平成 25 年度　博士学位論文

グリコシダーゼ阻害活性を有する
イミノ糖の合成と活性評価

Synthesis and biological evaluations of iminosugars with inhibitory effecton glycosidases

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略語

本論文中で用いられる略語表記法一覧 (アルファベット順)

Ac	Acetyl
aq.	aqua
Allyl	Allyl
Bu	Butyl
Bn	Benzyl
Boc	tert-butoxycarbonyl
Cbz	Benzyloxycarbonyl
CM	Cross Metathesis
COSY	Correlation spectroscopy
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*, *N*-Diisopropylethylamine
DMF	*N*, *N*-Dimethylformamide
Et	Ethyl
eq.	equivalent
FT-IR	Fourier transfer infrared spectroscopy
Fuc	fucose
Me	Methyl
HMDS	Hexamethyldisilazide
HRMS	High resolution mass spectrometry
Ipc	Isopinocampheyl
MOM	methoxymethyl
Mp	Melting point
Ms	methanesulfonyl
MS	mass spectrometry
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser effect correlated spectroscopy
Nu	nucleophile
Ph	Phenyl
quant.	quantitative
r.t.	room temperature

sat	saturated
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl

序論

イミノ糖は、単糖のヘテロ環内酸素原子を窒素原子で置換したイミノシクリトールの総称であり、糖類と類似した構造を有する。イミノ糖は、自然界の植物や微生物に広く存在する化合物であり、近年、天然物化学の分野では、単糖類に類似した構造を持つアルカロイド類の研究が盛んに行われている。

1966 年に nojirimycin (**Figure 1**) が、*Streptomyces* 属の真正細菌から初めて発見され、α-及び β-グルコシダーゼに対して強力な阻害活性があることが判明し、一躍、脚光を浴びた [1], [2]。

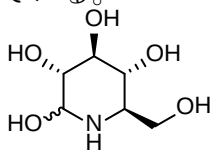
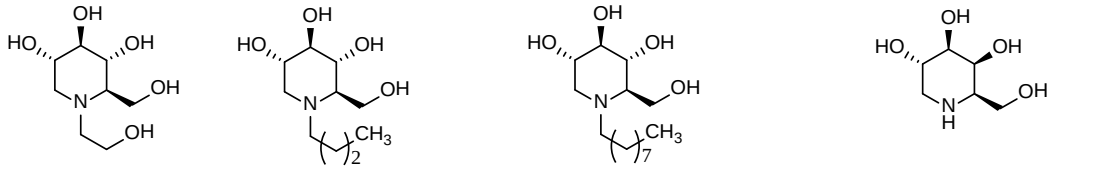


Figure 1. nojirimycin

その後、更なる探索が行われ、nojirimycin の構造類似体だけでも 25 種以上も発見され [3]、また piperidine 型以外の糖類似化合物として、pyrrolidine 型、indolizidine 型、pyrorrlizidine 型、nortropane 型の糖類似化合物が報告されている□[4]。これらも前述の nojirimycin と同様に、グリコシダーゼの活性部位に対して特異的に結合し、阻害活性を示すことが判明している。

グリコシダーゼは、生体内で重要な役割を担っており、糖の加水分解を通した、腸内消化や糖タンパク質の翻訳後プロセシング、ライソゾームでの複合多糖の異化に関係している。イミノ糖類の中には、グリコシダーゼ阻害活性を介して、抗ウイルス作用、抗癌作用、抗 HIV 作用、さらに抗肥満作用を発現する化合物も知られている [5]。すでに臨床利用されているものとしては、Miglitol (糖尿病治療薬) や Miglustat (ゴーシェ病治療薬) が挙げられる (**Figure 2**)。



Miglitol　Miglustat　*N*-(*n*-nonyl)-1-deoxynojirimycin (*N*-*N*-DNJ)　1-deoxygalactonojirimycin (DGJ)

Figure 2. Glycosidase inhibitors

近年、先天代謝異常疾患のライソゾーム蓄積症の新規治療薬として *N*-(*n*-nonyl)-1-deoxynojirimycin (*N*-*N*-DNJ) [6], [7] や 1-Deoxygalactonojirimycin (DGJ) (**Figure 2**) などのイミノ糖が、有効であると報告され [8]、薬理学的シャペロン療法が注目されている。現在、ライソゾーム蓄積症に対する有効な治療法としては、酵素補充療法があるが、この治療法は非常に高価である

ことに加えて、酵素自体が血液脳関門を通過できないため、Ⅰ型ゴーシェ病のような神経症状の伴わない疾患にしか使えないという問題がある。一方で、piperidine 型イミノ糖の Miglustat (**Figure 2**) は、脳などの中枢へ移行することが報告されていることから *N*-*N*-DNJ や DGJ の中枢への移行が期待されている [9], [10]。

薬理学的シャペロン療法として注目されている *N*-*N*-DNJ や DGJ は、分子シャペロンとして作用し、変異酵素の安定化作用を持つ。すなわち、遺伝子変異によって生じた、正しく折りたたまれていないグリコシダーゼに結合し、変異酵素を安定化させ、小胞体における品質管理機構による分解を回避する。その後、ゴルジ体における成熟過程を経て、ライソゾーム内に送りだされ、ライソゾーム内の酸性条件下で阻害剤が脱離することで酵素としての働きを取り戻し、治療効果を発する [11]。

ライソゾーム中には様々なグリコシダーゼが存在するが、遺伝子変異により様々な酵素が変異し、その酵素に対応した基質が蓄積する。すなわち変異酵素の種類の数だけ疾病が存在し、治療薬がその酵素に選択的に作用する必要があることから治療薬の開発が非常に立ち遅れている。中枢神経障害を始めとした重篤な症状を発することから、それぞれの変異酵素に対応した治療薬の開発が望まれている。

このように、イミノ糖類には医薬品のシードとなりうる化合物が多数存在するため、世界中で探索や合成研究が盛んに行われている。

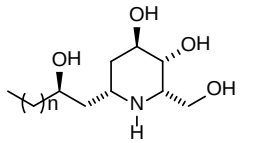
著者は、様々なイミノ糖の中から、海洋生物から得られた初のイミノ糖である Batzellaside 類、また L-フコースを擬態化した構造を有するイミノ糖に着目し、それらの合成および、様々なグリコシダーゼに対する阻害活性評価を行った。

各論

第一章　海洋産アルカロイド Batzellaside 類の全合成

第一節　アリル体 7 の合成

Batzellaside 類 (**Figure 3**) は、マダガスカル島西海岸に生息している海綿 *Batzella* sp. から、Crews らによって単離されたイミノ糖骨格を有するアルカロイドである。これまでに陸上の植物や微生物から多種多様な piperidine 型のイミノ糖が発見されているが、Batzellaside 類は海洋生物から得られたイミノ糖の最初の例として興味深い化合物である [12]。

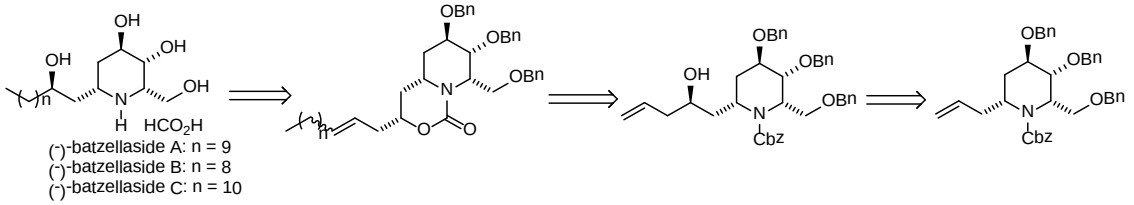


(-)-batzellaside A: n = 9
(-)-batzellaside B: n = 8
(-)-batzellaside C: n = 10

Figure 3. Structure of Batzellaside A, B, and C

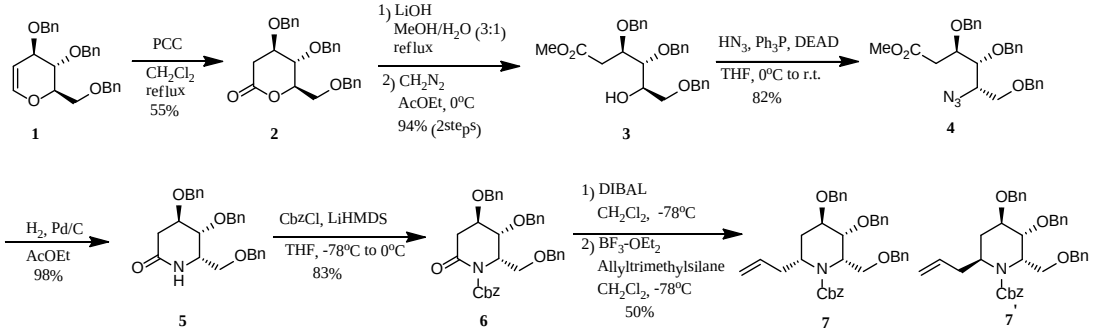
Crews らによって、NMR スペクトルデータから Batzellaside 類の piperidine 環上の不斉中心の相対配置は決定された。しかし、6 位側鎖上のヒドロキシ基の相対配置を決定することはできなかった (**Figure 3**) [12]。2011 年、依田等のグループ [13] [14] により (+)-Batzellaside B の最初の全合成は達成され、Batzellaside B の 6 位側鎖上ヒドロキシ基の相対配置および絶対配置が決定された。Batzellaside 類は、イミノ糖構造を有していることから各種グリコシダーゼを酵素選択的に阻害することが期待されるが、Crews らが Batzellaside 類を単離した際、*Staphylococcus epidermidis* の増殖阻害作用を報告している他に報告例はなく [12]、加えて天然からの供給量が微量であることから、生物活性試験は一向に進んでいない。このような背景から、Batzellaside 類のより効率的な合成経路による全合成および、各種グリコシダーゼ阻害活性を検討した。

Batzellaside 類のより効率的な合成経路の開拓を目指し、合成計画を以下のような逆合成解析により立案した (**Scheme 1**)。6 位側鎖上水酸基の両エピマー体の合成も視野に入れ、aldehyde に対する Brown's asymmetric allylation を考え、異なる炭素鎖 (Batzellaside A, B, C) の構築は、Olefin Cross Metathesis 反応を用いることで達成可能と考えた。



Scheme 1. Retrosynthetic analysis

上記の逆合成解析のもと、市販の Tri-*O*-benzyl-D-glucal **1** を出発原料として合成を開始した。文献 [15]に従い PCC 酸化によりラクトン **2** に誘導後、加水分解、メチルエステル化を行い メチルエステル **3** を合成した。メチルエステル **3** に対して光延条件下、アジド基を導入し **4** を合成した。次いで接触水素化を行うことにより、アジド基の還元と環化反応が一挙に進行し、さらに Cbz 化を経てラクタム **6** に導いた。ラクタム **6** に対して DIBAL 還元後、ルイス酸条件下において、アシルイミニウムイオンを生成させ、Allyltrimethylsilane を反応させたところ、アリル体 **7** と **7´** が、生成比 10:1 で得られた **(Scheme 2)**。



Scheme 2. Synthesis of **7**

主成績体 **7** の立体化学は、COSY 及び NOESY スペクトルによって決定した **(Figure 4)**。即ち、NOESY スペクトルにより **Figure 4** に示した主成績体 **7** の水素原子 H_A と H_B 間で NOE が観測されたことから、2, 6-*cis* 体であると決定した。

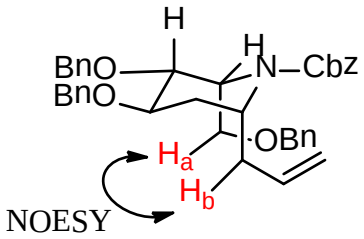


Figure 4. Conformation of **7**

この反応の立体選択性は、以下のように考察できる。ルイス酸存在下において生成するアシルイミニウムイオンは、**A** と **B** の立体配座が可能である **(Figure 5)**。Cbz 基ウレタン部位のアミド構造の C-N 結合は二重結合性を帯びているため、ほぼ平面構造をとる。そのため、α 位側鎖がエクアトリアル配置となった **B** では、α 位側鎖と Cbz 基間に特殊な $A^{(1,3)}$ strain [16] が生じる。その結果、反応時における立体配座は **A** に固定される。

立体配座 **A** に対して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 面から攻撃した場合は、twist boat 型の遷移状態を経て反応が進行する。一方で、α 位からの場合は、より安定な chair 型の遷移状態を経由する。そのため、β 面から求核攻撃した場合よりも、α 面から攻撃した場合の方が有利である [17]。

このような立体電子的効果によって本反応は制御され、2 位と 6 位が *cis* 配置のアリル体 **7** が優先的に得られたと考えられる。

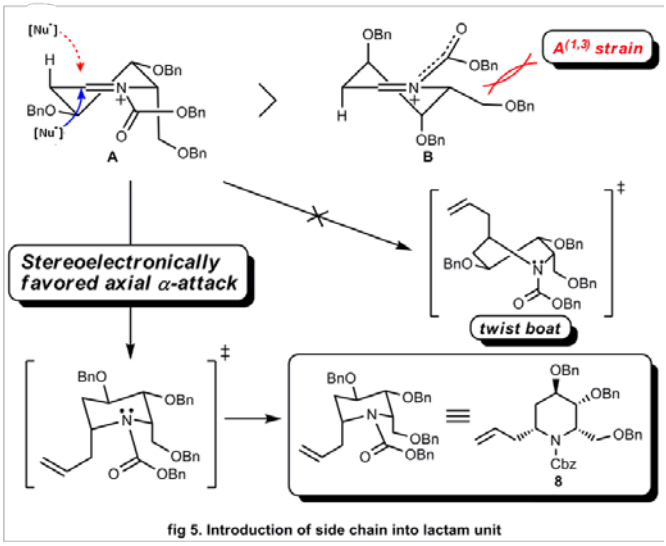
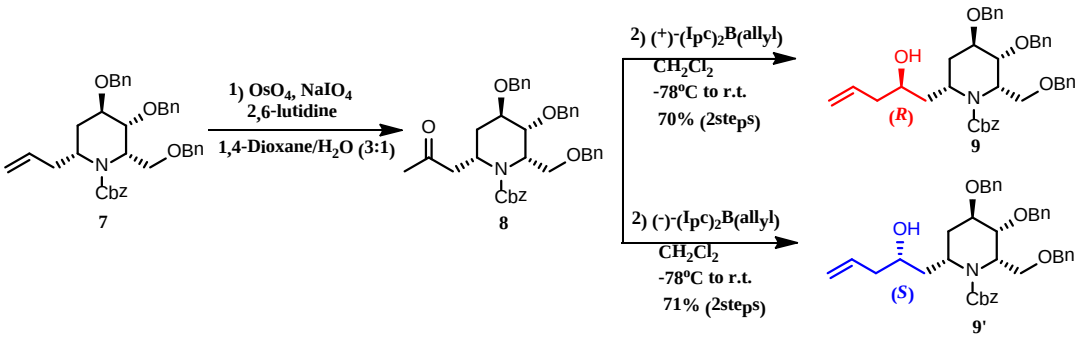


Figure 5. Stereoselective allylation

第二節　Brown 不斉アリル化を用いたホモアリルアルコール 9, 9´ の合成

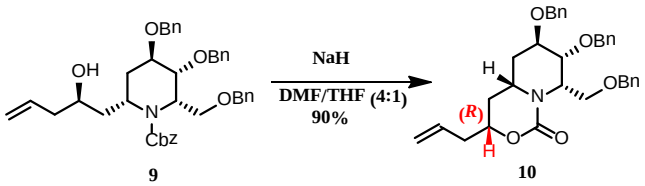
序論で述べたように、Batzellaside 類、およびその類縁体の生物活性評価は一向に進んでいない。6 位側鎖上ヒドロキシ基の立体化学がもたらす、生物活性の違いは興味深く、著者は、Batzellaside 類、および C8 エピマーの合成を柔軟に行うため、アリル体 **7** を鍵中間体として、Brown 不斉アリル化 [18]を行うこととした。

アリル体 **7** に対して、Lemieux-Johnson 酸化 [19]を行い、アルデヒド体 **8** を合成した。次に、アルデヒド体 **8** に対して、Brown 不斉アリル化を行い、ホモアリルアルコール **9** と **9´** をそれぞれ合成した (**Scheme 3**)。



Scheme 3. Synthesis of **9** and **9´**

(+)-$(Ipc)_2B(allyl)$ を用いて合成したホモアリルアルコール **9** の 6 位側鎖上に存在するヒドロキシ基の相対配置を決定するために、環状カルバメート **10** を合成した (**Scheme 4**)。



Scheme 4. Synthesis of **10**

環状カルバメート **10** の COSY 及び NOESY スペクトルを測定した結果を以下に示す (**Figure 6**)。NOESY スペクトルにより、H_a と H_b 間で NOE が観測

されたことから、ホモアリルアルコール **9** の 6 位側鎖上のヒドロキシ基の相対配置は ***R*** 配置であると決定された。

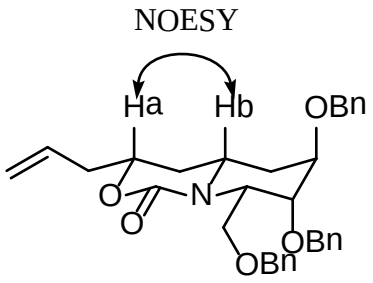
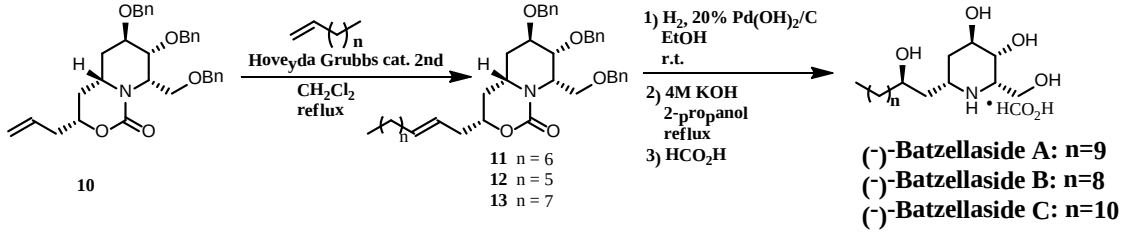


Figure 6. Stereochemistry of **10**

第三節　(-)-Batzellaside A, B, C, および C8 エピマーの合成

環状カルバメート **10** に対して、第二世代 Hoveyda-Grubbs 触媒[20]を用いた olefin cross metathesis を行い **11, 12, 13** を合成し、$Pd(OH)_2$ を用いた接触水素化後、続いて塩基性条件下での加水分解を行うことで(-)-Batzellaside A, B, C の全合成を達成した (**Scheme 5**)。また、依田らが報告した(+)-Batzellaside B と著者が合成した(-)-Batzellaside B の ^{1}H-NMR, ^{13}C-NMR スペクトルデータは一致した(**Table 1**)。



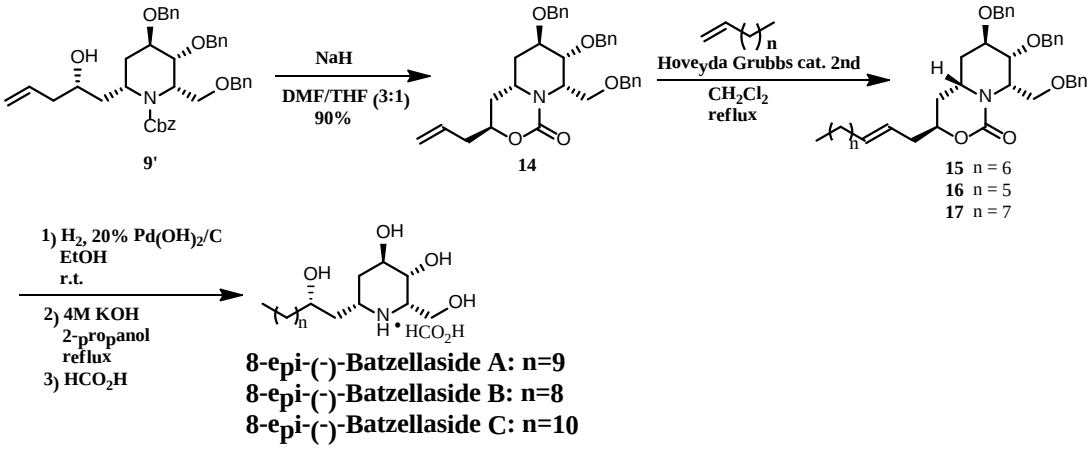
	Cross metathesis		Hydrogenation & Hydrolysis
(-)-Batzellaside A	n=6	85%	75%
(-)-Batzellaside B	n=5	90%	67%
(-)-Batzellaside C	n=7	91%	69%

Scheme 5. Synthesis of (-)-Batzellaside A, B, and C

Table 1. NMR data for of (-)-Batzellaside B

Table 1. NMR DATA for Batzellaside B in MeOH-d_4			
(-)-(L)-Batzellaside B formic acid salt		(+)-(D)-Batzellaside B formic acid salt Ref. 3 (a)	
δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
3.91 brm	72.1	3.91 ddd (3.0, 3.0,	72.0
3.83-3.75 m	67.3	3.86-3.75 m	67.3
3.59-3.50 m	67.2	3.65-3.49 m	67.2
2.01 t (14.9)	60.8	2.01 ddd (14.7, 13.	60.8
1.84 d (14.3)	58.5	1.83 dt (14.4, 3.0, 3	58.5
1.73-1.69 m	53.5	1.76-1.64 m	53.4
1.48 brs	39.5	1.46 brs	39.4
1.32 brs	39.4	1.30 brs	39.4
0.90 t (6.8)	33.0	0.90 t (6.8)	33.0
	32.6		32.5
	30.8		30.7
	30.7		30.7
	30.5		30.6
	30.4		30.4
	26.3		26.2
	23.7		23.7
	14.4		14.4

ホモアリルアルコール **9′** に対し同様の方法で環状カルバメート **14** に導き、olefin cross metathesis の後、$Pd(OH)_2$ を用いた接触水素化、続いて塩基性条件下での加水分解を行うことで 8-epi-(-)-Batzellaside A, B, C の全合成を達成した (**Scheme 6**)。



	Cross metathesis		Hydrogenation & Hydrolysis
8-epi-(-)-Batzellaside A	n=6	90%	72%
8-epi-(-)-Batzellaside B	n=5	90%	67%
8-epi-(-)-Batzellaside C	n=7	88%	55%

Scheme 6. Synthesis of 8-epi-(-)-Batzellaside A, B, and C

第四節　グリコシダーゼ阻害活性評価

Crews らは Batzellaside 類を単離した際、*Staphylococcus epidermidis* の増殖阻害作用を報告しているが[12]、それ以外の生理活性作用は現在まで全く報告されていない。そこで、著者は合成した Batzellaside A, B, C および C8-epi 体の様々なグリコシダーゼに対する阻害活性評価をおこなった **(Table 2)**。

Table 2. Concentration of batzellaside giving 50 % inhibition of various glycosidases

	IC_{50} (μM)					
enzyme	(-)-batzellaside A	C8-epi-A	(-)-batzellaside B	C8-epi-B	(-)-batzellaside C	C8-epi-C
α-glucosidase						
Yeast	NI[a]	NI	897	NI	NI	NI
β-glucosidase						
Bovine liver	43	50	83	NI	NI	43
α-galactosidase						
Coffee beans	NI	NI	NI	NI	NI	NI
β-galactosidase						
Bovine liver	6.7	18	26	45	35	7.5
α-mannosidase						
Jack beans	NI	NI	NI	NI	NI	NI
β-mannosidase						
Snail	NI	NI	NI	NI	NI	NI
α-L-fucosidase						
Bovine kidney	NI	NI	NI	NI	NI	NI
α-L-rhamnosidase						
Penicillium decumben	NI	NI	NI	NI	NI	NI
β-glucronidase						
E.coli	NI	85	NI	NI	NI	NI
trehalase						
Porcine kidney	NI	NI	NI	NI	NI	NI
amyloglucosidase						
Aspergillus niger	NI	NI	NI	NI	NI	NI

[a] NI : No inhibition (less than 50% inhibition at 1000 μM).

いずれの Batzellaside 類も β-galactosidase に対し阻害活性を示した。特に Batzellaside A、C8-epi- Batzellaside C は IC_{50} 値 6.7 μM、7.5 μM と中程度の阻害作用が認められた。この結果から構造活性相関を示すことは難しいが、piperidine 環上の水酸基の立体化学が deoxy L-xylo 型であることが重要であると考えられる。また、C8-epi- Batzellaside A のみ β-glucronidase に対し阻害活性を示した。β-glucronidase 阻害剤は、生体内の異物排泄と深く関わりがあることから医薬品として重要である。例えば、大腸がんの化学療法に用いられる CPT-11 (イリノテカン) はプロドラッグであり SN-38 に分解後トポイソメラーゼ阻害活性を示すが、胆汁排泄後、腸内細菌の β-glucronidase によって脱抱合を受け、再び SN-38 として腸管上皮細胞を障害する。この作用が原因で重篤な副作用を引き起こすことが知られているが、β-glucronidase 阻害によりこの副作用が軽減されることが報告されていることから[21]、C8-epi-Batzellaside A の β-glucronidase 阻害作用は、

薬学的見地から有用性があると考えられる。

第二章　α-L-フコシダーゼ阻害活性を有するポリヒドロキシピペリジン誘導体の合成

第一節　ピペリジン環の構築

糖は、天然では主にD体として存在しているため、D-グルコースやD-ガラクトースといったD糖の糖代謝酵素に関する研究が盛んに行われてきた。例えば、D-グルコースと類似構造を持つ天然物、1-deoxynojirimycin (DNJ) の *N*-ヒドロキシエチル誘導体であるミグリトールは、α-グリコシダーゼを強力に阻害し、経口糖尿病治療薬として臨床利用されている。

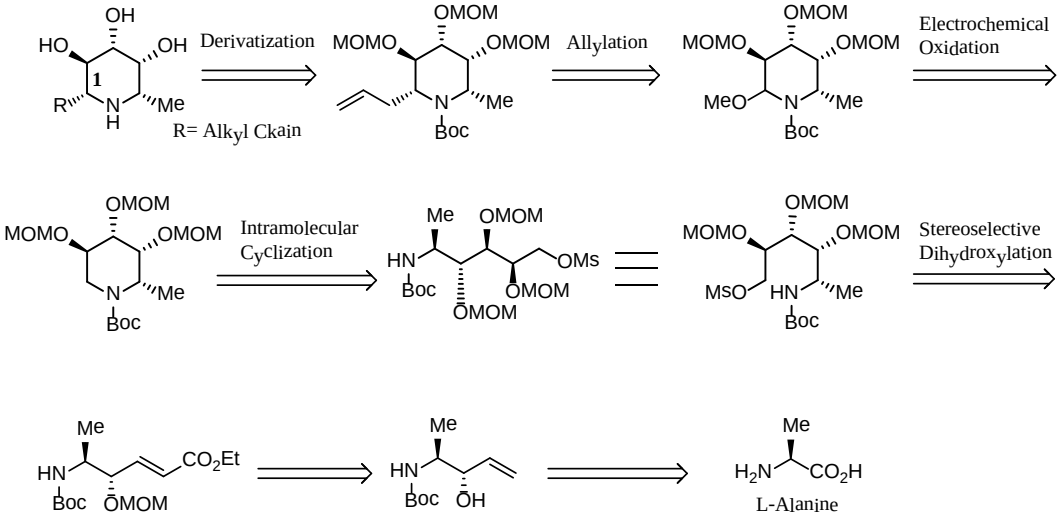
一方、L糖であるL-フコースやL-ラムノースの糖代謝酵素に関する創薬研究は圧倒的に少ないのが現状である。著者が注目したL-フコースは生体内では糖鎖上sialyl Lewis X抗原などに存在し、炎症やがんなど様々な疾病と関連をもつことが知られている[22]。α-L-フコシダーゼは、糖タンパクや糖脂質上のL-フコースとガラクトースまたは、*N*-アセチルグルコサミンとのα結合を切断する酵素であるが、この糖代謝酵素の欠損が原因で引き起こされる疾病にフコシドーシスが挙げられる。フコシドーシスとは、遺伝子変異により、α-L-フコシダーゼが欠損し、本来分解されるL-フコースを含んだ糖タンパクや糖脂質が蓄積することで、中枢神経障害を始めとした重篤な症状を引き起こす難病であるが、現在、効果的治療薬は皆無である。著者は、グリコシダーセ阻害剤がライソゾーム蓄積症治療薬として有効であるという報告例に着目し[23]、α-L-フコシダーゼ阻害剤は、フコシドーシスに対する薬理学的シャペロン療法を担う医薬品となり得る可能性があると考えた。

近年、α-L-フコシダーゼは、がん細胞が細胞外マトリックスを形成する複合糖質を分解し、組織へ浸潤を開始する際に使用されていること[24]、また細菌細胞壁の強度維持に関与していることが報告されていることから[25]、α-L-フコシダーゼ阻害剤はがん細胞の組織浸潤を防ぐ効果や抗菌薬としても期待される。

このような背景から、著者はピペリジン環周辺にα-L-フコシダーゼのフェニルポケットが存在するのではないかという独自の知見に基づき、L-フコースと類似構造を有し、ピペリジン環の窒素原子上、またはα位にアルキル基とベンゼン環を導入した新規フコシダーゼ阻害剤の創製を行った。

目的とするポリヒドロキシピペリジン誘導体の1-*C*位に様々なアルキル鎖を

柔軟に導入するために、合成計画を以下のような逆合成解析により立案した(**Scheme 7**)。1-*C* 位に様々なアルキル鎖を有するポリヒドロキシピペリジン誘導体を任意に合成可能なアリル体を共通の合成中間体として想定し、アリル体はピペリジンの電極酸化、続くアリル化にて得られると考えた。ピペリジンは、α、β 不飽和エステルの立体選択的ジヒドロキシル化、続く環化反応により合成することとし、α、β 不飽和エステルは L-アラニンを出発物質とし、文献既知であるアリルアルコール [26]を経由し合成できると考えた。

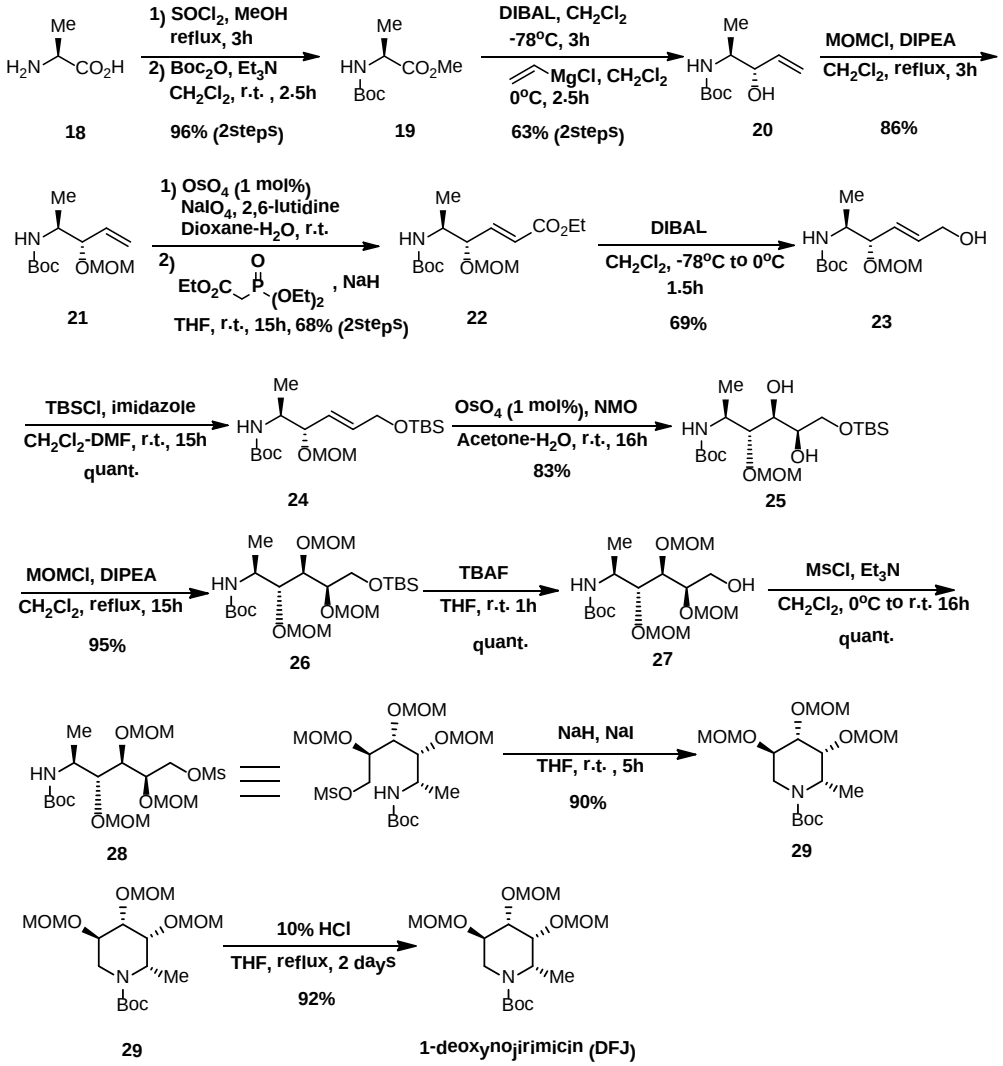


Scheme 7. Retrosynthetic analysis

上記の逆合成解析のもと、まず始めに、ピペリジン環の構築を行い、立体化学の決定を行った。以下にその概略を示す。

L-アラニン **18** を出発原料として、メチルエステル化、*N*-Boc 化を行い Boc 体 **19** を得た。井深らの方法に従い [26]、one-pot で DIBAL 還元、Grignard 反応を行い、目的とするアリルアルコール **20** を立体選択的に合成した。ヒドロキシ基を MOM 保護し、Lemieux-Johnson 酸化、続く Horner-Wadsworth-Emmons 反応を行い、1 炭素増炭した α、β 不飽和エステル **22** へ導いた。エステル部を DIBAL 還元し、TBS 保護した後、不斉炭素に隣接したオレフィンにおいて岸らの方法に従い [27]、ジヒドロキシル化を行い、ジオール **25** を単一の生成物として得た。得られたジオール **25** のヒドロキシ基を MOM 保護し、TBAF により TBS 基の脱保護を行い、1 級アルコール **27** へと導き、メシル体 **28** を経由し環化反応をおこない、収率よくピペリジン **29** の合成を達成した。これら 3 つのヒドロキシ基の立体化学は、塩酸を用いた脱保護を行い、文献既知 [28], [29]である 1-Deoxyfuconojirimicin (DFJ) へと導き、^{1}H-NMR の比較を行うことでその相対な

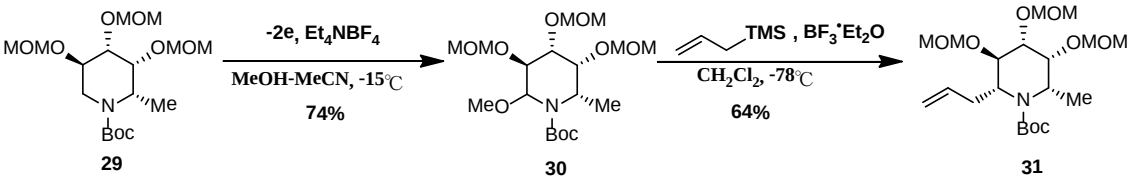
らびに絶対立体配置を決定した (**Scheme 8**)。



Scheme 8. Construction of Piperidine Ring

第二節　鍵中間体　アリル体 31 の合成

ピペリジン **29** に対し電極酸化を用い α 位にメトキシ基を導入後、ルイス酸条件下において、アシルイミニウムイオンを生成させ、Allyltrimethylsilane を反応させることで、アリル体 **30** を単一のジアステレオマーとして得た **(Scheme 9)**。



Scheme 9. Preparation of Common Intermediate

この時点で立体化学を決定することはできなかったため、次に記述する誘導体に変換し NOE により決定した。すなわち、アリル体 **31** を以下に示す 1-*C*-(*p*-methoxyphenyl)propyl 体へ誘導し、水素原子 H_A と H_B 間で NOE が観測されたことから、1, 5-*cis* 体であると決定した **(Figure 7)**。

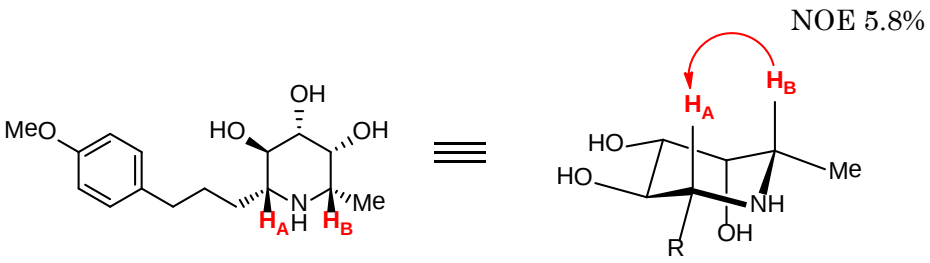


Figure 7. Stereochemistry of **31**

この反応の立体選択性は、以下のように考察できる。ルイス酸存在下において生成するアシルイミニウムイオンは、**A** と **B** の立体配座が可能である **(Figure 8.)**。Boc 基ウレタン部位のアミド構造の C-N 結合は二重結合性を帯びているため、ほぼ平面構造をとる。そのため、メチル基がエクアトリアル配置となった **B** では、メチル基と Boc 基間に特殊な $A^{(1,3)}$ strain [16]が生じる。その結果、反応時における立体配座は **A** に固定される。

立体配座 **A** に対して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 面から攻撃した場合は、twist boat 型の遷移状態を経て反応が進行する。一方で、α 面からの攻撃した場合は、より安定な chair 型の遷移状態を経由する。そのため、β 面から求核攻撃した場合よりも、α 面から攻撃した場合の方が有利である [17]。

このような立体電子的効果によって本反応は制御され、1 位と 5 位が *cis* 配置のアリル体 **31** が選択的に得られたと考えられる。

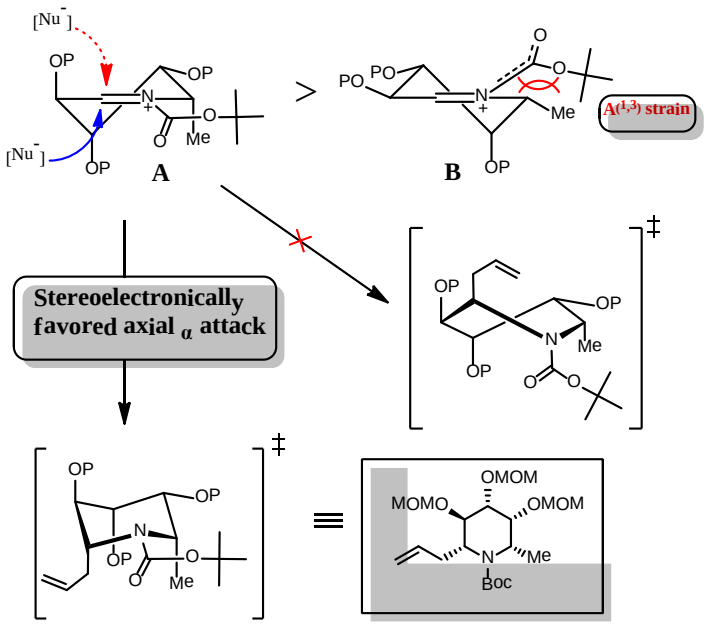
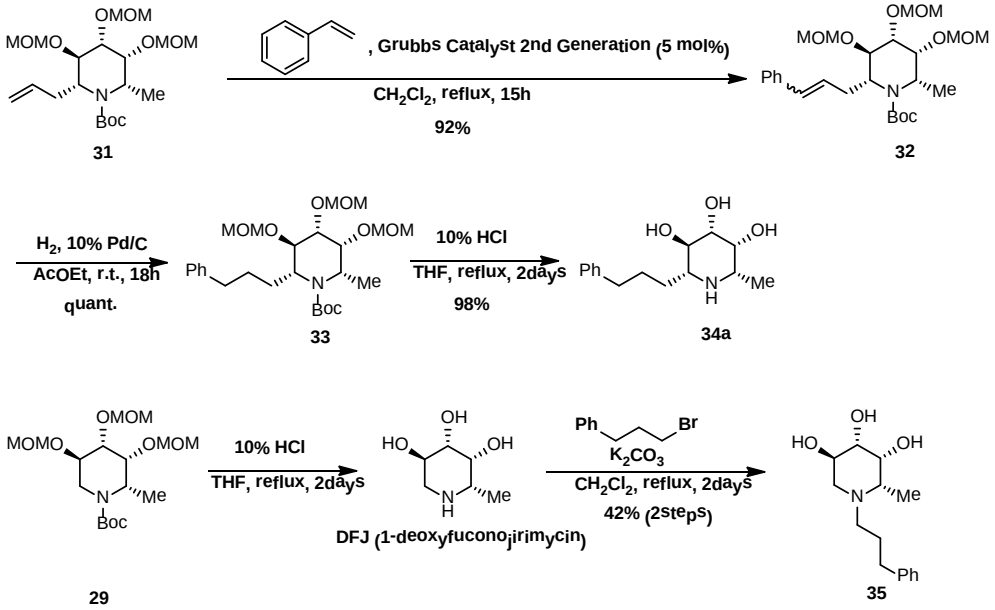


Figure 8. Stereoselective allylation

第三節　ポリヒドロキシピペリジン誘導体の合成、およびフコシダーゼ阻害活性評価

著者は、ピペリジン環の窒素原子上、または α 位のどちらに置換基を有することがフコシダーゼ阻害活性に重要であるかを検証するため、まず 2 つの誘導体を合成し、フコシダーゼ阻害活性評価を行った。

アリル体 **31** に対し第二世代 Grubbs 触媒を用いた olefin cross metathesis [30] を行い **32** を合成し、Pd/C を用いた接触水素化後、酸性条件下で MOM 基、Boc 基を同時に脱保護し、フェニルプロピル体 **34a** を合成した。また、DFJ に対し *N*-アルキル化を行い、*N*-フェニルプロピル体 **35** を得た **(Scheme 10)**。



Scheme 10. Synthesis of **34a** and **35**

34a、**35** の α-L-フコシダーゼに対する阻害活性評価を行った結果、**34a** は IC_{50} 値 180nM、 **35** は IC_{50} 値 180nM であった **(Figure 9)**。この結果からピペリジン環の α 位にアルキル基とベンゼン環を有することが α-L-フコシダーゼ阻害活性に重要であることが示唆された。

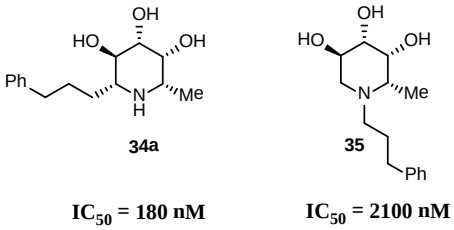
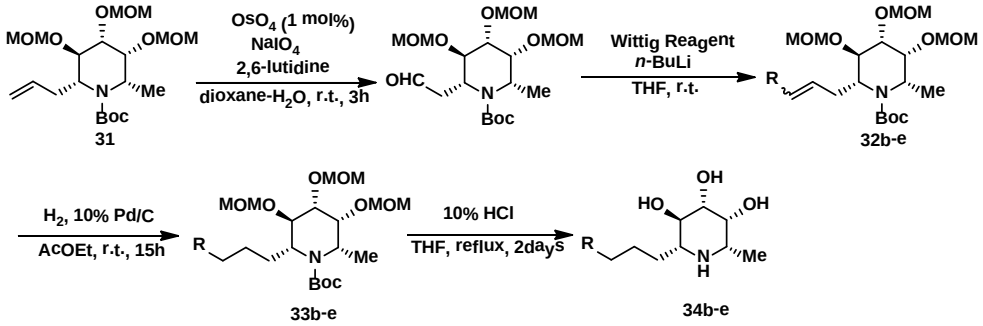


Figure 9. IC_{50} value of **34a** and **35**

次に著者は末端のベンゼン環の重要性を検証するため、アルキル基のみ導入した誘導体を合成した。

アリル体 **31** に対し Lemieux-Johnson 酸化 [18]を行いアルデヒド体へ導き、Wittig 反応を行うことでオレフィン体 **32b**, **32c**, **32e** を得た。なお、 **32d** のみアリル体 **31** から olefin cross metathesis によって合成した。オレフィン体 **32b-e** に対し Pd/C を用いた接触水素化後、酸性条件下で MOM 基、Boc 基を同時に脱保護し、アルキル体 **34b-e** を得た (**Scheme 11**)。



Scheme 11. Synthesis of **34b-e**

Table 2. Synthesis of iminosugar derivatives

	method	**R**	**32**	**33**	**34**
b	Wittig	methyl	80% (2 steps)	99%	81%
c	Wittig	*n*-propyl	quant. (2 steps)	91%	78%
d	CM	*n*-pentyl	92%	98%	96%
e	Wittig	*n*-hexyl	65% (2 steps)	98%	68%

34b-e の α-L-フコシダーゼに対する阻害活性評価を行った結果、アルキル鎖の延長に伴い、阻害活性の向上は認められたが、既存の強力なフコシダーゼ阻害剤である DFJ を上回る阻害活性は認められなかった (**Figure 10**)。

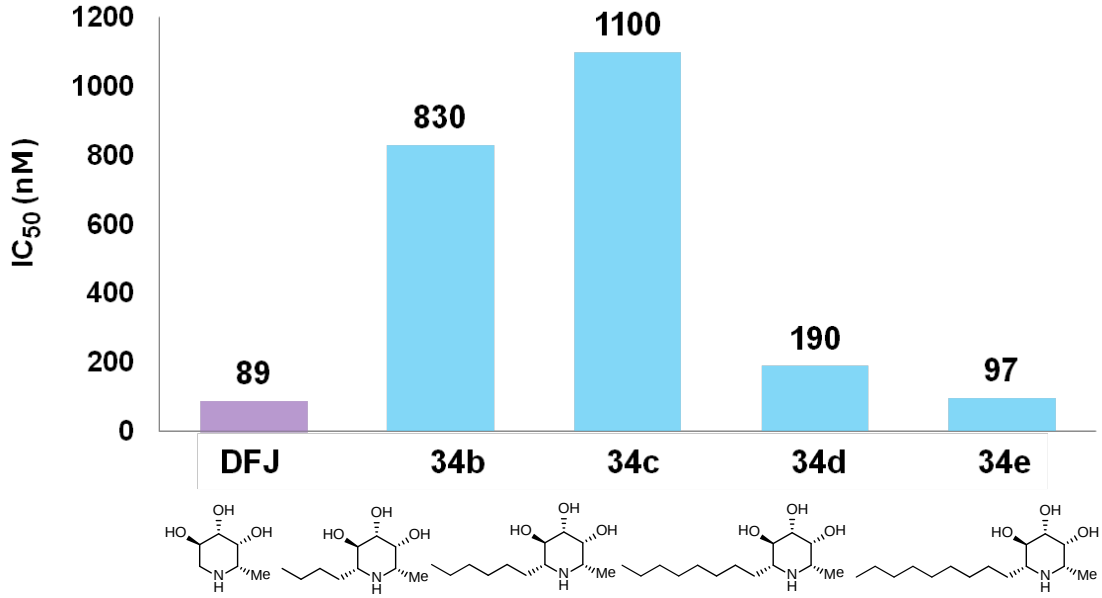


Figure 10. IC_{50} value of **34b-e**

次に著者は末端のベンゼン環を固定し、アルキル鎖の長さの異なる誘導体の合成を試みた。

同様の手順でアリル体 **31** から、フェニルブチル体 **34f**、フェニルペンチル体 **34g** を得た **(Table 3)**。

Table 3. Synthesis of iminosugar derivatives

	R	32	33	34
f	benzyl	79% (2 steps)	95%	62%
g	phenylethyl	65 %(2 steps)	96%	65%

34f-g の α-L-フコシダーゼに対する阻害活性評価を行った結果、末端にベンゼン環が存在する場合、アルキル鎖の長さの変化に伴う、阻害活性の変化は認められなかった **(Figure 11)**。

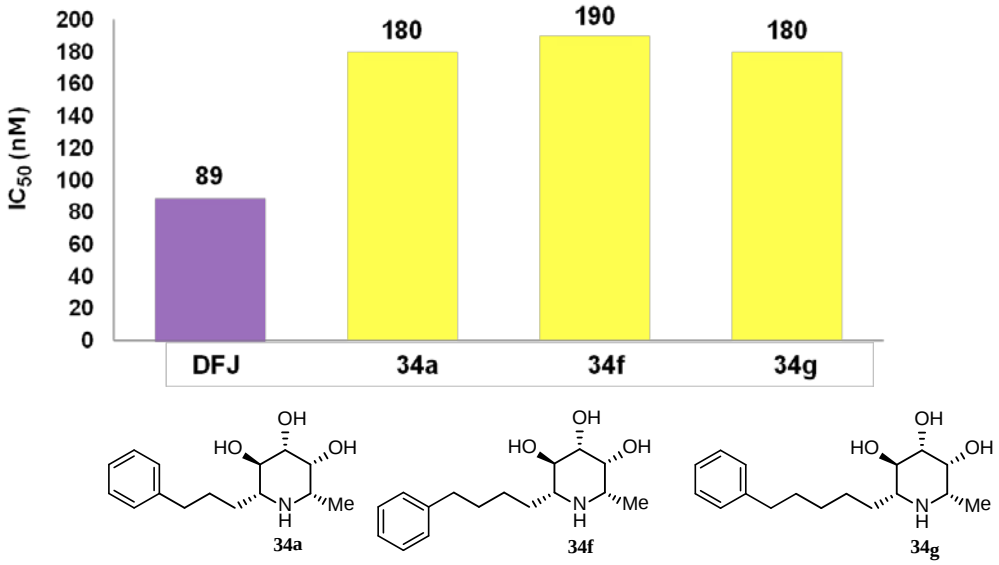


Figure 11. IC_{50} value of **34a, 34f,** and **34g**

そこで著者は、フェニルプロピル体に固定し、末端のベンゼン環上にさまざまな置換基を導入した誘導体の合成を試みた。

同様の手順でアリル体 **31** から、ベンゼン環上にさまざまな置換基を導入した誘導体を合成した **(Table 4)**。

Table 4. Synthesis of iminosugar derivatives

	R	32	33	34
h	1-naphthyl	87% (2 steps)	quant.	73%
i	*p*-isopropylphenyl	79% (2 steps)	99%	65%
j	*p*-methoxyphenyl	99% (2 steps)	quant.	42%
k	*p*-trifluoromethylphenyl	85% (2 steps)	quant.	73%
l	*p*-fluorophenyl	96% (2 steps)	quant.	66%
m	*p*-chlorophenyl	80% (2 steps)	92%	67%

34h-m の α-L-フコシダーゼに対する阻害活性評価を行った結果、ナフチル体は IC_{50} 値 20nM、*p*-トリフルオロメチル体は IC_{50} 値 43nM、*p*-クロロ体は IC_{50} 値 44nM と強力なフコシダーゼ阻害活性が認められた **(Figure 12)**。

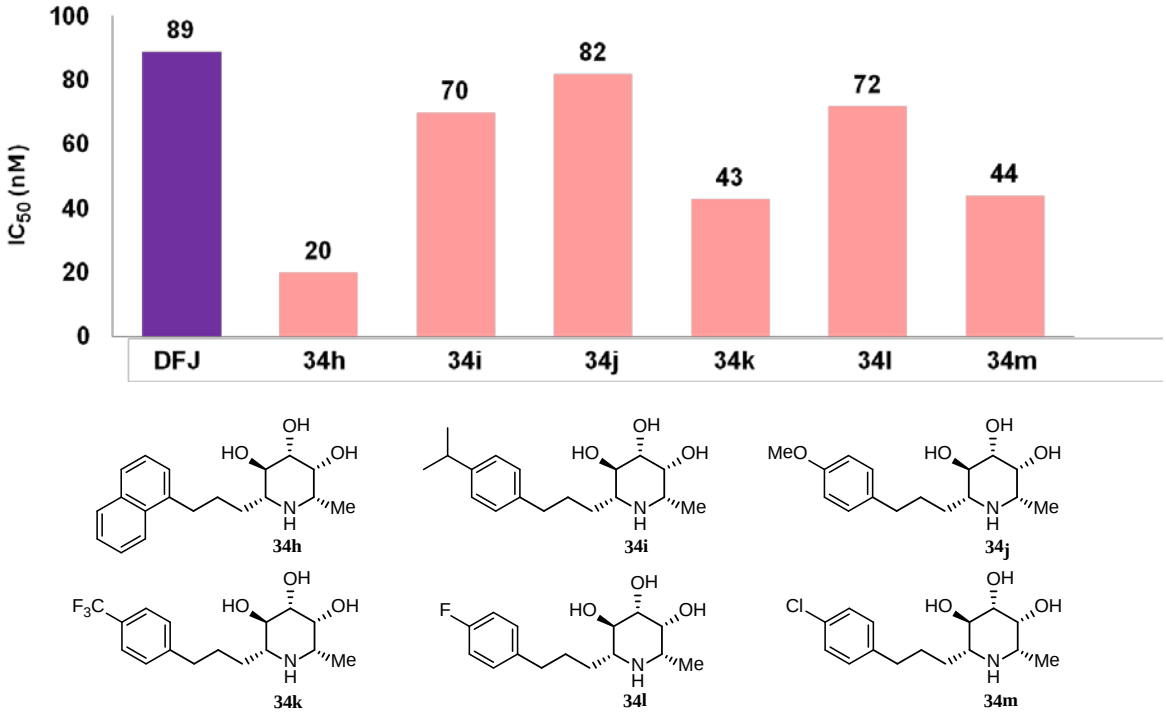


Figure 12. IC_{50} value of **34h-m**

そこで著者は、合成の簡便性から *p*-クロロ体に注目し、ベンゼン環上の塩素原子の数、または位置の異なる誘導体の合成を試みた。

同様の手順でアリル体 **31** から、ベンゼン環上の塩素原子の数、または位置の異なる誘導体を合成した **(Table 5)**。

Table 5. Synthesis of iminosugar derivatives

	R	32	33	34
n	*o*-chlorophenyl	91% (2 steps)	97%	82%
o	*m*-chlorophenyl	85% (2 steps)	quant.	70%
p	2, 4-dichlorophenyl	93% (2 steps)	95%	72%
q	2, 4, 6-trichlorophenyl	72% (2 steps)	98%	63%

34n-q の α-L-フコシダーゼに対する阻害活性評価を行った結果、2, 4-ジクロロ体は IC_{50} 値 13nM、2, 4, 6-トリクロロ体は、実に IC_{50} 値 5 nM、K_i 値 1.1 nM と非常に強力なフコシダーゼ阻害活性が認められた **(Figure 13)**。

Figure 13. IC_{50} value of **34n-q**

そこで著者は、もっとも阻害活性の強かった 2, 4, 6-トリクロロ体の酵素選択性を検証した。その結果、β-ガラクトシダーゼや β-グルコシダーゼに対し非常に弱い阻害活性を示すものの、やはり α-L フコシダーゼに対し酵素選択的に阻害活性を示すことが判明した **(Table 6)**。

Table 6. Inhibition activities of **34q** against various enzymes

enzyme	IC_{50} (μM)
α-Glucosidase (Yeast)	[a]NI
β-Glucosidase (Bovine liver)	412
α-Galactosidase (Coffee beans)	NI
β-Galactosidase (Bovine liver)	70
α-Mannosidase (Jack beans)	NI
β-Mannosidase (Snail)	NI
α-L-Fucosidase (Bovine kidney)	**0.005**
Trehalase (Porcine kidney)	NI
Amyloglucosidase (*Aspergillus niger*)	NI
α-L-Rhamnosidase (*Penicillium decumbens*)	NI

[a] NI : No inhibition (less than 50% inhibition at 1000 μM).

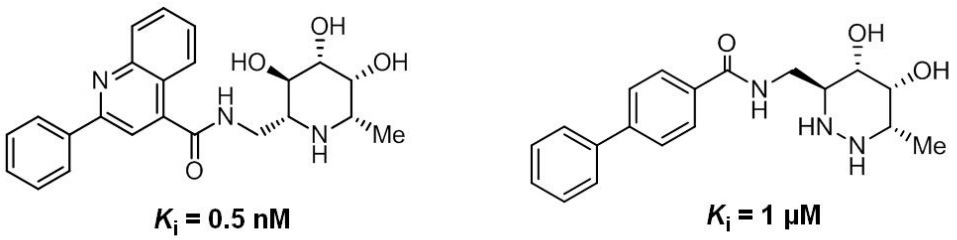
第三章　α-L-フコシダーゼ阻害活性を有する新規アミド型イミノ糖の合成

第一節　鍵中間体　カルボン酸 49 の合成

L 糖の糖代謝酵素を標的とした研究例は圧倒的に少ないことは先に述べた通りであるが、数少ない報告例の中、近年、アミド構造を有するイミノ糖が α-L フコシダーゼに対し強力かつ酵素選択的に阻害活性を示すことが報告されている **(Figure 14)** [31], [32]。

第二章において、著者は IC_{50} 値 5 nM の非常に強力な α-L-フコシダーゼ阻害剤の創製を報告した。しかし酵素選択性に関しては、高い選択性を示すものの、β-ガラクトシダーゼや、β-グルコシダーゼに対して、弱い阻害活性を示すことが判明した。医薬品の創製を目的とした場合、このわずかな β-ガラクトシダーゼや、β-グルコシダーゼに対する阻害活性が、予期せぬ副作用の発症原因となる可能性が懸念される。

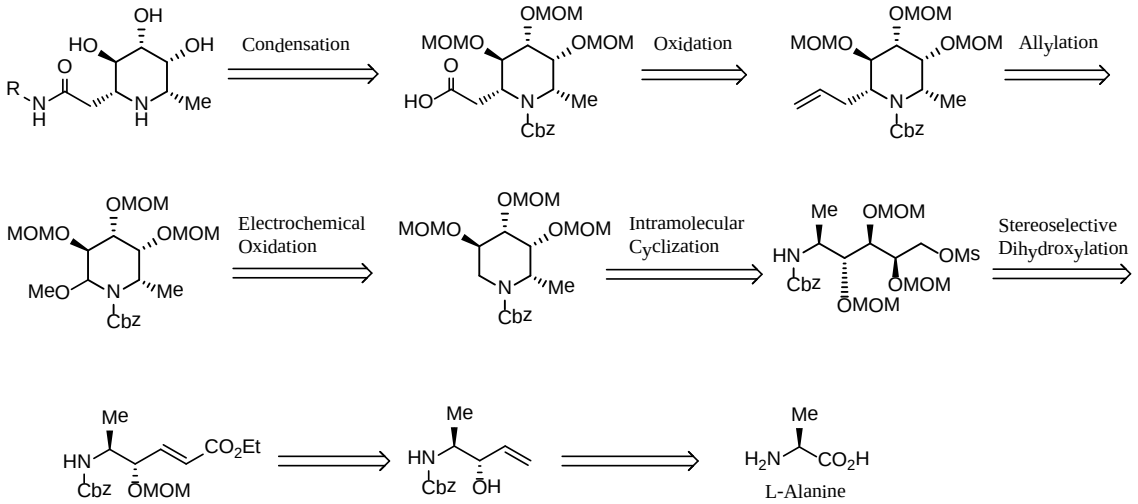
このような背景から著者は、強力な阻害活性を保持し、より酵素選択性の高いフコシダーゼ阻害剤の創製を目指し、第二節での合成経路を活かした、また例に示されるアミド様式と異なる、すなわちアミド様式を入れ替えた新規アミド型イミノ糖の合成、および α-L-フコシダーゼに対する阻害活性評価を検討した。また、報告されている α-L-フコシダーゼ阻害剤は、いずれも Bovine kidney 由来の α-L-フコシダーゼを用いて評価されていることから、今回著者は、Bovine kidney 由来のほかに、Human lysosome 由来の酵素源 [32]を用い、阻害活性評価を検討した。



Angew. Chem. Int. Ed. **2003**, *42*, 4661-4664　　*Bioorg. Med. Chem.* **2010**, *18*, 4648-4660

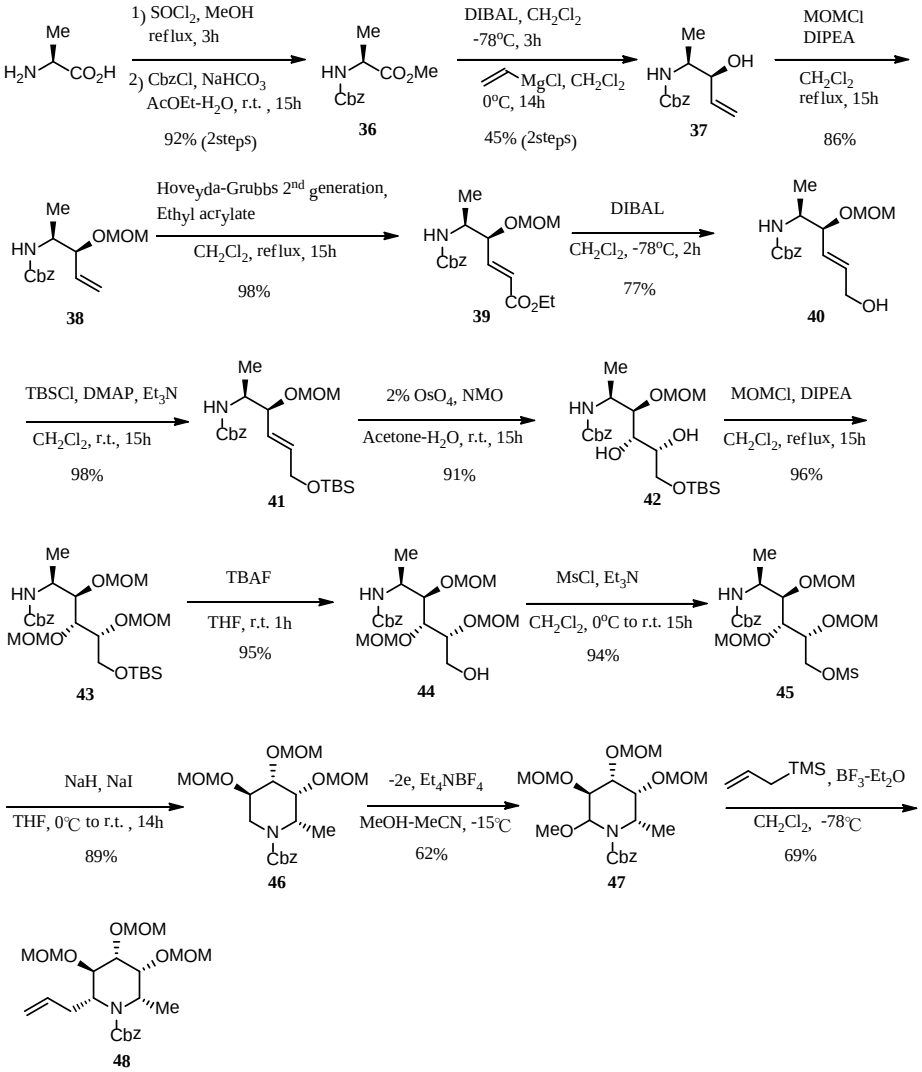
Figure 14. Fucosidase inhibitor

第二節での合成経路を活かし、合成計画を以下のような逆合成解析により立案した (**Scheme 12**)。最終段階の保護基の脱保護を想定し、*N* 保護基として Boc 基ではなく接触水素化で脱保護可能である Cbz 基を用いることとし、アミド部位は、カルボン酸とアミンの縮合で構築できると考えた。カルボン酸は、アリル体から Lemieux-Johnson 酸化でアルデヒドへ導き、Pinnick 酸化で得ることができると考えた。アリル体は、L-アラニンから同様に合成可能と考え、以上の逆合成解析のもと新規アミド型イミノ糖の合成を開始した (**Scheme 12**)。



Scheme 12. Retrosynthetic analysis

L-アラニンを出発原料として、メチルエステル化、*N*-Cbz 化を行い Cbz 体 **36** を得た。Gryko らの方法に従い [34]、one-pot で DIBAL 還元、Grignard 反応を行い、目的とするアリルアルコール **37** を立体選択的に合成した。ヒドロキシ基を MOM 保護し、第二世代 Grubbs 触媒を用いた olefin cross metathesis [30]を行い、1 炭素増炭した α、β 不飽和エステル **38** へ導いた。エステル部を DIBAL 還元し、TBS 保護した後、不斉炭素に隣接したオレフィンにおいて岸らの方法に従い [27]、ジヒドロキシル化を行い、ジオール **42** を単一の生成物として得た。得られたジオール **42** のヒドロキシ基を MOM 保護し、TBAF により TBS 基の脱保護を行い、1 級アルコール **44** へと導き、メシル体 **45** を経由し環化反応をおこない、ピペリジン **46** の合成を達成した。ピペリジン **46** に対し電極酸化を用い α 位にメトキシ基を導入後、ルイス酸条件下において、アシルイミニウムイオンを生成させ、Allyltrimethylsilane を反応させることで、アリル体 **48** を単一のジアステレオマーとして得た (**Scheme 13**)。



Scheme 13. Synthesis of **48**

この時点でアリル体 **48** の立体化学を決定することはできなかったため、次に記述する誘導体に変換し NOE により決定した。すなわち、アリル体 **48** を以下に示す buthyl 体へ誘導し、水素原子 H_A と H_B 間で NOE が観測されたことから、1, 5-*cis* 体であると決定した **(Figure 15)**。このアリル化の立体選択性は、先のアリル体 **30** と同様に考えられる。

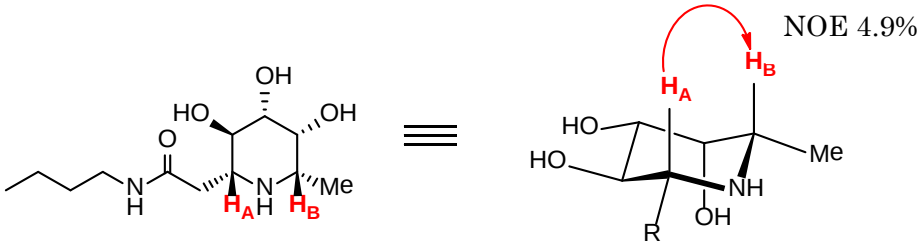
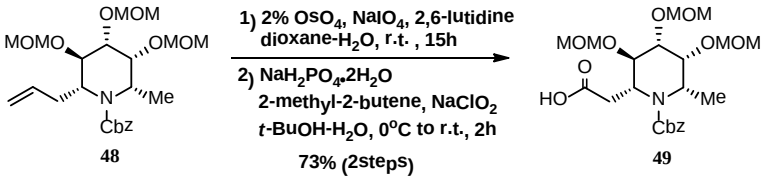


Figure 15. Stereochemistry of **48**

アリル体 **48** に対し Lemieux-Johnson 酸化□[19]を行い、アルデヒドへと導き、Pinnick 酸化 [35]を行うことで鍵中間体であるカルボン酸 **49** を得た (**Scheme 14**)。

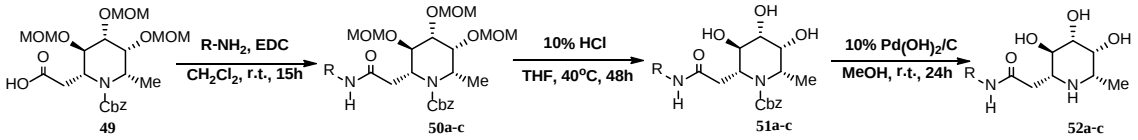


Scheme 14. Synthesis of **49**

第二節　アミド型イミノ糖誘導体の合成、およびフコシダーゼ阻害活性評価

著者は、アルキル鎖を導入した場合とアミド結合を導入した場合のフコシダーゼ阻害活性の違いを検証するため、まず 3 つの誘導体を合成した。

カルボン酸 **49** とアミンを縮合させ、MOM 基、Cbz 基の脱保護を順次行いアミド型イミノ糖 **52a-c** を得た **(Scheme 15)**。



Scheme 15. Synthesis of **52a-c**

Table 7. Synthesis of Amide type iminosugar derivatives

	R	**50**	**51**	**52**
a	phenyl	74%	quant.	90%
b	benzyl	76%	78%	87%
c	butyl	70%	85%	71%

フェニル体 **52a**、ベンジル体 **52b**、ブチル体 **52c** の α-L-フコシダーゼ (Bovine kidney 由来) に対する阻害活性評価を行った結果を以下に示す **(Figure 16)**。**52a** と **34a**、**52c** と **34c** の比較で示されるように、アミド結合の導入による阻害活性の向上が同様の傾向としてみられた。末端にベンジル基を導入することで阻害活性の低下がみられ、加えて **52a** と **52b** との比較から、やはり末端にベンゼン環を有することが阻害活性の向上に重要であることが示唆された。酵素選択性に関しては、ベンゼン環の導入により阻害活性は向上する一方で酵素選択性はアルキル基を導入した場合よりも劣る結果がみられた **(Table 8)**

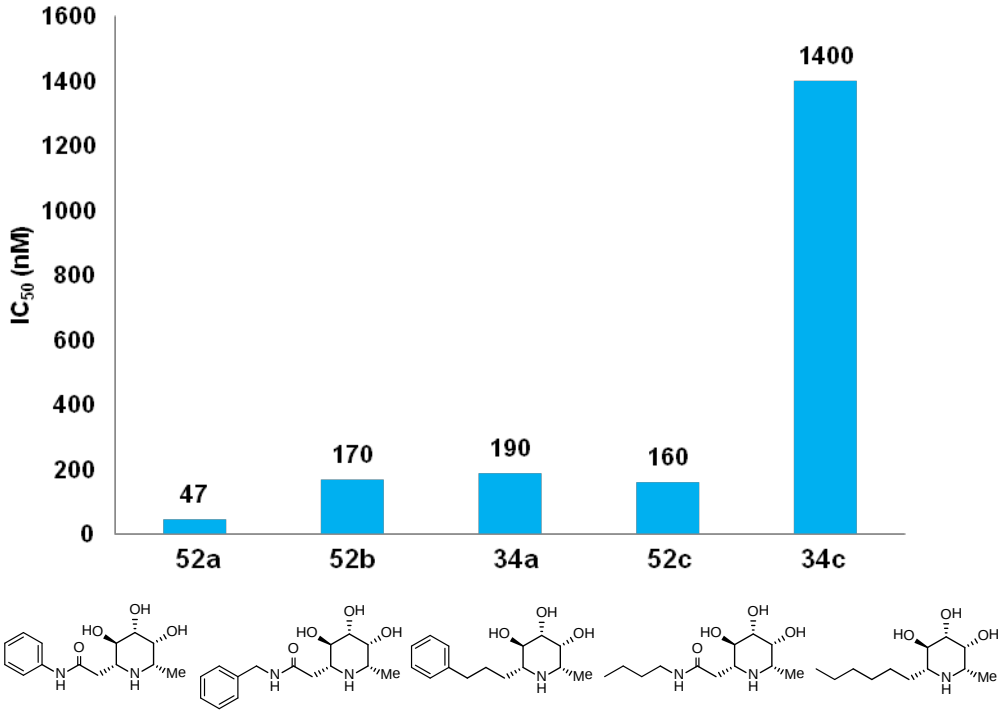


Figure 16. Concentration of **52a-c** giving 50% inhibition of α-L-fucosidase (Bovine kidney)

Table 8. Concentration of **52a, c** and **34a, c** giving 50% inhibition of various glycosidase

Enzyme		IC_{50} (μM)			
		52a	**34a**	**52c**	**34c**
α-Glucosidase	Rat intestinal maltase	NI[a] (0%)[b]	NI (1.9%)	NI (21.0%)	NI (8.3%)
β-Glucosidase	Bovine liver	754	NI (41.3%)	NI (28.6%)	NI (37.8%)
α-Galactosidase	Coffee beans	NI (6.7%)	NI (3.7%)	NI (6.6%)	NI (9.8%)
β-Galactosidase	Bovine liver	299	883	NI (45.1%)	NI (49.7%)
α-Mannosidase	Jack beans	NI (9.2%)	NI (9.6%)	NI (0%)	NI (11.3%)
β-Mannosidase	snail	NI (0%)	NI (0%)	NI (0%)	NI (0%)
α-L-Fucosidase	Bovine kidney	0.047	0.19	0.16	1.4
β-Glucuronidase	*E.coli*	NI (20.9%)	NI (26.8%)	NI (19.4%)	NI (19.8%)

a NI : No inhibition (less than 50% inhibition at 1000 mM).

b ( ) : inhibition % at 1000 mM

次に著者は **52a** の末端ベンゼン環の周囲にさまざまな置換基を導入した誘導体の合成を試みた。

同様の手順でカルボン酸 **49** から **52d-f** を合成し (**Table 9**)、α-L-フコシダーゼ (Bovine kidney 由来) に対する阻害活性評価を行った (**Figure 17**)。

Table 9. Synthesis of Amide type iminosugar derivatives

	R	**50**	**51**	**52**
d	*p*-methoxyphenyl	52%	76%	93%
e	*p*-tolyl	77%	75%	78%
f	*p*-fluorophenyl	68%	75%	94%

p-メトキシ体 **52d**、*p*-トリル体 **52e**、*p*-フルオロ体 **52f** の α-L-フコシダーゼ (Bovine kidney 由来) に対する阻害活性評価を行った結果、**52e**、**52f** は、**52a** と比べ 1.6-1.8 倍、阻害活性の向上が認められた (**Figure 17**)。

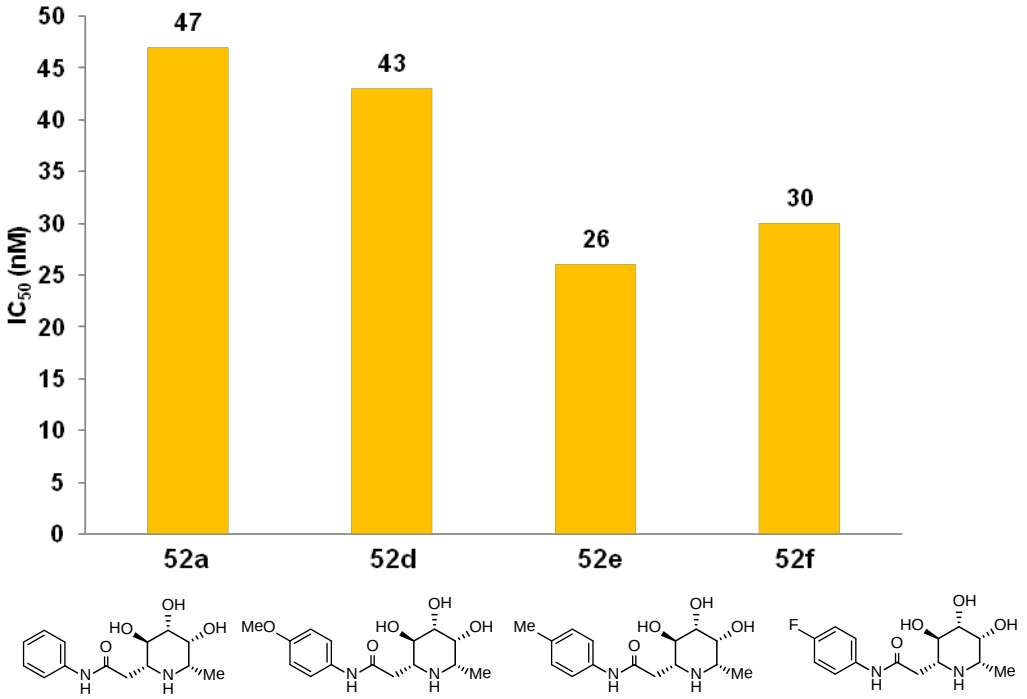


Figure 17. Concentration of **52d-f** giving 50% inhibition of α-L-fucosidase (Bovine kidney)

そこで著者は末端ベンゼン環上のメチル基、フッ素原子の数、または、位置の異なる誘導体の合成を試みた。

同様の手順でカルボン酸 **49** から **52g-n** を合成し (**Table 10**)、α-L-フコシダーゼ (Bovine kidney 由来) に対する阻害活性評価を行った (**Figure 18**)。

Table 10. Synthesis of Amide type iminosugar derivatives

	R	**50**	**51**	**52**
g	*o*-tolyl	54%	77%	64%
h	*m*-tolyl	74%	75%	87%
i	2, 4-dimethylphenyl	58%	72%	90%
j	2, 4, 6-trimethylphenyl	72%	68%	70%
k	*o*-fluorophenyl	63%	82%	55%
l	*m*-fluorophenyl	65%	78%	85%
m	2, 4-fluorophenyl	51%	72%	77%
n	2, 4, 6-fluorophenyl	31%	82%	85%

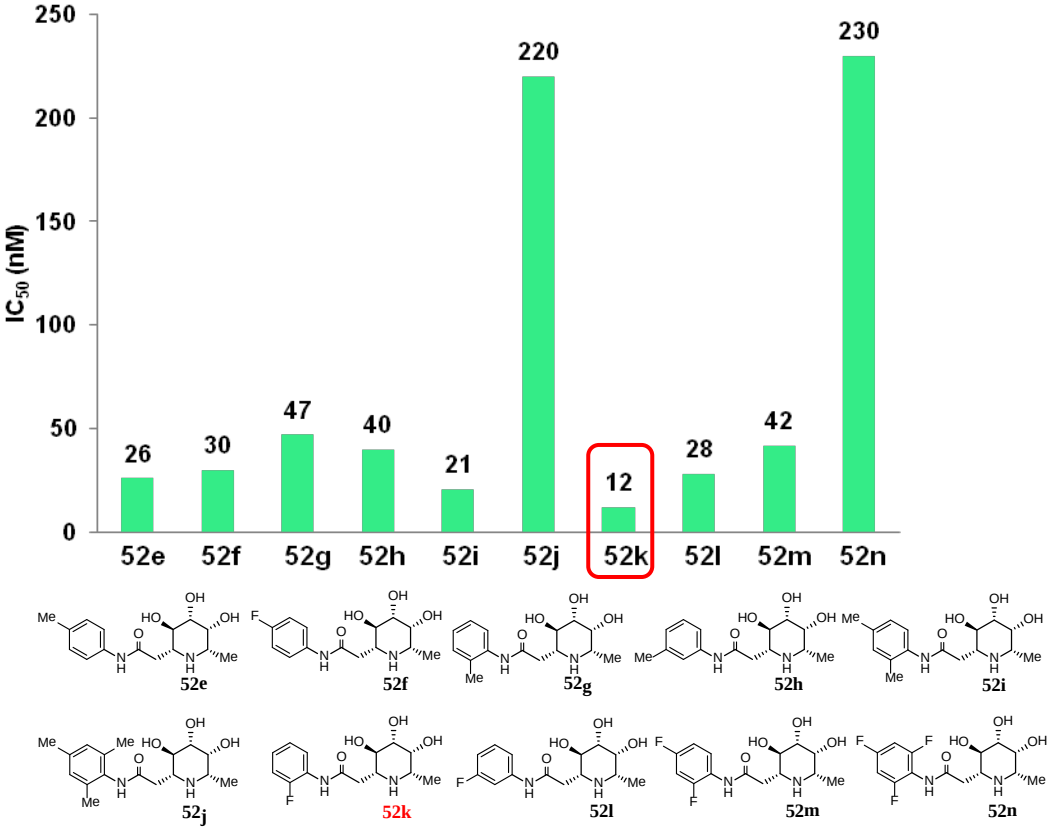


Figure 18. Concentration of **52g-n** giving 50% inhibition of α-L-fucosidase (Bovine kidney)

Table 11. Concentration of iminosugar derivatives giving 50% inhibition of various glycosidase

Enzyme		IC_{50} (μM)					
		52g	**52i**	**52j**	**52k**	**52m**	**52n**
α-Glucosidase	Rat intestinal maltase	NI[a] (0.3%)[b]	NI (0%)	NI (9.0%)	**NI (21.7%)**	NI (0%)	NI (0%)
β-Glucosidase	Bovine liver	7.1	NI (19.8%)	NI (0%)	**NI (34.3%)**	NI (48.7%)	NI (7.4%)
α-Galactosidase	Coffee beans	NI (0.8%)	NI (0%)	NI (0%)	**NI (0.3%)**	NI (0%)	NI (0%)
β-Galactosidase	Bovine liver	8.2	798	NI (29.1%)	**NI (49.5%)**	346	NI (42.6%)
α-Mannosidase	Jack beans	NI (6.9%)	NI (0%)	NI (11.3%)	**NI (0%)**	NI (11.0%)	NI (0%)
β-Mannosidase	snail	NI (11.4%)	NI (12.5%)	588	**NI (4.8%)**	NI (24.3%)	NI (0%)
α-L-Fucosidase	Bovine kidney	0.047	0.021	0.22	**0.012**	0.042	0.23
β-Glucuronidase	*E.coli*	796	NI (44.4%)	NI (21.5%)	**NI (39.6%)**	NI (30.9%)	NI (0%)

[a] NI : No inhibition (less than 50% inhibition at 1000 mM).

[b] ( ) : inhibition % at 1000 μM

52g-n の α-L-フコシダーゼ (bovine kidney 由来) に対する阻害活性評価を行った結果、*o*-フルオロ体 **52k** は IC_{50} 値 12 nM、*K*i 値 2.1 nM と強力な阻害活性を示した (**Figure 18**)。また、酵素選択性を検証した結果、*o*-フルオロ体 **52k** は α-L-フコシダーゼに対し非常に高い酵素選択性を示した (**Table 11**)。

最後に、アミド型イミノ糖誘導体 **52a-n** の Rat epididymis、 Human lysosome 由来の α-L-フコシダーゼに対する阻害活性評価を行った結果、Bovine kidney 由来の α-L-フコシダーゼと同様の傾向を示し、やはり *o*-フルオロ体 **52k** は Human lysosome 由来の α-L-フコシダーゼに対し IC_{50} 値 7.9 nM と強力な阻害活性を示し (**Table 12**)、フコシドーシス治療薬 [34] として非常に期待できる α-L-フコシダーゼ阻害剤の創製を達成した。

Table 12. Concentration of **52g-n** giving 50% inhibition of α-L-fucosidase (Bovine kidney, Rat epididymis and Human lysosome)

	IC_{50} (μM)		
	Bovine kidney	Rat epididymis	Human lysosome
DFJ	0.11	0.34	0.14
34a	0.19	0.43	0.086
34c	1.4	4.1	0.89
52a (R = phenyl)	0.047	0.34	0.030
52b (R = benzyl)	0.17	1.3	0.19
52c (R =butyl)	0.16	0.78	0.13
52d (R = *p*-methoxyphenyl)	0.043	0.17	0.026
52e (R = *p*-tolyl)	0.026	0.081	0.015
52f (R = *p*-fluorophenyl)	0.030	0.10	0.014
52g (R = *o*-tolyl)	0.047	0.39	0.058
52h (R = *m*-tolyl)	0.040	0.17	0.030
52i (R = 2,4-dimethylphenyl)	0.021	0.19	0.019
52j (R = 2,4,6-trimethylphenyl)	0.22	1.5	0.20
52k (R = *o*-fluorophenyl)	0.012	0.044	0.0079
52l (R = *m*-fluorophenyl)	0.028	0.28	0.031
52m (R = 2,4-difluorophenyl)	0.042	0.35	0.035
52n (R = 2,4,6-trifluorophenyl)	0.23	3.3	0.18

結論

今回著者は、様々なイミノ糖の中から、海洋生物から得られた初のイミノ糖である Batzellaside 類、また L-フコースを擬態化した構造を有するイミノ糖に着目し、それらの合成および、様々なグリコシダーゼに対する阻害活性評価を行った。

Batzellaside 類の全合成では、市販の Tri-*O*-benzyl-D-glucal **1** から 1 工程で得られる文献既知のラクトンから、13 工程、総収率 12.6%, 13.2%, 13.8% で Batzellaside A, B, および C の全合成を達成した。また総収率 13.0%, 12.1%, 9.7% で 8-epi-(-)-BatzellasideA, B, および C の合成を達成した。Batzellaside 類およびエピマーの各種グリコシダーゼ阻害活性を評価したところ、Batzellaside A、C8-epi- Batzellaside C は、β-galactosidase に対して IC_{50} 値 6.7μM、7.5μM の中程度の阻害作用を示した。また C8-epi- Batzellaside A は、β-glucronidase に対し IC_{50} 値 85μM の弱い阻害活性を示すことを見出した。

フコシダーゼ阻害剤の創製においては、2, 4, 6-トリクロロ体は、β-galactosidase に対し、弱い阻害活性を示すものの、α-L-フコシダーゼに対し高い酵素選択性を示し、IC_{50} 値 5 nM の非常に強力な阻害活性を有することを見出した。さらに、アミド型イミノ糖の合成では、Human lysosome 由来の α-L-フコシダーゼに対し IC_{50} 値 7.9 nM の強力な阻害活性を保持し、且つより高い酵素選択性を有した *o*-フルオロ体の創製を達成した。

謝辞

本研究に際し、終始御懇篤な御指導、御鞭撻を賜りました富山大学工学部教授、豊岡尚樹先生に謹んで感謝いたします。また、本研究の計画、実施および考察の細部にわたり御指導、御尽力いただきました富山大学薬学部教授、松谷裕二先生、准教授、杉本健士先生、助教、湊大志郎先生に深く感謝いたします。また、*in vitro* での活性試験を行って頂きました富山大学病院薬剤部准教授、加藤敦先生、薬剤部研究室の諸氏、立体構造解析をしてくださった富山大学医薬学総合研究所化学応用分野准教授、手塚康弘先生、電極酸化の検討をしてくださった長崎大学薬学部教授、尾野村治先生、Peter G. Kiria 氏に深く感謝いたします。

実験の部

General

Flash chromatography was performed with Kanto Kagaku silica gel 60N (63-210 mm). NMR spectra were recorded on a Varian Gemini300 or JEOL ECX400 spectrometer in the solvent indicated. Chemical shifts (δ) are given in ppm downfield from TMS and referenced with $CHCl_3$ (7.26 ppm) as an internal standard. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and coupling constants are given in (*J*) Hz. High resolution mass spectral data was obtained on a JEOL JMS-GC MATE Ⅱ or JEOL JMS-AX505HAD. All commercial reagents were used as received unless otherwise noted.

(4*R*, 5*S*, 6*R*)-4, 5-Bis-benzyloxy-6-benzyloxymethyltetrahydro-pyran-2-one (2)

PCC (43.6 g, 0.20 mol) and silica gel (60 g) were added to a solution of **1** (42.1 g, 0.10 mol) in CH_2Cl_2 (100 mL). The resulting suspension was refluxed for 12 h. After cooling, the reaction mixture was filtered through Celite pad. The Celite pad was washed several times with AcOEt, and the filtrates were combined and concentrated resulting in a black oil, which was chromatographed on silica gel (160 g, *n*-hexane/acetone 10:1) to give **2** (23.9 g, 55.5 mmol, 55%) as a pale yellow solid. The spectral data were identical with those of reported values.[4]

(3*R*, 4*R*, 5*R*)-3, 4, 6-Tris-benzyloxy-5-hydroxyhexanoic acid methyl ester (3)

The procedure in ref. 4 was modified as shown below.

Aqueous LiOH (1 N, 1.4 mL) was added to a solution of **2** (0.62 g, 1.44 mmol) in MeOH (4.2 mL). The reaction mixture was refluxed for 2 h. After cooling, the reaction mixture was acidified with 10 % HCl to pH 4 and then the aqueous mixture was extracted with AcOEt (10 mL x 3). The organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was dissolved in Et_2O (5 mL) and treated with ethereal CH_2N_2, prepared from *N*-Nitroso-*N*-methylurea (371 mg, 3.6 mmol) and a solution of KOH (0.57 g, 10.2 mmol) in a mixture of H_2O (2 mL) and Et_2O (3 mL), at 0 °C for 30 min. The reaction mixture was concentrated resulting in a pale yellow oil, which was chromatographed on silica gel (30 g, AcOEt/*n*-hexane 1:4) to give **3** (0.63 g, 1.35 mmol, 94%) as a pale yellow oil. The spectral data were identical with those of reported values.[4]

(3*R*, 4*R*, 5*S*)-5-Azido-3, 4, 6-tris-benzyloxyhexanoic acid methyl ester (4)

The procedure in ref. 4 was modified as shown below.

Ph_3P (6.51 g, 24.8 mmol) was added to a solution of **3** (8.87 g, 19.1 mmol) in THF (25 mL). A solution of HN_3 (0.8 N, 38.2 mmol) in benzene (48 mL), prepared from NaN_3 (3.26 g, 50.2 mmol) and conc. H_2SO_4 (1.26 mL, 23.7 mmol) in a mixture of H_2O (36 mL) and Benzene (60 mL) at 0 °C, was added to the stirred mixture. Dietyl azodicarboxylate (c.a. 2.2 mol/L, 11.2 mL, 24.9 mmol) at 0 °C was added slowly to the stirred mixture. The reaction mixture was stirred for 12 h at room temperature. The solvent was removed to give a pale yellow oil, which was chromatographed on silica gel (80 g, AcOEt/*n*-hexane 1:10) to give **4** (7.67 g, 15.7 mmol, 82%) as a colorless oil. The spectral data were identical with those for the reported values.[4]

(4*R*, 5*R*, 6*S*)-4, 5-Bis-benzyloxy-6-benzyloxymethylpiperidin-2-one (5)

10% Pd/C (491 mg) was added to a solution of **4** (6.15 g, 12.6 mmol) in AcOEt (13 mL), and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 48 h. The catalyst was filtered off with Celite pad and the filtrate was evaporated to give **5** (5.34 g, 12.4 mmol, 98%) as a colorless oil. This compound was used directly in the next step without further purification. The spectral data were identical with those for the reported values.[4]

(4*R*, 5*R*, 6*S*)-3, 4-Bis-benzyloxy-2-benzyloxymethyl-6-oxopiperidine-1-carboxylic acid benzyl ester (6)

A solution of lithium bis(trimethylsilyl)amide (10.4 mL, 16.6 mmol, 1.6 mol/L, in THF) at -78 °C was added to a stirred solution of **5** (5.55 g, 12.9 mmol) in THF (26 mL). The resulting mixture was stirred at -78 °C for 0.5 h. Benzyl chloroformate (2.75 mL, 19.3 mmol) was added dropwise to the mixture, and the reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with sat. $NaHCO_3$ (aq) and then the aqueous mixture was extracted with CH_2Cl_2 (30 mL x 3). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (80 g, AcOEt/*n*-hexane 1:10) to give **6** (6.1 g, 10.8 mmol, 83%) as a colorless oil.

^{1}H-NMR (300 MHz) ($CDCl_3$) δ 7.43-7.17 (20H, m), 4.76-4.58 (6H, m), 4.74-4.39 (3H, m), 4.25 (1H, ddd, *J* = 9.0, 7.6, 7.6 Hz), 3.92 (1H, dd, *J* = 9.9, 1.2 Hz), 3.85 (1H, dd, *J* = 9.0, 5.4 Hz), 3.64 (1H, dd, *J* = 9.9, 3.6 Hz), 3.01 (1H, dd, *J* = 17.1, 7.6 Hz), 2.52 (1H, dd, *J* = 17.1, 7.6 Hz); ^{13}C-NMR (75 MHz) ($CDCl_3$) δ 169.1, 153.5, 138.0, 137.5, 137.3, 135.0, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.3, 127.1, 78.4, 74.4, 73.2, 72.9, 72.2, 68.5, 65.9, 54.8, 40.5; IR (neat): 1774, 1721 cm^{-1}; MS (ESI): *m/z* 565

(M^+); HRMS (ESI) Calcd for $C_{35}H_{35}NO_6$ 565.2464; Found 565.2454; $[\alpha]_D^{24}$ +11.84 (*c* 0.98, $CHCl_3$).

(2*S*, 3*R*, 4*R*, 6*R*)-6-Allyl-3, 4-bis-benzyloxy-2-benzyloxymethylpiperidine-1-carboxylic acid benzyl ester (7)

A solution of DIBAL (1 M, 11.2 mL, 1.16 mmol, in *n*-hexane) at -78 °C was added to a solution of **6** (5.07 g, 8.98 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at the same temperature for 0.5 h. The reaction was quenched with MeOH (6 mL) and 30% Rochella salt (aq) and then the aqueous mixture was extracted with CH_2Cl_2 (30 mL x 3). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on silica gel (80 g, AcOEt/*n*-hexane 1:15) to give **7** (2.66 g, 4.49 mmol, 50%) as a pale yellow oil.

^{1}H-NMR (300 MHz) ($CDCl_3$) δ 7.34-7.22 (20H, m), 5.70 (1H, br), 5.20-5.09 (2H, m), 5.02-4.86 (2H, m), 4.78-4.44 (7H, m), 4.32 (1H, dd, *J* = 6.4, 6.4 Hz), 3.95-3.87 (1H, m), 3.82 (1H, dd, *J* = 10.2, 5.7), 3.65 (1H, br), 3.66 (1H, dd, *J* = 10.2, 5.1 Hz), 2.46-2.41 (1H, m), 2.26-2.15 (1H, m), 2.04 (1H, ddd, *J* = 12.0, 6.6, 6.4), 1.57 (1H, ddd, *J* = 12.0, 6.6, 6.4 Hz); ^{13}C-NMR (75 MHz) ($CDCl_3$) δ 155.8, 138.6, 138.2, 138.1, 136.5, 135.6, 128.3, 128.2, 128.1, 127.77, 127.67, 127.59, 127.53, 127.45, 127.41, 127.38, 127.25, 117.1, 100.5, 80.6, 73.0, 72.94, 72.86, 72.5, 69.5, 67.4, 53.2, 50.8, 39.1; IR (neat): 1679 cm^{-1}: MS (ESI): *m/z* 591 (M^+); HRMS (ESI) Calcd for $C_{38}H_{41}O_5N$ 591.2985; Found 591.2980; $[\alpha]_D^{23}$ -8.24 (*c* 1.10, $CHCl_3$).

(2*S*, 3*R*, 4*R*, 6*R*)-3, 4-Bis-benzyloxy-2-benzyloxymethyl-6-((2*R*)-2-hydroxypent-4-enyl)piperidine-1-carboxylic acid benzyl ester (9)

A 3:1 1, 4-dioxane/H_2O mixture (40 mL) in a solution of **7** (1.92 g, 3.24 mmol) was added to 2, 6-lutidine (0.75 mL, 6.48 mmol) and OsO_4 (4.0 mL, 0.648 mmol, 4% in H_2O) at 0 °C. $NaIO_4$ (2.77 g, 13.0 mmol) was added to the resulting mixture. The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, 10% HCl (aq) (20 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give the aldehyde (**8**) as a colorless oil, which was used directly in the next step.

(+)-$(Ipc)_2$B(allyl) (1.0 M, 2.7 mL, 2.67 mmol, in *n*-pentane) was added to a solution of the above aldehyde (**8**) in Et_2O (5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. After the reaction was complete, MeOH (2.0 mL) and 2-aminoethanol

(4.0 mL) were added. The resulting mixture was stirred at room temperature for 17 h. The reaction solvent was removed to give a pale yellow oil, which was chromatographed on silica gel (60 g, AcOEt/*n*-Hexane 1:15) to give **9** (1.44 g, 2.27 mmol, 70%) as a pale yellow oil.

^{1}H-NMR (300 MHz) ($CDCl_3$) δ 7.32-7.26 (20H, m), 5.74 (1H, br), 5.10-5.00 (5H, m), 4.76-4.57 (6H, m), 4.45 (1H, dd, *J* = 6.3, 6.3 Hz), 3.90-3.86 (2H, m), 3.64-3.58 (2H, m), 2.18-2.12 (3H, m), 1.94 (1H, ddd, *J* = 13.1, 6.5, 6.3 Hz), 1.67 (1H, ddd, *J* = 13.1, 6.5, 6.3 Hz), 1.66-1.65 (3H, m); ^{13}C-NMR (75 MHz) ($CDCl_3$) δ 156.3, 138.5, 138.1, 137.9, 136.3, 134.6, 128.3, 128.24, 128.21, 128.0, 127.6, 127.53, 127.46, 117.5, 80.6, 77.4, 76.6, 73.2, 73.07, 72.97, 72.6, 69.0, 68.7, 67.6, 53.3, 48.7, 42.3, 33.9; IR (neat): 3447, 1692 cm^{-1}; MS (ESI): *m/z* 635 (M^+); HRMS (ESI) Calcd for $C_{40}H_{45}O_6N$ 635.3247; Found 635.3261; $[\alpha]_D^{22}$ -15.27 (*c* 1.60, $CHCl_3$).

3-Allyl-6, 7-bis-benzyloxy-8-benzyloxymethylhexahydropyrido[1,2-c]-[1,3]oxazin-1-one (10)

A 3:1 THF/DMF mixture (4 mL) in a solution of **9** (0.20 g, 0.314 mmol) was added to NaH (17.6 mg, 0.441 mmol, 60% suspension in mineral oil). The stirred reaction mixture was refluxed for 20 h. After cooling, H_2O (10 mL) was added, and then the aqueous mixture was extracted with AcOEt (10 mL x 3). The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to give a brown oil, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt, 10:1) to give **10** (0.149 g, 0.283 mmol, 90%) as a pale brown oil.

^{1}H-NMR (300 MHz) ($CDCl_3$) δ 7.35-7.26 (15H, m), 5.79 (1H, ddt, *J* = 16.9, 10.3, 6.7 Hz), 5.14 (1H, d, *J* = 16.9 Hz), 5.13 (1H, d, *J* = 10.3 Hz), 4.73-4.44 (6H, m), 4.29-4.28 (1H, m), 4.23 (1H, dtd, *J* = 11.1, 6.7, 2.8), 3.97 (1H, dd, *J* = 10.3, 4.3 Hz), 3.96-3.93 (1H, m), 3.81 (1H, dd, *J* = 10.3, 2.6), 3.68 (1H, dddd, *J* = 11.1, 10.5, 2.8, 2.2 Hz), 2.49 (1H, dt, *J* = 14.2, 6.7 Hz), 2.32 (1H, dt, *J* = 14.2, 6.7 Hz), 2.18 (1H, dd, *J* = 14.0, 5.5 Hz), 1.93 (1H, dt, *J* = 13.5, 2.8 Hz), 1.76 (1H, dd, *J* = 14.0, 2.2 Hz), 1.42 (1H, dt, *J* = 13.5, 11.1 Hz); ^{13}C-NMR (75 MHz) ($CDCl_3$) δ 152.9, 138.3, 138.2, 137.9, 132.2, 128.3, 128.2, 127.6, 127.58, 127.53, 127.4, 127.3, 118.6, 78.1, 77.4, 75.8, 75.5, 73.3, 72.3, 71.5, 66.8, 54.0, 48.0, 39.5, 35.3, 34.3, 29.8; IR (neat): 1682 cm^{-1}; MS (ESI): *m/z* 527 (M^+); HRMS (ESI) Calcd for $C_{33}H_{37}O_5N$ 527.2672; Found 527.2661; $[\alpha]_D^{23}$ -20.45 (*c* 0.46, $CHCl_3$).

6,7-Bis-benzyloxy-8-benzyloxymethyl-3-dec-2-enyl-hexahydro-pyrido[1,2-c][1,3]oxazin-1-one (11)

1-Nonene (0.099 mL, 0.569 mmol) was added to a solution of **10** (30 mg, 56.9 μmol) in CH_2Cl_2 (2 mL) at room temperature. Hoveyda-Grubbs Catalyst, 2nd generation (3.7 mg, 5.69 μmol) was added to the stirred mixture. The stirred reaction mixture was refluxed for 24 h. After cooling, the reaction solvent was removed in vacuum to give a black oil, which was chromatographed on silica gel (5 g, AcOEt/*n*-Hexane 1:10) to give **11** (30.2 mg, 48.3 μmol, 85%) as a pale brown oil.

^{1}H-NMR (300 MHz) ($CDCl_3$) δ 7.26-7.17 (15H, m), 5.44 (1H, dt, *J* = 16.5, 5.3 Hz), 5.31 (1H, ddd, *J* = 16.5, 10.5, 5.1 Hz), 4.64-4.40 (6H, m), 4.21 (1H, br), 4.10 (1H, dtd, *J* = 11.1, 6.7, 2.8 Hz), 3.89 (1H, dd, *J* = 7.5, 3.0 Hz), 3.85-3.84 (1H, m), 3.73 (1H, dd, *J* = 7.5, 1.8 Hz), 3.62-3.56 (1H, m), 2.38-2.33 (1H, m), 2.20-2.12 (1H, m), 1.93-1.82 (2H, m), 1.69 (1H, d, *J* = 10.8 Hz), 1.36-1.19 (14H, m), 0.82-0.79 (3H, m); ^{13}C-NMR (75 MHz) ($CDCl_3$) δ 153.1, 152.9, 138.4, 138.3, 138.0, 135.0, 134.9, 133.8, 131.7, 128.3, 128.2, 127.7, 127.6, 127.57, 127.47, 127.3, 127.2, 78.1, 76.1, 75.8, 75.6, 73.3, 73.0, 72.2, 71.4, 38.4, 35.6, 35.3, 35.1, 34.3, 32.9, 32.6, 32.1, 31.8, 31.77, 31.67, 31.57, 31.4, 30.9, 29.6, 29.5, 29.3, 29.26, 29.1, 28.8, 27.4; IR (neat): 1691 cm^{-1}; MS (ESI): *m/z* 625 (M^+); HRMS (ESI) Calcd for $C_{40}H_{51}O_5N$ 625.3767; Found 625.3778; $[\alpha]_D^{22}$ -22.96 (*c* 1.50, $CHCl_3$).

6,7-Bis-benzyloxy-8-benzyloxymethyl-3-non-2-enyl-hexahydro-pyrido[1,2-c][1,3]oxazin-1-one (12)

1-Octene (0.146 mL, 0.93 mmol) was added to a solution of **10** (49 mg, 93.0 μmol) in CH_2Cl_2 (4 mL) at room temperature. Hoveyda-Grubbs Catalyst, 2nd generation (5.0 mg, 9.3 μmol) was added to the stirred mixture. The stirred reaction mixture was refluxed for 15 h. After cooling, the reaction solvent was removed in vacuum to give a black oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 20:1) to give **12** (51 mg, 83.7 μmol, 90%) as a pale brown oil.

^{1}H-NMR (500 MHz $CDCl_3$) δ 7.33-7.27 (15H, m), 5.34 (1H, dt, *J* = 14.3, 7.2 Hz), 5.50-5.31 (1H, m), 4.75-4.41 (6H, m), 4.28 (1H, br), 4.22-4.15 (1H, m), 3.96 (1H, dd, *J* = 10.1, 4.4 Hz), 3.94-3.87 (2H, m), 3.80 (1H, dd, *J* = 10.1, 2.6 Hz), 3.72-3.65 (1H, m), 2.53-2.11 (2H, m), 2.04-1.55 (6H, m), 1.37-1.26 (8H, m), 0.88 (3H, t, *J* = 6.5 Hz).

6,7-Bis-benzyloxy-8-benzyloxymethyl-3-undec-2-enyl-hexahydro-pyrido[1,2-c][1,3]oxazin-1-one (**13**)

1-Decene (0.40 mL, 2.12 mmol) was added to a solution of **10** (112 mg, 0.21 mol) in CH_2Cl_2 (6 mL) at room temperature. Hoveyda-Grubbs Catalyst, 2nd generation (13.0 mg, 21.2 μmol) was added to the stirred mixture. The stirred reaction mixture was refluxed

for 15 h. After cooling, the reaction solvent was removed in vacuum to give a black oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 20:1) to give **13** (123 mg, 0.19 mmol, 91%) as a pale brown oil.

^{1}H-NMR (500 MHz $CDCl_3$) δ 7.34-7.27 (15H, m), 5.33 (1H, dt, *J* = 14.4, 7.2 Hz), 5.43-5.33 (1H, m), 4.75-4.41 (6H, m), 4.29 (1H, br), 4.20-4.16 (1H, m), 3.98-3.90 (3H, m), 3.81 (1H, dd, *J* = 10.3, 2.9 Hz), 3.69-3.65 (1H, m), 2.51-2.18 (2H, m), 2.05-1.59 (6H, m), 1.35-1.26 (12H, m), 0.88 (3H, t, *J* = 6.6 Hz).

(-)-batzellaside A formic acid salt

20% $Pd(OH)_2$/C (3 mg) was added to a solution of **11** (20 mg, 31.9 μmol) in EtOH (3 mL), and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 5 days. The catalyst was filtered off with Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of 4 M KOH (aq, 0.5 mL) was added to a solution of this product in 2-propanol (0.5 mL), and the resulting mixture was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with a mixture of 1% v/v formic acid-methanol at room temperature, and concentrated in vacuo to yield (-)-batzellaside A as the formic acid salt (9 mg, 23.9 μmol, 75%).

^{1}H-NMR (500 MHz) (CD_3OD) δ 3.91 (1H, brs), 3.83-3.75 (3H, m), 3.65-3.51 (2H, m), 2.03-1.98 (1H, m), 1.85-1.82 (1H, m), 1.73-1.68 (2H, m), 1.47 (2H, brs), 1.31 (16H, brs), 0.90 (3H, t, *J* = 6.8 Hz); ^{13}C-NMR (125 MHz) (CD_3OD) δ 72.0, 67.3, 67.2, 60.9, 58.5, 53.4, 39.5, 39.4, 33.1, 33.0, 32.6, 30.8, 30.75, 30.70, 30.5, 26.3, 23.7, 14.4; $[\alpha]_D^{25.7}$ -5.9 (*c* 0.2, MeOH).

(-)-batzellaside B formic acid salt

20% $Pd(OH)_2$/C (5 mg) was added to a solution of **12** (82 mg, 134 μmol) in EtOH (5 mL), and the resulting suspension was hydrogenated at 1 atm under hydrogen for 7 days. The catalyst was filtered off with Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of 4 M KOH (aq, 1 mL) was added to a solution of this product in 2-propanol (1 mL), which was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with a mixture of 1% v/v formic acid-methanol at room temperature, and concentrated in vacuo to yield (-)-batzellaside B as the formic acid salt (33 mg, 89.8 μmol, 67%).

^{1}H-NMR (500 MHz) (CD_3OD) δ: 3.91 (1H, brs), 3.83-3.75 (3H, m), 3.59-3.50 (2H, m),

2.04-1.98 (1H, m), 1.85-1.73 (1H, m), 1.73-1.69 (2H, m), 1.48 (2H, brs), 1.32 (16H, brs), 0.90 (3H, t, *J* = 6.8 Hz); ^{13}C-NMR (125 MHz) (CD_3OD) δ 72.1, 67.3, 67.2, 60.8, 58.5, 53.5, 39.5, 39.4, 33.0, 32.6, 30.8, 30.7, 30.5, 30.4, 26.3, 23.7, 14.4; $[\alpha]_D^{25.3}$ -13.5 (*c* 0.1, MeOH).

(-)-batzellaside C formic acid salt

20% $Pd(OH)_2$/C (3 mg) was added to a solution of **13** (21 mg, 32.8 μmol) in EtOH (3 mL), and the resulting suspension was hydrogenated at 1 atm under hydrogen for 7 days. The catalyst was filtered off with Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of 4 M KOH (aq, 0.5 mL) was added to a solution of this product in 2-propanol (0.5 mL), which was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with a mixture of 1% v/v formic acid-methanol at room temperature, and concentrated in vacuo to yield (-)-batzellaside C as the formic acid salt (9 mg, 22.6 μmol, 69%).

^{1}H-NMR (500 MHz) (CD_3OD) δ: 3.91 (1H, brs), 3.83-3.77 (3H, m), 3.65-3.50 (2H, m), 2.03-1.98 (1H, m), 1.85-1.82 (1H, m), 1.73-1.66 (2H, m), 1.47 (2H, brs), 1.32 (18H, brs), 0.89 (3H, t, *J* = 6.8 Hz); ^{13}C-NMR (125 MHz) (CD_3OD) δ 72.1, 67.3, 67.2, 60.8, 58.5, 53.4, 39.5, 33.1, 33.0, 32.6, 30.8, 30.7, 30.5, 30.4, 26.3, 23.7, 14.4; $[\alpha]_D^{22.6}$ -7.4 (*c* 0.1, MeOH).

(2*S*, 3*R*, 4*R*, 6*R*)-3, 4-Bis-benzyloxy-2-benzyloxymethyl-6-((2*S*)-2-hydroxypent-4-enyl)piperidine-1-carboxylic acid benzyl ester (9')

In a 3:1 ratio of 1, 4-dioxane/H_2O mixture (20 mL), a solution of **7** (0.49 g, 0.84 mmol) was added to 2, 6-lutidine (0.19 mL, 1.68 mmol) and OsO_4 (1.0 mL, 0.17 mmol, 4% in H_2O) at 0 °C. Then to the resulting mixture was added $NaIO_4$ (0.718 g, 3.36 mmol). The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, 10% HCl (aq) (10 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give the aldehyde (**8**) as a colorless oil, which was used directly in the next step.

(-)-$(Ipc)_2$B(allyl) (1.0 M, 0.81 mL, 0.81 mmol, in *n*-pentane) was added to a solution of the above aldehyde (**8**) in Et_2O (3 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h. After the reaction was complete, MeOH (1.0 mL) and 2-Aminoethanol (2.0 mL) were added. The resulting mixture was stirred at room temperature for 17 h. The reaction solvent was removed to give a pale yellow oil, which was

chromatographed on silica gel (15 g, AcOEt/*n*-Hexane 1:15) to give **14** (0.38 g, 0.60 mmol, 71%) as a pale yellow oil.

^{1}H-NMR (300 MHz) ($CDCl_3$) δ 7.36-7.29 (20H, m), 5.78 (1H, br), 5.18-5.02 (4H, m), 4.86 (1H, br), 4.78-4.64 (6H, m), 4.44 (1H, dd, *J* = 5.1, 5.1 Hz), 3.92-3.85 (1H, m) 3.79-3.69 (1H, m), 3.64-3.56 (2H, m), 2.24-2.10 (4H, m), 1.98 (1H, ddd, *J* = 13.5, 5.1, 4.2 Hz) 1.86-1.73 (2H, m), 1.38 (1H, ddd, *J* = 13.5, 5.2, 4.2 Hz); ^{13}C-NMR (75 MHz) ($CDCl_3$) δ 156.3, 138.5, 138.1, 138.0, 136.1, 128.4, 128.26, 128.22, 128.0, 127.6, 127.5, 127.4, 127.2, 116.6, 80.3, 77.4, 73.6, 73.4, 72.9, 72.5, 69.1, 66.8, 53.4, 48.1, 42.9, 41.4, 35.0, 32.6, 31.0, 21.5; IR (neat): 3448, 1667 cm^{-1}; MS (ESI): *m/z* 635 (M^+) ; HRMS (ESI) Calcd for $C_{40}H_{45}O_6N$ 635.3247; Found 635.3242; $[\alpha]_D^{22}$ -10.26 (*c* 1.00, $CHCl_3$).

3-Allyl-6,7-bis-benzyloxy-8-benzyloxymethyl-hexahydro-pyrido[1,2-c][1,3]oxazin-1-one (14)

NaH (42 mg, 1.0 mmol, 60% suspension in mineral oil) was added to a solution of **9'** (0.442 g, 0.70 mmol) in a 4:1 THF/DMF mixture (10 mL). The stirred reaction mixture was refluxed for 15 h. After cooling, H_2O (10 mL) was added, and then the aqueous mixture was extracted with AcOEt (10 mL x 3). The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to give a brown oil, which was chromatographed on silica gel (15 g, *n*-Hexane/Acetone 10:1) to give **14** (0.320 g, 0.61 mmol, 87%) as a pale brown oil.

^{1}H-NMR (400 MHz) ($CDCl_3$) δ 7.27-7.21 (15H, m), 5.74 (1H, ddt, *J* = 17.3, 10.3, 6.6 Hz), 5.08 (1H, d, J = 17.1 Hz), 5.07 (1H, d, *J* = 10.3 Hz), 4.59-4.38 (6H, m), 4.34 (1H, m), 4.09-3.95 (3H, m), 3.86-3.83 (1H, m), 3.79-3.77 (1H, m), 3.70-3.68 (1H, m), 2.48 (1H, dt, *J* = 13.2, 6.6 Hz), 2.25 (1H, dt, *J* = 13.2, 6.6 Hz), 2.15-2.07 (1H, m), 1.88-1.81 (1H, m), 1.65-1.56 (2H, m); ^{13}C-NMR (125 MHz) ($CDCl_3$) δ 152.6, 138.5, 138.2, 138.1, 132.6, 128.4, 128.2, 127.7, 127.66, 127.63, 127.55, 127.54, 127.4, 118.6, 75.1, 74.3, 73.0, 72.6, 71.3, 67.4, 56.8, 47.4, 39.1, 34.2, 31.4; IR (neat): 1699 cm^{-1}; MS (ESI): *m/z* 527 (M^+); HRMS (ESI) calcd for $C_{33}H_{37}O_5N$ 527.2672; Found 527.2671; $[\alpha]_D^{29.6}$ -59.5 (*c* 1.1, $CHCl_3$).

6,7-Bis-benzyloxy-8-benzyloxymethyl-3-dec-2-enyl-hexahydro-pyrido[1,2-c][1,3]oxazin-1-one (15)

1-Nonene (0.14 mL, 0.834 mmol) was added to a solution of **14** (44 mg, 83.4 μmol) in CH_2Cl_2 (5 mL) at room temperature. Hoveyda-Grubbs Catalyst, 2nd generation (5.0 mg, 8.34 μmol) was added to the stirred mixture. The stirred reaction mixture was refluxed for 24 h. After cooling, the reaction solvent was removed in vacuum to give a black oil,

which was chromatographed on silica gel (5 g, *n*-Hexane/Acetone 20:1) to give **15** (47 mg, 75.1 μmol, 90%) as a pale brown oil.

^{1}H-NMR (500 MHz) ($CDCl_3$) δ 7.32-7.25 (15H, m), 5.55-5.33 (2H, m), 4.68-4.44 (6H, m), 4.30 (1H, br), 4.13-4.02 (3H, m), 3.91-3.89 (1H, m), 3.84 (1H, dd, *J* = 10.1, 4.9 Hz), 3.74-3.72 (1H, m), 2.53-2.11 (2H, m), 2.09-1.51 (6H, m), 1.31-1.26 (10H, m), 0.88 (3H, t, *J* = 6.9 Hz).

6,7-Bis-benzyloxy-8-benzyloxymethyl-3-non-2-enyl-hexahydro-pyrido[1,2-c][1,3]oxazin-1-one (16)

1-Octene (0.25 mL, 1.57 mmol) was added to a solution of **14** (83 mg, 157 μmol) in CH_2Cl_2 (8 mL) at room temperature. Hoveyda-Grubbs Catalyst, 2nd generation (10 mg, 17.7 μmol) was added to the stirred mixture. The stirred reaction mixture was refluxed for 15 h. After cooling, the reaction solvent was removed in vacuum to give a black oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 10:1) to give **16** (86 mg, 141.3 μmol, 90%) as a pale brown oil.

^{1}H-NMR (500 MHz) ($CDCl_3$) δ 7.33-7.27 (15H, m), 5.55-5.33 (2H, m), 4.72-4.44 (6H, m), 4.29 (1H, br), 4.14-4.02 (3H, m), 3.93-3.90 (1H, m), 3.84 (1H, dd, *J* = 10.1, 4.9 Hz), 3.74-3.72 (1H, m), 2.53-2.12 (2H, m), 2.09-1.56 (6H, m), 1.33-1.26 (8H, m), 0.88 (3H, t, *J* = 6.9 Hz).

6,7-Bis-benzyloxy-8-benzyloxymethyl-3-undec-2-enyl-hexahydro-pyrido[1,2-c][1,3]oxazin-1-one (17)

1-Decene (0.17 mL, 0.91 mmol) was added to a solution of **14** (48 mg, 0.091 mol) in CH_2Cl_2 (5 mL) at room temperature. Hoveyda-Grubbs Catalyst, 2nd generation (5 mg, 9.1 μmol) was added to the stirred mixture. The stirred reaction mixture was refluxed for 15 h. After cooling, the reaction solvent was removed in vacuum to give a black oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 20:1) to give **17** (51 mg, 0.08 mmol, 88%) as a pale brown oil.

^{1}H-NMR (500 MHz) ($CDCl_3$) δ 7.33-7.27 (15H, m), 5.52-5.30 (2H, m), 4.64-4.47 (6H, m), 4.29 (1H, br), 4.13-4.02 (3H, m), 3.98-3.89 (1H, m), 3.84 (1H, dd, *J* = 10.1, 4.9 Hz), 3.73-3.71 (1H, m), 2.48-2.13 (2H, m), 2.04-1.54 (6H, m), 1.33-1.26 (12H, m), 0.88 (3H, t, *J* = 6.6 Hz).

6-(2-Hydroxydodecyl)-2-hydroxymethylpiperidine-3,4-diol formic acid salt

20% $Pd(OH)_2$/C (5 mg) was added to a solution of **16** (110 mg, 178 μmol) in EtOH (5 mL), and the resulting suspension was hydrogenated at 1 atm under hydrogen for 7 days.

The catalyst was filtered off with Celite pad and the filtrate was evaporated to give a hydrogenated product. A solution of 4 M KOH (aq, 1.5 mL) was added to a solution of this product in 2-propanol (1.5 mL), which was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with a mixture of 1% v/v formic acid-methanol at room temperature, and concentrated in vacuo to yield **19** (48 mg, 128.2 μmol, 71%).

^{1}H-NMR (500 MHz) (CD_3OD) δ 3.93-3.76 (5H, m), 3.64 (1H, brs), 3.49 (1H, t, *J* = 6.3 Hz), 2.15-2.10 (1H, m), 1.98-1.84 (2H, m), 1.69-1.66 (1H, m), 1.47 (2H, brs), 1.31 (16H, brs), 0.89 (3H, t, *J* = 6.9 Hz); ^{13}C-NMR (125 MHz) (CD_3OD) δ 69.7, 67.2, 67.1, 61.0, 58.1, 51.3, 39.2, 38.4, 33.1, 32.0, 30.7, 30.5, 30.4, 26.3, 23.7, 14.4; $[\alpha]_D^{28.0}$ -16.0 (*c* 0.1, MeOH).

2-Hydroxymethyl-6-(2-hydroxyundecyl)piperidine-3,4-diol formic acid salt

20% $Pd(OH)_2/C$ (5 mg) was added to a solution of **17** (82 mg, 134 μmol) in EtOH (5 mL), and the resulting suspension was hydrogenated at 1 atm under hydrogen for 6 days. The catalyst was filtered off with Celite pad and the filtrate was evaporated to give hydrogenated product. A solution of 4 M KOH (aq, 1 mL) was added to a solution of this product in 2-propanol (1 mL), which was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with a mixture of 1% v/v formic acid-methanol at room temperature, and concentrated in vacuo to yield **20** (33 mg, 89.8 μmol, 67%).

^{1}H-NMR (500 MHz) (CD_3OD) δ 3.92-3.78 (5H, m), 3.64 (1H, brs), 3.50 (1H, m), 2.15-2.10 (1H, m), 1.95-1.82 (2H, m), 1.70 (1H, m), 1.47 (2H, brs), 1.31 (14H, brs), 0.90 (3H, t, *J* = 6.3 Hz); ^{13}C-NMR (125 MHz) (CD_3OD) δ 69.7, 67.2, 67.1, 61.0, 58.1, 51.3, 39.2, 38.4, 33.1, 32.0, 30.8, 30.75, 30.70, 30.4, 26.7, 23.7, 14.4; $[\alpha]_D^{23.4}$ -7.0 (*c* 0.1, MeOH).

2-Hydroxymethyl-6-(2-hydroxytridecyl)piperidine-3,4-diol formic acid salt

20% $Pd(OH)_2/C$ (3 mg) was added to a solution of **18** (51 mg, 79.7 μmol) in EtOH (3 mL), and the resulting suspension was hydrogenated at 1 atm under hydrogen for 6 days. The catalyst was filtered off with Celite pad and the filtrate was evaporated to give hydrogenated product. A solution of 4 M KOH (aq, 1 mL) was added to a solution of this product in 2-propanol (1 mL), which was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was purified by DOWEX 50W resin (X-8, H^+ form,

eluent: 0.7 N aqueous NH_3), subjected to counterion exchange with a mixture of 1% v/v formic acid-methanol at room temperature, and concentrated in vacuo to yield **21** (17 mg, 43.8 μmol, 55%).

^{1}H-NMR (500 MHz) (CD_3OD) δ 3.91-3.76 (5H, m), 3.63 (1H, brs), 3.49 (1H, t, *J* = 6.6 Hz), 2.15-2.12 (1H, m), 1.96-1.82 (2H, m), 1.70-1.66 (1H, m), 1.47 (2H, m), 1.31 (18H, brs), 0.89 (3H, t, *J* = 6.9 Hz); ^{13}C-NMR (125 MHz) (CD_3OD) δ 69.7, 67.2, 67.1, 61.0, 58.1, 51.3, 39.2, 38.4, 33.1, 32.0, 30.74, 30.70, 30.5, 26.7, 23.7, 14.4; $[\alpha]_D^{24.9}$ -4.4 (*c* 0.15, MeOH).

(3*S*, 4*S*)-4-*tert*-butoxycarbonylamino-3-methoxymethoxy-1-pentene (21)

N-Ethyldiisopropylamine (14 mL, 79 mmol) and chloromethyl methyl ether (5.5 mL, 72 mmol) were added to a solution of **20**[1] (4.83 g, 24 mmol) in CH_2Cl_2 (48 mL) at 0 °C. The stirred reaction mixture was refluxed for 18 h. After cooling, the volatiles were removed in vacuo to give a yellow oil, which was chromatographed on silica gel (40 g, *n*-Hexane/Acetone 20:1) to give **21** (4.83 g, 21 mmol, 86%) as a pale yellow oil.

1H-NMR (300 MHz, $CDCl_3$): δ 1.15 (3H, d, *J* = 6.6 Hz), 1.41 (9H, s), 3.36 (3H, s), 3.71~3.77 (1H, br), 3.92~3.96 (1H, br), 4.52, 4.59 (2H, ABq, *J* = 6.9 Hz), 4.64~4.71 (1H, br), 5.24 (1H, dd, *J* = 1.1, 15.9 Hz), 5.25 (1H, dd, *J* = 1.1, 11.3 Hz), 5.64~5.76 (1H, m); 13C-NMR (75 MHz, $CDCl_3$): δ 17.75, 28.41, 49.40, 55.64, 79.04, 79.31, 93.86, 100.54, 118.94, 134.73, 155.29; IR ($CHCl_3$): 150, 1706, 3447 cm^{-1}; MS (EI) m/z 189 (M^+-56), 246 (M^++1), 144 (M^+-101); HRMS (EI) Calcd for $C_7H_{14}NO_2$: 144.1025 (M^+-101), found: 144.1023; $[\alpha]_D^{20}$ +50.9 (c 1.0, $CHCl_3$).

Ethyl (2*E*, 4*S*, 5*S*)-5-*tert*-butoxycarbonylamino-4-methoxymethoxy-2-hexenoate (22)

In a 3:1 1, 4-dioxane/H_2O mixture (40 mL), a solution of **3** (1.64 g, 6.69 mmol) was added to 2, 6-lutidine (1.60 mL, 13.4 mmol) and OsO_4 (2.0 mL, 0.67 mmol, 2% in H_2O) at 0 °C. Then to the resulting mixture was added $NaIO_4$ (5.70 g, 26.8 mmol). The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, 10% $Na_2S_2O_3$ (aq) (10 mL) was added, and then the aqueous mixture was extracted with AcOEt (20 mL x 3). The organic layers were combined, washed with 10% HCl (aq), dried over anhydrous Na_2SO_4, and evaporated to give the aldehyde as a colorless oil, which was used directly in the next step.

Ethyl diethylphosphonoacetate (2.70 mL, 13.4 mmol), and NaH (0.508 g, 12.7 mmol, 60% dispersion in paraffin liquid) were added to a solution of the above aldehyde in THF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 15 h.

After the reaction was complete, H_2O was added, and then the aqueous mixture was extracted with Et_2O (20 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give **22** as a yellow oil, which was chromatographed on silica gel (40 g, *n*-Hexane/Acetone 15:1) to give **22** (1.54 g, 4.82 mmol, 72%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, d, *J* = 6.9 Hz), 1.29 (3H, t, *J* = 7.1 Hz), 1.45 (9H, s), 3.39 (3H, s), 3.89 (1H, br), 4.15~4.23 (1H, br), 4.19 (2H, q, *J* = 7.1 Hz), 4.59~4.65 (1H, m), 4.60, 4.62 (2H, ABq, *J* = 6.9 Hz), 6.01 (1H, dd, *J* = 1.4, 15.7 Hz), 6.83 (1H, dd, *J* = 6.0, 15.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.10, 17.18, 28.20, 48.93, 55.73, 60.24, 77.31, 79.21, 94.86, 123.41, 144.35, 155.10, 165.69; IR ($CHCl_3$): 1504 cm^{-1}, 1711 cm^{-1}, 3447 cm^{-1}; MS (EI) m/z 317 (M^+); HRMS (EI) Calcd for $C_{15}H_{27}NO_6$: 317.1838 (M^+), found: 317.1827; $[\alpha]_D^{21}$ +16.5 (c 1.2, $CHCl_3$).

(*2E, 4S, 5S*)-5-*tert*-butoxycarbonylamino-4-methoxymethoxy-2-hexen-1-ol (23)

A solution of DIBAL (1.0 M in *n*-hexane, 1.70 mL, 20.5 mmol,) at -78 °C was added to a solution of **22** (0.188 g, 0.590 mmol) in CH_2Cl_2 (3 mL), and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with MeOH (6 mL) and then the insoluble materials were filtered off with Celite pad. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated to give a pale yellow oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 3:1) to give **23** (0.124 g, 0.45 mmol, 76%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, d, *J* = 6.6 Hz), 1.44 (9H, s), 1.81 (1H, br), 3.38 (3H, s), 3.79 (1H, br), 4.00~4.03 (1H, br), 4.16 (2H, br), 4.53, 4.61 (2H, ABq, *J* = 6.6 Hz), 4.67~4.70 (1H, br), 5.63 (1H, dd, *J* = 7.7, 15.7 Hz), 5.88 (1H, dt, *J* = 5.2, 15.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.86, 28.37, 49.69, 55.66, 62.62, 78.26, 79.22, 93.80, 127.73, 133.94, 155.61; IR ($CHCl_3$): 1507 cm^{-1}, 1697 cm^{-1}, 3443 cm^{-1}; MS (EI) m/z 144 (M^+-131), 218 (M^+-57), 275 (M^+); HRMS (EI) Calcd for $C_7H_{14}NO_2$: 144.1025 (M^+-131), found: 144.1023; $[\alpha]_D^{19}$ +57.2 (c 0.4, $CHCl_3$).

(*2E, 4S, 5S*)-5-*tert*-butoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-4-methoxymethoxy-2-hexene (24)

tert-Butyldimethylchlorosilane (1.67 g, 11.1 mmol) and imidazole (1.89 mL, 27.8 mmol) were added to a solution of **23** (1.53 g, 5.56 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 15 h. After the reaction was complete, H_2O was added, and then the aqueous mixture was extracted with Et_2O (20 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and

evaporated to give the residue, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 40:1) to give **24** (2.18 g, 5.59 mmol, quant.) as a pale yellow oil.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.90 (9H, s), 1.17 (3H, d, *J* = 6.6 Hz), 1.44 (9H, s), 3.38 (3H, s), 3.76 (1H, br), 3.97~4.01 (1H, m), 4.19 (2H, d, *J*=3.0 Hz), 4.52, 4.61 (2H, ABq, *J* = 6.6 Hz), 4.66~4.70 (1H, br), 5.59 (1H, dd, *J* = 8.0, 15.4 Hz), 5.79 (1H, dt, *J* = 4.7, 15.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ -5.20, 17.74, 18.38, 25.66, 25.91, 28.42, 55.64, 62.94, 78.34, 98.71, 125.97, 134.70, 155.40; IR ($CHCl_3$): 1502 cm^{-1}, 1707 cm^{-1}, 3448 cm^{-1}; MS (EI) m/z 389 (M^+); HRMS (FAB) Calcd for $C_{19}H_{40}NO_5Si$: 390.2676 (M^++1), found: 390.2669; $[\alpha]_D^{21}$ +49.7 (c 0.9, $CHCl_3$).

(*2R, 3S, 4R, 5S*)-5-*tert*-butoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-4-methoxymethoxyhexane-2, 3-diol (25)

A solution of NMO (1.70 mL, 8.16 mmol, 4.8 mM in H_2O) and OsO_4 (0.25 mL, 0.04 mmol, 2% in H_2O) were added to a solution of **24** (1.59 g, 4.08 mmol) in acetone (9 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 13 h. After the reaction was complete, 10% $Na_2S_2O_3$ (aq) (4 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 10:1) to give **25** (1.43 g, 3.39 mmol, 83%) as a white solid.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.08 (6H, s), 0.90 (9H, s), 1.22 (3H, d, *J* = 6.9 Hz), 1.44 (9H, s), 2.63 (1H, d, *J* = 4.4 Hz), 3.42 (3H, s), 3.57 (2H, br), 3.78~3.80 (3H, m), 3.94 (1H, br), 4.10 (1H, br), 4.71, 4.73 (2H, ABq, *J* = 6.3 Hz), 4.89 (1H, d, *J* = 9.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ -5.48, 17.72, 18.17, 25.82, 28.27, 46.23, 56.28, 65.08, 69.37, 69.78, 79.54, 80.57, 98.25, 156.38; IR ($CHCl_3$): 1507 cm^{-1}, 1686 cm^{-1}, 3443 cm^{-1}; MS (EI) m/z 424 (M^++1); HRMS (FAB) Calcd for $C_{19}H_{42}NO_7Si$: 424.2731 (M^++1), found: 424.2686; $[\alpha]_D^{18}$ -33.5 (c 1.4, $CHCl_3$); m.p. 70~73 °C

(*2R, 3R, 4R, 5S*)-5-*tert*-butoxycarbonylamino-1-*tert*-butyldimethylsilyloxy-2, 3, 4-methoxymethoxyhexane (26)

N -Ethyldiisopropylamine (0.65 mL, 3.71 mmol) and chloromethyl methyl ether (0.27 mL, 3.38 mmol) were added to a solution of **25** (0.204 g, 0.48 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the stirred reaction mixture was refluxed for 17 h. After cooling, the volatiles were removed in vacuo to give a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 15:1) to give **26** (0.283 g, 0.54 mmol, quant.) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.07 (6H, s), 0.89 (9H, s), 1.22 (3H, d, *J* = 6.6 Hz), 1.43 (9H, s), 3.38 (3H, s), 3.39(3H, s), 3.41 (3H, s), 3.64~3.65 (1H, m), 3.72~3.85 (4H, m), 4.01 (1H, br), 4.62~4.89 (6H, m), 5.04 (1H, br); ^{13}C-NMR (100 MHz, $CDCl_3$): δ -5.51, -5.42, 18.14, 18.84, 25.82, 28.38, 46.15, 55.70, 56.14, 56.24, 62.86, 77.38, 77.99, 78.75, 80.55, 97.55, 97.99, 98.70, 155.23; IR ($CHCl_3$): 1499 cm^{-1}, 1704 cm^{-1}, 3445 cm^{-1}; MS (EI) m/z 410 (M^+-101), 455 (M^+-57); HRMS (EI) Calcd for $C_{17}H_{36}NO_8Si$: 410.2210 (M^+-101), found: 410.2208; $[\alpha]_D^{22}$ +4.6 (c 1.1, $CHCl_3$).

(*2R, 3R, 4R, 5S*)-5-*tert*-butoxycarbonylamino-2, 3, 4-methoxymethoxyhexan-1-ol (27)

A solution of tetrabutylammonium fluoride (1.0 M in THF, 6.40 mL, 6.40 mmol,) was added to a solution of **26** (1.64 g, 3.20 mmol) in THF (6 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, brine (4 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give **9** as a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 3:1) to give **27** (1.31 g, 3.30 mmol, quant.) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.07 (6H, s), 0.89 (9H, s), 1.22 (3H, d, *J* = 6.6 Hz), 1.43 (9H, s), 3.38 (9H, s), 3.64~3.65 (1H, m), 3.72~3.85 (4H, m), 4.01 (1H, br), 4.62~4.89 (6H, m), 5.04 (1H, br); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.28, 28.30, 31.49, 45.67, 55.81, 56.25, 62.98, 78.25, 79.14, 80.28, 81.38, 97.72, 98.70, 98.86, 155.16; IR ($CHCl_3$): 1498 cm^{-1}, 1703 cm^{-1}, 3439 cm^{-1}; MS (EI) m/z 247 (M^+-150), 278 (M^+-119); HRMS (EI) Calcd for $C_{11}H_{21}NO_5$: 247.1420 (M^+-150), found: 247.1382; $[\alpha]_D^{20}$ -6.7 (c 1.4, $CHCl_3$).

(*2R, 3R, 4R, 5S*)-5-*tert*-butoxycarbonylamino-1-methylsulfonyloxy-2, 3, 4-methoxymethoxyhexane (28)

Methanesulfonyl chloride (0.34 mL, 3.05 mmol) and Et_3N (0.55 mL, 3.97 mmol) were added to a solution of **27** (0.602 g, 1.53 mmol) in CH_2Cl_2 (4 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 15 h. After the reaction was complete, sat. $NaHCO_3$ (aq) (10 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give a yellow oil, which was chromatographed on silica gel (15 g, *n*-Hexane/Acetone 6:1) to give **28** (0.745 g, 1.57 mmol, quant.) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.6 Hz), 1.44 (9H, s), 3.06 (3H, s), 3.41 (9H, s), 3.64 (2H, m), 4.02~4.12 (2H, m), 4.39~4.52 (2H, m), 4.64~4.82 (6H, m), 4.90

(1H, d, *J* = 10.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.97, 19.01, 28.20, 31.39, 37.02, 45.81, 55.76, 55.95, 56.10, 68.96, 75.09, 78.86, 80.96, 97.47, 98.31, 154.89; IR ($CHCl_3$): 1504 cm^{-1}, 1708 cm^{-1}, 3393 cm^{-1}; MS (FAB) m/z 476 (M^++1); HRMS (FAB) Calcd for $C_{18}H_{38}NO_{11}S$: 476.2166 (M^++1), found: 476.2147; $[\alpha]_D^{22}$ -9.7 (c 1.0, $CHCl_3$).

(*2S, 3R, 4S, 5R*)-2-Methyl-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (29)

NaH (0.313 g, 7.83 mmol, 60% dispersion in paraffin liquid) and NaI (0.466 g, 3.13 mmol) were added to a solution of **28** (0.745 g, 1.57 mmol) in DMF (4 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. After the reaction was complete, sat. $NaHCO_3$ (aq) (6 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 15:1) to give **29** (0.535 g, 1.41 mmol, 90%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, d, *J* = 7.1 Hz), 1.45 (9H, s), 3.19 (1H, d, *J* = 13.7 Hz), 3.39 (6H, s), 3.41 (3H, s), 3.83 (1H, m), 3.89~3.94 (2H, m), 4.04 (1H, d, *J* = 14.0 Hz), 4.45 (1H, br), 4.60~4.78 (6H, m); ^{13}C-NMR (75 MHz, $CDCl_3$): δ12.23, 28.32, 37.10, 48.90, 55.46, 55.51, 71.57, 72.74, 75.88, 79.43, 94.76, 95.34, 97.06, 154.99; IR ($CHCl_3$): 1694 cm^{-1}; MS (EI) m/z 379 (M^+); HRMS (EI) Calcd for $C_{17}H_{33}NO_8$: 379.2206 (M^+), found: 379.2192; $[\alpha]_D^{22}$ -38.0 (c 1.1, $CHCl_3$).

(*3S, 4R, 5R, 6S*)-2-Methoxy-6-methyl-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (30)

Et_4NBF_4 (0.800 g, 3.68 mmol) was added to a solution of **29** (0.318 g, 0.84 mmol) in a 4:1 MeCN/MeOH mixture (60 mL) and the reaction mixture was stirred at -15 °C for 15 h under 100 mA electricity passed through by use of graphite anode and cathode electrodes. Then the reaction solvent was removed to give a yellow oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 10:1) to give **30** (0.252 g, 0.61 mmol, 73%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, d, *J* = 7.1 Hz), 1.48 (9H, s), 3.30 (3H, s), 3.39 (3H, s), 3.40 (3H, s), 3.41 (3H, s), 3.86 (1H, t, *J* = 3.6 Hz), 3.97 (1H, dd, *J* = 3.3, 6.3 Hz), 4.05 (1H, d, *J* = 2.8 Hz), 4.43~4.53 (1H, br), 4.70~4.75 (6H, m), 5.36 (1H, br);

(*2R, 3R, 4R, 5R, 6S*)-2-Allyl-6-methyl-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (31)

Allyltrimethylsilane (0.56 mL, 3.52 mmol) and BF_3•Et_2O (0.13 mL, 1.10 mmol) were added to a solution of **30** (0.360 g, 0.88 mmol) in CH_2Cl_2 (3 mL) at -78 °C, and the reaction mixture was stirred at the same temperature. After 3 and 5 h, BF_3•Et_2O (0.13 mL, 1.10 mmol) was added to the reaction mixture, and the resulting solution was stirred at -60 °C for 17h. After the reaction was complete, sat. $NaHCO_3$ (aq) (6 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give a yellow oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 4:1) to give **31** (0.236 g, 0.56 mmol, 64%) as a pale yellow oil.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, d, *J* = 6.9 Hz), 1.41 (9H, s), 2.46 (1H, ddd, *J* = 6.9, 13.7 Hz), 2.60 (1H, m), 3.33 (3H, s), 3.36 (6H, s), 3.79 (1H, br), 3.85 (1H, br), 3.95 (1H, dd, *J* = 2.8, 6.4 Hz), 4.23~4.34 (2H, br), 4.61~4.73 (6H, m), 5.00 (1H, d, *J* = 8.2 Hz), 5.03 (1H, d, *J* = 15.1 Hz), 5.71~5.81 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.07, 28.33, 38.41, 54.93, 55.53, 55.66, 71.93, 75.73, 79.60, 85.06, 95.64, 95.88, 96.42, 107.60, 116.97, 135.89, 154.99; IR ($CHCl_3$): 1691 cm^{-1}; MS (EI) m/z 379 (M^+-41), 419 (M^+); HRMS (EI) Calcd for $C_{17}H_{32}NO_8$: 378.2128 (M^+-41), found: 378.2120; $[\alpha]_D^{20}$ -1.6 (c 0.4, $CHCl_3$).

General procedure for Lemieux-Johnson oxidation and Wittig reaction

2, 6-Lutidine (0.030 mL, 0.31 mmol), OsO_4 (0.2 mL, 0.015 mmol, 2% in H_2O), and $NaIO_4$ (0.132g, 0.61 mmol) were added to a solution of **31** (0.063 g, 0.15 mmol) in a 3:1 1, 4-dioxane/H_2O mixture (4 mL) at 0 °C, and the stirring was continued at room temperature for 1 h. After the reaction was complete, 10% $Na_2S_2O_3$ (aq) was added, and then the aqueous mixture was extracted with AcOEt. The organic layers were combined, washed with 10% HCl (aq), dried over anhydrous Na_2SO_4, and evaporated to give the aldehyde as a colorless oil, which was used directly in the next step.
A solution of *n*-BuLi (1.6 M in *n*-hexane, 3.9 eq) was added to a suspension of Wittig reagent (4 eq) in THF at 0 °C. Then a solution of the above aldehyde in THF was added at the same temperature to the reaction mixture, and the reaction mixture was stirred at room temperature for 15 h. After the reaction was complete, H_2O was added, and then the aqueous mixture was extracted with Et_2O. The organic layers were combined, dried over anhydrous Na_2SO_4, evaporated, and chromatographed on silica gel to give **32**.

(*2R, 3R, 4R, 5R, 6S*)-2-(2-Buten-1-yl)-6-methyl-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (32b)

Yield 80% (*E, Z* mixtures) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, d, *J* = 7.1

Hz), 1.46 (9H, s), 1.65 (3H, d, *J* = 6.3 Hz), 2.38 (1H, m), 2.75~2.83 (1H, m), 3.37~3.41 (9H, m), 3.80 (1H, br), 3.89 (1H, br), 4.01 (1H, dd, *J* = 2.5, 6.3 Hz), 4.24 (1H, br), 4.41 (1H, br), 4.65~4.79 (6H, m), 5.47 (1H, m), 5.55 (1H, br).

(*2R, 3R, 4R, 5R, 6S*)-2-(2-Hexen-1-yl)-6-methyl-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (32c)

Yield 89% (*E*, *Z* mixtures) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.1 Hz), 1.33 (3H, d, *J* = 6.9 Hz), 1.46 (9H, s), 2.04 (2H, q, *J* = 7.1 Hz), 2.32~2.37 (1H, br), 2.73~2.78 (1H, m), 3.37~3.41 (9H, m), 3.81 (1H, br), 3.88 (1H, br), 4.01 (1H, dd, *J* = 2.5, 6.3 Hz), 4.24 (1H, br), 4.39 (1H, br), 4.66~4.80 (6H, m), 5.40~5.45 (2H, m).

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-(2-nonen-1-yl)-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (32e)

Yield 65% (*E*, *Z* mixtures) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, br), 1.27~1.34 (11H, br), 1.46 (9H, s), 2.05 (2H, br), 2.34 (1H, m), 2.72 (1H, m), 3.36~3.41 (9H, m), 3.80 (1H, br), 3.88 (1H, br), 4.00 (1H, m), 4.21 (1H, br), 4.41 (1H, br), 4.65~4.79 (6H, m), 5.38~5.46 (2H, m).

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-(4-phenyl-2-buten-1-yl)-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32f)

Yield 79% (*E*, *Z* mixtures) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 6.9 Hz), 1.47 (9H, s), 2.51 (2H, m), 2.86~2.94 (2H, m), 3.37~3.41 (9H, m), 3.87 (2H, br), 4.02 (1H, br), 4.31~4.47 (2H, br), 4.66~4.88 (6H, m), 5.57 (1H, m), 5.66 (1H, m), 7.18~7.30 (5H, m).

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-(5-phenyl-2-hepten-1-yl)-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32g)

Yield 65% (*E*, *Z* mixtures) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.3 (3H, t, *J* = 6.9 Hz), 1.45 (9H, s), 2.35 (4H, m), 2.67 (2H, t, *J* = 7.7 Hz), 3.36~3.38 (9H, m), 3.78 (1H, br), 3.86 (1H, br), 4.00 (1H, dd, *J* = 2.5, 6.6 Hz), 4.22 (1H, br), 4.35 (1H, br), 4.64~4.77 (6H, m), 5.43~5.50 (2H, m), 7.17~7.29 (5H, m).

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-[3-(naphthalene-1-yl)allyl]-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32h)

Yield 87% (*E* : *Z* = 3 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.41~1.52 (12H, m), 2.62 (0.5H, m), 2.87 (1.5H, m), 3.37~3.42 (9H, m), 3.95 (2H, br), 4.06 (1H, dd, *J* = 2.5,

6.6 Hz), 4.42 (2H, br), 4.67~4.83 (6H, m), 5.97 (0.3H, m), 6.25 (0.7H, m), 7.00 (0.3H, d, *J* = 11.8 Hz), 7.17 (0.7H, d, *J* = 15.4 Hz), 7.34~7.51 (3.9H, m), 7.58 (0.7H, d, *J* = 6.9 Hz), 7.74 (0.7H, d, *J* = 8.2 Hz), 7.83 (0.7H, m), 7.98 (0.3H, m), 8.10 (0.7H, m).

(*2R, 3R, 4R, 5R, 6S*)-2-[3-(4-Isopropylphenyl)allyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32i)

Yield 79% (*E* : *Z* = 4 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24 (9H, m), 1.44 (9H, m), 2.73~2.92 (4H, m), 3.36~3.42 (9H, m), 3.76 (1H, br), 3.90 (1H, br), 4.02 (1H, dd, *J* = 2.2, 6.6 Hz), 4.33~4.42 (2H, br), 4.66~4.80 (6H, m), 5.61 (0.2H, m), 6.18 (0.8H, m), 6.40 (0.8H, d, *J* = 15.7 Hz), 6.48 (0.2H, d, *J* = 11.5 Hz), 7.13~7.27 (4H, m).

(*2R, 3R, 4R, 5R, 6S*)-2-[3-(4-Methoxyphenyl)allyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32j)

Yield 99% (*E* : *Z* = 5 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, d, *J* = 7.1 Hz), 1.41 (9H, s), 2.64~2.73 (2H, m), 3.36~3.42 (9H, m), 3.80 (3H, s), 3.89 (2H, br), 4.03 (1H, d, *J* = 7.1 Hz), 4.36~4.56 (2H, br), 4.66~4.80 (6H, m), 5.81 (0.2H, m), 6.08 (0.8H, m), 6.36 (1H, d, *J* = 16.5 Hz), 6.43 (0.2H, d, *J* = 10.4 Hz), 6.82 (2H, d, *J* = 7.4 Hz), 7.26 (2H, d, *J* = 7.4 Hz).

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-[3-(4-trifluoromethylphenyl)allyl]-3, 4, 5-trimethoxymethoxypiperidine-
1-carboxylic acid *tert*-butyl ester (32k)

Yield 96% (*E* : *Z* = 2 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.15 (1H, d, *J* = 7.1 Hz), 1.36 (2H, d, *J* = 6.9 Hz), 1.40 (9H, s), 2.77(2H, t, *J* = 7.7 Hz), 3.38~3.43 (9H, m), 3.74~3.77 (1H, br), 3.88 (1H, br), 4.03 (1H, d, *J* = 6.3 Hz), 4.45~4.54 (2H, br), 4.67~4.82 (6H, m), 5.83 (0.3H, m), 6.36 (7H, m), 6.45 (0.7H, d, *J* = 15.7 Hz), 6.53 (0.3H, d, *J* = 11.5 Hz), 7.37~7.43 (2H, m), 7.52~7.58 (2H, m).

(*2R, 3R, 4R, 5R, 6S*)-2-[3-(4-Fluorophenyl)allyl]-6-methyl-3, 4, 5-trimethoxy-methoxypiperidine-1-carboxylic acid *tert*-butyl ester (32l)

Yield 85% (*E* : *Z* = 2 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, d, *J* = 6.9 Hz), 1.40 (9H, s), 2.72 (2H, t, *J* = 7.7 Hz), 3.42 (9H, m), 3.87 (2H, br), 4.02 (1H, br), 4.39~4.56 (2H, br), 4.59~4.79 (6H, m), 5.68 (0.3H, m), 6.15 (0.7H, m), 6.32 (0.7H, d, *J* = 15.9 Hz), 6.45 (0.3H, d, *J* = 11.8 Hz), 6.93~7.02 (2H, m), 7.21~7.30 (2H, m).

(*2R, 3R, 4R, 5R, 6S*)-2-[3-(4-Chlorophenyl)allyl]-6-methyl-3, 4,

5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32m)

Yield 80% (*E* : *Z* = 3 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, m), 1.42 (9H, m), 2.74 (2H, t, *J* = 7.1 Hz), 3.41~3.42 (9H, m), 3.65~3.87 (2H, br), 3.94 (0.3H, br), 4.02 (0.7H, br), 4.35~4.53 (2H, br), 4.67~4.79 (6H, m), 5.73 (0.3H, m), 6.21 (0.7H, m), 6.37 (0.7H, d, *J* = 15.7 Hz), 6.45 (0.3H, d, *J* = 11.3 Hz), 7.24~7.27 (4H, m).

(*2R, 3R, 4R, 5R, 6S*)-2-[3-(2-Chlorophenyl)allyl]-6-methyl-3, 4 ,5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32n)

Yield 85% (*E* : *Z* = 1.3 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.14 (1.3H, br), 1.39 (1.7H, br), 1.47 (9H, s), 2.76~2.90 (2H, m), 3.37~3.43 (9H, m), 3.91 (2H, br), 4.03 (1H, d, *J* = 6.6 Hz), 4.38~4.60 (2H, br), 4.62~4.89 (6H, m), 5.86 (0.4H, m), 6.22 (0.6H, m), 6.60 (0.4H, d, *J* = 12.9 Hz), 6.79 (0.6H, d, *J* = 15.9 Hz), 7.13~7.52 (4H, m).

(*2R, 3R, 4R, 5R, 6S*)-2-[3-(3-Chlorophenyl)allyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32o)

Yield 91% (*E* : *Z* = 3 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.16 (0.8H, d, *J* = 7.1 Hz), 1.36 (2.2H, d, *J* = 7.1 Hz), 1.41 (9H, s), 2.74 (2H, t, *J* = 7.1 Hz), 3.38~3.42 (9H, m), 3.87~3.88 (2H, br), 4.03 (1H, dd, *J* = 2.2, 6.3 Hz), 4.41~4.51 (2H, br), 4.68~4.81 (6H, m), 5.78 (0.3H, m), 6.26 (0.7H, m), 6.36 (0.7H, d, *J* = 15.7 Hz), 6.44 (0.7H, d, *J* = 12.4 Hz), 7.16~7.31 (4H, m).

(*2R, 3R, 4R, 5R, 6S*)-2-[3-(2, 4-Dichlorophenyl)allyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32p)

Yield 93% (*E* : *Z* = 1 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.11 (1.5H, d, *J* = 6.6 Hz), 1.37 (1.5H, d, *J* = 6.6 Hz), 1.47 (9H, s), 2.72~2.81 (2H, m), 3.38~3.43 (9H, m), 3.72 (1H, m), 3.89 (1H, br), 4.02~4.04 (1H, m), 4.40~4.54 (2H, br), 4.66~4.80 (6H, m), 5.89 (0.5H, br), 6.22 (0.5H, br), 6.53 (0.5H, d, *J* = 11.3 Hz), 6.71 (0.5H, d, *J* = 16.2 Hz), 7.15~7.45 (3H, m).

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-[3-(2, 4, 6-trichlorophenyl)allyl]-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (32q)

Yield 72% (*E* : *Z* > 99 : 1) (2 steps); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, d, *J* = 7.1 Hz), 1.43 (9H, s), 2.71 (1H, dd, *J* = 6.6, 13.5 Hz), 2.87~2.97 (1H, m), 3.36~3.42 (9H, m), 3.96 (2H, br), 4.04 (1H, d, *J* = 6.6 Hz), 4.38 (2H, br), 4.66~4.80 (6H, m), 6.18~6.26 (1H, m), 6.34 (1H, d, *J* = 16.5 Hz), 7.32 (2H, s).

General procedure for olefin cross metathesis

Grubbs Catalyst, 2nd generation (6 mol%) and 1-alkene (5 eq) were added to a solution of **31** in CH_2Cl_2 at room temperature, and the stirred reaction mixture was refluxed for 15 h. After cooling, the volatiles were removed in vacuo, and chromatographed on silica gel to give **32**.

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-(3-phenyl-allyl)-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (32a)

Yield 92% (*E* : *Z* > 99 : 1); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.37 (3H, t, *J* = 6.9 Hz), 1.41 (9H, s), 2.70~2.80 (2H, m), 3.40~3.43 (9H, m), 3.89 (2H, br), 4.03 (1H, d, *J* = 5.5 Hz), 4.40 (2H, br), 4.67~4.80 (6H, m), 6.23 (1H, br), 6.42 (1H, d, *J* = 16.8 Hz), 7.16~7.34 (5H, m).

(*2S, 3R, 4R, 5R, 6R*)-2-Methyl-6-(2-octen-1-yl)-3, 4, 5-trimethoxy-methoxypiperidine-1-carboxylic acid *tert*-butyl ester (32d)

Yield 98% (*E*, *Z* mixtures) ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.1 Hz), 1.25~1.32 (9H, m), 1.45 (9H, s), 1.98 (2H, br), 2.42 (1H, m), 2.56 (1H, m), 3.36~3.40 (9H, m), 3.87 (2H, br), 3.99 (1H, dd, *J* = 2.8, 6.3 Hz), 4.24 (1H, br), 4.40 (1H, br), 4.65~4.77 (6H, m), 5.36~5.52 (2H, m).

General procedure for the synthesis of 34

10% Pd/C was added to a solution of **32** in MeOH, and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 2 days. The catalyst was filtered off with Celite pad and the filtrate was evaporated to give a hydrogenated product **33**, which was used directly in the next step.

10% HCl (aq) was added to a solution of hydrogenated product **33** in THF at room temperature, and the reaction mixture was refluxed for 48 h. After the reaction was complete, the reaction mixture was basified with 10% NaOH (aq) to pH 11. The volatiles were removed in vacuo and purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3) to give **34**.

(*1R, 2R, 3R, 4R, 5S*)-1-(3-Phenylpropyl)fuconojirimycin (34a)

Yield 98%; ^{1}H-NMR (400 MHz, D_2O):δ 1.21 (3H, d, *J* = 6.4 Hz), 1.56 (1H,br), 1.71 (1H, br), 1.82~1.86 (2H, m), 2.68 (3H, m), 3.13 (1H, br), 3.55 (1H, m), 3.88 (1H, br), 7.27 (1H, d, *J* = 7.3 Hz), 7.31 (2H, d, *J* = 7.3 Hz), 7.38 (1H, dd, *J* = 7.3 Hz); ^{13}C-NMR (100 MHz, D_2O): δ 18.91, 29.43, 33.39, 38.00, 55.26, 61.42, 74.25, 75.13, 77.64,

128.76, 131.40, 131.43, 145.67; IR (neat): 1652 cm^{-1}, 3399 cm^{-1}; MS (EI) m/z 265 (M^+); HRMS (EI) Calcd for $C_{15}H_{23}NO_3$: 265.1678 (M^+), found: 265.1639; $[\alpha]_D^{26}$ +5.1 (c = 0.5, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-Butylfuconojirimycin (34b)

Yield 81%; ^{1}H-NMR (400 MHz, D_2O):δ 0.87 (3H, t, *J* = 6.9 Hz), 1.11 (3H, d, *J* = 6.4 Hz), 1.43 (1H, br), 1.59 (2H,m), 1.75 (1H, br), 2.43~2.48 (1H, m), 2.84 (1H, td, *J* = 5.5, 6.9 Hz), 3.37 (1H, t, *J* = 9.6 Hz), 3.51 (1H, m), 3.62 (3H, br), 3.79 (1H, br); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 14.39, 18.13, 23.91, 32.77, 54.25, 60.85, 73.66, 74.18, 77.79; IR (neat): 3304 cm^{-1}; MS (EI) m/z 203 (M^+); HRMS (EI) Calcd for $C_{10}H_{21}NO_3$: 203.1521 (M^+), found: 203.1529; $[\alpha]_D^{19}$ -0.3 (c = 0.4, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-Hexylfuconojirimycin (34c)

Yield 78%; ^{1}H-NMR (400 MHz, D_2O):δ 0.87 (3H, t, *J* = 6.9 Hz), 1.11 (3H, d, *J* = 6.4 Hz), 1.25~1.43 (4H, m), 1.59 (3H,m), 1.78 (1H, m), 2.46 (1H, m), 2.84 (1H, td, *J* = 5.5, 6.9 Hz), 3.37 (1H, t, *J* = 9.6 Hz), 3.51 (1H, m), 3.63 (3H, br), 3.79 (1H, br); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 14.34, 18.13, 23.31, 25.80, 32.62, 33.09, 35.21, 54.21, 60.85, 62.32, 73.55, 74.16; IR (neat): 1644 cm^{-1}, 3427 cm^{-1}; MS (EI) m/z 231 (M^+); HRMS (EI) Calcd for $C_{12}H_{25}NO_3$: 231.1834 (M^+), found: 231.1836; $[\alpha]_D^{18}$ +1.6 (c = 0.2, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-Octylfuconojirimycin (34d)

Yield 96%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 0.87 (3H, t, *J* = 6.4 Hz), 1.06 (3H, d, *J* = 6.4 Hz), 1.15~1.28 (12H, m), 1.56 (1H,m), 1.85 (1H, m), 2.27 (1H, td, *J* = 2.8, 9.2 Hz), 2.72 (1H, m), 3.17 (1H, t, *J* = 9.2 Hz), 3.26 (1H, dd, *J* = 2.8, 9.2 Hz), 3.53 (1H, br); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 14.33, 18.13, 23.30, 26.67, 27.84, 30.72, 30.75, 32.62, 33.09, 54.24, 60.86, 73.62, 74.17, 77.77; IR (neat): 1638 cm^{-1}, 3406 cm^{-1}; MS (EI) m/z 259 (M^+); HRMS (EI) Calcd for $C_{14}H_{29}NO_3$: 259.2147 (M^+), found: 259.2160; $[\alpha]_D^{20}$ +1.3 (c = 1.1, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-Nonylfuconojirimycin (34e)

Yield 68%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 0.87 (3H, t, *J* = 6.9 Hz), 1.06 (3H, d, *J* = 6.4 Hz), 1.13~1.28 (14H, m), 1.53 (1H,m), 1.85 (1H, br), 2.28 (1H, td, *J* = 2.8, 9.2 Hz), 2.71 (1H, qd, *J* = 1.4, 6.9 Hz), 3.18 (1H, t, *J* = 9.2 Hz), 3.27 (1H, dd, *J* = 2.8, 9.2 Hz), 3.56 (1H, br); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 14.29, 18.10, 23.26, 26.64, 29.19, 29.38, 30.35, 30.72, 32.58, 33.05, 54.23, 60.86, 73.63, 74.13, 77.76; IR (neat): 1637

cm^{-1}, 3433 cm^{-1}; MS (EI) m/z 273 (M^+); HRMS (EI) Calcd for $C_{15}H_{31}NO_3$: 273.2304 (M^+), found: 273.2307; $[\alpha]_D^{20}$ +1.3 (c = 1.1, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-(4-Phenylbutyl)fuconojirimycin (34f)

Yield 62%; ^{1}H-NMR (400 MHz, D_2O):δ 1.19 (3H, d, *J* = 6.4 Hz), 1.28~1.37 (2H,m), 1.86 (1H, m), 2.52 (1H, t, *J* = 7.3 Hz), 2.85 (1H, br), 3.28 (1H, br), 3.46~3.57 (2H, m), 3.83 (1H, br), 7.09~7.24 (5H, m); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.13, 26.40, 32.76, 32.91, 36.52, 54.22, 60.83, 73.66, 74.21, 77.79, 126.29, 128.97, 129.12, 143.64; IR (neat): 1637 cm^{-1}, 3434 cm^{-1}; MS (EI) m/z 279 (M^+); HRMS (EI) Calcd for $C_{16}H_{25}NO_3$: 279.1834 (M^+), found: 279.1834; $[\alpha]_D^{21}$ +3.8 (c = 0.4, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-(5-Phenylpentyl)fuconojirimycin (34g)

Yield 65%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.9 Hz), 1.19 (1H,m), 1.34 (3H, m), 1.60 (3H, m), 1.85 (1H, br), 2.27 (1H, td, *J* = 2.3, 9.2 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.71 (1H, m), 3.16 (1H, t, *J* = 9.2 Hz), 3.25 (1H, br), 3.56~3.66 (3H, br), 7.12~7.26 (5H, m); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.04, 26.47, 30.30, 32.37, 33.02, 36.47, 54.23, 60.83, 73.65, 74.15, 77.76, 126.30, 128.97, 129.13, 143.59; IR (neat): 1636 cm^{-1}, 3423 cm^{-1}; MS (EI) m/z 293 (M^+); HRMS (EI) Calcd for $C_{17}H_{27}NO_3$: 293.1991 (M^+), found: 293.2008; $[\alpha]_D^{18}$ +4.2 (c = 0.3, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(1-Naphthyl)propyl]fuconojirimycin (34h)

Yield 73%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.4 Hz), 1.32~1.41 (1H, m), 1.74~1.85 (1H, m), 1.85~2.00 (1H, m), 2.39 (1H, td, *J* = 2.8, 9.2 Hz), 2.72~2.76 (1H, m), 3.00~3.16 (2H, m), 3.21 (1H, t, *J* = 9.2 Hz), 3.29 (1H, dd, *J* = 2.8, 9.2 Hz), 3.57 (1H, br), 7.36~7.53 (4H, m), 7.72 (1H, d, *J* = 7.3 Hz), 7.87 (1H, dd, *J* = 1.4, 7.8 Hz), 8.15 (1H, d, *J* = 8.2 Hz); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.14, 28.29, 33.15, 33.88, 54.27, 60.71, 73.66, 74.26, 77.75, 124.83, 126.33, 126.43, 126.64, 127.09, 129.37, 132.78, 134.86, 139.87; IR (neat): 1636 cm^{-1}, 3434 cm^{-1}; MS (EI) m/z 315 (M^+); HRMS (EI) Calcd for $C_{19}H_{25}NO_3$: 315.1834 (M^+), found: 315.1851; $[\alpha]_D^{18}$ +5.0 (c = 1.1, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(4-Isopropyl)phenylpropyl]fuconojirimycin (34i)

Yield 65%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.9 Hz), 1.19~1.28 (8H, m), 1.60~1.62 (1H, m), 1.84~1.92 (2H, m), 2.32 (1H, td, *J* = 2.8, 9.2 Hz), 2.55 (2H, m), 2.71 (1H, q, *J* = 6.6 Hz), 2.84 (2H, m), 3.19 (1H, t, *J* = 9.2 Hz), 3.27 (1H, dd, *J* = 3.2,

9.2 Hz), 3.56 (1H, br), 7.11~7.13 (4H, m); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.09, 24.43, 28.91, 32.91, 34.46, 36.47, 54.35, 60.87, 73.69, 74.22, 77.79, 126.89, 129.07, 140.98, 146.62; IR (neat): 1513 cm^{-1}, 3364 cm^{-1}; MS (EI) m/z 307 (M^+); HRMS (EI) Calcd for $C_{18}H_{29}NO_3$: 307.2147 (M^+), found: 307.2151; $[\alpha]_D^{19}$ +5.4 (c = 1.1, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(4-Methoxy)phenylpropyl]fuconojirimycin (34j)

Yield 42%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.07 (3H, d, *J* = 6.9 Hz), 1.21~1.29 (1H, m), 1.57~1.64 (1H, m), 1.80~1.95 (2H, m), 2.35 (1H, td, *J* = 2.8, 9.2 Hz), 2.47~2.60 (2H, m), 2.75 (1H, qd, *J* = 1.3, 6.6 Hz), 3.20 (1H, t, *J* = 9.2 Hz), 3.28 (1H, dd, *J* = 3.0, 9.2 Hz), 3.57 (1H, dd, *J* = 1.3, 3.0 Hz), 3.74 (3H, s), 6.81 (2H, d, *J* = 8.7 Hz), 7.10 (2H, d, *J* = 8.7 Hz); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 17.99, 28.99, 32.71, 35.94, 54.35, 55.37, 60.82, 73.57, 74.08, 77.70, 114.39, 130.04, 135.54; IR (neat): 1511 cm^{-1}, 3374 cm^{-1}; MS (EI) m/z 295 (M^+); HRMS (EI) Calcd for $C_{16}H_{25}NO_4$: 295.1784 (M^+), found: 295.1770; $[\alpha]_D^{18}$ +6.2 (c = 0.4, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(4-Trifluoromethyl)phenylpropyl]fuconojirimycin (34k)

Yield 73%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.9 Hz), 1.23~1.30 (1H, m), 1.62~1.72 (1H, m), 1.84~1.96 (2H, m), 2.33 (1H, td, *J* = 2.3, 8.7 Hz), 2.67~2.76 (2H, m), 3.20 (1H, t, *J* = 9.2 Hz), 3.29 (1H, dd, *J* = 3.2, 9.2 Hz), 3.57~3.58 (2H, br), 7.43 (2H, d, *J* = 7.8 Hz), 7.58 (2H, d, *J* = 7.8 Hz); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.11, 28.48, 32.72, 36.52, 54.25, 60.72, 73.64, 74.10, 77.72, 125.79, 128.12, 129.87, 148.53; IR (neat): 1637 cm^{-1}, 3434 cm^{-1}; MS (EI) m/z 333 (M^+); HRMS (EI) Calcd for $C_{16}H_{22}F_3NO_3$: 333.1552 (M^+), found: 333.1552; $[\alpha]_D^{18}$ +4.3 (c = 0.5, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(4-Fluoro)phenylpropyl]fuconojirimycin (34l)

Yield 66%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.05 (3H, d, *J* = 6.4 Hz), 1.15~1.27 (2H, m), 1.79~1.94 (2H, m), 2.32 (1H, td, *J* = 2.8, 9.2 Hz), 2.61 (2H, m), 2.71 (1H, q, *J* = 6.4 Hz), 3.18 (1H, t, *J* = 9.2 Hz), 3.26~3.31 (2H, br), 3.56 (1H, s), 3.67 (2H, br), 7.00 (2H, t, *J* = 8.7 Hz), 7.20~7.24 (2H, m); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.12, 28.91, 32.73, 35.92, 54.24, 60.76, 73.65, 74.17, 77.75, 115.56, 130.71, 139.66, 163.09; IR (neat): 1640 cm^{-1}, 3468 cm^{-1}; MS (EI) m/z 283 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}FNO_3$: 283.1584 (M^+), found: 283.1587; $[\alpha]_D^{18}$ +4.0 (c = 0.8, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(4-Chloro)phenylpropyl]fuconojirimycin (34m)

Yield 67%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.4 Hz), 1.10~1.26 (1H, m), 1.63 (1H, br), 1.88~1.90 (2H, br), 2.31 (1H, t, *J* = 9.2 Hz), 2.61 (2H, m), 2.71 (1H, d,

J = 6.4 Hz), 3.17 (1H, t, *J* = 8.2 Hz), 3.26 (2H, br), 3.56~3.63 (3H, br), 7.22 (2H, d, *J* = 8.2 Hz), 7.27 (2H, d, *J* = 8.2 Hz); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.13, 28.67, 32.70, 36.04, 54.24, 60.74, 73.65, 74.16, 77.74, 128.92, 130.90, 131.53, 142.60; IR (neat): 1638 cm^{-1}, 3457 cm^{-1}; MS (EI) m/z 299 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}ClNO_3$: 299.1288 (M^+), found: 299.1286; $[\alpha]_D^{18}$ +4.8 (c = 0.5, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(2-Chloro)phenylpropyl]fuconojirimycin (34n)

Yield 70%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.4 Hz), 1.25~1.34 (1H, m), 1.58~1.68 (1H, m), 1.80~1.99 (2H, m), 2.34 (1H, td, *J* = 2.8, 9.2 Hz), 2.66~2.76 (2H, m), 3.21 (1H, t, *J* = 9.2 Hz), 3.29 (1H, dd, *J* = 3.2, 9.2 Hz), 3.57 (1H, br), 7.16 (1H, dd, *J* = 1.8, 7.3 Hz), 7.19 (1H, d, *J* = 1.8 Hz), 7.22 (1H, dd, *J* = 1.4, 7.3 Hz), 7.25 (1H, d, *J* = 1.4 Hz); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.12, 27.15, 32.84, 34.36, 54.27, 60.80, 73.64, 74.12, 77.74, 127.78, 128.18, 129.99, 131.41, 134.15, 141.04; IR (neat): 1637 cm^{-1}, 3538 cm^{-1}; MS (EI) m/z 299 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}ClNO_3$: 299.1288 (M^+), found: 299.1279; $[\alpha]_D^{19}$ +6.0 (c = 1.1, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(3-Chloro)phenylpropyl]fuconojirimycin (34o)

Yield 82%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.9 Hz), 1.20~1.27 (1H, m), 1.64~1.67 (1H, m), 1.88~1.90 (2H, m), 2.32 (1H, td, *J* = 2.8, 9.2 Hz), 2.59~2.65 (2H, m), 2.72 (1H, m), 3.18 (1H, t, *J* = 9.2 Hz), 3.27 (1H, dd, *J* = 3.2, 9.2 Hz), 3.56~3.80 (2H, br), 7.15~7.29 (4H, m); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.12, 28.56, 32.71, 36.37, 54.25, 60.72, 73.64, 74.14, 77.73, 126.37, 127.76, 129.10, 130.61, 134.26, 146.23; IR (neat): 1637 cm^{-1}, 3434 cm^{-1}; MS (EI) m/z 299 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}ClNO_3$: 299.1288 (M^+), found: 299.1296; $[\alpha]_D^{20}$ +3.6 (c = 1.3, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(2, 4-Dichloro)phenylpropyl]fuconojirimycin (34p)

Yield 72%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.06 (3H, d, *J* = 6.9 Hz), 1.24~1.32 (1H, m), 1.63~1.65 (1H, m), 1.85~1.94 (2H, m), 2.33 (1H, td, *J* = 2.8, 9.2 Hz), 2.69~2.75 (3H, m), 3.19 (1H, t, *J* = 9.2 Hz), 3.28 (1H, dd, *J* = 3.2, 9.2 Hz), 3.57 (2H, br), 7.28 (1H, dd, *J* = 2.3, 8.2 Hz), 7.35 (1H, d, *J* = 8.2 Hz), 7.42 (1H, d, *J* = 1.8 Hz); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.13, 26.95, 32.70, 33.74, 54.25, 60.73, 73.64, 74.12, 77.73, 127.93, 129.47, 132.40, 132.59, 135.00, 140.11; IR (neat): 1638 cm^{-1}, 3433 cm^{-1}; MS (EI) m/z 333 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}Cl_2NO_3$: 333.0898 (M^+), found: 333.0931; $[\alpha]_D^{21}$ +5.7 (c = 1.4, MeOH).

(*1R, 2R, 3R, 4R, 5S*)-1-[3-(2, 4, 6-Trichloro)phenylpropyl]fuconojirimycin (34q)

Yield 63%; ^{1}H-NMR (400 MHz, Acetone-d_6):δ 1.05 (3H, d, *J* = 6.9 Hz), 1.32~1.34 (1H, m), 1.55~1.60 (1H, m), 1.81 (1H, m), 1.98 (1H, m), 2.34 (1H, td, *J* = 2.8, 9.2 Hz), 2.68~2.92 (4H, m), 3.20 (1H, t, *J* = 9.2 Hz), 3.28 (1H, dd, *J* = 2.8, 8.7 Hz), 3.56 (1H, br), 7.46 (2H, s); ^{13}C-NMR (100 MHz, Acetone-d_6): δ 18.13, 25.67, 31.82, 32.90, 54.26, 60.77, 73.65, 77.76, 128.84, 132.68, 136.33, 138.41; IR (neat): 1638 cm^{-1}, 3475 cm^{-1}; MS (EI) m/z 367 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}Cl_3NO_3$: 367.0509 (M^+), found: 367.0481; $[\alpha]_D^{18}$ +0.6 (c = 0.4, MeOH).

_N_-(3-phenylpropyl)-1-deoxyfuconojirimycin (35)

10% HCl (aq) (1mL) was added to a solution of **29** (95mg, 0.25 mmol) in THF (1 mL) at room temperature, and the reaction mixture was refluxed for 52 h. After the reaction was complete, the reaction mixture was basified with 10% NaOH (aq) to pH 11. The volatiles were removed in vacuo and dissolved in CH_2Cl_2 (1 mL). Then K_2CO_3 (69 mg, 0.50 mmol) and 3-phenylpropyl bromide (0.042 mL, 0.28 mmol) were added to the solution. After the reaction was complete, the volatiles were removed in vacuo and purified by DOWEX 50W resin (X-8, H^+ form, eluent: 0.7 N aqueous NH_3) to give **35** (28mg, 0.11 mmol, 42 % in 2 steps).

^{1}H-NMR (400 MHz, $CDCl_3$):δ 1.28 (3H, d, *J* = 6.9 Hz), 1.41 (9H, s), 2.46 (1H, ddd, *J* = 6.9, 13.7 Hz), 2.60 (1H, m), 3.33~3.36 (9H, m), 3.79 (1H, br), 3.85 (1H, br), 3.95 (1H, dd, *J* = 2.8, 6.4 Hz), 4.23~4.34 (2H, br), 4.61~4.73 (6H, m), 5.00 (1H, d, *J* = 8.2 Hz), 5.03 (1H, d, *J* = 15.1 Hz), 5.71~5.81 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.26, 26.14, 33.36, 51.71, 56.14, 58.33, 69.56, 74.04, 125.88, 128.24, 128.36, 141.77; IR (neat): 3400 cm^{-1}; MS (EI) m/z 265 (M^+); HRMS (EI) Calcd for $C_{15}H_{23}NO_3$: 265.1678 (M^+), found: 265.1679; $[\alpha]_D^{20}$ +36.8 (c = 0.4, MeOH).

(3*S*, 4*S*)-4-Benzyloxycarbonylamino-3-methoxymethoxy-1-pentene (38)

N-Ethyldiisopropylamine (3.00 mL, 17.4 mmol) and chloromethyl methyl ether (1.09 mL, 13.2 mmol) were added to a solution of **3**[32] (1.35 g, 5.74 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The stirred reaction mixture was refluxed for 15 h. After cooling, the volatiles were removed in vacuo to give a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 15:1) to give **38** (1.391 g, 4.98 mmol, 87%) as a pale yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) *δ*: 7.38-7.29 (5H, m), 5.72 (1H, ddd, *J* = 13.7, 10.1, 6.7 Hz), 5.27 (1H, dd, *J* = 13.7, 0.7 Hz), 5.26 (1H, dd, *J* = 10.1, 0.7 Hz), 5.10 (2H, s), 4.94 (1H, br), 4.53, 4.68 (2H, ABq, *J* = 6.6 Hz), 3.98 (1H, dd, *J* = 6.7, 3.1 Hz), 3.89 (1H, br), 3.36 (3H, s), 1.22 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ* 155.99, 137.18, 137.03, 128.46, 128.02, 118.15, 117.84, 92.30, 76.74, 66.55, 55.64, 53.29, 16.33; IR

(neat): 3334, 1712 cm^{-1}; MS (EI): *m/z* 279 (M^+); HRMS (EI) Calcd for $C_{15}H_{21}O_4N$ 279.1471; Found 279.1508; $[\alpha]_D^{26}$ +45.6 (*c* 1.00, $CHCl_3$).

Ethyl (2*E*, 4*S*, 5*S*)-5-Benzyloxycarbonylamino-4-methoxymethoxy-2-hexenoate (39)
Hoveyda-Grubbs Catalyst, 2nd generation (7.0 mg, 10.5 μmol) and ethyl acrylate (0.190 mL, 1.79 mmol) were added to a solution of **38** (100 mg, 0.356 mmol) in CH_2Cl_2 (7 mL) at room temperature, and the stirred reaction mixture was refluxed for 15 h. After cooling, the volatiles were removed in vacuo to give a black oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 10:1) to give **39** (122 mg, 0.347 mmol, 98%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.32 (5H, m), 6.81 (1H, dd, *J* = 15.8, 6.4 Hz), 6.01 (1H, d, *J* = 15.8 Hz), 5.09 (2H, s), 4.89 (1H, br), 4.59, 4.63 (2H, ABq, *J* = 7.0 Hz), 4.20 (2H, q, *J* = 7.1 Hz), 3.95 (1H, br), 3.75 (1H, dd, *J* = 6.6, 6.4 Hz), 3.37 (3H, s), 1.29 (3H, t, *J* = 7.1 Hz), 1.22 (3H, d, *J* = 6.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.57, 155.63, 144.03, 136.31, 128.33, 127.91, 127.87, 123.74, 94.79, 77.12, 66.50, 60.38, 55.72, 49.59, 17.20, 14.01; IR (neat): 3337, 1718, 1700 cm^{-1}; MS (EI): *m/z* 351 (M^+); HRMS (EI) Calcd for $C_{18}H_{25}O_6N$ 351.1682; Found 351.1665; $[\alpha]_D^{21}$ +19.4 (*c* 1.00, $CHCl_3$).

(*2E, 4S, 5S*)-5-Benzyloxycarbonylamino-4-methoxymethoxy-2-hexen-1-ol (40)
A solution of DIBAL (1.0 M in *n*-hexane, 20.5 mL, 20.5 mmol,) at -78 °C was added to a solution of **39** (1.60 g, 4.56 mmol) in CH_2Cl_2 (16 mL), and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with sat. NH_4Cl (aq) and then the insoluble materials were filtered off with a Celite pad. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 3:1) to give **40** (1.09 g, 3.52 mmol, 77%) as a colorless oil.^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.30 (5H, m), 5.87 (1H, dt, *J* = 14.7, 5.2 Hz), 5.61 (1H, dd, *J* = 14.7, 6.8 Hz), 5.09 (2H, s), 4.96 (1H, br), 4.52, 4.67 (2H, ABq, *J* = 6.8 Hz), 4.13 (2H, d, *J* = 5.2 Hz), 4.03 (1H, br), 3.88 (1H, br), 3.36 (3H, s), 1.23 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.09, 136.42, 134.35, 128.38, 127.98, 127.92, 127.14, 93.64, 78.07, 66.55, 62.27, 55.53, 50.25, 17.69; IR (neat): 3339, 1702 cm^{-1}; MS (EI): *m/z* 309 (M^+); HRMS (EI) Calcd for $C_{16}H_{23}O_5N$ 309.1576; Found 309.1614; $[\alpha]_D^{21}$ +44.7 (*c* 1.00, $CHCl_3$).

(*2E, 4S, 5S*)-5-Benzyloxycarbonylamino-1-*tert*-butyldimethylsilyloxy-4-methoxymethoxy-2-hexene (41)
tert-Butyldimethylchlorosilane (0.935 g, 6.20 mmol), DMAP (0.126 g, 1.03 mmol) and

Et_3N (1.10 mL, 7.83 mmol) were added to a solution of **40** (1.07 g, 3.46 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 15 h. The volatiles were removed in vacuo to give a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 20:1) to give **41** (1.43 g, 3.38 mmol, 98%) as a pale yellow oil.^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.30 (5H, m), 5.79 (1H, dt, J = 14.4, 3.4 Hz), 5.58 (1H, dd, J = 14.4, 7.2 Hz), 5.09 (2H, s), 4.93 (1H, br), 4.50, 4.68 (2H, ABq, J = 6.4 Hz), 4.17 (2H, d, J = 3.4 Hz), 4.00 (1H, br), 3.85 (1H, br), 3.35 (3H, s), 1.21 (3H, d, J = 6.6 Hz), 0.91 (9H,s), 0.05 (6H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.83, 136.57, 134.89, 128.40, 128.01, 127.96, 125.74, 93.57, 78.13, 66.48, 62.76, 55.54, 50.26, 25.81, 18.27, 17.76, -5.33; IR (neat): 3337, 1718 cm^{-1}; MS (EI): *m/z* 423 (M^+); HRMS (EI) Calcd for $C_{22}H_{37}O_5NSi$ 423.2411; Found 423.2435; $[\alpha]_D^{21}$ +36.6 (*c* 1.00, $CHCl_3$).

(*2R, 3S, 4R, 5S*)-5-Benzyloxycarbonylamino-1-*tert*-butyldimethylsilyloxy-4-methoxymethoxyhexane-2, 3-diol (42)

NMO (0.782 g, 6.68 mmol) and OsO_4 (2.0 mL, 0.171 mmol, 2% in H_2O) were added to a solution of **41** (1.41 g, 3.33 mmol) in acetone (16mL) at 0 °C, and the reaction mixture was stirred at room temperature for 15 h. After the reaction was complete, 10% $Na_2S_2O_3$ (aq) (4 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 10:1) to give **42** (1.39 g, 3.04 mmol, 91%) as a colorless oil.^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.31 (5H, m), 5.05, 5.13 (2H, ABq, J = 12 Hz), 4.70, 4.74 (2H, ABq, J = 6.4 Hz), 4.18 (1H, br), 3.79 (3H, br), 3.62 (2H, br), 3.41 (3H, s), 1.25 (3H, d, J = 6.8 Hz), 0.90 (9H, s), 0.09 (6H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.45, 136.25, 128.29, 127.94, 127.92, 97.96, 79.96, 70.19, 69.02, 66.64, 65.33, 56.12, 46.91, 25.69, 18.03, 17.25, -5.61; IR (neat): 3417, 1700 cm^{-1}; MS (EI): *m/z* 457 (M^+); HRMS (EI) Calcd for $C_{22}H_{39}O_7NSi$ 457.2496; Found 457.2468; $[\alpha]_D^{22}$ -22.6 (*c* 1.00, $CHCl_3$).

(*2R, 3R, 4R, 5S*)-5-Benzyloxycarbonylamino-1-*tert*-butyldimethylsilyloxy-2, 3, 4-methoxymethoxyhexane (43)

N -Ethyldiisopropylamine (2.10 mL, 12.2 mmol) and chloromethyl methyl ether (0.80 mL, 9.69 mmol) were added to a solution of **42** (1.37 g, 3.00 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The stirred reaction mixture was refluxed for 15 h. After cooling, the volatiles were removed in vacuo to give a yellow oil, which was chromatographed on silica gel

(20 g, *n*-Hexane/Acetone 15:1) to give **43** (1.57 g, 2.88 mmol, 96%) as a pale yellow oil.^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.30 (5H, m), 5.09 (2H, s), 4.79-4.66 (6H, m), 4.09 (1H, br), 3.82-3.76 (3H, m), 3.74-3.68 (2H, m), 3.39 (3H, s), 3.38 (3H, s), 3.37 (3H, s), 1.25 (3H, d, J = 6.3 Hz), 0.89 (9H, s), 0.06 (6H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.56, 136.60, 127.76, 127.70,128.17, 98.34, 97.60, 97.30, 80.03, 77.90, 77.25, 66.15, 62.63, 55.86, 55.42, 46.72, 25.60, 18.53, 17.92, 13.86,-5.74; IR (neat): 3338, 1719 cm^{-1}; MS (EI): *m/z* 545 (M^+); HRMS (EI) Calcd for $C_{26}H_{47}O_9NSi$ 545.3020; Found 545.3014; $[\alpha]_D^{22}$ +3.0 (*c* 1.00, $CHCl_3$).

(*2R, 3R, 4R, 5S*)-5-Benzyloxycarbonylamino-2, 3, 4-methoxymethoxyhexan-1-ol (44)

A solution of tetrabutylammonium fluoride (1.0 M in THF, 5.70 mL, 5.70 mmol,) was added to a solution of **40** (1.55 g, 3.39 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, brine (4 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give **44** as a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 3:1) to give **44** (1.38 g, 3.20 mmol, 94%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.31 (5H, m), 5.09 (2H, s), 4.75-4.65 (6H, m), 4.06 (1H, dd, J = 7.6, 7.5 Hz), 3.83 (2H, br), 3.75-3.66 (3H, m), 3.53 (1H, br), 3.45 (3H, s), 3.43 (3H, s), 3.40 (3H, s), 1.24 (3H, d, J = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.62, 136.37, 128.32, 127.94, 127.94, 98.62, 98.43, 97.56, 80.96, 80.17, 78.05, 66.46, 62.75, 56.28, 56.14, 55.70, 46.30, 19.10; IR (neat): 3436, 1715 cm^{-1}; MS (FAB): *m/z* 432 (M^++1); HRMS (FAB) Calcd for $C_{20}H_{34}O_9N$ 432.2234; Found 432.2234; $[\alpha]_D^{23}$ -4.4 (*c* 1.00, $CHCl_3$).

(*2R, 3R, 4R, 5S*)-5-Benzyloxycarbonylamino-1-methylsulfonyloxy-2, 3, 4-methoxymethoxyhexane (45)

Methanesulfonyl chloride (0.40 mL, 5.15 mmol) and Et_3N (0.98 mL, 6.97 mmol) were added to a solution of **44** (1.14 g, 2.65 mmol) in CH_2Cl_2 (15 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 15 h. After the reaction was complete, sat. $NaHCO_3$ (aq) (4 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give **45** as a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 3:1) to give **45** (1.27 g, 2.50 mmol, 94%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.37-7.31 (5H, m),

5.09 (2H, s), 4.79-4.67 (6H, m), 4.49-4.40 (2H, m), 4.08 (2H, br), 3.65 (2H, br), 3.42 (3H, s), 3.40 (3H, s), 3.39 (3H, s), 3.03 (3H, s), 1.24 (3H, d, *J* = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 155.69, 136.45, 128.40, 128.03, 128.02, 98.59, 98.45, 97.64, 80.95, 77.62, 75.27, 68.93, 66.54, 56.25, 56.13, 55.92, 46.59, 37.16, 19.02; IR (neat): 3397, 1707 cm^{-1}; MS (FAB): *m/z* 510 (M^++1); HRMS (FAB) Calcd for $C_{21}H_{36}O_{11}NS$ 510.2009; Found 510.2012; $[\alpha]_D^{22}$ -10.4 (*c* 1.00, $CHCl_3$)

(*2S, 3R, 4S, 5R*)-2-Methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (46)

NaH (0.497 g, 12.4 mmol, 60% dispersion in paraffin liquid) and NaI (0.746 g, 4.97 mmol) were added to a solution of **45** (1.27 g, 2.50 mmol) in THF (20 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. After the reaction was complete, sat. $NaHCO_3$ (aq) (6 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give **46** as a yellow oil, which was chromatographed on silica gel (20 g, *n*-Hexane/Acetone 15:1) to give **46** (0.940 g, 2.28 mmol, 91%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.35-7.27 (5H, m), 5.19, 5.09 (2H, ABq, *J* = 12.4 Hz), 4.80-4.67 (6H, m), 4.56 (2H, br), 4.09 (1H, br), 3.97-3.91 (2H, m), 3.83 (1H, br), 3.40 (3H, s), 3.39 (3H, s), 3.38 (3H, s), 1.29 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 155.67, 136.74, 128.36, 127.84, 127.68, 97.10, 95.43, 95.11, 75.74, 72.98, 71.52, 67.05, 55.61, 55.53, 55.52, 49.37, 37.74, 12.41; IR (neat): 1700 cm^{-1}; MS (EI): *m/z* 413 (M^+); HRMS (EI) Calcd for $C_{20}H_{31}O_8N$ 413.2050; Found 413.2023; $[\alpha]_D^{22}$ -34.6 (*c* 1.00, $CHCl_3$)

(*3S, 4R, 5R, 6S*)-2-Methoxy-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (47)

Et_4NBF_4 (0.400 g, 1.84 mmol) was added to a solution of **46** (0.300 g, 0.73 mmol) in a 4:1 MeCN/MeOH mixture (20 mL) and the reaction mixture was stirred at -15 °C for 4.5 h with 100 mA electricity passed through by use of graphite anode and cathode electrodes. Then the reaction solvent was removed to give **47** as a yellow oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 10:1) to give **47** (0.200 g, 0.45 mmol, 62%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.39-7.33 (5H, m), 5.19 (2H, s), 4.78-4.66 (6H, m), 4.52 (1H, br), 4.09 (1H, br), 3.99-3.90 (2H, m), 3.83 (1H, br), 3.40-3.38 (9H, m), 3.32 (3H, s), 1.43 (3H, d, *J* = 7.0 Hz)

(*2R, 3R, 4R, 5R, 6S*)-2-Allyl-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-

carboxylic acid benzyl ester (48)

Allyltrimethylsilane (0.46 mL, 2.9 mmol) and BF_3•Et_2O (0.10 mL, 0.80 mmol) were added to a solution of **47** (0.335 g, 0.76 mmol) in CH_2Cl_2 (4 mL) at -78 °C, and the reaction mixture was stirred at the same temperature for 5 h. After the reaction was complete, sat. $NaHCO_3$ (aq) (6 mL) was added, and then the aqueous mixture was extracted with CH_2Cl_2 (5 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated to give **48** as a yellow oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 15:1) to give **48** (0.238 g, 0.53 mmol, 70%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.30 (5H, m), 5.78 (1H, br), 5.17-5.02 (4H, m), 4.77-4.64 (6H, m), 4.51 (1H, br), 4.38 (1H, br), 4.03 (1H, dd, J = 6.8, 2.3 Hz), 3.92 (1H, br), 3.87 (1H, br), 3.40 (9H, s), 2.72-2.51 (2H, m), 1.37 (3H, d, J = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.81, 136.71, 135.54, 128.35, 127.80, 127.65, 117.33, 96.48, 95.90, 95.67, 75.56, 75.54, 71.75, 67.11, 55.69, 55.56, 55.54, 49.63, 38.30, 29.19, 16.02; IR (neat): 1696 cm^{-1}; MS (EI): *m/z* 453 (M^+); HRMS (EI) Calcd for $C_{23}H_{35}O_8N$ 453.2363; Found 453.2358; $[\alpha]_D^{23}$ -8.7 (*c* 0.50, $CHCl_3$)

(*2R, 3R, 4R, 5R, 6S*)-2-Carboxymethyl-6-methyl-3, 4, 5-trimethoxymethoxy-piperidine-1-carboxylic acid benzyl ester (49)

2, 6-Lutidine (0.030 mL, 0.26 mmol), $NaIO_4$ (0.132 g, 0.62 mmol) and OsO_4 (0.20 mL, 0.017 mmol, 2% in H_2O) were added to a solution of **48** (0.070 g, 0.15 mmol) in a 3:1 1, 4-dioxane/H_2O mixture (4 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. After the reaction was complete, 10% $Na_2S_2O_3$ (aq) (1 mL) was added, and then the aqueous mixture was extracted with AcOEt (5 mL x 3). The organic layers were combined, washed with 10% HCl (aq), dried over anhydrous Na_2SO_4, and evaporated to give the aldehyde as colorless oil, which was used directly in the next step. 2-Methyl-2-butene (0.65 mL, 6.12 mmol), NaH_2PO_4•$2H_2O$ (0.238 g, 1.53 mmol), and $NaClO_2$ (0.118 g, 0.91 mmol) were added to a solution of the above aldehyde in a 3:1 *t*-BuOH/H_2O mixture (4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete, sat. $NaHSO_3$ (aq) and 10% HCl (aq) were added, and then the aqueous mixture was extracted with AcOEt (5 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to give **49** as a yellow oil, which was chromatographed on silica gel (10 g, *n*-Hexane/Acetone 15:1) to give **49** (0.053 g, 0.11 mmol, 73%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.30 (5H, m), 5.20, 5.13 (2H, ABq, J = 12.4 Hz), 4.77-4.63 (7H, m), 4.51 (1H, br), 4.04 (1H, dd, J = 6.4, 2.4 Hz), 3.96 (2H, br), 3.40 (3H,

s), 3.39 (3H, s), 3.38 (3H, s), 3.21 (1H, dd, *J* = 14.2, 10.2 Hz), 2.70 (1H, dd, *J* = 14.2, 4.6 Hz), 1.35 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 175.56, 155.70, 136.44, 128.38, 127.87, 127.59, 96.74, 95.60, 95.50, 76.74, 75.38, 71.15, 67.37, 55.68, 55.61, 55.56, 51.35, 37.72, 29.10, 15.96; IR (neat): 3485, 1732, 1695 cm^{-1}; MS (EI): *m/z* 471 (M^+); HRMS (EI) Calcd for $C_{22}H_{33}O_{10}N$ 471.2104; Found 471.2105; $[\alpha]_D^{24}$ -16.4 (*c* 0.50, $CHCl_3$)

General procedure for the synthesis of amides (50a-n)

EDC (2 eq), DMAP (0.1 eq) and amine (1 eq) were added to a solution of **15** in CH_2Cl_2 at room temperature, and the reaction mixture was stirred at the same temperature for 15 h. After the reaction was complete, the volatiles were removed in vacuo, and the residue was chromatographed on silica gel to give the amide (**50**).

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-(Phenylcarbamoylmethyl))-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = Phenyl, 50a)

Yield 74%; ^{1}H-NMR (500 MHz, $CDCl_3$) *δ*: 7.43 (2H, d, *J* = 6.8, Hz), 7.29-7.21 (7H, m), 7.03 (1H, t, *J* = 6.8 Hz), 5.17, 5.10 (2H, ABq, *J* = 12.3 Hz), 4.74-4.61 (7H, m), 4.47 (1H, t, *J* = 6.8 Hz), 4.02-3.91 (3H, m), 3.37 (3H, s), 3.36 (3H, s), 3.12 (3H, s), 3.09 (1H, dd, *J* = 14.4, 9.7 Hz), 2.58 (1H, br), 1.32 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 168.82, 157.96, 136.31, 130.86, 128.88, 128.54, 128.09, 127.76, 124.08, 119.82, 96.94, 96.60, 95.71, 75.57, 74.26, 71.25, 67.66, 55.86, 55.82, 55.78, 53.76, 49.63, 42.43, 16.26; IR (neat): 3323, 1693, 1682 cm^{-1}; MS (EI): *m/z* 546 (M^+); HRMS (EI) Calcd for $C_{28}H_{38}O_9N_2$ 546.2577; Found 546.2580; $[\alpha]_D^{25}$ +8.8 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-(Benzylcarbamoylmethyl))-6-methyl-3, 4, 5-trimethoxy-methoxypiperidine-1-carboxylic acid benzyl ester (R = Benzyl, 50b)

Yield 76%; ^{1}H-NMR (500 MHz, $CDCl_3$) *δ*: 7.34-7.23 (10H, m), 5.11 (2H, s), 4.75-4.61 (7H, m), 4.54-4.29 (3H, m), 4.04-3.96 (3H, m), 3.39 (3H, s), 3.35 (3H, s), 3.32 (3H, s), 3.03 (1H, dd, *J* = 14.8, 10.2 Hz), 2.63 (1H, br), 1.29 (3H, d, *J* = 7.1 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 170.24, 156.01, 138.40, 136.43, 128.58, 128.51, 128.01, 127.79, 127.72, 127.37, 96.77, 96.32, 95.59, 75.53, 75.42, 71.20, 67.43, 55.75, 55.71, 55.64, 52.70, 49.37, 43.44, 40.85, 16.15; IR (neat): 3325, 1693, 1682 cm^{-1}; MS (EI): *m/z* 560 (M^+); HRMS (EI) Calcd for $C_{29}H_{40}O_9N_2$ 560.2734; Found 560.2736; $[\alpha]_D^{25}$ +2.3 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-(Butylcarbamoylmethyl))-6-methyl-3, 4,

5-trimethoxy-methoxypiperidine-1-carboxylic acid benzyl ester (R = Butyl, 50c)
Yield 70%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.36-7.30 (5H, m), 5.19, 5.15 (2H, ABq, J = 12.5 Hz), 4.76-4.63 (7H, m), 4.50 (1H, br), 4.04-3.97 (3H, m), 3.41 (3H, s), 3.39 (3H, s), 3.33 (3H, s), 3.27-3.14 (2H, m), 2.97 (1H, dd, J = 14.0, 10.0 Hz), 2.63 (1H, br), 1.45-1.27 (7H, m), 0.89 (3H, t, J = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.27, 155.85, 136.36, 128.40, 127.91, 127.59, 96.64, 96.21, 95.46, 75.49, 75.23, 71.06, 67.33, 55.63, 55.60, 55.59, 52.68, 49.14, 40.77, 39.08, 31.44, 19.91, 16.08, 13.60; IR (neat): 3325, 1693, 1683 cm^{-1}; MS (EI): *m/z* 526 (M^+); HRMS (EI) Calcd for $C_{26}H_{42}O_9N_2$ 526.2890; Found 526.2867; $[\alpha]_D^{23}$ +2.2 (*c* 0.90, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(4-Methoxyphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = *p*-Methoxy-phenyl, 50d)
Yield 52%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.45-7.28 (7H, m), 6.82 (2H, d, J = 9.0 Hz), 5.21, 5.14 (2H, ABq, J = 12.3 Hz), 4.79-4.65 (7H, m), 4.52 (1H, br), 4.00-3.98 (3H, m), 3.77 (3H, s), 3.41 (3H, s), 3.35 (3H, s), 3.32 (3H, s), 3.11 (1H, dd, J = 14.5, 9.5 Hz), 2.76 (1H, br), 1.36 (3H, d, J = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.58, 156.21, 136.31, 131.11, 128.51, 128.04, 128.03, 127.70, 121.67, 113.98, 96.87, 96.53, 95.65, 76.01, 75.52, 71.20, 67.59, 55.77, 55.74, 55.41, 53.39, 53.05, 49.48, 42.09, 16.22; IR (neat): 3325, 1693, 1682 cm^{-1}; MS (EI): *m/z* 576 (M^+); HRMS (EI) Calcd for $C_{29}H_{40}O_{10}N_2$ 576.2683; Found 576.2682; $[\alpha]_D^{23}$ +13.9 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(4-Methylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = *p*-Tolyl, 50e)
Yield 77%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.37-7.29 (7H, m), 7.09 (2H, d, J = 8.5 Hz), 5.21, 5.14 (2H, ABq, J = 12.5 Hz), 4.79-4.65 (7H, m), 4.54-4.47 (1H, m), 4.06-3.98 (3H, m), 3.42 (3H, s), 3.40 (3H, s), 3.32 (3H, s), 3.12 (1H, dd, J = 15.0, 9.8 Hz), 2.77 (1H, br), 2.30 (3H, s), 1.37 (3H, d, J = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.63, 156.16, 136.25, 133.53, 129.24, 128.41, 128.37, 127.93, 127.61, 119.84, 96.78, 96.41, 95.54, 75.41, 71.33, 71.11, 67.48, 55.70, 55.67, 55.63, 53.34, 49.40, 41.97, 20.71, 16.10; IR (neat): 3325, 1698, 1684 cm^{-1}; MS (EI): *m/z* 560 (M^+); HRMS (EI) Calcd for $C_{29}H_{40}O_9N_2$ 560.2734; Found 560.2751; $[\alpha]_D^{23}$ +10.0 (*c* 1.00, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(4-Fluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = *p*-Fluorophenyl, 50f)

Yield 68%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.42-7.31 (7H, m), 6.97 (2H, t, J = 8.5 Hz), 5.23, 5.15 (2H, ABq, J = 12.5 Hz), 4.79-4.66 (7H, m), 4.52 (1H, br), 4.07-3.97 (3H, m), 3.42 (3H, s), 3.41 (3H, s), 3.33 (3H, s), 3.11 (1H, dd, J = 15.0, 9.0 Hz), 2.82 (1H, br), 1.37 (3H, d, J = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.78, 160.16 (d, J = 242.8 Hz), 156.79, 136.21, 134.07, 128.48, 128.04, 127.61, 121.53, 115.36 (d, J = 23.0 Hz), 96.83, 96.50, 95.66, 76.14, 75.52, 71.19, 67.61, 55.77, 55.76, 55.70, 53.37, 49.59, 42.08, 16.23; IR (neat): 3323, 1699, 1680 cm^{-1}; MS (EI): *m/z* 564 (M^+); HRMS (EI) Calcd for $C_{28}H_{37}O_9N_2F$ 564.2483; Found 564.2482; $[\alpha]_D^{23}$ +15.0 (*c* 0.90, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2-Methylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = *o*-Tolyl, 50g)

Yield 54%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.71 (2H, d, J = 7.5 Hz), 7.35-7.30 (6H, m), 7.18 (1H, t, J = 7.5 Hz), 7.07 (1H, t, J = 7.5 Hz), 5.21, 5.14 (2H, ABq, J = 12.5 Hz), 4.84-4.66 (7H, m), 4.53 (1H, br), 4.08-3.92 (3H, m), 3.41 (3H, s), 3.40 (3H, s), 3.34 (3H, s), 3.20 (1H, dd, J = 15.0, 10.5 Hz), 2.73 (1H, br), 2.23 (3H, s), 1.39 (3H, d, J = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.97, 156.09, 136.29, 135.55, 130.35, 129.82, 128.40, 127.94, 127.68, 126.49, 125.20, 123.55, 96.77, 96.41, 95.51, 75.69, 75.21, 71.08, 67.47, 55.73, 55.69, 55.64, 53.35, 49.36, 41.95, 22.61, 17.69; IR (neat): 3307, 1693, 1681 cm^{-1}; MS (EI): *m/z* 560 (M^+); HRMS (EI) Calcd for $C_{29}H_{40}O_9N_2$ 560.2734; Found 560.2739; $[\alpha]_D^{16}$ +2.4 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(3-Methylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = *m*-Tolyl, 50h)

Yield 74%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.36-7.29 (7H, m), 7.17 (1H, t, J = 7.5 Hz), 6.90 (1H, d, J = 7.5 Hz), 5.22, 5.16 (2H, ABq, J = 12.3 Hz), 4.79-4.66 (7H, m), 4.52 (1H, t, J = 6.5 Hz), 4.07-4.00 (3H, m), 3.42 (3H, s), 3.41 (3H, s), 3.32 (3H, s), 3.14 (1H, dd, J = 14.5, 9.5 Hz), 2.76 (1H, br), 2.33 (3H, s), 1.37 (3H, d, J = 6.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.73, 156.17, 138.67, 136.27, 128.61, 128.46, 127.99, 127.98, 127.65, 120.37, 116.82, 96.83, 96.51, 95.57, 76.10, 75.45, 71.13, 67.53, 55.77, 55.72, 55.70, 52.93, 49.43, 42.25, 21.40, 16.15; IR (neat): 3323, 1693, 1682 cm^{-1}; MS (EI): *m/z* 560 (M^+); HRMS (EI) Calcd for $C_{29}H_{40}O_9N_2$ 560.2734; Found 560.2721; $[\alpha]_D^{17}$ +15.7 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4-Dimethylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = 2, 4,-Dimethylphenyl, 50i)

Yield 58%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.45 (1H, d, J = 6.8 Hz), 7.35-7.28 (5H, m), 6.99 (1H, s), 6.98 (1H, d, J = 6.8 Hz), 5.21, 5.15 (2H, ABq, J = 12.0 Hz), 4.79-4.65 (7H, m), 4.53 (1H, br), 4.08-4.02 (3H, m), 3.42 (3H, s), 3.41 (3H, s), 3.32 (3H, s), 3.19 (1H, dd, J = 15.0, 10.5 Hz), 2.72 (1H, br), 2.28 (3H, s), 2.17 (3H, s), 1.38 (3H, d, J = 7.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 169.01, 156.03, 136.33, 135.03, 132.86, 131.04, 130.22, 128.44, 127.97, 127.70, 127.05, 123.90, 96.78, 96.41, 95.51, 75.24, 74.14, 71.09, 67.48, 55.82, 55.72, 55.67, 53.37, 49.31, 41.78, 26.43, 22.62, 16.13; IR (neat): 3318, 1699, 1684 cm^{-1}; MS (EI): *m/z* 574 (M^+); HRMS (EI) Calcd for $C_{30}H_{42}O_9N_2$ 574.2890; Found 574.2881; $[\alpha]_D^{25}$ +3.9 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4, 6-Trimethylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R =2, 4, 6-Trimethylphenyl, 50j)

Yield 49%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35-7.29 (5H, m), 6.85 (2H, s), 5.18 (2H, s), 4.86 -4.66 (7H, m), 4.56 (1H, br), 4.10-4.03 (3H, m), 3.42 (3H, s), 3.41 (3H, s), 3.34 (3H, s), 3.27-3.23 (1H, br), 2.80 (1H, br), 2.24 (3H, s), 2.12 (6H, s), 1.39 (3H, d, J = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.55, 153.90, 137.61, 136.34, 128.77, 128.47, 128.43, 127.96, 127.75, 127.67, 96.79, 96.30, 95.70, 74.15, 73.04, 71.39, 67.45, 55.73, 55.64, 55.61, 53.38, 51.55, 41.48, 26.45, 22.63, 17.59; IR (neat): 3327, 1699, 1683 cm^{-1}; MS (EI): *m/z* 588 (M^+); HRMS (EI) Calcd for $C_{31}H_{44}O_9N_2$ 588.3047; Found 588.3049; $[\alpha]_D^{20}$ +5.9 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2-Fluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = *o*-Fluorophenyl, 50k)

Yield 63%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.23 (1H, d, J = 8.0 Hz), 7.35-7.28 (5H, m), 7.13-7.04 (3H, m), 5.21, 5.13 (2H, ABq, J = 12.5 Hz), 4.79-4.65 (7H, m), 4.53 (1H, br), 4.08-4.01 (3H, m), 3.41 (3H, s), 3.40 (3H, s), 3.32 (3H, s), 3.20 (1H, dd, J = 14.5, 10.0 Hz), 2.75-2.72 (1H, br), 1.39 (3H, d, J = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.88, 155.79, 152.52 (d, J = 241.0 Hz), 136.35, 128.34, 127.85, 127.64, 126.10, 126.02, 124.38, 122.21, 114.72 (d, J = 19.38 Hz), 96.77, 96.26, 95.50, 75.59, 75.29, 71.13, 67.36, 55.67, 55.62, 55.61, 52.54, 49.31, 16.06; IR (neat): 3315, 1695, 1684 cm^{-1}; MS (EI): *m/z* 564 (M^+); HRMS (EI) Calcd for $C_{28}H_{37}O_9N_2F$ 564.2483; Found 564.2470; $[\alpha]_D^{21}$ +5.5 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(3-Fluorophenylcarbamoyl)methyl]-6-methyl-3, 4,

5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = *m*-Fluorophenyl, 50l)

Yield 65%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.46-7.31 (6H, m), 7.26-7.14 (1H, m), 6.78 (1H, td, *J* = 8.0, 2.0 Hz), 5.23, 5.15 (2H, ABq, *J* = 12.5 Hz), 4.79-4.67 (7H, m), 4.51 (1H, t, *J* = 6.5 Hz), 4.06 (1H, dd, *J* = 6.5, 1.5 Hz), 3.98 (2H, br), 3.43 (3H, s), 3.41 (3H, s), 3.33 (3H, s), 3.12 (1H, dd, *J* = 15.0, 9.0 Hz), 2.83 (1H, br), 1.37 (3H, d, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.94, 162.89 (d, *J* = 243.0 Hz), 156.01, 139.26, 136.19, 129.01, 128.54, 128.13, 127.72, 114.91, 110.66 (d, *J* = 20.6 Hz), 107.15 (d, *J* = 25.5Hz), 96.92, 96.66, 95.73, 75.59, 72.23, 71.23, 67.74, 55.87, 55.83, 55.78, 52.99, 49.77, 42.60, 16.29; IR (neat): 3325, 1695, 1674 cm^{-1}; MS (EI): *m/z* 564 (M^+); HRMS (EI) Calcd for $C_{28}H_{37}O_9N_2F$ 564.2483; Found 564.2493; $[\alpha]_D^{21}$ +18.4 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4-Difluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = 2, 4-Difluorophenyl, 50m)

Yield 51%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.12 (1H, d, *J* = 8.4 Hz), 7.35-7.28 (5H, m), 6.86 (1H, d, *J* = 8.4 Hz), 6.83 (1H, s), 5.21, 5.13 (2H, ABq, *J* = 12.5 Hz), 4.79-4.67 (7H, m), 4.55-4.49 (1H, br), 4.08-4.00 (3H, m), 3.41 (3H, s), 3.40 (3H, s), 3.33 (3H, s), 3.18 (1H, dd, *J* = 14.5, 10.0 Hz), 2.75 (1H, br), 1.38 (3H, d, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.99, 155.99, 154.75 (d, *J* = 258.1 Hz), 148.92 (d, *J* = 274.3 Hz), 136.36, 128.45, 127.99, 127.74, 123.59, 111.11 (d, *J* = 18.3Hz), 103.63 (d, *J* = 26.8 Hz), 96.91, 96.41, 95.66, 75.81, 75.46, 71.25, 67.53, 55.88, 55.80, 55.74, 53.40, 49.51, 41.85, 16.19; IR (neat): 3302, 1695, 1670 cm^{-1}; MS (EI): *m/z* 582 (M^+); HRMS (EI) Calcd for $C_{28}H_{36}O_9N_2F_2$ 582.2389; Found 582.2394; $[\alpha]_D^{20}$ +5.0 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4, 6-Trifluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trimethoxymethoxypiperidine-1-carboxylic acid benzyl ester (R = 2, 4, 6-Trifluorophenyl, 50n)

Yield 31%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.37-7.29 (5H, m), 6.72 (2H, t, *J* = 8.5 Hz), 5.19-5.14 (2H, m), 4.78-4.67 (7H, m), 4.53 (1H, br), 4.08-3.92 (3H, m), 3.41 (3H, s), 3.40 (3H, s), 3.38 (3H, s), 3.24 (1H, br), 2.82 (1H, br), 1.37 (3H, d, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 169.92, 161.46 (d, *J* = 243.1 Hz), 159.17 (d, *J* = 203.0 Hz), 155.15, 128.47, 128.00, 127.82, 127.72, 108.66, 101.01 (t, *J* = 19.38 Hz), 96.88, 96.18, 95.53, 75.45, 71.41, 71.08, 67.48, 56.06, 55.79, 55.69, 53.40, 51.18, 40.86, 14.02; IR (neat): 3290, 1697, 1679 cm^{-1}; MS (EI): *m/z* 600 (M^+); HRMS (EI) Calcd for

$C_{28}H_{35}O_9N_2F_3$ 600.2295; Found 600.2328; $[\alpha]_D^{17}$ +8.3 (*c* 0.30, $CHCl_3$)

General procedure for the synthesis of triols (51a-n)

10% HCl (aq) was added to a solution of **50** in THF at room temperature, and the reaction mixture was stirred at 40 °C for 48 h. After the reaction was complete, $NaHCO_3$ (aq) was added, and then the aqueous mixture was extracted with AcOEt (5 mL x 3). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to give the residue, which was chromatographed on silica gel to give **51**

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-(Phenylcarbamoylmethyl))-6-methyl-3, 4, 5-trihydroxy-piperidine-1-carboxylic acid benzyl ester (R = Phenyl, 51a)

Yield quant.; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.42 (2H, d, *J* = 7.8 Hz), 7.31-7.28 (5H, m), 7.22 (2H, t, *J* = 7.8 Hz), 7.03 (1H, t, *J* = 7.8 Hz), 5.13, 5.08 (2H, ABq, *J* = 12.4 Hz), 4.62 (1H, br), 4.26 (1H, t, *J* = 7.0 Hz), 4.04 (2H, br), 3.73 (1H, br), 3.12 (1H, dd, *J* = 14.8, 10.2 Hz), 2.67 (1H, dd, *J* = 14.8, 4.4 Hz), 1.25 (3H, d, *J* = 6.4 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.61, 156.30, 130.87, 128.87, 128.81, 128.78, 128.51, 128.04, 127.69, 120.25, 74.15, 72.90, 72.55, 67.59, 53.75, 53.02, 38.69, 16.35; IR (neat): 3566, 1697, 1683 cm^{-1}; MS (EI): *m/z* 414 (M^+); HRMS (EI) Calcd for $C_{22}H_{26}O_6N_2$ 414.1791; Found 414.1795; $[\alpha]_D^{23}$ +27.6 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-(Benzylcarbamoylmethyl))-6-methyl-3, 4, 5-trihydroxy-piperidine-1-carboxylic acid benzyl ester (R = Benzyl, 51b)

Yield 78%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.27-7.14 (10H, m), 5.02 (2H, s), 4.52 (1H, br), 4.34-4.20 (3H, m), 4.02 (2H, br), 3.73 (1H, br), 2.98 (1H, dd, *J* = 15.4, 10.5 Hz), 2.50 (1H, dd, *J* = 15.4, 5.6 Hz), 1.21 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 167.74, 159.70, 136.29, 132.41, 130.86, 128.77, 128.57, 128.02, 127.73, 127.62, 75.51, 72.87, 72.15, 68.13, 55.74, 53.78, 43.49, 40.93, 16.36; IR (neat): 3376, 1695, 1681 cm^{-1}; MS (EI): *m/z* 428 (M^+); HRMS (EI) Calcd for $C_{23}H_{28}O_6N_2$ 428.1947; Found 428.1940; $[\alpha]_D^{23}$ +7.5 (*c* 1.10, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-(Butylcarbamoylmethyl))-6-methyl-3, 4, 5-trihydroxy-piperidine-1-carboxylic acid benzyl ester (R = Butyl, 51c)

Yield 85%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.27-7.22 (5H, m), 5.06, 5.03 (2H, ABq, *J* = 12.5 Hz), 4.45 (1H, br), 4.24 (1H, t, *J* = 6.9 Hz), 3.99 (1H, br), 3.94 (1H, br), 3.71 (1H, br), 3.09-2.89 (3H, m), 2.45 (1H, dd, *J* = 14.5, 4.5 Hz), 1.33-1.19 (7H, m), 0.80 (3H, t, *J* = 7.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 171.73, 156.12, 136.29, 128.47, 127.98,

127.66, 72.84, 71.94, 69.50, 67.45, 53.76, 51.37, 40.99, 39.32, 31.25, 19.95, 16.29, 13.66; IR (neat): 3387, 1697, 1682 cm^{-1}; MS (EI): *m/z* 394 (M^+); HRMS (EI) Calcd for $C_{20}H_{30}O_6N_2$ 394.2104; Found 394.2096; $[\alpha]_D^{23}$ +6.4 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(4-Methoxyphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = *p*-Methoxyphenyl, 51d)
Yield 76%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.33-7.23 (7H, m), 6.70 (2H, d, *J* = 8.0 Hz), 5.11, 5.02 (2H, ABq, *J* = 12.0 Hz), 4.65 (1H, br), 4.22 (1H, br), 3.99 (2H, br), 3.73 (1H, br), 3.65 (3H, s), 3.08 (1H, dd, *J* = 14.0, 10.0 Hz), 2.65 (1H, br), 1.22 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.05, 156.40, 136.25, 131.36, 130.76, 128.52, 128.03, 127.69, 122.14, 113.96, 72.89, 72.44, 70.20, 67.61, 55.66, 55.34, 51.58, 41.76, 16.36; IR (neat): 3379, 1690, 1682 cm^{-1}; MS (EI): *m/z* 444 (M^+); HRMS (EI) Calcd for $C_{23}H_{28}O_7N_2$ 444.1897; Found 444.1894; $[\alpha]_D^{23}$ +34.9 (*c* 0.25, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(4-Methylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = *p*-Tolyl, 51e)
Yield 75%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.30-7.23 (7H, m), 6.96 (2H, d, J = 8.0 Hz), 5.11, 5.02 (2H, ABq, J = 12.0 Hz), 4.65 (1H, br), 4.21 (1H, br), 3.98 (2H, br), 3.72 (1H, br), 3.11 (1H, dd, J = 14.5, 10.5 Hz), 2.65 (1H, br), 2.19 (3H, s), 1.22 (3H, d, J = 6.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.13, 156.32, 136.22, 135.17, 133.87, 129.27, 128.46, 127.98, 127.65, 120.30, 73.47, 72.89, 72.32, 67.60, 53.75, 51.53, 41.75, 20.76, 16.31; IR (neat): 3407, 1695, 1682 cm-1; MS (EI): m/z 428 (M+); HRMS (EI) Calcd for $C_{23}H_{28}O_6N_2$ 428.1947; Found 428.1945; $[\alpha]_D^{24}$ +29.8 (c 0.30, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(4-Fluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = *p*-Fluorophenyl, 51f)
Yield 75%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.40-7.26 (7H, m), 6.85 (2H, d, *J* = 7.0 Hz), 5.12, 5.02 (2H, ABq, *J* = 12.0 Hz), 4.65 (1H, br), 4.21 (1H, br), 3.99 (2H, br), 3.73 (1H, br), 3.10 (1H, dd, *J* = 13.5, 9.5 Hz), 2.67 (1H, br), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.12, 158.41 (d, *J* = 257.0 Hz), 155.38, 128.49, 128.44, 128.06, 127.96, 127.63, 121.97, 121.97, 115.51 (d, *J* = 12.0 Hz), 74.02, 72.79, 72.38, 67.61, 53.40, 52.58, 40.63, 16.58; IR (neat): 3420, 1698, 1670 cm^{-1}; MS (EI): *m/z* 432 (M^+); HRMS (EI) Calcd for $C_{22}H_{25}O_6N_2F$ 432.1697; Found 432.1694; $[\alpha]_D^{23}$ +17.1 (*c* 0.30, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2-Methylphenylcarbamoyl)methyl]-6-methyl-3, 4,

5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = *o*-Tolyl, 51g)

Yield 77%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35-7.21 (7H, m), 7.10 (1H, t, J = 7.0 Hz), 7.02 (1H, t, J = 7.0 Hz), 5.12, 5.08 (2H, ABq, J = 12.5 Hz), 4.60 (1H, dd, J = 8.5, 2.5 Hz), 4.28 (1H, t, J = 8.5 Hz), 4.07 (1H, br),4.03 (1H, br), 3.74 (1H, br), 3.16 (1H, dd, J = 14.3, 11.0 Hz), 2.68 (1H, dd, J = 14.3, 4.0 Hz), 2.15 (3H, s), 1.26 (3H, d, J = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.58, 156.16, 136.24, 135.16, 132.40, 130.86, 130.49, 128.77, 128.76, 128.50, 128.04, 127.75, 72.82, 72.14, 68.12, 67.58, 55.93, 51.48, 38.69, 22.95, 17.80; IR (neat): 3393, 1700, 1678 cm^{-1}; MS (EI): *m/z* 428 (M^+); HRMS (EI) Calcd for $C_{23}H_{28}O_6N_2$ 428.1947; Found 428.1945; $[\alpha]_D^{27}$ +13.6 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(3-Methylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = *m*-Tolyl, 51h)

Yield 75%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.34-7.21 (7H, m), 7.07 (1H, t, J = 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz), 5.12, 5.06 (2H, ABq, J = 15.0 Hz), 4.63 (1H, br), 4.23 (1H, t, J = 7.0 Hz), 4.00 (2H, br),3.73 (1H, br), 3.10 (1H, dd, J = 15.0, 10.0 Hz), 2.64 (1H, br), 2.17 (3H, s), 1.22 (3H, d, J = 6.9 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.17, 156.31, 138.61, 137.64, 136.17, 128.60, 128.46, 127.99, 127.66, 125.11, 120.80, 117.31, 72.89, 72.72, 72.34, 67.60, 53.76, 51.52, 41.84, 21.30, 16.28; IR (neat): 3379, 1690, 1680 cm^{-1}; MS (EI): *m/z* 428 (M^+); HRMS (EI) Calcd for $C_{23}H_{28}O_6N_2$ 428.1947; Found 428.1939; $[\alpha]_D^{27}$ +24.4 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4-Dimethylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = 2, 4-Dimethylphenyl, 51i)

Yield 72%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.31-7.23 (6H, m), 6.87 (1H, s), 6.85 (1H, d, J = 8.5 Hz), 5.08, 5.04 (2H, ABq, J = 12.5 Hz), 4.58 (1H, br), 4.38 (1H, br), 4.03 (1H, br), 3.98 (1H, br), 3.71 (1H, br), 3.10 (1H, dd, J = 14.5, 11.0 Hz), 2.63 (1H, dd, J = 14.5, 4.0 Hz), 2.19 (3H, s), 2.06 (3H, s), 1.22 (3H, d, J = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.56, 156.15, 136.24, 135.47, 132.48, 131.10, 130.85, 128.75, 128.47, 127.99, 127.72, 126.95, 72.80, 72.12, 69.51, 67.52, 53.76, 51.46, 41.68, 23.69, 20.80, 16.35; IR (neat): 3371, 1690, 1681 cm^{-1}; MS (EI): *m/z* 442 (M^+); HRMS (EI) Calcd for $C_{24}H_{30}O_6N_2$ 442.2104; Found 442.2113; $[\alpha]_D^{20}$ +25.4 (*c* 0.40, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4, 6-Trimethylphenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = 2, 4, 6-Trimethylphenyl, 51j)

Yield 68%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.41-7.27 (5H, m), 6.81 (2H, s), 5.13, 5.09 (2H, ABq, *J* = 12.5 Hz), 4.57 (1H, br), 4.31 (1H, br), 4.05 (1H, br), 4.03 (1H, br), 3.69 (1H, br), 3.13 (1H, dd, *J* = 14.5, 10.5 Hz), 2.73 (1H, dd, *J* = 14.5, 3.0 Hz), 2.22 (3H, s), 2.07 (6H, s), 1.28 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 171.56, 155.84, 136.29, 135.18, 128.46, 128.11, 127.96, 127.82, 127.65, 127.63, 73.23, 72.86, 69.51, 67.45, 53.75, 53.41, 38.43, 26.42, 22.64, 16.25; IR (neat): 3393, 1691, 1676 cm^{-1}; MS (EI): *m/z* 456 (M^+); HRMS (EI) Calcd for $C_{25}H_{32}O_6N_2$ 456.2260; Found 456.2251; $[\alpha]_D^{19}$ +6.5 (*c* 0.20, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2-Fluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = *o*-Fluorophenyl, 51k)

Yield 82%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.19 (1H, t, *J* = 8.0 Hz), 7.35-7.29 (5H, m), 7.13-7.05 (3H, m), 5.15 (2H, s), 4.62 (1H, dd, *J* = 7.3,3.0 Hz), 4.36 (1H, t, *J* = 7.3 Hz), 4.16 (1H, br), 4.07 (1H, br), 3.78 (1H, br), 3.22 (1H, dd, *J* = 15.5, 11.0 Hz), 2.73 (1H, dd, *J* = 15.5, 3.5 Hz), 1.32 (3H, d, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.31, 156.13, 152.88 (d, *J* = 243.0 Hz), 136.20, 128.72, 128.39, 127.91, 127.63, 124.78, 122.67, 114.73 (d, *J* = 19.5 Hz), 72.77, 72.21, 69, 51, 67.50, 53.72, 51.34, 41.55, 16.21; IR (neat): 3375, 1697, 1682 cm^{-1}; MS (EI): *m/z* 432 (M^+); HRMS (EI) Calcd for $C_{22}H_{25}O_6N_2F$ 432.1697; Found 432.1694; $[\alpha]_D^{21}$ +10.0 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(3-Fluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = *m*-Fluorophenyl, 51l)

Yield 78%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.42 (1H, d, *J* = 8.0 Hz), 7.35-7.25 (6H, m), 7.08 (1H, d, *J* = 8.0 Hz), 6.80 (1H, t, *J* = 8.0 Hz), 5.16 (2H, s), 4.57 (1H, dd, *J* = 6.8,3.0 Hz), 4.37 (1H, t, *J* = 7.0 Hz), 4.14 (1H, br), 4.07 (1H, br), 3.78 (1H, br), 3.14 (1H, dd, *J* = 15.3, 10.5 Hz), 2.72 (1H, br), 1.30 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.05, 162.34 (d, *J* = 249.1Hz), 155.00, 133.94, 132.35, 128.54, 127.81, 127.70, 123.56, 115.28, 109.89 (d, *J* = 7.3 Hz), 106.35 (d, *J* = 9.8Hz), 75.97, 73.39, 72.62, 69.58, 55.60, 53.85, 41.04, 16.35; IR (neat): 3370, 1688, 1680 cm^{-1}; MS (EI): *m/z* 432 (M^+); HRMS (EI) Calcd for $C_{22}H_{25}O_6N_2F$ 432.1697; Found 432.1694; $[\alpha]_D^{21}$ +8.6 (*c* 0.50, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4-Difluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = 2, 4-Difluorophenyl, 51m)

Yield 72%; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.97 (1H, m), 7.35-7.27 (5H, m), 6.78 (2H,

m), 5.13, 5.08 (2H, ABq, *J* = 12.5 Hz), 4.64 (1H, br), 4.31 (1H, t, *J* = 6.5 Hz), 4.05 (2H, br), 3.78 (1H, br), 3.20 (1H, dd, *J* = 14.8, 10.5 Hz), 2.70 (1H, dd, *J* = 14.8, 4.5 Hz), 1.28 (3H, d, *J* = 7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 171.59, 155.58, 155.51 (d, *J* = 281.0 Hz), 150.18 (d, *J* = 266.4 Hz), 134.00, 133.91, 128.63, 128.53, 128.12, 127.81, 112.09 (d, *J* = 7.3 Hz), 106.38 (t, *J* = 13.4 Hz), 76.03, 73.60, 68.12, 67.63, 58.05, 53.75, 42.81, 14.10; IR (neat): 3350, 1690, 1676 cm^{-1}; MS (EI): *m/z* 450 (M^+); HRMS (EI) Calcd for $C_{22}H_{24}O_6N_2F_2$ 450.1602; Found 450.1602; $[\alpha]_D^{18}$ +11.6 (*c* 0.20, $CHCl_3$)

(2*R*, 3*R*, 4*R*, 5*R*, 6*S*)-2-[(2, 4, 6-Trifluorophenylcarbamoyl)methyl]-6-methyl-3, 4, 5-trihydroxypiperidine-1-carboxylic acid benzyl ester (R = 2, 4, 6-Trifluorophenyl 51n)

Yield 72%; ^{1}H-NMR (500 MHz, $CDCl_3$) *δ*: 7.31-7.27 (5H, m), 6.62 (2H, m), 5.10 (2H, s), 4.67 (1H, br), 4.04 (3H, br), 3.78 (1H, br), 3.20 (1H, dd, *J* = 15.0, 9.5 Hz), 2.81 (1H, dd, *J* = 15.0, 5.0 Hz), 1.22 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 169.14, 161.61 (d, *J* = 229.6 Hz), 157.16 (d, *J* = 299.0 Hz), 156.22, 128.52, 128.07, 128.00, 127.73, 106.4 (t, J = 7.1 Hz), 97.81 (t, *J* = 6.1 Hz), 75.36, 73.07, 72.19, 68.14, 54.57, 51.67, 39.93, 16.23; IR (neat): 3351, 1695, 1684 cm^{-1}; MS (EI): *m/z* 468 (M^+); HRMS (EI) Calcd for $C_{22}H_{23}O_6N_2F_3$ 468.1508; Found 468.1504; $[\alpha]_D^{18}$ +5.8 (*c* 0.20, $CHCl_3$)

General procedure for the synthesis of iminosugars (52a-n)

20% $Pd(OH)_2$/C was added to a solution of **51** in MeOH, and the resulting suspension was hydrogenated at 1 atm under hydrogen atmosphere for 2 days. The catalyst was filtered off with a Celite pad, and the filtrate was evaporated to give a hydrogenated product, which was purified using Dowex 50W resin (X-8, H^+ form, eluent: 0.5 N aqueous NH_3) to give **52**.

***N*-Phenyl-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(phenylcarbamoylmethyl)-deoxyfuconojirimycin] (52a)**

Yield 90%; ^{1}H-NMR (500 MHz, DMSO-d_6) *δ*: 7.56 (2H, d, *J* = 7.6 Hz), 7.28 (2H, t, *J* = 7.6 Hz), 7.01 (1H, t, J = 7.6 Hz), 4.64-4.33 (3H, br), 3.51 (1H, br), 3.18-3.12 (1H, m), 2.71-2.61 (1H, m), 2.27-2.20 (1H, m), 0.99 (3H, d, *J* = 6.4 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) *δ*: 171.18, 130.19, 129.15, 120.40, 119.41, 75.86, 72.73, 70.09, 58.76, 53.30, 40.00, 15.92; IR (KBr): 3421, 1662 cm^{-1}; MS (EI): *m/z* 280 (M^+); HRMS (EI) Calcd for $C_{14}H_{20}O_4N_2$ 280.1423; Found 280.1421; $[\alpha]_D^{25}$ +7.5 (*c* 0.10, MeOH); m.p. 221-223 ℃

***N*-Benzyl-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(benzylcarbamoylmethyl)**

deoxyfuconojirimycin] (52b)

Yield 87%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.30-7.21 (5H, m), 4.68-4.42 (3H, m), 4.35-4.21 (2H, m), 3.48 (1H, br), 3.21-3.14 (1H, m), 2.71-2.54 (1H, m), 2.12 (1H, br), 1.01 (3H, d, J = 6.8 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 171.84, 128.63, 127.72, 127.55, 127.09, 74.69, 72.19, 71.71, 61.46, 52.93, 52.84, 40.89, 13.41; IR (KBr): 3420, 1662 cm^{-1}; MS (EI): *m/z* 294 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}O_4N_2$ 294.1580; Found 294.1583; $[\alpha]_D^{25}$ +5.7 (*c* 0.10, MeOH); m.p. 231-232 ℃

***N*-Butyl-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(butylcarbamoyl-methyl)deoxyfuconojirimycin] (52c)**

Yield 71%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 4.57-4.20 (3H, br), 3.49 (1H, br), 3.16-3.14 (1H, br), 3.08-3.00 (2H, m), 2.61 (1H, dd, J = 13.0, 6.5 Hz), 2.00-1.96 (1H, m), 1.38-1.25 (4H, m), 0.96 (3H, d, J = 6.5 Hz), 0.86 (3H, t, J = 7.0 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 171.82, 76.40, 72.84, 72.14, 58.25, 53.32, 39.54, 38.48, 31.72, 20.07, 18.37, 14.21; IR (KBr): 3419, 1652 cm^{-1}; MS (EI): *m/z* 260 (M^+); HRMS (EI) Calcd for $C_{12}H_{24}O_4N_2$ 260.1736; Found 260.1737; $[\alpha]_D^{21}$ +13.0 (*c* 0.40, MeOH); m.p. 230-231 ℃

***N*-(4-Methoxyphenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(4-methoxy-phenylcarbamoylmethyl)deoxyfuconojirimycin] (52d)**

Yield 93%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.47 (2H, d, J = 8.8 Hz), 6.86 (2H, d, J = 8.8 Hz), 4.69-4.41 (3H, br), 3.71 (3H, s), 3.48 (1H, br), 3.20 (1H, br), 2.69 (1H, m), 2.24 (1H, m), 1.01 (3H, d, J = 5.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 173.24, 136.27, 131.19, 128.92, 120.96, 74.02, 72.44, 72.04, 62.47, 58.65, 55,61, 44.21, 16.74; IR (KBr): 3410, 1653 cm^{-1}; MS (EI): *m/z* 310 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}O_5N_2$ 310.1529; Found 310.1527; $[\alpha]_D^{25}$ +9.4 (*c* 0.25, MeOH); m.p. 233-234 ℃

***N*-(4-Tolyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(4-methylphenyl-carbamoylmethyl)deoxyfuconojirimycin] (52e)**

Yield 68%; ^{1}H-NMR (500 MHz, DMSO-d6) δ: 7.45 (2H, d, J = 8.5 Hz), 7.08 (2H, d, J = 8.5 Hz), 4.64-4.33 (3H, br), 3.46 (1H, br), 3.12-3.24 (1H, m), 2.69-2.61 (1H, m), 2.23-2.14 (4H, m), 0.99 (3H, d, J = 6.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d6) δ: 170.71, 137.32, 132.15, 129.51, 119.39, 76.32, 72.86, 71.98, 58.15, 53.24, 40.43, 20.93, 18.41; IR (KBr): 3411, 1656 cm-1; MS (EI): m/z 294 (M+); HRMS (EI) Calcd for $C_{15}H_{22}O_4N_2$ 294.1580; Found 294.1585; $[\alpha]_D^{25}$ +4.8 (c 0.10, MeOH); m.p. 241-242 ℃

***N*-(4-Fluorophenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(4-fluorophenyl-carbamoylmethyl)deoxyfuconojirimycin] (52f)**

Yield 94%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.59 (2H, dd, J = 8.8, 5.0 Hz), 7.12 (2H, t, J = 8.8 Hz), 4.75-4.51 (3H, br), 3.49 (1H, br), 3.21 (1H, br), 2.72-2.63 (1H, m), 2.30-2.26 (1H, m), 1.02 (3H, d, J = 7.0 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 170.72, 158.25 (d, J = 236.9Hz), 136.33, 121.15, 115.71 (d, J = 23.1 Hz), 76.15, 72.72, 71.76, 57.99, 53.34, 18.20; IR (KBr): 3409, 1661 cm^{-1}; MS (EI): *m/z* 298 (M^+); HRMS (EI) Calcd for $C_{14}H_{19}O_4N_2F$ 298.1329; Found 298.1352; $[\alpha]_D^{24}$ +3.2 (*c* 0.10, MeOH); m.p. 204-205 ℃

***N*-(2-Tolyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(2-methylphenyl-carbamoylmethyl)deoxyfuconojirimycin] (52g)**

Yield 64%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.30 (1H, d, J = 7.5 Hz), 7.19 (1H, d, J = 7.5 Hz), 7.14 (1H, t, J = 7.5 Hz), 7.04 (1H, t, J = 7.5 Hz), 5.22-4.88 (3H, br), 3.60 (1H, br), 3.11-2.95 (1H, br), 2.84 (1H, br), 2.22 (3H, s), 2.21-2.09 (1H, m),1.15 (3H, d, J = 6.0 Hz); ^{13}C-NMR (125MHz, DMSO-d_6) δ: 168.63, 131.26, 130.71, 126.54, 126.40, 121.74, 119.92, 74.83, 71.51, 71.27, 58.03, 53.90, 18.43, 15.40; IR (KBr): 3402, 1654 cm^{-1}; MS (EI): *m/z* 294 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}O_4N_2$ 294.1580; Found 294.1583; $[\alpha]_D^{26}$ +2.8 (*c* 0.20, MeOH); m.p. 217-218 ℃

***N*-(3-Tolyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(3-methylphenyl-carbamoylmethyl)deoxyfuconojirimycin] (52h)**

Yield 87%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.42 (1H, s), 7.33 (1H, d, J = 7.5 Hz), 7.15 (1H, t, J = 7.5 Hz), 6.83 (1H, d, J = 7.5 Hz), 4.68-4.39 (3H, br), 3.47 (1H, br), 3.21-3.14 (1H, m), 2.69-2.62 (1H, m), 2.26 (3H, s), 2.21-2.12 (1H, m), 1.00 (3H, d, J = 6.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 170.87, 139.74, 138.31, 129.00, 124.08, 119.95, 116.62, 76.26, 72.81, 71.89, 58.12, 53.31, 39.83, 21.71, 18.34; IR (KBr): 3397, 1655 cm^{-1}; MS (EI): *m/z* 294 (M^+); HRMS (EI) Calcd for $C_{15}H_{22}O_4N_2$ 294.1580; Found 294.1578; $[\alpha]_D^{26}$ +13.5 (*c* 0.20, MeOH); m.p. 200-201 ℃

***N*-(2,4-Dimethyphenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(2, 4-dimethylphenylcarbamoylmethyl)deoxyfuconojirimycin] (52i)**

Yield 90%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.65 (1H, d, J = 8.0 Hz), 6.98 (1H, s), 6.93 (1H, d, J = 8.0 Hz), 4.70-4.46 (3H, br), 3.49 (1H, br), 3.22-3.12 (1H, m), 2.74-2.58 (1H, m), 2.34-2.26 (1H, m), 2.22 (3H, s), 2.18 (3H, s), 1.03 (3H, d, J = 6.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 170.69, 134.95, 133.14, 131.13, 129.17, 126.88,

122.91, 76.09, 72.86, 71.84, 58.09, 53.26, 39.02, 20.92, 18.36, 18.21; IR (KBr): 3412, 1653 cm^{-1}; MS (EI): *m/z* 308 (M^+); HRMS (EI) Calcd for $C_{16}H_{24}O_4N_2$ 308.1736; Found 308.1747; $[\alpha]_D^{25}$ +9.8 (*c* 0.10, MeOH); m.p. 215-216 ℃

***N*-(2,4,6-Trimethyphenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(2, 4, 6-trimethylphenylcarbamoylmethyl)deoxyfuconojirimycin] (52j)**

Yield 70%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 6.84 (2H, s), 4.87-4.69 (3H, br), 3.53 (1H, br), 3.27 (1H, br), 2.85-2.57 (1H, m), 2.21 (3H, s), 2.14-2.07 (7H, m), 1.05 (3H, d, *J* = 5.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 169.56, 139.28, 135.17, 128.63, 122.48, 79.13, 72.32, 72.18, 57.97, 53.57, 40.59, 20.98, 18.63, 16.36; IR (KBr): 3418, 1653 cm^{-1}; MS (EI): *m/z* 322 (M^+); HRMS (EI) Calcd for $C_{17}H_{26}O_4N_2$ 322.1893; Found 322.1883; $[\alpha]_D^{25}$ +5.0 (*c* 0.10, MeOH); m.p. 237-240 ℃

***N*-(2-Fluorophenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(2-fluorophenyl-carbamoylmethyl)deoxyfuconojirimycin] (52k)**

Yield 65%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.60 (1H, dd, *J* = 8.5, 2.0 Hz), 7.34-7.23 (2H, m), 6.84 (1H, td, *J* = 8.5, 2.0 Hz), 4.73-4.49 (3H, br), 3.48 (1H, br), 3.20-3.16 (1H, m), 2.88-2.58 (1H, m), 2.31-2.24 (1H, m), 1.01 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 171.18, 160.86 (d, *J* = 216.0 Hz), 141.76, 141.53, 130.83 (d, *J* = 35.1 Hz), 115.38 (d, *J* = 37.8 Hz), 109.97, 76.07, 72.69, 71.67, 57.87, 53.40, 37.80, 18.54; IR (KBr): 3412, 1653 cm^{-1}; MS (EI): *m/z* 298 (M^+); HRMS (EI) Calcd for $C_{14}H_{219}O_4N_2F$ 298.1329; Found 298.1334; $[\alpha]_D^{23}$ +13.5 (*c* 0.10, MeOH); m.p. 208-209 ℃

***N*-(3-Fluorophenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(3-fluorophenyl-carbamoylmethyl)deoxyfuconojirimycin] (52l)**

Yield 85%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.20 (1H, td, *J* = 8.0, 1.5 Hz), 7.25-7.03 (3H, m), 4.71-4.45 (3H, br), 3.50 (1H, br), 3.22-3.11 (1H, m), 2.59-2.53 (1H, m), 2.40-2.35 (1H, m), 1.05 (3H, d, *J* = 6.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 171.50, 152.93 (d, *J* = 243.0 Hz), 127.49, 125.05, 122.37, 115.69 (d, *J* = 18.3 Hz), 108.42 (d, *J* = 12.5 Hz), 76.17, 72.92, 71.96, 58.01, 53.31, 18.16; IR (KBr): 3406, 1654 cm^{-1}; MS (EI): *m/z* 298 (M^+); HRMS (EI) Calcd for $C_{14}H_{219}O_4N_2F$ 298.1329; Found 298.1313; $[\alpha]_D^{25}$ +3.3 (*c* 0.10, MeOH); m.p. 197-198 ℃

***N*-(2,4-Difluorophenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(2,**

4-difluorophenylcarbamoylmethyl)deoxyfuconojirimycin] (52m)

Yield 77%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.17-8.13 (1H, m), 7.33-7.28 (1H, m), 7.05-7.02 (1H, m), 4.72-4.46 (3H, br), 3.49 (1H, br), 3.17-3.11 (1H, m), 2.70-2.57 (1H, m), 2.32-2.22 (1H, m), 1.03 (3H, d, J = 6.5 Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 171.30, 157.89 (d, J = 374 Hz), 155.62 (d, J = 193.3 Hz), 123.41, 120.33, 111.60 (d, J = 47.0 Hz), 103.44 (t, J = 8.5 Hz), 79.67, 72.79, 71.86, 57.93, 53.22, 18.10; IR (KBr): 3419, 1654 cm^{-1}; MS (EI): *m/z* 316 (M^+); HRMS (EI) Calcd for $C_{14}H_{18}O_4N_2F_4$ 316.1235; Found 316.1224; $[\alpha]_D^{24}$ +1.7 (*c* 0.10, MeOH); m.p. 224-226 ℃

***N*-(2,4,6-Trimethyphenyl)-2β-DFJ acetamide [(1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-1-(2, 4, 6-trifluorophenylcarbamoylmethyl)deoxyfuconojirimycin] (52n)**

Yield 85%; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 7.25 (2H, t, J = 8.5 Hz), 4.70-4.26 (3H, br), 3.52 (1H, br), 2.90-2.85 (1H, m), 2.73-2.57 (1H, m), 2.33-2.26 (1H, m), 1.05 (3H, d, J = 6.5Hz); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 170.1, 160.0 (d, J = 234.6 Hz), 157.9 (d, J = 232.1 Hz), 114.7 (t, J = 6.3 Hz), 100.0 (t, J = 6.1 Hz), 71.58, 71.04, 70.43, 53.24, 51.44, 17.91; IR (KBr): 3408, 1653 cm^{-1}; MS (EI): *m/z* 334 (M^+); HRMS (EI) Calcd for $C_{14}H_{17}O_4N_2F_3$ 334.1140; Found 334.1127; $[\alpha]_D^{25}$ +4.0 (*c* 0.10, MeOH); m.p. 267-270 ℃

Biological assays

The enzymes β-glucosidase (bovine liver), α-galactosidase (from coffee beans), β-galactosidase (from bovine liver), α-mannosidase (from jack bean), β-mannosidase (from snail), α-L-rhamnosidase (from *Penicillium decumbens*), α-L-fucosidase (from bovine kidney), β-glucuronidases (from bovine liver; from *Escherichia coli*), *p*-nitrophenyl glycosides, and various disaccharides were purchased from Sigma-Aldrich Co. Brush border membranes were prepared from the rat small intestine according to the method of Kessler et al [37] and were assayed at pH 5.8 for rat intestinal maltase using maltose. Rat epididymis α-L-fucosidase was partially prepared from epididymis according to the method of Skudlared et al [38]. Human lysosome α-L-fucosidase was prepared according to our previous methods [33] and was assayed using 4-methylumbelliferyl-α-L-fucopyranoside as substrate. For rat intestinal maltase activities, the reaction mixture (0.2 mL) contained 25 mM maltose and the appropriate amount of enzyme, and the incubations were performed for 10-30 min at 37 ˚C. The reaction was stopped by heating at 100 ˚C for 3 min. After centrifugation (600 g; 10 min), 0.05 mL of the resulting reaction mixture were added to 3 mL of the Glucose CII-test Wako (Wako Pure Chemical Ind., Osaka, Japan). The absorbance at 505 nm was

measured to determine the amount of the released D-glucose. Other glycosidase activities (including the rat epididymis α-L-fucosidase) were determined using an appropriate *p*-nitrophenyl glycoside as substrate at the optimum pH of each enzyme. The reaction mixture (1 mL) contained 2 mM of the substrate and the appropriate amount of enzyme. The reaction was stopped by adding 2 mL of 400 mM Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm.

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原著論文

1. Stereoselective Total Synthesis of (–)-Batzellasides A, B, and C
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2. Synthesis and biological evaluation of *N*-(2-fluorophenyl)-2β-deoxyfuconojirimycin acetamide as a potent inhibitor for α-L-fucosidases
Kato, A.; Okaki, T.; Ifuku, S.; Sato, K.; Hirokami, Y.; Iwaki, R.; Kamori, A.; Nakagawa, S.; Adachi, I.; Kiria, P. G.; Onomura, O.; Minato, D.; Sugimoto, K.; Matsuya, Y.; Toyooka, N.
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3. Synthesis of phenylalkyl-substituted polyhydroxypiperidines as potent inhibitors for α-L-fucosidase
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