 13.5, 1H), 4.77 (s, 1H), 5.07 (s, 1H). ¹³C NMR: 22.2 (CH₃), 27.0 (CH₂), 27.3 (CH₃), 29.4 (CH₃), 31.5 (CH₂), 35.9 (CH₂), 36.0 (CH), 37.3 (C), 44.8 (CH₂), 46.0 (CH), 47.1 (C), 48.0 (CH₂), 76.0 (C), 107.2 (CH₂), 150.4 (C). IR (neat): 3449, 2951, 2928, 2866, 1462, 1443, 1381, 1366, 1261, 1230, 1138, 1084, 1026. EIMS m/z : 220 (M⁺), 205 (M–Me), 192, 177, 163, 135, 121, 107, 95. HRMS-ESI (m/z): [M+Na]⁺ calcd. for C₁₅H₂₄NaO, 243.1725; found, 243.1725.

120: Yellow oil. R_f 0.46 (hexane/EtOAc 5:1). ¹H NMR: 0.90 (s, 3H), 1.04 (s, 3H), 1.13 (m, 1H), 1.15 (s, 3H), 1.24 (m, 1H), 1.36–1.48 (m, 3H), 1.53 (m, 1H), 1.77 (dd, *J* = 10.5, 11.0, 1H), 1.84 (ddd, *J* = 7.0, 13.5, 13.5, 1H), 1.93 (m, 1H), 2.10 (m, 1H), 2.18 (m, 1H), 2.27 (ddd, *J* = 3.5, 10.0, 12.5, 1H), 2.56 (m, 1H), 4.29 (dd, *J* = 7.5, 11.0, 1H), 4.53 (dd, *J* = 5.0, 11.0, 1H), 7.39 (dd, *J* = 8.0, 8.0, 1H), 7.53 (d, *J* = 8.0, 1H), 7.90 (d, *J* = 8.0, 1H), 8.00 (s, 1H). ¹³C NMR: 22.0 (CH₃), 26.3 (CH₃), 27.2 (CH₂), 27.7 (CH₂), 29.1 (CH₃), 29.4 (CH₂), 32.6 (CH), 37.8 (C), 37.9 (CH), 45.0 (CH), 45.4 (C), 46.2 (CH₂), 48.9 (CH₂), 66.6 (CH₂), 75.7 (C), 127.6 (CH), 129.6 (CH), 129.7 (CH), 132.1 (C), 133.0 (CH), 134.6 (C), 165.6 (C). IR (neat): 3431, 2953, 2926, 2866, 1719, 1460, 1283, 1260, 1132, 1086.

(4.8 mL) at rt. Hydrogen evolution commenced immediately. After 1 h, to *exo*-olefin **110** (48.6 mg, 0.220 mmol) was added the KAPA, using a double-ended needle. The reaction mixture was stirred at rt for 17 h. Then, the reaction was quenched by the addition of saturated aqueous NH₄Cl (10 mL) at 0 °C. The whole was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 99:1) to afford the title compound (41.0 mg, 85%) as colorless solids of mp 81–83 °C: R_f 0.48 (benzene/Et₂O 9:1). ¹H NMR: 0.96 (s, 3H), 1.00 (s, 3H), 1.21 (s, 3H), 1.24–1.30 (m, 2H), 1.36–1.40 (m, 2H), 1.45 (m, 1H), 1.51 (br s, 1H), 1.74 (br s, 3H), 1.75 (dd, *J* = 8.5, 13.0, 1H), 1.96–2.08 (m, 3H), 2.64 (m, 1H), 5.26 (br s, 1H). ¹³C NMR: 17.2 (CH₃), 21.1 (CH₃), 24.7 (CH₂), 31.5 (CH₃), 31.9 (CH₃), 33.8 (CH₂), 37.9 (C), 38.7 (CH), 42.2 (CH₂), 44.6 (C), 44.7 (CH), 47.8 (CH₂), 72.5 (C), 129.4 (CH), 133.2 (C). IR (KBr): 3387, 2955, 2866, 1447, 1234, 1188, 1130, 1099. EIMS *m/z*: 220 (M⁺), 205 (M–Me), 192, 177, 135, 124, 109, 91, 77, 55, 41. HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₅H₂₄NaO, 243.1725; found, 243.1728.

¹H NMR, MS, and IR spectral data were identical to those reported.⁴¹



Paesslerin A (4): To a stirred solution of alcohol **32** (17.8 mg, 80.8 μmol) in acetic anhydride (0.6 mL) was added pyridine (97 μL, 1.2 mmol). The mixture was heated at 130 °C for 26 h. After cooling to rt, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc 149:1) to afford the title compound (15.4 mg, 73%) as colorless oil: R_f 0.33 (hexane/EtOAc 95:5). ¹H NMR: 0.96 (s, 3H), 1.03 (s, 3H), 1.14 (s, 3H), 1.27 (m, 1H), 1.34 (dd, *J* = 4.0, 12.5, 1H), 1.37 (m, 1H), 1.55 (m, 1H), 1.61 (s, 3H), 1.62 (m, 1H), 1.77 (dd, *J* = 8.5, 12.5, 1H), 2.00 (m, 1H), 2.02 (s, 3H), 2.07 (ddd, *J* = 2.0, 8.5, 10.5, 1H), 2.50 (ddd, *J* = 10.5, 10.5, 10.5, 1H), 2.70 (br s, 1H), 5.32 (br s, 1H). ¹³C NMR: 18.2 (CH₃), 21.4 (CH₃), 21.6 (CH₃), 26.4 (CH₂), 30.5 (CH₃), 31.1 (CH₃), 31.5 (CH₂), 37.8 (CH), 38.0 (C), 41.7 (CH₂), 44.4 (CH), 44.7 (C), 47.7 (CH₂), 80.0 (C), 130.3 (CH), 130.7 (C), 169.7 (C). IR (neat): 2953, 2928, 2864, 1728, 1449, 1368, 1260, 1234, 1084, 1042. EIMS *m/z*: 262 (M⁺), 234, 220, 202, 192, 166, 135, 124, 109, 91, 43 (Ac). HRMS-ESI (*m/z*): [M+Na]⁺ calcd. for C₁₇H₂₆NaO₂, 285.1830; found, 285.1837.

¹H NMR, ¹³C NMR, and MS spectral data were identical to those reported.⁴⁰

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発表論文リスト

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Manuscript in preparation

略語一覧

Ac	acetyl
acac	acetylacetone
AIBN	2,2'-azobisisobutyronitrile
BHA	2,6-di- <i>tert</i> -butyl-4-methoxyphenyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
calcd.	calculated
cat.	catalytic amount of
cod	1,5-cyclooctadiene
conc.	concentrated
Cp	cyclopentadienyl
CSA	(1 <i>S</i>)-(+)-10-camphorsulfonic acid
cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DBADBU	6-(dibutylamino)-1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N</i> -dimethylpropyleneurea
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
ee	enantiomeric excess
EIMS	electron impact mass spectrometry
equiv.	equivalent
ESI-MS	electrospray ionization mass spectrometry
esp	$\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
FAB-MS	fast atom bombardment mass spectrometry
h	hour
HMDS	hexamethyldisilazide

HMPA	hexamethylphosphoric triamide
HOTT	<i>S</i> -(1-oxide-2-pyridinyl)-1,1,3,3-tetramethylthiuroniumhexafluor -ophosphate
HPLC	high resolution liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
<i>i</i> -Pr	isopropyl
IR	infrared
LDA	lithium diisopropylamide
<i>m</i> CPBA	<i>m</i> -chloroperbenzoic acid
Me	methyl
min	minute
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMO	<i>N</i> -methyldimorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Oct	octyl
pfb	perfluorobutylate
Ph	phenyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
py	pyridine
PTLC	preparative thin layer chromatography
quant	quantitative yield
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	<i>tert</i> -butylhydroperoxide

TBS	<i>tert</i> -butyldimetylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
TES	triethylsilyl
Tf	trifluoromethaneulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
tol	toluene
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl
Ts	<i>p</i> -toluenesulfonyl