令和 4 年度 博士論文

生理活性を有する複素環式天然有機化合物の合成およびその構造活性相関

Synthesis of bioactive heterocyclic natural products and their SAR study

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目次

序論

新たな医薬品リード化合物の開拓を志向した試みとして、天然資源からの生理活性有機化合物の探索研究が全世界を通じて古くから行われている。その研究対象は、伝統医学で用いられる生薬や古くから民間に伝えられてきた伝承薬物で、その原材料は陸上生物、海洋生物、鉱物、そして微生物の代謝産物など多肢にわたる。例えば、２０世紀後半に新たに認証された新薬のほとんどが、天然資源から得られた有機化合物とその合成誘導体によって占められていた (**Figure 1**) [1]。しかし、昨今、抗体医薬品やワクチンの発展は目覚ましく、新たな医薬品として脚光を浴びているが、2019 年においても天然有機化合物およびその誘導体が新薬の多くの割合を占めていることから、新たな生理活性天然物の探求は依然として重要であることが窺える。

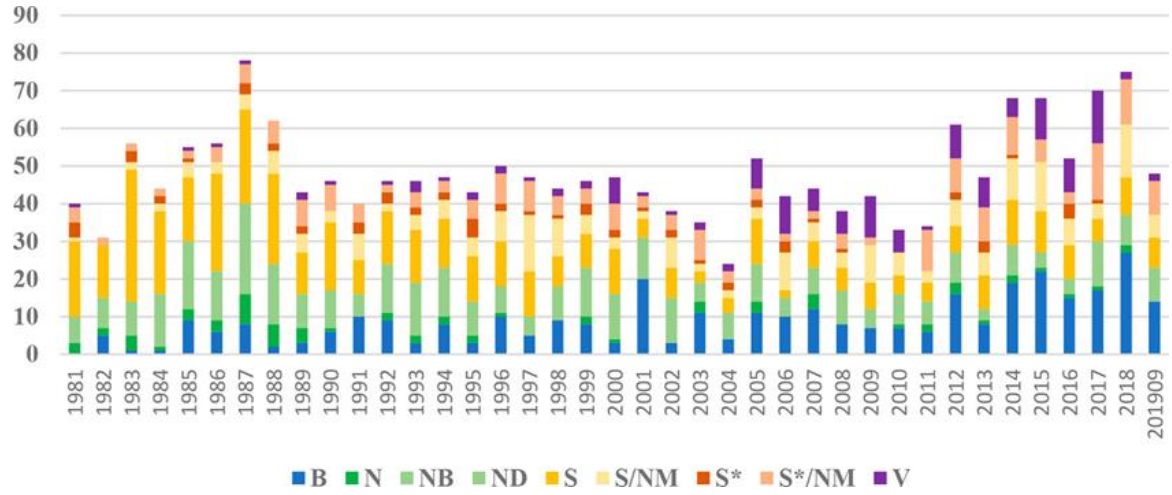


Figure 1. 年代別で新しく承認された薬の種類とその割合の推移 (1981 ~ 2019)[1]
B. 高分子医薬品, N. 未改変の天然物, NB. 植物薬, ND. 天然物誘導体,
S. 化学合成薬, S*. 天然物のファーマコフォアを用いた合成薬, V. ワクチン

生理活性を有する天然有機化合物の中には、分子構造中に酸素、窒素あるいは硫黄を含むものが少なくない。それらの詳細な薬理作用を調べるために必要な物質量を天然資源から確保することが困難な場合が多く、有機合成による目的物の量的確保が重要となる。さらに、生理活性天然有機物の合成法の確立後、その合成法に基づいた誘導体合成による構造活性相関研究を行うことは医薬品開発において有効的な手段の一つとなっている。天然資源から得られた医薬品としてもっとも有名な例に Penicillin がある。Penicillin は 1929 年に A. Fleming によって青カビの一種 *Penicillium* 属から単離[2]された抗生物質であり、1945 年に Hodgkin [3] らが X 線構造解析によりその構造を解き明かし、それまでに知られていた天然有機化合物とは異なり、当時では珍しい β ラクタム環を有する化合物であることを見出した。その作用機構は、細菌内に存在するトランスペプチターゼがペニシリンの β ラクタムを含む L-Cys-D-Val 構造と D-Ala-D-Ala 構造を誤認識することで、細菌細胞壁の生合成を阻害することが知られている (**Figure 2**)。

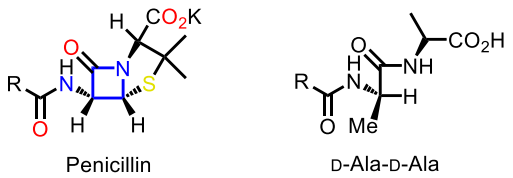


Figure 2. Penicillin および D-Ala-D-Ala の構造

また、マラリアの治療薬としてして用いられる Artemether および Artesunate はヨモギ族植物の黄花蒿 (*Artemisia annua* L.) から単離されたセスキテルペンラクトン Artemisinin から医薬品として生み出された化合物である [4]。Artemisinin の特殊な構造は X 線構造解析およびその全合成により確定された。その後、構造活性相関研究を通して Artemisinin をリード化合物とする構造の最適化が行われ、活性発現に重要な構造の特定および作用機序の解明に貢献した [5]。現在では酵母発酵で生成した前駆体からの半合成により供給されている。Artemisinin は多薬剤耐性をもつマラリアに対しても効果的であり、赤血球内に侵入したマラリア原虫をほぼ一掃する強力な薬効を示すことから、マラリア治療に革新をもたらした (**Figure 3**)。

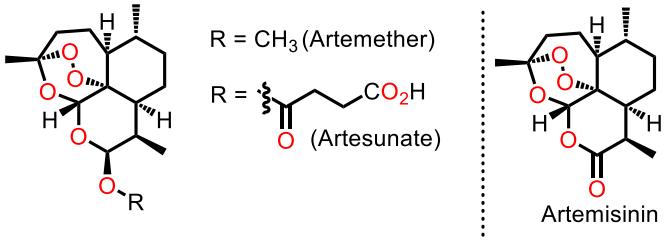


Figure 3. Artemisinin およびその誘導体化合物の構造

さらに、世界各国で現在も使用されている抗がん剤の Haraven® は、海綿動物のクロイソカイメンから単離された Halichondrin B の活性発現部位の構造を基盤にして生まれた医薬品である。岸　義人により、その複雑な分子の初の全合成 [6] が達成された後、構造活性相関により活性保持に必要な部分が特定された。その結果、複雑な構造が簡略化され、医薬品として供給が可能となった。まさに、有機合成化学から生まれた医薬品の金字塔といえる成果である (**Figure 4**)。

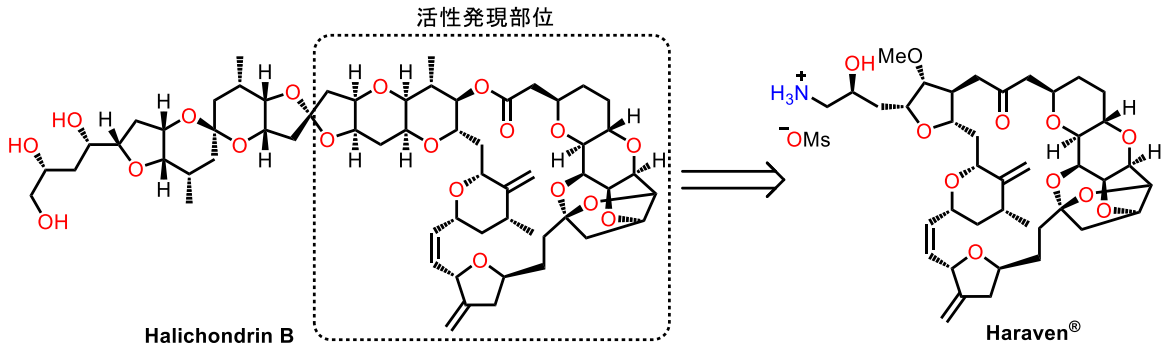


Figure 4. Halichondrin B を基に化学合成された抗がん物質 Haraven®

天然有機化合物を標的とした創薬研究は現在においても世界中の研究者によって行われており、またその過程で生まれた新たな合成手法や誘導体はさらなる創薬化学の発展に繋がっている。上述の背景の下、本博士論文では数種の複素環式生理活性天然物の形式合成ならびに誘導体合成に加えて、それらの構造活性相関に関する研究を行った。また、本博士論文は以下に示すように二部構成で、第一章から第三章ではピペリジン環構造を含む含窒素型化合物の合成およびその構造活性相関研究について論じている。そして、第四章および五章では、強力な α-グルコシダーゼ阻害活性を示す含硫黄型複素環式化合物 Salacinol をリード化合物とした構造活性相関研究について述べている。

第一章ではニコチン受容体への生理活性が期待される 3 環性毒ガエルアルカロイド Gephyrotoxin 287C の形式不斉合成に着手した。その結果、エナミノエステルへの高立体選択的 Michael 付加反応と分子内 Aldol 環化反応を鍵反応とした合成戦略により、Gephyrotoxin 287C の新たな形式不斉合成法を確立した (**Figure 5-1**)。

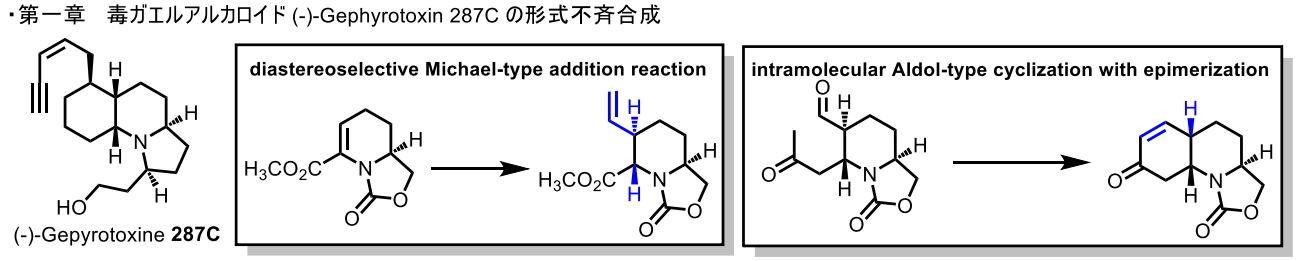


Figure 5-1

第二章では抗腫瘍活性を示す三環性海洋産アルカロイド Lepadiformine A、C および Fasicularin の形式不斉合成を行った。本研究を通して、エナミノエステルへの立体選択的ジアリル化反応の鍵反応とし、連続する 3 級および 4 級炭素の構築に成功すると共に、ピペリジン環を合成出発点とする Lepadiformine 類の新たな合成手法を開拓した (**Figure 5-2**)。

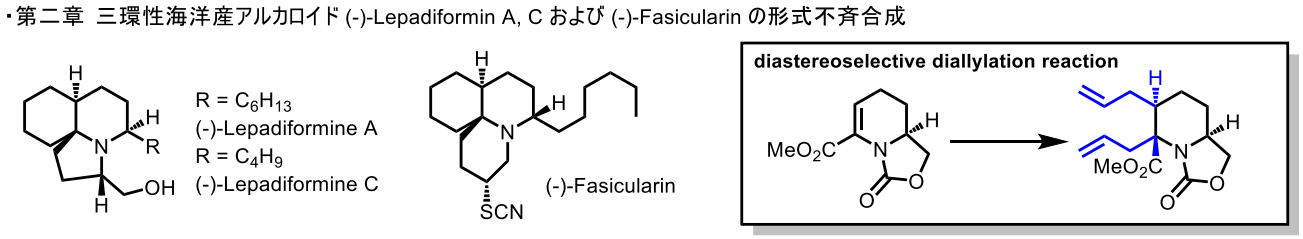


Figure 5-2

第三章ではニコチン受容体を標的とした Decahydroquinoline (DHQ) 型毒ガエルアルカロイドの網羅的合成を行った。本研究を通して、4 つの不斉中心からなる 4 つの立体異性体に属した DHQ 型アルカロイドの網羅的合成法を確立し、その骨格に属した 10 種類のアルカロイドの合成を達成した。さらに、合成したアルカロイドが血液脳関門のニコチン輸送システムおよび血液網膜関門のベラパミル輸送システムに対して基質認識される可能性を示した (**Figure 5-3**)。

・第三章 ニコチン受容体への構造活性相関研究を目的としたデカヒドロキノリン型毒ガエルアルカロイドの網羅的全合成

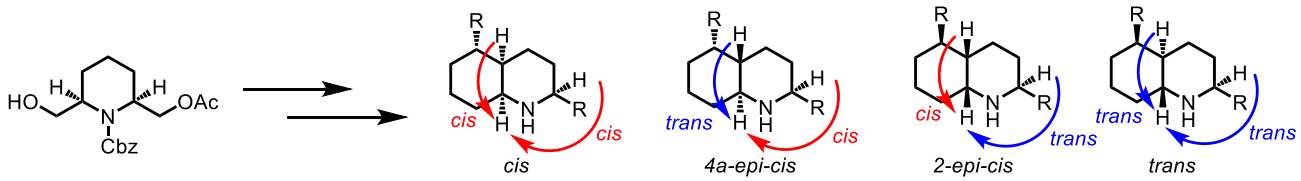


Figure 5-3

第四章では α-グルコシダーゼ阻害活性を示すチオ糖スルホニウム塩型化合物 Salacinol の構造活性相関研究の一環として、側鎖部のアルキル側鎖をさらに伸長した誘導体を合成し、そのα-グルコシダーゼに対する阻害活性を評価した。その結果、合成品は親化合物である Salacinol よりもさらに強力な α-グルコシダーゼ阻害活性を示すことが明らかになった。さらに、その活性強度の増加には、酵素の活性部位から遠く離れて存在する疎水性アミノ酸残基が関与している可能性が計算化学的手法により示唆された **(Figure 5-4)**。

・第四章 サラシア由来 α-グルコシダーゼ阻害剤サラシノールの C4'位アルキル側鎖伸長型誘導体の合成およびその活性評価

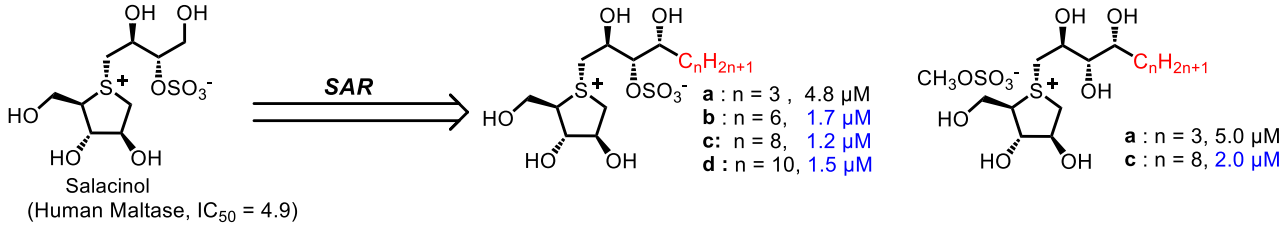


Figure 5-4

第五章では、これまで哺乳類の小腸刷子粘膜由来のα-グルコシダーゼに焦点を当てた研究が盛んに行われてきた。そこで、Salacinol の新たなケミカルスペースの拡張を目的とし、GH31 族ヒトリソソーム α-グルコシダーゼへの構造活性相関研究を検討した。その結果、Salacinol を始めとしたチオ糖スルホニウム塩型化合物が、ヒトリソソームα-グルコシダーゼに対してリガンド適合性があることを明らかにした **(Figure 5-5)**。

・第五章 Salacinol およびその誘導体化合物を用いたGH31 α-グルコシダーゼへの活性評価

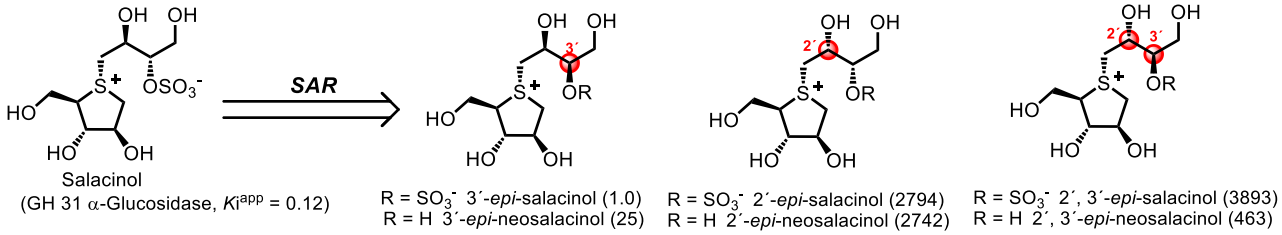


Figure 5-5

各論

第一章　　毒ガエルアルカロイド (-)-Gephyrotoxin **287C** の形式不斉合成

第一節　　毒ガエルアルカロイドの歴史

古来より、毒ガエルの皮膚分泌物は、未開のジャングルに生きる人々が狩猟の際に使用する矢じりに塗布する矢毒として用いられてきた。毒ガエルの分泌物に含まれる生理活性物質には、脂溶性のアルカロイドの他、ペプチド類、ブファジエノイド類、テトロドトキシン類などがあり、これらは他の生物に対して強い毒性を示し、細菌感染や天敵から毒カエル自身を守る役割を果たしていると考えられている。1960 年代の初頭から、米国国立衛生研究所 (NIH: National Institutes of Health) の J. W. Daly らは、オーストライア、中南米、ニューギニア島およびマダガスカル島に生存する毒ガエル (大部分は *Dendrobates* 科) の皮膚抽出液に関する研究を行い、多岐にわたる脂溶性の毒ガエルアルカロイドを見出している。1968 年には、同グループの徳山らが、Batrachotoxin A の *p*-bromo benzoate 体を単結晶化することにに成功し、その X 線構造解析によって全ての立体化学構造が解き明かされた **(Figure 6)** [7]。Batrachotoxin A は、陸上生物から得られた有機化合物の中で最も強い非タンパク質性の毒性成分であり、Na^+ イオンチャネルを活性化すると共に、アセチルコリンとカルバモイルコリンのムスカリン様受容体との結合を促す。その後、筋肉の細胞膜と神経との不可逆的な脱分極が起こることで毒性が生じる [8]。1992 年には、T. F. Spande らによってエクアドル産の毒カエル皮膚抽出液から Epibatidine が単離された [9]。本化合物は E. J. Corey らによって、両対掌体が合成された後、天然物と比較することでその絶対配置が決定された **(Figure 6)** [10]。また、Epibatidine は Morphine よりも約 200-500 倍も強力な鎮痛作用を示し、そのメカニズムは選択的に α4β2 ニコチン受容体に作用することが知られている。このように、Epibatidine のニコチン受容体へのアゴニスト様作用は、毒ガエルアルカロイドがニコチン受容体リガンドのリード化合物になる新たな発見であった [11]。上述の化合物以外にも毒ガエルアルカロイドには Pyrrolidine、Piperidine 環をもつ単環性のアルカロイドの他、Pyrrolizidine、Indolizidine、Quinolizidine、Decahydroquinoline 環を主骨格とする双環性アルカロイドや三環性のアルカロイドがある。現在までに、それらは約 20 種類を超えるサブクラスに分類され、800 種以上のアルカロイドが明らかにされている **(Figure 7)**。 特に、Indolizidine および Quinolizidine 型アルカロイドは最大のサブクラスであり、また、相対および絶対配置が不明な化合物も未だ残されていることから、近年においてもその合成研究が盛んに行われている [12]。

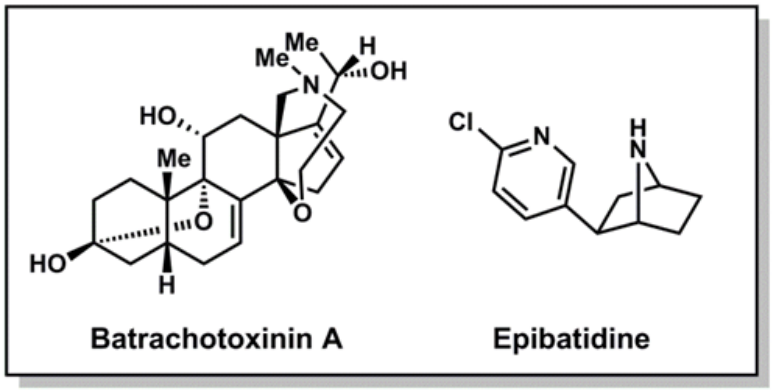


Figure 6. Batrachotoxinin A および Epibatidine の構造

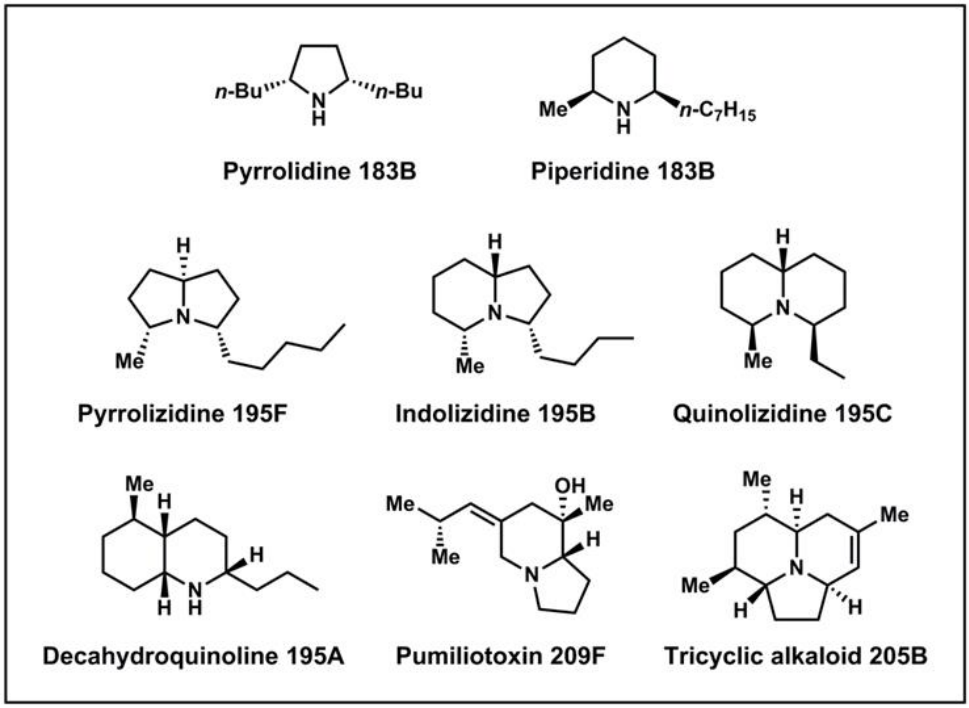


Figure 7. 脂溶性毒ガエルアルカロイドの例

第二節　　Gephyrotoxine **287C** の形式合成

Gephyrotoxine (GTX) **287C** (**1**) は 1974 年に J. W. Daly らによってコロンビアに生息する毒ガエルの皮膚抽出液から単離されたアルカロイドである [13]。その後、同グループによって **1** の絶対立体構造が X 線構造解析により確定されている [14]。また、GTX **287C** (**1**) が、ムスカリン拮抗作用をはじめとする様々な神経生物活性を示すことが報告されている [13,14,15]。構造的な特徴として、*cis*-Decahydroquinoline (DHQ) 環と Indolizidine 環が縮合した三環性の基本骨格 (decahydropyrrolo[1,2-*a*]quinolone 骨格) をもち、その 1, 3a, 5a, 6, 9a 位に５つの不斉中心を有している。また、側鎖として、１位にヒドロキシルエチル基の他、６位に特徴的な共役 *cis*-エンイン型の (*Z*)-pent-2-ene-4-ynly 基を備えた極めて興味深い構造のため、これまでに多くの有機合成化学者の興味を集め、その全合成が試みられてきた (**Figure 8**) [16-19]。

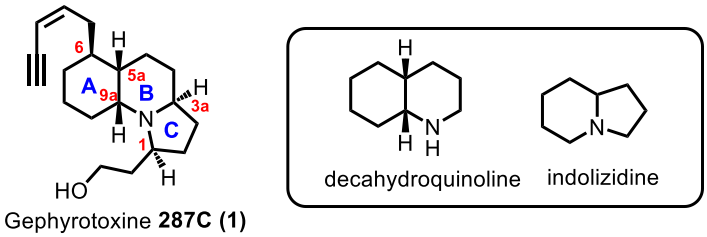


Figure 8. 毒ガエルアルカロイド Gephyrotoxine 287C (**1**) の構造

1980 年に、GTX **287C** (**1**) の初のラセミ全合成が **Figure 9** に示す経路を経て、岸らによって達成された [16]。すなわち、彼らは C 環の合成から開始し、スクシンイミド誘導体から導いた *cis* 配置のピペリジン誘導体をシクロヘキサノン体へと Aza-Michael 付加反応させることで A 環および C 環を連結させた。その後、ピペリジン側鎖をシクロヘキサノンの２位で閉環させることで残る B 環を巧みに構築した。その後、 Pt/Al_2O_3 触媒を用いた接触還元により、5a および 9a 位の *cis* 配置の合成に成功した。最後に ６位の *cis*-エンイン型側鎖部位の導入を行うことで、**1** を全合成した。加えて、岸らは 1981 年に L-Pyroglutamic acid を原料として用いることで、スクシンイミド誘導体の不斉誘導に成功し、(-)-**1** の不斉合成も達成した [17]。この岸らの全合成を皮切りに、Overman や Hart らによっても **1** の全合成が 1983 年に相次いで達成された [18]。

また 2010 年以降にも、４つのグループによっても GTX **287C** (**1**) の全合成が行われている [19]。すなわち、2014 年に千田ら [19a] は、4-pentenoic acid から合成した *N*-メトキシアミドから *N*-アシル-*N*-オキシニウムイオンを発生させ、分子内アリル化反応により 5a および 9a の *cis* 配置および B 環の構築を行った。次に、数工程で６位に目的の立体を保持した A 環を合成した後、鍵反応となる *N*-メトキシアミド選択的な還元的アリル化反応により、効率よく 3a 位の構築に成功した。その後、**1** の全合成を達成した (**Figure 10**)。

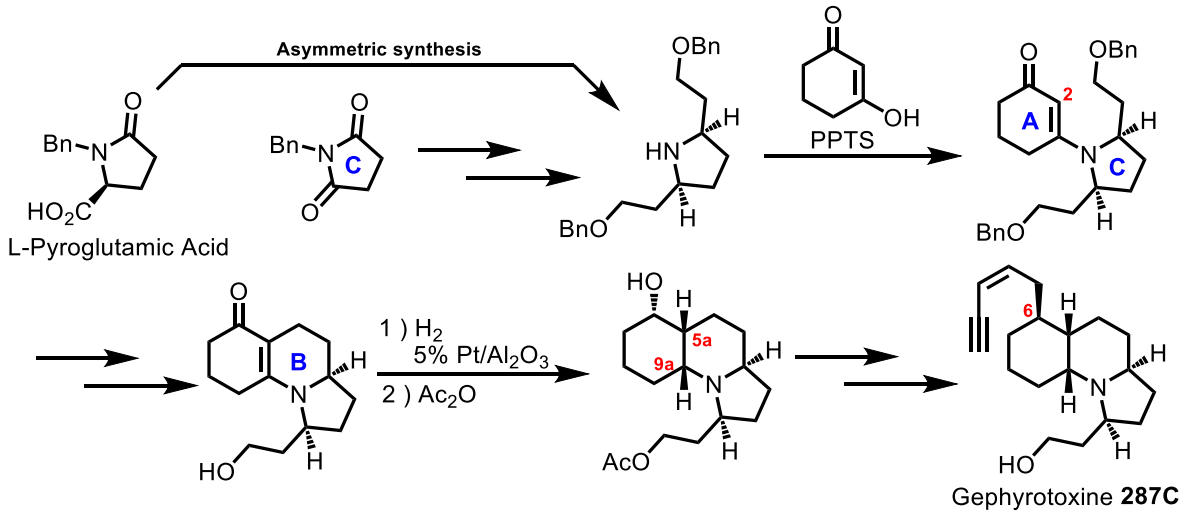


Figure 9. 岸らによる GTX **287C** (**1**) の全合成

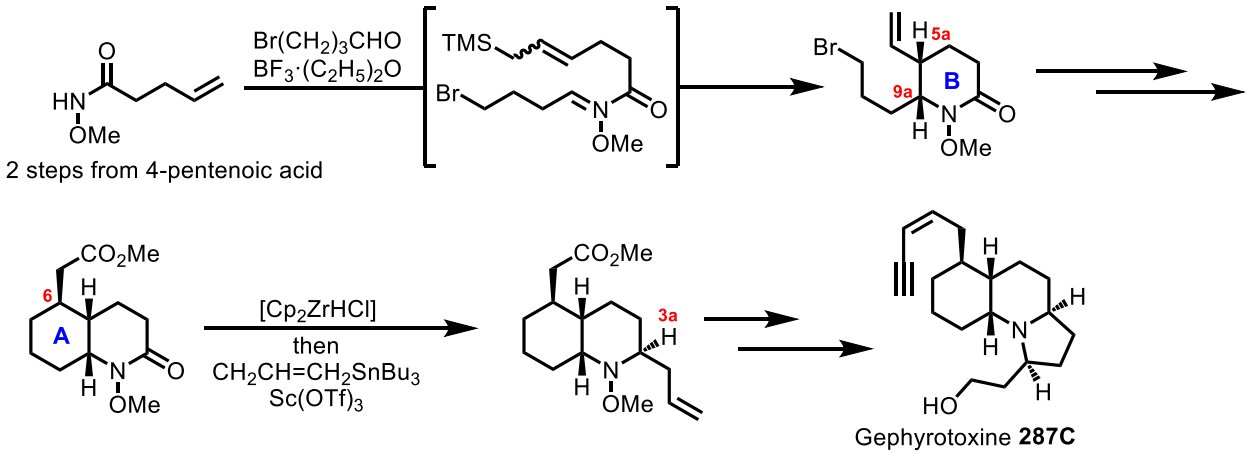


Figure 10. 千田らによる GTX **287C** (**1**) のラセミ全合成

Smith ら [19b] は、L-pyrogulutaminol から 2 工程で導いた側鎖非対称型のピペリジン誘導体に対して、オゾン分解および Wittig 反応を行うことで、α,β-不飽和ケトンへと導いた。その後、 TFA 中に付すことで、環化およびエナミンの Michael 付加反応が連続的に進行し、5a および 6 位に所望の不斉中心をもつ二環性のイミニウムカチオンを発生させた後、ヒドリド還元を行うことで一挙に GTX **287C** (**1**) の母格を合成した。最後に側鎖の構築を行うことで (-)-**1** を全合成した (**Figure 11**)。

Amat ら [19d] は 1,3-シクロヘキサンジオンから合成した A 環に相当する臭化物から数工程で導いたシリル保護体と (*S*)-フェニルグリシノールを縮合環化させることで所望の *cis*-Decahydroquinoline 骨格を構築した。その後、数工程で導いたエノールトリフラート体に対して Stille カップリングを施した後、ヒドリド還元を行うことで 3a 位に立体選択的にアリル基を導入することに成功した。そこから数工程で (+)-GTX 287C (**1**) の全合成を達成した (**Figure 12**)。

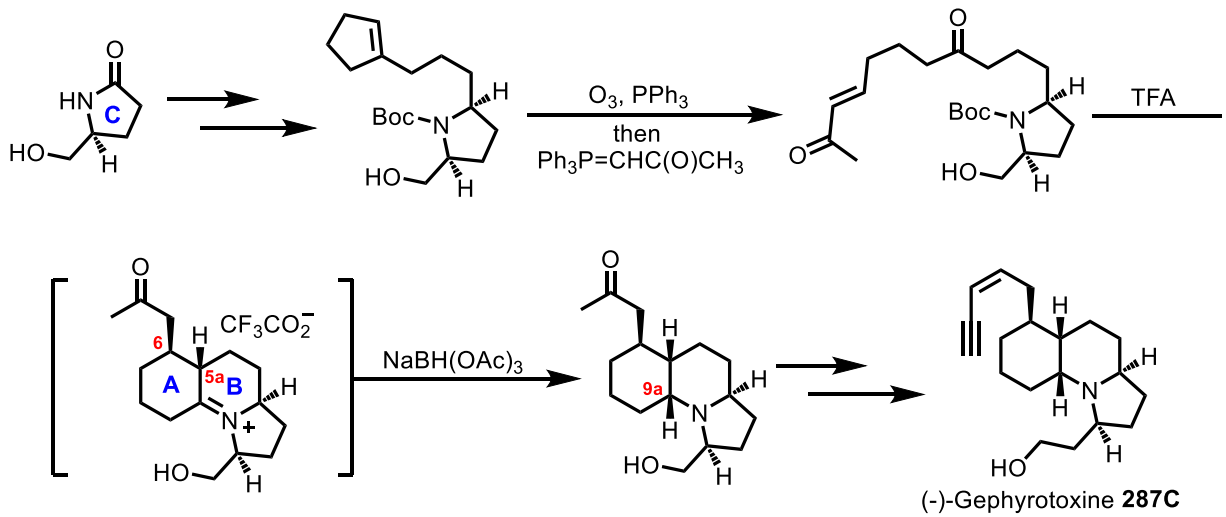


Figure 11. Smith らによる (-)-GTX **287C** (**1**) の全合成

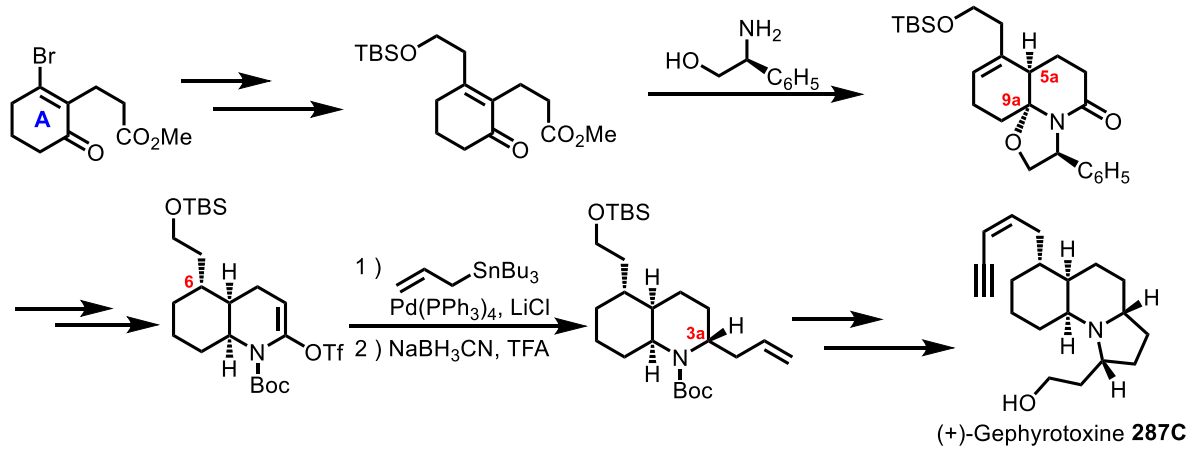


Figure 12.Amat らによる (-)-GTX **287C** (**1**) の全合成

以上のように、現在までに様々な合成法で GTX 287C (**1**) の全合成が行われてきたことから、本化合物の類稀な構造が世界中の有機合成化学者の興味を集めていることが窺える。そのような中、今回、著者はピペリジン (B) 環を起点とした脂溶性アルカロイドの不斉合成法を用いて **1** の新規合成法の開発に着手した。

第三節　　環状エナミノエステルへの高立体選択的共役付加反応を鍵とした (–)-Gephyrotoxine **287C** の形式不斉合成

著者らは、これまでに数多くの脂溶性アルカロイドを標的とした不斉合成を行い、その詳細な生理活性を明らかにするとともに、ターゲット分子の絶対立体構造を明らかにしてきた。その過程で、環状エナミノエステル (**2**) への Gilman 試薬の高立体選択的共役付加反応により、生成物の２,３および６位の不斉炭素の立体化学を完全に制御できる３置換ピペリジン誘導体の合成法を確立している。(**Figure 13**)。すなわち、環状エナミノエステル (**2**) への Gilman 試薬の共役付加反応 (type 1 型反応) の際に、６位も水素原子に対して、２位および３位の水素原子がそれぞれ、*cis* および *trans* の立体配置に導入され、３つの不斉中心をもつ化合物が高立体選択的に得られる。したがって、本反応を利用して、毒ガエルアルカロイド **235B´**[20]、**223A**[21] および 海洋産アルカロイドの Lepadin B[22] の不斉全合成が達成されている。一方、このコンセプトを、オキサゾリジノン環をもつ化合物 (**3**) に適用すると、type 1 型反応とは全く逆の立体選択性が見られ、６位水素原子に対して、２位および３位の水素原子がそれぞれ、*trans* および *cis* 配置になるように導入された化合物が生成することも明らかにしている。最終的に、これら二つの反応性を利用して、我々は５つの不斉点をもつ三環性毒ガエルアルカロイド *ent*-**205B** の世界初の全合成にも成功している[23]。

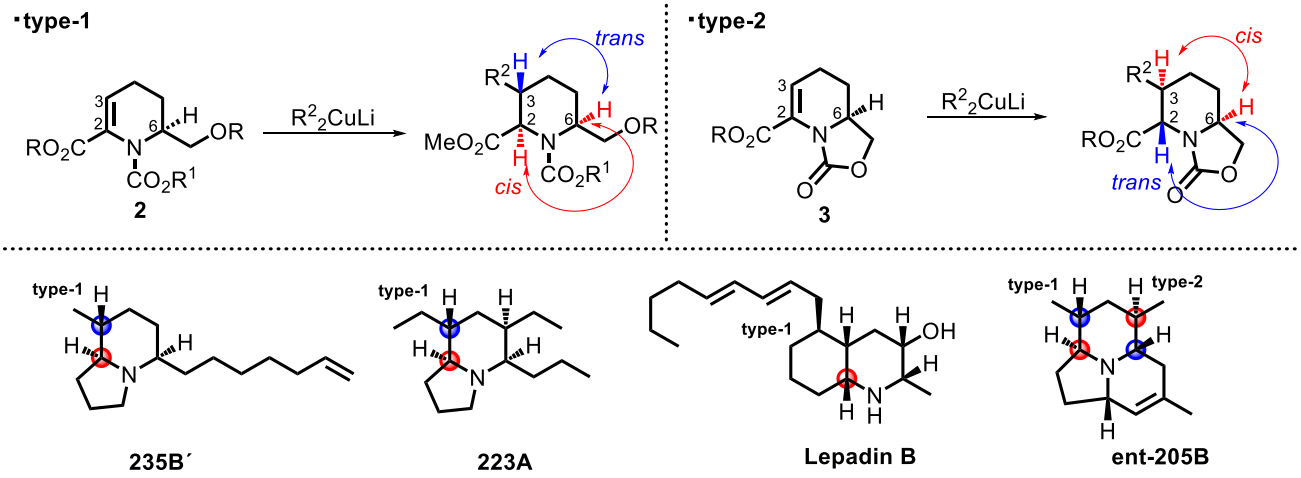
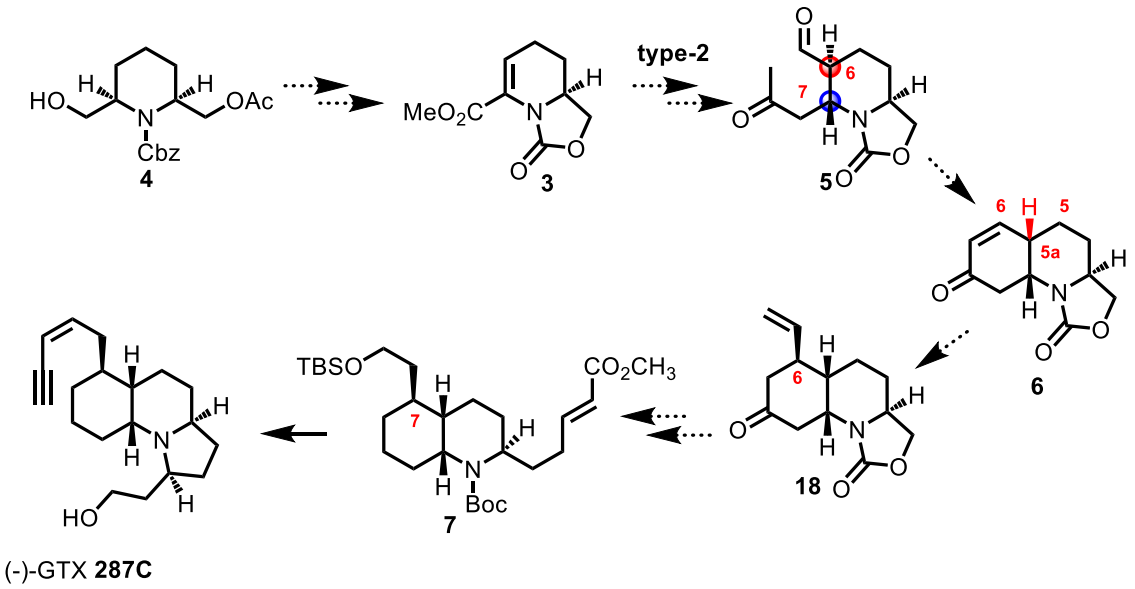


Figure 13. 環状エナミノエステルへの立体選択的共役付加反応を用いた脂溶性アルカロイドの全合成

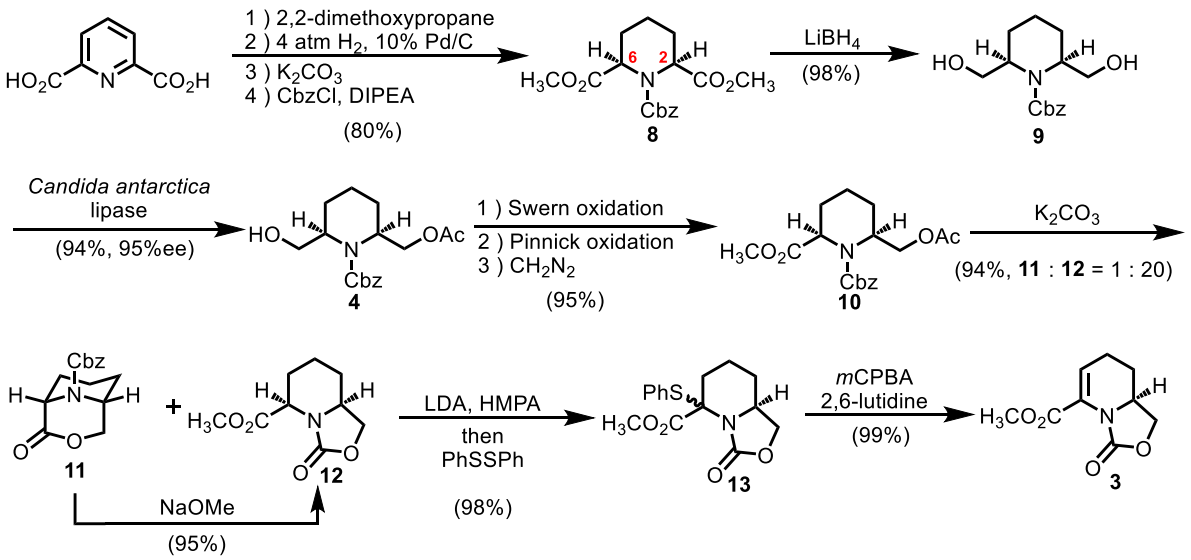
そこで本合成研究では、オキサゾリジノン環をもつ化合物 (**3**) の上記の反応性を利用した *2-epi-cis*-DHQ 環の効率的構築法を鍵とした GTX 287C (**1**) の形式不斉合成を計画した。すなわち、キラルなモノアシル体 (**4**) から導いたエナミノエステル (**3**) に対する高立体選択的共役付加反応により、６位および７位が *trans* 配置のケトアルデヒド (**5**) を調製した後、６位のエピメリ化を伴う環化反応によって *cis*-DHQ 環を有する化合物 (**6**) に導く。さらに、**6** のエノン部への 1,4-付加反応を利用することで６位に側鎖を導入した化合物 (**18**)

に変換する。最後に、**18** から数工程で近年 Amat らによって報告された中間体 (**7**) のエナンチオマーに導くことで **1** の形式不斉合成を達成できると考えた (**Scheme 1**)。



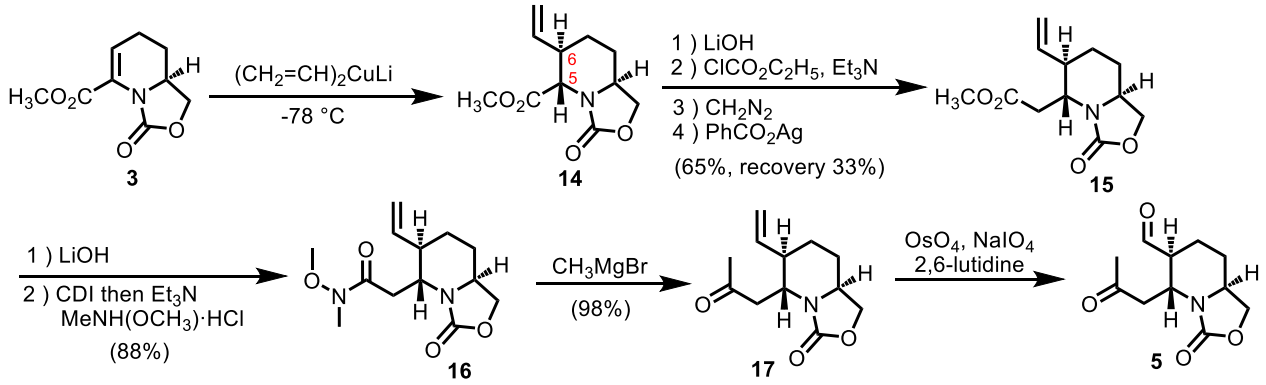
Scheme 1. (-)-GTX **287C** (**1**) 形式合成の合成戦略

前述の合成戦略に従い、2,6-ピリジンジカルボン酸を 4 工程で 2,6-*cis*-ピペリジンジエステル (**8**) へと変換した後、ヒドリド還元によりジオール (**9**) へと導いた。その後、リパーゼを用いた光学分割により目的のモノアシル体[24] (**4**) を高収率かつ高鏡像異性体過剰率で得た。さらに、**4** の水酸基を 2 段階酸化して得られるカルボン酸をジアゾメタンで処理することでメチルエステル体 (**10**) へと変換した。次に、炭酸カリウムの存在下に、**10** を過溶媒分解することにより、オキサゾリジノン誘導体 (**12**) に導いたが、この反応ではビシクロ化合物 (**11**) が複製したので、両者を分離精製後、**11** にナトリウムメトキシドを作用させることで **12** に変換した。さらに、メチルエステル (**12**) の α 炭素にチオフェニル基を導入して得たスルフィド (**13**) に メタクロロ過安息香酸を作用させることで、相当するスルホキシドの syn-β 脱離を経て、目的の鍵中間体となるエナミノエステル体 (**3**) を合成した (**Scheme 2**)。



Scheme 2. 鍵中間体 **(3)** の合成

次に、得られた鍵中間体 **(3)** に対して、**Scheme 3** に示したように高立体選択的共役付加反応を行った。すなわち、−78 °C で **3** に $(CH_2{=}CH)_2CuLi$ を作用させ、5 および 6 位にビニル基とメチルエステル部が *trans* の関係となった連続した 2 つの不斉中心を一挙に構築した。また、本反応の高い立体選択性は、次のように考えている。化合物 **3** の hexahydro-3*H*-oxazolo[3,4-*a*]pyridin-3-one からなる基本骨格特有の配座拘束により、反応時における **3** の立体配座は **Figure 13** のように固定されていると考えられる。また、求核種が **3** を攻撃する方向には α 面と β 面の両方が考えられる。α 面からの場合は、twist boat 型の遷移状態を経て反応が進行すると考えられる。一方、β 面からの場合は、より安定な chair 型の遷移状態を経て反応が進行すると考えられる。そのため、α 面よりもより有利な β 面からの求核攻撃が優先しものと推測される。その後、**14** の加水分解により得られたカルボン酸に対して Arndt-Eistert 反応を行い増炭後、**15** をさらに 2 工程で Weinreb アミド体 **(16)** へと変換した。引き続き、**16** に Grignard 試薬を作用させることでメチルケトン体 **(17)** に変換後、Lemieux–Johnson 酸化に付し、**17** のビニル基をアルデヒド基に変換することで、目的の環化前駆体 **(5)** に導いた。



Scheme 3. 有機銅試薬を用いた不斉 Michael 付加反応および環化前駆体 **(5)** の合成

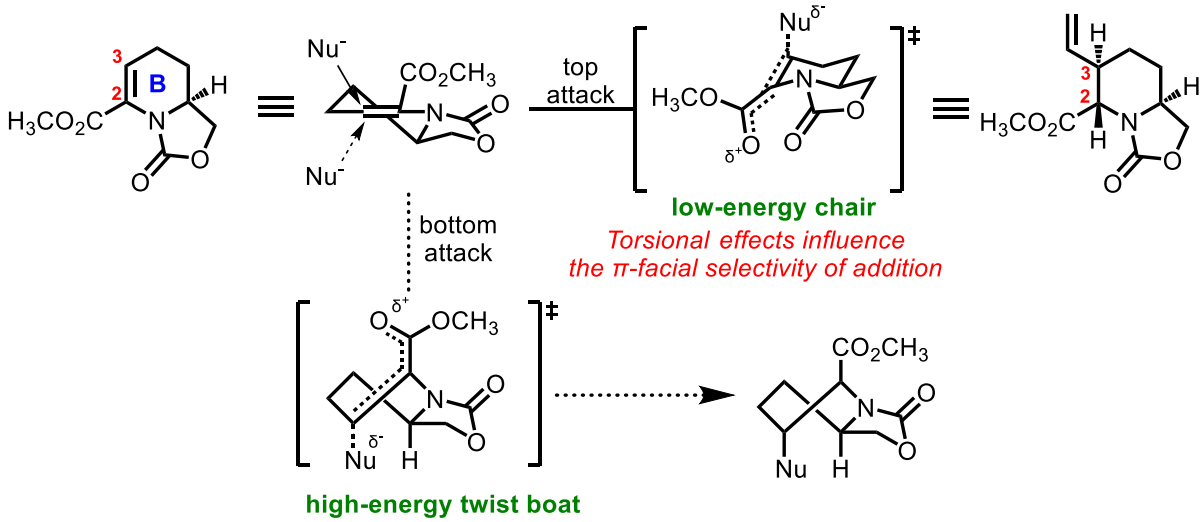
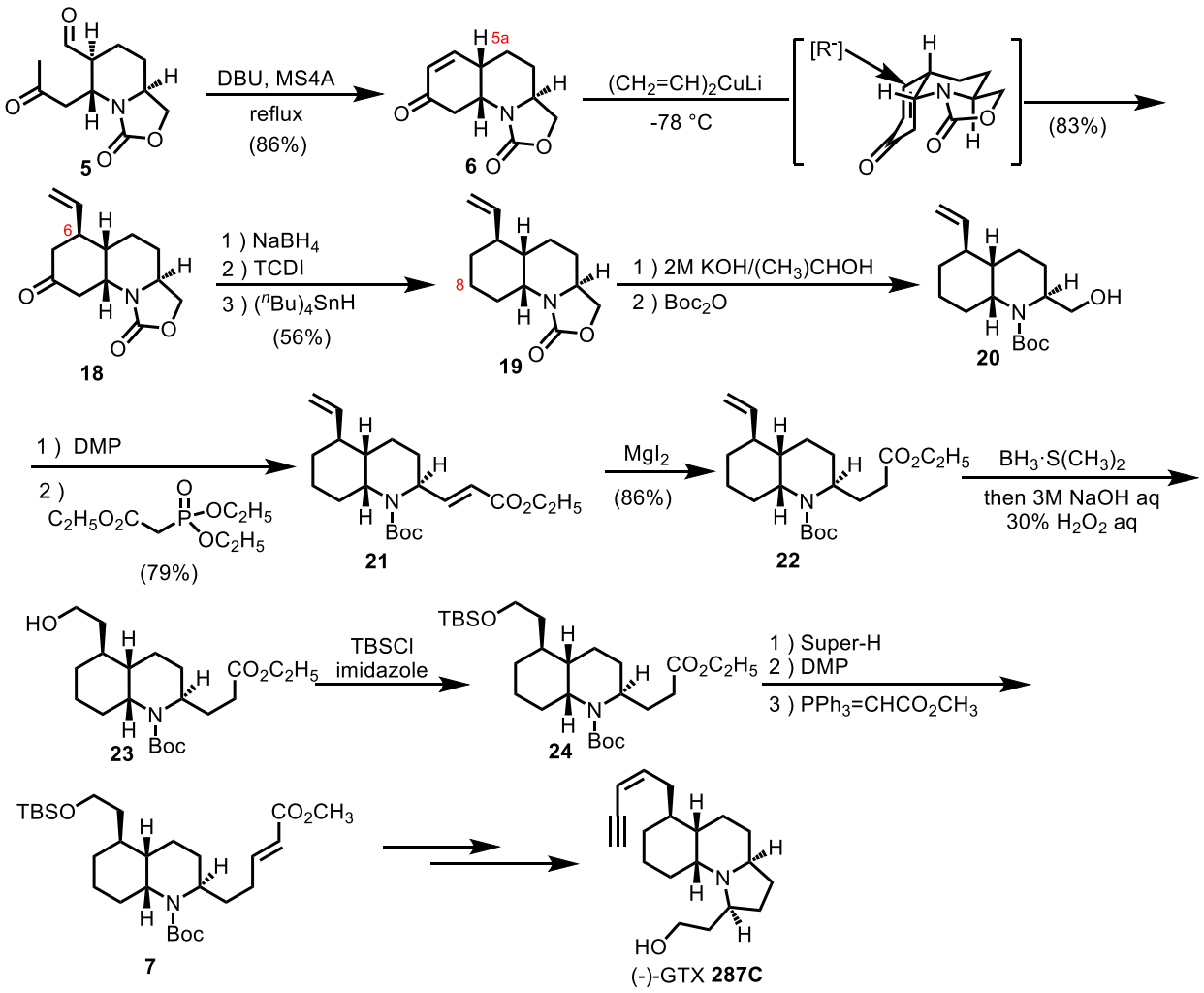


Figure 13. エナミノエステル (**3**) への共役付加反応における高立体選択性について

次に、文献記載の方法[25]に従い、環化前駆体 (**5**) を本合成経路の鍵反応である Aldol 型環化反応に付した結果、５a 位の水素のエピメリ化が進行し、*cis* 型の DHQ 骨格をもつ所望のエノン体 (**6**) を高収率で得ることに成功した。**Figure 15** に示すように、化合物 (**5**) のアルデヒド基および２-オキソプロピル基は、いずれもアキシアル方向を向いており、両置換基間での閉環は不利な立体配置である。したがって、まず DBU がカルボニル α 位の水素を引き抜き、６位でのエピメリ化が起きる。その結果、アルデヒドがエカトリアル方向を向き、メチルケトン部との間で分子内 Aldol 反応が進行し、化合物 (**6**) のみを選択的に与えたものと考えている。

引き続き、**6** に対する有機銅試薬を用いた 1,4-付加反応を検討した結果、本反応は立体選択的に進行し、ビニル体 (**18**) のみが 83% の収率で得られた。本反応の高い立体選択性には、基質 **6** のシクロヘキセノン環の α 面がピペリジン環およびオキサゾリジノン環による遮蔽効果を受ける。そのため、有機銅試薬が凸面（β 面）から優先してエノン部の β 炭素を求核攻撃した結果であると考察している。その後、Barton-McCombie 脱酸素化反応を含む３工程を経て **18** の８位のカルボニル基を還元し、**19** に導いた。次に、塩基性での加溶媒分解によりオキサゾリジノン環を開環後、生じた第２級アミンを Boc 保護して **20** を合成した。得られた **20** の第１級アルコールをアルデヒドへと酸化後、 Horner-Wadsworth-Emmons 反応により α, β-不飽和エチルエステル (**21**) へと変換した。さらに、化合物 (**21**) の不飽和結合をヨウ化マグネシウムの還元で生じた **22** をヒドロホウ素化条件に付すことでアルコール体 (**23**) に導いた後、 水酸基を TBS 基で保護し **24** へと導いた。最後に、**24** のメチルエステル部を還元後、得られたアルコール (**25**) を酸化および Wittig 反応に付すことで Amart らが報告した GTX **287C** (**1**) の中間体 (**7**) のエナンチオマーに導いた。

以上のように、本メチルエステル体 (**7**) の合成をもって GTX **287C** (**1**) の形式不斉合成が達成されたことになる (**Scheme 4**)[26]。



Scheme 4. (-)-GTX 287C の形式不斉合成

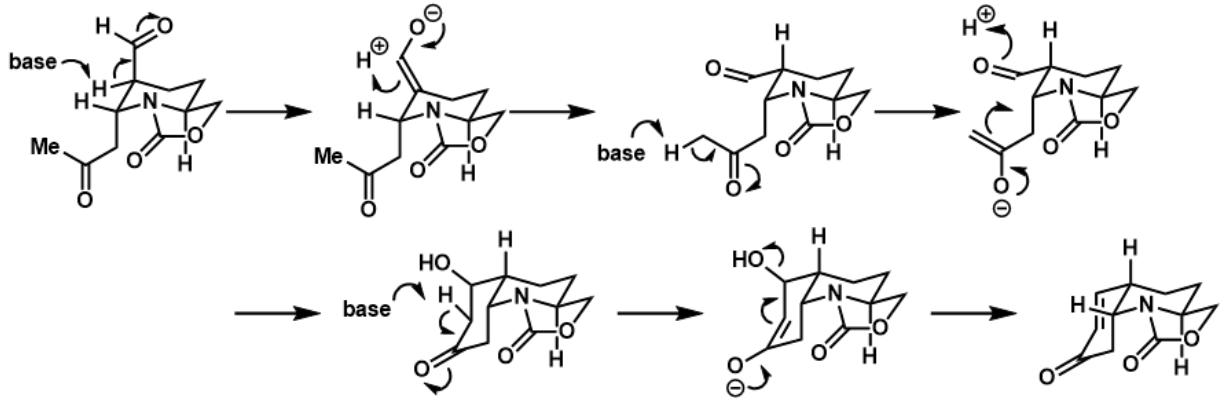


Figure 15. 分子内 Aldol 環化反応の推定反応機構

第二章　三環性海洋産アルカロイド (-)-Lepadiformine A, C および (-) Fasicularin の形式不斉合成

第一節　(-)-Lepadiformine A およびその類縁体について

Lepadiformine A (**25**) は、1994 年にチュニジア近海に生息するホヤ (*Clavelina lepadiformis* Müller in the Mediterranean) から単離された三環性の海洋産アルカロイドである [27]。化合物 (**25**) は様々な腫瘍細胞に対して細胞増殖抑制活性を示すことに加えて、抗不整脈作用や血圧降下作用なども報告されている [28]。当初、**25** の構造は、^{1}H および ^{13}C-NMR スペクトルを中心にした構造解析が行われ、アミノアルコール部位が双極性のイオンとなった構造が提出された [27]。その後、Weinreb[29]、Pearson[30]、樹林 [31]らの全合成研究により、**25** の構造が絶対配置を含め、**Figure 16** に示すようにに改訂された。化合物 (**25**) の構造上の特徴は、*trans*-DHQ 環 (AB 環) にピロリジン環が縮合し、AC 環はアザスピロ環様に結合した珍しい骨格をもっていることである。さらに、化合物 (**25**) には、AC 環のアザスピロ構造部に不斉炭素を含むα-tertiary アミン構造が存在する他、３つの不斉中心を備えている。また、B 環がボート配座をとっており、歪んだ立体構造も特徴である。また、2006 年に、**25** の類縁化合物の Lepadiformine C (**26**) がジブチ共和国海域に生息する *Clavelina moluccensis* から単離された [32]。興味深いことに、**26** が **25** と真逆の絶対配置を有することが、森本らの両対掌体合成によって明らかにされた [33]。さらに、1997 年に SmithKlineBeecham 社の研究グループにより、ミクロネシア海域に生息するホヤ *Nephteis fasicularis* から **25** の類似のピリドキノリン類縁体の Fasicularin (**28**) が単離された [34]。また、C 環にチオシアネート基を有することを特徴としていた。化合物 (**25**) を代表とする三環性海洋産アルカロイドは、その奇妙な構造も相まって、過去 20 年間様々な有機合成化学者によって合成研究が成されてきた。

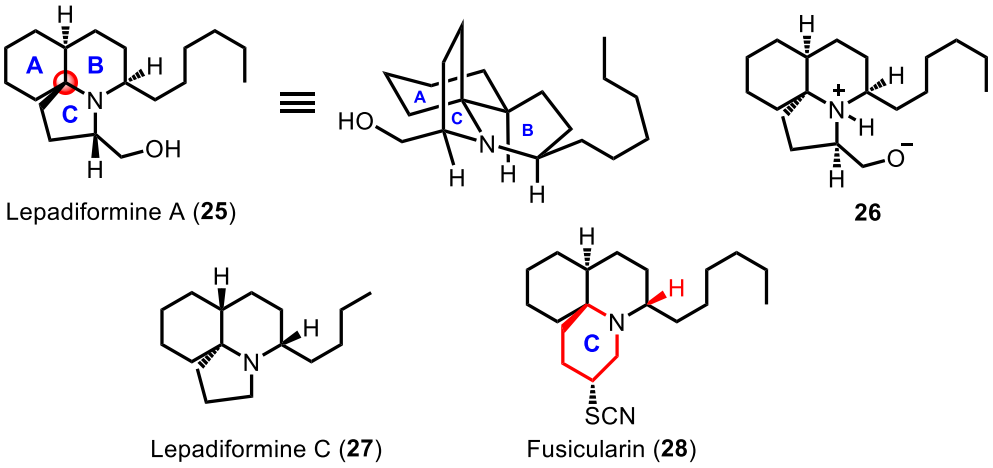


Figure 16. (-)-Lepadiformine A (**25**) およびその類縁体の構造

第二節　　Lepadiformine 類の合成戦略

2019 年までに 11 例の Lepadiformine 類の全合成研究が報告されている。その合成戦略はすべてが A 環および C 環に相当する合成素子から合成を開始し、画期的な方法で Lepadiformine 骨格上の α-tertiary アミンからなるアザスピロ環を構築している。すなわち、2000 年に樹林らは A 環部となる既知の一置換シクロヘキサノンを原料とし、Lepadiformine A (**25**) の初のラセミ全合成を達成した[31b]。彼らは原料をヒドロキサム酸へと変換した後、分子内 Hetero Diels-Alder 反応により、B 環部と同時に縮環部に α-tertiary アミンを構築することに成功した。その後、2001 年 Funk らはジメチルアセタール体から合成したエナミノアルデヒドへの分子間 Hetero Diels-Alder により **25** の A 環部および α-tertiary アミンの合成に成功した[35]。また、Renaud らは A 環部に当たるシクロヘキサノンから導いたエキソオレフィン体へのラジカル型カルボアジド化反応により α-tertiary アミン部の構築に成功している[36]。さらに、2007 年に Craig らは一置換シクロヘキサノンを 3 工程でアジリジン化した後、メチルフェニルスルホンを求核付加させることで A 環上に巧みに α-tertiary アミン を構築している[37]。2010 年に Zhao らは、Craig らと類似の一置換シクロヘキサノン体からキラルなケチミンを合成後、亜鉛粉末を用いたアリル化反応に付し、A 環上の α-tertiary アミンを合成した[38]。彼らはそこから数工程で **25** と Fusicularin (**28**) の不斉全合成を同時に達成している。同じく 2010 年に Rychnovsky らはキラルなアルコール体から合成したジブロモ体をアミノニトリルと求核置換反応させることで A 環部 α-tertiary アミンを合成した[39]。上記のように、A 環を合成開始地点とした合成研究はこれまでに６例報告されている (**Figure 17**)。

一方、C 環を合成拠点とする Lepadiformine 類の合成も、2002 年に樹林らによって行われた[40]。彼らは C 環部となる既知のキラルなピロリジノンを Grignard 試薬の付加により一度開環した。その後、得られたジエンをギ酸で処理することで分子内 Hetero Diels-Alder 反応が進行し、α-tertiary アミンを含む AC スピロ環の構築に成功した。そこから、数工程で Lepadiformine A (**25**) の初の不斉全合成を達成し、天然物の絶対配置が 3*S*,5*R*,7a*S*,11a*S* であることを確定した。また、同じく 2002 年に Weinreb らはキラルな臭素体から導いた環状ラクタムへのリチウム試薬の付加および生じたイミニウムカチオンへの分子内桜井・細見アリル化反応により AC スピロ環を効率よく合成した[41]。さらに、2010 年に徳山らはスクシンイミドから導いた α, β-不飽和スルホンへのラジカル分子内環化反応により AC スピロ環を構築し、その後種々の変換を行い **25** のラセミ全合成を達成した[42]。2014 年に Kim らはアリルエステル体に対する Ireland-Claisen 転位により C 環上に α-tertiary アミン構造の構築に成功した[43]。さらに閉環メタセシス反応を用いて A 環を合成することで AC スピロ環を形成した。また、Kim らは 2017 年に以前とは異なる合成戦略を用いて Lepadiformine C (**27**) の形式不斉合成も達成している[44]。近年、森本らによって **25** の新たな不斉全合成が達成された[45]。彼らはキラルな環状ヘミアセタールからアルキン体へと導いた後、トリフルオロメタンスルホン酸銀 (II) 触媒を用いた環状異性化反応により一挙に

AC スピロ環を構築した。上記に記載したように、 C 環を合成開始地点とした合成研究は 5 例報告されている **(Figure 18)**。

以上のように、様々なグループによりエレガントな方法で Lepadiformine 類の全合成が達成されてきたものの、未だ B 環を出発点とした合成例は未だ報告されていない。そこで我々は前章で述べたオキサゾリジノン誘導体へのタイプ２型の高立体選択的共役付加反応を拡張することで、B 環からの Lepadiformine 類への効率的アプローチがが可能になると考え、**25** および **27** 合成研究に着手した。

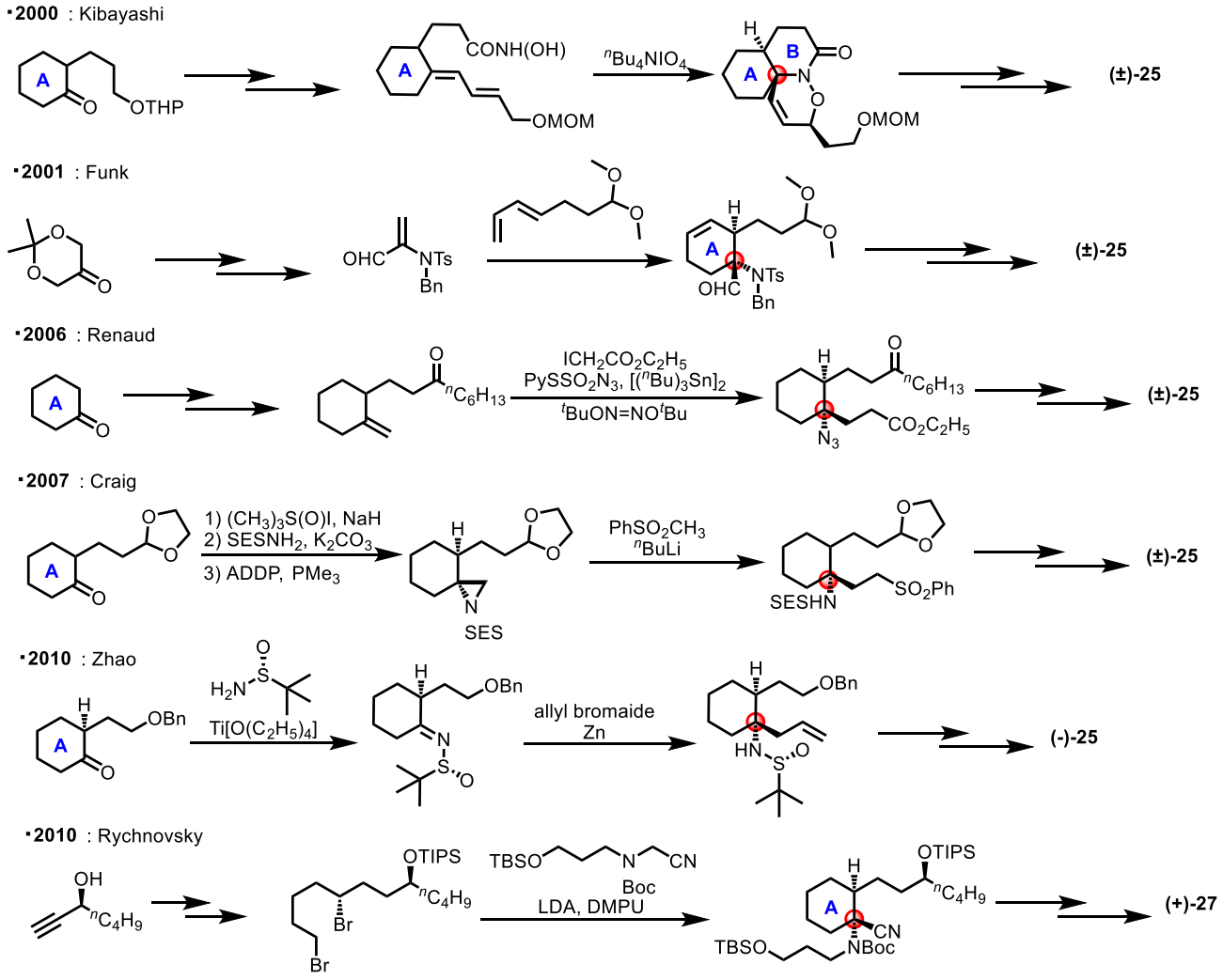


Figure 17. A 環部を合成開始地点として Lepadiformine 類の合成法

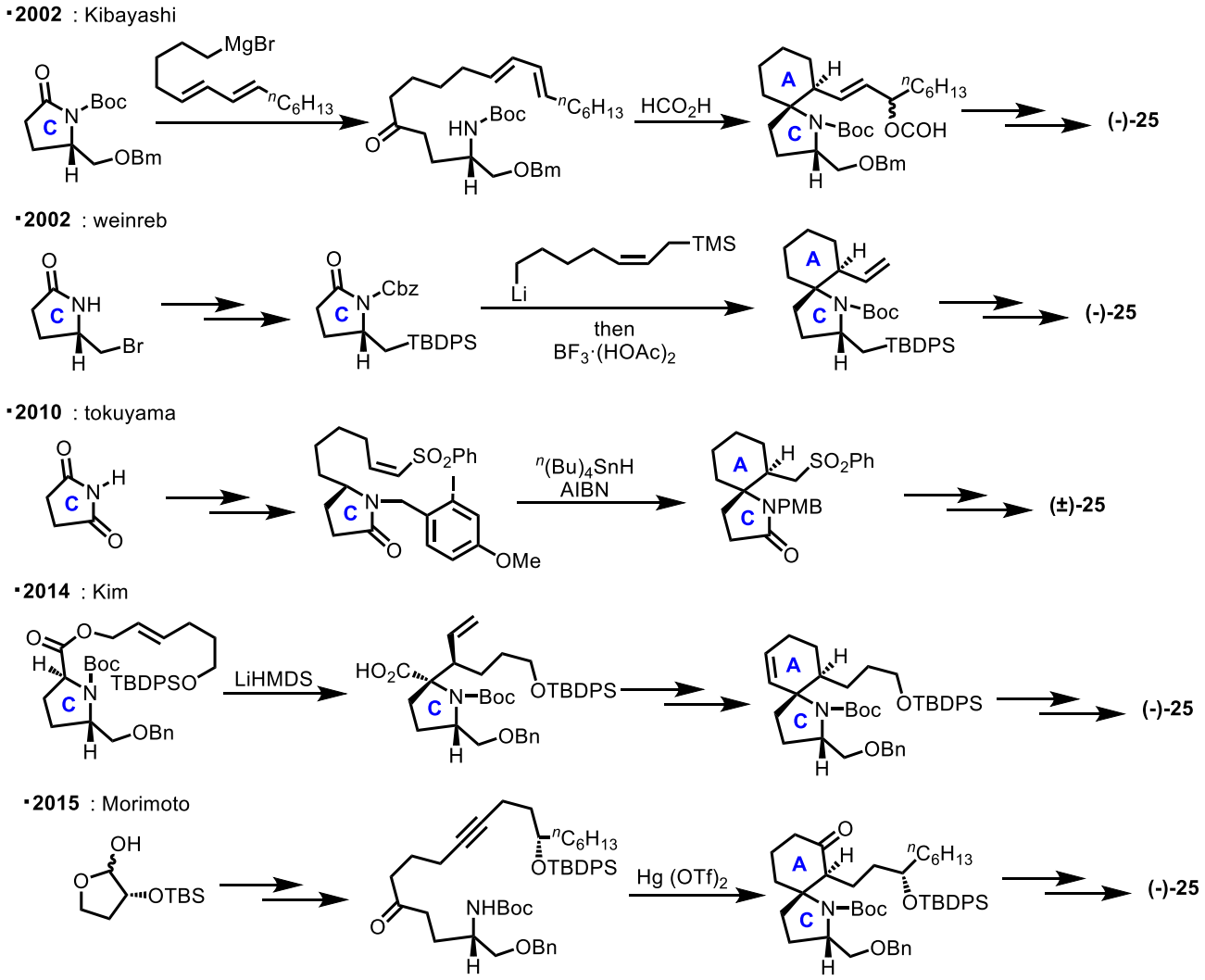
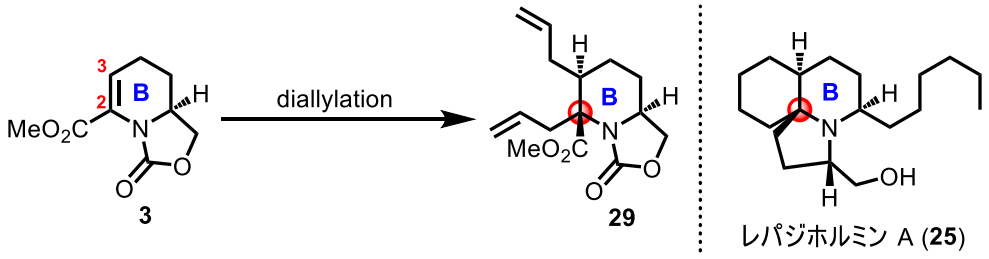


Figure 18. C 環部を合成開始地点として Lepadiformine 類の合成法

第三節　高立体選択的ジアリル化反応を用いた Lepadiformine 類の形式不斉合成

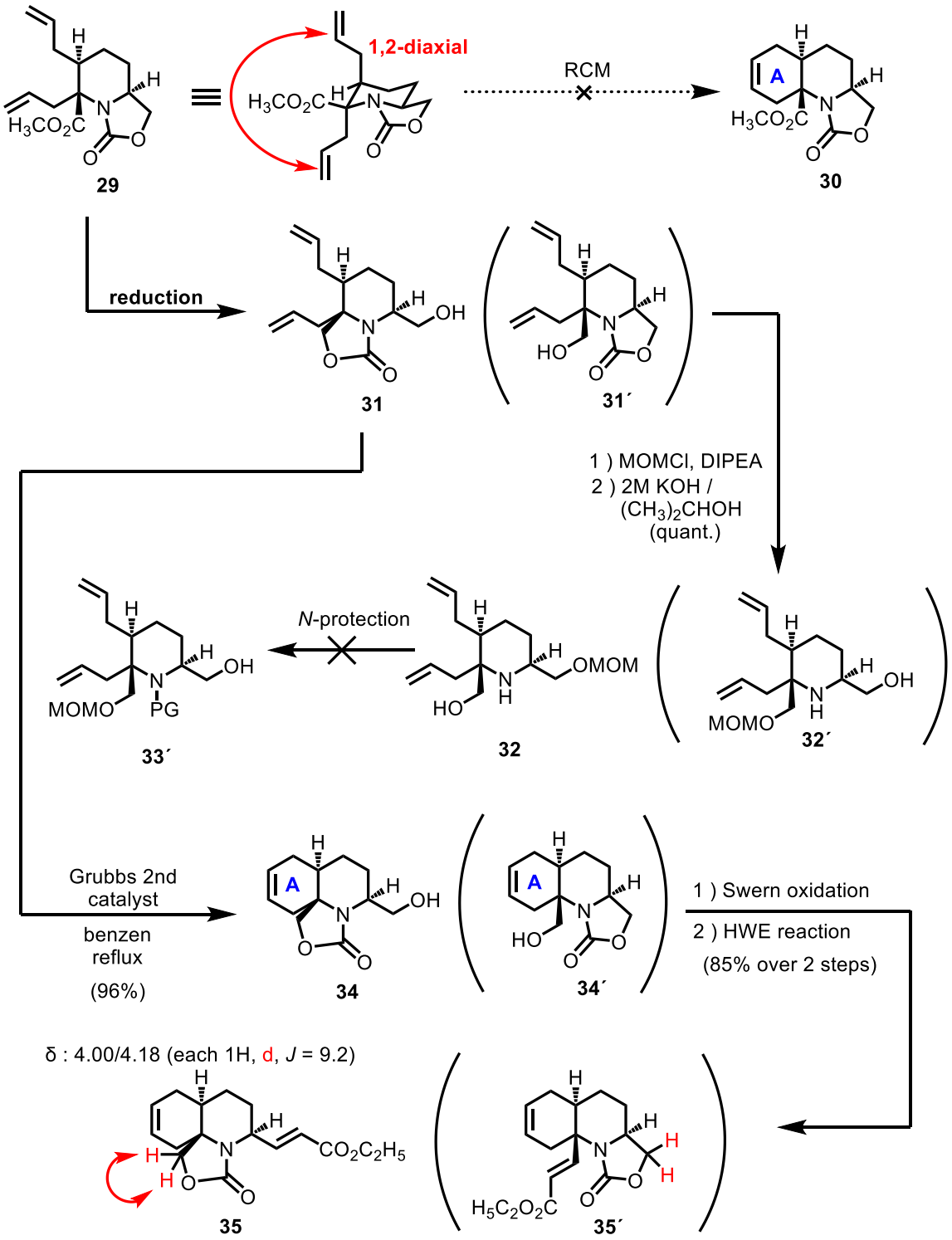
B 環を起点とする Lepadiformine 類の合成に向けての鍵反応となるエナミノエステル (**3**) への高立体選択的ジアリル化反応の検討を行った (**Table 1**)。すなわち、**3** の３位にアリル基を導入後、生じたエステルエノラート中間体を臭化アリルでトラップすることで連続した２つの不斉中心を一挙に構築することができると考えた。本反応により、２位に α-tertiary アミン構造を構築できることから、Lepadiformine 類への変換が比較的容易に展開することが可能である。まず初めに、Grignard 試薬をアリル源とした Gilman 試薬を用いて共役付加反応を行った後、生じるエステルエノラートをアリルブロミドで処理することを試みた。その結果、原料は消失したものの、複雑な混合生成物が得られた（entry 1）。次に、桜井・細見アリル化反応による共役付加反応を行った後、アリルブロミドで処理した。しかし、反応は進行せず、原料回収に留まった (entry 2)。そこで、共役付加反応に用いる Gilman 試薬をテトラアリルスズとメチルリチウムのトランスメタル化を用いて調製した。その結果、低収率であるものの目的のジアリル体を単一のジアステレオマーとして 39% 収率で得ることに成功した (entry 3)。さらに、 Gilman 試薬調製に用いるリチウム源の検討を行い、メチルリチウムをブチルリチウムに変更することで収率が著しく改善され、76% 収率で目的のジアリル体 (**29**) を得た。また、３位アリル基の高い立体選択性は、第一章 **Scheme 3** に示した反応性と同様に、オキサゾリジノン環によるピペリジン環の配座固定と立体電子効果から説明することができる。



entry	reagent	solvent	result
1	allylMgBr, CuI then allylBr	Et_2O/THF	complex mixture
2	allyltrimethylsilane $TiCl_4$ then allylBr	CH_2Cl_2	no reaction
3	tetraallyltin, CH_3Li CuI then allylBr	Et_2O/THF	39%
4	tetraallyltin, $^nC_4H_9Li$ CuI then allylBr	Et_2O/THF	76%

Table 1. エナミノエステルへの高立体選択的ジアリル化反応の条件検討

目的のジアリル化体 (**29**) が得られたので、(−)-Lepadiformine A (**25**) および C (**27**) の合成に向けて A 環の構築に移った。第一章で述べた環状エナミノエステルへの立体選択的共役付加反応における反応性を考慮すると、**29** の３位のアリル基は β 配置にあると考えられる。また、**29** の hexahydro-3*H*-oxazolo[3,4-*a*]pyridin-3-one 骨格には配座拘束があるため、２位のアリル基は α 配置になることが予想されるので、２つのアリル基はいずれもアキシアル方向を向いて配置されていることが考えられた。そのため、**29** の閉環メタセシス反応による A 環の形成は困難だと考えた。そこで、一度オキサゾリジノン環を開環させて、ピペリジン環の配座拘束を除去後、閉環メタセシス反応を行うことを計画した。そこで、最初に **29** のメチルエステルの還元を試みた。まず、$LiBH_4$ をヒドリド還元剤として用いたが、反応は進行せずに原料回収に留まった (entry 1)。次に、Super-H を用いてヒドリド還元を行ったところ、室温では全く進行しなかったが、加熱還流により目的の **31′** と考えられるアルコール体が 66% の収率で得られた(entry 2)。一方、 $LiAlH_4$ 還元では、**31′** と考えられるアルコールが 22% 収率でしか得られなかったため、entry 2 を最適条件した。次に、**31′** のカルビノールの水酸基を MOM 基で保護した後、2M の水酸化カリウム/イソプロピルアルコール溶液で加熱処理することで目的のアミノアルコールらしき化合物 (**32′**) を得た。最後に、第２級アミンの保護を検討したが、目的の構造をもつ化合物 (**33′**) を得ることは出来なかった。次に、アルコール体 (**31′**) らしき化合物から直接的に閉環メタセシス反応を試みた。その結果、予期に反して本反応は加熱還流条件下で進行し、環化体らしき化合物 (**34′**) が得られた。A 環の構築に成功したため、残る C 環構築に向けて、アルコールを酸化した後、 Horner-Wadsworth-Emmons 反応に付すことで、 α,β-不飽和エステル体らしき化合物 (**35′**) を得た。しかし、得られた α,β-不飽和エステル体の ^{1}H-NMR スペクトルには、 δ_H 4.00 および δ_H 4.18 にオキサゾリジノン環部のメチレン水素由来の２種類のシグナルが AB カルテットとして分離位置に確認されたことから、 **29** の還元反応で得られた化合物は **35′** ではなく **35** の構造を有していることが示唆された (**Scheme 5**)。



reduction

entry	reagent	temp	yield
1	$LiBH_4$	rt	no reaction
2	Super-H	reflux	66%
3	$LiAlH_4$	0 °C	22%

***N*-protection**

entry	reagent	yield
1	CbzCl, sat. $NaHCO_3$ aq	no reaction
2	$ClCO_2CH_3$, sat. $NaHCO_3$ aq	no reaction
3	BnCl, K_3CO_3	no reaction

Scheme 5. α,β-不飽和エステル体 (**35**) の合成

そこで、還元体 (**31′**) の構造について二次元 NMR 実験を行ったところ、**31′** の正しい構造は **31** であることが判明した。したがって、化合物 (**31**) は、**29** のメチルエステル部の還元反応で生成した２位カルビノール水酸基がオキサゾリジノン環のカルボニル基を攻撃して、オキサゾリジノン環の巻き直しが進行して生成したものと考えられた。また、**31** のオキサゾリジノン環のメチレン水素 H_A とアリル位水素 H_B 由来のシグナル間に NOE が観測されたことから、ジアリル化反応によって導入された２つのアリル基は予想通りシアキシアルの関係にあり、２つの不斉中心が共に *R* 配置であることを確認した (**Figure 19**)。また、還元体 (**31** および **31′**) の再安定配座のエネルギー計算を行ったところ 巻き直しが進行した **31′** の方が有利であることも支持された (**Figure 20**)。

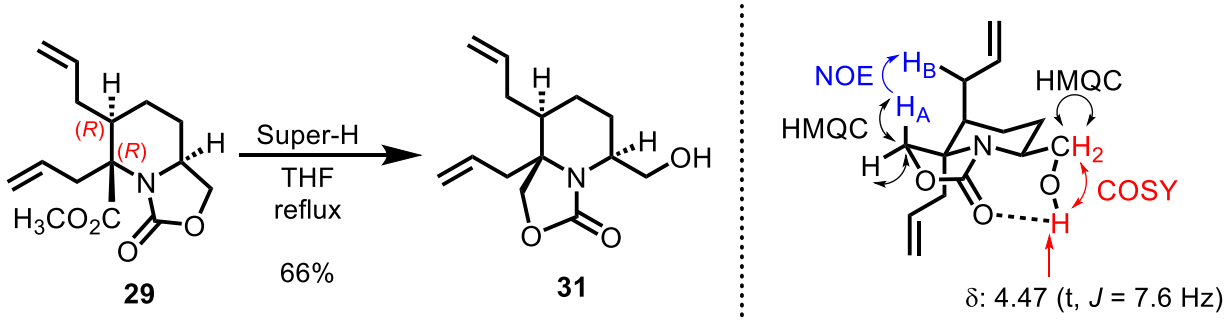


Figure 19. 2 次元 NMR 実験による還元体 **31** の構造決定

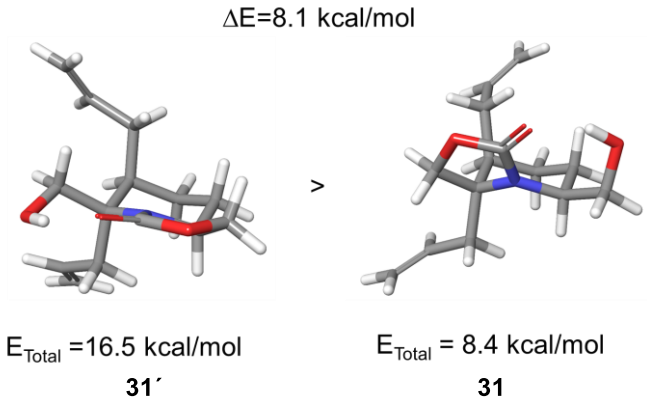
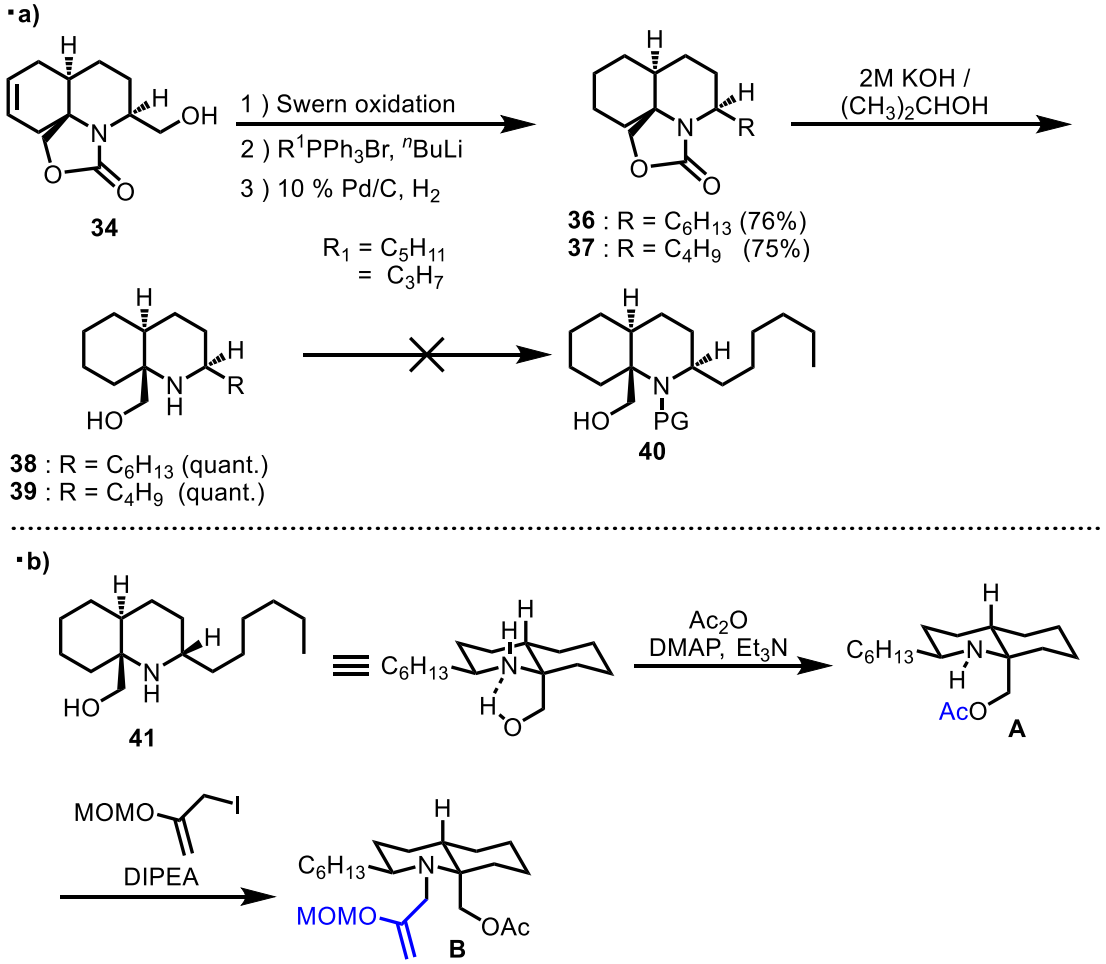


Figure 20. 還元体 **31** および **31′** の再安定配座エネルギーの計算結果

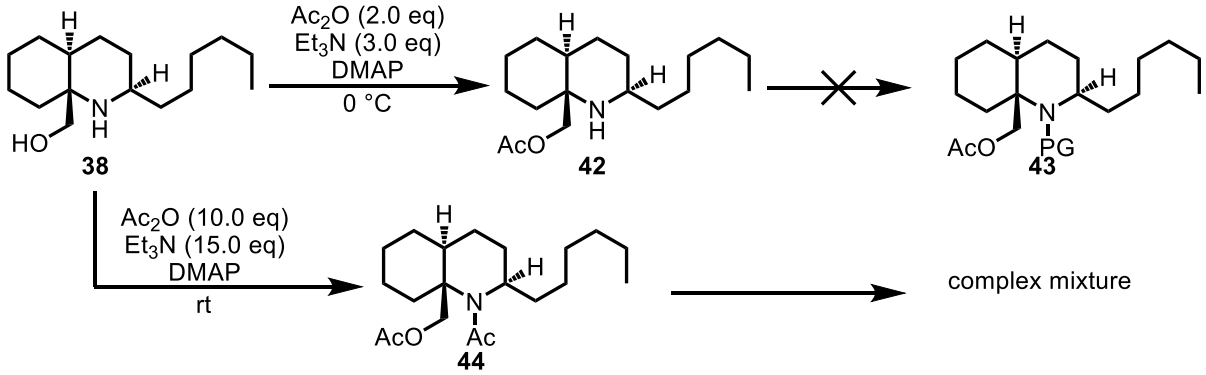
幸いにも、オキサゾリジノンの巻き直しが起きた還元体 (**31**) の閉環メタセシス反応が進み、目的の DHQ 環をもつ化合物 (**34**) が得られたことから、**34** を用いて合成研究を進めた。まず、目的アルカロイド (**25** および **27**) の側鎖部の構築を目的とし、**34** の Swern 酸化により生じるアルデヒドに対して Wittig 反応を行った。その後、オレフィン体を接触水素化反応に付すことでアルキル化体 (**36** および **37**) を合成した。さらに、2M の水酸化カリウム/イソプロピルアルコール溶液で **36** および **37** を加熱処理することでアミノアルコール体 (**38** および **39**) へと導いた。次に、C 環の構築に向けて、**38** から第２級アミンへの保護基の導入を試みたが、保護体 (**40**) を得ることは出来なかった (**Scheme 6a**)。Funk らは

40 とはピペリジン環窒素の α 位水素の立体が異なるアミノアルコール体 **(41)** を合成し、その第２級アミンの保護を試みたが、保護体を得ることができなかったことを報告している[35]。その理由として第２級アミンの窒素原子とカルビノール水酸基との間に生じる強い水素結合によりアミンの反応性が低下している可能性が示唆されている **(Scheme 6b)**。しかし、彼らはカルビノール水酸基をアシル基で保護した化合物 **(A)** を経由することで、第２級アミン上の修飾に成功している。



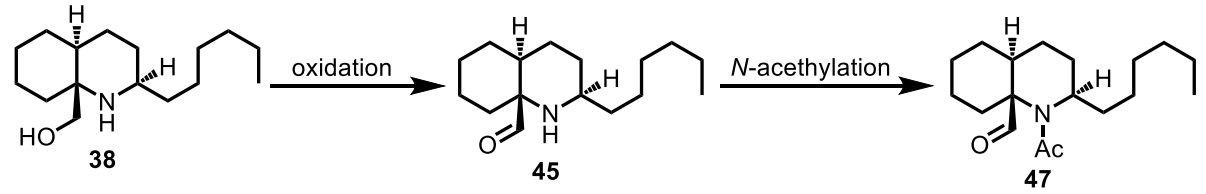
Scheme 6. C 環構築を目的としたアミノアルコールの変換: **a)** アミノアルコール **38** および 39 の合成。 **b)** Funk らによって報告されたアミノアルコール **(41)**

そこで、Funk らの知見を基にして、アミノアルコール体 **(38)** のカルビノール水酸基を小過剰の無水酢酸で選択的にアシル化することで **42** へと変換した後、第２級アミンの保護を試みたが、反応は全く進行しなかった。一方、大過剰の無水酢酸を室温で作用させることにより、窒素原子のアシル化も進行し、ジアシル体 **(44)** が得られ、カルビノール水酸基を保護し不活性化することができれば、第２級アミンをアシル基で保護できることが判明した。しかし、**44** に対して *O*-選択的脱アシル化を行ったが、目的の *O*-脱保護体を得ることは出来なかった **(Scheme 7)**。



Scheme 7. 2 級アミンの保護の検討

次に、**38** に対して *O*-選択的な酸化を試みた。一般にアルコールの酸化に用いられる Swern 酸化や Dess-Martin 酸化では複雑な混合生成物が生成した。そこで、AZADOL を用いたアミノアルコールの *O*-選択的な空気酸化を **38** に適用したところ、定量的に目的のアミノアルデヒド体 (**45**) が得られた。次に、**45** に対して無水酢酸を用いてアシル化を行ったところ、長時間の加熱が必要であったが、目的の **47** を中程度の収率で得た。その後、アシル源を無水酢酸から塩化アセチルへと変更することで高収率かつ短時間で **47** を得ることができた (**Figure 21**)。



O-selective oxidation

entry	reagent	result
1	$(COCl)_2$, DMSO, Et_3N	complex mixture
2	DMP	complex mixture
3	AZADOL, ,2-bpy DMAP, CuCl	99%

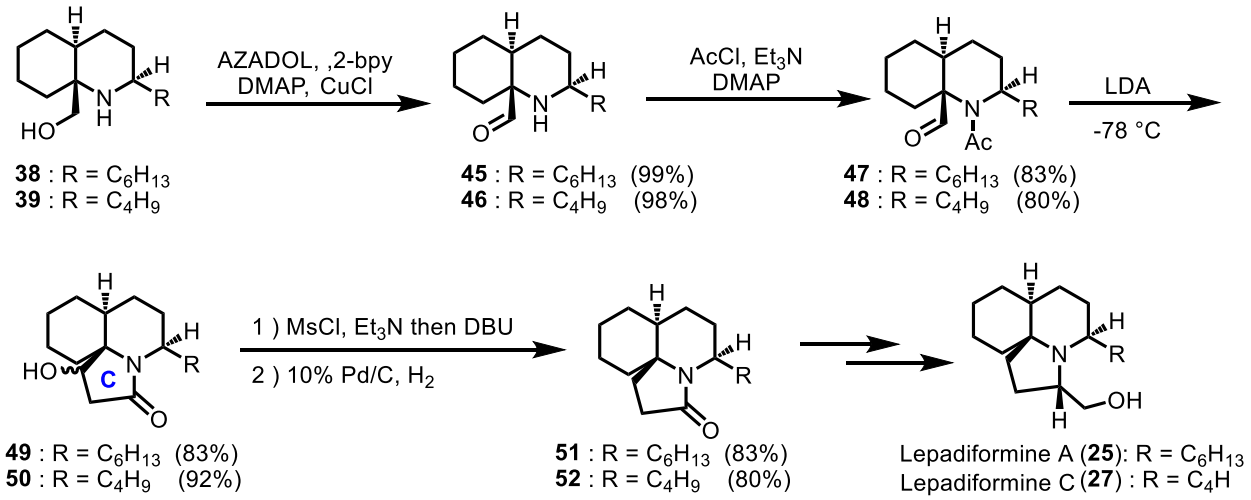
N-acethylation

entry	reagent and solv.	temp. and time	result
1	Ac_2O, Et_3N, DMAP CH_2Cl_2	reflux, 1 d	63%
2	AcCl, Et_3N, DMAP CH_2Cl_2	rt, 5 h	83%

Figure 21. アシル体 (**47**) の合成

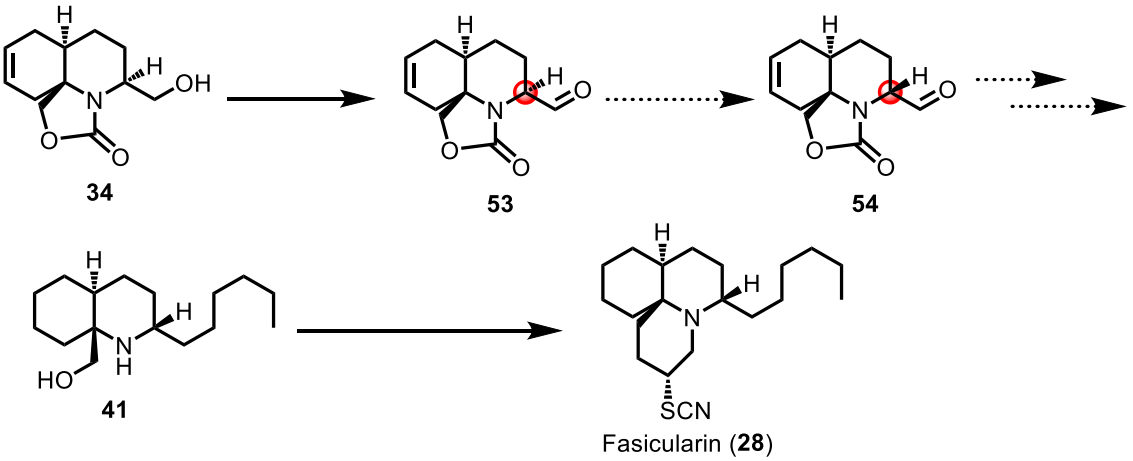
アミノアルコール (**39**) に対しても AZADOL を用いた空気酸化を行うことでアミノアルデヒド (**46**) へと導いた後、アセチルクロライドで処理することで **48** へと変換した。その後、アシル体 (**47** および **48**) は LDA を作用させて、それぞれ **49** および **50** へと導くことで C 環を構築することに成功した。その後、２級アルコールをメシル化した後、DBU を添加することで E1cb 脱離が進行しエノンを合成した。さらにエノンを水添反応により還元することでラクタム **51** および **52** へと変換した。化合物 (**51**) から Lepadiformine A (**25**) の合成は Renaud ら [36]によって報告されている。また、**52** から Lepadiformine C (**27**) の合成は Rychnovsky ら [39]によって報告されているので、**25** および **27** の形式不斉合成を達成

したことになる (**Scheme 8**)。



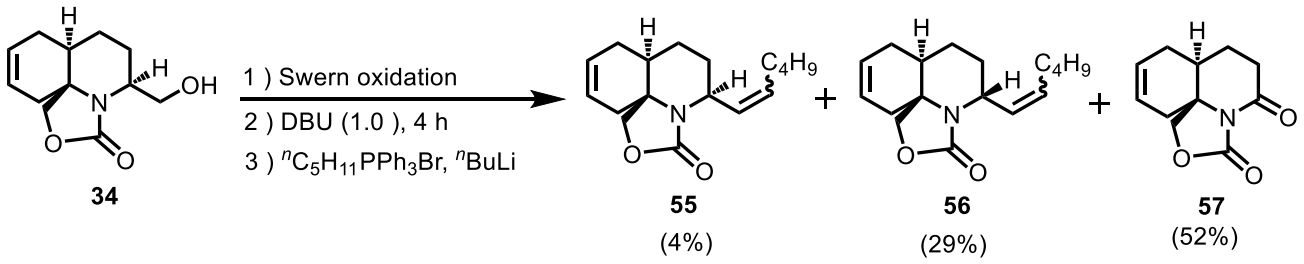
Scheme 8. 2 級アミンの保護の検討

次に、アルコール中間体 (**34**) から酸化により合成可能なアルデヒド (**53**) の α 位をエピメリ化することができれば、 Funk らによって報告された Fasicularin (**28**) の合成中間体 (**41**) へと導くことが可能だと考えられる。そのため、**53** へのエピメリ化反応の検討を行った (**Scheme 9**)。



Scheme 9. エピメリ化によるアミノアルコール (**41**) の合成計画

アルコール中間体 (**34**) を Swern 酸化後、DBU を 1 等量用いてエピメリ化反応を行った。4 時間後に反応を後処理し、得られた粗生成物に対して Wittig 反応を行うことで、オレフィン体 (**55**) および そのエピメリ化体 (**56**) を合成した。その結果、目的の **56** をジアステレオ優先的に得ることができたが、本反応の主生成物は予期に反したラクタム体 (**57**) が得られた (**Scheme 10**)。なお **57** の構造は X 線構造解析により決定した (**Figure 22**)。



Scheme 10. エピメリ化反応の検討

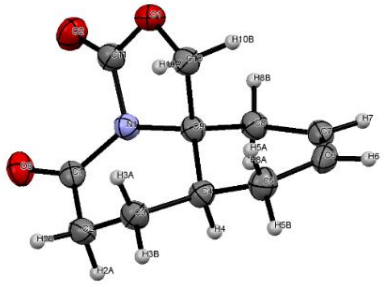


Figure 22. X 線構造解析により解かれたラクタム (**57**) の構造

Wender らは、Taxol の合成研究[46]においてアルデヒドを塩基性条件酸素雰囲気下でケトンへと変換することに成功している。そのため、予期に反して生成したラクタム体 (**57**) は、反応溶媒中の溶存酸素により **34** から生成している可能性が示唆できた (**Figure 22**)。

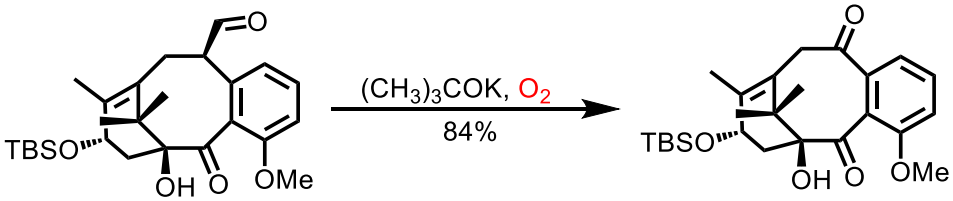
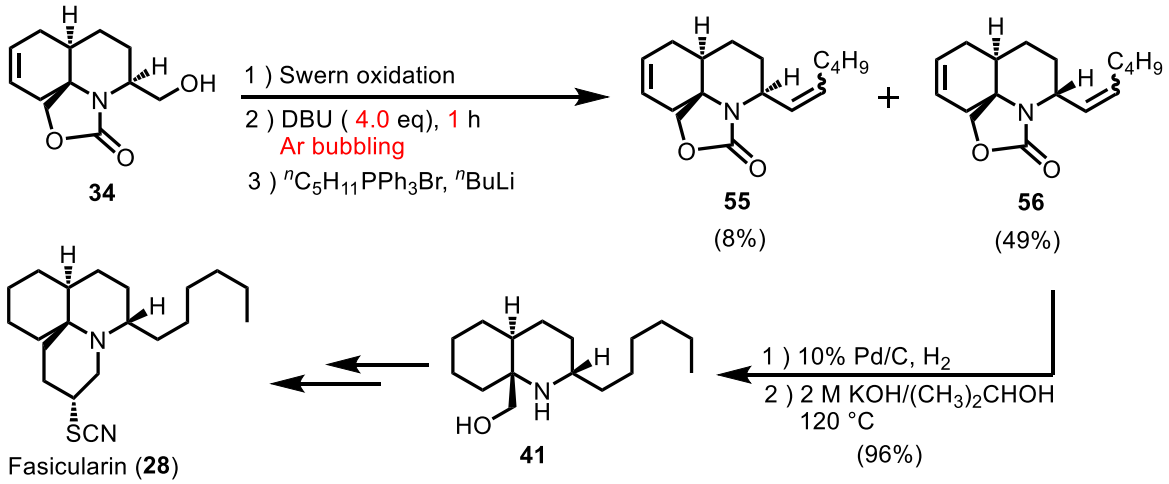


Figure 23. Wender らによって報告されたアルデヒドからケトンへの変換

前述の反応を参考に、エピメリ化反応において酸素の脱気を目的としたアルゴンバブリングを行った結果、予想通りにラクタム体 (**57**) の生成を抑えることに成功した。さらに、DBU を 4 等量加えることで 1 時間以内に 49% 収率で目的のエピメリ化体 (**56**) をジアステレオ優先的に得ることができた。最後に水添反応によりオレフィンを還元後、オキサゾリジノン環を開環することで Funk らの報告したアミノアルコール[35] (**41**) へと導き、fasicularin (**28**) の形式不斉合成を達成した (**Scheme 11**)[47]。



Scheme 11. Fasicularin (**28**)の形式不斉合成

第三章　　ニコチン受容体への構造活性相関研究を目的とした Decahydroquinoline 型毒ガエルアルカロイドの網羅的全合成

第一節　生理活性毒ガエルアルカロイド

中南米あるいはマダガスカル島産の毒ガエル皮膚抽出液の中から多様な骨格をもつ脂溶性アルカロイドが数多く単離されている。その数は現在までに 800 種以上確認されており、20 種類を超えるサブクラスに分類されている[48]。その中でも、Batrachotoxin、Histrionicotoxin、Pumiliotoxin は強力な神経毒として知られている[49] **(Figure 24)** 。

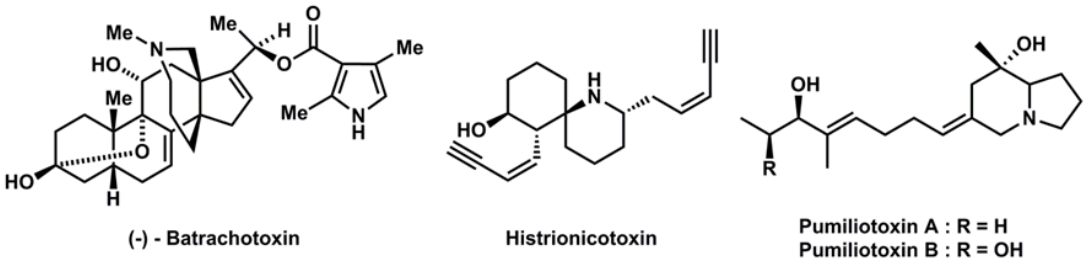


Figure 22. 毒ガエルアルカロイドの構造

特に、古くから矢毒として用いられてきた Batrachotoxin をはじめ、これら毒ガエルアルカロイドは、近年様々な生理作用が明らかになりつつあり、その中でも特に脳−神経研究上の重要なバイオロジカルツールとしての応用研究に期待が集まっている[4]。しかし、飼育下のカエルには、これらアルカロイドが含まれず、カエルを採集後、現地で直ちにカエルからの成分抽出を行わなければアルカロイドが単離されないという事実を踏まえると、これら毒ガエルアルカロイドは、主にエサとなるアリ、やすで、ダニ、クモ、などの昆虫に由来するという仮説、すなわち dietary hypothesis が有力視されている[50]。さらに、同種の毒ガエルでも生息地により異なるアルカロイドが抽出されると報告されていることもこの仮説を強く支持している[51]。一方、カエル特有の変換酵素により体内で生産されるアルカロイドも知られている[52]。これらの毒ガエルアルカロイドはニコチン受容体 (nAChR) を筆頭に中枢神経系に対して興味深い生物活性を示す可能性が報告されているが、上記 dietary hypothesis により天然からの供給量が極めて微量であることに加え、毒ガエルがワシントン条約によって保護されてから、増々天然からの量的供給が困難となり、詳細な生物活性の検討がなされていないのが現状である。

第二節　ニコチン性アセチルコリン受容体について

イオンチャネル内蔵型受容体である nAChR は神経伝達物質のアセチルコリンによって刺激されるアセチルコリン受容体の一種であり、ニコチンがアゴニストとして働くことがその由来である。さらに、哺乳類において nAChR は 16 種類 (α1−α7, α9, α10, β1−β4, γ, δ, ε) のサブユニットが確認されており、それらがホモまたはヘテロ 5 量体化することで形成されている**(Figure 23)** 。また、nAChR は α2−α7, α9, α10 と β2−β4 の組み合わせで構成される神経型と α1β1γδ/ε の骨格筋型の 2 つのサブタイプに大きく分けられる。特に、神経型ニコチン受容体はアセチルコリンやニコチンに対して反応性や感受性の異なる様々なサブタイプが、神経系に幅広く分布している。脳内においては α4β2 及び α7 nAChR が主なサブタイプであり、学習、記憶や認知機能など脳神経機能の調節に重要な役割を担っている**(Figure 24)**。また、2009 年にはバクテリアの nAChR ホモログを用いて、本チャネルがアロステリック機構であることが分子レベルで解明された [53]。

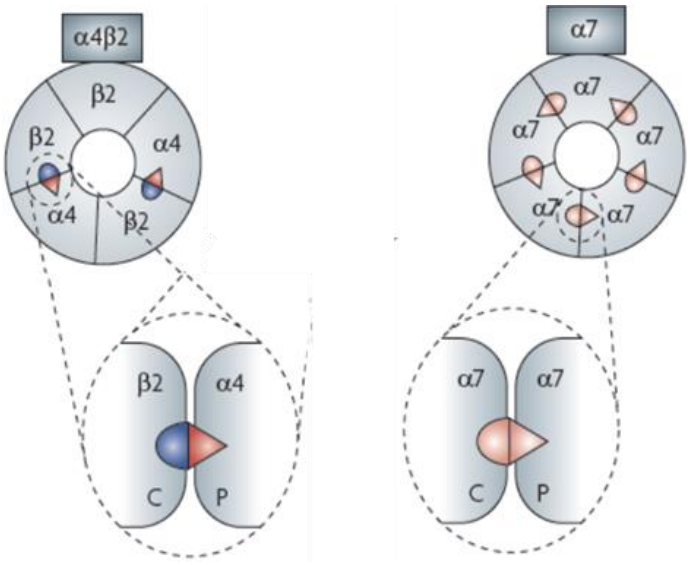


Figure 23. ニコチン受容体の構造[53

α4β2 ニコチン受容体 (nAChR) は、ニコチンに対して高親和性な受容体であり、脳内では、海馬、大脳皮質、腹側被蓋野 (VTA) および中脳黒質などに幅広く分布し、特に VTA のドーパミンニューロンへのニコチンによる報酬効果は α4β2 nAChR により調節される [54]。さらに、ヒト常染色体優性夜間前頭葉てんかん (autosomal dominant nocturnal frontal lobe epilepsy: ADNFLE) と ニコチン受容体サブユニット (α4 および β2) 遺伝子との連鎖解析により、これら２つの遺伝子が本疾患の病因である可能性が示唆された [55]。また、ニコチンは α4β2 nAChR を介した JAK2/STAT3 シグナル伝達により、リポ多糖 (Lipopolysaccharide : LPS) 刺激の炎症を緩和し、抗炎症効果を示す可能性が報告された [56]。2006 年には α6β2*

nAChR も中枢神経系のドーパミン様作用に密接に関与していることが示された。さらに、現在 α6β2* nAChR 選択的アンタゴニストである Conotoxin MII は α6β2* nAChR の研究に欠かすことのできない分子ツールとなっている [57]。

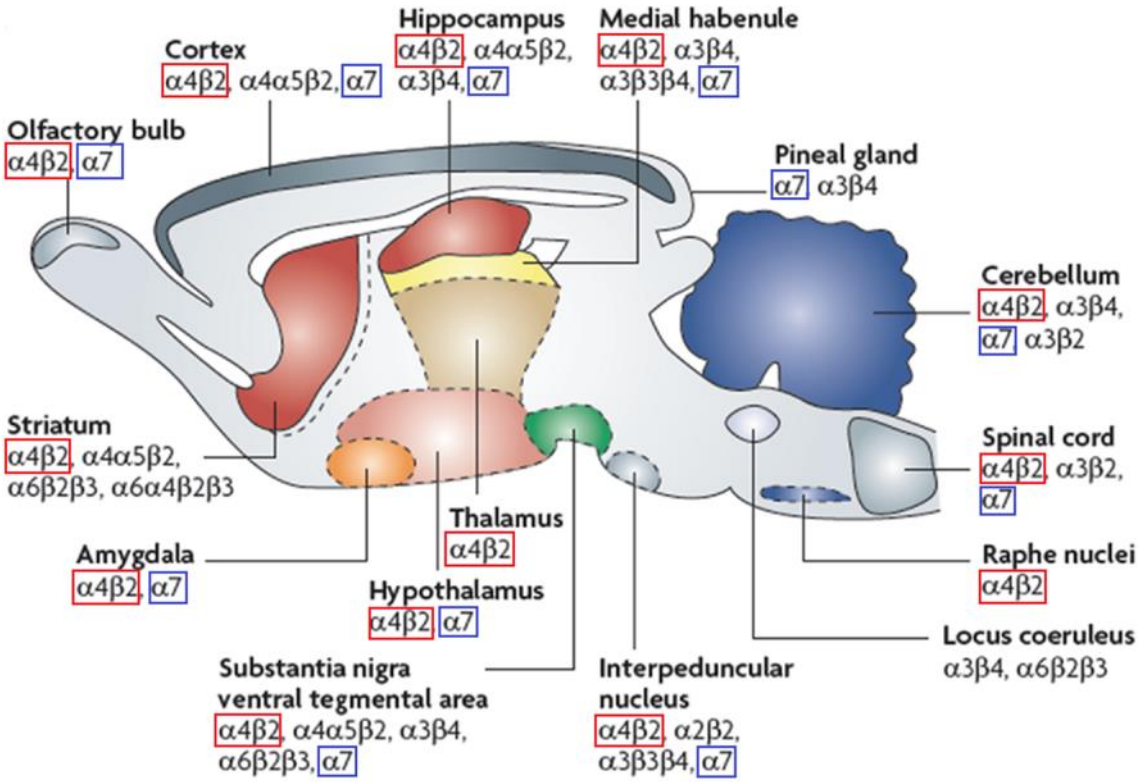


Figure 24. 中枢神経系におけるニコチン受容体サブタイプの分布 [56]

第三節　ニコチン受容体を標的とした創薬研究

てんかんやニコチン依存症などの中枢神経系疾患の治療において、α4β2 および α6β2* ニコチン受容体 (nAChR) は、重要な創薬標的の一つである。アメリカの製薬会社 Pfizer は世界で初めて α4β2 nAChR の部分作動薬である Varenicline を開発し、2006 年に商品名「CHANTIX®」として発売した。本医薬品は、現在唯一、臨床利用されている α4β2 および α6β2* nAChR サブタイプへの選択的な作用薬である [58]。しかし、副作用としてうつ病や奇異行動などの神経精神症状を発症し、重度の場合は自殺傾向を含むことが、販売後に報告された。そのため、2008 年 5 月に Pfizer は新たな安全警告を添付文書に追加した [59]。また、2012 年に Dougherty らは α4β2 nAChR のリガンドを用いた構造活性相関研究を行い、本受容体とリガンドの間にカルボニル基の水素結合相互作用およびカチオン–π 相互作用が働いていることを明らかにした [60]。一方で、Kozikowski らは Sazetidine A 誘導体とナミイトゴカイ (*Capitella teleta*) 由来アセチルコリン結合タンパク質 (Ct-AChBP) との間の相互作用を足掛かりに、Sazetidine 誘導体 **5** との共結晶を作成し、その X 線解析によりタンパクモデルを同定した。さらに、得られた結果を基により強力な薬理活性をもつ Sazetidine 誘導体 **12** を見出した [61]。また、2013 年に Paige らは、合成した Sazetidine 誘導体 **(S)-9** を用いてアルコール依存のマウスにおけるアルコール摂取量を減少させることに成功し、その作用機構が選択的に α4β2 nAChR を脱感作させていることを報告した。[62] 現在、α4β2 nAChR への構造活性相関研究によって見出された **AZD-1446** が本受容体の選択的なフルアゴニストとして作用することから、認知障害疾患の新たな治療薬として期待されている **(Figure 25)** [63]。

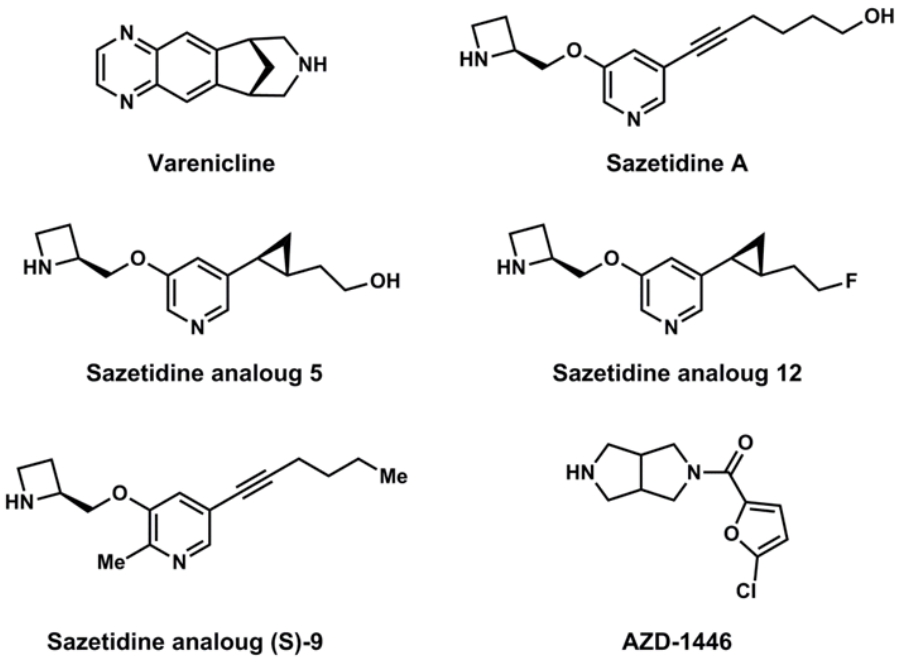


Figure 25.Varenicline、Sazetidine A およびその誘導体および AZD-1446 の構造

一方、我々の研究グループは、これまでに毒ガエルアルカロイド Indolizidine **235B′** の不斉合成を達成し、本化合物が α4β2 nAChR を抑制することを報告している。これに加えて、本化合物は α7、α3β2 および α4β4 nAChR よりもそれぞれ 6 、40 および 50 倍以上も強力に α4β2 nAChR を抑制することからサブタイプへの高い選択的を示すことも明らかになっている **(Figure 26)** [64]。

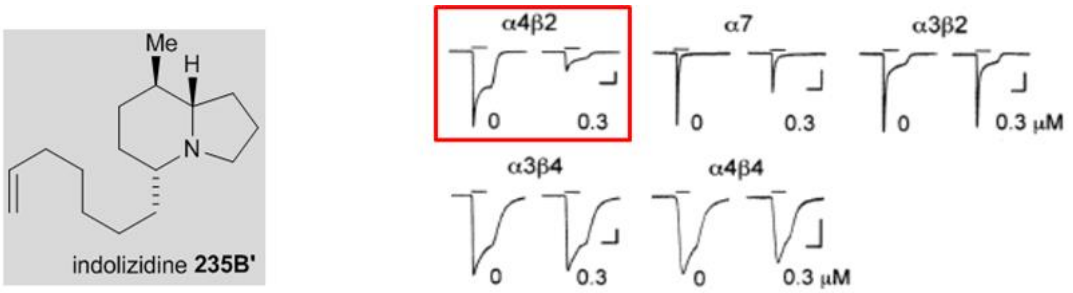


Figure 26. Indolizidine **235B′** のニコチン受容体抑制活性評価の結果

さらに、新規禁煙補助薬の開発を目的とした Kentucky 大学との共同研究により、Indolizidine **235B′** を含む 6 種の類縁体のニコチン誘発性ドパミン遊離阻害活性が測定された。その結果、Indolizidine **237D** が α-conotoxin MII 感受性 α6β2* nAChR と相互作用し、強いニコチン誘発性ドパミン遊離阻害作用を示したことから、5，8 位置換 indolizidine が、α6β2* nAChR のアンタゴニストとして作用する可能性が示唆された [65] **(Figure 27)**。

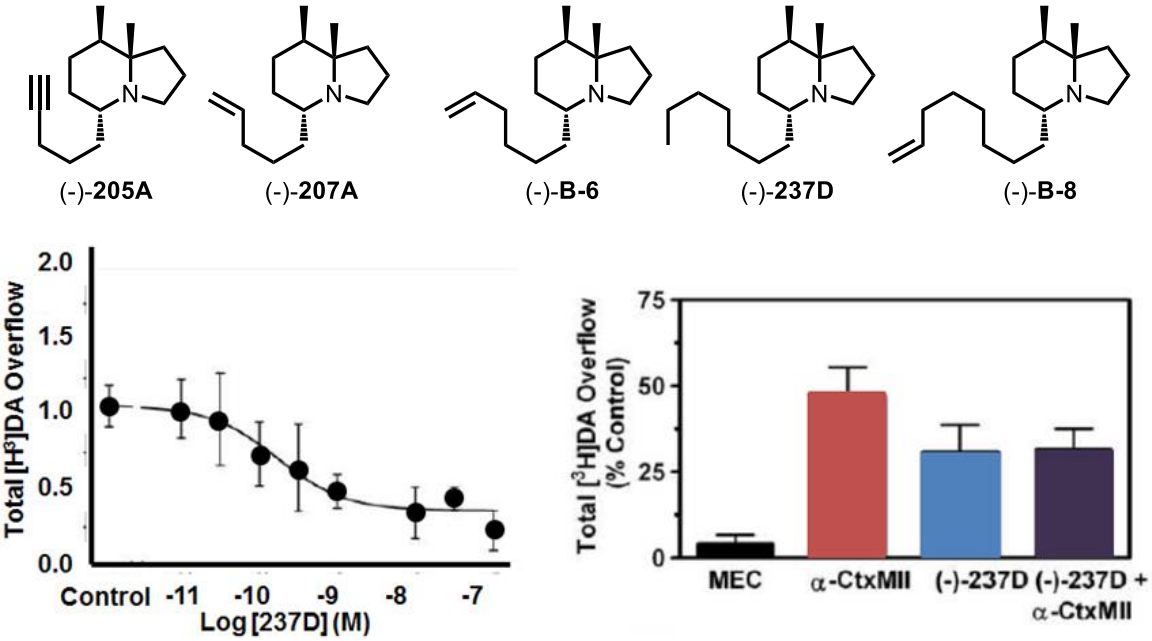


Figure 27. Indolizidine **235B′** 誘導体を用いたニコチン誘発性ドパミン遊離阻害活性の結果

さらに、Indolizidine **235B′** および Indolizidine **237D** 共に窒素のα位の側鎖の炭素数が 7 であることに着目し、当研究室で全合成を達成した Indolizidine **239Q** の 8 位側鎖の炭素数を 7 に変更した誘導体を合成し、合成品の α4β2 nAChR に対する抑制活性効果が測定された。その結果、 Indolizidine **239Q-1**, ***epi*-239Q-1** が α4β2 nAChR に対して天然物 Indolizidine **239Q** よりも約 20 倍も強力な抑制活性を示すことが判明している **(Figure 28)** [66] 。

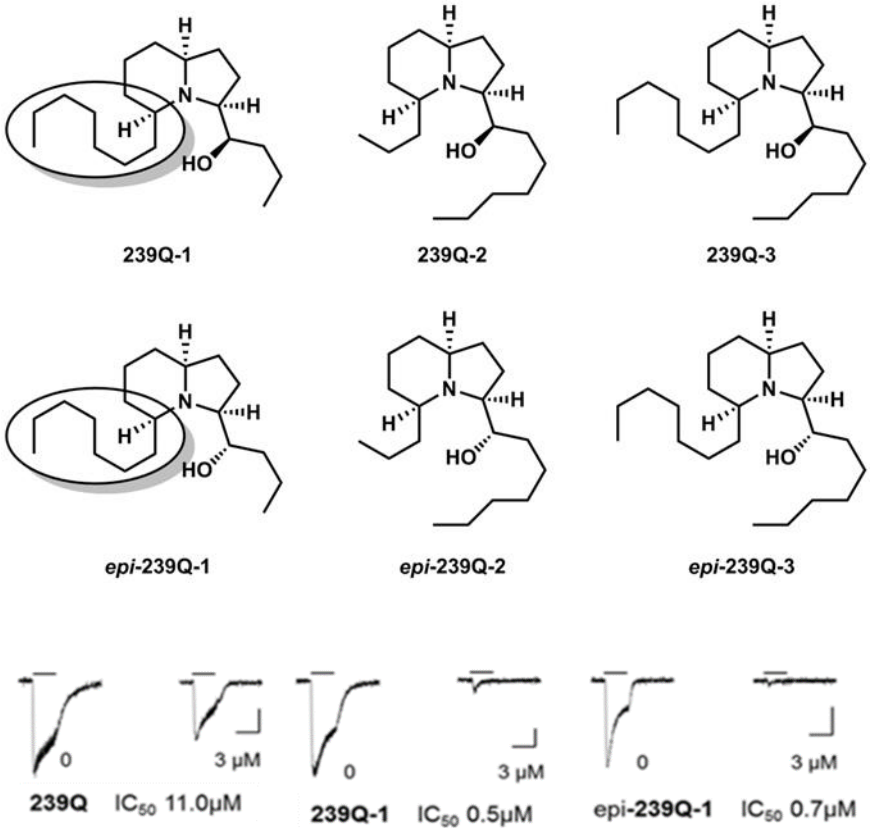


Figure 28. Indolizidine **239Q** およびその誘導体 Indolizidine **239Q-1**, ***epi*-239Q-1** の構造とニコチン受容体抑制活性結果

さらに、近年、我々は新たな中枢神経系疾患の治療薬なりうるリード化合物の探索を目的に、2, 5 位二置換 Decahydroquinoline (DHQ) 型毒アルカロイドに着目した。2,5 位二置換 DHQ 型毒ガエルアルカロイドは４つの不斉中心を有するので、16 種類ものジアステレオマーが存在する。そのため比較的大きなサブクラスではあるものの、代表例である ***cis*-195A** のみに焦点を当てた合成しか行われておらず、その他の DHQ 型毒ガエルアルカロイドについての合成例はほとんどないことから、詳細な薬理作用は検討されていない。そのような中、 2021 年に我々はエナミノエステル **(57)** へのタイプ１型の Michael 付加反応を鍵反応とし、得られたビニル体 **(58)** から ent-*cis*-**195A (60)**の不斉全合成を達成した。さらに、トリフラート中間体 **(59)** から異なる経路により *cis*-**211A (61)**の初の全合成およびその６位水酸基の立体が異なる 6-*epi*-**211A (62)** の合成に成功した [67]。また、天然物の絶対立体配置が *2R*、

4aR、*5R*、*6S* および *8aS* であることも確定した **(Figure 29)**.。

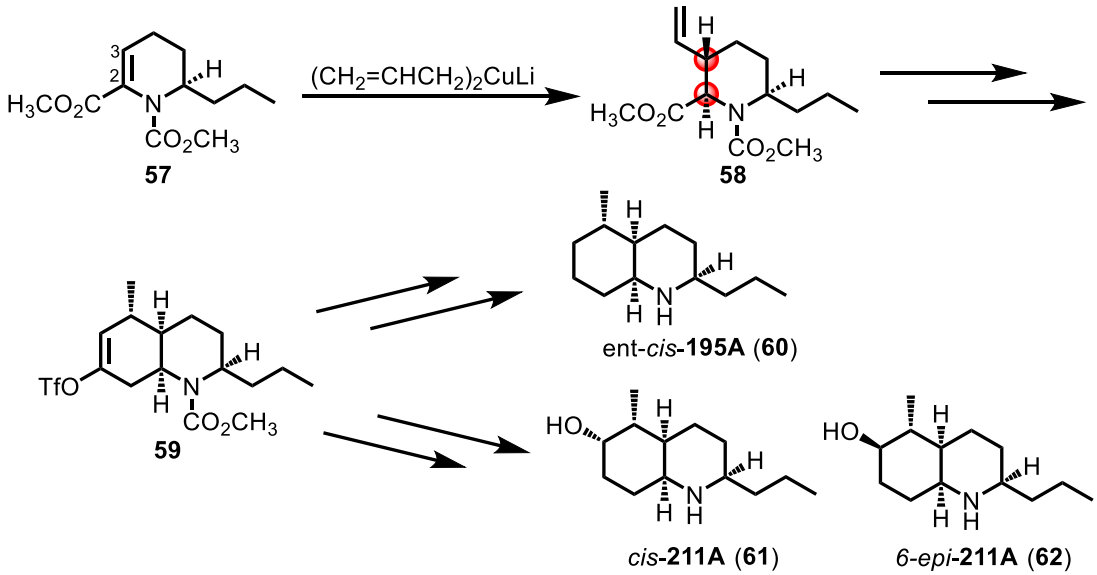
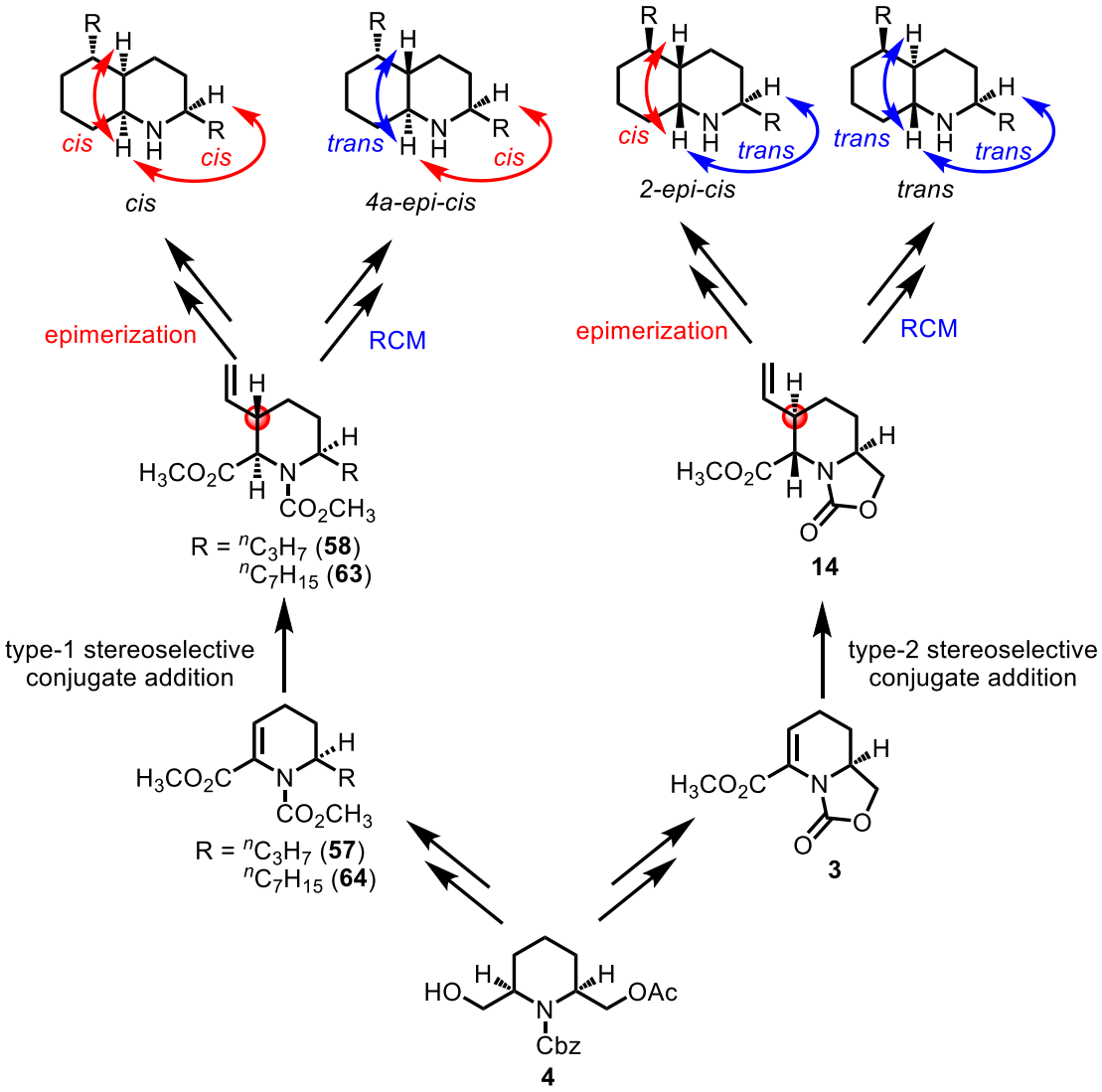


Figure 29. DHQ 型アルカロイド ent-*cis*-**195A** (**60**)、cis-**211A** (**61**) および 6-*epi*-**211A** (**62**) の全合成

上記の合成研究の結果、我々は *cis* 型の DHQ 型アルカロイドの合成法を確立した。また、第一章で述べた GTX 287C (**1**) の合成研究で用いた環化体 (**6**) からは 2-*epi*-*cis* 型の DHQ 型アルカロイドが合成可能と考えられる。そこで、今回我々はニコチン受容体への構造活性相関研究を目的とした DHQ 型アルカロイドの網羅的合成へと展開した。また、これまでの知見から、作用強度および選択制に正の効果を与える可能性が高い窒素 α 位の側鎖の炭素数を 7 に変更した誘導体も合成することを企画した。

第四節　Decahydroquinoline 型アルカロイドの網羅的合成と活性評価

DHQ 型毒ガエルアルカロイド **195A (60)**, **211A (61)** の全合成および GTX **287C (1)** の形式合成を参考に計画した、４つの不斉中心に基づいた４つの立体異性体 (*cis*, 4a-*epi-cis*, 2-*epi-cis*, *trans*) に属した関連アルカロイドの網羅的合成法を **Scheme 12** に示す。まず、*cis* および 2-*epi-cis* 型 DHQ 骨格の構築は第一章で述べた水素のエピメリ化を伴う Aldol 型環化反応により、それぞれ **58**、**63** および **14** から導くことができる。さらに、4a-*epi-cis* および *trans* 型 DHQ 骨格の構築は、**58**、**63** および **14** から閉環メタセシス反応により構築できると考察した。また、**58**、 **63** および **14** はそれぞれ環状エナミノエステル **(57)**、 **(64)** および **(3)** から高立体選択的共役付加反応により構築可能である。最後に **57**、 **64** および **3** は共通のキラルアルコール **(4)** から合成することとした。



Scheme 12 .DHQ 型アルカロイドの網羅的合成法の計画

上述の合成戦略に従い、*cis*-DHQ 型アルカロイド **209J (65)**、**223F (66)**、**237U (67)**、さらに側鎖炭素数が 7 の誘導体 **251A (68)**、**209J-1 (69)** および **223F-1 (70)** の合成に着手した **(Figure 30)**。

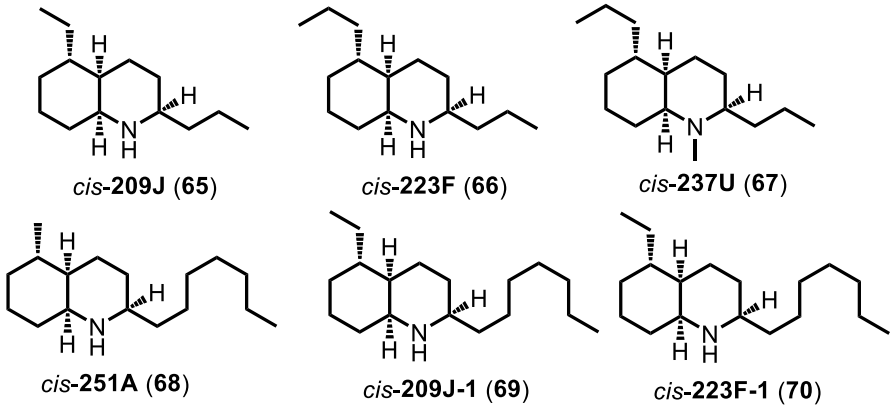
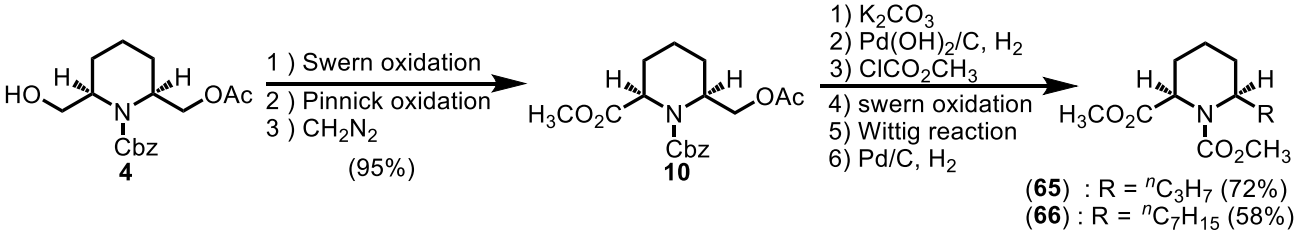


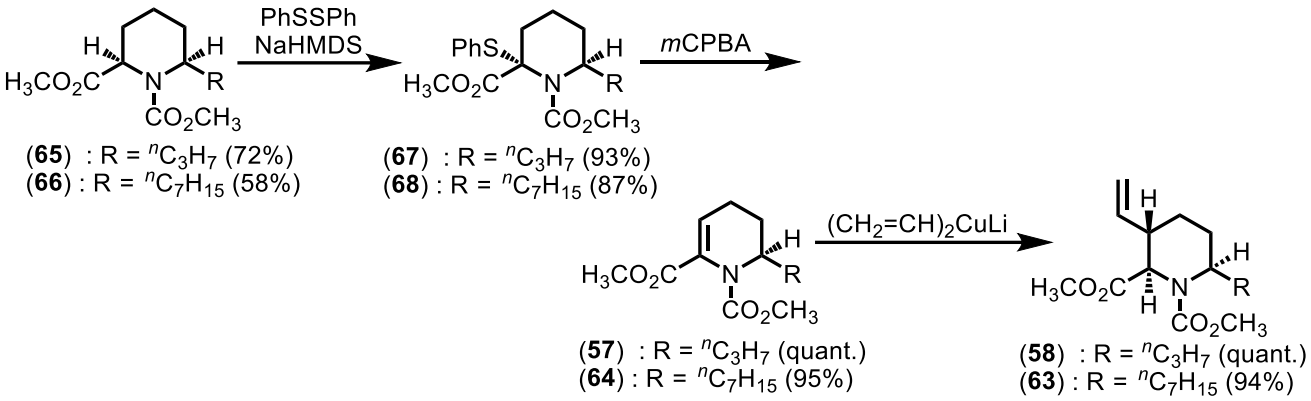
Figure 30. 標的 *cis*-DHQ 型アルカロイドの構造

原料であるモノアセチル体 **(4)** から第一章と同様の手法でメチルエステル体 **(10)** へと導いた。すなわち、**4** の二段階酸化後、ジアゾメタンを用いたメチルエステル化により定量的に **10** に変換した。次に、**10** のアセチル基を選択的に除去した後、Pearlman 触媒を用いて脱 Cbz 化した後、窒素原子をメチルウレタンで保護した。さらに、第 1 級アルコールを Swern 酸化後、Wiitig 反応および接触還元を経て 3 炭素および 7 炭素の側鎖 3 および 7 をピペリジン環に導入し、**65** および **66** を、6 工程、72% および 58% の収率で得た **(Scheme 13)**。



Scheme 13. モノアセチル体 **(4)** からの 2 位側鎖構築

次に、化合物 **(65** および **66)** を、極低温下で NaHMDS と処理した後、ジフェニルジスルフィドを作用させ、高収率で *S*-フェニル体 **(67** および **68)** へと変換した。その後、*m*CPBA を作用させることで生じたスルホキシドの syn-β 脱離反応が進行し、エナミノエステル **(57** および **64)** がほぼ定量的に得られた。さらに、**57** および **64** に対して鍵反応である高立体選択的共役付加反応を行うことで、連続した２つの不斉中心を一挙に構築し、**58** および **63** に導いた**(Scheme 14)**。



Scheme 14. エナミノエステルへの高立体選択的 Michael 付加反応

本共役付加反応の立体選択性は以下のように説明できる。**A** では α 位側鎖であるプロピル基とメチルウレタンとの間に特殊な *A*$^{(1,3)}$*strain* が生じる。その結果、反応時における立体配座は **B** に固定される。また、求核種が攻撃する方向は α 面と β 面の両方が考えられる。β 面からの場合は、twist boat 型の遷移状態を経て反応が進行すると考えられる。一方、α 面からの場合は、より安定な chair 型の遷移状態を経て反応が進行すると考えられる。そのため、β 面よりもより有利な α 面からの求核攻撃が優先したと考えられる (**Figure 31**)。

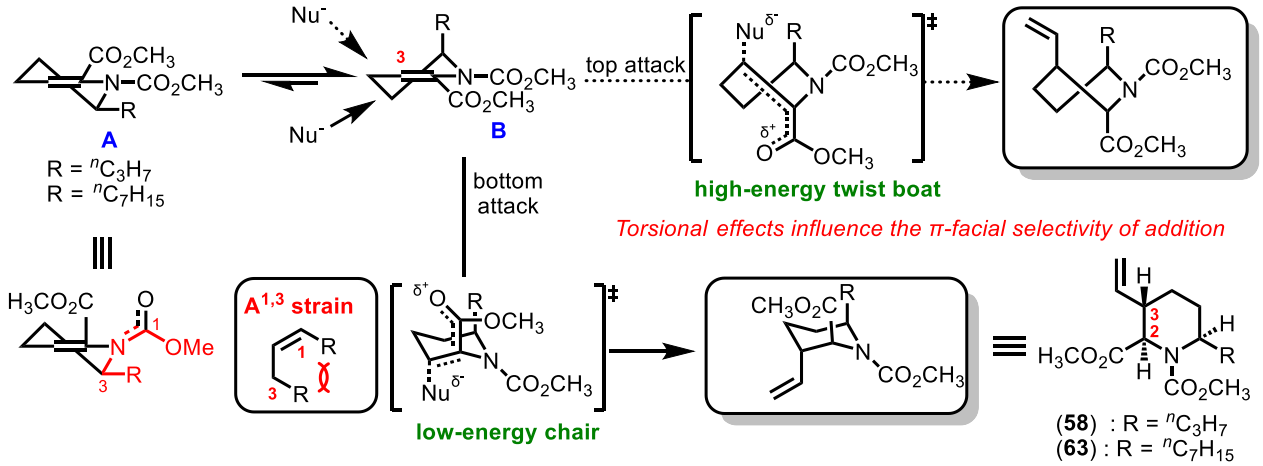
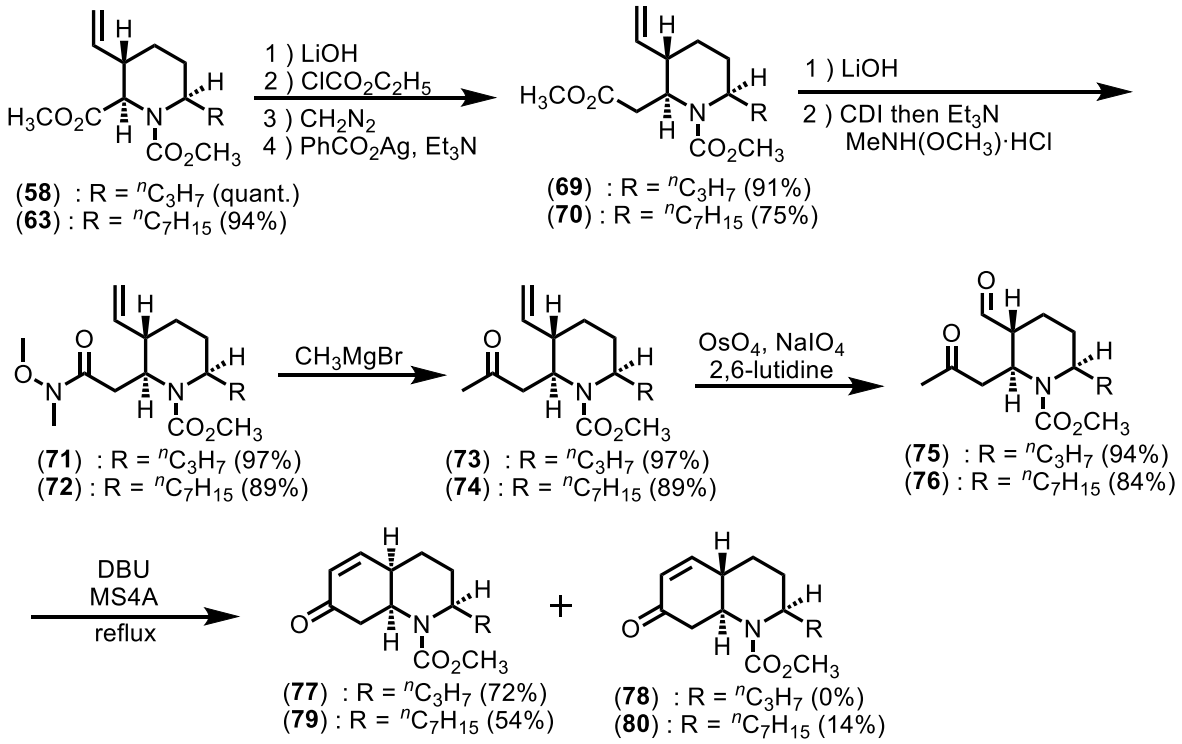


Figure 31. エナミノエステルへの共役付加反応における高立体選択性について

合成した **58** および **63** に対して Arndt-Eistert 反応を行うことで一炭素増炭した後、２工程で Weinreb アミド体 (**71** および **72**) へと導いた。その後、メチルマグネシウムブロミドを作用させることでメチルケトン体 (**73** および **74**) へと導いた後、Lemieux-Johnson 酸化によりケトアルデヒド (**75** および **76**) へと変換した。次に、**75** および **76** を本行程の鍵反応である水素のエピメリ化を伴う分子内 Aldol 反応に付した。すなわち、**75** および **76** に対して、 DBU 存在下加熱還流を行った。その結果、側鎖の炭素鎖が３の **75** からは *cis* 環化体 **77** のみが高収率で得られた。しかし、側鎖炭素鎖が７の **76** からは *cis* 環化体 **79** が優先的に得られたものの、*4a-epi-cis* 体の生成も認められた (**Scheme 15**)。



Scheme 15. ケトアルデヒドへの分子内 Aldol 環化反応

また、本環化反応の選択性については以下のように考察している。特殊な *A*$^{(1,3)}$*strain* が生じることにより **A** より **B** のコンフォメーションが優先されると考えられが、**B** のコンフォメーションでは環化に必要な２つの置換基が 1,2-*trans* ジアキシャルの関係になり、環化は不可能である。従って、DBU がカルボニル α 位の水素を引き抜きエピメリ化が起こることにより、分子内 Aldol 環化反応が起こり、シス体が優先的に生成したものと推測できる **(Figure 32)** 。

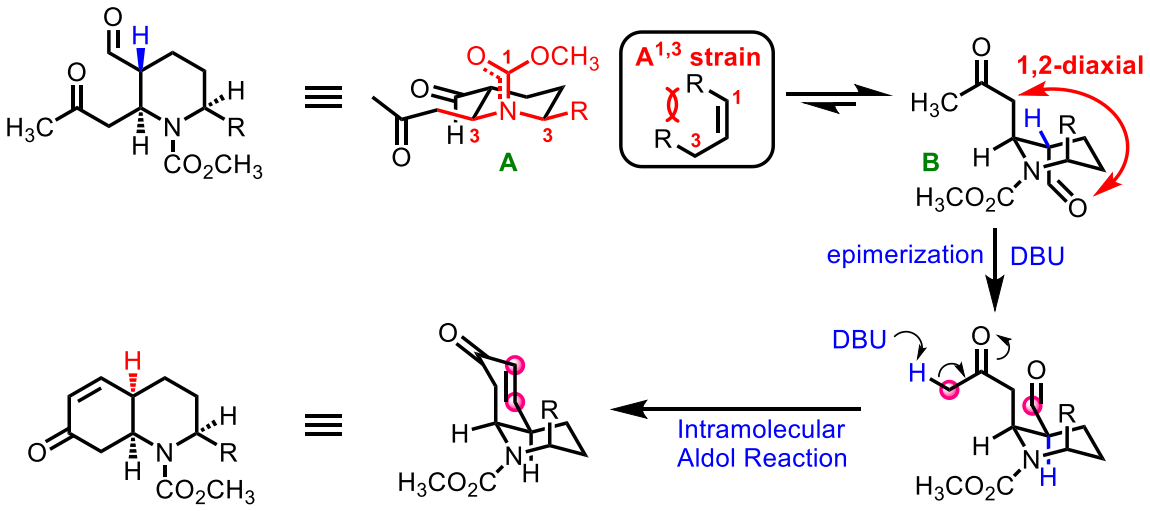
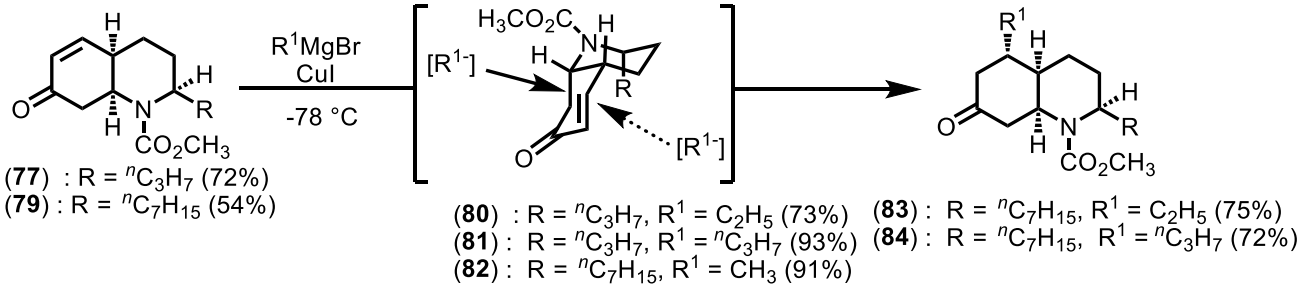


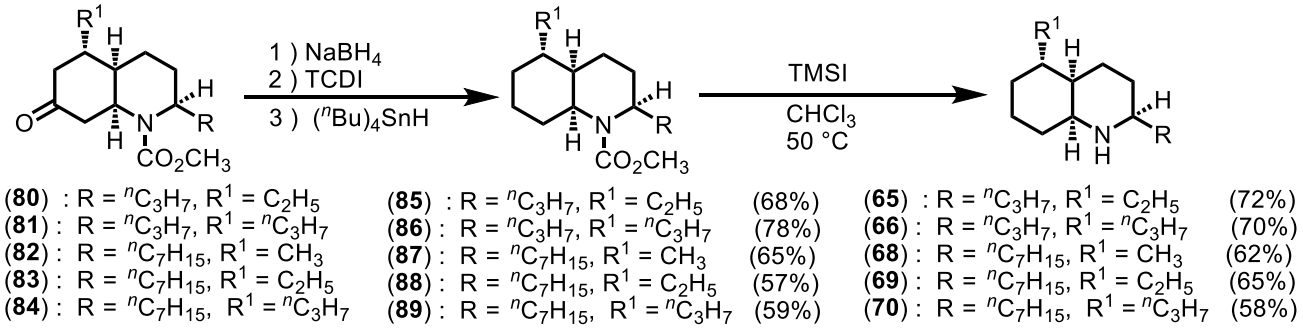
Figure 32.分子内 Aldol 環化反応における高立体選択性について

次に、５位の置換基の構築を行った。すなわち、環化体 **(77** および **79)** に対して極低温下で共役付加反応を行うことで、単一のジアステレオマーとしてアルキル化体 **(80~84)** を高収率で得た。本反応の高い立体選択性は下記の立体配座に対して凸面からの求核攻撃が優先したためだと考察している **(Scheme 16)**。



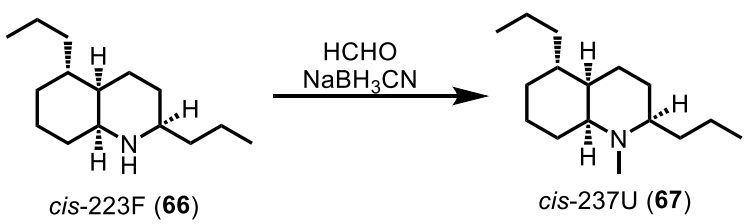
Scheme 16. 共役付加反応を利用した５位側鎖の構築

アルキル化体 **(80~84)** に対して、$NaBH_4$ 還元を行い、得られた各種アルコール体を 1,1-thiocarbonyldiimidazole (TCDI) と縮合させた後、 Barton-McCombie 脱酸素化反応を行った。得られた **(85~89)** に対してクロロホルム中 TMSI を加えた後、加熱攪拌することで目的の *cis*-DHQ 型アルカロイド **209J (65)**、**223F (66)**、さらに側鎖７誘導体の **251A (68)**、**209J-1 (69)** および **223F-1 (70)** の合成を達成した **(Scheme 17)**。



Scheme 17. *cis*-DHQ 型アルカロイドの合成

また、**223F (66)** はホルムアルデヒド存在下 $NaBH_3CN$ を用いて還元[68]することで **237U (67)** への変換も行った **(Scheme 18)**。



Scheme 18. *cis*-DHQ 型アルカロイド **237U (67)**の合成

次に、合成戦略に従い、4a-*epi*-*cis*-DHQ 型アルカロイド **195A (90)**、さらに側鎖部炭素数が 7 の誘導体 **251A (91)**の合成に着手した **(Figure 33)**。

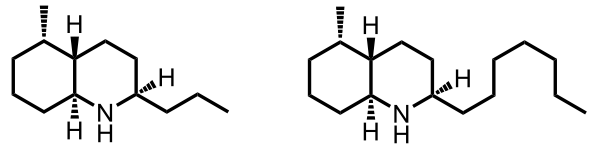
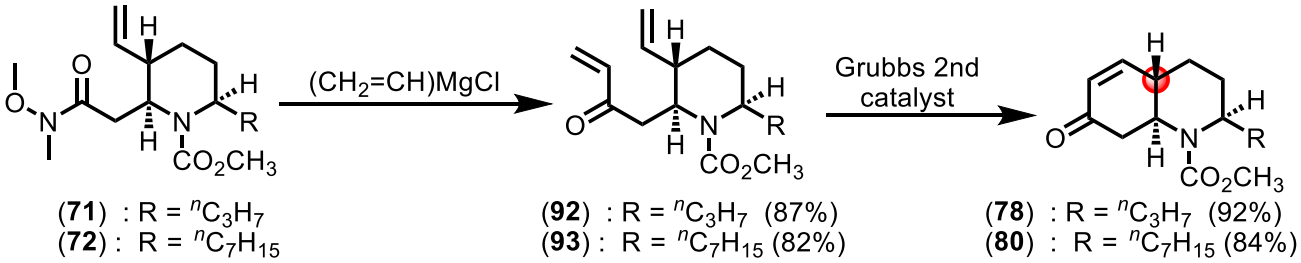


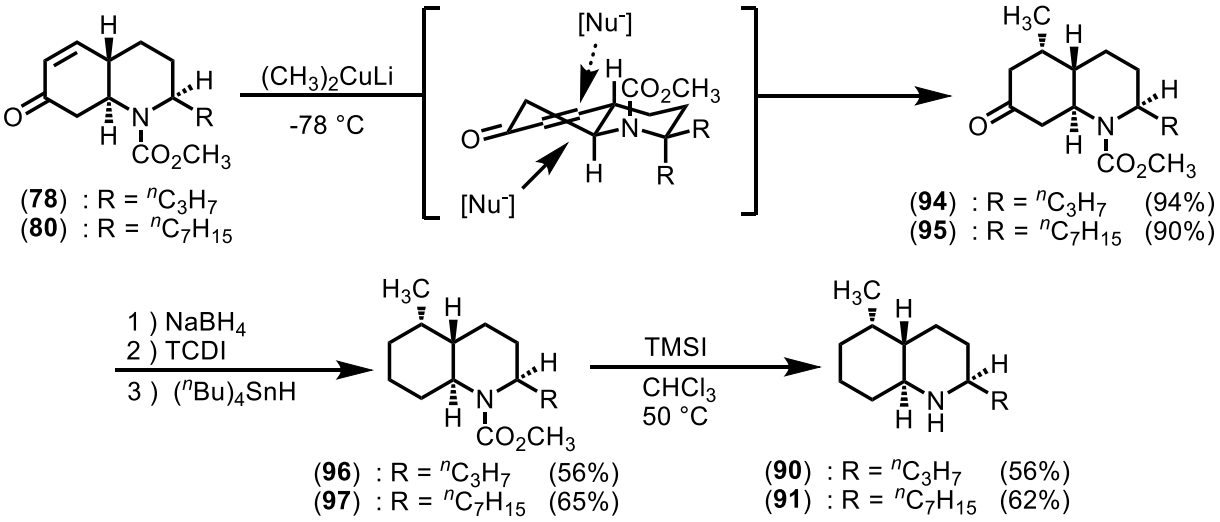
Figure 33. 標的 4a-*epi*-*cis*-DHQ 型アルカロイドの構造

cis-DHQ 合成中間体 **(71** および **72)** に対してビニルマグネシウムクロライドを作用させることでビニルケトン体 **(92** および **93)** へと変換した。その後、閉環メタセシス反応により高収率で 4a-*epi*-*cis*-環化体 **(78** および **80)** を合成した **(Scheme 19)**。



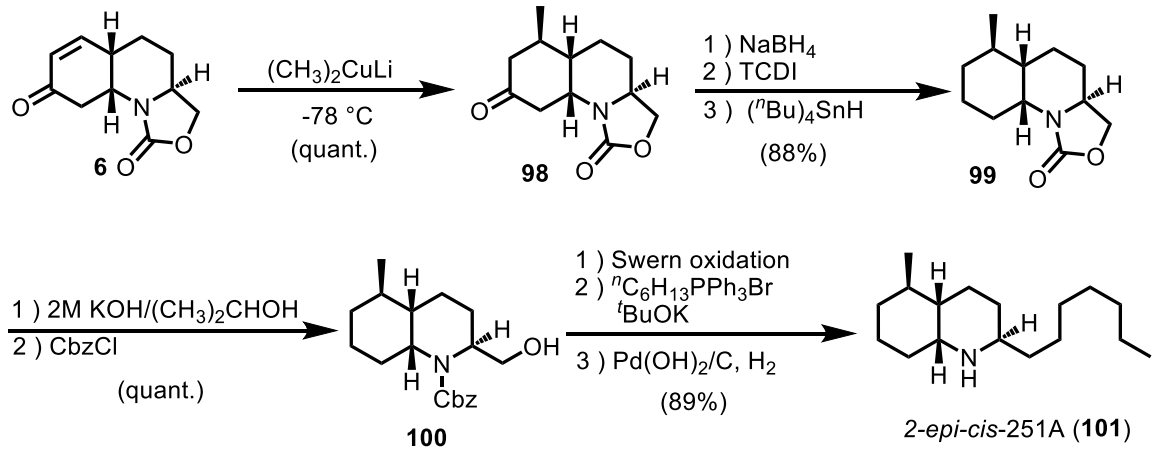
Scheme 19. 4a-*epi*-*cis*-DHQ 骨格の構築

5 位の置換基の構築に向けて、Gilman 試薬を用いた共役付加反応を行ったところ、単一のジアステレオマーとしてメチル体 **(94** および **95)** を得ることに成功した。本反応の高い立体選択性は、より安定な chair 型の遷移状態を経由する α 面からの求核攻撃が優先したためと推察される。最後に *cis* 体 **(80**～**84)**と同様に、3 工程で化合物 **(96** および **97)** へと導いた後、メチルエステルの脱保護を行うことで、目的の 4a-*epi*-*cis*-DHQ 型アルカロイド **195A (90)**、**251A (91)**の合成を達成した **(Scheme 20)**。



Scheme 20. 4a-*epi*-*cis*-DHQ 型アルカロイドの合成

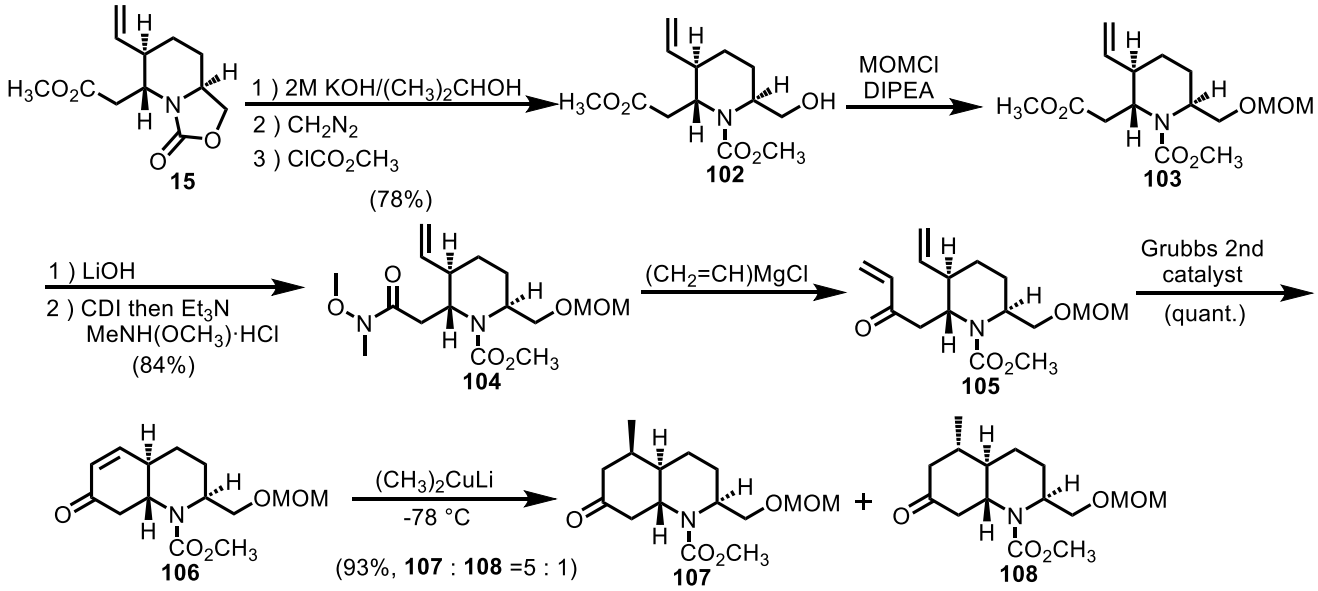
次に 2-*epi-cis*-DHQ 型アルカロイド 251A (**101**) の合成を行った。第一章で述べた GTX **287C** (**1**) の合成中間体 (**6**) への Gilman 試薬を用いた共役付加反応により、単一のジアステレオマーでアルキル化体 (**98**) を定量的に得ることに成功した。その後、３工程で化合物 (**99**) へと変換した後、２工程でオキサゾリジノン環の開環および生じた第２級アミンの Cbz 保護を行い **100** へと導いた。最後に、残る２位側鎖の構築と Cbz 基の脱保護を行うことで目的の **101** を合成することに成功した (**Scheme 21**)。



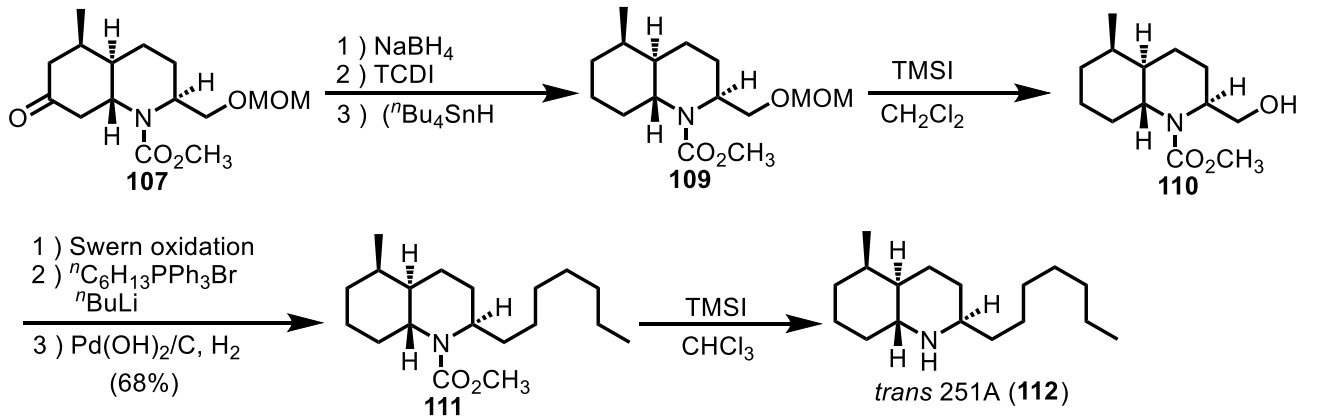
Scheme 21. 2-*epi-cis*-251A (**103**) の合成

最後に、*trans*-DHQ 型アルカロイド **251A** の合成に取り組んだ。第一章で述べた GTX **287C** (**1**) の合成中間体 (**15**) に対して、オキサゾリジノン環を開環させた後、加水分解され生成したカルボン酸に対してジアゾメタンを用いたメチルエステル化を行った。さらに、生じた第２級アミンをメチルエステルで保護することにより、アルコール体 (**102**) へと導いた。その後、MOM 基でアルコールを保護し、化合物 (**103**) へと導いた後、２工程で Weinreb アミド体 (**104**)へと変換した。次に、ビニルマグネシウムクロライドを作用させることでビニルケトン体 (**105**) へと導いた後、閉環メタセシス反応により高収率で *trans*-環化体 (**106**) を構築することに成功した。その後、５位の置換基の構築に向けて、Gilman 試薬を用いた共役付加反応を行ったところ、β-アルキル化体 (**107**) と α-アルキル化体 (**108**) が 5 : 1 の割合で生成した。また、**107** および **108** はカラムによる分離が可能であったため、優先的に得られた **107** を用いて次の反応に進んだ (**Scheme 22**)。

アルキル化体 (**107**) に対して３工程で脱酸素化反応を行い化合物 (**109**) へと導いた後、ジクロロメタン中 TMSI を作用させることで、 MOM 基の脱保護を行った。得られたアルコール体 (**110**) に対して、３工程で２位の側鎖構築を行った後、残るメチルエステル基の脱保護を行うことで、所望の *trans*-251A (**112**) の合成を達成した (**Scheme 23**)。



Scheme 22. *trans*-DHQ 骨格の合成



Scheme 23. *trans*-251A (**114**) の合成

最後に TR-BBB1 3 細胞および TR-iBBB13 細胞における [^{3}H] 化合物取り込み解析を行った。すなわち、合成した DHQ 型アルカロイド存在下において、血液脳関門モデル細胞（条件的不死化ラット脳毛細血管内皮細胞株、TR-BBB13 細胞）への [^{3}H] ニコチンの取り込み変動解析を行うことで、血液脳関門（blood-brain barrier: BBB）に対するデカヒドロキノリンアルカロイドの透過性を検討した。また、同アルカロイド存在下において、血液網膜関門モデル細胞（条件的不死化ラット網膜毛細血管内皮細胞株、 TR-iBRB2 細胞）への [^{3}H] ベラパミルの取り込み変動解析を実施し、BBB のニコチン輸送システムおよび BRB のベラパミル輸送システムの基質認識性の差異を比較した。結果として、 TR-BBB13 細胞および TR-iBBB13 細胞における [^{3}H] 化合物取り込みは、 DHQ 骨格を有する化合物存在下において 47% 以上有意に減少した。また、２位の側鎖炭素数が３である化合物よりも７の方が [^{3}H] ニコチン取り込みを減少させることが示唆された。血液脳関門のニコチン輸送システムおよび血液網膜関門のベラパミル輸送システムの基質認識性に関して、化合物構造の違い

による比較は困難であるものの、これら輸送機構はデカヒドロキノリン骨格を認識しやすいことが示唆された **(Table 1)**。

Table 1. DHQ 型 アルカロイドの [^{3}H] ニコチンの取り込み変動解析の結果

Conditions	*n*	Percentage of control [3H]Nicotine uptake	[3H]Verapamil uptake
control	9	100±14	100±10
cis-**209J**	3	14.2±1.3※	40.6±4.9※
cis-**251A**	3	3.11±0.42※	20.8±1.0※
cis-**209J-1**	3	3.48±0.62※	16.0±1.2※
cis-**223F-1**	3	9.97±2.17※	37.9±2.2※
4a-epi-cis-**195A**	3	16.1±2.5※	53.1±4.2※
4a-epi-cis-**209J**	3	18.0±2.6※	40.4±3.2※
4a-epi-cis-**223F**	3	11.5±2.6※	29.3±0.8※
4a-epi-cis-**251A**	3	9.07±0.72※	33.8±2.1※
2-epi-cis-**251A**	3	5.05±2.22※	28.1±6.9※
trans-**251A**	3	9.48±1.82※	17.1±1.6※

[3H]Nicotine uptake (0.1 μCi/well, 6.0 nM) by TR-BBB13 cells, an in vitro cell model of the rat blood-brain barrier, was tested at 37 °C for 10 sec in the absence (control) or presence of test compounds at 200 μM with 1.0% DMSO. Similarly, [3H]verapamil uptake by TR-iBRB2 cells, an in vitro cell model of the rat inner blood-retinal barrier, was measured at 37°C for 3 min. Each value represents the mean±standard deviation. *p < 0.01, significantly different from the control evaluated by Dunnett's test.

結果として、文献記載のモノアセチル体をから、***cis***, **4a-*epi-cis*,** **2-*epi-cis***, ***trans*** DHQ 型毒ガエルアルカロイドの網羅的合成経路を確立し、毒ガエルアルカロイド ***cis* 209J**, ***cis* 223F**, ***cis* 251A**, ***cis* 209J-1**, ***cis* 223F-1**, ***4a-epi-cis* 195A**, ***4a-epi-cis* 251A**, ***2-epi-cis* 251A**, ***trans*251A** の全合成を達成した。さらに、DHQ 型アルカロイド存在下における細胞への [^{3}H] ニコチンおよび [^{3}H] ベラパミル取り込み変動解析を行い、 BBB および BRB の輸送機構がデカヒドロキノリン骨格を認識しやすいことを見出した [69]。

第四章　　サラシア由来 α-グルコシダーゼ阻害剤 Salacinol の C4'位アルキル側鎖伸長型誘導体の合成およびその活性評価

第一節　糖尿病の現状とその治療薬について

糖尿病はインスリン作用不足による慢性の高血糖状態を主徴とする代謝疾患群であり、合併症として網膜症、腎症、神経障害など多くの障害を併発することが知られている。これらの合併症の発症により、QOL (Quality of life) は著しく低下し、心臓病や脳卒中などの直接死亡リスクにつながる動脈硬化を併発する可能性が高まることから、進展予防および治療の向上は取り組むべき課題である。糖尿病は１型（β 細胞の破壊、絶対的インスリン欠乏）および２型（インスリン分泌の低下）に大きく分類される。特に２型が糖尿病患者全体の 95 %以上を占めている。２型糖尿病はインスリン分泌不全やインスリン抵抗性になりやすい体質に、過食や運動不足といった環境的な要因、さらに加齢が加わることで発症する。また、我が国において「糖尿病が強く疑われる者」は平成 14 年には 740 万人、同 24 年には 950 万人にのぼり、さらに平成 28 年には 1000 万人と年々増加の一途をたどり、令和元年においても有意な減少は見られていない [70]。さらに、世界中では約５億 3,700 万人の成人が糖尿病を患っており、10 人に１人が本疾患に悩まされている。この数は、2030 年までに６億 4,300 万人、2045 年までに７億 8,300 万人にまで増加すると予測されている (**Figure 34**)[71]。

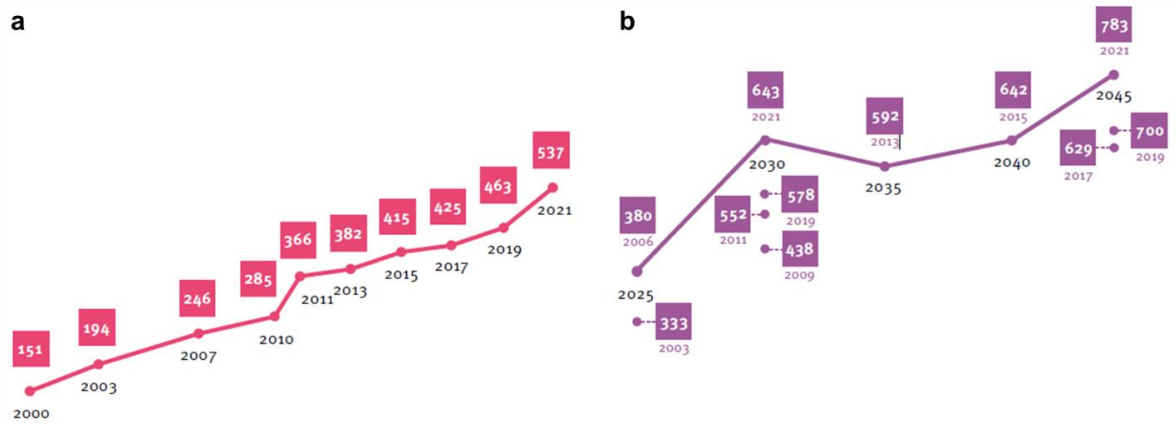


Figure 34.　世界的な糖尿病有病率の推定と予測 (IDF diabetes atlas eighth edition 2021 より, 一部改変)。
a : 2000 ~ 2021 年までの世界的な糖尿病有病率の推定
b : 2000 ~ 2079 年までの世界的な糖尿病有病率の予想

糖尿病の治療は主にインスリン抵抗性改善薬、インスリン分泌促進薬、糖吸収・排泄調製薬に分類される。インスリン抵抗性はインスリン分泌不全とともに 2 型糖尿病における基盤病態である。そのインスリン抵抗性の改善薬の種類としては、ビグアナイド薬とチアゾリジン系薬があり、副作用として下痢や消化管症状が問題視されている。インスリン分泌促進薬としてはスルホニルウレア系およびグリニド系薬剤が知られている。これらは古くより使用されている薬剤であり、膵臓ランゲルハンス島を刺激してインスリンの分泌を高める。しかし、強力な作用による二次無効を引き起こしやすい欠点が知られている。また、インスリン分泌刺激ホルモンであるインクレチンによる血糖コントロール作用を利用した新しい作用機序の糖尿病治療薬 (DPP-4) 阻害薬も見出されている。糖吸収・排泄調製薬には 2014 年から上市された原尿中のグルコース再吸収阻害作用を示す Na^+/グルコーストランスポーター阻害剤 (SGLT2 阻害剤) が知られている。また、α-グリコシターゼ阻害薬は副作用が極めて少ないことから糖尿病治療の第 1 選択薬として用いられることも多い。その作用は小腸での炭水化物の分解を抑制することで、糖の吸収を抑制し、血糖値を下げる。現在糖尿病治療薬に用いられている α-グリコシターゼ阻害薬は Acarbose、Voglibose、Miglitol の 3 種類である。これらは糖質または糖質に似た構造をもち、ショ糖よりも数百倍もの親和性で α-グリコシターゼに結合することで、二糖類のその部位への結合を拮抗的に阻害する (**Figure 35**)。

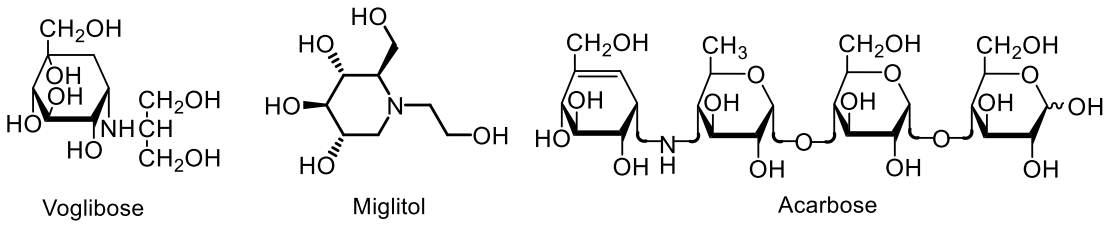


Figure 35. 現在糖尿病治療薬として用いられる α-グリコシターゼ阻害薬

上述のように、現在様々な作用機序に基づいた糖尿病治療薬が開発されているものの、未だその疾患を患う患者の減少が見られないことから、さらに安全で薬効の強い新規糖尿病治療薬の開発が求められている。

第二節　アーユルベーダ天然薬物 “サラシア” 由来 α-グルコシダーゼ阻害剤 Salacinol およびその類縁体化合物を用いた構造活性相関研究

Salacia 属植物 (*Salacia chinensis*, *S. reticulate* および *S. oblonga*) は、インドやスリランカをはじめ、タイやインドネシアなどの東南アジア一帯に広く分布するつる性の多年生木本である。現地では、その根や幹の煎じ液が糖尿病の予防や改善を目的とした民間薬として古くより利用されている[72]。1997 年に、吉川らは、その有効成分の探索研究の一環として、スリランカ産 *S. reticulate* 根部の抽出エキスに強力な α-グリコシターゼ阻害活性を見出した。また、その有効成分として Salacinol (**113**) の単離および構造決定に成功した[73]。本化合物は新奇なチオ糖スルホニウム分子内硫酸塩構造を有しており X 線構造解析によりその構造が確認された。また、**113** はラット小腸由来 α-グリコシターゼに対して、現在糖尿病の治療薬として用いられる Acarbose や Voglibose に匹敵するほどの強力な阻害作用を示したことから、新たなグリコシターゼ阻害剤として期待を集めた。現在までにチオ糖スルホニウム塩型化合物は **113** の他にも Salaprinol[74] (**115**)、Ponkoranol[74] (**117**)、Kotalanol[75] (**119**) およびその脱硫酸エステル体の Neosaracimol[76] (**114**)、Neosalaprinol[77] (**116**)、Neoponkolanol[77] (**116**) および Neokotalanol[78] (**118**) が相次いで単離された (**Figure 36, Table 2**)。また、これらの化合物群の構造決定および詳細な薬理作用の検討を行うための量的確保を目的とした全合成研究および合成方法論の開発も多数報告されている[79]。

Salacia reticulata

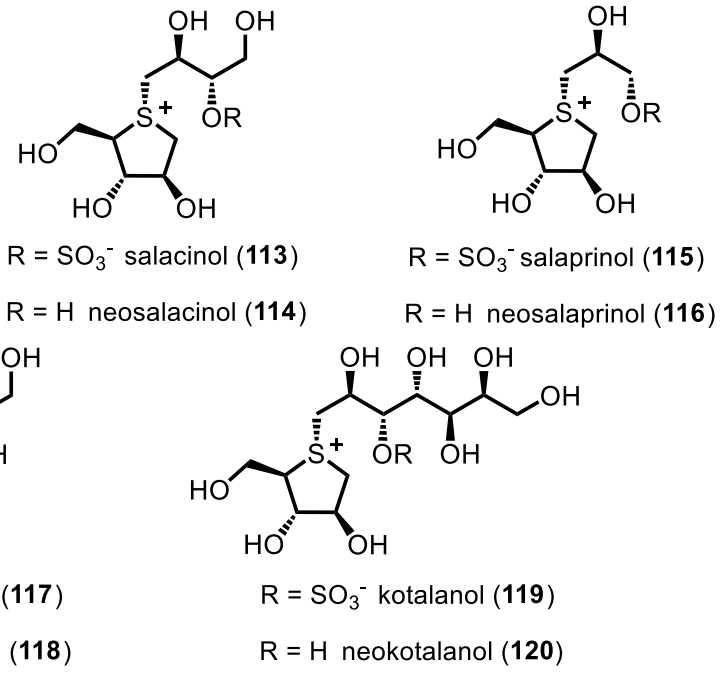


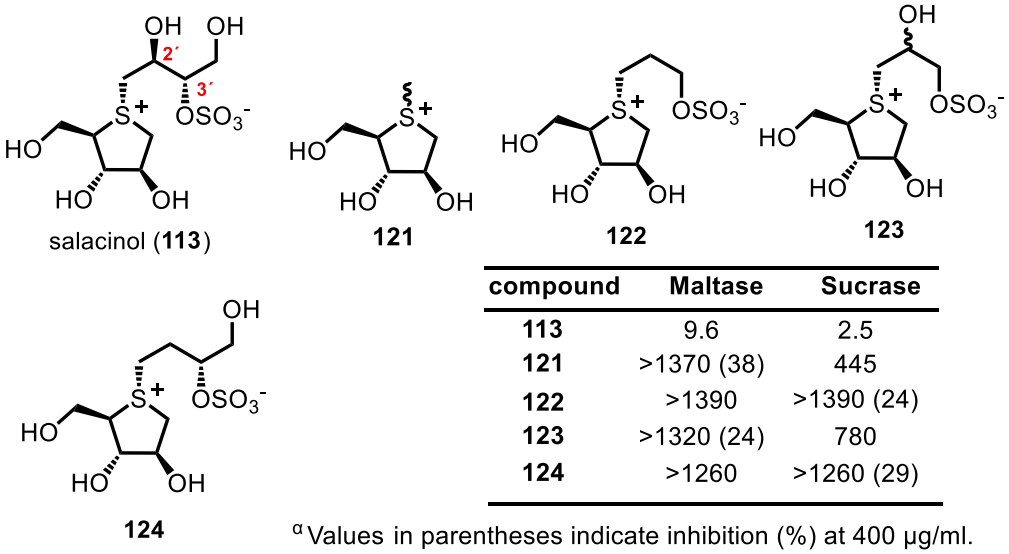
Figure 36. チオ糖スルホニウム塩型化合物群 (**113-120**) の構造

Table 2. チオ糖スルホニウム塩型化合物群 **(113-120)** の α-グルコシダーゼ阻害活性

Inhibitor	IC_{50} (μM)			Inhibitor	IC_{50} (μM)		
	Maltase	Sucrase	Isomaltase		Maltase	Sucrase	Isomaltase
Acarbose	2.0	1.7	155	Salapinol	>329 (42)[a]	>329 (23)[a]	15
Voglibose	1.2	0.2	2.1	Neosalacinol	8.0	1.3	0.3
Salacinol	5.2	1.6	1.3	Neokotalanol	4.8	4.5	1.8
Kotalanol	7.2	0.75	5.7	Neoponkoranol	5.1	1.0	1.4
Ponkoranol	3.2	0.29	2.6	Neosalaprinol	>384 (34.5)[a]	90	6.5

[α]Values in parentheses indicate inhibition (%) at the corresponding concentrations (μM).

チオ糖スルホニウム塩型化合物は、極めて強力な α-グリコシターゼ阻害作用を示すことから、構造活性相関研究がこれまでに盛んに行われてきた。田邉らは 2006 年に Salacinol **(113)** の脱酸素型誘導体 **(121-124)** の合成に成功し、それらのマルターゼおよびスクラーゼに対する阻害活性を評価した[80]。その結果、これら誘導体のマルターゼに対する阻害活性が **113** と比べて大幅に減少していたことから、C2' 位 の (*S*)-配置ヒドロキシル基と C3' 位のヒドロキシメチル基の双方が α-グリコシターゼ阻害活性に重要であることが示唆された。また、スクラーゼに対しては C3 位のヒドロキシメチル基をもたない **121** および **123** に弱いながらも阻害活性が認められた **(Figure 37)**。

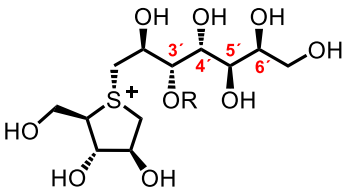


compound	Maltase	Sucrase
113	9.6	2.5
121	>1370 (38)	445
122	>1390	>1390 (24)
123	>1320 (24)	780
124	>1260	>1260 (29)

[α]Values in parentheses indicate inhibition (%) at 400 μg/ml.

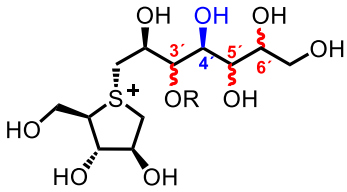
Figure 37. 脱酸素型 Salacinol 誘導体 **(121-124)** を用いた構造活性相関研究

また、Pinto らは側鎖炭素鎖が 7 の kotalanol **(119)** の構造活性相関研究の一環として、6-*epi*-**119** および 5-*epi*-**119** を合成し、そのヒトマルターゼ-グルコアミラーゼ (hNtMGAM) に対する阻害活性を測定したところ、天然物 **119** と *epi* 体 の活性強度にほとんど違いが見られなかった[79c,82]。一方、田邉らは、4′-*epi*-kotalanol 誘導体 **(126-132)** を合成し、ラット各種 α-グリコシターゼに対して阻害活性を測定した結果、4′-*epi*-体の活性がコタラノールに比べて顕著に低下した[81]。これらの結果から、側鎖炭素鎖 4 以上の場合、 C′4 位の立体配置が (*R*) であることが活性発現に重要であることが示唆された **(Figure 38)**。



R = SO_3^- kotalanol (**119**)

compound	NtMGAM
119	0.19±0.03
6-*epi*-**119**	0.20±0.03
5-*epi*-**119**	0.13±0.03



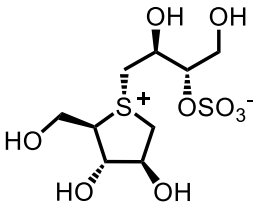
3′α, 5′β, 6′β (**119**) 3′α, 5′α, 6′α (**129**)
3′β, 5′α, 6′α (**125**) 3′α, 5′β, 6′β (**130**)
3′β, 5′β, 6′β (**126**) 3′α, 5′α, 6′β (**131**)
3′β, 5′α, 6′β (**127**) 3′α, 5′β, 6′α (**132**)
3′β, 5′β, 6′α (**126**)

compound	Maltase	Sucrase	Isomaltase	compound	Maltase	Sucrase	Isomaltase
119	7.2	0.75	5.7	**129**	49	67	1.6
125	>236 (25)[a]	>236 (8)[a]	16	**130**	>236 (42)[a]	136	11
126	>236 (32)[a]	>236 (28)[a]	20	**131**	58	32	6.5
127	>236 (45)[a]	>236 (34)[a]	21	**132**	>236 (45)[a]	214	16
128	134	55	58				

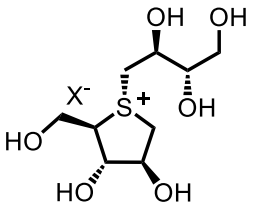
Values in parentheses indicate inhibition (%) at 100 μg/ml [236 μM, (MW for **125-132**: 424)].

Figure 38. kotalanol 誘導体を用いた構造活性相関研究

さらに、田邉らは 2007 年にカウンターアニオンの異なる 2 種類の neosalacinol (**114**) の合成を行った。その結果、硫酸ハーフエステルイオンをもつ **114a** および塩化物イオンをもつ **114b** の活性強度にほとんど差はなく、スルホニウム塩部が活性の本体であることが示唆された(**Figure 39**)[83]。



salacinol (**113**)



neosalacinol
X = $CH_3OSO_3^-$ **114a**
X = Cl^- **114b**

compound	Maltase	Sucrase
113	9.6	2.5
114a	15.6	3.7
114b	14.0	3.5

Values in parentheses indicate inhibition (%) at 400 μg/ml.

Figure 39. Salacinol (**113**) の脱硫酸エステル体を用いた構造活性相関研究

以上の構造活性相関研究の結果から、① C2'位の (*S*)-配置ヒドロキシル基と C3' 位のヒドロキシメチル基両方が α-グリコシターゼ阻害活性に重要であること、② 側鎖炭素が 4 以上の場合は、C4 位の立体配置は (*R*) 配置が必須であること、③ 硫酸エステル以外のカウンターアニオンを用いても活性には影響がでないことなどが判明している。

一方、2010 年にヒトマルターゼ-グルコアミラーゼ (hNtMGAM) と Salacinol (**113**) との共結晶構造が X 線構造解析 [84] により明らかにされるとともに *in silico* を用いた hNtMGAM と **113** とのドッキングシュミレーション [85] も行われた。これら二つの結果から、**113** の 3′位の硫酸アニオンは周囲の疎水性残基 (Tyr299, Phe575, Trip406) に囲まれていることが判明した。すなわち、グリコシターゼ阻害活性に対して **113** の 3′位の硫酸アニオンと周囲の疎水性残基との間に負の相互作用が働いている可能性が視覚的に示唆された (**Figure 40**)。

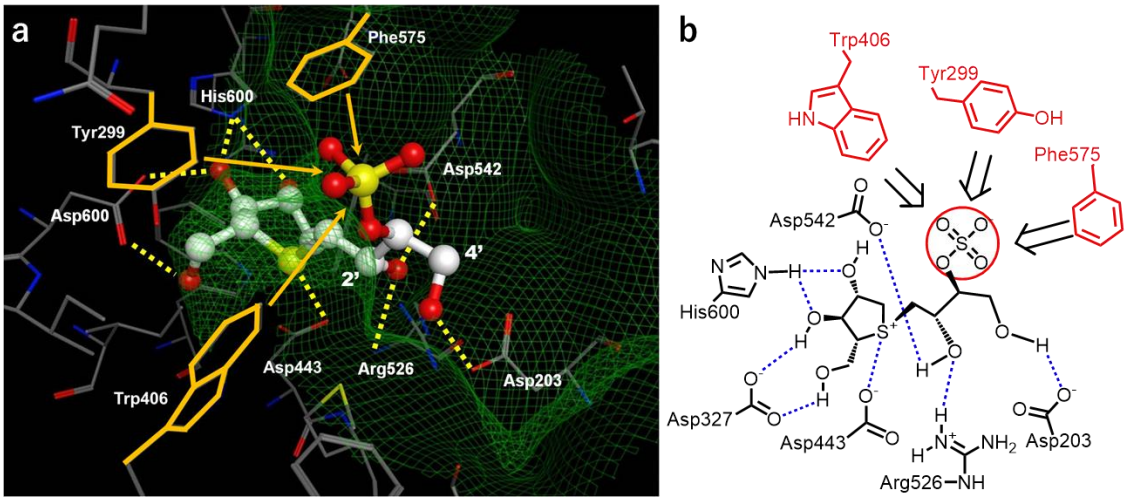
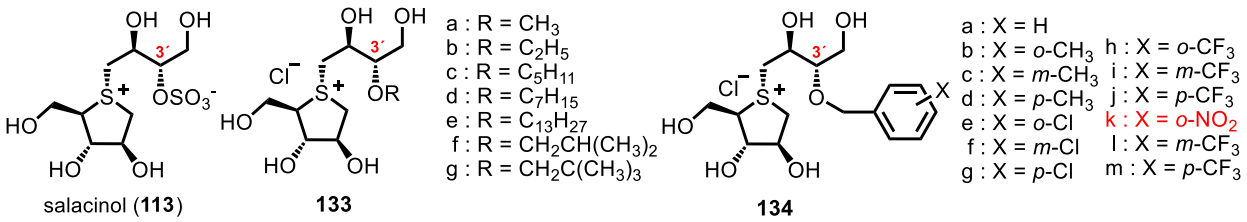


Figure 40. Salacinol (**113**) と hNtMGAM との *in silico* ドッキングシュミレーションの結果
a) 3D ドッキングシュミレーションモデル図. b) ドッキングシュミレーションモデルの平面図

その知見に基づき、3′位の *O*-アルキル型誘導体 (**133a-g**) および *O*-ベンジル型誘導体 (**134a-m**) が合成され、そのマルターゼに対する阻害活性が測定された (**Figure 41**) [86]。その結果、合成された *O*-アルキル誘導体 (**133** および **134**) が、Salacinol (**113**) と同等または強力な阻害活性を示した。中でも、オルト位にニトロ基が置換された *O*-ベンジル型誘導体 (**134k**) は **113** よりも約 40 倍も強力に α-グリコシターゼを阻害した。さらに、**134a** および **134k** の酵素とのドッキングシュミレーションモデルでは、フェニル基が Salacinol の硫酸エステル基とは全く異なった位置で酵素と相互作用していることが示唆された (**Figure 42**)。このように、酵素の活性部位から遠く離れたアミノ酸の疎水性残基が基質との相互作用を増強する可能性を支持する結果が得られている。



compound	E_{bind}	Rat Maltase	compound	E_{bind}	Rat Maltase	compound	E_{bind}	Rat Maltase
113	-37.0	5.2	**134a**	-37.2	0.32	**134i**	-35.4	0.98
133a	-35.4	5.3	**134b**	-37.2	0.66	**134j**	-40.5	0.98
133b	-38.2	1.7	**134c**	-36.7	0.84	**134k**	-38.9	0.13
133c	-38.0	1.5	**134d**	-35.5	0.86	**134l**	-37.4	0.94
133d	-41.3	0.80	**134e**	-41.6	0.31	**134m**	-42.2	0.68
133e	-41.9	1.0	**134f**	-42.6	0.53			
133f	-36.6	0.8	**134g**	-40.0	0.89			
133g	-38.6	0.3	**134h**	-37.5	0.33			

Figure 41. Salacinol (**113**) の脱硫酸エステル体を用いた構造活性相関研究

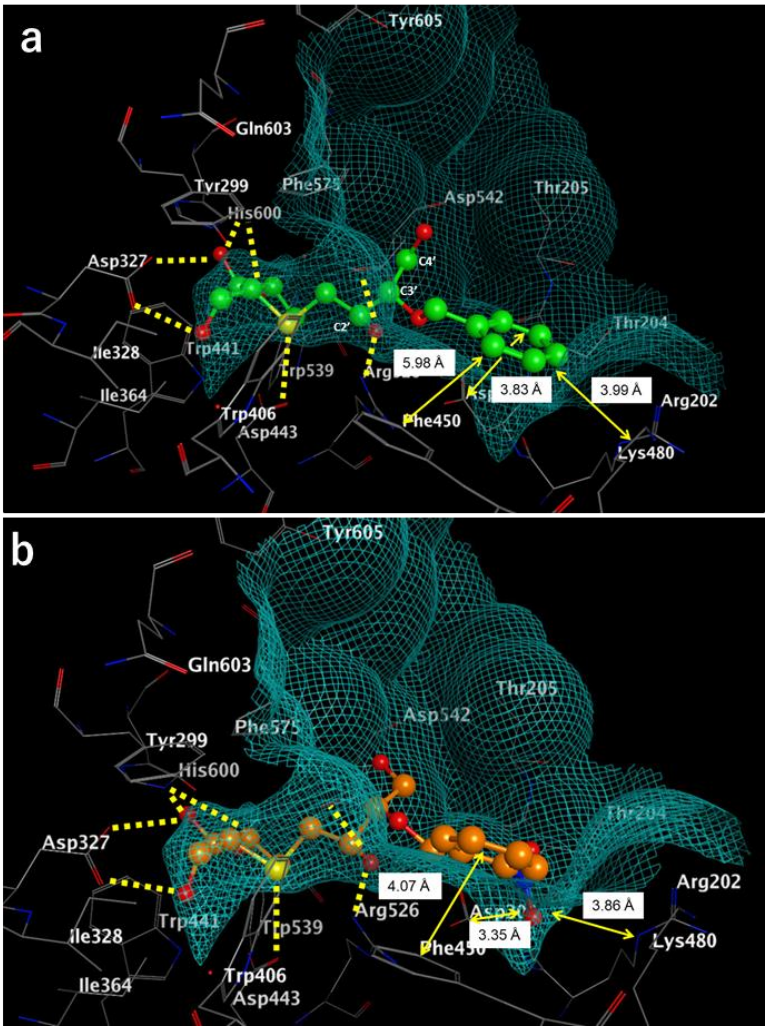
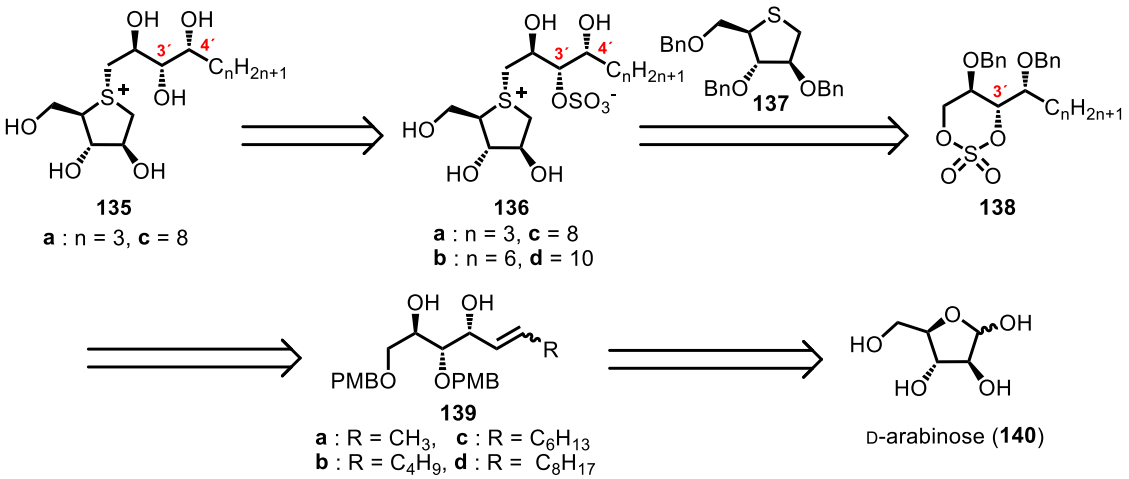


Figure 42. 誘導体 **134**a (a)および **134k** (b) の *in silico* ドッキングシュミレーションの結果

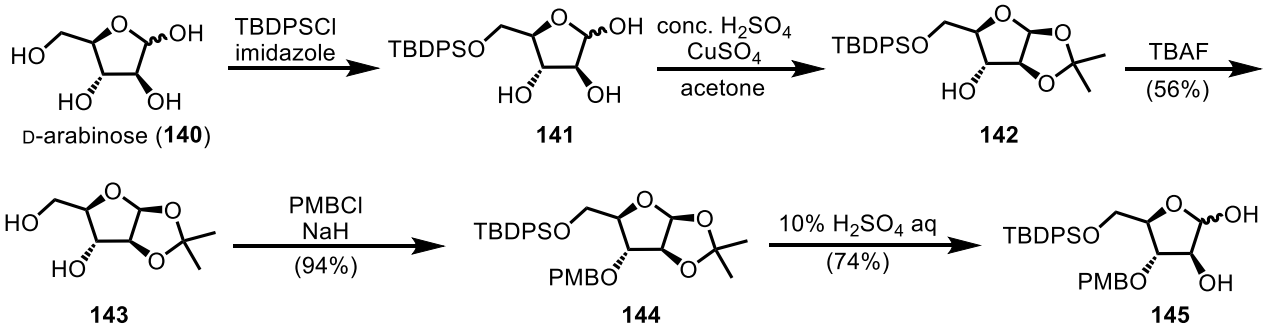
第三節　C4'位アルキル側鎖伸長型 Salacinol 類縁体の合成

本研究では、酵素のアミノ酸疎水性残基と salacinol 側鎖との間の相互作用についてさらなる知見を得るために、新たに C4'-アルキル側鎖伸長型誘導体 (**135a**, **135c**) および (**136a-d**) の合成を企画した (**Scheme 24**)。まず、脱硫酸エステル型誘導体 (**135a**, **135c**) は硫酸エステル誘導体 (**136a-d**) から導くことにした。また、 **136a-d** のチオ糖スルホニウム塩構造の構築はチオ糖 (**137**) と相当する環状硫酸エステル (**138a-d**) とのカップリング反応により合成することを想定した。さらに、**138** は、D-arabinose (**140**) の Wittig 反応を用いて合成した PMB 体 (**139**) を経由して合成することにした。



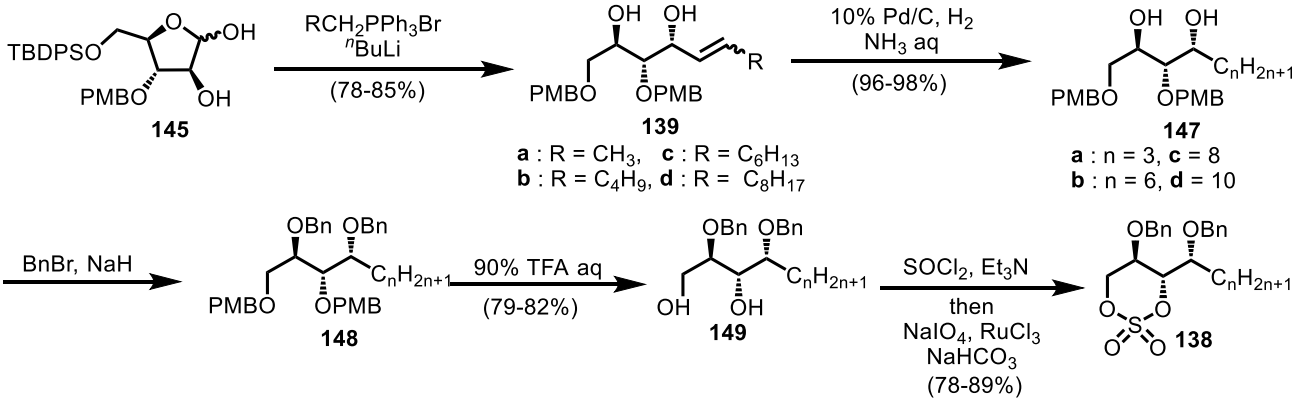
Scheme 24. C4'-アルキル型 salacinol 誘導体 (**135a, c**) および (**136a-d**) の逆合成解析

まず、D-arabinose (**140**) の水酸基を TBDPSCl を用いて５位選択的に保護して得られたシリル体[87] (**141**) を、アセトン中硫酸触媒を用いてアセトニド (**142**) へと変換した。その後、**142** を TBAF で処理することで化合物 **143** を **140** から３工程 56％ の収率で得た[88]。その後、**143** のジオールを PMB 基で保護し、化合物 (**144**) に導いた後、加水分解によりアセトニドを脱保護し、鍵中間体化合物 (**145**) を合成した (**Scheme 25**)。



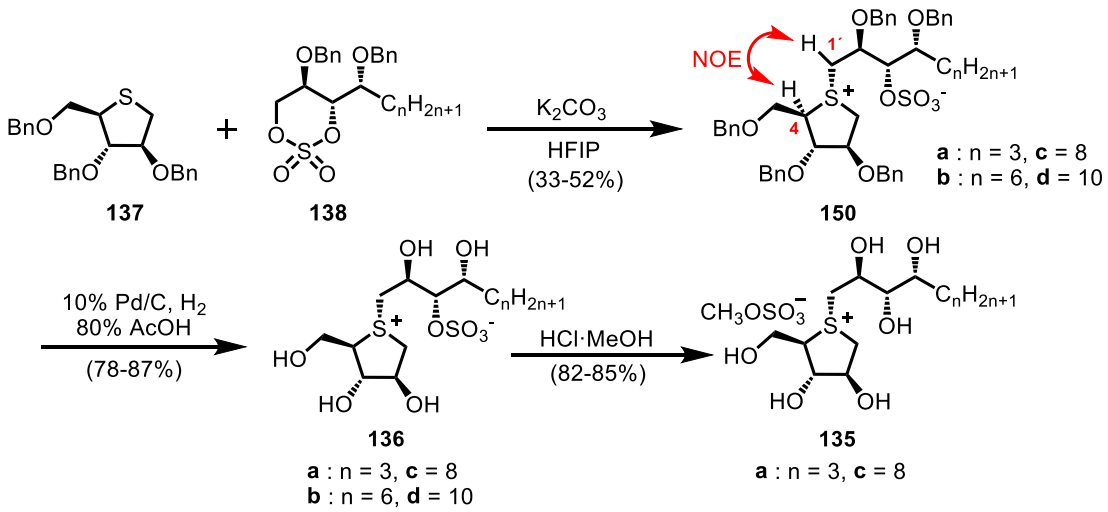
Scheme 25. 鍵中間体 **(145)** の合成

合成した鍵中間体 **(145)** に対して、異なるアルキル側鎖をもつリンイリドを用いて Wittig 反応を行い、オレフィン体 **(139a-d)** を合成した。次に、アンモニアで被毒した条件で接触水素化を行うことで、オレフィンを選択的に還元し、アルキル体 **(147a-d)** を高収率で得た。その後、1,3-ジオールをベンジル基で保護することで化合物 **(148a-d)** へと変換した後、90% トリフルオロ酢酸で処理して、脱 PMB 体 **(149a-d)** を合成した。最後に、塩化チオニルで処理した後、四酸化ルテニウムで酸化して、目的の環状硫酸エステル **(138a-d)** に導いた **(Scheme 26)**。



Scheme 26. 環状硫酸エステル **(138a-d)** の合成

環状硫酸エステル **(138a-d)** は、チオ糖 **(137)** [89]とのカップリング反応に付した。すなわち、HFIP 中で炭酸カリウムの存在下で、**138a-d** と **137** を 60 °C に加熱して、チオ糖スルホニウム塩体 **(150a-d)** へと導いた。また、得られた **150a-d** の側鎖部の立体化学は、NOESY スペクトルにて H-4 と H-1´水素由来のシグナル間に NOE 相関が観測されたことから、α配置と決定した。その後、80% 酢酸中、接触水素化により脱ベンジル化して目的の salacinol アルキル型誘導体 **(136a-d)** を合成した。さらに、**136a-d** をメタノール性の塩化水素溶液で処理した後、加溶媒分解して、脱硫酸エステル型誘導体 **(135a, c)** に変換した **(Scheme 27)**。

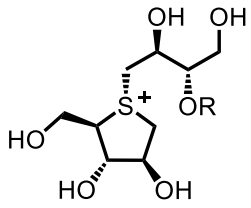


Scheme 27. C4'-アルキル型 salacinol 誘導体 (**135a, c**) および (**136a-d**) の合成

合成した C4' 位アルキル側鎖伸長型 salacinol 誘導体 (**135a, 135c**) および (**136a-d**) の各種 α-グリコシターゼ阻害活性を測定した。その結果、ラット由来 α-グリコシターゼに対して **136 a-d** は 5.4~7.7 μM の範囲で良好に阻害し、salacinol (**113**) と同等の阻害活性を示した。また、ラット由来マルターゼに対しては C4'-アルキル側鎖を伸長しても阻害活性に変化がほとんど見られなかった。一方、興味深いことに脱硫酸エステル型誘導体 (**135c**, n = 8) は、neosalacinol (**113**) や neokotalanol (**119**) と同じ長さの側鎖を有する **135a** (n = 3) に比べて強力なラット由来マルターゼ阻害作用を示した。そのため、脱硫酸エステル型化合物の場合、C4' 位へのアルキル側鎖のさらなる伸長は阻害活性効果を増大する可能性が考えられた。また、ラット由来スクラーゼについては (**135a, 135c**) および (**136a-d**) 共に側鎖伸長依存的に阻害活性が増大し、側鎖 n = 8 の **136c** および **135c** が最も強力な阻害活性を示した。ラット由来イソマルターゼに対しては、側鎖の伸長による阻害活性の変化はほとんどなく、活性の強弱が硫酸エステルの有無に依存していることが示唆された。

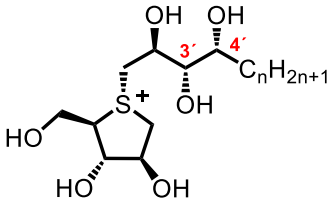
ヒト小腸由来マルターゼに対しては (**135a, 135c**) および (**136a-c**) 共に側鎖部アルキル基の伸長に依存して阻害活性が増大したが、側鎖アルキル基の炭素数が 10 の **136d** では阻害能が低下した。また、側鎖の導入により天然の salacinol (**113**) および neosalacinol (**114**) に比べて、最大で約 4 倍も強力に阻害活性を示した。さらに、その阻害活性は現在 α-グルコシダーゼ阻害剤として知られている 3 つの糖尿病治療薬の中で最も強力な Voglibose (IC_{50} = 1.3) と同等であった。

Table 3. C4'-アルキル型 salacinol 誘導体 (**135a, c**) および (**136a-d**) の各種 α-グルコシダーゼに対する阻害活性



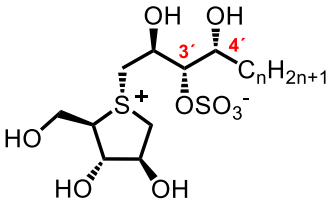
R = SO_3^- salacinol (**113**)

R = H neosalacinol (**114**)



135

a : n = 3, **c** = 8



136

a : n = 3, **c** = 8

b : n = 6, **d** = 10

Compound	E_{bind}	Rat			Human Maltase
		Maltase	Sucrase	Isomaltase	
salacinol (**113**)	-37.5	5.2	1.6	1.3	4.9
neosalacinol (**114**)	-34.9	8.0	1.3	0.3	9.0
136a (n = 3)	-39.3	5.4	0.73	2.9	4.8
136b (n = 6)	-41.1	7.7	0.29	4.8	1.7
136c (n = 8)	-43.0	7.2	0.15	5.4	1.2
136d (n = 10)	-44.4	6.3	0.17	4.4	1.5
135a (n = 3)	-37.6	4.8	1.4	0.49	5.0
135c (n = 8)	-41.9	2.5	0.38	0.40	2.0

次に、C4'-アルキル型硫酸エステル誘導体 (**136a-d**) と (hNtMGAM) との *in silico* ドッキングシュミレーションを行い、その計算結果から阻害活性試験の結果を考察した (**Figure 43)**。**136a-d** の C2′、C3′ および C4′ 位水酸基はそれぞれアルギニン 526、アスパラギン 542 および アスパラギン 203 残基と水素結合を形成し得る。この結果は Salacinol (**113**) の計算結果と一致し、阻害活性に寄与している可能性が高い。また、C2′ および C4′ の２つの水酸基の重要性はこれまでの構造活性相関の結果 (①および②) とも一致する。次に、**136a** (n = 3) のドッキングシュミレーションモデルでは側鎖 C7′ 位メチル基とスレオニン 205 残基との距離が 4.07Å であることから、ファンデルワールス相互作用が働く可能性が示唆される。しかし、ヒト小腸由来マルターゼに対する **136a** の阻害活性は Salacinol (**113**) と同等であったことから、スレオニン 205 残基との相互作用による活性用度の寄与はほとんどないと考えられる。一方、**136b-d** の側鎖 (n＝6~10) はスレオニン 205 および スレオニン 204 残基との立体反発をさけるために、**136a** とは異なる位置に配置される。したがって、**136b-d** の側鎖部位と遠方のフェニルアラニン 450 および リジン 480 残基との距離がそれぞれ 4.41~3.65、4.45~3.78 Å 以内になることから、新たな２つのファンデルワールス相互作用が働いている可能性が考えられる。また、この相互作用は **136b-d** のヒト小腸由来マルターゼに対する阻害活性が **113** および **136a** よりも強力であることを支持している。

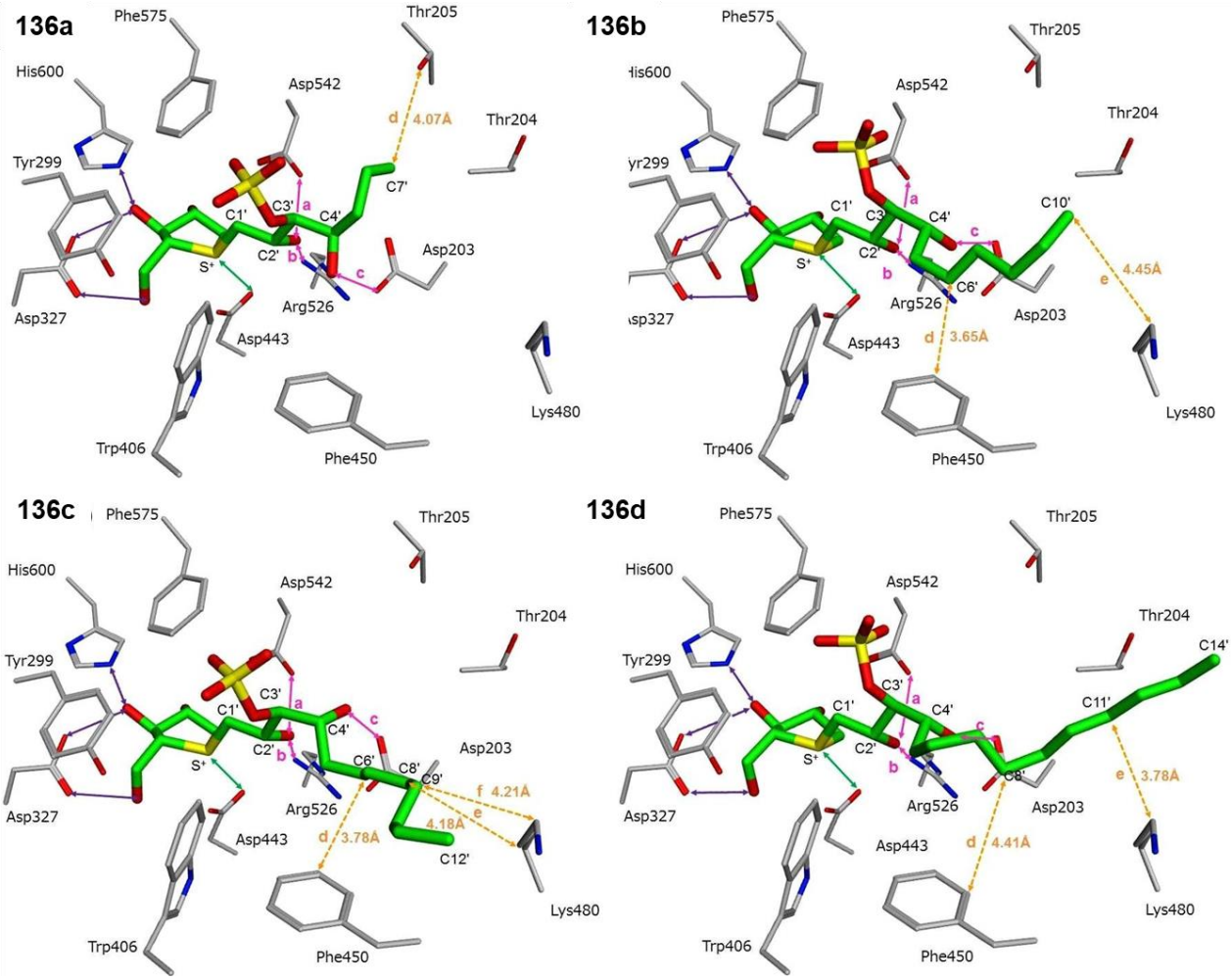


Figure 42. 誘導体 **(136a-d)** の *in silico* ドッキングシュミレーションの結果

また、ラット由来マルターゼに対して **136b-d** が顕著な活性を示さなかった理由としては、以下のように考察している。ラット マルターゼ-グルコアミラーゼ (rNtMGAM)とヒト (hNtMGAM) の *N* 末端触媒ドメインのアミノ酸配列は、約 60% の相同性があることが報告されている[90,91,92]。しかし、本実験の計算結果から得られた **136b-d** の阻害活性に係わる hNtMGAM のフェニルルアラニン 450 は rNtMGAM においてはロイシン 444 に置換されている。すなわち、フェニルルアラニン由来の CH-π 相互作用が rNtMGAM では働かない。また、hNtMGAM のリジン 480 においては rNtMGAM 中で完全に欠如しているため、側鎖とのファンデルワールス相互作用が引き起こらない。これら２つの相互作用の欠如により、 C4'-アルキル側鎖による活性強度の増加効果は得られなかったと考えられる **(Table 4)**。

Table 4. rNtMGAM および hNtMGAM の N 末端触媒ドメインのアミノ酸配列の相互表

	NtMGAM		
human	Phe450	Lys480	Thr205
rat	Leu444	—	Thr205

一方、脱硫酸エステル型誘導体 (**135a, 135c**) と (hNtMGAM) との *in silico* ドッキングシュミレーションモデルを作成した結果、**136b-d** のときに見られたフェニルアラニン 450 との相互作用が起こりにくいことが判明した。また、**135a** および **135c** はそれぞれチロシン 204 とリジン 480 としか相互作用しないと考えられることから、ドッキングシュミレーションモデルによる活性強度の増加理由を検討することは出来なかった (**Figure 43**)。そのため、脱硫酸エステル型誘導体の阻害活性が増加した理由としては、Pinto らによって報告された脱硫酸エステル化効果による周囲の疎水性アミノ酸残基との位置的圧迫の解消が要因になっている可能性が示唆された [84]。

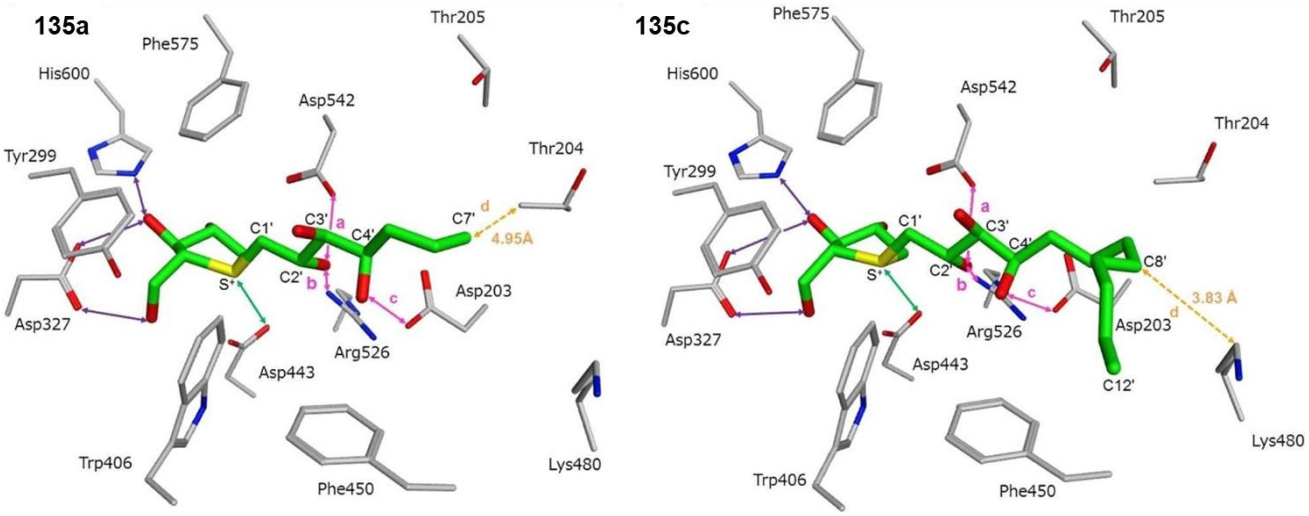


Figure 43. 誘導体 (**135a, c**) の *in silico* ドッキングシュミレーションの結果

以上、我々は salacinol (**113**) の構造活性相関研究の一環として新規側鎖 C4'-アルキル型 salacinol 誘導体 (**136a-d**) およびその脱硫酸エステル体 (**135a, c**) を合成し、それらのラットおよびヒト由来 α-グリコシターゼ阻害活性を測定した。その結果、合成した新規化合物は全て **113** よりも強力にヒト由来マルターゼを阻害した。また、最も強い阻害活性を示した **136c** は **113** よりも 4 倍も強力に作用し、さらに、その阻害活性は現在 α-グルコシダーゼ阻害剤として知られている糖尿病治療薬の中で最も強力な Voglibose (IC_{50} = 1.3 μM) と同等であった。本構造活性相関研究により **113** の側鎖 C4′ へのアルキル側鎖の導入が阻害活性の増加に寄与することが判明した。また、*in silico* ドッキングシュミレーションモデルにより、 hNtMGAM の Lys 480 および Phe 450 の残基とアルキル側鎖との間のファンデルワールス相互作用が阻害活性の増加に寄与している可能性を示唆することができた [93]。

第五章　Salacinol およびその誘導体化合物を用いた GH31 α-グルコシダーゼへの活性評価

第一節　GH31 α-グルコシダーゼについて

多様な遺伝子をコードする遺伝子は、共通の祖先遺伝子から分岐してきたものが数多く存在し、それらは相同タンパクとよばれる。その中でも、相互のアミノ酸配列の類似性が高い一群はファミリーとよばれる。1980 年代後半に Henrissat らはセルラーゼとヘミセルラーゼを対象に、アミノ酸配列の類似性を主な基準とした分類を行った[94]。その後、1991 年には 35 種の糖質加水分解酵素（Glycoside Hydrolase; GH）ファミリーが定義された[95]。さらに、2013 年までに、170,000 を超える膨大な数の糖質加水分解酵素が 130 種程度の GH ファミリーに分類された[96]。一般的にファミリー内のすべてのタンパク質の触媒機構や立体構造はファミリー内で明らかとなっているタンパク質と類似することが知られている。GH ファミリーの中でも α-グルコシダーゼの大部分は GH13 と GH31 に分類される。特に糖尿病治療薬の標的とされているヒト小腸 α-グルコシダーゼは GH31 に分類され、このファミリーはグリコシド結合をアノマー保持型機構で加水分解することが知られている (**Figure 44**)。

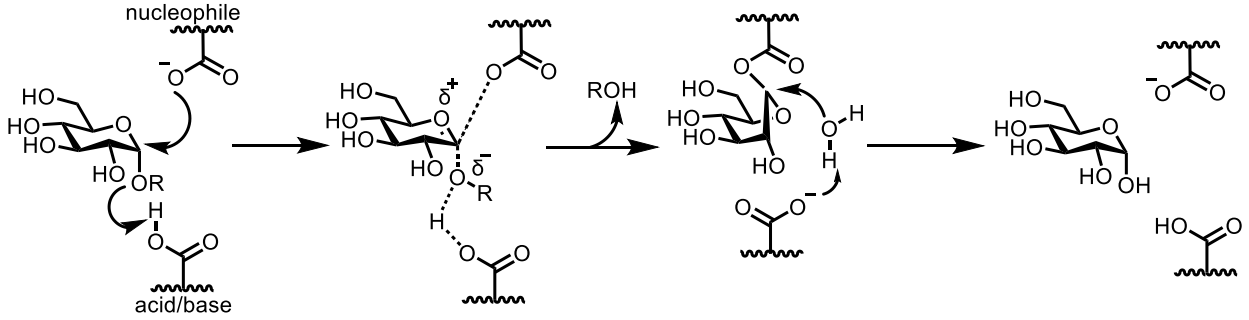


Figure 44. 担持保持型加水分解機構

ヒト小腸の他にも GH 31 族にはリソソーム α-グルコシダーゼが知られており、本酵素は小胞体内で生合成された糖タンパク質の分解やリソソームでのグリコーゲンの処理を担っている[97]。また、リソソーム α-グルコシダーゼの欠損はポンペ病として知られる糖原病 II 型を引き起こすことも解明されている[98]。第 4 章で述べたように、これまでに Salacinol (**113**) の構造活性相関研究を通して、ヒト腸内 α-グルコシダーゼに対して強力な阻害作用を示す誘導体化合物が創製されている。しかし、ヒト腸内 α-グルコシダーゼと同じく GH31 に分類されるヒトリソソーム α-グルコシダーゼへのチオ糖スルホニウム塩型化合物の効果についてはこれまでに全く研究がなされていない。そのため、チオ糖スルホニウム塩型化合物の新たなケミカルスペースの拡張を目的としたヒトリソソーム α-グルコシダーゼへの構造活性相関研究へと展開した。

第二節　リソソームα-グルコシダーゼへのチオ糖スルホニウム塩型化合物の構造活性相関

リソソーム α-グルコシダーゼへの構造活性相関を行うにあたり、まず salacinol (**113**) とは側鎖の C2′ および C3′ 位の立体が異なる誘導体 (**151~153**) およびその脱硫酸エステル体 (**154~156**) の合成を行った(**Figure 45**)。

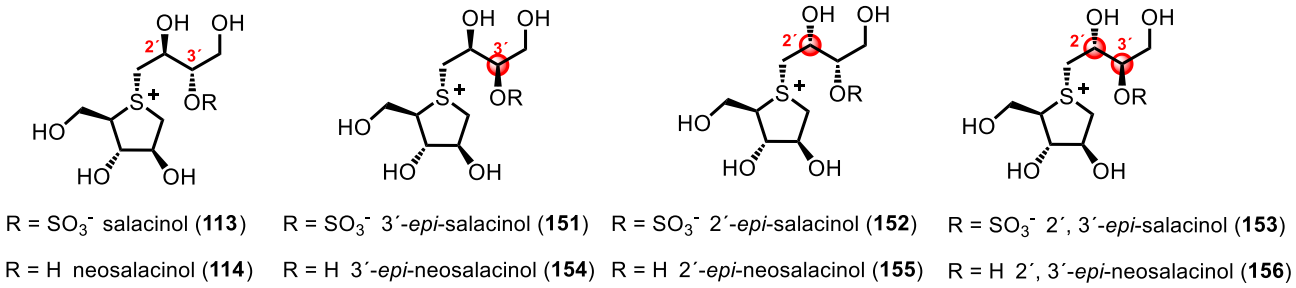
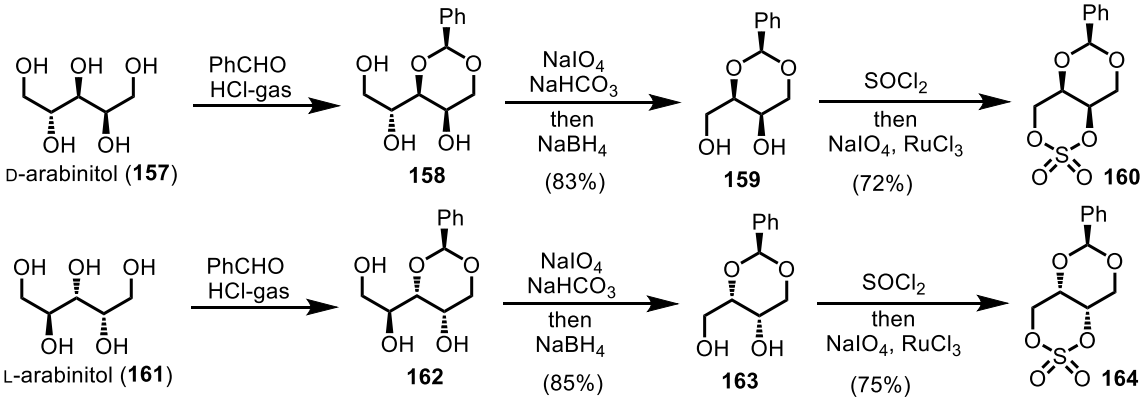


Figure 45. 側鎖の立体が異なる salacinol (**113**) 誘導体のデザイン

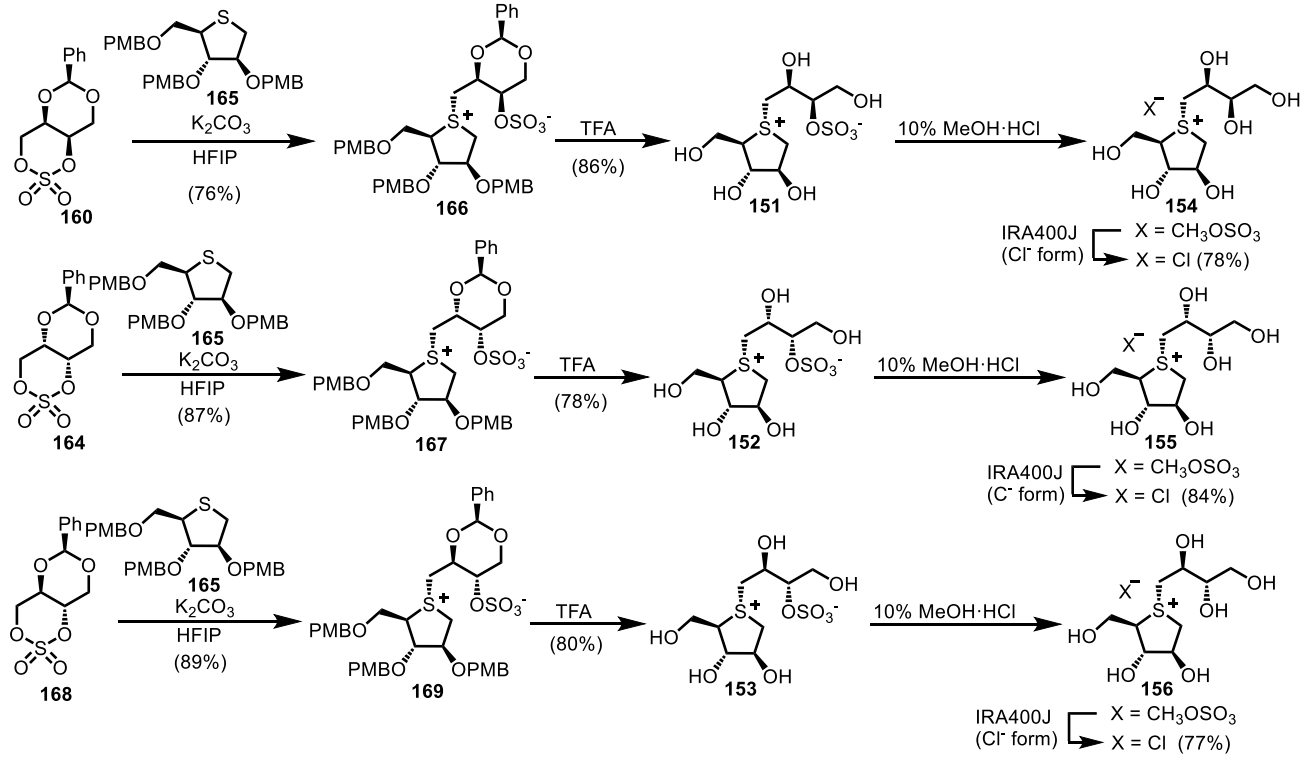
まず、側鎖部中間体の合成に向けて、D-arabinotol (**157**) をベンジリデンアセタール (**158**) へと変換した後、過ヨウ素酸ナトリウムおよび $NaBH_4$ を用いて減炭した後、塩化チオニルおよび四酸化ルテニウムで処理することで、目的の側鎖部中間体 (**160**) を合成した。また、L-arabinitol (**161**) を原料とすることで、側鎖部中間体 (**164**) を合成した (**Figure 28**)。また、文献記載の方法[99] に従い salacinol 型側鎖の中間体 (**168**) も合成した



Scheme 28. 側鎖部鍵中間体 (**160**) および (**164**) の合成

３種の側鎖中間体 (**160**, **164**, **168**) が得られたので、Pinto らの方法を参考に[79]、チオ糖 (**165**) とのカップリング反応を行った。すなわち、側鎖鍵中間体 (**160**, **164** および **168**) を HFIP 中炭酸カリウムの存在下で、チオ糖 (**165**) と反応させたところ、高収率で目的のチオ糖スルホニウム塩体 (**166**, **167**, **169**) を得ることができた。その後、 **166**, **167**, **169** を TFA で処理することで、PMB 基およびベンジリデンアセタールの脱保護が一挙に進行し、目的の

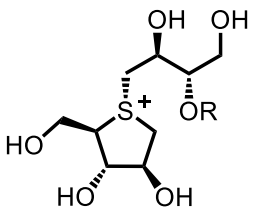
硫酸エステル体 (**151**, **152**, **153**) を合成した。さらに、10% 塩化水素メタノール水溶液中で加溶媒分解に付した後、イオン交換樹脂を用いたカウンターアニオンの交換を行い、脱硫酸エステル体 (**154**~**156**) へと導いた (**Scheme 29**)。



Scheme 29. 側鎖の立体が異なる Salacinol 誘導体 (**151**~**156**) の合成

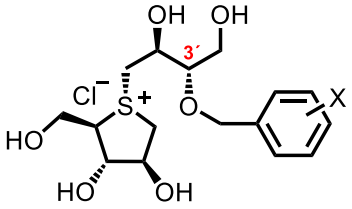
Salacinol 誘導体化合物 (**151**~**156**) の合成を達成したので、次に salacinol (**113**) 、neosalacinol (**114**)、さらにヒト腸 α グルコシダーゼに対して強力な阻害活性を示した *O*-ベンジル型誘導体 (**134a-k**) と共にヒトリソソーム α-グルコシダーゼに対するリガンド適合性の検討を行った(**Table 5**)。まず、**113** と **114** の阻害能を比較したところ、**113** が **114** よりも約 30 倍も強力にリソソーム α-グルコシダーゼを阻害した。さらに興味深いことに、現在 α-グルコシダーゼ阻害剤として糖尿病治療に用いられている voglibose や Acarbose の *K*i 値 は 7.6 μM 以上であり、同じ阻害剤であるチオ糖スルホニウム塩型化合物 (**113** および **114**) よりも高い値であった。すなわち、スルホニウム塩類が voglibose や Acarbose よりヒトリソソーム α-グルコシダーゼに対してリガンド適合性があることが明らかになった。

Table 5. ヒトリソソーム α-グルコシダーゼおよびβ-グルコシダーゼへの活性評価結果



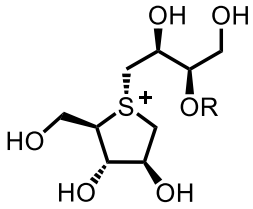
R = SO_3^- salacinol (**113**)

R = H neosalacinol (**114**)



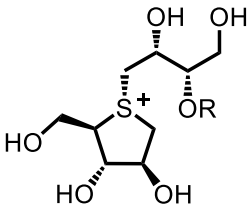
134

a : X = H
b : X = *o*-CH_3
e : X = *o*-Cl
h : X = *o*-CF_3
k : X = *o*-NO_2



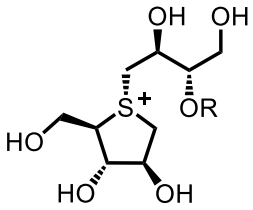
R = SO_3^- 3′-*epi*-salacinol (**151**)

R = H 3′-*epi*-neosalacinol (**154**)



R = SO_3^- 2′-*epi*-salacinol (**152**)

R = H 2′-*epi*-neosalacinol (**155**)



R = SO_3^- 2′, 3′-*epi*-salacinol (**153**)

R = H 2′, 3′-*epi*-neosalacinol (**156**)

Compound	α-Glucosidase GAA [b]	*A. niger* β-glucosidase [c]
salacinol (**113**)	0.12 ± 0.02	> 1000
neosalacinol (**114**)	3.6 ± 0.3	> 1000
134a	0.022 ± 0.007	> 1000
134b	0.034 ± 0.009	> 1000
134e	0.030 ± 0.009	> 1000
134h	0.017 ± 0.010	> 1000
134k	0.17 ± 0.05	> 1000
151	1.0 ± 0.1	> 1000
152	2794 ± 294	> 1000
153	3893 ± 262	> 1000
154	25 ± 2	> 1000
155	2742 ± 230	> 1000
156	463 ± 36	> 1000
Voglibose	7.6 ± 0.8	> 1000
Acarbose	40 ± 2	> 1000

[a]Mean_ SEM. [b]Apparent Ki. Assays conducted at pH 5.2 using a-p-NPG as the substrate.

[c] Apparent IC_{50}. Assays conducted at pH 4.6 using b-p-NPG as the substrate.

次に、ヒト腸 α-グルコシダーゼに対して強力な阻害活性を示した *O*-ベンジル型誘導体 **(134a-k)** の阻害定数を算出したところ、0.017～0.17 μM であり、**113** や 1**14** よりも強力にリソソーム α-グルコシダーゼを阻害した。すなわち、側鎖の *O*-ベンジル基が活性増加に影響を与えている可能性が示唆された。また、**113** と **134h** のリソソーム α-グルコシダーゼとの *in silico* ドッキングモデルを計算した結果、酵素ポケットへの適合性が **134h** の方が高く、阻害定数の結果がよく支持された。しかしながら、ヒト腸 α-グルコシダーゼに対して最も強力な阻害活性を示した **134k** はリソソーム α-グルコシダーゼに対しては最も阻害活性が低かった **(Figure 45)**。

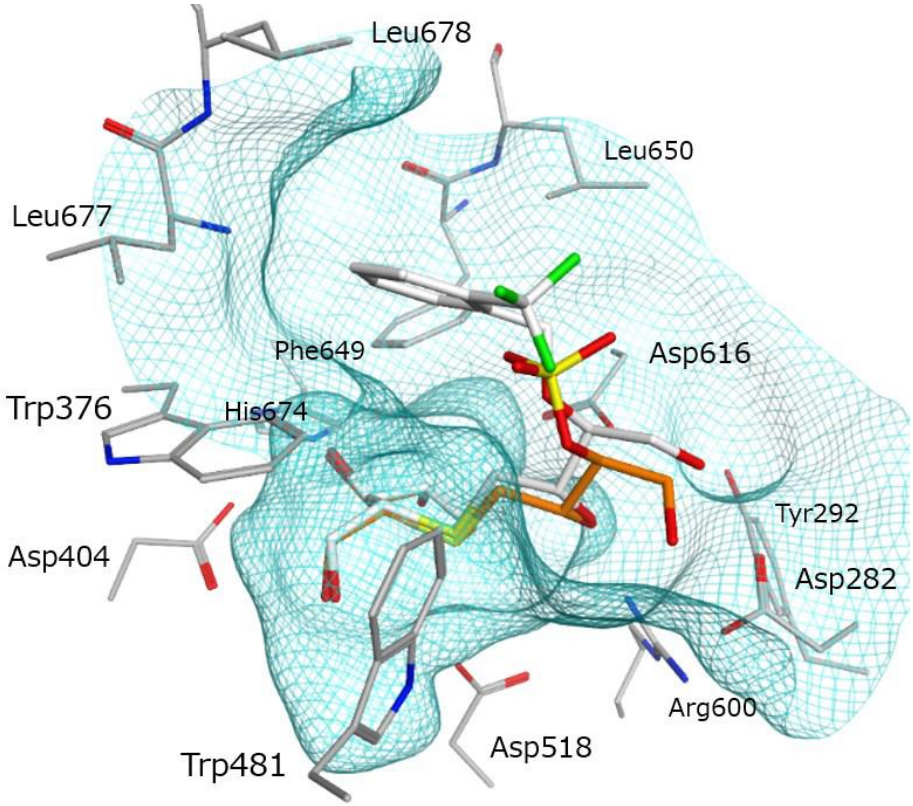


Figure 45. Salacinol **(113)** および *O*-ベンジル型誘導体 **(134h)** のリソソーム α-グルコシダーゼとの *in silico* ドッキングモデルの計算結果

次に、側鎖部の立体化学と活性強度の相関を検討するために、合成した２′および３′位側鎖の立体が異なる Salacinol 誘導体 **(151~156)** の阻害活性を測定した。その結果、３′位が反転した **151** および **154** のリソソーム α-グルコシダーゼの阻害定数がそれぞれ、1.0 ± 0.1 および 2 5± 2 μM の濃度であるのに対して、２′位が反転した **152** および **155** のものはそれぞれ、2794±294 および 2742 ± 230 μM と著しく大きな値を示した。。また、２′および３′位のどちらもエピメリ化した **153** および **156** はそれぞれ 3893 ± 262 および 463 ± 36 の濃度で阻害したことから、リソソーム α-グルコシダーゼのチオ糖スルホニウム塩型化合物の基質側鎖部の認識は３′位に対しては寛容であり、２′位に対しては厳格であることが示唆された。

最後に、チオ糖スルホニウム塩型化合物が GH31 α-グルコシダーに特異的に作用しているかを評価するために、*Aspergillus niger* 由来の β-グルコシダーゼ[100] に対する阻害活性能も測定した。その結果、全ての化合物において IC_{50} が 1000 μM 以上であったことからこれらチオ糖スルホニウム塩型化合物が GH31 α-グルコシダーゼを特異的に認識していることが示唆された。

以上、リソソーム α-グルコシダーゼへの Salacinol を始めとしたチオ糖スルホニウム塩型化合物の構造活性相関研究を通して、それらの化合物がヒト腸内 α-グルコシダーゼ以外の GH31 ファミリーに対して適合性があることを示すことができた。また、側鎖の立体が異なる Salacinol 誘導体 (**151**~**156**) との比較により、リソソーム α-グルコシダーゼ阻害活性に側鎖２′および３′位アルコールの立体化学が大きく関与している可能性を示すことができた[101]。

謝辞

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実験の部

第一章から第三章までの実験に際し、赤外線吸収スペクトル (IR) は日本分光 FT/IR-460 Plus、津島 FTIR 8400 を用いて測定した。水素及び炭素核磁気共鳴スペクトル (^{1}H- および ^{13}C-NMR) スペクトルは、 Varian Gemini 300 , JEOL JNM-A400 , Varian UNITY plus 500 核磁気共鳴装置を用いた。化学シフトは ppm 値で示し、シグナルの分裂様式は、次の略号を示した。 s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double doublet, ddd = double double doudlet, dt = double triplet.質量分析の測定には島津 GCMS- QP 500 型、JEOL JMS-GCmate II 、 JEOL AX 505 (70 eV direct inlet system) を使用した。旋光度は、HORIBA SEPA-500 を用いて測定した。シリカゲルクロマトグラフィーは、 Cica Silica Gel 60 N (spherical, neutral) 63-210 μm を用いて行った。薄層クロマトグラフィー (TLC) のスポット検出には紫外吸収法、アニスアルデヒド発色法、あるいは、リンモリブデン酸発色法を併用した。

第四章から第五章までの実験に際し、赤外吸収 (IR) スペクトルは、島津 IRAffinity-1 分光光度計を用いて測定した。水素及び炭素核磁気共鳴 (^{1}H– および ^{13}C–NMR) スペクトルは, 日本電子 AL 400 型 (^{1}H–NMR; 400 MHz, ^{13}C–NMR; 100 MHz) 及び JEOL JNM-ECA 500 (500 MHz ^{1}H, 125 MHz ^{13}C), JEOL JNM-ECA 800 (800 MHz ^{1}H, 200 MHz ^{13}C)を用いた。シグナルの分裂様式は、次の略号を示した。 s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double doublet, ddd = double double doudlet, dt = double triplet, dtd = quadruple doublet.質量分析の測定には、日本電子 JEOL JMS-700T 型を用い、高速原子衝撃法 (FAB) 及び サーモフィッシャーサイエンティフィック Exactive Plus Orbitrap 型を用い、エレクトロスプレイイオン化法 (ESI) にて測定した。シリカゲルカラムクロマトグラフィーの吸着剤は、富士シリシア BW -200 を用いて行った。 反応の後処理における乾燥は、すべて無水硫酸ナトリウムを用いた。

第一章

1-Benzyl 2-methyl (2*R*, 6*S*)-6-Acetoxymethylpiperidine-1,2-dicarboxylate (10)

To a stirred solution of $(COCl)_2$ (1.41 mL, 16.39 mmol) in CH_2Cl_2 (30 mL) was added DMSO (2.33 mL, 32.78 mmol) at -78 °C, and the resulting mixture was stirred at -78 °C for 15 min. To the mixture was added a solution of **4**[24] (3.51g, 10.93 mmol) in CH_2Cl_2 (30 mL) at -78 °C, and the stirring was continued for 1 h. Triethylamine (6.91 mL, 49.16 mmol) was added to the reaction mixture at -78 °C, and the reaction temperature was gradually increased to 0 °C. The reaction mixture was diluted with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (15 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step. To a stirred suspension of $NaH_2PO_4{\cdot}2H_2O$ (17.04 g, 109.25 mmol), 2-methyl-2-butene (23.22 mL, 218.50 mmol), and the crude aldehyde obtained above in *t*-BuOH (45 mL) was added a solution of $NaClO_2$ (70%, 8.47 g, 65.55 mmol) in H_2O (15 mL), and the resulting suspension was stirred at room temperature for 2 h. The reaction was quenched with satd. $NaHSO_3$ (aq) and 10% HCl (aq) at 0 °C, and the aqueous mixture was extracted with EtOAc (15 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step.To a stirred solution of the carboxylic acid obtained above in EtOAc (30 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction mixture was stirred at room temperature for 15 min. The solvent was evaporated, and the residue was chromatographed on SiO_2 (60 g, acetone/hexane = 1:10) to give **10** (3.63 g, 10.38 mmol, 95% in 3 steps) as pale yellow oil.

IR (neat) : 2953, 1743, 1699, 1456, 1409, 1313, 1229, 1071, 1036 cm^{-1}; ^{1}H-NMR (500 MHz $CDCl_3$) δ: 1.39-1.78 (5H, m), 1.99 (3H, s), 2.27 (1H, m), 3.68 (3H, s), 4.13 (2H, m), 4.47 (1H, m), 4.82-4.90 (1H, m), 5.14-5.22 (2H, m), 7.30-7.34 (5H, m); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 15.72, 20.82, 24.74, 25.88, 48.96, 52.24, 52.94, 63.40, 67.48, 127.78, 127.98, 128.40, 136.38, 156.25, 170.68, 172.80; MS (FAB): *m*/*z* 350 $[M+1]^+$; HRMS (FAB) Calcd for $C_{18}H_{24}NO_6$ 350.1603; Found 350.1605; $[\alpha]_D^{20}$ +20.4 (*c* 2.79, $CHCl_3$).

Benzyl (1*R*, 5*S*)-2- Oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (11) and Methyl (5*R*, 9*S*)-3-Oxohexahydroxazolo[3,4-α]pyridine-5-carboxylate (12)

To a stirred solution of **10** (4.29 g, 12.27 mmol) in MeOH (30 mL) was added K_2CO_3 (5.09 g, 36.80 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 20 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (60 g, EtOAc/hexane = 1:1) to give **12** (2.18 g, 10.92 mmol, 89%) as pale yellow oil and **11** (169 mg, 0.61 mmol, 5%) as pale yellow oil.

11: IR (neat) : 3648, 2928, 1739, 1734, 1418, 1254, 1047 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.26-1.37 (2H, m), 1.68-1.76 (1H, m), 1.77-1.89 (2H, m), 2.18-2.22 (1H, m), 3.89 (1H, t, *J* = 8.0), 4.03-4.07 (1H, m), 4.45 (1H, t, *J* = 8.0), 4.66 (1H, d, *J* = 6.0), 5.19 (2H, s), 7.34-7.39 (5H, m); ^{13}C-NMR (100 MHz $CDCl_3$) δ: 19.46, 26.19, 29.52, 51.87, 52.29, 67.11, 68.90, 128.09, 128.41, 128.60, 135.25, 157.06, 170.40; MS (FAB): *m*/*z* 276 $[M+1]^+$; HRMS (FAB) Calcd for $C_{15}H_{18}NO_4$ 276.1236; Found 276.1234; $[\alpha]_D^{20}$-15.7 (*c* 1.20, $CHCl_3$).

12: IR (neat) : 2952, 1742, 1767, 1419, 1280, 1254, 1047 cm^{-1}; ^{1}H-NMR (500 MHz $CDCl_3$) δ: 1.29-1.42 (2H, m), 1.68-1.75 (1H, m), 1.81-1.89 (2H, m), 2.17-2.22 (1H, m), 3.76 (3H, s), 3.90 (1H, t, *J* = 8.0), 4.02-4.08 (1H, m), 4.50 (1H, t, *J* = 8.0), 4.62 (1H, d, *J* = 6.0); ^{13}C-NMR (100 MHz $CDCl_3$) δ: 19.55, 26.16, 29.60, 51.90, 52.21, 52.43, 68.92, 157.06, 171.05; MS (FAB): *m*/*z* 200 $[M+1]^+$; HRMS (FAB) Calcd for $C_9H_{14}NO_4$ 200.0923; Found 200.0924; $[\alpha]_D^{20}$-8.3 (*c* 0.40, $CHCl_3$).

Conversion of **11** to **12**:To a stirred solution of **5** (330 mg, 1.20 mmol) in MeOH (5 mL) was added NaOMe (65 mg, 1.20 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 18 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (12 g, EtOAc/hexane = 1:1) to give **12** (228 mg, 1.14 mmol, 95%) as pale yellow oil.

Methyl (8a*S*)-3-Oxo-5-(phenylthio)hexahydro-1*H*-oxazolo[3,4-α]pyridine-5-carboxylate (13)

To a stirred solution of diisopropylamine (1.14 mL, 8.13 mmol) in THF (15 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 5.05 mL, 8.13 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min. To a stirred solution of **12** (1.08 g, 5.42 mmol) in THF (15 mL) was added a solution of LDA in THF prepared above at -78 °C, and the reaction mixture was stirred at -78 °C for 5 min. To the reaction mixture was added HMPA (1.41 mL, 8.13 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 25 min. To the reaction mixture was added a solution of $(PhS)_2$ (1.78 g, 8.13 mmol) in THF (10 mL) via cannula at -78 °C, and the temperature was gradually raised to 0 °C. The solvent was evaporated, and the residue was chromatographed on SiO_2 (30 g, EtOAc/hexane = 1:3) to give **13** (1.63 g, 5.30 mmol, 98%) as pale yellow oil as a mixture of diastereomers.

Methyl (*S*)-3-Oxo-3,7,8,8a-tetrahydro-1*H*-oxazolo[3,4-*α*]pyridine-5-carboxylate (3)

To a solution of **13** (4.20 g, 13.68 mmol) in CH_2Cl_2 (50 mL) was added 2,6-lutidine (4.11 mL, 35.29 mmol). *m*CPBA (70%, 8.09 g, 32.83 mmol) was added to the resulting mixture in 4 equal portions once every 15 min at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$ (aq) (90 mL), and extracted with CH_2Cl_2 (10 mL × 3). The organic extracts were combined, and washed with 10% HCl (aq) (20 mL). The organic layer was dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g EtOAc/hexane = 1:3) to give **7** (2.62 g, 13.29 mmol, 97%) as a colorless solid. whose spectral data were identical with those for the reported ones.[25]

(3a*S*, 5a*S*, 6*S*, 9a*R*)-6-Vinyloctahydro-1*H*-oxazolo[3,4-α]quinolone-1,8(3*H*)-dione (18)

To a stirred suspension of CuI in Et_2O (3 mL) was added a solution of vinyl lithium at -78 °C, prepared from tetravinyltin (49 μL, 0.27 mmol) and MeLi (1.13 M in Et_2O, 97 μL, 1.07 mmol) in Et_2O (1 mL) at 0 °C for 30 min, and the resulting suspension was warmed to -35 °C for 30 min. The resulting suspension was re-cooled to -78 °C, and a solution of **6**[25] (37 mg, 0.18 mmol) in Et_2O (0.5 mL) was added to the resulting suspension. The reaction mixture was warmed to 0 °C for 1 h, and the reaction

was quenched with sat. NH_4Cl (aq) (3 mL). The aqueous mixture was extracted with CH_2Cl_2 (3 mL × 3), and the organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (5 g, acetone/hexane = 1:5) to give **18**（36 mg, 0.15 mmol, 83%）as pale yellow oil.

IR (neat) : 1747, 1717, 1684, 1418, 1231, 1084, 1028 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.42-1.57 (1H, m), 1.80-1.88 (2H, m), 1.90-2.02 (2H, m), 2.41-2.58 (4H, m), 2.61-2.65 (1H, m), 3.78-3.85 (1H, m), 3.92 (1H, dd, *J* = 8.4, 6.0), 4.29-4.35 (1H, m), 4.42 (1H, t, *J* = 8.4), 5.04 (1H, dd, *J* = 17.2, 1.4), 5.12 (1H, dd, *J* = 10.8, 1.4), 5.77 (1H, ddd, *J* = 17.2, 10.8, 5.6) ; ^{13}C-NMR (125 MHz $CDCl_3$) δ: 24.04, 30.48, 38.12, 39.69, 39.99, 41.55, 47.95, 49.98, 68.09, 116.69, 139.00, 156.154, 207.29; MS (EI): *m*/*z* 235 $[M]^+$; HRMS (EI) Calcd for $C_{13}H_{17}NO_3$ 235.1208; Found 235.1202; $[\alpha]_D^{21}$-55.9 (*c* 1.00, $CHCl_3$).

(3a*S*, 5a*S*, 6*S*, 9a*R*)-6-Vinyldacahydro-1*H*-oxazolo [3,4-α]quinolin-1-one (10)

To a stirred solution of **18** (220 mg, 0.94 mmol) in CH_2Cl_2 (8 mL) and MeOH (0.8 mL) was added $NaBH_4$ (106 mg, 2.81 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. NH_4Cl (aq) (5 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give white solid, which was used directly in the next step. To a stirred solution of the above solid in 1,2-dichloroethane (8 mL) was added 1,1-thiocarbonyldiimidazole (500 mg, 2.81 mmol) at room temperature. The resulting mixture was refluxed for 16 h. After cooling, the solvent was evaporated to give yellow paste, which was chromatographed on silica gel (8 g, acetone/hexane = 1:7) to give yellow oil, which was used in the next step. A stirred solution of *n*-Bu_3SnH (0.74 mL, 2.81 mmol) in toluene (7 mL) was heated to reflux for 30 min, and then a solution of above yellow oil in toluene (1.5 mL) was added to the above solution, and the reaction mixture was refluxed for 4 h. After cooling, the solvent was evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, EtOAc/hexane = 1:15) to give **19** (115 mg, 0.52 mmol, 56% in 3 steps) as a colorless oil.

IR (neat) : 2932, 1830, 1749, 1541, 1418, 846, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.29-1.41 (2H, m), 1.45-1.64 (6H, m), 1.72-1.88 (3H, m), 2.28 (1H, br), 3.72-3.78 (1H, m), 3.81 (1H, t, *J* = 7.6), 3.94-4.00 (1H, m), 4.34 (1H, t, *J* = 7.6), 5.04 (1H, dm, *J* = 10.0), 5.05 (1H, dm, *J* = 18.2), 5.93 (1H, ddd, *J* = 18.2, 10.0, 5.7); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 20.02, 24.11, 24.23, 24.70, 30.94, 38.66, 42.47, 48.02, 50.43, 68.16, 114.46, 140.86, 156.60; MS (EI): *m*/*z* 221 $[M]^+$; HRMS (EI) Calcd for $C_{13}H_{19}NO_2$ 221.1416; Found 221.1419; $[\alpha]_D^{22}$-3.9 (*c* 1.00, $CHCl_3$).

***t*-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-2-(Hydroxymethyl)-5-vinyloctahydroquinoline-1(*2H*)-carboxylate (20)**

A solution of 2M KOH in *i*-PrOH (7 mL) was added to **19** (24 mg, 0.11 mmol), and the resulting mixture was heated at 120 °C in a sealed tube for 24 h. After cooling, the solvent was evaporated, and residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (3 mL × 5). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the oil obtained above in THF (3 mL) were added

satd. $NaHCO_3$ (aq) (3 mL) and Boc_2O (118 mg, 0.54 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 5). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (5 g, EtOAc/hexane = 1:7) to give **20** (23 mg, 0.08 mmol, 72% in 2 steps) as pale yellow oil.

IR (neat) : 3449, 1830, 1670, 1558, 1541, 1456, 1396, 1173, 856, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.44 (9H, s), 1.48-1.82 (10H, m), 1.91-1.96 (1H, m), 2.23 (1H, br), 3.59-3.80 (4H, m), 5.06 (1H, dm, *J* = 10.8 Hz), 5.07 (1H, dm, *J* = 17.5 Hz), 5.94 (1H, ddd, *J* = 17.5, 10.8, 5.7 Hz); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 20.93, 22.51, 24.72, 25.79, 27.04, 28.52, 37.44, 42.41, 51.97, 54.42, 66.46, 80.04, 114.27, 141.64, 156.40; MS (EI): *m*/*z* 295 $[M]^+$; HRMS (EI) Calcd for $C_{17}H_{29}NO_3$ 295.2147; Found 295.2140; $[\alpha]_D^{23}$-5.8 (*c* 1.00 , $CHCl_3$).

<u>*t*-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-2-((*E*)-3-Ethoxy-3-oxoprop-1-en-1-yl)-5-vinyloctahydroquinoline-1(2*H*)- carboxylate (21)</u>

To a stirred solution of **20** (23 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (50 mg, 0.12 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd.$Na_2S_2O_3$ (aq) (3 mL), and the aqueous mixture was extracted with CH_2Cl_2 (3 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give an aldehyde as pale yellow oil, which was used directly in the next step. To a stirred suspension of NaH (60%, 5 mg, 0.130 mmol) in THF (3 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (33 μL, 0.16 mmol) at 0 °C, then the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added the above aldehyde in THF (1 mL) at 0 °C, then the mixture was stirred at room temperature for 16 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (8 g, EtOAc/hexane = 1:7) to give **21** (22 mg, 0.06 mmol, 79% in 2 steps) as pale yellow oil.

IR (neat) : 1830, 1717, 1697, 1653, 1558, 1506, 1456, 1394 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.26 (3H, t, *J* = 7.2 Hz), 1.29-1.33 (1H, m), 1.40 (9H, s), 1.47-1.52 (3H, m), 1.56-1.69 (3H, m), 1.75-1.83 (2H, m), 1.93-2.02 (2H, m), 2.21 (1H, br), 3.98 (1H, br), 4.16 (2H, q, *J* = 7.2), 4.37 (1H, br), 5.03 (1H, dm, *J* = 17.2), 5.04 (1H, dm, *J* = 10.8), 5.76 (1H, dd, *J* = 15.6, 1.6), 5.95 (1H, ddd, *J* = 17.2, 10.8, 6.0), 6.96 (1H, dd, *J* = 15.6, 5.4); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 14.19, 20.40, 20.63, 24.44, 26.66, 28.33, 36.00, 42.15, 50.77, 51.87, 53.37, 60.23, 79.79, 114.38, 119.24, 141.30, 151.24, 155.09, 166.59; MS (EI): *m*/*z* 363 $[M]^+$; HRMS (EI) Calcd for $C_{21}H_{33}NO_4$ 363.2410; Found 363.2412; $[\alpha]_D^{24}$-46.8 (*c* 1.00, $CHCl_3$).

第二章

_t_-Butyl (2_S_, 4a_S_, 5_S_, 8a_R_)-2-(3-Methoxy-3-oxopropyl)-5-vinyloctahydroquinoline-1(2_H_)-carboxylate (22)

To a stirred suspension of magnesium turnings (362 mg, 14.88 mmol) in MeOH (8 mL) was added iodine (19 mg, 0.07 mmol), and the resulting brown colored mixture was stirred at room temperature for 30 min. as the solution becomes colorless. A solution of **21** (90 mg, 0.25 mmol) in MeOH (1 mL) was added to the resulting suspension, and the reaction mixture was heated to 60 °C for 2 h. After cooling, the MeOH was evaporated and the residue was acidified with 10% HCl (aq) (5 mL). The aqueous mixture was extracted with CH_2Cl_2 (5 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale red oil, which was chromatographed on SiO_2 (8 g, EtOAc/hexane = 1:10) to give **22** (75 mg, 0.21 mmol, 86%) as pale yellow oil.

IR (neat) : 1734, 1697, 1684, 1541, 1506, 1456, 1364, 1173, 856, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.19-1.29 (2H, m), 1.39-1.41 (2H, m), 1.43 (9H, s), 1.45-1.90 (7H, m), 1.91-2.00 (1H, br), 2.10 (1H, br), 2.21 (1H, br), 2.32 (2H, t, J = 8.2 Hz), 3.64 (3H, s), 3.73 (1H, br), 3.81-3.86 (1H, m), 5.03 (1H, dm, J = 9.8), 5.04 (1H, dm, J = 18.2), 5.97 (1H, ddd, J = 18.2, 9.8, 6.8); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 19.60, 20.39, 23.46, 24.51, 28.44, 29.10, 30.68, 31.81, 35.56, 42.18, 50.42, 50.67, 51.49, 79.08, 114.20, 141.55, 154.99, 173.88; MS (EI): m/z 351 $[M]^+$; HRMS (EI) Calcd for $C_{20}H_{33}NO_4$ 351.2410; Found 351.2415; $[\alpha]_D^{24}$-11.1 (c 1.00, $CHCl_3$).

_t_-Butyl (2_S_, 4a_S_, 5_S_, 8a_R_)-5-(2-Hydroxyethyl)-2-(3-methoxy-3-oxopropyl)octahydroquinoline-1(2_H_)-carboxylate (23)

To a stirred solution of **22** (70 mg, 0.20 mmol) in THF (5 mL) was added $BH_3 \cdot SMe_2$ (28 μL, 0.30 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. To the reaction mixture were added 10% NaOH (aq) (1 mL) and 30% H_2O_2 (aq) (1 mL) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 5). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (8 g, EtOAc/acetone = 1:7) to give **23** (44 mg, 0.12 mmol, 60%) as pale yellow oil.

IR (neat) : 3734, 1830, 1734, 1697, 1653, 1558, 1456, 1173, 856, 772 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 1.15-1.28 (2H, m), 1.35-1.52 (12H, m), 1.54-1.86 (9H, m), 1.90-1.99 (2H, m), 2.32 (2H, t, J = 8.0), 3.62-3.68 (6H, m), 3.70-3.76 (1H, m), 3.79-3.84 (1H, m); ^{13}C-NMR (125 MHz $CDCl_3$) δ: 19.92, 20.17, 23.59, 24.06, 28.60, 29.46, 30.87, 31.96, 34.97, 35.32, 35.54, 50.59, 50.72, 51.66, 61.52, 79.30, 155.20, 174.06; MS (EI): m/z 369 $[M]^+$; HRMS (EI) Calcd for $C_{20}H_{35}NO_5$ 369.2515; Found 369.2524; $[\alpha]_D^{23}$-10.7 (c 1.00 , $CHCl_3$).

<u>*t*-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-5-(2-((*t*-Butyldimethylsilyl)oxy)ethyl)-2-(3-methoxy-3-oxopropyl)-octahydroquinoline-1(2*H*)-carboxylate (24)</u>

To a stirred solution of **23** (35 mg, 95 μmol) in CH_2Cl_2 (3 mL) were added imidazole (13 mg, 0.19 mmol) and TBSCl (29 mg, 0.19 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (8 g, acetone/hexane = 1:10) to give **24** (37 mg, 77 μmol, 80%) as pale yellow oil.

IR (neat) : 1747, 1717, 1684, 1558, 1456, 1364, 1175, 1099, 839, 770 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 1.19-1.43 (4H, m), 1.45 (9H, s), 1.53-1.70 (7H, m), 1.74-1.91 (3H, m), 1.93-2.00 (2H, m), 2.34 (2H, t, *J* = 7.8), 3.58-3.68 (5H, m), 3.76 (1H, br), 3.80-3.85 (1H, m); ^{13}C-NMR (125 MHz $CDCl_3$) δ: -5.34, 18.31, 19.80, 20.15, 23.47, 24.06, 25.94, 28.50, 29.43, 30.78, 31.91, 34.97, 35.08, 35.40, 50.48, 50.68, 51.53, 61.80, 79.10, 155.08, 173.92; MS (EI): *m*/*z* 483 $[M]^+$; HRMS (EI) Calcd for $C_{26}H_{49}NO_5Si$ 483.3380; Found 483.3377; $[\alpha]_D^{23}$-2.7 (*c* 1.00 , $CHCl_3$).

<u>*t*-Butyl (2*S*, 4a*S*, 5*S*, 8a*R*)-5-(2-((*t*-Butyldimethylsilyl)oxy)ethyl)-2-((*E*)-5-methoxy-5- oxopent-3-en-1-yl)octahydroquinoline-1(2*H*)-carboxylate (7)</u>

To a stirred solution of **24** (23 mg, 48 μmol) in THF (3 mL) was added Super-Hydride (0.14 mL, 0.14 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give yellow oil, which was used directly in the next step. To a stirred solution of the above oil in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (30 mg, 72 μmmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd.$Na_2S_2O_3$ (aq) (3 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give an aldehyde as pale yellow oil, which was used directly in the next step.To a stirred solution of the above oil in THF (3 mL) was added (methoxycarbonylmethylene) triphenylphosphorane (24 mg, 72 μmL) at room temperature, and the resulting mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (5 g, EtOAc/hexane = 1:7) to give **7** (17 mg, 33 μmol, 69% in 3 steps) as pale green oil.

The ^{1}H- and ^{13}C-NMR spectra of our synthetic material were good accordance with those for reported values.[19] IR (neat) : 2930, 1732, 1684, 1653, 1558, 1506, 1456, 1175, 1099, 856 cm^{-1}; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 1.18-1.39 (4H, m), 1.45 (9H, s), 1.53-1.97 (12H, m), 2.13-2.38 (2H, m), 3.58-3.67 (2H, m), 3.71 (3H, s), 3.74 (1H, br), 3.81-3.85 (1H, m), 5.83 (1H, d, *J* = 15.6), 6.96 (1H, dt, *J* = 15.6, 7.0); ^{13}C-NMR (125 MHz $CDCl_3$) δ: -5.3, 18.3, 19.8, 20.15, 22.88, 24.13, 25.93, 28.55, 29.57, 29.97, 33.66, 35.01, 35.13, 35.39, 50.58, 51.37, 61.78, 79.08, 121.03, 148.97, 155.02, 167.01; MS (EI): *m*/*z* 509 $[M]^+$; HRMS (EI) Calcd for $C_{28}H_{51}NO_5Si$ 509.3537; Found 509.3535; $[\alpha]_D^{23}$ -5.4 (*c* 0.75, $CHCl_3$).

Methyl (5*R*,6*R*,8a*S*)-5,6-Diallyl-3-oxohexahydro-1*H*-oxazolo[3,4-*a*]pyridine-5-carboxylate (29)

To a stirred suspension of CuI (948 mg, 4.98 mmol) in tetrahydrofuran (THF) (20 mL) was added a solution of allyl lithium at −78 °C, prepared from tetraallyltin (0.90 mL, 3.74 mmol) and *n*-BuLi (1.6 M in *n*-hexane, 6.23 mL, 9.96 mmol) in THF (7 mL) at 0 °C for 30 min, and the resulting suspension was warmed to −15 °C for 45 min. The resulting suspension was re-cooled to −78 °C, and a solution of **3** (491 mg, 2.49 mmol) in THF (3 mL) was added to the resulting suspension. The reaction mixture was warmed to −30 °C, and allyl bromide (1.48 mL, 17.43 mmol) was added to the reaction mixture. The reaction mixture was warmed to 0 °C for 1 h, and the reaction was quenched with sat. NH_4Cl (aq) (15 mL). The aqueous mixture was extracted with CH_2Cl_2 (10 mL × 3), and the organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, *n*-hexane/EtOAc = 7:1) to give **29** (531 mg, 1.90 mmol, 76%) as pale yellow oil. IR (neat): 3076, 2949, 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.44–1.55 (2H, m), 1.57–1.70 (1H, m), 1.83–1.88 (2H, m), 1.97–2.03 (1H, m), 2.40–2.45 (1H, m), 2.77 (1H, dd, *J* = 14.6, 8.6), 3.17 (1H, dd, *J* = 14.6, 5.2), 3.75 (3H, s), 3.91–3.98 (2H, m), 4.40–4.51 (1H, m), 5.02 (1H, dd, *J* = 15.2, 1.8), 5.03 (1H, dd, *J* = 11.6, 1.8), 5.18 (1H, d, *J* = 11.6), 5.19 (1H, d, *J* = 16.8), 5.65 (1H, m), 5.77 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.2, 27.0, 34.4, 36.2, 36.3, 50.6, 52.3, 64.7, 69.0, 117.1, 120.1, 132.2, 135.7, 156.4, 171.1; MS (EI/double focusing) *m*/*z*: 279 $[M]^+$; HRMS (EI/double focusing) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{21}NO_4$, 279.1471; found, 279.1476; $[\alpha]_D^{23}$ −87.7 (*c* 1.0, $CHCl_3$).

(5*S*,8*R*,8a*R*)-8,8a-Diallyl-5-(hydroxymethyl)tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (31)

To a stirred solution of **29** (1.11 g, 3.97 mmol) in THF (15 mL) was added Super-Hydride (1 M in THF, 10.56 mL, 11.90 mmol) at 0 °C, and the resulting mixture was refluxed for 30 min. The reaction was quenched with sat. NH_4Cl (aq) (5 mL), and the aqueous mixture was extracted with CH_2Cl_2 (7 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford colorless oil, which was chromatographed on SiO_2 (15 g, *n*-hexane/acetone = 7:1) to give **31** (658 mg, 2.62 mmol, 66%) as pale yellow oil. IR (neat): 3041, 1734, 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.37 (1H, ddd, *J* = 10.2, 6.0, 3.0), 1.60–1.69 (2H, m), 1.75 (1H, ddd, *J* = 11.2, 6.0, 2.8), 1.84 (1H, tt, *J* = 11.2, 2.8), 2.12 (1H, ddd, *J* = 19.2, 11.6, 4.4), 2.30 (1H, td, *J* = 11.6, 4.2), 2.45 (1H, dd, *J* = 14.3, 7.5), 2.62 (1H, dd, *J* = 14.3, 7.5), 3.30–3.35 (1H, m), 3.81–3.93 (2H, m), 4.08 (1H, d, *J* = 9.3), 4.24 (1H, d, *J* = 9.3), 4.44 (1H, t, *J* = 7.5), 5.05 (1H, d, *J* = 10.0), 5.07 (1H, dd, *J* = 17.0, 1.0), 5.20 (1H, d, *J* = 15.5), 5.22 (1H, d, *J* = 9.0), 5.60–5.71 (2H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.5, 22.2, 31.4, 36.5, 39.1, 54.4, 63.1, 64.1, 68.5, 117.1, 120.8, 130.6, 136.0, 157.4; MS (EI/ double focusing) *m*/*z*: 251 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{14}H_{21}NO_3$, 251.1521; found, 251.1521; $[\alpha]_D^{21}$ −1.3 (*c* 1.0, $CHCl_3$).

(2*R*,3*R*,6*S*)-(2,3-Diallyl-6-((methoxymethoxy)methyl)piperidin-2-yl)methanol (32)

To a stirred solution of **31** (12 mg, 48 μmol) in CH_2Cl_2 (2 mL) were added diisopropylethylamine (25 μL, 0.14 mmol) and chloromethyl methyl ether (11 μL, 0.144) at 0 °C, and the resulting mixture was

refluxed for 48 h. The solvent was evaporated to afford a yellow oil, which was chromatographed on SiO_2 (5 g, *n*-hexane/acetone = 5:1) to give (5*S*,8*R*,8a*R*)-8,8a-diallyl-5-((methoxymethoxy)methyl)-tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one (**IM1**) (14 mg, 0.48 mmol, quant.) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58–1.69 (3H, m), 1.73–1.88 (2H, m), 2.14–2.22 (1H, m), 2.30–2.36 (1H, m), 2.52 (1H, dd, *J* = 14.4, 7.0), 2.59 (1H, dd, *J* = 14.8, 7.0), 3.33–3.42 (1H, m), 3.37 (3H, s), 3.72 (1H, dd, *J* = 10.0, 7.2), 4.02 (1H, d, *J* = 9.2), 4.17 (1H, d, *J* = 9.2), 4.30 (1H, d, *J* = 10.0, 5.6), 4.65 (1H, d, *J* = 6.4), 4.69 (1H, d, *J* = 6.4), 5.05–5.23 (4H, m), 5.63–5.74 (1H, m). A solution of 2 M KOH in *i*-PrOH (3 mL) was added to **IM1** (14 mg, 47 μmol), and the resulting mixture was heated at 120 °C in a sealed tube for 12 h. After cooling, the solvent was evaporated and the residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (4 mL × 5). The organic extracts were combined, dried over K_2CO_3, and evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (3 g, CH_2Cl_2/MeOH = 3:1) to give **32** (13 mg, 47 μmol, 100%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (1H, m), 1.39–1.48 (2H, m), 1.65–1.78 (3H, m), 2.20–2.36 (2H, m), 2.50 (1H, dd, *J* = 13.6, 8.0), 2.56 (1H, dd, *J* = 13.6, 7.0), 3.15–3.21 (1H, m), 3.37 (3H, s), 3.50 (1H, t, *J* = 9.2), 3.52 (1H, d, *J* = 11.6), 3.61 (1H, d, *J* = 11.6), 3.62 (1H, br), 3.63 (1H, dd, *J* = 9.2, 3.6), 4.63 (1H, d, *J* = 6.2), 4.64 (1H, d, *J* = 6.2), 5.02 (1H, d, *J* = 9.6), 5.06 (1H, dd, *J* = 16.8, 1.2), 5.17 (2H, dd, *J* = 13.8, 1.2), 5.65–5.76 (1H, m), 5.78–5.86 (1H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.5, 23.1, 32.4, 36.6, 38.0, 49.2, 55.4, 57.2, 66.1, 72.8, 96.7, 115.8, 118.5, 134.2, 138.5; MS (EI/double focusing) *m*/*z*: 269 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{15}H_{27}NO_3$, 269.1991; found, 269.1994.

(5*S*,7a*R*,11a*R*)-5-(Hydroxymethyl)-5,6,7,7a,8,11-hexahydrooxazolo[4,3-*j*]quinolin-3(1*H*)-one (34)

To a stirred solution of **31** (69 mg, 0.28 mmol) in benzene (5 mL) was added Grubbs Catalyst, 2nd generation (24 mg, 0.03 mmol), and the resulting solution was refluxed for 1 h. After cooling, the solvent was evaporated to afford brown oil, which was chromatographed on SiO_2 (7 g, *n*-hexane/acetone = 7:1) to give **34** (60 mg, 0.27 mmol, 96%) as a pale yellow oil. IR (neat): 3118, 2841, 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31–1.41 (1H, m), 1.56–1.68 (2H, m), 1.74–1.84 (1H, m), 1.88–2.01 (2H, m), 2.13–2.20 (1H, m), 2.26 (1H, dd, *J* = 16.8, 4.8), 2.35–2.41 (1H, m), 3.35–3.42 (1H, m), 3.92 (2H, m), 4.07 (1H, d, *J* = 8.8), 4.11 (1H, d, *J* = 8.8), 4.12–4.15 (1H, m), 5.59–5.75 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.2, 23.9, 29.0, 35.8, 36.0, 51.7, 61.2, 61.7, 69.8, 124.7, 128.4, 158.9; MS (EI/double focusing) *m*/*z*: 223 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{12}H_{17}NO_3$, 223.1208; found, 223.1204; $[\alpha]_D^{22}$ −114.3 (*c* 1.0, $CHCl_3$).

(*E*)-Ethyl 3-((5*S*,7a*R*,11a*R*)-3-Oxo-1,3,5,6,7,7a,8,11-octahydrooxazolo[4,3-*j*]quinolin-5-yl)acrylate (35)

To a stirred solution of $(COCl)_2$ (43 μL, 0.50 mmol) in CH_2Cl_2 (6 mL) was added dimethyl sulfoxide (DMSO) (69 μL, 1.00 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 15 min.

To the mixture was added a solution of **31** (37 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. Triethylamine (0.21 mL, 1.49 mmol) was added at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step. To a stirred suspension of NaH (60%, 13 mg, 0.33 mmol) in THF (3 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (83 μL, 0.42 mmol) at 0 °C, and then the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added the above aldehyde in THF (1 mL) at 0 °C, and the mixture was stirred at room temperature for 16 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (3 mL × 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (5 g, *n*-hexane/EtOAc = 5:1) to give **35** (39 mg, 0.13 mmol, 81% in 2 steps) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* = 7.0), 1.31–1.40 (1H, m), 1.60–1.71 (2H, m), 1.85–1.92 (3H, m), 2.08–2.22 (3H, m), 2.63–2.59 (1H, m), 4.00 (1H, d, *J* = 9.2), 4.17 (q, 2H, *J* = 7.0), 4.18 (1H, d, *J* = 9.2), 5.20 (1H, q, *J* = 9.4), 5.59–5.71 (2H, m), 5.90 (1H, d, *J* = 11.6), 7.28 (1H, dd, *J* = 11.6, 9.4); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.2, 21.2, 26.5, 29.0, 35.6, 37.6, 50.3, 60.5, 60.8, 69.7, 121.2, 124.8, 128.3, 145.7, 159.1, 166.0; MS (EI/double focusing) *m*/*z*: 291 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{16}H_{21}NO_4$, 291.1471; found, 291.1471.

(5*S*,7a*R*,11a*R*)-5-(Hex-1-en-1-yl)-5,6,7,7a,8,11-hexahydrooxazolo[4,3-*j*]quinolin-3(1*H*)-one (55)

To a stirred solution of $(COCl)_2$ (0.07 mL, 0.81 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.12 mL, 1.61 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 15 min. To the mixture was added a solution of **34** (60 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. Triethylamine (0.34 mL, 2.42 mmol) was added at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step. To a stirred suspension of amylPPh_3Br (445 mg, 1.08 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 0.50 mL, 0.81 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 30 min. To the suspension was added a solution of the above oil in THF (1.5 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 15 h. The reaction was quenched with sat. NH_4Cl (aq) (5 mL), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (15 g, *n*-hexane/acetone = 10:1) to give **55** (56 mg, 2.03 mmol, 76%) as a mixture of E- and Z-isomers.

(5*R*,7a*S*,11a*R*)-5-Hexyloctahydrooxazolo[4,3-*j*]quinolin-3(1*H*)-one (36)

To a stirred solution of **IM2** (82 mg, 0.30 mmol) in EtOAc (5 mL) was added 10% Pd/C (10 mg), and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 24 h. The catalyst

was filtered off, and the filtrate was evaporated to give **36** (83 mg, 0.30 mmol, quant.) as a pale yellow oil. IR (neat): 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.6), 0.95 (1H, qd, *J* = 12.4, 3.6), 1.21–1.43 (10H, m), 1.44–1.62 (6H, m), 1.65–1.81 (5H, m), 2.27–2.35 (1H, m), 3.10–3.20 (1H, m), 4.03 (1H, d, *J* = 9.0), 4.07 (1H, d, 9.0); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.2, 22.5, 22.6, 25.5, 27.1, 27.5, 29.0, 31.3, 31.8, 35.6, 40.7, 50.9, 63.0, 67.1, 158.8; MS (EI/double focusing) *m*/*z*: 279 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{17}H_{29}NO_2$, 279.2198; found, 279.2196; $[\alpha]_D^{24}$ −31.3 (*c* 1.0, $CHCl_3$).

((2*R*,4a*S*,8a*R*)-2-Hexyldecahydroquinolin-8a-yl)methanol (38)

A solution of 2 M KOH in *i*-PrOH (7 mL) was added to **36** (80 mg, 0.29 mmol), and the resulting mixture was heated at 120 °C in a sealed tube for 12 h. After cooling, the solvent was evaporated and the residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (4 mL × 5). The organic extracts were combined, dried over K_2CO_3, and evaporated to afford a pale yellow oil, which was chromatographed on SiO_2 (12 g, CH_2Cl_2/MeOH = 2:1) to give **38** (73 mg, 0.29 mmol, quant.) as a pale yellow oil. IR (neat): 3672, 3506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.8), 0.99 (2H, dtd, *J* = 25.4, 12.6, 4.0), 1.20–1.74 (20H, m), 1.86 (1H, br d, *J* = 12), 3.00–3.06 (1H, m), 3.25 (1H, d, *J* = 11.0), 3.56 (1H, d, *J* = 11.0); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 22.3, 22.6, 23.8, 26.0, 26.4, 27.7, 28.5, 29.4, 31.8, 36.4, 37.4, 40.7, 49.9, 55.5, 59.4; MS (EI/double focusing) *m*/*z*: 253 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{16}H_{31}NO$, 253.2406; found, 253.2402; $[\alpha]_D^{23}$ +46.7 (*c* 1.3, $CHCl_3$).

(2*R*,4a*S*,8a*R*)-(1-Acetyl-2-hexyldecahydroquinolin-8a-yl)methyl Acetate (42)

To a stirred solution of **38** (6 mg, 24 μmol) in CH_2Cl_2 (1.5 mL) were added Et_3N (51 μL, 0.36 mmol), 4-dimethylaminopyridine (DMAP) (0.1 mg, 12 μmol), and Ac_2O (23 μL, 0.24 mmol) at 0 °C, and the resulting solution was refluxed for 18 h. The reaction was quenched with sat. $NaHCO_3$ (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (3 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale green oil, which was chromatographed on SiO_2 (3 g, *n*-hexane/EtOAc = 3:1) to give **42** (6 mg, 18 μmol, 75%) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J* = 7.2), 1.22–2.15 (23H, m), 2.06 (3H, s), 2.16 (3H, s), 3.34–3.52 (1H, m), 3.84 (1H, br), 4.25 (1H, d, *J* = 12.4), 4.73 (1H, d, *J* = 12.4); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 21.1, 22.6, 23.2, 23.4, 25.8, 26.7, 27.9, 28.5, 29.4, 30.2, 31.8, 35.3, 36.5, 47.2, 55.6, 62.7, 63.3, 171.2, 173.4; MS (EI/double focusing) *m*/*z*: 337 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{20}H_{35}NO_3$, 337.2617; found, 337.2617.

(2*R*,4a*S*,8a*R*)-2-Hexyldecahydroquinoline-8a-carbaldehyde (45)

To a mixture of **38** (69 mg, 0.27 mmol), DMAP (3 mg, 27 μmol), 2,2-bipyridyl (2 mg, 14 μmol), and AZADOL (2 mg, 14 μmol) in MeCN (3 mL) was added CuCl (1 mg, 14 μmol) at room temperature. The mixture was stirred at room temperature under air atmosphere for 16 h. The reaction was quenched

with sat. $NaHCO_3$ (aq) (2 mL) and 20% $Na_2S_2O_3$ (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 3). The organic extracts were combined, dried over K_2CO_3, and evaporated to afford pale green oil, which was chromatographed on SiO_2 (7 g, *n*-hexane/EtOAc = 5:1) to give **45** (67 mg, 0.26 mmol, 99%) as a pale yellow oil. IR (neat): 3421, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.6), 1.12–1.18 (2H, m), 1.24–1.31 (11H, m), 1.38–1.43 (1H, m), 1.46–1.61 (4H, m), 1.65–1.78 (5H, m), 1.91 (1H, br), 2.95–2.99 (1H, m), 9.68 (1H, d, *J* = 1.6); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.2, 22.6, 23.4, 26.1, 27.0, 28.6, 29.2, 29.5, 31.8, 35.5, 36.7, 43.4, 52.3, 61.8, 206.4; MS (EI/double focusing) *m*/*z*: 251 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{16}H_{29}NO$, 251.2249; found, 251.2254; $[\alpha]_D^{21}$ +36.9 (*c* 1.0, $CHCl_3$).

(2*R*,4a*S*,8a*R*)-1-Acetyl-2-hexyldecahydroquinoline-8a-carbaldehyde (47)

To a stirred solution of **45** (65 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) were added triethylamine (73 μL, 0.52 mmol), DMAP (3 mg, 26 μmol), and acetyl chloride (28 μL, 0.39 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The solvent was evaporated to afford a pale yellow oil, which was chromatographed on SiO_2 (7 g, *n*-hexane/EtOAc = 7:1) to give **47** (63 mg, 0.21 mmol, 83%) as a pale yellow oil. IR (neat): 1722, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.0), 1.25–1.36 (13H, m), 1.39–1.52 (3H, m), 1.69–1.81 (5H, m), 1.89 (1H, ddd, *J* = 25.6, 13.0, 3.8), (1H, m), 2.18 (3H, s), 3.60 (1H, br), 3.83–3.87 (1H, m), 9.83 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 22.9, 23.1, 25.2, 25.9, 27.5, 27.8, 29.1, 30.0, 31.7, 32.8, 35.2, 46.1, 56.6, 69.0, 174.66, 202.7; MS (EI/double focusing) *m*/*z*: 293 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{18}H_{31}NO_2$, 293.2355; found, 293.2359; $[\alpha]_D^{22}$ +200.0 (*c* 0.5, $CHCl_3$).

(5*R*,7a*S*,11a*R*)-5-Hexyl 5,6,7,7a,8,9,10,11-octahydro-3*H*-pyrrolo[2,1-*j*]quinolin-3-one (IM3)

To a stirred solution of diisopropylamine (52 μL, 0.37 mmol) in THF (1 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 0.23 mL, 0.37 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min. To a stirred solution of **47** (60 mg, 0.20 mmol) in THF (3 mL) was added a solution of lithium diisopropylamide (LDA) in THF prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched with 10% HCl (aq) (1 mL), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford a pale yellow oil, which was chromatographed on SiO_2 (15 g, *n*-hexane/acetone = 5:1) to give (5*R*,7a*S*,11a*R*)-5-hexyl-1-hydroxyoctahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3(2*H*)-one (**IM2**) (50 mg, 0.17 mmol, 83%) as a mixture of diastereomers. To a stirred solution of **IM2** (6 mg, 20 μmol) in CH_2Cl_2 (1 mL) were added trimethylamine (4 μL, 26 μmol) and methanesulfonyl chloride (2 μL, 24 μmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. 2,3,4,6,7,8,9,10-Octahydropyrimido[1,2-*a*]azepine (DBU) (15 μL, 100 μmol) was added to the reaction mixture at 0 °C, and the reaction mixture was refluxed for 2 h. The solvent was evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (3 g, *n*-hexane/acetone = 5:1) to give **IM3** (5 mg, 18 μmol, 83%) as a pale yellow oil. IR (neat): 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.814–0.90 (1H, m), 0.87

(3H, t, *J* = 6.8), 1.25–1.38 (7H, m), 1.41–1.54 (4H, m), 1.61–1.76 (5H, m), 1.81–1.94 (5H, m), 2.46–2.55 (1H, m), 3.21–3.29 (1H, m), 6.11 (1H, d, *J* = 5.8), 7.29 (1H, d, *J* = 5.8); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 22.63, 23.8, 26.7, 27.4, 29.1, 29.4, 31.7, 31.9, 32.2, 35.6, 43.6, 52.2, 72.3, 129.1, 149.3, 176.5; MS (EI/double focusing) *m*/*z*: 275 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{18}H_{29}NO$, 275.2249; found, 275.2242; $[\alpha]_D^{24}$ −36.0 (*c* 1.0, $CHCl_3$).

(5*R*,7a*S*,11a*S*)-5-Hexyloctahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3(2*H*)-one (49)

To a stirred solution of **IM3** (30 mg, 0.11 mmol) in EtOAc (3 mL) was added 10% Pd/C (7 mg), and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 24 h. The catalyst was filtered off, and the filtrate was evaporated to give **49** (30 mg, 0.11 mmol, quant.) as a pale yellow oil. IR (neat): 1692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.6), 1.15 (1H, qd, *J* = 12.2, 3.6), 1.27–1.70 (20H, m), 1.75 (2H, tdd, *J* = 13.0, 9.2, 1.6), 1.87 (1H, dd, *J* = 12.6, 8.0), 2.10 (1H, dd, *J* = 16.2, 9.0), 2.44 (1H, ddd, *J* = 16.4, 12.8, 8.4), 2.50 (1H, dd, *J* = 13.6, 5.2), 3.16 (1H, quint-like, *J* = 8.0); ^{13}C- NMR (100 MHz, $CDCl_3$): δ 14.1, 22.1, 22.6, 23.5, 24.4, 26.1, 27.2, 27.8, 29.1, 30.4, 31.6, 31.8, 31.9, 33.2, 42.5, 51.6, 66.1, 176.3; MS (EI/double focusing) *m*/*z*: 277 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{18}H_{31}NO$, 277.2406; found, 277.2411; $[\alpha]_D^{25}$ −57.1 (*c* 1.0, $CHCl_3$).

(5*R*,7a*S*,11a*R*)-5-Butyloctahydrooxazolo[4,3-*j*]quinolin-3(1*H*)-one (37)

To a stirred solution of $(COCl)_2$ (0.14 mL, 1.68 mmol) in CH_2Cl_2 (7 mL) was added DMSO (0.24 mL, 3.36 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 15 min. To the mixture was added a solution of **34** (125 mg, 0.56 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. Triethylamine (0.71 mL, 5.04 mmol) was added at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step. To a stirred suspension of propylPPh_3Br (863 mg, 2.24 mmol) in THF (7 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 1.05 mL, 1.68 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 30 min. To the suspension was added a solution of the above oil in THF (2 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 15 h. The reaction was quenched with sat. NH_4Cl (aq) (10 mL), and the aqueous mixture was extracted with CH_2Cl_2 (7 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (15 g, *n*-hexane/acetone = 10:1) to give (5*S*,7a*R*,11a*R*)-5-(but-1-en-1-yl)-5,6,7,7a,8,11-hexahydrooxazolo[4,3-*j*]quinolin-3(1*H*)-one (IM4) (104 mg, 0.42 mmol, 75%) as a mixture of E- and Z-isomers. To a stirred solution of IM4 (125 mg, 0.51 mmol) in EtOAc (5 mL) was added 10% Pd/C (30 mg), and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 24 h. The catalyst was filtered off, and the filtrate was evaporated to give **37** (127 mg, 0.51 mmol, quant.) as a pale yellow oil. IR (neat): 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 7.0), 0.93 (1H, qd, *J* = 12.8, 4.0), 1.19–1.71 (16H, m), 1.75–1.79 (1H, m), 2.24–2.33 (1H, m), 3.12 (1H, tt, *J* = 10.2, 6.2), 4.01 (1H, d, *J*

= 8.8), 4.04 (1H, d, *J* = 8.8); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.1, 22.3, 22.5, 25.4, 27.4, 28.9, 29.3, 31.0, 35.5, 40.6, 50.9, 62.9, 67.0, 158.7; MS (EI/double focusing) *m*/*z*: 251 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{15}H_{25}NO_2$, 251.1885; found, 251.1884; $[\alpha]_D^{23}$ −37.1 (*c* 1.0, $CHCl_3$).

(2*R*,4a*S*,8a*R*)-(2-Butyldecahydroquinolin-8a-yl)methanol (39)

A solution of 2 M KOH in *i*-PrOH (8 mL) was added to **37** (115 mg, 0.46 mmol), and the resulting mixture was heated at 120 °C in a sealed tube for 12 h. After cooling, the solvent was evaporated and the residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (7 mL × 5). The organic extracts were combined, dried over K_2CO_3, and evaporated to afford a pale yellow oil, which was chromatographed on SiO_2 (12 g, CH_2Cl_2/MeOH = 2:1) to give **39** (103 mg, 0.46 mmol, quant.). IR (neat): 3699, 3292 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, *J* = 6.6), 0.94–1.05 (2H, m), 1.18–1.49 (12H, m), 1.51–1.58 (1H, m), 1.62–1.73 (3H, m), 1.86 (1H, br d, *J* = 12.0), 3.02–3.08 (1H, m), 3.28 (1H, d, *J* = 10.4), 3.59 (1H, d, *J* = 10.4); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.2, 22.7, 23.4, 25.9, 27.4, 28.4, 28.7, 35.9, 36.4, 40.8, 50.1, 56.1, 59.0; MS (EI/double focusing) *m*/*z*: 225 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{14}H_{27}NO$, 225.2093; found, 225.2089; $[\alpha]_D^{24}$ +43.8 (*c* 1.0, $CHCl_3$).

(2*R*,4a*S*,8a*R*)-2-Butyldecahydroquinoline-8a-carbaldehyde (46)

To a mixture of **39** (85 mg, 0.38 mmol), DMAP (5 mg, 38 μmol), 2,2-bipyridyl (3 mg, 19 μmol), and AZADOL (3 mg, 19 μmol) in MeCN (3 mL) was added CuCl (2 mg, 19 μmol) at room temperature. The mixture was stirred at room temperature under air atmosphere for 16 h. The reaction was quenched with sat. $NaHCO_3$ (aq) (3 mL) and 20% $Na_2S_2O_3$ (aq) (3 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 3). The organic extracts were combined, dried over K_2CO_3, and evaporated to afford pale green oil, which was chromatographed on SiO_2 (12 g, *n*-hexane/EtOAc = 5:1) to give **46** (82 mg, 0.37 mol, 98%) as pale yellow oil. IR (neat): 3498, 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, *J* = 7.2), 1.12–1.19 (2H, m), 1.21–1.33 (7H, m), 1.36–1.41 (1H, m), 1.43–1.59 (4H, m), 1.63–1.80 (5H, m), 1.86 (1H, br), 2.92–2.98 (1H, m), 9.65 (1H, d, *J* = 1.6); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.2, 22.6, 23.3, 26.1, 28.5, 29.2, 29.5, 35.5, 36.4, 43.4, 52.3, 61.7, 206.3; MS (EI/double focusing) *m*/*z*: 223 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{14}H_{25}NO$, 223.1936; found, 223.1939; $[\alpha]_D^{25}$ +46.5 (*c* 1.0, $CHCl_3$).

(2*R*,4a*S*,8a*R*)-1-Acetyl-2-butyldecahydroquinoline-8a-carbaldehyde (48)

To a stirred solution of **46** (90 mg, 0.40 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (0.11 mL, 0.81 mmol), DMAP (5 mg, 40 μmol), and acetyl chloride (43 μL, 0.61 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h. The solvent was evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (12 g, *n*-hexane/EtOAc = 7:1) to give **48** (86 mg, 0.32 mmol, 80%) as a pale yellow oil. IR (neat): 1722, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85

(3H, t, J = 7.4 Hz), 1.10–1.49 (11H, m), 1.65–1.78 (6H, m), 1.81–1.93 (1H, m), 2.14 (3H, s), 3.57–3.60 (1H, m), 3.82–3.85 (1H, m), 9.82 (1H, s); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 22.8, 23.0, 25.2, 25.8, 27.4, 29.9, 30.0, 32.7, 34.9, 46.1, 56.5, 68.9, 174.6, 202.8; MS (EI/double focusing) m/z: 265 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{16}H_{27}NO_2$, 265.2042; found, 265.2041; $[\alpha]_D^{25}$ +271.8 (*c* 1.0, $CHCl_3$).

(5*R*,7a*S*,11a*R*)-5-Butyl-5,6,7,7a,8,9,10,11-octahydro-3*H*-pyrrolo[2,1-*j*]quinolin-3-one (IM5)

To a stirred solution of diisopropylamine (74 μL, 0.53 mmol) in THF (1.5 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 0.33 mL, 0.53 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min. To a stirred solution of **48** (78 mg, 0.29 mmol) in THF (4 mL) was added a solution of LDA in THF prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched with 10% HCl (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (15 g, *n*-hexane/acetone = 5:1) to give (5*R*,7a*S*,11a*R*)-5-butyl-1-hydroxyoctahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3(2*H*)-one (**IM4**) (72 mg, 2.71 mmol, 92%) as a mixture of diastereomers. To a stirred solution of IM5 (47 mg, 0.18 mmol) in CH_2Cl_2 (4 mL) were added trimethylamine (32 μL, 0.23 mmol) and methanesulfonyl chloride (16 μL, 0.21 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. DBU (0.132 mL, 0.89 mmol) was added to the reaction mixture at 0 °C, and the reaction mixture was refluxed for 2 h. The solvent was evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (7 g, *n*-hexane/acetone = 5:1) to give **IM5** (35 mg, 0.14 mmol, 80%) as a pale yellow oil. IR (neat): 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78–0.87 (1H, m), 0.89 (3H, t, J = 7.0), 1.24–1.38 (5H, m), 1.39–1.52 (3H, m), 1.60–1.76 (4H, m), 1.80–1.92 (5H, m), 2.45–2.54 (1H, m), 3.19–3.27 (1H, m), 6.09 (1H, d, J = 5.6), 7.27 (1H, d, J = 5.6); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 14.1, 22.5, 22.6, 23.8, 26.7, 29.4, 29.7, 31.8, 31.9, 35.6, 43.6, 52.2, 72.4, 129.1, 149.3, 176.6; MS (EI/double focusing) m/z: 247 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{16}H_{25}NO$, 247.1936; found, 247.1931; $[\alpha]_D^{25}$ −36.9 (*c* 1.0, $CHCl_3$).

(5*R*,7a*S*,11a*S*)-5-Butyloctahydro-1*H*-pyrrolo[2,1-*j*]quinolin-3(2*H*)-one (33)

To a stirred solution of **IM5** (26 mg, 0.11 mmol) in EtOAc (3 mL) was added 10% Pd/C (7 mg), and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 24 h. The catalyst was filtered off, and the filtrate was evaporated to give **50** (26 mg, 0.11 mmol, quant.) as a pale yellow oil. IR (neat): 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.0 Hz), 1.15 (1H, qd, J = 12.6, 3.6 Hz), 1.22–1.38 (7H, m), 1.39–1.54 (4H, m), 1.55–1.79 (9H, m), 1.87 (1H, m), 2.10 (1H, dd, J = 16.2, 8.2 Hz), 2.40–2.52 (2H, m), 3.15 (1H, quint-like, J = 8.1 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 14.11, 22.1, 22.5, 23.5, 24.4, 26.1, 27.2, 30.0, 30.4, 31.6, 31.6, 33.2, 42.5, 51.6, 66.2, 176.3; MS (EI/double focusing) m/z: 249 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{16}H_{27}NO$, 249.2093; found, 249.2094; $[\alpha]_D^{25}$ −53.5 (*c* 1.0, $CHCl_3$).

(5*R*,7a*R*,11a*R*)-5-(Hex-1-en-1-yl)-5,6,7,7a,8,11-hexahydrooxazolo[4,3-*j*]quinolin-3(1*H*)-one (55)

To a stirred solution of $(COCl)_2$ (46 μL, 0.54 mmol) in CH_2Cl_2 (4 mL) was added DMSO (76 μL, 1.07 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 15 min. To the mixture was added a solution of **19** (40 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. Triethylamine (0.23 mL, 1.61 mmol) was added at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (3 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step. A stirred solution of above oil in THF (1 mL) was bubbled by argon gas at room temperature for 15 min. To the above solution was added DBU (0.11 mL, 0.716 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched with 10% HCl (aq) (1 mL), and the aqueous mixture was extracted with CH_2Cl_2 (2 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale yellow oil, which was used directly in the next step. To a stirred suspension of amylPPh$_3$Br (296 mg, 0.72 mmol) in THF (3 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 0.34 mL, 0.53 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 30 min. To the suspension was added a solution of the above oil in THF (1 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 15 h. The reaction was quenched with sat. NH_4Cl (aq) (3 mL), and the aqueous mixture was extracted with CH_2Cl_2 (4 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (7 g, *n*-hexane/EtOAc = 15:1) to give **56** (28 mg, 87 μmol, 49%) and **55** (4 mg, 14 μmol, 8%) as a mixture of E-and Z-isomers.

(7a*R*,11a*R*)-6,7,7a,8-Tetrahydrooxazolo[4,3-*j*]quinoline-3,5(1*H*,11*H*)-dione (57)

To a stirred solution of $(COCl)_2$ (75 μL, 0.87 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.12 mL, 1.74 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 15 min. To the mixture was added a solution of **34** (65 mg, 0.29 mmol) in CH_2Cl_2 (1 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. Triethylamine (0.29 mL, 2.61 mmol) was added to the reaction mixture at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (3 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step. To a stirred solution of above oil in THF (1 mL) was added DBU (43 μL, 0.29 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched with 10% HCl (aq) (1 mL), and the aqueous mixture was extracted with CH_2Cl_2 (2 mL × 3). The organic extracts were combined, dried over Na_2SO_4, and evaporated to afford pale yellow oil, which was chromatographed on SiO_2 (7 g, *n*-hexane/acetone = 5:1) to give aldehydes (30 mg, 0.14 mmol, 47%) as a mixture of diastereomers and **57** (31 mg, 0.15 mmol, 52%). mp: 102–103 °C; IR (KBr): 1798, 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (1H, qd, *J* = 13.6, 3.6), 1.74–1.80 (1H, m), 1.86–1.96 (1H, m), 2.15–2.35 (1H, m), 2.37–2.51 (1H, m), 2.75 (1H, ddd, *J* = 18.0, 3.6, 2.4), 4.04 (1H, dd, *J* = 8.2, 2.4), 4.16

(1H, d, *J* = 8.2), 5.83–5.64 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 22.4, 28.9, 35.6, 38.0, 38.3, 62.5, 69.5, 124.8, 127.9, 152.3, 169.3; MS (EI/double focusing) *m*/*z*: 209 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{11}H_{15}NO_3$, 209.1052; found, 209.1054; $[\alpha]_D^{25}$ −129.8 (*c* 1.0, $CHCl_3$).

(5*S*,7a*S*,11a*R*)-5-Hexyloctahydrooxazolo[4,3-*j*]quinolin-3(1*H*)-one (IM6)

To a stirred solution of **34** (45 mg, 0.16 mmol) in EtOAc (2 mL) was added 10% Pd/C (10 mg), and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 24 h. The catalyst was filtered off, and the filtrate was evaporated to give **IM6** (46 mg, 0.16 mmol, quant.) as a pale yellow oil. IR (neat): 1751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, s, *J* = 7.0), 0.93 (1H, qd, *J* = 13.2, 4.0), 1.27–1.81 (20H, m), 1.94 (1H, d, *J* = 8.0), 2.09–2.18 (1H, m), 3.90–3.98 (1H, m), 3.96 (1H, d, *J* = 7.8), 4.19 (1H, d, *J* = 7.8); ^{13}C- NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 22.9, 25.6, 26.6, 28.5, 29.0, 31.7, 37.40, 39.3, 41.1, 50.1, 61.5, 68.0, 160.2; MS (EI/double focusing) *m*/*z*: 279 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{17}H_{29}NO_2$, 279.2198; found, 279.2197; $[\alpha]_D^{23}$ −23.8 (*c* 1.0, $CHCl_3$).

(2*S*,4a*S*,8a*R*)-2-Hexyl(decahydroquinolin-8a-yl)methanol (41)

A solution of 2 M KOH in *i*-PrOH (5 mL) was added to **IM6** (63 mg, 0.23 mmol), and the resulting mixture was heated at 120 °C in a sealed tube for 12 h. After cooling, the solvent was evaporated, and the residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (4 mL × 5). The organic extracts were combined, dried over K_2CO_3, and evaporated to afford a pale yellow oil, which was chromatographed on SiO_2 (8 g, CH_2Cl_2/MeOH = 2:1) to give **41** (55 mg, 0.22 mmol, 96%) as a white solid. mp: 75–77 °C; IR (KBr): 3150, 1456 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, t, *J* = 6.8), 0.95–1.05 (2H, m), 1.25–1.76 (20H, m), 1.85 (1H, br d, *J* = 13.0), 2.62 (1H, br d, *J* = 7.5), 3.53 (1H, d, *J* = 10.5), 3.65 (1H, d, *J* = 10.5); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 22.4, 22.6, 26.1, 26.4, 27.2, 28.5, 29.4, 31.8, 34.3, 35.4, 37.7, 46.2, 49.8, 55.6, 55.8; MS (EI/double focusing) *m*/*z*: 253 $[M]^+$; HRMS (EI/double focusing): $[M]^+$ calcd for $C_{16}H_{31}NO$, 253.2406; found, 253.2409; $[\alpha]_D^{23}$ +4.0 (*c* 1.0, $CHCl_3$).

X-ray crystallographic analyses of 57

Data Collection

A colorless block crystal of $C_{11}H_{13}NO_3$ having approximate dimensions of 0.240 x 0.040 x 0.040 mm was mounted in a loop. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using multi-layer mirror monochromated Cu-Kα radiation. The crystal-to-detector distance was 127.00 mm.Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

a = 7.35354(15) Å

b = 5.87211(11) Å β = 95.496(7)°

c = 11.1184(2) Å

$$V = 477.895(17)\ \text{Å}^3$$

For Z = 2 and F.W. = 207.23, the calculated density is 1.440 g/cm^3. Based on the reflection conditions of:

0k0: k = 2n

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P2_1$$

The data were collected at a temperature of -100 $\pm$ 1^{o}C to a maximum 2θ value of 136.4^o. A total of 90 oscillation images were collected. A sweep of data was done using ω scans from 80.0 to 260.0^o in 10.00^o step, at χ=54.0^o and ϕ = 0.0^o. The exposure rate was 20.0 [sec./^{o}]. A second sweep was performed using ω scans from 80.0 to 260.0^o in 10.00^o step, at χ=54.0^o and ϕ = 90.0^o. The exposure rate was 20.0 [sec./^{o}]. Another sweep was performed using ω scans from 80.0 to 260.0^o in 10.00^o step, at χ=54.0^o and ϕ = 180.0^o. The exposure rate was 20.0 [sec./^{o}]. Another sweep was performed using ω scans from 80.0 to 260.0^o in 10.00^o step, at χ=54.0^o and ϕ = 270.0^o. The exposure rate was 20.0 [sec./^{o}]. Another sweep was performed using ω scans from 80.0 to 260.0^o in 10.00^o step, at χ=0.0^o and ϕ = 0.0^o. The exposure rate was 20.0 [sec./^{o}]. The crystal-to-detector distance was 127.00 mm. Readout was performed in the 0.100 mm pixel mode.

Data Reduction

Of the 5415 reflections were collected, where 1695 were unique (R_{int} = 0.0331); equivalent reflections were merged. The linear absorption coefficient, μ, for Cu-Kα radiation is 8.736 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.745 to 0.966. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 1695 observed reflections and 136 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma\ ||Fo| - |Fc|| / \Sigma\ |Fo| = 0.0346$$

$$wR2 = [\ \Sigma\ (\ w\ (Fo^2 - Fc^2)^2\ )/\ \Sigma\ w(Fo^2)^2]^{1/2} = 0.0837$$

The goodness of fit was 1.09. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.13 and -0.21 e$^-$/Å^3, respectively. The final Flack parameter was 0.16(14), indicating that the present absolute structure is correct.

Neutral atom scattering factors were taken from International Tables for Crystallography (IT), Vol. C, Table 6.1.1.4 . Anomalous dispersion effects were included in Fcalc; the values for Δf' and Δf'' were those of Creagh and McAuley. The values for the mass attenuation coefficients are those of Creagh and Hubbell. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL Version 2018/3.

A. Crystal Data

Empirical Formula	$C_{11}H_{13}NO_3$
Formula Weight	207.23
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.240 X 0.040 X 0.040 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 7.35354(15) Å b = 5.87211(11) Å c = 11.1184(2) Å β = 95.496(7) ° V = 477.895(17) Å^3
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.440 g/cm^3
F_{000}	220.00
μ(CuKα)	8.736 cm^{-1}

B. Intensity Measurements

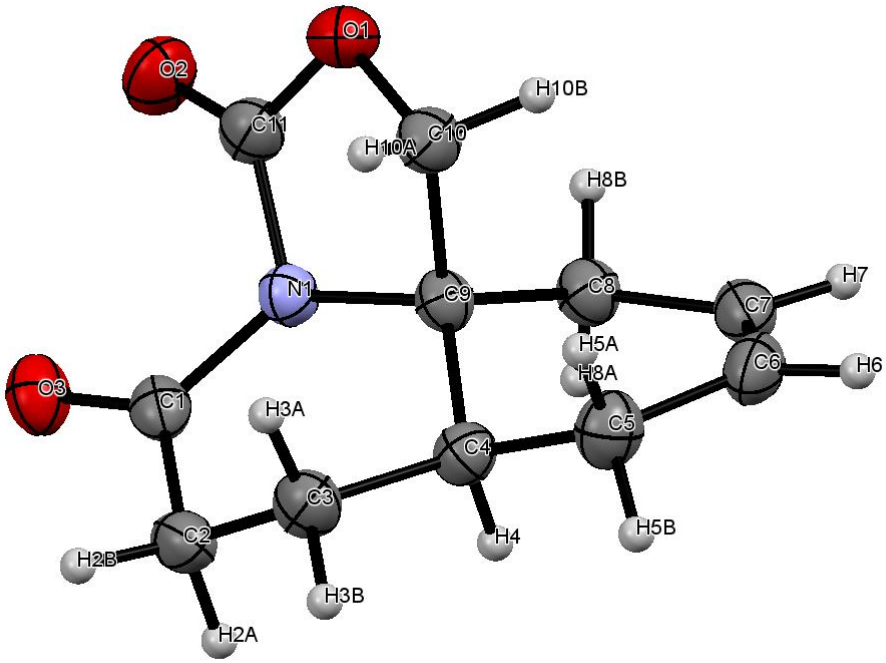
Diffractometer	R-AXIS RAPID
Radiation	CuKα (λ = 1.54187 Å) multi-layer mirror monochromated
Voltage, Current	40kV, 30mA
Temperature	-100.0°C
Detector Aperture	460.0 x 256.0 mm
Data Images	90 exposures
ω oscillation Range (χ=54.0, ϕ=0.0)	80.0 - 260.0°
Exposure Rate	20.0 sec./°
ωoscillation Range (χ=54.0, ϕ=90.0)	80.0 - 260.0°

Exposure Rate	20.0 sec./^{o}
ωoscillation Range (χ=54.0, ϕ=180.0)	80.0 - 260.0^{o}
Exposure Rate	20.0 sec./^{o}
ωoscillation Range (χ=54.0, ϕ=270.0)	80.0 - 260.0^{o}
Exposure Rate	20.0 sec./^{o}
ωoscillation Range (χ=0.0, ϕ=0.0)	80.0 - 260.0^{o}
Exposure Rate	20.0 sec./^{o}
Detector Position	127.00 mm
Pixel Size	0.100 mm
$2\theta_{max}$	136.4^{o}
No. of Reflections Measured	Total: 5415 Unique: 1695 (R_{int} = 0.0331) Parsons quotients (Flack x parameter): 634
Corrections	Lorentz-polarization Absorption (trans. factors: 0.745 - 0.966)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXT Version 2018/2)
Refinement	Full-matrix least-squares on F^2
Function Minimized	Σ w (Fo^2 - Fc^2)^2
Least Squares Weights	$w = 1/ [\sigma^2(Fo^2) + (0.0310 \cdot P)^2 + 0.1025 \cdot P]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	136.4^{o}
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	1695
No. Variables	136
Reflection/Parameter Ratio	12.46
Residuals: R1 (I>2.00□(I))	0.0346
Residuals: R (All reflections)	0.0386
Residuals: wR2 (All reflections)	0.0837
Goodness of Fit Indicator	1.087
Flack parameter (Parsons' quotients = 634)	0.16(14)

Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.13 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.21 $e^-/Å^3$



X-ray thermal ellipsoid plot of **36** (50% probability)

MM calculations of 31´ and 31

The three-dimensional (3D) structures of **31´** and **31** were first constructed by Schrödinger maestro and Ligprep program (Schrödinger Co.). Following the 3D structure constructions, the conformational analyses of **31´** and **31** were carried out by Confgen program. Energy minimizations were then performed for all of the generated conformers by Prime program. The lowest energy structures of **31´**and **31** obtained by energy minimization were defined as the most stable structures of them. OPLS3 force field was applied for all MM calculations.

The calculated total energies of the most stable structures of compound **31´**and **31** are 16.5 and 8.4 kcal/mol, respectively. These Cartesian coordinates are placed below.

Cartesian coordinate of the most stable structure of compound 31´ [Å]

N	-0.06710	-1.03010	0.10690
C	-0.47270	-1.89920	-0.99980

C	-0.00580	-1.31240	-2.34850
C	-0.34700	0.17680	-2.48840
C	0.21420	0.98400	-1.29000
C	-0.32870	0.45490	0.10450
C	1.76990	1.07640	-1.41130
C	2.38410	2.37800	-0.92340
C	3.36220	2.46630	-0.00780
C	-1.88660	0.60440	0.18510
C	-2.40160	2.03480	0.15350
C	-3.15160	2.55720	-0.83000
H	-0.16410	2.00010	-1.42010
C	0.40230	1.21850	1.27190
O	-0.17240	1.02890	2.55450
C	0.19580	-3.19960	-0.61280
O	0.21440	-3.10440	0.79150
C	0.24050	-1.82580	1.22090
H	-1.55810	-2.01690	-0.98600
O	0.45830	-1.54050	2.39600
H	1.07310	-1.43820	-2.45580
H	-0.45210	-1.87510	-3.16980
H	0.04030	0.56420	-3.43240
H	-1.42730	0.30380	-2.56100
H	2.24350	0.22170	-0.92480
H	2.06840	1.01010	-2.45860
H	1.99180	3.28570	-1.36300
H	3.78590	1.58620	0.45540
H	3.75720	3.42560	0.29590
H	-2.39200	0.03510	-0.59350
H	-2.24170	0.16880	1.12070
H	-2.13350	2.64890	1.00440
H	-3.44150	1.97250	-1.69110
H	-3.48900	3.58300	-0.78660
H	1.44570	0.90850	1.33790
H	0.41220	2.29090	1.07220
H	-0.01460	0.09730	2.79350
H	-0.35420	-4.07490	-0.96030
H	1.21820	-3.26450	-0.99000

Cartesian coordinate of the most stable structure of compound 31 [Å]

N	0.24100	0.52950	0.82400
C	1.23120	-0.52530	1.18800
C	1.36270	-1.44800	-0.05170
C	0.00080	-1.92250	-0.60320
C	-0.96920	-0.73290	-0.86280
C	-1.12060	0.14580	0.43990
C	-0.59790	-0.00870	-2.19030
C	-0.71920	-0.86350	-3.44060
C	0.30910	-1.18900	-4.24030
H	-1.95230	-1.16500	-1.05390
H	0.75970	-1.09790	1.98610
C	2.59510	-0.04450	1.76150
O	3.41110	0.60370	0.80570
C	-1.85920	-0.57990	1.60510
C	-3.33890	-0.83570	1.36500
C	-4.33430	-0.25110	2.05060
C	-1.73020	1.53160	0.22860
O	-0.62030	2.36280	-0.02340
C	0.51990	1.85840	0.47890
O	1.56100	2.50980	0.52320
H	1.90480	-0.92000	-0.83870
H	1.98120	-2.31170	0.19560
H	0.15420	-2.51260	-1.50770
H	-0.44870	-2.61820	0.10530
H	-1.25260	0.84780	-2.34840
H	0.40990	0.40460	-2.12420
H	-1.71190	-1.21810	-3.68340
H	1.31450	-0.85160	-4.02950
H	0.16300	-1.79920	-5.12010
H	2.43280	0.62350	2.60940
H	3.14690	-0.89960	2.15480
H	2.96370	1.43730	0.57240
H	-1.39980	-1.54230	1.82530
H	-1.74770	0.00210	2.52270
H	-3.58370	-1.54760	0.58770
H	-4.13760	0.46260	2.83840
H	-5.36890	-0.47850	1.83460

H	-2.45500	1.55600	-0.58520
H	-2.23420	1.89360	1.12650

第三章

General procedure for the synthesis of methyl urethanes (65-66)

To a stirred solution of **10** (500 mg, 1.43 mmol) in MeOH (5 mL) was added K_2CO_3 (297 mg, 2.15 mmol) at -50 °C, and the resulting mixture was stirred at -50 °C for 20 min. The reaction was quenched with sat. NH_4Cl (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL x 5). The organic extracts were combined, dried over Na_2SO_4, and evaporated to give pale yellow oil, which was used directly in the next step. To a stirred solution of the above primary alcohol in EtOAc (5 mL) was added 20% $Pd(OH)_2/C$ (5 mg), and the resulting mixture was hydrogenated at 1 atm for 16 h. The catalyst was removed through a celite pad and washed with MeOH (3 mL x 3). The filtrate and washings were combined and evaporated to give pale yellow oil, which was used directly in the next step. To a stirred solution of the above amino alcohol in THF and (2.5 mL) and sat. $NaHCO_3$ (aq.) (2.5 mL) was added $ClCO_2Me$ (0.12 mL, 1.50 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 16 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of DMSO (0.30 mL, 4.29 mmol) in CH_2Cl_2 (5 mL) was added $(COCl)_2$ (0.18 mL, 2.15 mmol) at -78 °C for 15 min, and then a solution of the above alcohol in CH_2Cl_2 (3 mL) was added to the reaction mixture at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, and then Et_3N (0.90 mL, 6.44 mmol) was added to the reaction mixture at -78 °C. The resulting mixture was gradually warmed to 0 °C. The reaction was quenched with H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The organic layer and extracts were combined, washed with brine, 10% HCl (aq.), and brine, successively, dried over Na_2SO_4, and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the corresponding Wittig reagent (2.86 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 1.61 mL, 2.57 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min. To the solution was added a solution of the above aldehyde in THF (3 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 15 h. The reaction was quenched with sat. NH_4Cl (aq.), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give a yellow paste, which was passed through a thin celite pad and washed with Et_2O (3 mL x 3). The filtrate and washings were combined and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the above olefin in EtOAc (5 mL) was added 10% Pd/C (10 mg), and the resulting mixture was hydrogenated at 1 atm for 30 h. The catalyst was removed through a celite pad and washed with EtOAc (3 mL x 3). The filtrate and washings were combined and evaporated to give a yellow oil, which was chromatographed on SiO_2 (15 g, EtOAc/*n*-hexane = 1/10 – 1/5) to give the corresponding methyl esters **65-66** as a colorless oil.

(*2R*,*6R*)-dimethyl 6-propylpiperidine-1,2-dicarboxylate (65)

Yield: 72% in 6 steps; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* = 7.2), 1.26-1.35 (3H, m), 1.48-1.65 (6H, m), 2.28-2.30 (1H, m), 3.70 (3H, s), 3.72 (3H, s), 4.20 (1H, br), 4.89 (1H, br); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.01, 15.71, 20.13, 25.84, 27.71, 34.29, 51.05, 52.04, 52.78, 53.51, 157.03, 173.21; IR (neat): 1210, 1699, 1733 cm^{-1}; MS (EI): *m/z* 243; HRMS (EI): Calcd for $C_{12}H_{21}NO_4$ 243.1470, Found 243.1474; $[\alpha]_D^{23}$ +77.1 (*c* 1.00, $CHCl_3$).

(*2R*,*6R)*-dimethyl 6-heptylpiperidine-1,2-dicarboxylate (66)

Yield: 58% in 6 steps; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.9 Hz), 1.24-1.36 (10H, m), 1.47-1.69 (7H, m), 2.27-2.29 (1H, m), 3.69 (3H, s), 3.71 (3H, s), 4.16 (1H, br), 4.88 (1H, br); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.13, 15.72, 22.71, 25.87, 27.05, 29.39, 29.66, 29.73, 31.95, 51.34, 52.05, 52.13, 52.81, 53.49, 156.90, 173.24; IR (neat): 1207, 1701, 1734 cm^{-1}; MS (EI); *m/z* 299; HRMS (EI): Calcd for $C_{16}H_{29}NO_4$ 299.2097, Found 299.2098; $[\alpha]_D^{20}$ +65.2 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of thiophenyl ethers (67-68)

To a stirred solution of **65-66** (10.39 mmol) in THF (30 mL) was added a solution of sodium bis(trimethylsilyl)amide (1.9 M in THF, 8.20 mL, 15.59 mmol) at -78 °C, and the reaction mixture was stirred at -78 °C for 30 min. To the reaction mixture was added a solution of diphenyl disulfide (3.40 g, 15.59 mmol) in THF (15 mL), and the resulting mixture was stirred at 0 °C for 30 min. The solvent was evaporated and the residue was chromatographed on SiO_2 (50 g, acetone/*n*-hexane = 1/30 – 1/20) to give the corresponding thiophenyl ethers **67-68** as a yellow oil as a mixture of diastereomers.

(*6R*)-dimethyl 2-(phenylthio)-6-propylpiperidine-1,2-dicarboxylate (67)

Yield: 93%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 & 0.94 (3H, each t, *J* = 7.2 Hz), 1.28-1.79 (8H, m), 1.90-1.98 (1H, m), 2.26-2.38 (1H, m), 3.49 & 3.62 (3H, each s), 3.73 & 3.74 (3H, each s), 4.06-4.20 (1H, m), 7.29-7.35 (3H, m), 7.73-7.78 (2H, m).

(*6R*)-dimethyl 6-heptyl-2-(phenylthio)piperidine-1,2-dicarboxylate (68)

Yield: 87%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87-0.92 (3H, m), 1.22-1.37 (10H, m), 1.50-1.79 (6H, m), 1.91-1.98 (1H, m), 2.24-2.37 (1H, m), 3.39 & 3.49 (3H, each s), 3.74 & 3.76 (3H, each s), 4.07-4.14 (1H, m), 7.29-7.33 (3H, m), 7.70-7.81 (2H, m).

General procedure for the synthesis of enaminoesters (57 and 64)

To a stirred solution of **57** or **64** (3.61 mmol) in CH_2Cl_2 (12 mL) was added 2,6-lutidine (0.84 mL, 9.03 mmol), and then *m*CPBA (70%, 1.50 g, 8.67 mmol) was added to the reaction mixture in four portions in 15 min interval at 0 °C. The resulting mixture was stirred at room temperature for 8 h. The reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$ (aq.) (25 mL), and the aqueous mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (5 mL x 3).

The organic layer and extracts were combined, washed with brine, 10% HCl (aq.), and brine, successively, dried and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, acetone/*n*-hexane = 1/30 – 1/25) to give the corresponding enaminoesters **57**, **64** as pale yellow oil.

(*6R*)-dimethyl 6-propyl-5,6-dihydropyridine-1,2(4H)-dicarboxylate (57)

Yield: quant. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J* = 7.3), 1.17-1.28 (1H, m), 1.37-1.58 (3H, m), 1.69-1.76 (1H, m), 1.79-1.89 (1H, m), 2.15-2.22 (2H, m), 3.70 (3H, s), 3.76 (3H, s), 4.42 (1H, br), 6.06 (1H, t, *J* = 3.6); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.75, 19.10, 19.53, 25.70, 31.62, 50.99, 51.87, 52.85, 122.08, 129.87, 154.63, 165.56; IR (neat): 1231, 1275, 1330, 1442, 1714, 1733 cm^{-1}; MS (EI): *m/z* 241; HRMS (EI): Calcd for $C_{12}H_{19}NO_4$ 241.1314, Found 241.1315; $[\alpha]_D^{19}$ -68.0 (*c* 1.00, $CHCl_3$).

(*6R*)-dimethyl 6-heptyl-5,6-dihydropyridine-1,2(4H)-dicarboxylate (64)

Yield: 95%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.9), 1.21-2.04 (14H, m), 2.12-2.32 (2H, m), 3.71 (3H, s), 3.76 (3H, s), 4.39 (1H, br), 6.06 (1H, t, *J* = 3.6); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.95, 22.51, 25.66, 25.84, 29.23, 29.28, 29.04, 29.46, 31.66, 51.32, 51.89, 52.88, 122.12, 129.92, 154.62, 165.60; IR (neat): 1700, 1717 cm^{-1}; MS (EI): *m/z* 297; HRMS (EI): Calcd for $C_{16}H_{27}NO_4$ 297.1940, Found 297.1939; $[\alpha]_D^{28}$ -62.7 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of Michael adducts (58 and 63)

To a stirred solution of CuI (1.31 g, 6.90 mmol) in Et_2O (15 mL) was added a solution of vinyl lithium, prepared from tetravinyltin (0.61 mL, 3.45 mmol) and MeLi (1.13 M in Et_2O, 12.20 mL, 13.80 mmol) in Et_2O (15 mL) at 0 °C for 30 min, at -78 °C, and the reaction mixture was warmed to -35 °C for 30 min. The reaction mixture was re-cooled to -78 °C, and a solution of **57** or **64** (2.30 mmol) in Et_2O (7 mL) was added to the reaction mixture. The resulting mixture was gradually warmed to 0 °C and stirred at same temperature for 1 h. The reaction was quenched with sat. NH_4Cl (aq.) (30 mL). The aqueous mixture was diluted with CH_2Cl_2 (30 mL), and the resulting mixture was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (20 g, acetone/*n*-hexane = 1/30 – 1/25) to give the Michael adducts **58**, **63**as a colorless oil.

(*2R,3S,6R*)-dimethyl 6-propyl-3-vinylpiperidine-1,2-dicarboxylate (58)

Yield: 99%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* = 7.0), 1.25-1.56 (6H, m), 1.78-1.92 (2H, m), 3.08 (1H, br), 3.71 (3H, s), 3.74 (3H, s), 4.17-4.18 (1H, m), 4.88 (1H, br), 5.09-5.15 (2H, m), 5.81 (1H, ddd, *J* = 17.1, 10.7, 6.4); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.86, 19.88, 21.03, 22.45, 34.59, 36.52, 50.96, 51.99, 52.75, 55.07, 115.16, 139.00, 157.08, 172.86; IR (neat): 1200, 1340, 1363, 1448, 1506, 1558, 1683, 1699, 1734 cm^{-1}; MS (EI): *m/z* 269; HRMS (EI): Calcd for $C_{14}H_{23}NO_4$ 269.1627, Found 269.1631; $[\alpha]_D^{25}$ +53.6 (*c* 1.00, $CHCl_3$).

(*2R*,*3S*,*6R*)-dimethyl 6-heptyl-3-vinylpiperidine-1,2-dicarboxylate (63)

Yield: 97%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.7), 1.25-1.56 (14H, m), 1.77-1.92 (2H, m), 3.08 (1H, br), 3.70 (3H, s), 3.74 (3H, s), 4.14-4.15 (1H, m), 4.87 (1H, br), 5.10 (1H, dd, *J* = 10.6, 1.4), 5.12 (1H, dd, *J* = 17.1, 1.4), 5.85 (1H, ddd, *J* = 17.1, 10.6, 6.4); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.06, 21.09, 22.39, 22,63, 26.37, 29.29, 29.57, 31.84, 32.40, 36.61, 51.30, 52.06, 52.83, 55,15, 115.24, 139.09, 157.15, 172.94; IR (neat): 1701, 1735 cm^{-1}; MS (EI): *m/z* 325; HRMS (EI): Calcd for $C_{18}H_{31}NO_4$ 325.2250, Found 325.2244; $[\alpha]_D^{22}$ +43.2 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of homologated esters (69-70)

To a stirred solution of **58** or **63** (1.59 mmol) in MeOH (6 mL) and H_2O (2 mL) was added $LiOH{\cdot}H_2O$ (266 mg, 6.36 mmol), and the resulting mixture was refluxed for 2 h. After cooling, MeOH was evaporated and the residue was acidified with 10% HCl (aq.) (5 mL). The aqueous mixture was extracted with EtOAc (3 mL x 5). The organic extracts were combined, dried, and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the above oil in THF (10 mL) were added $ClCO_2Et$ (0.18 mL, 1.91 mmol) and Et_3N (0.27 mL, 1.91 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (3 mL), and $Et_3N{\cdot}HCl$ was filtered off. The filtrate was evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the above oil in Et_2O (10 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated to give a yellow oil, which was dissolved in MeOH (10 mL). To the MeOH solution were added $AgCO_2Ph$ (37 mg, 0.16 mmol) and Et_3N (0.45 mL, 3.18 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with Et_2O and the insoluble material was filtered off. The filtrate was evaporated to give a black oil, which was chromatographed on SiO_2 (20 g, EtOAc/*n*-hexane = 1/30 – 1/25) to give the corresponding homologated esters **69**-**70** as a colorless oil.

(*2S*,*3S*,*6R*)-methyl 2-(2-methoxy-2-oxoethyl)-6-propyl-3-vinylpiperidine-1-carboxylate (69)

Yield: 91% in 4 steps; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J* = 7.3), 1.20-1.42 (4H, m), 1.43-1.52 (2H, m), 1.78-1.92 (2H, m), 2.32 (1H, br), 2.54 (1H, dd, *J* = 14.9, 4.8), 2.65 (1H, dd, *J* = 14.9, 10.1), 3.66 (3H, s), 3.68 (3H, s), 4.12 (1H, br), 4.61 (1H, br), 5.06 (1H, dt, *J* = 10.6, 1.4), 5.09 (1H, dt, *J* = 17.2, 1.4), 5.84 (1H, ddd, *J* = 17.2, 10.6, 6.6); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.96, 20.05, 20.32, 22.18, 37.46, 39.73, 39.90, 50.73, 50.92, 51.67, 52.62, 115.07, 140.04, 156.76, 171.64; IR (neat): 1101, 1363, 1443, 1696, 1740 cm^{-1}; MS (EI): *m/z* 283; HRMS (EI): Calcd for $C_{15}H_{25}NO_4$ 283.1784, Found 269.1780; $[\alpha]_D^{19}$ -31.4 (*c* 1.00, $CHCl_3$).

(*2S*,*3S*,*6R*)-methyl 6-heptyl-2-(2-methoxy-2-oxoethyl)-3-vinylpiperidine-1-carboxylate (70)

Yield: 75% in 4 steps; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.9), 1.21-1.91 (16H, m), 2.31 (1H, br), 2.55 (1H, dd, *J* = 14.9, 4.6), 2.66 (1H, dd, *J* = 14.9, 9.7), 3.67 (3H, s), 3.69 (3H, s), 4.11 (1H,

br), 4.62 (1H, br), 5.07 (1H, dt, *J* = 10.6, 1.4), 5.09 (1H, dt, *J* = 17.2, 1.4), 5.85 (1H, ddd, *J* = 17.2, 10.6, 6.6); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.05, 20.03, 22.12, 22,61, 27.18, 29.24, 29.52, 31.79, 35.20, 39.70, 39.90, 50.50, 50.90, 51.65, 52.60, 115.05, 140.04, 156.73, 171.62; IR (neat): 1696, 1700 cm^{-1}; MS (EI): *m/z* 339; HRMS (EI): Calcd for $C_{18}H_{31}NO_4$ 339.2410, Found 339.2405; $[\alpha]_D^{23}$ -27.3 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of Weinreb amides (71-72)

To a stirred solution of **69-70** (2.02 mmol) in MeOH (4.5 mL) and H_2O (1.5 mL) was added $LiOH{\cdot}H_2O$ (338 mg, 8.06 mmol), and the resulting mixture was refluxed for 2 h. After cooling, MeOH was evaporated and the residue was acidified with 10% HCl (aq.) (3 mL). The aqueous mixture was extracted with EtOAc (3 mL x 5). The organic extracts were combined, dried, and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the above oil in CH_2Cl_2 (7 mL) was added 1,1-carbonyldiimidazole (457 mg, 2.82 mmol) at 0 °C, and the reaction mixture was stirred for 30 min. To the reaction mixture were added MeO(Me)NH·HCl (275 mg, 2.82 mmol) and Et_3N (0.40 ml, 2.82 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 16 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (10 g, acetone/*n*-hexane = 1/10 - 1/7) to give the corresponding Weinreb amides **71-72** as a colorless oil.

(*2S*,*3S*,*6R*)-methyl 2-(2-(methoxy(methyl)amino)-2-oxoethyl)-6-propyl-3-vinylpiperidine-1-carboxylate (71)

Yield: 97% in 2 steps; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.91 (3H, t, *J* = 7.3), 1.16-1.43 (4H, m), 1.48 (2H, q, *J* = 6.0), 1.76-1.92 (2H, m), 2.37 (1H, br), 2.53-2.56 (1H, m), 2.80 (1H, m), 3.12 (3H, br), 3.65 (3H, s), 3.67 (3H, s), 4.12 (1H, br), 4.63 (1H, br), 5.04 (1H, dd, *J* = 10.7, 1.4), 5.07 (1H, dd, *J* = 17.2, 1.4), 5.84 (1H, ddd, *J* = 17.2, 10.7, 1.4); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.96, 19.85, 20.26, 22.15, 29.20, 32.12, 37.36, 39.15, 50.20, 50.55, 52.51, 61.22, 114.82, 140.30, 156.75, 172.01; IR (neat): 1100, 1348, 1362, 1444, 1667, 1694, 1698 cm^{-1}; MS (EI): *m/z* 312; HRMS (EI): Calcd for $C_{16}H_{28}N_2O_4$ 312.2049, Found 312.2046; $[\alpha]_D^{23}$ -36.0 (*c* 1.00, $CHCl_3$).

(*2S*,*3S*,*6R*)-methyl 6-heptyl-2-(2-(methoxy(methyl)amino)-2-oxoethyl)-3-vinylpiperidine-1-carboxylate (72)

Yield: 89% in 2 steps; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.9), 1.25-1.71 (14H, m), 1.81-2.00 (2H, m), 2.14-2.60 (2H, m), 2.84 (1H, br), 3.18 (3H, s), 3.69 (3H, s), 3.70 (3H, s), 4.14 (1H, br), 4.67 (1H, br), 5.04-5.12 (2H, m), 5.86 (1H, ddd, *J* = 17.5, 10.7, 6.5); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.07, 19.88, 22.18, 22.62, 27.17, 29.26, 29.56, 31.83, 32.11, 32.17, 35.18, 37.35, 39.16, 50.49, 52.55, 61.25, 114.85, 140.35, 156.79, 172.10; IR (neat): 1670, 1694 cm^{-1}; MS (EI): *m/z* 368; HRMS (EI): Calcd for $C_{20}H_{36}N_2O_4$ 368.2675, Found 368.2672; $[\alpha]_D^{24}$ -25.5 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of methyl ketones (73-74)

To a stirred solution of **71**- **72** (0.60 mmol) in THF (3 mL) was added a solution MeMgBr (0.91 M in THF, 0.97 mL, 0.72 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. NH_4Cl (aq.) (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 3). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (7 g, acetone/*n*-hexane = 1/10 - 1/7) to give the corresponding methyl ketones **73**-**74**as a colorless oil.

(*2S*,*3S*,*6R*)-methyl 2-(2-oxopropyl)-6-propyl-3-vinylpiperidine-1-carboxylate (73)

Yield: 99%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J* = 7.3), 1.19-1.62 (6H, m), 1.79-1.91 (2H, m), 2.18 (3H, s), 2.24 (1H, br), 2.61 (1H, dd, *J* = 12.0, 2.8), 2.74 (1H, dd, *J* = 12.0, 8.4), 3.69 (3H, s), 4.12 (1H, br), 4.62-4.64 (1H, m), 5.07 (1H, dd, *J* = 10.6, 1.5), 5.09 (1H, dd, *J* = 17.2, 1.5), 5.86 (1H, ddd, *J* = 17.2, 10.6, 1.5); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.97, 19.82, 20.29, 22.00, 29.86, 37.30, 39.59, 49.44, 50.00, 50.26, 52.56, 115.08, 140.07, 156.74, 206.60; IR (neat): 1102, 1277, 1361, 1407, 1443, 1640, 1694 cm^{-1}; MS (EI): *m/z* 267; HRMS (EI): Calcd for $C_{15}H_{25}NO_3$ 267.1834, Found 267.1835; $[\alpha]_D^{19}$ -70.0 (*c* 1.00, $CHCl_3$).

(*2S*,*3S*,*6R*)-methyl 6-heptyl-2-(2-oxopropyl)-3-vinylpiperidine-1-carboxylate (74)

Yield: 94%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.9), 1.25-1.59 (14H, m), 1.79-1.89 (2H, m), 2.18 (3H, s), 2.59-2.63 (1H, m), 2.74-2.79 (1H, m), 3.69 (3H, s), 4.10 (1H, br), 4.63 (1H, br), 5.06-5.11 (2H, m), 5.86 (1H, ddd, *J* = 17.2, 10.6, 6.6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.98, 19.71, 21.88, 22.53, 27.05, 29.15, 29.43, 29.77, 31.71, 34.94, 39.48, 49.34, 49.88, 50.40, 52.46, 114.98, 139.99, 156.63, 206.46; IR (neat): 1701, 1735 cm^{-1}; MS (EI): *m/z* 323; HRMS (EI): Calcd for $C_{19}H_{33}NO_3$ 323.2460, Found 323.2461; $[\alpha]_D^{19}$ -55.8 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of ketoaldehydes (75-76)

To a stirred solution of **73-74** (1.38 mmol) in 1,4-dioxane (6 mL) and H_2O (2 mL) was added 2,6-lutidine (0.32 mL, 2.75 mmol), OsO_4 (2% aqueous solution, 1.7 mL, 0.14 mmol) and $NaIO_4$ (1.18 g, 5.51 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$ (aq.) (10 mL), and the aqueous mixture was diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 3). The organic layer and extracts were combined, washed with brine, 10% HCl (aq.), and brine, successively, dried and evaporated to give a yellow oil, which was chromatographed on SiO_2 (10 g, acetone/*n*-hexane = 1/10 – 1/8) to give the corresponding ketoaldehydes **75-76** as a colorless oil.

(*2S*,*3R*,*6R*)-methyl 3-formyl-2-(2-oxopropyl)-6-propylpiperidine-1-carboxylate (75)

Yield: 94%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* = 7.3), 1.16-1.26 (1H, m), 1.26-1.36 (1H, m), 1.38-1.57 (4H, m), 1.74-1.82 (1H, m), 1.93-1.99 (1H, m), 2.17 (3H, s), 2.37 (1H, br), 2.70-2.80 (2H, m), 3.67 (3H, s), 4.06 (1H, br), 5.15 (1H, br), 9.66 (1H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.94,

14.37, 20.22, 23.39, 30.15, 36.61, 45.10, 48.19, 48.90, 49.93, 52.74, 156.29, 202.79, 206.29; IR (neat): 1100, 1328, 1354, 1447, 1684, 1694, 1717, 2873, 2957 cm^{-1}; MS (EI): *m/z* 269; HRMS (EI): Calcd for $C_{14}H_{23}NO_4$ 269.1627, Found 269.1629; $[\alpha]_D^{23}$ -114.8 (*c* 1.00, $CHCl_3$).

(*2S*,*3R*,*6R*)-methyl 3-formyl-6-heptyl-2-(2-oxopropyl)piperidine-1-carboxylate (76)

Yield: 84%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.3), 1.25-1.61 (14H, m), 1.79-1.86 (1H, m), 1.95-2.00 (1H, m), 2.19 (3H, s), 2.39 (1H, br), 2.72-2.81 (2H, m) 3.69 (3H, s), 4.06 (1H, br), 5.17 (1H, br), 9.68 (1H, s). Since the ketoaldehyde **76** was not stable, **76** was used for the next reaction immediately after the structure of **76** was confirmed by 1H-NMR.

General procedure for the synthesis of cis-fused enones (77 and 79)

To a stirred solution of **77**, **79** (1.30 mmol) in benzene (30 mL) was added DBU (0.78 mL, 5.18 mmol) and MS 4Å (50 mg), and the resulting mixture was refluxed for 48 h. After cooling, benzene was evaporated and the residue was acidified with 10% HCl (aq.) (5 mL). The aqueous mixture was extracted with EtOAc (3 mL x 5). The organic extracts were combined, dried, and evaporated to give a brown oil, which was chromatographed on SiO_2 (25 g, EtOAc/*n*-hexane = 1/30 - 1/10) to give the corresponding *cis*-fused enones **77**, **79** as a yellow oil together with *trans*-fused enone **80** as a yellow oil.

(*2R*,*4aR*,*8aS*)-methyl 7-oxo-2-propyl-2,3,4,4a,8,8a-hexahydroquinoline-1(7H)-carboxylate (77)

Yield: 72% from **21a**; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.91 (3H, t, *J* = 7.2), 1.24-1.41 (2H, m), 1.44-1.55 (2H, m), 1.59 (1H, td, *J* = 10.0, 2.4), 1.67 (1H, tdd, *J* = 10.0, 4.8, 2.4), 1.73-1.78 (1H, m), 1.78-1.83 (1H, m), 2.40-2.45 (1H, m), 2.61 (2H, br), 3.70 (3H, s), 4.25 (1H, br), 4.63 (1H, br), 6.13 (1H, d, *J* = 9.7), 6.77 (1H, dd, *J* = 9.7, 5.7); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.88, 19.95, 20.24, 27.09, 36.53, 37.00, 40.30, 48.43, 49.73, 52.60, 128.64, 152.18, 156.04, 198.22; IR (neat): 771, 1089, 1115, 1246, 1275, 1314, 1444, 1685, 2934 cm^{-1}; MS (EI): *m/z* 251; HRMS (EI): Calcd for $C_{14}H_{21}NO_3$ 251.1521, Found 251.1522; $[\alpha]_D^{24}$ +29.9 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*8aS*)-methyl 2-heptyl-7-oxo-2,3,4,4a,8,8a-hexahydroquinoline-1(7H)-carboxylate (79)

Yield: 54% together with **23b** in 14% from **21b**; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8), 1.26-1.83 (16H, m), 2.41-2.46 (1H, m), 2.67 (2H, br), 3.71 (3H, s), 4.22-4.25 (1H, m), 4.65 (1H, br), 6.02 (1H, d, *J* = 10.3), 6.93 (1H, dd, *J* = 10.3, 5.7); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.06, 20.01, 22.59, 26.81, 27.16, 29.19, 29.49, 31.72, 31.78, 34.35, 37.07, 48.49, 50.02, 52.67, 128.73, 152.21, 156.10, 198.31; IR (neat): 1701, 1735 cm^{-1}; MS (EI): *m/z* 307; HRMS (EI): Calcd for $C_{18}H_{29}NO_3$ 307.2147, Found 307.2149; $[\alpha]_D^{23}$ +20.0 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of Michael adducts (80-84)

To a stirred suspension of CuI (765 mg, 4.02 mmol) in Et_2O (12 mL) was added a solution of the

corresponding Grignard reagent (8.04 mmol) at -78 °C, and the reaction mixture was warmed to 0 °C for 30 min. The resulting suspension was re-cooled to -78 °C, and a solution of **22a-b** (0.80 mmol) in Et_2O (3 mL) was added to the reaction mixture at -78 °C, and the resulting mixture was gradually warmed to 0 °C. The reaction was quenched with sat. NH_4Cl (aq) (5 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL x 3), and the organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, EtOAc/*n*-hexane = 1/15 - 1/10) to give the corresponding Michael adducts **24a-e** as pale yellow oil.

(*2R*,*4aR*,*5S*,*8aS*)-methyl 5-ethyl-7-oxo-2-propyloctahydroquinoline-1(2H)-carboxylate (80)

Yield: 73%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.6), 0.88 (3H, t, *J* = 7.6), 1.22-1.59 (8H, m), 1.62-1.91 (5H, m), 2.17 (1H, dd, *J* = 14.6, 4.4), 2.47 (2H, dd, *J* = 14.6, 4.4), 3.65 (3H, s), 4.15 (1H, br), 4.48 (1H, br); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.81, 13.90, 20.49, 20.86, 26.69, 27.46, 29.17, 37.17, 38.78, 41.22, 41.44, 49.30, 50.18, 52.52, 156.03, 209.30; IR (neat): 1697, 1715 cm^{-1}; MS (FAB): *m/z* 282; HRMS (FAB): Calcd for $C_{16}H_{28}NO_3$: 282.2069, Found 282.2070; $[\alpha]_D^{23}$ -8.8 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-methyl 7-oxo-2,5-dipropyloctahydroquinoline-1(2H)-carboxylate (81)

Yield: 93%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (3H, t, *J* = 6.8), 0.89 (3H, t, *J* = 7.2), 1.23-1.85 (15H, m), 2.13-2.17 (1H, dd, *J* = 14.0, 4.0), 2.45 (2H, dd, *J* = 14.0, 5.2), 3.67 (3H, s), 4.12 (1H, br), 4.45 (1H, br); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.80, 13.82, 20.23, 20.42, 20.77, 27.40, 35.98, 37.12, 39.11, 39.31, 41.41, 49.33, 50.12, 52.43, 53.33, 155.98, 209.19; IR (neat): 1313, 1445, 1697, 1712 cm^{-1}; MS (FAB): *m/z* 296; HRMS (FAB): Calcd for $C_{17}H_{30}NO_3$ 296.2226, Found 296.2227; $[\alpha]_D^{23}$ +0.6 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-methyl 2-heptyl-5-methyl-7-oxooctahydroquinoline-1(2H)-carboxylate (82)

Yield: 91%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8), 1.03 (3H, d, *J* = 7.2), 1.19-1.32 (9H, m), 1.49-1.66 (4H, m), 1.71 (2H, ddd, *J* = 12.8, 5.6, 3.0), 1.79-1.91 (2H, m), 2.10 (2H, d, *J* = 12.8), 2.52 (2H, br), 2.54 (1H, br), 3.69 (3H, s), 4.16 (1H, br), 4.58 (1H, br); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.02, 20.16, 20.85, 22.56, 27.36, 29.18, 29.48, 29.53, 31.75, 34.36, 34.93, 40.72, 43.50, 49.10, 50.45, 52.53, 156.09, 209.25; IR (neat): 1682, 1694 cm^{-1}; MS (EI): *m/z* 323; HRMS (EI): Calcd for $C_{19}H_{33}NO_3$ 323.4702, Found 323.2461; $[\alpha]_D^{26}$ -8.0 (*c* 1.00, $CHCl_3$).

(2R,4aR,5S,8aS)-methyl 5-ethyl-2-heptyl-7-oxooctahydroquinoline-1(2H)-carboxylate (83)

Yield: 75%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, t, *J* = 6.6), 0.88 (3H, t, *J* = 7.6), 1.20-1.40 (12H, m), 1.40-1.57 (3H, m), 1.63-1.90 (5H, m), 2.16 (1H, dd, *J* = 14.4, 4.0), 2.44-2.49 (3H, m), 3.64 (3H, s), 4.12 (1H, br), 4.46 (1H, br); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.77, 13.98, 20.84, 22.51, 26.67, 27.33, 29.14, 29.42,31.69, 34.91, 38.78, 40.02, 41.19, 41.40, 49.43, 50.38, 52.46, 53.35, 156.03, 209.22 ; IR (neat): 1312, 1444, 1697 cm^{-1}; MS (EI): m/z 337; HRMS (EI): Calcd for $C_{20}H_{35}NO_3$ 337.2617, Found 337.2618 ; $[\alpha]_D^{19}$ -3.4 (c 1.00, $CHCl_3$).

(2R,4aR,5S,8aS)-methyl 2-heptyl-7-oxo-5-propyloctahydroquinoline-1(2H)-carboxylate (84)

Yield: 72%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.84 (3H, t, *J* = 6.0), 0.85 (3H, t, *J* = 5.8), 1.22-1.87 (23H, m), 2.13 (1H, dd, *J* = 14.4, 4.0), 2.44-2.49 (2H, m), 3.65 (3H, s), 4.09-4.12 (1H, m), 4.47 (1H, br); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 13.84, 13.99, 20.28, 20.81, 22.50, 27.34, 29.15, 29.15, 29.38, 31.57, 31.71, 34.93, 36.04, 39.15, 39.35, 40.33, 41.46, 49.39, 50.40, 52.49, 156.04, 209.27; IR (neat): 1445, 1699, 1714 cm^{-1}; MS (EI): m/z 351; HRMS (EI): Calcd for $C_{21}H_{37}NO_3$ 351.2773, Found 351.2774; $[\alpha]_D^{20}$ +2.4 (c 1.00, $CHCl_3$).

General procedure for the synthesis of the deoxygenated compounds 85-89

To a stirred solution of **80-84** (0.15 mmol) in CH_2Cl_2 (2 mL) and MeOH (0.2 mL) was added $NaBH_4$ (11 mg, 0.30 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (2 mL x 5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step. To a stirred solution of the above alcohol in 1,2-dichloroethane (5 mL) was added 1,1-thiocarbonyldiimidazole (107 mg, 0.60 mmol) at room temperature. The resulting mixture was refluxed for 10 h. After cooling, the solvent was evaporated to give yellow paste, which was used directly in the next step. To a stirred solution of the above thiocarbonylimidazolate in toluene (10 mL) was added *n*-Bu_3SnH (0.16 mL, 0.60 mmol) at room temperature, and then the resulting mixture was refluxed for 8 h. The solvent was evaporated and the residue was diluted with MeCN. The MeCN layer was washed with hexane and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, CH_2Cl_2/*n*-hexane = 1/5 - 1/1) to give the corresponding deoxygenated compounds **85-89** as a colorless oil.

***(2R,4aR,5S,8aS)*-methyl 5-ethyl-2-propyloctahydroquinoline-1(2H)-carboxylate (85)**

Yield: 68% in 3 steps; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 7.0), 0.89 (3H, t, *J* = 7.4), 1.16-1.81 (17H, m), 1.86 (1H, qd, *J* = 13.2, 3.2), 3.66 (1H, s), 4.06-4.12 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.55, 14.01, 20.48, 20.56, 21.24, 24.29, 25.24, 28.08, 28.51, 37.67, 40.32, 42.16, 50.04, 50.34, 52.18, 156.58; IR (neat): 1332, 1443, 1697 cm^{-1}; MS (FAB): m/z 268; HRMS (FAB): Calcd for $C_{16}H_{30}NO_2$ 268.2277, Found 268.2279; $[\alpha]_D^{20}$ -26.4 (c 1.00, $CHCl_3$).

***(2R,4aR,5S,8aS)*-methyl 2,5-dipropyloctahydroquinoline-1(2H)-carboxylate (86)**

Yield: 78% in 3 steps; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8), 0.90 (3H, t, *J* = 7.2), 1.18-1.69 (19H, m), 1.86 (1H, qd, *J* = 13.6, 3.6), 3.66 (3H, s), 4.06-4.20 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.04, 14.19, 20.57, 21.25, 21.25, 24.73, 28.15, 34.90, 37.71, 39.90, 40.65, 50.10, 50.37, 52.22, 156.61; IR (neat): 1443, 1694 cm^{-1}; MS (FAB): *m/z* 282; HRMS (FAB): Calcd for $C_{17}H_{32}NO_2$ 282.2433, Found 282.2429; $[\alpha]_D^{25}$ -25.4 (*c* 1.00, $CHCl_3$).

***(2R,4aR,5S,8aS)*-methyl 2-heptyl-5-methyloctahydroquinoline-1(2H)-carboxylate (87)**

Yield: 65% in 3 steps; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.9), 1.06 (2H, d, *J* = 7.5), 1.21-1.87 (24H, m), 3.67 (3H, s), 4.04 (1H, br), 4.17-4.22 (1H, m); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 12.25, 14.09, 19.30, 20.30, 21.25, 22.64, 26.71, 27.48, 28.04, 29.28, 29.61, 31.83, 34.50, 35.42, 42.08, 49.70, 50.60, 52.24, 156.65; IR (neat): 1699 cm^{-1}; MS (EI): *m/z* 309; HRMS (EI): Calcd for $C_{19}H_{35}NO_2$: 309.2668, Found 309.2665; $[\alpha]_D^{19}$ -9.9 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-methyl 5-ethyl-2-heptyloctahydroquinoline-1(2H)-carboxylate (88)

Yield: 57% in 3 steps; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.4), 0.87 (3H, t, *J* = 6.4), 1.18-1.78 (25H, m), 1.87 (1H, qd, *J* = 11.6, 5.5), 3.66 (3H, s), 4.04-4.32 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.59, 14.02, 20.52, 21.28, 22.62, 24.34, 25.27, 28.13, 28.88, 29.27, 29.57, 31.83, 35.42, 3867, 40.36, 42.20, 50.07, 50.59, 52.22, 156.61; IR (neat): 1312, 1443, 1697 cm^{-1}; MS (EI): *m/z* 323; HRMS (EI): Calcd for $C_{20}H_{37}NO_2$ 323.2824, Found 323.2824; $[\alpha]_D^{19}$ -17.2 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-methyl 2-heptyl-5-propyloctahydroquinoline-1(2H)-carboxylate (89)

Yield: 59% in 3 steps; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.2), 0.89 (3H, t, *J* = 6.2), 1.18-1.49 (20H, m), 1.53-1.74 (7H, m), 1.86 (1H, qd, *J* = 13.2, 2.8), 3.67 (3H, s), 4.04 (1H, s), 4.17-4.27 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.08, 14.21, 20.59, 21.11, 21.26, 22.63, 22.95, 28.89, 29.28, 29.58, 30.32, 31.83, 34.91, 35.44, 38.69, 39.91, 40.67, 50.12, 50.63, 52.24, 156.63; IR (neat): 1443, 1697 cm^{-1}; MS (EI): *m/z* 337; HRMS (EI): Calcd for $C_{21}H_{39}NO_2$ 337.2981, Found 337.2981; $[\alpha]_D^{19}$-6.0 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of cis-decahydroquinoline poison-frog alkaloids cis-209J, ent-cis-223F, cis-251A, cis-209J-1, and cis-223F-1

To a stirred solution of **85-89** (0.17 mmol) in $CHCl_3$ (3 mL) was added NaI (197 mg, 1.32 mmol) and TMSCl (0.10 mL, 0.83 mmol), and the resulting mixture was heated to 50 °C for 24 h. After cooling, the reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$ (aq.) (3 mL), and aqueous mixture was extracted with CH_2Cl_2 (2 mL x 10). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (3 g, MeOH/CH_2Cl_2 = 1/30 - 1/20) to give the corresponding *cis*-decahydroquinoline poison-frog alkaloids as pale yellow oil.

(*2R*,*4aR*,*5S*,*8aS*)-5-ethyl-2-propyldecahydroquinoline (*cis*-209J)

Yield: 72%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.82 (3H, t, *J* = 7.4), 0.89 (3H, t, *J* = 7.0), 0.98-1.14 (2H, m), 1.22-1.77 (16H, m), 1.96 (1H, ddd, *J* = 15.2, 4.8, 2.0), 2.52-2.56 (1H, m), 2.87 (1H, d, *J* = 2.4); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.28, 14.28, 19.14, 21.16, 25.35, 26.73, 27.30, 31.33, 32.98, 33.22, 39.55, 39.75, 56.25, 57.81; IR (neat): 1456, 3666 cm^{-1}; MS (FAB): *m/z* 210; HRMS (FAB): Calcd for $C_{14}H_{28}N$ 210.2222, Found 210.2223; $[\alpha]_D^{18}$ +6.5 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-2,5-dipropyldecahydroquinoline (*ent-cis*-223F)

Yield: 70%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.8 Hz), 0.90 (3H, t, *J* = 7.6 Hz), 0.96-1.64 (16H, m), 1.51-1.61 (2H, m), 1.72-1.79 (2H, m), 1.95-2.00 (1H, m), 2.51-2.55 (1H, m), 2.86 (1H, d, *J* = 3.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.28, 14.64, 19.15, 19.26, 21.18, 26.83, 27.41, 31.65, 32.11, 33.29, 35.58, 39.65, 40.42, 56.25, 57.80; IR (neat): 1457, 3628 cm^{-1}; MS (FAB): *m/z* 224; HRMS (FAB): Calcd for $C_{15}H_{30}N$ 224.2378, Found 224.2381; $[\alpha]_D^{25}$ +9.7 (*c* 0.45, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-2-heptyl-5-methyldecahydroquinoline (*cis*-251A)

Yield: 62%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, d, *J* = 6.0), 0.87 (3H, t, *J* = 6.4), 0.91-0.95 (1H, m), 1.04-1.16 (1H, m), 1.26-1.42 (15H, m), 1.48-1.69 (5H, m), 1.80-1.90 (1H, m), 1.94 (1H, dt, *J* = 11.2, 2.9), 2.47-2.53 (1H, m), 2.85 (1H, d, *J* = 2.8); ^{13}C-NMR (100 MHz $CDCl_3$) δ: 14.09, 19.90, 21.22, 22.66, 26.02, 27.00, 27.26, 27.35, 29.30, 29.84, 31.83, 33.30, 35.89, 37.41, 56.01, 58.09; IR (neat): 1457, 3853 cm^{-1}; MS (EI): *m/z* 251; HRMS (EI): Calcd for $C_{17}H_{33}N$: 251.2613, Found 251.2614; $[\alpha]_D^{25}$ -1.6 (*c* 1.00, MeOH).

(*2R*,*4aR*,*5S*,*8aS*)-5-ethyl-2-heptyldecahydroquinoline (*cis*-209J-1)

Yield: 65%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, t, *J* = 7.6), 0.87 (3H, t, *J* = 7.6), 0.93-1.14 (2H, m), 1.22-1.38 (15H, m), 1.43-1.56 (4H, m), 1.59-1.63 (2H, m), 1.96 (1H, ddd, *J* = 13.6, 4.8, 2.8), 2.45-2.54 (1H, m), 2.87 (1H, d, *J* = 2.8); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.29, 14.09, 21.17, 22.65, 25.36, 26.04, 26.75, 27.35, 29.29, 29.84, 31.34, 31.83, 32.98, 33.25, 37.39, 39.77, 56.27, 58.14; IR (neat): 3583 cm^{-1}; MS (EI): *m/z* 265; HRMS (EI): Calcd for $C_{18}H_{35}N$ 265.2770, Found 265.2770; $[\alpha]_D^{20}$ +2.2 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-2-heptyl-5-propyldecahydroquinoline (*cis*-223F-1)

Yield: 58%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (6H, t, *J* = 7.2), 0.94-1.67 (26H, m), 1.74-1.79 (2H, m), 1.78 (2H, d, *J* = 10.8), 1.98 (1H, dd, *J* = 13.6, 2.4), 2.54 (1H, t, *J* = 8.0), 2.89 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.09, 14.65, 19.24, 21.14, 22.66, 26.00, 26.72, 27.21, 29.31, 29.51, 31.64, 31.84, 32.05, 33.02, 35.57, 37.16, 40.31, 56.37, 58.23; IR (neat): 1456, 3574 cm^{-1}; MS (EI): *m/z* 279; HRMS (EI): Calcd for $C_{19}H_{37}N$ 279.2926, Found 279.2926; $[\alpha]_D^{17}$ +12.1 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5S*,*8aS*)-1-methyl-2,5-dipropyldecahydroquinoline (*cis*-237U)

To a stirred solution of *ent-cis*-**223F** (25 mg, 0.11 mmol) in MeOH (4.5 mL) and H_2O (1.5 mL) were added formaldehyde (37% aqueous solution, 0.03 mL, 0.67 mmol) and $NaBH_3CN$ (26 mg, 0.42 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (2 mL), and aqueous mixture was extracted with CH_2Cl_2 (2 mL x 5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (3 g, MeOH/CH_2Cl_2 = 1/10) to give *cis*-**237U** (21 mg, 0.09 mmol, 78%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8), 0.89 (3H, t, *J* = 7.2), 0.94-1.05 (1H, m), 1.14-2.02 (21H, m), 2.19 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.53, 14.59, 18.98, 19.25, 20.33, 26.08,

26.86, 30.01, 31.46, 33.14, 35.22, 36.02, 37.66, 41.82, 64.00, 64.31; IR (neat): 1456, 2619, 2706, 2770, 2870, 2930, 2955 cm^{-1}; MS (EI): *m/z* 237; HRMS (EI): Calcd for $C_{16}H_{31}N$ 237.2464, Found 237.4310; $[\alpha]_D^{24}$ +9.7 (*c* 1.20, $CHCl_3$).

General procedure for the synthesis of vinyl ketones 92-93

To a stirred solution of **71-72** (0.60 mmol) in THF (3 mL) was added a solution vinylMgCl (1.7 M in THF, 0.42 mL, 0.72 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 3 h. The reaction was quenched with sat. NH_4Cl (aq.) (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, acetone/*n*-hexane = 1/15 - 1/10) to give the corresponding vinyl ketones **92-93** as a colorless oil.

(*2S,3S,6R*)-methyl 2-(2-oxobut-3-en-1-yl)-6-propyl-3-vinylpiperidine-1-carboxylate (92)

Yield: 87%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J* = 7.2), 1.21-1.58 (6H, m), 1.78-1.94 (2H, m), 2.27 (1H, s), 2.80-2.92 (2H, m), 3.68 (3H, s), 4.13 (1H, d, *J* = 5.6), 4.62-4.65 (1H, m), 5.04-5.08 (2H, m), 5.79-5.88 (2H, m), 6.30-6.42 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.00, 19.72, 20.31, 21.96, 37.36, 39.03, 45.54, 50.27, 50.51, 52.55, 115.09, 128.95, 136.07, 140.04, 156.76, 198.59; IR (neat): 1393, 1445, 1690 cm^{-1}; MS (FAB): *m/z* 280; HRMS (FAB): Calcd for $C_{16}H_{26}NO_3$ 280.1913, Found 280.1911; $[\alpha]_D^{20}$ -82.7 (*c* 1.00, $CHCl_3$).

(*2S,3S,6R*)-methyl 6-heptyl-2-(2-oxobut-3-en-1-yl)-3-vinylpiperidine-1-carboxylate (93)

Yield: 82%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 6.6), 1.21-1.52 (14H, m), 1.78-1.92 (2H, m), 2.26 (1H, s), 2.83 (1H, t, *J* = 14.6), 2.87 (1H, t, *J* = 14.6), 3.68 (3H, s), 4.10 (1H, d, *J* = 5.6), 4.64 (1H, dd, *J* = 8.0, 4.4), 5.03 (1H, d, *J* = 1.6), 5.07 (1H, d, *J* = 6.8), 5.79-5.88 (2H, m), 6.30-6.41 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.05, 19.69, 21.92, 22.61, 27.14, 29.23, 29.48, 31.79, 35.10, 45.53, 50.49, 52.53, 115.06, 128.94, 136.07, 140.03, 156.74, 198.58; IR (neat): 1404, 1444, 1694 cm^{-1}; MS (FAB): *m/z* 336; HRMS (FAB): Calcd for $C_{20}H_{34}NO_3$ 336.2539, Found 336.2535; $[\alpha]_D^{15}$ -80.4 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of 4a-epi-cis-fused enones 78 and 80

To a stirred solution of **92-93** (0.44 mmol) in CH_2Cl_2 (10 mL) was added 2nd generation Grubbs catalyst (19 mg, 0.02 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 15 h. The solvent was evaporated to give a black oil, which was chromatographed on SiO_2 (15 g, *n*-hexane/acetone = 10/1 – 5/1) to give the corresponding 4a-*epi-cis* enones **78, 80** as a yellow oil.

(*2R*,*4aS*,*8aS*)-methyl 7-oxo-2-propyl-2,3,4,4a,8,8a-hexahydroquinoline-1(7H)-carboxylate (78)

Yield: 92%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* = 7.6), 1.30-1.45 (3H, m), 1.48-1.57 (1H, m), 1.62-1.73 (2H, m), 1.94-2.01 (1H, m), 2.08-2.17 (1H, m), 2.23 (1H, dd, *J* = 16.8, 12.8), 2.82 (1H, t, *J* = 12.4), 3.26 (1H, dd, *J* = 16.8, 2.8), 3.68 (3H, s), 3.75 (1H, td, *J* = 12.4, 2.8), 4.23 (1H, qd, *J* = 9.2, 2.4), 6.00 (1H, 9.6, 1.6), 6.80 (1H, dd, *J* = 9.6, 1.6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.88, 19.99, 23.84, 26.49, 36.36, 42.24, 46.37, 50.68, 52.53, 56.53, 129.85, 153.04, 157.03, 198.51; IR (neat): 1450, 1679, 1697 cm^{-1}; MS (FAB): *m/z* 252; HRMS (FAB): Calcd for $C_{14}H_{22}NO_3$ 252.1600, Found 252.1597; $[\alpha]_D^{19}$ +121.2 (*c* 1.00, $CHCl_3$).

(*2R*,*4aS*,*8aS*)-methyl 2-heptyl-7-oxo-2,3,4,4a,8,8a-hexahydroquinoline-1(7H)-carboxylate (80)

Yield: 84%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, t, *J* = 6.6), 1.24-1.70 (14H, m), 1.92-1.99 (1H, m), 2.05-2.14 (1H, m), 2.21 (1H, dd, *J* = 16.4, 12.0), 2.79 (1H, t, *J* = 12.0), 3.24 (1H, dd, *J* = 16.4, 3.4), 3.66 (3H, s), 3.73 (1H, td, *J* = 12.0, 3.4), 4.18 (1H, q, *J* = 7.5), 5.97 (1H, dd, *J* = 9.6, 2.4), 6.78 (1H, d, *J* = 9.6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.93, 22.45, 23.74, 26.38, 26.67, 29.05, 31.66, 36.28, 39.87, 46.23, 50.86, 52.40, 56.45, 129.71, 152.98, 156.90, 198.38; IR (neat): 1447, 1683, 1699 cm^{-1}; MS (FAB): *m/z* 308; HRMS (FAB): Calcd for $C_{18}H_{30}NO_3$ 308.2226, Found 308.2225; $[\alpha]_D^{25}$ +99.1 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of Michael adducts 94-95

To a stirred suspension of CuI (383 mg, 2.01 mmol) in Et_2O (7.5 mL) was added a solution of MeLi (1.17 M in Et_2O, 3.44 mL, 4.02 mmol) at -78 °C, and the reaction mixture was warmed to 0 °C for 30 min. The resulting suspension was re-cooled to -78 °C, and a solution of **78, 80** (0.40 mmol) in Et_2O (3 mL) was added to the reaction mixture at -78 °C, and the resulting mixture was gradually warmed to 0 °C. The reaction was quenched with sat. NH_4Cl (aq) (5 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL x 3), and the organic layer and extracts were combined, dried, and evaporated to give a yellow oil, which was chromatographed on SiO_2 (10 g, EtOAc/*n*-hexane = 1/15 - 1/10) to give the corresponding Michael adducts **94-95** as pale yellow oil.

(*2R*,*4aS*,*5S*,*8aS*)-methyl 5-methyl-7-oxo-2-propyloctahydroquinoline-1(2H)-carboxylate (94)

Yield: 94%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, d, *J* = 7.2), 0.90 (3H, t, *J* = 7.2), 1.24-1.40 (3H, m), 1.47-1.71 (4H, m), 2.14-2.29 (5H, m), 2.54 (1H, dd, *J* = 14.4, 6.4), 2.97-3.02 (1H, m), 3.68 (3H, s), 3.81 (1H, dd, *J* = 11.6, 3.6), 4.32 (1H, qd, *J* = 8.8, 2.0); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.83, 13.90, 19.95, 23.52, 27.53, 32.40, 39.57, 42.95, 49.07, 49.26, 52.15, 52.55, 157.03, 208.96; IR (neat): 1450, 1681, 1699 cm^{-1}; MS (FAB): *m/z* 268; HRMS (FAB): Calcd for $C_{15}H_{26}NO_3$ 268.1913, Found 268.1920; $[\alpha]_D^{20}$ +50.3 (*c* 1.00, $CHCl_3$).

(*2R*,*4aS*,*5S*,*8aS*)-methyl 2-heptyl-5-methyl-7-oxooctahydroquinoline-1(2H)-carboxylate (95)

Yield: 90%; ^{1}H-NMR (400 MHz $CDCl_3$) δ: 0.83 (6H, t, *J* = 6.4), 1.19-1.45 (12H, m), 1.48-1.71 (4H,

m), 2.12-2.26 (4H, m), 2.52 (1H, dd, *J* = 14.8, 7.2), 2.97 (1H, ddd, *J* = 12.2, 3.8, 1.9), 3.65 (3H, s), 3.78 (1H, td, *J* = 12.2, 3.8), 4.27 (1H, dd, *J* = 16.0, 7.2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.77, 13.99, 22.52, 27.49, 32.34, 39.52, 40.67, 49.01, 49.19, 49.46, 52.10, 52.48, 156.94, 208.86; IR (neat): 1448, 1683, 1699 cm^{-1}; MS (FAB): *m/z* 324; HRMS (FAB): Calcd for $C_{19}H_{34}NO_3$ 324.2539, Found 324.2534; $[\alpha]_D^{25}$ +39.5 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of the deoxygenated compounds 96-97

To a stirred solution of **94-95** (0.30 mmol) in CH_2Cl_2 (3 mL) and MeOH (0.3 mL) was added $NaBH_4$ (22 mg, 0.60 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (2 mL x 5). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the above alcohol in 1,2-dichloroethane (5 mL) was added 1,1-thiocarbonyldiimidazole (214 mg, 1.20 mmol) at room temperature. The resulting mixture was refluxed for 10 h. After cooling, the solvent was evaporated to give a yellow paste, which was used directly in the next step. To a stirred solution of the above thiocarbonylimidazolate in toluene (10 mL) was added *n*-Bu_3SnH (0.32 mL, 1.20 mmol) at room temperature, and then the resulting mixture was refluxed for 8 h. The solvent was evaporated and the residue was diluted with MeCN. The MeCN layer was washed with hexane and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, CH_2Cl_2/*n*-hexane = 1/5 - 1/1) to give the corresponding deoxygenated compounds **96-97**as a colorless oil.

(*2R*,*4aS*,*5S*,*8aS*)-methyl 5-methyl-2-propyloctahydroquinoline-1(2H)-carboxylate (96)

Yield: 56% in 3 steps; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (3H, d, *J* = 7.4 Hz), 0.90 (3H, t, *J* = 7.6 Hz), 1.09-1.68 (12H, m), 1.73-1.82 (1H, m), 1.93-2.01 (1H, m), 2.10-2.19 (2H, m), 3.53 (1H, td, *J* = 12.4, 3.2 Hz), 3.68 (3H, s), 4.23 (1H, qd, *J* = 9.2, 2.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.22, 13.94, 19.90, 20.75, 24.43, 28.14, 33.02, 33.37, 34.29, 40.68, 43.06, 49.04, 52.17, 54.38, 157.45; IR (neat): 1696 cm^{-1}; MS (FAB): *m/z* 254; HRMS (FAB): Calcd for $C_{15}H_{28}NO_2$ 254.2120, Found 254.2120; $[\alpha]_D^{25}$ +66.0 (*c* 1.00, $CHCl_3$).

(*2R*,*4aS*,*5S*,*8aS*)-methyl 2-heptyl-5-methyloctahydroquinoline-1(2H)-carboxylate (97)

Yield: 65% in 3 steps; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (6H, t, *J* = 7.6), 1.05-1.67 (20H, m), 1.77 (1H, tdd, *J* = 18.4, 6.4, 2.8), 1.96 (1H, ddd, *J* = 14.0, 6.4, 2.8), 2.09-2.18 (2H, m), 3.52 (1H, td, *J* = 11.6, 2.8), 3.67 (3H, s), 4.20 (1H, qd, *J* = 8.8, 1.2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.25, 14.09, 20.77, 22.64, 22.46, 26.72, 28.16, 29.27, 29.51, 31.84, 33.05, 33.39, 34.30, 40.72, 40.85, 49.29, 52.20, 54.41, 157.45; IR (neat): 1699 cm^{-1}; MS (FAB): *m/z* 310; HRMS (FAB): Calcd for $C_{19}H_{36}NO_2$ 310.2746, Found 310.2744; $[\alpha]_D^{25}$ +42.6 (*c* 1.00, $CHCl_3$).

General procedure for the synthesis of *4a-epi-cis*-decahydroquinoline poison-frog alkaloids *4a-epi-cis*-195A and *4a-epi-cis*-251A

To a stirred solution of **28a-b** (0.34 mmol) in $CHCl_3$ (3 mL) was added NaI (394 mg, 2.64 mmol) and TMSCl (0.20 mL, 1.66 mmol), and the resulting mixture was heated to 50 °C for 24 h. After cooling, the reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$ (aq.) (3 mL), and aqueous mixture was extracted with CH_2Cl_2 (2 mL x 5). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (3 g, MeOH/CH_2Cl_2 = 1/30 - 1/25) to give the corresponding 4a-*epi-cis*-decahydroquinoline poison-frog alkaloids as pale yellow oil.

(*2R*,*4aS*,*5S*,*8aS*)-5-methyl-2-propyldecahydroquinoline (*4a-epi-cis*-195A)

Yield: 56%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.85-0.88 (6H, m), 1.26-1.52 (13H, m), 1.64-1.73 (2H, m), 1.74-1.82 (1H, m), 2.41-2.48 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.30, 19.14, 19.91, 21.24, 27.02, 27.28, 27.36, 33.33, 35.90, 39.64, 42.53, 55.99, 57.75; IR (neat): 1448, 3566 cm^{-1}; MS (FAB): *m/z* 196; HRMS (FAB): Calcd for $C_{13}H_{26}N$ 196.2065, Found 196.2066; $[\alpha]_D^{17}$ -3.8 (*c* 1.00, $CHCl_3$).

(*2R*,*4aS*,*5S*,*8aS*)-2-heptyl-5-methyldecahydroquinoline (4a-epi-cis-251A)

Yield: 62%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.86 (3H, d, *J* = 6.8), 0.87 (3H, t, *J* = 6.8), 1.03-1.35 (17H, m), 1.42-1.54 (5H, m), 1.56-1.73 (2H, m), 1.77-1.80 (1H, m), 2.45 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.56, 14.08, 19.59, 22.64, 26.06, 29.25, 29.30, 29.78, 31.82, 32.28, 33.30, 33.57, 34.40, 37.27, 45.26, 54.92, 56.83; IR (neat): 1452, 3421 cm^{-1}; MS (FAB): *m/z* 252; HRMS (FAB) Calcd for $C_{17}H_{34}N$ 252.2691, Found 252.2689; $[\alpha]_D^{25}$ -1.5 (*c* 1.00, $CHCl_3$).

(*3aS*,*5aS*,*6R*,*9aR*)-6-methyldecahydro-1H-oxazolo[3,4-a]quinolin-1-one (99)

To a stirred solution of **98** (67 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) and MeOH (0.3 mL) was added $NaBH_4$ (22 mg, 0.60 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (2 mL x 3). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step. To a stirred solution of the above alcohol in 1,2-dichloroethane (5 mL) was added 1,1-thiocarbonyldiimidazole (214 mg, 1.20 mmol) at room temperature. The resulting mixture was refluxed for 10 h. After cooling, the solvent was evaporated to give a yellow paste, which was used directly in the next step. To a stirred solution of the above thiocarbonylimidazolate in toluene (5 mL) was added *n*-Bu_3SnH (0.32 mL, 1.20 mmol) at room temperature, and then the resulting mixture was refluxed for 8 h. The solvent was evaporated and the residue was diluted with MeCN. The MeCN layer was washed with hexane and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, CH_2Cl_2/*n*-hexane = 1/1) to give **99** (55 mg, 0.26 mmol, 88% in 3 steps) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.08 (3H, d, *J* = 7.5), 1.25-1.39 (3H, m), 1.48-1.60 (6H, m), 1.75-1.86 (3H, m), 3.76-3.78 (1H, m), 3.84 (1H, t, *J* = 7.0), 4.01-4.02 (1H, m), 4.37 (1H, t, *J* = 7.0); ^{13}C-NMR

(100 MHz, $CDCl_3$) δ: 18.93, 19.38, 24.41, 24.73, 26.04, 31.14, 33.64, 40.33, 47.79, 50.63, 68.29, 156.79; IR (neat): 1747, 2971 cm^{-1}; MS (EI): *m/z* 209; HRMS (EI): Calcd for $C_{12}H_{19}NO_2$ 209.1416, Found 209.1420; $[\alpha]_D^{25}$ -15.8 (*c* 1.00, $CHCl_3$).

(*2S*,*4aS*,*5R*,*8aR*)-benzyl 2-(hydroxymethyl)-5-methyloctahydroquinoline-1(2H)-carboxylate (100)

To a stirred solution of **99** (13 mg, 0.06 mmol) in *i*-PrOH (5 mL) was added KOH (35 mg, 0.62 mmol) at room temperature, and the resulting mixture was heated at 120 °C in sealed tube for 24 h. After cooling, the solvent was evaporated, and residue was dissolved in H_2O. The aqueous mixture was extracted with CH_2Cl_2 (3 mL x 10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a red oil, which was used directly in the next step. To a stirred solution of the above amino alcohol in THF (2 mL) and sat. $NaHCO_3$ (aq.) (2 mL) was added CbzCl (0.01 mL, 0.08 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 mL x 5). The organic layer and extracts were combined, dried, and evaporated to give a yellow oil, which was chromatographed on silica gel (6 g, EtOAc/*n*-hexane = 1/5) to give the alcohol **100** (19 mg, 0.06 mmol, quant. in 2 steps) as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.04 (3H, d, *J* = 7.5), 1.19-1.25 (1H, m), 1.48-1.75 (11H, m), 3.67-3.80 (3H, m), 4.25 (1H, br), 5.15 (2H, s), 7.31-7.38 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 18.96, 20.01, 22.78, 25.86, 27.13, 33.41, 38.93, 51.51, 54.87, 66.08, 66.92, 77.21, 127.44, 127.87, 128.48, 136.75, 156.59; IR (neat): 1698, 2966, 3630 cm^{-1}; MS (FAB): *m/z* 318; HRMS (FAB): Calcd for $C_{19}H_{28}NO_3$ 318.2069, Found 318.2069; $[\alpha]_D^{25}$ -7.1 (*c* 1.00, $CHCl_3$).

(2R,*4aS*,*5R*,*8aR*)-2-heptyl-5-methyldecahydroquinoline (2-epi-cis 251A)

To a stirred solution of DMSO (0.03 mL, 0.34 mmol) in CH_2Cl_2 (3 mL) was added $(COCl)_2$ (0.02 mL, 0.17 mmol) at -78 °C for 15 min, and then a solution of **100** (18 mg, 0.06 mmol) in CH_2Cl_2 (1.5 mL) was added to the reaction mixture at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, and then Et_3N (0.07 mL, 0.51 mmol) was added to the reaction mixture at -78 °C. The resulting mixture was gradually warmed to 0 °C. The reaction was quenched with H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 mL x 5). The organic layer and extracts were combined, washed with brine, 10% HCl (aq.), and brine, successively, dried over Na_2SO_4, and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of $HexP^+Ph_3Br^-$ (96 mg, 0.22 mmol) in THF (3 mL) was added *t*-BuOK (24 mg, 0.21 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min. To the solution was added a solution of the above aldehyde in THF (1.5 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 15 h. The reaction was quenched with sat. NH_4Cl (aq.), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 mL x 5). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give a yellow paste, which was passed through a thin celite pad and washed

with Et_2O (2 mL x 5). The filtrate and washings were combined and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the above olefin in EtOAc (5 mL) was added 20% $Pd(OH)_2/C$ (3 mg), and the resulting mixture was hydrogenated at 1 atm for 24 h. The catalyst was removed through a celite pad and washed with EtOAc (2 mL x 5). The filtrate and washings were combined and evaporated to give a yellow oil, which was chromatographed on SiO_2 (5 g, EtOAc/*n*-hexane = 1/5) to give 2-*epi-cis* **251A** as pale yellow oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* = 7.0), 1.04 (3H, d, *J* = 6.5), 1.13-1.47 (15H, m), 1.52-1.76 (4H, m), 1.74-1.90 (5H, m), 2.80-2.86 (1H, m), 3.15-3.19 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.08, 19.23, 20.36, 22.62, 25.04, 26.09, 27.91, 29.27, 29.68, 31.81, 32.39, 35.70, 41.41, 49.97, 50.12; IR (neat): 1449, 3630 cm^{-1}; MS (EI): *m/z* 251; HRMS (EI) Calcd for $C_{17}H_{33}N$ 251.2613, Found 251.2613; $[\alpha]_D^{23}$ +11.9 (*c* 1.00, $CHCl_3$).

(*2R*,*3R*,*6S*)-methyl 6-(hydroxymethyl)-2-(2-methoxy-2-oxoethyl)-3-vinylpiperidine-1-carboxylate (102)

To a stirred solution of **15** (124 mg, 0.58 mmol) in *i*-PrOH (10 mL) was added KOH (325 mg, 5.80 mmol) at room temperature, and the resulting mixture was heated at 120 °C in sealed tube for 24 h. After cooling, the solvent was evaporated to give a red paste, which was passed through a thin Dowex 50W x 8-100 ion-exchange resin pad and washed with water and ammonium hydroxide aqueous solution. The basic fractions were evaporated to give a aminoalchol, which was used directly in the next step. To a stirred solution of the aminoalchol in MeOH (3 mL) was added a solution of CH_2N_2, prepared from *N*-methyl-*N*-nitrosourea (179 mg, 1.74 mmol) and KOH (292 mg, 5.22 mmol) in Et_2O (5 mL) and H_2O (5 mL), in Et_2O at 0 °C, and the resulting mixture was stirred at room temperature for 30 min. The solvent was evaporated to give pale yellow oil, which was used directly in next step. To a stirred solution of the above methyl ester in THF (2 mL) and sat. $NaHCO_3$ (aq.) (2 mL) was added $ClCO_2Me$ (0.05 mL, 0.66 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The organic layer and extracts were combined, dried, and evaporated to give a yellow oil, which was chromatographed on SiO_2 (7 g, acetone/*n*-hexane = 1/7) to give **102** (123 mg, 0.45 mmol, 78% in 3 steps) as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.55-1.61 (2H, m), 1.65-1.78 (2H, m), 2.33 (1H, quin, *J* = 7.0), 2.59 (1H, dd, *J* = 16.4, 5.2), 3.17 (1H, br), 3.65 (3H, s), 3.66 (3H, s), 3.68-3.72 (2H, m), 3.68 (1H, br), 3.69 (1H, t, *J* = 5.2), 3.95 (1H, br), 5.06 (1H, d, *J* = 11.0, 1.2), 5.10 (1H, d, *J* = 18.2,), 5.67 (1H, ddd, *J* = 18.2, 11.0, 7.0); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.19, 26.22, 35.73, 42.51, 51.83, 52.47, 53.48, 55.81, 62.20, 116.34, 138.87, 156.92, 172.78; IR (neat): 1171, 1319, 1566, 1682, 1695, 2860, 2953 cm^{-1}; MS (EI): *m/z* 271; HRMS (EI): Calcd for $C_{13}H_{21}NO_5$ 271.1420, Found 271.1417; $[\alpha]_D^{26}$ -14.4 (*c* 1.00, $CHCl_3$).

(*2R*,*3R*,*6S*)-methyl 2-(2-methoxy-2-oxoethyl)-6-((methoxymethoxy)methyl)-3-vinylpiperidine-1-carboxylate (103)

To a stirred solution of **102** (250 mg, 0.92 mmol) in CH_2Cl_2 (7 mL) was added DIPEA (0.36 mL, 2.02 mmol) at room temperature, and then MOMCl (0.14 mL, 1.84 mmol) was added to the reaction mixture at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The solvent was evaporated to give a red oil, which was chromatographed on SiO_2 (10 g, acetone/*n*-hexane = 1/7) to give **103** (258 mg, 0.82 mmol, 89%) as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.58 (1H, quin, *J* = 8.4), 1.68-1.77 (3H, m), 2.32 (1H, tt, *J* = 8.6, 7.0), 2.69 (1H, dd, *J* = 16.2, 7.0), 2.98 (1H, dd, *J* = 16.2, 7.0), 3.36 (3H, s), 3.64 (3H, s), 3.65 (3H, s), 3.73 (1H, dd, *J* = 9.8, 7.6), 3.81 (1H, dd, *J* = 9.8, 6.0), 3.85 (1H, dd, *J* = 7.6, 6.0), 4.13 (1H, quin, *J* = 7.0), 4.63 (1H, d, *J* = 6.4), 4.66 (1H, d, *J* = 6.4), 5.02 (1H, d, *J* = 11.0, 1.2), 5.08 (1H, d, *J* = 18.2), 5.64 (1H, ddd, *J* = 18.2, 11.0, 8.6); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.79, 25.82, 37.33, 43.65, 51.52, 52.29, 53.39, 53.76, 55.22, 67.48, 96.51, 116.08, 139.47, 156.90, 172.19; IR (neat): 1109, 1417, 1703, 1738 cm^{-1}; MS (EI): *m/z* 315; HRMS (EI): Calcd for $C_{15}H_{25}NO_6$ 315.1682, Found 315.1687; $[\alpha]_D^{25}$ -23.6 (*c* 1.00, $CHCl_3$).

(*2R*,*3R*,*6S*)-methyl 2-(2-(methoxy(methyl)amino)-2-oxoethyl)-6-((methoxymethoxy)methyl)-3-vinylpiperidine-1-carboxylate (104)

To a stirred solution of **103** (318 mg, 1.01 mmol) in MeOH (4.5 mL) and H_2O (1.5 mL) was added LiOH·H_2O (169 mg, 4.03 mmol), and the resulting mixture was refluxed for 2 h. After cooling, MeOH was evaporated and the residue was acidified with 10% HCl (aq.) (3 mL). The aqueous mixture was extracted with EtOAc (3 mL x 5). The organic extracts were combined, dried, and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the above oil in CH_2Cl_2 (5 mL) was added EDC·HCl (270 mg, 1.41 mmol) at 0 °C, and the reaction mixture was stirred for 30 min. To the reaction mixture were added MeO(Me)NH·HCl (138 mg, 1.41 mmol) and Et_3N (0.20 ml, 1.41 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 15 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (10 g, acetone/*n*-hexane = 1/7) to give **104** (285 mg, 0.83 mmol, 84% in 2 steps) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.57 (1H, quin, *J* = 8.2), 1.67-1.74 (3H, m), 2.34 (1H, dt, *J* = 14.2, 7.6), 2.75 (1H, dd, *J* = 14.2, 5.2), 3.11 (3H, s), 3.13 (1H, br), 3.33 (3H, s), 3.61 (3H,s), 3.72 (3H, s), 3.75 (1H, t, *J* = 8.8), 3.83 (1H, dd, *J* = 8.8, 5.4), 3.98 (1H, d, *J* = 5.4), 4.07 (1H, br), 4.60 (1H, d, *J* = 6.4), 4.63 (1H, d, *J* = 6.4), 4.97 (1H, d, *J* = 10.4), 5.05 (1H, d, *J* = 17.8), 5.64 (1H, ddd, *J* = 17.8, 10.4, 8.2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.85, 25.77, 32.21, 34.71, 43.36, 52.16, 53.56, 55.17, 61.07, 67.65, 96.50, 115.54, 139.97, 156.83, 172.56; IR (neat): 1456, 1683, 1697, 2927 cm^{-1}; MS (EI): *m/z* 344; HRMS (EI): Calcd for $C_{16}H_{28}N_2O_6$ 344.1947, Found 344.1946; $[\alpha]_D^{26}$ -25.0 (*c* 1.00, $CHCl_3$).

(*2R*,*3R*,*6S*)-methyl 6-((methoxymethoxy)methyl)-2-(2-oxobut-3-en-1-yl)-3-vinylpiperidine-1-carboxylate (105)

To a stirred solution of **104** (206 mg, 0.60 mmol) in THF (3 mL) was added a solution vinylMgCl (1.7 M in THF, 0.42 mL, 0.72 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 3 h. The reaction was quenched with sat. NH_4Cl (aq.) (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, acetone/*n*-hexane = 1/10) to give **105** (186 mg, 0.60 mmol, 100%) as a colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.58 (1H, quin, *J* = 8.0), 1.69-1.71 (3H, m), 2.29 (1H, ddd, *J* = 16.8, 7.8, 5.6), 2.84 (1H, dd, *J* = 16.8, 5.6), 3.35 (3H, s), 3.38 (1H, br), 3.73 (1H, dd, *J* = 10.0, 7.8), 3.82 (1H, dd, *J* = 10.0, 5.6), 3.90 (1H, dd, *J* = 13.2, 5.6), 4.21 (1H, br), 4.62 (1H, d, *J* = 6.8), 4.66 (1H, d, *J* = 6.8), 4.97 (1H, d, *J* = 9.8), 5.05 (1H, d, *J* = 17.8), 5.57 (1H, ddd, 17.8, 9.8, 7.8), 5.76 (1H, d, *J* = 10.8), 6.20 (1H, d, *J* = 17.6), 6.32 (1H, dd, *J* = 17.6, 10.8); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 24.11, 26.36, 42.45, 44.41, 52.36, 52.58, 53.76, 55.37, 67.30, 96.68, 116.16, 127.95, 136.65, 139.87, 156.91, 198.29; IR (neat): 918, 1045, 1109, 1402, 1448, 1703, 2932 cm^{-1}; MS (EI): *m/z* 311; HRMS (EI): Calcd for $C_{16}H_{25}NO_5$ 311.1733; Found 311.1724; $[\alpha]_D^{25}$ -17.3 (*c* 1.00, $CHCl_3$).

(*2S*,*4aR*,*8aR*)-methyl 2-((methoxymethoxy)methyl)-7-oxo-2,3,4,4a,8,8a-hexahydroquinoline-1(7H)-carboxylate (106)

To a stirred solution of **105** (137 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) was added 2nd generation Grubbs catalyst (19 mg, 0.02 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 16 h. The solvent was evaporated to give a black oil, which was chromatographed on SiO_2 (15 g, *n*-hexane/acetone = 7/1) to give **106** (125 mg, 0.44 mmol, 100%) as a yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.48 (1H, qd *J* = 12.8, 5.6), 1.77-1.96 (3H, m), 1.92 (1H, ddd, *J* = 17.2, 7.6, 3.6) 2.49 (1H, t, *J* = 10.2), 3.07 (1H, d, *J* = 14.0), 3.33 (3H, s), 3.38 (1H, t, *J* = 14.0), 3.40-3.45 (1H, m), 3.61 (1H, dd, *J* = 10.2, 6.8), 3.67 (3H, s), 3.73 (1H, dd, *J* = 10.2, 7.6), 4.58 (1H, d, *J* = 6.4), 4.61 (1H, d, *J* = 6.4), 4.59-4.65 (1H, m), 5.98 (1H, dd, *J* = 9.8, 2.0), 6.574 (1H, dd, *J* = 9.8, 2.0); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 25.84, 26.39, 39.69, 43.51, 52.39, 52.81, 54.57, 55.34, 65.41, 96.25, 129.07, 151.68, 156.76, 199.01; IR (neat): 766, 916, 1111, 1447, 1682, 1703, 2930 cm^{-1}; MS (EI): *m/z* 283; HRMS (EI): Calcd for $C_{14}H_{21}NO_5$ 283.1420, Found 283.1420; $[\alpha]_D^{26}$ +56.0 (*c* 1.00, $CHCl_3$).

(2S,4aR,5R,8aR)-methyl 2-((methoxymethoxy)methyl)-5-methyl-7-oxooctahydroquinoline-1(2H)-carboxylate (107)

To a stirred suspension of CuI (192 mg, 1.01 mmol) in Et_2O (5 mL) was added a solution of MeLi (1.17 M in Et_2O, 1.72 mL, 2.01 mmol) at -78 °C, and the reaction mixture was warmed to 0 °C for 30 min. The resulting suspension was re-cooled to -78 °C, and a solution of **106** (60 mg, 0.20 mmol) in Et_2O (3 mL) was added to the reaction mixture at -78 °C, and the resulting mixture was gradually warmed to 0 °C. The reaction was quenched with sat. NH_4Cl (aq) (3 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 mL x 3), and the organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15

g, EtOAc/*n*-hexane = 1/20 - 1/10) to give **107** (46 mg, 0.16 mmol, 78%) as pale yellow oil and **108** (9 mg, 0.03 mmol, 15%) as pale yellow oil, respectively.

39a: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, d, *J* = 7.6), 1.58-1.64 (2H, m), 1.76-1.81 (2H, m), 2.01-2.09 (1H, m), 2.16-2.22 (1H, m), 2.24 (1H, dt, *J* = 14.0, 2.0) , 2.60 (1H, dd, *J* = 14.0, 5.8), 2.22-3.18 (2H, m), 3.35 (3H, s), 3.52 (1H, td, *J* = 11.2, 5.8), 3.58 (1H, dd, *J* = 10.0, 6.8), 3.66 (3H, s), 3.66 (1H, dd, *J* = 10.0, 6.8), 4.39 (1H, ddd, *J* = 11.6, 5.8, 4.8), 4.59 (1H, d, *J* = 6.4), 4.61 (1H, d, *J* = 6.4); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.93, 23.42, 25.05, 33.17, 41.34, 46.67, 48.62, 51.35, 52.15, 53.16, 55.20, 66.59, 96.24, 157.51, 209.64; IR (neat): 918, 1109, 1302, 1443, 1705, 2934 cm^{-1}; MS (EI): *m/z* 299; HRMS (EI): Calcd for $C_{15}H_{25}NO_5$ 299.1733, Found 299.1732; $[\alpha]_D^{24}$ +5.9 (*c* 1.00, $CHCl_3$).

(*2S*,*4aR*,*5R*,*8aR*)-methyl 2-((methoxymethoxy)methyl)-5-methyloctahydroquinoline-1(2H)-carboxylate (108)

To a stirred solution of **107** (45 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) and MeOH (0.3 mL) was added $NaBH_4$ (11 mg, 0.30 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. NH_4Cl (aq) (2 mL), and the aqueous mixture was extracted with CH_2Cl_2 (2 mL x 3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the above alcohol in 1,2-dichloroethane (3 mL) was added 1,1-thiocarbonyldiimidazole (107 mg, 0.60 mmol) at room temperature. The resulting mixture was refluxed for 15 h. After cooling, the solvent was evaporated to give a yellow paste, which was used directly in the next step. To a stirred solution of the above thiocarbonylimidazolate in toluene (5 mL) was added *n*-Bu_3SnH (0.16 mL, 0.60 mmol) at room temperature, and then the resulting mixture was refluxed for 12 h. The solvent was evaporated and the residue was diluted with MeCN. The MeCN layer was washed with hexane and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, CH_2Cl_2/*n*-hexane = 1/1) to give **108** (30 mg, 0.11 mmol, 71% in 3 steps) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, d, *J* = 7.2), 1.17-1.76 (10H, m), 1.82-1.91 (1H, br), 2.43 (1H, dd, *J* = 12.8, 3.2), 3.22 (1H, td, *J* = 11.2, 3.2), 3.34 (3H, s), 3.58 (1H, dd, *J* = 10.0, 6.5), 3.62 (3H, s), 3.68 (1H, dd, *J* = 10.0, 6.5), 4.26 (1H, quin, *J* = 6.5), 4.59 (1H, d, *J* = 6.8), 4.61 (1H, d, *J* = 6.8); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.19, 20.79, 23.94, 25.45, 32.07, 33.09, 33.73, 42.86, 51.89, 53.12, 53.31, 55.17, 67.13, 96.31, 157.74; IR (neat): 918, 1111, 1277, 1443, 1645, 1711, 2876, 2926 cm^{-1}; MS (EI): *m/z* 285; HRMS (EI): Calcd for $C_{15}H_{27}NO_4$ 285.1940, Found 285.1940; $[\alpha]_D^{23}$ -28.8 (*c* 1.00, $CHCl_3$).

(*2S*,*4aR*,*5R*,*8aR*)-methyl 2-(hydroxymethyl)-5-methyloctahydroquinoline-1(2H)-carboxylate (109)

To a solution of NaI (63 mg, 0.42 mmol) in CH_2Cl_2 (1 mL) was added TMSCl (0.42 mL, 0.42 mmol), and the resulting mixture was stirred at room temperature for 15 min. To a solution of **108** (60 mg, 0.21 mmol) in CH_2Cl_2 was transferred a solution of TMSI, prepared above, via a cannula, and then stirred at room temperature for 1 h. The reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$

(aq.) (3 mL), and aqueous mixture was extracted with CH_2Cl_2 (2 mL x 5). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (10 g, acetone/*n*-hexane = 1/5) to give **109** (32 mg, 0.13 mmol, 63%) as a colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, d, *J* = 7.2), 1.24-2.00 (12H, m), 3.39-3.45 (1H, m), 3.67-3.85 (7H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.51, 20.60, 23.76, 25.10, 31.70, 32.86, 33.32, 41.33, 52.28, 54.49, 55.16, 62.89, 157.46; IR (neat): 918, 1111, 1277, 1443, 1645, 1711, 2876, 2926 cm^{-1}; MS (EI): *m/z* 285; HRMS (EI): Calcd for $C_{15}H_{27}NO_4$ 285.1940, Found 285.1940; $[\alpha]_D^{23}$ -84.7 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5R*,*8aR*)-methyl 2-heptyl-5-methyloctahydroquinoline-1(2H)-carboxylate (110)

To a stirred solution of DMSO (0.05 mL, 0.72 mmol) in CH_2Cl_2 (3 mL) was added $(COCl)_2$ (0.03 mL, 0.36 mmol) at -78 °C for 15 min, and then a solution of **109** (29 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added to the reaction mixture at -78 °C. The reaction mixture was stirred at -78 °C for 1 h, and then Et_3N (0.15 mL, 1.08 mmol) was added to the reaction mixture at -78 °C. The resulting mixture was gradually warmed to 0 °C. The reaction was quenched with H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 mL x 5). The organic layer and extracts were combined, washed with brine, 10% HCl (aq.), and brine, successively, dried over Na_2SO_4, and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of $HexP^+Ph_3Br^-$ (205 mg, 0.48 mmol) in THF (3 mL) was added *n*-BuLi (1.6M in hexane, 0.26 mL, 0.42 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min. To the solution was added a solution of the above aldehyde in THF (1.5 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 15 h. The reaction was quenched with sat. NH_4Cl (aq.), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 mL x 5). The organic layer and extracts were combined, dried over Na_2SO_4, and evaporated to give a yellow paste, which was passed through a thin celite pad and washed with Et_2O (2 mL x 5). The filtrate and washings were combined and evaporated to give a yellow oil, which was used directly in the next step. To a stirred solution of the above olefin in EtOAc (5 mL) was added 10% Pd/C (3 mg), and the resulting mixture was hydrogenated at 1 atm for 24 h. The catalyst was removed through a celite pad and washed with EtOAc (2 mL x 5). The filtrate and washings were combined and evaporated to give a yellow oil, which was chromatographed on SiO_2 (5 g, EtOAc/*n*-hexane = 1/5) to give **110** (25 mg, 0.08 mmol, 68% in 3 steps) as pale yellow oil.
^{1}H-NMR (400 MHz $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6), 0.92 (3H, d, *J* = 6.8), 1.27-1.35 (12H, m), 1.37-1.70 (9H, m), 1.85 (1H, quin, *J* = 3.2), 2.01 (1H, qd, *J* = 12.0, 3.2), 2.24 (1H, dd, *J* = 13.2, 3.2), 3.14 (1H, td, *J* = 12.0, 3.2), 3.61 (3H, s), 4.12-4.18 (1H, m);^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.56, 14.08, 20.95, 22.65, 23.97, 26.27, 28.01, 29.47, 30.85, 31.82, 31.94, 33.30, 33.54, 42.61, 51.69, 52.21, 54.24, 157.54; IR (neat): 1089, 1247, 1446, 1712, 2856, 2925 cm^{-1}; MS (EI): *m/z* 309; HRMS (EI): Calcd for $C_{15}H_{27}NO_4$ 309.2668, Found 309.2662; $[\alpha]_D^{23}$ -12.4 (*c* 1.00, $CHCl_3$).

(*2R*,*4aR*,*5R*,*8aR*)-2-heptyl-5-methyldecahydroquinoline (trans-251A)

To a stirred solution of **110** (24 mg, 0.08 mmol) in $CHCl_3$ (3 mL) was added NaI (99 mg, 0.66 mmol) and TMSCl (0.05 mL, 0.42 mmol), and the resulting mixture was heated to 50 °C for 24 h. After cooling, the reaction was quenched with 10% $Na_2S_2O_3$ in sat. $NaHCO_3$ (aq.) (3 mL), and aqueous mixture was extracted with CH_2Cl_2 (2 mL x 10). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (3 g, MeOH/CH_2Cl_2 = 1/20) to give *trans*-**251A** (16 mg, 0.07 mmol, 84%) as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6), 0.89 (3H, d, *J* = 6.6), 1.25-1.37 (14H, m), 1.48-1.62 (6H, m), 1.68-1.78 (2H, m), 1.83-1.97 (3H, m), 2.86 (1H, t, *J* = 10.8), 3.20 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.48, 14.09, 19.72, 22.66, 23.68, 26.93, 29.32, 29.66, 30.65, 31.83, 32.49, 33.42, 34.43, 45.70, 47.66, 52.42; IR (neat): 2854, 2923, 3059, 3665 cm^{-1}; MS (EI): *m/z* 251; HRMS (EI): Calcd for $C_{17}H_{33}N$ 251.2613, Found 251.2613; $[\alpha]_D^{23}$ -3.2 (*c* 0.80, $CHCl_3$).

第四章

1,2-O-Isopropylidene-D-arabinofuranose (143)

To a suspension of D-arabinofuranose **140** (15 g, 0.1 mmol), imidazole (10.3 g, 0.15 mol) in DMF (700 mL) was gradually added a solution of *tert*-butyldiphenylsilyl chloride (TBDPSCl, 39.3 mL, 0.15 mol) at 0 °C. After being stirred at 0 °C for 2 h, the resulting suspension turned into clear solution, which was further stirred at room temprature for another 5 h. The reaction mixture was poured into ice-cooled water (3500 mL), and the resulting mixture was divided into two parts. Each part was extracted with diethyl ether (1×300 mL, 2×200 mL, 4×100 mL,). The extract was washed with brine and condensed to give a pale yellow oil (55 g), which on trituration with *n*-hexane (3×100 mL, 1×50 mL) gave 5-*O*-*tert*-butyldiphenylsilyl-D-arabinofuranose (**141**, 39 g) as a pale yellow oil, which was used in the next step without further purification.

To a mixture of the oil (34.1 g) and anhydrous cupper (II) sulfate (15 g, 0.88 mmol), and acetone (300 mL) was added concentrated H_2SO_4 (1 mL) at room temperature, and the mixture was stirred at room temperature for 3 h. The resulting mixture was filtered into aqueous $NaHCO_3$ solution (200 mL) to quench the reaction. The deposited precipitate was filter off, and washed with acetone. To remove excess acetone, the combined filtrate and washings were evaporated at reduced pressure, and the aqueous residue was extracted with diethyl ether (1×200 mL, 2×50 mL). The extract was washed with brine and condensed to give 5-*O*-*tert*-butyldiphenylsilyl -1,2-*O*-isopropylidene-D-arabinofuranose (**142**, 40 g) as a pale yellow oil, which was used in the next step without purification.

A mixture of the oil (40 g), 1 M solution of TBAF in THF (100 mL), and water (3 mL) was stirred at room temperature for 2.5 h, and the resulting mixture was condensed in vacuo. The residue was purified by means of column chromatography (*n*-hexane–acetone, 30/1→10/1→2/1) to give the title compound (**143**, 10.6 g, 56%) as a colorless prisms. Mp. 111.5–112.5 °C (from dichloromethane), ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.34/1.53 [each 3H, s, C(C*H*$_3$)$_2$], 2.38 (1H, br dd, *J* = *ca*. 5.9, 2.1, OH), 2.52 (1H, d, *J* = 4.0, OH), 3.75 (1H, ddd, *J* = 11.3, 5.9, 5.3, H-5a), 3.81 (H, ddd, *J* = 11.3, 7.3, 2.1, H-

5b), 4.10 (1H, ddd, J = 7.3, 5.3, 2.7, H-4), 4.26 (1H, br dd, J = *ca*. 4.0, 2.7, H-3), 4.59 (1H, d, J = 4.2, H-2), 5.95 (1H, d, J = 4.2, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.1/26.9 [C(*C*H_3)$_2$], 62.4 (C-5), 75.8 (C-3), 87.2 (C-2), 87.9 (C-4), 105.5 (C-1), 112.8 [*C*(CH_3)$_2$].

1,2-O-Isopropylidene-3,5-di-O-(p-methoxybenzyl)-D-arabinofuranose (144).

A solution of **143** (5.7 g, 30 mmol) in dry DMF (50 mL) was added to a mixture of *p*-methoxybenzyl chloride (10 mL, 74 mmol), sodium hydride (3.6 g, 90 mmol, 60% in mineral oil), and dry DMF (50 mL) at 0 °C. After being stirred at room temperature for another 2 h, the reaction mixture was poured into ice-cooled water (500 mL), and extracted with diethyl ether (1×300 mL, 5 × 50 mL). The extract was washed with brine and condensed to give a pale yellow oil (16.1 g), which on column chromatography (*n*-hexane–ethyl acetate, 5:1) gave the title compound **144** (12.1 g, 94%) as a pale yellow oil. $[\alpha]_D^{25}$ +9.4 (c = 1.02, $CHCl_3$). IR (neat): 1614, 1516, 1456, 1373, 1301, 1248, 1211, 1173, 1094, 1034 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32/1.44 [each 3H, s, C(C*H*$_3$)$_2$], 3.58/3.60 (each 1H, dd-like, J = 10.0, 6.3, H-5a and H-5b), 3.798/3.803 (each 3H, s, OC*H*$_3$), 3.98 (1H, d, J = 3.0, H-3), 4.23 (1H, td, J = 6.3, 3.0, H-4), 4.47/4.50 (each 1H, d, J = 11.5, C*H*$_2$PMP), 4.48/4.52 (each 1H, d, J = 11.5, C*H*$_2$PMP), 4.62 (1H, d, J = 4.0, H-2), 5.88 (1H, d, J = 4.0, H-1), 6.83–6.89 (4H, m, arom.), 7.21–7.25 (4H, m arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.3/27.0 [C(*C*H_3)$_2$], 55.2 (2×C, O*C*H_3), 69.7 (C-5), 71.3/72.9 (*C*H_2PMP), 82.6 (C-3), 83.5 (C-4), 85.2 (C-2), 105.7 (C-1), 112.6 [*C*(CH_3)$_2$], 113.7/113.8/129.3/129.5 (d, arom.), 129.3/130.1/159.2/159.3 (s, arom.). HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{30}O_7Na$ 453.1884; Found 453.1888.

3,5-Di-O-(p-methoxybenzyl)-D-arabinofuranose (145).

A mixture of **144** (11.8 g, 27.4 mmol), 10% aqueous sulfuric acid (60 mL), and 1,4-dioxane (200 mL) was heated at 45 °C for 6 h, and the resulting mixture was further heated at 55 °C for another 1.5 h. After being cooled, the reaction mixture was poured into aqueous sodium hydrogen carbonate (300 mL), and extracted with ethyl acetate (3×100 mL). The extract was washed with brine, and condensed to give a pale yellow oil (11.4 g), which on column chromatography (*n*-hexane–ethyl acetate, 2:1→1:1) gave an anomeric mixture (α/β = *ca*. 1/1) of the title compound (**145**, 7.9 g, 74%) as a colorless viscous oil, which solidified on standing at room temperature. Waxy solid. Mp 53–56 °C. IR (neat): 3399, 1612, 1516, 1456, 1304, 1250, 1174, 1078, 1031 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.46 (0.5H, dd, J = 10.3, 2.2, H-5a), 3.50 (0.5H, dd, J = 10.4, 1.9, H-5a), 3.54 (0.5H, d, J = 10.3, OH), 3.62 (0.5H, d, J = 11.0, OH), 3.63 (0.5H, dd, J = 10.3, 2.0, H-5b), 3.66 (0.5H, dd, J = 10.4, 2.3, H-5b), 3.805/3.807/3.808/3.810 (each 1.5H, s, OC*H*$_3$), 3.89 (0.5H, br s-like, H-3), 3.94 (0.5H, br dd, J = 3.4, 3.0, H-3), 4.00 (0.5H, ddd, J = 10.3, 3.6, 3.4, H-2), 4.05 (0.5H, d, J = 10.7, OH), 4.07 (0.5H, d, J = 10.6, H-2), 4.09 (0.5H, ddd, J = 3.0, 2.2, 2.0, H-4), 4.15 (0.5H, d, J = 11.6, OH), 4.38 (0.5H, br dd, J = 2.3, 1.9, H-4), 4.42/4.56 (each 0.5H, d, J = 11.4, C*H*$_2$PMP), 4.44–4.48/4.54–4.63 (each 2H, m, C*H*$_2$PMP), 5.22 (0.5H, br d, J = 11.0, H-1), 5.28 (0.5H, dd, J = 10.7, 3.6, H-1), 6.85–6.91 (4H, m, arom.), 7.18–7.25 (4H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.23/55.25 (O*C*H_3), 69.1/69.9 (C-

5), 71.5/71.9/73.4/73.5 (*C*H$_2$PMP), 75.6/76.3 (C-2), 81.4/83.4 (C-4), 83.3/84.3 (C-3), 97.9/104.1 (C-1), 113.8/113.95/113.97/113.98/129.4/129.58(2×C)/129.65 (d, arom.), 128.49/128.52/128.7/129.53 (s, arom.), 159.3/159.53/159.55/159.58 (s, arom.). HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{26}O_7Na$ 413.1571; Found 413.1570.

Preparation of (2*R*,3*S*,4*R*)-1,3-di-*O*-(p-methoxybenzyl)alkane-1,2,3,4-tetraol (147a-d)

(2*R*,3*S*,4*R*)-1,3-di-*O*-(p-methoxybenzyloxy)heptane-2,4-diol (139a). Under argon atmosphere, a 1.6 M solution of *n*-butyl lithium in hexane (2.0 mL, 3.2 mmoL) was added dropwise to a suspension of ethyltriphenylphosphonium bromide (1.18 g, 3.1 mmol) in dry THF (20 mL) at 0 °C, and the mixture was stirred for 0.5 h. At that temperature, a solution of **145** (300 mg, 0.77 mmol) in dry THF (5 mL) added, and the resulting mixture was stirred at room temperature for 1.5 h. After the reaction was quenched with ice-cooled aqueous ammonium chloride (100 mL), the resulting mixture was extracted with diethyl ether (1×50 mL, 2×20 mL). The extract was washed with brine and evaporated to give a pale yellow oil (980 mg), which on column chromatography (*n*-hexane–ethyl acetate, 10:1→5:1), gave a *ca*. 3:1 mixture of (2*R*,3*S*,4*R*,5*Z*)- and (2*R*,3*S*,4*R*,5*E*)-1,3-di-*O*-(*p*-methoxybenzyl)hept-5-ene-1,2,3,4-tetraol (***Z*-** and ***E*-139a**, 262 mg, 85%) as a colorless oil.

The oil (250 mg, 0.50 mmol) was hydrogenated in the presence of 28% aqueous ammonia (10 μL) in methanol (3 mL) over 10% palladium-on-carbon (60 mg) for 15 min. The catalysts were filtered off and washed with methanol. The combined filtrate and the washings were condensed to give a practically pure title compound **147a** (246 mg, 98%) as a colorless oil, which was used in the next step without purification. $[\alpha]_D^{26}$ +13.2 (*c* = 0.21, $CHCl_3$). IR (neat): 3426, 1613, 1514, 1464, 1302, 1248, 1175, 1078, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.91 (3H, t, *J* = 7.2, H-7), 1.28–1.37 (1H, m, H-6a), 1.43–1.58 (3H, m, H-5 and H-6b), 3.41 (1H, dd, *J* = 6.6, 2.6, H-3), 3.57 (1H, dd, *J* = 9.7, 6.0, H-1a), 3.61 (1H, dd, *J* = 9.7, 4.0, H-1b), 3.75–3.79 (1H, m, H-4), 3.802/3.804 (each 3H, s, OC*H*$_3$), 3.99 (1H, ddd, *J* = 6.6, 6.0, 4.0, H-2), 4.45/4.49 (each 1H, d, *J* = 11.5, C*H*$_2$PMP), 4.49/4.53 (each 1H, d, *J* = 10.9, C*H*$_2$PMP), 6.86/6.88 (each 1H, d-like, *J* = 8.9, arom.), 7.18/7.25 (each 1H, d-like, *J* = 8.9, arom.), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0 (C-7), 19.2 (C-6), 35.9 (C-5), 55.3 (2×C, O*C*H$_3$), 70.7 (C-1, C-2), 70.9 (C-4), 73.1/73.3 (*C*H$_2$PMP), 79.7 (C-3), 113.79/113.85/129.6/129.7 (d, arom.), 129.8/130.1/159.4(2×C) (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{32}O_6Na$ 427.2097; Found 427.2113.

(*2*R*,3*S*,4*R*)-1,3-Di-O-(p-methoxybenzyloxy)decane-2,4-diol (147b).** Following the method similar to that used for the preparation of **147a**, D-arabinose derivative **145** (300 mg, 0.77 mmol) was treated with pentylidenetriphenylphosphorane, which was prepared from pentyltriphenylphosphonium bromide (1.27 g, 3.1 mmol). Work-up gave a pale yellow oil (740 mg), which on column chromatography (*n*-hexane–ethyl acetate, 10:1→5:1) gave a *ca*. 3:1 mixture of (2*R*,3*S*,4*R*,5*Z*)- and (2*R*,3*S*,4*R*,5*E*)-1,3-di-*O*-(*p*-methoxybenzyloxy)dec-5-ene-1,2,3,4-tetraol (Z*-** and ***E*-139b,** 266 mg, 78%). The olefin mixture (220 mg) was then hydrogenated over the ammonia poisoning palladium

catalyst. Work-up gave the title compound **147b** (216 mg, 98%) as a colorless oil. $[\alpha]_D^{26}$ +19.8 (*c* = 0.59, $CHCl_3$). IR (neat): 3404, 1614, 1587, 1516, 1508, 1456, 1302, 1246, 1175, 1058, 1038, 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.88 (3H, t, *J* = 7.2, H-10), 1.21–1.35 (7H, m, H-6a, H-7, H-8 and H-9), 1.41–1.57 (3H, m, H-5 and H-6b), 2.15 (1H, d, *J* = 8.3, OH), 2.82 (1H, d, *J* = 5.0, OH), 3.41 (1H, dd, *J* = 6.7, 2.6, H-3), 3.57 (1H, dd, *J* = 9.6, 5.7, H-1a), 3.61 (1H, dd, *J* = 9.6, 4.0, H-1b), 3.75 (1H, m, H-4), 3.801/3.804 (each 1H, s, OC*H*$_3$), 4.00 (1H, dddd-like, *J* = ca. 6.7, 5.7, 5.0, 4.0, H-2), 4.45/4.49 (each 1H, d, *J* = 11.5, C*H*$_2$PMP), 4.48/4.53 (each 1H, d, *J* = 11.0, C*H*$_2$PMP), 6.85/6.88 (each 1H, d-like, *J* = 8.6, arom.), 7.18/7.25 (each 1H, d-like, *J* = 8.6, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 14.1 (C-10), 22.6 (C-9), 25.9 (C-6), 29.3/31.8 (C-7, C-8), 33.8 (C-5), 55.3(2×C, OCH_3), 70.68 (C-2), 70.70 (C-1), 71.2 (C-4), 73.1/73.3 (*C*H_2PMP), 79.5 (C-3), 113.77/113.83/129.6/129.7 (d, arom.), 129.9/130.1/159.4(2×C) (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{38}O_6Na$ 469.2566; Found 469.2578.

(2*R*,3*S*,4*R*)-1,3-Di-*O*-(p-methoxybenzyloxy)dodecane-2,4-diol (147c). Following the method similar to that used for the preparation of **147a**, D-arabinose derivative **145** (500 mg, 1.28 mmol) was treated with heptylidenetriphenylphosphorane, prepared from heptyltriphenylphosphonium bromide (2.26 g, 5.1 mmol). Work-up gave a pale yellow oil (1.26 g), which on column chromatography (*n*-hexane–ethyl acetate, 5:1) gave a *ca*. 4:1 mixture of (2*R*,3*S*,4*R*,5*Z*)- and (2*R*,3*S*,4*R*,5*E*)-1,3-di-*O*-(*p*-methoxybenzyl)dodec-5-ene-1,2,3,4-tetraol (***Z*-** and ***E*-139c**, 486 mg, 80%). The olefin mixture (466 mg) was then hydrogenated over the ammonia poisoning palladium catalyst. Work-up gave the title compound **147c** (454 mg, 97%) as a colorless oil. $[\alpha]_D^{26}$ +14.5 (*c* = 0.55, $CHCl_3$). IR (neat): 3323, 1616, 1559, 1514, 1301, 1247, 1171, 1090, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.88 (3H, t, *J* = 7.2, H-12), 1.22–1.32 (11H, m, H-6a, H-7, H-8, H-9, H-10 and H-11), 1.42–1.57 (3H, m, H-5 and H-6b), 3.41 (1H, dd, *J* = 6.9, 2.6, H-3), 3.57 (1H, dd, *J* = 9.7, 5.7, H-1a), 3.61 (1H, dd, *J* = 9.7, 4.0, H-1b), 3.73–3.77 (1H, m, H-4), 3.802/3.806 (each 3H, s, OC*H*$_3$), 4.00 (1H, ddd, *J* = 6.9, 5.7, 4.0, H-2), 4.45/4.50 (each 1H, d, *J* = 11.5, C*H*$_2$PMP), 4.49/4.53 (each 1H, d, *J* = 10.9, C*H*$_2$PMP), 6.85/6.89 (each 1H, d-like, *J* = 8.6, arom.), 7.18/7.25 (each 1H, d-like, *J* = 8.6, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 14.1 (C-12), 22.6 (C-11), 26.0 (C-6), 29.3/29.56/29.64/31.9 (C-7, C-8, C-9, C-10), 33.8 (C-5), 55.3 (2 × C) (O*C*H_3), 70.70 (C-1), 70.72 (C-2), 71.2 (C-4), 73.1/73.3 (*C*H_2PMP), 79.6 (C-3), 113.8/113.9/129.6/129.7 (d, arom.), 129.8/130.1/159.4(2C) (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{42}O_6Na$ 497.2879; Found 497.2884.

(2*R*,3*S*,4*R*)-1,3-Di-*O*-(p-methoxybenzyloxy)tetradecane-2,4-diol (147d). Following the method similar to that used for the preparation of **147a**, D-arabinose derivative **145** (200 mg, 0.51 mmol) was treated with nonylidenetriphenylphosphorane, prepared from nonyltriphenylphosphonium bromide (0.96 g, 2.0 mmol). Work-up gave a pale yellow oil (529 mg), which on column chromatography (*n*-hexane–ethyl acetate, 5:1) gave a *ca*. 6:1 mixture of (2*R*,3*S*,4*R*,5*Z*)- and (2*R*,3*S*,4*R*,5*E*)-1,3-di-*O*-(*p*-

methoxybenzyl)tetradec-5-ene-1,2,3,4-tetraol (***Z***- and ***E*-139d**, 202 mg, 79%). The olefin mixture (184 mg) was hydrogenated over the ammonia poisoning palladium catalyst. Work-up gave the title compound **147d** (177 mg, 96%) as a colorless oil. $[\alpha]_D^{26}$ +12.2 (*c* = 0.51, $CHCl_3$). IR (neat): 3377, 1613, 1514, 1456, 1250, 1173, 1090, 1065, 1032 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) *δ*: 0.88 (3H, t, *J* = 7.1, H-14), 1.23–1.33 (15H, m, H-6a, H-7, H-8, H-9, H-10, H-11, H-12 and H-13), 1.43–1.58 (3H, m, H-5 and H-6b), 3.41 (1H, dd, *J* = 6.6, 2.6, H-3), 3.57 (1H, dd, *J* = 9.6, 6.0, H-1a), 3.61 (1H, dd, *J* = 9.6, 3.8, H-1b), 3.75 (1H, ddd, *J* = 8.4, 4.4, 2.6 H-4), 3.801/3.805 (each 3H, s, O*C*H_3), 4.00 (1H, ddd, *J* = 6.6, 6.0, 3.8, H-2), 4.46/4.49 (each 1H, d, *J* = 11.6, *C*H_2PMP), 4.49/4.53 (each 1H, d, *J* = 11.0, *C*H_2PMP), 6.86/6.88 (each 1H, d-like, *J* = 8.6, arom.), 7.18/7.25 (each 1H, d-like, *J* = 8.6, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) *δ*: 14.1 (C-14), 22.7 (C-13), 26.0 (C-6), 29.3/29.61/29.63(2C)/29.7/31.9 (C-7, C-8, C-9, C-10, C-11, C-12), 33.8 (C-5), 55.3(2×C, O*C*H_3), 70.7 (C-1, C-2), 71.2 (C-4), 73.1/73.3 (*C*H_2PMP), 79.6 (C-3), 113.82/113.88/129.6/129.7 (d, arom.), 129.9/130.1/159.4(2×C) (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{30}H_{46}O_6Na$ 525.3192; Found 525.3202.

Preparation of (2*R*,3*S*,4*R*)-2,4-di-*O*-benzyloxyalkane-1,3-diol (149a–d)

(2*R*,3*S*,4*R*)-2,4-Di-*O*-benzyloxyheptane-1,3-diol (148a). A solution of **147** (125 mg, 0.31 mmol) in dry DMF (2 mL) was added to a mixture of benzyl bromide (81 μl, 0.68 mmol), sodium hydride (37 mg, 0.93 mmol, 60% in mineral oil), and dry DMF (1 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was poured into ice-cooled water (20 mL) and extracted with a mixture of *n*-hexane–diethyl ether (1:2, 3×20 mL). The extract was washed with brine and evaporated to give (2*R*,3*S*,4*R*)-2,4-di-*O*-benzyloxy- 1,3-di-*O*-(*p*-methoxybenzyloxy)heptane (**148a**, 230 mg) as a pale yellow oil. The oil was then treated with 90% aqueous trifluoroacetic acid (2.8 mL) at room temperature for 30 min. After the reaction mixture was poured into aqueous $NaHCO_3$ (30 mL), the resulting mixture was extracted with chloroform (3×10 mL). The extract was washed with brine and evaporated to give a pale yellow oil (224 mg), which on column chromatography (chloroform) gave the title compound **149a** (85 mg, 80 % from **147a**) as a colorless oil. $[\alpha]_D^{25}$ –68.3 (*c* = 0.36, $CHCl_3$). IR (neat): 3422, 1497, 1454, 1396, 1338, 1247, 1094, 1059 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.94 (3H, t, *J* = 7.4, H-7), 1.32–1.47 (2H, m, H-6), 1.61–1.73 (2H, m, H-5), 2.35/2.47 (each 1H, br s, OH), 3.47 (1H, dt, *J* = 8.0, 4.0, H-2), 3.62–3.68 (2H, m, H-3 and H-4), 3.87 (2H, d, *J* = 4.0, H-1), 4.29/4.59 (each 1H, d, *J* = 11.2, C*H*$_2$Ph), 4.36/4.59 (each 1H, d, *J* = 11.5, C*H*$_2$Ph), 7.25–7.37 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 14.2 (C-7), 18.7 (C-6), 32.6 (C-5), 61.7 (C-1), 71.7/71.8 (*C*H_2Ph), 72.8 (C-3), 76.9 (C-4), 78.4 (C-2), 127.83/127.87/127.91/127.93/128.4/128.5 (d, arom.), 137.9/138.2 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{28}O_4Na$ 367.1885; Found 367.1906.

(2*R*,3*S*,4*R*)-2,4-Dibenzyloxydecane-1,3-diol (149b). Following the method similar to that used for the preparation of **149a**, **147b** (198 mg, 0.44 mmol) was benzylated to give (2*R*,3*S*,4*R*)-2,4-di-*O*-benzyloxy -1,3-di-*O*-(*p*-methoxybenzyloxy)- decane (**148b**, 380 mg) as a pale yellow oil, which was

then treated with 90% aqueous trifluoroacetic acid. Work-up and column chromatography gave the title compound **149b** (141 mg, 82% from **147b**) as a colorless oil. $[\alpha]_D^{26}$ –38.9 (*c* = 0.45, $CHCl_3$). IR (neat): 3443, 1496, 1456, 1394, 1338, 1207, 1094, 1063, 1028 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) *δ*: 0.89 (3H, t, *J* = 7.2, H-10), 1.24–1.38 (8H, m, H-6, H-7, H-8 and H-9), 1.63–1.72 (2H, m, H-5), 2.04 (2H, br s, OH), 3.47 (1H, dt, *J* = 8.0, 4.4, H-2), 3.63 (1H, ddd, *J* = 7.2, 5.6, 2.0, H-4), 3.65 (1H, dd, *J* = 8.0, 2.0, H-3), 3.87 (2H, d, *J* = 4.4, H-1), 4.29/4.59 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.36/4.59 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 7.26–7.35 (10H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) *δ*: 14.1 (C-10), 22.6 (C-9), 25.3 (C-6) 29.4/31.8 (C-7, C-8), 30.3 (C-5), 61.7 (C-1), 71.7/71.8 (*C*H_2Ph), 72.8 (C-3), 77.1 (C-4), 78.5 (C-2), 127.8/127.87/128.89/127.92/128.4/128.5 (d, arom.), 138.0/ 138.2 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{34}O_4Na$ 409.2355; Found 409.2368.

(2*R*,3*S*,4*R*)-2,4-Di-*O*-benzyloxydodecane-1,3-diol (149c). Following the method similar to that used for the preparation of **149a**, **147c** (438 mg, 0.92 mmol) was benzylated to give (2*R*,3*S*,4*R*)-2,4-di-*O*-benzyloxy -1,3-di-*O*-(*p*- methoxybenzyloxy)decane (**148c**, 782 mg) a pale yellow oil, which was then treated with 90% aqueous trifluoroacetic acid. Work-up and column chromatography gave the title compound **149c** (302 mg, 79% from **147c**) as a colorless oil. $[\alpha]_D^{23}$ –30.0 (*c* = 0.12, $CHCl_3$). IR (neat): 3435, 1456, 1338, 1251, 1207, 1065, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.89 (3H, t, *J* = 6.9, H-12), 1.23–1.38 (12H, m, H-6, H-7, H-8, H-9, H-10 and H-11), 1.63–1.72 (2H, m, H-5), 2.40 (2H, br s, OH), 3.48 (1H, dt, *J* = 8.0, 4.0, H-2), 3.63–3.67 (2H, m, H-3 and H-4), 3.87 (2H, d, *J* = 4.0, H-1), 4.29/4.59 (each 1H, d, *J* = 11.5, C*H*$_2$Ph), 4.38/4.59 (each 1H, d, *J* = 11.5, C*H*$_2$Ph), 7.25–7.36 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 14.1 (C-12), 22.7 (C-11), 25.3 (C-6), 29.3/29.5/29.8/31.9 (C-7, C-8, C-9, C-10), 30.3 (C-5), 61.7 (C-1), 71.68/71.74 (*C*H_2Ph), 72.8 (C-3), 77.1 (C-4), 78.4 (C-2), 127.8/127.88/127.90/127.92/128.4/128.5 (d, arom.), 137.9/138.2 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{38}O_4Na$ 437.2668; Found 437.2653.

(2*R*,3*S*,4*R*)-2,4-Di-O-benzyloxytetradecane-1,3-diol (149d). Following the method similar to that used for the preparation of **149a**, **147d** (150 mg, 0.30 mmol) was benzylated to give (2*R*,3*S*,4*R*)-2,4-di-*O*-benzyloxy-1,3-di-*O*-(*p*- methoxybenzyloxy)tetradecane (**148d**, 228 mg) as a pale yellow oil, which was then treated with 90% aqueous trifluoroacetic acid. Work-up and column chromatography gave the title compound **149d** (106 mg, 80% from **147d**) as a colorless oil. $[\alpha]_D^{25}$ –30.2 (*c* = 0.45, $CHCl_3$). IR (neat): 3438, 1456, 1338, 1276, 1247, 1094, 1065, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) □: 0.89 (3H, t, *J* = 7.2, H-14), 1.25–1.38 (16H, m, H-6, H-7, H-8, H-9, H-10, H-11, H-12 and H-13), 1.60–1.72 (2H, m, H-5), 2.33 (1H, br s, OH), 2.47 (1H, br d, *J* = 8.9, OH), 3.47 (1H, dt, *J* = 8.0, 4.4, H-2), 3.60–3.70 (2H, m, H-3 and H-4), 3.87 (2H, d, *J* = 4.4, H-1), 4.29/4.59 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.36/4.59 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 7.27–7.36 (10H, m, arom.), ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 14.1 (C-14), 22.7 (C-13), 25.4/29.3/29.56/29.60(2×C)/29.8/31.9 (C-6, C-7, C-8, C-9, C-10, C-11, C-12), 30.3 (C-5), 61.7 (C-1), 71.7/71.8 (*C*H_2Ph), 72.8 (C-3), 77.1 (C-4), 78.5 (C-2), 127.82/127.87/127.89/127.92/128.43/128.49 (d, arom.), 138.0/138.2 (s, arom.). HRMS (FAB) *m/z*:

$[M+Na]^+$ Calcd for $C_{28}H_{42}O_4Na$ 465.2981; Found 465.3005.

Preparation of cyclic sulfates (138a–d)

(2*R*,3*S*,4*R*)-2,4-Di-*O*-benzyloxyheptane-1,3-diol 1,3-cyclic sulfate (138a). A solution of freshly distilled thionyl chloride (34 μL, 0.47 mmol) in dry dichloromethane (1 mL) was added dropwise to a stirred mixture of **149a** (80 mg, 0.23 mmol), triethyl amine (113 μL, 0.81 mol), and dichloromethane (1 mL) at 0 °C. After being stirred at 0 °C for 30 min, the mixture was poured into ice-cooled and vigorously stirred aqueous sodium hydrogen carbonate (10 mL) and extracted with dichloromethane. The extract was washed with brine, and evaporated to give a pale yellow oil (103 mg), which was used in the next step without purification.

To a well stirred mixture of the oil (103 mg), sodium hydrogen carbonate (70 mg, 0.84 mmol), carbon tetrachloride (1 mL), acetonitrile (1 mL), and water (1 mL) was added dropwise a brown mixture of sodium metaperiodate (150 mg, 0.70 mmol), ruthenium chloride *n*-hydrate (15 mg) and water (1 mL) at 0 °C. After being stirred at room temperature for 15 min, the reaction was quenched by the addition of aqueous sodium thiosulfate-sodium hydrogen carbonate (10 ml). The resulting purple mixture was filtered through celite, and the filtrate was extracted with diethyl ether. The extract was washed with brine and condensed to give a colorless solid (83.5 mg), which on column chromatography (*n*-hexane–ethyl acetate, 10:1) gave the title compound **138a** (79 mg, 84 %) as a colorless oil. $[\alpha]_D^{24}$ –31.3 (*c* = 0.31, $CHCl_3$). IR (neat): 1456, 1404, 1202, 1103, 1064, 1028, 990 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) *δ*: 0.98 (3H, t, *J* = 7.4, H-7), 1.32–1.47 (2H, m, H-6), 1.71 (1H, dddd, *J* = 15.8, 11.9, 9.8, 6.2, H-5a), 1.83 (1H, dddd, J = 15.8, 11.0, 5.8, 5.8, H-5b), 3.86 (1H, ddd, *J* = 9.8, 5.8, 2.0, H-4), 4.20 (1H, ddd, *J* = 10.0, 9.4, 5.2, H-2), 4.30 (1H, dd, *J* = 11.1, 5.2, H-1eq), 4.34/4.42 (each 1H, d, *J* = 11.4, C*H*$_2$Ph), 4.38/4.70 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.40 (1H, dd, *J* = 11.1, 10.0, H-1ax), 4.67 (1H, dd, *J* = 9.4, 2.0, H-3), 7.14–7.38 (10H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) *δ*: 14.1 (C-7), 18.5 (C-6), 30.5 (C-5), 67.2 (C-2), 71.2/73.2 (*C*H$_2$Ph), 71.8 (C-1), 74.6 (C-4), 85.7 (C-3), 127.8/127.91/127.93/128.5/128.6/128.7 (d, arom.), 136.7/137.9 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{26}O_6SNa$ 429.1348; Found 429.1351.

(2*R*,3*S*,4*R*)-2,4-Di-*O*-benzyloxydecane-1,3-diol 1,3-cyclic sulfate (138b). Following the method similar to that used for the preparation of **138a**, cyclic sulfate formation reaction of (123 mg, 0.32 mmol) was carried out. Work-up and column chromatography gave the title compound **138b** (122 mg, 85%) as a colorless oil. $[\alpha]_D^{25}$ –27.6 (*c* = 0.34, $CHCl_3$). IR (neat): 1456, 1398, 1202, 1103, 1063, 1024, 984 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) *δ*: 0.89 (3H, t, *J* = 7.0, H-10), 1.26–1.40 (8H, m, H-6, H-7, H-8 and H-9), 1.68–1.75 (1H, m, H-5a), 1.81–1.88 (1H, m, H-5b), 3.84 (1H, ddd, *J* = 8.4, 5.8, 1.8, H-4), 4.20 (1H, ddd, *J* = 9.8, 9.6, 5.2, H-2), 4.30 (1H, dd, *J* = 11.0, 5.2, H-1eq), 4.34/4.42 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.38/4.70 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.40 (1H, dd, *J* = 11.0, 9.8, H-1ax), 4.67 (1H, dd, *J* = 9.6, 1.8, H-3), 7.14–7.38 (10H, m, arom.), ^{13}C NMR (175 MHz, $CDCl_3$) *δ*: 14.0 (C-10), 22.5/29.3/31.6 (C-7, C-8, C-9), 25.1 (C-6), 28.3 (C-5), 67.2 (C-2), 71.2/73.2 (*C*H$_2$Ph), 71.7 (C-1), 74.8 (C-4), 85.7 (C-3), 127.8/127.9(2×C)/128.53/128.55/128.7 (d, arom.), 136.7/137.9 (s, arom.). HRMS

(FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{32}O_6SNa$ 471.1817; Found 471.1822.

(2*R*,3*S*,4*R*)-2,4-Di-*O*-benzyloxydodecane-1,3-diol 1,3-cyclic sulfate (138c). Following the method similar to that used for the preparation of **138a**, cyclic sulfate formation reaction of **149c** (302 mg, 0.73 mmol) was carried out. Work-up and column chromatography gave the title compound **138c** (270 mg, 78%) as a colorless oil. $[\alpha]_D^{24}$ –23.2 (*c* = 0.25, $CHCl_3$). IR (neat): 1456, 1398, 1200, 1090, 1067, 1026, 986 cm^{-1}.^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J* = 7.2, H-12), 1.23–1.39 (12H, m, H-6, H-7, H-8, H-9, H-10 and H-11), 1.68–1.74 (1H, m, H-5a), 1.81–1.87 (1H, m, H-5b), 3.84 (1H, ddd, *J* = 8.6, 5.8, 2.0, H-4), 4.20 (1H, ddd, *J* = 9.8, 9.5, 5.2, H-2), 4.29 (1H, dd, *J* = 11.2, 5.2, H-1eq), 4.34/4.42 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.38/4.70 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.40 (1H, dd, *J* = 11.2, 9.8, H-1ax), 4.67 (1H, dd, *J* = 9.5, 2.0, H-3), 7.14–7.38 (10H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.0 (C-12), 22.6 (C-11), 25.1 (C-6), 28.3 (C-5), 29.2/29.4/29.6/31.8 (C-7, C-8, C-9, C-10), 67.2 (C-2), 71.2/73.2 (*C*H$_2$Ph), 71.7 (C-1), 74.8 (C-4), 85.7 (C-3), 127.8/127.91/127.93/128.5/128.6/128.7 (d, arom.), 136.7/137.9 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{36}O_6SNa$ 499.2130; Found 499.2155.

(*2R*,3*S*,4*R*)-2,4-Di-*O*-benzyloxytetradecane-1,3-diol 1,3-cyclic sulfate (138d). Following the method similar to that used for the preparation of **138a**, cyclic sulfate formation reaction of **149d** (70 mg, 0.16 mmol) was carried out. Work-up and column chromatography gave the title compound **138d** (71 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ –17.3 (*c* = 0.40, $CHCl_3$). IR (neat): 1456, 1406, 1202, 1090, 1071, 1028, 988 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J* = 7.1, H-14), 1.23–1.40 (16H, m, H-6, H-7, H-8, H-9, H-10, H-11, H-12 and H-13), 1.68–1.75 (1H, m, H-5a), 1.80–1.87 (1H, m, H-5b), 3.84 (1H, ddd, *J* = 8.4, 5.8, 1.8, H-4), 4.20 (1H, ddd, *J* = 9.8, 9.4, 5.2, H-2), 4.30 (1H, dd, *J* = 11.2, 5.2, H-1eq), 4.34/4.42 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.38/4.70 (each 1H, d, *J* = 11.6, C*H*$_2$Ph), 4.40 (1H, dd, *J* = 11.2, 9.8, H-1ax), 4.67 (1H, dd, *J* = 9.4, 1.8, H-3), 7.14–7.38 (10H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 (C-14), 22.7 (C-13), 29.3/29.4/29.52/29.56/29.62/31.9 (C-7, C-8, C-9, C-10, C-11, C-12), 25.1 (C-6), 28.3 (C-5), 67.2 (C-2), 71.2/73.2 (*C*H$_2$Ph), 71.7 (C-1), 74.8 (C-4), 85.7 (C-3), 127.80/127.91/127.93/128.5/128.6/128.7 (d, arom.), 136.7/137.9 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{40}O_6SNa$ 527.2443; Found 527.2458.

Coupling reaction of cyclic sulfates 138a–d with thiosugar 137.

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dibenzyloxy-3-(sulfooxy)heptyl]episulfoniumylidene}-D- arabinitol inner salt (150a). In a heavy wall mini-vial sealed with an inside screw cap with O-ring seal, a suspension of cyclic sulfate **138a** (40 mg, 0.099 mmol), thiosugar **137** (38 mg, 0.090 mmol), potassium carbonate (2 mg, 0.014 mmol), and HFIP (0.1 ml) was heated at 60 °C for 8 days. Removal of the solvent *in vacuo* left a pale orange oil (80 mg), which on column chromatography ($CHCl_3$→$CHCl_3$-MeOH, 100 : 1→30 : 1) gave the title compound **150a** (39 mg, 52 %) as a colorless viscous oil. $[\alpha]_D^{23}$ –15.7 (*c* = 0.37, $CHCl_3$). IR (neat): 1497, 1456, 1398, 1362, 1261, 1229, 1088, 1069,

1026 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 0.99 (3H, t, J = 7.2, H-7'), 1.47–1.60 (2H, m, H-6'), 1.83–1.90 (1H, m, H-5'a), 1.95–2.01 (1H, m, H-5'b), 3.46 (1H, dd, J = 9.4, 7.0, H-5a), 3.51 (1H, dd, J = 9.4, 9.4, H-5b), 3.62 (1H, br dd-like, J = *ca*. 9.4, 7.0, H-4), 3.68 (1H, dd, J = 13.4, 3.4, H-1a), 3.77 (1H, dd, J = 13.0, 4.0, H-1'a), 3.92 (1H, td, J = 7.1, 2.2, H-4'), 4.13 (1H, br d-like, J = *ca*. 13.4, H-1b), 4.15/4.25 (each 1H, d, J = 11.8, CH_2Ph), 4.26–4.30 (1H, m, H-2'), 4.27, (1H, br s-like, H-3), 4.31/4.44 (each 1H, d, J = 11.8, CH_2Ph), 4.31 (1H, br d-like, J = 13.0, H-1'b), 4.39/4.52 (each 1H, d, J = 11.2, CH_2Ph), 4.41-4.43 (1H, m, H-2), 4.45/4.49 (each 1H, d, J = 12.0, CH_2Ph), 4.51/4.69 (each 1H, d, J = 11.8, CH_2Ph), 4.62 (1H, dd, J = 9.0, 2.2, H-3'), 7.10–7.35 (25H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 (C-7'), 19.4 (C-6'), 30.8 (C-5'), 48.4 (C-1), 51.6 (C-1'), 65.0 (C-4), 66.7 (C-5), 69.6/71.8/72.1/73.29/73.32 (*C*H_2Ph), 74.1 (C-2'), 75.9 (C-3'), 77.1 (C-4'), 81.4 (C-2), 83.4 (C-3), 127.3/127.7/127.9/128.1/128.26/128.28/128.37/128.39/128.47/128.54/128.7/128.8 (d, arom.), 135.8/136.1/136.7/136.8/139.0 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{47}H_{54}O_9S_2Na$ 849.3107; Found 849.3123.

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dibenzyloxy-3-(sulfooxy)decyl]episulfoniumylidene}-D-arabinitol inner salt (150b). Following the method similar to that used for the preparation of **150a**, coupling reaction of **138b** (102 mg, 0.23 mmol) with thiosugar **137** (64 mg, 0.15 mmol) was carried out to give the title compound **150b** (43 mg, 33%) as a colorless viscous oil. $[\alpha]_D^{26}$ –20.0 (c = 0.33, $CHCl_3$). IR (neat): 1456, 1362, 1206, 1229, 1094, 1067, 1020 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 7.0, H-10'), 1.27–1.32 (4H, m, H-8' and H-9'), 1.31–1.43 (2H, m, H-7'), 1.42–1.48 (1H, m, H-6'a), 1.50–1.56 (1H, m, H-6'b), 1.86–1.91 (1H, m, H-5'a), 1.96–2.02 (1H, m, H-5'b), 3.47 (1H, dd, J = 9.5, 7.0, H-5a), 3.51 (1H, dd, J = 9.5, 9.5, H-5b), 3.62 (1H, br dd-like, J = *ca*. 9.5, 7.0, H-4), 3.66 (1H, dd, J = 13.7, 3.9, H-1a), 3.75 (1H, dd, J = 13.4, 4.2, H-1'a), 3.90 (1H, ddd, J = 8.4, 5.2, 2.2, H-4'), 4.14 (1H, br d-like, J = *ca*. 13.7, H-1b), 4.16/4.25 (each 1H, d, J = 11.6, CH_2Ph), 4.27–4.30 (1H, m, H-2'), 4.28 (1H, br s-like, H-3), 4.30/4.43 (each 1H, d, J = 11.8, CH_2Ph), 4.32 (1H, br d-like, J = *ca.* 13.4, H-1'b), 4.38–4.41 (1H, m, H-2), 4.39/4.53 (each 1H, d, J = 11.2, CH_2Ph), 4.44/4.47 (each 1H, d, J = 12.0, CH_2Ph), 4.51/4.70 (each 1H, d, J = 11.8, CH_2Ph), 4.62 (1H, dd, J = 9.0, 2.2, H-3'), 7.09–7.35 (25H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 (C-10'), 22.7 (C-9'), 26.2 (*C*-6'), 28.7 (*C*-5'), 29.4 (C-7'), 31.9 (C-8'), 48.4 (C-1), 51.7 (C-1'), 65.0 (C-4), 66.7 (C-5), 69.6/71.8/72.1/73.3(2×C) (*C*H_2Ph), 74.1 (C-2'), 75.9 (C-3'), 77.2 (C-4'), 81.4 (C-2), 83.4(C-3), 127.3/127.66/127.68/127.9/128.06/128.08/128.26/128.30/ 128.40/128.42/128.5/128.6/128.7/128.8 (d, arom.), 135.8/136.1/136.7/136.8/139.0 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{50}H_{60}O_9S_2Na$ 891.3576; Found 891.3590.

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dibenzyloxy-3-(sulfooxy)dodecyl]episulfoniumylidene}-D-arabinitol inner salt (150c). Following the method similar to that used for the preparation of **150a**, coupling reaction of **138c** (191 mg, 0.40 mmol) with thiosugar **137** (153 mg, 0.36 mmol) was carried out to give the title compound **150c** (114 mg, 35%) as a colorless viscous oil. $[\alpha]_D^{23}$

–24.6 (*c* = 0.26, $CHCl_3$). IR (neat): 1456, 1362, 1258, 1211, 1094, 1067, 1030 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.2, H-12'), 1.18–1.42 (10H, m, H-7', H-8', H-9', H-10' and H-11'), 1.42–1.48 (1H, m, H-6'a), 1.49–1.56 (1H, m, H-6'b), 1.85–1.91 (1H, m, H-5'a), 1.95–2.01 (1H, m, H-5'b), 3.47 (1H, dd, *J* = 9.6, 7.0, H-5a), 3.51 (1H, dd, *J* = 9.6, 9.0, H-5b), 3.62 (1H, br dd-like, *J* = *ca.* 9.0, 7.0, H-4), 3.65 (1H, dd, *J* = 13.8, 3.8, H-1a), 3.74 (1H, dd, *J* = 13.4, 4.2, H-1'a), 3.90 (1H, ddd, *J* = 8.2, 5.7, 2.5, H-4'), 4.13 (1H, br d-like, *J* = *ca.* 13.8, H-1b), 4.16/4.26 (each 1H, d, *J* = 11.8, CH_2Ph), 4.27–4.30 (1H, m, H-2'), 4.28 (1H, br s-like, H-3), 4.29/4.42 (each 1H, d, *J* = 11.9, CH_2Ph), 4.32 (1H, dd-like, *J* = 13.4, 1.4, H-1'b), 4.36–4.38 (1H, m, H-2), 4.39/4.53 (each 1H, d, *J* = 11.2, CH_2Ph), 4.43/4.46 (each 1H, d, *J* = 12.0, CH_2Ph), 4.52/4.70 (each 1H, d, *J* = 11.8, CH_2Ph), 4.63 (1H, dd, *J* = 9.0, 2.5, H-3'), 7.09–7.35 (25H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 (C-12'), 22.7 (C-11'), 26.3 (C-6'), 28.7 (*C*-5'), 29.3/29.68/29.73/31.9 (C-7', C-8', C-9', C-10'), 48.4 (C-1), 51.7 (C-1'), 65.0 (C-4), 66.7 (C-5), 69.6/71.8/72.2/73.3(2×C) (*C*H_2Ph), 74.0 (C-2'), 75.9 (C-3'), 77.4 (C-4'), 81.4 (C-2), 83.4 (C-3), 127.3/127.67/127.72/127.9/128.0/128.1/128.28/ 128.31/128.41/128.44/128.5/128.6/128.7/128.8 (d, arom.), 135.7/136.1/136.7/136.8/139.0 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{52}H_{64}O_9S_2Na$ 919.3889; Found 919.3880.

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dibenzyloxy-3-(sulfooxy)tetradecyl]episulfoniumylidene}-D-arabinitol inner salt (150d). Following the method similar to that used for the preparation of **150a**, coupling reaction of **138d** (57mg, 0.11 mmol) with thiosugar **137** (32 mg, 0.076 mmol) was carried out to give the title compound **150d** (26 mg, 37%) as a colorless viscous oil. $[\alpha]_D^{23}$ –4.2 (*c* = 0.24, $CHCl_3$). IR (neat): 1456, 1362, 1271, 1224, 1101, 1090, 1070, 1028 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.2, H-14'), 1.24–1.42 (14H, m, H-7', H-8', H-9', H-10', H-11', H-12' and H-13'), 1.43–1.48 (1H, m, H-6'a), 1.49–1.55 (1H, m, H-6'b), 1.86–1.92 (1H, m, H-5'a), 1.95–2.01 (1H, m, H-5'b), 3.48 (1H, dd, *J* = 9.4, 7.0, H-5a), 3.52 (1H, dd, *J* = 9.4, 9.4, H-5b), 3.60 (1H, br dd-like, *J* = *ca.* 9.4, 7.0, H-4), 3.62 (1H, dd, *J* = 13.4, 3.8, H-1a), 3.77 (1H, dd, *J* = 13.0, 4.2, H-1'a), 3.91 (1H, ddd, *J* = 8.1, 6.2, 2.2, H-4'), 4.15 (1H, br d-like, *J* = *ca.* 13.4, H-1b), 4.17/4.27 (each 1H, d, *J* = 11.6, CH_2Ph), 4.27–4.30 (1H, m, H-2'), 4.28 (1H, br s-like, H-3), 4.29/4.42 (each 1H, d, *J* = 11.6, CH_2Ph), 4.34 (1H, br d-like, *J* = *ca.* 13.0, H-1'b), 4.34-4.36 (1H, m, H-2), 4.39/4.54 (each 1H, d, *J* = 11.2, CH_2Ph), 4.43/4.45 (each 1H, d, *J* = 12.0, CH_2Ph), 4.53/4.72 (each 1H, d, *J* = 11.8, CH_2Ph), 4.62 (1H, dd, *J* = 9.0, 2.2, H-3'), 7.09–7.36 (25H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 (C-14'), 22.7 (C-13'), 26.3 (C-6'), 28.7 (C-5'), 29.4/29.65/29.71/29.8(2C)/31.9 (C-7', C-8', C-9', C-10', C-11', C-12'), 48.5 (C-1), 51.9 (C-1'), 65.0 (C-4), 66.7 (C-5), 69.5/71.8/72.2/73.38/73.40 (*C*H_2Ph), 74.0 (C-2'), 75.9 (C-3'), 77.2 (C-4'), 81.3 (C-2), 83.5 (C-3), 127.3/127.7/127.9/128.0/128.1/128.26/128.34/128.4/128.49/128.51/128.6/128.71/128.73/128.84 (d, arom.), 135.7/136.0/ 137.0/38.2/139.1 (s, arom.). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{54}H_{68}O_9S_2Na$ 947.4202; Found 947.4217.

Hydrogenolysis of the coupled products (136a-d)

1,4-Dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dihydroxy-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (136a). A suspension of 10% palladium-on-carbon (50 mg) in 80% aqueous acetic acid (1 ml) was pre-equilibrated with hydrogen. To the suspension was added a solution of the coupled product **150a** (34 mg, 0.041 mmol) in 80% aqueous acetic acid (2 ml), and the mixture was hydrogenated at 60°C under atmospheric pressure for 3 h. The catalysts were filtered off and washed with methanol. The combined filtrate and the washings were condensed to give a colorless oil (21 mg), which on column chromatography (ethyl acetate-methanol, 20:1→ethyl acetate-methanol-water, 20:4:1) gave the title compound **136a** (12.6 mg, 81%) as a colorless amorphous. $[\alpha]_D^{24}$ +6.7 (*c* = 0.27, CH_3OH). IR (neat): 3381, 1456, 1417, 1258, 1211, 1065, 1026 cm^{-1}. ^1H NMR (700 MHz, CD_3OD) δ: 0.95 (3H, t, *J* = 7.4, H-7'), 1.40–1.47 (1H, m, H-6'a), 1.47–1.55 (1H, m, H-6'b), 1.62–1.71 (2H, m, H-5'), 3.80 (2H, d-like, *J* = 2.8, H-1 and H-1b), 3.88 (1H, ddd, *J* = 8.5, 5.3, 1.6, H-4'), 3.95 (1H, dd, *J* = 10.0, 7.0, H-5a), 3.98 (1H, dd, *J* = 13.4, 5.6, H-1'a), 3.97–4.00 (1H, m, H-4), 4.02 (1H, dd, *J* = 10.0, 5.0, H-5b), 4.03 (1H, dd, *J* = 13.4, 3.8, H-1'b), 4.26 (1H, dd, *J* = 8.0, 1.6, H-3'), 4.37 (1H, ddd, *J* = 8.0, 5.6, 3.8, H-2'), 4.40 (1H, dd, *J* = 2.6, 1.4, H-3), 4.58 (1H, td-like, *J* = 2.8, 2.6, H-2). ^{13}C NMR (175 MHz, CD_3OD) δ: 14.3 (C-7'), 20.2 (C-6'), 36.6 (C-5'), 51.2 (C-1), 53.1 (C-1'), 60.9 (C-5), 68.6 (C-2'), 70.9 (C-4'), 73.1 (C-4), 79.0 (C-2), 79.8 (C-3), 81.6 (C-3'). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{12}H_{24}O_9S_2Na$ 399.0760; Found 399.0778.

1,4-Dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dihydroxy-3-(sulfooxy)decyl]episulfoniumylidene}-D-arabinitol inner salt (136b). Following the method similar to that used for the preparation of **136a**, hydrogenolysis of **150b** (33 mg, 0.38 mmol) was carried out to give the title compound **136b** (13.8 mg, 87%) as a colorless amorphous. $[\alpha]_D^{25}$ +7.8 (*c* =1.39, $CHCl_3$). IR (nujol): 3374, 1458, 1261, 1126, 1092, 1030 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 0.90 (3H, t, *J* = 7.2, H-10'), 1.27–1.45 (7H, m, H-6'a, H-7', H-8' and H-9'), 1.45–1.52 (1H, m, H-6'b), 1.65–1.71 (2H, m, H-5'), 3.80 (2H, d-like, *J* = 2.9, H-1a and H-1b), 3.86 (1H, ddd-like, *J* = 7.5, 5.9, 1.5, H-4'), 3.95 (1H, dd, *J* = 8.6, 6.9, H-5a), 3.97 (1H, dd-like, *J* = 13.5, 5.7, H-1'a), 3.97–4.00 (1H, m, H-4), 4.02 (1H, dd, *J* = 8.6, 4.3, H-5b), 4.04 (1H, dd, *J* = 13.5, 4.0, H-1'b), 4.26 (1H, dd, *J* = 8.0, 1.5, H-3'), 4.36 (1H, ddd, *J* = 8.0, 5.7, 4.0, H-2'), 4.40 (1H, dd, *J* = 2.6, 0.9, H-3), 4.58 (1H, td-like, *J* = 2.9, 2.6, H-2). ^{13}C-NMR (125 MHz, CD_3OD) δ: 14.4 (C-10'), 23.7 (C-9'), 27.1 (C-6'), 30.4/33.0 (C-7', C-8'), 34.5 (C-5'), 51.2 (C-1), 53.1 (C-1'), 60.9 (C-5), 68.5 (C-2'), 71.2 (C-4'), 73.0 (C-4), 79.0 (C-2), 79.8 (C-3), 81.5 (C-3'). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{30}O_9S_2Na$ 441.1229; Found 441.1204.

1,4-Dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dihydroxy-3-(sulfooxy)dodecyl]episulfoniumylidene}-D-arabinitol inner salt (136c). Following the method similar to that used for the preparation of **136a**, hydrogenolysis of **150c** (40 mg, 0.45 mmol) was carried out to give the title compound **136c** (15.5 mg, 78%) as a colorless amorphous. $[\alpha]_D^{24}$ +2.5 (*c* = 0.24, CH_3OH). IR (neat): 3381, 1458, 1417, 1258, 1211, 1065, 1026 cm^{-1}. ^1H NMR (700 MHz, CD_3OD) δ: 0.89 (3H, t, *J* = 7.2, H-12'), 1.26–1.44 (11H,

m, H-6'a, H-7', H-8', H-9', H-10' and H-11'), 1.45–1.52 (1H, m, H-6'b), 1.65–1.70 (2H, m, H-5'), 3.80 (2H, d-like, *J* = 2.8, H-1a and H-1b), 3.85 (1H, ddd-like, *J* = 7.4, 6.0, 1.5, H-4'), 3.95 (1H, dd, *J* = 9.2, 7.6, H-5a), 3.96–4.00 (1H, m, H-4), 3.98 (1H, dd-like, *J* = 13.6, 5.6, H-1'a), 4.01 (1H, dd, *J* = 9.2, 4.0, H-5b), 4.03 (1H, dd, *J* = 13.6, 4.0, H-1'b), 4.26 (1H, dd, *J* = 8.0, 1.5, H-3'), 4.36 (1H, ddd, *J* = 8.0, 5.6, 4.0, H-2'), 4.40 (1H, dd, *J* = 2.8, 1.1, H-3), 4.58 (1H, td-like, *J* = 2.8, 2.8, H-2). ^{13}C NMR (175 MHz, CD_3OD) *δ*: 14.4 (C-12'), 23.7 (C-11'), 27.2 (C-6'), 30.5/30.7/30.8/33.1 (C-7', C-8', C-9', C-10'), 34.5 (C-5'), 51.2 (C-1), 53.2 (C-1'), 60.9 (C-5), 68.5 (C-2'), 71.3 (C-4'), 73.1 (C-4), 79.0 (C-2), 79.8 (C-3), 81.5 (C-3'). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{34}O_9S_2Na$ 469.1542; Found 469.1513.

1,4-Dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*R*)-2,4-dihydroxy-3-(sulfooxy)tetradecyl]episulfoniumylidene}-D-arabinitol inner salt (136d). Following the method similar to that used for the preparation of **136a**, hydrogenolysis of **150d** (24 mg, 0.26 mmol) was carried out to give the title compound **136d** (9.9 mg, 80%) as a colorless amorphous. $[\alpha]_D^{25}$ +10.0 (*c* = 0.75, CH_3OH). IR (nujol): 3356, 1458, 1258, 1209, 1093, 1058, cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *δ*: 0.89 (3H, t, *J* = 7.2, H-14'), 1.26–1.34 (14H, m, H-7', H-8', H-9', H-10', H-11', H-12' and H-13'), 1.34–1.52 (2H, m, H-6'), 1.65–1.70 (2H, m, H-5'), 3.80 (2H, d-like, *J* = 2.9, H-1a and H-1b), 3.86 (1H, td-like, *J* = 7.5, 1.8, H-4'), 3.95 (1H, dd, *J* = 8.6, 6.9, H-5a), 3.97 (1H, dd-like, *J* = 13.2, 5.5, H-1'a), 3.96–4.00 (1H, m, H-4), 4.02 (1H, dd, *J* = 8.6, 4.0, H-5b), 4.04 (1H, dd, *J* = 13.2, 3.7, H-1'b), 4.26 (1H, dd, *J* = 8.0, 1.8, H-3'), 4.36 (1H, ddd, *J* = 8.0, 5.5, 3.7, H-2'), 4.40 (1H, dd, *J* = 2.9, 1.2, H-3), 4.58 (1H, td-like, *J* = 2.9, 2.9, H-2). ^{13}C-NMR (125 MHz, CD_3OD) *δ*: 14.4 (C-14'), 23.7/30.5/30.7/30.76/30.80 (C-7', C-8', C-9', C-10', C-11', C-12', C-13'), 27.2 (C-6'), 34.5 (C-5'), 51.2 (C-1), 53.1 (C-1'), 60.9 (C-5), 68.5 (C-2'), 71.2 (C-4'), 73.1 (C-4), 79.0 (C-2), 79.8 (C-3), 81.5 (C-3'). HRMS (FAB) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{38}O_9S_2Na$ 497.1855; Found 497.1871.

Methanolysis of sulfonium sulfate inner salts (135a, c)

1,4-Dideoxy-1,4-{(*R*)-[(2*S*,3*S*,4*R*)-2,3,4-trihydroxyheptyl]episulfoniumylidene}-D-arabinitol methyl sulfate (135a). A mixture of **136a** (15.6 mg, 0.041 mmol) and 5% methanolic hydrogen chloride (1.5 mL) was stirred at 60 °C for 3 h. Removal of the solvent left a colorless oil (17.2 mg), which on column chromatography ($CHCl_3$-MeOH, 20:1 → $CHCl_3$-MeOH-H_2O, 6:4:1) gave the title compound **135a** (14.3 mg, 85%) as a colorless oil. $[\alpha]_D^{24}$ +4.6 (*c* = 1.58, CH_3OH). IR (neat): 3368, 1653, 1418, 1260, 1202, 1126, 1063, 1009 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *δ*: 0.96 (3H, t, *J* = 7.2, H-7'), 1.34–1.43 (1H, m, H-6'a), 1.43–1.52 (2H, m, H-5'a and H-6'b), 1.55–1.63 (1H, m, H-5'b), 3.38 (1H, dd, *J* = 7.5, 1.7, H-3''), 3.68 (3H, s, CH_3OSO_3), 3.72 (1H, dd, *J* = 13.2, 8.6, H-1'a), 3.76 (1H, ddd, *J* = 8.6, 4.9, 1.7, H-4'), 3.85 (2H, d-like, *J* = 2.6, H-1a and H-1b), 3.90 (1H, dd, *J* = 13.2, 3.5, H-1'b), 3.92 (1H, dd, *J* = 10.6, 9.2, H-5a), 4.01 (1H, br dd-like, *J* = 9.2, 4.9, H-4), 4.05 (1H, dd, *J* = 10.6, 4.9, H-5b), 4.14 (1H, ddd, *J* = 8.6, 7.5, 3.5, H-2'), 4.37 (1H, dd, *J* = 2.6, 1.5, H-3), 4.62 (1H, td-like, *J* = 2.6, 2.6, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 14.4 (C-7'), 20.9 (C-6'), 37.0 (C-5'), 51.9 (C-1), 52.6 (C-1'), 55.2 (CH_3OSO_3), 61.1 (C-5), 69.7 (C-2''), 70.7 (C-4'), 73.7 (C-4), 76.7 (C-3'), 79.4 (C-2), 79.5

(C-3). HRMS (FAB) *m/z*: $[M–CH_3OSO_3]^+$ Calcd for $C_{12}H_{25}O_6S$ 297.1372, found 297.1401.

1,4-dideoxy-1,4-{(*R*)-[(2*S*,3*S*,4*R*)-2,3,4-trihydroxydodecyl]episulfoniumylidene}-D-arabinitol inner salt (135c). Following the method similar to that used for the preparation of **135a**, methanolysis of **136c** (28 mg, 0.63 mmol) was carried out to give the title compound **135c** (24.5 mg, 82%) as a colorless oil. $[\alpha]_D^{24}$ +12.5 (*c* = 0.53, CH_3OH). IR (neat): 3364, 1651, 1458, 1258, 1223, 1069, 1011 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) *δ*: 0.89 (3H, t, *J* = 6.9, H-12'), 1.24–1.42 (11H, m, H-6'a, H-7', H-8', H-9', H-10' and H-11'), 1.42–1.55 (2H, m, H-5'a, H-6'b), 1.55–1.64 (1H, m, H-5'b), 3.38 (1H, dd, *J* = 7.5, 1.7, H-3'), 3.68 (3H, s, C*H*$_3$OSO$_3$), 3.72 (1H, dd, *J* = 13.0, 8.6, H-1'a), 3.73 (1H, ddd, *J* = 8.1, 4.6, 1.7, H-4'), 3.85 (2H, d-like, *J* = 2.6, H-1a and H-1b), 3.89 (1H, dd, *J* = 13.0, 3.5, H-1'b), 3.92 (1H, dd, *J* = 10.6, 9.2, H-5a), 4.00 (1H, br dd-like, *J* = 9.2, 4.9, H-4), 4.05 (1H, dd, *J* = 10.6, 4.9, H-5b), 4.14 (1H, ddd, *J* = 8.6, 7.5, 3.5, H-2'), 4.36 (1H, dd, *J* = 2.3, 1.2, H-3), 4.61 (1H, td-like, *J* = 2.6, 2.3, H-2). ^{13}C NMR (125 MHz, CD_3OD) *δ*: 14.4 (C-12'), 23.7 (C-11'), 27.0 (C-6'), 30.4/30.7/30.8/33.1 (C-7', C-8', C-9', C-10'), 34.9 (C-5'), 52.0 (C-1), 52.6 (C-1'), 55.1 (*C*H_3OSO_3), 61.1 (C-5), 69.7 (C-2'), 71.0 (C-4'), 73.8 (C-4), 76.7 (C-3'), 79.47 (C-2), 79.51 (C-3). HRMS (FAB) *m/z*: $[M–CH_3OSO_3]^+$ Calcd for $C_{17}H_{35}O_6S$ 367.2154; Found 367.2170.

Bioassay

Inhibitory effects on rat intestinal α-glucosidases

Rat small intestinal brush border membrane vesicles were prepared and their suspensions in 0.1 M maleate buffer (pH 6.0) were used as small intestinal α-glucosidases of maltase, sucrose, and isomaltase. A test sample was dissolved in dimethyl sulfoxide (DMSO), and the resulting solution was diluted with 0.1 M maleate buffer to prepare the test sample solution (concentration of DMSO 10 %). A substrate solution in the maleate buffer (maltose 74 mM, sucrose 74 mM, isomaltase 7.4 mM, 50 μL), the test sample solution (25 μL), and the enzyme solution (25 μL) were mixed at 37 °C for 30 min, and then immediately heated by boiling water for 2 min to stop the reaction. The glucose concentrations were determined by a glucose-oxidase method. The final concentration of DMSO in the test solution was 2.5 % and no influence of DMSO on the inhibitory activity was detected.

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1,3-*O*-Benzylidene-D-threitol [2,4-*O*-benzylidene-D-threitol] (159). A hydrogen chloride solution in benzaldehyde (20.9 g) was pre-prepared by bubbling of a slow stream of hydrogen chloride (2.9 g) into freshly distilled benzaldehyde (18.0 g, 170 mmol) under ice-water cooling. To the solution (4.9 g), D-arabinitol (5.0 g, 32.9 mmol) was added at room temperature and D-arabinitol dissolved in 20 min. The resulting mixture solidified during stirring at room temperature for another 20 min and was allowed to stand at room temperature for further 18 h. The solid mass was finely crushed and triturated with a mixture of the solution of sodium hydroxide (2.0 g, 50 mmol) in water (30 mL) and methanol (10 mL). The deposited solid was collected by filtration, and then successively washed with water and

diethyl ether to give 1,3-benzylidene-D-arabinitol (**S2**, 5.2 g) as a colorless solid. The combined filtrate and washings were washed with diethyl ether and was condensed to give **158** (2.1 g). Compound **158** was pure enough for further reaction.

To a mixture of the crude **158** (3.71 g), saturated aqueous sodium hydrogen carbonate (15 mL), and dichloromethane (45 mL) was added portionwise sodium metaperiodate (6.6 g, 30.8 mmol) at room temperature. The heterogeneous mixture was stirred for 1 h at room temperature, and the insoluble solid was filtered off, and washed with ethyl acetate. The combined filtrate and washings were condensed, and the residue was dissolved in methanol (300 mL). To the mixture was added portionwise sodium borohydride (3.51 g, 92.8 mmol) at 0 °C. After being stirring for 1 h at room temperature, the reaction was quenched by addition of saturated aqueous ammonium chloride. Methanol was evaporated at reduced pressure, and the residue was extracted with ethyl acetate (3×50 mL). The extract was successively washed with aqueous sodium thiosulfate-sodium hydrogen carbonate and brine, and condensed to give the title compound **159** (2.90 g, 83% from D-arabinitol as a colorless microcrystalline solid, which was pure enough for further reaction. For analytical purpose a small portion of **S3** was recrystallized from a mixture of ethyl acetate and *n*-hexane to give colorless needles, mp 133–135 °C, $[\alpha]^{25}_{D}$ –6.3 (*c* = 1.13, $CHCl_3$), IR (nujol): 3263, 1087, 1060, 1002 cm^{-1}. ^1H NMR (800 MHz, DMSO-d_6) δ: 3.49 (1H, dtd, *J* = 6.6, 1.6, 1.5, H-2), 3.50 (1H, ddd, *J* = 11.6, 6.6, 5.5, H-4a), 3.56 (1H, ddd, *J* = 11.6, 5.9, 5.9, H-4b), 3.86 (1H, ddd, *J* = 6.6, 5.9, 1.5, H-3), 4.10 (2H, d, *J* = 1.6, H-1), 4.63 (1H, dd, *J* = 5.9, 5.5, O*H*), 4.73 (1H, d, *J* = 6.6, O*H*), 5.54 (1H, s, C*H*Ph), 7.32–7.37 (3H, m, arom.), 7.46–7.48 (2H, m, arom.). ^{13}C NMR (200 MHz, $CDCl_3$) δ: 61.2 (C-4), 62.6 (C-2), 72.4 (C-1), 80.2 (C-3), 100.5 (*C*HPh), 126.6/128.0/128.7 (d, arom.), 139.0 (s, arom.).

1,3-*O*-Benzylidene-L-threitol [2,4-*O*-benzylidene-L-threitol] (163). In a similar mannar used for the preparation of **159**, L-arabinitol (5.0 g, 32.9 mmol) was treated with a solution of hydrogen chloride in benzaldehyde (4.9 g). A similar work-up gave a practically pure 1,3-benzylidene-L-arabinitol (**162**, 7.5 g) as colorless solid, a part (2.47 g) of which was oxidized with sodium metaperiodate (4.4 g, 20.5 mmol) in a mixture of saturated aqueous sodium hydrogen carbonate (10 mL), and dichloromethane (30 mL). Work-up gave an aldehyde intermediate, which was then reduced with sodium borohydride (2.34 g, 61.9 mmol) in methanol (200 mL) to give the title compound **163** (1.92 g, 85%) as a colorless microcrystalline solid, which was pure enough for further reaction. ^1H and ^{13}C NMR spectroscopic properties of **162** were completely in accord with those of **158**. For analytical purpose a small portion of **163** was recrystallized from a mixture of ethyl acetete and *n*-hexane to give colorless needles, mp 133–135 °C, $[\alpha]^{24}_{D}$ +7.44 (*c* = 1.05, $CHCl_3$), ^1H and ^{13}C NMR spectroscopic properties of **163** were completely in accord with those of **159**.

2,4-*O*-Benzylidene-D-threitol 1,3-Cyclic Sulfate (160). A solution of freshly distilled thionyl chloride (0.39 mL, 5.4 mmol) in dry dichloromethane (10 mL) was added dropwise to a stirred mixture of diol **159** (0.8 g, 3.8 mmol), triethylamine (1.42 mL, 10.3 mmol) and dry dichloromethane (15 mL)

at 0 °C. After being stirred at 0 °C for 15 min, the mixture was poured into ice-cooled and vigorously stirred saturated aqueous sodium hydrogen carbonate (50 mL), and extracted with dichloromethane (1×30 mL, 2×10 mL). The extract was washed with brine, and condensed to give the corresponding sulfite (1.07 g) as a pale brown solid, which was immediately used in the next step without purification.

To a well stirred mixture of the crude sulfite (1.02 g), sodium hydrogen carbonate (800 mg, 9.5 mmol), carbon tetrachloride (20 mL), acetonitrile (20 mL), and water (10 mL) was added dropwise a brown mixture of sodium metaperiodate (1.96 g, 9.2 mmol), ruthenium chloride *n*-hydrate (30 mg), and water (15 mL) at 0 °C. After being stirred at 0 °C for 30 min, the reaction was quenched by the addition of aqueous sodium thiosulfate–sodium hydrogen carbonate. The resulting purple suspension was filtered by suction, and the filter cake was washed with ethyl acetate. The combined filtrate and washings was extracted with ethyl acetate (3×30 mL). The extract was washed with brine, and condensed to give a colorless solid (930 mg), which on column chromatography (*n*-hexane/CH_2Cl_2, 2/1→1/1→1/2) gave the title compound **160** (745 mg, 72 %) as a colorless microcrystalline solid, mp. 125–127 °C. $[\alpha]^{25}_D$ –37.1 (*c* = 1.00, $CHCl_3$). IR (nujol): 1404, 1199, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.08 (1H, ddd, *J* = 2.0, 1.4, 1.2, H-2), 4.20 (1H, dd, *J* = 13.5, 1.8, H-4a), 4.40 (1H, dd, *J* = 13.5, 1.4, H-4b), 4.66 (1H, dd, *J* = 12.6, 1.2, H-1a), 4.84 (1H, ddd, *J* = 1.8, 1.4, 1.4, H-3), 4.93 (1H, dd, *J* = 12.6, 2.0, H-1b), 5.62 (1H, s, C*H*Ph), 7.38–7.55 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 67.2 (C-2), 68.0 (C-4), 74.9 (C-1), 77.1 (C-3), 101.3 (*C*HPh), 126.2/128.4/129.7 (d, arom.), 136.4 (s, arom.). HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{13}O_6S$ 273.0433; Found 273.0445.

2,4-*O*-Benzylidene-L-threitol 1,3-Cyclic Sulfate (164). In a similar mannar used for the preparation of **160**, diol **163** (0.8 g, 3.81 mmol) was treated with a solution of thionyl chloride (0.39 mL, 5.4 mmol) in dichloromethane (25 mL) in the presence of triethylamine (1.42 mL, 10.3 mmol). A similar work-up gave the corresponding sulfite (1.02 g) as a pale brown solid, which was immediately used in the next step without purification. The crude sulfite (1.00 g) was oxidized with ruthenium tetroxide, which was generated from mixing sodium metaperiodate (1.92 g, 9.0 mmol) and ruthenium chloride *n*-hydrate (30 mg) in water (15 mL), in a mixture of sodium hydrogen carbonate (800 mg, 9.5 mmol), carbon tetrachloride (20 mL), acetonitrile (20 mL), and water (10 mL) to give a colorless solid (934 mg). Column chromatography (*n*-hexane/CH_2Cl_2, 2/1→1/1→1/2) gave the title compound **15** (777 mg, 75 %) as a colorless microcrystalline solid, mp. 124–126 °C. $[\alpha]^{23}_D$ ＋37.8 (*c* = 1.07, $CHCl_3$). ^1H and ^{13}C NMR spectroscopic properties of **164** were completely in accord with those of **160**.

Syntheses of sulfonium sulfate inner salts (2', 3'-*epi*-Salacinol (151), 3'-*epi*-Salacinol (152), 2'-*epi*-Salacinol (153)) and sulfonium chlorides (2', 3'-*epi*-Neosalacinol (154), 3'-*epi*-Neosalacinol (155), 2'-*epi*-Neosalacinol (156)).

By applying Pinto's conditions for the synthesis of salacinol (**113**), coupling reactions of thiosugar (**165**) with cyclic sulfates (**160**, **164**, **168**) were carried out in 1,1,3,3,3-hexafluoroisopropanol (HFIP), where an α-facial attack of **160**, **164**, **168** to the sulfur atom of **165** preferentially took place to give

coupled products **166**, **167** and **169** in 76%, 87% and 89% yield, respectively. Subsequently, compounds (**166**, **167** and **169**) was treated with aqueous TFA, where *p*-methoxybenzyl (PMB) group and benzylidene acetal moiety were simultaneously removed to afford desired sulfonium salts (**151, 152** and **153**) in good yield. As shown **Table S1**, the ^{13}C NMR spectral properties of **151, 152** and **153** were similar to that of salacinol (**113**), well supporting the formation of salacinol-type sulfonium inner salt structure. To remove sulfo group at the C-3' oxygen atom, **151, 152** and **153** were subjected to acidic methanolysis to give corresponding sulfonium salts (**154, 155** and **156**, X = CH_3OSO_3), the anion of which was then exchanged with resin IRA400I (Cl^- form) to give the corresponding chlorides (**154, 155** and **156**) in good yield. The ^{13}C NMR spectroscopic properties of **154, 155** and **156** were similar with each other.

Table S1. ^{13}C NMR data for salacinol (**113**) and its analogs **3'-*epi*-113 (151), 2'-*epi*-113 (152)** and **2', 3'-*epi*-113 (153)** in D_2O and neosalacinol (**114**) and its analogs **3'-*epi*-114 (154), 2'-*epi*-114 (155)** and **2', 3'-*epi*-114 (156)** in CD_3OD (125 MHz, δ in ppm)

	113[a,c]	**153**[d]	**3'-*epi*-113 (151)**[c]	**2'-*epi*-113 (152)**[c]	**156**[2]	**3'-*epi*-114 (154)**[d]	**2'-*epi*-114 (155)**[d]	**114**[d]
C1	50.5	49.8	50.4	49.4	51.8	52.3	50.3	50.8
C2	79.5	79.5	79.5	79.4	79.4	79.4	79.4	79.4
C3	80.3	80.5	80.1	80.4	79.5	79.6	79.8	79.7
C4	72.7	72.3	72.3	72.6	73.7	73.5	73.5	73.5
C5	61.7	61.7	61.7	61.7	61.0	61.1	61.1	61.1
C1’	52.4	52.1	52.0	51.5	52.1	52.2	51.3	51.4
C2’	68.3	68.6	68.4	68.7	69.6	69.2	69.1	69.5
C3’	82.6	82.8	82.1	82.0	75.3	74.2	74.3	75.1
C4’	62.2	62.2	62.2	62.2	64.0	63.6	63.6	64.0

a) BMCL2009 19 2195-2198; b) BMC2007(15) 3926-3973; c) 125 MHz; d) 200 MHz

Coupling raction between cyclic sulfates (160, 164, 168) and thiosugar (165).

Cyclic sulfates (**160, 164, 168**) were treated with thiosugar (**165**) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).

With cyclic sulfate (168). In a sealed tube, a mixture of **168** (234 mg, 0.86 mmol), **165** (376 mg, 0.74 mmol), potassium carbonate (20 mg, 0.14 mmol), and HFIP (1.2 ml) was stirred at 70 °C for 120 h. After removal of the solvent, the residue was purified on column chromatography (CH_2Cl_2→CH_2Cl_2/MeOH, 20/1) to give 1,4-dideoxy-2,3,5-tri-*O*-(*p*-methoxybenzyl)-1,4-{(*S*)-[2,4-*O*-benzylidene-1-deoxy-3-*O*-sulfo-D-erythritol-1-yl]episulfoniumylidene}-D-arabinitol inner salt (**169**, 516 mg, 89%) as a colorless amorphous, $[\alpha]^{24}_D$ –42.7 (*c* = 1.07, $CHCl_3$). IR (nujol): 1612, 1512, 1249, 1087, 1018 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ: 3.55 (1H, dd, *J* = 10.3, 7.8, H-5a), 3.68 (1H, dd, *J* = 10.3, 7.2, H-5b), 3.70 (1H, dd-like, *J* = *ca*. 10.5, 10.5, H-4'a), 3.72 (3H, s, OCH_3), 3.73 (6H, s, OCH_3), 3.81 (1H, dd, *J* = 13.2, 4.0, H-1a), 3.94 (1H, dd, *J* = 13.8, 7.2, H-1'a), 3.99 (1H, dd, *J* = 13.2, 2.6, H-1b), 4.10 (1H, dd, *J* = 13.8, 2.9, H-1'b), 4.16 (1H, ddd, *J* = 10.5, 10.5, 5.5, H-3'), 4.26/4.29 (each 1H, d, *J* = 11.5 Hz, OCH_2PMP), 4.28 (1H, ddd-like, *J* = *ca*. 10.5, 7.2, 2.9, H-2'), 4.34 (1H, dd, *J* = 10.5, 5.5, H-4'b), 4.36 (1H, dd-like, *J* = ca. 2.3, 2.3, H-3), 4.39/4.45 (each 1H, d, *J* = 11.2 Hz, OCH_2PMP),

4.43 (1H, br dd, *J* = 7.8, 7.2, H-4), 4.49/4.51 (each 1H, d, *J* = 11.5, OC*H*$_2$PMP), 4.62 (1H, ddd, *J* = 4.0, 2.6, 2.3, H-2), 5.60 (1H, s, C*H*Ph), 6.84–7.24 (12H, m, arom.), 7.35–7.45 (5H, m, arom.). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 46.7 (C-1), 47.0 (C-1'), 55.3 (O*C*H$_3$), 63.3 (C-4), 66.1 (C-5), 67.3 (C-3'), 69.0 (C-4'), 70.97/71.10/72.2 (O*C*H$_2$PMP), 75.7 (C-2'), 82.4 (C-2), 82.5 (C-3), 100.6 (*C*HPh), 113.9/114.0(2C)/126.5/128.4 /129.39/129.6/129.7/130.0 (d, arom.), 129.1(2C)/129.40/137.2/159.1/159.22/159.24 (s, arom). HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{40}H_{47}O_{12}S_2$ 783.2509; Found 783.2522.

With cyclic sulfate (160). In a similar mannar, 1,4-dideoxy-2,3,5-tri-*O*-(*p*-methoxybenzyl)-1,4-{(*S*)-[2,4-*O*-benzylidene-1-deoxy-3-*O*-sulfo-D-threitol-1-yl]episulfoniumylidene}-D-arabinitol inner salt (**166** 438 mg, 76%) was obtained by the condensation between **160** (234 mg, 0.86 mmol) and **165** (376 mg, 0.74 mmol) as colorless amorphous, $[\alpha]^{22}_D$ +26.5 [*c* = 1.00, $CHCl_3$]. IR (nujol): 1612, 1512, 1246, 1069, 1029 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.55 (1H, dd, *J* = 10.0, 10.0, H-5a), 3.70/3.74/3.75 (each 3H, s, OC*H*$_3$), 3.70–3.77 (2H, m, H-1a and 1'a), 3.79 (1H, dd, *J* = 10.0, 5.2, H-5b), 3.89 (1H, dd, *J* = 13.5, 8.6, H-1'b), 3.98 (1H, dd, *J* = 12.0, 1.4, H-4'a), 4.05 (1H, dd, *J* = 13.2, 3.0, H-1b), 4.21 (1H, dd-like, *J* = 3.0, 1.4, H-3'), 4.35 (1H, dd-like, *J* = 3.0, 2.0, H-3), 4.37 (1H, br d-like, *J* = *ca.* 12.1 Hz, H-4'b), 4.38/4.46 (each 1H, d, *J* = 11.7, OC*H*$_2$PMP), 4.43/4.48 (each 1H, *J* = 11.5, OC*H*$_2$PMP), 4.51 (1H, ddd-like, *J* = 10.0, 5.2, 2.0, H-4), 4.52–4.55 (1H, m, H-2'), 4.55/4.58 (2H, dd, *J* = 11.2, OC*H*$_2$PMP), 4.62 (1H, ddd, *J* = 3.0, 3.0, 3.0, H-2), 5.38 (1H, s, C*H*Ph), 6.81/6.88/6.91/7.15/7.16/7.27 (each 2H, d-like, *J* = *ca.* 8.6, arom.), 7.33–7.39 (5H, m, arom.). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 46.5 (C-1), 47.0 (C-1'), 55.2/55.3(2C) (O*C*H$_3$), 63.9 (C-4), 66.5 (C-5), 68.3 (C-3'), 69.5 (C-4'), 70.9/71.3/72.2 (O*C*H$_2$PMP), 73.4 (C-2'), 81.8 (C-2), 82.5 (C-3), 100.1 (*C*HPh), 113.9/114.0(2C)/126.2/128.1/129.0/129.66/129.74/130.0 (d, arom.), 129.2/129.3/137.9/159.11/159.21/159.24 (s, arom.). HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{40}H_{47}O_{12}S_2$ 783.2509; Found 783.2488.

With cyclic sulfate (164). In a similar mannar, 1,4-dideoxy-2,3,5-tri-*O*-(*p*-methoxybenzyl)-1,4-{(*S*)-[2,4-*O*-benzylidene-1-deoxy-3-*O*-sulfo-L-threitol-1-yl]episulfoniumylidene}-D-arabinitol inner salt (**167,** 503 mg, 87%) was obtained by the condensation between **164** (234 mg, 0.86 mmol) and **165** (376 mg, 0.74 mmol) as colorless amorphous, $[\alpha]^{23}_D$ –48.6 (*c* = 1.01, $CHCl_3$). IR (nujol): 1612, 1512, 1246, 1068, 1026 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.60 (1H, dd, *J* = 10.0, 8.9, H-5a), 3.73/3.735/3.743 (each 3H, s, OC*H*$_3$), 3.78 (1H, dd, *J* = 10.0, 6.6, H-5b), 3.82 (2H, d-like, *J* = 6.0, H-1'a and H-1'b), 3.95 (1H, dd, *J* = 13.5, 3.2, H-1a), 3.96 (1H, dd-like, *J* = *ca*. 12.0, 1.4, H-4'a), 3.98 (1H, dd, *J* = 13.5, 4.0, H-1b), 4.17 (1H, ddd, *J* = 1.8, 1.4, 1.4, H-3'), 4.29 (1H, dd, *J* = 12.0, 1.4, H-4'b), 4.34 (2H, s, OC*H*$_2$PMP), 4.39 (1H, dd-like, *J* = *ca*. 2.3, 2.3, H-3), 4.41/4.47 (each 1H, d, *J* = 11.5, OC*H*$_2$PMP), 4.42–4.47 (1H, m H-4), 4.50/4.55 (each 1H, d, *J* = 11.2, OC*H*$_2$PMP), 4.55 (1H, td-like, *J* = 6.0, 1.8, H-2'), 4.63 (1H, ddd, *J* = 4.0, 3.2, 2.3, H-2), 5.49 (1H, s, C*H*Ph), 6.84–6.92 (6H, m, arom.), 7.14/7.18/7.26 (each 2H, d-like, *J* = 8.6 Hz, arom.), 7.35–7.42 (5H, m, arom.). ^{13}C NMR (125 MHz,

DMSO-d_6) δ: 45.7 (C-1'), 45.9 (C-1), 55.2 (O*C*H$_3$), 63.6 (C-4), 66.5 (C-5), 68.1 (C-3'), 69.6 (C-4'), 70.9/71.1/72.2 (O*C*H$_2$PMP), 73.9 (C-2'), 82.5 (C-3), 82.6 (C-2), 100.3 (*C*HPh), 113.9/113.95/114.01/126.3/128.3/129.2/129.67/129.69/130.0 (d, arom.), 128.97/129.03/129.4/137.9/159.1/159.2/159.3 (s, arom.). HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_{40}H_{47}O_{12}S_2$ 783.2509; Found 783.2488.

De-protection of PMB and benzylidene moieties of coupling products (151, 152 and 153) by aqueous TFA.

1,4-Dideoxy-1,4-{(*S*)-[1-deoxy-3-*O*-sulfo-D-erythritol-1-yl]episulfoniumylidene}-D-arabinitol inner salt (153). A mixture of coupling product (**169,** 460 mg, 0.59 mmol), trifluoroacetic acid (5 mL), and water (0.5 mL) was stirred at room temperature for 1.5 h. After removal of the solvent *in vacuo*, the residue was washed with dichroromethane to give a colorless solid, which was triturated with methanol to give the title compound (**169**, 157 mg, 80%) as a white powder, mp 149–151 °C. $[\alpha]^{24}_D$ –27.3 (*c* = 0.60, H$_2$O), IR (KBr): 3645, 1261, 1215, 1049, 1010 cm^{-1}. ^{1}H NMR (800 MHz, D$_2$O) δ: 3.89 (1H, dd, *J* = 12.8, 3.2, H-4'a), 3.90 (1H, dd, *J* = 13.6, 4.0, H-1a), 3.918 (1H, dd, *J* = 12.8, 8.8, H-1'a), 3.922 (1H, dd, *J* = 13.6, 4.8, H-1b), 3.99 (1H, dd, *J* = 12.8, 3.2, H-1'b), 4.00 (1H, dd, *J* = 12.8, 3.2, H-4'b), 4.02 (1H, dd, *J* = 12.8, 8.0, H-5a), 4.03 (1H, dd, *J* = 12.8, 5.6, H-5b), 4.19 (1H, ddd, *J* = 8.0, 5.6, 3.2, H-4), 4.37 (1H, ddd, *J* = 7.2, 3.2, 3.2, H-3'), 4.44 (1H, ddd, *J* = 8.8, 7.2, 3.2, H-2'), 4.51 (1H, dd-like, *J* = *ca*. 3.2, 3.2, H-3), 4.78 (1H, ddd, *J* = 4.8, 4.0, 3.2, H-2). ^{13}C NMR (200 MHz, D$_2$O) δ: 49.8 (C-1), 52.1 (C-1'), 61.7 (C-5), 62.2 (C-4'), 68.6 (C-2'), 72.3 (C-4), 79.5 (C-2), 80.5 (C-3), 82.8 (C-3'). HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_9H_{19}O_9S_2$ 335.0471; Found 335.0472.

1,4-Dideoxy-1,4-{(*S*)-[1-deoxy-3-*O*-sulfo-D-threitol-1-yl]episulfoniumylidene}-D-arabinitol inner salt (151). In a similar mannar, the title compound (**151,** 151 mg, 86%) was obtained from coupling product (**166**, 410 mg, 0.52 mmol) as a white powder, mp. 161–162 °C. $[\alpha]^{25}_D$ +17.5 (*c* = 0.40, H$_2$O). IR (nujol): 3418, 1249, 1219, 1056, 1007 cm^{-1}. ^{1}H NMR (500 MHz, D$_2$O) δ: 3.82 (1H, dd, *J* = 12.0, 6.3, H-4'a), 3.81–3.85 (1H, m, H-1'a), 3.85 (1H, dd, *J* = 12.0, 6.0, H-4'b), 3.87 (1H, dd, *J* = 13.5, 4.0, H-1a), 3.85–3.89 (1H, m, H-1'b), 3.90 (1H, dd, *J* = 13.5, 3.8, H-1b), 3.92 (1H, dd, *J* = 11.8, 8.9, H-5a), 4.07 (1H, ddd, *J* = 8.9, 4.9, 3.2, H-4), 4.11 (1H, dd, *J* = 11.8, 4.9, H-5b), 4.38 (1H, ddd-like, *J* = *ca*. 6.3, 6.0, 3.0, H-3'), 4.42 (1H, dd-like, *J* = *ca*. 3.5, 3.2, H-3), 4.46 (1H, ddd, *J* = 9.2, 4.1, 3.0, H-2'), 4.73 (1H, ddd, *J* = 4.0, 3.8, 3.5, H-2). ^{13}C NMR (125 MHz, D$_2$O) δ: 50.4 (C-1), 52.0 (C-1'), 61.7 (C-5), 62.2 (C-4'), 68.4 (C-2'), 72.3 (C-4), 79.5 (C-2), 80.1 (C-3), 82.1 (C-3'). HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_9H_{19}O_9S_2$ 335.0471; Found 335.0473.

1,4-Dideoxy-1,4-{(*S*)-[1-deoxy-3-*O*-sulfo-L-threitol-1-yl]episulfoniumylidene}-D-arabinitol inner salt (152). In a similar mannar, the title compound (**152,** 166 mg, 78%) was obtained from coupling product (**167**, 498 mg, 0.64 mmol) as a white powder, mp. 145–147 °C. $[\alpha]^{27}_D$ –39.0 (*c* = 0.40, H$_2$O). IR (nujol): 3360, 1288, 1200, 1064, 1015 cm^{-1}. ^{1}H NMR (500 MHz, D$_2$O) δ: 3.82 (1H, dd,

J = 11.8, 6.0, H-4'a), 3.83 (1H, dd, *J* = 13.5 4.3, H-1'a), 3.85 (1H, dd, *J* = 11.8, 5.2, H-4'b), 3.86 (1H, dd-like, *J* = *ca*. 13.2, 3.7, H-1a), 3.89 (1H, dd, *J* = 13.2, 3.7, H-1b), 3.92 (1H, dd, *J* = 13.2, 9.5, H-1'b), 3.97 (1H, dd, *J* = 12.3, 8.0, H-5a), 4.09 (1H, dd, *J* = 12.3, 5.2, H-5b), 4.15 (1H, ddd, *J* = 8.0, 5.2, 3.2, H-4), 4.38 (1H, ddd, *J* = 6.0, 5.2, 2.9, H-3'), 4.460 (1H, ddd-like, *J* = *ca*. 9.5, 4.3, 2.9, H-2'), 4.462 (1H, dd-like, *J* = *ca*. 3.2, 3.2, H-3), 4.74 (1H, ddd, *J* = 3.7, 3.7, 3.2, H-2). ^{13}C NMR (125 MHz, D_2O) δ: 49.4 (C-1), 51.5 (C-1'), 61.7 (C-5), 62.2 (C-4'), 68.7 (C-2'), 72.6 (C-4), 79.4 (C-2), 80.4 (C-3), 82.0 (C-3'). HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for $C_9H_{19}O_9S_2$ 335.0471; Found 335.0476.

Acidic methanolysis of sulfonium inner salts (154, 155, 156).

1,4-Dideoxy-1,4-{(*R*)-[1-deoxy-D-erythritol-1-yl]episulfoniumylidene}-D-arabinitol chloride (156). A mixture of **153** (75 mg, 0.22 mmol) and 5% methanolic hydrogen chloride (4 ml) was stirred at 50 °C for 3 h. After removal of the solvent *in vacuo*, the residue (92 mg) was treated with ion exchange resin IRA400J (Cl^- form, 2.0 g) in methanol (4 mL) at room temperature for 15 h. The resin was filtered off and washed with methanol. The combined filtrate and washings were condensed to give the title compound **156** (50 mg, 77%) as a colorless oil, $[\alpha]^{27}_D$ –52.9 (*c* = 0.24, MeOH). IR (neat): 3418, 1643, 1415, 1258, 1222, 1072 cm^{-1}. ^{1}H NMR (800 MHz, CD_3OD) δ: 3.60–3.63 (1H, m, H-3'), 3.62–3.64 (1H, m, H-4'a), 3.67–3.70 (1H, m, H-4'b), 3.79 (1H, dd, *J* = 12.8, 4.8, H-1'a), 3.81 (1H, dd, *J* = 12.8, 6.4, H-1'b), 3.82 (1H, dd-like, *J* = *ca*. 12.0, 2.0, H-1a), 3.83 (1H, dd, *J* = 12.0, 3.2, H-1b), 3.95 (1H, dd, *J* = 12.0, 8.8, H-5a), 4.03 (1H, dd, *J* = 12.0, 6.4, H-5b), 4.07 (1H, ddd-like, *J* = *ca*. 6.4, 6.4, 4.8, H-2'), 4.09 (1H, br dd, *J* = 8.8, 6.4, H-4), 4.40 (1H, dd, *J* = 2.4, 0.8, H-3), 4.62 (1H, ddd-like, *J* = *ca*. 3.2, 2.4, 2.0, H-2). ^{13}C NMR (200 MHz, CD_3OD) δ: 50.8 (C-1), 51.4 (C-1'), 61.1 (C-5), 64.0 (C-4'), 69.5 (C-2'), 73.5 (C-4), 75.1 (C-3'), 79.4 (C-2), 79.7 (C-3). HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_9H_{19}O_6S$ 255.0903; Found 255.0893.

1,4-Dideoxy-1,4-{(*R*)-[1-deoxy-D-threitol-1-yl]episulfoniumylidene}-D-arabinitol chloride (154). In a similar mannar, the title compound (**151**, 58 mg, 78%) was obtained from coupling product (**154**, 86 mg, 0.26 mmol) as a colorless oil, $[\alpha]^{23}_D$ +2.7 (*c* = 1.0, MeOH). IR (neat): 3287, 1631, 1404, 1257, 1072, 1042 cm^{-1}. ^{1}H NMR (800 MHz, CD_3OD) δ: 3.59 (1H, ddd, *J* = 6.4, 4.8, 3.2, H-3'), 3.62 (1H, dd, *J* = 11.2, 4.8z, H-4'a), 3.64 (1H, dd, *J* = 11.2, 6.4, H-4'b), 3.74 (1H, dd, *J* = 12.8, 4.0, H-1'a), 3.79 (1H, dd, *J* = 12.8, 9., H-1'b), 3.84 (1H, dd, *J* = 12.8, 3.2, H-1a), 3.86 (1H, dd, *J* = 12.8, 1.6, H-1b), 3.93 (1H, dd, *J* = 12.0, 9.6, H-5a), 3.98 (1H, br dd, *J* = 9.6, 4.8, H-4), 4.05 (1H, dd, *J* = 12.0, 4.8, H-5b), 4.18 (1H, ddd, *J* = 9.6, 4.0, 3.2, H-2'), 4.37 (1H, dd-like, *J* = *ca*. 2.4, 0.8, H-3), 4.61 (1H, ddd-like, *J* = ca. 3.2, 2.4, 1.6, H-2). ^{13}C NMR (200 MHz, CD_3OD) δ: 52.2 (C-1'), 52.3 (C-1), 61.1 (C-5), 63.6 (C-4'), 69.2 (C-2'), 73.5 (C-4), 74.2 (C-3'), 79.4 (C-2), 79.6 (C-3). HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_9H_{19}O_6S$ 255.0903; Found 255.0921.

1,4-Dideoxy-1,4-{(*R*)-[1-deoxy-L-threitol-1-yl]episulfoniumylidene}-D-arabinitol Chloride (155). In a similar mannar, the title compound (**155,** 56 mg, 84%) was obtained from coupling product (**152**,

77 mg, 0.23 mmol) as a colorless oil, $[\alpha]^{24}_{D}$ –17.0 (*c* = 0.17, MeOH). IR (neat): 3360, 1643, 1416, 1254, 1072 cm^{-1}. ^{1}H NMR (800 MHz, CD_3OD) δ: 3.60 (1H, ddd-like, *J* = *ca*. 6.5, 4.8, 3.2, H-3'), 3.62 (1H, dd-like, *J* = ca. 11.2, 4.8, H-4'a), 3.64 (1H, dd, *J* = 11.2, 6.5, H-4'b), 3.70 (1H, dd, *J* = 12.8, 3.2, H-1'a), 3.80 (1H, dd, *J* = 12.8, 1.6, H-1a), 3.82 (1H, dd, *J* = 12.8, 8.8, H-1'b), 3.85 (1H, dd, *J* = 12.8, 4.0, H-1b), 3.95 (1H, dd, *J* = 11.2, 8.8, H-5a), 4.03 (1H, dd, *J* = 11.2, 6.4, H-5b), 4.06 (1H, br dd-like, *J* = *ca.* 8.8, 6.4, H-4), 4.17 (1H, ddd, *J* = 8.8, 3.2, 3.2, H-2'), 4.41 (1H, br s-like, H-3), 4.62 (1H, br dd-like, *J* = *ca*. 4.0, 1.6, H-2). ^{13}C NMR (200 MHz, CD_3OD) δ: 50.3 (C-1), 51.3 (C-1'), 61.1 (C-5), 63.6 (C-4'), 69.1 (C-2'), 73.5 (C-4), 74.3 (C-3'), 79.4 (C-2), 79.8 (C-3). HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_9H_{19}O_6S$ 255.0903; Found 255.0910.

Biochemistry Procedures

***In vitro* enzymatic assay toward recombinant human GAA (rGAA, Myozyme).**

Standard assay conditions: Reactions contained 0.5 μM rGAA (Myozyme, SANOFI GENZYME), 150 mM McIlvaine bufer (pH 5.2), 3 mM 4-nitrophenyl-α-D-glucopyranoside (α-p-NPG), and varying amounts of inhibitors (compounds **113-114**, **134a-134k**, **151-156**, voglibose, and acarbose). The reactions (80 μL) were run in 96-well plates (FALCON, 353072). Absorbance at 405 nm (A_{405}) was measured on a Multiskan FC (Thermo Fisher Scientific).

Determination of apparent K_i (K_i^{app}) values of compounds **113-114**, **134a-134k**, **151-156***, voglibose, and acarbose*: K_i^{app} determination was performed under standard assay conditions. The enzyme, substrate, and inhibitor concentrations are listed here: rGAA was used at 0.5 μM with 3 mM of α-p-NPG in either the absence or presence of compounds **113-114**, **134a-134k**, **151-156**, viglibose, and acarbose (salacinol (**113**): 0.031–1000 μM; neosalacinol (**114**): 0.031–1000 μM; **134a** (H): 0.024–100 μM; **134b** (*o*-CH_3): 0.024–100 μM; **134c** (*o*-Cl): 0.024–100 μM; **134d** (*o*-CF_3): 0.024–100 μM; **134e** (*o*-NO_2): 0.024–100 μM; 3'-*epi*-salacinol (**151**): 0.031–1000 μM; 3'-*epi*-neosalacinol (**154**): 0.031–1000 μM; 2'-*epi*-salacinol (**151**): 0.122–4000 μM; 3'-*epi*-neosalacinol (**152**): 0.122–4000 μM; 2',3'-*epi*-salacinol (**153**): 0.122–4000 μM; 2',3'-*epi*-neosalacinol (**154**): 0.061–2000 μM; voglibose: 0.031–1000 μM; acarbose: 0.122–4000 μM). Inhibition studies were performed by pre-incubation of rGAA (0.5 μM) with varying amounts of inhibitors (compounds **113-114**, **134a-134k**, **151-156**, voglibose, and acarbose) for 10 min at room temperature. After 10 min at room temperature, the reaction was initiated by adding α-p-NPG (3 mM). After 30 min incubation at 37 ℃, the reaction was quenched by adding 120 μL of 80 mM glycine-NaOH buffer (pH 10). Control reactions were treated except no inhibitors (compounds**113-114**, **134a-134k**, **151-156**, voglibose, and acarbose) were added to the reaction mixture. In all experiments, the total DMSO concentration was kept at 2.0%. All K_i^{app} values were determined by replicating each assay twice. Data was fit to the Morrison equation using Prism 7 (GraphPad Software).

***In vitro* enzymatic assay toward *β*-glucosidase from *Aspergillus niger*.**

Standard assay conditions: Reactions contained 0.5 U/mL *β*-glucosidase from *Aspergillus niger* (Sigma-Aldrich, 49291), 150 mM McIlvaine bufer (pH 4.6), 10 mM 4-nitrophenyl-*β*-D-glucopyranoside (*β*-p-NPG), and 1 mM inhibitors (compounds **113-114**, **134a-134k**, **151-156**, voglibose, and acarbose). The reactions (80 μL) were run in 96-well plates (FALCON, 353072). Absorbance at 405 nm (A_{405}) was measured on a Multiskan FC (Thermo Fisher Scientific).

Inhibition profile of β-glucosidase from *A. niger toward compounds* **113-114**, **134a-134k**, **151-156***, voglibose, and acarbose*: Inhibition studies were performed by pre-incubation of *β*-glucosidase from *A. niger* (0.5 U/mL) with 1 mM of inhibitors (compounds **113-114**, **134a-134k**, **151-156**, voglibose, and acarbose) for 10 min at room temperature. After 10 min at room temperature, the reaction was initiated by adding *β*-p-NPG (10 mM). After 30 min incubation at 37 ℃, the reaction was quenched by adding 120 μL of 80 mM glycine-NaOH buffer (pH 10). Control reactions were treated except no inhibitors (compounds **113-114**, **134a-134k**, **151-156**, voglibose, and acarbose) were added to the reaction mixture. In all experiments, the total DMSO concentration was kept at or below 1.0%.

参考文献

1. David J. N. and Gordon M. C. *J. Nat. Prod*. **2020**, *83*, 770–803.
2. Tan, S. Y.; Tatsumura, Y. *Singapore Med. J*. **2015**, *56*, 366–367.
3. Hodgkin, C. D.; *Adv. Sci.* **1949**, *22*, 85–89.
4. Tu, Y. *Nat. Med.* **2011**, *17*, 1217–1220.
5. a) 李英、虞佩林、陳一心 薬学学報, **1981** *16*: 429−439. b) 顧浩明、呂宝芬, 瞿志祥 中国薬理学報, **1980**, *1*, 48−50.
6. Aicher, D. T.; Buszek R. K.; Fang, G. F.; Forsyth J. C.; Jung, H. S.; Kishi, Y.; Matelich, C. M.; Scola, M. P.; Spero, M. D.; Yoon, K. S. *J. Am. Chem. Soc.* **1992**, 114, 8, 3162-3164.
7. Tokuyama, T.; Daly, J. W.; Witkop, B.; Karle, I. L.; Karle, K. J. *J. Am. Chem. Soc.* **1968**, *90*, 439–457.
8. 黒須 三千夫, 岸 義人, *有機合成化学協会誌* **2004**, *62*, 1205.
9. Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. M. *J. Am. Chem. Soc*. **1992**, *114*, 3475–3478.
10. Corey, E. J.; Loh, T-P.; Achyutharao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600–5602.
11. Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, *45*, 563–569.
12. a) Toyooka, N.; Tanaka, K.; Momose, T.; Daly, J. W.; Garraffo, H. M. *Tetrahedron* **1997**, *53*, 9553–9574.; b) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett*. **2002**, *4*, 1715–1718.; c) Toyooka, N.; Nemoto, H. *Tetrahedron Lett*. **2003**, *44*, 569–570.; d) Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem. Int. Ed*. **2003**, *42*, 3808–3810.; e) Toyooka, N.; Nemoto, H.; Kawasaki, M.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **2005**, *61*, 1187–1198.; f) Toyooka, N.; Dejun, Z.; Nemoto, H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron Lett*. **2006**, *47*, 577–580.; g) Toyooka, N.; Dejun, Z.; Nemoto, H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron Lett*. **2006**, *47*, 581–582.; h) Toyooka, N.; Kobayashi, S.; Zhou, D.; Tsuneki, H.; Wada, T.; Sakai, H.; Nemoto, H.; Sasaoka, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5872–5875.; i) Toyooka, N.; Zhou, D.; Kobayashi, S.; Tsuneki, H.; Wada, T.; Sakai, H.; Nemoto, H.; Sasaoka, T.; Tezuka, Y.; Subehan; Kadota, S.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Synlett* **2008**, *12*, 61–64.; j) Toyooka, N.; Zhou, D.; Nemoto, H.; Tezuka, Y.; Kadota, S.; Andriamaharavo, N. R.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *J. Org. Chem*. **2009**, *74*, 6784–6791.; For a review see: Michael, J. P. *Nat. Prod. Rep*. **2008**, *25,* 139–165.
13. Tokuyama,T.; Uenoyama,K.; Brown, G.; Daly, J. W.; Witkop, B.; *Helv. Chim. Acta* **1974**, *57*, 2597–2604.
14. Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**,

60, 1128–1140.

15. a) Mensah-Dwumah, M.; Daly, J. W.; *Toxicon* **1978**, *16*, 189–194. b) Souccar, C.; Maleque, M. A.; Daly, J. W.; Albuquerque, E. X.; *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **1982**, *41*, 1299. c) Daly, J. W.;Nishizawa, Y.; Edwards, M. W.; Waters, J. A.; Aronstam, R. S.; *Neurochem. Res.* **1991**, *16*, 489–500.
16. Fujimoto, R.; Kishi, Y. Blount, J. F.; *J. Am. Chem. Soc.* **1980**, *102*, 7154–7156.
17. Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 4197–4198.
18. a) Overman, L. E.; Lesuisse, D.; Hashimoto, M.; *J. Am. Chem. Soc.* **1983**, *105*, 5373–5379. b) Hart, D. J.; Kanai, K.; *J. Am. Chem. Soc.* **1983**, *105*, 1255–1263.
19. a) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 512–516. b) Chu, S.; Wallace, S.; Smith, M. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 13826–13829. c) Nemoto, T. Yamaguchi, M.; Kakugawa, K.; Harada, S.; Hamada, Y. *Adv.Synth.Catal.* **2015**, *357*, 2547–2555. d) Piccichè, M.; Pinto, A.; Griera, R.; Bosch, J.; Amat, M. *Org. Lett*. **2017**, *19*, 6654–6657.
20. Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, 59, 943–945.
21. Toyooka, M.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715–1717.
22. Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem.* **1999**, *64*, 2182–2183.
23. Toyooka, N.; Fukutome, A.; Shinoda, H.; Nemoto, H. *Angew. Chem., Int. Ed.* **2003**, 42, 3938–3940
24. Chênvert, R.; Ziarani, G. M.; Morin, M. P.; Dasser, M. *Tetrahedron: Asymmetry*, **1999**, *10*, 3117–3122.
25. Toyooka, N.; Okumura, M.; Nemoto, H. *J. Org. Chem.* **2002**, 67, 6078–6081.
26. Takashima, K.; Toyooka, N. *Heterocycles* **2019***, 99*, 649–660.
27. Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691–2694.
28. Juge, M.; Grimaud, N.; Biard, J. F.; Sauviat M. P.; Nabil. M. Verbist, J.F.; Petit, J. Y. *Toxicon* **2001**, *39*, 1231–1237.
29. a) Werner, K. M.;de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686–687. b) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865–4873.
30. a) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369–3372. b) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688–689.
31. a) Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205–1208. b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583–4592. c) Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059–2074.
32. Sauviat, M.-P.; Vercauteren, J.; Grimaud, N.; Jugé, M.; Nabil, M.; Petit, J.-Y.; Biard, J.-F. *J. Nat. Prod.* **2006**, *69*, 558–562.

33. Nishikawa, K.; Yamauchi, K.; kikuchi, S.; Ezaki, S.; Koyama, T.; Nokubo, H.; Matsumura, K.; Kodama, T.; Kumagai, M.; Morimoto, Y. *Chem. Eur. J.* **2017**, *23*, 9535–9545.
34. Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363–364.
35. Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511–3514.
36. Schär, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569–1571.
37. Caldwell, J. J.; Craig, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 2631–2634.
38. Mei, S.-L.; Zhao, G. *Eur. J. Org. Chem.* **2010**, 1660–1668.
39. Perry, M. A.; Morin, M. D.; Slafer, B. W.; Wolckenhauer, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 9591–9593.
40. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Int. Ed.* **2002**, *41*,3017–3020.
41. Sun, P.; Sun, C.; Weinreb, M. S. *J. Org. Chem.* **2002**, 67, 4337–4345.
42. Tokuyama, H.; Fujitani, M.; Tsuchiya, M.; Okano, K.; Takasu, K.; Ihara, M. *Synlett* **2010**, 822–826.
43. In, J.; Lee, S.; Kwon, Y.; Kim, S. *Chem. Eur. J.* **2014**, *20*, 17433–17442.
44. Lee, S.; Bae, M.; In, J.; Kim, J.; Kim, S. *Org. Lett.* **2017**, *19*, 254–257.
45. Nishikawa, K.;.kikuchi, S.; Ezaki, S.; Koyama, T.; Nokubo, H.; Kodama, T.; Kumagai, M.; Morimoto, Y. *Chem. Eur. J.* **2017**, *23*, 9535–9545.
46. Wender, P. A.; Glass, E. T.; Krauss, E. N.; Mühlebach, M.; Peschke, B.; Rawlins, B. D. *J. Org. Chem.* **1996**, *61*, 7662–7663.
47. Takashima, K.; Hayakawa, D.; Gouda, H.; Toyooka, N. *J. Org. Chem.* **2019**, *84*, 5222–5229.
48. a) Daly, J. W. *J. Nat. Prod.* **1998**, *68*, 162–172. b) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575.
49. Daly, J. W. *Cell. Mol. Neurobiol.* **2005**, *25*, 513–552.
50. Daly, J. W.; Kaneko, T.; Wilham, J.; Garraffo, H. M.; Spaande, T. F.; Espinosa, A.; Donnelly, M. A. *Proc. Nat'l Acad. Sci. USA.* **2002**, *99*, 13996–14001.
51. Saporito, R. A.; Donnelly, M. A.; Jain, P.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Toxicon.* **2007**, *50*, 757–778.
52. Daly, J. W. *Personal communications*.
53. Taly, A.; Corringer, P. J.; Guedin, D.; Lestage, D.; Changeux, J. P. *Nat. Rev. Drug. Discov.* **2009**, *8*, 733–750.
54. Albuquerque, E. X.; Pereira, E. F.; Alkondon, M. *Physiol. Rev.* **2009**, *89*, 73–120.
55. Fusco, M. D.; Becchetti, A.; Patrignani, A.; Annesi, G.; Gambardella, A.; Quattrone, A.; Ballabio, A.; Wanke, E.; Casari, G. *Nat. Genet.* **2000**, *26*, 275.
56. Hosur, V.; Loring, R, H. *Mol. Pharm.* **2011**, *79*, 167–174.
57. Quik, M.; Mclntosh, J. M. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 481–489.
58. Rollema, H.; Coe, J. W.; Chambers, L. K.; Hurst, R. S.; Stahl, S, M.; Williams, K. E. *Trends. Pharmacol. Sci.* **2007**, *28*, 316–324.

59. Alkam, T.; Nabeshima, T. *The Lung perspectives.* **2010**, *18*, 57–61.
60. Tavares, X. D. S.; Blum, A. P.; Nakamura, D. T.; Puskar, N. L.; Shanata, J. A. P.; Lester, H. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 11474–11480.
61. Zhang, H. K.; Yu, L. F.; Eaton, J. P.; Whiteaker, P.; Onajole, O. K.; Hanania, T.; Brunner, D.; Lukas, R. J.; Kozikowski, A. P. *J. Med. Chem.* **2013**, *56*, 5495–5504.
62. Liu, Y.; Richardson, J.; Tran, T.; Al-Muhtasib, N.; Xie, T.; Yenugonda, V. M.; Sexton, H. G.; Rezvani, A. H.; Levin, E. D.; Sahibzada, N.; Kellar, K. J.; Brown, M. L.; Xiao, Y.; Paige, M. *J. Med. Chem.* **2013**, *56*, 3000–3011.
63. Mazurov, A. A.; Miao, L.; Bhatti, B. S.; Strachan, J. P.; Akireddy, S.; Murthy, S.; Kombo, D.; Xiao, Y. d.; Hammond, P.; Zhang, J.; Hauser, T. A.; Jordan, K. G.; Miller, C. H.; Speake, J. D.; Gatto, G. J.; Yohannes, D. *J. Med. Chem*. **2012**, *55*, 9181–9194.
64. Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol*. **2004**, *66*, 1061–1069.
65. Pivavarchyk, M.; Smith, A. M.; Zhang, Z.; Zhou, D.; Wang, X.; Toyooka, N.; Tsuneki, H.; Sasaoka, T.; McIntosh, J. M.; Crooks, P. A.; Dwoskin, L. P. *Eur. J. Pharmacol.* **2011**, *658,* 132.
66. Wang, X. et al. *Eur. J. Org. Chem*. **2012**, *36*, 7082–7092.
67. Okada, T.; Wu, N.; Takashima, K.; Ishimura, J.; Morita, H.; Ito, T.; Kodama, T.; Yamasaki, Y.; Akanuma, S.; Kubo, Y.; Hosoya, K.; Tsuneki, H.; Wada, T.; Sasaoka, T.; Shimizu, T.; Sakai, H.; Dwoskin, P. L.; Hussami, R. S.; Saporito, A. R.; Toyooka, N. *Molecules* 2**021**, *26*, 7529–7544.
68. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
69. Takashima, K.; Okada, T.; Kato, A.; Yamasaki, Y.; Sugouchi, T.; Akanuma, S.; Kubo, Y.; Hosoya, K.; Morita, H.; Ito, T.; Kodama, T.; Tanabe, G.; Toyooka, N. *ChemistrySelect* **2022**, *7*, e202104533.
70. 厚生労働省、令和元年 年国民健康・栄養調査
71. International Diabetes Federation, *IDF diabetes atlas eighth edition 2021*
72. Matsuda, H.; Yoshikawa, M.; Morikawa, T.; Tanabe, G.; Muraoka, O.; *J. Trad. Med.* **2005**, *22*,145–153.
73. a) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett*. **1997**, *38*, 8367–8370. b) Yoshikawa, M.; Morikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioorg. Med. Chem.* **2002**, *10*, 1547–1554.
74. Yoshikawa, M.; Xu, F.; Nakamura, S.; Wang, T.; Matsuda, H.; Tanabe, G.; Muraoka, O.; *Heterocycles* **2008**, *75*, 1397–1405.
75. Yoshikawa, M.; Muraoka, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1339–1340.
76. Minami, Y.; Kuriyama, C.; Ikeda, K.; Kato, A.; Takebayashi, K.; Adachi, I.; Fleet, J. W. G.; Kettawan, A.; Okamoto, T.; Asano, N. *Bioorg. Med. Chem.* **2008**, *16*, 2734–2740.

77. Xie, W.; Tanabe, G,; Akaki, J.; Morikawa, T.; Ninomiya, K.; Minematsu, T.; Yoshikawa, M.; Wu, X.; Muraoka, O. *Bioorg. Med. Chem.* **2011**, *19*, 2015–2022.

78. a) Ozaki, S.; Oe, H.; Kitamura, S. *J. Nat. Prod.* **2008**, *71,* 981–984. b) Muraoka, O.; Xie, W.; Tanabe, G.; Amer, A.F.M.; Minematsu, T.; Yoshikawa, M. *Tetrahedron Lett.* **2008**, *49*, 7315–7317.

79 a) Ghavami, A.; Sadalapure, K. S.; Johnston, B. D.; Lobera, M.; Snider, B. B.; Pinto, B. M. *Synlett* **2003**, *9*, 1259-1262. b) Tanabe, G.; Xie, W.; Ogawa, A.; Cao, C.; Minematsu, T.; Yoshikawa, M.; Muraoka, O. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2195–2198. c) Eskandari, R.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Org. Lett*. **2010**, *12*, 1632–1635. d) Johnston, B. D.; Jensen, H. H.; Pinto, B. M. *J. Org. Chem.* **2006**, *71*, 1111–1118. e) Jayakanthan, K.; Mohan,S.; Pinto, B. M. *J. Am. Chem. Soc.* **2009**, *131*, 5621–5626. f) Tanabe, G.; Matsuda, Y.; Oka, M.; Kunikata, Y.; Tsutsui, N.; Xie, W.; Balakishan, G.; Amer, M. F. A.; Marumoto, S.; Muraoka, O. *J. Org. Chem*. **2016**, *81*, 3407–3415. g) Tanabe, G.; Ueda, S.; Kurimoto, K.; Sonoda, N.; Marumoto, S.; Ishikawa, F.; Xie, W.; Muraoka, O. *ACS Omega* **2019**, *4*, 7533–7542. and referenced cited therein.

80. Muraoka, O.; Yoshikai, K.; Takahashi, H.; Minematsu, T.; Lu, G.; Tanabe, G.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2006**, *14*, 500–509

81. a) Xie, W.; Tanabe, G.; Matsuoka, K.; Amer, A. F. M.; Minematsu, T,; Wu, X.; Yoshikawa, M.; Muraoka, O. *Bioorg. Med. Chem* **2011**, *19*, 2252–2262. b) Tanabe, G.; Matsuoka, K.; Yoshinaga, M.; Xie, W.; Tsutsui, N.; Amer, A. F. M.; Nakamura, S.; Nakanishi, I., Wu, X.; Yoshikawa, M. *Bioorg. Med. Chem.* **2012**, *20*, 6321–6334.

82. a) Sim, L.; jayakanthan, K.; Mohsn, S.; Nasi, R.; Johnson, D. B.; Mario Pinto, D.; Rose, R. D. *Biochemistry*, **2010**, *49*, 443–451. b) Eskandari, R.; Jayakanthan, K.; Kuntz, A. D.; Rose, R. D.; Mario Pinto, B. *Bioorganic Med. Chem.* **2010**, *18*, 2829–2835.

83. Tanabe, G.; Yoshikai, K.; Hatanaka, T.; Yamamoto, M.; Shao, Y.; Minemastu, T.; Muraoka, O.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2007**, *15*, 3926–3937.

84. Sim. L; Jayakanthan, K.; Mohan, S.; Nasi, R.; Johnston, D. B.; Pinto, M. B.; Rose, R. D. *Biochemistry* **2010**, 49, 443–451.

85. Nakamura, S.; Takahira, K.; Tanabe, G.; Morikawa, T.; Sakano, M.; Ninomiya, K.; Yoshikawa, M.; Muraoka, O.; Nakanishi, I. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4420–4423.

86. a) Tanabe, G.; Otani, T.; Conh, W.; Minemastu, T.; Ninimiya, K.; Yoshikawa, M.; Muraoka, O. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3159–3162. b) Tanabe, G.; Nakamura, S.; Tsutsui, N.; Balakishan, G.; Xie, W.; Tsuchiya, S.; Akaki, J.; Morikawa, T.; Ninomiya, K.; Nakanishi, I.; Yoshikawa, M.; Muraoka, O.; C*hem. Commun*. **2012**, *48*, 8646–8648.

87. Soares, P. F.; Silva, J. M.; Doboszewski, B. *Carbohydr. Res.* **2013**, *380*, 143–148.

88. Oliver, R. M.; Rao, P. S.; EI-Shenawy, A. H.; Kurz, G. K.; Cutler, B. A. *J. Org. Chem.* **1988**, *53*, 3287–3292

89. a) Yoshimura, Y.; Kitano, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki ,T.;

Matsuda, A. *J. Org. Chem*. **1996**, *61*, 822-823. b) Muraoka, O.; Yoshikai, K.; Takahashi, H.; Minematsu, T.; Lu, G.; Tanabe, G.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2006**, *14*, 500-509.

90. a) Sim, L.; Willemama, C.; Mohan, S.; Naim, Y. H.; Mario Pinto, B.; Rose, R. D. J. *Biol. Chem*. **2010**, *4*, 17763–17770. b) Ren, L.; Cao, X.; Geng, P.; Bai, F.; Bai, G. *Carbohydr. Res.* **2011**, *346*, 2688–2692. c) Jones, K.; Sim, L.; Mohan, S.; Kumarasamy, J.; Liu, H.; Avery, S.; Naim, Y. H.; Quezada-Calvillo, R.; Nichols, L. B.; Mario Pinto, B.; Rose, R. D. *Bioorg. Med. Chem.* **2011**, *19*, 3929–3934.
91. Maltase-glucoamylase Gene ID: (a) Entrez Gene 312272 [Rattus norvegicus (Norway rat)]; (b) Entrez Gene 8972 [Homo sapiens (human)].
92. a) Nakamura, S.; Shimada, K.; Tanabe, G. Muraoka, O.; Nakanishi, I. *Open J Med Chem.* **2017**, *7*, 19–28. b) Nakamura, S.; Takahira, K.; Tanabe, G.; Muraoka, O.; Nakanishi, I. *Open J. Med. Chem.* **2012**, *2*, 50–60.
93. Takashima, K.; Sakano, M.; Kinouchi, Eri.; Nakamura, S.; Marumoto, S.; Ishikawa, F.; Ninomiya, K.; Nakanishi, I.; Morikawa, T. *Bioorg. Med. Chem. Lett*. **2021**, *33*, 127751.
94. Henrissat, B.; Claeyssens, M.; Tomme, P.; Lemesle, L.; Mornon, J.P. *Gene* 1989. *81*, 83-95.
95. Henrissat, B. *Biochem. J.* **1991**, *280*, 309-316.
96. Lombard, V.; Ramulu, H. R.; Drula, E.; Coutinho, P. M.; Henrissat, B. *Nucleic Acids Res*. **2013**, *42*, 490-495.
97. Jiang, J.; Kuo, C. L.; Wu, L.; Franke, C.; Kallemeijn, W. W.; Florea, B. I.; van Meel, E.; van der Marel, G. A.; Codee, J. D.; Boot, R. G.; Davies, G. J.; Overkleeft, H. S.; Aerts, J. M. *ACS Cent. Sci*. **2016**, *2*, 351 – 358.
98. Hers, H. G. *Biochem. J*. **1963**, *86*, 11– 16
99. Tanabe, G.; Yoshikai, K.; Hatanaka, T.; Yamamoto, M.; Shao, Y.; Minematsu, T.; Muraoka, O.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2007**, *15*, 3926–3937
100. Watanabe, T.; Sato, T.; Yoshioka, S.;Koshijima, T.; Kuwahara, M. *Eur. J. Biochem.* **1992**, *209*, 651 – 659.
101. Ishikawa, F.; Hirano, A.; Yoshimori, Y.; Nishida, K.; Nakamura, S.; Takashima, K.; Marumoto, S.; Ninomiya, K.; Nakanishi, I.; Xie, W.; Morikawa, T.; Muraoka, O. *RSC Adv.* **2021**,*11*, 3221-3225.