連続反応による骨格構築を鍵とした
lyconesidine B の全合成

２０２０

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目次

略語表

Ac	acetyl
acac	acetylacetonate
ADMP	2-azido-1,3-dimethylimidazolinium hexafluorophosphate
aq	aqueous
AZADOL	2-hydroxy-2-azaadamantane
BAr_F	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bpy	2,2'-bipyridyl
Bu	butyl
cap	caprolactamate
Cbz	benzyloxycarbonyl
CSA	10-camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMSO	dimethyl sulfoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	dimethyl formamide
dr	diastereomeric ratio
eq	equivalent
er	enantiomeric ratio
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
hfacac	hexafluoroacetylacetonato
HMDS	hexamethyldisilazane
i	*iso*
JohnPhos	2-(di-*tert*-butylphosphino)biphenyl
LDA	lithium diisopropylamide
L-Selectride®	lithium tri-*sec*-butylborohydride
Me	methyl
Mes	methanesulfonyl
MS	molecular sieve
n	*normal*
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Ns	2-nitrobenzenesulfonyl
P	*para*
Ph	phenyl
pin	pinacolato
PMHS	polymethylhydrosiloxane
Pr	propyl

t	*tertiary*
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl (tosyl)

序論

第一節　リコポジウムアルカロイドについて

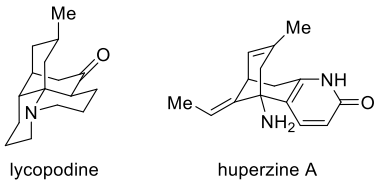
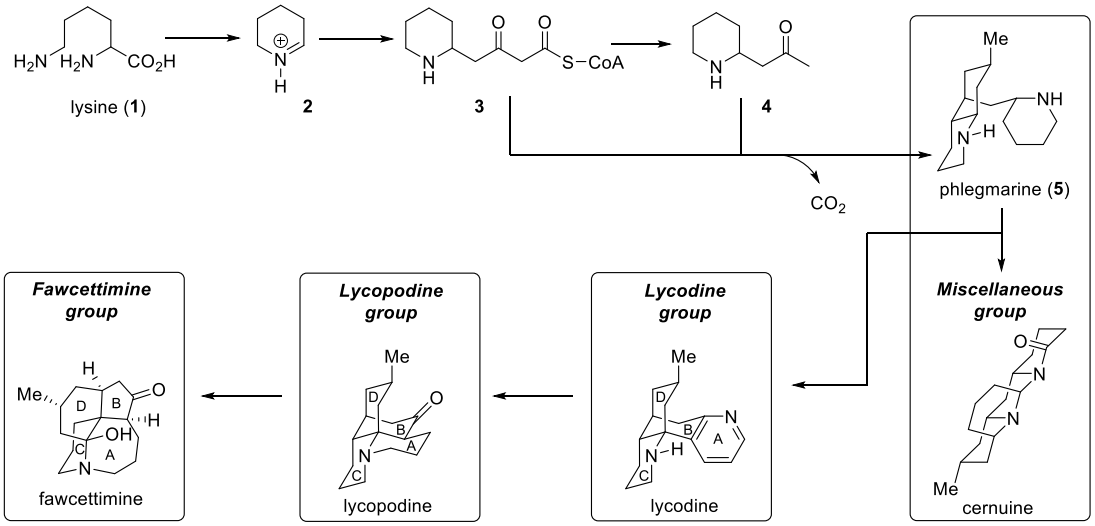


Figure 1. examples of *lycopodium* alkaloids

ヒカゲノカズラ科の植物は、世界中に広く分布するシダ植物であり、古くから止血、消炎、解毒作用などを目的とした伝統薬として利用されてきた [1]。このような背景から、これら植物からの生理活性天然物の単離研究が精力的に行われており、1881 年 Bödeker らによる lycopodine[2] の単離以来、「リコポジウムアルカロイド」と呼ばれる特徴的な多環性骨格の天然物が現在までに 250 種類以上単離されてきた (Figure 1)[1a]。本天然物群の中には、有用な生物活性を持つものが多数報告されている。その代表的な例は、1981 年に *Huperzia Serrata* より単離された huperzine A である [3]。本天然物は、既存のアルツハイマー病治療薬と同等の高い可逆性アセチルコリンエステラーゼ阻害活性を有しており、毒性や副作用が少ない為、米国では記憶障害改善のためのサプリメントとして販売されている [4]。また、huperzine A の他にも、抗 HIV 活性 [5] や抗腫瘍活性 [6]、抗炎症作用 [7] などを持つ天然物が報告されている。リコポジウムアルカロイドは、その生物活性が注目される一方で、その生合成研究は発展途上であり、生合成酵素もほとんど明らかになっていない [1c]。これは、ヒカゲノカズラ科の植物の成長速度が非常に遅く、栽培も難しいことが原因である。しかしながら、放射性同位体標識したリシンを用いたトレーサー実験より、リシン (**1**) 由来の 4-(2-piperidyl)acetoacetate (**3**) と pelletierine (**4**) との脱炭酸を伴うカップリング成績体 phlegmarine (**5**) が生合成中間体と提唱されている (Scheme 1)[8]。**5** から脱窒素や骨格転位を伴って生合成されるリコポジウムアルカロイドは、その構造的特徴から lydcodine グループ、lycopodine グループ、fawcettimine グループ、その他 (miscellaneous group) の 4 種類に大別される [9]。Lycodine に代表される lycodine グループは、二つの窒素原子を含んでおり、ピリジン環やピリドン環を有することがその特徴である。Lycopodine に代表される lycopodine グループは、lycodine 型天然物の A 環が開環してピペリジン環を形成した構造である。また、fawcettimine に代表される fawcettimine グループは、BD 環部の *cis*-ヒドリンダン骨格と AC 環部のヒドロアゾニン環を有することがその特徴である。なお、これらに属さないリコポジウムアルカロイドはその他に分類される。

Scheme 1. Biosynthesis and classification of *lycopodium* alkaloids.



第二節　Fawcettimine 型リコポジウムアルカロイドについて

Fawcettimine は 1959 年に Burnell によって *Lycopodium fawcetti* より過塩素酸塩の結晶として単離された [10]。その後、犬伏、Burnell、Ayer らによってヘミアミナール **6a** とケトアミン **6b** の平衡混合物であることが提唱された (Figure 2)[11]。この時点では、4 位の立体化学については明らかでなかったが、後述の Heathcock らの全合成により 4*S* 体であることが明らかとなった。Fawcettimine の単離以来、fawcettimine グループに属する天然物は 80 種類以上が単離されており、構造的多様性に富んでいる。著者は、本化合物群の構造の中で、13 位の酸化度に着目し、それぞれをヘミアミナール型、エナミン型、アミン型の三種類に分類した (Figure 3a, b, c)。

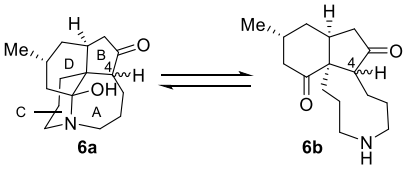


Figure 2. The structure of fawcettimine.

	(a) hemiaminal-type	(b) enamine-type	(c) amine-type
examples of basic skeleton	1979, Inubushi 1986, Heathcock 2007, Toste[a] 2008, Liu, Chau[a,b] 2010, Mukai[a] 2010, Jung[a,b] 2011, Yang[a] 2012, Williams 2012, Lei[a] 2013, Tu, Wang[a] 2014, Taniguchi[a,b] 2014, Zhai 2015, Zhao[a] 2020, Qiu fawcettimine 2009, Takayama lycoposerramine C 2014, Taniguchi[a] 2019, Takayama[a] lycopodavamine A	2008, Dake[a] 2012, Lei[a] 2013, Mukai 2013, Tu, Wang[a] 2013, Zhao[a] fawcettidine 2013, Mikai 2013, Zhao[a] lycoposerramine Q	2012, Yao[a] lannotinidine B •improvement of NGF mRNA expression
examples of oxygen-functionalized skeleton	2011, Takayama[a] 2015, Lei[a] 2015, Zhao[a] 2017, Yokoshima, Fukuyama huperzine Q 2011, Tu alopecuridine 2013, Taniguchi 2014, Taniguchi[a] lycopodavamine B 2013, Zhao[a] lycopladine D •cytotoxicity againstmurine lymphoma L1210 cells •human epidermoid carcinoma KB cells (IC_{50} > 10 μg/ml) 2014, Lei[a] 8α-hydroxyfawcettimine 2015, Zhao[a] N-oxyhuperzine Q 2017, Fan 2018, Hsieh palhinine D	2015, Lei[a] lycopladine B	***no tatal synthesis*** R = H: lyconesidine A R = OH: lyconesidine B •cytotoxicity againstmurine lymphoma L1210 cells (IC_{50} = 18.0, 9.5 μg/ml) •inhibition the polumerization oftubulin (IC_{50} = 300, 250 μM)

[a]Asymmetric synthesis. [b]Formal synthesis

Figure 3. Classification of fawcettimine-type *lycopodium* alkaloids based on the structure of C13 and examples of total synthesis. The numbers and names in the right side of each compound are the years of publication and the authors of their synthetic studies. The biactivities (onyl for reported compounds) are showed below each compound.

ヘミアミナール型は、fawcettimine に代表される 13 位にヘミアミナール構造を有する天然物群であり、fawcettimine を基準として、その炭素骨格の酸素官能基化の度合いによって、「基本骨格 (basic skeleton)」と「酸素官能基化骨格 (oxygen-functionalized skeleton)」に細分化した。エナミン型、アミン型の天然物も同様に、それぞれ fawcettidine と lannotinidine B を基準として分類した。これらのグループについてその全合成報告数を比較すると、ヘミアミナール型の天然物は比較的合成研究が進んでおり、その合成報告数は、基本骨格天然物が 16 報、酸素官能基化天然物が 12 報である [12]。エナミン型天然物の合成報告数は、ヘミアミナール型程多くないが、基本骨格天然物、酸素官能基化天然物の合成がそれぞれ 5 報と 1 報である。一方で、アミン型の天然物は、lannotinidine B の全合成の 1 報に留まり、酸素官能基化骨格のアミン型天然物の合成は、本博士課程の研究で著者が報告するまで達成されていなかった。

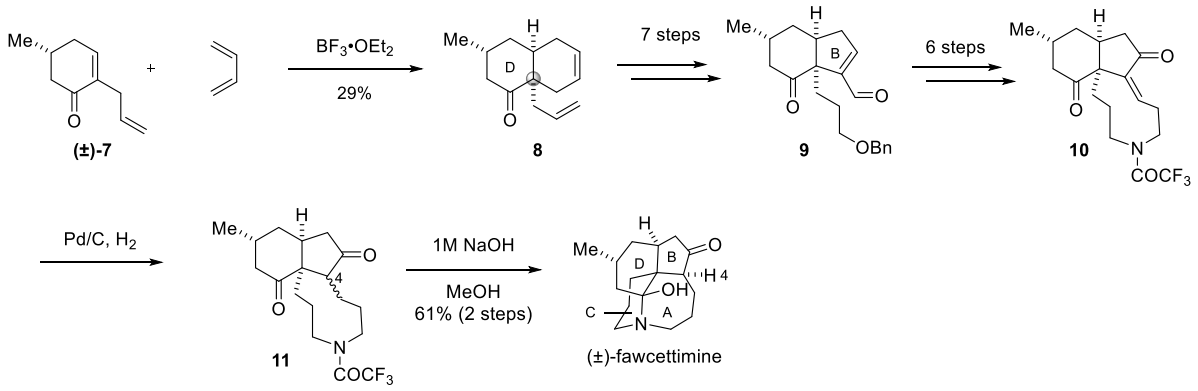
第三節　Fawcettimine 型リコポジウムアルカロイドのこれまでの合成戦略について

Fawcettimine 型リコポジウムアルカロイドの合成報告数には偏りがあるが、おおまかな合成戦略で分類して、これまでの合成研究を紹介する [13]。

① 犬伏らによる(±)-fawcettimine の初の全合成

Fawcettimine 型リコポジウムアルカロイドの初の全合成は、1979 年に京都大学の犬伏らによって報告された fawcettimine の全合成である (Scheme 2)[12a]。本合成では、BD 環部から構築し、最後にヘミアミナールを形成する戦略が採用された。具体的には、まずシクロヘキセノン誘導体 **7** とブタジエンとの Diels-Alder 反応により、四つの置換基全てが炭素原子の sp^3 炭素（以下、第四級炭素）の導入と D 環部の構築を一挙に行った。その後、オゾン分解と分子内アルドール縮合による B 環部の五員環形成で、シスヒドリンダン化合物 **9** へと導いた。さらに、Horner-Wadsworth-Emmons 反応による増炭と分子内アミド化による 9 員環ラクタムの形成を含む 6 工程の変換で、三環性化合物 **10** へと変換した。アルケンの接触水素化後、トリフルオロアセチル基を除去すると、分子内でヘミアミナール構造が形成され、(±)-fawcettimine の初の全合成が達成された。なお、本合成では接触水素化後に 4 位のジアステレオ混合物となったため、天然物の 4 位の立体化学は明らかになっていなかった。

Scheme 2. Inubushi's first total synthesis of (±)-fawcettimine.

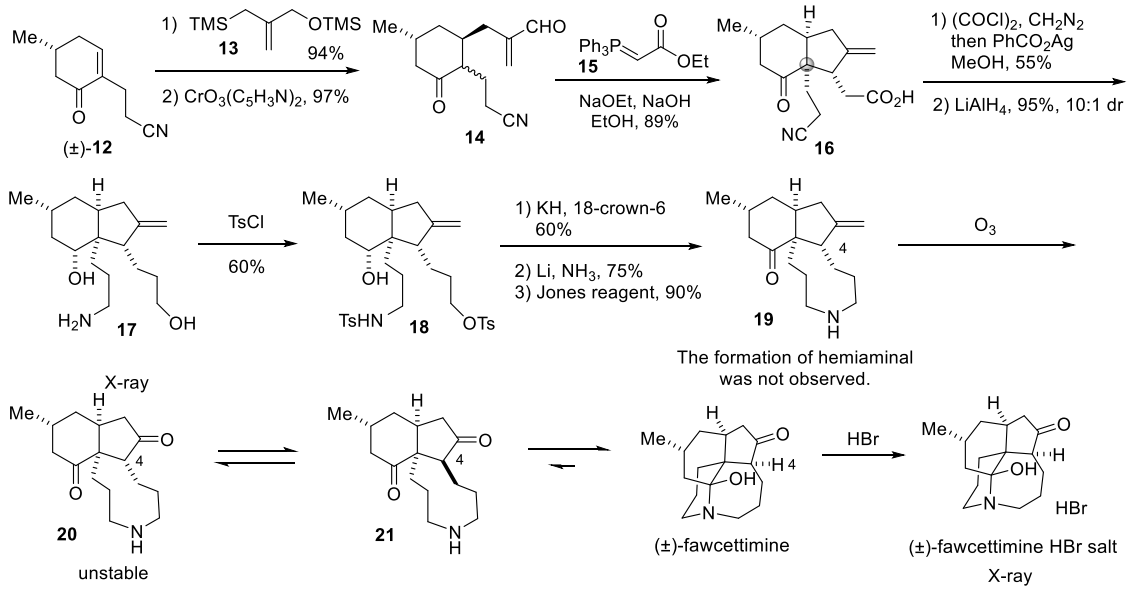


② Heathcock らによる(±)-fawcettimine の全合成と 4 位の立体化学の決定

1986 年、Heathcock らは、4 位の立体化学の決定を目的として fawcettimine を全合成した (Scheme 3)[12c]。彼らは、まず、シクロヘキセノン誘導体 **12** とアリルシラン **13** との細見・櫻井反応によって得

られたアリルアルコールを酸化して α,β-不飽和アルデヒド **14** を得た。**14** とイリド **15** との Wittig 反応に続く分子内 Michael 付加による第四級炭素の導入と加水分解でカルボン酸 **16** を合成した。その後、Arndt-Eistert 合成で増炭して生じたエステルと二トリル、ケトンの還元で、アミノジオール **17** を 9:1 のジアステレオ混合物として得た。なお、主ジアステレオマーの構造は、X 線結晶構造解析によって確認された。**17** を TsCl で処理して、トシルアミド **18** とした後、分子内求核置換反応によりヒドロアゾニン環を形成した。その後、トシル基の除去、第二級アルコールの酸化でアミノケトン **19** を合成した。このとき、**19** はヘミアミナール体として観測されなかったことから、4 位の立体化学はヘミアミナール形成に影響を与えていることが示唆された。最後に、**19** をオゾン分解すると、アミノジケトン **20** が生成したが、**20** は不安定であり、室温、数時間で 4 位が異性化した後、分子内でヘミアミナールを形成し、(±)-fawcettimine を与えた。最終的には、合成した (±)-fawcettimine の臭化水素塩の X 線結晶構造解析により、fawcettimine の相対立体配置が確認された。

Scheme 3. Heathcock's total synthesis of (±)-fawcettimine and its structural confirmation.

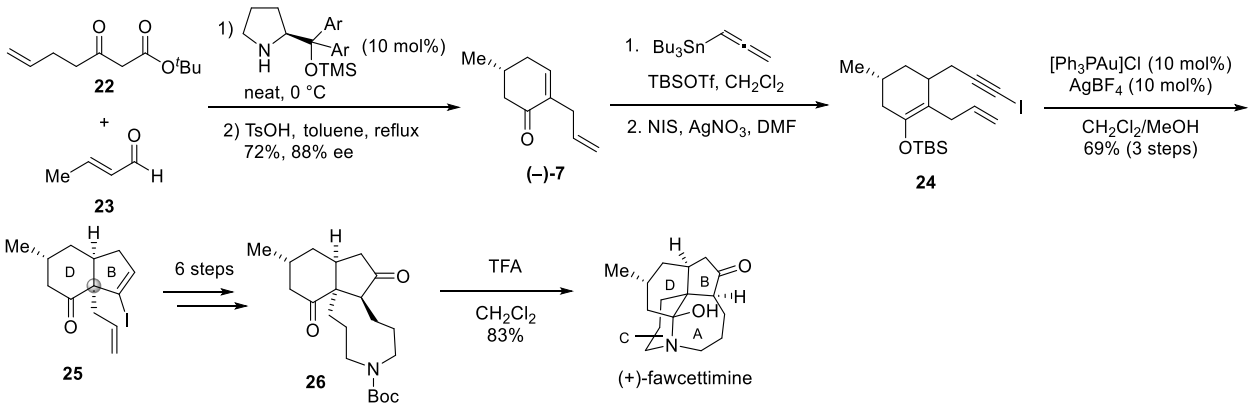


犬伏・Heathcock らは共に、5-6-9 員環の三環性合成中間体を合成し、最後にヘミアミナール構造を形成することで fawcettimine の四環性骨格を構築した。本合成戦略は fawcettimine 型リコポジウムアルカロイドの効率的な骨格構築法であり、その後のヘミアミナール型天然物の全ての合成で採用された。

③ Toste らによる(+)-fawcettimine の初の不斉全合成

2007 年 Toste らは fawcettimine の初の不斉全合成を達成した。本合成でも犬伏・Heathcock らの合成戦略が用いられている。まず、ケトエステル **22** とクロトンアルデヒド (**23**) とのエナンチオ選択的な Robinson 環化反応でシクロヘキセノン誘導体 (−)**-7** を 72% 収率、88% ee で得た (Scheme 4)[12e]。(−)**-7** にプロパルギル基を導入した後、生じたエノラートはシリル基で捕捉し、続いてアセチレン末端をヨウ素化して、エノールシリルエーテル **24** を合成した。得られた **24** の金触媒による環化反応で、第四級炭素を導入しつつ B 環部を構築した。その後、鈴木-宮浦クロスカップリングによる増炭と分子内求核置換反応によるヒドロアゾニン環の構築を含む数工程で三環性化合物 **26** を合成し、最後に Boc 基の除去で(+)-fawcettimine の初の不斉全合成を達成した。

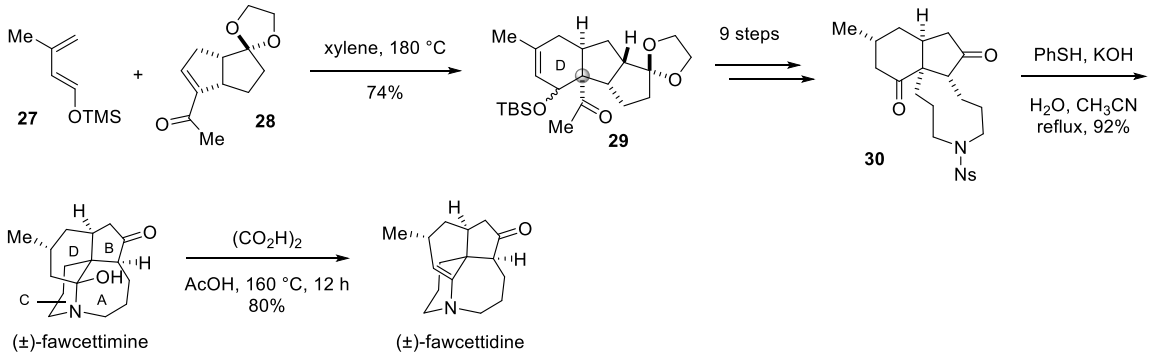
Scheme 4. Toste's first asymmetric total synthesis of (+)-fawcettimine.



④ Williams らによる(±)-fawcettimine の全合成と(±)-fawcettidine への誘導化

犬伏・Heathcock らの合成戦略は、エナミン型天然物の合成へも応用可能である。2012 年、Williams らは、脱水反応によってヘミアミナール構造を持つ fawcettimine からエナミン構造を持つ fawcettidine への誘導化を達成した (Scheme 5)[12n]。まず、ジエン **27** と不飽和ケトン **28** との Diels-Alder 反応によって第四級炭素を導入しつつ D 環部を構築し、シクロペンタン環の開裂とヒドロアゾニン環の形成を含む 9 工程の変換で三環性化合物 **30** とした。最後に Ns 基の除去で(±)-fawcettimine を全合成した。さらに、 (±)-fawcettimine を、酢酸中、過剰量のシュウ酸存在下 160 °C で 12 時間攪拌することで (±)-fawcettidine への誘導化にも成功した。本脱水反応では、fawcettimine の窒素原子の n 軌道とヒドロキシ基の $\sigma^*_{C\text{-}O}$ 軌道の重なりが悪いため過酷な条件が必要であった。

Scheme 5. Williams' total synthesis of (±)-fawcettimine and (±)-fawcettidine

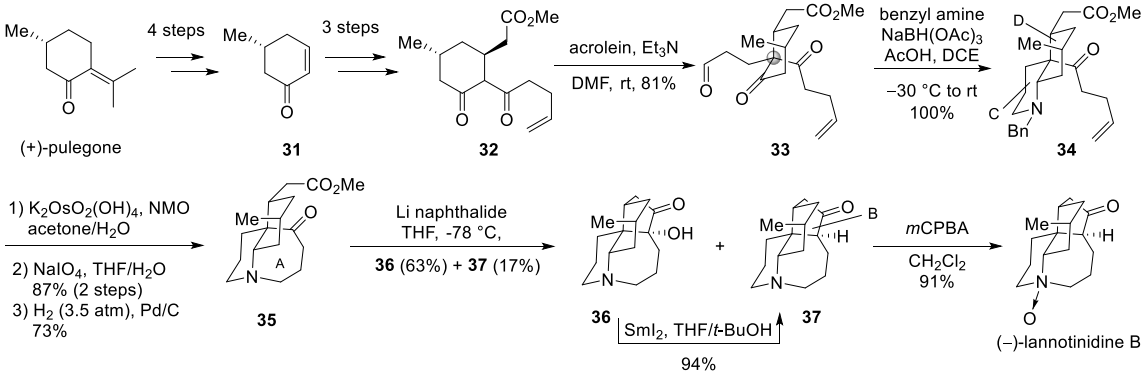


⑤ Yao らによる(−)-lannotinidine B の全合成

Fawcettimine 型リコポジウムアルカロイド特有の構造的特徴のためヘミアミナール型、およびエナミン型天然物を直接アミン型天然物に変換する手法は報告されていない。アミン型の合成では、BD 環部から合成する犬伏・Heathcock らの合成戦略とは異なり、CD 環部から構築する合成が 1 例報告されている。2012 年、Yao らは、官能基選択的かつ立体選択的な還元的アミノ化反応を鍵とした(−)-lannotinidine B の全合成を報告した (Scheme 6)[18]。(+)-Pulegone より合成したメチルシクロヘキセノン **31** から導いたジケトン **32** をアクロレインに求核付加させ、第四級炭素を有するジケトアルデヒド **33** を合成した。続いて **33** とベンジルアミンとの還元的アミノ化で C 環部を構築し、ヒドロキノリン **34** とした。さらに、**34** の末端アルケンの酸化的開裂に続く還元的アミノ化で三環性化合物 **35** を合成し

た。その後、Birch 条件で処理することで還元的に C-C 結合を形成し、ケトアルコール **36** とケトン **37** をそれぞれ得た。**36** については SmI_2 による還元的なケトン α 位水酸基の除去により **37** へと変換し、最後に *m*CPBA でアミンを酸化して(−)-lannotinidine B の全合成を達成した。

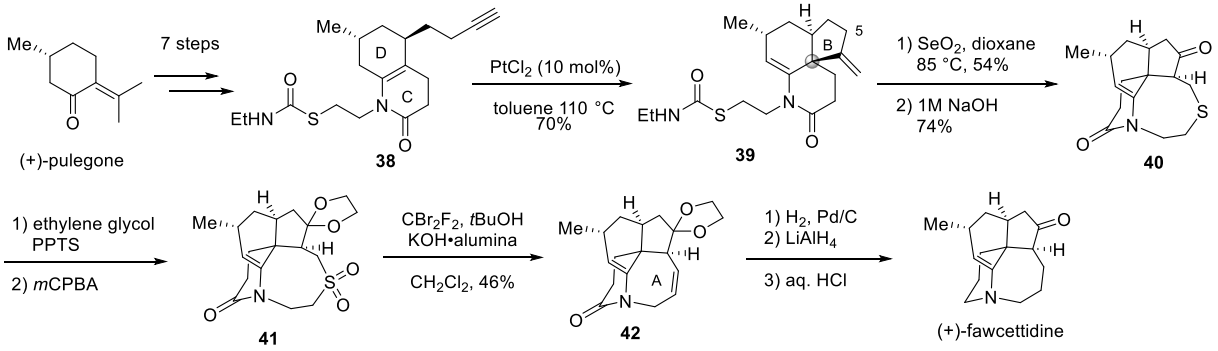
Scheme 6. Yao's first total synthesis of (−)-lannotinidine B constructed from CD ring.



⑥ Dake らによる(+)-fawcettidine の全合成

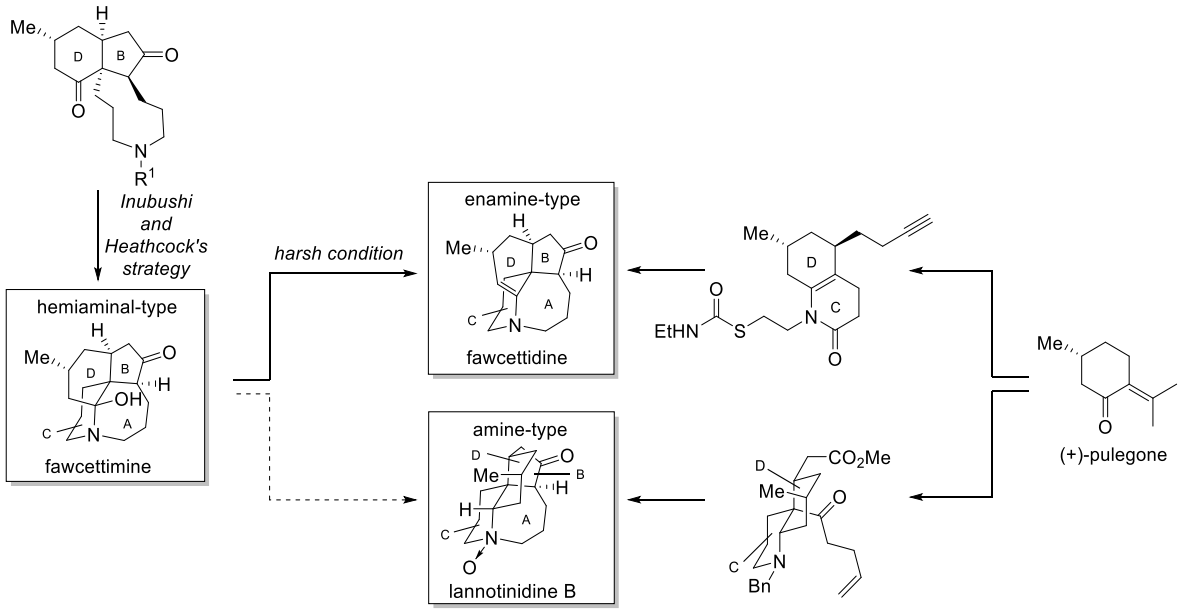
上記のように CD 環部からの合成については、2008 年 Dake らによりエナミン型天然物でも 1 例報告されている [12f]。本合成でも(+)-pulegone を出発原料とし、7 工程でアルキン **38** を合成した (Scheme 7)。続いて、白金触媒による環化反応で、第四級炭素を導入しつつ B 環部を構築し、三環性化合物 **39** へと導いた。その後、5 位を酸化して生じたエノンに対して分子内でチオールを共役付加させ、スルフィド **40** を合成した。ケトンのアセタール保護とスルフィドの酸化でスルホン **41** とし、Ramberg-Bäcklund 転位で A 環部の 7 員環を合成した。その後のオレフィンの接触水素化とアミドの還元およびアセタールの脱保護で、(+)-fawcettidine の全合成を達成した。

Scheme 7. Dake's first total synthesis of (+)-fawcettidine constructed from CD ring.



以上の合成報告をまとめると、犬伏・Heathcock らの合成戦略は特にヘミアミナール型の fawcettimine 型リコポジウムアルカロイド合成の効率的な手法である (Scheme 8)。しかしながら、本天然物群は橋頭位に窒素原子を有するため通常のヘミアミナールとは反応性が異なり、エナミン型への変換には過酷な条件が必要である。また、ヘミアミナール型からアミン型への変換は報告がない。一方、犬伏・Heathcock らの合成戦略と異なり、CD 環部から構築する合成報告はエナミン型とアミン型の天然物でそれぞれ 1 例ずつのみ報告されている。そのいずれも(+)-pulegone が出発原料として用いられた。

Scheme 8. Synthetic strategies of fawcettimine-type *lycopodium* alkaloids.



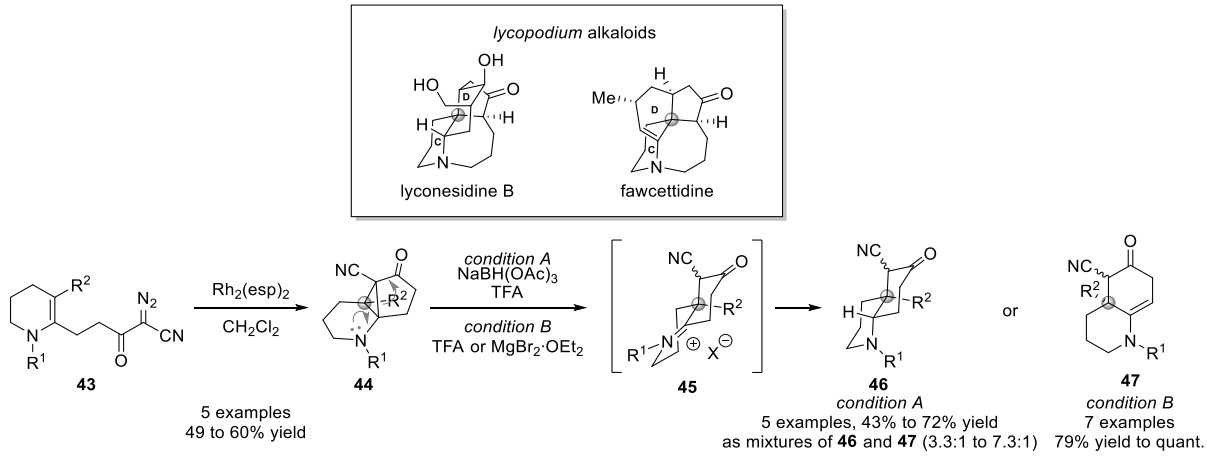
第四節　本研究の概要と構成

前述のように、これまで多くの fawcettimine 型リコポジウムアルカロイド合成で用いられてきた BD 環部から構築する犬伏・Heathcock らの合成戦略は、ヘミアミナール型天然物の合成には効果的である一方で、エナミン型や、アミン型天然物の合成では必ずしも有効とは限らない。CD 環部から構築することが、本課題の 1 つの解決策であるが、本合成経路が用いられた 2 つの合成では、いずれも同じキラルシントンを用いており、これを高度に官能基化された天然物合成へ展開させるには対応する原料の調製が必要である。そこで著者は、酸素官能基化されたエナミン型、アミン型天然物の合成に対応し得る新たな合成法を立案し、これを用いて全合成が達成されていなかった酸素官能基化されたアミン型天然物である lyconesidine B の全合成を目指すこととした。以下にその概略を述べる。

第一章では、核間位に第四級炭素を有するオクタ-およびデカヒドロキノリン骨格の新規合成法の開発について述べる (Scheme 9)。本骨格は、fawcettimine 型リコポジウムアルカロイドの CD 環部に相当する骨格である。これらの触媒的不斉合成が可能となれば幅広い出発原料を利用して、様々な本アルカロイドの誘導体合成に柔軟に対応可能な合成ルートを確立できる。本骨格の合成課題は、核間位への第四級炭素の導入とその不斉合成法の確立である。著者は、触媒的な不斉合成を目指し、テトラヒドロピリジンの分子内シクロプロパン化による核間位第四級炭素の導入の後、生じたシクロプロパンの開環条件によってオクタヒドロキノリンとデカヒドロキノリンをつくり分けることを計画した。実際に、テトラヒドロピリジン **43** を $Rh_2(esp)_2$ で処理すると第四級炭素の構築が進行し多置換シクロプロパン **44** が得られた。これを、$NaBH(OAc)_3$ と TFA の組み合わせで処理すると、シクロプロパン環の開裂によって生じるイミニウムイオン中間体 **45** が還元され、デカヒドロキノリン **46** を得ることに成功した。また、**44** を TFA や $MgBr_2$·OEt などの酸のみで処理すると、オクタヒドロキノリン **47** への変換も可能であった。本反応で合成したヒドロキノリン誘導体 **46**、**47** は、シクロヘキサン、または、シクロヘキセン環上にケトンやニトリルを有しており、これら官能基を更なる誘導化や置換基導入の足掛かりとして利用できる点で有用である。なお、本反応の不斉化については、lyconesidine

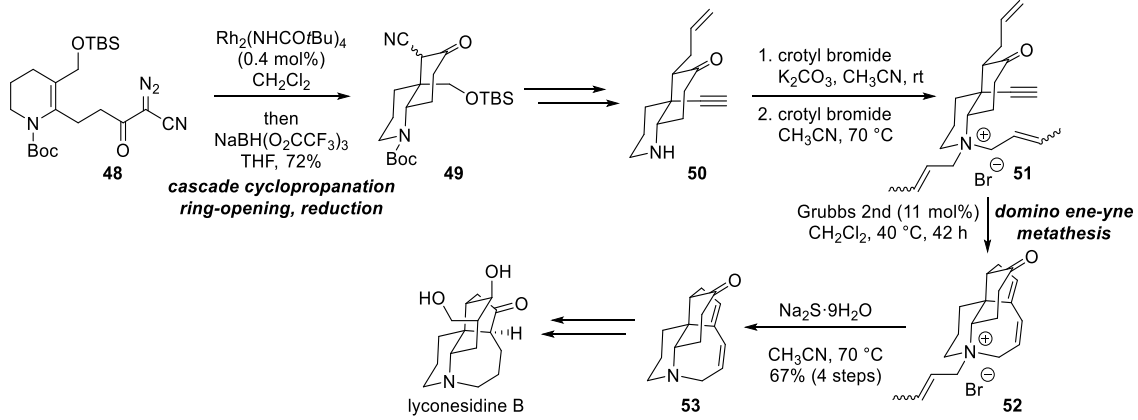
B の全合成の基質で検討しており、第二章で述べる。

Scheme 9. Chapter 1: Synthesis of octa- and decahydroquinoline with quaternary carbon center at angular position.



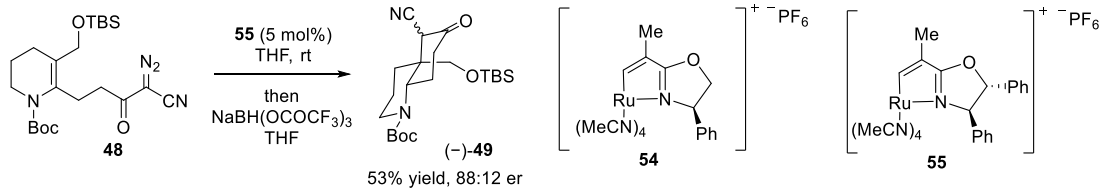
第二章では、第一章のデカヒドロキノリン合成法とドミノエニンメタセシス反応による骨格構築を鍵とした lyconesidine B の全合成と、その不斉合成の検討について述べる (Scheme 10)。まず、第一章のシクロプロパン化とその開環反応を基盤とした合成戦略で、テトラヒドロピリジン **48** からデカヒドロキノリン **49** を合成し、これをエニン化合物 **50** へと導いた。さらに、**50** を第四級アンモニウム塩 **51** としてドミノエニンメタセシス反応で四環性第四級アンモニウム塩 **52** を得た。その後、Na_2S でクロチル基を除去して得られた四環性アミン **53** を誘導化して lyconesidine B の初の全合成を達成した。本全合成のドミノエニンメタセシス反応では、**51** を経由することで Grubbs 触媒の失活を抑えると同時にクロチル基をアキシアル位に配置させて、反応点を接近させることが重要であった。

Scheme 10. Chapter 2: Total synthesis of (±)-lyconesidine B.



最後にテトラヒドロピリジン **48** からデカヒドロキノリン **49** への変換の不斉化を目指した (Scheme 11)。**48** のように窒素原子が置換したアルケンに対する分子内不斉シクロプロパン化は報告例が少なく、実際に、不斉シクロプロパン化でしばしば用いられる不斉 Cu 触媒や不斉 Rh 触媒では低～中程度のエナンチオ選択性しか得られなかった。そこで種々の触媒検討の結果、豊橋技術科学大学の岩佐らが開発した不斉 Ru 触媒 **54** のリガンドを修飾した触媒 **55** を用いると 53%収率、88:12 er で(−)-**49** が得られることを見出した。

Scheme 11. Chapter 2: Studies toward asymmetric total synthesis of (−)-lyconesidine B using asymmetric cyclopropanation.



続く、第 1 章、第 2 章でその詳細を述べる。

第一章　四置換エンカーバメートのシクロプロパン化とその開環を利用したオクタ-およびデカヒドロキノリンの合成

核間位に第四級炭素を持つオクタおよびデカヒドロキノリン骨格は、fawcettimine 型リコポジウムアルカロイドの CD 環部に見られる構造である (Figure 4)。特に酸素官能基化されたアミン型とエナミン型の天然物合成への展開を目指し、シクロプロパン化による CD 環部の新規骨格構築法を開発することとした。本法の鍵となるシクロプロパン化についてその関連研究を以下に紹介する。

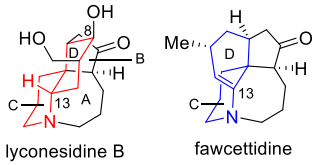


Figure 4. Fawcettimine-type *lycopodium* alkaloids with amine or enamine structure at C13.

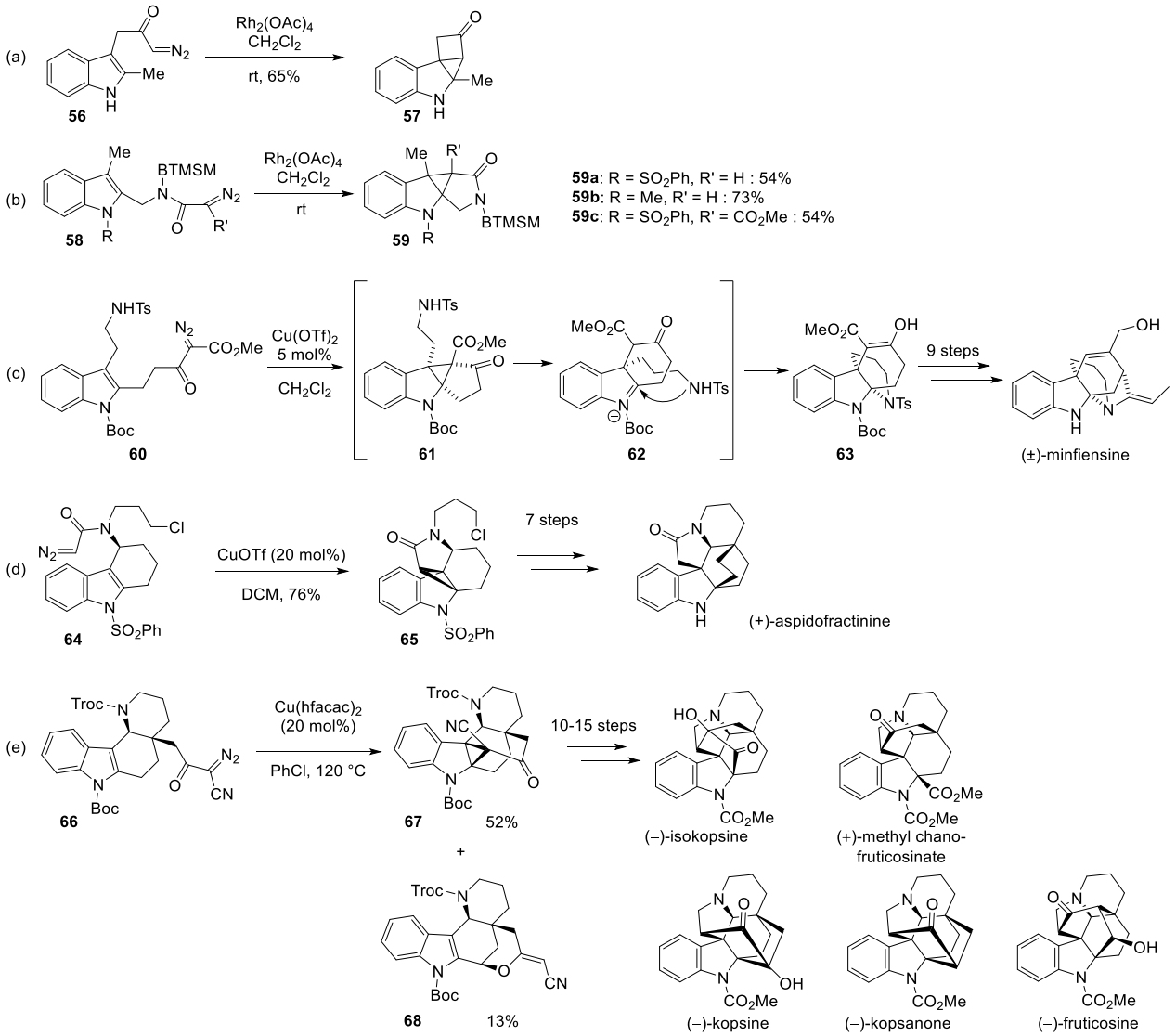
第一節　シクロプロパン化による第四級炭素の導入と、その全合成への応用

ジェミナル二置換アルケンのシクロプロパン化は、第四級炭素を構築可能な反応の 1 つである。また、不斉シクロプロパン化による不斉第四級炭素の合成も期待できることから近年注目を集めている [15]。中でも、電子求引基を有するアミノシクロプロパン誘導体は、ドナー-アクセプターシクロプロパンに特徴的な炭素-炭素結合開裂反応を利用した骨格の組み換え反応が可能なため、アルカロイド合成にもしばしば利用されている [16]。

①電子豊富な 2,3-二置換インドールと金属カルベン錯体とのシクロプロパン化とその誘導化について

インドール関連化合物では 2,3-二置換インドール、すなわち四置換二重結合と金属カルベン錯体のシクロプロパン化と、その変換は多く報告されている。例えば、2000 年に Capretta らは、インドール 3 位の側鎖にジアゾ基を持つ **56** を $Rh_2(OAc)_4$ で処理してシクロプロパン化合物 **57** を 65%で合成した (Scheme 12a)[17]。また、2008 年 Wee らは、ジアゾ基を持つインドール誘導体 **58** を $Rh_2(OAc)_4$ で処理して 5 置換シクロプロパン **59a**、**59b** および 6 置換シクロプロパン **59c** が合成出来ることを報告した (Scheme 12b)[18]。2008 年 Qin らは、インドールのシクロプロパン化とその開環反応を利用した(±)-minfiensine の全合成を報告した (Scheme 12c)[19]。Qin らは、インドール誘導体 **60** を $Cu(OTf)_2$ で処理して、分子内シクロパン化による第四級炭素の導入に続く、シクロプロパン環の開裂と生じたイミニウムイオンへのトシルアミド基の分子内求核付加反応により、四環性化合物 **63** を合成した。その後、9 工程の変換で(±)-minfiensine へと導いた。2009 年 Spino らは、三環性インドール **64** のシクロプロパン化でインドール 3 位に第四級炭素を導入し中間体 **65** を経て、(+)-aspidofractinine の全合成を達成した (Scheme 12d)[20]。最近では、2017 年に Qin らが複数のインドールアルカロイド合成に用いた(Scheme 12e)[21]。すなわち、四環性インドール **66** の分子内シクロプロパン化でシクロプロパン化体 **67** を 52%で得た。このときエノールエーテル **68** が副生成物として 13%得られた。その後の 10-15 工程の変換で(−)-isokopsine、(+)-methyl chanofruticosinate、(−)-kopsine、(−)-kopsanone、(−)-fruticosine を全合成した。上記のように 2,3-二置換インドールのシクロプロパン化については多くの知見が得られており、確立した手法となりつつある。

Scheme 12. Cyclopropanation of 2,3-substituted indoles.

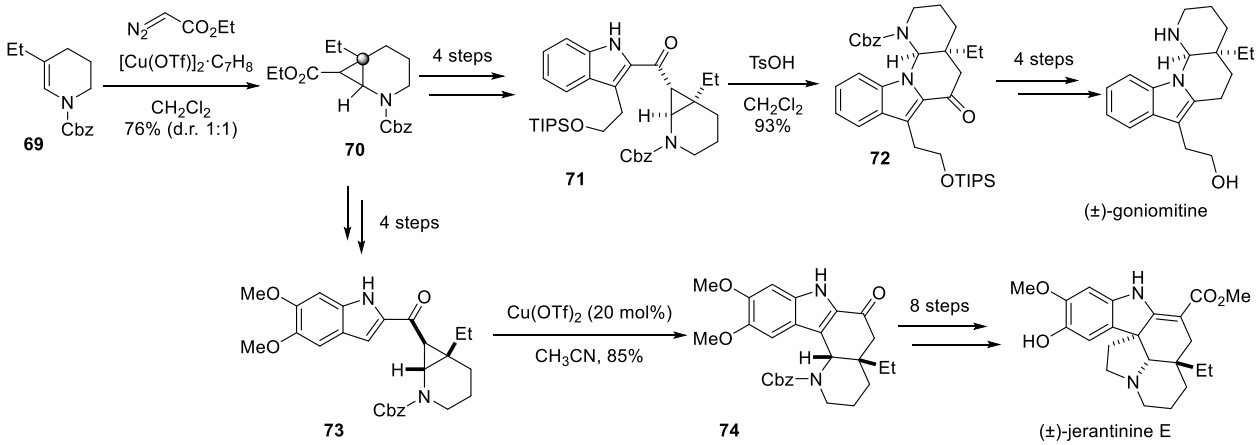


② 二置換、三置換エナミド・エンカーバメートのシクロプロパン化とその生成物の誘導化について

インドール誘導体を基質としない、二置換や三置換エナミド・エンカーバメートについてもそのシクロプロパン化と生成物の誘導化が報告されている[16]。

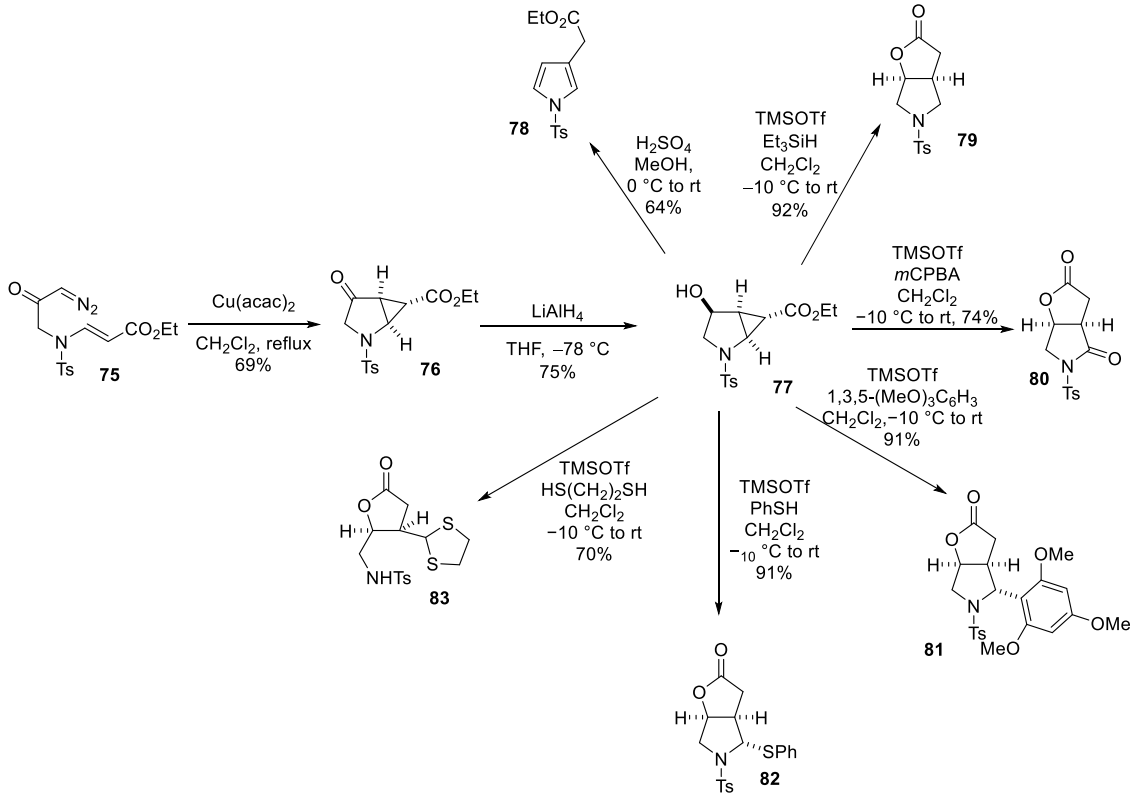
例えば、2010 年、Waser らは、アミノシクロプロパン誘導体の開環で生じるイミニウムイオンに対するインドール 1 位の求核付加を利用した(±)-goniomitine の全合成を報告した (Scheme 13)[22]。まず、テトラヒドロピリジン誘導体 **69** とジアゾ酢酸エチルのシクロプロパン化で、第四級炭素を持つアミノシクロプロパン誘導体 **70** を合成した。その後、4 工程の変換でインドール部位を導入して化合物 **71** へと導いた。**71** を TsOH で処理すると、シクロプロパンの開環で生じたイミニウムイオンへのインドール 1 位の求核付加で、天然物の骨格を持つ化合物 **72** を構築した。その後、4 工程の変換で、(±)-goniomitine の全合成を達成した。また、2013 年には、アミノシクロプロパン **70** を共通の合成中間体として用いた(±)-jerantinine E の全合成を報告した。すなわち、**70** をインドール誘導体 **73** へと変換したのち、CH_3CN 中 $Cu(OTf)_2$ で処理することでシクロプロパン環の開環で生じたイミニウムに対するインドール 3 位の付加が進行し、四環性化合物 **74** を得た。その後、8 工程の変換で(±)-jerantinine E の全合成を達成した。

Scheme 13. Cylopropane-ring-opening and C-N or C-C bond formation in total synthesis of (±)-goniomitine and (±)-jerantinine E.



2012 年 Reddy らは、ジアゾケトン **75** の分子内シクロプロパン化でシクロプロパン **76** としたのち、ケトンの還元でアルコール **77** を得た (Scheme 14)[23]。**77** を、MeOH 中触媒量の硫酸で処理すると、ピロール誘導体 **78** が得られた。また、CH_2Cl_2 中、TMSOTf と Et_3SiH で処理すると、生じたイミニウムイオンが還元されてトシルピロリジン誘導体 **79** へと変換された。さらに、Et_3SiH の代わりに、*m*CPBA を用いるとトシルピロリドン **80** が得られ、1,3,5-トリメトキシベンゼンや PhSH、1,2-ジチオエタンを求核剤として用いると、付加体 **81**、**82** および **83** がそれぞれ得られることを報告した。

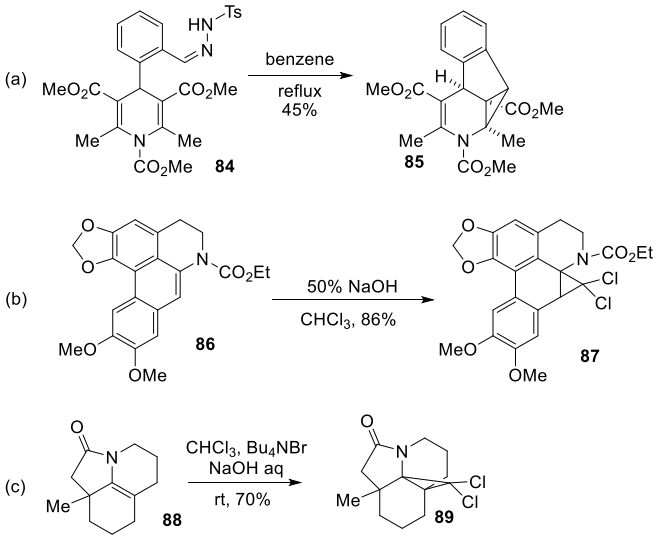
Scheme 14. Derivatization of cyclopropyl tosyl amide **77**.



③ 四置換エナミド・エンカーバメートのシクロプロパン化について

電子豊富な 2,3-二置換インドールや二置換および三置換エナミド・エンカーバメートと比較し、四置換エナミドの状況は大きく異なる。すなわち、含窒素芳香環を基質としない四置換エナミンおよびエナミド、エンカーバメートと金属カルベン錯体とのシクロプロパン化は報告例がない。フリーカルベンを用いたシクロプロパン化の報告が 3 例あるのみである (Scheme 15)。具体的には、1985 年に Cochran らは、トシルヒドラゾン **84** の熱分解で四置換エンカーバメートの分子内シクロプロパン化が進行することを報告した (Scheme 15a)[24]。また、同年 Castro らは、ジクロロカルベンとデヒドロアポルフィン **86** とのシクロプロパン化でジクロロシクロプロパン **87** を 86%で得た (Scheme 15b)[25]。また、2005 年に Padwa らも同様に、ジクロロカルベンと四置換エナミド **88** とのシクロプロパン化を報告した (Scheme 15c)[26]。このように、単純な四置換エンカーバメートのシクロプロパン化でも知見が少なく、これを用いるには、反応条件や基質の検討が必要である。

Scheme 15. Cyclopropanation of tetrasubstituted enamides or enecarbamates.



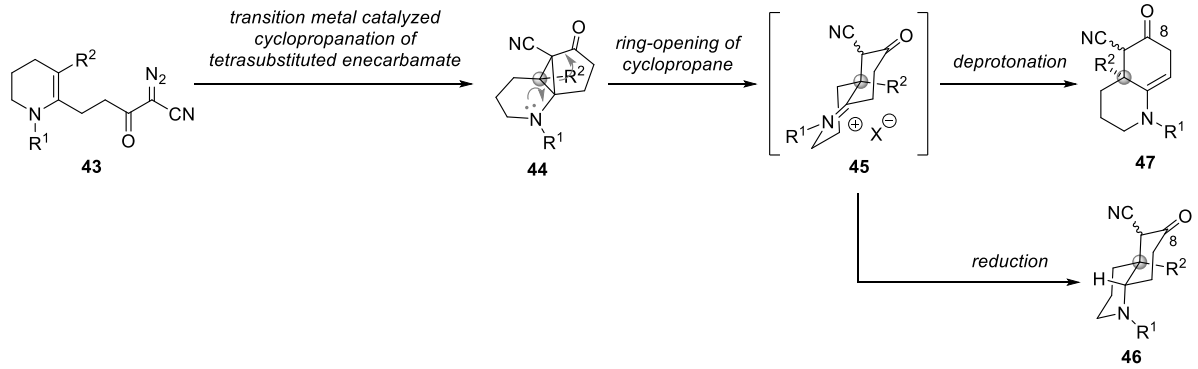
以上まとめると、四置換以外のエナミンや、エナミド、エンカーバメートのシクロプロパン化は、天然物の合成などで有用な反応として用いられてきた。一方で、四置換エナミン（およびエナミド、エンカーバメート）の利用はほとんどない。これは四置換エナミンが、その合成の煩雑さのために基質として十分検討されていない点に加えて、立体障害のために反応性が低い点が理由として想定された。このような背景のもと、著者は、前例のない四置換エナミン誘導体を用いたシクロプロパン化–環開裂連続反応に着目し、酸素官能基化された fawcettimine 型リコポジウムアルカロイド合成に応用可能な新規骨格構築法を開発することとした。

第二節　シクロプロパン化と開環反応を基盤とした合成計画

以上の背景から、四置換エナミン（もしくはエナミド、エンカーバメート）のシクロプロパン化による第四級炭素の導入、さらにその開環反応の反応条件の変更によるオクタヒドロキノリン骨格とデカヒドロキノリン骨格の作り分けを計画した (Scheme 16)。すなわち、テトラヒドロピリジン **43** の分子内シクロプロパン化で全置換シクロプロパン **44** を合成する。本シクロプロパンには電子供与基で

ある窒素原子と電子求引基であるケトンが置換している。したがって、**44** を酸性条件で処理すると、窒素原子からの電子の押し出しにより、シクロプロパン環が開裂して、イミニウムイオン **45** が生じる。その後、脱プロトン化が進行すれば、オクタヒドロキノリン **47** を与え、還元すればデカヒドロキノリン **46** を与える。イミニウムイオン中間体 **45** は置換基 R^2 の立体障害を活かして、立体選択的に還元することを狙った。本法で合成される **47** と **46** は、8 位にケトンを有しており、酸素官能基化された fawcettimine 型リコポジウムアルカロイド合成への応用が期待できる。また、ケトン α 位の官能基化や炭素鎖の導入も容易であることが予想された。

Scheme 16. Strategy for construction of octa- and decahydroquinolines with quaternary carbon center at the angular position.

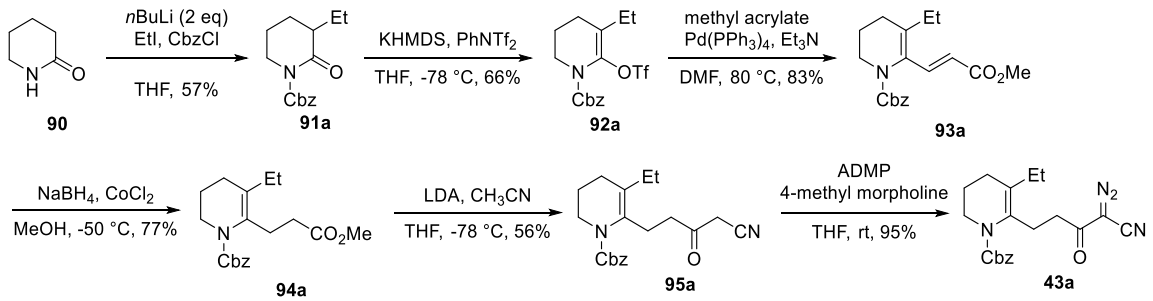


第三節　核間位に第四級炭素を持つオクタ-およびデカヒドロキノリン骨格の合成

① モデル基質の合成

シクロプロパン化の検討のために、モデル基質 **43a** を合成した (Scheme 17)。まず、既知の条件に従い、δ-バレロラクタム (**90**) の THF 溶液に 2 当量の *n*BuLi を加えて調製したジアニオンに対して、EtI と CbzCl を順次添加してベンジルカーバメート **91a** とした [22]。**91a** をエノールトリフラート **92a** へと変換した後、アクリル酸メチルとの Heck 反応で、不飽和エステル **93a** を得た。次に **93a** を $CoCl_2$ 存在下 $NaBH_4$ で処理することで 1,4-還元してエステル **94a** を得た [27]。最後に、脱プロトン化したアセトニトリルの **94a** への付加と、ジアゾ転位でシクロプロパン化前駆体 **43a** を合成した [28]。**43a** は、アミン存在下高濃度に濃縮すると不安定であったため、本化合物を収率良く単離する為には、分液操作後、完全に濃縮することなくシリカゲルカラムクロマトグラフィーで精製することが効果的であった。

Scheme 17. Synthesis of cyclopropane precursor **43a**.

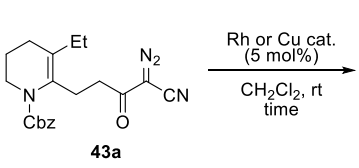


② シクロプロパン化の条件検討

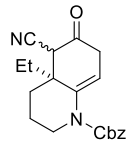
続いて、得られたジアゾケトン **43a** を、金属カルベン錯体が生じることが知られている種々の遷移金属触媒 (5 mol%) で処理してシクロプロパン化体 **44a** を得ることを検討した (Table 1)。まず、

$Cu(OTf)_2$ を用いたとき、**44a** の生成の後シクロプロパン環が開裂して水和されたと予想されるジケトン **96a** が 70%収率で得られた (entry 1)。これは、$Cu(OTf)_2$ の Lewis 酸性によるものと予想し、代わりに $Cu(hfacac)_2$ を用いると、望みのシクロプロパン化体 **44a** とオクタヒドロキノリン **47a** がおよそ 1:1 の比率で得られた (entry 2)。次に、種々の Rh 二核錯体によるシクロプロパン化を試みた。ラクタム配位子を持つ $Rh_2(cap)_4$[29] を用いると、42% 収率で **44a** が得られた (entry 3)。このとき **47a** の生成は観測されなかった。$Rh_2(OAc)_4$ では、反応時間の短縮と収率向上がみられ、最終的に、$Rh_2(esp)_2$[30] を用いたとき 59% 収率で **44a** が得られることを見出した (entries 4, 5)。本触媒での反応は非常に速く、触媒 0.1 mol%でも、15 分で原料が完全に消費され、触媒 5 mol% の場合と比較しても遜色ない収率を与えた (entry 6)。収率には改善の余地があるものの、中程度の収率でシクロプロパン化体 **44a** を得ることに成功したので、次に **44a** の開環反応について検討した。

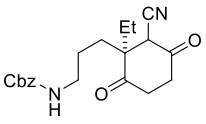
Table 1. Transition metal catalyzed cyclopropanation of tetrahydropyridine **43a**.



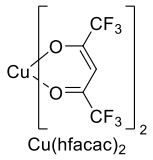
43a **44a**



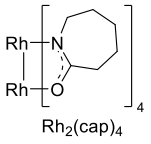
47a



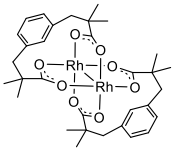
96a



$Cu(hfacac)_2$



$Rh_2(cap)_4$



$Rh_2(esp)_2$

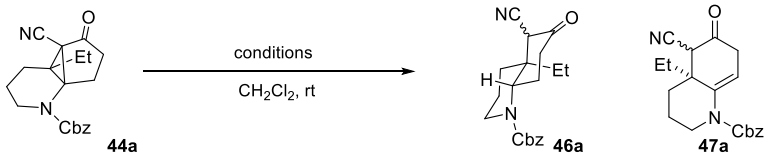
			yield[a]		
entry	Rh or Cu cat.	time	**44a**	**47a**	**96a**
1	$Cu(OTf)_2$	10 h	–	–	70%
2	$Cu(hfacac)_2$[b]	24 h	32%	37%	–
3	$Rh_2(cap)_4$	2.5 h	42%	–	–
4	$Rh_2(OAc)_4$	30 min	52%	–	–
5	$Rh_2(esp)_2$	10 min	59%	–	–
6	$Rh_2(esp)_2$ (0.1 mol%)	15 min	57%	–	–

[a]Isolated yield. [b]60 mol%. –: not detected.

③ シクロプロパン環の開裂条件の検討

シクロプロパン化体 **44a** からオクタヒドロキノリン **47a** およびデカヒドロキノリン **46a** への変換を試みた (Table 2)。**44a** から **47a** への変換は、TFA や $BF_3 \cdot OEt_2$ などの酸で処理すると収率良く **47a** を与えた (entries 1, 2)。このことから、**46a** は酸性条件で定量的にイミニウムイオンへと変換されることが示唆された。そこで、酸性条件下での開環後、生じたイミニウムイオン中間体を還元して **46a** へと変換することとした。まず、酸を TFA に固定して、種々の還元剤を検討した。その結果、Et_3SiH や Ph_3SiH、$NaBH_3CN$ では **46a** は得られず、**47a** が生成した (entries 3-5)。一方で、$NaBH(OAc)_3$ を還元剤として用いると、**47a** との混合物ではあるものの、**46a** が 72%収率で得られた (entry 6)。その後、種々の酸を検討したが、$BF_3 \cdot OEt_2$ では、**46a** は低収率で得られ、$MgBr_2 \cdot OEt_2$、$AlCl_3$、$Sc(OTf)_3$ では **46a** を与えなかった為、entry 6 の TFA と $NaBH(OAc)_3$ を組み合わせた条件を **46a** への変換の最適条件とした (entries 7-10)。

Table 2. Selective formation of octahydroquinoline **47a** and decahydroquinoline **46a**.



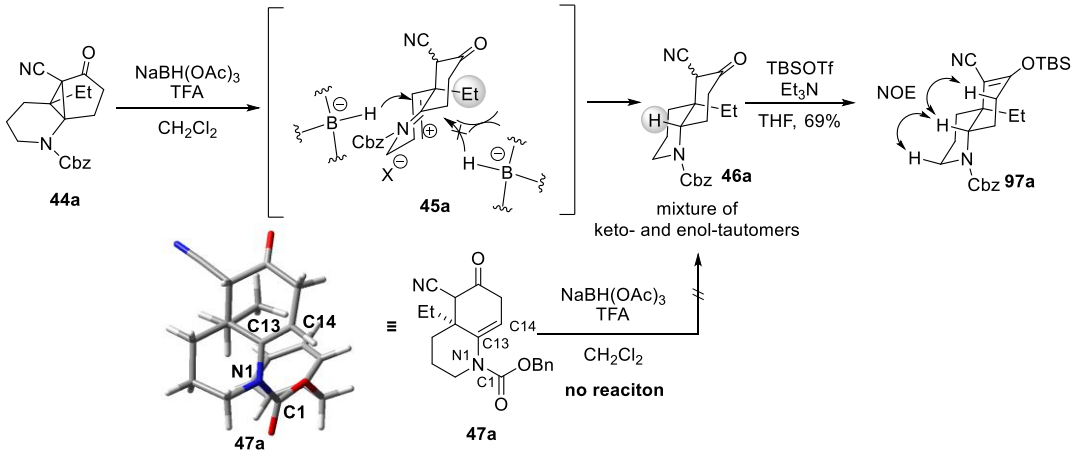
entry	conditions		yield[a]	
	Lewis acid or H^+ (6 eq.)	reductant (10 eq.)	**46a**	**47a**
1	TFA[b]	–	–	96%
2	$BF_3{\cdot}OEt_2$[b]	–	–	95%
3	TFA	Et_3SiH	–	56%
4	TFA	Ph_3SiH	–	40%
5	TFA	$NaBH_3CN$	–	17%
6	TFA	$NaBH(OAc)_3$	72%[c]	22%[c]
7	$BF_3{\bullet}OEt_2$[d]	$NaBH(OAc)_3$[e]	31%[c]	23%[c]
8	$MgBr_2{\bullet}OEt_2$	$NaBH(OAc)_3$	–	60%
9	$AlCl_3$	$NaBH(OAc)_3$	–	59%
10	$Sc(OTf)_3$	$NaBH(OAc)_3$	–	28%

[a]Isolated yield. [b]1 equiv. [c]The yield was calculated by ^{1}H NMR. [d]10 equiv. [e]6 equiv. –; not detected

④ デカヒドロキノリン **46a** の相対立体配置の決定と還元のジアステレオ選択性の考察

デカヒドロキノリン **46a** は、重クロロホルム中でケト-エノール互変異体の混合物であったため、^{1}H NMR で観測されるシグナルは複雑化していた。そこで、エノールシリルエーテル **97a** とした後、NOESY を測定しその相対立体配置を決定した (Scheme 18)。すなわち、図に示すような NOE 相関が確認されたため **97a** はトランス体であり、その原料となる **46a** もトランス体であると決定した。**44a** から **46a** への変換反応のジアステレオ選択性は次のように推察した。シクロプロパン **44a** が酸性条件で開環して生じたイミニウムイオン **45a** が還元されるとき、期待通り核間位のエチル基が立体障害となり、還元が紙面左側から進行してトランスデカヒドロキノリン **46a** がジアステレオ選択的に得られた。なお、オクタヒドロキノリン **47a** を還元して **46a** とするために、**44a** の還元と同様に TFA と $NaBH(OAc)_3$ で処理したが、反応は進行しなかった。**47a** の最安定配座を計算すると、二面角 C1-N1-C13-C14 はおよそ 73.5°であり、N1 の孤立電子対と C13-C14 のオレフィン部分は共役の寄与が小さいことが予想された。このことから、**47a** からイミニウムイオン **45a** の生成が困難であったと推測している。

Scheme 18. Determination of relative configuration of **46a** and diastereoselectivity of reduction of iminium Intermediate **45a**.

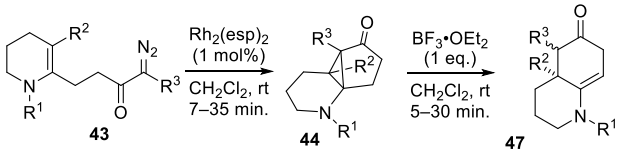


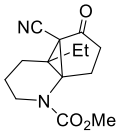
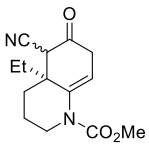
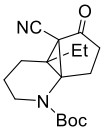
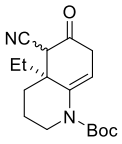
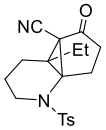
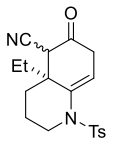
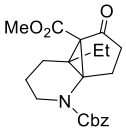
Calculated by Gausian 09 ωB97X-D/6-311G(d,p) level of theory.

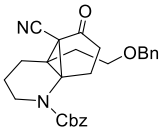
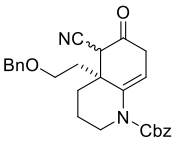
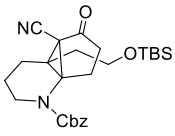
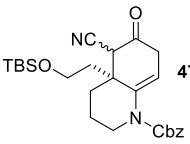
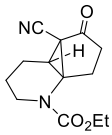
⑤ シクロプロパン合成およびオクタヒドロキノリン合成の基質適用範囲

シクロプロパン合成とオクタヒドロキノリン合成について基質適用範囲を調査した（Table 3）。まず、アミンの保護基 R^1 について検討した。R^1 がメトキシカルボニル基および Boc 基を有する基質では **43a** と同程度の収率でシクロプロパン化体 **44b**、**44c** を与え、その後の **47b**、**47c** への変換も収率良く進行した (entries 1, 2)。このとき Boc 基を持つ **44c** を $BF_3{\cdot}OEt_2$ で処理すると、Boc 基の除去反応が競合したため、$BF_3{\cdot}OEt_2$ の代わりに $MgBr_2{\cdot}OEt_2$ を用いた (entry 3)。一方で、R^1 が Ts 基の **43d** を $Rh_2(esp)_2$ で処理すると、酸で処理することなく、シクロプロパン環が開裂し、オクタヒドロキノリン **47d** を 76%収率で与えた。続いて、ジアゾ基の β 位の置換基 R^3 をメトキシカルボニル基に変更したところ、複雑な混合物を与え、シクロプロパン化体 **44e** の単離には至らなかった (entry 4)。これは、メトキシカルボニル基がシアノ基より嵩高いため、混みあった四置換オレフィンとの反応が不利になったためと予想している。本結果から、シクロプロパン化には置換基 R^3 がニトリルであることが重要と明らかになった。最後に、アルケン上の置換基 R^2 ついて検討した。本反応は、ベンジルエーテルやシリルエーテルを持つ **43f**、**43g** からも進行し、**44f**、**44g** を中程度の収率で与え、その後の **47f**、**47g** への変換もそれぞれ 80%収率および定量的に進行した。一方で、R^2 が H の **43h** を $Rh_2(esp)_2$ で処理すると複雑な混合物を与え、シクロプロパン化体 **44h** の生成は確認できなかった。

Table 3. Scope and limitations of synthesis of cyclopropane **44** and octahydroquinoline **47**.



	first step		second step	
entry	product	yield[a]	product	yield[a]
1		**44b**, 60%		**47b**, 96%
2		**44c**, 50%		**47c**, quant.[b]
3		**44d**, –[c]		**47d**, 76%[c]
4		**44e**, n.d.[d]		

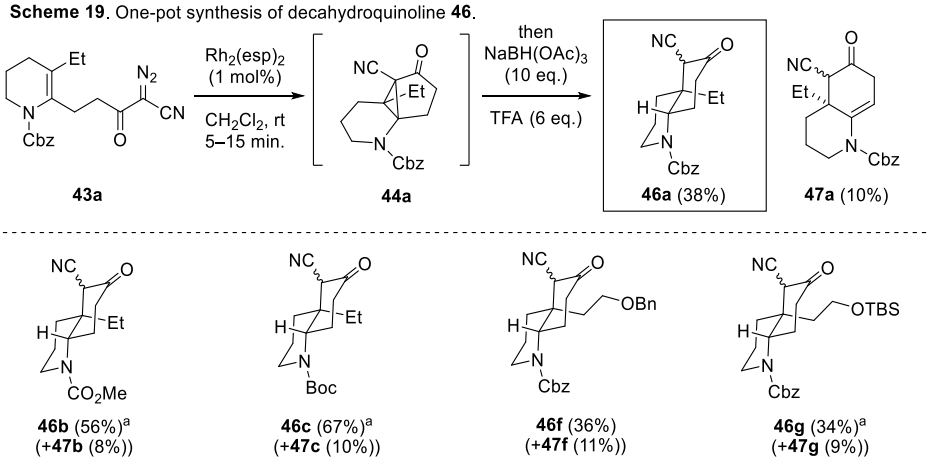
	first step		second step	
entry	product	yield[a]	product	yield[a]
5		**44f**, 49%		**47f**, 80%
6		**44g**, 52%		**47g**, quant.[b]
7		**44h**, n.d.[d]		

[a]Isolated yield. [b]$MgBr_2{\cdot}OEt_2$ was used instead of $BF_3{\cdot}OEt_2$ [c] **47d** was observed instead of **44d** under the first step reaction conditions.
[d]not detected. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

⑥ ワンポットでのデカヒドロキノリン合成とその基質適用範囲

続いて、デカヒドロキノリン **46** 合成の基質適用範囲を検討した (Scheme 19)。本反応では、シクロプロパン化と開環・還元反応をワンポットで実施することで、不安定なシクロプロパン中間体 **44** の単離を回避した。まず、テトラヒドロピリジン **43a** を $Rh_2(esp)_2$ で処理して原料の消費を確認した後、同一フラスコに $NaBH(OAc)_3$ と TFA を加えると、**46a** が 38%収率で **47a** との混合物として得られた。本反応は、アミンの保護基がメトキシカルボニル基、 Boc 基のとき良好に進行し、デカヒドロキノリン **46b**、**46c** をそれぞれ 56%、67%で与えた。また、ベンジルエーテルおよびシリルエーテルを持つ **46f**、**46g** の合成も可能であった。

Scheme 19. One-pot synthesis of decahydroquinoline **46**.

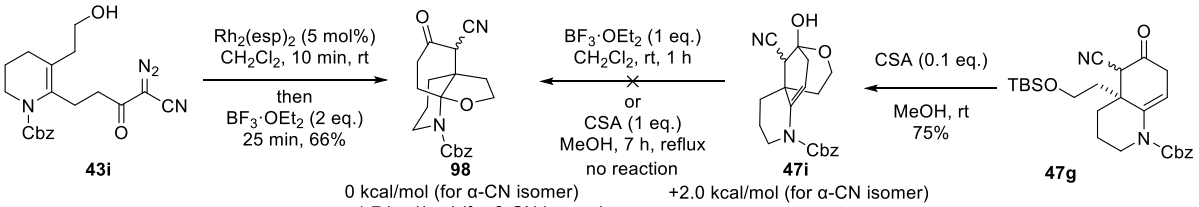


Ratio of **46** and **47** was calculated by ^{1}H NMR. [a]$Rh_2(OAc)_4$ was used instead of $Rh_2(esp)_2$.

⑦ 三環性化合物 **98** の合成

最後に本反応を三環性化合物の合成へと応用した。すなわち、無保護の水酸基を持つテトラヒドロピリジン **43i** を $Rh_2(esp)_2$ で処理してシクロプロパンへと変換した後、$BF_3{\cdot}OEt_2$ を加えると、シクロプロパン環の開裂で生じたイミニウムイオンに対して水酸基の付加が進行して、三環性化合物 **98** が 66%収率で得られた (Scheme 20)。また、**47g** のシリル基を除去して調製したヘミアセタール **47i** から **98** を得る目的で CH_2Cl_2 中 $BF_3{\cdot}OEt_2$ 存在下室温で撹拌、もしくは MeOH 中 CSA 存在下加熱還流したが、反応は進行しなかった。**47i** と比較して **98** の方が熱力学的に安定であるにも関わらず **98** が得られなかったことから、**47i** からもイミニウムイオンが容易に生じないことが示唆された。以上の結果は、本反応を全合成に応用する際の基質選択のための重要な知見となった。

Scheme 20. One-pot synthesis of tricyclic compound **98**.



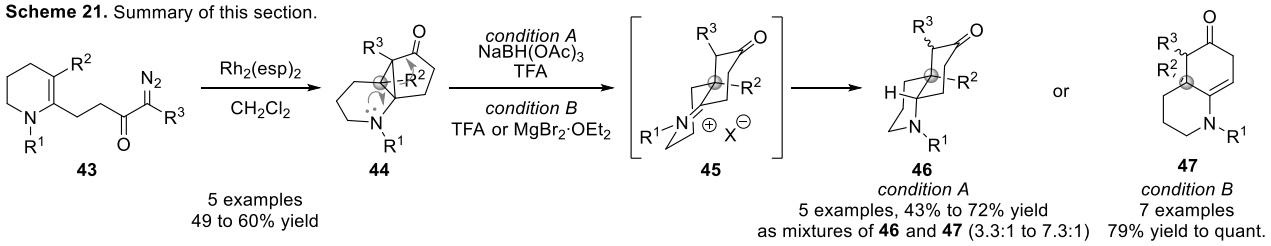
0 kcal/mol (for α-CN isomer)　　+2.0 kcal/mol (for α-CN isomer)
+1.7 kcal/mol (for β-CN isomer)　　+4.0 kcal/mol (for β-CN isomer)

Calculated by Gausian 09 ωB97X-D/6-311G(d,p) level of theory.

第四節　結論

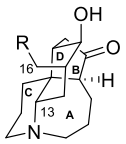
著者は、シクロプロパン化に続く開環反応を利用し、核間位に第四級炭素を持つオクタヒドロキノリンおよびデカヒドロキノリン合成法を開発した (Scheme 21)[31]。$Rh_2(esp)_2$ を触媒として用いて立体的に込み合った四置換エンカーバメートのシクロプロパン化が中程度から良好な収率で進行することを見出した。本反応の進行にはジアゾ基の β 位の置換基 R^3 にシアノ基を採用することが重要であった。また、得られたシクロプロパン化合物を TFA や $MgBr_2{\cdot}OEt_2$ で処理して、オクタヒドロキノリンへ、TFA と $NaBH(OAc)_3$ の組み合わせで処理してデカヒドロキノリンへの作り分けが可能であることを明らかにした。本反応の基質として、エナミン構造の保護基 R^1 にはカーバメートを用いることが可能であり、トシル基を用いた場合は系中でシクロプロパン環が容易に開裂することが明らかとなった。また、アルケンの置換基 R^2 にはエチル基だけでなく、シロキシエチル基やベンジロキシエチル基も用いることができた。本法で合成したデカヒドロキノリン誘導体は酸素官能基化された fawcettimine 型リコポジウムアルカロイド合成への応用が期待できる。

Scheme 21. Summary of this section.



第二章　Lyconesidine B の全合成

第一節　Lyconesidine 類について



R = H: Lyconesidine A
R = OH: Lyconesidine B
Figure 5. Lyconesidines

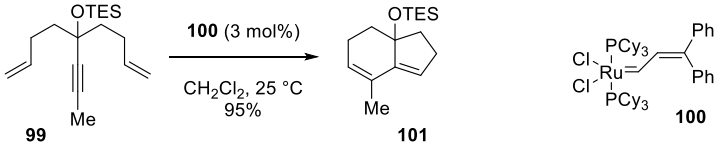
Lyconesidine A、B は、2002 年に北海道大学の小林らによってヒカゲノカズラ科の植物の *Lycopodium chinense* より単離された (Figure 5)[32]。その相対、および絶対立体配置は、2 次元 NMR を含む各種 NMR スペクトル、X 線結晶構造解析によって決定された。本天然物は、一般的な fawcettimine 型リコポジウムアルカロイドと比較して 13 位の酸化度が低いアミン型に分類される（序論第二節参照）。また、CD 環がトランス縮環していることから、16 位のメチル基またはヒドロキシメチル基がアキシアル位に位置している点も特徴的である。生物活性としては、マウスリンパ腫 L1210 細胞に対する細胞毒性（lyconesidine A: IC_{50} = 18.0 μg/mL, lyconesidine B: IC_{50} = 9.5 μg/mL）と、弱いながらもチューブリンの重合阻害作用（lyconesidine A: IC_{50} = 300 μM , lyconesidine B: IC_{50} = 250 μM）を有することが報告されている [32]。Lyconesidine A、B のように、基本骨格が酸素官能基化されたアミン型の fawcettimine 型リコポジウムアルカロイドは未だ合成例がない。著者は、より酸化度が高く生物活性の強い lyconesidine B を標的として、その特異な構造の合成経路の開拓を目指し、全合成研究に着手した。

第二節　ドミノエニンメタセシスについて

本合成では、終盤でアミン化合物のドミノエニンメタセシス反応を利用するので、その背景を概説する。ドミノエニンメタセシスに用いる触媒は、アミンの塩基性・求核性により失活することがあるため適切な保護が必要な可能性がある。以下に例を挙げて説明する。

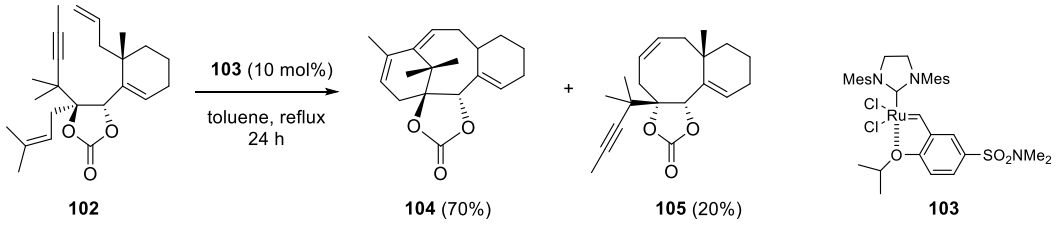
ドミノエニンメタセシスは、1994 年に Grubbs らによって 2 つのアルケンと 1 つのアルキンを持つ化合物からビシクロ[m.n.0]骨格を構築する反応として報告された (Scheme 22)[33]。例えば、ジエニン化合物 **99** を CH_2Cl_2 中 3 mol%の Ru 触媒 **100** 存在下室温で攪拌すると、ビシクロ[4.3.0]ノナジエン **101** が 95%収率で得られた。

Scheme 22. Grubbs' first report of domino-enyne metathesis.



本反応は、鎖状化合物から一挙に二つの環構造を構築できる点で有用な反応であり、天然物など複雑骨格の構築にも応用されている [34]。例えば、2014 年 Prunet らは、シクロヘキセン誘導体 **102** をトルエン中、触媒 **103** 存在下加熱還流すると、タキサン骨格 **104** が 70%収率で、副生成物 **105** (20%)と共に得られることを報告している (Scheme 23)[34r]。

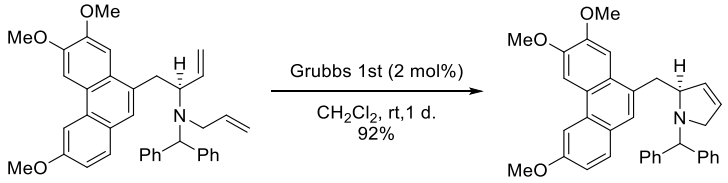
Scheme 23. Synthesis of taxane skeleton using domino enyne metathesis reaction.



102 **104** (70%) **105** (20%) **103**

窒素原子周辺が嵩高い場合には、アミンを基質としても触媒の失活は大きな問題とならない。例えば、2003 年 Kim らは、ジフェニルメチルアミン **106** を CH_2Cl_2 中、2 mol%の第一世代 Grubbs 触媒存在下室温で 1 日攪拌すると、ジヒドロピロール誘導体 **107** が 92%収率で得られると報告している (Scheme 24)[34b]。

Scheme 24. Domino enyne metathesis of bulky amine substrate.

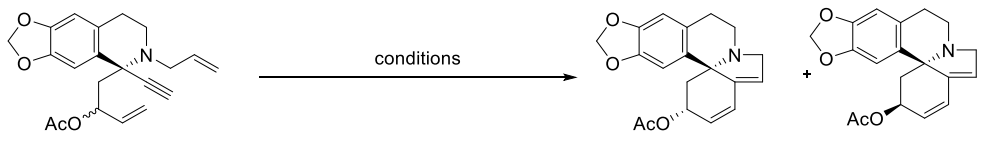


106 **107**

一方、窒素原子周辺の立体障害が小さいために基質のアミンが触媒を失活させる場合があり、Lewis 酸や Brønsted 酸の添加による改善が報告されている。

2003 年、森らは、ジエニン化合物 **108** を CH_2Cl_2 中、第一世代 Grubbs 触媒存在下加熱還流したが、目的のジエン **109** は得られず、69%の原料が回収された (Table 4, entry 1)[34a]。また、第二世代 Grubbs 触媒を用いても **109** は得られなかった (entry 2)。そこで、触媒の金属中心へのアミンの配位を防ぐために **108** を一度塩酸塩とした後に第一世代 Grubbs 触媒で処理すると、ドミノエニンメタセシスが進行した。その後、K_2CO_3 水溶液で後処理すると、四環性ジエン **109a** と **109b** を 1:1 のジアステレオマー比で定量的に得ることができた (entry 3)。

Table 4. Domino enyne metathesis reaction of HCl salt of amine **108**.



108 **109a** **109b**

entry	conditions	yield (**109a**:**109b**)
1	Grubbs 1st, CH_2Cl_2, reflux, 15 h	–
2	Grubbs 2nd, CH_2Cl_2, reflux, 1.5 h	–
3	HCl, Et_2O then Grubbs 1st, CH_2Cl_2, rt, 18 h	quant. (1:1)

また、2005 年、Xiao、Yu らは、ジアリルアミン **110** の閉環メタセシスにおいて $Ti(O^iPr)_4$ が効果的に働くことを報告した[35]。まず、ジアリルアミン **110** を CH_2Cl_2 中、5 mol%の触媒 **111** 存在下 40 °C で 48 時間加熱したが、**111** の失活により 24%収率でジヒドロピロール誘導体 **112** が得られるのみであっ

た (Scheme 25a)。**110** を塩酸塩 **113** とした後に **111** で処理すると、酸化剤についての言及はないが、環化後に酸化されてピロール誘導体 **114** がジヒドロピロール誘導体の代わりに生成した (Scheme 25b)。そこで、添加剤として種々の Lewis 酸を検討した (Table 5)。まず、LiI を添加したところ、53%収率で **112** が得られた (entry 1)。また、$AlCl_3$ や $La(OTf)_3$ を用いると、**112** の生成は確認できなかった (entries 2, 3)。これは、Lewis 酸性が強すぎるために触媒が速やかに失活したと Xiao、Yu らは推測した。一方で、$Ti(O^iPr)_4$ を用いると、2 時間、91%収率で **112** を与えた (entry 4)。さらに、$Ti(O^iPr)_4$ の当量を 50 mol%、20 mol%と低減しても、反応時間の延長で **112** を高い収率で得ることに成功した。

Scheme 25. Ring closing metathesis of diallylamine **110**.

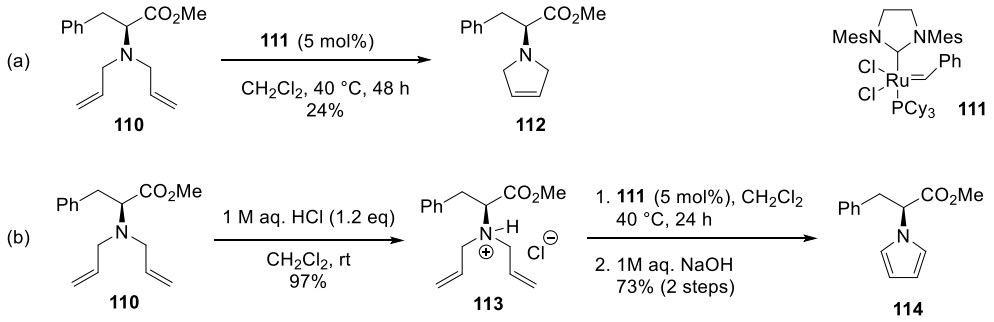
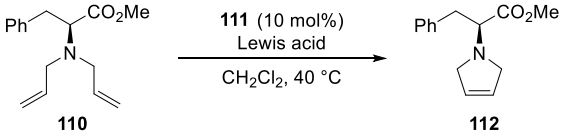


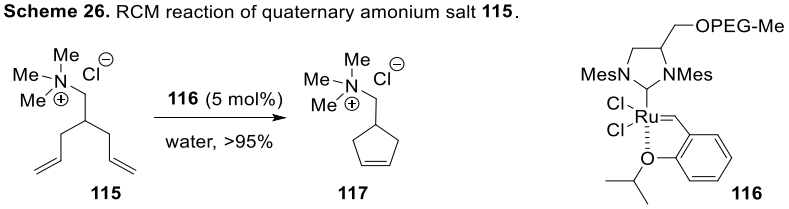
Table 5. Investigation of Lewis acid for ring closing metathesis of diallylamine **110**.



entry	Lewis acid	amount (mol%)	time (h)	yield of **112** (%)
1	LiI	100	36	53
2	$AlCl_3$	100	2	0[c]
3	$La(OTf)_3$	100	2	0[c]
4	$Ti(O^iPr)_4$	100	2	91
5	$Ti(O^iPr)_4$	50	5	82
6	$Ti(O^iPr)_4$	20	6	93

一方、第四級アンモニウム塩を基質として用いると、触媒は失活することなく反応が進行する。2006 年 Grubbs らは、第四級アンモニウム塩 **115** を水溶性の触媒 **116** で処理すると、ほとんど定量的に閉環メタセシス反応が進行することを報告した (Scheme 26)[36]。しかし、複雑な構造を持つ第四級アンモニウム塩を用いた例はなく、実践的な合成への展開は未検討であった。

Scheme 26. RCM reaction of quaternary amonium salt **115**.



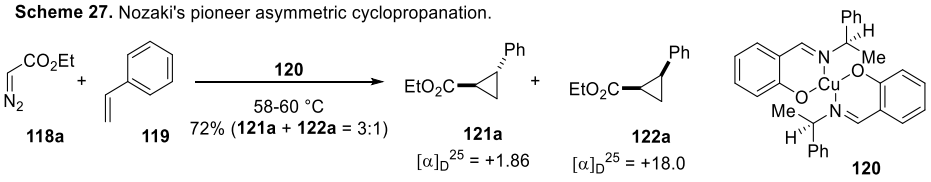
第三節　遷移金属触媒によるジアゾ化合物とアルケンの不斉シクロプロパン化について

Lyconesidine B の全合成では、不斉シクロプロパン化による不斉合成研究にも取り組んだ。以下、遷移金属を用いた不斉シクロプロパン化について、その背景を紹介する。

① これまでに開発されている主要な不斉シクロプロパン化の触媒について

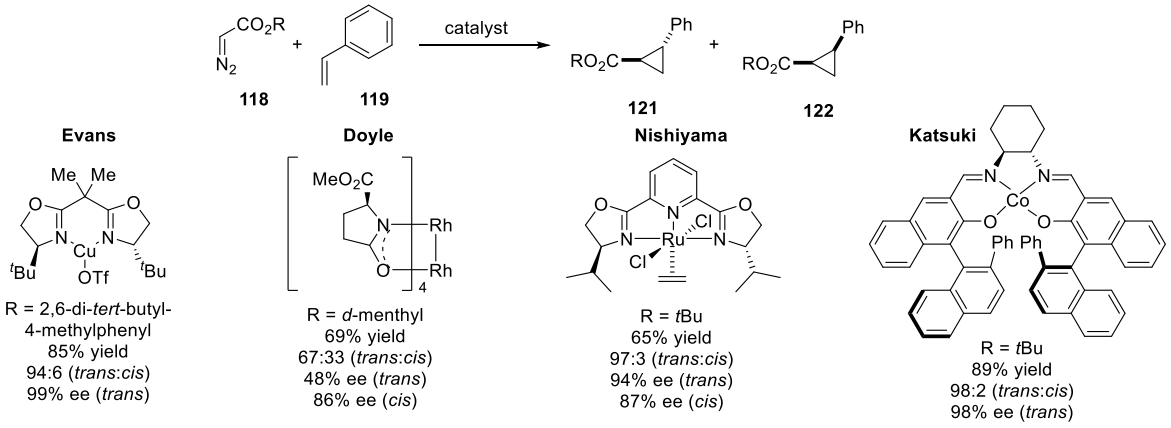
遷移金属触媒を用いたジアゾケトンとアルケンの不斉シクロプロパン化の先駆的な研究は、1966 年に野崎らによって報告された (Scheme 27)[37]。野崎らは、エチルジアゾ酢酸 (**118a**) とスチレンを Cu 触媒 **120** 存在下、反応させて光学活性なシクロプロパン **121a** と **122a** を 72%収率、3:1 dr で得た。

Scheme 27. Nozaki's pioneer asymmetric cyclopropanation.



野崎らの研究から、Cu や、Rh、Ru、Co などの金属錯体を用いた不斉シクロプロパン化が精力的に研究されてきた (Scheme 28)[38]。例えば、1991 年、Evans らは Cu-bisoxazoline 錯体による高エナンチオ選択的なシクロプロパン化反応を報告した [39]。1990 年、Doyle らは Rh 二核錯体による不斉シクロプロパン化を報告した [40]。また、1994 年、西山らは Ru-bis(oxazolinyl)pyridine 錯体、1995 年、香月らは Co-salen 錯体による不斉シクロプロパン化を報告した [41, 42]。

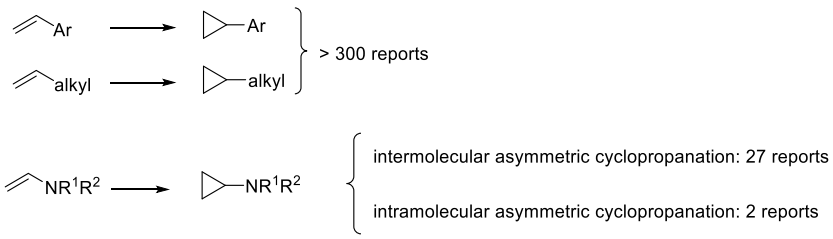
Scheme 28. Representative Cu, Rh, Ru, Co catalysts for asymmetric cyclopropanation of styrene.



② 窒素原子が置換したアルケンの分子内不斉シクロプロパン化について

以上のような例を代表として、これまでにスチレン誘導体やアルキル置換アルケンの不斉シクロプロパン化は、合わせて 300 以上が報告されている (Scheme 29)[43]。一方で、窒素原子が置換したアルケンに対する不斉シクロプロパン化の例は、分子間反応が 27 例 [44] であり、分子内反応はわずか 2 例 [45] にとどまる (2021 年 2 月時点)。

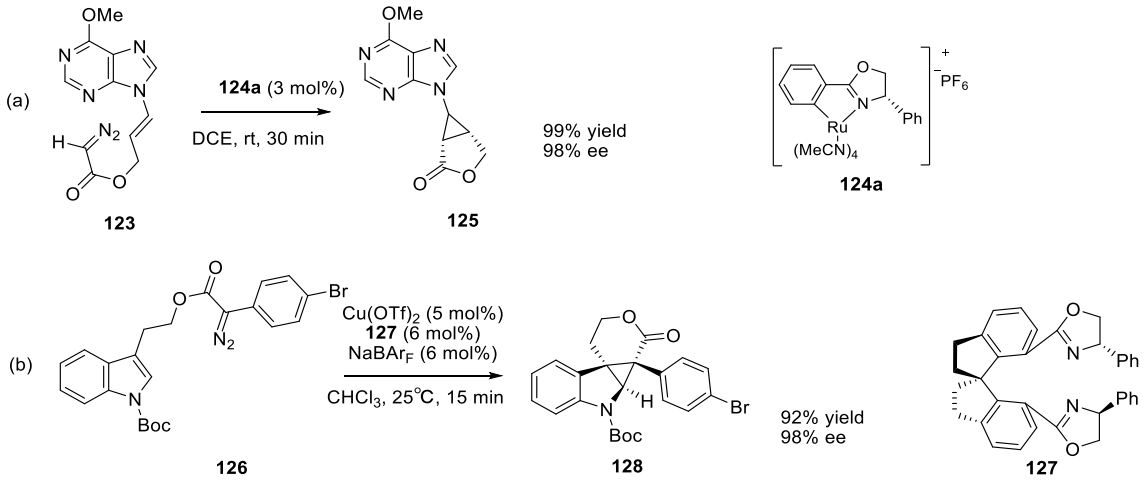
Scheme 29. The number of asymmetric cyclopropanation of *N*-substituted alkene.



窒素原子が置換したアルケンの分子内不斉シクロプロパン化は、2016 年、Guo らにより初めて報告された。彼らは、プリン誘導体 **123** を Ru 錯体 **124a** で処理することで高収率、高エナンチオ選択的な分子内不斉シクロプロパン化を達成した (Scheme 30a)[45a]。また、2017 年、Zhou らは、リガンド **127** を用いた Cu 触媒によるインドール誘導体 **126** の分子内シクロプロパン化を達成した (Scheme 30b)[45b]。しかし、両報告は、基質がジアゾエステルと制約があり、オレフィン部位もプリンやインドールの置換した二置換、三置換アルケンのみとなっている。

このように窒素原子が置換したアルケンの分子内不斉シクロプロパン化は未だ例が少なく、発展途上の分野である。

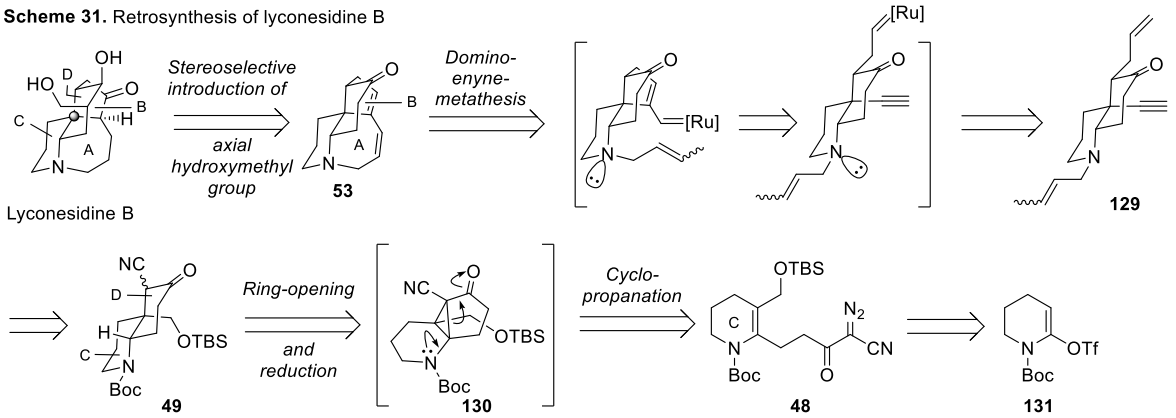
Scheme 30. Examples of inramolecular cyclopropanation of *N*-substituted alkene.



第四節　Lyconesidine B の合成計画

Lyconesidine B の合成上の課題は、(i) その複雑な四環性骨格の構築と (ii) 核間位第四級炭素や (iii) D 環上のアキシアルヒドロキシメチル基を含む連続した 6 つの不斉中心の導入である (Scheme 31)。著者は、ドミノエニンメタセシスによる AB 環部の合成と第一章で開発した反応を利用した CD 環部構築を鍵工程とし、本天然物の合成を計画した。すなわち、lyconesidine B は四環性ジエン **53** から立体選択的なアキシアルヒドロキシメチル基の導入を含む数工程で合成することとした。また、AB 環部のヒドロアザアズレン骨格はジエニン化合物 **129** のドミノエニンメタセシスで合成する。**129** の前駆体となるトランスデカヒドロキノリン **49** は、テトラヒドロピリジン **48** の分子内シクロプロパン化による核間位第四級炭素の導入と、その開環で生じたイミニウムイオンの立体選択的な還元で合成する。**48** は、既知のエノールトリフラート **131** より合成することとした。

Scheme 31. Retrosynthesis of lyconesidine B

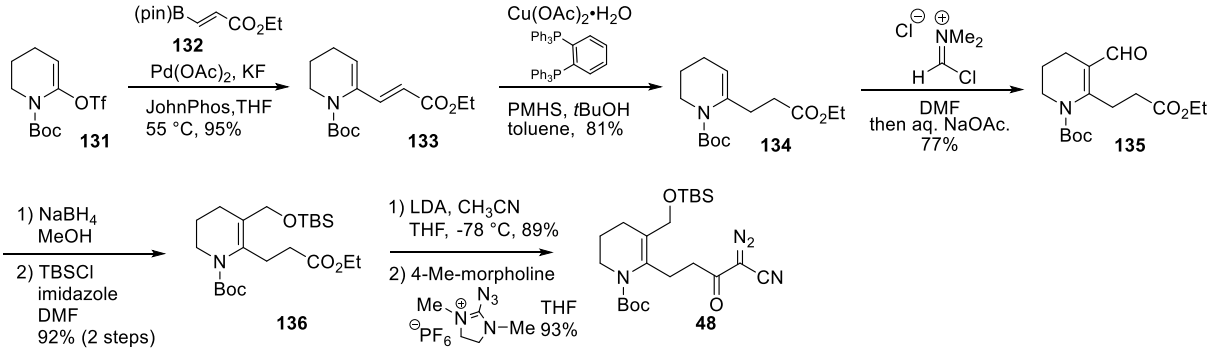


第五節　(±)-Lyconesidine B の全合成

① ワンポットシクロプロパン化-開環-還元反応による核間位第四級炭素を持つデカヒドロキノリンの合成

まず、シクロプロパン化前駆体 **48** の合成から着手した (Scheme 32)。既知のエノールトリフラート **131**[46] とボロン酸エステル **132**[47] とを鈴木-宮浦クロスカップリングで連結して α,β-不飽和エステル **133** を得た後、1,4-還元[48] してエステル **134** を合成した。さらに、ホルミル化でアルデヒド **135** とした。**135** を $NaBH_4$ で還元し、生じた水酸基をシリル化してシリルエーテル **136** へと変換した。続いて、脱プロトン化したアセトニトリルを **136** に付加させた後、ジアゾ化[28] してシクロプロパン化前駆体 **48** を得た。

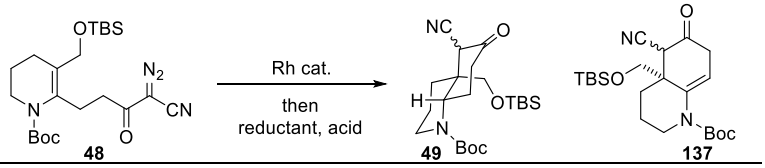
Scheme 32. Preparation of cyclopropanation precursor **48**.



合成した **48** を基質として第一章で開発したシクロプロパン化と続く開環･還元反応を試みた (Table 6)。まず、第一章で用いたデカヒドロキノリン合成の条件で処理したところ、目的のデカヒドロキノリン **49** と望まない副生成物 **137** が混合物として得られた (entry 1)[31]。**137** の生成を抑える目的で更に還元剤を精査し、$NaBH_4$ に対して 3 当量の TFA を加えて調製した $NaBH(OCOCF_3)_3$[49] を $NaBH(OAc)_3$ と TFA の代わりに用いると **137** の生成が抑えられた (entry 2)。還元剤の変更により **137** の生成が抑えられた理由は次のように考察している (Scheme 33)。シクロプロパン化体 **130** を TFA と $NaBH(OAc)_3$ の組み合わせで処理したとき、これら試薬間で酢酸イオンとトリフルオロ酢酸イオンの交換が起こり、反応系中には、対アニオンがトリフルオロ酢酸イオンの **138a** と、酢酸イオンの **138b** の両方が生成する。対アニオンの塩基性度の違いから、**138a** では還元のみが進行するが、**138b** では還元と酢酸イオンによる脱プロトン化が競合し望まない生成物 **137** を与えた。一方、酢酸イオンが系中に存在しない

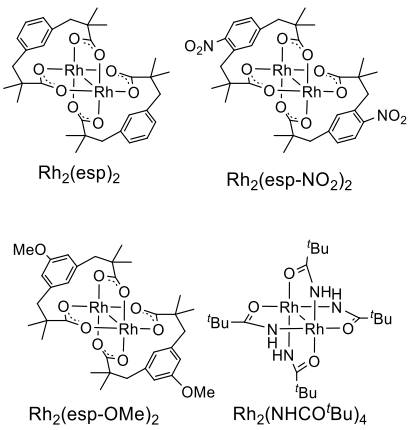
$NaBH(OCOCF_3)_3$ による還元は、脱プロトン化が進行しないために高い選択性で目的物 **49** を与えた。続いて、本反応の更なる収率向上を目指してシクロプロパン化の触媒についても再検討した。$Rh_2(esp)_2$ より電子豊富または電子不足な配位子を持つ $Rh_2(esp\text{-}OMe)_2$[50] や $Rh_2(esp\text{-}NO_2)_2$[50] では収率は向上しなかったが、$Rh_2(NHCO\mathit{t}Bu)_4$[51] を用いると収率は 72%まで向上した (entries 3-5)。第一章の検討において、ラクタムを配位子として持つ $Rh_2(cap)_4$ は $Rh_2(esp)_2$ よりも低い収率でシクロプロパン化体を与えていたため、$Rh_2(NHCO\mathit{t}Bu)_4$ で収率が改善されたことは配位子のアミド水素が重要な役割を果たしたと推測している。

Table 6. Optimization of one-pot cyclopropanation-ring-opening-reduction.

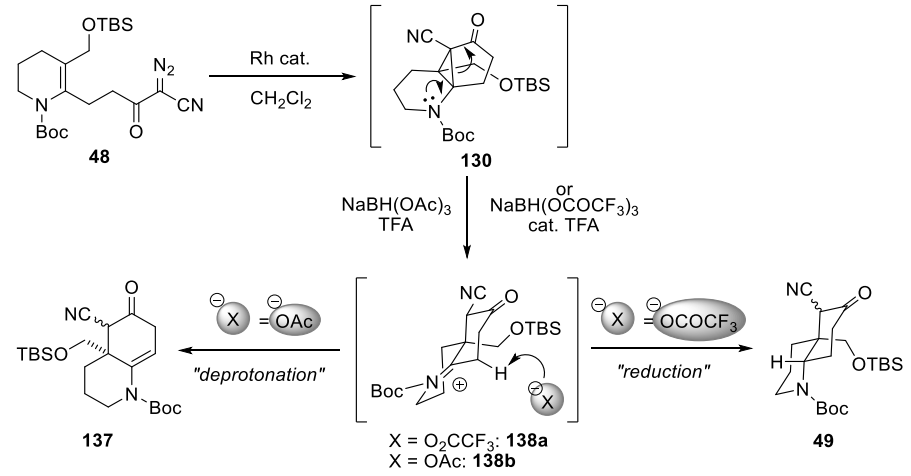


entry	Rh cat.	reductant, acid	product (%) **49**	**137**
1	$Rh_2(esp)_2$ (1 mol%)	$NaBH(OAc)_3$ (10 eq.), TFA (6 eq.)	45	6
2	$Rh_2(esp)_2$ (1 mol%)	$NaBH(OCOCF_3)_3$[a] (1 eq.)	47	0
3	$Rh_2(esp\text{-}OMe)_2$ (1 mol%)	$NaBH(OCOCF_3)_3$[a] (1 eq.)	31	0
4	$Rh_2(esp\text{-}NO_2)_2$ (1 mol%)	$NaBH(OCOCF_3)_3$[a] (1 eq.)	44	0
5	$Rh_2(NHCO\mathit{t}Bu)_4$ (0.5 mol%)	$NaBH(OCOCF_3)_3$[a] (1 eq.)	72	0

[a]1M THF solution.



Scheme 33. Counter ion effect of iminium ion **138**.

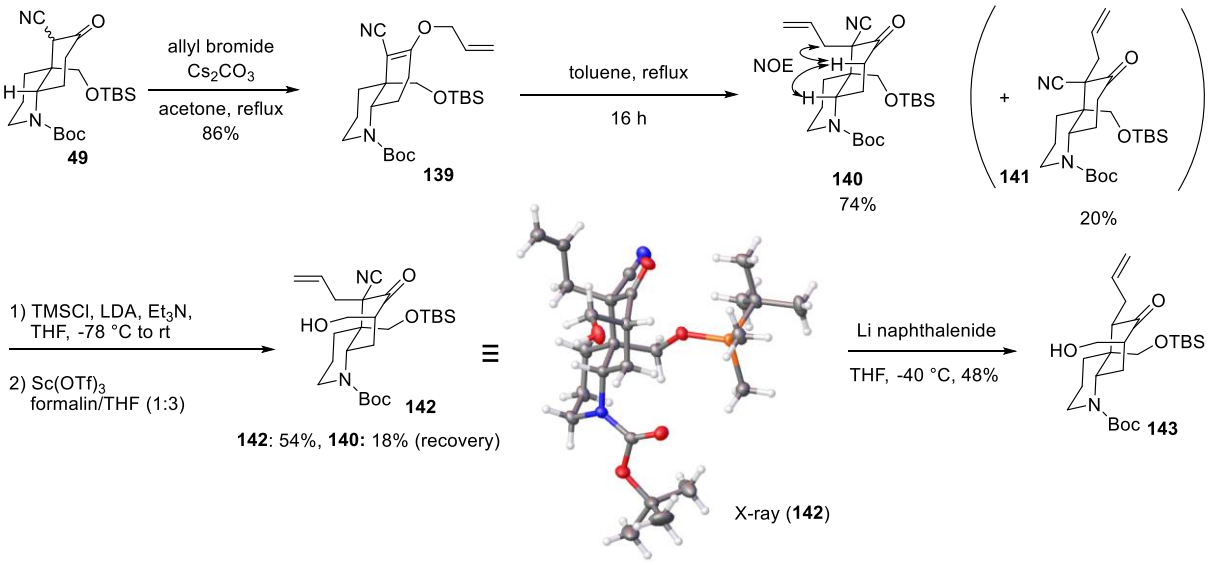


② ドミノエニンメタセシス前駆体 **129** の合成

続いて、ドミノエニンメタセシス前駆体を合成することとした。本誘導化では、核間位にアルキンを導入するが、その段階について検討が必要であった。まず、ケトニトリル **49** をアリルビニルエーテル **139** へと変換した (Scheme 34)。その後、Claisen 転位でアリルケトン **140** と **141** を得た。なお、**140** のアリル基の立体化学は、図に示した NOE 相関により決定した。得られた **140** をエノールシリルエーテルへと変換した後に $Sc(OTf)_3$ とホルマリンで処理すると向山アルドール反応[52] が進行し、18%の原料が回収されたものの、ヒドロキシメチル化体 **142** を単一のジアステレオマーとして 54%収率で得た。その立体化学を含む構造については、X 線結晶構造解析によって確認した。本ヒドロキシ

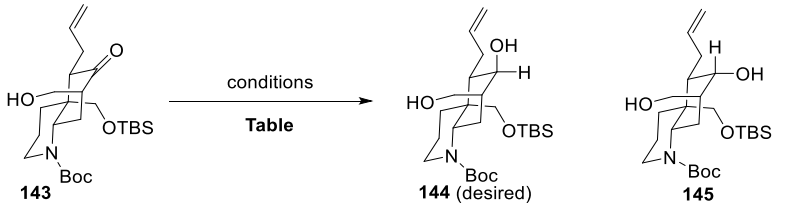
メチル化のジアステレオ選択性発現は、シロキシメチル基の立体障害によるものと推測している。続いて、**142** からリチウムナフタレニド処理によりシアノ基を還元的除去し、ケトン **143** へと導いた [53]。

Scheme 34. Synthesis of ketone **143**.



得られた **143** のケトン部位のジアステレオ選択的な還元を検討した。まず、DIBAL-H による還元では、エクアトリアル側から還元剤が攻撃して望まない立体化学のジオール **145** が 71%収率で生成した (Table 7, entry 1)。**145** は推定構造であるが、得られた化合物の高分解能 MS スペクトルが **145** と一致することを確認した。また、第二級水酸基の立体化学は、得られた化合物を CH_2Cl_2 中 $PhCH(OMe)_2$、CSA 存在下室温で 23 時間攪拌してもベンジリデンアセタール化が進行しなかったことから、第二級水酸基とヒドロキシメチル基がアンチの関係にある **145** の構造と推測した。望みの生成物 **144** は、ケトンの還元で生じる第二級アルコールが、エクアトリアル位にあり、かつ第一級アルコールと水素結合を形成できるため、**145** と比べて熱力学的に安定と推測し、Meerwein-Ponndorf-Verley 還元の条件を二種類検討したが、反応が進行しない、もしくは複雑な混合物を与えるのみであった (entries 2, 3)[54]。そこで、β-ヒドロキシケトンとジエチルメトキシボランとのキレートを利用した還元を試みたが、**145** が主生成物であった (entry 4)[55]。一方、$CeCl_3$ と $NaBH_4$ で処理すると、望みのジアステレオマー**144** がわずかに優先して得られた [56]。なお、**144** の構造は、その後に実施した以下の誘導化が進行したことから本構造と推定した。

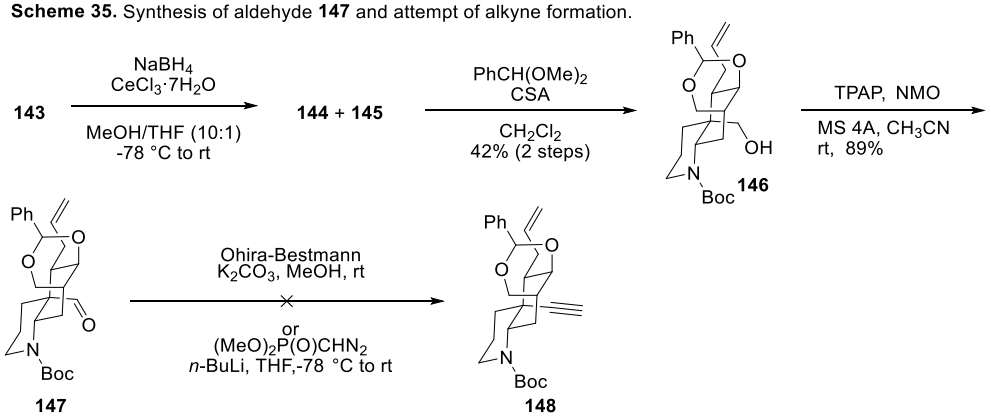
Table 7. Diastereoselective reduction of ketone **143**.



entry	conditions	result
1	DIBAL-H, THF, -78 °C to 0 °C 2 h then additional DIBAL-H, 0 °C, 5 min.	**144**: 0%, **145**: 71%, **143**: 9%
2	SmI_2, *i*PrOH-THF (1:10), rt, 4 days	no reaction
3	$Al(OiPr)_3$, *i*PrOH, reflux, 4 days	complex mixture
4	Et_2BOMe, $NaBH_4$, THF-MeOH (4:1), -78 °C to rt, 4 h	**144** + **145** (2:5): 69%
5	$NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH/THF (10:1), -78 °C to rt, 1 h	**144**+ **145** (3:2): 77%

上記の条件で得られた **144** と **145** の混合物を分離精製することなく CSA 存在下ベンズアルデヒドジメチルアセタールで処理するとベンジリデンアセタールの形成と TBS 基の除去が進行し、アルコール **146** が得られた (Scheme 35)。さらに、**146** の TPAP 酸化によりアルデヒド **147** へと変換し[57]、さらにアルキン **148** への変換を試みた。しかし、塩基性条件下、Ohira-Bestmann 試薬、あるいは、Seyferth-Gilbert 試薬で処理しても、反応は全く進行しなかった。これは、反応点であるアルデヒドがネオペンチル位にあり、かつアキシアル水素やアリル基が立体障害になっているために試薬が接近できないことが原因と推測した (Figure 6)。そこで、基質の変更により、本課題の解決を試みることとした。すなわち、7 位と 8 位が sp^2 炭素のアリルビニルエーテル **149** であれば、アルデヒド周辺の立体障害が低減され、アルキン合成反応が進行すると予想した。

Scheme 35. Synthesis of aldehyde **147** and attempt of alkyne formation.



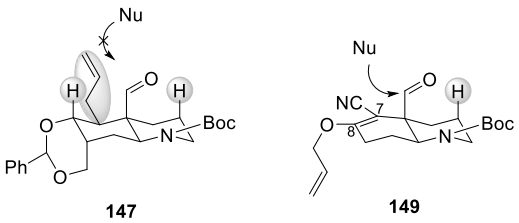
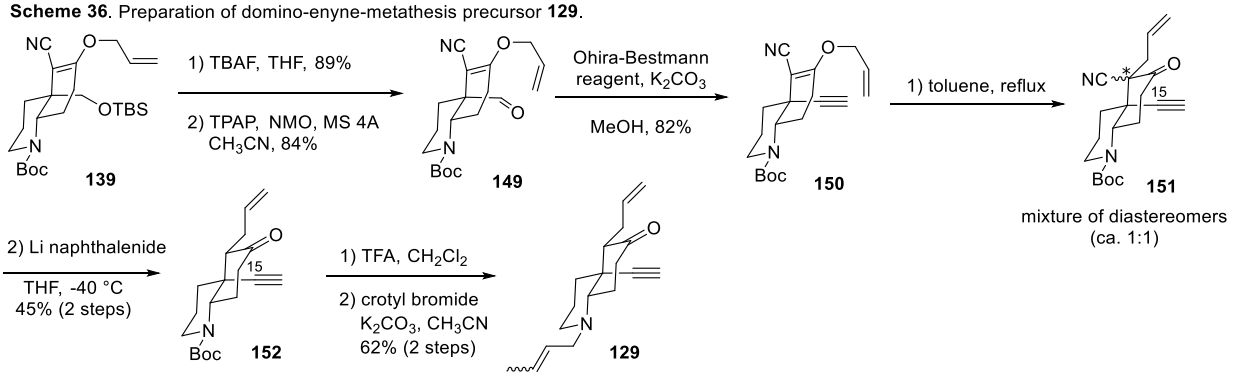


Figure 6. Strategy for formation of alkyne.

そこで、アリルビニルエーテル **139** の TBS 基を除去したのち、生じたアルコールを酸化してアルデヒド **149** を合成した (Scheme 36)。これを MeOH 中 K_2CO_3 存在下、Ohira-Bestmann 試薬で処理すると狙い通り反応が進行しアルキン **150** を 82%収率で得ることに成功した。続いて、Claisen 転位でアリルケトン **151** をジアステレオ混合物として得たのち、シアノ基を Birch 条件で除去してエニン化合物 **152** を得た。なお、向山アルドール反応を実施する目的で **151** や **152** を LDA や LHMDS と TMSCl で処理してエノールシリルエーテルへ変換することを試みたが、複雑な混合物を与えたため 15 位へのヒドロキシメチル基の導入は四環性骨格構築後に実施することとした。**152** の Boc 基の除去と *N*-クロチル化で、ドミノエニンメタセシス前駆体 **129** へと変換した。

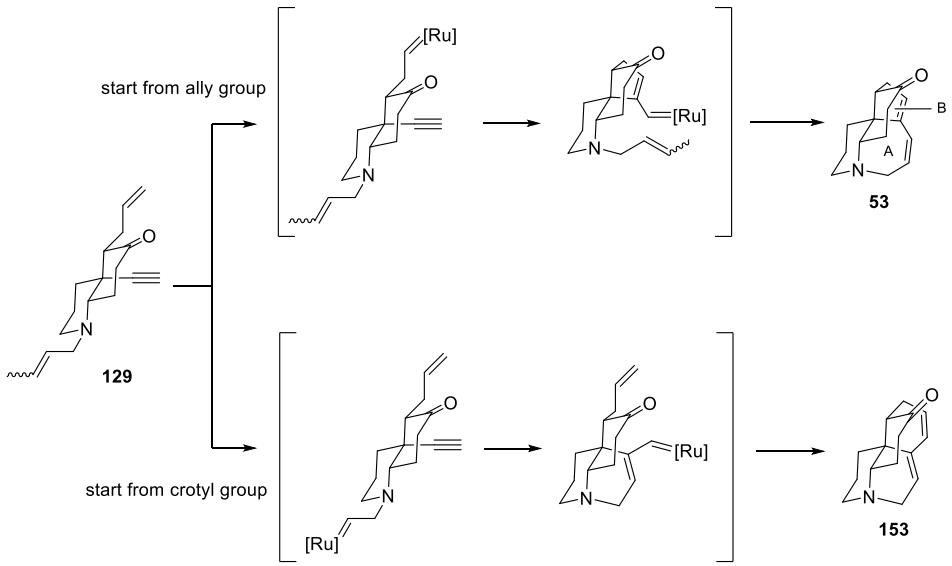
Scheme 36. Preparation of domino-enyne-metathesis precursor **129**.



③ ドミノエニンメタセシス反応の検討

続いて、**129** を基質としてドミノエニンメタセシス反応を検討した。本反応で望みの四環性化合物 **53** を得るには、その反応順序が重要である (Scheme 37)。すなわち、**129** のアリル基から反応するとヒドロアザアズレン環 (AB 環部) を形成して **53** が得られるが、クロチル基から反応するとヒドロイソキノリン環を形成して **153** へと変換される。本反応順序を制御するために、3 位側にはアリル基より立体的に嵩高いクロチル基を用いた。

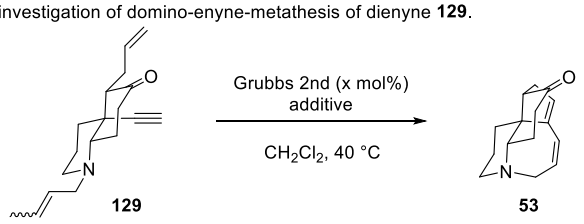
Scheme 37. The role of crotyl group for the construction of hydroazaazulene structure (AB rings).



実際に、ジエニン化合物 **129** を 5 mol%の第二世代 Grubbs 触媒で処理すると 5%の収率ながら所望の順序で反応が進行し、目的の **53** が得られた (Table 8, entry 1)。また、第二世代 Grubbs 触媒を 50

mol%用いると収率は 50%となり、触媒の当量依存的に目的物 **53** を与えた (entry 2)。これは、基質 **129** あるいは生成物 **53** の第三級アミンにより触媒が失活したためと推測した。そこで、第三級アミンによる Grubbs 触媒の失活を効率的に抑えることが報告されている $Ti(OiPr)_4$[58] を添加したが大きな収率の向上は見られず、さらに、**129** の塩酸塩 [34a] を用いた場合は、複雑な混合物を与えるのみであった (entries 3, 4)。

Table 8. Initial investigation of domino-enyne-metathesis of dienyne **129**.

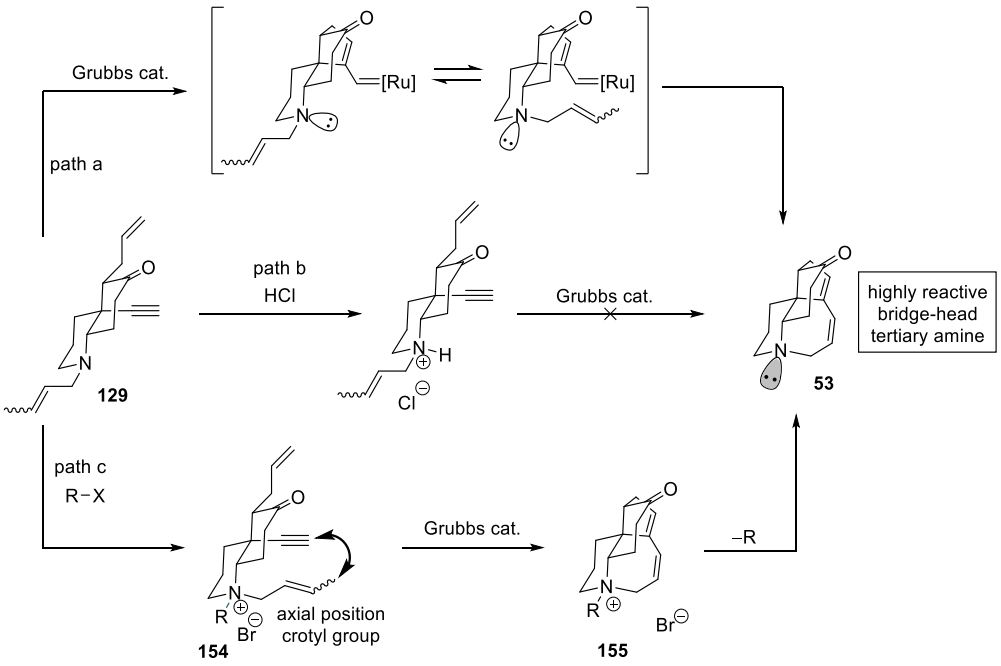


entry	Grubbs 2nd (mol%)	additive	time	yield (%)
1	5	–	17 h	5
2	50	–	16.5 h	50
3	30	$Ti(OiPr)_4$ (1 eq.)	5 days	35
4[a]	10	HCl	2 days	complex mixture

HCl salt of **129** was used as a substrate.

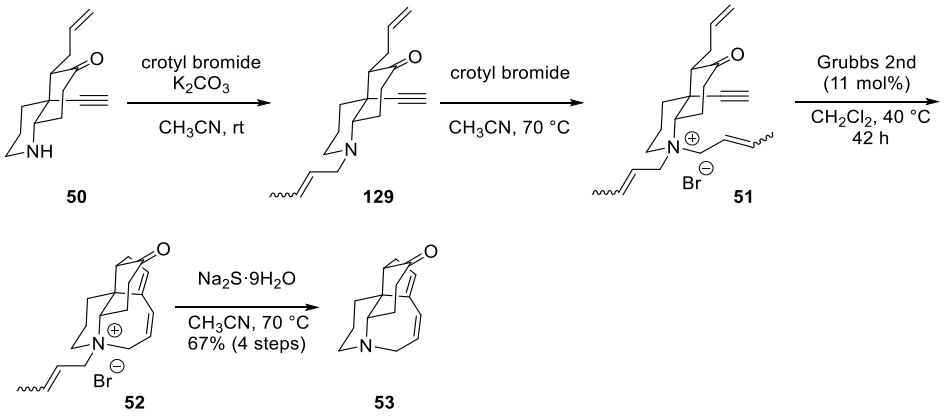
以上の結果を次のように考察した。まず、**129** を第二世代 Grubbs 触媒のみで処理した場合、生成物 **53** が橋頭位に窒素原子をもつ反応性の高いアミンであるために、触媒を失活させたと予想した (Scheme 38, path a)。また、**129** を塩酸塩としたときは、クロチル基がエクアトリアル位にある熱力学的に安定な塩酸塩が生成し、二回目の環化反応が進行しなかったと推測した (path b)。これらのことから、本反応を円滑に進行させるためには、**53** による Grubbs 触媒の失活を抑えつつ、クロチル基をアキシアル位に位置させる必要がある。そこで著者は、第四級アンモニウム塩 **154** がこれらを満たすと考えた (path c)。すなわち、**129** を *N*-アルキル化して第四級アンモニウム塩 **154** とすることで、クロチル基をアキシアル位に位置させることが可能である。さらに、環化後の生成物 **155** はアンモニウム塩なので、Grubbs 触媒の失活が抑えられる。最後に置換基 R を除去すれば、望みの四環性ジエン **53** を得られる。なお、置換基 R には、1 つ目のクロチル基との識別の必要がなく、求核剤で容易に除去可能な、クロチル基を採用することとした。

Scheme 38. Strategy for synthesis of tetracyclic diene **53**.



実際に、エニン化合物 **50** を二段階でクロチル化して第四級アンモニウム塩 **51** を合成した (Scheme 39)。**129** から **51** への変換では、反応初期に一部生じた分岐型ブテニル化体を熱力学的に安定な直鎖型クロチル化体に変換するために、塩基 (K_2CO_3) を用いない条件で加熱することが重要であった。得られた第四級アンモニウム塩 **51** を、11 mol%の第二世代 Grubbs 触媒で処理すると、望みの環化反応が円滑に進行し四環性アンモニウム塩 **52** を得た。最後に、Na_2S で **52** のクロチル基を除去し四環性ジエン **53** を 4 工程 67%収率で得た。本法により、四環性骨格の構築法を確立することができた。

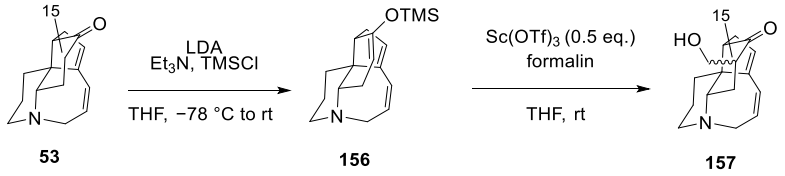
Scheme 39. Domino-enyne-metathesis via tertiary ammonium salt.



④ Lyconesidine B の全合成

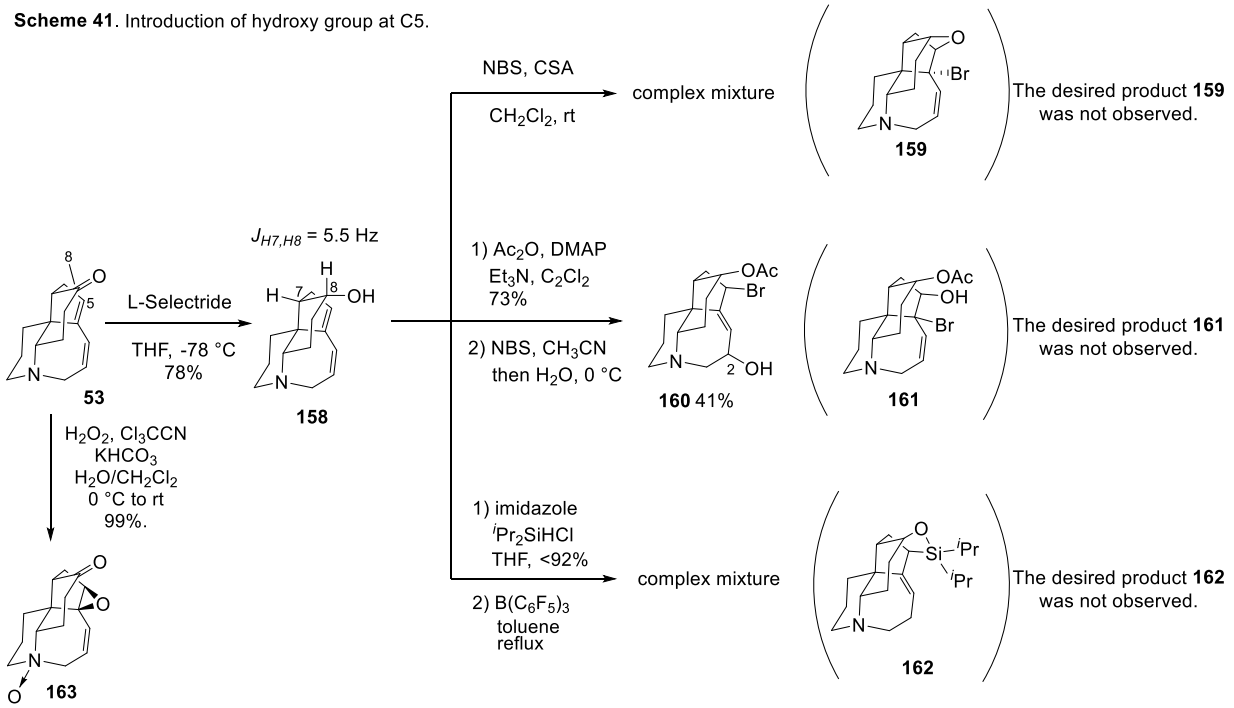
四環性骨格の構築に成功したので、その骨格の修飾と lyconesidine B の全合成を目指した。まず、四環性ジエン **53** に対する 15 位のヒドロキシメチル化を試みた。本基質に対するヒドロキシメチル化は convex 面である紙面左側から進行することを期待した (Scheme 40)。しかし、実際のエノールシリルエーテル **156** に対する向山アルドール反応は、シリル基が convex 面を遮蔽したためか、β-ヒドロキシケトン **157** を 2:5 のジアステレオ混合物として与えた。そこで、紙面左右でより立体障害に差のある基質に変更してヒドロキシメチル化のジアステレ選択性向上を目指すこととした。

Scheme 40. Hydroxymethylation of tetracyclic diene **53**.



53 の 5 位に β-水酸基を導入し、これを立体障害として 15 位にヒドロキシメチル基をジアステレオ選択的に導入することを計画した (Scheme 41)。**53** を L-Selectride®で還元すると、ヒドリドの攻撃は優先的に convex 面から進行し、第二級アルコール **158** を与えた。この水酸基を足掛かりに 5 位への β 選択的な水酸基の導入を試みた。まず、アミンの酸化を防ぐことを目的として CSA を添加した条件で、NBS で処理してブロモエーテル **159** を得ることを試みたが、複雑な混合物を与えた。8 位水酸基と三置換アルケンの距離が遠かったことが原因と考え、8 位水酸基をアセチル化した後 NBS と H_2O で処理したが、2 位に水酸基が導入されたブロモヒドリン **160** が得られ、目的とする **161** は得られなかった。続いて、**158** をイミダゾール存在下、*i*Pr_2SiHCl で処理した。その後、$B(C_6F_5)_3$ で処理して生じたシリルカチオンとジエンの反応でアリルカチオンが生成し、これが立体的に空いている側からホウ素ヒドリド種によって還元されて、アリルシロキサン **162** が得られることを期待したが、複雑な混合物と **158** が回収されるのみであった。以上のような水酸基を足掛かりとした 5 位へのジアステレオ選択的な酸素官能基導入は困難であった。一方、ジエン **53** を過剰量の *m*CPBA で処理して、アミンが酸化された後も攪拌を続けると 18%と低収率ながら、三置換アルケンがエポキシ化されたエポキシド **163** が単一のジアステレオマーとして得られることが明らかとなった。そこで、CH_2Cl_2/H_2O 中 CCl_3CN、H_2O_2、$KHCO_3$ で処理してより温和な条件で酸化を試みたところ、99%収率でエポキシド **164** が得られることを見出した [59]。

Scheme 41. Introduction of hydroxy group at C5.



酸化された三置換アルケンの両ジアステレオトピック面の嵩高さに大きな差はないため、本ジアステレオ選択性は予想外であった。そこで、本反応について三置換アルケンの両面がエポキシ化される

ときの活性化エネルギーをそれぞれ DFT 計算によって算出すると、実際に得られたエポキシド **163** を与える活性化エネルギーは、**164** を与えるそれより 1.4 kcal/mol 安定であることが示唆された (Figure 7)。

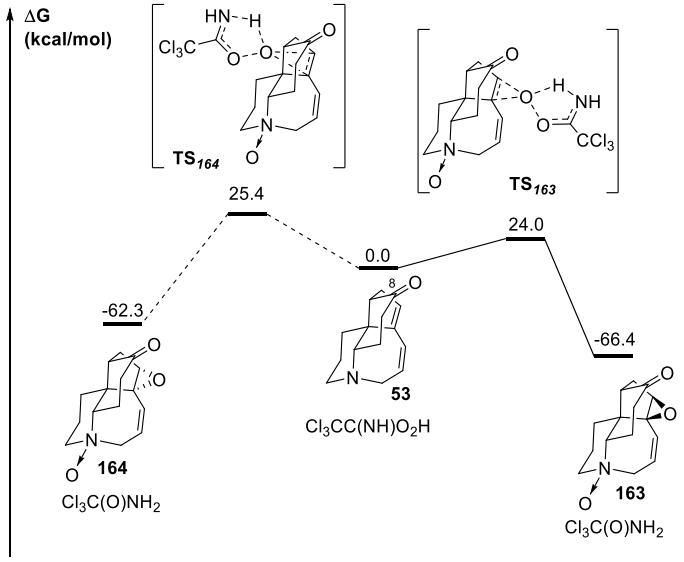
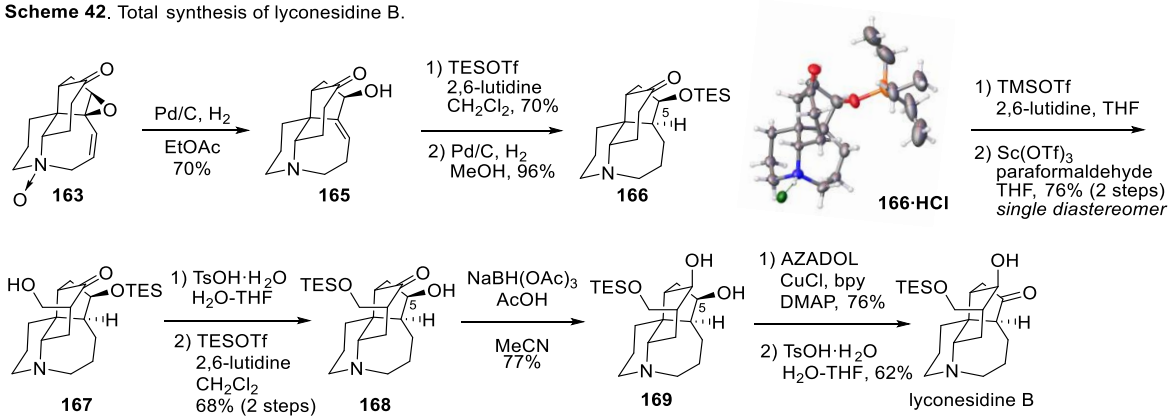


Figure 7. DFT calculation of transition state energy for epoxydation calculated by Gaussian 09 at the ωB97XD/6-311G(d,p) level of theory.

エポキシド **163** から lyconesidine B への誘導化を検討した。**163** を水素雰囲気下 Pd/C で処理すると、*N*-オキシドが還元された後にエポキシドの開環と還元が進行し、アリルアルコール **165** が 70%収率で得られた (Scheme 42)。生じたアリルアルコールを TES 基で保護した後、三置換オレフィンを接触水素化してシリルエーテル **166** を得た。シリルエーテル **166** について、その塩酸塩 **166**· **HCl** の X 線結晶構造解析により立体化学を確認した。続いて、シリルエーテル **166** をエノールシリルエーテルとした後、TES 基を立体障害としたホルムアルデヒドとの向山アルドール反応に付すことで、β-ヒドロキシケトン **167** を単一ジアステレオマーとして得た。通常、ランタノイドトリフラートや $Sc(OTf)_3$ を用いたエノールシリルエーテルとホルムアルデヒドの向山アルドール反応では、ホルムアルデヒド水溶液が用いられるが、本基質ではエノールシリルエーテルのプロトン化で **166** に戻る反応が競合した。そのため、収率良く本反応を進行させるために、禁水条件でパラホルムアルデヒドを用いた。続いて、TES 基の脱着でケトアルコール **168** としたのち、5 位の水酸基を配向基としたケトンのジアステレオ選択的なヒドリド還元により、ジオール **169** を得た。最後に、5 位水酸基の選択的酸化 [60] と TES 基の除去を経て lyconesidine B の世界初の全合成を達成した。また、合成品は、天然由来の lyconesidine B と ^{1}H、^{13}C NMR および高分解能 MS スペクトルが完全に一致した。本合成経路では、既知のエノールトリフラート **131** から 30 工程、総収率 0.52%であった。合成経路では、官能基化可能な四環性骨格の供給が数 100 mg スケールで実施でき、多様な類縁体の合成にも発展が期待できる。

Scheme 42. Total synthesis of lyconesidine B.

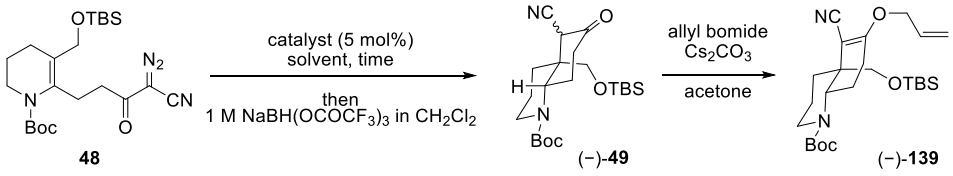


第六節　(−)-Lyconesidine B の不斉合成研究

著者が確立した lyconesidine B のラセミ全合成経路おいて、不斉炭素を生じるのは、テトラヒドロピリジン **48** のシクロプロパン化の段階である。したがって、本反応を不斉反応へと展開できれば、本天然物の不斉全合成へと発展できる。そこで、不斉配位子を持った遷移金属触媒を用いて、不斉シクロプロパン化を検討することとした。なお、シクロプロパン化・開環・還元の後に得られるデカヒドロキノリン **49** は、エナンチオマーの分離条件を見出すのが困難であったため、アリルビニルエーテル **139** へと変換して、エナンチオマー比を決定した。

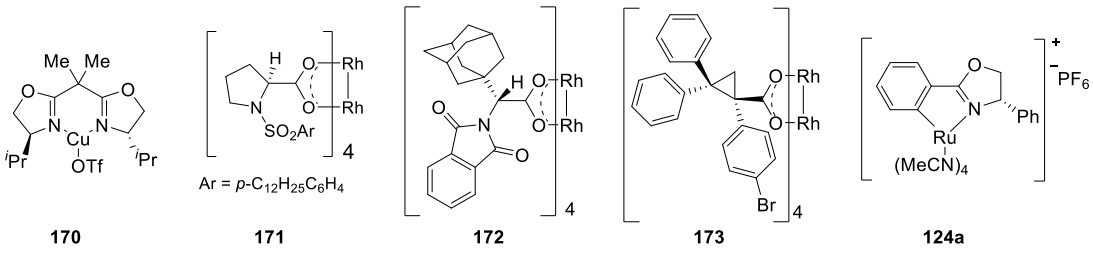
初期検討として、不斉シクロプロパン化に頻用される不斉遷移金属錯体によるシクロプロパン化を試みた。まず、$[CuOTf]_2 \cdot C_6H_6$ と 2,2-bis[(4*S*)-(−)-4-isopropyloxazoline]propane から用時調製した触媒 **170**[61] を用いると、5 時間攪拌しても反応は進行しなかった (Table 9, entry 1)。次に、市販の不斉 Rh 二核錯体 **171**[62]、**172**[63]、**173**[64] を検討したが、得られた **49** のエナンチオマー比は、それぞれ 50:50、59:41、65:35 に留まった (entries 2-4)。不斉 Rh 二核錯体は、この他にも多くの種類が開発されているが、そのほとんどが触媒 **171**、**172**、**173** の類縁体なので、同様の配位子でのエナンチオ選択性の大幅な向上は見込めないと推測した。次に、ビニルプリン誘導体の分子内不斉シクロプロパン化（第二章第三節 page 27）で用いられた不斉カチオン性 Ru 錯体 **124a**[65] を用いたところ、26:74 と比較的良好なエナンチオ選択性で **49** を与えた (entry 5)。さらに、**124a** を用いて溶媒を検討した。EtOAc を用いると、エナンチオ選択性がわずかに向上し、25:75 er で **49** が得られた (entry 6)。次に、toluene を用いると、23:77 er で **49** が得られ、THF 中では 21:79 er まで向上した (entries 7, 8)。なお、CH_3CN 中ではほとんど原料が消費しなかったが、これはおそらく Ru 金属中心からの CH_3CN の解離が不利になり、Ru カルベン錯体の形成が遅くなったことが原因と推測される (entry 9)。

Table 9. Initial screening of catalysts and solvents for asymmetric cyclopropanaiton of **48**.



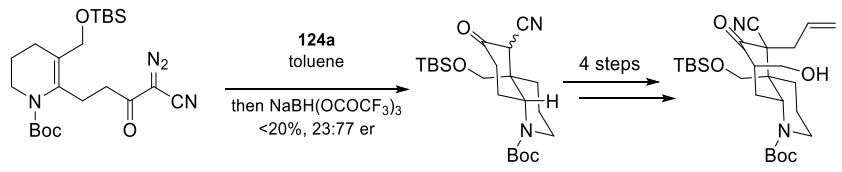
entry	catalyst	solvent	time	yield (%)	er (−)-**49**:(+)-**49**
1	**170**	toluene	5 h	no reaction	
2	**171**	CH_2Cl_2	20 min	45	50:50
3	**172**	CH_2Cl_2	20 min	22	59:41
4	**173**	CH_2Cl_2	3 h	29	65:35
5	**124a**	CH_2Cl_2	1 h	29	26:74
6	**124a**	EtOAc	1 h	26	25:75
7	**124a**	toluene	4 h	<20[a]	23:77
8	**124a**	THF	40 min	28	21:79
9	**124a**	CH_3CN	1.5 h	–[b]	

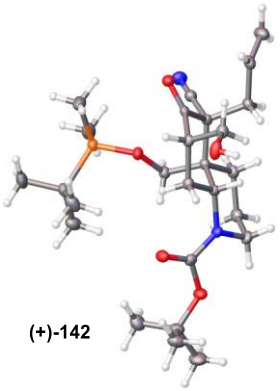
[a]including small amount of impurity. [b]Although small amount of **48** was consumed, **49** was not detected.



得られたデカヒドロキノリン **49** の主エナンチオマーの絶対立体配置を決定する目的で、第二章第五節② (page 29) の方法に従い、4 工程で β-ヒドロキシケトン **142** へと誘導化し、その結晶を得た (Scheme 43)。この X 線結晶構造解析から、主エナンチオマーは、望みと逆の絶対立体配置であることが明らかとなった。

Scheme 43. Determination of absolute stereochemistry of **142**.

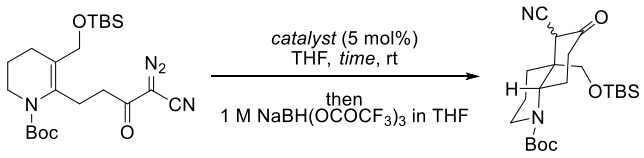




触媒 **124a** は、豊橋技術科学大学の岩佐らが開発したものであるが、市販のアミノアルコールから数工程（通常 3 工程）で合成可能であり、その構造最適化が比較的容易である。そこで、更なるエナンチオ選択性の向上を目指し、触媒構造の改変に着手した。触媒は、岩佐らの報告に従い合成した。まず、オキサゾリン環上に *t*Bu 基を持つ触媒 **124b**[66] を用いたが、その嵩高さのためか反応は進行せず

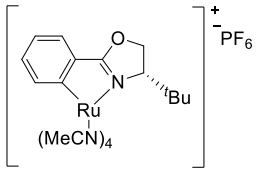
原料が回収された (Table 11, entry 1)。続いて、金属中心と結合したベンゼン環上の置換基 R^1 がそれぞれメトキシ基、ニトロ基の **124c**[67] と **124d**[68] を検討したが、いずれも **124a** より低いエナンチオ選択性を与えたため、R^1 は H に固定することとした (entries 2, 3)。続いて、オキサゾリン環上の置換基 R^2 がフェニル基の **124e**[69] を用いたところ、16:84 er とエナンチオ選択性が向上した (entry 4)。一方で R^1、R^2 共にフェニル基の **124f**[70] では、エナンチオ選択性が低下した (entry 5)。このことからオキサゾリン環上の置換基は、**124e** のように二つのフェニル基がトランス置換した構造を採用した。次に、Ru 周辺の立体障害によるエナンチオ選択性への影響を調査する目的で、Ru に直接結合したベンゼン環にメチル基を導入した **124g** を合成した。なお、望みの(−)-**49** を主生成物として得るために、触媒は 1R, 2R 体とした。**124g** を用いると 63:37 er と顕著な反応時間の延長とエナンチオ選択性の低下が確認された (entry 6)。そこで、立体的に嵩が低い **55** によるシクロプロパン化を試みたところ、88:12 er まで向上した (entry 7)。

Table 11. Optimization of the structure of catalyst.

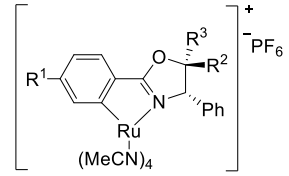


entry	catalyst	time	yield (%)	er (−)-**49**:(+)-**49**
1	**124b**	1.5 h	no reaction	—
2	**124c**	30 min	36	26:74
3	**124d**	7 h	20	25:75
4	**124e**	1.5 h	46	16:84
5	**124f**	30 min	<29[a]	27:73
6	**124g**	7.5 h	<17[a]	63:37
7	**55**	30 min	53	88:12

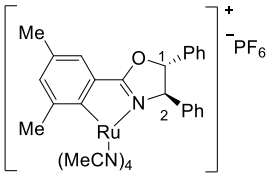
[a]containing a small amount of unidentified impurity.



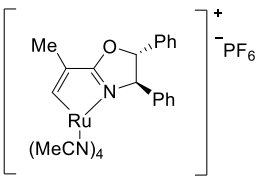
124b



124c: R^1 = OMe, R^2 = H, R^3 = H
124d: R^1 = NO_2, R^2 = H, R^3 = H
124e: R^1 = H, R^2 = Ph, R^3 = H
124f : R^1 = H, R^2 = Ph, R^3 = Ph



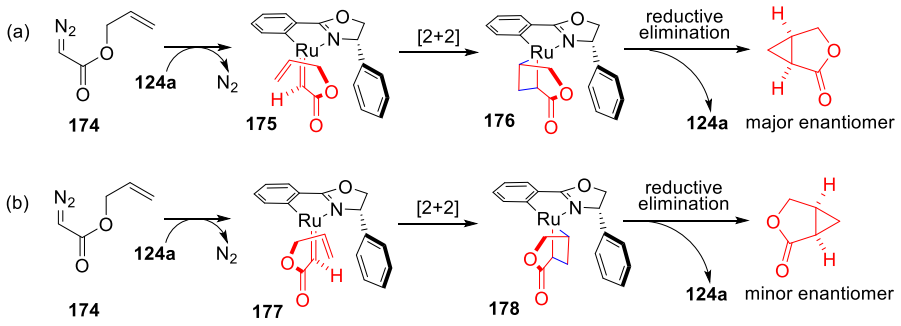
124g



55

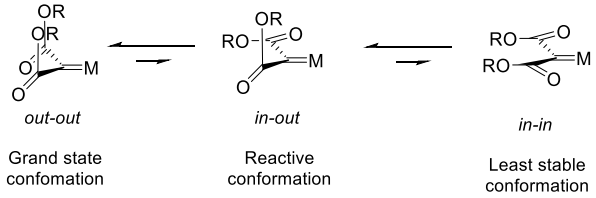
本反応の反応機構について、中間体を観測するなど直接的な証拠は得られていないが過去の報告を参考に考察した。触媒 **124a** を用いた分子内不斉シクロプロパン化について 2018 年、岩佐らは計算化学を用いて次のようにエナンチオ選択性が発現すると提唱した (Scheme 44)[71]。ジアゾエステル **174** と触媒 **124a** から Ru カルベン錯体 **175** が生成した後、メタラシクロブタン **176** を経て、還元的脱離で主エナンチオマーを与える (Scheme 44a)。一方、**177** ように、主エナンチオマーを与えた **175** と逆のエナンチオトピック面でオレフィンが反応すると、メタラシクロブタン **178** を経てもう一方のエナンチオマーが生成する (Scheme 44b)。

Scheme 44. Reported mechanism of asymmetric cyclopropanation using catalyst **124a**



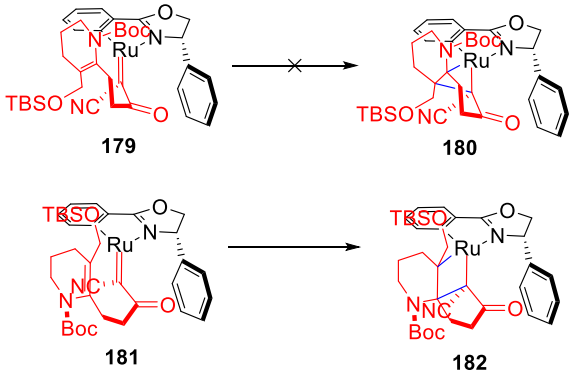
しかし、岩佐らが報告した本モデルを著者の基質 **48** に適用すると主エナンチオマーが実際の実験結果と逆転する。これは、岩佐らの基質がジアゾエステルであることに対して、著者の基質 **48** がジアゾケトニトリルであることに起因すると考えた。一般に、2 つの電子求引基が置換した金属カルベン錯体では、カルベンの不安定化を避けるために基底状態でカルベンと両電子求引基が直交している (Scheme 45, out-out)。しかし、立体的な要因から、シクロプロパン化等の反応は 1 つの電子求引基がカルベンと平面構造をとって進行する (in-out)。一方、両電子求引基とカルベンが平面構造をとると大きく不安定化されるため、この状態からは反応しないとされている(in-in)[72]。

Scheme 45. Conformations of metal carbene complex with two electron withdrawing groups.



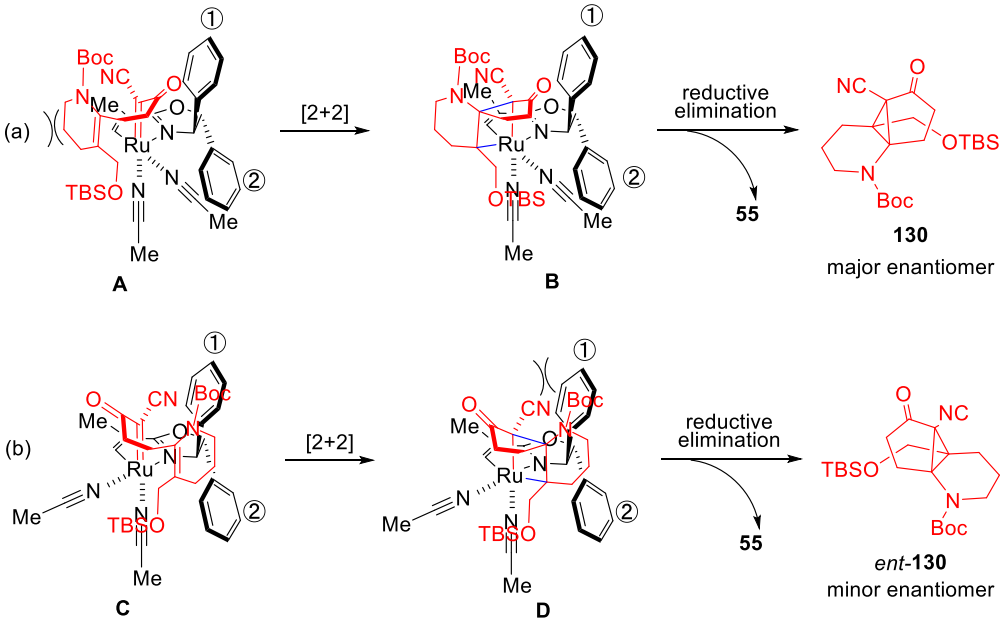
岩佐らの報告では、エステルがカルベンと平面構造をとることが想定されているが、著者の基質はニトリルが常にカルベンと共役しており、ケトンはカルベンと直交した状態で反応することが予想される (Scheme 46)。この状態で Ru カルベン錯体 **179** からメタラシクロブタン **180** への変換には大きなひずみを伴う。したがって Ru カルベン錯体 **181** からメタラシクロブタン **182** を経て、大きなひずみを伴わずシクロプロパン化が進行しているものと予想した。

Scheme 46. Metallacyclobutane formation from **179** and **181**.



即ち、最も良いエナンチオ選択性を与えた触媒 **55** を用いたとき、Ru カルベン錯体 **A** からメタラシクロブタン **B** を形成し、続く還元的脱離で主エナンチオマーとしてシクロプロパン **130** を与えたと推察した (Scheme 47a)。一方、Ru カルベン錯体 **C** からは、メタラシクロブタン **D** を経てシクロシクロプロパン *ent*-**130** を与える (47b)。

Scheme 47. Proposed mechanism of asymmetric cyclopropanation.



触媒を **124e** から **55** に変更したときエナンチオ選択性が向上した。これは、ルテニウムに直接結合したベンゼン環をメチルビニル基に変更したことで、**A** において基質のテトラヒドロピリジン環と触媒との立体反発が低減されたためと推測した。また、触媒を **124a** から **124e** に変更したときエナンチオ選択性が向上した。フェニル基②が触媒のオキサゾリン環上に導入されるとオキサゾリン環の配座が変化し、フェニル基①が擬アキシアル位に位置することが DFT 計算から示唆された (Figure 8)。これにより、**C** において基質のシアノ基と触媒のフェニル基①の立体反発が大きくなり *ent*-**130** の生成が抑制されため、エナンチオ選択性が向上したと推察した (Scheme 47)。以上の理由から、触媒 **55** が最も良いエナンチオ選択性を与えたと考えた。

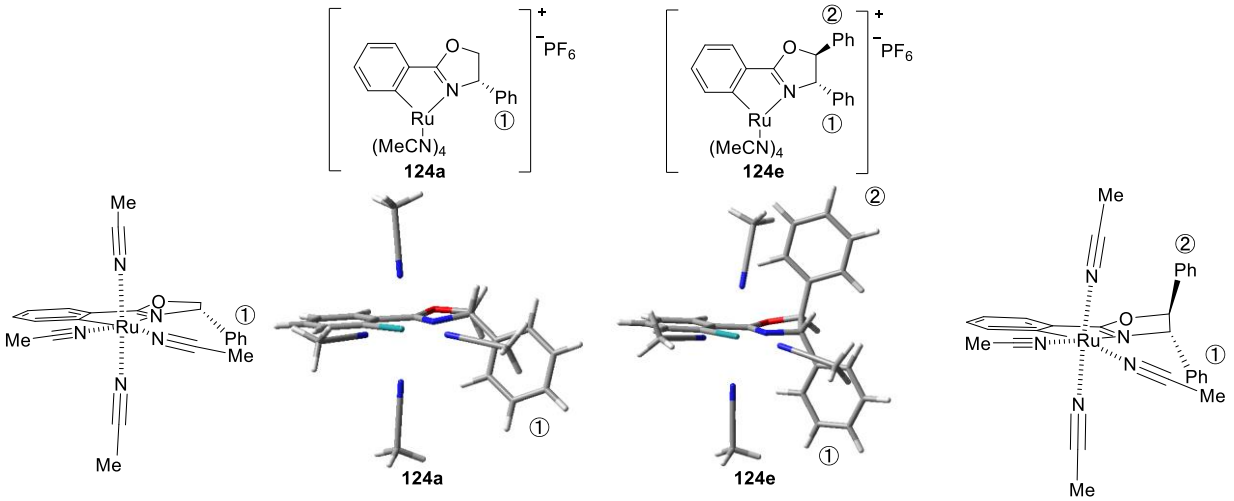


Figure 8. Structures of **124a** and **124e**.
Calculated by Gausian 09 ωB97X-D/(LANL2DZ: Ru; 6-31G(d): others)

第七節　結論

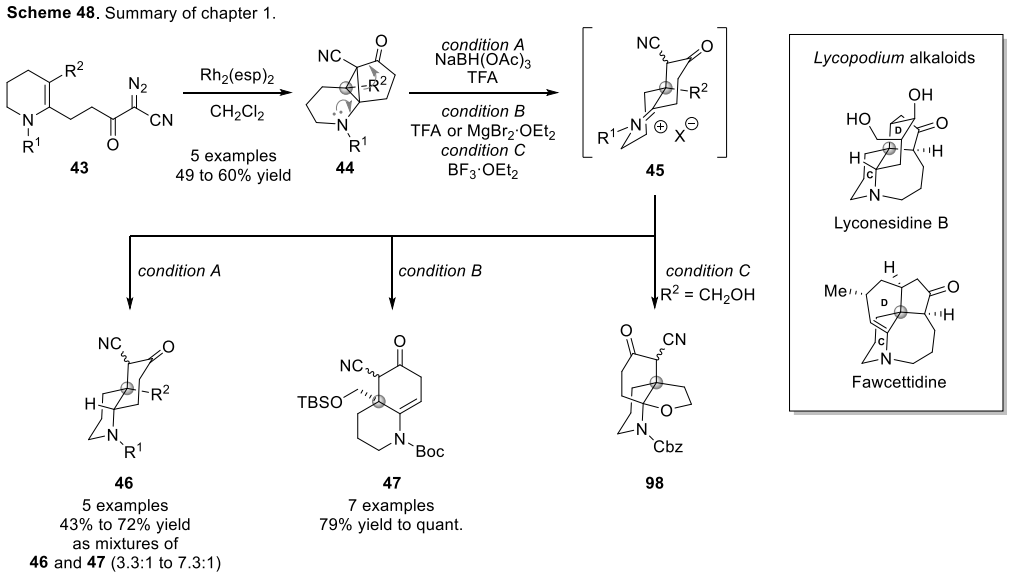
著者は、(i) シクロプロパン化による第四級炭素の構築とその開環・還元による D 環部の構築、(ii) ドミノエニンメタセシス反応による AB 環部の一挙構築を鍵として、(±)-lyconesidine B の初の全合成を達成した。酸素官能基化されたアミン型の fawcettimine 型リコポジウムアルカロイドの全合成は、本報告が初であり、シクロプロパン化を利用したオクタヒドロキノリン合成法の有用性が示された。また、Ru 触媒による不斉シクロプロパン化により、合成中間体のデカヒドロキノリン **49** を 88:12 er で得ることに成功した。これにより、本法での fawcettimine 型リコポジウムアルカロイドの不斉全合成への発展も期待できる。

第三章　結論

以上のように、著者は、Fawcettimine グループの中でもエナミン型やアミン型の天然物に注目して、新たな合成戦略を検討した。これまで多くの合成で用いられてきた犬伏・Heathcock らの合成戦略とは別の CD 環部から構築する戦略を開発し、合成戦略におけるアミン型の合成法へ 1 つの解決策を提示した。原料もキラルシントンを用いないため、幅広い酸化された天然物合成へ対応可能である。その要点は下記の通りである。

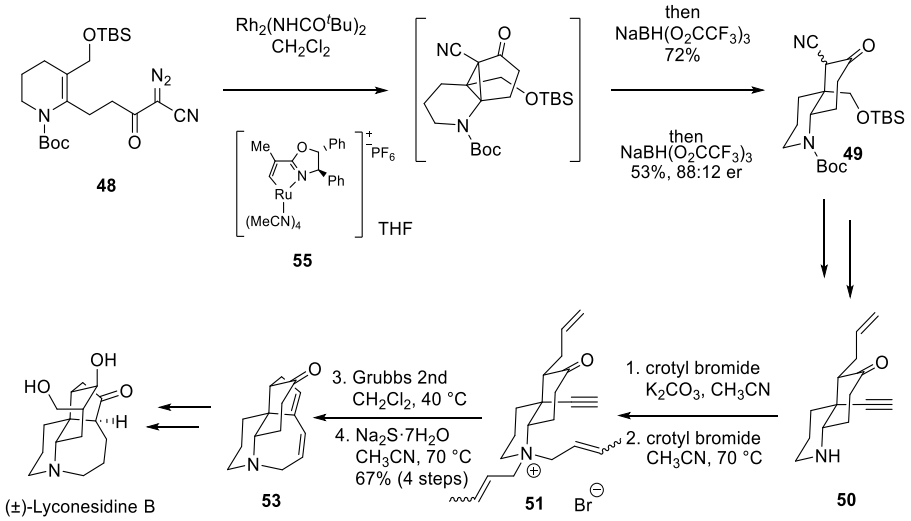
第一章では、テトラヒドロピリジンの分子内シクロプロパン化による第四級炭素の構築と生じたシクロプロパンの開裂によって核間位に第四級炭素を有するオクタおよびデカヒドロキノリン骨格の新規合成法を開発した (Scheme 48)。さらに、分子内に水酸基を有する基質を用いて、三環性化合物 **98** の合成にも発展させた。本法で合成したヒドロキノリン誘導体は、シクロヘキサン、または、シクロヘキセン環上にケトンやニトリルを有しており、これら官能基を更なる誘導化や置換基導入の足掛かりとして利用できる点で有用な合成中間体である。

Scheme 48. Summary of chapter 1.



第二章では、第一章のデカヒドロキノリン合成法とドミノエニンメタセシス反応による骨格構築を鍵として (±)-lyconesidine B の初の全合成を達成した (Scheme 49)。酸素官能基化されたアミン型の fawcettimine 型リコポジウムアルカロイドの全合成は、本報告が初であり、シクロプロパン化を利用したオクタヒドロキノリン合成法の有用性が示された。また、Ru 触媒 **55** による不斉シクロプロパン化で合成中間体 **49** を 88:12 er で得ることにも成功した。これにより、本法での fawcettimine 型リコポジウムアルカロイド類の不斉全合成への展開も期待できる。ドミノエニンメタセシス反応による AB 環部合成では、第四級アンモニウム塩を経由することが鍵であった。本研究により Grubbs 触媒の失活を抑え、かつ反応点を接近させる合成戦略の有用性を示せたことから、エニンメタセシスを用いたアミン化合物合成における 1 つの課題の解決策を提示した。

Scheme 49. Summary of chapter 2.



実験項

General Information

All non-aqueous reactions were carried out under argon in dried glassware. Analytical thin-layer chromatography was performed using Silica gel 60 plates (Merck, Darmstadt, Germany). Silica gel column chromatography was performed using Kanto silica gel 60 (particle size 63–210 μm, Kanto, Tokyo, Japan), Chromatorex BW-300 (Fuji silysia, Aichi, Japan), DualPore OPEN (DPS Inc., Kyoto, Japan), Chromatorex DIOL SMB10020/45 (Fuji silysia) and Chromatorex NH-DU3050 (Fuji silysia). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JNM-AL 400 (JEOL) at 400 MHz, a JNM-ECA 500 (JEOL, Tokyo, Japan) at 500 MHz, Avance I 600 (Bruker Biospin AG, Switzerland) at 600 MHz or a JNM-ECZ 600 (JEOL) at 600 MHz. Chemical shifts were reported relative to Me_4Si (δ 0.00) in $CDCl_3$ or the residual solvent peak in C_6D_6 (δ 7.16) or CD_3OD (δ 3.31). Multiplicity was indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JNM-AL 400 (JEOL) at 100 MHz, a JNM-ECA 500 at 126 MHz, an Avance I 600 (Bruker Biospin AG, Switzerland) at 151 MHz or a JNM-ECZ 600 at 151 MHz. Chemical shifts were reported relative to $CDCl_3$ (δ 77.0), C_6D_6 (δ 128.0) or CD_3OD (δ 49.0). Infrared spectra were recorded on a FT/IR-4100 Fourier-transform infrared spectrometer (JASCO, Tokyo, Japan) ATR (attenuated total reflectance). Low and High resolution mass spectra were recorded on JMS-700 mass spectrometer (JEOL) for FAB-MS and a LCMS-IT-TOF (Shimadzu, Kyoto, Japan) for ESI-MS. X-ray crystallography was recorded on XtaLAB P200 deffractometer (Rigaku, Tokyo, Japan).

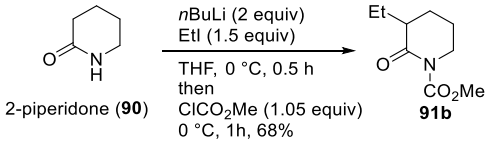
Materials

Anhydrous acetone, CH_2Cl_2, THF, DMF, toluene, methanol and CH_3CN, were purchased from KANTO Chemical Co., Aldrich and Wako chemicals. Materials were obtained from Tokyo Chemical Industry Co., Ltd. Aldrich Inc., and other commercial suppliers, and used without further purification.

第一章　四置換エンカーバメートのシクロプロパン化とその開環を利用したオクタ-およびデカヒドロキノリンの合成

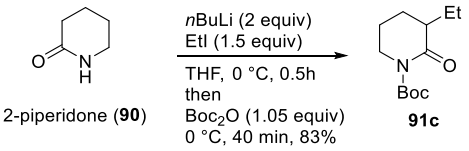
1. Experimental Procedure

Compound **91a** was prepared by following Waser's procedure.[27] Compound **91b-d**, **91f** and **91h** was synthesized by modifying this procedure as follows.

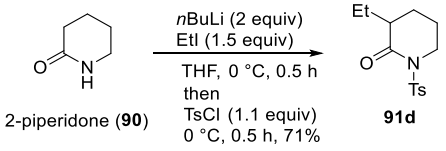


Compound 91b: To a solution of 2-piperidone (4.00 g, 40.4 mmol) in THF (80 mL) was added *n*BuLi (1.6 M hexane solution, 55.5 mL, 88.8 mmol) dropwise at 0 °C, and the solution was stirred at the same temperature for

30 min. EtI (4.90 mL, 60.6 mmol) was then added dropwise, and the resultant solution was stirred at the same temperature for 0.5 h. $ClCO_2Me$ (3.30 mL, 42.4 mmol) was then added at 0 °C, and the resultant solution was warmed to room temperature. After stirring at room temperature for 1 h, aq. NH_4Cl was added to the reaction mixture. The resultant mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **91b** (5.10 g, 27.5 mmol, 68%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.81 (m, 1H), 3.69 (m, 1H), 2.36 (m, 1H), 2.03 (m, 1H), 1.95-1.87 (m, 2H), 1.82 (m, 1H), 1.54-1.49 (m, 2H), 0.97 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 153.6, 52.3, 44.8, 43.9, 24.3, 22.9, 20.4, 10.3; IR (ATR) 2957, 2876, 1774, 1715, 1283, 1257, 1089 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_9H_{16}NO_3$ 186.1130; Found 186.1127.

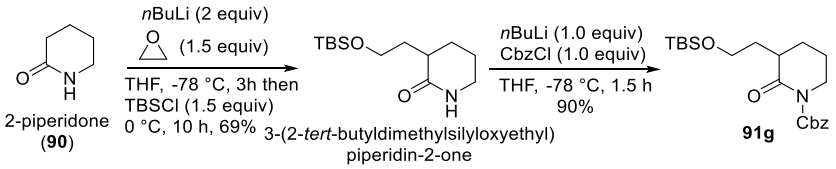


Compound 91c: To a solution of 2-piperidone (1.00 g, 10.1 mmol) in THF (20 mL) was added *n*BuLi (1.6 M hexane solution, 13.9 mL, 22.0 mmol) dropwise at 0 °C, and the solution was stirred at the same temperature for 30 min. EtI (1.23 mL, 15.1 mmol) was then added dropwise, and the resultant solution was stirred at the same temperature for 0.5 h. Boc_2O (2.31 g, 10.6 mmol) was then added at 0 °C, and the resultant solution was warmed to room temperature. After stirring at room temperature for 40 min, aq. NH_4Cl was added to the reaction mixture. The resultant mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **91c** (1.89 g, 8.32 mmol, 83%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77-3.72 (m, 1H), 3.63-3.58 (m, 1H), 2.34-2.29 (m, 1H), 2.04-1.79 (m, 4H), 1.58-1.50 (m, 2H), 1.52 (s, 9H), 0.96 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 152.6, 82.1, 45.3, 44.7, 27.6, 25.1, 23.7, 21.3, 11.1; IR (ATR) 2967, 2875, 1768, 1712, 1296, 1150 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{22}NO_3$ 228.1600; Found: 228.1602.



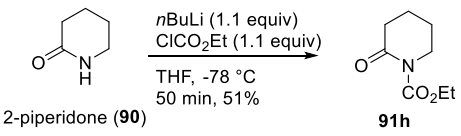
Compound 91d: To a solution of 2-piperidone (500 mg, 5.04 mmol) in THF (10 mL) was added *n*BuLi (1.6 M hexane solution, 6.95 mL, 11.1 mmol) dropwise at 0 °C, and the solution was stirred at the same temperature for 30 min. EtI (0.615 mL, 7.65 mmol) was then added dropwise, and the resultant solution was stirred at the same temperature for 0.5 h. A solution of TsCl (1.01 g, 5.29 mmol) in THF (5.0 mL) was then added at 0 °C, and the resultant solution was warmed to room temperature. After stirring at room temperature for 0.5 h, aq. NH_4Cl was added to the reaction mixture. The resultant mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (hexane/EtOAc = 10:1) to afford **91d** (1.00 g, 3.57 mmol, 71%) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 3.95 (m, 1H), 3.87 (m, 1H), 2.42 (s, 3H), 2.25 (m, 1H), 2.03-1.93 (m, 2H), 1.84-1.77 (m, 2H), 1.50-1.42 (m, 2H), 0.85 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 144.5, 136.3, 129.3, 128.6, 128.5, 46.7, 44.8, 25.1, 23.9, 22.3, 21.6, 11.1; IR (ATR) 2962, 2875, 1693, 1349, 1167 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{20}NO_3S$ 282.1164; Found: 282.1169.



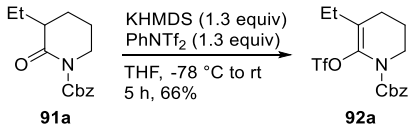
Compound 91g: To a solution of 2-piperidone (2.97 g, 30.0 mmol) in THF (60 mL) was added *n*BuLi (1.6 M hexane solution, 41.0 ml, 66.0 mmol) dropwise at 0 °C, and the solution was stirred at the same temperature for 30 min. Ethylene oxide (1.2 M THF solution, 25.0 ml, 30.0 mmol) was then added dropwise, and the resultant solution was stirred at the same temperature for 3 h. TBSCl (7.05 g, 45.0 mmol) was then added at 0 °C, and the resultant solution was warmed to room temperature. After stirring at room temperature for 10 h, aq. NH_4Cl was added to the reaction mixture. The resultant mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:2) to afford 3-(2-tert-butyldimethylsilyloxyethyl)-piperidin-2-one (5.30 g, 20.6 mmol, 69%) as a colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (brs, 1H), 3.75 (t, 2H, *J* = 6.2 Hz), 3.30 (brs, 2H), 2.43 (m, 1H), 2.21 (m, 1H), 2.00 (m, 1H), 1.88 (m, 1H), 1.74 (m, 1H), 1.64-1.52 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 60.8, 41.8, 37.7, 34.2, 27.0, 26.2, 25.7, 21.2, 18.0, −5.58, −5.64; IR (ATR) 3284, 3191, 3070, 2951, 2856, 1645, 1491, 1249 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{28}NO_4Si$ $[M+H]^+$ 258.1889; Found: 258.1887.

To a solution of 3-(2-tert-butyldimethylsilyloxyethyl)piperidin-2-one (5.30 g, 20.6 mmol) in dry THF (80 mL) was added *n*BuLi (1.6 M hexane solution, 12.9 ml, 20.6 mmol) dropwise at −78 °C. The solution was stirred at the same temperature for 30 min. CbzCl (2.90 ml, 20.6 mmol) was then added dropwise. After stirring at −78 °C for 1.5 h, water was added to the reaction mixture. The resultant solution was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **91g** (7.30 g, 16.8 mmol, 90%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.43 (m, 2H), 7.38-30 (m, 3H), 5.28 (s, 2H), 3.88 (m, 1H), 3.77-3.64 (m, 3H), 2.63 (m, 1H), 2.19 (m, 1H), 2.05 (m, 1H), 1.91-1.80 (m, 2H), 1.60-1.49 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 154.2, 135.5, 128.5, 128.2, 128.0, 68.4, 60.6, 45.7, 40.3, 33.8, 26.0, 25.9, 21.7, 18.3, −5.3, −5.4; IR (ATR) 2953, 2857, 1772, 1714, 1253, 1169 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{34}NO_4Si$ 392.2257; Found: 392.2266.



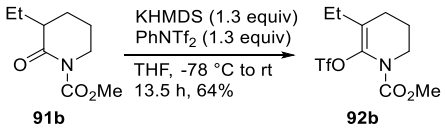
Compound 91h: To a solution of 2-piperidone (20.0 g, 202 mmol) in THF (500 mL) was added *n*BuLi (1.6 M

hexane solution, 152 mL, 244 mmol) dropwise at 0 °C, and the solution was stirred at the same temperature for 30 min. $ClCO_2Et$ (20.0 mL, 212 mmol) was then added at −78 °C, and the resultant solution was warmed to room temperature. After stirring at room temperature for 50 min, aq. NH_4Cl was added to the reaction mixture. The resultant mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **91h** (17.7 g, 103 mmol, 51%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (q, 2H, *J* = 7.1 Hz), 3.72 (m, 2H), 2.54 (t, 2H, *J* = 6.2 Hz), 1.84 (m, 4H), 1.35 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 153.8, 62.6, 46.1, 34.5, 22.3, 20.0, 13.9; IR (ATR) 2958, 1770, 1712, 1235, 1090 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}NO_3Na$ 172.0974; Found: 172.0976.



91a **92a**

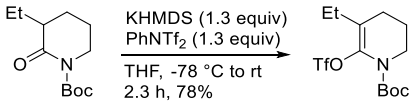
Compound 92a: To a solution of KHMDS (0.5 M toluene solution, 47.0 mL, 23.5 mmol) in THF (75 mL) was added a solution of **91a** (4.90 g, 18.8. mmol) in THF (15 mL) dropwise at −78 °C. The solution was stirred at the same temperature for 2 h. A solution of $PhNTf_2$ (5.10 g, 23.5 mmol) in THF (25 mL) was then added dropwise via cannula and the resultant solution was warmed to room temperature. After stirring at room temperature for 5 h, the solution was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 15:1) to afford **92a** (4.86 g, 12.4 mmol, 66%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.22 (s, 2H), 3.65 (t, 2H, *J* = 5.3 Hz), 2.28-2.24 (m, 4H), 1.82 (tt, 2H, *J* = 6.5, 5.5 Hz), 1.10 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 135.3, 134.0, 128.4, 128.2, 128.0, 123.2, 118.2 (q, *J* = 318 Hz), 68.2, 46.1, 25.2, 23.14, 23.09, 11.9; IR (ATR) 2976, 2920, 1725, 1414, 1390 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{18}NO_5F_3Na$ 416.0750; Found: 416.0737.



91b **92b**

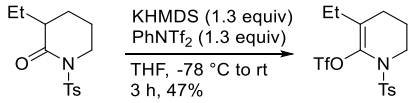
Compound 92b: To a solution of KHMDS (0.5 M toluene solution, 67.0 mL, 33.5 mmol) in THF (100 mL) was added a solution of **91b** (4.96 g, 26.8. mmol) in THF (20 mL) dropwise at −78 °C. The solution was stirred at the same temperature for 2 h. A solution of $PhNTf_2$ (7.31 g, 33.5 mmol) in THF (20 mL) was then added dropwise via cannula and the resultant solution was warmed to room temperature. After stirring at room temperature for 13.5 h, the solution was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **92b** (5.40 g, 17.0 mmol, 64%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.61 (t, 2H, *J* = 5.6 Hz), 2.26-2.21 (m, 4H), 1.83-1.78 (m, 2H), 1.08 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 133.9, 122.8, 118.2 (q, *J* = 320 Hz), 53.2, 45.9, 25.2, 23.1, 23.0, 11.8; IR (ATR) 2957, 1730, 1692, 1414, 1208, 1088

cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{10}H_{15}F_3NO_5S$ 318.0623; Found: 318.0630.



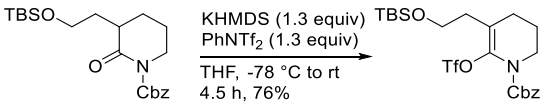
91c **92c**

Compound 92c: To a solution of KHMDS (0.5 M toluene solution, 18.7 mL, 9.36 mmol) in THF (75 mL) was added a solution of **91c** (1.70 g, 7.49 mmol) in THF (10 mL) dropwise at −78 °C. The solution was stirred at the same temperature for 2 h. A solution of $PhNTf_2$ (3.34 g, 9.36 mmol) in THF (10 mL) was then added dropwise via cannula and the resultant solution was warmed to room temperature. After stirring at room temperature for 15 min, the solution was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to afford **92c** (2.11 g, 5.88 mmol, 78%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53 (br, 2H), 2.24-2.20 (m, 4H), 1.79-1.75 (m, 2H), 1.47 (s, 9H), 1.08 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 134.9, 122.2, 118.25 (q, *J* = 318 Hz) , 82.3, 45.8, 27.9, 25.5, 23.22, 23.19, 12.1; IR (ATR) 2942, 2879, 1717, 1415, 1362, 1205, 1156, 1138 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{21}F_3NO_5S$ 360.1093; Found: 360.1091.



91d **92d**

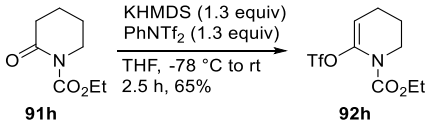
Compound 92d: To a solution of KHMDS (0.5 M toluene solution, 12.8 mL, 6.40 mmol) in THF (30 mL) was added a solution of **91d** (1.52 g, 5.10. mmol) in THF (10 mL) dropwise at −78 °C. The solution was stirred at the same temperature for 2 h. $PhNTf_2$ (2.29 g, 6.40 mmol) in THF (10 mL) was then added dropwise via cannula and the resultant solution was warmed to room temperature. After stirring at room temperature for 1 h, the solution was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **92d** (1.04 g, 2.39 mmol, 47%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* = 7.7 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 3.56 (t, 2H, *J* = 5.9 Hz), 2.45 (s, 3H), 2.23 (q, 2H, *J* = 7.4 Hz), 1.93 (t, 2H, *J* = 6.7 Hz), 1.39-1.34 (m, 2H), 1.03 (t, 3H, *J* = 7.4 Hz), 0.88 (t, 2H, *J* = 6.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 135.0, 133.5, 129.8, 129.3, 128.0, 118.2 (*J* = 320 Hz), 48.0, 24.7, 24.0, 21.6, 19.9, 12.0; IR (ATR) 2943, 2879, 1711, 1691, 1412, 1367, 1203, 1167 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{19}F_3NO_5S_2$ 414.0657; Found: 414.0663.



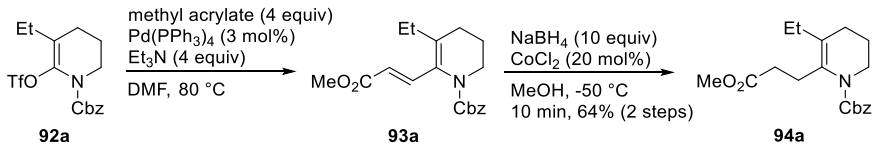
91g **92g**

Compound 92g: To a solution of KHMDS (0.5 M toluene solution, 46.6 mL, 23.3 mmol) in THF (93 mL) was added a solution of **91g** (7.30 g, 18.6. mmol) in THF (30 mL) dropwise at −78 °C. The solution was stirred at the same temperature for 2 h. $PhNTf_2$ (5.10 g, 23.4 mmol) in THF (30 mL) was then added dropwise via cannula and

the resultant solution was warmed to room temperature. After stirring at room temperature for 2.5 h, the solution was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to afford **92g** (7.40 g, 14.1 mmol, 76%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.32 (m, 5H), 5.18 (s, 2H), 3.73 (t, 2H, *J* = 6.3 Hz), 3.62 (t, 2H, *J* = 5.7 Hz), 2.40 (t, 2H, *J* = 6.6 Hz), 2.31 (t, 2H, *J* = 6.9 Hz), 1.80-1.75 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 135.3, 128.5, 128.3, 128.1, 120.1, 118.2 (q, *J* = 320 Hz), 68.4, 61.2, 46.1, 33.6, 27.0, 25.8, 23.3, 18.2, −5.5; IR (ATR) 2954, 2858, 1729, 1695, 1415, 1252, 1208 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{33}F_3NO_6SSi$ 524.1750; Found: 524.1755.

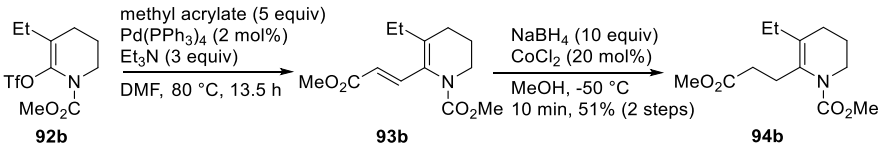


Compound 92h: To a solution of KHMDS (0.5 M toluene solution, 73.0 mL, 36.5 mmol) in THF (90 mL) was added a solution of **91h** (5.00 g, 29.2 mmol) in THF (20 mL) dropwise at −78 °C. The solution was stirred at the same temperature. for 2 h A solution of $PhNTf_2$ (8.00 g, 36.5 mmol) in THF (20 mL) was then added dropwise via cannula and the resultant solution was warmed to room temperature. After stirring at room temperature for 20 min, the solution was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to afford **92h** (5.80 g, 19.1 mmol, 65%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (t, 1H, *J* = 3.9 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 3.67 (t, 2H, *J* = 5.4 Hz), 2.28 (td, 2H, *J* = 6.7, 3.9 Hz), 1.81-1.77 (m, 2H), 1.31 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 139.7, 118.3 (*J* = 320 Hz), 107.1 , 62.8, 45., 22.2, 21.9, 14.0; IR (ATR) 2941, 1727, 1682, 1420, 1375, 1205, 1138 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_9H_{13}F_3NO_5S$ 304.0467; Found: 304.0463.

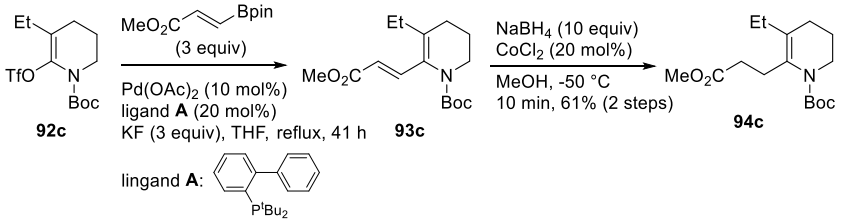


Compound 94a: To a solution of **92a** (1.82 g, 4.63 mmol) in DMF (14 mL) was added methyl acrylate (1.24 mL, 13.9 mmol), Et_3N (1.90 mL, 13.9 mmol) and $Pd(PPh_3)_4$ (104 mg, 0.0926 mmol). The solution was stirred at 80 °C for 20 h. The reaction mixture was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to afford **93a** as a colorless oil (1.26 g, 3.83 mmol, 83%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, 1H *J* = 15.5 Hz), 7.30 (m, 5H), 5.77 (d, 1H, *J* = 15.5 Hz), 5.10 (s, 2H), 3.71 (s, 3H), 3.53 (t, 2H, *J* = 5.7 Hz), 2.30-2.22 (m, 4H), 1.83 (tt, 2H, *J* = 6.5, 5.5 Hz), 1.06 (t, 3H, 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 154.9, 141.2, 137.3,

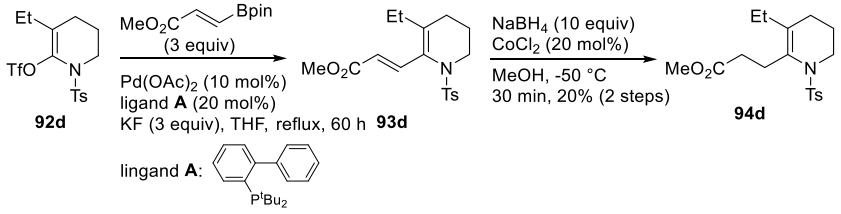
136.0 ,131.4, 128.2, 127.9, 127.8, 117.1, 67.3, 51.2, 44.3, 27.6, 25.7, 23.5, 13.5; IR (ATR) 2949, 2879, 1708, 1630, 1393, 1308, 1252, 1170 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Ccalcd for $C_{19}H_{24}NO_4$ 330.1700; Found: 390.1690. To a solution of the above **93a** (1.08 g, 3.29 mmol) in MeOH (30 mL) was added $NaBH_4$ (1.24 g, 32.9 mmol) at −50 °C. The resultant solution was stirred at the same temperature for 15 min. $CoCl_2$ (85.0 mg, 0.670 mmol) was added, and the resultant solution was then stirred at −50 °C for 10 min. At the same temperature, aq. NH_4Cl was added to the reaction mixture. The resultant solution was extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **94b** (843 mg, 2.60 mmol, 64% for 2 steps) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 5.14 (s, 2H), 3.61 (s, 3H), 3.48 (t, 2H, *J* = 5.7 Hz), 2.34 (br, 2H), 2.37 (t, 2H, *J* = 6.9 Hz), 2.08-2.04 (m, 4H), 1.76 (tt, 2H, *J* = 6.5, 6.0 Hz), 1.00 (t, 3H, 7.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 154.5, 136.3, 131.9, 128.3, 128.2, 127.9, 127.8, 67.0, 51.2, 44.9, 32.4, 26.4, 25.4, 23.8, 13.9; IR (ATR) 2949, 2876, 1737, 1698, 1397, 1254, 1185 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{25}NO_4Na$ 354.1676; Found: 354.1659.



Compound 94b: To a solution of **92b** (4.83 g, 15.2 mmol) in DMF (45 mL) was added methyl acrylate (6.80 mL, 76.1 mmol), Et_3N (6.30 mL, 45.6 mmol) and $Pd(PPh_3)_4$ (351 mg, 0.300 mmol). The solution was stirred at 80 °C for 13.5 h. The reaction mixture was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by a short pad of silica gel (hexane/EtOAc = 5:1) to give crude **93b** (2.20 g) as a colorless oil. To a solution of the above crude **93b** (2.20 g) in MeOH (23 mL) was added $NaBH_4$ (1.46 g, 38.7 mmol) at −50 °C. The resultant solution was stirred at the same temperature for 15 min. $CoCl_2$ (50.0 mg, 0.387 mmol) was added, and the resultant solution was then stirred at −50 °C for 10 min. At the same temperature, aq. NH_4Cl was added to the reaction mixture. The resultant solution was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **94b** (1.66 g, 6.50 mmol, 51% for 2 steps) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.65 (s, 3H), 3.44 (t, 2H, *J* = 5.6 Hz), 2.83 (t, 2H, *J* = 7.3 Hz), 2.41 (t, 2H, *J* = 7.6 Hz), 2.08-2.04 (m, 4H), 1.79-1.74 (m, 2H), 1.01 (t, 3H, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 155.2, 132.0, 127.8, 52.4, 51.3, 44.9, 32.5, 26.4, 25.3, 25.1, 23.8, 13.1; IR (ATR) 2952, 2875, 1737, 1701, 1440, 1376, 1255, 1191 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{22}NO_4$ 256.1549; Found: 256.1551.

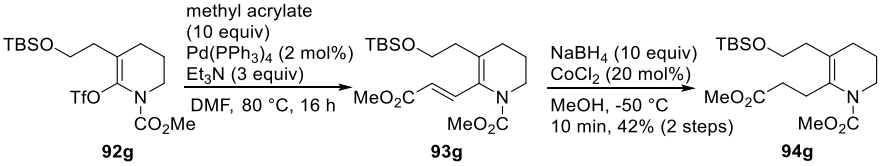


Compound 94c: A solution of $Pd(OAc)_2$ (26.5 mg, 0.118 mmol) and 2-(di-tert-butylphosphino)biphenyl **A** (70.4 mg, 0.236 mmol) in THF (8.0 mL) was stirred at room temperature for 10 min. A solution of **92c** (426 mg, 1.18 mmol) and methyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (3.55 mmol, prepared from methyl propionate and bis(pinacolato)diboron by following Yun's procedure[77]) in THF (4.0 mL), and KF (206 mg, 3.55 mmol) were added to the pre-mixed solution. The solution was refluxed for 41 h. The reaction mixture was diluted with Et_2O. The organic layer was washed with water and brine and dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by a short pad of silica gel (hexane/EtOAc = 10:1) to give crude **93c** (350 mg) as a yellow oil. To a solution of the above crude **93c** (350 mg) in MeOH (30 mL) was added $NaBH_4$ (449 mg, 11.9 mmol) at −50 °C. The resultant solution was stirred for 5 min at the same temperature. $CoCl_2$ (30.9 mg, 0.238 mmol) was added, and the resultant solution was then stirred at −50 °C for 30 min. At the same temperature, aq. NH_4Cl was added to the reaction mixture. The resultant solution was extracted with $CHCl_3$. The combined organic layers were washed with brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **94c** (215 mg, 0.723 mmol, 61% for 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.39 (t, 2H, *J* = 5.8 Hz), 2.84 (t, 2H, *J* = 7.8 Hz), 2.39 (t, 2H, *J* = 7.8 Hz), 2.10-2.02 (m, 4H), 1.81-1.73 (m, 2H), 1.48 (s, 9H), 1.01 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 153.9, 132.2, 127.0, 79.9, 51.2, 44.7, 32.2, 28.1, 26.6, 25.4, 25.1, 23.9, 13.1; IR (ATR) 2937, 2874, 1740, 1697, 1366, 1156 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{28}NO_4$ 298.2013; Found: 298.2018.

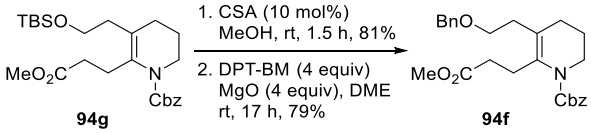


Compound 94d: A solution of $Pd(OAc)_2$ (17.2 mg, 0.0768 mmol) and 2-(di-*tert*-butylphosphino)biphenyl (45.8 mg, 0.154 mmol) in THF (4.0 mL) was stirred at room temperature for 10 min. A solution of **92d** (317 mg, 0.768 mmol) and methyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (2.30 mmol, prepared from methyl propionate and bis(pinacolato)diboron by following Yun's procedure[77]) in THF (2.0 mL), and KF (134 mg, 2.30 mmol) were added to the pre-mixed solution. The solution was refluxed for 60 h. The reaction mixture was diluted with Et_2O. The organic layer was washed with water and brine and dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by a short pad of silica gel (hexane/EtOAc = 10:1) to give crude **93d** (159 mg) as a yellow oil. To a solution of the above crude **93d** (159 mg) in MeOH (10 mL) was added $NaBH_4$ (175 mg, 4.62 mmol) at −50 °C. The resultant solution was stirred at

the same temperature for 10 min. $CoCl_2$ (12.0 mg, 0.0924 mmol) was added, and the resultant solution was then stirred at −50 °C for 30 min. Then aq. NH_4Cl was added to the reaction mixture. The resultant solution was extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **94d** (53.3 mg, 0.152 mmol, 20% for 2 steps) as a colorless oil:^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.0 Hz), 3.65 (s, 3H), 3.45 (t, 2H, *J* = 6.0 Hz), 2.95 (t, 2H, *J* = 7.4 Hz), 2.57 (t, 2H, *J* = 7.4 Hz), 2.42 (s, 3H), 2.05 (d, 2H, *J* = 7.4 Hz), 1.69 (t, 2H, *J* = 7.0 Hz), 1.39-1.34 (m, 2H), 0.95 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 143.2, 137.1, 132.2, 130.9, 129.3, 127.1, 51.4, 46.7, 32.4, 26.4, 26.3, 25.8, 21.4, 21.0, 13.2; IR (ATR) 2961, 1736, 1337, 1236, 1160 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{26}NO_4S$ 352.1583; Found: 352.1588.

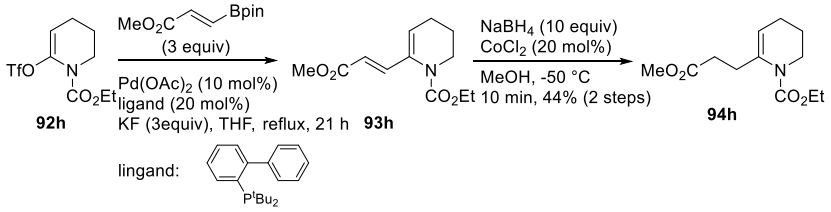


Compound 94g: To a solution of **92g** (7.40 g, 14.1 mmol) in DMF (47 mL) was added methyl acrylate (12.7 mL, 141 mmol), Et_3N (5.90 mL, 42.3 mmol) and $Pd(PPh_3)_4$ (326 mg, 0.282 mmol). The solution was stirred at 80 °C for 16 h. The reaction mixture was diluted with Et_2O, and water was added for quenching the reaction. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by a short pad of silica gel (hexane/EtOAc = 10:1) to give crude **93g** (6.30 g) as a colorless oil. To a solution of the above crude **93g** (6.30 g) in MeOH (137 mL) was added $NaBH_4$ (5.20 g, 137 mmol) at −50 °C. The resultant solution was stirred for at the same temperature 15 min. $CoCl_2$ (356 mg, 2.74 mmol) was added, and the resultant solution was then stirred at −50 °C for 10 min. At the same temperature, aq. NH_4Cl was added to the reaction mixture. The resultant solution was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **94g** (2.76 g, 6.00 mmol, 42% for 2 steps) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.24 (m, 5H), 5.11 (s, 2H), 3.62-3.59 (m, 2H), 3.58 (s, 3H), 3.44 (t, 2H, *J* = 5.2 Hz), 2.81 (t, 2H, *J* = 6.6 Hz), 2.33 (t, 2H, *J* = 7.2 Hz), 2.24 (t, 2H, *J* = 6.9 Hz), 2.04 (t, 2H, *J* = 6.6 Hz), 1.72 (t, 2H, *J* = 5.6 Hz), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 154.6, 136.5, 134.2, 128.4, 128.4, 128.03, 128.00, 123.3, 67.3, 62.0, 51.4, 45.0, 36.1, 32.5, 28.0, 25.9, 24.0, 18.3, 14.1, −5.4; IR (ATR) 2951, 2857, 1738, 1703, 1398, 1254, 1088 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{40}NO_5Si$ 462.2676; Found: 462.2680.

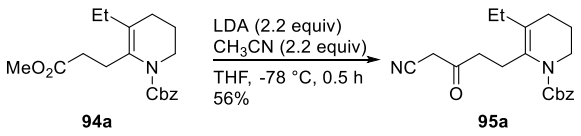


Compound 94f: To a solution of **94g** (129.4 mg, 0.280 mmol) in MeOH (2.8 mL) was added (−)-10-camphorsulfonic acid (6.5 mg, 0.0280 mmol) at room temperature. After the solution was stirred for 1.5 h, Et_3N

was added for quenching the reaction. The resultant mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:2) to afford an alcohol (79.3 mg, 0.228 mmol, 81%) as a colorless oil. To a solution of the above alcohol (21.4 mg, 0.0616 mmol) in DME (1.0 mL) were added 4-(4,6- diphenoxy-1,3,5-triazin-2-yl)-4-benzylmorholinium trifluoromethanesulfonate (DPT-BM)[21] (107 mg, 0.246 mmol) and MgO (10.0 mg, 0.246 mmol) at room temperature. The solution was stirred for 17 h. The solution was diluted with EtOAc and washed with aq. $NaHCO_3$. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) and GPC to afford **94f** (21.4 mg, 0.0489 mmol, 79%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 10H), 5.14 (s, 2H), 4.50 (s, 2H), 3.60 (s, 3H), 3.50 (t, 2H, *J* = 7.0 Hz), 3.47 (t, 2H, *J* = 6.0 Hz), 2.86 (t, 2H, *J* = 7.3 Hz), 2.38 (d, 2H, *J* = 7.5 Hz), 2.36 (d, 2H, *J* = 7.5 Hz), 2.07 (t, 2H, *J* = 6.9 Hz), 1.77-1.72 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 154.6, 138.3, 136.4, 134.3, 128.5, 128.4, 128.0, 127.7, 127.6, 127.4, 123.1, 72.9, 69.0, 67.3, 51.4, 45.1, 33.1, 32.4, 27.8, 25.3, 24.0; IR (ATR) 2921, 1730, 1420, 1257, 1210, 1089 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{32}NO_5$ 438.2280; Found: 438.2275.

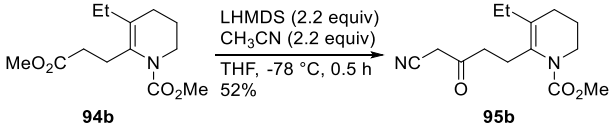


Compound 94h: A solution of $Pd(OAc)_2$ (57.3 mg, 0.255 mmol) and 2-(di-*tert*-butylphosphino)biphenyl (152 mg, 0.510 mmol) in THF (8.0 mL) was stirred at room temperature for 10 min. A solution of **92h** (773 mg, 2.55 mmol) and methyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (7.65 mmol, prepared from methyl propionate and bis(pinacolato)diboron by following Yun's procedure) in THF (4.0 mL), and KF (444 mg, 7.65 mmol) were added to the pre-mixed solution. The solution was refluxed for 21 h. The reaction mixture was diluted with Et_2O. The organic layer was washed with water and brine and dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by a short pad of silica gel (hexane/EtOAc = 5:1) to give crude **93f** (638 mg) as a yellow oil. To a solution of the above crude **93h** (638 mg) in MeOH (26 mL) was added $NaBH_4$ (1.01 g, 26.7 mmol) at −50 °C. The resultant solution was stirred at the same temperature for 10 min. $CoCl_2$ (69.3 mg, 0.534 mmol) was added, and the resultant solution was then stirred at −50 °C for 20 min. At the same temperature, aq. NH_4Cl was added to the reaction mixture. The resultant solution was extracted with $CHCl_3$. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **94f** (274 mg, 1.13 mmol, 44% for 2 steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (t, 1H, *J* = 3.3 Hz), 4.17 (q, 2H, *J* = 7.1 Hz), 3.66 (s, 3H), 3.56-3.54 (m, 2H), 2.84-2.81 (m, 2H), 2.43 (t, 2H, *J* = 7.6 Hz), 2.09-2.05 (m, 2H), 1.78-1.75 (m, 2H), 1.29 (t, 2H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 154.3, 138.1, 113.4, 61.5, 51.4, 44.9, 32.8, 30.7, 23.1, 22.8, 14.4; IR (ATR) 2950, 1738, 1703, 1402, 1378, 1339, 1090 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{20}NO_4$ 242.1392; Found: 242.1395.



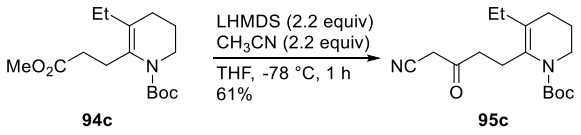
94a **95a**

Compound 95a: To a THF solution of LDA (4.31 mmol in THF (7.0 mL)), prepared from *i*Pr$_2$NH (0.634 mL, 4.51 mmol and *n*BuLi (1.6 M hexane solution, 2.70 mL, 4.31 mmol at −78 °C, was added CH_3CN (0.229 mL, 0.4.31 mmol) dropwise at −78 °C. After the solution was stirred at the same temperature for 30 min, **95a** (650 mg, 1.96 mmol) in THF (3.0 mL) was added dropwise via cannula. The solution was stirred for 15 min, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **95a** (497 mg, 1.46 mmol, 74%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 5H), 5.12 (s, 2H), 3.47 (t, 2H, *J* = 5.4 Hz), 3.26 (br, 2H), 2.74 (br, 2H), 2.58 (br, 2H), 2.06-1.99 (m, 4H), 1.76 (tt, 2H, *J* = 7.0, 5.5 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 154.4, 136.2, 130.9, 128.4, 128.1, 127.8, 113.8, 67.1, 44.9, 40.5, 31.4, 26.4, 25.3, 23.9, 23.7, 13.0; IR (ATR) 2961, 2872, 2257, 1731, 1695, 1399, 1189 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{24}N_2O_3Na$ 363.1679; Found: 363.1665.



94b **95b**

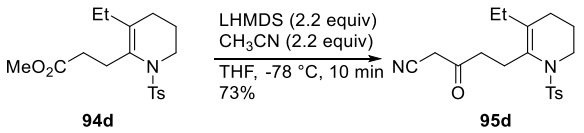
Compound 95b: To a solution of LHMDS (10.4 mL, 13.5 mmol, 1.3 M THF solution) in THF (20 mL) was added CH_3CN (0.718 mL, 13.5 mmol) dropwise at −78 °C. After the solution was stirred at the same temperature for 0.5 h, a solution of **94b** (1.38 g, 5.40 mmol) in THF (7.0 mL) was added dropwise via cannula. The solution was stirred for 0.5 h, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **95b** (745 mg, 2.82 mmol, 52%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.48 (s, 2H), 3.43 (t, *J* = 5.7 Hz, 2H), 2.82-2.79 (m, 2H), 2.76-2.73 (m, 2H), 2.08-2.01 (m, 4H), 1.79-1.74 (m, 2H), 1.01 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 155.2, 131.2, 127.9, 113.8, 52.6, 45.0, 40.7, 31.8, 26.4, 25.4, 23.9, 23.7, 13.1; IR (ATR) 2956, 2259, 1731, 1693, 1442, 1375, 1193 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}N_2O_3$ 265.1552; Found: 265.1552.



94c **95c**

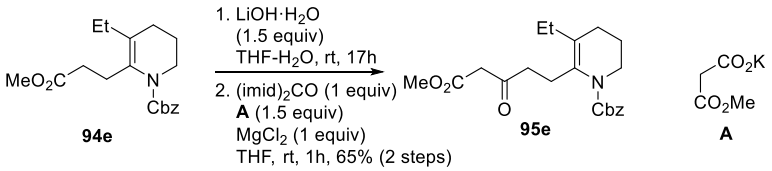
Compound 95c: To a solution of LHMDS (1.00 mL, 1.30 mmol, 1.3 M THF solution) in THF (2.5 mL) was added CH_3CN (0.070 mL, 1.32 mmol) dropwise at −78 °C. After the solution was stirred at the same temperature for 1.5 h, a solution of **94c** (157 mg, 0.528 mmol) in THF (2.0 mL) was added dropwise via cannula. The solution was stirred for 1 h, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **95c** (98.2 mg, 0.320 mmol, 61%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52 (s, 2H), 3.36 (t, 2H, *J* = 5.5 Hz), 2.81 (t, 2H, *J* = 7.0 Hz), 2.70 (t, 2H, *J* = 7.3 Hz), 2.07-2.01 (m, 4H), 1.77-1.72 (m, 2H), 1.47 (s, 9H), 1.01 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 154.1, 131.4, 127.4, 113.8, 80.2, 45.0, 40.5, 31.8, 28.2, 26.6, 25.5, 24.0, 23.8, 13.1; IR (ATR) 2969, 2259, 1695, 1367, 1088 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{27}N_2O_3$ 307.2022; Found: 307.2021.



94d **95d**

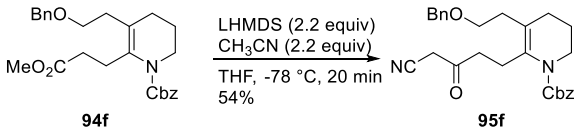
Compound 95d: To a solution of LHMDS (0.439 mL, 0.571 mmol, 1.3 M THF solution) in THF (1.0 mL) was added CH_3CN (0.030 mL, 0.571 mmol) dropwise at −78 °C. After the solution was stirred at the same temperature for 0.5 h, a solution of **94d** (80.3 mg, 0.228 mmol) in THF (2.0 mL) was added dropwise via cannula. The solution was stirred for 10 min, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **95d** (59.6 mg, 0.165 mmol, 73%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, 2H, *J* = 8.0 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), 3.59 (s, 2H), 3.43 (t, 2H, *J* = 5.9 Hz), 2.94 (t, 2H, *J* = 6.7 Hz) , 2.88 (t, 2H, *J* = 6.7 Hz), 2.43 (s, 3H), 2.04 (q, 2H, *J* = 7.4 Hz), 1.69 (t, 2H, *J* = 6.9 Hz), 1.31-1.26 (m, 2H), 0.95 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.5, 143.6, 136.5, 132.5, 129.9, 129.5, 127.2, 113.8, 46.8, 40.5, 32.0, 26.5, 26.0, 25.2, 21.5, 20.5, 13.2; IR (ATR) 2959, 2873, 2260, 1730, 1335, 1158 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{25}N_2O_3S$ 361.1586; Found: 361.1588.



94e **95e** **A**

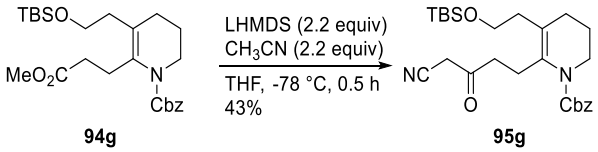
Compound 95e: To a solution of **94e** (300 mg, 0.905 mmol) in THF-H_2O (3:1, 10 mL) was added LiOH·H_2O (57.0 mg, 1.36 mmol) at room temperature. After stirring for 24 h, additional LiOH·H_2O (28.5 mg, 0.679 mmol) was added and the solution was stirred for 17 h. After addition of aq. HCl, the mixture was extracted with $CHCl_3$, dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was dissolved in THF (3 ml). To the solution was added 1,1'-carbonyldiimidazole (152 mg, 0.941 mmol) at room temperature. The solution was stirred at the same temperature for 1 h. $MgCl_2$ (83.0 mg, 0.869 mmol) and monomethyl potassium malonate (202 mg, 1.36 mmol) were then added at room temperature. After the solution was stirred at the same temperature for 28 h, the solution was diluted with EtOAc and washed with aq. $NaHSO_4$ and brine. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **95e** (220 mg, 0.589 mmol, 65%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 5.14 (s, 2H), 3.71 (s, 3H), 3.47 (t, 2H, *J* = 5.7 Hz), 3.32 (brs, 2H), 2.76 (br, 2H) 2.57 (br, 2H), 2.06-2.01 (m, 4H), 1.79-1.74 (m, 2H), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 202.1, 167.5, 154.5, 136.3, 131.6, 128.42, 128.36, 128.0, 127.7, 67.1, 52.1, 48.6, 45.0, 41.3, 26.5, 25.4, 23.9, 23.8, 13.1; IR (ATR) 2952, 2873, 1747, 1699, 1398, 1254 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{28}NO_5$ 374.1967; Found: 374.1972.



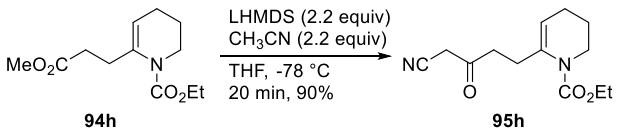
94f **95f**

Compound **95f**: To a solution of LHMDS (1.38 mL, 1.79 mmol, 1.3 M THF solution) in THF (5.0 mL) was added CH_3CN (0.095 mL, 1.79 mmol) dropwise at −78 °C. After the solution was stirred at the same temperature for 0.5 h, a solution of **94f** (313 mg, 0.715 mmol) in THF (2.0 mL) was added dropwise via cannula. The solution was stirred for 20 min, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **95f** (173 mg, 0.387 mmol, 54%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 5.11 (s, 2H), 4.46 (s, 2H), 3.52 (t, 2H, *J* = 6.6 Hz), 3.48 (m, 2H), 3.03 (brs, 2H), 2.75 (t, 2H, *J* = 7.0 Hz), 2.51 (br, 2H), 2.33 (t, 2H, *J* = 6.6 Hz), 2.05 (t, 2H, *J* = 6.9 Hz), 1.78-1.73 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.0, 154.3, 138.1, 136.1, 133.4, 128.5, 128.24, 128.16, 128.1, 127.6, 127.5, 123.0, 113.7, 72.8, 68.4, 67.2, 44.9, 40.5, 32.9, 31.3, 27.2, 23.9, 23.6; IR (ATR) 2944, 2259, 1729, 1693, 1397, 1357, 1188, 1083 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{31}N_2O_4$ 447.2284; Found: 447.2282.



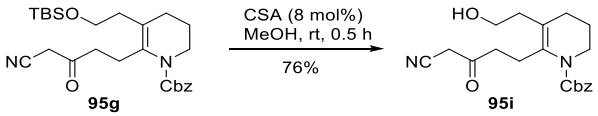
94g **95g**

Compound 95g: To a solution of LHMDS (3.50 mL, 4.58 mmol, 1.3 M THF solution) in THF (15 mL) was added CH_3CN (0.244 mL, 4.58 mmol) dropwise at −78 °C. After the solution was stirred at the same temperature for 1 h, a solution of **94g** (845 mg, 1.83 mmol) in THF (6.0 mL) was added dropwise via cannula. The solution was stirred for 30 min, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **95g** (366 mg, 0.778 mmol, 43%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 5.13 (s, 2H), 3.65 (t, 2H, *J* = 6.9 Hz), 3.48 (t, 2H, *J* = 5.4 Hz), 3.21 (s, 2H), 2.77 (t, 2H, *J* = 6.9 Hz), 2.59 (br, 2H), 2.24 (t, 2H, *J* = 6.9 Hz), 2.08 (t, 2H, *J* = 6.6 Hz), 1.79-1.74 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 154.5, 136.3, 133.2, 128.7, 128.33, 123.29, 113.6, 67.4, 61.7, 45.5, 40.6, 36.0, 31.6, 27.8, 25.9, 24.3, 23.8, 18.3, -5.4; IR (ATR) 2952, 2857, 2257, 1733, 1698, 1398, 1253, 1081 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{39}N_2O_4Si$ 471.2679; Found: 471.2682.



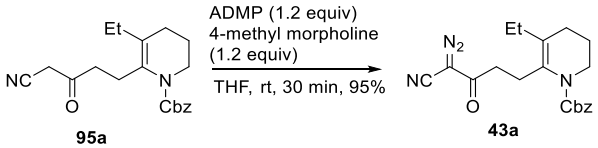
94h 95h

Compound 95h: To a solution of LHMDS (0.549 mL, 0.714 mmol, 1.3 M THF solution) in THF (3.0 mL) was added CH_3CN (0.038 mL, 0.714 mmol) dropwise at −78 °C. After the solution was stirred at the same temperature for 0.5 h, a solution of **94h** (119 mg, 0.286 mmol) in THF (2.0 mL) was added dropwise via cannula. The solution was stirred for 20 min, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to afford **95h** (64.5 mg, 0.258 mmol, 90%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (t, 1H, *J* = 3.6 Hz), 4.15 (q, 2H, *J* = 7.1 Hz), 3.54-3.56 (m, 2H), 3.52 (s, 2H), 2.82 (t, 2H, *J* = 7.2 Hz), 2.73 (t, 2H, *J* = 7.0 Hz), 2.09-2.06 (m, 2H), 1.78-1.74 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 154.1, 137.3, 113.8, 113.7, 61.6, 44.9, 41.0, 31.8, 29.2, 22.9, 22.7, 14.4; IR (ATR) 2940, 2259, 1727, 1693, 1403, 1377, 1252, 1194 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{19}N_2O_3$ 251.1396; Found: 251.1393.



95g 95i

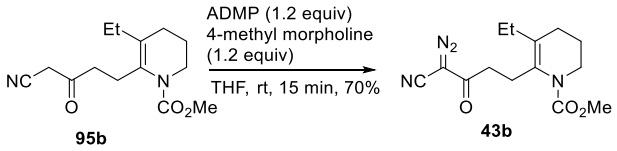
Compound 95i: To a solution of **95g** (29.5 mg, 0.0827 mmol) in MeOH (1 mL) was added (-)-10-camphorsulfonic acid (1.5 mg, 0.0063 mmol) at room temperature. After the solution was stirred for 30 min, Et_3N was added for quenching the reaction. The resultant mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:2) to afford **95i** (16.9 mg, 76%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.34 (m, 5H), 5.14 (s, 2H), 3.71 (t, 2H, *J* = 6.3 Hz), 3.46 (t, 2H, *J* = 5.7 Hz), 3.26 (s, 2H), 2.86 (br, 2H), 2.61 (br, 2H), 2.32 (t, 2H, *J* = 6.3 Hz), 2.09 (d, 2H, *J* = 7.0 Hz), 1.81-1.76 (m, 2H), 1.71 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 154.6, 136.2, 133.8, 128.7, 128.4, 123.1, 113.6, 67.5, 60.8, 45.1, 39.9, 35.7, 31.8, 29.7, 27.2, 24.2, 23.7; IR (ATR) 3453, 2921, 2260, 1696, 1402, 1236, 1089 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O_4$ 357.1814; Found: 357.1809.



95a 43a

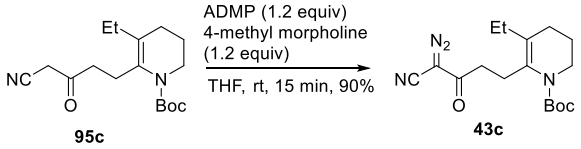
Compound **43a**: To a solution of **95a** (1.07 g, 3.14 mmol) in THF (31 mL) were added 4-methylmorpholine (0.414 mL, 3.77 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (1.06 g, 3.77 mmol) at room temperature. After the solution was stirred for 30 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **43a** (944 mg, 2.58 mmol, 82%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 5.14 (s, 2H), 3.49 (t, 2H, *J* = 6.0 Hz), 2.87 (t, 2H, *J* = 7.5

Hz), 2.68 (t, 2H, J = 7.0 Hz), 2.08-2.00 (m, 4H), 1.77 (tt, 2H, J = 6.5, 6.0 Hz), 1.00 (t, 3H, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.5, 154.6, 136.3, 131.2, 128.5, 128.2, 128.1, 128.0, 108.3, 67.3, 56.9, 45.1, 37.9, 26.6, 25.5, 24.5, 23.8, 13.2; IR (ATR) 3032, 2937, 2874, 2221, 2125, 1696, 1497, 1455, 1397, 1356, 1337, 1254, 1183, 1120, 1023 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_4O_3Na$ 389.1584; Found: 389.1598;



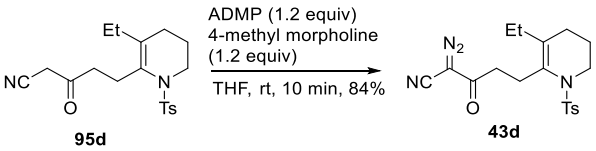
95b 43b

Compound 43b: To a solution of **95b** (122 mg, 0.463 mmol) in THF (4.6 mL) were added 4-methylmorpholine (0.061 mL, 0.555 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (158 mg, 0.555 mmol) at room temperature. After the solution was stirred for 15 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **43b** (106.3 mg, 0.366 mmol, 79%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.46 (t, 2H, J = 5.5 Hz), 2.90 (t, 2H, J = 7.5 Hz), 2.72 (t, 2H, J = 7.3 Hz), 2.08-2.03 (m, 4H), 1.77 (tt, 2H, J = 7.0, 6.0 Hz), 1.01 (t, 3H, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.7, 155.2, 131.2, 128.1, 108.3, 57.0, 52.6, 45.0, 37.9, 26.5, 25.4, 24.5, 23.7, 13.2; IR (ATR) 2956, 2221, 2127, 1698, 1440, 1276, 1292, 1256, 1236, 1186, 1088 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{18}N_4O_3Na$ 313.1271; Found: 313.1264.

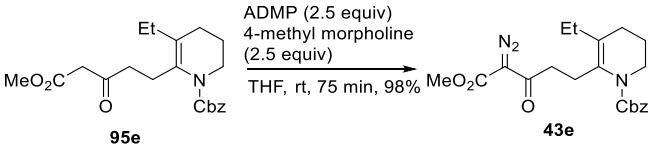


95c 43c

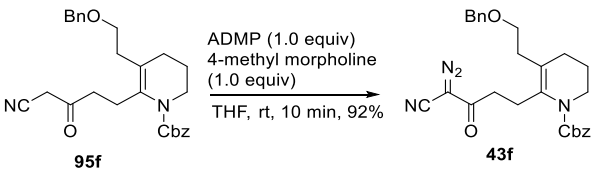
Compound 43c: To a solution of **95c** (19.4 mg, 0.0633 mmol) in THF (1 mL) were added 4-methylmorpholine (8.4 μL, 0.076 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (1.06 g, 3.77 mmol) at room temperature. After the solution was stirred for 15 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **43c** (18.8 mg, 0.0566 mmol, 90%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39 (t, 2H, J = 5.8 Hz), 2.89 (t, 2H, J = 7.3 Hz), 2.72 (t, 2H, J = 7.5 Hz), 2.07-2.03 (m, 4H), 1.75 (tt, 2H, J = 6.0, 5.8 Hz), 1.48 (s, 9H), 1.01 (t, 3H, J = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8, 154.2, 131.9, 127.6, 108.4, 80.4, 45.1, 37.1, 28.3, 26.8, 25.6, 24.7, 24.0 13.3; IR (ATR) 2979, 2920, 1729, 1469, 1382, 1236, 1089, 889 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{25}N_4O_3$ 333.1921; Found: 333.1910.



Compound 43d: To a solution of **95d** (15.4 mg, 0.0427 mmol) in THF (1 mL) were added 4-methylmorpholine (5.6 μL, 0.051 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (14.6 mg, 0.0512 mmol) at room temperature. After the solution was stirred for 10 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **43d** (13.9 mg, 0.0360 mmol, 84%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, 2H, *J* = 8.5 Hz), 7.27 (d, 2H, *J* = 7.5 Hz), 3.47 (t, 2H, *J* = 6.0 Hz), 3.01 (t, 2H, *J* = 7.3 Hz), 2.88 (t, 2H, *J* = 7.3 Hz), 2.43 (s, 3H), 2.03 (q, 2H, *J* =7.5 Hz), 1.72 (t, 2H, *J* = 6.8 Hz), 1.36 (tt, 2H, *J* = 6.4 Hz), 0.95 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8, 143.4, 136.9, 132.4,130.2, 129.5, 127.3, 108.4, 57.1, 46.7, 37.9, 26.5, 26.0, 25.5, 21.5, 20.8, 13.3; IR (ATR) 2962, 2930, 2873, 2222, 2127, 1673, 1592, 1455, 1336, 1301, 1184, 1159, 1088, 881, 815 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}N_4O_3S$ 388.1564; Found: 388.1548.

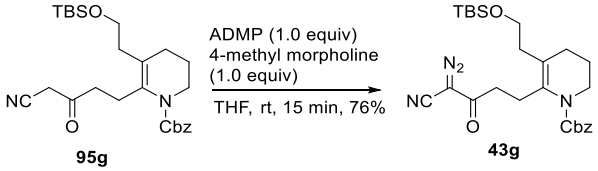


Compound 43e: To a solution of **95e** (95.5 mg, 0.266 mmol) in THF (2.7 mL) were added 4-methylmorpholine (0.0725 mL, 0.659 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (190 mg, 0.659 mmol) at room temperature. After the solution was stirred for 75 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **43e** (104.4 mg, 0.261 mmol, 98%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 5.13 (s, 2H), 3.80 (s, 3H), 3.49 (t, 2H, *J* = 5.5 Hz), 2.91 (br, 2H), 2.82 (br, 2H), 2.06-2.01 (m, 4H), 1.77 (tt, 2H, *J* = 6.8, 5.5 Hz), 1.00 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.9, 161.5, 154.6, 136.4, 132.0, 128.3, 128.0, 127.8, 127.7, 75.4, 67.1, 52.0, 45.0, 38.7, 26.5, 25.4, 24.4, 23.9, 13.2; IR (ATR) 2960, 2929, 2134, 1702, 1655, 1437, 1398, 1318, 1253, 1192, 1088 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{25}N_3O_5Na$ 422.1686; Found: 422.1690.

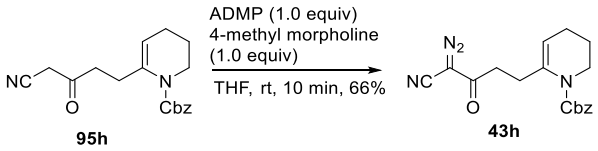


Compound 43f: To a solution of **95f** (23.8 mg, 0.0533 mmol) in THF (1 mL) were added 4-methylmorpholine (5.9 μL, 0.053 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (15.2 g, 0.0533

mmol) at room temperature. After the solution was stirred for 10 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **43f** (23.1 mg, 0.0679 mmol, 92%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.23 (m, 10H), 5.14 (s, 2H), 4.50 (s, 2H), 3.52-3.49 (m, 4H), 2.89 (br, 2H), 2.66 (br, 2H), 2.35 (t, 2H, *J* = 6.5 Hz), 2.07 (t, 2H, *J* = 6.5 Hz), 1.76 (t, 2H, *J* = 5.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.4, 154.5, 138.2, 136.2, 133.6, 128.5, 128.3, 128.2, 128.1, 127.6, 127.5, 123.3, 108.3, 72.9, 68.6 , 67.4, 56.1, 45.1, 37.9, 33.1, 27.6, 24.6, 23.8; IR (ATR) 2919, 2856, 2222, 2125, 1698, 1455, 1397, 1356, 1256, 1186, 1087, 4154, 890 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{29}N_4O_4$ 473.2183; Found: 473.2190.

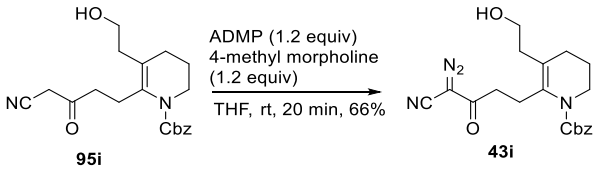


Compound 43g: To a solution of **95g** (37.8 mg, 0.0803 mmol) in THF (1 mL) were added 4-methylmorpholine (8.8 μL, 0.080 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (22.9 mg, 0.0803 mmol) at room temperature. After the solution was stirred for 15 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **43g** (30.2 mg, 0.0608 mmol, 76%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.33 (m, 5H), 5.14 (s, 2H), 3.64 (t, 2H, *J* = 7 Hz), 3.50 (t, 2H, *J* = 5.5 Hz), 2.90 (br, 2H), 2.67 (br, 2H), 2.26 (t, 2H, *J* = 7.0 Hz), 2.09 (t, 2H, *J* = 6.8 Hz), 1.77 (t, 2H, *J* = 5.5 Hz), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.4, 154.5, 136.2, 133.3, 128.5, 128.2, 128.1, 123.4, 108.3, 67.4, 61.9, 56.9, 45.1, 37.8, 36.1, 27.9, 25.9, 24.7, 23.9, 18.3, −5.4; IR (ATR) 2948, 2928, 2860, 2222, 2126, 1701, 1466, 1397, 1357, 1254, 1186, 1089, 892 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{36}N_4O_4SiNa$ 519.2398; Found: 519.2386.

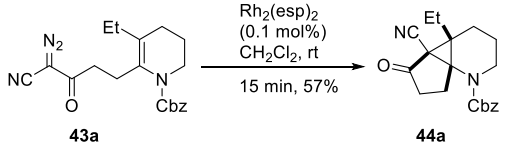


Compound 43h: To a solution of **95h** (25.9 mg, 0.103 mmol) in THF (1 mL) were added 4-methylmorpholine (0.011 mL, 0.10 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (29.5 mg, 0.103 mmol) at room temperature. After the solution was stirred for 10 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **43h** (18.8 mg, 0.0680 mmol, 66%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (t, 1H, *J* = 3.5 Hz), 4.17 (q, 2H, *J* = 4.2 Hz), 3.57 (t, 2H, *J* = 5.8 Hz), 2.90 (t, 2H, *J* = 7.0 Hz), 2.75 (t, 2H, *J* = 7.5 Hz), 2.08 (t, 2H, *J* = 1.8 Hz), 1.76 (tt, 2H, *J* = 6.5, 5.3 Hz), 1.29 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6, 154.2, 137.4, 113.9, 108.4, 61.7, 57.2, 45.0, 38.2, 30.0,

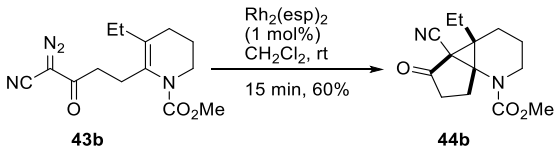
23.0, 22.9, 14.5; IR (ATR) 2981, 2921, 2223, 2129, 1699, 1402, 1380, 1339, 1236, 1194, 1089, 893 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{17}N_4O_3$ 277.1295; Found: 277.1285.



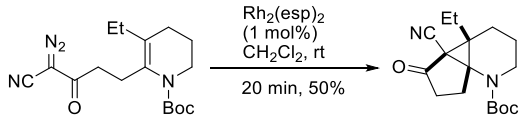
Compound 43i: To a solution of **95i** (25.2 mg, 0.0707 mmol) in THF (1 mL) were added 4-methylmorpholine (9.3 μL, 0.085 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (24.2 mg, 0.0848 mmol) at room temperature. After the solution was stirred for 20 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:2) to afford **43i** (56.1 mg, 0.147 mmol, 66%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.34 (m, 5H), 5.17 (s, 2H), 3.71 (t, 2H, *J* = 6.0 Hz), 3.49 (t, 2H, *J* = 5.8 Hz), 2.98 (br, 2H), 2.77 (br, 2H), 2.35 (m, 3H), 2.11 (t, 2H, *J* = 6.9 Hz), 1.80 (tt, 2H, *J* = 6.9, 5.4 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.1, 154.6, 136.3, 134.0, 128.6, 128.2, 123.3, 108.3, 67.6, 60.9, 57.3, 45.2, 37.2, 35.8, 27.3, 24.7, 23.8; IR (ATR) 3485, 2919, 2223, 2129, 1697, 1400, 1357, 1258, 1187, 1089, 1042, 890 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{22}N_4O_4Na$ 405.1533; Found: 405.1531.



Compound 44a: To a solution of **43a** (405 mg, 1.11 mmol) in CH_2Cl_2 (22 mL) was added $Rh_2(esp)_2$ (0.8 mg, 0.0011 mmol) at room temperature. After 15 min, the reaction was quenched with Et_3N. The solution was purified directly by silica gel column chromatography without concentration (hexane/EtOAc = 2:1, 1% Et_3N) to afford **44a** (213 mg, 0.629 mmol, 57%, mixture of rotamers) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (br, 5H), 5.27-5.06 (m, 2H), 4.02-3.99 (m, 0.7H), 3.83 (t, 0.3H, *J* = 6.0 Hz), 2.99 (t, 0.3H, *J* = 10.7 Hz), 2.88-2.84 (m, 1.4H), 2.72 (t, 0.3H, *J* = 11.6 Hz), 2.39-2.33 (m, 0.7H), 2.25-2.10 (m, 1.6H), 2.05-2.00 (m, 2.7H), 1.85-1.82 (m, 1H), 1.73-1.55 (m, 2H), 1.46-1.32 (m, 1H), 1.07-1.03 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 155.5, 1351, 128.85, 128.79, 128.0, 114.4, 69.0, 61.9, 44.6, 42.0, 38.4, 29.7, 26.2, 25.8, 24.8, 22.0, 10.1; IR (ATR) 2960, 2939, 2232, 1712, 1456, 1395, 1299, 1195, 1129, 1089, 892 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2O_3Na$ 361.1523; Found: 361.1513.

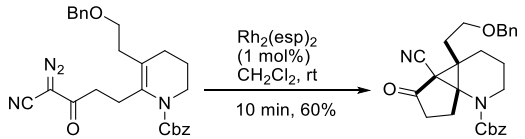


Compound 44b: To a solution of **43b** (17.7 mg, 0.0610 mmol) in CH_2Cl_2 (1 mL) was added $Rh_2(esp)_2$ (0.5 mg, 0.0006 mmol) at room temperature. After 15 min, the reaction was quenched with Et_3N. The solution was purified directly by silica gel column chromatography without concentration (hexane/EtOAc = 2:1, 1% Et_3N) to afford **44b** (9.7 mg, 0.037 mmol, 60%, mixture of rotamers) as a yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (t, 0.5H, *J* = 6.5 Hz), 3.82-3.78 (m, 3.5H), 3.00 (t, 0.5H, *J* = 9.8 Hz), 2.87 (t, 1H, *J* = 9.5 Hz), 2.77-2.67 (m, 1H), 2.54-2.48 (m, 0.5H), 2.31-2.13 (m, 2H), 2.01 (t, 2H, *J* = 7.0 Hz), 1.86-1.80 (m, 1H), 1.79-1.60 (m, 2H), 1.47-1.38 (m, 1H), 1.07 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 156.2, 53.7, 44.7, 42.1, 38.4, 29.7, 26.4, 26.2, 25.7, 24.7, 24.3, 21.9, 10.1; IR (ATR) 2979, 2920, 2232, 1716, 1469, 1381, 1236, 1089, 891, 785 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{18}N_2O_3Na$ 285.1210; Found: 285.1217.



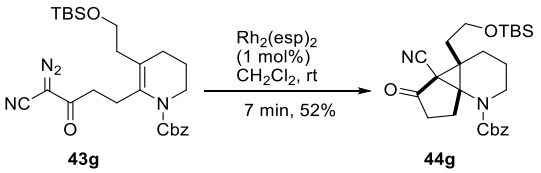
43c **44c**

Compound 44c: To a solution of **43c** (20.0 mg, 0.0602 mmol) in CH_2Cl_2 (1 mL) was added $Rh_2(esp)_2$ (0.5 mg, 0.0006 mmol) at room temperature. After 20 min, the reaction was quenched with Et_3N. The solution was purified directly by silica gel column chromatography without concentration (hexane/EtOAc = 3:1, 1% Et_3N) to afford **44c** (9.2 mg, 0.030 mmol, 50%, mixture of rotamers) as a yellow oil: ^1H NMR (500 MHz, C_6D_6) δ 3.92-3.89 (m, 0.75H), 3.49 (br, 0.25H), 2.61-2.56 (m, 0.25H), 2.44-2.39 (m, 0.5H), 2.28-2.22 (m, 1.5H), 2.10-2.04 (m, 0.75H), 1.65-1.15 (m, 14H), 0.95-0.92 (m, 1H), 0.87-0.67 (m, 2H), 0.58 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ 202.9, 154.7, 115.4, 81.8, 62.4, 44.6, 42.0, 21.8, 38.6, 30.6, 28.6, 28.4, 26.7, 26.2, 25.0, 22.4, 10.2; IR (ATR) 3370, 2968, 2938, 2877, 2232, 1706, 1457, 1368, 1301, 1254, 1159 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{24}N_2O_3Na$ 327.1679; Found: 327.1679.

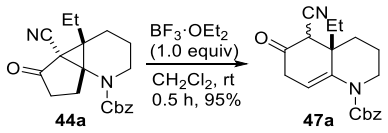


43f **44f**

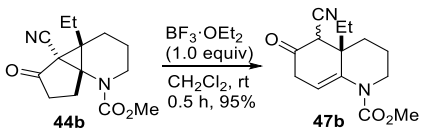
Compound 44f: To a solution of **43f** (19.4 mg, 0.0411 mmol) in CH_2Cl_2 (1 mL) was added $Rh_2(esp)_2$ (0.3 mg, 0.0004 mmol) at room temperature. After 10 min, the reaction was quenched with Et_3N. The solution was purified directly by silica gel column chromatography without concentration (hexane/EtOAc = 2:1, 1% Et_3N) to afford **44f** (8.9 mg, 0.020 mmol, 49%, mixture of rotamers) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (m, 10H), 5.26 (d, 0.6H, *J* = 11.6 Hz), 5.20 (s, 0.8H), 5.07 (d, 0.6H, *J* = 11.6 Hz), 4.47 (s, 2H), 3.96-3.93 (m, 0.6H), 3.78 (m, 0.4H), 3.64-3.62 (m, 1H), 3.53 (m, 1H), 2.99 (m, 0.4H), 2.86 (m, 1.2H), 2.70 (m, 0.4H), 2.35-2.23 (m, 2H), 2.15-2.06 (m, 2H), 1.95-1.89 (m, 1H), 1.85-1.82 (m, 2H), 1.68-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 155.5, 137.5, 135.1, 128.84, 128.75, 128.5, 128.0, 127.8, 127.7, 114.3, 73.4, 69.0, 66.1, 61.2, 41.7, 41.6, 38.1, 31.6, 30.0, 26.5, 25.9, 21.8; IR (ATR) 3032, 2957, 2918, 2873, 2232, 1711, 1588, 1497, 1454, 1396, 1362, 1345, 1212, 1192, 1088, 1025, 967, 891, 740 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{28}N_2O_4Na$ 467.1941; Found: 467.1954.



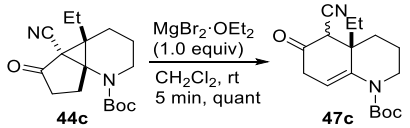
Compound 44g: To a solution of **43g** (25.9 mg, 0.0521 mmol) in CH_2Cl_2 (1 mL) was added $Rh_2(esp)_2$ (0.4 mg, 0.0005 mmol) at room temperature. After 7 min, the reaction was quenched with Et_3N. The solution was purified directly by silica gel column chromatography without concentration (hexane/EtOAc = 2:1, 1% Et_3N) to afford **44g** (12.7 mg, 0.0271 mmol, 52%, mixture of rotamers) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 5H), 5.25 (d, 0.7H, *J* = 11.5 Hz), 5.08 (s, 0.6H), 5.07 (d, 0.7H, *J* = 11.5 Hz), 3.97-3.95 (m, 0.7H), 3.81-3.78 (m, 1.3H), 3.72 (t, 1H, *J* = 5.5 Hz), 3.03 (m, 0.3H), 2.92-2.82 (m, 1.4H), 2.70 (m, 0.3H), 2.34-1.95 (m, 5H), 1.82-1.56 (m, 4H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.9, 155.5, 135.1, 128.9, 128.8, 128.0, 114.3, 69.0, 61.2, 59.4, 41.8, 41.6, 38.1, 33.9, 29.7, 26.4, 25.94, 25.91, 21.9, 18.2, −5.5; IR (ATR) 2952, 2930, 2855, 2233, 1711, 1457, 1395, 1340, 1082, 930, 835, 782, 735 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{37}N_2O_4Si$ 469.2517; Found: 469.2511.



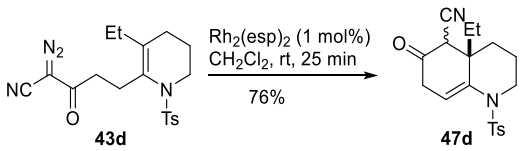
Compound 47a: To a solution of **44a** (356.9 mg, 1.05 mmol) in CH_2Cl_2 (10.5 ml) was added $BF_3{\cdot}OEt_2$ (0.125 mL, 1.05 mmol) at room temperature. After 30 min, the reaction was quenched with aq. $NaHCO_3$.The resultant mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **47a** (337 mg, 0.996 mmol, 95%, mixture of tautomers) as yellow viscous foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.33 (m, 5H), 6.09 (br, 0.4H), 5.76 (br, 0.6H), 5.61 (br, 0.4H), 5.14 (s, 2H), 4.36-4.24 (m, 1H), 3.65 (s, 0.6H), 3.13-2.93 (m, 2.6H), 2.81 (t, 0.4H, *J* = 12.3 Hz), 2.06-2.00 (m, 1H), 1.95-1.79 (m, 1.6H), 1.78-1.68 (m, 1H), 1.64-1.56 (m, 1.4H), 1.33-1.23 (m, 1H), 0.89-0.78 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 163.5, 154.9, 136.7, 136.6, 136.4, 136.1, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 119.0, 117.0, 115.8, 114.1, 89.6, 67.8, 67.4, 53.7, 46.7, 46.4, 46.1, 41.6, 38.2, 29.8, 29.2, 28.3, 20.8, 8.95, 8.86; ^{1}H NMR (500 MHz, pyridine-d5) δ 7.51 (d, 2H, *J* = 7.5 Hz), 7.38 (t, 2H, *J* = 7.5 Hz), 7.31 (t, 1H, *J* = 7.0 Hz), 5.71 (br, 1H), 5.37 (d, 1H, *J* = 12.5 Hz), 5.33 (d, *J* = 13.0 Hz), 4.49 (br, 1H), 3.28 (d, 1H, *J* = 20.5 Hz), 3.13 (dd, 1H, *J* = 22.5, 4.3 Hz), 2.80 (br, 1H), 2.14 (br, 1H), 1.93 (br, 1H), 1.78 (br, 2H), 1.45 (td, 1H, *J* = 16.0, 6.5 Hz), 1.37 (br, 1H), 0.96 (br, 3H); ^{13}C NMR (126 MHz, pyridine-d5) δ 165.5, 155.3, 138.1, 137.80, 129.3, 128.78, 128.75, 118.5, 118.4, 88.9, 67.8, 47.5, 42.4, 39.1, 31.3, 29.0, 21.6, 9.8; IR (ATR) 3233, 2920, 2871, 2208, 1695, 1659, 1458, 1409, 1348, 1278, 1235, 1089, 891 cm^{-1}; HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{20}H_{21}N_2O_3$ 337.1558; Found: 337.1553.



Compound 47b: To a solution of **44b** (9.7 mg, 0.0370 mmol) in CH_2Cl_2 (10.5 ml) was added $BF_3{\cdot}OEt_2$ (4.6 μL, 0.037 mmol) at room temperature. After 30 min, the reaction was quenched with aq. $NaHCO_3$.The resultant mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **47b** (9.3 mg, 0.035 mmol, 96%, mixture of tautomers) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (br, 0.5H), 5.77 (br, 0.5H), 5.61 (br, 0.5H), 4.30 (br, 0.5H), 4.22-4.20 (m, 0.5H), 3.72-3.67 (m, 3.5H), 3.18-3.10 (m, 1.5H), 3.02-2.96 (m, 1H), 2.80 (t, 0.5H, J = 11.9 Hz), 2.07-2.03 (m, 1H), 1.95-1.80 (m, 1.5H), 1.76-1.70 (m, 1H), 1.67-1.56 (m, 1.5H), 1.36-1.24 (m, 1H), 0.89-0.81 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 163.7, 155.6, 136.7, 136.6, 118.8, 117.0, 116.0, 114.1, 89.4, 53.8, 53.1, 52.8, 46.6, 46.4, 46.1, 41.6, 38.3, 29.7, 29.3, 28.3, 22.7, 20.7, 18.4, 14.1, 8.9, 8.7; IR (ATR) 3237, 2960, 2871, 2208, 1659, 1444, 1392, 1220, 1089, 896, 772 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{19}N_2O_3$ 263.1390; Found: 263.1389.

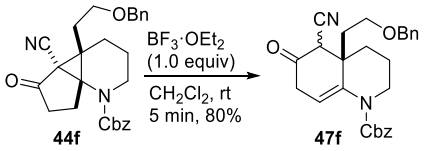


Compound 47c To a solution of **44c** (2.4 mg, 0.0079 mmol) in CH_2Cl_2 (1.0 ml) was added $MgBr_2{\cdot}OEt_2$ (2.0 mg, 0.0079 mmol) at room temperature. After 5 min, the reaction was quenched with aq. $NaHCO_3$, and the resultant solution was extracted with EtOAc. The organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **47c** (2.4 mg, 0.0079 mmol, quant. mixture of tautomers) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (br, 0.5H), 5.63 (br, 0.5H), 5.49 (br, 0.5H), 4.24-4.21 (m, 0.5H), 4.13-4.12 (m, 0.5H), 3.57 (s, 0.5H), 3.12-2.88 (m, 2H), 2.84 (t, 0.5H, J = 9.8 Hz), 2.65 (t, 0.5H, J = 11.7 Hz), 1.99-1.85 (m, 1.5H), 1.80-1.74 (m, 1H), 1.67-1.63 (m, 1H), 1.61-1.48 (m, 1.5H), 1.37 (s, 9H), 1.28-1.18 (m, 1H), 0.82-0.77 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.0, 154.0, 137.0, 118.6, 89.6, 53.8, 46.1, 45.8, 41.6, 38.3, 29.7, 28.3, 20.8, 9.1, 9.0; IR (ATR) 3266, 2976, 2920, 2210, 1698, 1470, 1394, 1236, 1090, 890 cm^{-1}; HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{17}H_{23}N_2O_3$ 303.1714; Found: 303.1720.

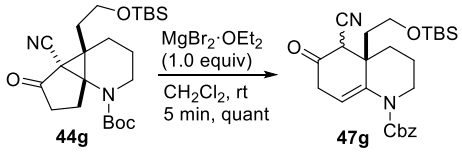


Compound 47d: To a solution of **43d** (31.2 mg, 0.0807 mmol) in CH_2Cl_2 (1.0 ml) was added $Rh_2(esp)_2$ (0.6 mg, 0.0008 mmol) at room temperature. After 25 min, the reaction was quenched with Et_3N. The solution was purified directly by silica gel column chromatography without concentration ($CHCl_3$/MeOH = 9:1, 1% Et_3N) to afford **47d** as a triethylammonium salt. The salt was diluted with EtOAc and washed with aq. HCl to afford **47d** (22.1 mg, 0.0617 mmol, 76%, mixture of tautomers) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 2H, J =

8.1 Hz), 7.34-7.27 (m, 2H), 5.90 (t, 0.4H, J = 3.8 Hz), 5.69 (t, 0.6H, J = 3.5 Hz), 4.18-4.14 (m, 0.4H), 4.06-4.04 (m, 0.6H), 3.58 (s,0.4H), 3.12-3.03 (m, 1.8H), 2.95-2.86 (m, 1.2H), 2.44 (s, 3H), 2.09-1.49 (m, 6H), 0.73 (t, 1.8H, J = 7.2 Hz), 0.66 (t, 1.2H, J = 7.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 163.9, 144.0, 143.6, 137.9, 137.5, 136.4, 136.0, 129.8, 129.8, 127.2, 127.1, 117.1, 116.0, 115.2, 113.9, 88.9, 53.9, 48.4, 47.5, 45.6, 41.4, 38.6, 38.3, 37.5, 29.7, 28.3, 27.7, 21.54, 21.52, 20.9, 20.8, 8.8, 8.5; IR (ATR) 3272, 2925, 2857, 2206, 1714, 1691, 1656, 1600, 1450, 1397, 1339, 814, 752 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_3S$ 359.1424; Found: 359.1421.

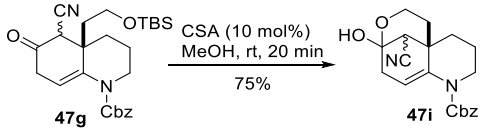


Compound 47f: To a solution of **44f** (8.9 mg, 0.0190 mmol) in CH_2Cl_2 (1 ml) was added $BF_3{\cdot}OEt_2$ (4.9 mg, 0.0190 mmol) at room temperature. After 5 min, the reaction was quenched with aq. $NaHCO_3$.The resultant mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **47f** (6.4 mg, 0.014 mmol, 80%, mixture of tautomers) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.23 (m, 10H), 6.40 (br, 0.5H), 5.75 (br, 0.5H), 5.57 (br, 0.5H), 5.15-5.05 (m, 2H), 4.42-4.25 (m, 2.5H), 4.12 (t, 0.5H, J = 7.0 Hz), 3.57 (s, 0.5H), 3.51-3.35 (m, 2H), 3.05-2.88 (m, 2.5H), 2.81 (t, 0.5H, J = 11.9 Hz), 2.23-2.18 (m, 0.5H), 2.14-2.05 (m, 1H), 1.99-1.58 (m, 4.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 162.8, 154.8, 154.7, 138.3, 137.6, 136.7, 136.4, 136.0, 136.0, 128.6, 128.5, 128.34, 128.31, 128.28, 128.1, 128.1, 127.9, 127.8, 127.6, 127.53, 127.46, 119.1, 117.0, 115.9, 114.5, 90.0, 73.0, 71.9, 67.8, 67.5, 67.3, 65.7, 54.4, 46.7, 46.3, 43.7, 39.4, 37.7, 37.6, 34.8, 34.0, 29.7, 29.1, 20.9, 20.8; IR (ATR) 3241, 2974, 2921, 2208, 1698, 1469, 1406, 1278, 1236, 1090, 891 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O_4$ 445.2122; Found: 445.2102.

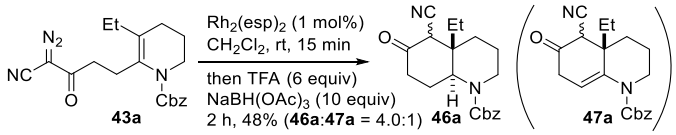


Compound 47g: To a solution of **44g** (8.9 mg, 0.019 mmol) in CH_2Cl_2 (1 ml) was added $MgBr_2{\cdot}OEt_2$ (4.9 mg, 0.019 mmol) at room temperature. After 5 min, the reaction was quenched with aq. $NaHCO_3$.The resultant mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **47g** (8.6 mg, 0.018 mmol, quant, mixture of tautomers) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.36 (m, 5H), 5.78 (br, 0.5H), 5.61 (br, 0.5H), 5.20-5.12 (m, 2H), 4.37 (br, 0.5H), 4.24 (br, 0.5H), 3.62-3.56 (m, 2.5H), 3.13-2.93 (m, 2.5H), 2.84 (t, 0.5H, J = 11.9 Hz), 2.18-2.07 (m, 1.5H), 1.99-1.63 (m, 4.5H), 0.91-0.87 (m, 9H), 0.04-0.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 162.5, 154.8, 136.8, 136.3, 136.0, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 118.9, 116.8, 115.9, 114.4, 90.3, 67.8, 67.6, 59.8, 59.3,

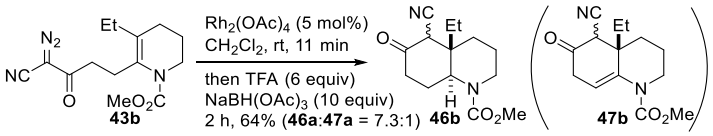
54.0, 46.7, 46.4, 43.6, 39.3, 38.0, 37.7, 37.3, 29.7, 29.1, 26.0, 25.9, 25.8, 20.75, 20.70, 18.5, 18.2, -5.4, -5.5; IR (ATR) 3223, 2951, 2856, 2210, 1703, 1659, 1450, 1407, 1345, 1277, 1214, 1148, 1026, 836 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{37}N_2O_4Si$ 469.2517; Found: 469.2539.



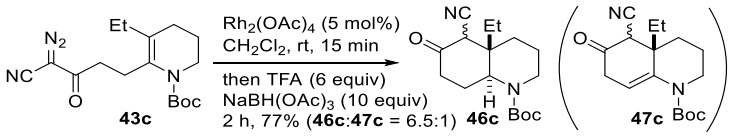
Compound 47i: To a solution of compound **47g** (7.4 mg, 0.016 mmol) was added CSA (0.4 mg, 0.0016 mmol) at room temperature. After the solution was stirred for 20 min, satd. aq. $NaHCO_3$ was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **47i** (4.2 mg, 0.0119 mmol, 75%) as a yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.83 (br, 0.5H), 5.73 (br, 0.5H), 5.15 (dd, 1H, *J* = 12.0, 6.6 Hz), 5.08 (dd, 1H, *J* = 12.0, 1.2 Hz), 4.20 (1H, d, *J* = 12.6 Hz), 3.83 (m, 2H), 3.02-2.85 (m, 2.5H), 2.64 (dd, 0.5H, *J* = 3.0, 19.2 Hz), 2.56 (s, 0.5H), 2.47 (t, 0.5H, *J* = 16.2 Hz), 2.14-2.09 (m, 0.5H), 1.92 (br, 1H), 1.79-1.57 (m, 4H), 1.45 (d, 0.5H, *J* = 13.8 Hz), 1.36 (td, 0.5H, *J* = 13.1, 4.8 Hz), 1.25 (2H, s), 0.87 (1H, d, *J* = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.2, 155.1, 136.2, 136.1, 133.9, 132.2, 128.62, 128.61, 128.4, 128.3, 128.04, 128.00, 121.6, 121.2, 117.8, 116.8, 94.4, 93.3, 67.8, 67.7, 62.6, 62.4, 47.3, 47.1, 46.0, 45.9, 40.7, 39.9, 36.9, 35.8, 35.7, 34.9, 32.4, 29.7, 21.2, 20.8; IR (ATR) 3393, 2923, 2242, 1698, 1402 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{22}N_2O_4Na$ 377.1472; Found: 377.1455.



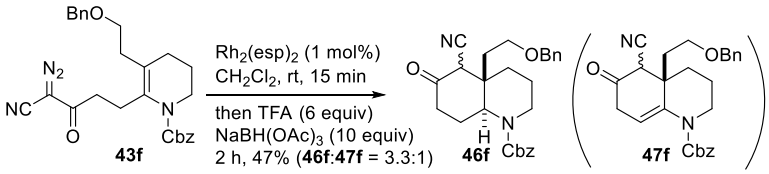
Compound 46a: To a solution of **43a** (370 mg, 1.01 mmol) in CH_2Cl_2 (20 mL) was added $Rh_2(esp)_2$ (0.8 mg, 0.010 mmol) at room temperature. After 15 min, the resulting solution was added to a suspended solution of $NaBH(OAc)_3$ (2.14 g, 10.1 mmol) and TFA (0.463 mL, 6.06 mmol) via canula at room temperature. After 2 h, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$. The organic layers were dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **46a** along with **47a** (164.9 mg, 0.0485 mmol, 48%, **82a**:**81a** = 4.0:1, mixture of tautomers and rotamers) as yellow viscous foam: ^1H NMR (600 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5H), 5.14-5.06 (m, 2H), 4.43-4.35 (m, 1H), 3.79 (d, 0.15H, *J* = 9.0 Hz), 3.42-3.37 (m, 0.6H), 3.25 (s, 0.15H), 3.13-2.57 (m, 3H), 2.48-2.26 (m, 2H), 2.16 (br, 0.3H), 2.02-1.50 (m, 6.8H), 1.05 (t, 0.9H, *J* = 8.0 Hz), 0.97 (t, 0.45H, *J* = 8.0 Hz), 0.78 (t, 1.65H, *J* = 7.5 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.6, 198.3, 166.1, 155.4, 155.3, 155.2, 136.7, 136.5, 136.4, 128.58, 128.56, 128.51, 128.21, 128.16, 128.1, 128.3, 127.98, 127.9, 117.2, 116.3, 114.6, 90.8, 67.1, 67.0, 66.9, 66.5, 65.0, 62.6, 53.7, 49.4, 48.93, 48.88, 48.8, 45.2, 44.9, 40.4, 38.6, 38.1, 36.0, 34.1, 31.7, 29.7, 29.0, 27.0, 26.9, 24.6, 22.4, 22.1, 21.5, 20.7, 19.0, 8.55, 8.49, 6.6; IR (ATR) 3224, 2942, 2205, 1681, 1658, 1469, 1384, 1269, 1236, 1200, 1090, 891 cm^{-1}; HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{20}H_{23}N_2O_3$ 339.1714; Found: 339.1703.



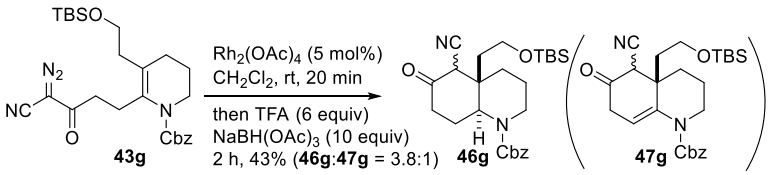
Compound 46b: To a solution of **43b** (25.2 mg, 0.0844 mmol) in CH_2Cl_2 (20 mL) was added $Rh_2(OAc)_4$ (1.9 mg, 4.3 μmol) at room temperature. After 11 min, the resulting solution was added to a suspended solution of $NaBH(OAc)_3$ (178 mg, 0.844 mmol) and TFA (0.039 mL, 0.516 mmol) via canula at room temperature. After 2 h, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$. The organic layers were dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **46b** along with **47b** (10.3 mg, 0.0390 mmol, 64%, **46b**:**47b** = 7.3:1, mixture of tautomers and rotamers) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.40-4.21 (m, 1H), 3.78 (dd, 0.38H, *J* = 12.7, 4.0 Hz), 3.71-3.65 (m, 3.24H), 3.38 (dd, 0.38H, *J* = 12.8, 3.4 Hz), 3.3 (s, 0.38H), 3.26 (s, 0.38H), 3.08-2.98 (m, 1H), 2.92 (td, 0.38H), 2.85-2.60 (m, 1.38H), 2.50-2.27 (m, 2.24H), 2.20-2.18 (m, 0.24H), 2.10-2.00 (m, 0.76H), 1.89-1.84 (m, 1H), 1.67-1.52 (m, 3H), 1.40-1.25 (m, 1H), 1.10 (t, 1.14H, *J* = 7.7 Hz), 1.00 (t, 1.14H, *J* = 7.6 Hz), 0.81 (t, 0.72H, *J* = 7.5 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.6, 198.3, 166.1, 156.1, 155.9, 116.3, 115.8, 90.8, 66.4, 64.8, 62.5, 53.8, 53.7, 52.4, 52.3, 52.1, 49.4, 48.8, 48.7, 45.2, 44.9, 40.4, 38.6, 38.1, 35.9, 34.1, 31.7, 29.7, 29.0, 26.69, 26.8, 24.6, 22.3, 22.1, 21.5, 20.7, 19.0, 8.55, 8.49, 6.6; IR (ATR) 2950, 2867, 2205, 1690, 1475, 1445, 1383, 1236, 1090, 892 cm^{-1}; HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{14}H_{19}N_2O_3$263.1401; Found: 263.1392.



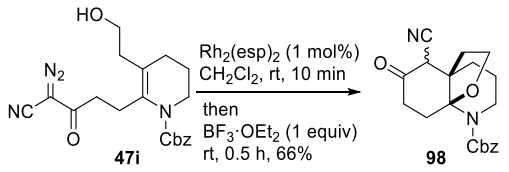
Compound 46c: To a solution of **43c** (9.5 mg, 0.0256 mmol) in CH_2Cl_2 (1.0 mL) was added $Rh_2(OAc)_4$ (0.6 mg, 1.4 μmol) at room temperature. After 15 min, the resulting solution was added to a suspended solution of $NaBH(OAc)_3$ (54.3 mg, 0.256 mmol) and TFA (0.0118 mL, 0.154 mmol) via canula at room temperature. After 2 h, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$. The organic layers were dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **47c** along with a **47c** (6.8 mg, 0.022 mmol, 77%, **46c**:**47c** = 6.5:1, mixture of tautomers and rotamers) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.39-4.20 (m, 1H), 3.75 (dd, 0.25H, *J* = 12.0, 3.7 Hz), 3.38-3.35 (m, 1H), 3.26 (s, 0.25H), 3.26-3.24 (m, 0.25H), 3.02-2.83 (m, 1H), 2.79-2.59 (m, 2H), 2.47-2.26 (m, 2.75H), 2.18-2.14 (m, 0.25H), 2.05-1.25 (m, 14H), 1.10 (t, 0.75H, *J* = 7.7 Hz), 1.02 (t, 0.75H, *J* = 7.6 Hz), 0.92-0.80 (m, 1.5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.2, 198.6, 166.0, 155.0, 154.7, 116.4, 114.7, 91.0, 80.4, 80.2, 79.8, 66.2, 64.6, 62.3, 53.8, 49.4, 49.0, 48.9, 48.7, 45.3, 45.0, 40.6, 38.7, 38.3, 36.4, 35.7, 34.4, 31.9. 29.7, 28.9, 28.5, 28.3, 27.4, 27.3, 24.6, 22.8, 22.0, 21.4, 20.8, 19.0, 8.73, 8.69, 6.7; IR (ATR) 3257, 2932, 2853, 2205, 1730, 1680, 1657, 1469, 1367, 1256, 11665, 1089, 892 cm^{-1}; HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{17}H_{25}N_2O_3$ 305.1871; Found: 305.1862.



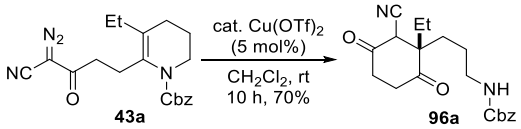
Compound 46f: To a solution of **43f** (25.8 mg, 0.0546 mmol) in CH_2Cl_2 (1.0 mL) was added $Rh_2(esp)_2$ (0.4 mg, 0.5 μmol) at room temperature. After 5 min, the resulting solution was added to a suspended solution of $NaBH(OAc)_3$ (115.7 mg, 0.546 mmol) and TFA (0.025 mL, 0.328 mmol) via canula at room temperature. After 2 h, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$. The organic layers were dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **46f** along with a **47f** (10.2 mg, 0.0229 mmol, 47%, **46f**:**47f** = 3.3:1, mixture of tautomers and rotamers) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.25 (m, 10H), 5.15-5.09 (m, 2H), 4.52-4.22 (m, 3H), 3.91-3.17 (m, 3H), 3.08-2.71 (m, 2H), 2.66-2.30 (m, 2H), 2.24-1.35 (m, 8H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.8, 197.7, 166.1, 155.3, 155.2, 154.8, 138.4, 138.1, 137.7, 136.6, 136.5, 136.4, 128.7, 128.59, 128.56, 128.52, 128.48, 128.41, 128.39, 128.33, 128.31, 128.2, 128.1, 128.03, 1247.99, 127.8, 127.73, 127.71, 127.6, 127.5, 116.4, 115.8, 114.5, 90.8, 73.2, 73.1, 72.0, 67.8, 67.5, 67.2, 67.1, 66.7, 65.6, 65.5, 65.1, 62.9, 54.0, 50.4, 48.9, 48.8, 48.7, 44.9, 44.1, 43.7, 40.3, 39.4, 38.3, 37.2, 35.25, 32.3, 31.7, 29.0, 28.0, 26.9, 26.0, 24.8, 22.5, 22.1, 21.6; IR (ATR) 3226, 2944, 2866, 2205, 1688, 1454, 1385, 1274, 1236, 1197, 1090, 891 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{30}N_2O_4Na$ 469.2098; Found: 469.2078.



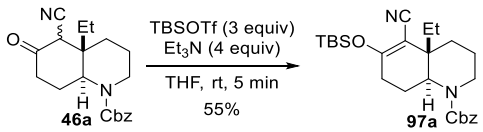
Compound 46g: To a solution of **47g** (17.1 mg, 0.0344 mmol) in CH_2Cl_2 (1.0 mL) was added $Rh_2(OAc)_4$ (0.8 mg, 1.7 μmol) at room temperature. After 20 min, the resulting solution was added to a suspended solution of $NaBH(OAc)_3$ (72.9 mg, 0.344 mmol) and TFA (0.016 mL, 0.206 mmol) via canula at room temperature. After 2 h, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$. The organic layers were dried over Mg_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to afford **46g** along with **47g** (7.1 mg, 0.015 mmol, 43%, **46g**:**47g** = 3.8:1, mixture of tautomers and rotamers) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.32 (m, 5H), 5.34-5.04 (m, 2H), 4.47-4.23 (m, 1H), 3.99-3.53 (m, 2.1H), 3.37-3.33 (m, 0.9H), 2.98-2.58 (m, 2H), 2.49-2.28 (m, 2H), 2.22-1.26 (m, 8H), 0.89-0.85 (m, 9H), 0.07-0.03 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.6, 198.0, 166.1, 155.3, 155.1, 154.8, 136.8, 136.5, 136.4, 128.64, 128.56, 128.5, 128.3, 128.15, 128.12, 128.08, 128.0, 127.9, 118.9, 116.8, 116.5, 90.5, 68.8, 67.9, 67.6, 67.0, 66.7, 63.0, 59.9, 59.4, 58.6, 54.1, 54.0, 50.2, 49.1, 48.8, 46.7, 46.4, 44.8, 44.1, 43.7, 39.3, 38.3, 37.8, 35.8, 33.3, 32.3, 29.7, 29.1, 28.1, 26.9, 26.0, 25.93, 25.87, 22.2, 21.4, 20.7, 18.5, 18.2, 18.1, −5.40, −5.42, −5.6; IR (ATR) 3227, 2951, 2856, 2207, 1704, 1395, 1360, 1257, 1195, 1146, 1052, 835 cm^{-1}; HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{26}H_{37}N_2O_4Si$ 469.2528; Found: 469.2511.



Compound 93: To a solution of **47i** (14.6 mg, 0.0382 mmol) in CH_2Cl_2 (1.0 ml) was added $Rh_2(esp)_2$ (1.4 mg, 0.0019 mmol) at room temperature. After the solution was stirred for 10 min, $BF_3{\cdot}OEt_2$ (0.090 mL, 0.076 mmol) was added to the solution. The solution was stirred for 30 min. The reaction was quenched with aq. $NaHCO_3$. The reaction mixture was extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford **93** (8.9 mg, 0.025 mmol, 66%, mixture of tautomers) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.33 (m, 5H), 5.22-5.13 (m, 2H), 4.26-4.19 (m, 1.4H), 4.11 (td, 0.6H, J = 9.6, 3.7 Hz), 4.01 (td, 0.4H, J = 9.1, 2.7 Hz), 3.98-3.87 (m, 1.2H), 2.86-2.77 (m, 2H), 2.66-2.60 (m, 0.4H), 2.57-2.51 (m, 0.6H), 2.48-2.40 (m, 1H), 2.27-2.19 (m, 2H), 2.06 (td, 0.6H, J = 12.6, 6.4 Hz), 1.98-1.94 (m, 0.4H), 1.72-1.53 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.7, 166.4, 156.3, 156.1, 136.7, 136.4, 128.54, 128.46, 128.1, 127.9, 127.93, 127.84, 116.8, 114.5, 92.9, 92.5, 90.2, 67.3, 67.0, 65.0, 63.6, 54.6, 51.1, 47.5, 44.3, 43.9, 36.3, 32.4, 32.3, 31.5, 26.1, 25.9, 25.6, 23.0, 20.1, 19.7; IR (ATR) 3263, 2942, 2205, 1688, 1455, 1391, 1342, 1274, 1235, 1186, 1090, 1026, 890 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{23}N_2O_4$ 355.1652; Found: 355.1642.

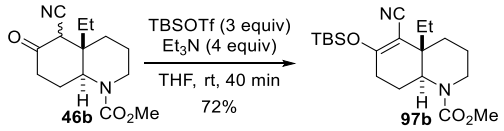


Compound 96a: To a solution of **43a** (17.2 mg, 0.0469 mmol) in CH_2Cl_2 (1.0 ml) was added $Cu(OTf)_2$ (0.8 mg, 0.0023 mmol) at room temperature. After the solution mixture was stirred for 10 h, the reaction mixture was purified directly by column chromatography without concentration (hexane/EtOAc = 3:1) to afford **96a** (11.4 mg, 0.0320 mmol, 70%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 7.25 (d, 2H, J = 7.7 Hz), 7.12 (t, 2H, J = 7.4 Hz), 7.06 (t, 1H, J = 7.1 Hz), 5.09 (s, 2H), 4.22 (s, 1H), 2.91-2.87 (m, 2H), 2.32 (s, 2H), 2.22 (t, 2H, J = 5.2 Hz), 2.04 (br, 1H), 1.46-1.35 (m, 3H), 1.18-1.07 (m, 3H), 0.71 (t, 3H, J = 7.4 Hz); ^{13}C NMR (151MHz, C_6D_6) δ 211.1, 198.4, 175.0, 138.2, 129.2, 129.0, 128.9, 109.0, 67.2, 53.3, 41.6, 36.7, 33.2, 30.8, 28.8, 28.3, 25.5, 12.3; IR (ATR) 3362, 2966, 2921, 2223, 2129, 1708, 1527, 1468, 1384, 1236, 1089, 891 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{24}N_2O_4Na$ 379.1628; Found: 379.1615.

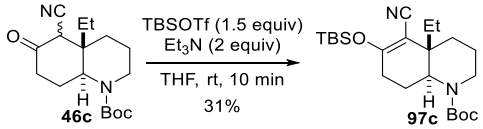


Compound 97a: To a solution of **46a** (5.2 mg, 0.015 mmol) in THF (1.0 ml) were added Et_3N (0.045 mL, 0.061 mmol) and TBSOTf (0.011 mL, 0.046 mmol) at room temperature. After 5 min, the reaction was quenched with aq. $NaHCO_3$, and the resultant solution was extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford **97a** (3.8 mg, 0.0084 mmol, 55%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 5.09 (s, 2H), 4.36 (d, 1H, *J* = 10.3 Hz), 3.01 (d, 1H, *J* = 12.9 Hz), 2.76-2.66 (m, 2H), 2.31 (d, 1H, *J* = 13.5 Hz), 2.26 (m, 2H), 2.16 (d, 1H, *J* = 13.7 Hz), 1.75-1.50 (m, 4H), 1.32-1.25 (m, 1H), 0.99-0.98 (m, 12H), 0.24-0.23 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 155.3, 136.7, 128.5, 128.02, 127.98, 117.6, 98.9, 66.8, 65.0, 48.8, 39.1, 34.2, 31.8, 25.5, 24.8, 23.0, 21.5, 18.2, 8.8, −3.7; IR (ATR) 2925, 2860, 2209, 1704, 1618, 1471, 1382 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{39}N_2O_3Si$ 455.2724; Found: 455.2703.



Compound 97b: To a solution of **46b** (10.3 mg, 0.0390 mmol) in THF (1.0 mL) were added Et_3N (0.011 mL, 0.078 mmol) and TBSOTf (0.0134 mL, 0.0584 mmol) at room temperature. After 40 min, the reaction was quenched with aq. $NaHCO_3$, and the resultant solution was extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **97b** (10.7 mg, 0.0283 mmol, 72%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32-4.29 (m, 1H), 3.65 (s, 3H), 3.01-2.98 (m, 1H), 2.79-2.65 (m, 2H), 2.32-2.27 (m, 3H), 2.17-2.13 (m, 1H), 1.75-1.51 (m, 4H), 1.32-1.25 (m, 1H), 1.03-0.99 (m, 12H), 0.28-0.23 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 156.0, 117.6, 98.9, 64.8, 52.1, 48.6, 39.1, 34.2, 31.8, 25.5, 24.7, 22.9, 21.4, 18.1, 8.7, −3.7; IR (ATR) 2931, 2860, 2209, 1707, 1619, 1472, 1443, 1373, 1263, 1235, 1200, 1151, 1089, 890, 864, 843 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{35}N_2O_3Si$ 379.2411; Found: 379.2398.

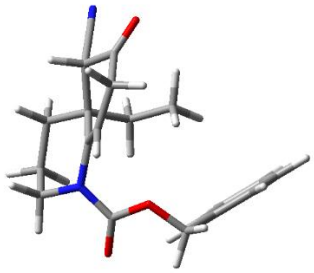


Compound 97c: To a solution of **46c** (6.8 mg, 0.022 mmol) in THF (1.0 mL) were added Et_3N (0.062 mL, 0.044 mmol) and TBSOTf (0.077 mL, 0.033 mmol) at room temperature. After 10 min, the reaction was quenched with aq. $NaHCO_3$, and the resultant solution was extracted with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **97c** (2.9 mg, 0.0069 mmol, 31%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (d, 1H, *J* = 12.9 Hz), 2.97 (d, 1H, *J* = 10.6 Hz), 2.68-2.63 (m, 2H), 2.31-2.25 (m, 3H), 2.12 (d, 1H, *J* = 13.5 Hz), 1.67-1.45 (m, 13H), 1.31-1.25 (m, 1H), 1.05-0.98 (m, 12H), 0.25-0.24 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 154.9, 117.6, 99.1, 79.7, 64.6, 48.7, 39.2, 34.7, 32.1, 28.5, 25.5, 24.7, 23.4, 21.4, 18.4, 9.0, −3.7; IR (ATR) 2934, 2859, 1685, 1619, 1457, 1370, 1255, 1150, 839, 7875 cm^{-1}; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{40}N_2O_3SiNa$ 443.2700; Found: 443.2702.

2. Details for DFT calculation

All of optimization was performed at ωB97XD/6-311G(d,p) level using Gaussian09 software package.[73]

Compound 47a



E(RωB97XD) = -1110.48235868

Zero-point correction=	0.392474 (Hartree/Particle)
Thermal correction to Energy=	0.414373
Thermal correction to Enthalpy=	0.415317
Thermal correction to Gibbs Free Energy=	0.341538
Sum of electronic and zero-point Energies=	-1110.089884
Sum of electronic and thermal Energies=	-1110.067986
Sum of electronic and thermal Enthalpies=	-1110.067042
Sum of electronic and thermal Free Energies=	-1110.140821

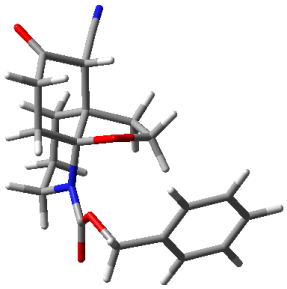
The coordinates of the structure

0 1

N	0.42395100	2.13232900	0.32749500
C	1.25582700	1.02389500	0.66640600
C	1.53960700	0.75246100	1.93453200
H	1.15195400	1.41273400	2.70232500
C	1.71896600	0.20050900	-0.52576100
C	2.27261600	-0.46948000	2.39234200
H	1.65845100	-1.05832700	3.07977000
H	3.17202000	-0.19356800	2.95899300
C	2.71403800	-1.39405100	1.28009700
O	2.96021800	-2.55378100	1.46118500
C	2.90695700	-0.70143000	-0.07328200
H	3.76038100	-0.02914500	0.09414800
C	3.29953800	-1.64687800	-1.11326000
N	3.58903600	-2.35970400	-1.96668600
C	2.25362000	1.14956300	-1.62895700

H	2.47172100	0.56298100	-2.52594700
H	3.20544500	1.57694200	-1.28890300
C	0.96311500	3.05642900	-0.66982500
H	0.21918200	3.83088900	-0.84028800
H	1.86163400	3.52033300	-0.24846500
C	1.30537100	2.30287900	-1.94805200
H	0.38346000	1.94006200	-2.41161800
H	1.77819100	2.98102900	-2.66350100
C	-0.93315800	2.13217500	0.52793200
O	-1.69162200	2.92581400	0.01823300
O	-1.31655200	1.15137100	1.36343900
C	-2.73171100	0.91497900	1.46866200
H	-3.26040100	1.84863300	1.27586200
H	-2.89162100	0.60901400	2.50212800
C	-3.15145700	-0.17058200	0.51404700
C	-3.82400400	-2.20737400	-1.27265400
C	-3.44351900	-1.44917900	0.97849200
C	-3.20877700	0.08427900	-0.85717900
C	-3.53580400	-0.93081000	-1.74532400
C	-3.78376800	-2.46395300	0.09155200
H	-3.39757900	-1.65640500	2.04298700
H	-2.99418000	1.08385500	-1.22014900
H	-3.57426200	-0.72485200	-2.80899400
H	-4.00848300	-3.45618700	0.46558500
H	-4.08226900	-2.99857900	-1.96718200
C	0.53441400	-0.62794700	-1.08061700
H	0.85301400	-1.08484900	-2.02321500
H	-0.27237300	0.06504500	-1.33453400
C	-0.02005000	-1.70372800	-0.15338300
H	0.68405400	-2.52682900	-0.01368900
H	-0.93366100	-2.12128500	-0.58082400
H	-0.28285900	-1.28762700	0.82238300

Compound 98 (α -CN)



E(RωB97XD) = -1185.71219127

Zero-point correction=	0.399972 (Hartree/Particle)
Thermal correction to Energy=	0.421749
Thermal correction to Enthalpy=	0.422693
Thermal correction to Gibbs Free Energy=	0.348772
Sum of electronic and zero-point Energies=	-1185.312219
Sum of electronic and thermal Energies=	-1185.290442
Sum of electronic and thermal Enthalpies=	-1185.289498
Sum of electronic and thermal Free Energies=	-1185.363419

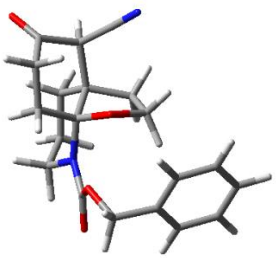
The coordinates of the structure

0 1

N	0.05802300	1.50290900	-0.33170900
C	0.81716000	2.45598500	-1.14784400
H	1.42805300	3.09155600	-0.49008100
H	0.08911500	3.09668200	-1.63920200
C	1.71643300	1.77002500	-2.15806000
H	1.10871200	1.30006300	-2.93554400
H	2.33346400	2.52409100	-2.65304600
C	2.60598400	0.74376700	-1.46939000
H	3.32706300	1.26205700	-0.82462400
H	3.19490700	0.18568300	-2.20169100
C	1.78806600	-0.23133800	-0.62287300
C	0.81144600	0.44980900	0.39117200
C	0.79736600	-1.10188000	-1.41785700
H	1.27802800	-2.00236100	-1.80437500
H	0.39172600	-0.55309700	-2.26598600
C	-0.31073400	-1.40371100	-0.39462400
H	-0.33320900	-2.44594800	-0.07196200
H	-1.30264200	-1.14087600	-0.77227800

O	-0.01078300	-0.61813900	0.76193500
C	2.73030300	-1.18465700	0.18791300
H	2.10454100	-1.96911200	0.62763700
C	3.40328900	-0.46977300	1.36740600
O	4.59298300	-0.34237000	1.46247300
C	2.40154400	0.07002900	2.35577100
H	2.93666400	0.56076600	3.16858600
H	1.82394600	-0.76597200	2.76217400
C	1.45230100	1.03797100	1.64563600
H	0.64517700	1.34409200	2.31230200
H	2.00371200	1.93827500	1.35943000
C	-1.21543400	1.89804300	0.00884100
O	-1.88579200	2.65319800	-0.65788300
O	-1.62894200	1.37025500	1.17173100
C	-3.05146100	1.25184700	1.33762000
H	-3.19749400	1.17178900	2.41389400
H	-3.53664500	2.15446600	0.96551500
C	-3.53478400	0.01853400	0.62317900
C	-4.24136600	-2.29953200	-0.76042300
C	-3.46091600	-1.22568700	1.24628700
C	-3.96790600	0.09285400	-0.69964200
C	-4.31911500	-1.06242600	-1.38875900
C	-3.81418000	-2.37970100	0.56081700
H	-3.10955500	-1.28874700	2.27080800
H	-4.00810900	1.05874500	-1.19070500
H	-4.65468900	-0.99553400	-2.41744600
H	-3.75504000	-3.34274200	1.05526500
H	-4.51699500	-3.20004100	-1.29758400
C	3.69771600	-1.83926000	-0.68569500
N	4.42415800	-2.36473600	-1.40457600

Compound 98 (β -CN)



E(RωB97XD) = -1185.71046486

Zero-point correction=	0.400342 (Hartree/Particle)
Thermal correction to Energy=	0.421900
Thermal correction to Enthalpy=	0.422844
Thermal correction to Gibbs Free Energy=	0.349779
Sum of electronic and zero-point Energies=	-1185.310122
Sum of electronic and thermal Energies=	-1185.288565
Sum of electronic and thermal Enthalpies=	-1185.287620
Sum of electronic and thermal Free Energies=	-1185.360686

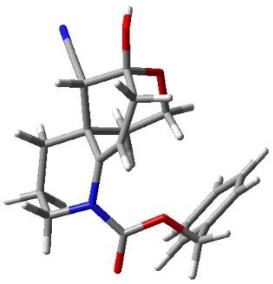
The coordinations of the structure

0 1

N	0.21466500	-1.59978400	0.05537500
C	0.94650800	-2.71252700	0.66386300
H	1.64960300	-3.13346700	-0.07022000
H	0.21321600	-3.48114500	0.89542300
C	1.70968000	-2.28962200	1.90324300
H	1.00544600	-2.03955800	2.70091500
H	2.30800300	-3.13192500	2.25994200
C	2.61512500	-1.10894800	1.58315000
H	3.41861700	-1.44128100	0.91399000
H	3.10298100	-0.73697200	2.48976000
C	1.85135500	0.04214700	0.92164400
C	0.97248200	-0.37535500	-0.30775800
C	0.78378100	0.68616900	1.82862400
H	1.19666800	1.51378600	2.40841200
H	0.38370800	-0.04362800	2.53089200
C	-0.30745000	1.14526500	0.84455900
H	-0.42504700	2.22681200	0.80184700
H	-1.27656800	0.69006100	1.06905500
O	0.13326400	0.72884700	-0.44848700
C	2.91262100	1.11151300	0.48533700
C	3.62207400	0.70537100	-0.82212500
O	4.80265800	0.48496500	-0.84340200
C	2.68581200	0.52547300	-1.98351100
H	3.26128000	0.28516600	-2.87713900
H	2.12501700	1.44974500	-2.14824700
C	1.71099300	-0.60142400	-1.62617300
H	0.95492600	-0.71528500	-2.40356800

H	2.26068300	-1.54502000	-1.55788200
C	-1.01348600	-1.92045600	-0.47833600
O	-1.70001300	-2.83466900	-0.08178700
O	-1.35830300	-1.12304100	-1.50041700
C	-2.76757700	-0.99482900	-1.75283800
H	-2.83057500	-0.64021800	-2.78067500
H	-3.24167900	-1.97307800	-1.67005200
C	-3.35722800	-0.00068300	-0.78939500
C	-4.26426700	1.85783400	1.08292900
C	-3.24316700	1.36567900	-1.03906800
C	-3.93105400	-0.42941100	0.40598200
C	-4.38317100	0.49723600	1.33880100
C	-3.69519900	2.29179800	-0.10983900
H	-2.77853600	1.70305500	-1.95943900
H	-4.00135800	-1.49212200	0.60955800
H	-4.82792700	0.15541300	2.26657000
H	-3.59896200	3.35240400	-0.31228200
H	-4.61624300	2.58041900	1.81057600
H	3.68161600	1.15990300	1.26107500
C	2.38716500	2.46646800	0.33097300
N	2.01452000	3.54806000	0.21232100

Compound 47h (α -CN)



E(RωB97XD) = -1185.71058861

Zero-point correction=	0.400650 (Hartree/Particle)
Thermal correction to Energy=	0.422043
Thermal correction to Enthalpy=	0.422987
Thermal correction to Gibbs Free Energy=	0.350419
Sum of electronic and zero-point Energies=	-1185.309939
Sum of electronic and thermal Energies=	-1185.288546

Sum of electronic and thermal Enthalpies= -1185.287601

Sum of electronic and thermal Free Energies= -1185.360169

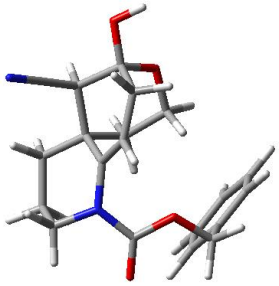
The coordinates of the structure

0 1

N	0.11904800	2.22560800	-0.38212400
C	-0.10387800	3.17397700	0.70951200
H	-0.98893600	3.77056200	0.46579300
H	0.75869200	3.83357400	0.76035000
C	-0.31481400	2.40477000	2.00692100
H	0.59937400	1.84944800	2.24175800
H	-0.49317800	3.09821700	2.83301900
C	-1.50679600	1.46370900	1.85426800
H	-2.41292700	2.07363500	1.74700600
H	-1.64422000	0.85492800	2.75238600
C	-1.40590300	0.53304900	0.63012000
C	-0.45574500	-0.65931700	0.87867200
H	-0.76326500	-1.17159200	1.79587200
H	0.57324200	-0.31716500	1.02270300
C	-0.48361800	-1.63101500	-0.29532900
H	0.01311900	-2.56273400	-0.02867800
H	0.04360700	-1.19984500	-1.15266600
O	-1.80541100	-2.00235200	-0.67352100
C	-2.80525200	-0.04138200	0.30562100
H	-3.49031400	0.77896900	0.07000900
C	-2.32684200	-0.09380200	-2.14664900
H	-3.25029200	0.31022300	-2.57232700
H	-1.90117800	-0.75959600	-2.90420900
C	1.42456700	1.97888300	-0.72463800
O	2.36274500	2.62642300	-0.31790200
O	1.54560100	0.93500100	-1.56687400
C	2.87035300	0.38424900	-1.68913100
H	2.88432500	-0.08822000	-2.67053500
H	3.59916800	1.19390500	-1.65912100
C	3.10381700	-0.62391500	-0.59494300
C	3.35381600	-2.47576300	1.48044700
C	2.86274400	-1.97649700	-0.82117300
C	3.49027700	-0.20713800	0.68042100
C	3.60971400	-1.12867200	1.71249600

C	2.98744600	-2.90031700	0.20936500
H	2.56447800	-2.30915700	-1.81052700
H	3.68177400	0.84502700	0.85757100
H	3.90735200	-0.79531000	2.70020300
H	2.79594900	-3.95051900	0.02026000
H	3.44738900	-3.19396500	2.28699400
C	-2.70899700	-0.95504500	-0.94103800
O	-3.92189000	-1.55764200	-1.23861900
H	-4.04965000	-2.26871400	-0.60345900
C	-1.36586600	1.01298800	-1.83105100
H	-0.95502800	1.57049700	-2.66565700
C	-0.92744700	1.28424300	-0.60685100
C	-3.37355800	-0.78396600	1.42776900
N	-3.82075500	-1.38672900	2.29922900

Compound 47h (β -CN)



E(RωB97XD) = -1185.70700004

Zero-point correction=	0.400257 (Hartree/Particle)
Thermal correction to Energy=	0.421830
Thermal correction to Enthalpy=	0.422774
Thermal correction to Gibbs Free Energy=	0.349892
Sum of electronic and zero-point Energies=	-1185.306743
Sum of electronic and thermal Energies=	-1185.285170
Sum of electronic and thermal Enthalpies=	-1185.284226
Sum of electronic and thermal Free Energies=	-1185.357108

The coordinations of the structure

0 1

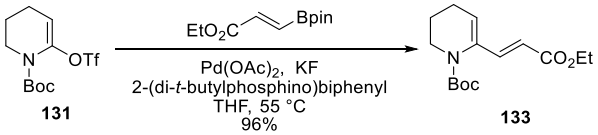
N	-0.23908700	1.97917500	-0.61087200
C	-0.54636000	3.04565900	0.34327700

H	-1.55403600	3.41316100	0.12709000
H	0.16464800	3.85241500	0.18435800
C	-0.46983000	2.48344400	1.75697700
H	0.55291000	2.13992300	1.94592700
H	-0.68900900	3.26620200	2.48793300
C	-1.47875200	1.34632500	1.90224500
H	-2.48220600	1.78081300	1.84463000
H	-1.39541600	0.87018900	2.88453900
C	-1.34635200	0.25972000	0.81663600
C	-0.18050400	-0.70670400	1.13225700
H	-0.31752300	-1.10341000	2.14400300
H	0.77663900	-0.17698800	1.11382800
C	-0.12541900	-1.85308400	0.13340900
H	0.55838000	-2.62769300	0.47852200
H	0.23307700	-1.49402300	-0.83692500
O	-1.38780700	-2.49378900	-0.00525800
C	-2.63630400	-0.59908200	0.77714800
C	-2.35556300	-0.99164100	-1.69439100
H	-3.36583900	-0.80164300	-2.06936100
H	-1.88831300	-1.70729800	-2.38102600
C	1.05869200	1.90096500	-1.04452500
O	1.89186100	2.75587500	-0.84316300
O	1.30737100	0.76255000	-1.72282000
C	2.69765500	0.43198200	-1.89015000
H	2.72961500	-0.19234200	-2.78230500
H	3.26597900	1.34643000	-2.05910100
C	3.18896700	-0.31972400	-0.68081400
C	3.92079300	-1.71841300	1.62332200
C	3.18463300	-1.71208300	-0.66718500
C	3.58127200	0.36900100	0.46869200
C	3.94049000	-0.32784800	1.61503100
C	3.54953600	-2.41066000	0.47738100
H	2.88420800	-2.25509600	-1.55790600
H	3.58785200	1.45295200	0.45854300
H	4.24130500	0.21590900	2.50337600
H	3.54247100	-3.49483800	0.47457500
H	4.20284400	-2.26108000	2.51839300
C	-2.48772400	-1.66761900	-0.31832700
O	-3.60653000	-2.48826600	-0.25808500

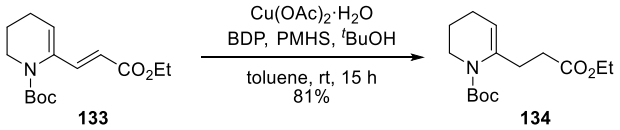
H	-3.42220800	-3.25842300	-0.80088300
C	-1.57280600	0.28832000	-1.67817600
H	-1.33581700	0.74339700	-2.63329200
C	-1.10723300	0.84995600	-0.56893200
C	-3.83599500	0.20781200	0.56095000
N	-4.76805400	0.85973100	0.39286400
H	-2.75392300	-1.12982700	1.72678700

第二章　Lyconesidine B の全合成

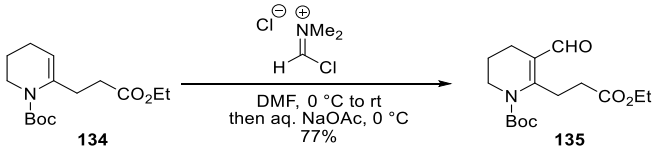
1. Experimental Procedure



Compound 133: To a solution of Compound **131**[51] (21.4 g, 64.5 mmol) in THF (600 mL) were added a solution of (*E*)-ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate, prepared from ethyl propiolate (104 mmol) and bis(pinacolato)diboron (104 mmol) by following Yun's procedure[52] in THF (90 mL), 2-(di-*tert*-butylphosphino)biphenyl (1.92 g, 6.45 mmol), KF (11.2 g, 193.5 mmol) and $Pd(OAc)_2$ (726 mg, 3.23mmol) at room temperature. After stirring for 40 h at 55 °C (oil bath), the reaction mixture was diluted with Et_2O. The resultant mixture was washed with water and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (hexane/EtOAc = 8:1) to give **133** (17.4 g, 61.8 mmol, 96%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (1H, d, *J* = 15.1 Hz), 5.91 (1H, d, *J* = 15.8 Hz), 5.63 (1H, t, *J* = 3.8 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 3.56-3.55 (2H, m), 2.25 (2H, td, *J* = 6.9, 4.1 Hz), 1.82-1.79 (2H, m), 1.44 (9H, s), 1.29 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.1, 153.7, 143.7, 137.0, 120.9, 116.1, 81.3, 60.2, 44.0, 28.2, 23.8, 22.9, 14.3; IR (ATR) 2979, 1698, 1636, 1364 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{24}NO_4$ 282.1705; Found 282.1704.

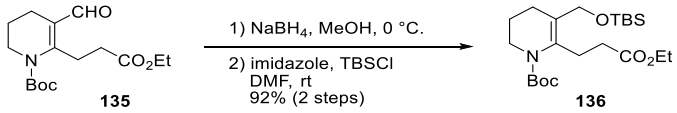


Compound 134: To a suspension of $Cu(OAc)_2 \cdot H_2O$ (31.7 mg, 0.159 mmol) and 1,2-bis(diphenylphosphino)benzene (BDP) (80.2 mg, 0.180 mmol) in toluene (20 mL) was added *t*-BuOH (1.03 mL, 10.8 mmol). After stirring at room temperature for 20 min, poly(methylhydrosiloxane) (PMHS) (9.5 mL, 124 mmol) was added and stirred for 5 min at the same temperature. To the reaction mixture was added a solution of **133** (1.02 g, 3.61 mmol) in toluene (16 mL). After stirring at room temperature for 15 h, the reaction was quenched by addition of water. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **134** (831 mg, 2.93 mmol, 81%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, s), 4.04 (2H, q, *J* = 7.2 Hz), 3.42 (2H, t, *J* = 5.3 Hz), 2.72 (2H, t, *J* = 7.6 Hz), 2.32 (2H, t, *J* = 7.6 Hz), 1.98 (2H, m), 1.69-1.64 (2H, m), 1.41 (9H, s), 1.17 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 153.3, 138.2, 112.9, 80.4, 60.0, 44.7, 32.8, 30.9, 28.1, 23.1, 22.9, 14.1; IR (ATR) 2978, 2924, 1737, 1698, 1367 cm^{-1}; HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{25}NO_4Na$ 306.1681; Found 306.1687.



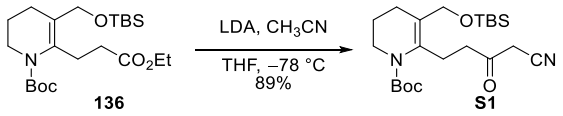
134 135

Compound 135: To a solution of **134** (12.6 g, 44.5 mmol) in DMF (440 mL) was added (chloromethylene)dimethyliminium chloride (8.78 g, 68.6 mmol) at 0 °C. After stirring at room temperature for 6.5 h, a solution of NaOAc (20.5 g, 250 mmol) in water (200 mL) was added at 0 °C and stirred for 10 min at 0 °C. The reaction mixture was diluted with water and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to afford **135** (10.7 g, 34.4 mmol, 77%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (1H, s), 4.10 (2H, q, *J* = 7.1 Hz), 3.52 (2H, t, *J* = 5.6 Hz), 3.40 (2H, t, *J* = 7.6 Hz), 2.57 (2H, t, *J* = 7.6 Hz), 2.24 (2H, t, *J* = 6.7 Hz), 1.77-1.72 (2H, m), 1.49 (9H, s), 1.22 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8, 172.1, 156.5, 152.5, 123.4, 82.6, 60.6, 45.8, 34.2, 28.0, 24.0, 22.1, 20.8, 14.2; IR (ATR) 2979, 2938, 1733, 1710, 1657, 1601 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{26}NO_5$ 312.1811; Found 312.1818.

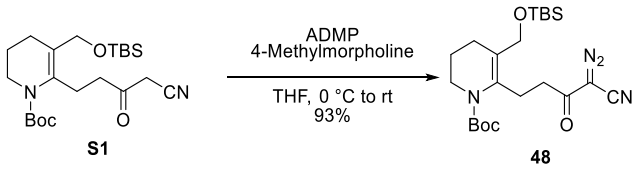


135 136

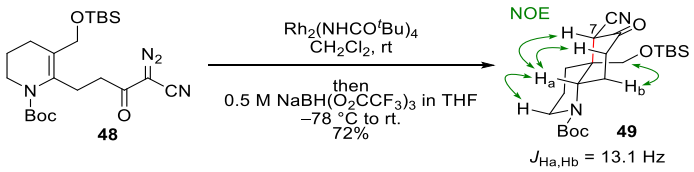
Compound 136: To a solution of **135** (11.9 g, 37.9 mmol) in MeOH (150 mL) was added $NaBH_4$ (1.47 g, 38.9 mmol) at 0 °C. After stirring at 0 °C for 10 min, the reaction was quenched by addition of aq. NH_4Cl. The resultant mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. To a solution of the resultant residue in DMF (80 mL) were added imidazole (3.64 g, 53.5 mmol) and TBSCl (6.95 g, 46.1 mmol) at room temperature. After stirring at room temperature for 1 h, additional imidazole (1.43 g, 21.0 mmol) and TBSCl (2.45 g, 16.3 mmol) were added to the reaction mixture. After stirring for 14 h at room temperature, additional imidazole (1.21 g, 17.8 mmol) and TBSCl (2.34 g, 15.5 mmol) were added to the reaction mixture and stirred for 20 min and additional imidazole (1.01 g, 14.8 mmol) and TBSCl (2.38 g, 15.8 mmol) were added. After stirring for 1 h, the reaction was quenched by addition of water. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to afford **136** (14.9 g, 34.8 mmol, 92% in 2 steps) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.18 (2H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.42 (2H, t, J = 5.5 Hz), 2.86 (2H, t, *J* = 7.9 Hz), 2.41 (2H, t, *J* = 7.6 Hz), 2.16 (2H, t, *J* = 6.9 Hz), 1.78-1.75 (2H, m), 1.48 (9H, s), 1.24 (3H, t, *J* = 7.2 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 154.1, 135.0, 124.8, 80.5, 62.8, 60.2, 44.9, 33.0, 28.3, 25.9, 25.6, 25.5, 23.7, 18.3, 14.2, −5.3; IR (ATR) 2933, 2858, 1736, 1699, 1657 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{42}NO_5Si$ 428.2832; Found 428.2834.



Compound S1: To a solution of diisopropyamine (12.4 mL, 88.2 mmol) in THF (170 mL) was added *n*BuLi (1.3 M hexane solution) (55.0 mL, 88.0 mmol), dropwise at −78 °C. After stirring at −78 °C for 40 min, CH_3CN (4.70 mL, 89.3 mmol) was added dropwise at −78 °C. After stirring at the same temperature for 1 h, a solution of **136** (16.5 g, 35.2 mmol) in THF (120 mL) was added dropwise via cannula. The solution was stirred for 30 min, then aq. NH_4Cl was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **S1** (13.3 g, 31.5 mmol, 89%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (2H, s), 3.49 (2H, s), 3.41-3.39 (2H, m), 2.87 (2H, t, *J* = 7.2 Hz), 2.76 (2H, t, *J* = 7.4 Hz), 2.15 (2H, t, *J* = 6.9 Hz), 1.79-1.74 (2H, m), 1.47 (9H, s), 0.90 (9H, s), 0.08 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2, 154.0, 134.5, 124.9, 113.7, 80.6, 62.8, 45.1, 41.1, 31.7, 28.3, 25.9, 25.6, 24.3, 23.5, 18.3, −5.3; IR (ATR) 2932, 2858, 2259, 1732, 1693 cm^{-1}; HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{38}N_2O_4SiNa$ 445.2499; Found 445.2495.

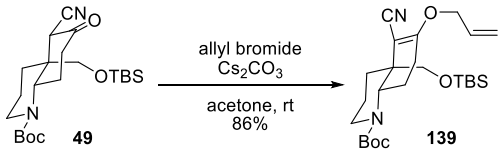


Compound 48: To a solution of **S1** (6.93 g, 16.4 mmol) in THF (160 mL) were added 4-methylmorpholine (1.96 mL, 18.0 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP)[33] (5.15 g, 18.1 mmol) at 0 °C then allowed to warm to room temperature. After stirring for 15 min, water was added for quenching the reaction. The resultant mixture was extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to afford **48** (6.84 g, 15.2 mmol, 93%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (2H, s), 3.42 (2H, t, *J* = 5.4 Hz), 2.93 (2H, t, *J* = 7.4 Hz), 2.77 (2H, t, *J* = 7.4 Hz), 2.16 (2H, t, *J* = 6.9 Hz), 1.79-1.74 (2H, m), 1.48 (9H, s), 0.90 (9H, s), 0.08 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6, 154.0, 134.4, 125.1, 108.3, 80.7, 62.7, 57.0, 45.1, 38.2, 28.3, 25.9, 25.6, 24.8, 23.6, 18.3, −5.3; IR (ATR) 2932, 2858, 2223, 2127, 1670cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{37}N_4O_4Si$ 449.2584; Found 449.2589.

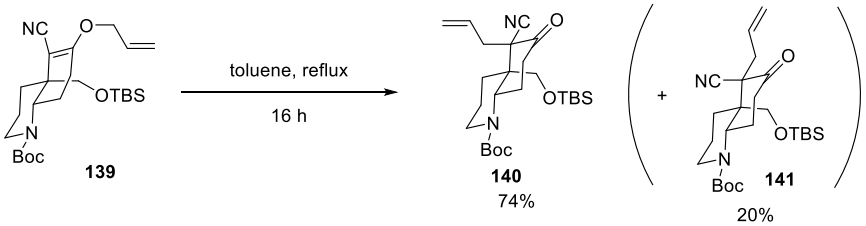


Compound 49: To a solution of **48** (1.29 g, 2.88 mmol) in CH_2Cl_2 (144 mL) was added $Rh_2(NHCO^tBu)_4$[4] (7.2 mg, 0.0117 mmol) at room temperature. After 10 min, the reaction solution was cooled to −78 °C then $NaBH(O_2CCF_3)_3$ (6 mL, 3.02 mmol, 0.5 M THF solution), which was prepared from $NaBH_4$ (114 mg, 3.01 mmol)

and TFA (0.960 mL, 9.02 mmol),[5] was added dropwise at −78 °C then warmed to room temperature. After 30 min, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to afford **49** (876 mg, 2.07 mmol, 72%) as a yellow oil. Epimers on C7 and an enol isomer were observed in $CDCl_3$. ^1H and ^{13}C spectra are described about a major isomer: ^1H NMR (600 MHz, $CDCl_3$) δ 4.35 (1H, d, *J* = 15.1 Hz), 4.08 (1H, d, *J* = 10.3 Hz), 3.65 (1H, dd, *J* = 10.3, 1.4 Hz), 3.48-3.41 (1H, m), 3.37 (1H, d, *J* = 13.1 Hz), 3.13 (1H, s), 2.71-2.66 (1H, m), 2.63-2.61 (1H, m), 2.30-2.23 (2H, m), 2.14-2.12 (1H, m), 1.56-1.53 (1H, m), 1.48-1.46 (11H, m), 0.90 (9H, s), 0.10 (6H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.3, 154.3, 114.5, 80.1, 64.4, 64.1, 52.7, 49.0, 46.5, 40.1, 37.7, 28.4, 26.9, 25.8, 22.3, 18.4, −5.9, −6.1; IR (ATR) 2931, 2859, 2208, 2129, 1732, 1701 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{39}N_2O_4Si$ 423.2679; Found 423.2676.

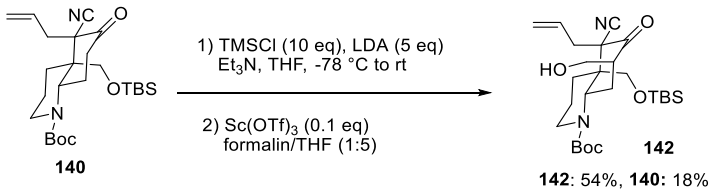


Compound 139: To a solution of **49** (14.3 g, 33.9 mmol) in acetone (340 mL) were added Cs_2CO_3 (16.5 g, 50.7 mmol) and allyl bromide (4.90 mL, 57.5 mmol) at room temperature. After 7 h, the reaction mixture was filtered through celite with EtOAc and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to afford **139** (13.5 g, 29.2 mmol, 86%) as a yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 5.97-5.91 (1H, m), 5.40 (1H, dd, *J* = 17.2, 1.4 Hz), 5.26 (1H, dd, *J* = 10.3, 1.4 Hz), 4.58-4.50 (2H, m), 4.27 (1H, dd, *J* = 13.4, 4.5 Hz), 3.79 (1H, d, *J* = 9.6 Hz), 3.65 (1H, d, *J* = 10.3 Hz), 3.00 (1H, dd, *J* = 13.1, 2.8 Hz), 2.80-2.76 (1H, m), 2.67 (1H, td, *J* = 13.3, 3.0 Hz), 2.51-2.47 (1H, m), 2.43 (1H, d, *J* = 13.8 Hz), 2.34-2.30 (1H, m), 2.15-2.13 (1H, m), 1.67-1.43 (11H, m), 1.29 (1H, td, *J* = 13.6, 4.6 Hz), 0.91 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 154.7, 132.7, 117.9, 116.6, 95.0, 79.8, 68.7, 64.0, 63.0, 48.8, 41.1, 33.5, 28.5, 27.3, 25.9, 23.4, 21.7, 18.2, −5.5, −5.8; IR (ATR) 2932, 2858, 2212, 2128, 1733, 1694, 1625 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{43}N_2O_4Si$ 463.2992; Found 463.2997.

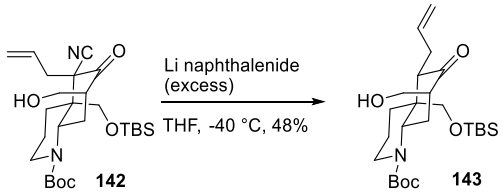


Compound 140: A solution of **139** (442 mg, 0.955 mmol) in toluene (9.5 mL) was stirred under reflux. After 16 h, the reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to afford **140** (327 mg, 0.707 mmol, 74%) as white solid and **158b** (89.1 mg, 0.193 mmol, 20%) as a colorless oil. **140**: ^1H NMR (600 MHz, $CDCl_3$) δ 5.75-5.68 (1H, m), 5.17 (1H, br s), 5.15 (1H, br d, *J* = 4.8 Hz), 4.32 (1H, br d, *J* = 13.8 Hz), 4.17 (1H, d, J = 10.3 Hz), 3.69-3.64 (2H, m), 3.43 (1H, qd, *J* = 13.4, 4.0 Hz), 2.80 (1H, dd, *J* = 14.5, 5.5 Hz), 2.69-2.64 (1H, m), 2.55 (1H, dd, *J* = 13.8, 9.0 Hz), 2.49

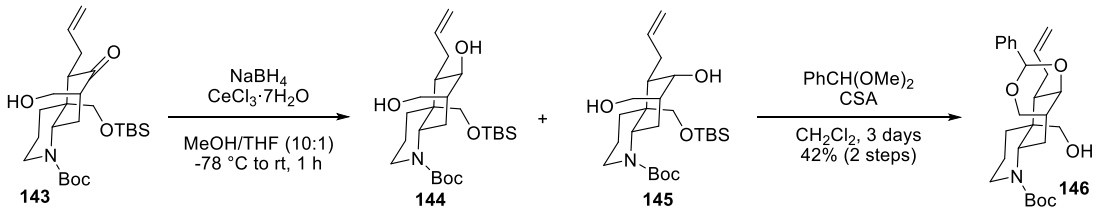
(1H, dq, *J* = 15.5, 2.4 Hz), 2.30-2.26 (1H, m), 2.23-2.17 (1H, m), 1.81-1.72 (2H, m), 1.59-1.54 (1H, m), 1.52-1.43 (10H, m), 0.91 (9H, s), 0.11 (3H,s), 0.10 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.6, 154.6, 130.3, 119.7, 117.9, 80.0, 65.7, 59.8, 48.9, 48.9, 47.3, 37.5, 37.0, 31.4, 28.5, 26.9, 25.7, 21.8, 18.5, −6.0, −6.2; IR (ATR) 2930, 2857, 2242, 1726, 1703 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{43}N_2O_4Si$ 463.2992; Found 463.2988.
141: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.95-5.88 (1H, m), 5.21-5.17 (2H, m), 4.29 (1H, d, *J* = 13.8 Hz), 3.92 (1H, dd, *J* = 13.1, 4.1 Hz), 3.79 (1H, d, *J* = 11.7 Hz), 3.55 (1H, d, *J* = 11.0 Hz), 3.25-3.17 (1H, m), 3.00-2.92 (2H, m), 2.77 (1H, td, *J* = 13.1, 2.1 Hz), 2.51 (1H, dq, *J* = 13.9, 2.4 Hz), 2.34-2.25 (2H, m), 2.11 (1H, d, *J* = 13.8 Hz), 1.91 (1H, td, *J* = 13.4, 4.8 Hz), 1.62-1.59 (1H, m), 1.44 (9H, s), 0.87 (9H, s), 0.05 (3H, s), 0.04 (1H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.5, 154.5, 133.8, 119.2, 119.0, 79.9, 62.4, 61.1, 58.8, 49.7, 48.8, 38.5, 32.1, 30.8, 28.4, 27.9, 25.7, 22.4, 18.2, −5.8, −6.1; IR (ATR) 2938, 2865, 2222, 1735, 1700 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{43}N_2O_4Si$ 463.2992; Found 463.2990.



Compound 142 To a solution of ^{i}Pr$_2$NH (462 μL, 3.27 mmol) in THF (9 mL) was added *n*BuLi (1.6 M hexane solution, 2.00 mL, 3.60 mmol) at −78 °C. After stirring for 30 min at the same temperature, a solution of **158a** (304 mg, 0.657 mmol) in THF (9 mL) was added via canula at −78 °C and stirred for 2.5 h. Et_3N (5.4 mL) and TMSCl (804 μL, 6.57 mmol) was added at −78 °C the stirred at room temperature. Afer stirring for 1.5 h, the reaction was quenched with water. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in THF (9 mL). To the resultant solution were added 36-38% aq. formaldehyde (1.8 mL) and $Sc(OTf)_3$ (32.1 mg, 0.0652 mmol). After stirring at room temperature for 18 h, the reaction mixture was concentrated under reduced pressure. To the residue was added water and extracted with Et_2O. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **159** (173.4 mg, 0.352 mmol, 54%) as white solid and **158a** (56.0 mg, 0.121 mmol, 18%) was recovered: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80-5.73 (1H, m), 5.21 (1H, s), 5.18 (1H, d, *J* = 6.0 Hz), 4.36 (1H, d, *J* = 10.3 Hz), 4.03 (1H, td, *J* = 9.0, 4.4 Hz), 3.84-3.76 (3H, m), 3.36-3.26 (2H, m), 3.07 (1H, q, *J* = 6.2 Hz), 2.92-2.87 (1H, m), 2.80 (1H, dd, *J* = 13.8, 6.9 Hz), 2.60 (1H, dd, *J* = 13.8, 6.9 Hz), 2.28 (1H, br s), 2.14 (1H, br d, *J* = 11.0 Hz), 1.86 (1H, br d, *J* = 13.1 Hz), 1.65-1.61 (2H, dq, *J* = 13.9, 4.0 Hz), 1.48 (9H, s), 0.92 (10H, s), 0.15 (1H, s), 0.11 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 154.7, 132.0, 120.0, 118.6, 80.3, 64.0, 63.8, 59.0, 57.5, 49.5, 47.9, 46.4, 33.8, 28.9, 28.4, 28.0, 25.8, 20.9, 18.4, −5.9, −6.1; IR (ATR) 3470, 2930, 2250, 1703 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{45}N_2O_5Si$ 493.3098; Found 493.3105.

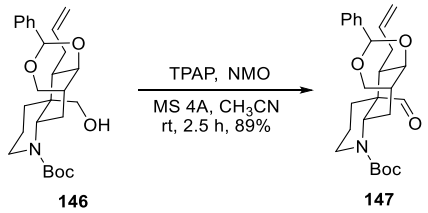


Compound 143: To a solution of **142** (141 mg, 0.286 mmol) in THF (2.9 mL) was added Li naphthalenide (prepared from 34.1 mg of Li, 650 mg of naphthalene and 5 mL of THF under sonication) at −40 °C until the reaction solution become green. After stirring for 10 min, the reaction was quenched with aq. NH_4Cl. The mixture was extracted with EtOAc, the organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to afford **143** (64.1 mg, 0.137 mmol, 48%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.94-5.87 (1H, m), 4.99 (1H, d, J = 17.2 Hz), 4.92 (1H, d, *J* = 9.6 Hz), 4.28 (1H, d, *J* = 13.1 Hz), 3.88-3.81 (3H, m), 3.60 (1H, dd, J = 13.8, 4.1 Hz), 3.48-3.42 (2H, m), 2.76-2.67 (3H, m), 2.16 (1H, dd, J = 13.4, 3.8 Hz), 2.12-2.06 (3H, m), 1.73-1.64 (1 H, br m), 1.53-1.49 (1H, m), 1.45 (9H, s), 0.87 (9H, s), 0.045 (3H, s), 0.025 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.5, 154.6, 139.2, 114.6, 79.5, 46.8, 62.7, 62.2, 57.1, 52.1, 49.0, 47.2, 35.8, 29.1, 28.5, 27.4, 25.8, 22.6, 08.2, −5.8, −6.1; IR (ATR) 3432, 2929, 2858, 1702 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_2H_{50}N_5O_5Si$ 468.3145; Found 468.3143.

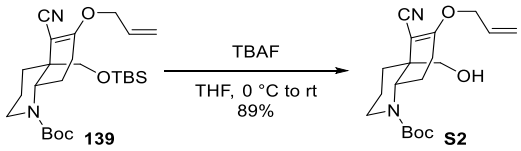


Compound 146: To a solution of **143** (18.0 mg, 0.0384 mmol) in MeOH (1 mL) and THF (100 μL) was added $CeCl_3·7H_2O$ (28.7 mg, 0.0770 mmol) at room temperature. The reaction mixture was cooled to −78 °C. To the reaction mixture was added $NaBH_4$ (8.4 mg, 0.222 mmol) at −78 °C then arrowed to warm to room temperature. After stirring for 1 h, water was added. The resultant mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL). To the solution was added $PhCH(OMe)_2$ (11.5 μL, 0.0768 mmol) and (+)-10-camphorsulfonic acid (8.8 mg, 0.0379 mmol) at room temperature. After stirring for 3 days, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **146** (7.1 mg, 0.160 mmol, 42%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49-7.48 (2H, m), 7.37-7.31 (3H, m), 6.02-5.96 (1H, m), 5.73 (1H, s), 5.03 (1H, dd, *J* = 17.2, 1.4 Hz), 4.92 (1H, br d, *J* = 9.0 Hz), 4.75 (1H, dd, *J* = 12.4, 5.5 Hz), 4.23-4.17 (2H, m), 3.90 (1H, dd, *J* = 11.4, 5.2 Hz), 3.78-3.70 (2H, m), 3.32 (1H, td, *J* = 14.5, 6.9 Hz), 3.21 (1H, dd, *J* = 9.0, 6.2 Hz), 3.06 (1H, dd, *J* = 14.5, 4.8 Hz), 2.81-2.73 (2H, m), 2.49-2.37 (2H, m), 2.32-2.28 (1H, m), 2.02 (1H, br d, *J* = 13.8 Hz), 1.66-1.56 (3H, m), 1.46 (9H, s), 1.25-1.17 (1H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.5, 139.5, 138.7, 128.7, 128.2, 126.2, 115.2, 93.3, 80.2, 75.7, 66.4, 62.5, 62.2, 50.5, 44.3, 43.8, 35.9, 33.3, 31.8, 28.4, 27.9, 22.7; IR (ATR) 3469, 2929, 1669 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for

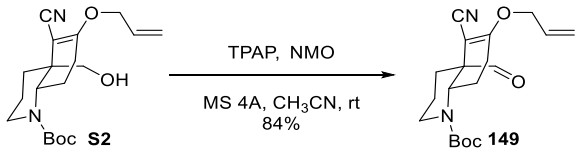
$C_{26}H_{38}NO_5$ 444.2750; Found 444.2749.



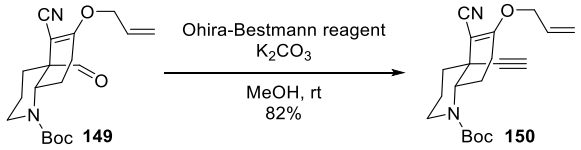
Compound 147: To a solution of **146** (29.5 mg, 0.0665 mmol) in CH_3CN (1 mL) were added 4-methylmorpholine *N*-oxide (12.3 mg, 0.105 mmol) and activated MS 4A. After stirring at room temperature for 30 min, TPAP (2.2 mg, 0.00626 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 h the concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **147** (26.0 mg, 0.0589 mmol, 89%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.05 (1H, s), 7.41-7.40 (2H, m), 7.31-7.26 (3H, m), 5.78-5.71 (1H, m), 5.64 (1H, s), 4.95 (1H, d, *J* = 17.4 Hz), 4.89 (1H, d, *J* = 10.2 Hz), 4.44 (1H, dd, *J* = 12.4, 5.5 Hz), 4.18 (1H, t, *J* = 12.1 Hz), 3.98 (1H, d, *J* = 13.1 Hz), 3.93 (1H, dd, *J* = 11.0, 4.8 Hz), 3.28 (1H, td, *J* = 14.3, 6.0 Hz), 3.20 (1H, dd, *J* = 14.5, 3.4 Hz), 2.86-2.83 (1H, m), 2.73-2.68 (1H, m), 2.59 (1H, br d, *J* = 13.8 Hz), 2.40-2.37 (1H, m), 2.26-2.22 (2H, m), 1.84 (1H, br d, *J* = 14.5 Hz), 1.74-1.66 (1H, m), 1.56-1.53 (1H, m), 1.34 (9H, s), 1.20-1.14 (1H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 155.0, 138.2, 137.5, 128.9, 128.3, 126.1, 116.7, 93.5, 80.3, 74.8, 66.0, 61.1, 55.4, 49.1, 43.3, 33.6, 33.1, 31.3, 28.3, 27.5, 23.1; IR (ATR) 2929, 1694 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{36}NO_5$ 442.2593; Found 442.2599.



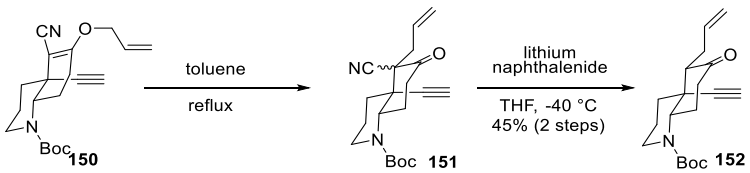
Compound S2: **139** (13.5 g, 29.2 mmol) was dissolved in a 1 M solution of TBAF in THF (88.0 ml, 88.0 mmol) at room temperature. After stirring at room temperature for 5 h, water was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to afford **S2** (9.01 g, 25.9 mmol, 89%) as brown foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89-5.84 (1H, m), 5.33 (1H, d, *J* = 17.5 Hz), 5.19 (1H, d, *J* = 10.6 Hz), 4.53-4.45 (2H, m), 4.13 (1H, dd, *J* = 13.3, 3.9 Hz), 3.76 (1H, d, *J* = 12.3 Hz), 3.49 (1H, d, *J* = 9.5 Hz), 3.05 (1H, brs), 2.96-2.85 (2H, m), 2.74-2.69 (1H, m), 2.50 (1H, dd, *J* = 17.9, 4.7 Hz), 2.31-2.24 (1H, m), 2.03-1.94 (2H, m), 1.68-1.60 (1H, m), 1.52-1.27 (11H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 155.7, 132.3, 117.6, 116.1, 92.8, 80.2, 68.4, 63.6, 63.0, 49.2, 40.3, 34.1, 28.1, 26.8, 23.3, 21.5; IR (ATR) 3460, 2940, 2867, 2208, 1673 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{29}N_2O_4$ 349.2127; Found 349.2123.



Compound 149: To a solution of compound **S2** (4.65 g, 13.3 mmol) in CH_3CN (66 mL) were added 4-methylmolpholine *N*-oxide (2.53 g, 21.6 mmol) and dried MS 4A (10 g) at room temperature. After stirring at room temperature for 30 min, tetrapropylammonium perruthenate (502 mg, 1.43 mmol) was added. After stirring at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure directly. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **149** (3.86 g, 11.1 mmol, 84%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (1H, s), 5.97-5.92 (1H, m), 5.41 (1H, d, *J* = 17.2 Hz), 5.30 (1H, d, *J* = 10.6 Hz), 4.67-4.59 (2H, m), 4.21 (1H, d, *J* = 10.0 Hz), 3.15 (1H, dd, *J* = 13.2, 2.3 Hz), 2.97-2.93 (1H, m), 2.76 (1H, td, *J* = 13.5, 2.5 Hz), 2.68 (1H, dd, *J* = 18.3, 4.6 Hz), 2.62 (1H, d, *J* = 13.2 Hz), 2.51-2.44 (1H, m), 2.32 (1H, dd, *J* = 13.5, 6.0 Hz), 1.84-1.74 (1H, m), 1.62 (1H, d, *J* = 14.0 Hz), 1.44-1.43 (10H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.1, 170.0, 154.3, 131.8, 118.1, 114.8, 87.6, 80.3, 68.9, 61.6, 50.3, 48.7, 31.6, 28.1, 26.9, 23.3, 22.4; IR (ATR) 2976, 2922, 2209, 1689 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{27}N_2O_4$ 347.1971; Found 347.1966.

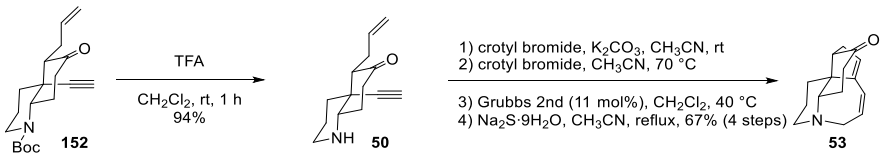


Compound 150: To a solution of compound **149** (6.72 g, 19.4 mmol) in MeOH (100 mL) were added dimethyl (1-diazo-2-oxopropyl)phosphonate (Ohira-Bestmann reagent) (3.52 ml, 23.3 mmol) and K_2CO_3 (4.05 g, 29.3 mmol) at room temperature. After stirring at room temperature for 9.5 h, water was added for quenching the reaction. The resultant mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford **150** (5.46 g, 15.9 mmol, 82%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87-5.83 (1H, m), 5.32 (1H, d, *J* = 17.2 Hz), 5.20 (1H, d, *J* = 10.6 Hz), 4.54-4.47 (2H, m), 4.23 (1H, d, *J* = 12.3 Hz), 2.82 (1H, d, *J* = 12.6 Hz), 2.67-2.48 (3H, m), 2.32-2.25 (4H, m), 1.93 (1H, q, *J* = 13.6 Hz), 1.53 (1H, d, *J* = 14.0 Hz), 1.45-1.37 (10H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 154.3, 132.0, 117.8, 115.4, 92.5, 82.9, 79.6, 73.3, 68.6, 62.8, 47.9, 38.2, 37.7, 28.1, 27.2, 24.9, 21.9; IR (ATR) 3236, 2967, 2936, 2880, 2203, 1674, 1623 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{27}N_2O_3$ 343.2022; Found 343.2016.



Compound 152: A solution of **150** (5.46 g, 15.9 mmol) in toluene (80 mL) was stirred for 9.5 h under reflux (oil bath). The reaction solution was concentrated under reduced pressure. The resultant residue was used for the next

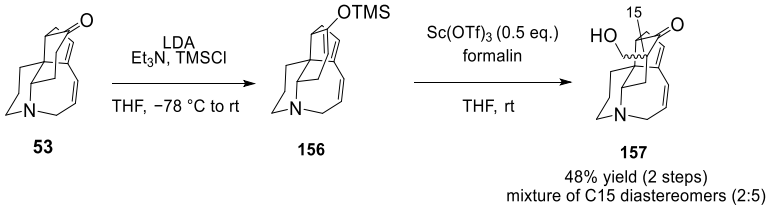
reaction without purification. To a solution of the residue in THF (520 mL) was added solution lithium naphthalenide in THF (20 mL), which was prepared from lithium pole (996 mg, 150 mmol), naphthalene (19.2 g, 150 mmol) and THF (150 mL) under sonication, at −40 °C. After stirring for 30 min at the same temperature, to the reaction solution was added MeOH for quenching. The resultant mixture was diluted with EtOAc and washed with aq. NH_4Cl. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **152** (2.26 g, 7.12 mmol, 45% for 2 steps) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87-5.79 (1H, m), 5.02 (1H, d, *J* = 17.2 Hz), 4.95 (1H, d, *J* = 10.0 Hz), 4.15 (1H, d, *J* = 13.7 Hz), 3.52 (1H, d, *J* = 12.0 Hz), 2.96-2.74 (3H, m), 2.52-2.49 (1H, m), 2.44-2.27 (4H, m), 2.21 (1H, s), 2.11 (1H, dd, *J* = 14.5, 7.3 Hz), 1.90-1.83 (1H, m), 1.68-1.66 (1H, m), 1.53-1.44 (10H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.7, 154.6, 137.4, 115.4, 81.6, 79.6, 74.9, 64.4, 58.5, 45.6, 45.5, 41.1, 36.1, 29.2, 28.2, 27.8, 21.8; IR (ATR) 3259, 2966, 2948, 2871, 1713, 1678 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{28}NO_3$ 318.2069, Found 318.2075.



Compound 50: To a solution of compound **152** (204 mg, 0.643 mmol) in CH_2Cl_2 (6 mL) was added TFA (1 mL) at room temperature. After stirring at the same temperature for 1 h, aq. NaOH was added for quenching the reaction. The resultant mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 8:1) to afford **50** (132 mg, 0.607 mmol, 94%) as a colorless oil: ^{1}H NMR (600MHz, $CDCl_3$) δ 5.88-5.82 (1H, m), 5.02 (1H, dq, *J* = 17.2, 1.6 Hz), 4.95 (1H, dd, *J* = 10.3, 1.4 Hz), 3.16-3.12 (1H, m), 2.82 (1H, dd, *J* = 11.4, 4.5 Hz), 2.72-2.64 (2H, m), 2.48-2.37 (2H, m), 2.29-2.27 (2H, m), 2.24-2.21 (1H, m), 2.16-2.11 (1H, m), 2.00-1.91 (2H, m), 1.82-1.71 (1H, m), 1.63-1.58 (2H, m), 1.45 (1H, td, *J* = 13.1, 3.4 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.8, 137.7, 115.5, 82.2, 75.8, 62.1, 57.7, 46.4, 45.6, 40.4, 35.7, 30.7, 27.4, 23.4; IR (ATR) 3288, 3075, 2939, 2858, 1713, 1639 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{20}NO$ 218.1545, Found 218.1548.

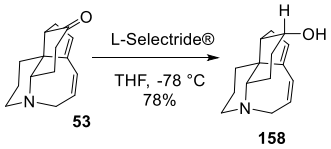
Compound 53: To a solution of compound **50** (132 mg, 0.607 mmol) in CH_3CN (6 mL) were added K_2CO_3 (690 mg, 4.99 mmol) and crotyl bromide (309 μL, 3.04 mmol) at room temperature. After stirring at the same temperature for 1 h, the mixture was filtered through celite with EtOAc. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_3CN (6 mL). To the solution was added crotyl bromide (309 μL, 3.04 mmol) at room temperature. After stirring at 70 °C (oil bath) for 9 h, the rection mixture was cooled to room temperature. The volatile components were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (24 mL). To the solution was added Grubbs 2nd (38.6 mg, 0.0454 mmol) at room temperature. After stirring at 40 °C (oil bath) for 18 h, additional Grubbs 2nd (19.0 mg, 0.0224 mmol). The reaction mixture was stirred at 40 °C (oil bath) for 48 h. After cooling to room temperature, to the reaction solution was added SH-silica gel (SCAVENGER SH Silica, Fuji Silysia Chemical) and stirred for 10 min at room temperature for the

removal of Ru. The mixture was filtered through cotton with $CHCl_3$/MeOH = 5:1 and concentrated under reduced pressure. The residue was dissolved in CH_3CN (6 mL). To the solution was added $Na_2S \cdot 9H_2O$ (300 mg, 1.22 mmol) at room temperature. After stirring under reflux (oil bath) for 1 h, the reaction solution was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 5:1) to afford compound **53** (93.4 mg, 0.407 mmol, 67% for 4 steps) as a brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (1H, dd, *J* = 12.0, 2.3 Hz), 5.73 (1H, s), 5.47 (1H, dd, *J* = 12.3, 4.9 Hz), 3.88 (1H, d, *J* = 20.0 Hz), 3.45 (1H, dd, *J* = 19.8, 4.9 Hz), 3.36 (1H, dd, *J* = 12.5, 2.8 Hz), 3.23-3.16 (2H, m), 2.94 (1H, dd, *J* = 17.5, 2.5 Hz), 2.60-2.52 (2H, m), 2.43 (1H, td, *J* = 13.5, 3.0 Hz), 2.34 (1H, d, *J* = 6.3 Hz), 2.05-1.85 (4H, m), 1.70 (1H, td, *J* = 12.5, 4.0 Hz), 1.36 (1H, d, *J* = 14.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 221.9, 146.3, 133.7, 130.9, 126.6, 61.5, 60.1, 56.2, 55.1, 52.8, 41.3, 39.3, 31.0, 26.3, 22.6; IR (ATR) 2920, 2360, 1458, 1234 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{20}NO$ 230.1545, Found 230.1548.



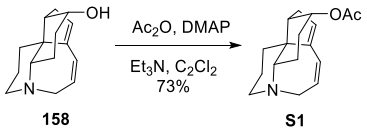
Compound 157: To a solution of *i*Pr$_2$NH (40 µL, 0.285 mmol) in THF (1 mL) was added *n*BuLi (1.6M haexane solution, 170 µL, 272 mmol) at −78 °C. After stirring for 30 min, a solution of **53** (31.4 mg, 0.137 mmol) in THF (2 mL) was added then the reaction solution was stirred for 45 min Et_3N (95 µ, 0.685 mmol) and TMSCl (85 µL, 0.673 mmol) were added. The reaction solution was arrowed to worm to room temperature and stirred for 30 min the reaction was quenched by addition of water. The resultant mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue (**156**) was used for the next reaction without further purification. $Sc(OTf)_3$ (6.6 mg, 0.0134 mmol) was dissolved in THF (1 mL) and 37% formalin (0.5 mL). To the solution was added a solution of **156** in THF (1.5 mL). After stirring at room temperature for 13 h, additional $Sc(OTf)_3$ (26.6 mg, 0.0540 mmol) was added. After stirring for 4.5 h., the reaction was quenched by addition of aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Dual Pore) (EtOAc/MeOH = 10:1) to afford **157** as a mixture of C15 diastereomers (2:5) (16.9 mg, 0.0652 mmol, 48%,) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.33 (minor, 1H, dd, *J* = 12.3, 2.1 Hz), 6.21 (major, 1H, dd, *J* = 11.7, 2.7 Hz), 5.74 (major, 1H, br s), 5.72 (minor, 1H, br s), 5.53 (minor, 1H, dd, *J* = 13.2, 6.0 Hz), 5.45 (major, 1H, dd, *J* = 11.4, 4.8 Hz), 3.94 (minor, 1H, br d, *J* = 10.8 Hz), 3.84 (major, br d, *J* = 19.2 Hz), 3.79-3.71 (minor, 2H, m), 3.79-3.71 (major, 1H, m), 3.65 (major, 1H, dd, *J* = 11.1, 4.5 Hz), 3.51-3.42 (major, 2H, m), 3.51-3.42 (minor, 1H, m), 3.23-3.11 (major, 2H, m), 3.23-3.11 (minor, 1H, m), 3.00 (major, 1H, dd, *J* = 11.1, 3.3 Hz), 2.83-2.76 (minor, 2H, m), 2.65 (minor, 1H, dd, *J* = 18.3, 2.7 Hz), 2.63-2.58 (major, 1H, m), 2.50-2.48 (minor, 1H, m), 2.50-2.48 (major, 1H, m), 2.40 (major, 1H, d, *J* = 6.0 Hz), 2.15 (minor, 1H, td, *J* = 12.6, 8.8 Hz), 2.05-1.87 (major, 4H, m), 2.05-1.87 (minor, 3H, m), 1.79-1.65 (major, 2H, m), 1.79-1.65 (minor, 1H, m), 1.41-1.37 (minor, 1H, m), 1.41-1.37 (major, 1H, m); ^{13}C

NMR (151 MHz, $CDCl_3$) δ 215.5 (minor), 214.1 (major), 146.5 (minor), 146.1 (major), 133.8 (major), 132.2 (minor), 130.9 (major), 129.7 (minor), 126.7 (minor), 126.6 (major), 62.85 (minor), 62.81 (major), 61.1 (major), 60.4 (major), 60.2 (minor), 57.6 (minor), 56.3 (minor), 56.1 (major), 56.0 (major), 54.5 (minor), 52.6 (major), 52.2 (minor), 52.0 (major), 48.5 (minor), 39.5 (minor), 39.2 (major), 33.5 (minor), 29.8 (major), 29.6 (major), 26.9 (minor), 22.6 (major), 21.7 (minor); IR (ATR) 3369, 2927, 2852, 1698 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}NO_2$ 260.1645, Found 261.1634.



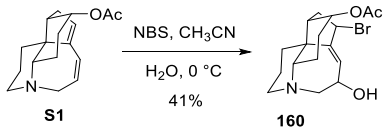
53 158

Compound 158: To a solution of compound **53** (13.6 mg, 0.0593 mmol) in THF (1 mL) was added L-Selectride® (1.0 M THF solution, 89 μL, 0.089 mmol) at −78 °C. After stirring for 40 min at −78 °C, water was added for quenching the reaction at −78 °C. To the resultant mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 5:1) to afford **158** (10.7 mg, 0.0463 mmol, 78%) as a brown oil: ^1H NMR (600 MHz, $CDCl_3$) δ 6.24 (1H, dd, *J* = 12.1, 2.4 Hz), 5.86 (1H, br s), 5.51 (1H, dd, *J* = 12.4, 4.8 Hz), 3.91 (1H, br d, *J* = 19.8 Hz), 3.82 (1H,br s), 3.41 (1H, dd, *J* = 19.6, 5.2 Hz), 3.20-3.10 (2H, m), 2.94 (1H, dd, *J* = 12.7, 3.1 Hz), 2.65 (1H, br dd, *J* = 17.2, 4.8 Hz), 2.34 (1H, dd, *J* = 17.2, 3.4 Hz), 2.09 (1H br s), 2.06 (1H, t, *J* = 5.4 Hz), 2.00-1.79 (4H, m), 162-1.55 (1H, m), 1.55-1.47 (2H, m), 1.30 (1H, br d, *J* = 13.8 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.1, 133.3, 132.2, 126.3, 69.8, 63.0, 56.4, 53.4, 52.6, 51.8, 40.7, 32.3, 31.8, 23.3, 21.5; IR (ATR) 3400, 2924, 2852, 1708, 1647 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{22}NO$ 232.1701; Found 232.1703.

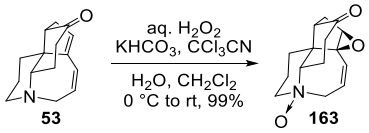


158 S1

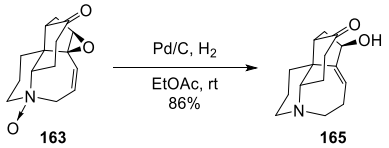
Compound S1: To a solution of compound **158** (10.7 mg, 0.0463 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (19.3 μL, 0.139 mmol), Ac_2O (8.8 μL, 0.926 mmol) and DMAP (0.7 mg, 0.00573 mmol). After stirring at room temperature for 16 h, the reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Dual Pore) (EtOAc) to afford **S1** (9.3 mg, 0.0340 mmol, 73%) as a brown oil: ^1H NMR (600 MHz, $CDCl_3$) δ 6.32 (1H, d, *J* = 12.4 Hz), 5.75 (1H, br s), 5.40 (1H, dd, *J* = 12.1, 4.5 Hz), 5.11-5.09 (1H, m), 3.94 (1H, br d, *J* = 19.3 Hz), 3.49 (1H, dd, *J* = 19.6, 5.2 Hz), 3.27-3.20 (2H, m), 3.15-3.12 (1H, m), 2.58 (1H, dd, *J* = 17.9, 6.2 Hz), 2.23 (1H, t, *J* = 5.9 Hz), 2.06-1.86 (7H, m), 1.83-1.77 (1H, m), 1.72-1.63 (3H, m), 1.57 (1H, td, *J* = 13.1, 4.1 Hz), 1.42 (1H, dd, *J* = 13.8, 2.1 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 146.1, 133.5, 127.7, 126.3, 70.3, 61.9, 55.3, 52.3, 51.7, 50.3, 40.2, 31.5, 28.2, 22.1, 21.4, 21.3; IR (ATR) 2934, 2853, 1730 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{24}NO_2$ 274.1807; Found 274.1812.



Compound 160: To a solution of compound **S1** (9.3 mg, 0.0340 mmol) in CH_3CN (2.5 mL) was added NBS (6.4 mg, 0.0360 mmol) at 0 °C. After stirring for 10 min, aq. $Na_2S_2O_3$ was added. The resultant mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20:1) to afford **160** (5.1 mg, 0.0138 mmol, 41%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.12 (1H, d, *J* = 6.2 Hz), 4.99 (1H, t, *J* = 7.9 Hz), 5.00-4.94 (1H, m), 4.17 (1H, t, *J* = 5.2 Hz), 3.54 (1H, dd, *J* = 16.2, 4.5 Hz), 3.24 (1H, dd, *J* = 14.5, 4.8 Hz), 3.16-3.11 (2H, m), 2.83 (1H, d, *J* = 10.3 Hz), 2.54-2.49 (1H, m), 2.26-2.22 (2H, m), 2.07-1.97 (6H, m), 1.83-1.76 (2H, m), 1.60-1.55 (1H, m), 1.52-1.45 (2H, m), 1.37 (1H, d, *J* = 10.3 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0, 149.7, 126.8, 71.6, 68.9, 62.1, 53.6, 52.8, 52.4, 51.7, 50.7, 37.7, 37.1, 29.5, 21.6, 21.0, 20.2; IR (ATR) 3412, 2934, 1735 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{25}BrNO_3$ 370.1018; Found 370.1020.

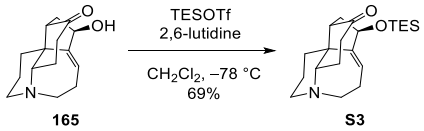


Compound 163: To a solution of compound **53** (40.1 mg, 0.175 mmol) in CH_2Cl_2 (1 mL) were added a solution of $KHCO_3$ (162 mg, 1.62 mmol) in H_2O (1 mL), CCl_3CN (52.4 μL, 0.523 mmol) and 30% aq. H_2O_2 (59.2 μL, 0.523 mmol) at 0 °C and the reaction mixture was stirring at the same temperature for 1 h. Then the reaction mixture was warmed to room temperature. After stirring for 1 h at room temperature, additional a solution of $KHCO_3$ (169 mg, 1.69 mmol) in H_2O (1 mL), CCl_3CN (52.4 μL, 0.523 mmol) and 30% aq. H_2O_2 (59.2 μL, 0.523 mmol). the reaction mixture was stirred at room temperature at room temperature for 3 h. Then reaction mixture was concentrated under reduced pressure directly. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to afford **163** (45.4 mg, 0.174 mmol, 99%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.93 (1H, ddd, *J* = 12.0, 7.2, 2.4 Hz), 5.75 (1H, dd, *J* = 11.7, 3.4 Hz), 4.44 (1H, d, *J* = 17.9 Hz), 4.08 (1H, dd, *J* = 17.9, 6.9 Hz), 3.98 (1H, dd, *J* = 13.4, 4.5 Hz), 3.85 (1H, d, *J* = 11.0 Hz), 3.69 (1H, t, *J* = 13.2 Hz), 3.52 (1H, s), 3.28-3.25 (1H, m), 2.96-2.92 (1H, m), 2.85-2.81 (1H, m), 2.66-2.57 (1H, m), 2.50-2.44 (1H, m), 2.32-2.25 (1H, m), 2.05 (2H, m), 1.92-1.89 (1H, m), 1.85-1.80 (1H, m), 1.76 (1H, td, *J* = 13.8, 5.5 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.3, 130.3, 128.6, 78.2, 73.0, 67.1, 64.8, 60.8, 54.1, 47.1, 39.8, 32.4, 29.2, 22.5, 19.8; IR (ATR) 3381, 3272, 2211, 2127, 1696 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{20}NO_3$ 262.1443, Found 262.1449.



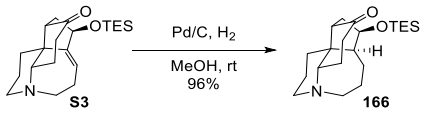
Compound 165: To a suspension of compound **163** (84.4 mg, 0.323 mmol) in EtOAc (1 mL) was added Pd/C (Aldrich 10 wt%, 102 mg). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature

for 3.5 h. The reaction mixture was filtered through celite with $CHCl_3$/MeOH = 5:1. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DualPore) ($CHCl_3$/MeOH = 5:1) to afford compound **165** (68.4 mg, 0.277 mmol, 86%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 5.71 (1H, d, *J* = 7.6 Hz), 4.15 (1H, dd, *J* = 6.0, 1.2 Hz), 3.04 (2H, td, *J* = 14.1, 4.4 Hz), 2.97 (1H, td, *J* = 13.4, 3.2 Hz), 2.88-2.85 (1H, m), 2.78 (1H, dd, *J* = 12.0, 3.6 Hz), 2.64 (1H, dd, *J* = 15.1, 5.5 Hz), 2.43-2.33 (3H, m), 2.13-2.00 (2H, m), 1.77 (1H, d, *J* = 7.6 Hz), 1.67 (2H, m), 1.56-1.49 (3H, m), 1.10-1.02 (2H, m); ^{13}C NMR (151 MHz, C_6D_6) δ 210.4, 149.8, 126.2, 75.7, 62.2, 58.4, 53.8, 52.3, 46.3, 41.1, 40.6, 34.2, 31.6, 27.1, 23.5; IR (ATR) 3387, 2934, 1699, 1457 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{22}NO_2$ 248.1651; Found 248.1646.



165 **S3**

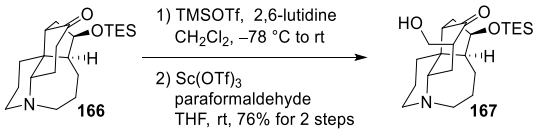
Compound S3: To a solution of compound **165** (68.4 mg, 0.277 mmol) in CH_2Cl_2 (3 mL) were added 2,6-lutidine (70 μL, 0.601 mmol) and TESOTf (60 μL, 0.266 mmol) at −78 °C. After stirring at −78 °C for 10 min, MeOH was added for quenching the reaction at −78 °C. To the resultant solution was added aq. $NaHCO_3$ then extracted with $CHCl_3$/MeOH = 5/1. The combined organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DualPore) ($CHCl_3$/MeOH = 5:1) to afford **S3** (69.1 mg, 0.191 mmol, 69%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 5.79 (1H, d, *J* = 8.3 Hz), 4.34-4.31 (1H, m), 3.29 (1H, td, *J* = 14.1, 4.4 Hz), 3.21-3.12 (2H, m), 2.92-2.88 (2H, m), 2.81-2.74 (1H, m), 2.67 (1H, dd, *J* = 17.9, 5.5 Hz), 2.58-2.51 (1H, m), 2.42-2.35 (1H, m), 2.20 (1H, t, *J* = 7.6 Hz), 2.11-2.06 (2H, m), 1.91-1.82 (3H, m), 1.72-1.69 (1H, m), 1.58 (1H, td, *J* = 13.8, 4.4 Hz), 1.45-1.41 (1H, m), 0.96 (9H, t, *J* = 7.9 Hz), 0.61 (6H, q, *J* = 7.8 Hz); ^{13}C NMR (151 MHz, C_6D_6) δ 212.4, 148.9, 122.6, 74.5, 63.1, 57.4, 51.9, 50.4, 46.4, 41.4, 38.8, 37.9, 31.2, 24.8, 23.3, 6.8, 4.8; IR (ATR) 2952, 2877, 1707 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{36}NO_2Si$ 362.2515; Found 362.2521.



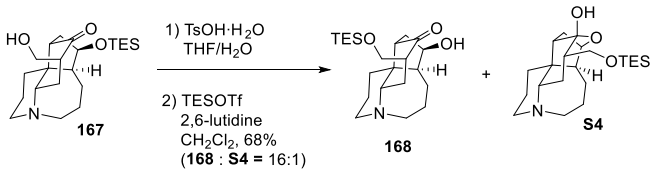
S3 **166**

Compound 166: To a solution of compound **S3** (5.4 mg, 0.0149 mmol) in MeOH (1 mL) was added Pd/C (Aldrich 10 wt%, 5.2 mg). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20 h. The reaction mixture was filtered through celite with $CHCl_3$/MeOH = 5:1 then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DualPore) ($CHCl_3$/MeOH = 10:1) to afford compound **166** (5.2 mg, 0.0143 mmol, 96%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 3.64 (1H, t, *J* = 3.1 Hz), 3.03-2.92 (2H, m), 2.84 (1H, dd, *J* = 13.8, 4.8 Hz), 2.77 (1H, d, *J* = 15.1 Hz), 2.71 (1H, dd, *J* = 12.4, 2.8 Hz), 2.57 (1H, dd, *J* = 17.2, 3.4 Hz), 2.51 (1H, d, *J* = 13.1 Hz), 2.35 (1H, qd, *J* = 12.6, 4.3 Hz), 2.05-1.91 (2H, m), 1.71 (1H, d, *J* = 7.6 Hz), 1.63-1.47 (4H, m), 1.40-1.32 (3H, m), 1.27-1.25 (1H, m), 1.12-0.97 (11H, m), 0.63-0.53 (6H, m); ^{13}C NMR (151 MHz, C_6D_6) δ 208.5, 77.7, 63.5, 59.7, 54.9, 53.9, 52.2, 46.8, 44.8, 41.7, 37.9, 30.5, 28.0, 26.0, 23.8, 7.3, 5.1; IR (ATR) 2928, 2879, 1704 cm^{-1}; HRMS (FAB) *m/z*:

$[M+H]^+$ Calcd for $C_{21}H_{38}NO_2Si$ 364.2672; Found 364.2679.

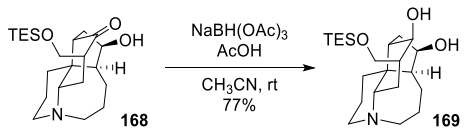


Compound 167: To a solution of compound **166** (9.7 mg, 0.0267 mmol) in CH_2Cl_2 (1 mL) were added 2,6-lutidine (15 μL, 0.13 mmol) and TMSOTf (18 μL, 0.089 mmol) at −78 °C. After stirring at room temperature for 5.5 h, the reaction was quenched with aq. $NaHCO_3$ at room temperature. The resultant mixture was extracted with $CHCl_3$/MeOH = 5:1. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was resolved in THF (1.2 mL). To the solution were added paraformaldehyde (16.2 mg, 0.539 mmol) and $Sc(OTf)_3$ (14.4 mg, 0.0293 mmol) at room temperature. After stirring at room temperature for 3 h, aq. $NaHCO_3$ was added for quenching the reaction. The resultant mixture was extracted with $CHCl_3$/MeOH = 5:1. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DualPore) ($CHCl_3$/MeOH = 5:1) to afford **167** (8.0 mg, 0.0203 mmol, 76%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 4.21 (1H, brs), 3.91-3.87 (2H, m), 3.64 (1H, t, *J* = 2.8 Hz), 3.38 (1H, dd, *J* = 13.4, 2.4 Hz), 3.06 (1H, td, *J* = 13.8, 3.4 Hz), 3.01-2.96 (1H, m), 2.85-2.79 (2H, m), 2.72 (1H, d, *J* = 14.5 Hz), 2.55 (1H, td, *J* = 13.3, 6.7 Hz), 2.43 (1H, d, *J* = 12.4 Hz), 1.97 (1H, d, *J* = 8.3 Hz), 1.94-1.90 (1H, m), 1.60-1.44 (3H, m), 1.36-1.27 (4H, m), 1.21-1.18 (1H, m), 1.14-1.09 (2H, m), 0.99 (9H, t, *J* = 7.9 Hz), 0.61-0.54 (6H, m); ^{13}C NMR (151 MHz, C_6D_6) δ 212.4, 77.7, 64.6, 60.1, 59.3, 54.8, 53.5, 51.6, 51.3, 46.2, 43.8, 39.4, 29.1, 27.6, 27.5, 22.8, 7.2, 5.0; IR (ATR) 2951, 2875, 1764, 1696 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{40}NO_3Si$ 394.2777; Found 394.2781.

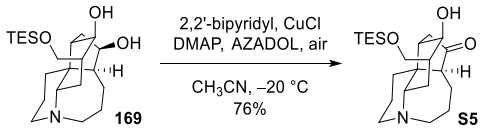


Compound 168: To a solution of compound **167** (4.7 mg, 0.0119 mmol) in THF (400 μL) and H_2O (200 μL) was added $TsOH·H_2O$ (22.3 mg, 0.117 mmol) at room temperature. After stirring at room temperature for 2.5 h, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$/MeOH = 5:1. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2. To the solution were added 2,6-lutidine (14.0 μL, 0.0601 mmol) and prepared 0.5 M solution of TESOTf in CH_2Cl_2 (25.0 μL, 0.0125 mmol) at −78 °C. After stirring at −78 °C for 10 min, additional 0.5 M TESOTf in CH_2Cl_2 (12.5 μL, 0.00625 mmol) was added at −78 °C and stirred for 10 min at the same temperature. MeOH was added for quenching the reaction. The resultant solution was poured on aq. $NaHCO_3$ and extracted with $CHCl_3$/MeOH = 5:1. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DualPore) ($CHCl_3$/MeOH = 40:1) to afford the mixture of **168** and **S4 (**16:1) (3.2 mg, 0.00813 mmol, 68% for 2 steps) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ: 4.06-4.01 (1H, m), 3.92 (0.6H, s), 3.77-3.72 (1H, m), 3.59 (0.4H, s), 3.55 (0.4H, dd, *J* = 13.4, 3.1 Hz), 3.20-3.10 (1.4H, m), 3.01 (0.6H, td, *J* = 13.8, 3.4 Hz), 2.92 (0.4H, dd, *J* = 14.7, 5.1), 2.88-2.81 (2H, m),

2.73-2.60 (1.6H, m), 2.50-2.47 (0.6H, m), 2.42-2.36 (1H, m), 2.18 (0.6H, q, *J* = 13.1 Hz), 2.09 (0.4H, q, *J* = 13.1 Hz), 2.00 (0.4H, d, *J* = 7.6 Hz), 1.97 (0.4H, dd, *J* = 13.1, 2.8 Hz), 1.93 (0.6H, s), 1.66-1.28 (7.4H, m), 1.23-1.15 (2.2H, m), 1.02-0.95 (9H, m), 0.61-0.53 (6H, m); ^{13}C NMR (151 MHz, C_6D_6) δ 212.7, 103.9, 81.7, 76.7, 66.3, 64.9, 60.3, 59.0, 58.4, 54.7, 54.3, 54.1, 53.7, 53.2, 51.6, 51.3, 51.0, 46.8, 44.9, 43.4, 43.2, 40.6, 39.1, 33.9, 30.7, 30.2, 29.1, 28.1, 27.5, 27.1, 23.8, 23.5, 7.1, 7.0, 4.7, 4.6; IR (ATR) 2954, 2925, 2872, 1737 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{40}NO_3Si$ 394.2777; Found 394.2771.

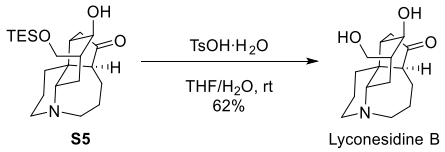


Compound 169: To a solution of compound **168** (4.3 mg, 0.0109 mmol) in CH_3CN (1 mL) were added $NaBH(OAc)_3$ (46.7 mg, 0.220 mmol) and AcOH (25.0 μL, 0.437 mmol) at rt. Additional $NaBH(OAc)_3$ (46.7 mg, 0.220 mmol) and AcOH (25.0 μL, 0.437 mmol) were added three times for 45 min. After stirring for 15 min the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane/EtOAc = 1:1) to afford **169** (3.3 mg, 0.00834 mmol, 77%) as a colorless oil: ^{1}H NMR (600MHz, C_6D_6) δ 4.58 (1H, dd, *J* = 9.6, 4.8 Hz), 4.19 (1H, dd, *J* = 10.3, 8.3 Hz), 3.96 (1H, t, *J* = 5.5 Hz), 3.78 (1H, dd, *J* = 10.0, 5.8 Hz), 3.19-3.07 (3H, m), 2.84 (1H, dd, *J* = 14.1, 4.5 Hz), 2.74 (1H, d, *J* = 14.4 Hz), 2.53-2.50 (1H, m), 2.18 (1H, d, *J* = 13.8 Hz), 2.12 (1H, td, *J* = 13.4, 5.0 Hz), 1.87-1.76 (5H, m), 1.63-1.59 (1H, m), 1.53 (1H, m), 1.39-1.30 (3H, m), 1.23-1.15 (2H, m), 1.00 (9H, t, *J* = 7.9 Hz), 0.58 (6H, q, *J* = 8.0 Hz). ^{13}C NMR (151 MHz, C_6D_6) δ: 76.1, 73.1, 63.5, 59.6, 54.2, 53.9, 52.5, 50.6, 48.3, 43.7, 41.0, 36.9, 30.2, 29.5, 27.0, 23.7, 7.1, 4.6; IR (ATR) 2977, 2920, 1469 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{42}NO_3Si$ 396.2934; Found: 396.2937.



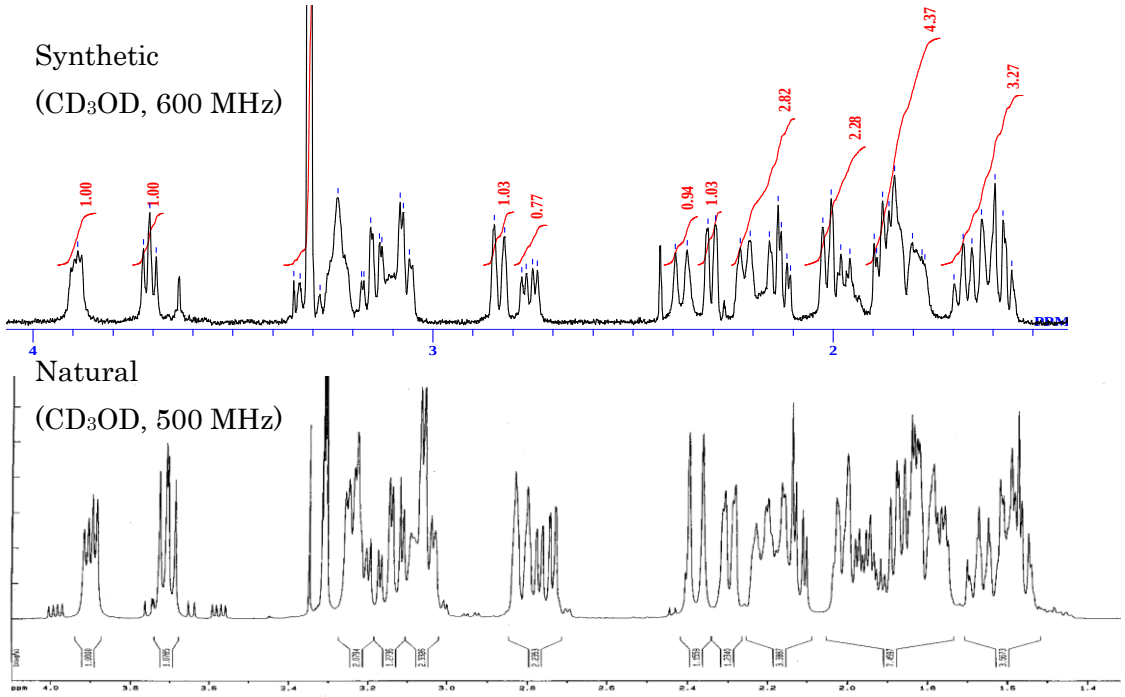
Compound S5: To a solution of compound **169** (3.3 mg, 0.00834 mmol) in CH_3CN (2 mL) were added 2,2'-bipyridyl (2.1 mg, 0.134 mmol), DMAP (3.0 mg, 0.0246 mmol) and AZADOL (0.6 mg, 0.00417 mmol) at room temperature then cooled to −20 °C. To the reaction mixture was added CuCl (1.3 mg, 0.0131 mmol) at −20 °C. After stirring for 30 min at the same temperature under air, the reaction was quenched with aq. $NaHCO_3$ and aq. $Na_2S_2O_4$. The resultant mixture was extracted with CH_2Cl_2 and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DualPore) ($CHCl_3$/MeOH = 40:1) to afford **S5** (2.5 mg, 0.00635 mmol, 76%) as a colorless oil: ^{1}H NMR (600 MHz, C_6D_6) δ 4.01 (1H, t, *J* = 7.6 Hz), 3.61 (1H, dd, *J* = 10.0, 5.9 Hz), 3.20 (1H, dd, *J* = 9.6, 3.4 Hz), 3.08-2.99 (2H, m), 2.91 (1H, brm), 2.76 (1H, dd, *J* = 14.1, 5.2 Hz), 2.68 (1H, d, *J* = 16.5 Hz), 2.62-2.59 (1H, m), 2.38-2.33 (2H, m), 2.10 (1H, brs), 1.85 (1H, td, *J* = 13.4, 5.3 Hz), 1.77-1.73 (2H, m), 1.65-1.62 (1H, m), 1.49-1.46 (1H, m), 1.43-1.29 (4H, m), 1.14-1.07 (2H, m), 0.96 (9H, t, *J* = 7.9 Hz), 0.54 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (151 MHz, C_6D_6) δ 216.0, 74.3, 63.4, 59.4, 56.8, 53.9, 50.3, 45.8, 45.6, 42.4, 41.5, 40.8, 32.1, 30.2, 26.8, 23.8, 6.9, 4.5; IR

(ATR) 2919, 1734, 1467 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{40}NO_3Si$ 394.2777; Found 349.2771.



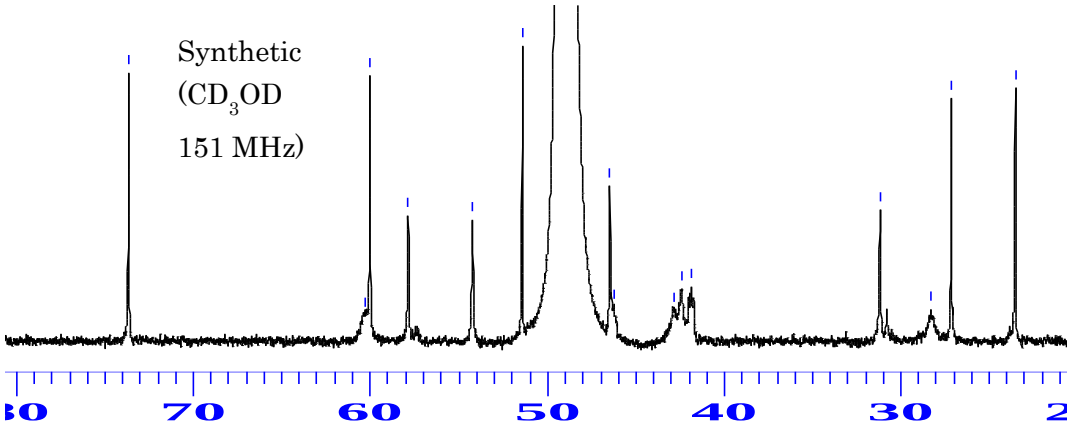
Lyconesidine B: To a solution of compound **S5** (4.1 mg, 0.0104 mmol) in THF (1 mL) and H_2O (0.5 mL) was added $TsOH \cdot H_2O$ (2.1 mg, 0.0122 mmol) at room temperature. After stirring for 20 min at room temperature, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$/MeOH = 5:1 then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by diol silica gel column chromatography ($CHCl_3$/MeOH = 20:1) to afford **lyconesidine B** (1.8 mg, 0.00644 mmol, 62%) as a colorless solid: ^{1}H NMR (600 MHz, CD_3OD) δ 3.89 (1H, dd, *J* = 9.97, 6.3 Hz), 3.71 (1H, dd, *J* = 9.6, 9.6 Hz), 3.28-3.20 (2H, m), 3.16 (1H, ddd, *J* = 13.2, 13.2, 3.0 Hz), 3.09 (1H, m), 3.07 (1H, m), 2.84 (1H, br d, *J* = 15.0 Hz), 2.76 (1H, dd, *J* =16.2, 7.2 Hz), 2.38 (1H, d, *J* =18.0 Hz), 2.31 (1H, dd, *J* =12.6, 2.4 Hz), 2.22 (1H, m), 2.18 (1H, m), 2.13 (1H, ddd, *J* = 13.5, 13.5, 4.4 Hz), 2.02 (1H, d, *J* = 12.0 Hz), 1.96 (1H, m). 1.90-1.76 (4H, m), 1.68 (1H, dd, *J* = 13.5, 13.5 Hz), 1.60 (1H, m), 1.58 (1H, ddd, *J* =13.8, 13.8, 3.0 Hz). ^{13}C NMR (151 MHz, CD_3OD) δ 220.20, 73.84, 60.47, 59.65, 57.91, 54.20, 51.21, 46.59, 46.10, 42.92, 42.69, 41.74, 31.80, 28.45, 27.30, 23.87; IR (ATR) 3304, 2958, 1717, 1522 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{26}NO_3$ 280.1913, Found 280.1911.

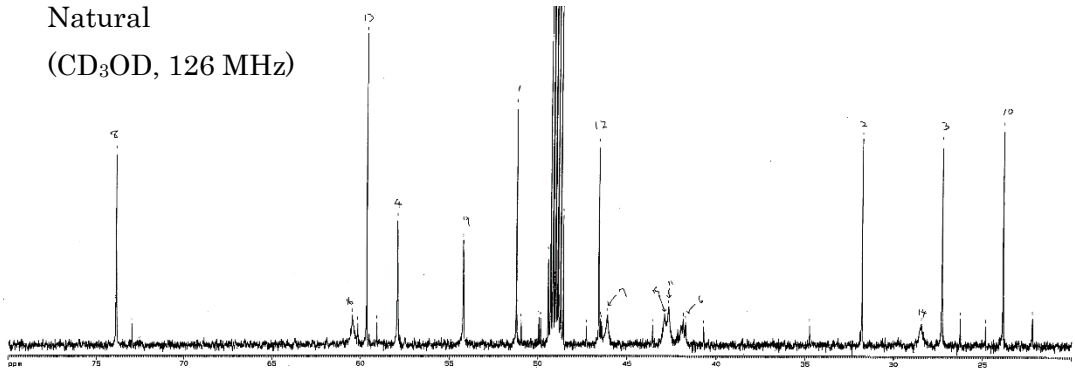
Comparison of ^{1}H NMR data of synthetic with natural lyconesidine B.



	^{1}H NMR (CD_3OD, 600MHz)		^{1}H NMR (CD_3OD, 500 MHz)	
No.	synthetic lyconesidine B		natural lyconesidine B	
16b	3.89	(1H, dd, *J* = 9.9, 6.3 Hz)	3.90	(1H, dd, *J* = 10.9, 5.8 Hz)
16a	3.71	(1H, dd, *J* = 9.6, 9.6 Hz)	3.71	(1H, dd, *J* = 10.9, 8.9 Hz)
8	3.28-3.20	(2H, m)	3.23	(1H, m)
1b			3.20	(1H, m)
9b	3.16	(1H, ddd, *J* = 13.2, 13.2, 3.0 Hz)	3.14	(1H, ddd, *J* = 13.6, 13.6, 3.6 Hz)
13	3.09	(1H, m)	3.07	(1H, m)
9a	3.07	(1H, m)	3.04	(1H, m)
1a	2.84	(1H, br d, *J* = 15.0 Hz)	2.81	(1H, br d, *J* = 15.4 Hz)
6b	2.76	(1H, dd, *J* =16.2, 7.2 Hz)	2.75	(1H, dd, *J* =18.1, 7.2 Hz)
6a	2.38	(1H, d, *J* =18.0 Hz)	2.36	(1H, d, *J* =18.1 Hz)
4	2.31	(1H, dd, *J* =12.6, 2.4 Hz)	2.29	(1H, dd, *J* =12.4, 3.1 Hz)
3b	2.22	(1H, m)	2.20	(1H, m)
15	2.18	(1H, m)	2.17	(1H, m)
14b	2.13	(1H, ddd, *J* = 13.5, 13.5, 4.4 Hz)	2.13	(1H, ddd, *J* = 13.5, 13.5, 4.6 Hz)
11b	2.02	(1H, d, *J* = 12.0 Hz)	2.01	(1H, d, *J* = 13.1 Hz)
10b	1.96	(1H, m)	1.94	(1H, m)
7	1.90-1.76	(4H, m)	1.86	(1H, d, *J* = 10.2 Hz)
2			1.80	(2H, m)
14a			1.77	(1H, m)
3a	1.68	(1H, dd, *J* = 13.5, 13.5 Hz)	1.67	(1H, dd, *J* = 12.3, 12.3 Hz)
10a	1.60	(1H, m)	1.59	(1H, m)
11a	1.58	(1H, ddd, *J* =13.8, 13.8, 3.0 Hz)	1.57	(1H, ddd, *J* =13.1, 13.1, 3.2 Hz)

Comparison of ^{13}C NMR data of synthetic with natural lyconesidine B.

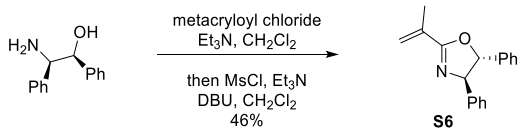




	^{13}C NMR (CD_3OD, 151 MHz)	^{13}C NMR (CD_3OD, 151 MHz)
	synthetic lyconesidine B	natural lyconesidine B
5	220.20	219.84
8	73.84	73.68
16	60.47	60.30
13	59.65	60.03
4	57.91	57.87
9	54.20	54.22
1	51.21	51.42
12	46.59	46.46
7	46.10	46.23
15	42.92	42.84
11	42.69	42.43
6	41.74	41.86
2	31.80	31.19
14	28.45	28.30
3	27.30	27.15
10	23.87	23.54

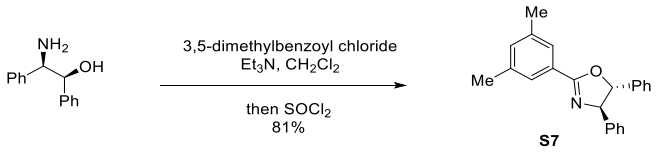
Asymmetric cyclopropanation

Ru catalyst **124a** is commercially available. Known **127c-f** were prepared by reported procedure.[71-75] **124g** and **55** were synthesized by follow procedure.



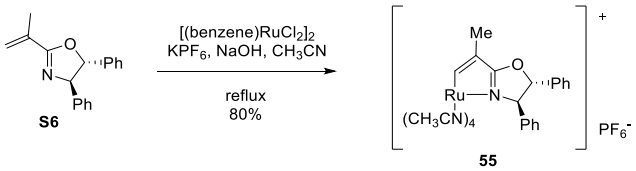
S6

Compound S6: To a suspension of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (235 mg, 1.1 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (554 µL, 4.0 mmol) and methacryloyl chloride (100 µL, 1.0 mmol) at 0 °C. After stirring at room temperature overnight, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 then Et_3N (170 µL), MsCl (90 µL in 5 mL CH_2Cl_2) and DBU (180 µL) were added. After stirring for 3.5 h, MsCl (50 µL), Et_3N (90 µL) and DBU (90 µL) were added at 0 °C. After stirring for 10 min, the reaction mixture was extracted with CH_2Cl_2 then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **S6** (122 mg, 0.463 mmol, 46%) as a white solid: $[\alpha]_D^{16}$ +118.3 (*c* 0.42, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.34 (5H, m), 7.32-7.30 (3H, m), 7.26-7.24 (2H, m), 6.03 (1H, s), 5.58 (1H, s), 5.28 (1H, d, *J* = 8.3 Hz), 5.11 (1H, d, *J* = 7.6 Hz), 2.16 (3H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.96, 141.79, 140.52, 132.62, 128.85, 128.78, 128.33, 127.73, 126.71, 125.58, 122.68, 88.71, 79.09, 19.48; IR (ATR) 3071, 3031, 2969, 2925, 1653, 1606 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{18}NO$ 264.1388, Found 264.1391.

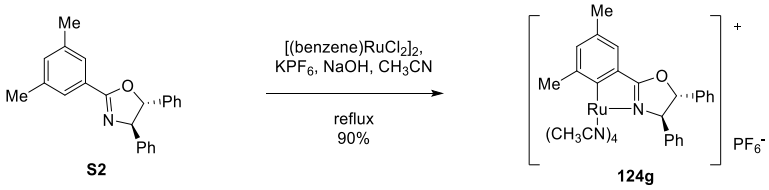


S7

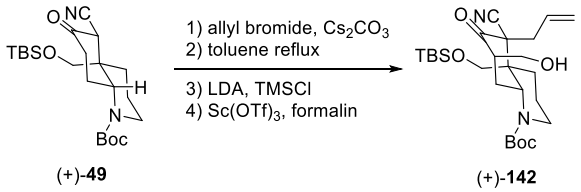
Compound S7: To a solution of compound (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (235 mg, 1.1 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (550 µL, 4.0 mmol) and 3,5-dimethylbenzoyl chloride (150 µL, 1.0 mmol). After stirring at room temperature overnight, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (6 mL) then $SOCl_2$ (360 µL, 5.0 mmol) was added at 0 °C. After stirring at room temperature overnight, the reaction was quenched with aq. $NaHCO_3$, extracted with $CHCl_3$ then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **S7** (265 mg, 0.809 mmol, 81%) as a white solid: $[\alpha]_D^{15}$ −13.8 (*c* 0.52, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (2H, s), 7.42-7.35 (7H, m), 7.33-7.29 (3H, m), 7.18 (1H, s), 5.40 (1H, d, J = 7.6 Hz), 5.20 (1H, d, J = 7.6 Hz), 2.38 (6H, s).^{13}C NMR (151 MHz, $CDCl_3$) δ 164.37, 142.01, 140.51, 138.16, 133.41, 128.91, 128.84, 128.42, 127.75, 127.12, 126.76, 126.31, 125.69, 88.88, 78.94, 21.16; IR (ATR) 3031, 2920, 1641, 1597 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{22}NO$ 328.1701, Found 328.1699.



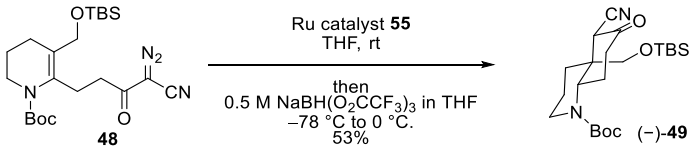
Compound 55: To a solution of **S6** (53 mg, 0.2 mmol), $[(benzene)RuCl_2]_2$ (50 mg, 0.1 mmol) and KPF_6 (147 mg, 0.8 mmol) in CH_3CN (3.5 mL) was added 1 M aq. NaOH (200 µL, 0.2 mmol). After refluxing for at 80 °C 24 h, the reaction mixture was extracted with CH_2Cl_2 then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3CN = 20:1) to afford **55** (107 mg, 0.159 mmol, 80%) as a yellow solid: ^{1}H NMR (600 MHz, CD_3CN) δ 9.99 (1H, s), 7.43-7.40 (5H, m), 7.34 (1H, t, *J* = 6.9 Hz), 7.29 (2H, d, *J* = 7.6 Hz), 7.25 (2H, d, *J* = 8.3 Hz), 5.58 (1H, d, *J* = 6.9 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 2.36 (3H, s), 2.19 (3H, s), 2.11 (3H, s), 2.09 (4H, s), 1.96 (3H, s). ^{13}C NMR (151 MHz, CD_3CN) δ 208.89, 176.65, 142.60, 140.70, 130.00, 129.85, 129.38, 129.01, 128.57, 126.71, 125.90, 123.07, 123.00, 122.94, 91.86, 76.79, 18.29, 4.20, 4.00, 3.91; IR (ATR) 2913, 2270, 1603 cm^{-1}; Anal. Calcd for $C_{26}H_{28}F_6N_5OPRu$: C, 46.43; H, 4.20; N, 10.41; F, 16.95. Found: C, 46.46; H, 4.21; N, 10.35; F, 16.78.



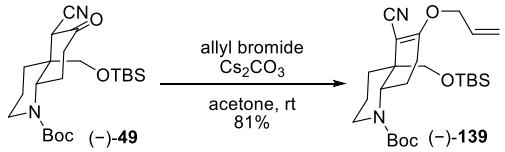
Compound 124g: To a solution of **S7** (57 mg, 0.2 mmol), $[(benzene)RuCl_2]_2$ (50 mg, 0.1 mmol) and KPF_6 (147 mg, 0.8 mmol) in CH_3CN (3.5 mL) was added 1 M aq. NaOH (200 µL, 0.2 mmol). After refluxing at 85 °C for 24 h, the reaction mixture was extracted with CH_2Cl_2 then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3CN = 10:1) to afford **124g** (106 mg, 0.179 mmol, 90%) as a yellow solid: ^{1}H NMR (600 MHz, CD_3CN) δ 7.46-7.38 (5H, m), 7.37 (1H, m), 7.33-7.32 (2H, m), 7.29 (2H, m), 7.22 (1H, s), 6.91 (1H, s), 5.70 (1H, d, *J* = 6.2 Hz), 4.97 (1H, d, *J* = 6.2 Hz), 2.50 (3H, s), 2.34 (3H, s), 2.28 (3H, s), 2.14 (4H, s), 2.04 (3H, s), 1.95 (3H, d, *J* = 4.8 Hz); ^{13}C NMR (151 MHz, CD_3CN) δ 179.57, 176.00, 150.90, 141.90, 140.33, 135.19, 133.18, 131.00, 130.13, 130.07, 129.53, 129.25, 128.57, 126.79, 124.89, 124.44, 92.19, 77.38, 26.48, 20.51, 4.23, 3.96, 3.91; IR (ATR) 2933, 2269, 1627 cm^{-1}; Anal. Calcd for $C_{31}H_{32}F_6N_5OPRu$: C, 50.54; H, 4.38; N, 9.51; F, 15.47. Found: C, 50.44; H, 4.46; N, 9.42; F, 15.44.



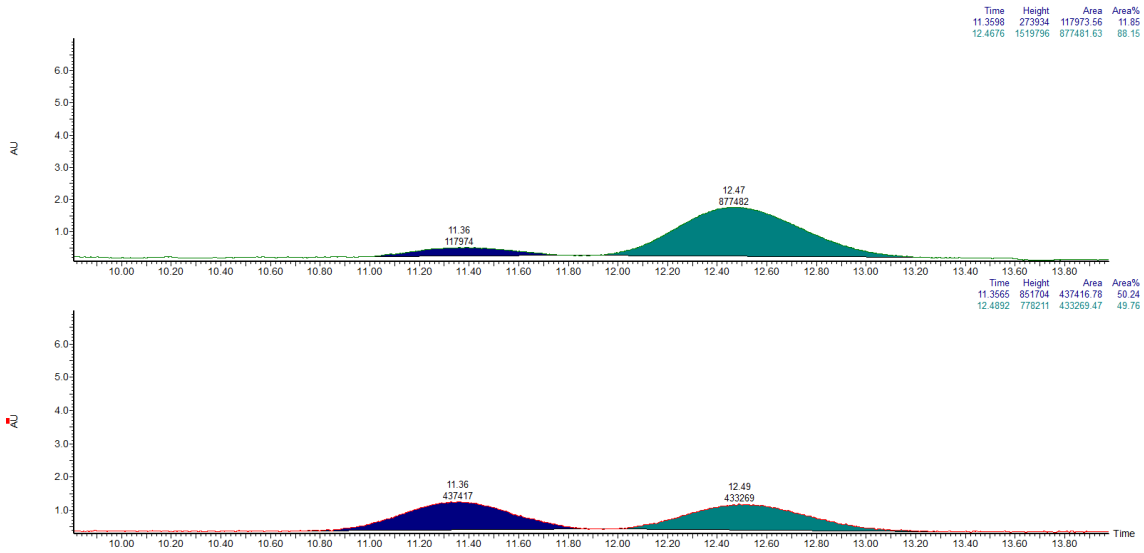
Compound (+)-**142**: (+)-**142** was prepared from (+)-**49** (23:77 er) by the same procedure to racemic **142**: $[\alpha]_D^{19}$ 0.21 (*c* 1.62, $CHCl_3$).



Compound (−)-**49**: To a solution of **48** (95 mg, 0.21 mmol) in THF (5.3 mL) was added Ru catalyst **55** (6.9 mg, 0.010 mmol) at room temperature. After 30 min, the reaction solution was cooled to −78 °C then $NaBH(O_2CCF_3)_3$ (450 µL, 0.23 mmol, 0.5 M THF solution), which was prepared from $NaBH_4$ (37.8 mg, 1.0 mmol) and TFA (230 µL, 3.0 mmol),[5] was added dropwise at −78 °C then warmed to 0 °C. After 30 min, the reaction was quenched with aq. $NaHCO_3$. The resultant mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford (−)-**49** (47.3 mg, 0.11 mmol, 53%) as a yellow oil. Epimers on C7 and an enol isomer were observed in $CDCl_3$: $[\alpha]_D^{17}$ −11.0 (*c* 4.73, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, major isomer) δ 4.35 (1H, d, *J* = 13.1 Hz), 4.08 (1H, d, *J* = 11.0 Hz), 3.69-3.65 (1H, m), 3.48-3.41 (1H, m), 3.37-3.36 (1H, m), 3.14 (1H, s), 2.72-2.67 (1H, m), 2.64-2.61 (1H, m), 2.31-2.25 (2H, m), 2.14-2.12 (1H, m), 1.56-1.53 (1H, m), 1.49-1.43 (11H, m), 0.90 (9H, s), 0.09 (6H, m) ; ^{13}C NMR (151 MHz, $CDCl_3$, major isomer) δ 196.4, 154.4, 114.6, 80.1, 64.3, 64.1, 52.7, 49.0, 46.5, 40.1, 37.7, 28.4, 26.9, 25.7, 22.3, 18.4, −6.0, −6.1; IR (ATR) 2940, 2862, 2251, 1698 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{39}N_2O_4Si$ 423.2679; Found 423.2676.



Compound (−)-**139**: To a solution of (−)-**49** (47.3 mg, 0.11 mmol) in acetone (1.1 mL) were added Cs_2CO_3 (107 mg, 0.33 mmol) and allyl bromide (19 µL, 0.22 mmol) at room temperature. After stirring overnight, the reaction was filtered through celite with EtOAc and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford (−)-**139** (43.4 mg, 0.091 mmol, 81%, 76 %ee) as a yellow solid: $[\alpha]_D^{16}$ −96.3 (*c* 3.98, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.97-5.91 (1H, m), 5.39 (1H, dd, 17.4, 1.2 Hz), 5.27-5.24 (1H, m), 4.55-4.50 (2H, m), 4.28-4.26 (1H, m), 3.79 (1H, d, *J* = 9.6 Hz), 3.65 (1H, d, *J* = 10.3 Hz), 3.00 (1H, dd, *J* = 13.1, 2.8 Hz), 2.82-2.74 (1H, m), 2.67 (1H, td, *J* = 13.3, 3.2 Hz), 2.51-2.48 (1H, m), 2.43 (1H, d, *J* = 13.8 Hz), 2.36-2.29 (1H, m), 2.16-2.12 (1H, m), 1.62-1.48 (11H,m), 1.29 (1H, td, *J* = 13.1, 2.8 Hz), 0.91 (9H, s), 0.06 (6H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 154.6, 132.7, 117.9, 116.6, 95.0, 79.7, 68.7, 63.9, 62.9, 48.8, 41.1, 33.4, 28.4, 27.2, 25.8, 23.3, 21.7, 18.2, −5.5, −5.8; IR (ATR) 2936, 2862, 2210, 1691, 1626 cm^{-1}; HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{43}N_2O_4Si$ 463.2992; Found 463.2988. The enantiomeric excess was determined by UPC analysis: IC-3/SFC, 1.0 mL/min, 5% MeOH/CO_2, λ = 210-400 nm, t_R(*ent*-**139**) = 11.4 min, t_R(**139**) = 12.5 min



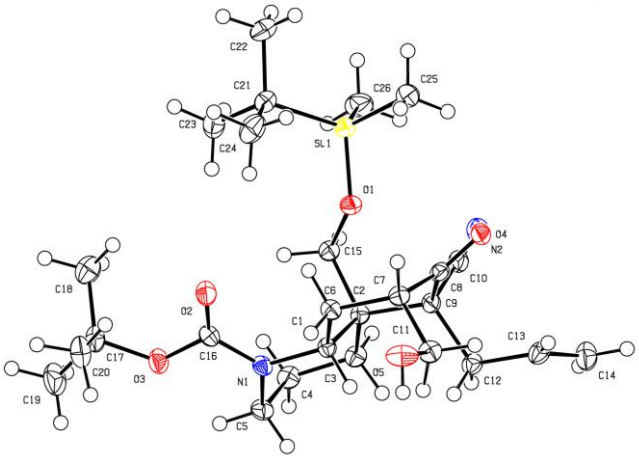
2. Crystallographic Data

The data of compound **142**, (+)-**142**, **22**·**HCl** were collected with a Rigaku XtaLAB P200 diffractometer using multi-layer mirror monochromated Cu-Kα radiation at 100 K.

2-1. Compound 142

142 was crystalized from hexane/EtOAc solvent system as clear plate crystal.

ORTEP Diagram of **142** Showing Thermal Ellipsoids at the 50% Probability Level



CCDC 2059098 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

==========

Bond precision: C-C = 0.0023 A Wavelength=1.54184

Cell: a=12.7065(2) b=13.0358(2) c=33.6268(5)

alpha=90 beta=90 gamma=90

Temperature: 93 K

	Calculated	Reported
Volume	5569.92(15)	5569.92(15)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C26 H44 N2 O5 Si	C26 H44 N2 O5 Si
Sum formula	C26 H44 N2 O5 Si	C26 H44 N2 O5 Si
Mr	492.72	492.72
Dx, g cm-3	1.175	1.175
Z	8	8
Mu (mm-1)	1.034	1.034
F000	2144.0	2144.0
F000'	2151.96	
h,k,lmax	15,16,41	15,16,41
Nref	5611	5556
Tmin,Tmax	0.883,0.902	0.738,1.000
Tmin'	0.733	

Correction method= # Reported T Limits: Tmin=0.738 Tmax=1.000

AbsCorr = MULTI-SCAN

Data completeness= 0.990 Theta(max)= 73.560

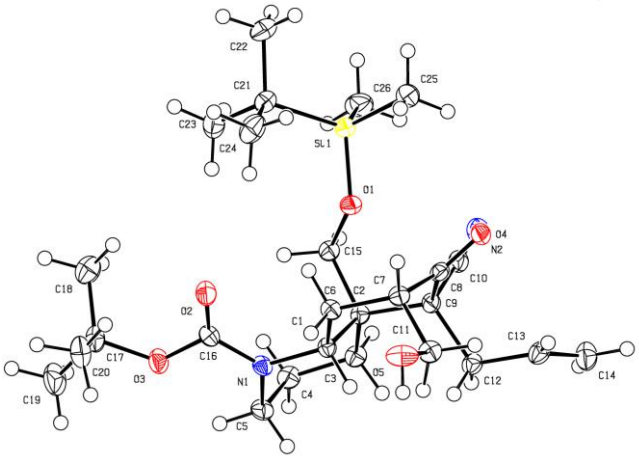
R(reflections)= 0.0489(5192) wR2(reflections)= 0.1344(5556)

S = 1.063 Npar= 324

2-2. Compound (+)-142

(+)-142 was crystalized from hexane/EtOAc solvent system as clear plate crystal.

ORTEP Diagram of **(+)-142** Showing Thermal Ellipsoids at the 50% Probability Level



CCDC 2059096 contains the supplementary crystallographic data for this paper. These data can be obtained free

of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

==========

Bond precision: C-C = 0.0025 A Wavelength=1.54184

Cell: a=7.60718(4) b=12.22825(3) c=31.00880(18)

alpha=90 beta=90 gamma=90

Temperature: 93 K

	Calculated	**Reported**
Volume	2884.52(3)	2884.52(3)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ac	P 2ac 2ac
Moiety formula	C26 H44 N2 O5 Si	C26 H44 N2 O5 Si
Sum formula	C26 H44 N2 O5 Si	C26 H44 N2 O5 Si
Mr	492.72	492.72
Dx, g cm-3	1.135	1.135
Z	4	4
Mu (mm-1)	0.999	0.999
F000	1072.0	1072.0
F000'	1075.98	
h,k,lmax	9,15,38	9,15,38
Nref	5809[3319]	5671
Tmin,Tmax	0.791,0.867	0.606,1.000
Tmin'	0.500	

Correction method= # Reported T Limits: Tmin=0.606 Tmax=1.000

AbsCorr = GAUSSIAN

Data completeness= 1.71/0.98 Theta(max)= 73.432

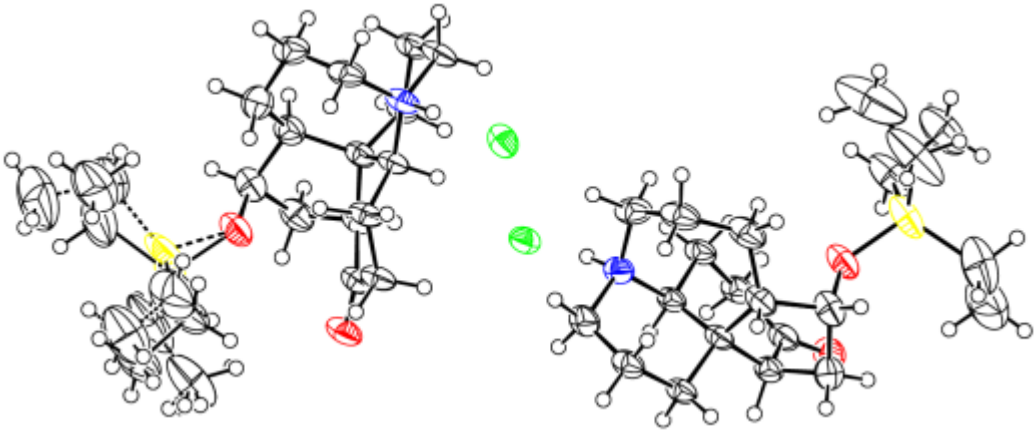
R(reflections)= 0.0297(5646) wR2(reflections)= 0.0807(5671)

S = 1.061 Npar= 316

2-3. Compound 166·HCl

166·HCl was crystalized from hexane/toluene solvent system as clear plate crystal.

ORTEP Diagram of **166·HCl** Showing Thermal Ellipsoids at the 50% Probability Level



CCDC 2040075 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

==========

Bond precision: C-C = 0.0041 A Wavelength=1.54184

Cell: a=8.8964(2) b=12.6421(3) c=20.2671(4)
alpha=82.849(2) beta=79.063(2) gamma=89.715(2)
Temperature: 100 K

	Calculated	Reported
Volume	2220.21(9)	2220.21(9)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C21 H38 N O2 Si, Cl	Cl, C21 H38 N O2 Si
Sum formula	C21 H38 Cl N O2 Si	C21 H38 Cl N O2 Si
Mr	400.06	400.06
Dx, g cm-3	1.197	1.197
Z	4	4
Mu (mm-1)	2.145	2.145
F000	872.0	872.0
F000'	876.42	
h,k,lmax	11,15,25	10,15,25
Nref	8959	8549
Tmin,Tmax	0.712,0.778	0.581,1.000
Tmin'	0.188	

Correction method= # Reported T Limits: Tmin=0.581 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.954 Theta(max)= 73.642

R(reflections)= 0.0664(7552) wR2(reflections)= 0.1963(8549)

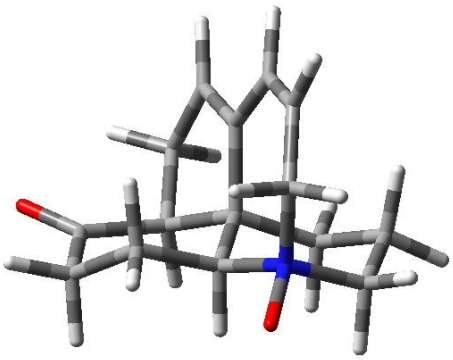
S = 1.070 Npar= 528

3. Details for DFT calculation

3-1. Epoxidation of tetracyclic diene 53

The molecular geometries for the transition states were first estimated by Reaction plus software package, based on the nudged elastic band (NEB) method,[73] and were subsequently re-optimized at ωB97XD/6-311G(d,p) level using Gaussian09 software package.[74]

Diene *N*-Oxide



E(RwB97XD)=-788.089080

Zero-point correction=	0.322587 (Hartree/Particle)
Thermal correction to Energy=	0.336210
Thermal correction to Enthalpy=	0.337155
Thermal correction to Gibbs Free Energy=	0.283692
Sum of electronic and zero-point Energies=	-787.766493
Sum of electronic and thermal Energies=	-787.752869
Sum of electronic and thermal Enthalpies=	-787.751925
Sum of electronic and thermal Free Energies=	-787.805388

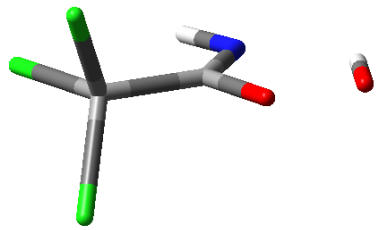
The coordinates of the structure

0 1

C	1.84901100	-0.18723200	-0.83039000
C	2.47075800	1.02553000	-0.11153700
C	1.58981900	2.23163800	0.12272700
C	0.20185400	1.84132200	0.62654100
C	-0.41889900	0.89003400	-0.37722200

C	0.34559100	-0.43326800	-0.50783100
H	2.11053700	2.89908000	0.80975200
H	1.98641200	0.00227900	-1.90228200
H	0.28614000	1.36881500	1.61138400
H	-0.44580300	2.71450400	0.70655200
H	-0.40263700	1.38632600	-1.35292400
H	1.48899600	2.75678100	-0.83637600
C	-0.30186200	-1.26715400	-1.63430400
H	0.21922200	-2.22171700	-1.73979200
H	-0.18286700	-0.72256600	-2.57955800
C	-1.78767600	-1.49200000	-1.37514500
H	-2.24688700	-2.00002900	-2.22799100
H	-1.93525000	-2.13664700	-0.50673600
C	-2.49522400	-0.15883900	-1.19879900
H	-3.54918900	-0.25952800	-0.94240700
H	-2.43583000	0.44174500	-2.10716600
O	3.63196800	1.02023300	0.21300700
N	-1.91457400	0.75949600	-0.15812600
C	-2.29390600	0.34427000	1.23593900
H	-2.08453300	1.23630800	1.82946200
H	-3.38113900	0.27284800	1.19409600
C	0.46906500	-1.29313300	0.74967700
C	-0.56525100	-1.51272800	1.74883800
H	-0.34668800	-2.31025700	2.45459800
C	2.54762600	-1.47261600	-0.36069000
H	3.57511800	-1.26751200	-0.05776400
H	2.57956700	-2.23594500	-1.14722100
C	1.66214000	-1.89928300	0.77420700
H	1.95934000	-2.62971300	1.51839100
C	-1.71514600	-0.85790500	1.91747500
H	-2.33708100	-1.17540400	2.75111200
O	-2.48232000	1.98130900	-0.34365300

$CCl_3C=NHOOH$



E(RwB97XD)=-1663.087637

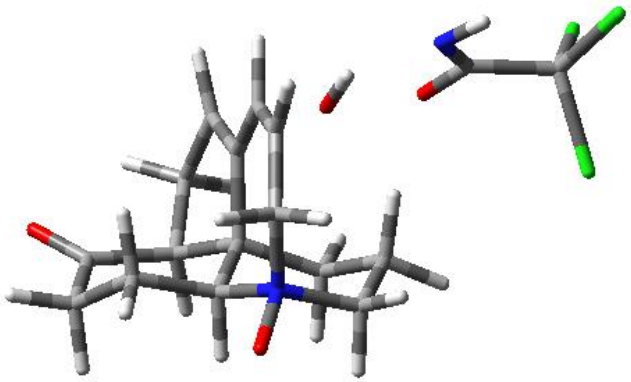
Zero-point correction=	0.050313 (Hartree/Particle)
Thermal correction to Energy=	0.058834
Thermal correction to Enthalpy=	0.059778
Thermal correction to Gibbs Free Energy=	0.015159
Sum of electronic and zero-point Energies=	-1663.037325
Sum of electronic and thermal Energies=	-1663.028803
Sum of electronic and thermal Enthalpies=	-1663.027859
Sum of electronic and thermal Free Energies=	-1663.072479

The coordinates of the structure

0 1

C	-0.51736400	-0.03299300	0.00020100
C	0.93648600	0.46836600	-0.00045600
O	1.76682900	-0.57583200	-0.00053600
O	3.11918700	-0.16932000	0.00019200
H	3.02909500	0.80768400	-0.00081000
N	1.37765100	1.64497100	-0.00073400
H	0.66292200	2.36086600	-0.00067900
Cl	-1.63502600	1.35639700	-0.00053000
Cl	-0.79866800	-1.01241300	-1.45862200
Cl	-0.79797800	-1.01071200	1.45979300

Epoxidation TS_{164} (+1.4 kcal/mol)



E(RwB97XD)=-2451.154869

Zero-point correction=	0.372297 (Hartree/Particle)
Thermal correction to Energy=	0.395679
Thermal correction to Enthalpy=	0.396623
Thermal correction to Gibbs Free Energy=	0.317472
Sum of electronic and zero-point Energies=	-2450.782572
Sum of electronic and thermal Energies=	-2450.759191
Sum of electronic and thermal Enthalpies=	-2450.758246
Sum of electronic and thermal Free Energies=	-2450.837397

Imaginary frequency =-544.88i

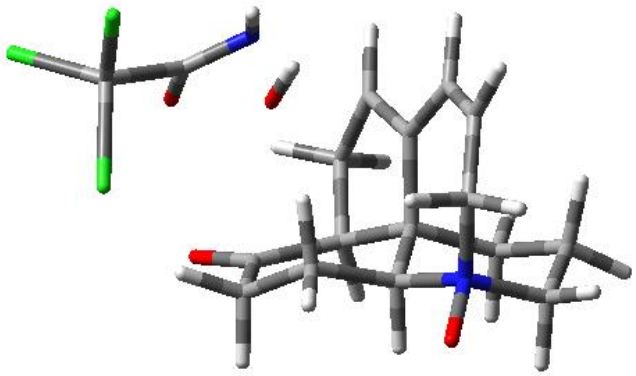
The coordinates of the structure

0 1

C	-2.66830300	1.72385600	-0.83705100
C	-4.10088000	1.94715500	-0.31278600
C	-5.03910300	0.76291700	-0.33168000
C	-4.37613800	-0.47933400	0.26358000
C	-3.12130200	-0.77727200	-0.53431000
C	-2.06079300	0.33502200	-0.46854700
H	-5.94799200	1.04310900	0.20070400
H	-2.72589800	1.83325000	-1.92652000
H	-4.14265900	-0.30191200	1.31949500
H	-5.03175900	-1.34699100	0.18944700
H	-3.42096900	-0.87234800	-1.58218600
H	-5.30980000	0.56013900	-1.37578200
C	-0.93189700	-0.03715400	-1.46023500

H	-0.16692900	0.73431400	-1.48195400
H	-1.38343200	-0.10311000	-2.45767400
C	-0.32204400	-1.38253000	-1.09228200
H	0.43727100	-1.66218300	-1.82754700
H	0.19258600	-1.32196900	-0.12985900
C	-1.39359000	-2.45871800	-1.10370700
H	-1.03468000	-3.43556300	-0.78184100
H	-1.81820400	-2.57870100	-2.10062300
O	-4.45529300	3.03068400	0.07859400
N	-2.61551300	-2.18191700	-0.26381700
C	-2.37750500	-2.46855000	1.18774100
H	-3.38583200	-2.57645600	1.59470600
H	-1.95527100	-3.47415700	1.19740300
C	-1.48950000	0.64661100	0.91062700
C	-1.25718700	-0.27594100	1.99701300
H	-0.74407500	0.15222000	2.85347700
C	-1.71425500	2.74171000	-0.19057500
H	-2.24708300	3.65231700	0.08148600
H	-0.88156000	3.00926200	-0.84480300
C	-1.20828400	1.99109500	1.00907300
H	-0.93156700	2.47843800	1.93433900
C	-1.59254800	-1.56730200	2.07954100
H	-1.33163100	-2.06792800	3.00905800
O	0.61005700	1.50121100	0.47124600
O	-3.57712700	-3.06230200	-0.65116800
H	0.85932700	0.83041800	1.16036800
O	2.31884000	1.42895300	-0.09641900
C	2.83193800	0.42699100	0.52275300
C	4.20963400	0.02740900	-0.08184200
N	2.24380400	-0.19553300	1.47080300
H	2.77638200	-0.96267400	1.85744500
Cl	3.89263700	-0.72809100	-1.67228400
Cl	5.23411800	1.46289500	-0.28870000
Cl	5.06703700	-1.15077400	0.95510400

Epoxidation TS*163*



E(RwB97XD)=-2451.159034

Zero-point correction=	0.372445 (Hartree/Particle)
Thermal correction to Energy=	0.395610
Thermal correction to Enthalpy=	0.396554
Thermal correction to Gibbs Free Energy=	0.319453
Sum of electronic and zero-point Energies=	-2450.786589
Sum of electronic and thermal Energies=	-2450.763424
Sum of electronic and thermal Enthalpies=	-2450.762480
Sum of electronic and thermal Free Energies=	-2450.839581

Imaginary frequency =-547.49i

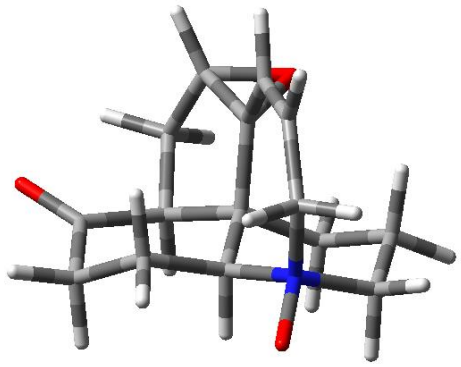
The coordinates of the structure

0 1

C	-2.04533700	2.11697500	0.37875900
C	-0.77514300	2.18236800	1.24821600
C	-0.32357500	0.95431700	2.00897200
C	-0.74206100	-0.38421300	1.40779000
C	-2.21455300	-0.33179300	1.04848100
C	-2.53699900	0.70241100	-0.03891400
H	0.75885200	1.02898300	2.11376400
H	-2.81423600	2.61441200	0.97928900
H	-0.13357600	-0.59810100	0.52734600
H	-0.60787500	-1.18918800	2.13027300
H	-2.76760200	-0.04591000	1.94937000
H	-0.75197000	1.05216100	3.01564200
C	-4.07037500	0.74436500	-0.26116400

H	-4.31786100	1.45413200	-1.05518200
H	-4.52104900	1.12590100	0.66255200
C	-4.65545700	-0.63082900	-0.56236200
H	-5.74769500	-0.57543100	-0.56564100
H	-4.35825400	-0.97607100	-1.55363800
C	-4.24906900	-1.62440500	0.51342100
H	-4.56965700	-2.64369600	0.30154500
H	-4.66197700	-1.34824000	1.48419500
O	-0.22124400	3.24293400	1.38227000
N	-2.77462600	-1.71967800	0.79804400
C	-2.04605900	-2.48330600	-0.27028700
H	-1.06813500	-2.68755800	0.17202900
H	-2.56342800	-3.44237600	-0.29433900
C	-1.87037100	0.52213900	-1.39132800
C	-1.74350900	-0.71370200	-2.13193500
H	-1.47919000	-0.60109700	-3.17966100
C	-1.81448900	2.85690600	-0.95154900
H	-1.02331200	3.60063000	-0.85791700
H	-2.71918100	3.36686500	-1.30034600
C	-1.46568800	1.73892500	-1.88488800
H	-1.15688100	1.89672100	-2.91065200
C	-1.84760300	-1.95851000	-1.65662000
H	-1.66912700	-2.76068700	-2.36836000
O	0.27324300	1.23499200	-1.07129500
O	-2.63740300	-2.45456700	1.93073700
H	0.46357500	0.38901000	-1.55937400
O	1.93909600	1.15565000	-0.42422000
C	2.37984700	-0.00355900	-0.76621300
C	3.69679000	-0.35947000	-0.01879400
N	1.75918400	-0.78350400	-1.56427900
H	2.22807800	-1.66213500	-1.73657400
Cl	4.50677900	-1.77151500	-0.76002000
Cl	4.81484600	1.01784400	-0.03117800
Cl	3.24902000	-0.76867100	1.66413200

Compound 164 (+4.1 kcal/mol)



E(RwB97XD)=-863.281388

Zero-point correction=	0.327555 (Hartree/Particle)
Thermal correction to Energy=	0.341712
Thermal correction to Enthalpy=	0.342657
Thermal correction to Gibbs Free Energy=	0.287867
Sum of electronic and zero-point Energies=	-862.953833
Sum of electronic and thermal Energies=	-862.939675
Sum of electronic and thermal Enthalpies=	-862.938731
Sum of electronic and thermal Free Energies=	-862.993521

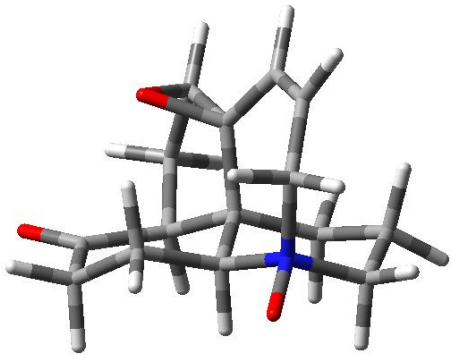
The coordinates of the structure

0 1

C	1.77938800	0.17548800	-0.89910100
C	2.23227600	1.44256500	-0.14250200
C	1.22408700	2.55332900	0.00893000
C	-0.08557900	1.99714700	0.56263300
C	-0.59982800	0.94367700	-0.40130600
C	0.31491900	-0.28414600	-0.58468200
H	1.65553400	3.32052000	0.65172200
H	1.86834300	0.42684100	-1.96415900
H	0.08283700	1.57957500	1.56073400
H	-0.84502100	2.77657200	0.62834600
H	-0.67088000	1.42640200	-1.38082900
H	1.04062800	2.99726700	-0.97749300
C	-0.26653200	-1.12213100	-1.73565000
H	0.36882300	-1.98225700	-1.93966000
H	-0.30185500	-0.50440300	-2.64067700
C	-1.67493500	-1.57394300	-1.36358400

H	-2.11748000	-2.15781800	-2.17521600
H	-1.64201000	-2.22878800	-0.48868500
C	-2.56770400	-0.36829700	-1.12957300
H	-3.57214300	-0.62997300	-0.79886200
H	-2.66627200	0.22461200	-2.03887200
O	3.34956100	1.53779700	0.30161500
N	-2.06501000	0.65038300	-0.13939600
C	-2.35052400	0.27411200	1.28586900
H	-2.34494400	1.23906200	1.79566400
H	-3.39317700	-0.04707600	1.28313500
C	0.52679400	-1.20221700	0.64532600
C	-0.32406400	-1.24147300	1.84819900
H	0.07278700	-1.89052500	2.62366200
C	2.68188800	-0.99841500	-0.49153400
H	3.66785700	-0.63410600	-0.20763300
H	2.79266700	-1.73284100	-1.29152100
C	1.94135100	-1.62524000	0.67298800
H	2.45637400	-1.87778700	1.59561600
C	-1.51253400	-0.68880500	2.06213900
H	-1.97486500	-0.90599800	3.02286100
O	0.93477600	-2.53488000	0.26849100
O	-2.77635700	1.79185000	-0.35901500

Compound 163



E(RwB97XD)=-863.288557

Zero-point correction=	0.327724 (Hartree/Particle)
Thermal correction to Energy=	0.341838
Thermal correction to Enthalpy=	0.342782
Thermal correction to Gibbs Free Energy=	0.288531

Sum of electronic and zero-point Energies=	-862.960833
Sum of electronic and thermal Energies=	-862.946719
Sum of electronic and thermal Enthalpies=	-862.945775
Sum of electronic and thermal Free Energies=	-863.000026

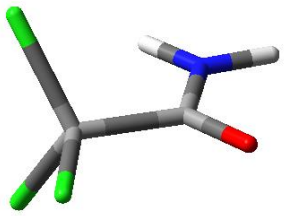
The coordinates of the structure

0 1

C	-1.71500700	0.00494300	0.98108900
C	-2.38721500	1.13797100	0.18891200
C	-1.51368200	2.26589900	-0.31959800
C	-0.13305800	1.82555700	-0.80042400
C	0.52109800	1.00116600	0.29260200
C	-0.23641100	-0.29367300	0.59608500
H	-2.07194900	2.79129500	-1.09484200
H	-1.77029500	0.31693400	2.02991700
H	-0.23673400	1.24640800	-1.72139000
H	0.50744700	2.68590300	-0.99323200
H	0.53755000	1.61188600	1.20162900
H	-1.39661100	2.96467600	0.52040500
C	0.44488200	-1.03234200	1.76913600
H	-0.03202800	-2.00224700	1.93376100
H	0.26734300	-0.43560500	2.67153900
C	1.95235100	-1.21118400	1.59961200
H	2.38921500	-1.53442000	2.54904200
H	2.17525000	-1.99093900	0.87244900
C	2.61624700	0.10055700	1.21345800
H	3.67170800	-0.00989000	0.96706000
H	2.54471500	0.83709400	2.01474800
O	-3.58583800	1.16467500	0.06548400
N	2.00713400	0.82153900	0.04293700
C	2.33989300	0.14606500	-1.26231200
H	2.00658400	0.85781500	-2.01925500
H	3.42822600	0.18395600	-1.27927000
C	-0.42361900	-1.24121600	-0.59207200
C	0.69892300	-1.83405500	-1.34955400
H	0.51355800	-2.81258900	-1.78214700
C	-2.46053000	-1.32021900	0.74615500
H	-3.51942300	-1.13747200	0.56094600
H	-2.36467400	-2.00359200	1.59371300

C	-1.74260000	-1.87489000	-0.45988700
H	-1.94967700	-2.87043800	-0.84033700
C	1.85596500	-1.23532100	-1.60990200
H	2.56026900	-1.77634000	-2.23694900
O	-1.52516600	-0.87620600	-1.44958400
O	2.58427700	2.04793800	-0.01691900

CCl_3CONH_2



E(RwB97XD)=-1587.995684

Zero-point correction=	0.046325 (Hartree/Particle)
Thermal correction to Energy=	0.054168
Thermal correction to Enthalpy=	0.055112
Thermal correction to Gibbs Free Energy=	0.012104
Sum of electronic and zero-point Energies=	-1587.949359
Sum of electronic and thermal Energies=	-1587.941516
Sum of electronic and thermal Enthalpies=	-1587.940572
Sum of electronic and thermal Free Energies=	-1587.983580

The coordinates of the structure

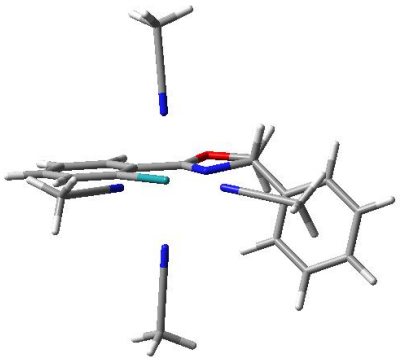
0 1

C	-0.21232200	0.01200600	0.00007100
C	1.26697000	-0.52625400	0.00024400
O	1.49572400	-1.70343700	0.00028100
N	2.20113400	0.44736400	0.00072600
H	1.97662900	1.42646800	-0.00139500
Cl	-0.47051600	1.01908300	-1.46158700
Cl	-1.34377500	-1.33455100	0.00079200
Cl	-0.47064200	1.02083100	1.46037300
H	3.16560700	0.16378200	-0.00065000

3-2. Structure of Ru catalysts

All of optimization was performed at ωB97XD/(LANL2DZ: Ru; 6-31G(d): others) level using Gaussian09 software package.[77]

Compound 174a



E(RωB97XD) = -1333.19077672

Zero-point correction=	0.430702 (Hartree/Particle)
Thermal correction to Energy=	0.463907
Thermal correction to Enthalpy=	0.464851
Thermal correction to Gibbs Free Energy=	0.360057
Sum of electronic and zero-point Energies=	-1332.760075
Sum of electronic and thermal Energies=	-1332.726870
Sum of electronic and thermal Enthalpies=	-1332.725926
Sum of electronic and thermal Free Energies=	-1332.830720

The coordinates of the structure

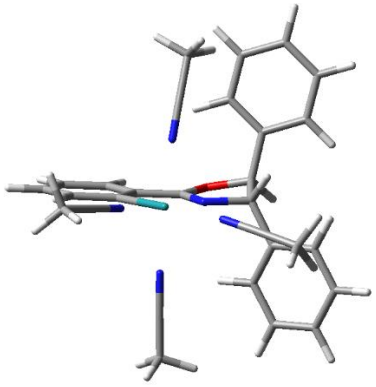
1 1

C	2.12444800	-0.70460400	-0.37361600
C	1.74035800	-2.06404000	-0.29838500
C	0.37229400	-2.23649200	0.14016600
N	-0.36975400	-1.19790600	0.35542300
O	-0.17955500	-3.42386300	0.38698400
C	-1.56124500	-3.16860200	0.71531600
C	-1.63239300	-1.63647000	0.94611100
Ru	0.64941700	0.62584900	0.11620800
H	-1.81797300	-3.76245100	1.59229500

N	1.23101400	0.48222700	2.07856300
C	1.61613100	0.32559600	3.15435600
C	2.11581100	0.12216700	4.50849500
H	1.31669000	-0.25788400	5.15019200
H	2.48098700	1.06790800	4.91718200
H	2.93594200	-0.60053400	4.49313700
N	0.14803100	0.67938200	-1.86849600
C	-0.07517100	0.65149800	-2.99966000
C	-0.35654300	0.60189600	-4.42889300
H	-0.26413400	1.60037200	-4.86391700
H	-1.37199800	0.23315600	-4.59693700
H	0.35230800	-0.06915100	-4.92115100
N	1.83606300	2.29904400	-0.13513100
C	2.51789900	3.22040600	-0.27000700
C	3.38809800	4.37786400	-0.44074400
H	3.12012700	5.15659500	0.27807100
H	3.28292700	4.77692300	-1.45297600
H	4.42964400	4.08705800	-0.27990700
N	-1.13039100	1.86621800	0.61563700
C	-2.16454100	2.35321700	0.77032600
C	-3.48432600	2.94404800	0.94778300
H	-3.91588500	2.60712800	1.89345100
H	-4.13425300	2.61644500	0.13229100
H	-3.41356400	4.03459400	0.94903200
C	3.44023300	-0.46431200	-0.78406400
H	3.80284200	0.55718300	-0.86624200
C	2.59492600	-3.12692100	-0.60396000
H	2.24389400	-4.15187000	-0.52479700
C	4.30530000	-1.51297000	-1.09402700
H	5.32193600	-1.29261500	-1.41009200
C	3.89170100	-2.84493700	-1.00626000

H	4.57793900	-3.64926800	-1.25044900
H	-1.60892100	-1.40312500	2.01918700
H	-2.17359200	-3.48072900	-0.13573600
C	-2.86440600	-1.00434700	0.34173900
C	-5.19362400	0.07048700	-0.77739100
C	-2.93679500	-0.75121900	-1.02860000
C	-3.96558200	-0.71219100	1.14624400
C	-5.12921600	-0.18450100	0.59023900
C	-4.09124900	-0.20967600	-1.58424800
H	-2.07629200	-0.97276500	-1.65277100
H	-3.91820700	-0.90625100	2.21546000
H	-5.98553900	0.02383900	1.22468600
H	-4.13955600	-0.01613700	-2.65195900
H	-6.10062700	0.47699500	-1.21454600

Compound 174e



E(RωB97XD) = -1564.17074127

Zero-point correction=	0.512676 (Hartree/Particle)
Thermal correction to Energy=	0.550274
Thermal correction to Enthalpy=	0.551218
Thermal correction to Gibbs Free Energy=	0.436701
Sum of electronic and zero-point Energies=	-1563.658065
Sum of electronic and thermal Energies=	-1563.620468
Sum of electronic and thermal Enthalpies=	-1563.619523
Sum of electronic and thermal Free Energies=	-1563.734040

The coordinates of the structure

1 1

C	1.52319100	-1.60159900	-1.01764000
C	0.40967900	-1.59887200	-1.89318400
C	-0.61084900	-0.66025100	-1.48450100
N	-0.40534500	0.09381700	-0.45677500
O	-1.80363200	-0.53358700	-2.07492400
C	-2.62170300	0.23607300	-1.16738900
C	-1.58029100	0.91466000	-0.21527200
Ru	1.38786300	-0.27131500	0.53244600
N	0.31631400	-1.66381900	1.59955100
C	-0.42123600	-2.41635600	2.06855600
C	-1.37132600	-3.35618600	2.64843300
H	-1.36613700	-3.27252500	3.73823200
H	-1.10331800	-4.37750700	2.36550900
H	-2.37399900	-3.13082800	2.27132500
N	2.31853300	1.13217400	-0.62682500
C	2.74743900	1.94774900	-1.31965100
C	3.25859100	2.99253900	-2.19652200
H	2.57322700	3.84465900	-2.17805300
H	3.33728900	2.61466000	-3.21928500
H	4.24610600	3.31851800	-1.86010900
N	3.18014700	-0.82921200	1.40309600
C	4.17659500	-1.16943900	1.87562500
C	5.43540600	-1.60930300	2.46538700
H	5.75564900	-0.90351000	3.23619500
H	6.20703100	-1.66880100	1.69325200
H	5.30825000	-2.59662100	2.91713600
N	1.00706100	1.32995600	2.03524400
C	0.73123100	2.29040200	2.61239600
C	0.37585700	3.51942100	3.31039400

H	-0.04130200	4.22926300	2.59021200
H	1.26211900	3.95599900	3.77777400
H	-0.36822800	3.31098400	4.08347100
C	2.54359900	-2.50398900	-1.33633300
H	3.42913300	-2.56112500	-0.70873300
C	0.29714100	-2.43506000	-3.00757000
H	-0.58606900	-2.39098600	-3.63896300
C	2.45071600	-3.34019300	-2.44814300
H	3.26213000	-4.02952100	-2.66798000
C	1.33308400	-3.31336500	-3.28710600
H	1.27702100	-3.97313900	-4.14676000
H	-1.89919500	0.79192100	0.82440600
H	-3.16669000	0.96737900	-1.76735100
C	-1.33028800	2.38260900	-0.48472300
C	-0.93801800	5.10828800	-0.99439300
C	-0.63554600	2.79557700	-1.62347100
C	-1.82950200	3.34639700	0.39082400
C	-1.63533600	4.70392200	0.14050700
C	-0.44375600	4.14995400	-1.87823900
H	-0.24544300	2.05206200	-2.31350200
H	-2.38164800	3.03255000	1.27468700
H	-2.03954500	5.44482800	0.82439700
H	0.07702500	4.46196600	-2.77946500
H	-0.79230200	6.16463800	-1.19737000
C	-3.56732300	-0.67230900	-0.41402900
C	-5.28388700	-2.27308300	1.10520200
C	-4.57933800	-0.09246300	0.35494900
C	-3.42176200	-2.05841300	-0.42245000
C	-4.28285300	-2.85488700	0.33218500
C	-5.43155500	-0.88685800	1.11343100
H	-4.70386000	0.98861700	0.35625100

H	-2.65372800	-2.51921400	-1.03518200
H	-4.17860600	-3.93585300	0.30070300
H	-6.21895600	-0.42623800	1.70182700
H	-5.95758000	-2.89585400	1.68549500

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論文目録

第一章

Synthesis of Octahydro- and Decahydroquinolines by a One-Pot Cascade Reaction of Tetrasubstituted Enecarbamate

Tomohiro Kurose, Chihiro Tsukano, Yoshiji Takemoto

Org. Lett. **2017**, *19*, 4762–4765.

第二章

Total Synthesis of Lyconesidine B, a *Lycopodium* Alkaloid with an Oxygenated, Amine-type Fawcettimine Core

Tomohiro Kurose, Chihiro Tsukano, Takeshi Nanjo, Yoshiji Takemoto

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Synthetic Studies toward Asymmetric Synthesis of Lyconesidine B.

Tomohiro Kurose, Chihiro Tsukano, Takeshi Nanjo, Moeko Itoga, Yoshiji Takemoto

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