新規 *C*-グリシトール骨格を有する SGLT1 阻害物質の創薬研究

黒田　翔一

本学位論文は、下記の原著論文を基に作成され、東北大学大学院薬学研究科に提出されたものである。

1. **Kuroda S.**, Kobashi Y., Oi T., Amada, H., Okumura-Kitajima L., Io, F., Yamamoto K., Kakinuma H., Discovery of a potent, low-absorbable sodium-dependent glucose cotransporter 1 (SGLT1) inhibitor (TP0438836) for the treatment of type 2 diabetes.

Bioorganic & Medicinal Chemistry Letters, **28**, 3534-3539 (2018).

2. **Kuroda S.**, Kobashi Y., Oi T., Kawabe K., Shiozawa F., Okumura-Kitajima L., Sugisaki-Kitano M., Io F., Yamamoto K., Kakinuma H., Discovery of potent, low-absorbable sodium-dependent glucose cotransporter 1 (SGLT1) inhibitor SGL5213 for type 2 diabetes treatment.

Bioorganic & Medicinal Chemistry, **27**, 394-409 (2019).

3. **Kuroda, S.**, Kobashi Y., Madoka K., Kawabe K., Shiozawa F., Makoto, H., Yuki, S., Okumura-Kitajima L., Hiroko, K., kayo, K., Yamamoto K., Kakinuma H., Synthesis and Structure-Activity Relationship of *C*-Phenyl D-Glucitol (TP0454614) Derivatives as Selective Sodium-Dependent Glucose Cotransporter 1 (SGLT1) Inhibitors.

Chem. Pharm. Bull., **68**, 635-652 (2020).

略語表

本論文中、以下の略語を使用した。

APCI：atmospheric pressure chemical ionization

AUC：area under the curve

BA：bioavailability

DPP-4：dipeptidyl peptidase-4

EI：electron ionization

ESI：electrospray ionization

GLP-1：glucagon-like peptide-1

HbA1c：hemoglobin A1c

HOBt：1-hydroxybenzotriazole

HPLC：high performance liquid chromatography

HRMS：high resolution mass spectrum

HTS：high-throughput screening

Hz：hertz

IC_{50}：inhibition concentration 50%

IR：infrared spectroscopy

IV：intravenous

J：coupling constant

LBDD：ligand-based drug design

LC/MS：liquid chromatography/mass spectrometry

mp：melting point

MS：mass spectrometry, microsomal stability

NMR：nuclear magnetic resonance

PAMPA：parallel artificial membrane permeability assay

PK：pharmacokinetics

PO：per os

SBDD：structure-based drug design

SD：Sprague-Dawley

SGLT1：sodium-glucose cotransporter 1

SGLT2：sodium-glucose cotransporter 2

TFA：trifluoroacetic acid

THF：tetrahydrofuran

TMS：tetramethylsilane

TPSA：topological Polar Surface Area

WSCI：1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

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序論

２型糖尿病を有する人の数は、世界中で年々増加しており社会問題となっている。国際糖尿病連盟(IDF) は、約 4 億 1500 万人の成人が糖尿病に罹患していると推定し、この合計は 2040 年までに 6 億 4200 万人に増加すると予測している [1)]。また、国内においても厚生労働省から平成 26 年に発表された「患者調査」によると糖尿病の総患者数は 316 万 6000 人であり、 3 年間で 46 万人以上増加していることが報告されている。2 型糖尿病の成因は、生活習慣、加齢、遺伝、ストレスなどによってインスリン不足になることが影響していると考えられている。例えば生活習慣が要因と考えられる場合として、糖尿病の発症リスクは糖含有飲料との糖摂取量との相関があるとする報告もあり、2014 年には、世界保健機関(WHO)が糖分摂取量を制限するために新しい勧告を発表した [2)]。２型糖尿病治療において血糖値を維持することは、合併症の抑制や生命予後に非常に有効であり、実際血糖値の指標である HbA1c を 6.9%未満に抑制することで細小血管症の進展を抑制できることが報告されている [3)]。血糖コントロールとしては、初めに運動療法と食事療法による改善を試みるが、不十分な場合には薬物療法を実施する。経口糖尿病治療薬はこれまでに下記に示すように様々なメカニズムの経口医薬品が発売されている。

・インスリン抵抗性改善系：ビグアナイド薬、チアゾリジン薬
・インスリン分泌促進系：DPP-4 阻害剤、GLP-1 作動薬、スルホニル尿素薬、グリニド薬
・糖吸収、排泄調節系：α-グルコシダーゼ阻害薬、SGLT2 阻害薬

近年、シェアを拡大している DPP-4 阻害薬及び SGLT2 阻害薬が登場する以前は、スルホニル尿素薬、α-グルコシダーゼ阻害薬が最も使用されていた。スルホニル尿素薬は、血糖非依存的にインスリン分泌を促進することから、高い血糖抑制作用を有する [4)]。一方で、副作用として低血糖、薬効の二次無効などが知られていた。2009 年に登場した DPP-4 阻害薬は、インクレチンの分解を阻害し、活性型の GLP-1 及び GIP の血中濃度を増加させることにより、インスリン分泌を促す。GLP-1 は、血糖依存的にインスリン分泌を促すことか

ら、DPP-4 阻害薬の低血糖リスクは、スルホニル尿素と比較して低いと考えられている[5]。

このように様々な薬剤が登場しているにも関わらず、糖尿病の患者数は増加しており糖尿病性腎臓病や網膜症などの合併症のリスクが高い。さらには糖尿病患者の 15%が心不全を併発することも知られており、異なるメカニズムの医薬品の創出が望まれている。

SGLT は、SGLT1~6 の 6 つのサブタイプが知られている。その中でも SGLT1 と SGLT2 に対し阻害活性を有する天然物であるフロリジンが動物モデルで血糖低下作用、インスリン抵抗性改善作用を示したことから SGLT1 と SGLT2 が 2 型糖尿病の魅力的な標的として注目されていた[6,7]。

SGLT1 及び SGLT2 は、腎臓に発現していることが知られており、SGLT2 に関しては腎臓の近位尿細管に限定的に発現している。グルコースは、近位尿細管でほぼ完全に再吸収され通常はほとんど尿に排泄されることはない。その中で、SGLT2 はグルコースの取り込みの９０％を担っており、残りの１０％は SGLT1 が担っている[8,9,10]。(Figure 1)

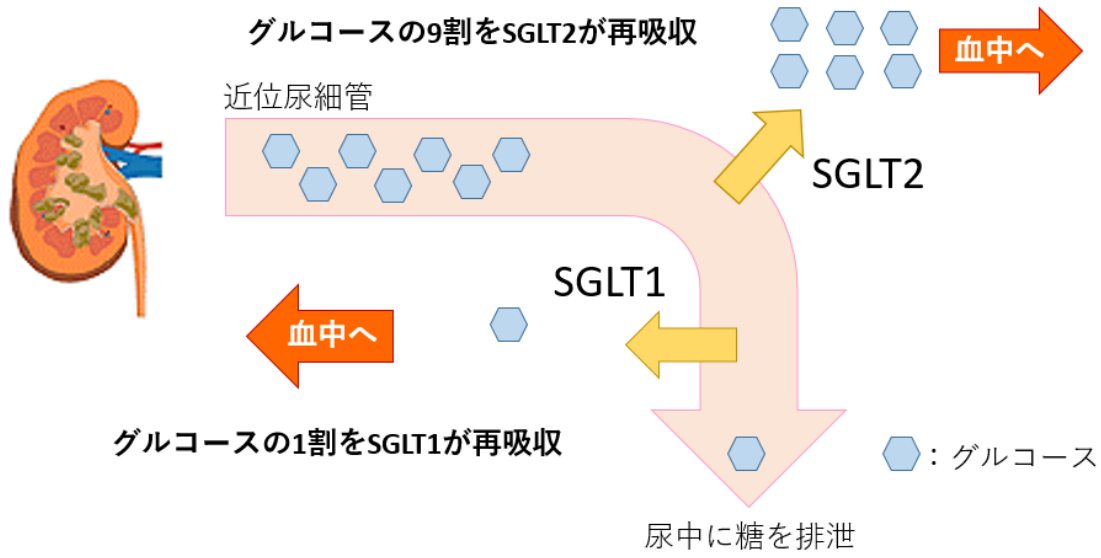


Figure 1. 近位尿細管での SGLT1 及び SGLT2 の糖の再吸収

現在、多くの SGLT2 阻害剤（dapagliflozin,[11]） canagliflozin,[12] empagliflozin,[13] ipragliflozin,[14] luseogliflozin,[15] and tofogliflozin,[16]）が上市され、腎臓での再吸収を阻害し、糖を尿から排出させることで血糖をコントロールできることが知られている。また、発売後の canagliflozin、empagliflozin、dapagliflozin の大規模臨床試験の結果、糖尿病性腎臓病や心不全に関するリスクも低下することが示唆されている [17,18,19]。一方で、腎機能が低下した患者に投与した場合、効果が減弱することが知られており [20]、副作用として尿路感染症などが発現することから課題も有していると言える。(Figure 2)

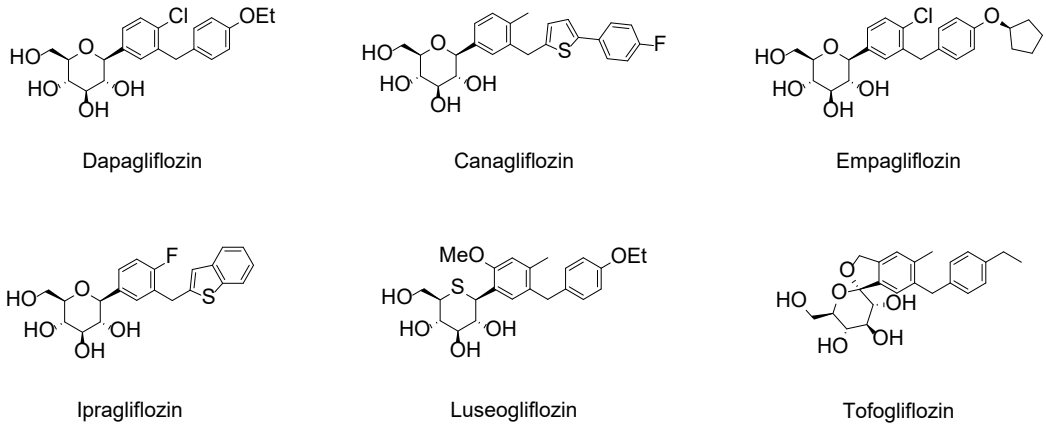


Figure 2. SGLT2 inhibitors

SGLT1 は SGLT2 と異なり小腸や心臓にも発現していることから、SGLT1 を阻害することにより小腸からの糖吸収を抑制し、血糖コントールできる可能性がある。SGLT2 阻害薬では血糖低下効果が低いと考えられる腎機能が低下した患者にも有用性があると考えられ、糖尿病の創薬標的として有望であると著者は考えた。実際、小腸の SGLT1 mRNA の発現と腸のブドウ糖の取り込みは、２型糖尿病患者で上昇していることが知られている [21]。小腸で作用する糖尿病薬としては、α-グルコシダーセ阻害剤が知られている。食事から得られる糖質の 6 割がデンプンなどの多糖類、約 3 割がショ糖などの二糖類である。そのうち、多糖類は唾液などに含まれるα-アミラーゼにより二糖類に分解され、二糖類は小腸に達するとα-グルコシダーセによって単糖に分解され、血中に吸収される。α-グルコシダーセ阻

害薬を用いることにより、二糖類の分解を抑えられ、食後血糖の上昇が抑制される。しかし、食直前投与や単糖には効かないことから課題を抱えてきた。一方で SGLT1 は、腸管腔から小腸の上皮細胞へのグルコース吸収に重要な役割を果たしている。単糖であるグルコースの小腸上皮での吸収を抑え、糞便中に糖を排泄することで血糖コントロールが可能になることが考えられた。すなわち、SGLT1 を特異的に阻害できれば、食事由来の糖吸収を抑制し、糖尿病治療の新しい選択肢として提供できることが期待される。(Figure 3)

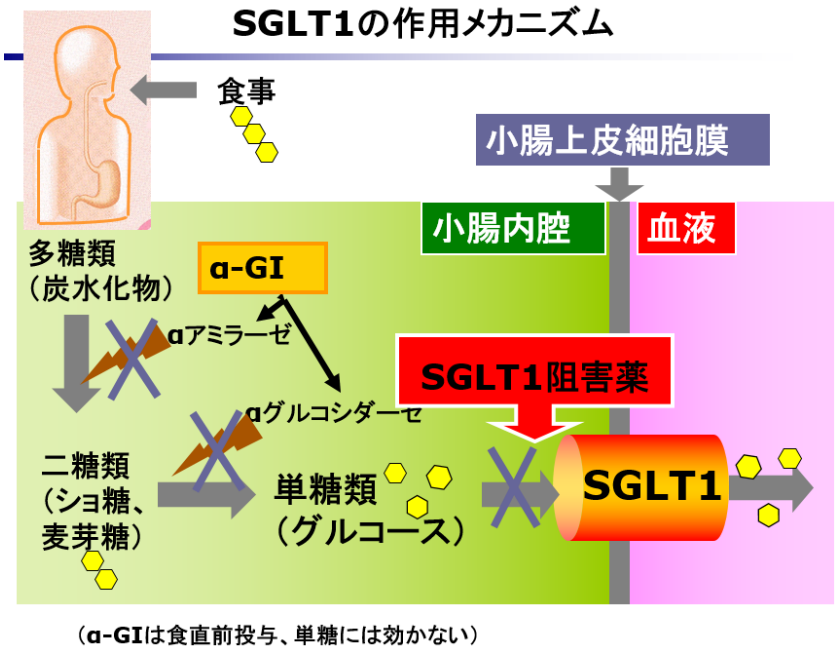


Figure 3. 小腸上皮での SGLT1 の役割

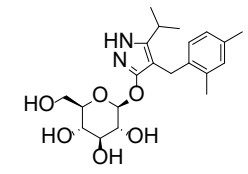
一般的に特定の標的を選択的に阻害するには、それ以外の標的と比較し、高い選択性を有する化合物を創出することが考えられる。SGLT1 が小腸に発現している一方で、SGLT2 は小腸に発現していないことから、本研究においては前述の戦略とは異なり、著者は化合物が小腸上皮でのみ作用することで薬物動態の観点から選択性が出せないかと考えた。つまり、小腸から吸収される化合物量を抑えることにより、腎臓などに発現する SGLT2、SGLT1 には作用しない化合物を創出する戦略を立てた。研究開始時には、小腸からの吸収を抑えた低吸収性の低分子化合物の報告はなかったので、新たな創薬戦略を用いる必要があった。そこで小腸からの吸収を抑えた低吸収低分子を創出する上で、著者は膜透過性の指標として用

いられる TPSA[22)]に着目した。極性表面積（PSA）の算出には、３次元での解析が必要となり多くのリソースを要することから、創薬の指標として用いるには難しいのが現状である。一方で、TPSA は３次元計算をすることなく、近似的な数値を得る簡便な手法であり、創薬において良く用いられている。さらに、Peter らの報告では、化合物の TPSA の増大により小腸からの吸収が低下することが報告されていることから[22,23)]、著者は SGLT1 阻害活性と高い TPSA を両立することにより、小腸からの吸収を抑えた低吸収性低分子を創出できると考えた。

また、SGLT1 は腎臓や小腸だけでなく、心臓、肝臓、肺、骨格筋、脳など、さまざまな他の臓器や細胞でも高発現しているが、その生理機能は明らかにされていない[24,25)]。SGLT1 に関する様々な報告がある中、心不全に対する SGLT1 の治療の可能性とその心保護作用のメカニズムが最近注目されている[26)]。例えば、Kashiwagi らから、非選択的な SGLT1 阻害剤であるフロリジンを用いて、心臓での SGLT1 の役割を考察した論文が報告されている。[27)]以上の背景を踏まえ、著者は SGLT1 阻害作用に基づく安全に長期間使用可能な新規糖尿病及び糖尿病合併症治療薬の創出を目指し、経口投与可能な SGLT1 阻害剤の創薬研究に着手した。加えて、心保護作用解明に寄与すると考えられる SGLT1 選択的阻害物質の創出についても併せて以下に論述する。

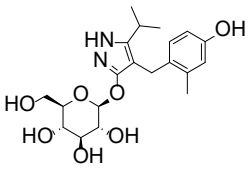
SGLT1阻害薬の現況

SGLT1阻害活性を示す低分子化合物**A**、**B**がキッセイ薬品株式会社のFushimiらから2012年に初めて報告された。経口吸収されるタイプの化合物であり、糖尿病モデルラットにおいて用量依存的な薬効が報告されている。一方で、ヒトとラットの間に種差があり、ヒトのSGLT1に対する阻害活性が弱い点が課題だと言える[28]。続いて2013年に、同じくキッセイ薬品株式会社のFushimiらから初めて小腸からの吸収を抑えた低吸収性SGLT1阻害化合物**C**が報告された[29]。SGLT1阻害活性は増強されていたものの、基本骨格が*O*-グリコシドタイプの化合物であり、化学的な安定性に欠けると推定された。実際、論文中でアグリコン部が小腸から吸収されることについて述べられていたことから、グルコシド結合が加水分解されることが示唆される。また、創薬研究段階で阻害活性に種差があると、動物を用いた薬効と安全性の評価の難易度が高くなる。SGLT1は、グルコースだけでなく、ガラクトースも基質とすることから、彼らはグルコース４位のヒドロキシル基の立体配置を反転させた誘導体を合成することにより種差を低減している。ただ、立体反転が必要となるため合成の難易度が増している点は課題である。その後、2017年にはLexicon社のGoodwinらから*C*-グリコシドタイプの低吸収性化合物**D**が報告された[30]。同グループは、SGLT1/SGLT2 dual阻害薬である経口薬sotagliflozin[31-33]を開発しており、それをリード化合物とし合成展開していることから、著者と同様のコンセプトで同時期に研究されていたことになる。ただし、グルコース部位にメチルチオ基を導入しており合成難易度が高いことが開発における課題と考えられる。(Figure 4)



A

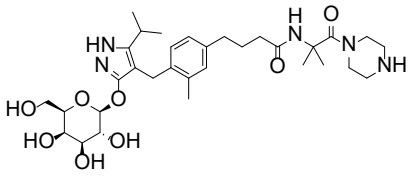
hSGLT1 IC_{50} = 246 nM
hSGLT2 IC_{50} = 6010 nM



B

hSGLT1 IC_{50} = 320 nM
hSGLT2 IC_{50} = 6890 nM

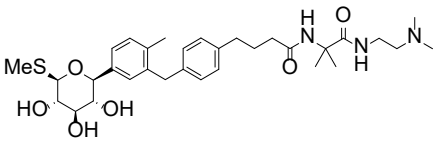
Kissei (2012)



C

hSGLT1 IC_{50} = 50 nM
hSGLT2 IC_{50} = 1730 nM

Kissei (2013)



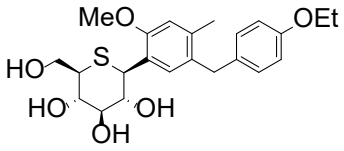
D

hSGLT1 IC_{50} = 2.2 nM
hSGLT2 IC_{50} = 2.7 nM

Lexicon (2017)

Figure 4. Reported SGLT1 inhibitors

そのような状況下で著者は、安価に入手可能なグルコースを原料に用い、低吸収性で消化管に発現するSGLT1のみを阻害する薬剤の創出ができないかと考えた。その際、自社で実施したSGLT2阻害薬ルセオグリフロジン(Figure 2)の創薬研究で得られたヒット化合物から誘導体展開を実施することを計画した。



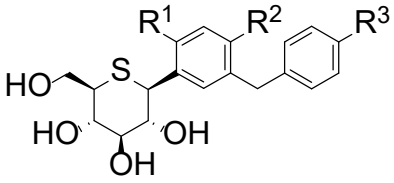
Luseogliflozin

Figure 2 より抜粋

ルセオグリフロジンの創薬研究[15,34]では、SGLT2選択的阻害物質の創出を目指していたことから、SGLT1阻害活性は弱いものが多かった。ただ、Table 1に示すように、R^2の置換基をメチル基（**4a**）に、R^1の置換基をOH基（**4b**）に変換することで、SGLT1阻害活性が向上することが示唆されていることから、これらのSARを足掛かりに更なる研究を実施した。

Table 1

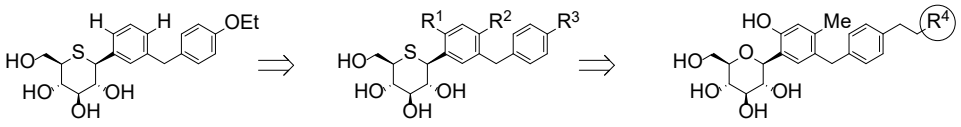
報告されている *C*-phenyl 1-thio-D-glucitol derivatives[15]の SGLT1/SGLT2 阻害活性



Cpd.	R^1	R^2	R^3	hSGLT2 IC_{50} (nM)	hSGLT1 IC_{50} (nM)
1	H	H	OEt	73.6	26100
1a	H	OH	OEt	283	14600
1b	H	OMe	OEt	13.4	565
1c	H	F	OEt	9.40	7960
4a	H	Me	OEt	2.29	671
1d	H	Cl	OEt	1.77	1210
4b	OH	H	OEt	17.4	4040
1e	OMe	H	OEt	37.9	100000
1f	OMe	OMe	OEt	10.8	4270
Luseogliflozin	OMe	Me	OEt	2.26	3990

本研究成果概要

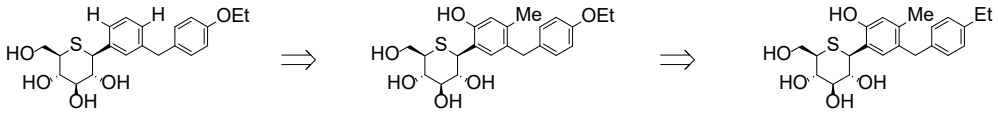
本論第１章では、自社医薬品であるルセオグリフロジンの創薬研究の際に得られていたSGLT2阻害化合物**1**をリード化合物として、化合物**2**のR^1、R^2、R^3部位、続いて化合物**3**のR^4部位の構造活性相関研究及び膜透過性について論じる。創薬戦略としては、高活性且つ低吸収性化合物を創製し小腸上皮に発現しているSGLT1を選択的に阻害することを目指している。つまり、SGLT1とSGLT2を両方抑えると、低血糖リスクが増大することから、体内暴露を低下させることで腎臓に発現するSGLT2への作用を減らし低血糖の副作用を抑制できると考えた。(Figure 5)



1 **2** **3**

Figure 5. 創薬戦略

化合物**2**のR^1にヒドロキシル基を導入すると化合物**1**(hSGLT1 IC_{50} = 26100 nM)と比較してSGLT1阻害活性が約6倍、R^2にメチル基を導入すると約35倍増強することが以前の研究（Table 1）から示唆されていたので組み合わせ合成を実施した。合成変換した化合物**14a**は、狙い通り強いSGLT1阻害活性（hSGLT1 IC_{50} = 162 nM）を示した。続いて、R^3部位の先に水溶性の側鎖を導入することを考え、最適なリンカーを探索したところアルコキシ基を有する化合物**14a**よりもアルキル基を有する化合物**14d**の方が強い阻害活性を持つことを見出した。(Figure 6)



1
hSGLT1 IC_{50} = 26100 nM

14a
hSGLT1 IC_{50} = 162 nM

14d
hSGLT1 IC_{50} = 32 nM

Figure 6

次に、細胞膜透過性を低減するため、膜透過性と関連する極性表面積（TPSA）（Å^2）を指標に加え合成展開を開始した[22]。直鎖タイプのアルキルリンカーの先に水溶性側鎖を導入することで、活性の減弱することなくTPSAの向上が可能かを検証することとした。**3**のR^4に水溶性の側鎖を導入したところ、SGLT1阻害活性を維持しつつTPSAの向上した化合物**22d**が得られたことから、この部位での最適化により、活性向上と膜透過性低減の両立が可能であることがわかった。次に、医薬品開発を行う上で非常に重要な合成コストの低減を視野に入れ、高価なチオグルコース部位を安価なグルコース部位に変換しても阻害活性が維持されるかを検証した。**22d**の硫黄原子を酸素原子に変換してもSGLT1阻害活性が維持したことから、グルコース部位を固定してR^4の側鎖の最適化を行った。最終的には、SGLT1阻害活性(hSGLT1 IC_{50} = 28 nM)と高いTPSAを両立した化合物**30b**を見出した。(Figure 7)

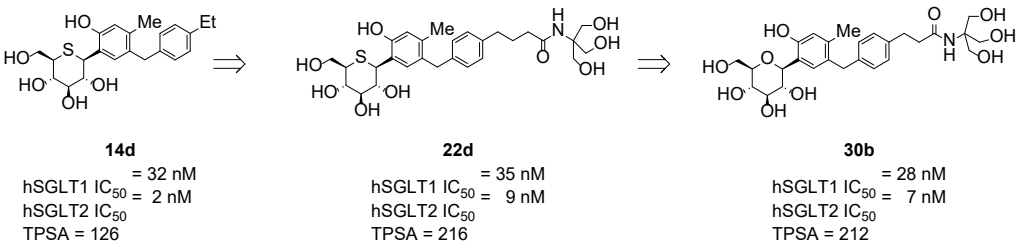


Figure 7

次に、**30b** の低吸収性を検証するためにSDラットを用いたPK試験を実施した。この結果、**30b**は非常に低いバイオアベイラビリティ（F = 0.05%）を示した。また、膜透過性の評価に用いられるPAMPA試験[35]を実施したところ、低吸収性を示唆するデータが得られた。最後にSDラットを用いた糖負荷試験を実施し、0.1mg/kgから用量依存的に血中グルコース濃度を低下させることを確認した。これらの結果から、**30b**は新たな低吸収性の経口糖尿病治療薬となることが期待できる。

第 1 章で得られた**30b**は、安全性試験の結果から、意外にもわずかに吸収された化合物の腎臓残留性が確認され、低血糖などのリスクを高める可能性が懸念された。第 2 章では、腎臓残留性の低い低吸収性SGLT1阻害物質の創出について述べる。これまで、腎臓に残留する化合物の回避というのは報告例があまりないことから著者は次のような仮説を立てた。主に尿から排泄される**30b**とは排泄経路の異なるプロファイルを持つ化合物を創出することで達成できないかという仮説を立て研究を開始した。すなわち、胆汁から排泄される化合物を創出することで腎臓残留性が回避できるのではないかと考えた。そこで、**30b**の阻害活性及び低吸収性は維持しつつ、脂溶性を付与することで胆汁排泄型の化合物となるかを検証した。合成戦略としては、脂溶性パラメーターである*C*logP＞3.5、小腸からの吸収性の指標となるTPSA＞160を目標値とした[22,23,36]。直鎖リンカー部位は、脂溶性向上が見込める上にMizoroki-Heak反応を用いることで合成容易なジメチルブテン骨格を採用しベンゼン環上の置換基(化合物**31**のR^1、R^2、R^3)の最適化を実施した。その後、*C*logP及びTPSAを調整するために化合物**32**のR^4部位に水溶性側鎖を導入することを計画し研究を開始した。(Figure 8)

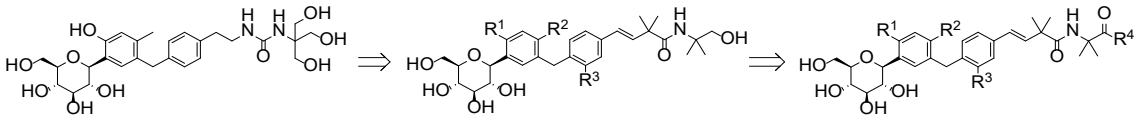


Figure 8. *C*logPとTPSAの両立を目指した創薬戦略

まず初めにR^1、R^2をメチル基で固定しR^3の置換基を探索したところ、嵩高い置換基を導入するとSGLT1阻害活性が減弱することがわかった。次に*C*logP向上を目指し、R^3は水素原子あるいはメチル基に固定した上で、R^1＝ヒドロキシ基、メトキシ基、およびR^2＝イソプロピル基を導入する組み合わせを探索したところ、いずれの組み合わせ（化合物**56f**、**56g**、**56h**）においても脂溶性が向上しSGLT1阻害活性も維持することがわかった。（Figure 9）

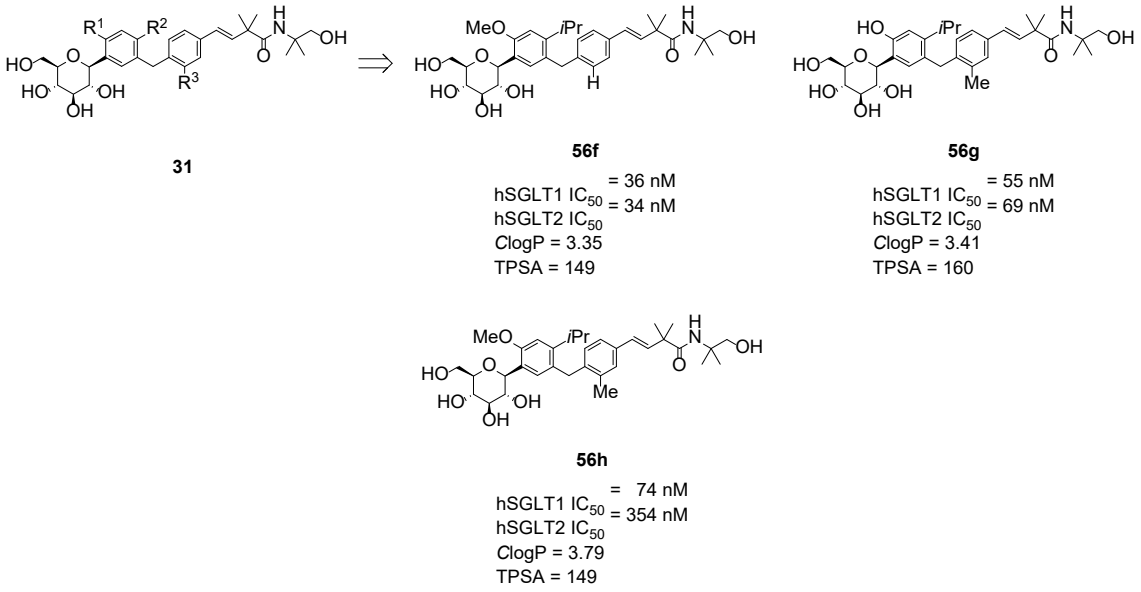


Figure 9

最後に低吸収性の指標となる*C*logP>3.5、TPSA>160を両立するために、側鎖の置換基を変換した。意外にも側鎖部位の許容性は広く、水溶性の高い側鎖を導入しても、全ての合成化合物のSGLT1阻害活性が維持された。その中で、目標プロファイルを満たす化合物**62d**、**62j**に絞り込んだ。（Figure 10）

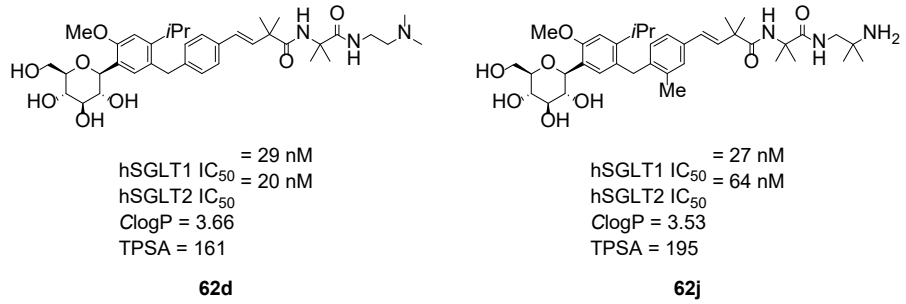


Figure 10

次に、化合物**62d**、**62j**のSDラットPK試験及びPAMPA試験を実施し低吸収性について検証した。ラットＰＫ試験において、化合物**62d**、**62j**はそれぞれバイオアベイラビリティ（以下BAと略す）が0.17%、0.09%と非常に低いことを確認し、PAMPA試験の結果からも膜透過性が非常に低いことが明らかとなった。続いて化合物**62d**、**62j**の排泄経路を調べるために、胆管にカニューレを挿入したラット（BDC SDラット）に静脈内投与をしたところ、狙い通り化合物**62d**、**62j**は主に胆汁を通して排泄されることが確認され、**30b**とは異なる排泄経路であることが確認できた。胆汁排泄タイプの化合物**62d**、**62j**の腎臓残留物特性を調査するために、SDラットへの静脈内投与後の腎臓における薬物濃度の時間経過を評価したところ、化合物**62d**、**62j**は、**30b**と比較して、腎臓での蓄積が急速に減少していることが確認された。これらの結果から本化合物クラスでは、3.5以上の*C*logP値が胆汁排泄につながり、それにより腎残留を回避できることが推察された。また、物性評価を行うと、化合物**62j**はいかなる検討でも結晶化せず非晶質であった。一方、化合物**62d**は容易にエタノールから再結晶できた。開発難易度を考慮し、化合物**62d**を開発化合物に選択し、SDラットを用いた糖負荷試験を実施したところ、0.3mg/kgから有意に血中グルコース濃度を低下させることを確認した。以上のことから、**62d**は低吸収性で腎残留性を回避した新たな経口糖尿病治療薬となることが期待できる。

本編第３章では、SGLT2に対して40倍以上の選択性を持つ選択的SGLT1阻害物質の創出について述べる。選択的SGLT1阻害物質の創出により、SGLT1が心保護作用にどのような影響を及ぼしているのか検証するためのツール化合物となることが期待できる。これまで化学的に安定な*C*-グリコシド誘導体によるSGLT1選択的阻害物質の報告はない上、リガンドとの共結晶なども報告がないことから、詳細にＳＡＲを取得していく必要があった。まず選択性のない化合物**63**をリード化合物として、化合物**64**のリンカーR^1部位を探索した後、ベンゼン環上の置換基R^2の最適化を実施した。最後に化合物**64**の末端側鎖R^3の変換により、選択性を獲得できるかどうかを検証した。(Figure 11)

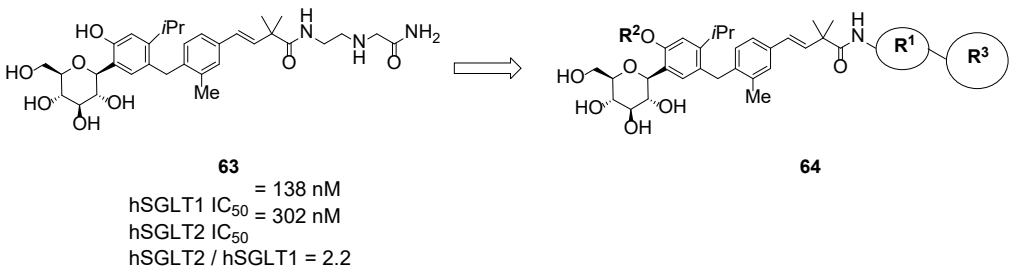


Figure 11. LBDDによる創薬戦略

化合物**64**のR^1部位の変換では、種々合成した中でジメチル基を導入した化合物**75**が最も高いSGLT1阻害選択性を示した。次に、化合物**75**のフェノール性ヒドロキシル基を変換した誘導体を合成したところ、メトキシ基を導入した化合物**92a**のSGLT1阻害選択性が向上することを見出した。(Figure 12)

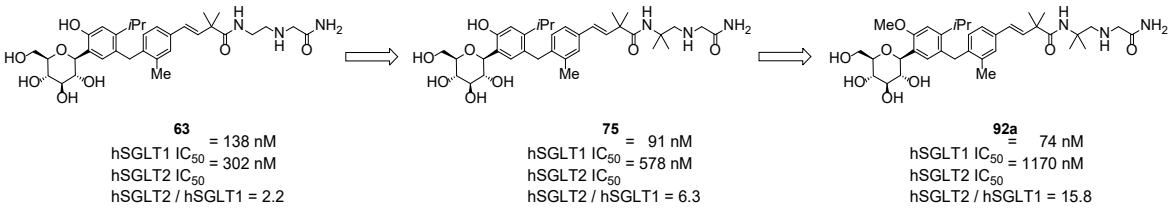
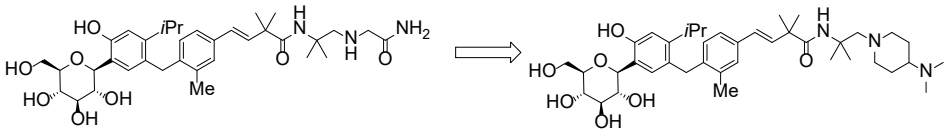


Figure 12.

最後に、還元的アミノ化により化合物**92a**の側鎖R^3を変換した化合物を種々合成したところ環状構造を持つ化合物**94j**がhSGLT1 IC_{50} = 26 nM、hSGLT2 IC_{50} = 1101 nM、hSGLT2 / hSGLT1 = 42.4を示し、高選択性の化合物を得ることに成功した。（Figure 13）今後このツール化合物を用い、例えば虚血再灌流誘発性心臓損傷モデルへの投与などにより心保護作用などの検証が可能となると考えられる。



92a
= 74 nM
hSGLT1 IC_{50} = 1170 nM
hSGLT2 IC_{50}
hSGLT2 / hSGLT1 = 15.8

94j
= 26 nM
hSGLT1 IC_{50} = 1101 nM
hSGLT2 IC_{50}
hSGLT2 / hSGLT1 = 42.4

Figure 13

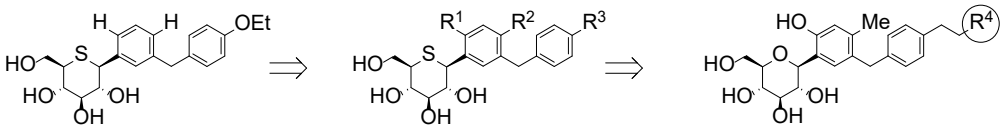
本論

第 1 章　経口投与可能なSGLT1阻害活性を有する新規*C*-グリコシド型誘導体の創出

第 1 節　リード化合物の課題と合成戦略

効率的な創薬を行う上で、近年一般的に用いられる手法としてはSBDDが挙げられる。つまり、X線結晶構造解析などから得られた標的タンパク質の3次元構造とリガンドの相互作用を可視化してドラッグデザインする手法である。しかし、ターゲットであるSGLT1は単結晶構造やリガンドとの共結晶などは報告されていないことからタンパク質の構造とリガンドとの相互作用を考察して創薬展開するSBDDは困難である。したがって、SBDD手法を用いることができない場合は、標的タンパク質と相互作用するリガンドの構造情報を基に創薬を行うことが試みられている。本研究もリガンドの変換部位に各種置換基を導入し、それらのSARを考察するLBDDの手法を用いて創薬展開することとした。著者が所属する大正製薬株式会社の医薬品であるルセオグリフロジンの創薬研究の際に得られていたSGLT2阻害化合物**1**をリード化合物として研究を開始した。化合物**1**の課題として、大きく2点考えられた。①SGLT1阻害活性が弱いこと。②膜透過性を有すること。SGLT1阻害活性については、SGLT2阻害薬の研究の中でサブタイプであるSGLT1阻害活性についても評価しており、化合物**2**のR^1、R^2部位に関するSARは取得していたので[15]、その知見を活用し最適化を実施することで解決可能と考えた。（Figure 5）2つ目の課題である膜透過性に関しては、これまでのSGLT2阻害薬の研究からR^3部位に親水性のスペースがあると予想し、そこに水溶性官能基を導入することで、膜透過性を低減できると考えた。その際、序論で示したように膜透過性と相関があるTPSAを指標とすることで活性とのバランスを考察することとした。最後に化合物 **3** のR^4部位の構造活性相関研究及び膜透過性について論じる。創薬戦略としては、

高活性且つ低吸収の化合物を創製し小腸上皮に発現しているSGLT1を選択的に阻害することを目指している。つまり、SGLT1とSGLT2を両方抑えると、低血糖リスクが増大することから、体内暴露を低下させることで腎臓に発現するSGLT2に対する阻害を減らし低血糖の副作用を抑制できると考えた。(Figure 14)

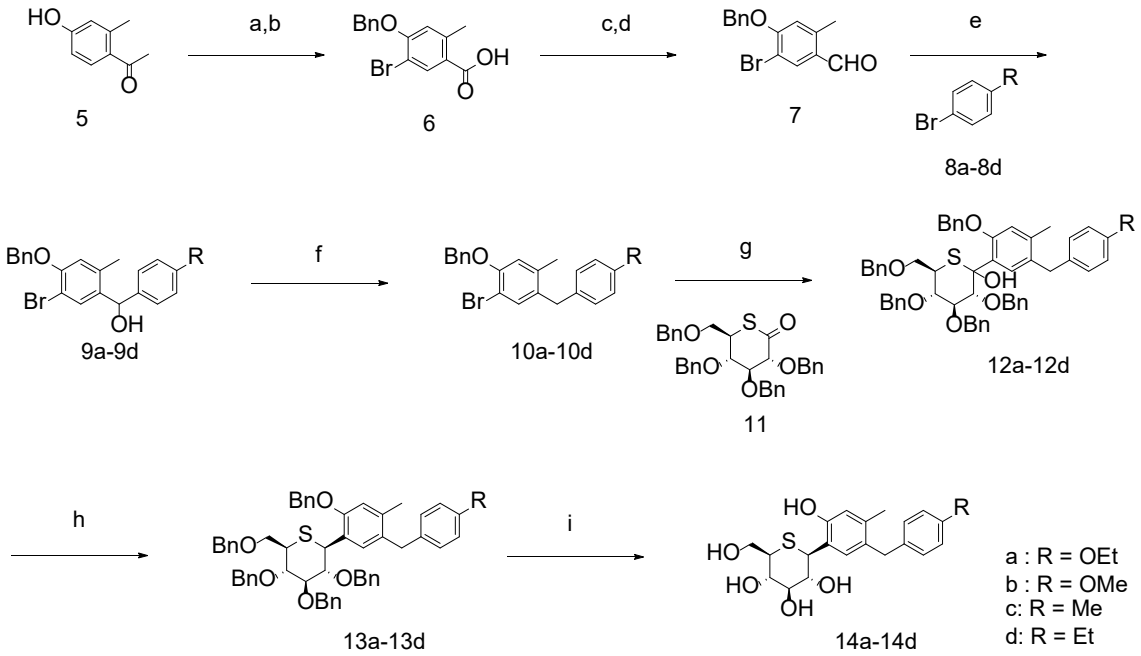


1 **2** **3**

Figure 14

第２節　新規*C*-グリコシド型誘導体の合成と構造活性相関

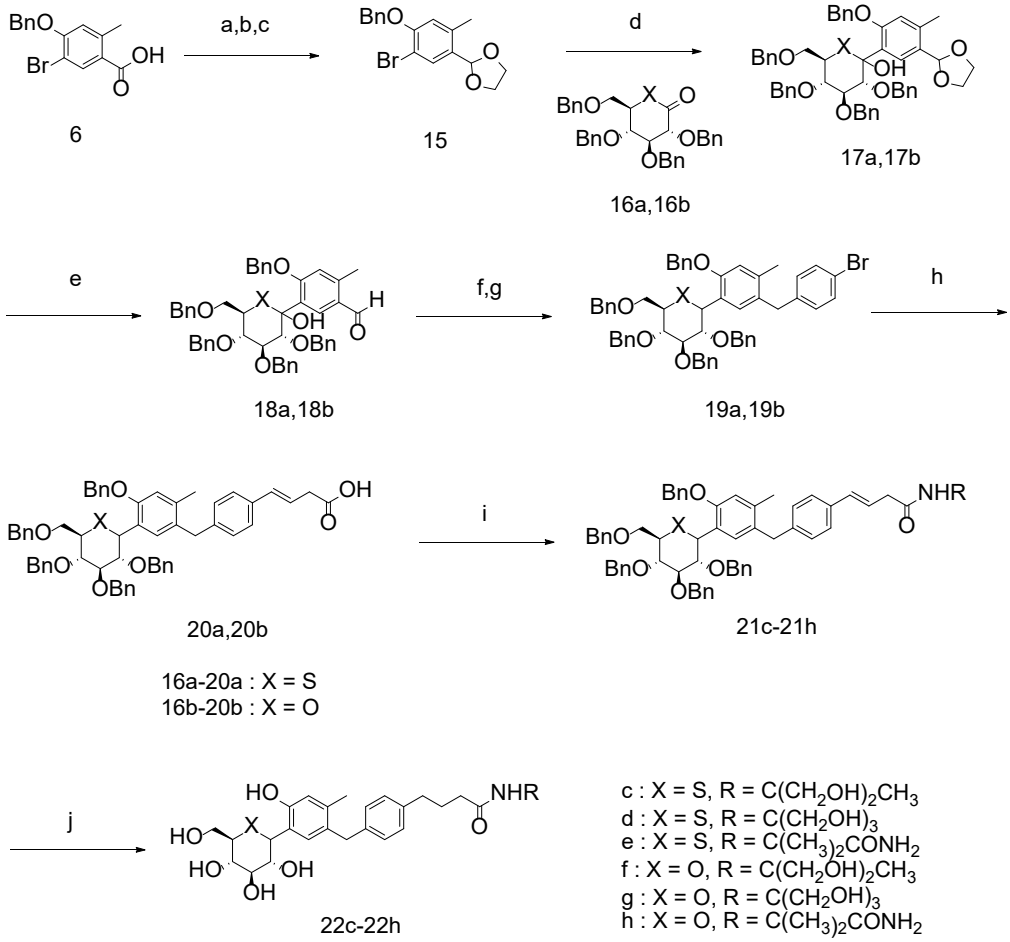
化合物**1**及び化合物**2**のR^2にメチル基を導入した**4a**(R^1=H, R^3=OEt)とR^1にヒドロキシル基を導入した**4b**(R^2=H, R^3=OEt)の合成法に関しては、ルセオグリフロジンの創薬研究の際にすでに報告されている[15]。化合物**2**のR^1にヒドロキシル基、R^2にメチル基を導入した誘導体**14a**－**14d**の合成では、市販の4-ヒドロキシ-2-メチル-アセトフェノン（**5**）と臭化ベンジルを使用してベンジル基で保護し、次にOXONE®の存在下でNaBrを使用して酸化的臭素化して**6**を合成した。カルボン酸**6**は、Weinrebアミドを経由した後、水素化リチウムアルミニウム還元によりアルデヒド**7**に変換した。市販の**8a**－**8d**のハロゲンリチウム交換後、**7**と1,2-付加させることで**9a**－**9d**へと導いた。**9a**－**9d**に対しトリエチルシランおよび三フッ化ホウ素ジエチルエーテラートを使用したヒドロキシル基の還元的除去を行い、アグリコン**10a**－**10d**を生成した。**12a**－**12d**は、既知の合成法[15]に従って合成したチオラクトン**11**を、アグリコン**10a**－**10d**とマグネシウム粉末から調製したグリニャール試薬のTHF溶液に加えることで得られた。得られた**12a-12d**のヒドロキシル基を還元して、選択的にβ-*C*-グルコシド化合物**13a**－**13d**を得た[37]。最後に、水素雰囲気下で水酸化パラジウムを用いた加水素分解により、**13a**－**13d**のベンジル基を除去し、**14a**－**14d**を得た。



Scheme 1. (a) BnBr, K_2CO_3, TBAI, DMF, rt; (b) NaBr, OXONE®, acetone-H_2O, rt, 59% in 2 steps; (c) $(COCl)_2$, DMF (cat.), $CHCl_3$, rt, then *N*-methoxy-*N*-methylamine hydrochloride, Et_3N, rt; (d) $LiAlH_4$, THF, 0˚C, 65% in 2 steps; (e) **8a-8d**, *n*-BuLi, THF, -78˚C, then **7**; (f) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, 0˚C; (g) Mg, THF; (h) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, -15˚C; (i) $Pd(OH)_2/H_2$, EtOH, rt.

化合物**3**のR[4]部位を変換した*C*-フェニル1-チオ-D-グルシトール誘導体**22c**－**22h**の合成をスキーム2に示す。化合物**6**からScheme 1に記載と同様の条件で合成した中間体**7**に対し酸性条件下でエチレングリコールを使用してアセタール保護し、化合物**6**からonepotでアセタール**15**を合成した。アセタール**15**と*n*-BuLiから調製されたリチウム試薬に対し、チオラクトン**16a**または市販のラクトン**16b**を付加させることで**17a**、**17b**が得られた。**17a**および**17b**のアセタール基を除去し、それぞれアルデヒド**18a**および**18b**を得た。1,4-ジブロモベンゼンに対し、*n*-BuLiを加えモノリチオ化した後、アルデヒド**18a**および**18b**に付加した。続いてアノマー位のヒドロキシル基を還元的除去し、β選択的にそれぞれ**19a**および**19b**を得た[37]。マイクロ波照射下での**19a**および**19b**とビニル酢酸とMizoroki-Heck反応によりC-C結合を構築し、それぞれ**20a**および**20b**へと導いた。**21c**－**21h**は、WSCI・HClを使用して**20a**および**20b**と対応するアミンを縮合することにより得られた。最後に、スキーム1の**14a**－**14d**の合

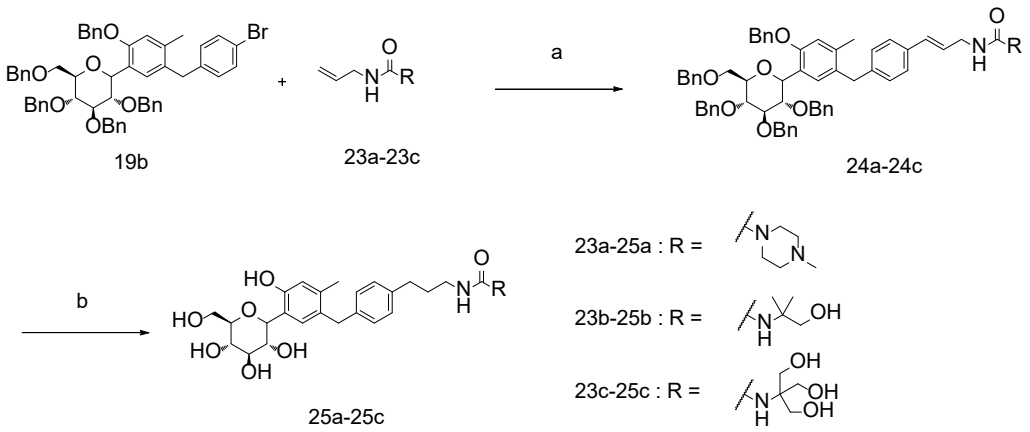
成と同様の条件下で、**21c**－**21h**のベンジル基の除去と二重結合の還元を同時に行い、目的の生成物**22c**－**22h**を得た。



Scheme 2. (a) $(COCl)_2$, DMF(cat.), $CHCl_3$, rt, then *N*-methoxy-*N*-methylamine hydrochloride, Et_3N, rt ; (b) $LiAlH_4$, THF, 0˚C; (c) *p*-TsOH, ethylene glycol, PhMe, reflux, 78% in 3 steps; (d) *n*-BuLi, THF, -78˚C, then **16a**,**16b**, 73-87%; (e) 6M HCl, THF, quant.; (f) 1,4-dibromobenzene, *n*-BuLi, THF, -78˚C; (g) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, 0˚C, 20-23% in 2 steps; (h) 3-Butenoic acid, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, 120˚C, 60-87%; (i) amine, WSCI·HCl, HOBt·H_2O, $CHCl_3$, rt; (j) $Pd(OH)_2/H_2$, EtOH, rt, 20-42% in 2 steps.

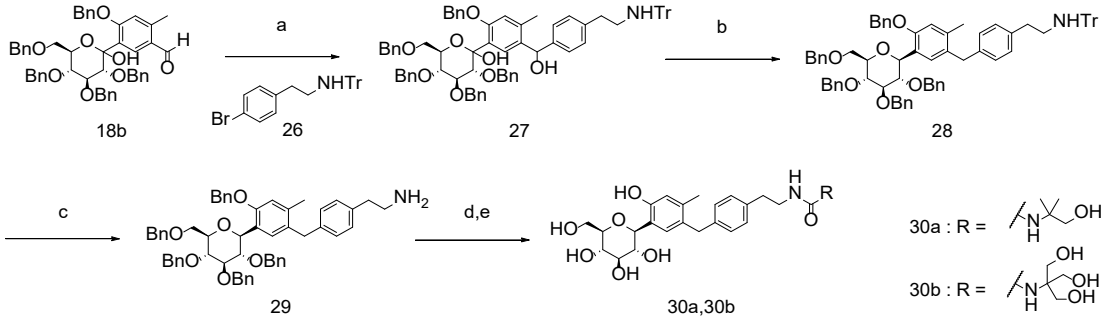
スキーム3は、ウレア結合を持つ化合物**25a**－**25c**の合成を示す。**19b**とアリール尿素誘導体**23a**－**23c**のMizoroki-Heck反応により、**24a**－**24c**へと導いた。**24a**－**24c**のベンジル基の除去と二重結合の還元は、スキーム1の**14a**－**14d**の合成と同様の条件下で行い、目的の生成物

25a－25cを得た。



Scheme 3. (a) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, 120˚C; (b) $Pd(OH)_2/H_2$, EtOH, rt, 20-54% in 2 steps.

スキーム4は、リンカーの炭素原子１つ短くしたウレア結合を有する化合物**30a**および**30b**の合成を示す。 化合物**27**は、**26**と*n*-BuLiから調製されたアリールリチウムに**18b**を加えることにより得た。**27**のベンジル位のヒドロキシル基とアノマー位のヒドロキシル基を同時に還元し、*β-C*-グルコシド**28**を得た。続いて、酸性条件下で**28**のトリチル基の除去を行って**29**を得た。**30a**と**30b**は、**29**と対応するアミンとウレア結合を構築した後、スキーム1の**14a**－**14d**の合成と同様の条件下で行いベンジル基を除去することにより合成した。

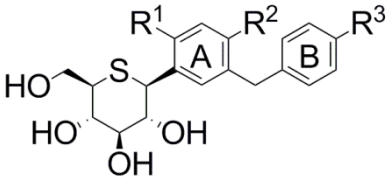


Scheme 4. (a) **26**, *n*-BuLi, THF, then **18b**, -78˚C, 64%; (b) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, 0˚C, 59%; (c) TFA, rt, quant.; (d) *p*-nitrophenyl chloroformate, pyridine, rt; (e) $Pd(OH)_2/H_2$, MeOH, rt, 38-55% in 2 steps.

化合物**1**、**4a**、**4b**及び合成した**14a**－**14d**のSGLT1、SGLT2阻害活性試験の結果及びTPSAをTable 2に示す。TPSAは膜透過と相関があると報告されており[30]、小腸での吸収を予測するのに最適であると考えた。実際、Tianらは、TPSA < 160 $Å^2$ and log P > −2.2でBAが良好となるとの相関を示していることから[22]、低吸収性を付与するためにTPSA>160 $Å^2$を目標値として設定した。また、TPSAはソフトウェア(ACD/ Percepta, version 2015, Advanced Chemistry Development, Inc.)を使用し簡便に算出できることも利点として挙げられる。化合物**1**のR^1にヒドロキシル基を導入すると化合物**1**(hSGLT1 IC_{50} = 26100 nM)と比較して活性が約6倍(**4b**)、R^2にメチル基を導入すると約35倍(**4a**)、SGLT1阻害活性が増強することが以前の研究から示唆されていた。化合物**14a**は、狙い通り強いSGLT1阻害活性 (hSGLT1 IC_{50} = 162 nM) を示した。次に、B環のR^3のアルキル基とアルコキシ基で置換された化合物**14b**－**14d**のSARを比較した。アルキル基を導入した**14c**、**14d**は、アルコキシ基を有する**14a**、**14b**よりもSGLT1阻害活性が強いことがわかった。この結果から、B環のパラ位には２～３炭素からなるアルキル基が許容されることが示唆された。そこで、R^3のアルキルリンカーの先に水溶性側鎖を導入することで、活性の減弱することなくTPSAの向上が可能かを次に検証することとした。

Table 2

化合物 **1**、**4a**、**4b**、**14a** － **14d** の SGLT1/SGLT2 阻害活性と TPSA



Cpd.	R^1	R^2	R^3	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	TPSA[b]
1	H	H	OEt	26100[c]	73.6	115
4a	H	Me	OEt	671[c]	2.29	115
4b	OH	H	OEt	4040[c]	17.4	136
14a	OH	Me	OEt	162	3	136
14b	OH	Me	OMe	65	NT[d]	136
14c	OH	Me	Me	25	2	126
14d	OH	Me	Et	32[c]	2	126

[a] IC_{50} values for hSGLT1 and hSGLT2 activities represent the mean values of at least two experiments.

[b] The TPSA value was calculated using software from ACD/ Percepta, version 2015, Advanced Chemistry Development, Inc.

[c] 0.1 mM methyl-α-D-glucopyranoside containing [^{14}C] methyl-α-D-glucopyranoside.

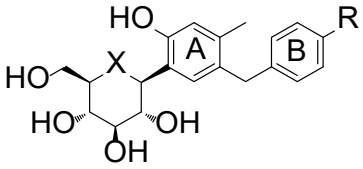
[d] Not tested.

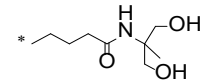
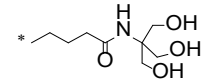
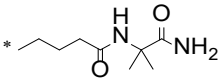
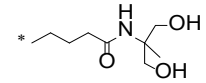
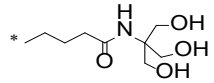
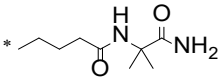
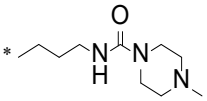
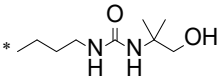
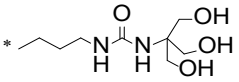
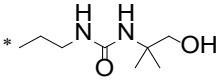
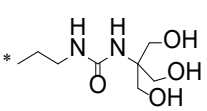
R^3に水溶性官能基を有するアルキル鎖を導入することで、低吸収性化合物が得られることを期待して合成した**22c**－**22h**、**25a**－**25c**、**30a**、**30b**のSGLT1、SGLT2阻害活性試験の結果及びTPSAをTable 3に示す。TPSAを増加させることを目的とし、水溶性の高いアミドを直鎖アルキルリンカーに導入した化合物**22c**、**22d**、**22e**は、SGLT1阻害活性を維持しながら、TPSAを増加させた。次に開発を見据え合成難易度を低減するために、中間体**11**がD-グルクロノ-3,6-ラクトンから14段階の合成を行う5-チオ-グルコース構造ではなく、グルコース構造に変換してもSGLT1阻害活性が維持するかを確認した。その結果、グルコースに変換し

た誘導体**22f**、**22g**、**22h**のSGLT1阻害活性は、チオグルコースを有する**22c**、**22d**、**22e**と同等であることが確認できた。さらに、TPSAの増大を狙いウレア結合の先に水溶性官能基を導入した誘導体**25b**および**25c**は、SGLT1阻害活性が減弱した。また、塩基性メチルピペラジンを含む**25a**は、SGLT1阻害活性が大きく減弱することがわかった。しかし、ベンゼン環から水溶性官能基までの距離を**22g**と合わせるため、**25b**及び**25c**よりも1本の炭素鎖が短くなった尿素誘導体**30a**、**30b**を合成したところ、これらの化合物は、アミド誘導体と同じ阻害活性を示した。この中で、化合物**30b**は、強力なSGLT1阻害活性（IC_{50} = 28 nM）と高いTPSA(212.2 $Å^2$)を有することから仮説を検証するためin vivo 動態試験、薬理試験を実施することとした。

Table 3

化合物 **22c**－**22h**、**25a**－**25c**、**30a**、**30b** の SGLT1/SGLT2 阻害活性と TPSA



Cpd.	X	R	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	TPSA[b]
22c	S		22	5	196.01
22d	S		35	9	216.24
22e	S		47	4	198.64
22f	O		32	NT[c]	179.94
22g	O		35	NT[c]	200.17
22h	O		51	7	182.57
25a	O		704	5	145.96
25b	O		65	5	171.74
25c	O		175	7	212.2
30a	O		51	4	171.74
30b	O		28	7	212.2

[a] IC_{50} values for hSGLT1 and hSGLT2 activities represent the mean values of at least two experiments.

[b] The ClogP value was calculated using software from Daylight Chemical Information Systems, Inc.

[c] Not tested.

第３節　新規*C*-グリコシド型誘導体のラットin vivo薬物動態試験及びラットin vivo薬効試験

化合物**30b**の有効性と小腸からの低吸収性を期待して、SDラットを用いた薬物動態（PK）と膜透過性を評価するためにPAMPA試験を実施した。その結果をTable 4に示す。クリアランス（CL_{total}）、分布体積（Vd_{ss}）、および化合物**30b**の単回静脈内投与後の消失半減期（$t_{1/2}$）は、それぞれ1080 mL/h/kg、439 mL/kg、0.362時間であった。また、化合物**30b**（1 mg/kg）の経口投与後の最大濃度（C_{max}）は1.46 ng/mLで、バイオアベイラビリティ（F）は0.05%であった。次に、PAMPAの結果は（0.3×10^{-6} cm/s）であり低い膜透過性が示唆された。ラットPK試験及びPAMPA試験の結果から、化合物**30b**が低い吸収性を有することを確認することができた。

Table 4

Pharmacokinetic parameters in SD rats and permeability of **30b**

Compound	Pharmacokinetic parameters						Permeability
	IV (2 mg/kg)[a]			PO (1 mg/kg)[b]			PAMPA
	CL_{total}	Vd_{ss}	$t_{1/2}$	C_{max}	T_{max}	F	at pH7.4
	(mL/h/kg)	(mL/kg)	(h)	(ng/mL)	(h)	(%)	($\times 10^{-6}$ cm/s)
30b	1080	439	0.362	1.46	0.25	0.05	0.3

[a] Dosing vehicle: saline

[b] Dosing vehicle: 0.5% CMC Na

The PK parameters were calculated using the mean value of the plasma concentration in three animals at each point.

次に、SDラットを用いた経口ブドウ糖負荷試験（oGTT）を実施し、**30b**の血糖低下効果を評価した。グルコース負荷の直前に化合物**30b**を経口投与し、次に血漿グルコース濃度を

2時間にわたって測定したところ、期待通りにグルコースの低下作用を確認できた。Vehicle投与と比較したグルコース濃度の低下作用（0～2時間のΔAUC）は、0.1、0.3、1 mg/kgでそれぞれ31.5%、58.5%、62.2%であり、用量依存的に血糖低下作用が増加することを明らかにした（Figure . 15）。さらに、0.1または0.3 mg/kgの用量で1日2回、**30b**を4日間繰り返し投与した後、5日目にブドウ糖を皮下投与したところ、尿中グルコース排泄がないことを確認した。また、1 mg/kgの用量を1日2回投与したところわずかに尿糖排泄が見られたが、0.5%CMC(カルボキシメチルセルロース)対照と比較して有意ではなかった。まとめると、これらの結果は、化合物**30b**が0.1および0.3 mg/kgの用量で投与された場合に、消化管でのみSGLT1の阻害を通じてその血糖低下作用を発揮したことを示唆している。一方、高用量群で1 mg/kgの用量を1日2回投与すると、わずかに尿糖排泄が確認されたことから、**30b**がいくらか吸収され腎尿細管でのSGLT2の活性が阻害された可能性があると考えられた。

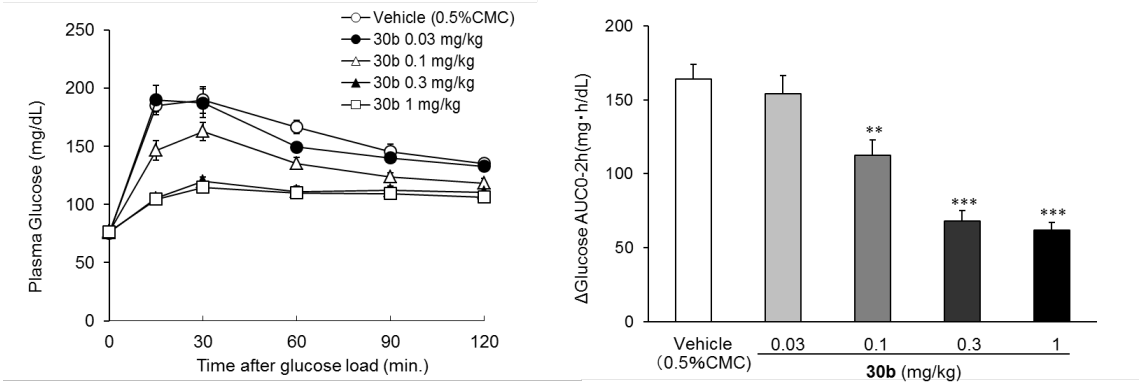


Figure 15. Effects of oral administration of **30b** (0.03, 0.1, 0.3, or 1 mg/kg) on plasma glucose during an oGTT in SD rats. Each point represents the mean ± SE. ***P* < 0.01, ****P* < 0.001 vs. Vehicle group, Dunnett's test.(n=8)

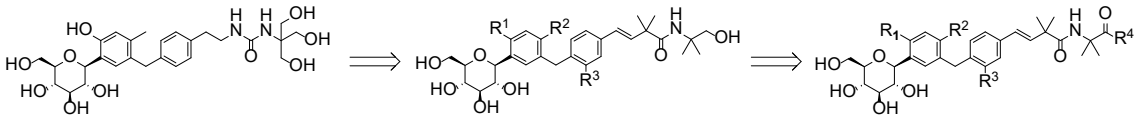
第 4 節　小括

SGLT2研究の際に得られた化合物**1**からベンゼン環上の置換基変換により、SGLT1阻害活性の向上した化合物**14d**を得た。次に低吸収性を付与するために側鎖に水溶性置換基の導入し、同時に開発難易度の観点からチオグルコース部位をグルコースに変換し、高いTPSAと強いSGLT1阻害活性を有する化合物**30b**を見出した。化合物**30b**は、ラットPK試験により低いBAが確認され、PAMPA試験の結果からも低吸収性化合物であることを確認した。最後にラット糖負荷試験により、**30b**が0.1 mg/kgから用量依存的に糖吸収を抑制することを明らかとした。

第２章　腎臓残留性を低減したSGLT1阻害活性を有する新規*C*-グリコシド型誘導体の創出

第１節　化合物**30b**の課題と合成戦略

第１章で述べたように**30b**は、安全性試験の結果から、高容量（1 mg/kg、2回/１日）を投与した際にわずかに吸収され腎臓残留性が確認された。**30b**は、SGLT2に対しても強い阻害活性を有することから、腎臓に残留した場合、SGLT1及びSGLT2を阻害することで低血糖などのリスクを高める可能性が懸念された。そのような経緯から本章では、腎臓残留性の低い低吸収SGLT1阻害物質の創出について述べる。これまで、低吸収性化合物において腎臓に残留する化合物の回避という報告例がないことから著者は次のような仮説を立てた。**30b**が残留している腎臓から尿へ排泄されることから、腎臓残留性を回避するには排泄経路の異なるプロファイルを有する化合物を創出することで達成できないかという仮説を立て研究を開始した。すなわち、主に尿から排泄される**30b**とは異なり、胆汁から排泄される低吸収化合物を創出することで腎臓残留性が回避できると考えた。一般的に、水溶性の高い化合物は尿排泄となり、脂溶性の高い化合物は胆汁排泄となる傾向があることは知られている。そこで**30b**（*C*logP = 1.57, TPSA = 212）の阻害活性及び低吸収性は維持しつつ、脂溶性を増加させることで胆汁排泄型の化合物となるかを検証した。合成戦略としては、脂溶性パラメーターである*C*logP＞3.5、膜透過性の指標となるTPSA＞160を目標値として誘導体展開に着手した。直鎖リンカー部位は、脂溶性向上が見込める上にMizoroki-Heak反応を用いることで合成容易なジメチルブテン骨格を採用し、ベンゼン環上の置換基(化合物**31**のR^1、R^2、R^3)の最適化を実施した。その後、*C*logP及びTPSAを調整するために化合物**32**のR^4部位に水溶性側鎖を導入することを計画し研究を開始した。(Figure　g 16)

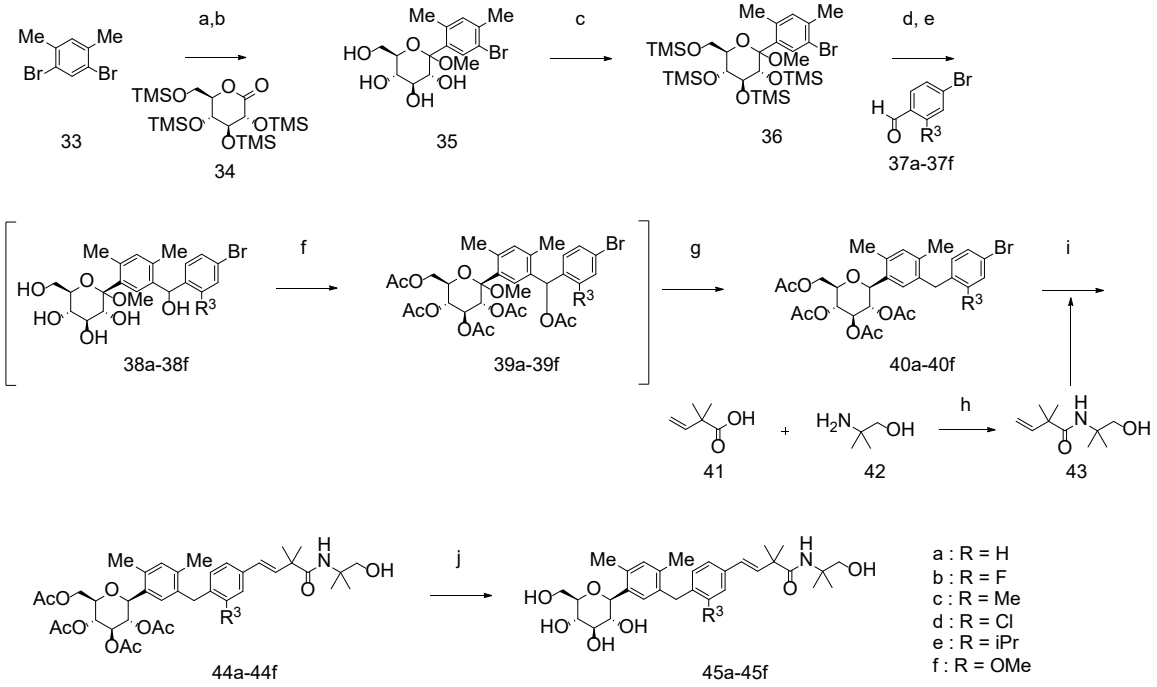


30b 31 32

Figure 16

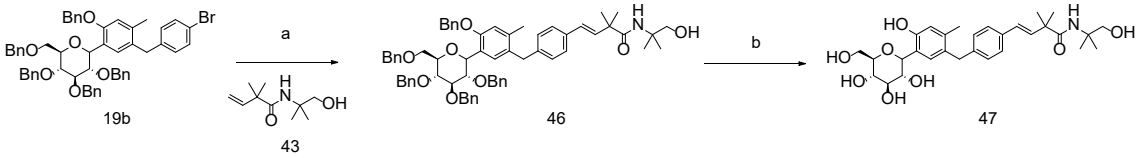
第２節　*C*-フェニル-D-グルシトール誘導体の合成及び構造活性相関

化合物**31**のR^1=Me、R^2=Meに固定しR^3部位の変換を行った*C*-フェニル-D-グルシトール誘導体**45a**－**45f**の合成をスキーム5に示す。市販の5-ジブロモ-2,4-ジメチルベンゼン（**33**）と*n*-BuLi から調製したリチウム試薬にラクトン**34**を添加した後、酸性条件下でメチルグルコシル化し化合物**35**を得た。**35**のヒドロキシル基をトリメチルシリル基で再保護して**36**を得た。**36**と*n*-BuLiから調製したリチウム試薬に市販のアルデヒド**37a**－**37f**を加え、酸性条件でトリメチルシリル基を除去して、粗中間体**38a**－**38f**を得た。得られた**38a**－**38f**のヒドロキシル基は、塩基性条件下で無水酢酸を使用してアセチル基で保護し、粗中間体**39a**－**39f**を合成した。化合物**39a**－**39f**のメチルグルコシドおよびベンジル位のアセトキシ基の還元には、前述の通りトリエチルシランおよび三フッ化ホウ素ジエチルエーテラートを用い、立体選択的にアリールβ-*C*-グルコシド**40a**-**40f**を得た。続いて、水溶性カルボジイミド塩酸塩（WSCI・HCl）を使用して**41**と**42**を縮合することにより得られた化合物**43**をマイクロ波照射下で**40a**－**40f**とMizoroki-Heck反応[38,39]させることにより**44a**－**44f**へと導いた。最後に、**44a**－**44f**のアセチル基をZemplén脱アセチル化反応により除去し、**45a**-**45f**を得た。



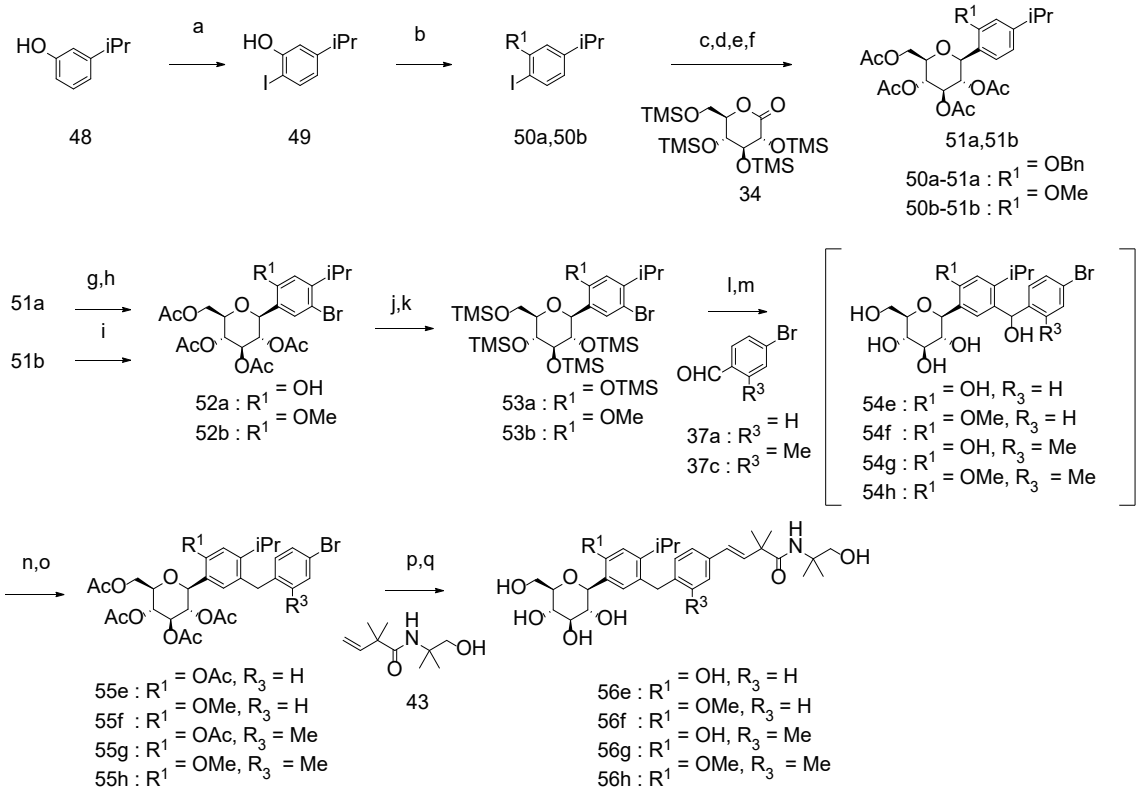
Scheme 5. (a) *n*-BuLi, THF, –78 ˚C, then **34**; (b) MsOH, MeOH, rt, 64% in 2 steps; (c) TMSCl, Et_3N, DMF, rt, 96% ; (d) *n*-BuLi, THF, –78 ˚C, then **37a–37f** ; (e) MsOH, MeOH, rt ; (f) Ac_2O, pyridine, rt ; (g) Et_3SiH, $BF_3{\cdot}OEt_2$, $CH_3CN/CHCl_3$, 37%-85% in 4 steps; (h) WSCI·HCl, $HOBt{\cdot}H_2O$, $CHCl_3$, rt, 51%; (i) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, **43**, DMF or MeCN, 120 ˚C, 36-87%; (j) NaOMe, MeOH, rt, 59-78%.

化合物**31**のR^1のメチル基をヒドロキシル基に変換した*C*-フェニル-D-グルシトール誘導体誘導体**47**の合成をスキーム6に示す。第 1 章で合成した化合物**19b**と**43**のMizoroki-Heck反応を行い、化合物**46**を得た。続いて、**46**のベンジル基をエタンチオールと三フッ化ホウ素ジエチルエーテラートで除去し**47**を合成した。



Scheme 6. (a) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, 120 ˚C, 72%; (b) EtSH, $BF_3{\cdot}OEt_2$, $CHCl_3$, rt, 4%.

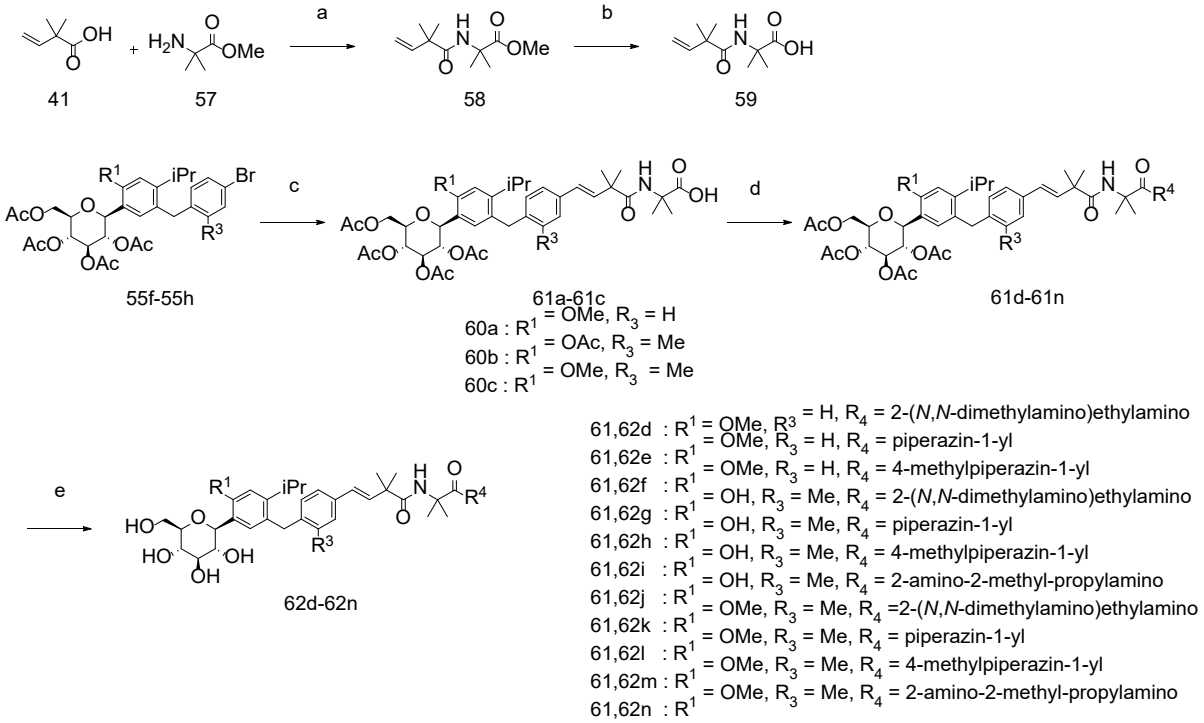
化合物**31**のR^2=*i*Prに固定しR^1及びR^3部位の変換を行った*C*-フェニル-D-グルシトール誘導体**56e**－**56h**の合成をスキーム7に示す。まず初めに、酸性の条件下で市販の3-イソプロピルフェノール（**48**）をヨウ化カリウムとヨウ素を用いてフェノール性ヒドロキシル基のオルト位をヨウ素化し、化合物**49**を得た。塩基性条件下でハロゲン化アルキルを使用して、化合物**49**のフェノール性ヒドロキシル基をベンジルエーテル基またはメチルエーテル基とし、**50a**および**50b**を得た。得られた**50a**または**50b**と*n*-BuLiから調製したリチウム試薬にラクトン**34**を加え、トリメチルシリル基を酸性条件下で除去して、同時にアノマー位のヒドロキシル基をメトキシ基に変換した。次に、脱保護されたヒドロキシル基を、塩基性条件下で無水酢酸を使用してアセチル基で保護し、続いてトリエチルシランと三フッ化ホウ素ジエチルエーテラートを用いてメチルグルコシドを還元し、立体選択的にアリールβ-*C*-グルコシド**51a**または**51b**を合成した[37]。**51a**のベンジル基の脱保護および芳香環の臭素化により、**52a**を得た。また、**51b**に対しても芳香環の臭素化により**52b**を得た。続いて、**52a**と**52b**のアセチル基をメタノール水中のトリメチルアミンを使用して除去し、塩基性条件下でトリメチルシリルクロリドを用いてヒドロキシル基を保護し、**53a**、**53b**を得た。化合物**54e**－**54h**は、アルデヒド**37a**または**37c**を**53a**または**53b**と*n*-BuLiから調製されたリチウム試薬に添加した後、トリメチルシリル基を酸性条件下で脱保護することで得た。得られた**54e**－**54h**のヒドロキシル基を塩基性条件下で無水酢酸を使用してアセチル基で保護し、ベンジル位のアセトキシ基は、トリエチルシランと三フッ化ホウ素ジエチルエーテラートを使用して還元し、**55e**－**55h**へと導いた。最後に、**55e**－**55h**から**56e**－**56h**への変換は、スキーム5で**45a**－**45f**を合成したと同様の方法で行った。



Scheme 7. (a) KI, I_2, H_2O, AcOH, rt, 57%; (b) BnBr or MeI, K_2CO_3, MeCN, rt, 85%; (c) *n*-BuLi, THF, –78 ˚C, then **34**; (d) MsOH, MeOH, rt; (e) Ac_2O, pyridine, 4-(dimethylamino)pyridine, rt ; (f) Et_3SiH, $BF_3{\cdot}OEt_2$, $CH_3CN/CHCl_3$, 4 ˚C, 40%-59% in 4 steps; (g) 10%Pd–C, H_2, MeOH, rt; (h) Br_2, AcOH, rt, 52% in 2 steps; (i) Br_2, AcOH, rt, 96%; (j) Et_3N, $MeOH/H_2O$, 50 ˚C or NaOMe, MeOH, rt; (k) TMSCl, Et_3N, DMF, 4 ˚C ; (l) *n*-BuLi, THF, –78 ˚C, then **37a** or **37c**; (m) MsOH, MeOH, rt ; (n) Ac_2O, pyridine, rt ; (o) Et_3SiH, BF_3OEt_2, $CH_3CN/CHCl_3$, 4 ˚C, 34-53% in 4 steps; (p) **43**, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, CH_3CN, 120 ˚C; (q) NaOMe, MeOH, rt, 38-54% in 2 steps.

化合物**32**のR[4]部位の変換を行った*C*-フェニルD-グルシトール誘導体**62d–62n**の合成をスキーム8に示す。市販の化合物**41**を酸塩化物に誘導し、市販の化合物**57**を反応させることで化合物**58**を得た。得られたメチルエステル**58**を加水分解して、カルボン酸**59**へと導いた。次にマイクロ波照射下でカルボン酸**59**と**55f**－**55h**とMizoroki-Heck反応させることにより**60a**－**60c**へと導いた。**60a**－**60c**と対応するアミンをWSCI・HClまたはカルボニルジイミダゾール（CDI）を使用して縮合することにより**61d**－**61n**を得た。 最後に、ナトリウムメトキシ

ドを使用して**61d**－**61n**のアセチル基を除去し、目的の生成物**62d**－**62h**を得た。



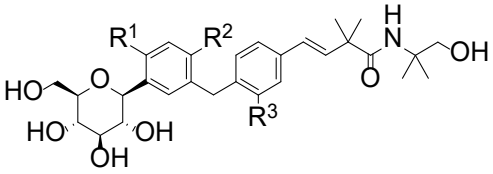
Scheme 8. (a) $(COCl)_2$, DMF(cat.), $CHCl_3$, rt, then Et_3N, **57**, 93%; (b) aq.NaOH, MeOH, rt, 94%; (c) **59**, $Pd(OAc)_2$, $(tolyl)_3P$, Et_3N, CH_3CN, 120˚C, 60-87%; (d) WSCI·HCl, HOBt·H_2O, amines, $CHCl_3$, rt or CDI, $CHCl_3$, rt, 21-99%; (e) NaOMe, MeOH, rt or Et_3N, H_2O, MeOH, rt, 47-98%.

化合物**45a**－**45f**及び**47**、**56e**－**56h**のSGLT1、SGLT2阻害活性試験の結果及び*C*logP、TPSAをTable 5に示す。最初に、SGLT1阻害活性と親油性への影響を調査するために、R^1、R^2、およびR^3にさまざまな置換基を持つ化合物を評価した。R^1とR^2をメチル基に固定した上で、R^3の置換基のを最適化するために、脂溶性の向上を期待した側鎖を導入した**45a**－**45f**を比較した。R^3部位のSARとしては、置換基が嵩高くなるにつれてSGLT1阻害活性が減弱する傾向があり、R^3がプロトンの**45a**が最も活性が強いことがわかった。また、脂溶性の高い側鎖を導入したことで*C*logPは向上したが、TPSAに関してはさらなる向上が必要であった。R^3をプロトン基に固定し、第１章で得られた知見を基にR^1には水溶性官能基（ヒドロキシル

基またはメトキシ基）を導入し、R^2には脂溶性官能基（メチル基またはイソプロピル基）を導入した。R^1にヒドロキシル基を導入すると、TPSAは**45a**に比べて増加し、幸いなことに、化合物**47**は**45a**と同じSGLT1阻害活性を持っていた。**47**の*C*logPが目標の*C*logP >3.5よりも低いため、親油性を高める置換基をR^2およびR^3に導入した（**56e**－**56h**）。R^2にイソプロピル基を導入した誘導体**56e**－**56h**は、**47**と比較してより高い*C*logP値を示し、SGLT1阻害活性（21 nM–74 nM）も維持することがわかった。

Table 5

化合物**45a**－**45f**及び**47**、**56e**－**56h**のSGLT1/SGLT2阻害活性及び*C*logPとTPSA



Cpd.	R^1	R^2	R^3	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	*C*logP[b]	TPSA[c] (Å^2)
45a	Me	Me	H	22	10	3.35	139
45b	Me	Me	F	34	17	3.49	139
45c	Me	Me	Me	111	84	3.80	139
45d	Me	Me	Cl	176	NT[d]	4.06	139
45e	Me	Me	iPr	12531	2126	4.72	139
45f	Me	Me	OMe	1166	798	3.27	149
47	OH	Me	H	21	NT[d]	2.18	160
56e	OH	iPr	H	23	19	2.96	160
56f	OMe	iPr	H	36	34	3.35	149
56g	OH	iPr	Me	55	69	3.41	160
56h	OMe	iPr	Me	74	354	3.79	149

[a] The IC_{50} values for the hSGLT1 and hSGLT2 activities represent the mean values of at least two experiments.

[b] The *C*logP value was calculated using software from Daylight Chemical Information Systems, Inc.

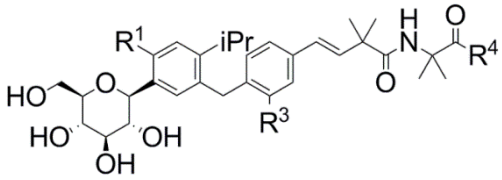
[c] The TPSA value was calculated using software from ACD/Percepta, version 2015, Advanced Chemistry Development, Inc.

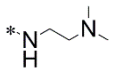
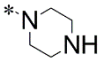
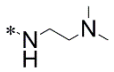
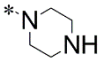
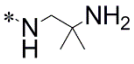
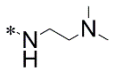
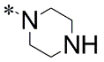
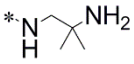
[d] Not tested.

次に、**56f**－**56h**の側鎖の変換（R^4）に焦点を当てて、*C*logP >3.5、TPSA >160Åを満たすべく最適化研究を行った。化合物**62d**－**62n**のSGLT1、SGLT2阻害活性試験の結果及び*C*logP、TPSAをTable 6に示す。R^4にさまざまな第一級または第二級アミンを導入することでTPSAを増加させることができ、また適度な*C*logP値を持つ化合物が合成できると考えた。実際、3種類または4種類のアミンを**56e**－**56h**に導入した化合物**62d**－**62n**は、強いSGLT1阻害活性を維持しながら、目標とするTPSA値と*C*logPを満たした。また、化合物**62d**－**62j**は、SGLT1阻害活性に匹敵するSGLT2阻害活性を示す一方、化合物**62l**－**62n**のSGLT2阻害活性は、SGLT1阻害活性よりも約6倍低かった。これらの結果から、SGLT1阻害活性はR^4の置換基によって影響を受けなかったが、R^3のメチル基の導入により、SGLT2阻害活性が減弱すると考えられた。Table 6に示すin vitroデータプロファイルを考慮すると、TPSA値と*C*logPの目標値を満たし、最もSGLT1阻害活性の強い化合物**62j**が有望と考えた。しかしながら、化合物**62j**は、様々な溶媒および温度条件下で結晶化検討を実施したが、結晶化しなかった。そのため、非晶質である**62j**は製造性の観点から開発難易度が高いことが予想された。この化合物群は誘導体合成の段階で結晶化が難しいことがわかっていた。そこで、Table 6に示す、他の化合物を再合成し、化学純度を99%以上に精製した上で結晶化スクリーニングを実施した。その結果、エタノール溶液中から**62d**が唯一結晶化した。高活性化合物**62j**と開発難易度の観点から結晶性の良い**62d**を高次評価に進めることとした。

Table 6

化合物**62d**－**62n**のSGLT1/SGLT2阻害活性及び*C*logPとTPSA



Cpd.	R^1	R^3	R^4	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	*C*logP[b]	TPSA[c] (Å^2)
62d	OMe	H		29	20	3.66	161
62e	OMe	H		38	17	3.55	161
62f	OMe	H		42	26	4.01	152
62g	OH	Me		35	74	3.72	172
62h	OH	Me		30	28	3.61	172
62i	OH	Me		35	81	4.07	163
62j	OH	Me		27	64	3.53	195
62k	OMe	Me		46	NT[d]	4.11	161
62l	OMe	Me		34	200	4.00	161
62m	OMe	Me		55	281	4.46	152
62n	OMe	Me		54	322	3.92	184

[a] The IC_{50} values for the hSGLT1 and hSGLT2 activities represent the mean values of at least two experiments.

[b] The *C*logP value was calculated using software from Daylight Chemical Information Systems, Inc.

[c] The TPSA value was calculated using software from ACD/Percepta, version 2015, Advanced Chemistry Development, Inc.[d] Not tested.

第３節　*C*-フェニル-D-グルシトール誘導体のラット薬物動態試験

SDラットにおける化合物**62d**および**62j**のPKプロファイルと、PAMPAの結果をTable 7に示す。化合物**62d**および**62j**のバイオアベイラビリティは、それぞれF=0.17%、0.09%と非常に低かった。また、化合物**62d**および**62j**は、PAMPA試験において非常に低い膜透過性を示した。これらのデータから、化合物**62d**および**62j**が低い吸収性を有することを確認した。

Table 7

Pharmacokinetic parameters in SD rats and permeability of **62d** and **62j**

Cpd.	Pharmacokinetic parameters								Permeability
	IV [a]				PO [b]				PAMPA
	Dose (mg/kg)	CL_{total} (mL/h/kg)	Vd_{ss} (mL/kg)	$t_{1/2}$ (h)	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	F (%)	at pH7.4 ($\times 10^{-6}$ cm/s)
62d	0.4	4020	1640	2.39	30	1.88	2.83	0.17	0.0
62j	0.4	3760	964	0.578	30	5.34	0.250	0.09	0.0

[a] Dosing vehicle: saline

[b] Dosing vehicle: 0.5% CMC Na

Each data point represents the mean value of three animals.

次に、**62d**および**62j**の排泄経路を調査するために、胆管カニューレ挿入（BDC）SDラットに静脈内投与した。**62d**および**62j**の尿及び胆汁からの排泄結果をTable 8に示す。幸いにも、**62d**および**62j**は主に胆汁から排泄されることが確認され、**30b**とは異なることが確認できた。この排泄経路の違いから、腎臓での化合物の蓄積が減少することを期待して、さらなる試験を行った。

Table 8

Accumulative excretion of **1**, **62d**, and **62j** after intravenous administration to BDC SD rats

Compound	Dose (mg/kg)	Urine (% of dose)	Bile (% of dose)
30b	2	36.2 ± 11.0	30.2 ± 10.4
62d	0.3	18.1 ± 9.3	65.1 ± 17.7
62j	0.3	5.3 ± 0.4	89.8 ± 5.7

Dosing vehicle: saline

Collection period: 24 hours

Each data represents the mean ± SD of three animals.

続いて、**30b**と**62d**および**62j**の腎臓残留性を調査するために、SDラットへの静脈内投与後、2時間、24時間、72時間後の腎臓における薬物濃度を評価した。その結果をTable 9に示す。**62d**および**62j**は、**30b**と比較して、腎臓での化合物の残留が急速に減少していることが確認できた。すなわち、投与後72時間後の化合物の腎臓濃度を比較すると、**30b**は803 ng/gと化合物が残留しているのに対し、**62d**および**62j**はそれぞれ29.2 ng/gおよび12.5 ng/gと時間経過と共に減少することが明らかとなった。この*C*-フェニル-D-グルシトール誘導体では、仮説として立てた3.5以上の*C*logP値が胆汁排泄につながり、それにより腎残留を回避できることを見出した。

次のステップであるin vivo薬効試験には、開発難易度の観点から結晶化している**62d**を進めることとした。

Table 9

Concentrations of **1**, **62d**, and **62j** in the kidneys after intravenous administration to SD rats

Compound	Dose (mg/kg)	Kidney concentration (ng/g tissue) 2h	24h	72h
1	0.3	1900 ± 90.7	1110 ± 72.3	803 ± 64.8
62d	0.3	1090 ± 55.7	104 ± 16.7	29.2 ± 9.43
62j	0.3	1060 ± 28.9	83.8 ± 12.9	12.5 ± 10.9

第４節　*C*-フェニル-D-グルシトール誘導体**62d**のラットも用いたin vivo薬効試験

SDラットを用いた経口ショ糖負荷試験（oGTT）を実施し、**62d**の血糖低下作用を評価した。スクロース負荷の直前に化合物**62d**を経口投与し、次いで血漿中グルコース濃度を2時間にわたって測定したところ、期待した通りに血中グルコース濃度の低下が確認できた。グルコース濃度の低下作用（0～2時間のΔAUC）は、0.3、1.0、3.0 mg/kgでそれぞれ27.5%、50.8%、45.7%であった。グルコース低下効果は0.3 mg/kgで有意に効果的であり、最大の効果は1 mg/kgで得られた。（Figure 16）これらの結果は、化合物**62d**が糖尿病患者の治療薬として潜在的に有用である可能性があることを示唆している。

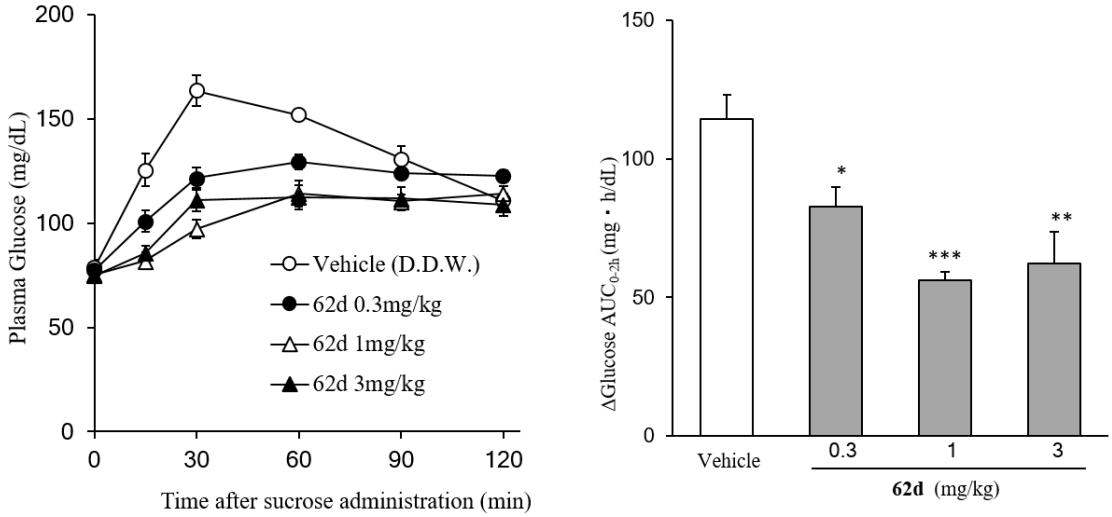


Figure 16. Effects of the oral administration of **62d** (0.3 or 1 or 3 mg/kg) on plasma glucose during an oral sucrose tolerance test in SD rats. Each point represents the mean ± SE. **p* < 0.05, ***p* < 0.01, ****p* < 0.001 vs. Vehicle group, Dunnett's test (n = 5).

第5節　小括

第1章で見出した**30b**の課題である腎残留性の回避を目的として、*C*-フェニル-D-グルシトール誘導体の新しいシリーズを設計し合成した。課題の克服のために、排泄経路が異なる分子を作成することで、腎臓の薬物貯留を回避できるのではないかという仮説を立て、検証した。低吸収で**30b**の排泄経路とは異なる胆汁から排泄される分子のクラスの創製を目指し、*C*logP値とTPSAが適切な範囲内になるように最適化した。最適化研究により、化合物**62d**および**62j**を見出した。これらは、SDラットを用いた薬物動態評価により、胆汁から主に排泄されることが確認された。また、ラットへの静脈内投与後の腎臓での薬物濃度を評価したところ、**62d**および**62j**は**30b**と比較して大幅に腎臓残留性が軽減されていることが確認できた。最後に、開発難易度の観点から選んだ**62d**は、SDラットで0.3 mg/kg（p.o.）でグルコース低下作用を示した。これらの結果から、糖尿病の治療に対する有効性が示唆された。

第 3 章　選択的SGLT1阻害活性を有する新規*C*-グリコシド型誘導体の創出

第 1 節　選択的SGLT1阻害活性を有する新規*C*-グリコシド型誘導体の創薬戦略

最近の研究では、SGLT1の活性化が虚血再灌流によって誘発される心臓の損傷を改善し、SGLT1遺伝子発現の増加がヒトの心臓の肥大性、虚血性、および糖尿病性心筋症で観察されることが示されており、著者は心不全に対するSGLT1の治療上の可能性とそのメカニズムにも興味を持った。ただ、SGLT1の心臓における役割は、SGLT1ノックダウンマウス[40,41]またはフロリジンをツール化合物として使用して研究されている[27]。ノックダウンマウスは、小腸や腎臓を含むすべての臓器で発現するSGLT1の生理作用を抑制するため、グルコース恒常性が間接的に心機能に影響を与える可能性があることは否定できない。また、非特異的SGLT阻害剤であり、生体内でα-グルコシダーゼによって容易に代謝されるフロリジンは、メカニズム分析に最適なツール化合物とは言えない。そうした背景から、著者は選択的なSGLT1阻害剤をこれまでの知見を利用し、創出できないかと考えた。ただ、化学的に安定な*C*-グリコシド誘導体の選択的なSGLT1阻害剤の報告はない。第 1 章でも述べたように、SGLT1はタンパク構造が報告されていないことから、LBDDでの創薬を実施する必要がある。そこで著者は化合物**63**をリード化合物として、第 1 章、第 2 章での知見から官能基許容性が高くスペースがあると考えられる側鎖部位（R^1、R^3）の変換とこれまでの研究から選択性に影響があると考察するフェノキシ部位（R^2）の変換を行う戦略を立てた。（Figure 17）その際、共通中間体**55g**の簡便な合成法を確立し効率的に合成展開できるようにした。

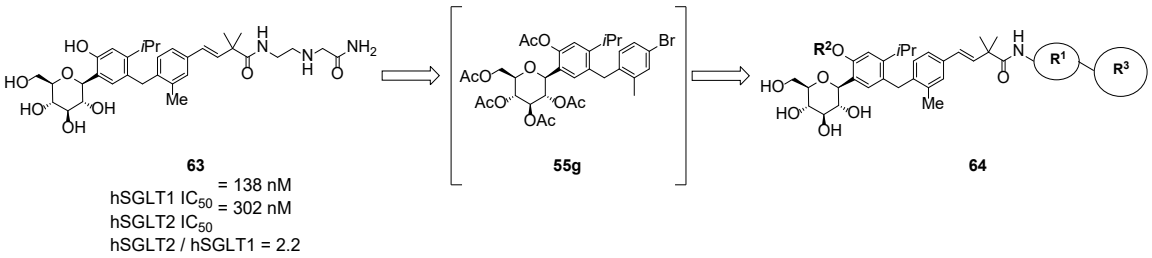
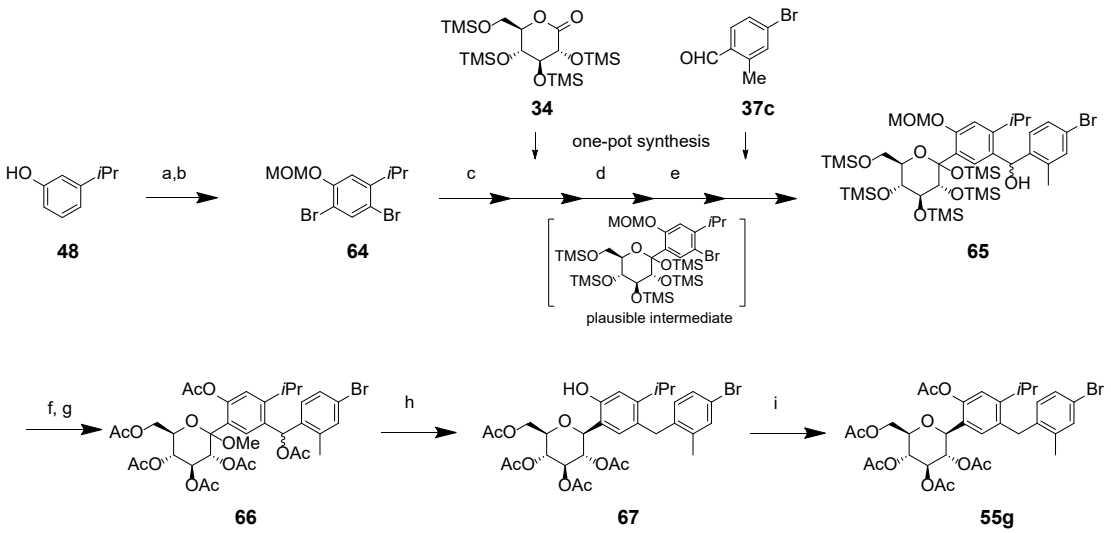


Figure 17

第２節　*C*-フェニル-D-グルシトール誘導体の合成

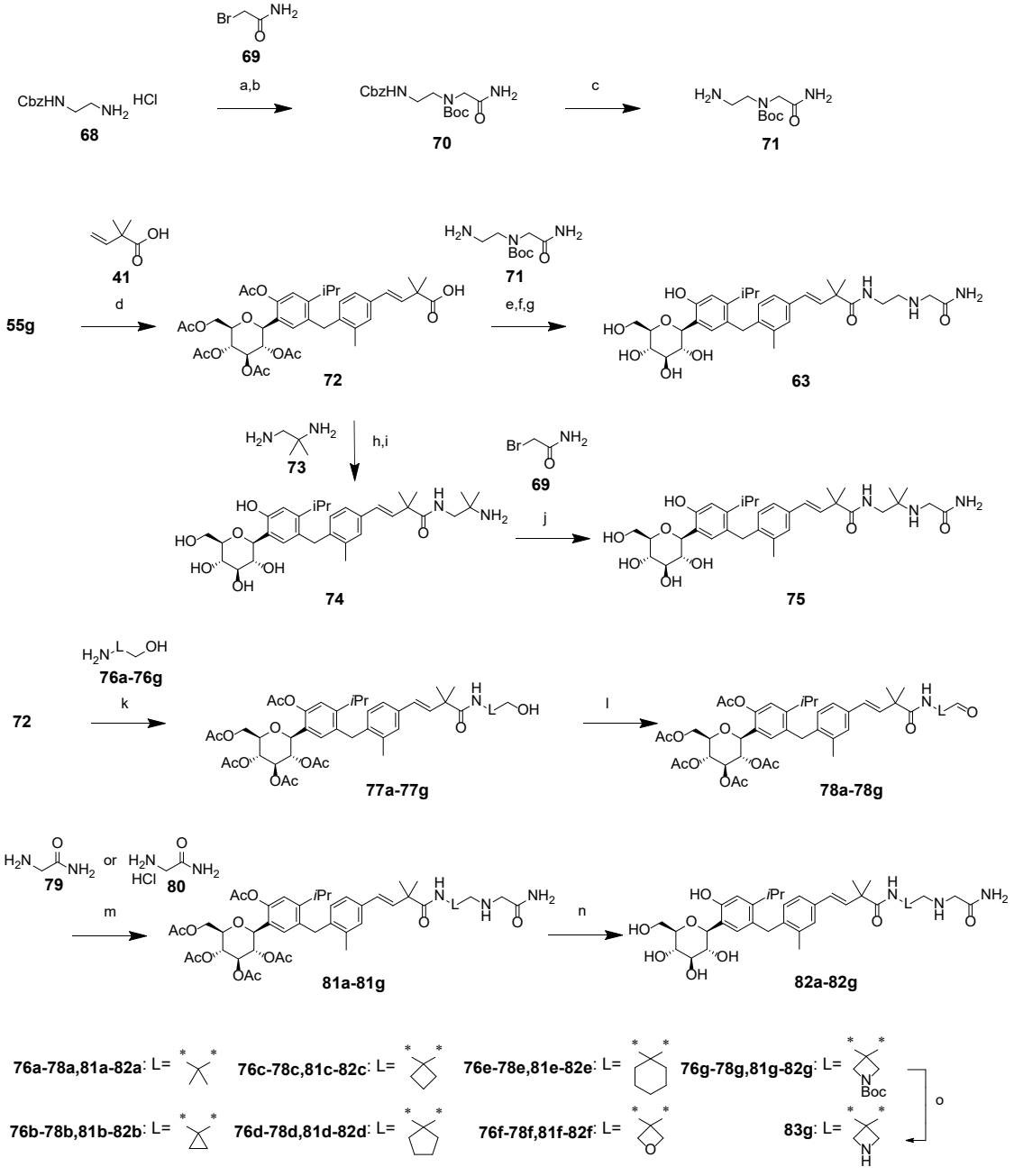
第２章で述べている主要中間体**55g**の改良した合成法をスキーム9に示す。誘導体合成を行う上で、効率的に中間体を供給することがスピードアップに寄与する。そこで著者は、第２章で報告した中間体**55g**の合成法を改良し、効率的な合成法を確立したので論述する。新たな合成法は、ワンポット3成分縮合反応を含む短工程での合成法であり、さらにカラム精製を必要としないことから大量合成が容易になった。ジブロモ体**64**は、市販の3-イソプロピルフェノール（**48**）を酸性条件下でBr_2を用いて臭素化し、塩基性条件下でMOMClを使用してフェノール性ヒドロキシル基をメトキシメチルエーテル基で保護して得た。続くワンポット反応ではメトキシメチルエーテル基のオルト位をリチオ化し[42]、ラクトン**34**とカップリングさせた後、生じたアノマー位のヒドロキシル基をトリメチルシリル基で保護した。得られた中間体を*n*-BuLiを用いて、もう一度ハロゲン金属交換によりリチオ化し、アルデヒド**37c**を加えて**65**を得た。化合物**65**のアノマー位のヒドロキシル基をメタノール中で酸性条件によりメチルエーテルに変換し、グルコース部位及びベンジルヒドロキシル基を無水酢酸とピリジンを用いてアセトキシ基で保護して**66**を得た。得られた**66**のアノマー位のメチルグルコシドとベンジル位のアセトキシ基を*t*-ブチルジメチルシランとトリメチルシリルトリフレートを使用して還元を行い、アリールβ-C-グルコシド**67**を立体選択的に合成した。**67**のフェノール性ヒドロキシル基をアセチル化して**55g**を得た。粗精製の**55g**は、2-プロパノールを用いて再結晶して精製することで、無色の粉末として得ることができた。これらの工程においては、カラム精製がないことから、操作的に簡便な合成ルートを確立した。



Scheme 9. (a) Br_2, AcOH, 4˚C, 1 h, 99%; (b) MOMCl, DIPEA, $CHCl_3$, rt, 1 h, 96%; (c) *n*-BuLi, THF, –78˚C, 35 min, then **34**; (d) TMSCl, –78˚C, 2 h; (e) *n*-BuLi, THF, –78˚C, 30 min, then **37c**; (f) MsOH, MeOH, reflux, 1.5 h; (g) Ac_2O, pyridine, rt, 18 h; (h) *t*$BuMe_2SiH$, TMSOTf, MeCN, 4˚C, 2 h, crude; (i) Ac_2O, pyridine, rt, 18 h, 45%.

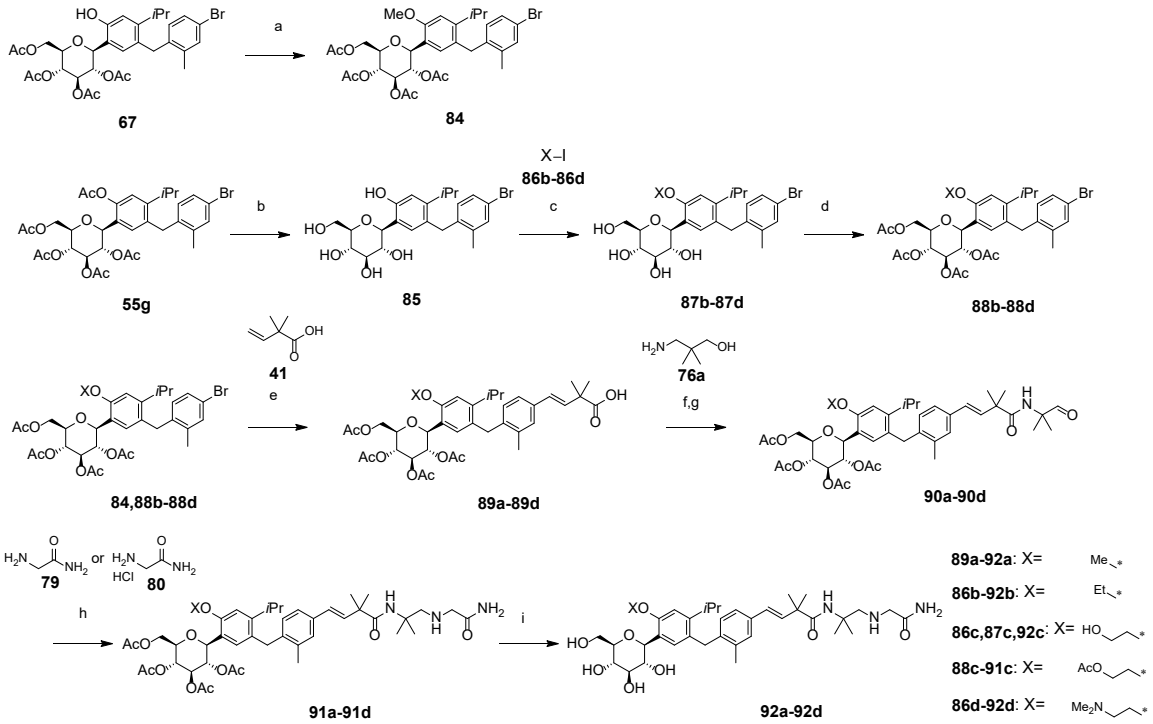
化合物**64**のR^1部位の構造変換を行った*C*-フェニル-D-グルシトール誘導体**63**および**75**、**82a**–**82f**、**83g**の合成をスキーム10に示す。市販の*N*-カルボベンゾキシ-1,2-ジアミノエタン塩酸塩（**68**）と市販の2-ブロモアセトアミド（**69**）を塩基性条件下で反応させた後、アミノ基を*t*-ブトキシカルボニル基で保護し、化合物**70**を合成した。水素雰囲気下で水酸化パラジウムを使用して**70**のベンジルオキシカルボニル基を脱保護し、中間体**71**を得た。次にマイクロ波照射条件下、**55g**と2,2-ジメチルブト-3-エン酸（**41**）をMizoroki-Heck反応によりカップリングし、カルボン酸**72**を得た。リード化合物**63**は、水溶性カルボジイミド塩酸塩（WSCI・HCl）を使用して**71**と**72**を縮合した後、トリフルオロ酢酸を用いて*t*-ブトキシカルボニル基を脱保護し、続いてナトリウムメトキシドを用いてアセトキシ基を脱保護することで合成した。化合物**74**は、**72**および市販の1,2-ジアミノ-2-メチルプロパン（**73**）を縮合した後、ナトリウムメトキシドを用いて脱保護して得た。化合物**75**は、塩基性条件下で2-ブロモアセトアミド（**69**）と**74**を反応させ合成した。側鎖の置換基を変換した化合物**82a**–

82fおよび**83g**は以下の手順で合成した。中間体**72**とアミン**76a–76g**と縮合して化合物**77a–77g**を得た。得られた**77a–77g**の末端アルコールをDess-Martin酸化[43]しアルデヒド**78a–78g**へと導いた。**78a–78g**に対しアミン**79**またはその塩酸塩**80**を用いて還元的アミノ化を行い、**81a–81g**を合成した。最後に、**81a–81g**のアセチル基をZemplén脱アセチル化条件または MeOH / H_2O中のEt_3Nで除去して、**82a–82g**を得た。*t*-ブトキシカルボニル基で保護してある**82g**は、トリフルオロ酢酸で脱保護し**83g**とした。



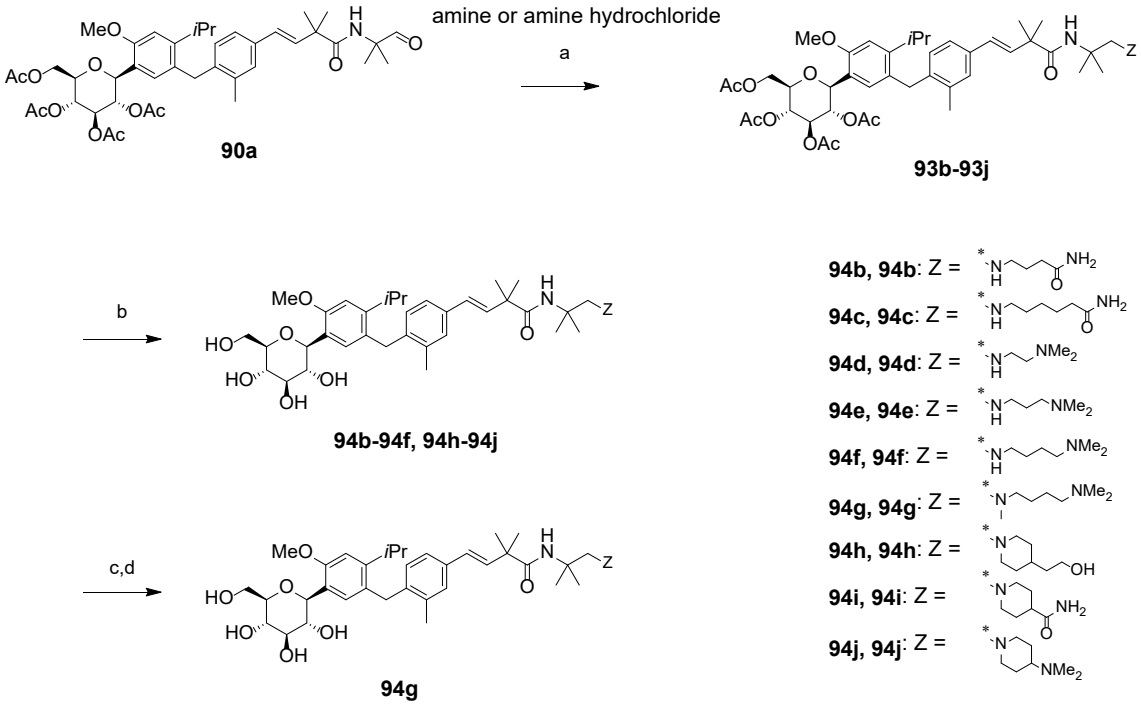
Scheme 10. (a) **69**, DIPEA, EtOH, rt, 18 h; (b) Boc_2O, DMAP, DMF, reflux, 18 h, 36% in 2 steps; (c) $Pd(OH)_2/C$, MeOH, rt, 18 h, crude; (d) **41**, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, reflux, 3 h, 88%; (e) **71**, WSCI·HCl,, HOBt·H_2O, Et_3N, DMF, rt, 18 h; (f) TFA, $CHCl_3$, rt, 18 h; (g) NaOMe, MeOH, rt, 3.5 h, 76% in 3 steps; (h) **73**, CDI, $CHCl_3$, rt, 5 h; (i) NaOMe, MeOH, rt, 1 h, 50% in 2 steps; (j) **69**, $CHCl_3$, 90˚C, 25 h, 22%; (k) **76a–76g**, WSCI·HCl,, HOBt·H_2O, Et_3N, DMF, rt, 18 h; (l) Dess-Martin periodinane, $CHCl_3$, rt, 3 h, 23-98% in 2 steps; (m) **25** or **26**, $NaBH_3CN$, MeOH or $NaBH(OAc)_3$, DMF, AcOH, rt; (n) Et_3N, MeOH/H_2O, 50˚C or NaOMe, MeOH, rt, 3-55% in 2 steps; (o) TFA, rt, 18 h, 63%.

化合物**64**のR^2部位の構造変換を行った*C*-フェニル-D-グルシトール誘導体**92a–92d**の合成をスキーム11に示す。主要中間体**67**のフェノール性ヒドロキシル基をメチルエーテル化して**84**へと導いた。R^2部位の置換基がメチルエーテル基以外の**92b–92d**の合成は 次のようにアルキル化した。MeOH/H_2O中のEt_3Nを使用して**55g**のアセチル基を除去し、**85**を得た。得られた**85**のフェノール性ヒドロキシル基を塩基性条件下、**86b–86d**を用いてアルキル化して**87b–87d**を得た。得られた**87b–87d**のグルコース部位のヒドロキシル基をアセチル化で保護し、**88b–88d**へと導いた。マイクロ波照射下、**84**、**88b–88d**と2,2-ジメチルブト-3-エン酸（**41**）のMizoroki–Heck反応により、**89a–89d**を得た。水溶性カルボジイミド塩酸塩（WSCI・HCl）を用いて**89a–89d**と**76a**を縮合した後、末端アルコールをDess-Martin酸化し、アルデヒド**90a–90d**を合成した。アルデヒド**90a–90d**対しアミン**79**またはその塩酸塩**80**を用いて還元的アミノ化を行い、**91a–91g**を合成した。最後に、**91a–91g**のアセチル基をZemplén脱アセチル化条件またはMeOH / H_2O中のEt_3Nで除去して、**92a–92g**を得た。



Scheme 11. (a) MeI, K_2CO_3, DMF, rt, 18 h then 50 ˚C, 2 h, 46%; (b) Et_3N, MeOH/H_2O, rt, 3 d; (c) **86b–86d**, K_2CO_3, DMF, 50–150˚C, 3–18 h; (d) Ac_2O, pyridine, rt, 18 h, 90% in 3 steps; (e) **41**, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, MeCN, reflux, 3 h, 99%; (f) **76a**, WSCI·HCl,, HOBt·H_2O, Et_3N, DMF, rt, 18 h; (g) Dess-Martin periodinane, $CHCl_3$, rt, 1 h, 77% in 2 steps; (h) **79** or **80**, $NaBH_3CN$, MeOH, rt, 18 h or $NaBH(OAc)_3$, DMF, AcOH, rt, 18 h; (i) Et_3N, MeOH/H_2O, rt, 18 h or NaOMe, MeOH, rt, 18 h, 27-56% in 2 steps.

化合物**64**のR[3]部位の構造変換を行った誘導体**94b–94j**の合成をスキーム12に示す。中間体**90a**に対し、種々のアミンまたはアミン塩酸塩による還元的アミノ化を行い、**93b–93j**を得た。次に、**93b–93f**、**93h–93j**のアセチル基を除去して、**94b–94f**、**94h–94j**をそれぞれ合成した。また、**93f**をNメチル化した後、アセチル基を除去することで**94g**を合成した。



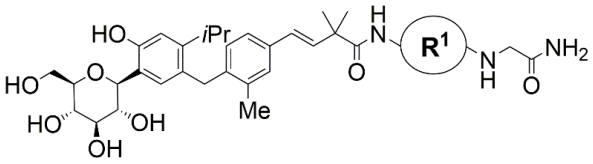
Scheme 12. (a) amine or amine hydrochloride, $NaBH_3CN$, MeOH or $NaBH(OAc)_3$, DMF or $CHCl_3$, AcOH, rt, 18 h; (b) Et_3N, $MeOH/H_2O$, rt, 18 h, 23-61% in 2 steps; (c) aq.HCHO, $NaBH(OAc)_3$, $CHCl_3$, rt, 6 h; (d) Et_3N, $MeOH/H_2O$, rt, 16 h, 27% in 3 steps.

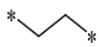
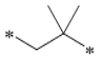
第３節　*C*-フェニル-D-グルシトール誘導体の構造活性相関及び膜透過性評価

リード化合物**63**の選択性（SGLT2/SGLT1）を向上させるために、側鎖R^1を変更してSARを探索した。（Table 10）立体障害の影響を調べるために、ジメチル基を持つ**75**および**82a**を合成した。化合物**75**はSGLT1阻害活性が改善されており、**63**と比較して選択性が3倍向上することが明らかとなった。一方で、**82a**はSGLT1阻害活性が大幅に低下することがわかった。次に、化合物**75**のジメチル基部位を環状アルキル、オキセタン、アゼチジンに変換した誘導体**82b-82f**、**83g**を合成し、立体障害と官能基の影響を評価した。結果は、SGLT1とSGLT2の阻害活性がシクロアルカンリングのサイズに反比例する傾向があることを示している。例えば、シクロプロパン化合物**82b**は、シクロヘキサン化合物**82e** と比較して、SGLT1阻害活性が2倍強く、一方でSGLT2阻害活性は2倍減弱した。結果として、選択性（hSGLT2/hSGLT1）は環を大きくすると低下することがわかった。また、環状構造に酸素原子を導入した**82f**は、**82b**と同様のSGLT1阻害活性を示した一方、窒素原子を導入した**82g**は、SGLT1阻害活性が有意に減弱した。最も選択性の高い化合物**75**の側鎖の最適化を次に実施した。

Table 10

化合物 **63**、**75**、**82a**－**82g**、**83g** の SGLT1/SGLT2 阻害活性及び選択性



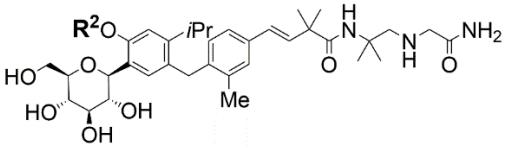
Compound	R^1	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	hSGLT2/hSGLT1
63		138	302	2.2
75		91	578	6.3
82a		553	NT[b]	NT[b]
82b		49	238	4.9
82c		47	150	3.2
82d		43	153	3.6
82e		97	109	1.1
82f		38	149	4
83g		505	NT[b]	NT[b]

[a] The IC_{50} values for the hSGLT1 and hSGLT2 activities are the mean values of data obtained in at least two experiments.

[b] Not tested.

次に、ベンゼン環のR²を変換することで選択性が向上するのかを検証した。（Table 11）最初に、R²をメトキシ基に変換すると選択性が向上することが第２章でで述べたSARの知見から示唆されていたため（Table 5）、**92a**を合成したところ、意図した通りに選択性が大幅に向上することが明らかとなった。一方予想に反して、エトキシ基に変換した**92b**は、選択性が**92a**ほど向上しなかった。また、エトキシ基の先端にヒドロキシル基やアミノ基を導入することで、選択性が影響を受けるかどうかも検討した。その結果、ヒドロキシエチル基が導入された**92c**は選択性が低く、アミノエチル基が導入された**92d**はSGLT1阻害活性を失った。選択性の観点から、メチル基がベンゼン環の最適なR²置換基であることを明らかとした。最後に、**92a**の側鎖の末端であるR³を変換することにより、選択性の向上を試みることとした。

Table 11. 化合物 **75**、**92a**－**92d** の SGLT1/SGLT2 阻害活性及び選択性



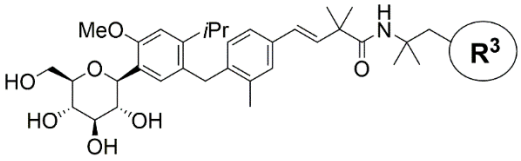
Compound	R^2	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	hSGLT2/hSGLT1
75	H	91	578	6.3
92a	Me	74	1170	15.8
92b	Et	174	1898	10.9
92c	CH_2CH_2OH	145	848	5.8
92d	$CH_2CH_2NMe_2$	>3000	NT[b]	NT[b]

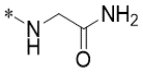
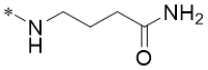
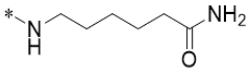
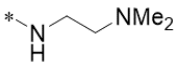
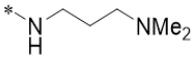
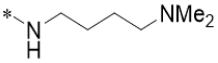
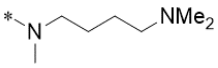
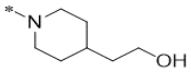
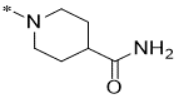
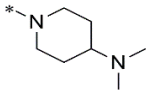
[a] The IC_{50} values for the hSGLT1 and hSGLT2 activities are the mean values of data obtained in at least two experiments.

[b] Not tested.

化合物**92a**のR^3をさまざまな構造に変換した結果をTable 12に示す。まず、**92a**の末端側鎖の長さが変更されたときのSARを調査した。**92a**よりも長い側鎖を有する化合物**94b**および**94c**のSGLT1阻害活性及び選択性は変化しなかった。次に、末端側鎖をアミド基からジメチルアミノ基に変換した場合の活性への影響を調べた。側鎖の長さが異なる**94d**、**94e**、**94f**を比較すると、最も短い化合物**94d**だけがSGLT1阻害活性を改善し、選択性が24.8倍に向上した。さらに、**94f**のNメチル化した**94g**は、選択性がわずかに向上した結果を考察し、末端側鎖の環化によって選択性を改善できるかどうかを検証した。3つの環化誘導体**94h**、**94i**、**94j**を準備したところ、4-ジメチルピペリジンを導入した**94j**は、SGLT1阻害活性（26 nM）とSGLT2に対するSGLT1の42.4倍の選択性を示した。SGLT2/SGLT1選択性を有するツール化合物を取得できたため、PAMPAを測定していくつかの化合物の膜透過性を評価した。いずれの化合物もPAMPAの値は低吸収の目安となる0.5×10^{-6} cm/sよりも低く、膜透過性が低いことが確認できた。小腸からの吸収が非常に低いことが予想されるため、動物への投与経路は皮下および静脈内投与で行うことが望ましいと考えられる。化学的に安定な*C*-フェニル-D-グルシトール誘導体**94j**を使用することにより、in vitroおよびin vivoの両方でSGLT1の機能解析を実施することが可能と考えられる。SGLT1は、虚血時の嫌気性解糖による唯一のATP供給源であるブドウ糖の取り込みを促進するため、急性心筋虚血性損傷後に有益である可能性がある。例えば、**94j**の虚血再灌流誘発性心臓損傷モデルへの投与は、SGLT1が心臓保護に不可欠であるか、別の促進拡散型グルコース輸送体1または4（GLUT1または4）によって補償されるかを検証することができると考えられる。

Table 12. 化合物 **92a**、**94b**－**94j** の SGLT1/SGLT2 阻害活性及び選択性と PAMPA



Compound	R^3	hSGLT1[a] IC_{50} (nM)	hSGLT2[a] IC_{50} (nM)	hSGLT2/hSGLT1	PAMPA at pH6.2 ($\times 10^{-6}$ cm/s)
92a		74	1170	15.8	0.2
94b		65	780	12.0	NT[b]
94c		60	954	15.9	NT[b]
94d		26	646	24.8	0.1
94e		65	927	14.3	0
94f		62	1016	16.4	NT[b]
94g		69	1335	19.3	0
94h		64	1563	24.4	0.2
94i		73	1180	16.2	NT[b]
94j		26	1101	42.4	0.2

[a] The IC_{50} values for the hSGLT1 and hSGLT2 activities are the mean values of data obtained in at least two experiments.

[b] Not tested.

第 4 節　小括

C-フェニル-D-グルシトール誘導体の新しいシリーズを設計および合成し、それらの化合物の選択性（hSGLT2 / hSGLT1）と膜透過性を評価した。選択性を獲得するために、R^1、R^2、R^3部位のSAR探索を実施した。構造最適化した結果、**94j**が40倍を超えるSGLT2 / SGLT1選択性を有し、IC_{50} = 26 nMのSGLT1阻害活性を示した。 SGLT1選択的化合物の報告は非常に少なく、**94j**は最初に発見された*C*-グリコシド型SGLT1阻害剤であり、SGLT1の生理学の解明に役立つ可能性がある。さらなる研究により、SGLT1が心不全患者の治療標的として有益であるかどうかを調査することが可能になると考えられる。

結論

ナトリウム依存性グルコース共輸送体の１つである小腸上皮細胞に存在するSGLT1を標的とし、SGLT1を阻害し小腸からの糖吸収を抑制することで、新規糖尿病治療薬の創出を目的とし研究を行った。

第１章では、SGLT2の創薬研究を行った際に得られていた化合物**1**から知見を生かし、芳香環の置換基を変換した化合物**14a**を見出した。リンカーを探索するためにアルキル基を導入した化合物**14d**のSGLT1阻害活性が向上したので、次に低吸収性を付与するために側鎖に水溶性置換基の導入することとした。また、開発難易度の観点からチオグルコース部位をグルコースに変換し、高いTPSAと強いSGLT1阻害活性を有する化合物**30b**を見出した。SGLT1阻害活性が強くTPSAも高い**30b**を見出し、PK試験、in vivo薬効試験を実施した。**30b**は、ラットPK試験により低いBAが確認され、PAMPA試験の結果からも低吸収性化合物であることを確認した。最後にラット糖負荷試験により、**30b**が0.1 mg/kgから用量依存的に糖吸収を抑制することを明らかとした。

第２章では、第１章で見出した**30b**の課題である腎残留性の回避を目的として、*C*-フェニル-D-グルシトール誘導体の新しいシリーズを設計し合成した。腎残留性という課題の克服のために、**30b**とは排泄経路が異なる分子を作成することで、腎残留性を回避できるのではないかと考えた。低吸収で**30b**の排泄経路とは異なる胆汁から排泄される分子のクラスの創製を目指し、*C*logP値とTPSAが適切な範囲内になるように最適化した。最適化研究により、化合物**62d**および**62j**を見出した。これらは、SDラットを用いた薬物動態評価により、胆汁から主に排泄されることが確認された。また、ラットへの静脈内投与後の腎臓での薬物濃度を評価したところ、**62d**および**62j**は**30b**と比較して大幅に腎臓残留性が軽減されていること

が確認できた。最後に、開発難易度の観点から選んだ**62d**は、SDラットで0.3 mg/kg（p.o.）でグルコース低下作用を示した。これらの結果から、糖尿病の治療に対する有効性が示唆された。

第３章では、*C*-フェニル-D-グルシトール誘導体の新しいシリーズを設計および合成し、それらの化合物の選択性（hSGLT2 / hSGLT1）と膜透過性を評価した。構造最適化した結果、**94j**が40倍を超えるSGLT2 / SGLT1選択性を有し、強いSGLT1阻害活性を示した。SGLT1選択的化合物の報告は非常に少なく、**94j**は最初に発見された*C*-グリコシド型SGLT1阻害剤であり、SGLT1の生理学の解明に役立つ可能性がある。さらなる研究により、SGLT1が心不全患者の治療標的として有益であるかどうかを調査することが可能になると考えられる。

本論文は、*C*-フェニル-D-グルシトール構造を持つSGLT1阻害薬の開発において、化合物の腎残留性にまで言及し、排泄経路を変えることで課題を解決した初めての報告である。また、*C*logP、TPSAのパラメーターを調整することで、低吸収で腎残留性の低い**62d**を創出した研究は、今後のSGLT1阻害薬研究に有用である。また、化学的に安定なC-グリコシド型の誘導体として初めて、高い選択性を持つ**94j**を見出した。ツール化合物としてSGLT1のメカニズム解析の進展に寄与するものと考えられる。

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実験の部

All commercially available starting materials and reagents were used without further purification unless otherwise noted. Thin layer chromatography was performed to monitor the reactions using Merck silica gel 60 F254 plates or Fuji Silysia chromatorex NH plates. Silica gel column chromatography was performed using Wakogel® C–200, or NH–silica gel Fuji Silysia chromatorex® DM1020, or an appropriately sized pre-packed silica cartridge on a Biotage system. Melting points were determined using a Yanako micro melting point apparatus and were not corrected. The ^{1}H NMR spectra were determined with a Varian Instruments INOVA300 spectrometer at 300 MHz or a JEOL ECA600 NMR spectrometer operating at 600 MHz. The ^{13}C NMR spectra were determined with a JEOL JNM-ECA500 NMR spectrometer operating at 126 MHz. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS, δ 0.00 ppm) as an internal reference. Multiplicity was defined as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), br s (broad singlet). IR spectra were recorded using a Perkin-Elmer Spectrum One. Electron impact (EI) mass spectra were taken on a Perkin-Elmer Sciex API-300 mass spectrometer. The other mass spectra (MS) were recorded using a Shimadzu LCMS-2010EV mass spectrometer with an ESI/APCI dual source. HRMS were recorded using a Shimadzu LCMS-IT-TOF mass spectrometer with an ESI/APCI dual source. Elemental analyses were performed using a Perkin–Elmer 2400II, and the results were within ±0.4% of the calculated values. Optical rotations were measured on a Rudolph Reseach Analytical AUTOPOL V.

4-(Benzyloxy)-5-bromo-2-methylbenzoic acid (6)

To an *N*,*N*-dimethylformamide solution (20 mL) of 4'-hydroxy-2'-methylacetophenone (**5**) (3.06 g, 20.0 mmol) were added potassium carbonate (3.66 g, 26.4 mmol), benzyl bromide (2.7 mL, 22.4 mmol), and *n*-Bu_4NI (0.75 g, 2.03 mmol), and the mixture was stirred for 14 hours at room temperature.

To the reaction solution cooled in ice were added a saturated solution of ammonium chloride, subsequently water. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with 20% aqueous solution of sodium thiosulfate and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 8:1 to 6:1) to obtain 1-[4-(benzyloxy)-2-methylphenyl]ethanone (5.05 g, quant.) as a colorless powder. To an acetone solution (300 mL) of 1-[4-(benzyloxy)-2-methylphenyl]ethanone (20.9 g, 87.1 mmol) were added an aqueous solution (100 mL) of NaBr (9.86 g, 95.9 mmol), water (200 mL), and Oxone (registered trade mark, oxone-persulfuric acid chloride, from Aldrich) (59.0 g, 95.9 mmol), and the mixture was stirred 2.5 hours at room temperature. To the reaction solution cooled in ice were added an aqueous solution (50 mL) of sodium sulfite (20 g), subsequently water. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with 20% aqueous solution of sodium sulfite and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain a mixture (27.2 g) of 1-[4-(benzyloxy)-5-bromo-2-methylphenyl]ethanone and 1-[4-(benzyloxy)-3-bromo-2-methylphenyl]ethanone. To the mixture were added a 5% aqueous solution (300 mL, 255 mol) of sodium hypochlorite and an aqueous solution (10 mL) of potassium hydroxide (4.80 g, 85.3 mmol), stirred at 120°C for an hour, cooled to room temperature, and precipitated insoluble matter was filtered. To this insoluble matter was added 2 M hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was washed with methanol to obtain the titled compound (16.6 g, 59%, 2 steps) as a colorless powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.45-2.57 (m, 3H), 5.28 (s, 2H), 7.18 (s, 1H), 7.31-7.54 (m, 5H), 8.03 (s, 1H), 12.83 (brs, 1H).

4-(Benzyloxy)-5-bromo-2-methylbenzaldehyde (7)

To a suspension of compound **6** (23.4 g, 72.9 mmol) in chloroform (160 mL) were added oxalyl chloride (6.56 mL, 76.5 mmol) and *N*,*N*-dimethylformamide (6 drops), and the mixture was stirred for an hour at room temperature. And then the reaction solution was concentrated to obtain 4-(benzyloxy)-5-bromo-2-methylbenzoyl chloride. Then to a chloroform suspension (80 mL) of *N*,*O*-dimethylhydroxylamine hydrochloride (7.46 g, 76.5 mmol) and triethylamine (21.3 mL, 153 mmol) cooled in ice was added dropwise a chloroform solution (60 mL) of 4-(benzyloxy)-5-bromo-2-methylbenzoyl chloride, and the mixture was stirred for an hour at room temperature. To the reaction solution cooled in ice were added water and chloroform to separate an organic layer. The organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 4-(benzyloxy)-5-bromo-*N*-methoxy-*N*-methylbenzamide. To a tetrahydrofuran solution (150 mL) of the 4-(benzyloxy)-5-bromo-*N*-methoxy-*N*-methylbenzamide was added at -10°C lithium aluminum hydroxide (1.44g, 38.0 mmol), and the mixture was stirred for an hour at the same temperature. To the reaction solution were added 1 M hydrochloric acid, and then ethyl acetate to separate an organic layer. The organic layer was washed with 1 M hydrochloric acid, a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain the titled compound (4.57g, 65% in 2 steps) as a colorless amorphous.

1-(benzyloxy)-2-bromo-5-methyl-4-(4-methoxybenzyl)benzene (10b)

To a solution of 4-(benzyloxy)-5-bromo-2-methylbenzaldehyden (**7**) (3.0 g, 9.83 mmol) in tetrahydrofuran (20 mL) was added to a solution of 0.5 M 4-methoxyphenylmagnesium bromide prepared from **8b** and $MgBr_2$ in tetrahydrofuran (29.5 mL, 14.7 mmol) at −18 °C and the mixture was

stirred at −15 °C for 15 minutes. A saturated aqueous ammonium chloride solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution and saturated saline, and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1) to obtain [1-(benzyloxy)-2-Bromo-5-methylphenyl](4-methoxyphenyl)methanol was obtained as a colorless oil. Next, to a solution of [1-(benzyloxy)-2-bromo-5-methylphenyl](4-methoxyphenyl)methanol (4.40 g) in acetonitrile (20 mL) and chloroform (20 mL) was added to Et_3SiH (3.10 mL, 19.7 mmol) and $BF_3 \cdot Et_2O$ (1.20 mL, 9.83 mmol) at −4 °C. After stirring at the same temperature for 30 minutes, 2 M aqueous potassium hydroxide solution (20 mL) was added. The resulting mixed liquid was extracted with chloroform, the organic layer was washed with 1 M hydrochloric acid and saturated saline, and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=10:1) to obtain the titled compound (3.46 g, 89 % in 2 steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.17 (s, 3 H), 3.79 (s, 3 H), 3.82 (s, 2 H), 5.12 (s, 2 H), 6.77 (s, 1 H), 6.82 (d, J = 8.4 Hz, 2 H), 7.02 (d, J = 8.4 Hz, 2 H), 7.19 - 7.45 (m, 4 H), 7.44 - 7.58 (m, 2 H). EI *m/z* 396 $[M+H]^+$.

1-(Benzyloxy)-2-bromo-5-methyl-4-(4-ethoxybenzyl)benzene (10a)

Compound **10a** (62% in 2 steps) was obtained from **7** and **8a** in a manner similar to that described for **10b**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.40 (t, J = 6.99 Hz, 3H), 2.16 (s, 3H), 3.81 (s, 2H), 3.94 - 4.07 (m, 2H), 5.12 (s, 2H), 6.73 - 6.85 (m, 3H), 7.00 (d, J = 8.70 Hz, 2H), 7.22 - 7.32 (m, 1H), 7.32 - 7.42 (m, 3H), 7.43 - 7.53 (m, 2H). EI *m/z* 410 $[M+H]^+$.

1-(Benzyloxy)-2-bromo-5-methyl-4-(4-methylbenzyl)benzene (10c)

Compound **10c** (50% in 2 steps) was obtained from **7** and **8c** in a manner similar to that described for **10b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.17 (s, 3 H), 2.31 (s, 3 H), 3.84 (s, 2 H), 5.12 (s, 2 H), 6.76 (s, 1 H), 6.95 - 7.03 (m, 2 H), 7.04 - 7.14 (m, 2 H), 7.22 - 7.58 (m, 6 H). EI *m/z* 380 $[M+H]^+$.

1-(Benzyloxy)-2-bromo-4-(4-ethylbenzyl)-5-methylbenzene (10d)

A solution of 1-bromo-4-ethylbenzene (**8d**) (5.00 g, 16.4 mmol) in tetrahydrofuran (30 mL) was added with a hexane solution of 2.66 M *n*- butyllithium (6.47 mL, 17.2 mmol) at −60°C. After stirring at the same temperature for 15 minutes, a solution of 4-(benzyloxy)-5-bromo-2-methylbenzaldehyde (**7**) (3.03 g, 16.4 mmol) in tetrahydrofuran (15 mL) was added dropwise to reaction solution at the same temperature. And stirred for 15 minutes. A saturated aqueous ammonium chloride solution was added to the reaction solution, the temperature was raised to room temperature, this was extracted with ethyl acetate, the organic phase was washed with saturated saline, and then dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure to obtain the crude intermediate. Et_3SiH (3.93 mL, 24.6 mmol) and $BF_3 \cdot Et_2O$ (2.49 mL, 19.7 mmol) were added to a chloroform solution of the intermediate (80 mL) at 0° C, and the mixture was stirred for 30 minutes. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction solution, the mixture was extracted with ethyl acetate, the organic phase was washed with saturated saline and then dried over anhydrous magnesium sulfate. The desiccant was filtered off, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=98:2) to obtain the titled compound (5.31 g, 82% in 2 steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.62 Hz, 3 H), 2.17 (s, 3 H), 2.61 (q, J = 7.62 Hz, 2 H), 3.85 (s, 2 H), 5.12 (s, 2 H), 6.76 (s, 1 H), 7.01 (d, 2 H), 7.10 (d, 2 H), 7.27 - 7.43 (m, 4 H), 7.48 (d, 2 H); ESI *m/z* = 414 $[M+NH_4]^+$.

(*1S*)-1,5-Anhydro-1-{2-hydroxy-5-[(4-methoxyphenyl)methyl]-4-methylphenyl}-1-thio-D-glucitol (14b)

To a THF (17 mL) solution of **10b** (3.46 g, 8.71 mmol) was added a 2.6 M *n*- butyllithium (3.7 mL, 9.58 mmol) in hexane at −50°C. After stirring for 30 minutes at −60° C, 2,3,4,6-tetra-*O*-benzyl-5n-thio-*D*-glucono-1,5-lactone (**11**) (3.22 g, 5.81 mmol) in THF (10 mL) was added to the reaction solution, and the mixture was stirred at the same temperature for 15 minutes. A saturated aqueous ammonium chloride solution was added to the reaction solution, the temperature was raised to room temperature. The mixture was extracted with ethyl acetate, the organic phase was washed with saturated saline, and then dried over anhydrous magnesium sulfate. The desiccant was filtered off, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=5:1) to obtain the compound (**12b**) (2.22g) as a pale yellow gum. To a solution of **12b** (2.20 g, 2.52 mmol) in chloroform (6.0 mL) and acetonitrile (12.0 mL) was added Et_3SiH (0.800 mL, 5.04 mmol) and $BF_3 \cdot Et_2O$ (0. 380 mL, 3.02 mmol) sequentially, and stirred for 1 hour. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction solution, the mixture was extracted with ethyl acetate, and the organic phase was washed with saturated saline and then dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=5:1) to give the compound **13b** (2.15 g) as a colorless powder. To a solution of **13b** (2.11 g, 2.46 mmol) in ethyl acetate (20 mL) and ethanol (20 mL) was added 20% palladium hydroxide activated carbon (2.1 g) under a hydrogen atmosphere, and the mixture was stirred at room temperature for 24 hours. The insoluble matter in the reaction solution was filtered through Celite, and the filtrate was concentrated. The obtained residue was purified by silica gel column chromatography (chloroform:methanol=10:1) to obtain the titled compound (690 mg, 30% in 3 steps) as a colorless powder. ^1H NMR (300 MHz, CD_3OD) δ ppm 2.08 (s, 3 H), 2.91 -

3.06 (m, 1 H), 3.26 (t, 1 H), 3.59 (dd, *J* = 10.3, 8.9 Hz, 1 H), 3.68 - 3.78 (m, 1 H), 3.74 (s, 3 H), 3.81 (s, 2 H), 3.82- 3.88 (m, 1 H), 3.94 (dd, *J* = 11.3, 3.7 Hz, 1 H), 4.29 (d, *J* = 10.6 Hz, 1 H), 6.60 (s, 1 H), 6.69 - 6.82 (m, 2 H), 6.96 - 7.03 (m, 2 H), 7.04 (s, 1 H); ESI *m/z* 429 $[M+Na]^+$.

(*1S*)-1,5-Anhydro-1-{5-[(4-ethoxyphenyl)methyl]-2-hydroxy-4-methylphenyl}-1-thio-D-glucitol (14a)

Compound **14a** (40% in 3 steps) was obtained as a colorless powder from **10a** in a manner similar to that described for **14b**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.35 (t, *J* = 7.0 Hz, 3H), 2.08 (s, 3 H), 2.92 - 3.04 (m, 1 H), 3.22-3.27 (m, 1 H), 3.59 (dd, *J* = 10.3, 8.9 Hz, 1 H), 3.69 - 3.88 (m, 4 H), 3.89-4.03 (m, 3 H), 4.29 (d, *J* = 10.6 Hz, 1 H), 6.60 (s, 1 H), 6.73 - 6.80 (m, 2 H), 6.95 - 7.02 (m, 2 H), 7.04 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 15.4, 19.7, 39.1, 43.4, 50.7, 62.9, 64.6, 76.1, 77.9, 81.3, 115.5, 118.5, 122.8, 130.6, 131.0, 132.1, 134.5, 138.0, 155.2, 158.7; HR-MS ESI/APCI Dual *m/z*: 443.1486 [M+Na]+ (calcd for $C_{22}H_{28}O_6SNa$ 443.1499).

(*1S*)-1,5-Anhydro-1-{2-hydroxy-4-methyl-5-[(4-methylphenyl)methyl]phenyl}-1-thio-D-glucitol (14c)

Compound **14c** (17% in 3 steps) was obtained as a colorless powder from **10c** in a manner similar to that described for **14b**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 2.07 (s, 3 H), 2.27 (s, 3 H), 2.92 - 3.04 (m, 1 H), 3.25-3.28 (m, 1 H), 3.58 (dd, *J* = 10.3, 9.0 Hz, 1 H), 3.73 (dd, *J* = 11.5, 6.6 Hz, 1 H), 3.78 - 3.88 (m, 3 H), 3.94 (dd, *J* = 11.5, 3.8 Hz, 1 H), 4.29 (d, *J* = 10.6 Hz, 1 H), 6.60 (s, 1 H), 6.94 - 6.98 (m, 2 H), 7.01 - 7.04 (m, 2 H), 7.05 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.7, 21.2, 39.5, 43.4, 50.8, 62.9, 76.1, 77.8, 81.4, 118.5, 122.8, 129.6, 130.0, 131.1, 131.9, 136.3, 138.0, 139.5, 155.2; HR-MS ESI/APCI Dual *m/z*: 413.1389 [M+Na]+ (calcd for $C_{21}H_{26}O_5SNa$ 413.1393).

(*1S*)-1,5-Anhydro-1-{5-[(4-ethylphenyl)methyl]-2-hydroxy-4-methylphenyl}-1-thio-D-glucitol (14d)

Compound **14d** (8% in 3 steps) was obtained as a colorless powder from **10d** in a manner similar to that described for **14b**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.19 (t, J = 7.6 Hz, 3H), 2.08 (s, 3 H), 2.58 (q, J = 7.5 Hz, 2 H), 2.95 - 3.02 (m, 1 H), 3.23-3.28 (m, 1 H), 3.58 (dd, J = 10.1, 9.2 Hz, 1 H), 3.73 (dd, J = 11.5, 6.4 Hz, 1 H), 3.81 - 3.87 (m, 3 H), 3.94 (dd, J = 11.4, 3.6 Hz, 1 H), 4.30 (d, J = 10.4 Hz, 1 H), 6.61 (s, 1 H), 6.98 - 7.06 (m, 5 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 16.4, 19.7, 29.6, 39.6, 43.4, 50.7, 62.9, 76.1, 77.9, 81.3, 118.5, 122.8, 128.8, 129.7, 131.1, 131.8, 138.1, 139.8, 142.9, 155.2; HR-MS ESI/APCI Dual *m/z*: 427.1541 [M+Na]+ (calcd for $C_{22}H_{28}O_5SNa$ 427.1550).

2-[4-(Benzyloxy)-5-bromo-2-methylphenyl]-1,3-dioxolane (15)

To a suspension of 4-(benzyloxy)-5-bromo-2-methylbenzoic acid (**6**) (16.6 g, 51.7 mmol) in chloroform (80 mL) were added oxalyl chloride (5.00 mL, 56.9 mmol) and *N*,*N*-dimethylformamide (6 drops), and the mixture was stirred for an hour at room temperature. And then the reaction solution was concentrated to obtain 4-(benzyloxy)-5-bromo-2-methylbenzoyl chloride. Then to a chloroform suspension (60 mL) of *N*,*O*-dimethylhydroxylamine hydrochloride (5.55 g, 56.9 mmol) and triethylamine (15.0 mL, 103 mmol) cooled in ice was added dropwise a chloroform solution (60 mL) of 4-(benzyloxy)-5-bromo-2-methylbenzoyl chloride, and the mixture was stirred for an hour at room temperature. To the reaction solution cooled in ice were added water and the resulting mixture was extracted with chloroform. The organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 4-(benzyloxy)-5-bromo-*N*-methoxy-*N*-methylbenzamide. To a tetrahydrofuran solution (150 mL) of the 4-(benzyloxy)-5-bromo-*N*-methoxy-*N*-methylbenzamide was added at −10°C lithium aluminum hydroxide (1.96 g, 51.7 mmol),

and the mixture was stirred for an hour at the same temperature. To the reaction solution were added 1 M hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with 1 M hydrochloric acid, a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 4-(benzyloxy)-5-bromo-2-methylbenzaldehyde. To a toluene solution (120 mL) of the 4-(benzyloxy)-5-bromo-2-methylbenzaldehyde were added ethylene glycol (30.0 mL, 517 mmol) and *p*-toluenesulfonic acid monohydrate (0.500 g, 2.58 mmol), and heated to reflux for 1.5 hours with a Dean-Stark apparatus. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 5:1). In addition, the residue was further purified with NH type silica gel column chromatography (chloroform) to obtain the titled compound (12.8 g, 71% in 3 steps) as a colorless powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.34 (s, 3H), 3.92-4.19 (m, 4H), 5.15 (s, 2H), 5.87 (s, 1H), 6.74 (s, 1H), 7.27-7.51 (m, 5H), 7.72 (s, 1H).

2,3,4,6-Tetra-*O*-benzyl-1-*C*-[2-(benzyloxy)-5-(1,3-dioxolan-2-yl)-4-methylphenyl]-5-thio-D-glucopyranose (17a)

To a solution of **15** (12.9 g, 36.9 mmol) in THF (100 mL), 2.67 M n-butyllithium in hexane (14.5 mL, 36.9 mmol) was added dropwise at −78°C under a nitrogen atmosphere and stirred at the same temperature for 30 minutes. Then, a solution of 2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucono-1,5-lactone (**16a**) (9.77 g, 17.6 mmol) in tetrahydrofuran (40 mL) was added dropwise and stirred at the same temperature for 15 minutes. After addition of saturated aqueous ammonium chloride, the reaction

mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1 → 2:1) to give the titled compound (10.6 g, 73%) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.39 (s, 3 H) 3.46-3.72 (m, 2 H) 3.86-4.22 (m, 8 H) 4.43-5.00 (m, 8 H) 5.10 (s, 2 H) 5.92 (s, 1 H) 6.66-6.90 (m, 3 H) 7.00-7.38 (m, 23 H) 7.57 (brs, 1 H); ESI *m/z* = 847 $[M+Na]^+$.

2,3,4,6-Tetra-*O*-benzyl-1-*C*-[2-(benzyloxy)-5-(1,3-dioxolan-2-yl)-4-methylphenyl]-D-glucopyranose (17b)

Compound **17b** (10.7 g, 87%) was obtained as a yellow oil from **15** and **16b** in a manner similar to that described for **17a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.40 (s, 3H), 3.65-3.86 (m, 3H), 3.89-4.21 (m, 8H), 4.45-4.69 (m, 4H), 4.78-5.03 (m, 5H), 5.91 (s, 1H), 6.71 (s, 1H), 6.97 (dd, J = 7.31, 2.18 Hz, 2H), 7.10-7.37 (m, 23H), 7.81 (s, 1H).

2,3,4,6-Tetra-*O*-benzyl-1-*C*-[2-(benzyloxy)-5-formyl-4-methylphenyl]-5-thio-D-glucopyranose (18a)

To a solution of **17a** (11.1 g, 13.5 mmol) in tetrahydrofuran (100 mL), 6 N hydrochloric acid (100 mL) was added under ice cooling and stirred at room temperature for 12 hours. After addition of water under ice cooling, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give the titled compound (10.1 g, quant.) as a light-yellow oil. ^{1}H NMR

(300 MHz, $CDCl_3$) δ ppm 2.64 (s, 3 H) 3.51-3.70 (m, 2 H) 3.84-4.29 (m, 4 H) 4.46-4.97 (m, 8 H) 5.04-5.24 (m, 2 H) 6.62-6.82 (m, 3 H) 6.99-7.38 (m, 23 H) 7.60 (brs, 1 H) 10.05 (s, 1 H); ESI *m/z* = 803 $[M+Na]^+$.

2,3,4,6-Tetra-*O*-benzyl-1-C-[2-(benzyloxy)-5-formyl-4-methylphenyl]-D-glucopyranose (18b)

Compound **18b** (10.2 g, quant.) was obtained as a yellow oil from **17b** in a manner similar to that described for **18a**. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 2.66 (s, 3H), 3.60-3.72 (m, 2H), 3.74-3.82 (m, 1H), 4.01 (t, J = 9.1 Hz, 1H), 4.07-4.20 (m, 3H), 4.40-4.61 (m, 5H), 4.71-5.05 (m, 5H), 6.70 (s, 1H), 6.87 (d, J = 6.7 Hz, 2H), 7.06-7.40 (m, 23H), 8.07 (s, 1H), 10.06 (s, 1H).

(*1S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-1-thio-D-glucitol (19a)

To a solution of 1,4-dibromobenzene (6.08 g, 25.8 mmol) in tetrahydrofuran (50 mL), 2.67 M n-butyllithium in hexane (10.0 mL, 25.8 mmol) was added dropwise at −78°C under a nitrogen atmosphere. Then, a solution of **18a** (10.0 g, 13.0 mmol) in tetrahydrofuran (30 mL) was added dropwise and stirred at the same temperature for 15 minutes. After addition of saturated aqueous ammonium chloride, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1 → 2:1) to give a crude intermediate (8.89 g) as a yellow amorphous. To a solution of this crude intermediate (8.89 g) in acetonitrile (60 mL), Et_3SiH (4.60 mL, 28.4 mmol) and $BF_3 \cdot Et_2O$ (2.88 mL, 22.7 mmol) were added at −10°C under a nitrogen atmosphere and stirred at the same temperature for 20 minutes. The reaction mixture was warmed to room temperature and

chloroform (30 mL) was added thereto, followed by stirring for 3.5 hours. After addition of saturated aqueous sodium bicarbonate under ice cooling, the reaction mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 15:1 → 10:1) to give the titled compound (2.34 g, 20% in 2 steps) as a colorless and transparent amorphous substance. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.14 (s, 3 H) 3.05-3.18 (m, 1 H) 3.55 (t, J=8.63 Hz, 1 H) 3.64-4.10 (m, 7 H) 4.48-4.69 (m, 5 H) 4.81-5.13 (m, 5 H) 6.71-6.95 (m, 4 H) 7.03-7.52 (m, 27 H); ESI *m/z* = 922 $[M+NH_4]^+$.

(*1S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-glucitol (19b)

Compound **19b** (2.70 g, 23% in 2 steps) was obtained as a yellow oil from **18b** in a manner similar to that described for **19a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.17 (s, 3H) 3.53-3.63 (m, 1H) 3.68-3.91 (m, 7H) 4.00 (d, *J*=11.04 Hz, 1H) 4.39-4.95 (m, 8H) 5.01 (s, 2H) 6.75 (s, 1H) 6.86-6.97 (m, 4H) 7.10-7.35 (m, 24H) 7.36-7.46 (m, 2H).

(*1S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-{2-(benzyloxy)-5-[4-((*1E*)-3-carboxyprop-1-en-1-yl)benzyl]-4-methylphenyl}-1-thio-D-glucitol (20a)

To a solution of **19a** (1.0 g, 1.10 mmol) in acetonitrile (11 mL), 3-butenoic acid (227 mg, 2.64 mmol), palladium(II) acetate (49 mg, 0.218 mmol), tri-*O*-tolylphosphine (135 mg, 0.218 mmol) and triethylamine (558 mg, 5.51 mmol) were added and reacted at 120°C for 20 minutes using a Biotage microwave system. The reaction mixture was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1 → 1:1 → 1:2)

to give the titled compound (598 mg, 60%) as an orange-yellow amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.15 (s, 3 H) 3.00-3.34 (m, 3 H) 3.35-4.18 (m, 8 H) 4.45-4.68 (m, 5 H) 4.82-4.95 (m, 3 H) 4.97-5.16 (m, 2 H) 6.00-6.26 (m, 1 H) 6.33-6.50 (m, 1 H) 6.68-7.51 (m, 31 H); ESI *m/z* = 909 $[M-H]^-$.

(*1S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[2-(benzyloxy)-5-[4-[(*1E*)-3-carboxyprop-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol (20b)

Compound **20b** (681 mg, 87%) was obtained as an orange-yellow amorphous from **19b** in a manner similar to that described for **20a**. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.17 (s, 3H) 3.25 (d, *J*=5.50 Hz, 2H) 3.53-3.84 (m, 6H) 3.84-3.95 (m, 2H) 4.00 (d, *J*=10.55 Hz, 1H) 4.43 (d, *J*=10.55 Hz, 1H) 4.50 (d, *J*=11.92 Hz, 1H) 4.57-4.65 (m, 2H) 4.80-4.93 (m, 4H) 4.99 (s, 2H) 6.12-6.22 (m, 1H) 6.42 (d, *J*=15.59 Hz, 1H) 6.74 (s, 1H) 6.89-7.03 (m, 4H) 7.11-7.47 (m, 26H);

ESI *m/z* = 893 $[M-H]^-$.

(*1S*)-1,5-Anhydro-1-{5-[(4-{4-[(1,3-dihydroxy-2-methylpropan-2-yl)amino]-4-oxobutyl}phenyl)methyl]-2-hydroxy-4-methylphenyl}-1-thio-D-glucitol (22c)

To a solution of **21a** (410 mg, 0.449 mmol) in chloroform (4.5 mL), 2-amino-2-methyl-1,3-propanediol (118 mg, 1.12 mmol), HOBt·H_2O (114 mg, 0.846 mmol) and WSCI·HCl (162 mg, 0.846 mmol) were added and the mixture was stirred overnight. After addition of water, the reaction mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:1 → 1:2) to give **21c** (310 mg) as an orange-yellow oily compound. To a solution of **21c** in ethanol (6 mL), palladium hydroxide (200 mg) was added and

stirred overnight at room temperature under a hydrogen atmosphere. After the reaction mixture was filtered through celite, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (chloroform:methanol = 5:1) to give the titled compound (62 mg, 36% in 2 steps) as a colorless powder. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.22 (s, 3 H), 1.83 - 1.90 (m, 2 H), 2.08 (s, 3 H), 2.17 - 2.21 (m, 2 H), 2.58 (t, J = 7.8 Hz, 2 H), 2.96 - 3.01 (m, 1 H), 3.26 (t, J = 8.9 Hz, 1 H), 3.56 - 3.67 (m, 5 H), 3.73 (dd, J = 11.5, 6.4 Hz, 1 H), 3.81 - 3.85 (m, 3 H), 3.94 (dd, J = 11.5, 3.7 Hz, 1 H), 4.29 (d, J = 10.6 Hz, 1 H), 6.61 (s, 1 H), 6.99 - 7.03 (m, 2 H), 7.03 - 7.10 (m, 3 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.6, 19.7, 28.9, 35.9, 37.1, 39.5, 43.4, 50.7, 60.2, 62.9, 66.2, 76.1, 77.9, 81.3, 118.5, 122.8, 129.6, 129.8, 131.1, 131.8, 138.0, 140.1, 140.5, 155.2, 176.7; HR-MS ESI/APCI Dual *m/z*: 550.2458 [M+H]+ (calcd for $C_{28}H_{39}NO_8S$ 550.2469).

(*1S*)-1,5-Anhydro-1-(5-{[4-(4-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}-4-oxobutyl)phenyl]methyl}-2-hydroxy-4-methylphenyl)-1-thio-D-glucitol (22d)

Compound **22d** (45 mg, 20% in 2 steps) was obtained as a colorless powder from **21a** and tris(hydroxymethyl)aminomethane in a manner similar to that described for **22c**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.84 - 1.93 (m, 2 H), 2.08 (s, 3 H), 2.21 - 2.27 (m, 2 H), 2.60 (t, J = 7.6 Hz, 2 H), 2.95 - 3.01 (m, 1 H), 3.26 (t, J = 8.7 Hz, 1 H), 3.55 - 3.61 (m, 2 H), 3.69 - 3.76 (m, 6 H), 3.79 - 3.87 (m, 3 H), 3.94 (dd, J = 11.5, 3.7 Hz, 1 H), 4.29 (d, J = 10.6 Hz, 1 H), 6.60 (s, 1 H), 6.99 - 7.10 (m, 5 H); HR-MS ESI/APCI Dual *m/z*: 566.2350 [M+H]+ (calcd for $C_{28}H_{39}NO_9S$ 566.2418).

(*1S*)-1-{5-[(4-{4-[(1-Amino-2-methyl-1-oxopropan-2-yl)amino]-4-oxobutyl}phenyl)methyl]-2-hydroxy-4-methylphenyl}-1,5-anhydro-1-thio-D-glucitol (22e)

Compound **22e** (59 mg, 27% in 2 steps) was obtained as a colorless powder from **21a** and 2-amino-2-methylpropionamide in a manner similar to that described for **22c**. ^{1}H NMR (600 MHz, CD_3OD) δ

ppm 1.44 (s, 6 H), 1.82 - 1.92 (m, 2 H), 2.08 (s, 3 H), 2.15 - 2.22 (m, 2 H), 2.58 (t, *J* = 7.8 Hz, 2 H), 2.95 - 3.02 (m, 1 H), 3.26 (t, *J* = 8.9 Hz, 1 H), 3.56 - 3.60 (m, 1 H), 3.74 (dd, *J* = 11.5, 6.4 Hz, 1 H), 3.79 - 3.87 (m, 3 H), 3.94 (dd, *J* = 11.5, 3.7 Hz, 1 H), 4.29 (d, *J* = 10.6 Hz, 1 H), 6.60 (s, 1 H), 6.99 - 7.09 (m, 5 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.7, 25.8, 28.6, 36.0, 36.6, 39.5, 43.4, 50.7, 57.7, 62.9, 76.1, 77.9, 81.3, 118.5, 122.8, 129.6, 129.8, 131.1, 131.8, 138.0, 140.1, 140.5, 155.2, 175.6, 180.3; HR-MS ESI/APCI Dual *m/z*: 547.2457 [M+H]+ (calcd for $C_{28}H_{38}N_2O_7S$ 547.2472).

(*1S*)-1,5-Anhydro-1-{5-[(4-{4-[(1,3-dihydroxy-2-methylpropan-2-yl)amino]-4-oxobutyl}phenyl)methyl]-2-hydroxy-4-methylphenyl}-D-glucitol (22f)

Compound **22f** (32 mg, 29% in 2 steps) was obtained as a colorless powder from **21b** and 2-amino-2-methyl-1,3-propanediol in a manner similar to that described for **22c**. ^{1}H NMR (600 MHz, CD_3OD) *δ* ppm 1.22 (s, 3 H), 1.80 - 1.91 (m, 2 H), 2.09 (s, 3 H), 2.15 - 2.23 (m, 2 H), 2.58 (t, *J* = 7.6 Hz, 2 H), 3.37 - 3.50 (m, 3 H), 3.51 - 3.73 (m, 6 H), 3.83 - 3.90 (m, 3 H), 4.51 (d, *J* = 9.6 Hz, 1 H), 6.63 (s, 1 H), 6.99 - 7.09 (m, 4 H), 7.12 (s, 1 H); ESI *m/z* 556 $[M+Na]^+$.

(*1S*)-1,5-Anhydro-1-(5-{[4-(4-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}-4-oxobutyl)phenyl]methyl}-2-hydroxy-4-methylphenyl)-D-glucitol (22g)

Compound **22g** (60 mg, 42% in 2 steps) was obtained as a colorless powder from **21b** and tris(hydroxymethyl)aminomethane in a manner similar to that described for **22c**. ^{1}H NMR (600 MHz, CD_3OD) *δ* ppm 1.84 - 1.93 (m, 2 H), 2.10 (s, 3 H), 2.21 - 2.27 (m, 2 H), 2.59 (t, *J* = 7.6 Hz, 2 H), 3.37 - 3.44 (m, 2 H), 3.48 (t, *J* = 8.5 Hz, 1 H), 3.53 - 3.59 (m, 1 H), 3.70 (s, 7 H), 3.83 - 3.90 (m, 3 H), 4.51 (d, *J* = 9.6 Hz, 1 H), 6.63 (s, 1 H), 6.99 - 7.10 (m, 4 H), 7.11 (s, 1 H); ESI *m/z* 572$[M+Na]^+$.

(*1S*)-1-{5-[(4-{4-[(1-Amino-2-methyl-1-oxopropan-2-yl)amino]-4-oxobutyl}phenyl)methyl]-2-

hydroxy-4-methylphenyl}-1,5-anhydro-D-glucitol (22h)

Compound **22h** (32 mg, 33% in 2 steps) was obtained as a colorless powder from **21b** and 2-amino-2-methylpropionamide in a manner similar to that described for **22c**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.44 (s, 6 H), 1.82 - 1.90 (m, 2 H), 2.09 (s, 3 H), 2.19 (t, J = 7.6 Hz, 2 H), 2.57 (t, J = 7.6 Hz, 2 H), 3.37 - 3.52 (m, 2 H), 3.56 (t, J = 9.2 Hz, 2 H), 3.70 (dd, J = 11.9, 5.0 Hz, 1 H), 3.82 - 3.90 (m, 3 H), 4.51 (d, J = 9.6 Hz, 1 H), 6.63 (s, 1 H), 6.98 - 7.08 (m, 4 H), 7.11 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.8, 25.8, 28.6, 36.0, 36.6, 39.5, 57.6, 63.1, 71.9, 75.8, 78.9, 80.2, 82.5, 119.0, 124.1, 129.5, 129.7, 131.5, 131.7, 138.7, 140.2, 140.5, 155.1, 175.5, 180.2; HR-MS ESI/APCI Dual *m/z*: 531.2683 [M+H]+ (calcd for $C_{28}H_{38}N_2O_8$ 531.2701).

(*1S*)-1,5-Anhydro-1-(2-hydroxy-5-{[4-(3-{[(1-hydroxy-2-methylpropan-2-yl)carbamoyl]amino}propyl)phenyl]methyl}-4-methylphenyl)-D-glucitol (25b)

To an acetonitrile solution (5.4 mL) of **19b** (0.48 g, 0.539 mmol) were added *N*-allyl-*N'*-(2-hydroxy-1,1-dimethylethyl) urea (223 mg, 1.29 mmol), palladium(II) acetate (24.0 mg, 0.108 mmol), tri-*O*-tolylphosphine (66.0 mg, 0.216 mmol) and triethylamine (273 mg, 2.69 mmol), and the mixture was stirred at 120°C for 20 minutes with microwave manufactured by Biotage. The reaction solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform and then chloroform:methanol = 50:1) to obtain **24b** (210 mg, 40%) as a pale yellow amorphous. To an ethanol solution (3 mL) of **24b** (210 mg, 0.214 mmol) was added 20% palladium hydroxide (210 mg), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction solution was filtered through celite, and the solvent was evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 5:1) to obtain the titled compound (83 mg, 29% in 2 steps) as a colorless powder. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.23 (s, 6 H), 1.68 - 1.76 (m, 2 H), 2.09

(s, 3 H), 2.54 - 2.60 (m, 2 H), 3.05 (t, *J* = 6.9 Hz, 2 H), 3.37 - 3.44 (m, 2 H), 3.45 - 3.58 (m, 4 H), 3.70 (dd, *J* = 11.9, 5.0 Hz, 1 H), 3.83 - 3.90 (m, 3 H), 4.51 (d, *J* = 9.6 Hz, 1 H), 6.63 (s, 1 H), 6.98 - 7.03 (m, 2 H), 7.03 - 7.08 (m, 2 H), 7.12 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.8, 25.1, 33.3, 33.8, 39.5, 40.4, 55.0, 63.1, 71.0, 71.9, 75.8, 78.9, 80.2, 82.5, 119.0, 124.0, 129.4, 129.7, 131.5, 131.8, 138.8, 140.1, 140.6, 155.1, 161.1; HR-MS ESI/APCI Dual *m/z*: 533.2833 [M+H]+ (calcd for $C_{28}H_{40}N_2O_8$ 533.2857).

(*1S*)-1,5-Anhydro-1-{2-hydroxy-4-methyl-5-[(4-{3-[(4-methylpiperazine-1-carbonyl)amino]propyl}phenyl)methyl]phenyl}-D-glucitol (25a)

Compound **25a** (180 mg, 54% in 2 steps) was obtained as a colorless powder from **19b** and *N*-allyl-4-methylpiperazine-1-carboxyamide in a manner similar to that described for **25b**. ^{1}H NMR (600 MHz, CD_3OD) *δ* ppm 1.74 - 1.82 (m, 2 H), 2.10 (s, 3 H), 2.29 (s, 3 H), 2.37 - 2.42 (m, 4 H), 2.54 - 2.60 (m, 2 H), 3.15 (t, *J* = 7.1 Hz, 2 H), 3.33 - 3.44 (m, 6H), 3.48 (t, *J* = 8.9 Hz, 1 H), 3.53 - 3.58 (m, 1 H), 3.70 (dd, *J* = 12.2, 5.3 Hz, 1 H), 3.83 - 3.89 (m, 3 H), 4.51 (d, *J* = 9.6 Hz, 1 H), 6.63 (s, 1 H), 6.99 - 7.09 (m, 4 H), 7.12 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.8, 33.1, 34.0, 39.5, 41.8, 44.4, 44.5, 46.2, 55.7, 55.7, 63.1, 71.9, 75.7, 78.9, 80.2, 82.5, 119.0, 124.1, 128.4, 129.4, 129.7, 131.5, 131.8, 138.7, 140.1, 140.8, 155.1, 160.2; HR-MS ESI/APCI Dual *m/z*: 544.3004 [M+H]+ (calcd for $C_{29}H_{41}N_3O_7$ 544.3017).

(*1S*)-1,5-Anhydro-1-[5-({4-[3-({[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]carbamoyl}amino)propyl]phenyl}methyl)-2-hydroxy-4-methylphenyl]-D-glucitol (25c)

Compound **25c** (60 mg, 20% in 2 steps) was obtained as a colorless powder from **19b** and *N*-allyl-*N′*-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl] urea in a manner similar to that described for **25b**. ^{1}H NMR (600 MHz, CD_3OD) *δ* ppm 1.70 - 1.77 (m, 2 H), 2.09 (s, 3 H), 2.54 - 2.62 (m, 2 H), 3.07 (t,

J = 6.9 Hz, 2 H), 3.36 - 3.60 (m, 5 H), 3.61 - 3.73 (m, 6 H), 3.82 - 3.91 (m, 3 H), 4.51 (d, *J* = 9.6 Hz, 1 H), 6.63 (s, 1 H), 6.99 - 7.08 (m, 4 H), 7.08 - 7.15 (m, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.8, 19.8, 33.1, 33.8, 39.5, 40.6, 41.3, 61.9, 63.1, 63.4, 63.5, 71.9, 75.7, 78.9, 80.2, 82.5, 119.0, 124.0, 128.3, 129.5, 129.7, 129.8, 131.5, 131.8, 138.8, 140.1, 140.6, 155.1, 161.5; HR-MS ESI/APCI Dual *m/z*: 565.2743 [M+H]+ (calcd for $C_{28}H_{40}N_2O_{10}$ 565.2756).

2,3,4,6-Tetra-*O*-benzyl-1-*C*-[2-(benzyloxy)-5-[hydroxy[4-[2-(tritylamino)ethyl]phenyl]methyl]-4-methylphenyl]-D-glucopyranose (27)

To a tetrahydrofuran solution (3 mL) of 2-(4-bromophenyl)-*N*-tritylethaneamine (**26**) (0.814 g, 1.84 mmol) was added dropwise under nitrogen atmosphere at −78°C a 2.66 M hexane solution of *n*-butyllithium (0.690 mL, 1.84 mmol), and the mixture was stirred for 30 minutes at the same temperature. Then a tetrahydrofuran solution (3 mL) of **18b** (0.670 g, 0.876 mmol) was added dropwise, and the mixture was stirred for 30 minutes at the same temperature. To the reaction solution was added water, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with NH type silica gel column chromatography (chloroform) to obtain the titled compound (0.634 g, 64%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.12-2.22 (m, 3H), 2.30-2.43 (m, 2H), 2.65-2.76 (m, 2H), 3.64-3.84 (m, 3H), 3.99-4.22 (m, 4H), 4.42-4.65 (m, 5H), 4.75-5.04 (m, 5H), 5.83-5.91 (m, 1H), 6.67-6.72 (m, 1H), 6.88-7.43 (m, 44H).

(*1S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[2-(benzyloxy)-4-methyl-5-[4-[2-(tritylamino)ethyl]benzyl]phenyl]-D-glucitol (28)

To an acetonitrile solution (6 mL) of **27** (0.638 g, 0.565 mmol) were added under a nitrogen

atmosphere at 0°C Et_3SiH (0.270 mL, 1.69 mmol) and $BF_3 \cdot Et_2O$ (1.58 mL, 1.24 mmol), and the mixture was stirred for 30 minutes at the same temperature. To the reaction solution cooled in ice was added a saturated sodium bicarbonate aqueous solution and the resulting mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 9:1) to obtain the titled compound (0.402 g, 59%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.16 (s, 3H), 2.36 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 3.52-3.65 (m, 1H), 3.67-3.92 (m, 7H), 4.00 (d, J = 10.9 Hz, 1H), 4.37-4.67 (m, 5H), 4.78-5.06 (m, 5H), 6.73 (s, 1H), 6.83-7.01 (m, 5H), 7.05-7.45 (m, 40H).

(*1S*)-1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-methylphenyl]-D-glucitol (29)

To a chloroform solution of **28** (0.402 g, 0.336 mmol) was added at room temperature trifluoroacetate (0.5 mL), and the mixture was stirred for 3 hours at the same temperature. To the reaction solution was added ethanol and then the solvent was evaporated under reduced pressure. Thus obtained residue was purified with NH type silica gel column chromatography (hexane:ethyl acetate = 4:6, chloroform:methanol = 20:1) to obtain the titled compound (0.296 g, quant.) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.20 (s, 3H), 2.65 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H), 3.52-3.95 (m, 8H), 4.00 (d, J = 10.7 Hz, 1H), 4.38-4.67 (m, 5H), 4.81-5.04 (m, 5H), 6.74 (s, 1H), 6.88-7.45 (m, 30H).

(*1S*)-1,5-Anhydro-1-[5-({4-[2-({[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]carbamoyl}amino)ethyl]phenyl}methyl)-2-hydroxy-4-methylphenyl]-D-glucitol (30b)

To a chloroform solution (3 mL) of 4-nitrophenyl chloroformate (0.177 g, 0.879 mmol) and pyridine

(0.071 mL, 0.88 mmol), which was cooled in ice, was added dropwise a chloroform solution (3 mL) of **29** (0.249 g, 0.292 mmol), and the mixture was stirred for 20 minutes at room temperature. After that, a chloroform solution (3 mL) of tris(hydroxymethyl)aminomethane (0.283 g, 2.34 mmol) and dimethyl sulfoxide (3 mL) were added thereto, and the mixture was stirred overnight at the same temperature. To the reaction solution was added water, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and brine (3 times), and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with NH type silica gel column chromatography (chloroform) to (*1S*)-1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-1-[2-(benzyloxy)-5-({4-[2-({[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]carbamoyl}amino)ethyl]phenyl}methyl)-4-methylphenyl]-D-glucitol (0.251 g) as a pale yellow oil. To a methanol solution (4 mL) of (*1S*)-1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-1-[2-(benzyloxy)-5-({4-[2-({[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]carbamoyl}amino)ethyl]phenyl}methyl)-4-methylphenyl]-D-glucitol (0.242 g, 0.242 mmol) was added 20% palladium hydroxide (0.180 g), and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through celite and evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 17:3) to obtain the titled compound (85 mg, 55% in 2 steps) as a colorless powder. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 2.09 (s, 3 H), 2.68 (t, J = 7.3 Hz, 2 H), 3.24 - 3.32 (m, 3 H), 3.36 - 3.66 (m, 9 H), 3.68 - 3.74 (m, 1 H), 3.81 - 3.90 (m, 3 H), 4.52 (d, J = 9.6 Hz, 1 H), 6.64 (s, 1 H), 7.00 - 7.14 (m, 5 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.8, 37.1, 39.5, 42.7, 62.0, 63.1, 63.5, 71.9, 75.7, 78.9, 80.2, 82.5, 119.0, 124.1, 129.8, 129.9, 131.5, 131.7, 138.2, 138.8, 140.6, 155.1, 161.4; IR (KBr) $\tilde{\nu}$ = 3319, 2923, 1639, 1566, 1511, 1442, 1285, 1083, 1029 cm^{-1}; HR-MS ESI/APCI Dual *m/z*: 551.2586 $[M+H]^+$ (calcd for $C_{27}H_{38}N_2O_{10}$ 551.2599); $[\alpha]_D^{25}$ = +13 (*c* = 0.10, MeOH).

(*1S*)-1,5-Anhydro-1-(2-hydroxy-5-{[4-(2-{[(1-hydroxy-2-methylpropan-2-yl)carbamoyl]amino}ethyl)phenyl]methyl}-4-methylphenyl)-D-glucitol (30a)

Compound **30a** (57 mg, 38% in 2 steps) was obtained as a colorless powder from **29** and 2-amino-2-methyl-1-propanol in a manner similar to that described for **25b**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.25 (s, 6 H), 2.13 (s, 3 H), 2.72 (t, J = 7.1 Hz, 2 H), 3.25 - 3.37 (m, 3 H), 3.38 - 3.80 (m, 6 H), 3.86 - 3.96 (m, 3 H), 4.56 (d, J = 9.3 Hz, 1 H), 6.68 (s, 1 H), 7.03 - 7.19 (m, 5 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.8, 25.1, 37.2, 39.5, 42.5, 55.0, 63.1, 71.0, 71.9, 75.8, 78.9, 80.2, 82.5, 119.0, 124.1, 129.8, 129.9, 131.6, 131.7, 138.3, 138.8, 140.6, 155.1, 161.0; HR-MS ESI/APCI Dual *m/z*: 519.2692 $[M+H]^+$ (calcd for $C_{27}H_{38}N_2O_8$ 519.2701).

Methyl 1-*C*-(5-bromo-2,4-dimethylphenyl)-D-glucopyranoside (35)

A 2.8-M *n*-butyllithium solution in hexane (26.8 mL, 74.2 mmol) was added dropwise to a THF (100 mL) solution of 1,5-dibromo-2,4-dimethylbenzene (**33**) (17.6 g, 74.2 mmol) at −78°C in a nitrogen atmosphere, and the mixture was stirred for 15 minutes at the same temperature. Then, a THF (60 mL) solution of 2,3,4,6-tetra-*O*-trimethylsilyl-D-glucono-1,5-lactone (**34**) (38.1 g, 81.7 mmol) was added dropwise over 25 minutes, and the mixture was stirred for 15 minutes at the same temperature. Ice water was added to the reaction solution, and the resulting mixture was warmed to room temperature and then extracted with ethyl acetate. The combined organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in a methanol (370 mL) solution containing methanesulfonic acid (0.480 mL, 7.42 mmol), and the solution was stirred for 16 hours at room temperature. Then, the solution was neutralized with triethylamine (1.40 mL, 10.3 mmol), and the reaction mixture was concentrated. The resulting residue was purified using neutral silica gel column chromatography (chloroform:methanol ratio = 9:1 to 8:1) to obtain the titled

compound as a light-yellow gummy substance (17.8 g, 64% in 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.32 (s, 3H), 2.33 (s, 3H), 2.93 (s, 1H), 3.08 (s, 3H), 3.26–3.38 (m, 1H), 3.55–3.62 (m, 2H), 3.82–3.92 (m, 4H), 4.83–4.91 (m, 1H), 4.97–5.08 (m, 1H), 7.00 (s, 1H), 7.57 (s, 1H).

Methyl 1-*C*-(5-bromo-2,4-dimethylphenyl)-2,3,4,6-tetrakis-*O*-(trimethylsilyl)-D-glucopyranoside (36)

Triethylamine (24.1 mL, 172 mmol) and chlorotrimethylsilane (18.8 mL, 147 mmol) were added to a *N, N*-dimethylformamide (102 mL) solution of compound **35** (9.30 g, 24.7mmol) under ice cooling. The reaction mixture was stirred for 16 hours at room temperature, and ice water was added. The mixture was extracted twice with toluene, and the combined organic layer was washed with water and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure to obtain the titled compound (15.8 g, 96%). This compound was used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm −0.32 (s, 9H), 0.13 (s, 9H), 0.19 (s, 9H), 0.20 (s, 9H), 2.33 (s, 3H), 2.43 (s, 3H), 3.10 (s, 3H), 3.38 (d, J = 9.0 Hz, 1H), 3.49–3.62 (m, 2H), 3.77 (d, J = 2.9 Hz, 2H), 3.97–4.07 (m, 1H), 6.99 (s, 1H), 7.67 (s, 1H).

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromophenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (40a)

A 2.77 M *n*-butyllithium hexane solution (2.8 mL, 7.8 mmol) was added dropwise to a THF (40 mL) solution of compound **7** (5.2 g, 7.8 mmol) at −78°C in an argon atmosphere, and the mixture was stirred for 30 minutes at the same temperature. Then, a THF (10 mL) solution of 4-bromobenzaldehyde (**37a**) (1.4 g, 8.6 mmol) was added dropwise over 15 minutes, and the mixture was stirred for 2 hours at the same temperature. Water was added to the reaction liquid; after the mixture was warmed to room temperature, the warmed mixture was extracted twice with ethyl acetate. The combined organic layer

was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in a methanol (39 mL) solution containing methanesulfonic acid (0.051 mL), and the solution was stirred for 2 hours at room temperature. The reaction liquid was neutralized with triethylamine (1.1 mL), and the reaction mixture was concentrated to obtain compound **38a** (4.17 g). Compound **38a** was used in the next reaction without purification. Compound **38a** (4.17 g, 7.80 mmol) was dissolved in pyridine (24 mL). Acetic anhydride (20 mL) was added to the resulting solution, and the mixture was stirred for 16 hours at room temperature. Ice water was added, and the mixture was extracted twice with toluene. The combined organic layer was washed with 2 M hydrochloric acid and a saturated sodium hydrogen carbonate solution and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure to obtain crude compound **39a** (4.43 g). Et_3SiH (4.20 mL, 25.4 mmol) was added to a solution of crude compound **39a** (4.43 g) in chloroform (22 mL) and acetonitrile (22 mL), and the mixture was cooled with ice in a nitrogen atmosphere. Under ice cooling, $BF_3 \cdot OEt_2$ (2.40 mL, 19.0 mmol) was added dropwise over 10 minutes, and the mixture was stirred for 2 hours at the same temperature. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, and the mixture was extracted with ethyl acetate. Then, the organic layer was dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using acidic silica gel column chromatography (hexane:ethyl acetate ratio = 40:1) to obtain the titled compound as a colorless powder (1.74 g, 37% in 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.76 (s, 3H), 2.01 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.35 (s, 3H), 3.79–3.90 (m, 3H), 4.10–4.27 (m, 2H), 4.58–4.67 (m, 1H), 5.18–5.36 (m, 3H), 6.92–6.97 (m, 3H), 7.11 (s, 1H), 7.33–7.36 (m, 1H), 7.37–7.40 (m, 1H).

MS ESI/APCI Dual *m/z* 627$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-fluorophenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (11b)

Compound **40b** (69% in 4 steps) was obtained from **36** and **37b** in a manner similar to that described for **40a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.77 (s, 3H), 2.01 (s, 3H), 2.05 (s, 4H), 2.07 (s, 3H), 2.13 (s, 3H), 2.36 (s, 3H), 3.78–3.96 (m, 3H), 4.11–4.28 (m, 2H), 4.60 (d, J = 9.5 Hz, 1H), 5.17–5.37 (m, 3H), 6.74 (t, J = 8.1 Hz, 1H), 6.95 (s, 1H), 7.08 (s, 1H), 7.12–7.17 (m, 2H), 7.21 (dd, J = 9.3, 1.9 Hz, 1H). MS ESI/APCI Dual *m/z* 645[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-methylphenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (40c)

Compound **40c** (85% in 4 steps) was obtained from **36** and **37c** in a manner similar to that described for **40a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.76 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 2.27 (s, 3H), 2.37 (s, 3H), 3.76–3.86 (m, 3H), 4.08–4.28 (m, 2H), 4.58 (d, J = 9.6 Hz, 1H), 5.14–5.36 (m, 3H), 6.61 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 9.2 Hz, 2H), 7.19 (dd, J = 8.16, 1.79 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H). MS ESI/APCI Dual *m/z* 641[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-chlorophenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (40d)

Compound **40d** (52% in 4 steps) was obtained from **36** and **37d** in a manner similar to that described for **40a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.78 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.10 (s, 3H), 2.37 (s, 3H), 3.78–3.87 (m,3H), 4.08–4.29 (m, 2H), 4.60 (d, J = 9.3 Hz, 1H), 5.16-5.38 (m, 3H), 6.65 (d, J = 8.2 Hz, 1H), 6.97 (s, 1H), 7.03 (s, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H). MS ESI/APCI Dual *m/z* 661[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-(5-{[4-bromo-2-(propan-2-yl)phenyl]methyl}-2,4-dimethylphenyl)-D-glucitol (40e)

Compound **40e** (56% in 4 steps) was obtained from **36** and **37e** in a manner similar to that described for **40a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 (d, J = 3.6 Hz, 3H), 1.23 (d, J = 3.6 Hz, 3H), 1.76 (s, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.13 (s, 3H), 2.36 (s, 3H), 3.06–3.18 (m, 1H), 3.73–3.84 (m, 1H), 3.87 (s, 2H), 4.07–4.14 (m, 1H), 4.18–4.27 (m, 1H), 4.58 (d, J = 9.8 Hz, 1H), 5.10–5.34 (m, 3H), 6.60 (d, J = 8.2 Hz, 1H), 6.92 (s, 1H), 6.96 (s, 1H), 7.17 (dd, J = 8.2, 2.2 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H). MS ESI/APCI Dual *m/z* 647[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-methoxyphenyl)methyl]-2,4-dimethylphenyl}-D-glucitol(40f)

Compound **40f** (84% in 4 steps) was obtained from **36** and **37f** in a manner similar to that described for **40a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.75 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 2.36 (s, 3H), 3.79-3.86 (m, 6H), 4.11–4.17 (m, 1H), 4.20–4.27 (m, 1H), 4.59 (d, J = 9.5 Hz, 1H), 5.17–5.36 (m, 3H), 6.58 (d, J = 7.9 Hz, 1H), 6.92–6.98 (m, 3H), 7.05 (s, 1H).

***N*-(1-Hydroxy-2-methylpropan-2-yl)-2,2-dimethylbut-3-enamide (43)**

2-Amino-2-methylpropan-1-ol (**42**) (1.00 g, 11.2 mol), WSCI·HCl (2.15 g, 11.2 mmol) and HOBt·H_2O (1.51 g, 11.2 mmol) were added to a chloroform (37 mL) solution of 2,2-dimethyl-3-butenoic acid (**41**) (1.11 g, 7.48 mmol) in a nitrogen atmosphere, and the mixture was stirred for 16 hours at room temperature. Water was added to the reaction liquid, and the mixture was extracted with chloroform. Then, the organic layer was washed with 2 M hydrochloric acid, a saturated aqueous solution of sodium hydrogen carbonate, and a saturated saline solution and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced

pressure. The resulting residue was purified using silica gel column chromatography (hexane:ethyl acetate ratio = 9:1 to 1:1) to obtain the titled compound as a colorless powder (0.70 g, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (s, 6H), 1.28 (s, 6H), 3.55 (s, 2H), 5.19-5.30 (m, 2H), 5.74 (br s, 1H), 5.99 (dd, J = 17.49, 10.65 Hz, 1H).

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (44a)

In an argon atmosphere, an acetonitrile (36 mL) suspension of compound **40a** (0.50 g, 0.83 mmol), compound **43** (0.370 g, 1.98 mmol), palladium (II) acetate (37.0 mg, 0.170 mmol), tri-*o*-tolylphosphine (101 mg, 0.330 mmol), and triethylamine (0.580 mL, 4.15 mmol) was stirred for 30 minutes at 120°C under microwave irradiation. The reaction mixture was filtered using Celite (registered trademark) and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the resulting residue was purified using neutral silica gel column chromatography (hexane:ethyl acetate ratio = 1:2) to obtain the titled compound as a partially purified product (1.5 g). The titled compound (1.5 g) was further purified using neutral silica gel column chromatography (hexane:ethyl acetate ratio = 7:3→2:8) to obtain the titled compound as a light-yellow amorphous substance (514 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (s, 6H), 1.36 (s, 6H), 1.78 (s, 3H), 2.01 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.14 (s, 3H), 2.36 (s, 3H), 3.79–3.87 (m, 1H), 3.93 (s, 2H), 4.09–4.27 (m, 3H), 4.59–4.67 (m, 1H), 4.83 (br s, 1H), 5.18–5.37 (m, 3H), 6.22–6.29 (m, 1H), 6.47–6.54 (m, 1H), 6.94 (s, 1H), 7.06 (d, J = 8.1 Hz, 2H), 7.14 (s, 1H), 7.29 (d, J = 8.2 Hz, 2H). MS ESI/APCI Dual m/z 710$[M+H]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(2-fluoro-4-{(*1E*)-4-[(1-hydroxy-2-

methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (44b)

Compound **44b** (70%) was obtained from **40b** and **43** in a manner similar to that described for **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (s, 5H), 1.37 (s, 4H), 1.78 (s, 2H), 2.00 (s, 2H), 2.06 (s, 2H), 2.06 (s, 2H), 2.16 (s, 2H), 2.36 (s, 3H), 3.55 (s, 2H), 3.79–4.00 (m, 1H), 3.80–4.00 (m, 2H), 4.12–4.27 (m, 2H), 4.61 (d, J = 9.5 Hz, 1H), 5.19–5.37 (m, 3H), 6.24–6.32 (m, 1H), 6.43–6.51 (m, 1H), 6.84 (t, J = 7.9 Hz, 1H), 6.95 (s, 1H), 7.01–7.12 (m, 3H). MS ESI/APCI Dual *m/z* 728$[M+H]^+$, 750$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (44c)

Compound **44c** (36%) was obtained from **40c** and **43** in a manner similar to that described for **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (s, 6H), 1.37 (s, 6H), 1.77 (s, 3H), 1.99 (s, 3H), 2.05 (s, 3H), 2.14 (s, 3H), 2.31 (s, 3H), 2.37 (s, 3H), 3.55 (d, J = 5.28 Hz, 2H), 3.78-3.87 (m, 3H), 4.07–4.25 (m, 2H), 4.58 (d, J = 9.6 Hz, 1H), 4.85 (s, 1H), 5.13–5.35 (m, 3H), 6.22–6.32 (m, 1H), 6.46–6.54 (m, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.97 (s, 2H), 7.10 (dd, J = 8.1, 1.7 Hz, 1H), 7.23 (s, 1H).

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(2-chloro-4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (44d)

Compound **44d** was obtained as a mixture with **43** from **40d** in a manner similar to that described for **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (s, 6H), 1.37 (s, 6H), 1.79 (s, 3H), 1.99 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.13 (s, 3H), 2.38 (s, 3H), 2.49 (s, 3H), 3.55 (s, 2H), 3.77–3.87 (m, 1H), 3.91–4.08 (m, 2H), 4.11–4.27 (m, 2H), 4.61 (d, J = 9.48 Hz, 1H), 5.28–5.38 (m, 3H), 6.26–6.33 (m, 1H),

6.42–6.50 (m, 1H), 6.76 (d, *J* = 8.08 Hz, 1H), 6.97 (s, 1H), 7.04–7.19 (m, 2H), 7.29–7.36 (m, 1H), 7.40–7.46 (m, 1H).

(*1S*)-2,3,4,6-Tetra-O-acetyl-1,5-anhydro-1-(5-{[4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-(propan-2-yl)phenyl]methyl}-2,4-dimethylphenyl)-D-glucitol (44e)

Compound **44e** was obtained as a mixture with **43** from **40e** in a manner similar to that described for **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.24–1.28 (m, 12H), 1.38 (s, 6H), 1.77 (s, 3H), 1.98 (s, 3H), 2.04 (s, 6H), 2.16 (s, 3H), 2.37 (s, 3H), 3.12–3.22 (m, 1H), 3.55 (d, *J* = 5.9 Hz, 2H), 3.77–3.83 (m, 1H), 3.93 (s, 2H), 4.07–4.14 (m, 1H), 4.16–4.25 (m, 1H), 4.59 (d, *J* = 9.9 Hz, 1H), 4.82–4.89 (m, 2H), 5.12–5.35 (m, 3H), 5.96 (d, *J* = 10.7 Hz, 1H), 6.02 (d, *J* = 10.6 Hz, 1H), 6.27 (d, *J* = 16.2 Hz, 1H), 6.50–6.58 (m, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 4.4 Hz, 2H), 7.13 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.29 (s, 1H). MS ESI/APCI Dual *m/z* 752$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methoxyphenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (44f)

Compound **44f** was obtained as a mixture with **43** from **40f** in a manner similar to that described for **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22–1.29 (m, 56H), 1.37 (s, 6H), 1.77 (s, 3H), 2.00 (s, 3H), 2.03–2.07 (m, 9H), 2.15 (s, 3H), 2.36 (s, 3H), 2.49 (s, 2H), 3.77–3.87 (m, 3H), 3.89 (s, 3H), 4.12 (q, *J* = 7.2 Hz, 1H), 4.21 (d, *J* = 4.7 Hz, 1H), 4.60 (d, *J* = 9.3 Hz, 1H), 5.16–5.37 (m, 3H), 6.22–6.31 (m, 1H), 6.47–6.55 (m, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.82–6.90 (m, 2H), 6.95 (s, 1H), 7.08 (s, 1H). MS ESI/APCI Dual *m/z* 740$[M+Na]^+$.

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (45a)

Sodium methoxide (4.88 M) in methanol solution (0.593 mL, 2.90 mmol) was added to a methanol (4.8 mL) solution of compound **44a** (0.514g, 0.724 mmol), and the mixture was stirred for 2 hours at room temperature. Dry ice was added to the reaction liquid, and the solvent was distilled off under reduced pressure. The resulting residue was purified using neutral silica gel column chromatography (ethyl acetate:ethanol:water ratio = 30:2:1) to obtain the titled compound as colorless amorphous substance (306 mg, 78%). ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.26 (s, 6H) 1.33 (s, 6H) 2.13 (s, 3H) 2.36 (s, 3H) 3.34 (s, 1H) 3.31–3.71 (m, 7H) 3.82–3.91 (m, 1H) 3.94 (s, 2H) 4.42 (d J = 9.1 Hz, 1H) 6.29–6.38 (m, 1H) 6.39–6.46 (m, 1H) 6.47–6.59 (m, 1H) 6.95 (s, 1H) 7.07 (d, J = 8.2 Hz, 2H) 7.21–7.34 (m, 3H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 19.4, 19.5, 23.8, 25.9, 40.1, 46.5, 55.9, 63.4, 69.8, 72.3, 76.1, 79.8, 80.3, 82.5, 127.5, 130.0, 130.4, 130.5, 133.4, 135.0, 136.2, 136.3, 136.8, 137.3, 137.5, 141.9, 179.0; HRMS ESI/APCI Dual *m/z*: 542.3105 $[M+H]^+$ (calcd for $C_{31}H_{43}NO_7$ 542.3112).

(*1S*)-1,5-Anhydro-1-{5-[(2-fluoro-4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (45b)

Compound **45b** (59%) was obtained from **44b** in a manner similar to that described for **45a**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.27 (s, 6H) 1.34 (s, 6H) 2.15 (s, 3H) 2.36 (s, 3H) 3.37–3.40 (m, 1H) 3.44–3.54 (m, 4H) 3.60–3.72 (m, 1H) 3.82–3.97 (m, 4H) 4.38–4.42 (m, 1H) 6.36–6.56 (m, 2H) 6.85–7.27 (m, 5H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 19.3, 19.4, 23.8, 25.8, 32.4, 46.6, 56.0, 63.4, 69.8, 72.3, 76.1, 79.8, 80.3, 82.5, 113.4, 113.6, 123.5 (d, J = 2.5 Hz), 128.2, 128.3, 129.5, 130.3, 131.9 (d, J = 5.0 Hz), 133.4, 136.1, 136.5, 136.7, 137.0, 137.2, 138.9 (d, J = 7.5 Hz), 161.6, 163.5, 178.7; HRMS ESI/APCI Dual *m/z*: 560.3004 $[M+H]^+$ (calcd for $C_{31}H_{42}FNO_7$ 560.3018).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (45c)

Compound **45c** (77%) was obtained from **44c** in a manner similar to that described for **45a**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.27 (s, 6H) 1.34 (s, 6H) 2.14 (s, 3H) 2.30 (s, 3H) 2.37 (s, 3H) 3.34–3.49 (m, 6H) 3.61 (dd, J = 11.8, 5.6 Hz, 1H) 3.80–3.91 (m, 3H) 4.34–4.41 (m, 1H) 6.29–6.39 (m, 1H) 6.43 (s, 1H) 6.46–6.57 (m, 1H) 6.76 (d, J = 7.9 Hz, 1H) 6.99 (s, 1H) 7.04–7.13 (m, 2H) 7.24 (s, 1H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 19.4, 19.4, 19.9, 23.9, 25.9, 37.3, 46.5, 55.9, 63.5, 69.8, 72.3, 75.9, 79.9, 80.3, 82.5, 125.1, 129.2, 130.0, 130.2, 130.7, 133.3, 134.8, 136.3, 136.4, 136.7, 137.0, 137.3, 137.9, 139.8, 179.0; HRMS ESI/APCI Dual *m/z*: 556.3252 $[M+H]^+$ (calcd for $C_{32}H_{45}NO_7$ 556.3269).

(*1S*)-1,5-Anhydro-1-{5-[(2-chloro-4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (45d)

Compound **45d** (5% in 2 steps) was obtained from **44d** in a manner similar to that described for **45a**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.27 (s, 6H) 1.34 (s, 6H) 2.11 (s, 3H) 2.37 (s, 3H) 3.33–3.69 (m, 7H) 3.81–3.92 (m, 1H) 4.02 (s, 2H) 4.41 (d, J = 9.17 Hz, 1H) 6.35–6.56 (m, 3H) 6.83 (d, J = 7.9 Hz, 1H) 7.00 (s, 1H) 7.14–7.25 (m, 2H) 7.45–7.47 (m, 1H); MS ESI/APCI Dual *m/z* 576[M+H]+, 574[M-H]$^-$.

(*1S*)-1,5-Anhydro-1-(5-{[4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-(propan-2-yl)phenyl]methyl}-2,4-dimethylphenyl)-D-glucitol (45e)

Compound **45e** (51% in 2 steps) was obtained from **44e** in a manner similar to that described for **45a**. ^{1}H NMR (300 MHz, CD3OD) δ ppm 1.23 (d, J = 2.3 Hz, 3H) 1.26 (d, J = 2.3 Hz, 3H) 1.28 (s, 6H) 1.36 (s, 6H) 2.17 (s, 3H) 2.37 (s, 3H) 3.14-3.23 (m, 1H) 3.34–3.50 (m, 6H) 3.55–3.64 (m, 2H) 3.84

(dd, *J* = 12.0, 2.0 Hz, 1H) 3.96 (s, 2H) 4.33–4.40 (m, 1H) 6.31–6.39 (m, 1H) 6.45 (s, 1H) 6.51–6.60 (m, 1H) 6.79 (d, *J* = 8.1 Hz, 1H) 7.00 (d, *J* = 5.9 Hz, 2H) 7.12 (dd, *J* = 7.9, 1.6 Hz, 1H) 7.34 (d, J=1.6 Hz, 1H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 19.4, 19.5, 23.9, 24.1, 24.2, 26.0, 30.2, 36.6, 46.5, 55.9, 63.5, 69.8, 72.3, 76.0, 79.9, 80.3, 82.5, 124.6, 124.7, 129.8, 130.9, 131.0, 133.3, 134.7, 136.3, 136.6, 136.8, 137.1, 137.5, 138.1, 148.6, 179.0; HRMS ESI/APCI Dual *m/z*: 584.3569 $[M+H]^+$ (calcd for $C_{34}H_{49}NO_7$ 584.3582).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methoxyphenyl)methyl]-2,4-dimethylphenyl}-D-glucitol (45f)

Compound **45f** (33% in 2 steps) was obtained from **44f** in a manner similar to that described for **45a**. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.27 (s, 6H) 1.35 (s, 6H) 2.13 (s, 3H) 2.35 (s, 3H) 3.36–3.67 (m, 7H) 3.83–3.89 (m, 5H) 4.40 (d, *J* = 9.0 Hz, 1H) 6.29–6.60 (m, 3H) 6.71–6.79 (m, 1H) 6.82–6.91 (m, 1H) 6.92–7.03 (m, 2H) 7.18 (s, 1H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 19.3, 19.4, 23.8, 25.9, 33.8, 46.5, 55.9, 56.0, 63.5, 69.8, 72.3, 76.1, 79.9, 80.3, 82.5, 109.2, 119.9, 130.1, 130.4, 130.8, 130.9, 133.2, 135.1, 136.2, 136.5, 137.3, 137.3, 137.8, 159.0, 179.0; HRMS ESI/APCI Dual *m/z*: 572.3198 $[M+H]^+$ (calcd for $C_{32}H_{45}NO_8$ 572.3218).

(*1S*)-1,5-Anhydro-2,3,4,6-tetra-O-benzyl-1-{2-(benzyloxy)-5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-4-methylphenyl}-D-glucitol (46)

In an argon atmosphere, an acetonitrile (36 mL) suspension of (*1S*)-1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-1-{2-(benzyloxy)-5-[(4-bromophenyl)methyl]-4-methylphenyl}-D-glucitol (**19b**) (518 mg, 0.58 mmol), compound **43** (162 mg, 0.870 mmol), palladium (II) acetate (13.1 mg, 0.0580 mmol), tri-*o*-tolylphosphine (35.4 mg, 0.116 mmol), and triethylamine (0.406 mL, 2.91 mmol) was stirred for 20

minutes at 120°C under microwave irradiation. The reaction mixture was filtered using Celite (registered trademark) and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the resulting residue was purified using neutral silica gel column chromatography (hexane:ethyl acetate ratio = 1:1) to obtain the titled compound as pale-yellow oil (416 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 (s, 6H), 1.36 (s, 6H), 2.20 (s, 3H), 3.55 (s, 3H), 3.72–3.79 (m, 4H), 3.92 (s, 2H), 4.00 (m, 1H), 4.41–4.52 (m, 2H), 4.57–4.65 (m, 2H), 4.83–4.92 (m, 3H), 5.00 (s, 2H), 5.21–5.29 (m, 2H), 5.73 (s, 2H), 6.21 (d, J = 16.3 Hz, 1H), 6.46 (d, J = 16.3 Hz, 1H), 6.75 (s, 1H), 6.93 (m, 2H), 7.05 (d, J = 8.1 Hz, 2H), 7.11–7.46 (m, 26H); MS ESI/APCI Dual *m/z* 994$[M+H]^+$.

(*1S*)-1,5-Anhydro-1-{2-hydroxy-5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-4-methylphenyl}-D-glucitol (47)

EtSH (4.10 mL, 26.5 mmol) was added to a solution of compound **46** (410 mg, 0.412 mmol) in chloroform (4.1 mL), and the mixture was cooled with ice in a nitrogen atmosphere. Under ice cooling, $BF_3 \cdot OEt_2$ (0.82 mL, 6.5 mmol) was added, and the mixture was stirred for 2 hours at room temperature. Methanol was added to the reaction liquid, and the mixture was distilled off under reduced pressure. The resulting residue was purified using acidic silica gel column chromatography (ethyl acetate:ethanol:water ratio = 20:2:1) to obtain the titled compound as a partially purified product (72 mg). The titled compound (72 mg) was further purified using acidic silica gel column chromatography (chloroform→chloroform:methanol ratio = 4:1) to obtain the titled compound as colorless amorphous substance (8.7 mg, 4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.26 (s, 6H) 1.35 (s, 6H) 2.10 (s, 3H) 3.34–3.71 (m, 7H) 3.84–3.91 (m, 2H) 4.07 (s, 1H) 4.52 (d, J = 9.5 Hz, 1H) 6.29–6.58 (m, 2H) 6.64 (s, 1H) 7.04–7.14 (m, 3H) 7.30 (d, J = 8.2 Hz, 1H); MS ESI/APCI Dual *m/z* 544$[M+H]^+$, 542$[M-H]^-$.

2-Iodo-5-(propan-2-yl)phenol (49)

An aqueous suspended solution (75 mL) of potassium iodide (7.88 g, 0.0368 mol) and iodine (18.7 g, 0.0736 mol) was added to an acetic acid (200 mL) solution of 3-isopropylphenol (25.0 g, 0.184 mol), and the resulting reaction solution was stirred for 20 hours at room temperature. After the addition of diethyl ether (400 mL) and water (300 mL), the organic layer was separated. The organic layer was washed with water, a saturated aqueous solution of sodium hydrogen carbonate, and a saturated saline solution and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using neutral silica gel column chromatography (hexane:ethyl acetate ratio = 95:5) to obtain a colorless oily titled compound (27.6 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.16 –1.25 (m, 6 H) 2.64–2.98 (m, 1 H) 5.21 (s, 1 H) 6.57 (dd, J = 8.1, 2.2 Hz, 1 H) 6.88 (d, J = 2.2 Hz, 1 H) 7.54 (d, J = 8.1 Hz, 1 H).

2-(Benzyloxy)-1-iodo-4-(propan-2-yl)benzene (50a)

Benzyl bromide (14.4 mL, 0.121 mol) was added to an acetonitrile suspension of compound **49** (26.5 g, 0.101 mol) and potassium carbonate (20.9 g, 0.152 mol), and the mixture was stirred at room temperature for 2 hours, followed by the addition of methanol (1.0 mL) and stirring for an additional 30 minutes. The insoluble materials were filtered off, and the filtrate was concentrated. The resulting residue was purified using silica gel column chromatography (hexane:ethyl acetate ratio = 95:5) to obtain the titled compound as a colorless oil (30.2 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 (d, J = 7.0 Hz, 6 H) 2.84 (m, 1 H) 5.14 (s, 2 H) 6.62 (dd, J = 8.4, 2.2 Hz, 1 H) 6.74 (d, J = 2.2 Hz, 1 H) 7.23–7.58 (m, 5 H) 7.68 (d, J = 8.4 Hz, 1 H).

1-Iodo-2-methoxy-4-(propan-2-yl)benzene (50b)

Methyl iodide (9.80 mL, 0.156 mol) was added to an acetonitrile suspension (200 mL) of compound **49** (27.4 g, 0.104 mol) and potassium carbonate (21.7 g, 0.156 mol), and the mixture was stirred for

2.5 hours at 40°C. Methyl iodide (3.5 mL, 0.052 mol) was further added, and the mixture was stirred for 1 hour at the same temperature. The insoluble materials were filtered off, and the filtrate was diluted with ethyl acetate. The organic layer was washed with water, a 10% aqueous solution of sodium thiosulfate, and a saturated saline solution and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using neutral silica gel column chromatography (hexane→hexane:ethyl acetate ratio = 95:5) to obtain a light-yellow oily compound (24.5 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.24 (d, J = 6.8 Hz, 6 H) 2.87 (m, 1 H) 3.88 (s, 3 H) 6.58–6.65 (m, 1 H) 6.70 (d, J = 1.9 Hz, 1 H) 7.65 (d, J = 8.1 Hz, 1 H); MS ESI/APCI Dual *m/z* 277$[M+H]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[2-(benzyloxy)-4-(propan-2-yl)phenyl]-D-glucitol (51a)

n-Butyllithium (2.6 M) in hexane (33.0 mL, 85.7 mmol) was added dropwise to a solution of compound **50a** (30.2 g, 85.7 mmol) in THF (450 mL) at −78°C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 15 minutes. Next, a solution of 2,3,4,6-tetra-*O*-trimethylsilyl-D-glucono-1,5-lactone (**34**) (40.0 g, 85.7 mmol) in THF (230 mL) was added dropwise over 15 minutes, and the mixture was stirred at the same temperature for 20 minutes. Saturated aqueous ammonium chloride (150 mL) and water (100 mL) were added to the reaction mixture, and the mixture was warmed to room temperature and then extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in a solution containing methanesulfonic acid (2.9 g) in methanol (840 mL), and the mixture was stirred at room temperature for 14.5 hours. After neutralization with triethylamine (2.5 mL), the reaction mixture was concentrated. The resulting residue (46.4 g) was dissolved in pyridine (125 mL) and

cooled to 4°C. Acetic anhydride (75 mL) and 4-dimethylaminopyridine (102 mg, 0.835 mmol) were added to the solution, and the mixture was stirred at room temperature for 19 hours. After the addition of ice water (500 mL), the mixture was extracted twice with ethyl acetate (500 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure to yield a crude compound (53 g). Et_3SiH (13.7 mL, 85.7 mmol) and $BF_3{\cdot}Et_2O$ (10.9 mL, 85.7 mmol) were added to a solution of the crude compound in chloroform (250 mL) and acetonitrile (250 mL) at 4°C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 1.5 hours. The reaction mixture was diluted with saturated aqueous sodium bicarbonate and extracted with chloroform. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure and the resulting residue was purified using silica gel column chromatography (hexane:ethyl acetate ratio = 5:1 → 2:1) to obtain the titled compound as a light-yellow amorphous substance (19.1 g, 40% in 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.21 (d, J = 6.99 Hz, 6 H) 1.78 (s, 3 H) 2.01 (s, 6 H) 2.05 (s, 3 H) 2.86 (m, 1 H) 3.80 (m, 1 H) 4.06–4.13 (m, 1 H) 4.19–4.27 (m, 1 H) 4.96 (d, J = 9.9 Hz, 1 H) 5.10 (s, 2 H) 5.16–5.25 (m, 1 H) 5.33 (t, J = 9.2 Hz, 1 H) 5.40–5.49 (m, 1 H) 6.79 (d, J = 1.4 Hz, 1 H) 6.85 (dd, J = 7.9, 1.4 Hz, 1 H) 7.26–7.52 (m, 6 H); MS ESI/APCI Dual *m/z* 579[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-O-acetyl-1,5-anhydro-1-[2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (51b)

A 2.6 M *n*-butyllithium solution in hexane (34.0 mL, 88.6 mmol) was added dropwise to a THF (100 mL) solution of compound **50b** (24.5 g, 88.6 mmol) at −78°C in a nitrogen atmosphere, and the mixture was stirred for 5 minutes at the same temperature. Then, a THF (60 mL) solution of 2,3,4,6-tetra-*O*-trimethylsilyl-D-glucono-1,5-lactone (**34**) (37.6 g, 80.5 mmol) was added dropwise over 25

minutes, and the mixture was stirred for 10 minutes at the same temperature. Ice water was added to the reaction solution, and the resulting mixture was warmed to room temperature and then extracted twice with ethyl acetate. The combined organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in a methanol (380 mL) solution containing methanesulfonic acid (1.55 g, 16.1 mmol), and the solution was stirred for 2 hours at room temperature. Then, the solution was neutralized with triethylamine (11.2 mL, 80.5 mmol), and the reaction mixture was concentrated. The resulting residue (30.2 g) was dissolved in pyridine (100 mL), and acetic anhydride (100 mL) was then added; the mixture was then stirred for 14 hours at room temperature. Ice water (400 mL) was added, and the mixture was extracted twice with ethyl acetate (200 mL). The combined organic layer was washed with 1 M hydrochloric acid, a saturated aqueous solution of sodium hydrogen carbonate, and a saturated saline solution and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using neutral silica gel column chromatography (hexane→hexane:ethyl acetate ratio = 6:4) . The obtained organic layer was distilled off under reduced pressure. Et_3SiH (21 mL, 128 mmol) and $BF_3 \cdot OEt_2$ (49 mL, 385 mmol) were added to a solution of the resulting residue (32.8 g) in chloroform (150 mL) and acetonitrile (150 mL) at 4°C in a nitrogen atmosphere, and the mixture was stirred for 1 hour at the same temperature. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction solution, and the mixture was extracted with chloroform. Then, the organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using neutral silica gel column chromatography (hexane:ethyl acetate ratio = 2:1) to obtain the titled compound as light-yellow gummy substance (22.9 g, 59% in 4 steps). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (d, J = 7.0 Hz, 6

H) 1.77 (s, 3 H) 2.01 (s, 3 H) 2.05 (s, 3 H) 2.07 (s, 3 H) 2.87 (dt, J = 13.8, 7.0 Hz, 1 H) 3.80–3.87 (m, 1 H) 3.84 (s, 3 H) 4.09–4.16 (m, 1 H) 4.22–4.29 (m, 1 H) 4.88–4.95 (m, 1 H) 5.18–5.27 (m, 1 H) 5.32–5.38 (m, 2 H) 6.71 (d, J = 1.6 Hz, 1 H) 6.83 (dd, J = 7.9, 1.6 Hz, 1 H) 7.23–7.30 (m, 1 H); MS ESI/APCI Dual *m/z* 503[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[5-bromo-2-hydroxy-4-(propan-2-yl)phenyl]-D-glucitol (52a)

Ten-percent palladium on activated carbon (1.8 g) was added to a solution of compound **51a** (19.1 g, 34.3 mmol) in methanol (200 mL), and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours. After the reaction mixture was filtered through celite, the solvent was distilled off under reduced pressure and the resulting residue was purified using silica gel column chromatography (hexane:ethyl acetate ratio = 2:1 → 1:1) to yield (*1S*)-2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-[2-hydroxy-4-(propan-2-yl)phenyl]-D-glucitol as a colorless amorphous substance (12.3 g). Bromine (4.2 g, 26.3 mmol) was then added dropwise to a solution of (*1S*)-2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-1-[2-hydroxy-4-(propan-2-yl)phenyl]-D-glucitol (12.3 g, 26.3 mmol) in acetic acid (120 mL) at room temperature. The reaction mixture was stirred for 1.5 hours, and ice water (150 mL) was added. This mixture was extracted twice with ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium bicarbonate and 10% aqueous sodium thiosulfate and brine and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure. The resulting residue was dissolved in 2-propanol (20 mL), to which hexane (50 mL) was then added dropwise. The mixture was stirred at 4°C for 1 hour, and the resulting precipitate was filtered to obtain the titled compound (9.8 g, 52% in 2 steps) as a colorless powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.12-1.26 (m, 6 H) 1.89 (s, 3 H) 2.01 (s, 3 H) 2.07 (s, 3 H) 2.13 (s, 3 H) 3.22 (sept, *J* = 6.74 Hz, 1 H) 3.87 (ddd, *J* = 9.5, 3.7, 2.2 Hz, 1 H) 4.14–4.22 (m, 1 H) 4.28–

4.36 (m, 1 H) 4.53 (d, J = 9.3 Hz, 1 H) 5.16–5.39 (m, 3 H) 6.82 (s, 1 H) 7.14 (s, 1 H); MS ESI/APCI Dual *m/z* 567[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[5-bromo-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (52b)

Bromine (2.40 mL, 47.6 mmol) was added dropwise to an acetic acid (90 mL) solution of compound **51b** (22.9 g, 47.7 mmol) at room temperature. The reaction mixture was stirred for 1 hour, and the resulting reaction liquid was added to a saturated aqueous solution of sodium hydrogen carbonate (400 mL). The mixture was extracted twice with ethyl acetate, and the combined organic layer was washed with a 10% saline solution; the system was then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using neutral silica gel column chromatography (hexane:ethyl acetate ratio = 3:2) to obtain the titled compound as a light-yellow amorphous substance (25.5 g, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.20 (d, J = 6.8 Hz, 3 H) 1.23 (d, J = 6.8 Hz, 3 H) 1.80 (s, 3 H) 2.01 (s, 3 H) 2.05 (s, 3 H) 2.09 (s, 3 H) 3.31 (quin, J = 6.8 Hz, 1 H) 3.77–3.82 (m, 1 H) 3.83 (s, 3 H) 4.10–4.17 (m, 1 H) 4.22–4.30 (m, 1 H) 4.83 (d, J = 9.5 Hz, 1 H) 5.17–5.38 (m, 3 H) 6.75 (s, 1 H) 7.49 (s, 1 H); MS ESI/APCI Dual *m/z* 581[M+Na]$^+$.

(*1S*)-1,5-Anhydro-1-{5-bromo-4-(propan-2-yl)-2-[(trimethylsilyl)oxy]phenyl}-2,3,4,6-tetrakis-*O*-(trimethylsilyl)-D-glucitol (53a)

Triethylamine (24 mL) and water (24 mL) were added to a solution of compound **52a** (12.2 g, 22.3 mmol) in methanol (120 mL). The reaction mixture was stirred at room temperature for 15 hours and then further stirred at 50°C for 10 hours; the solvent was distilled off under reduced pressure. The resulting residue was dissolved in *N*,*N*-dimethylformamide (106 mL), to which triethylamine (18.6

mL, 134 mmol) and chlorotrimethylsilane (14.3 mL, 112 mmol) were added at 4°C under a nitrogen atmosphere. The reaction mixture was stirred at 4°C for 1 hour, followed by the addition of ice water (150 mL). The mixture was extracted three times with toluene, and the combined organic layers were washed with water and saturated aqueous sodium bicarbonate and brine and then dried over anhydrous magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under reduced pressure to obtain the titled compound (17.4 g) as an oil. This compound was used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm -0.28 (s, 9 H) 0.08 (s, 9 H) 0.19 (s, 9 H) 0.20 (s, 9 H) 0.29 (s, 9 H) 1.16 (d, J = 6.8 Hz, 3 H) 1.21 (d, J = 6.8 Hz, 3 H) 3.17-3.37 (m, 1 H) 3.41–3.56 (m, 3 H) 3.62 - 3.72 (m, 1 H) 3.76-3.86 (m, 1 H) 4.46 (d, J = 8.2 Hz, 1 H) 6.64 (s, 1 H) 7.47 (s, 1 H).

(*1S*)-1,5-Anhydro-1-[5-bromo-2-methoxy-4-(propan-2-yl)phenyl]-2,3,4,6-tetrakis-*O*-(trimethylsilyl)-D-glucitol (53b)

A 25 wt.% sodium methoxide-methanol solution (1.0 mL, 4.9 mmol) was added to a methanol (250 mL) suspension of compound **52b** (25.5 g, 45.6 mmol), and the mixture was stirred for 2 hours at room temperature. Dry ice was placed in the reaction solution, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in *N,N*-dimethylformamide (135 mL); triethylamine (45 mL) and chlorotrimethylsilane (35 mL) were then added under ice cooling. The reaction mixture was stirred for 2 hours at room temperature, and ice water was added. The mixture was extracted twice with toluene, and the combined organic layer was washed with a saturated saline solution; the system was then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure to obtain the titled compound as a brown oily substance (30.3 g). This compound was used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm -0.32 (s, 9 H) 0.09 (s, 9 H) 0.18 (s, 9 H) 0.20 (s, 9 H) 1.19 (d, J = 6.8 Hz, 3 H) 1.23 (d, J = 6.8 Hz, 3 H) 3.26–3.44 (m, 3 H) 3.52–3.58 (m, 2 H) 3.65–3.75 (m, 3 H) 3.76–3.83 (m, 1

H) 3.80 (s, 3 H) 4.60 (d, *J* = 8.6 Hz, 1 H) 6.72 (s, 1 H) 7.51 (s, 1 H); MS ESI/APCI Dual *m/z* 701[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromophenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (55f)

A 2.7 M *n*-BU hexane solution (4.70 mL, 12.9 mmol) was added dropwise to a THF (40 mL) solution of compound **53b** (8.70 g, 12.9 mmol) at -78°C in an argon atmosphere, and the mixture was stirred for 10 minutes at the same temperature. Then, a THF (25 mL) solution of 4-bromobenzaldehyde (**37a**) (2.60 g, 14.2 mmol) was added dropwise over 15 minutes, and the mixture was stirred for 30 minutes at the same temperature. A saturated aqueous solution of ammonium chloride was added to the reaction liquid; after the mixture was warmed to room temperature, the warmed mixture was extracted twice with ethyl acetate. The combined organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in a methanol (65 mL) solution containing methanesulfonic acid (0.2 g), and the solution was stirred for 14 hours at room temperature. The reaction liquid was neutralized with triethylamine (1.8 mL), and the reaction mixture was concentrated. The resulting residue was purified using acidic silica gel column chromatography (chloroform→chloroform:methanol ratio = 9:1) to obtain an intermediate compound (**54f**) as a colorless amorphous substance (2.9 g). Compound **54f** (2.9 g, 5.8 mmol) was dissolved in pyridine (18 mL). Acetic anhydride (9 mL) was added to the resulting solution, and the mixture was stirred for 5 hours at room temperature. Ice water was added, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with 3 M hydrochloric acid and a saturated saline solution and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure to obtain a crude product (3.3 g). Et_3SiH (1.1 mL, 7.1

mmol) was added to a solution of the crude product (3.3 g) in chloroform (25 mL) and acetonitrile (25 mL), and the mixture was cooled with ice in a nitrogen atmosphere. Under ice cooling, $BF_3 \cdot OEt_2$ (0.9 mL, 7.1 mmol) was added dropwise over 10 minutes, and the mixture was stirred for 30 minutes at the same temperature. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction liquid, and the mixture was extracted with chloroform. Then, the organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using acidic silica gel column chromatography (hexane:ethyl acetate ratio = 9:1→6:4) to obtain the titled compound as a colorless oil (2.9 g, 34% in 4 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.04 (d, J = 6.8 Hz, 3 H) 1.09 (d, J = 6.8 Hz, 3 H) 1.76 (s, 3 H) 2.01 (s, 3 H) 2.05 (s, 3 H) 2.06 (s, 3 H) 2.91–3.06 (m, 1 H) 3.80–3.88 (m, 4 H) 3.91 (d, J = 5.1 Hz, 2 H) 4.06–4.18 (m, 1 H) 4.20–4.31 (m, 1 H) 4.82–4.93 (m, 1 H) 5.15–5.43 (m, 3 H) 6.77 (s, 1 H) 6.92 (d, J = 8.6 Hz, 2 H) 7.11 (s, 1 H) 7.36 (d, J = 8.6 Hz, 2 H); MS ESI/APCI Dual *m/z* 671[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-bromophenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (55e)

Compound **55e** (56% in 4 steps) was obtained from **53a** and **37a** in a manner similar to that described for **55f**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.77 (s, 3H), 2.01 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 2.36 (s, 3H), 2.95–3.05 (m, 1H), 3.75–3.83 (m, 1H), 3.96 (s, 2H), 4.08 (dd, J = 12.5, 2.2 Hz, 1H), 4.29 (dd, J = 12.5, 4.7 Hz, 1H), 4.51–4.58 (m, 1H), 5.15–5.24 (m, 1H), 5.28–5.34 (m, 2H), 6.91–6.98 (m, 3H), 7.15 (s, 1H), 7.38 (d, J = 8.2 Hz, 2H); MS ESI/APCI Dual *m/z* 699[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-bromo-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (55g)

Compound **55g** (50% in 4 steps) was obtained from **53a** and **37c** in a manner similar to that described for **55f**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.12 (d, J = 6.7 Hz, 3 H) 1.14 (d, J = 6.7 Hz, 3 H) 1.76 (s, 3 H) 1.99 (s, 3 H) 2.03 (s, 3 H) 2.06 (s, 3 H) 2.27 (s, 3 H) 2.37 (s, 3 H) 2.93 (sept, J = 6.7 Hz, 1 H) 3.76 (ddd, J = 9.9, 4.5, 2.2 Hz, 1 H) 3.87 (s, 2 H) 4.06 (dd, J = 12.5, 2.2 Hz, 1 H) 4.27 (dd, J = 12.5, 4.5 Hz, 1 H) 4.49 (d, J = 9.6 Hz, 1 H) 5.10–5.33 (m, 3 H) 6.59 (d, J = 8.4 Hz, 1 H) 6.97 (s, 1 H) 7.00 (s, 1 H) 7.20 (dd, J = 8.4, 2.5 Hz, 1 H) 7.34 (d, J = 2.5 Hz, 1 H); MS ESI/APCI Dual *m/z* 713[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (55h)

Compound **55h** (53% in 4 steps) was obtained from **53b** and **37c** in a manner similar to that described for **55f**.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.11 (d, J = 6.7 Hz, 3 H) 1.14 (d, J = 6.7 Hz, 3 H) 1.75 (s, 3 H) 1.99 (s, 3 H) 2.04 (s, 3 H) 2.05 (s, 3 H) 2.28 (s, 3 H) 2.90 (sept, J = 6.7 Hz, 1 H) 3.71–3.90 (m, 3 H) 3.86 (s, 3H) 3.85–3.87 (m, 1 H) 4.05–4.15 (m, 1 H) 4.19–4.28 (m, 1 H) 4.77–4.85 (m, 1 H) 5.11–5.23 (m, 1 H) 5.26–5.37 (m, 2 H) 6.54 (d, J = 8.2 Hz, 1 H) 6.81 (s, 1 H) 6.96 (s, 1 H) 7.17 (dd, J = 8.2, 2.6 Hz, 1 H) 7.32 (d, J = 2.6 Hz, 1 H); MS ESI/APCI Dual *m/z* 685[M+Na]$^+$.

(*1S*)-1,5-Anhydro-1-{2-hydroxy-5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-4-(propan-2-yl)phenyl}-D-glucitol (56e)

Compound **56e** (49% in 2 steps) was obtained from **55e** and **43** in a manner similar to that described for **45a**.

^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.03 (d, J = 6.9 Hz, 6H) 1.26 (s, 6H) 1.33 (s, 6H) 3.02 (dt, J = 13.6, 6.7 Hz, 1H) 3.34 (s, 2H) 3.39–3.45 (m, 2H) 3.46–3.51 (m, 3H) 3.58 (t, J = 9.2 Hz, 1H) 3.71 (dd, J = 12.2, 5.3 Hz, 1H) 3.87 (dd, J = 11.9, 1.8 Hz, 1H) 3.95 (s, 2H) 4.52 (d, J = 9.6 Hz, 1H) 6.34 (d, J = 16.5 Hz, 1H) 6.42 (s, 1H) 6.51 (d, J = 16.5 Hz, 1H) 6.76 (s, 1H) 7.06 (d, J = 8.3 Hz, 2H) 7.14 (s, 1H) 7.29 (d, J = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 23.9, 24.1, 24.2, 25.9, 30.3, 39.2, 46.5, 55.9, 63.1, 69.8, 71.9, 75.7, 78.9, 80.2, 82.5, 114.4, 124.0, 127.5, 129.8, 129.9, 130.5, 132.1, 135.0, 136.1, 143.1, 149.6, 155.8, 179.0; HRMS ESI/APCI Dual *m/z*: 572.3206 $[M+H]^+$ (calcd for $C_{32}H_{45}NO_8$ 572.3218).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (56f)

Compound **56f** (54% in 2 steps) was obtained from **55f** and **43** in a manner similar to that described for **45a**.

^{1}H NMR (600 MHz, CD3OD) δ ppm 1.08 (t, J = 6.0 Hz, 6H) 1.26 (s, 6H) 1.34 (s, 7H) 3.06–3.15 (m, 1H) 3.38 (d, J = 4.6 Hz, 1H) 3.47 (s, 2H) 3.56 (t, J = 9.2 Hz, 1H) 3.65 (d, J = 10.6 Hz, 1H) 3.81–3.88 (m, 3H) 3.98 (s, 2H) 4.65 (d, J = 9.6 Hz, 1H) 6.34 (d, J = 16.1 Hz, 1H) 6.42 (s, 1H) 6.52 (d, J = 15.6 Hz, 1H) 6.88 (s, 1H) 7.07 (d, J = 7.8 Hz, 2H) 7.23 (s, 1H) 7.30 (d, J = 6.4 Hz, 2H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 23.9, 24.1, 24.2, 25.9, 30.7, 39.2, 46.5, 55.9, 56.5, 63.4, 69.8, 72.3, 75.9, 76.8, 80.3, 82.5, 109.8, 126.2, 127.5, 129.9, 130.5, 130.8, 132.1, 135.0, 136.2, 142.9, 149.8, 158.7, 179.0; HRMS ESI/APCI Dual *m/z*: 586.3347 $[M+H]^+$ (calcd for $C_{33}H_{47}NO_8$ 586.3374).

(*1S*)-1,5-Anhydro-1-{2-hydroxy-5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl}-D-glucitol (56g)

Compound **56g** (48% in 2 steps) was obtained from **55g** and **43** in a manner similar to that described

for **45a**.

^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.10 (d, J = 6.9 Hz, 6H) 1.27 (s, 7H) 1.34 (s, 6H) 2.31 (s, 3H) 2.89–2.96 (m, 1H) 3.34 (s, 1H) 3.37–3.39 (m, 2H) 3.43–3.49 (m, 2H) 3.52–3.56 (m, 1H) 3.66–3.70 (m, 1H) 3.81–3.90 (m, 3H) 4.46 (d, J = 9.6 Hz, 1H) 6.32–6.36 (m, 1H) 6.42 (s, 1H) 6.50 (d, J = 16.1 Hz, 1H) 6.75 (d, J = 7.8 Hz, 1H) 6.80 (s, 1H) 6.96 (s, 1H) 7.07–7.12 (m, 1H) 7.23 (s, 1H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 20.0, 23.9, 24.1, 24.2, 26.0, 30.3, 36.3, 46.5, 55.9, 63.1, 69.8, 71.9, 75.5, 79.2, 80.2, 82.4, 114.3, 124.0, 125.0, 129.1, 129.2, 130.2, 130.7, 131.8, 134.7, 136.2, 137.6, 140.8, 149.6, 155.7, 179.0; HRMS ESI/APCI Dual *m/z*: 586.3354 $[M+H]^+$ (calcd for $C_{33}H_{47}NO_8$ 586.3374).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-hydroxy-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (56h)

Compound **56h** (38% in 2 steps) was obtained from **55h** and **43** in a manner similar to that described for **45a**.

^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.12–1.17 (m, 6H) 1.27 (s, 5H) 1.34 (s, 5H) 2.32 (s, 3H) 2.96–3.02 (m, 1H) 3.34–3.37 (m, 2H) 3.43–3.53 (m, 3H) 3.59–3.65 (m, 1H) 3.80–3.85 (m, 3H) 3.92 (s, 1H) 4.61 (d, J = 9.6 Hz, 1H) 6.34 (d, J = 16.5 Hz, 1H) 6.42 (s, 1H) 6.50 (d, J = 16.5 Hz, 1H) 6.74 (d, J = 7.8 Hz, 1H) 6.92 (s, 1H) 7.04–7.11 (m, 2H) 7.23 (s, 1H); MS ESI/APCI Dual *m/z* 600$[M+H]^+$, 598$[M-H]^-$.

Methyl *N*-(2,2-dimethylbut-3-enoyl)-2-methylalaninate (58)

Oxalyl chloride (4.43 mL, 49.9 mmol) and *N*,*N*-dimethylformamide (3 drops) were added to a chloroform (250 mL) solution of 2,2-dimethyl-3-butenoic acid (**41**) (5.42 g, 47.5 mmol) in a nitrogen atmosphere, and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was cooled with ice, and triethylamine (19.9 mL, 143 mmol) and α-aminoisobutyric acid methyl ester

hydrochloride (**57**) (10.9 g, 71.2 mmol) were added; the mixture was then stirred for 1 hour at room temperature. Water was added to the reaction liquid, and the mixture was extracted with chloroform. Then, the organic layer was washed with 3 M hydrochloric acid, a saturated aqueous solution of sodium hydrogen carbonate, and a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using silica gel column chromatography (hexane→hexane:ethyl acetate ratio = 4:1) to obtain the titled compound as a colorless powder (9.38 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.27 (s, 6 H) 1.51 (s, 6 H) 3.73 (s, 3 H) 5.17–5.32 (m, 2 H) 6.02 (dd, J = 17.6, 10.6 Hz, 1 H) 6.25 (s, 1 H); MS ESI/APCI Dual *m/z* 214$[M+H]^+$.

***N*-(2,2-Dimethylbut-3-enoyl)-2-methylalanine (59)**

A 4 M aqueous solution of sodium hydroxide (16.5 mL, 66.0 mmol) was added to a methanol (20 mL) solution of compound **58** (9.38 g. 43.9 mmol), and the mixture was stirred for 1 hour at room temperature. Then, the reaction mixture was concentrated. The resulting residue was dissolved in water, and the solution was neutralized by the addition of 3 M hydrochloric acid. The mixture was extracted twice with ethyl acetate, and the combined organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure to obtain the titled compound as a colorless powder (8.19 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.29 (s, 6 H) 1.54 (s, 6 H) 5.16–5.36 (m, 2 H) 6.01 (dd, J = 17.5, 10.7 Hz, 1 H) 6.14 (s, 1 H); MS ESI/APCI Dual *m/z* 200$[M+H]^+$, 222$[M+Na]^+$.

2-{[(*3E*)-4-(4-{[4-Methoxy-2-(propan-2-yl)-5-{(*2S*,*3S*,*4R*,*5R*,*6R*)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl}phenyl]methyl}phenyl)-2,2-dimethylbut-3-enoyl]amino}-2-methylpropanoic acid (60a)

In an argon atmosphere, an acetonitrile (36 mL) suspension of compound **59** (1.20 g, 1.85 mmol), compound **55f** (2.59 g, 13.0 mmol), palladium (II) acetate (44 mg, 0.19 mmol), tri-*o*-tolylphosphine (112 mg, 0.370 mmol), and triethylamine (1.30 mL, 9.25 mmol) was stirred for 30 minutes at 120°C under microwave irradiation. The reaction mixture was filtered using Celite (registered trademark) and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the resulting residue was purified using neutral silica gel column chromatography (chloroform→chloroform:methanol ratio = 9:1) to obtain the titled compound as a partially purified product (1.5 g). The titled compound (1.5 g) was further purified using neutral silica gel column chromatography (hexane:ethyl acetate ratio = 7:3→2:8) to obtain the titled compound as a light-yellow amorphous substance (854 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.08 (d, J = 6.8 Hz, 3 H) 1.12 (d, J = 6.8 Hz, 3 H) 1.38 (s, 6 H) 1.53 (s, 6 H) 1.77 (s, 3 H) 2.00 (s, 3 H) 2.05 (s, 6 H) 3.06 (quin, J = 6.6 Hz, 1 H) 3.78–3.83 (m, 1 H) 3.84 (s, 3 H) 3.97 (s, 2 H) 4.07–4.18 (m, 1 H) 4.17–4.27 (m, 1 H) 4.87 (dd, J = 6.8, 2.9 Hz, 1 H) 5.16–5.25 (m, 1 H) 5.27–5.40 (m, 2 H) 6.18–6.33 (m, 2 H) 6.54 (d, J = 16.5 Hz, 1 H) 6.77 (s, 1 H) 7.03 (d, J = 8.1 Hz, 2 H) 7.10 (s, 1 H) 7.29 (d, J = 8.1 Hz, 2 H); MS ESI/APCI Dual *m/z* 768[M+H]$^+$, 790[M+Na]$^+$.

2-{[(*3E*)-4-(4-{[4-(Acetyloxy)-2-(propan-2-yl)-5-{(*2S*,*3S*,*4R*,*5R*,*6R*)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl}phenyl]methyl}phenyl)-2,2-dimethylbut-3-enoyl]amino}-2-methylpropanoic acid (60b)

Compound **60b** (78%) was obtained from **55g** and **59** in a manner similar to that described for **60a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.16, 1.18 (each d, J = 6.84 Hz, 3 H) 1.40 (s, 6 H) 1.54–1.58 (m, 6 H) 1.76 (s, 3 H) 1.99 (s, 3 H) 2.03 (s, 3 H) 2.05 (s, 3 H) 2.28 (s, 3 H) 2.36 (s, 3 H) 2.98–3.10 (m, 1 H) 3.71–3.79 (m, 1 H) 3.94 (s, 2 H) 4.01–4.08 (m, 1 H) 4.24 (dd, J = 12.4, 4.5 Hz, 1 H) 4.47 (d, J = 9.2 Hz, 1 H) 5.07-5.32 (m, 3 H) 6.31 (d, J = 16.3 Hz, 1 H) 6.35 (s, 1 H) 6.55 (d, J = 16.3 Hz, 1 H) 6.77

(d, *J* = 7.6 Hz, 1 H) 6.92 (s, 1 H) 6.99 (s, 1 H) 7.12–7.18 (m, 1 H) 7.26 (s, 1 H); MS ESI/APCI Dual *m/z* 810[M+H]$^+$, 832[M+Na]$^+$.

2-{[(*3E*)-4-(4-{[4-Methoxy-2-(propan-2-yl)-5-{(*2S*,*3S*,*4R*,*5R*,*6R*)-3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]oxan-2-yl}phenyl]methyl}-3-methylphenyl)-2,2-dimethylbut-3-enoyl]amino}-2-methylpropanoic acid (60c)

Compound **60c** (87%) was obtained from **55h** and **59** in a manner similar to that described for **60a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.17, 1.14 (each d, *J* = 7.0 Hz, 3 H) 1.38 (s, 6 H) 1.55 (s, 6 H) 1.76 (s, 3 H) 1.98 (s, 3 H) 2.04 (s, 6 H) 2.30 (s, 3 H) 2.94–3.03 (m, 1 H) 3.76–3.83 (m, 1 H) 3.84–3.95 (m, 4 H) 4.06–4.15 (m, 1 H) 4.16–4.25 (m, 1 H) 4.81 (d, *J* = 9.8 Hz, 1 H) 5.12–5.20 (m, 1 H) 5.23–5.35 (m, 2 H) 6.29 (s, 1H) 6.31 (d, *J* = 16.3 Hz, 1 H) 6.52 (d, *J* = 16.3 Hz, 1 H) 6.67 (d, *J* = 8.1 Hz, 1 H) 6.81 (s, 1 H) 6.94 (s, 1 H) 7.06–7.14 (m, 1 H) 7.24 (s, 1 H); MS ESI/APCI Dual *m/z* 782[M+H]$^+$, 804[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[2-(dimethylamino)ethyl]amino}-2-methyl-1-oxopropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (61d)

WSCI·HCl (37.0 mg, 0.20 mmol) was added to a chloroform (1.5 mL)/*N*,*N*-dimethylformamide (1.5 mL) solution of compound **60a** (100 mg, 0.130 mmol), 1-hydroxybenzotriazole monohydrate (HOBt·H_2O) (30 mg, 0.20 mmol), and *N*,*N*-dimethylethylenediamine (42 μL, 0.39 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified using

neutral silica gel column chromatography (hexane:ethyl acetate = 7:3→2:8) to obtain the titled compound as a colorless amorphous substance (103 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 (d, J = 6.8 Hz, 3 H) 1.10 (d, J = 6.8 Hz, 3 H) 1.38 (s, 6 H) 1.49 (s, 6 H) 1.77 (s, 3 H) 2.00 (s, 3 H) 2.05 (s, 3 H) 2.06 (s, 3 H) 2.46 (s, 6 H) 2.64–2.78 (m, 2 H) 3.04 (sept, J = 6.8 Hz, 1 H) 3.38–3.49 (m, 2 H) 3.78-3.83 (m, 1 H) 3.85 (s, 3 H) 3.87–4.04 (m, 2 H) 4.08–4.18 (m, 1 H) 4.18–4.30 (m, 1 H) 4.87 (d, J = 9.5 Hz, 1 H) 5.16–5.27 (m, 1 H) 5.28–5.44 (m, 2 H) 6.35 (s, 1 H) 6.40–6.57 (m, 2 H) 6.77 (s, 1 H) 7.01 (d, J = 8.2 Hz, 2 H) 7.13 (s, 1 H) 7.32 (d, J = 8.2 Hz, 2 H) 7.40 (s, 1 H); MS ESI/APCI Dual *m/z* 839$[M+H]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl]amino}-4-oxobut-1-en-1-yl]phenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (61e)

Compound **61e** (55%) was obtained from **60a** and piperazine in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 (d, J = 6.6 Hz, 3 H) 1.11 (d, J = 6.6 Hz, 3 H) 1.35 (s, 6 H) 1.77 (s, 6 H) 2.00 (s, 3 H) 2.04 (s, 3 H) 2.06 (s, 3 H) 2.25 (s, 2 H) 2.78–2.88 (m, 4 H) 2.96–3.12 (m, 1 H) 3.55–3.65 (m, 4 H) 3.78–3.88 (m, 1 H) 3.85 (s, 3 H) 3.88–4.04 (m, 2 H) 4.09–4.18 (m, 1 H) 4.20–4.30 (m, 1 H) 4.88 (d, J = 9.5 Hz, 1 H) 5.15-5.27 (m, 1 H) 5.28–5.44 (m, 2 H) 6.22–6.33 (m, 1 H) 6.41–6.55 (m, 1 H) 6.72–6.85 (m, 2 H) 6.96–7.06 (m, 2 H) 7.14 (s, 1 H) 7.23–7.32 (m, 2 H); MS ESI/APCI Dual *m/z* 836$[M+H]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-yl]amino}-4-oxobut-1-en-1-yl]phenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (61f)

Compound **61f** (95%) was obtained from **60a** and 1-methylpiperazine in a manner similar to that

described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.05 (d, J = 6.8 Hz, 3 H) 1.10 (d, J = 6.8 Hz, 3 H) 1.36 (s, 6 H) 1.59 (s, 6 H) 1.77 (s, 3 H) 2.00 (s, 3 H) 2.05 (s, 3 H) 2.06 (s, 3 H) 2.26 (s, 3 H) 2.32–2.40 (m, 4 H) 2.96–3.12 (m, 1 H) 3.59–3.71 (m, 4 H) 3.79–3.84 (m, 1 H) 3.85 (s, 3 H) 3.90–4.05 (m, 2 H) 4.10–4.16 (m, 1 H) 4.21–4.28 (m, 1 H) 4.87 (d, J = 9.6 Hz, 1 H) 5.16–5.27 (m, 1 H) 5.29–5.44 (m, 2 H) 6.28 (d, J = 16.4 Hz, 1 H) 6.49 (d, J = 16.4 Hz, 1 H) 6.77 (s, 1 H) 6.83 (s, 1 H) 7.01 (d, J = 8.1 Hz, 2 H) 7.13 (s, 1 H) 7.25–7.32 (m, 2 H); MS ESI/APCI Dual *m/z* 850$[M+H]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-{(*1E*)-3,3-dimethyl-4-[(2-methyl-1-{[2-(methylamino)ethyl]amino}-1-oxopropan-2-yl)amino]-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (61g)

Compound **61g** (61%) was obtained from **60b** and *N*,*N*-dimethylethylenediamine in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.13, 1.15 (each d, J = 6.9 Hz, each 3 H) 1.38 (s, 6 H) 1.53 (s, 6 H) 1.77 (s, 3 H) 1.99 (s, 3 H) 2.03 (s, 3 H) 2.05 (s, 3 H) 2.23 (s, 6 H) 2.31 (s, 3 H) 2.37 (s, 3 H) 2.41 (t, J = 5.7 Hz, 2 H) 2.90–3.03 (m, 1 H) 3.25–3.34 (m, 2 H) 3.71–3.80 (m, 1 H) 3.92 (s, 2 H) 4.05 (dd, J = 12.6, 2.2 Hz, 1 H) 4.23–4.32 (m, 1 H) 4.44–4.52 (m, 1 H) 5.11–5.20 (m, 1 H) 5.22–5.33 (m, 2 H) 6.33 (d, J = 16.6 Hz, 1 H) 6.41 (s, 1 H) 6.51 (d, J = 16.6 Hz, 1 H) 6.68 (d, J = 7.8 Hz, 1 H) 6.77 (s, 1 H) 7.00 (s, 2 H) 7.12 (d, J = 7.8 Hz, 1 H) 7.26 (s, 1 H); MS ESI/APCI Dual *m/z* 880$[M+H]^+$, 902$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (61h)

Compound **61h** (47%) was obtained from **60b** and piperazine in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.14, 1.16 (each d, J = 7.0 Hz, each 3 H) 1.38 (s, 6 H)

1.61 (s, 6 H) 1.71 (s, 3 H) 1.99 (s, 3 H) 2.05 (s, 3 H) 2.12 (s, 3 H) 2.27 (s, 3 H) 2.79–2.87 (m, 4 H) 2.87–2.99 (m, 1 H) 3.56–3.66 (m, 4 H) 3.75–3.94 (m, 3 H) 4.12–4.20 (m, 1 H) 4.25–4.34 (m, 1 H) 4.44–4.52 (m, 1 H) 5.23–5.32 (m, 3 H) 6.30 (d, *J* = 16.3 Hz, 1 H) 6.48 (d, *J* = 16.3 Hz, 1 H) 6.53 (s, 1 H) 6.68 (d, *J* = 7.8 Hz, 1 H) 6.88 (s, 1 H) 6.97 (s, 1 H) 7.05–7.12 (m, 1 H) 7.22 (s, 1 H); MS ESI/APCI Dual *m/z* 836[M+H]$^+$, 858[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (61i)

Compound **61i** (61%) was obtained from **60b** and 1-methylpiperazine in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.13, 1.15 (each d, *J* = 6.8 Hz, each 3 H) 1.37 (s, 6 H) 1.60 (s, 6 H) 1.77 (s, 3 H) 1.99 (s, 3 H) 2.03 (s, 3 H) 2.05 (s, 3 H) 2.27 (s, 3 H) 2.30 (s, 3 H) 2.33–2.41 (m, 7 H) 2.88–3.04 (m, 1 H) 3.60–3.70 (m, 4 H) 3.72–3.80 (m, 1 H) 3.92 (s, 2 H) 4.05 (dd, *J* = 12.6, 2.3 Hz, 1 H) 4.27 (dd, *J* = 12.6, 4.5 Hz, 1 H) 4.43-4.54 (m, 1 H) 5.10–5.20 (m, 1 H) 5.22–5.32 (m, 2 H) 6.31 (d, *J* = 16.5 Hz, 1 H) 6.49 (d, *J* = 16.5 Hz, 1 H) 6.68 (d, *J* = 8.1 Hz, 1 H) 6.86 (s, 1 H) 7.00 (s, 2 H) 7.08–7.14 (m, 1 H) 7.24 (s, 1 H); MS ESI/APCI Dual *m/z* 892[M+H]$^+$, 914[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-({4-[(*1E*)-4-({1-[(2-amino-2-methylpropyl)amino]-2-methyl-1-oxopropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (61j)

Compound **61j** (21%) was obtained from **60b** and 1,2-diamino-2-methylpropane in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.11–1.17 (m, 6 H) 1.11 (s, 6 H) 1.39 (s, 6 H) 1.53 (s, 6 H) 1.77 (s, 3 H) 1.99 (s, 3 H) 2.03 (s, 3 H) 2.05 (s, 3 H) 2.31 (s, 3 H) 2.37 (s, 3 H) 2.89–3.05 (m, 1 H) 3.14 (d, *J* = 5.9 Hz, 2 H) 3.76 (ddd, *J* = 9.7, 4.5, 2.1 Hz, 1 H) 3.93 (s, 2 H) 4.05 (dd, *J* =

12.5, 2.1 Hz, 1 H) 4.27 (dd, *J* = 12.5, 4.5 Hz, 1 H) 4.49 (d, *J* = 7.5 Hz, 1 H) 5.11–5.20 (m, 1 H) 5.23–5.31 (m, 2 H) 6.26 (s, 1 H) 6.29–6.38 (m, 1 H) 6.48–6.57 (m, 1 H) 6.69 (d, *J* = 7.9 Hz, 1 H) 6.97–7.03 (m, 3 H) 7.12 (d, *J* = 7.9 Hz, 1 H) 7.25 (s, 1 H); MS ESI/APCI Dual *m/z* 880[M+H]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[2-(dimethylamino)ethyl]amino}-2-methyl-1-oxopropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (61k)

Compound **61k** (74%) was obtained from **60c** and *N*,*N*-dimethylethylenediamine in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.12, 1.14 (each d, *J* = 6.8 Hz, each 3 H) 1.37 (s, 6 H) 1.51 (s, 6 H) 1.76 (s, 3 H) 1.99 (s, 3 H) 2.04 (s, 3 H) 2.04 (s, 3 H) 2.23 (s, 6 H) 2.32 (s, 3 H) 2.41 (t, *J* = 6.2 Hz, 2 H) 2.86–2.99 (m, 1 H) 3.25–3.33 (m, 2 H) 3.76–3.90 (m, 6 H) 4.07–4.15 (m, 1 H) 4.18–4.26 (m, 1 H) 4.76–4.85 (m, 1 H) 5.13–5.22 (m, 1 H) 5.26–5.36 (m, 2 H) 6.31 (d, *J* = 16.5 Hz, 1 H) 6.37 (s, 1 H) 6.50 (d, *J* = 16.5 Hz, 1 H) 6.61–6.67 (m, 1 H) 6.81 (s, 1 H) 6.99 (s, 1 H) 7.06–7.12 (m, 1 H) 7.24 (s, 1 H); MS ESI/APCI Dual *m/z* 852[M+H]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (61l)

Compound **61l** (38%) was obtained from **60c** and piperazine in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.12, 1.14 (each d, *J* = 7.0 Hz, each 3 H) 1.37 (s, 6 H) 1.58 (s, 6 H) 1.76 (s, 3 H) 1.99 (s, 3 H) 2.04 (s, 3 H) 2.04 (s, 3 H) 2.32 (s, 3 H) 2.79–2.86 (m, 4 H) 2.88–2.99 (m, 1 H) 3.57–3.64 (m, 4 H) 3.76–3.95 (m, 6 H) 4.07–4.14 (m, 1 H) 4.18–4.26 (m, 1 H) 4.77–4.84 (m, 1 H) 5.13–5.22 (m, 1 H) 5.26–5.37 (m, 2 H) 6.29 (d, *J* = 16.2 Hz, 1 H) 6.49 (d, *J* = 16.2 Hz, 1 H) 6.64 (d, *J* = 7.9 Hz, 1 H) 6.77–6.83 (m, 2 H) 6.99 (s, 1 H) 7.05–7.11 (m, 1 H) 7.22 (s, 1 H);

MS ESI/APCI Dual *m/z* 850[M+H]$^+$, 872[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (61m)

Compound **61m** was obtained as a crude product from **60c** and 1-methylpiperazine in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.12 (d, J = 8.5 Hz, 3 H) 1.15 (d, J = 8.5 Hz, 3 H) 1.36 (s, 6 H) 1.56 (s, 6 H) 1.77 (s, 3 H) 1.99 (s, 3 H) 2.04 (s, 6 H) 2.30 (s, 3 H) 2.32 (s, 3 H) 2.38–2.50 (m, 4 H) 2.85–3.02 (m, 1 H) 3.61–3.74 (m, 4 H) 3.76–3.84 (m, 1 H) 3.81–3.96 (m, 1 H) 3.86 (s, 3 H) 4.07–4.15 (m, 1 H) 4.18–4.27 (m, 1 H) 4.75–4.88 (m, 1 H) 5.11–5.24 (m, 1 H) 5.26–5.37 (m, 2 H) 6.22–6.38 (m, 1 H) 6.43–6.54 (m, 1 H) 6.59–6.70 (m, 2 H) 6.81 (s, 1 H) 6.96–7.02 (m, 1 H) 7.04–7.12 (m, 1 H) 7.20–7.26 (m, 1 H).

(*1S*)-2,4,6-Tri-*O*-acetyl-1-[5-({4-[(*1E*)-4-({1-[(2-amino-2-methylpropyl)amino]-2-methyl-1-oxopropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-1,5-anhydro-3-*O*-formyl-D-glucitol (61n)

Compound **61n** (99%) was obtained from **60c** and 1,2-diamino-2-methylpropane in a manner similar to that described for **61d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 (s, 6 H) 1.12 (d, J = 6.8 Hz, 3 H) 1.14 (d, J = 6.8 Hz, 3 H) 1.36 (s, 6 H) 1.56 (s, 6 H) 1.77 (s, 3 H) 1.99 (s, 3 H) 2.04 (s, 6 H) 2.30 (s, 3 H) 2.85–3.02 (m, 1 H) 3.13 (d, J = 5.91 Hz, 2 H) 3.76–3.84 (m, 1 H) 3.81–3.96 (m, 1 H) 3.86 (s, 3 H) 4.07–4.15 (m, 1 H) 4.18–4.27 (m, 1 H) 4.75–4.88 (m, 1 H) 5.11–5.24 (m, 1 H) 5.26–5.37 (m, 2 H) 6.22–6.38 (m, 1 H) 6.43–6.54 (m, 1 H) 6.59–6.70 (m, 1 H) 6.81 (s, 1 H) 6.96–7.02 (m, 2 H) 7.04–7.12 (m, 1 H) 7.20–7.26 (m, 1 H).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[2-(dimethylamino)ethyl]amino}-2-methyl-1-oxopropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}phenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (62d)

A triethylamine/water/methanol mixture (1/1/5, 2.5 mL) was added to compound **61d** (103 mg, 0.12 mmol). The reaction mixture was stirred for 17 hours at room temperature, and the solvent was distilled off under reduced pressure. The resulting residue was purified using neutral silica gel column chromatography (chloroform→chloroform:methanol ratio = 8:2) to obtain the titled compound as a colorless amorphous substance (62.1 mg, 75%). mp = 111°C, ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.07 (d, J = 5.0 Hz, 3 H) 1.09 (d, J = 5.0 Hz, 3 H) 1.36 (s, 6 H) 1.44 (s, 6 H) 2.23 (s, 6 H) 2.41 (t, J = 6.9 Hz, 2 H) 3.10 (quin, J = 6.8 Hz, 1 H) 3.26 – 3.30 (m, 2 H) 3.38 (d, J = 6.0 Hz, 2 H) 3.45 – 3.52 (m, 1 H) 3.54 – 3.60 (m, 1 H) 3.62 – 3.69 (m, 1 H) 3.79 – 3.89 (m, 4 H) 3.99 (s, 2 H) 4.65 (d, J = 9.6 Hz, 1 H) 6.39 (d, J = 16.5 Hz, 1 H) 6.52 (d, J = 16.5 Hz, 1 H) 6.88 (s, 1 H) 7.07 (d, J = 8.3 Hz, 2 H) 7.23 (s, 1 H) 7.31 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 24.1, 25.3, 25.7, 30.7, 38.4, 39.3, 45.6, 46.1, 56.5, 58.1, 59.2, 63.4, 72.3, 75.9, 76.9, 80.3, 82.6, 109.8, 126.3, 127.5, 129.9, 130.4, 130.8, 132.1, 134.8, 136.3, 142.8, 149.8, 158.7, 177.2, 178.4; IR (KBr) $\nu^{\sim}$ = 3370, 2962, 2868, 1660, 1506, 1463, 1364, 1278, 1207, 1087, 1040 cm^{-1}; HRMS ESI/APCI Dual *m/z*: 670.4057 $[M+H]^+$ (calcd for $C_{37}H_{55}N_3O_8$ 670.4062); $[\alpha]_D^{25}$ = +5 (*c* = 0.10, MeOH).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl]amino}-4-oxobut-1-en-1-yl]phenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (62e)

Sodium methoxide (4.88 M/MeOH, 10 μL) was added to a solution of compound **61e** (90 mg, 0.11 mmol) in methanol (2.0 mL), and the mixture was stirred at room temperature for 1 hour. A small amount of dry ice was added to neutralize the reaction mixture, and the solvent was distilled off under

reduced pressure. The resulting residue was purified using NH-type silica gel column chromatography (chloroform:methanol ratio = 9:1 → 6:4) to obtain the titled compound as a colorless amorphous substance (52 mg, 70%). ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.06 (d, J = 6.8 Hz, 3 H) 1.07 (d, J = 6.8 Hz, 3 H) 1.34 (s, 6 H) 1.42 (s, 6 H) 2.67 (s, 4 H) 3.04–3.12 (m, 1 H) 3.27–3.30 (m, 2 H) 3.33–3.38 (m, 2 H) 3.43–3.49 (m, 1 H) 3.50–3.61 (m, 3 H) 3.61–3.66 (m, 1 H) 3.80 (s, 3 H) 3.83 (d, J = 11.9 Hz, 1 H) 3.92–4.00 (m, 2 H) 4.63 (d, J = 9.6 Hz, 1 H) 6.33–6.39 (m, 1 H) 6.44–6.49 (m, 1 H) 6.86 (s, 1 H) 7.06 (d, J = 8.3 Hz, 2 H) 7.21 (s, 1 H) 7.27 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 24.1, 24.2, 25.7, 26.3, 30.7, 39.2, 45.7, 46.6, 56.5, 58.1, 63.4, 72.3, 75.9, 76.8, 80.3, 82.6, 109.7, 126.3, 127.4, 130.0, 130.2, 130.8, 132.0, 134.7, 136.2, 142.9, 149.7, 158.7, 173.8, 177.8; HRMS ESI/APCI Dual *m/z*: 668.3880 $[M+H]^+$ (calcd for $C_{37}H_{53}N_3O_8$ 668.3905).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-yl]amino}-4-oxobut-1-en-1-yl]phenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (62f)

Compound **62f** (84%) was obtained from **61f** in a manner similar to that described for **62d**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.07 (d, J = 6.7 Hz, 3 H) 1.05 (d, J = 6.7 Hz, 3 H) 1.36 (s, 6 H) 1.45 (s, 6 H) 2.14 (s, 3 H) 2.29 (s, 4 H) 3.06–3.16 (m, 1 H) 3.34–3.42 (m, 2 H) 3.46–3.52 (m, 1 H) 3.51–3.73 (m, 6 H) 3.79–3.91 (m, 4 H) 3.98 (s, 2 H) 4.65 (d, J = 9.6 Hz, 1 H) 6.38 (d, J = 16.1 Hz, 1 H) 6.48 (d, J = 16.1 Hz, 1 H) 6.88 (s, 1 H) 7.08 (d, J = 8.3 Hz, 2 H) 7.23 (s, 1 H) 7.29 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 24.1, 24.2, 25.7, 26.3, 30.7, 39.2, 45.7, 46.1, 55.9, 56.5, 58.1, 63.4, 72.3, 75.9, 76.8, 80.3, 82.6, 109.8, 126.3, 127.5, 130.0, 130.1, 130.8, 132.0, 134.8, 136.2, 143.0, 149.7, 158.7, 173.8, 177.8; HRMS ESI/APCI Dual *m/z*: 682.4047 $[M+H]^+$ (calcd for $C_{38}H_{55}N_3O_8$ 682.4062).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)4-[(1-{[2-(dimethylamino)ethyl]amino}-2-methyl-1-oxopropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-D-glucitol (62g)

Compound **62g** (80%) was obtained from **61g** in a manner similar to that described for **62e**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.10 (d, J = 6.92 Hz, 6 H) 1.36 (s, 6 H) 1.45 (s, 6 H) 2.23 (s, 6 H) 2.31 (s, 3 H) 2.40 (t, J = 6.9 Hz, 2 H) 2.87–2.96 (m, 1 H) 3.28 (t, J = 6.7 Hz, 2 H) 3.34–3.41 (m, 2 H) 3.43–3.50 (m, 1 H) 3.51–3.57 (m, 1 H) 3.67 (dd, J = 12.2, 2.5 Hz, 1 H) 3.84 (d, J = 11.5 Hz, 1 H) 3.89 (s, 2 H) 4.47 (d, J = 9.6 Hz, 1 H) 6.39 (d, J = 16.1 Hz, 1 H) 6.50 (d, J = 16.1 Hz, 1 H) 6.75 (d, J = 8.3 Hz, 1 H) 6.80 (s, 1 H) 6.97 (s, 1 H) 7.11 (d, J = 7.8 Hz, 1 H) 7.25 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.0, 24.1, 24.2, 25.2, 25.7, 30.3, 36.3, 38.2, 45.5, 46.0, 58.1, 59.2, 63.1, 71.9, 75.6, 79.1, 80.2, 82.4, 114.3, 124.0, 125.1, 129.1, 129.2, 130.2, 130.6, 131.8, 134.5, 136.3, 137.6, 149.6, 155.7, 177.4, 178.6; HRMS ESI/APCI Dual *m/z*: 670.4039 $[M+H]^+$ (calcd for $C_{37}H_{55}N_3O_8$ 670.4062).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-hydroxy-4-(propan-2-yl)phenyl]-D-glucitol (62h)

Compound **62h** (47%) was obtained from **61h** in a manner similar to that described for **62e**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.10 (d, J = 6.4 Hz, 6 H) 1.36 (s, 6 H) 1.44 (s, 6 H) 2.31 (s, 3 H) 2.70 (s, 4 H) 2.90–2.95 (m, 1 H) 3.36–3.39 (m, 2 H) 3.43–3.61 (m, 7 H) 3.65–3.69 (m, 1 H) 3.84 (d, J = 11.9 Hz, 1 H) 3.88 (s, 2 H) 4.46 (d, J = 9.6 Hz, 1 H) 6.38 (d, J = 16.1 Hz, 1 H) 6.47 (d, J = 16.1 Hz, 1 H) 6.76 (d, J = 7.8 Hz, 1 H) 6.80 (s, 1 H) 6.95 (s, 1 H) 7.10 (d, J = 7.3 Hz, 1 H) 7.22 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.0, 24.1, 24.2, 25.8, 26.3, 30.3, 36.3, 45.7, 46.6, 58.1, 63.1, 71.9, 75.6, 79.1, 80.2, 82.5, 114.3, 124.0, 124.9, 129.1, 129.2, 130.3, 130.3, 131.7, 134.5, 136.3, 137.6, 140.9, 149.6, 155.7, 173.9, 177.8; HRMS ESI/APCI Dual *m/z*: 668.3900 $[M+H]^+$ (calcd for

$C_{37}H_{53}N_3O_8$ 668.3905).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-hydroxy-4-(propan-2-yl)phenyl]-D-glucitol (62i)

Compound **62i** (79%) was obtained from **61i** in a manner similar to that described for **62e**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.10 (d, J = 6.9 Hz, 6 H) 1.37 (s, 6 H) 1.44 (s, 6 H) 2.16 (s, 3 H) 2.22–2.38 (m, 7 H) 2.87–2.96 (m, 1 H) 3.35–3.41 (m, 2 H) 3.42–3.51 (m, 2 H) 3.51–3.56 (m, 1 H) 3.56–3.71 (m, 5 H) 3.84 (d, J = 12.4 Hz, 1 H) 3.88 (s, 2 H) 4.47 (d, J = 9.6 Hz, 1 H) 6.38 (d, J = 16.5 Hz, 1 H) 6.46 (d, J = 16.5 Hz, 1 H) 6.75 (d, J = 8.3 Hz, 1 H) 6.80 (s, 1 H) 6.97 (s, 1 H) 7.09 (d, J = 8.3 Hz, 1 H) 7.22 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.0, 24.1, 24.2, 25.7, 26.3, 30.3, 36.3, 45.7, 46.1, 55.9, 58.1, 63.1, 71.9, 75.6, 79.1, 80.2, 82.5, 114.3, 124.1, 125.0, 129.1, 129.2, 130.2, 130.3, 131.8, 134.6, 136.2, 137.6, 140.9, 149.6, 155.7, 173.8, 177.8; HRMS ESI/APCI Dual *m/z*: 682.4065 $[M+H]^+$ (calcd for $C_{38}H_{55}N_3O_8$ 682.4062).

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(2-Amino-2-methylpropyl)amino]-2-methyl-1-oxopropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-hydroxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (62j)

Compound **62j** (98%) was obtained from **61j** in a manner similar to that described for **62e**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.02 (s, 6 H) 1.05–1.10 (m, 6 H) 1.35 (s, 6 H) 1.44 (s, 6 H) 2.29 (s, 3 H) 2.85–2.93 (m, 1 H) 3.09 (s, 1 H) 3.27–3.30 (m, 1 H) 3.34–3.39 (m, 2 H) 3.42–3.47 (m, 1 H) 3.52 (t, J = 9.4 Hz, 1 H) 3.55–3.61 (m, 1 H) 3.63–3.69 (m, 1 H) 3.80–3.85 (m, 1 H) 3.86 (s, 2 H) 4.46 (d, J = 9.6 Hz, 2 H) 6.35–6.41 (m, 1 H) 6.44–6.51 (m, 1 H) 6.73 (d, J = 7.8 Hz, 1 H) 6.78 (s, 1 H) 6.96 (s, 1 H) 7.06–7.10 (m, 1 H) 7.23 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.0, 24.1, 24.2, 25.3,

25.8, 26.5, 30.3, 36.3, 46.0, 50.7, 53.9, 58.2, 63.1, 71.9, 75.6, 79.1, 80.2, 82.4, 114.3, 124.0, 125.1, 129.1, 130.2, 130.6, 131.8, 134.3, 136.2, 137.5, 140.9, 149.6, 155.7, 177.8, 178.9; HRMS ESI/APCI Dual *m/z*: 670.4052 $[M+H]^+$ (calcd for $C_{37}H_{55}N_3O_8$ 670.4062).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[2-(dimethylamino)ethyl]amino}-2-methyl-1-oxopropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (62k)

Compound **62k** (78%) was obtained from **61k** in a manner similar to that described for **62e**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.13, 1.15 (each d, J = 6.8 Hz, each 3 H) 1.36 (s, 6 H) 1.45 (s, 6 H) 2.21 (s, 6 H) 2.32 (s, 3 H) 2.39 (t, J = 6.9 Hz, 2 H) 2.93–3.02 (m, 1 H) 3.24–3.39 (m, 4 H) 3.42–3.48 (m, 1 H) 3.49–3.54 (m, 1 H) 3.58–3.65 (m, 1 H) 3.80–3.87 (m, 4 H) 3.91 (s, 2 H) 4.61 (d, J = 9.6 Hz, 1 H) 6.39 (d, J = 16.5 Hz, 1 H) 6.50 (d, J = 16.1 Hz, 1 H) 6.73 (d, J = 7.3 Hz, 1 H) 6.92 (s, 1 H) 7.08 (s, 1 H) 7.10 (d, J = 7.8 Hz, 1 H) 7.25 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.0, 24.1, 24.2, 25.3, 25.7, 30.7, 36.4, 38.4, 45.6, 46.1, 56.5, 58.1, 59.2, 63.5, 72.3, 75.8, 77.0, 80.3, 82.5, 109.7, 125.1, 126.3, 129.2, 130.1, 130.2, 130.6, 131.8, 134.6, 136.4, 137.6, 140.6, 149.8, 158.6, 177.3, 178.4; HRMS ESI/APCI Dual *m/z*: 684.4213 $[M+H]^+$ (calcd for $C_{38}H_{57}N_3O_8$ 684.4218).

(*1S*)-1,5-anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-oxo-1-(piperazin-1-yl)propan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (62l)

Compound **62l** (94%) was obtained from **61l** in a manner similar to that described for **62e**. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.14, 1.16 (each d, J = 6.4Hz, each 3 H) 1.36 (s, 6 H) 1.44 (s, 6 H) 2.32 (s, 3 H) 2.69 (s, 4 H) 2.95–3.03 (m, 1 H) 3.28–3.38 (m, 2 H) 3.42–3.52 (m, 2 H) 3.53 –3.65 (m, 5 H) 3.80–3.84 (m, 1 H) 3.84 (s, 3 H) 3.92 (s, 2 H) 4.61 (d, J = 9.2 Hz, 1 H) 6.39 (d, J = 16.1 Hz,

1 H) 6.47 (d, *J* = 16.1 Hz, 1 H) 6.74 (d, *J* = 7.8 Hz, 1 H) 6.92 (s, 1 H) 7.06 (s, 1 H) 7.10 (d, *J* = 7.8 Hz, 1 H) 7.22 (s, 1 H); ^{13}C NMR (126 MHz, CD3OD) δ ppm 20.0, 24.1, 24.2, 25.7, 25.8, 26.3, 30.7, 36.3, 45.7, 46.6, 56.5, 58.1, 63.4, 72.3, 75.8, 76.9, 80.3, 82.5, 109.7, 124.9, 126.3, 129.2, 130.2, 130.3, 130.3, 131.7, 134.5, 136.3, 137.7, 140.7, 149.7, 158.6, 173.9, 177.8; HRMS ESI/APCI Dual *m/z*: 682.4041 $[M+H]^+$ (calcd for $C_{38}H_{55}N_3O_8$ 682.4062).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-3,3-dimethyl-4-{[2-methyl-1-(4-methylpiperazin-1-yl)-1-oxopropan-2-yl]amino}-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (62m)

Compound **62m** (9% in 2 steps) was obtained from **61m** in a manner similar to that described for **62e**.

^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.09–1.16 (m, 6 H) 1.35 (s, 6 H) 1.42 (s, 6 H) 2.12–2.16 (m, 3 H) 2.23–2.33 (s, 4 H) 2.30 (s, 3 H) 2.92–3.01 (m, 1 H) 3.28 (s, 2 H) 3.30–3.38 (m, 1 H) 3.41–3.51 (m, 2 H) 3.55–3.66 (m, 5 H) 3.78–3.86 (m, 4 H) 3.90 (s, 2 H) 4.59 (d, *J* = 9.2 Hz, 1 H) 6.33–6.39 (m, 1 H) 6.42–6.47 (m, 1 H) 6.72 (d, *J* = 7.8 Hz, 1 H) 6.90 (s, 1 H) 7.04–7.11 (m, 2 H) 7.19–7.24 (m, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.0, 24.1, 24.2, 25.7, 26.3, 30.7, 36.3, 45.7, 46.1, 55.9, 56.5, 58.1, 63.4, 72.3, 75.8, 76.9, 80.3, 82.5, 109.7, 125.0, 126.3, 129.1, 130.2, 130.2, 130.3, 131.7, 134.6, 136.3, 137.6, 140.7, 149.7, 158.6, 173.8, 177.8; HRMS ESI/APCI Dual *m/z*: 696.4203 $[M+H]^+$ (calcd for $C_{39}H_{57}N_3O_8$ 696.4218).

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(2-Amino-2-methylpropyl)amino]-2-methyl-1-oxopropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (62n)

Compound **62n** (65%) was obtained from **61n** in a manner similar to that described for **62e**.

^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.01 (s, 6 H) 1.09 - 1.15 (m, 6 H) 1.35 (s, 6 H) 1.43 (s, 6 H) 2.31 (s, 3 H) 2.91–3.00 (m, 1 H) 3.08 (s, 2 H) 3.27–3.36 (m, 5 H) 3.41–3.46 (m, 1 H) 3.47–3.52 (m, 1 H) 3.60 (dd, J = 11.9, 6.0 Hz, 1 H) 3.80- 3.84 (m, 4 H) 3.90 (s, 2 H) 4.59 (d, J = 9.6 Hz, 1 H) 6.36 - 6.41 (m, 1 H) 6.45 - 6.50 (m, 1 H) 6.71 (d, J = 7.8 Hz, 1 H) 6.90 (s, 1 H) 7.06 (s, 1 H) 7.07 - 7.10 (m, 1 H) 7.20 - 7.25 (m, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.0, 24.0, 24.2, 25.3, 25.8, 27.3, 30.7, 36.4, 46.0, 51.7, 52.5, 56.5, 58.2, 63.4, 72.3, 75.8, 77.0, 80.3, 82.5, 109.7, 125.1, 126.3, 129.2, 130.1, 130.2, 130.6, 131.8, 134.5, 136.3, 137.5, 140.6, 149.8, 158.6, 177.7, 178.6; HRMS ESI/APCI Dual *m/z*: 684.4198 $[M+H]^+$ (calcd for $C_{38}H_{57}N_3O_8$ 684.4218).

1,5-Dibromo-2-(methoxymethoxy)-4-(propan-2-yl)benzene (64)

A solution of bromine (469 g, 2.94 mol) in acetic acid (320 mL) was added dropwise over 1 minute at room temperature to a solution of 3-isopropylphenol (**48**) (160 g, 1.18 mol) in acetic acid (1.6 L) and stirred for 1 hour so that the internal temperature did not exceed 19°C. After addition of toluene (1.6 L), the mixture was ice-cooled, and a 10% aqueous sodium sulfite solution (1.0 L) was added dropwise so as not to exceed an internal temperature of 20°C. The organic layer was separated, washed twice with 10% aqueous sodium sulfite solution (1.0 L) and 10% brine (1.0 L), and then dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure to give 2,4-dibromo-5-isopropylphenol (342 g, 99%) in the form of a pale yellow oil. *N*,*N*-diisopropylethylamine (364 mL, 2.09 mol) was added to a solution of 2,4-dibromo-5-isopropylphenol (512 g, 1.74 mol) in chloroform (1.74 L), and the mixture was ice-cooled. Chloromethyl methyl ether (159 mL, 2.09 mol) was added dropwise over a 1-hour period, and the solution was stirred at room temperature for 1 hour. The reaction solution was then ice-cooled, and after addition of 1 M aqueous sodium hydroxide solution (1.5 L) dropwise, the organic layer was separated, washed with 1 M aqueous sodium hydroxide solution (1.5 L) and water (1.5 L), and dried over anhydrous magnesium

sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue obtained was purified by distillation under reduced pressure (0.93 to 1.5 hPa, 122°C. to 137°C.) to obtain the titled compound (548 g, 96%) in the form of a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.22 (d, J = 6.8 Hz, 6 H), 3.28 (sept, J = 6.8 Hz, 1 H), 3.52 (s, 3 H), 5.23 (s, 2 H), 7.06 (s, 1 H), 7.69 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 339$[M+H]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-D-glucitol (67)

A 2.69 M *n*-butyllithium hexane solution (231 mL, 0.621 mol) was added dropwise over 20 minutes to a tetrahydrofuran solution (2.84 L) of compound **64** (200 g, 0.592 mol) at −80°C to −76°C under an argon atmosphere, and stirred at the same temperature for 35 minutes. A solution of 2,3,4,6-tetra-*O*-trimethylsilyl-D-glucono-1,5-lactone (**34**) (290 g, 0.621 mol) in tetrahydrofuran (800 mL) was then added dropwise over 55 minutes and stirred at the same temperature for 50 minutes. Next, trimethylchlorosilane (75.7 mL, 0.621 mol) was added dropwise over 15 minutes, and the mixture was stirred at the same temperature for 2 hours. Then, a 2.69 M *n*-butyllithium hexane solution (319 mL, 0.858 mol) was added dropwise over 29 minutes, and the mixture was stirred at the same temperature for 40 minutes. Finally, a solution of 4-bromo-2-methylbenzaldehyde (**37c**) (130 g, 0.651 mol) in tetrahydrofuran (800 mL) was added dropwise over 54 minutes, and the mixture was stirred at the same temperature for 30 minutes. Water (2.85 L) was added to the reaction solution and warmed to room temperature. Toluene (2.0 L) was added, the organic layer was separated, and the solvent was evaporated under reduced pressure to yield crude compound **65** (546 g). Compound **65** (546 g) was dissolved in methanol (3.0 L), and after adding methanesulfonic acid (3.84 mL, 0.0592 mol), the mixture was refluxed for 1.5 hours. The reaction solution was then cooled to room temperature and neutralized with triethylamine (25 mL, 0.179 mol), and the reaction mixture was concentrated. The

concentrate was dissolved in toluene (1.0 L) and washed with water (0.5 L, 1.0 L), and after addition of a 1 M aqueous sodium hydroxide solution (0.6 L) and toluene (1.0 L) to the organic layer, the aqueous layer was separated and washed with toluene (1.0 L, 0.5 L). The aqueous layer was acidified by addition with 10% hydrochloric acid (0.7 L) and extracted with toluene (1.0 L), and the organic layer was separated. The organic layer was then washed with 10% brine (1.0 L) and water (0.5 L), and the solvent was evaporated under reduced pressure to yield a crude intermediate (314 g). The crude intermediate (314 g) was dissolved in pyridine (1.0 L), and after addition of acetic anhydride (0.8 L, 8.51 mol) to the solution, the mixture was stirred at room temperature for 18 hours. The reaction solution was ice-cooled, and after addition of ice (1.5 L) and toluene (1.0 L), and the mixture was stirred for 3 hours. The aqueous layer was separated and extracted with toluene (1.0 L). The combined organic layer was then washed twice with 2 M hydrochloric acid (1.5 L), 5% aqueous sodium hydrogen carbonate solution (1.0 L), and 10% saline (1.0 L), and the solvent was distilled off under reduced pressure to yield compound **66** (350 g). Compound **66** (350 g) was dissolved in acetonitrile (3.4 L) and H_2O (9.1 mL, 0.506 mol), and Et_3SiH (328 mL, 2.05 mol) was added. The solution was cooled in an ice-bath, and TMSOTf (403 mL, 2.23 mol) was added dropwise over 85 minutes under ice-cooling. After stirring for 2 hours at the same temperature, a 3% aqueous sodium hydrogen carbonate solution (1.92 L) was added dropwise over 40 minutes, and after diluting the mixture with toluene (1.0 L) and stirring for 15 minutes, the organic layer was separated. The aqueous layer was extracted with toluene (1.5 L), and after washing the combined organic layer with saturated aqueous sodium hydrogen carbonate solution (1.5 L), the solvent was evaporated under reduced pressure to give the titled compound (392 g) in the form of a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.09 - 1.19 (m, 6 H), 1.69 (s, 3 H), 1.99 (s, 3 H), 2.05 (s, 3 H), 2.12 (s, 3 H), 2.25 (s, 3 H), 2.80 - 2.97 (m, 1 H), 3.66 - 3.96 (m, 3 H), 4.08 - 4.35 (m, 2 H), 4.42 - 4.57 (m, 1 H), 5.19 - 5.37 (m, 3 H), 6.52 (s, 1 H), 6.57 (d, J = 8.1 Hz, 1 H), 6.87 (s, 1H), 7.12 – 7.20 (m, 1 H), 7.30- 7.33 (m, 1 H).

Tert-butyl (2-amino-2-oxoethyl)(2-{[(benzyloxy)carbonyl]amino}ethyl)carbamate (70)

Compound **68** (2.51 g, 10.9 mmol) was added to a solution of compound **69** (500 mg, 3.62 mmol) and *N*,*N*-diisopropylethylamine (1.84 mL) in ethanol solution (18 mL). The reaction solution was stirred at the room temperature for 18 hours. The reaction solution was evaporated under reduced pressure. The resulting residue was purified by performing silica gel column chromatography (chloroform: methanol ratio = 8:2) to obtain the colorless amorphous (1.6 g). Di-tert-butyl dicarbonate (4.04 g) and *N*,*N*-dimethyl-4-aminopyridine (440 mg) were added to a solution of obtained amorphous (1.55 g) in *N*,*N*-dimethylformamide solution (18 mL). The reaction solution was refluxed for 18 hours. The reaction solution was diluted with ethyl acetate. The organic layer was separated and washed with 10% brine, and water. The solvent was evaporated under reduced pressure. The resulting residue was purified by performing silica gel column chromatography (hexane: ethyl acetate = 8: 2 to 5: 5) to obtain the titled compound (463 mg, 36% in 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.44 (s, 9H), 3.31 - 3.48 (m, 4H), 3.81 (s, 2H), 5.09 (br s, 2H), 7.28 - 7.44 (m, 5H); MS (ESI/APCI Dual) *m/z*: 374$[M+Na]^+$.

Tert-butyl (2-aminoethyl)(2-amino-2-oxoethyl)carbamate (71)

7.5% $Pd(OH)_2$/C (139 mg) was added to a solution of compound **70** (463 mg, 1.32 mmol) in methanol solution (13 mL) under hydrogen atomsphere. The reaction solution was stirred at the room temperature for 18 hours. The mixture was filtered through Celite®. The filtrate was evaporated under reduced pressure to give the titled compound (297 mg). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.34 - 1.43 (m, 9H), 2.85 - 2.94 (m, 2H), 3.17 (s, 1H), 3.37 - 3.47 (m, 2H), 3.78 (s, 2H), 7.08 - 7.88 (m, 5H); MS (ESI/APCI Dual) *m/z*: 218$[M+H]^+$.

(*1S*)-2,3,4,6-Tetra-O-acetyl-1-[2-(acetyloxy)-5-({4-[(*1E*)-3-carboxy-3-methylbut-1-en-1-yl]-2-methylphenyl}methyl)-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (72)

Under an argon atmosphere, a suspension of compound **55g** (216 g, 0.312 mol), 2,2-dimethyl-3-butenoic acid (**41**) (53.4 g, 0.467 mol), palladium (II) acetate (3.50 g, 15.6 mmol), tri-*o*-tolylphosphine (9.48 g, 31.2 mmol) and triethylamine (86.9 mL, 0.623 mol) in acetonitrile (623 mL) was heated to reflux for 3 hours. The reaction mixture was cooled to room temperature, diluted with chloroform (300 mL) and methanol (100 mL), and filtered through Celite®. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in ethyl acetate (1.32 L). It was washed with 1M hydrochloric acid (0.96 L), 10% brine (1.2 L), and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, ethyl acetate (1.2 L) was further added to the filtrate, isopropylamine (28.2 mL, 0.327 mol) was added, and the mixture was stirred from room temperature to 0 ° C for 1 hour. The deposited precipitate was filtered to obtain an isopropylamine salt of intermediate. This salt was dissolved in ethyl acetate (1.2 L) and 1 M hydrochloric acid (500 mL) and stirred for 30 minutes, and the organic layer was separated. The organic layer was washed with 10% brine (500 mL) and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure to obtain the titled compound (207 g, 88%) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.13 (d, J = 6.8 Hz, 3 H), 1.14 (d, J = 6.8 Hz, 3 H), 1.43 (s, 6 H), 1.76 (s, 3 H), 1.99 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.28 (s, 3 H), 2.37 (s, 3 H), 2.98 (spt, J = 6.8 Hz, 1 H), 3.70 - 3.80 (m, 1 H), 3.91 (s, 2 H), 4.05 (dd, J = 12.4, 2.2 Hz, 1 H), 4.28 (dd, J = 12.4, 4.4 Hz, 1 H), 4.43 - 4.50 (m, 1 H), 5.11 - 5.20 (m, 1 H), 5.22 - 5.33 (m, 2 H), 6.33 - 6.49 (m, 2 H), 6.68 (d, J = 7.9 Hz, 1 H), 6.96 (s, 1 H), 6.99 (s, 1 H), 7.06 - 7.14 (m, 1 H), 7.23 (d, J = 1.4 Hz, 1 H); MS (ESI/APCI Dual) *m/z*: 747[M+Na]$^+$.

(*1S*)-1-[5-({4-[(*1E*)-4-({2-[(2-Amino-2-oxoethyl)amino]ethyl}amino)-3,3-dimethyl-4-oxobut-1-

en-1-yl]-2-methylphenyl}methyl)-2-hydroxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (63)

Compound **71** (285 mg, 1.52 mmol), 1-hydroxy-1H-benzotriazole hydrate (205 mg), triethylamine (420 uL), water soluble carbodiimide hydrochloride (290 mg) were added to a solution of compound **72** (731 mg, 1.01 mmol) in *N*,*N*-dimethylformamide solution (5 mL). The reaction solution was stirred at the room temperature for 18 hours. The reaction solution was diluted with ethyl acetate. The organic layer was separated and washed with 10% brine, and water. The solvent was evaporated under reduced pressure. The resulting residue was purified by performing silica gel column chromatography (hexane: ethyl acetate = 2: 1 to 1: 2) to obtain the crude compound (830 mg) as a colorless amorphous. Trifluoroacetic acid (1.2 mL) was added to a solution of obtained crude compound (830 mg) in chloroform solution (9 mL). The reaction solution was stirred at the room temperature for 18 hours. The solvent was evaporated under reduced pressure to give the crude compound (1.5 g). 4.88 M sodium methoxide (1.1 mL) was add to a solution of the crude compound (1.5g) in methanol solution (9 mL). The reaction solution was stirred at the room temperature for 3.5 hours. The solvent was evaporated under reduced pressure. The resulting residue was purified by performing NH silica gel column chromatography (ethanol: H_2O = 9: 1 to 2: 1) to obtain the titled compound (652 mg, 76% in 3 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.08 - 1.12 (m, 6 H), 1.37 (s, 6 H), 2.30 (s, 3 H), 2.66 - 2.70 (m, 2 H), 2.90 - 2.96 (m, 1 H), 3.21 - 3.23 (m, 2 H), 3.27 - 3.30 (m, 2 H), 3.37 - 3.40 (m, 2 H), 3.44 - 3.48 (m, 1 H), 3.52 - 3.56 (m, 1 H), 3.66 - 3.70 (m, 1 H), 3.82 - 3.86 (m, 1 H), 3.88 (s, 2 H), 4.44 - 4.48 (m, 1 H), 6.33 - 6.39 (m, 1 H), 6.44 - 6.50 (m, 1 H), 6.73 - 6.78 (m, 1 H), 6.80 (s, 1 H), 6.95 (s, 1 H), 7.08 - 7.12 (m, 1 H), 7.23 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.97, 24.09, 24.20, 25.95, 30.30, 36.31, 40.59, 45.92, 49.84, 52.34, 63.09, 71.89, 75.51, 79.17, 80.17, 82.41, 114.28, 123.95, 125.04, 129.14, 129.24, 130.23, 130.26, 131.77, 134.72, 136.33, 137.54, 140.70, 149.64, 155.64, 177.00, 179.71,; HR-MS ESI/APCI dual *m/z*: 614.3454 $[M+H]^+$ (calcd for $C_{33}H_{47}N_3O_8$: 614.3436).

(*1S*)-1-{5-[(4-{(*1E*)-4-[(2-Amino-2-methylpropyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (74)

Compound **73** (128 mg, 1.45 mmol) was added to a solution of componud **72** (1.00 g, 1.38 mmol) and 1,1'-carbonylbis-1H-imidazole (235 mg) in chloroform solution (5 mL). The reaction solution was stirred at the room temperature for 5 hours. The reaction mixture was twice with 10% K_2CO_3, and the organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The resulting residue was purified by performing NH silica gel column chromatography (chloroform) to obtain the crude compound (0.7 g). To a solution of the crude compound (0.7g) in methanol solution (5 mL), 4.88M sodium methoxide (1.1 mL) was added. The reaction solution was stirred at the room temperature for 1 hours. After acetic acid (605 μL) was added, the solvent was evaporated under reduced pressure. The resulting residue was purified by performing NH silica gel column chromatography (ethyl acetate: ethanol: H_2O = 30: 2: 1 to 10: 2: 1) to obtain the titled compound (399 mg, 50% in 2 steps). ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.05 (s, 6H), 1.09 (d, J = 6.88 Hz, 6H), 1.39 (s, 6H), 2.31 (s, 3H), 2.87 - 2.94 (m, 1H), 3.13 (s, 2H), 3.35 - 3.40 (m, 2H), 3.43 - 3.49 (m, 1H), 3.51 - 3.56 (m, 1H), 3.65 - 3.71 (m, 1H), 3.82 - 3.89 (m, 3H), 4.47 (d, J = 9.63 Hz, 1H), 6.38 (d, J = 16.05 Hz, 1H), 6.46 - 6.52 (m, 1H), 6.75 (d, J = 7.79 Hz, 1H), 6.80 (s, 1H), 6.96 (s, 1H), 7.10 (d, J = 7.79 Hz, 1H), 7.23 (s, 1H); MS (ESI/APCI Dual) *m/z*: 585$[M+H]^+$, 583$[M-H]^-$.

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(2-Amino-2-oxoethyl)amino]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-hydroxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (75)

Compound **74** (0.20 g, 0.34 mmol) was addded to a solution of compound **69** (213 mg, 1.55 mmol) in *N*,*N*-dimethylformamide solution (1 mL). The reaction solution was stirred at 90 °C for 25 hours. The solvent was evaporated under reduced pressure. The resulting residue was purified by performing

HPLC column chromatography (Waters sunfine C-18, MeOH: 0.1%Et_3N = 3: 7, 20 mL/min) to obtain the titled compound (49 mg, 22%). ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.07 - 1.14 (m, 6 H), 1.33 (s, 6 H), 1.36 (s, 6 H), 2.31 (s, 3 H), 2.77 - 2.84 (m, 2 H), 2.90 - 2.96 (m, 1 H), 3.31 - 3.35 (m, 2 H), 3.37 - 3.40 (m, 2 H), 3.44 - 3.48 (m, 1 H), 3.52 - 3.57 (m, 1 H), 3.66 - 3.70 (m, 1 H), 3.82 - 3.87 (m, 1 H), 3.89 (s, 2 H), 4.44 - 4.48 (m, 1 H), 6.37 (d, *J* = 16.0 Hz, 1 H), 6.50 (d, *J* =16.0 Hz, 1 H), 6.74 - 6.78 (m, 1 H), 6.80 (s, 1 H), 6.96 (s, 1 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 7.23 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.97, 24.09, 24.21, 25.35, 25.91, 30.32, 36.31, 46.51, 52.35, 54.50, 59.25, 63.09, 71.91, 75.48, 79.21, 80.17, 82.42, 114.29, 117.25, 119.58, 123.95, 125.02, 129.14, 129.21, 130.26, 130.64, 131.82, 134.78, 136.24, 137.63, 140.84, 149.67, 155.66, 163.09, 163.36,; HR-MS ESI/APCI Dual *m/z*: 642.3730 $[M+H]^+$ (calcd for $C_{35}H_{51}N_3O_8$: 642.3749).

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-{(*1E*)-3,3-dimethyl-4-[(2-methyl-1-oxopropan-2-yl)amino]-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (78a)

Compound **76a** (184 mg, 2.07 mmol), 1-hydroxy-*1H*-benzotriazole hydrate (242 mg), water soluble carbodiimide hydrochloride (342 mg) were added to a solution of compound **72** (1.0 g, 1.38 mmol) in *N*,*N*-dimethylformamide solution (30 mL). The reaction solution was stirred at the room temperature for 18 hours. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure to obtain the crude intermediate (**77a**) (1.05 g). A chloroform suspension (20 mL) of obtained intermediate (**77a**) (660 mg, 0.830 mmol) and Dess-Martin periodinane (422 mg, 1.25 mmol) was stirred at room temperature for 3 hours. After the solvent was distilled off under reduced pressure, the residue was purified by silica gel column chromatography (hexane: ethyl acetate

= 4: 1 to 1: 4) to obtain the titled compound (602 mg, 85% over 2 steps) as a yellow amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.09 - 1.18 (m, 6 H), 1.33 (s, 6 H), 1.39 (s, 6 H), 1.78 (s, 3 H), 1.99 (s, 3 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 2.31 (s, 3 H), 2.37 (s, 3 H), 2.98 (spt, *J* = 6.9 Hz, 1 H), 3.73 - 3.80 (m, 1 H), 3.89 - 3.98 (m, 2 H), 4.06 (dd, *J* = 12.4, 2.3 Hz, 1 H), 4.26 (dd, *J* = 12.4, 4.6 Hz, 1 H), 4.46 - 4.53 (m, 1 H), 5.11 - 5.18 (m, 1 H), 5.23 - 5.30 (m, 2 H), 6.13 (br. s, 1 H), 6.33 (d, *J* = 16.5 Hz, 1 H), 6.53 (d, *J* = 16.5 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 6.99 – 7.01 (m, 2 H), 7,13 (d, J = 7.8 Hz, 1 H), 7.26 (s, 1 H), 9.34 (s, 1 H).

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-{(*1E*)-4-[(1-formylcyclopropyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (78b)

Compound **72** (500 mg, 0.69 mmol) and compound **76b** (72 mg, 0.83 mmol) were used as starting materials and synthesized in the same manner as compound **78a** to give the titled compound (305 mg, 98% for 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 - 1.16 (m, 6 H), 1.42 (s, 6 H), 1.46 - 1.55 (m, 4 H), 1.78 (s, 3 H), 1.99 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.31 (s, 3 H), 2.37 (s, 3 H), 2.91 - 3.06 (m, 1 H), 3.72 - 3.80 (m, 1 H), 3.91 - 3.95 (m, 2 H), 4.01 - 4.08 (m, 1 H), 4.20 - 4.28 (m, 1 H), 4.46 - 4.52 (m, 1 H), 5.09 - 5.18 (m, 1 H), 5.22 - 5.29 (m, 2 H), 6.26 - 6.30 (m, 1 H), 6.35 (d, *J* = 16.2 Hz, 1 H), 6.55 (d, *J* = 16.2 Hz, 1 H), 6.68 - 6.74 (m, 1 H), 7.00 (s, 2 H), 7.10 - 7.16 (m, 1 H), 7.26(s, 1H), 9.06 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 792$[M+H]^+$, 814$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-{(*1E*)-4-[(1-formylcyclobutyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (78c)

Compound **72** (1.0 g, 1.38 mmol) and compound **76c** (210 mg, 2.07 mmol) were used as starting

materials and synthesized in the same manner as compound **78a** to give the titled compound (355 mg, 32% for 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 - 1.19 (m, 6 H), 1.40 (s, 6 H), 1.78 (s, 3 H), 1.91 - 2.08 (m, 11 H), 2.22 - 2.40 (m, 8 H), 2.42 - 2.56 (m, 2 H), 2.91 - 3.05 (m, 1 H), 3.70 - 3.81 (m, 1 H), 3.94 (s, 2 H), 4.05 (dd, J = 12.4, 1.9 Hz, 1 H), 4.26 (dd, J = 12.4, 4.5 Hz, 1 H), 4.44 - 4.55 (m, 1 H), 5.10 - 5.20 (m, 1 H), 5.21 - 5.33 (m, 2 H), 6.28 - 6.41 (m, 2 H), 6.49 - 6.61 (m, 1 H), 6.71 (d, J = 7.9 Hz, 1 H), 7.00 (s, 2 H), 7.14 (d, J = 7.9 Hz, 1 H), 7.27 (s, 1 H), 9.55 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 806$[M+H]^+$, 828$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-{(*1E*)-4-[(1-formylcyclopentyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (78d)

Compound **72** (1.0 g, 1.38 mmol) and compound **76d** (207 mg, 1.79 mmol) were used as starting materials and synthesized in the same manner as compound **78a** to give the titled compound (850 mg, 71% for 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.10 - 1.18 (m, 6 H), 1.39 (s, 6 H), 1.64 - 2.18 (m, 8 H), 1.77 (s, 3 H), 1.99 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.32 (s, 3 H), 2.37 (s, 3 H), 2.89 - 3.04 (m, 1 H), 3.71 - 3.81 (m, 1 H), 3.93 (s, 2 H), 4.01 - 4.10 (m, 1 H), 4.25 - 4.30 (m, 1 H), 4.45 - 4.53 (m, 1 H), 5.10 - 5.20 (m, 1 H), 5.23 - 5.30 (m, 2 H), 6.18 (s, 1 H), 6.26 - 6.39 (m, 1 H), 6.47 - 6.60 (m, 1 H), 6.70 (d, J = 7.6 Hz, 1 H), 6.96 - 7.05 (m, 2 H), 7.10 - 7.16 (m, 1 H), 7.23 - 7.26 (m, 1 H), 9.43 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 820$[M+H]^+$, 842$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-{(*1E*)-4-[(1-formylcyclohexyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (78e)

Compound **72** (1.00 g, 1.38 mmol) and compound **76e** (267 mg, 2.07 mmol) were used as starting

materials and synthesized in the same manner as compound **78a** to give the titled compound (265 mg, 23% for 2 steps) as a light brown amorphous.MS (ESI/APCI Dual) *m/z*: 834[M+H]$^+$, 856[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-[(4-{(*1E*)-4-[(3-formyloxetan-3-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (78f)

Compound **72** (815 mg, 1.12 mmol) and compound **76f** (174 mg, 1.69 mmol) were used as starting materials and synthesized in the same manner as compound **78a** to give the titled compound (483 mg, 69% for 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 - 1.10 (m, 6 H), 1.43 (s, 6 H), 1.79 (s, 3 H), 1.98 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.31 (s, 3 H), 2.36 (s, 3 H), 2.93 - 3.06 (m, 1 H), 3.71 - 3.80 (m, 1 H), 3.93 (s, 2 H), 4.04 (dd, *J* = 12.3, 2.2 Hz, 1 H), 4.23 (dd, *J* = 12.4, 4.6 Hz, 1 H), 4.48-4.52 (m, 1 H), 4.76 (d, *J* = 6.7 Hz, 2 H), 4.87 (d, *J* = 6.7 Hz, 2 H), 5.08 - 5.18 (m, 1 H), 5.18 - 5.33 (m, 2 H), 6.36 (d, *J* = 16.0 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 6.60 (br. s, 1 H), 6.73 (d, *J* = 7.9 Hz, 1 H), 6.98 (s, 1 H), 7.00 (s, 1 H), 7.15 (d, *J* = 7.9 Hz, 1 H), 7.27 (s, 1 H), 9.74 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 808[M+H]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-[2-(acetyloxy)-5-({4-[(*1E*)-4-{[1-(tert-butoxycarbonyl)-3-formylazetidin-3-yl]amino}-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (78g)

Compound **72** (629 mg, 0.867 mmol) and compound **76g** (228 mg, 1.13 mmol) were used as starting materials and synthesized in the same manner as compound **78a** to give the titled compound (556 mg, 71% for 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.15 (dd, *J* = 6.84, 4.20 Hz, 6H), 1.44 (s, 6H), 1.78 (s, 3H), 1.99 (s, 3H), 2.02 - 2.05 (m, 6H), 2.31 (s, 3H), 2.37 (s, 3H), 2.88 (s, 1H), 2.93 - 3.04 (m, 2H), 3.72 - 3.81 (m, 1H), 3.94 (s, 2H), 4.04 (d, *J* = 9.17 Hz, 2H), 4.18 - 4.29

(m, 3H), 4.47 - 4.52 (m, 1H), 5.10 - 5.30 (m, 3H), 6.30 - 6.39 (m, 1H), 6.53 - 6.62 (m, 2H), 6.72 (d, *J*=7.93 Hz, 1H), 6.99 (d, *J* = 1.71 Hz, 2H), 7.14 (dd, *J* = 8.16, 1.63 Hz, 1H), 9.58 (s, 1H); MS (ESI/APCI Dual) *m/z*: 807[M+H-Boc]$^+$.

(*1S*)-1-[5-({4-[(*1E*)-4-({2-[(2-Amino-2-oxoethyl)amino]-2-methylpropyl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-hydroxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (82a)

Sodium cyanoborohydride (32 mg) was added to a solution of compound **78a** (300 mg, 0.392 mmol) and compound **79** (44.0 mg, 0.588 mmol) in methanol solution (4 mL). The reaction solution was stirred at the room temperature for 18 hours. After the solvent was distilled off under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure. The residue (**81a**) was purified by silica gel column chromatography (chloroform: methanol = 99: 1 to 9: 1) to obtain the crude intermediate (43 mg). The crude intermediate (43 mg) and 4.88 M sodium methoxide (64 μL) in methanol solution (0.5 mL) was stirred at the room temperature for 18 hours. After the solvent was distilled off under reduced pressure, the residue was purified by NH silica gel column chromatography (ethyl acetate: ethanol: water = 15: 2: 1 to 7: 2: 1) to obtain the titled compound (8 mg, 3% in 2 steps) as a colorless amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.01 (s, 6H), 1.09 (s, 3H), 1.10 (s, 3H), 1.39 (s, 6H), 2.30 (s, 3H), 2.88 - 2.98 (m, 1H), 3.13 (s, 2H), 3.20 (s, 2H), 3.36 - 3.42 (m, 2H), 3.43 - 3.49 (m, 1H), 3.51 - 3.57 (m, 1H), 3.65 - 3.71 (m, 1H), 3.81 - 3.86 (m, 1H), 3.88 (s, 2H), 4.46 (d, *J* = 9.56 Hz, 1H), 6.36 - 6.42 (m, 1H), 6.48 - 6.55 (m, 1H), 6.75 (d, *J* = 8.03 Hz, 1H), 6.80 (s, 1H), 6.96 (s, 1H), 7.12 (dd, *J* = 8.03, 1.53 Hz, 1H), 7.23 (s, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.98, 24.10, 24.21, 25.14, 25.96, 30.31, 36.32, 45.81, 46.09, 48.42, 54.99, 63.12,

71.91, 75.53, 79.14, 80.18, 82.43, 114.28, 123.98, 124.99, 129.16, 129.19, 130.24, 130.49, 131.78, 134.84, 136.28, 137.58, 140.79, 149.62, 155.68, 178.02, 179.46,; HR-MS ESI/APCI Dual *m/z*: 642.3759 $[M+H]^+$ (calcd for $C_{35}H_{51}N_3O_8$: 642.3749).

(*1S*)-1-{5-[(4-{(*1E*)-4-[(1-{[(2-Amino-2-oxoethyl)amino]methyl}cyclopropyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (82b)

Sodium triacetoxyborohydride (30 mg) was added to a solution of compound **78b** (100 mg, 0.126 mmol) and compound **80** (21.0 mg, 0.192 mmol) in *N*,*N*-dimethylformamide solution (4 mL). The reaction solution was stirred at the room temperature for 18 hours. Water was added and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform: methanol = 99: 1 to 50: 50) to obtain the crude intermediate (62 mg). The crude intermediate (62 mg) in methanol: triethylamine: water (5: 1: 1) solution (2 mL) was stirred at the room temperature for 18 hours. After the solvent was distilled off under reduced pressure, the residue was purified by OH silica gel column chromatography (chloroform: methanol = 100: 0 to 50: 50) to obtain the titled compound (30 mg, 28% in 2 steps) as a pale brown amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 0.71 - 0.80 (m, 4 H), 1.10 (d, J = 6.9 Hz, 6 H), 1.34 (s, 6 H), 2.30 (s, 3 H), 2.72 - 2.77 (m, 2 H), 2.89 - 2.96 (m, 1 H), 3.30 (s, 1 H), 3.35 - 3.40 (m, 2 H), 3.43 - 3.48 (m, 1 H), 3.51 - 3.56 (m, 1 H), 3.65 - 3.70 (m, 1 H), 3.82 - 3.86 (m, 1 H), 3.86 - 3.91 (s, 2 H), 4.46 (d, J = 9.2 Hz, 1 H), 6.35 (d, J = 16.0 Hz, 1 H), 6.45 (d, J = 16.0 Hz, 1 H), 6.72 - 6.78 (m, 1 H), 6.78 - 6.82 (s, 1 H), 6.91 - 6.97 (s, 1 H), 7.07 - 7.14 (m, 1 H), 7.20 - 7.26 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 13.36, 19.97, 24.09, 24.21, 25.85, 30.30, 33.61, 36.31, 45.84, 51.94, 56.33, 63.11, 71.90, 75.53,

79.14, 80.18, 82.42, 114.26, 123.98, 125.04, 129.14, 129.21, 130.16, 130.23, 131.75, 134.69, 136.32, 137.55, 140.72, 149.61, 155.65, 175.78, 180.63,; HR-MS ESI/APCI Dual *m/z*: 640.3598 $[M+H]^+$ (calcd for $C_{35}H_{49}N_3O_8$: 640.3592).

(*1S*)-1-{5-[(4-{(*1E*)-4-[(1-{[(2-Amino-2-oxoethyl)amino]methyl}cyclobutyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (82c)

Compound **78c** (135 mg, 0.167 mmol) and compound **80** (25 mg, 0.226 mmol) were used as starting materials and synthesized in the same manner as compound **82b** to give the titled compound (80 mg, 55% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.10 (d, J = 6.9 Hz, 6 H), 1.36 (s, 6 H), 1.75 - 1.91 (m, 2 H), 2.07 - 2.12 (m, 2 H), 2.21 - 2.28 (m, 2 H), 2.30 (s, 3 H), 2.89 - 2.94 (m, 3 H), 3.24 (s, 2 H), 3.29 - 3.31 (m, 1 H), 3.36 - 3.42 (m, 2 H), 3.46 (t, J = 8.7 Hz, 1 H), 3.55 (t, J = 8.7 Hz, 1 H), 3.68 (dd, J = 11.9, 5.0 Hz, 1 H), 3.84 (dd, J = 11.9, 1.8 Hz, 1 H), 3.88 (s, 2 H), 4.46 (d, J = 9.6 Hz, 1 H), 6.36 - 6.41 (m, 1 H), 6.46 - 6.51 (m, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.80 (s, 1 H), 6.96 (s, 1 H), 7.11 (dd, J = 7.8, 0.9 Hz, 1 H), 7.24 (d, J = 0.9 Hz, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 15.85, 19.98, 24.10, 24.21, 25.89, 30.31, 32.22, 36.31, 46.06, 53.06, 55.86, 58.39, 60.30, 63.11, 71.90, 75.52, 79.15, 80.18, 82.43, 114.27, 123.97, 125.03, 129.13, 129.20, 130.24, 130.32, 131.78, 134.91, 136.32, 137.57, 140.74, 149.62, 155.66, 176.88, 178.56,; HR-MS ESI/APCI Dual *m/z*: 654.3757 $[M+H]^+$ (calcd for $C_{36}H_{51}N_3O_8$: 654.3749).

(*1S*)-1-{5-[(4-{(*1E*)-4-[(1-{[(2-Amino-2-oxoethyl)amino]methyl}cyclopentyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (82d)

Compound **78d** (220 mg, 0.268 mmol) and compound **79** (30.0 mg, 0.402 mmol) were used as

starting materials and synthesized in the same manner as compound **82a** to give the titled compound (16 mg, 9% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.07 - 1.13 (m, 6 H), 1.32 - 1.38 (m, 6 H), 1.57 - 1.76 (m, 6 H), 1.93 - 2.02 (m, 2 H), 2.31 (s, 3 H), 2.82 (s, 2 H), 2.92 (s, 1 H), 3.19 (s, 2 H), 3.35 - 3.41 (m, 2 H), 3.43 - 3.49 (m, 1 H), 3.52 - 3.57 (m, 1 H), 3.65 - 3.71 (m, 1 H), 3.81 - 3.87 (m, 1 H), 3.88 (s, 2 H), 4.44 - 4.49 (m, 1 H), 6.36 - 6.42 (m, 1 H), 6.48 - 6.53 (m, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.80 (s, 1 H), 6.96 (s, 1 H), 7.08 - 7.13 (m, 1 H), 7.23 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.98, 24.10, 24.21, 25.07, 25.90, 30.32, 36.33, 37.14, 46.44, 53.20, 56.82, 63.12, 65.93, 71.92, 75.53, 79.15, 80.19, 82.45, 114.27, 123.99, 124.98, 129.13, 129.19, 130.26, 130.61, 131.80, 134.97, 136.25, 137.62, 140.85, 149.64, 155.68, 177.11, 178.93,; HR-MS ESI/APCI Dual *m/z*: 668.3916 $[M+H]^+$ (calcd for $C_{37}H_{53}N_3O_8$: 668.3905).

(*1S*)-1-{5-[(4-{(*1E*)-4-[(1-{[(2-Amino-2-oxoethyl)amino]methyl}cyclohexyl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (82e)

Compound **78e** (265 mg, 0.318 mmol) and compound **80** (46.0 mg, 0.413 mmol) were used as starting materials and synthesized in the same manner as compound **82b** to give the titled compound (13 mg, 5.6% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.09 (d, J = 6.4 Hz, 6 H), 1.26 - 1.40 (m, 14 H), 1.48 - 1.61 (m, 3 H), 2.11 - 2.16 (m, 2 H), 2.32 (s, 3 H), 2.85 (s, 2 H), 2.88 - 2.95 (m, 1 H), 3.25 (s, 2 H), 3.37 - 3.41 (m, 2 H), 3.46 (t, J = 8.9 Hz, 1 H), 3.52 - 3.57 (m, 1 H), 3.65 - 3.70 (m, 1 H), 3.84 (d, J = 12.4 Hz, 1 H), 3.89 (s, 2 H), 4.47 (d, J = 9.6 Hz, 1 H), 6.43 (d, J = 16.5 Hz, 1 H), 6.58 (d, J = 16.5 Hz, 1 H), 6.76 (d, J = 7.8 Hz, 1 H), 6.80 (s, 1 H), 6.97 (s, 1 H), 7.12 (d, J = 7.8 Hz, 1 H), 7.25 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 8.61, 20.00, 22.73, 24.10, 24.22, 25.94, 26.86, 30.33, 33.83, 36.36, 46.86, 53.21, 57.56, 60.30, 63.13, 71.93, 75.55, 79.14, 80.19, 82.46, 114.30, 124.02, 124.96, 129.15, 129.18, 130.29, 131.08, 131.84, 134.88, 136.10, 137.67, 141.02,

149.65, 155.70, 176.77, 178.89,; HR-MS ESI/APCI Dual *m/z*: 682.4083[M+H]$^+$ (calcd for $C_{38}H_{55}N_3O_8$: 682.4062).

(*1S*)-1-{5-[(4-{(*1E*)-4-[(3-{[(2-Amino-2-oxoethyl)amino]methyl}oxetan-3-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (82f)

Sodium cyanoborohydride (27 mg) was added to a solution of compound **78f** (117 mg, 0.145 mmol) and compound **80** (48.0 mg, 0.434 mmol) in methanol solution (4 mL). The reaction solution was stirred at the room temperature for 18 hours. After the solvent was distilled off under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform: methanol = 100: 0 to 50: 50) to obtain the crude intermediate (68 mg). The crude intermediate (68 mg) in methanol: triethylamine: water (5: 1: 1) solution (2 mL) was stirred at the room temperature for 18 hours. After the solvent was distilled off under reduced pressure, the residue was purified by NH silica gel column chromatography (ethyl acetate: ethanol: water = 10: 2: 1) to obtain the titled compound (16 mg, 17% in 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.10 (d, J = 6.7 Hz, 6 H), 1.38 (s, 6 H), 2.30 (s, 3 H), 2.86 - 2.98 (m, 1 H), 3.08 (s, 2 H), 3.25 (s, 2 H), 3.36 - 3.40 (m, 2 H), 3.41 - 3.49 (m, 1 H), 3.50 - 3.58 (m, 1 H), 3.63 - 3.72 (m, 1 H), 3.80 - 3.91 (m, 3 H), 4.46 (d, J = 9.5 Hz, 1 H), 4.50 (d, J = 7.0 Hz, 2 H), 4.67 (d, J = 7.0 Hz, 2 H), 6.38 (d, J = 16.3 Hz, 1 H), 6.50 (d, J = 16.3 Hz, 1 H), 6.76 (d, J = 7.9 Hz, 1 H), 6.80 (s, 1 H), 6.95 (s, 1 H), 7.11 (d, J = 7.9 Hz, 1 H), 7.24 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.97, 24.10, 24.21, 25.86, 25.98, 30.31, 36.32, 45.85, 46.66, 51.91, 53.29, 53.36, 54.68, 58.09, 61.85, 63.12, 63.78, 71.91, 75.53, 79.14, 80.16, 80.19, 82.44, 114.26,

123.98, 125.08, 125.11, 129.17, 129.21, 130.25, 130.43, 131.10, 131.76, 134.46, 134.53, 136.28, 137.58, 137.62, 140.79, 140.89, 149.62, 155.67, 177.26, 178.90, 179.89,; HR-MS ESI/APCI Dual *m/z*: 656.3561[M+H]$^+$ (calcd for $C_{35}H_{49}N_3O_9$: 656.3542).

(*1S*)-1-[5-({4-[(*1E*)-4-{[3-{[(2-Amino-2-oxoethyl)amino]methyl}-1-(tert-butoxycarbonyl)azetidin-3-yl]amino}-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-hydroxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (82g)

Sodium triacetoxyborohydride (30 mg) was added to a solution of compound **78g** (550 mg, 0.606 mmol) and compound **80** (87.0 mg, 0.788 mmol) and acetic acid (45 μL) in *N*,*N*-dimethylformamide solution (6 mL). The reaction solution was stirred at the room temperature for 18 hours. Water was added and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform: methanol = 99: 1 to 50: 50) to obtain the crude intermediate (313 mg). The crude intermediate (163 mg) and 4.88 sodium methoxide (415 μL) in methanol solution (1.7 mL) was stirred at the room temperature for 18 hours. After the solvent was distilled off under reduced pressure, the residue was purified by NH silica gel column chromatography (ethyl acetate: ethanol: water = 20: 2: 1 to 7: 2: 1) to obtain the titled compound (80 mg, 34% in 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.10 (d, J = 6.84 Hz, 6H), 1.38 (s, 6H), 1.42 (s, 9H), 2.30 (s, 3H), 2.86-3.01 (m, 3H), 3.22 (s, 2H), 3.37 - 3.72 (m, 6H), 3.81 - 4.00 (m, 6H), 4.46 (d, J = 9.33 Hz, 1H), 6.28 - 6.42 (m, 1H), 6.44 - 6.55 (m, 1H), 6.75 (d, J = 7.93 Hz, 1H), 6.80 (s, 1H), 6.95 (s, 1H), 7.11 (dd, J = 7.93, 1.55 Hz, 1H), 7.23 (s, 1H); MS (ESI/APCI Dual) *m/z*: 755[M+H]$^+$.

(*1S*)-1-{5-[(4-{(*1E*)-4-[(3-{[(2-amino-2-oxoethyl)amino]methyl}azetidin-3-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-hydroxy-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (83g)

The compound **82g** (80.0 mg, 0.106 mmol) in trifluoroacetic acid solution (1.0 mL) was stirred at the room temperature for 18 hours. After the solvent was distilled off under reduced pressure, the residue was purified by NH silica gel column chromatography (ethyl acetate: ethanol: water = 20: 2: 1 to 7: 2: 1) to obtain the titled compound (44 mg, 63%) as a colorless amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.04 - 1.11 (m, 6H), 1.35 - 1.39 (m, 3H), 1.46 (s, 3H), 2.31 (s, 3H), 2.88 - 2.95 (m, 1H), 3.20 - 3.94 (m, 12H), 4.46 (d, J = 9.56 Hz, 1H), 6.27 - 6.41 (m, 1H), 6.51 (br dd, J = 18.73, 16.44 Hz, 1H), 6.76 (br d, J = 8.03 Hz, 1H), 6.80 (s, 1H), 6.95 (s, 1H), 7.11 (br d, J = 7.64 Hz, 1H), 7.24 (s, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 19.96, 24.09, 24.21, 25.84, 26.42, 26.48, 30.31, 36.31, 40.19, 53.36, 54.95, 55.01, 55.61, 56.80, 57.80, 63.13, 66.34, 71.92, 71.96, 75.55, 75.73, 79.11, 80.19, 82.44, 114.28, 124.02, 125.06, 125.17, 129.13, 129.16, 129.25, 130.19, 130.24, 130.38, 131.76, 133.48, 137.61, 141.09, 149.61, 155.70, 155.74,; HR-MS ESI/APCI Dual *m/z*: 655.3718$[M+H]^+$ (calcd for $C_{35}H_{50}N_4O_8$: 655.3701).

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (84)

Methyl iodide (33.0 mL, 0.530 mol) in *N*,*N*-dimethylformamide (50 mL) was added to a suspension of compound **67** (392 g, 0.506 mol) and potassium carbonate (73.4 g, 0.531 mol) in *N*,*N*-dimethylformamide (0.95 L). The reaction solution was stirred for 1 hour, and after addition of potassium carbonate (70.0 g, 0.506 mol) and methyl iodide (31.5 mL, 0.506 mol), the mixture was stirred for 1 hour. Potassium carbonate (70.0 g, 0.506 mol) and methyl iodide (31.5 mL, 0.506 mol) were added again, and the mixture was stirred for 1 hour. Methyl iodide (15.8 mL, 0.254 mol) was

added, and the mixture was stirred overnight at room temperature. After stirring at 50°C for 2 hours, the mixture was diluted with toluene (1.25 L), and water (1.0 L) was added. The two layers were separated, and the organic layer was washed twice with water (1.0 L) and 10% brine (1.0 L), and then concentrated under reduced pressure. The residue was dissolved with isopropyl alcohol (350 mL) at 40°C, and the solution was cooled to room temperature and stirred overnight. The resulting precipitate was filtered off and dried to give the titled compound (155 g, 46%) in the form of a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.12 (d, J = 6.8 Hz, 3 H), 1.13 (d, J = 6.8 Hz, 3 H), 1.55 (s, 3 H), 1.75 (s, 3 H), 1.99 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.29 (s, 3 H), 2.83 - 2.96 (m, 1 H), 3.86 (s, 3 H), 4.08 - 4.17 (m, 1 H), 4.18 - 4.28 (m, 1 H), 4.78 - 4.89 (m, 1 H), 5.13 - 5.23 (m, 1 H), 5.27 - 5.35 (m, 2 H), 6.51 - 6.57 (m, 1 H), 6.80 (s, 1 H), 6.96 (s, 1 H), 7.12 - 7.20 (m, 1 H), 7.30 (s, 1 H).

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-methylphenyl)methyl]-2-ethoxy-4-(propan-2-yl)phenyl}-D-glucitol (88b)

The compound **55g** (100 g) in methanol: triethylamine: water (5: 1: 1) solution (12 L) was stirred at the room temperature for 3 days. The reaction solution was concentrated, and dissolved in 2 M hydrochloric acid and extracted twice with chloroform. The organic layers were combined, washed with saturated brine, and dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was distilled off under reduced pressure to obtain the intermediate **85** (80.4 g) as a light brown amorphous. To a suspension of the intermediate **85** (1.00 g, 2.08 mmol) and potassium carbonate (862 mg, 6.24 mmol) in *N*,*N*-dimethylformamide (6.0 mL) was added to ethyl iodide (**86b**) (500 μL, 6.24 mmol). The reaction mixture was stirred at 50°C for 8 hours. Water was added to the reaction solution and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol: chloroform = 0: 100 to 10: 90)

to obtain the intermediate (**87b**) (950 mg, 90%) as a colorless liquid. A solution of the intermediate (**87b**) (867 mg, 1.70 mmol) and acetic anhydride (4.3 mL) in pyridine (5.2 mL) was stirred at room temperature for 3 days. The reaction solution was added to ice water and extracted with toluene. The organic layer was washed with 2 M hydrochloric acid and saturated brine, and dried over sodium sulfate. After the desiccant was filtered off, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 85: 15 → 65: 35) to give the titled compound (1.00 g, 90% in 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.15 (m, 6 H), 1.46 (t, J = 6.9 Hz, 3 H), 1.75 (s, 3 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.28 (s, 3 H), 2.83 - 2.94 (m, 1 H), 3.72 - 3.90 (m, 3 H), 4.02 - 4.15 (m, 3 H), 4.19 - 4.28 (m, 1 H), 4.76 - 4.89 (m, 1 H), 5.15 - 5.22 (m, 1 H), 5.27 - 5.38 (m, 2 H), 6.54 (d, J = 8.2 Hz, 1 H), 6.79 (s, 1 H), 6.94 (s, 1 H), 7.16 (dd, J = 8.2, 1.7 Hz, 1 H), 7.31 (d, J = 1.7 Hz, 1 H); MS (ESI/APCI Dual) *m/z*: 699[M+Na]$^+$.

(*1S*)-2,3,4,6Tetra-*O*-acetyl-1-{2-[2-(acetyloxy)ethoxy]-5-[(4-bromo-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (88c)

To a suspension of Intermediate **85** (1.00 g, 2.08 mmol) and potassium carbonate (861 mg, 6.23 mmol) in *N*, *N*-dimethylformamide (5 mL) was added to 2-iodoethanol (**86c**) (485 μL, 6.23 mmol). The reaction mixture stirred at 150°C. for 3 hours. Water was added to the reaction mixture and extracted twice with ethyl acetate. The organic layers were combined, washed with 10% brine and water, and dried over anhydrous magnesium sulfate. The desiccant was filtered off and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate only → ethyl acetate: ethanol: water = 15: 2: 1) to give the intermediate (**87c**) (370 mg) as a colorless amorphous. Acetic anhydride (900 μL) was added to a solution of the intermediate (**87c**) (360 mg, 0.685 mmol) in pyridine (1.08 mL), and the mixture was stirred overnight at room temperature. The

reaction solution was added to ice water and extracted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid twice and saturated brine, and then dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the solvent was evaporated under reduced pressure to give the titled compound (480 mg, 37% in 3 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.07 - 1.15 (m, 6 H), 1.74 (s, 3 H), 1.99 (s, 3 H), 2.04 (s, 3 H), 2.06 (s, 3 H), 2.17 (s, 3 H), 2.28 (s, 3 H), 2.88 - 2.94 (m, 1 H), 3.72 - 3.92 (m, 3 H), 4.04 - 4.33 (m, 4 H), 4.36 - 4.49 (m, 1 H), 4.52 - 4.64 (m, 1 H), 4.75 (br. s., 1 H), 5.19 (t, J = 9.2 Hz, 1 H), 5.30 (t, J = 9.2 Hz, 1 H), 5.41 (br. s., 1 H), 6.53 (d, J = 8.2 Hz, 1 H), 6.79 (s, 1 H), 6.93 (s, 1 H), 7.18 (d, J = 8.2 Hz, 1 H), 7.32 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 757[M+Na]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-bromo-2-methylphenyl)methyl]-2-[2-(dimethylamino)ethoxy]-4-(propan-2-yl)phenyl}-D-glucitol (88d)

Intermediate **85** (2.00 g, 4.15 mmol) and 2-iodo-*N*,*N*-dimethylethan-1-amine (**86d**) (2.07 g, 10.4 mmol) were used as starting materials and synthesized in the same manner as compound **88c** to give the titled compound (520 mg, 17% for 2 steps) as a brown amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.12 (m, 6H), 1.75 (s, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.28 (s, 3H), 2.49 (s, 6H), 2.84-3.00 (m, 3H), 3.76 - 3.91 (m, 3H), 4.02 - 4.26 (m, 4H), 4.78 - 4.94 (m, 1H), 5.13 - 5.37 (m, 3H), 6.53 (d, J = 8.08 Hz, 1H), 6.81 (s, 1H), 6.94 (s, 1H), 7.17 (dd, J = 8.00, 1.94 Hz, 1H), 7.32 (d, J = 2.18 Hz, 1H); MS (ESI/APCI Dual) *m/z*: 720[M+H]$^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-[5-({4-[(*1E*)-3-carboxy-3-methylbut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (89a)

In an argon atmosphere, an acetonitrile (200 mL) suspension of compound **84** (10.0 g, 15.1 mmol), compound **41** (4.12 g, 36.1 mmol), palladium (II) acetate (337 mg, 1.51 mmol), tri-*o*-tolylphosphine

(917 mg, 3.02 mmol), and triethylamine (10.5 mL, 75.5 mmol) was refluxed for 3 hours. After cooling to room temperature, the reaction mixture was concentrated, the residue was dissolved in ethyl acetate (800 mL), and the solution was washed with 10% hydrochloric acid (200 mL), then dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by performing neutral silica gel column chromatography (hexane: ethyl acetate = 8: 2 to1: 9) to obtain the titled compound (10.4 g, 99%) in the form of a colorless amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.12 (d, J = 6.9 Hz, 3 H), 1.13 (d, J = 6.9 Hz, 3 H), 1.43 (s, 6 H), 1.75 (s, 3 H), 1.99 (s, 3 H), 2.01 - 2.06 (m, 6 H), 2.29 (s, 3 H), 2.90 - 2.98 (m, 1 H), 3.77 - 3.81 (m, 1 H), 3.81 - 3.91 (m, 5 H), 4.08 - 4.13 (m, 1 H), 4.21 (dd, J = 12.2, 4.4 Hz, 1 H), 4.79 (br. d, J = 8.3 Hz, 1 H), 5.17 (t, J = 9.6 Hz, 1 H), 5.27 - 5.36 (m, 2 H), 6.35 (d, J = 16.0 Hz, 1 H), 6.43 (d, J = 16.0 Hz, 1 H), 6.64 (d, J = 8.3 Hz, 1 H), 6.80 (s, 1 H), 6.95 (s, 1 H), 7.06 (d, J = 8.3 Hz, 1 H), 7.21 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 719$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-{(*1E*)-3,3-dimethyl-4-[(2-methyl-1-oxopropan-2-yl)amino]-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (90a)

Compound **76a** (1.72 g, 19.4 mmol), water soluble carbodiimide hydrochloride (3.21 g, 16.8 mmol) and 1-hydroxy-1H-benzotriazole hydrate (2.27 g, 16.8 mmol) were added to a *N*,*N*-dimethylformamide (100 mL) solution of compound **89a** (9.00 g, 12.9 mmol) in a nitrogen atmosphere, and the mixture was stirred for 16 hours at room temperature. Water was added to the reaction liquid, and after extracting the mixture with ethyl acetate, the organic layer was washed with 10% brine, then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified by performing silica gel column chromatography (hexane: ethyl acetate = 2: 8 to 8: 2) to obtain the colorless powder (8.07 g). Dess-

Martin periodinane (6.69 g, 15.8 mmol) was added to the colorless powder (8.07 g, 10.5 mmol) in a nitrogen atmosphere, and the mixture was stirred for 1 hour at room temperature. The resection mixture was distilled off under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane: ethyl acetate ratio = 2: 8 to 8: 2) to obtain the titled compound (7.6 g, 77% in 2 steps) in the form of a yellow amorphous. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 1.09 - 1.18 (m, 6 H), 1.32 (s, 6 H), 1.38 (s, 6 H), 1.77 (s, 3 H), 1.98 (s, 3 H), 2.00 - 2.07 (m, 6 H), 2.33 (s, 3 H), 2.95 (spt, *J* = 6.8 Hz, 1 H), 3.77 - 3.94 (m, 6 H), 4.08 - 4.15 (m, 1 H), 4.22 (dd, *J* = 11.9, 4.6 Hz, 1 H), 4.82 (br. s., 1 H), 5.14 - 5.20 (m, 1 H), 5.27 - 5.35 (m, 2 H), 6.11 (br. s, 1 H), 6.31 (d, *J* = 16.5 Hz, 1 H), 6.52 (d, *J* = 16.5 Hz, 1 H), 6.67 (d, *J* = 7.8 Hz, 1 H), 6.81 (s, 1 H), 6.99 (s, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 7.24 (s, 1 H), 9.33 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 766$[M+H]^+$, 788$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{5-[(4-{(*1E*)-3,3-dimethyl-4-[(2-methyl-1-oxopropan-2-yl)amino]-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-ethoxy-4-(propan-2-yl)phenyl}-D-glucitol (90b)

Compound **88b** (1.00 g, 1.48 mmol) was used as starting materials and synthesized in the same manner as compound **89a** and **90a** to give the titled compound (175 mg, 15% for 3 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.06 - 1.18 (m, 6 H), 1.32 (s, 6 H), 1.38 (s, 6 H), 1.47 (t, *J* = 6.9 Hz, 3 H), 1.77 (s, 3 H), 1.99 (s, 3 H), 2.04 (s, 3 H), 2.04 (s, 3 H), 2.33 (s, 3 H), 2.85 - 3.03 (m, 1 H), 3.72 - 3.97 (m, 3 H), 4.01 - 4.16 (m, 3 H), 4.17 - 4.28 (m, 1 H), 4.72 - 4.91 (m, 1 H), 5.11 - 5.21 (m, 1 H), 5.27 - 5.37 (m, 2 H), 6.11 (s, 1 H), 6.26 - 6.35 (m, 1 H), 6.48 - 6.57 (m, 1 H), 6.67 (d, *J* = 7.9 Hz, 1 H), 6.80 (s, 1 H), 6.97 (s, 1 H), 7.10 (d, *J* = 7.9 Hz, 1 H), 7.25 (s, 1 H), 9.33 (s, 1 H); MS ESI/APCI Dual *m/z*: 780$[M+H]^+$, 802$[M+Na]^+$, 778$[M-H]^-$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1-{2-[2-(acetyloxy)ethoxy]-5-[(4-{(*1E*)-3,3-dimethyl-4-[(2-methyl-1-

oxopropan-2-yl)amino]-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl}-1,5-anhydro-D-glucitol (90c)

Compound **88c** (480 mg, 0.653 mmol) was used as starting materials and synthesized in the same manner as compound **89a** and **90a** to give the titled compound (250 mg, 46% for 3 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.13 (d, J = 6.8 Hz, 3 H), 1.14 (d, J = 6.8 Hz, 3 H), 1.33 (s, 6 H), 1.39 (s, 6 H), 1.76 (s, 3 H), 1.98 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.18 (s, 3 H), 2.32 (s, 3 H), 2.88 - 3.01 (m, 1 H), 3.76 - 3.91 (m, 3 H), 4.05 - 4.13 (m, 1 H), 4.15 - 4.30 (m, 3 H), 4.37 - 4.48 (m, 1 H), 4.53 - 4.63 (m, 1 H), 4.73 (br. s., 1 H), 5.18 (t, J = 9.2 Hz, 1 H), 5.30 (t, J = 9.2 Hz, 1 H), 5.41 (br. s., 1 H), 6.11 (s, 1 H), 6.34 (d, J = 16.0 Hz, 1 H), 6.55 (d, J = 16.0 Hz, 1 H), 6.67 (d, J = 7.8 Hz, 1 H), 6.80 (s, 1 H), 6.96 (s, 1 H), 7.11 (d, J = 7.8 Hz, 1 H), 7.25 (s, 1 H), 9.33 (s, 1 H); MS (ESI/APCI Dual) *m/z*: 838$[M+H]^+$, 860$[M+Na]^+$.

(*1S*)-2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-1-{2-[2-(dimethylamino)ethoxy]-5-[(4-{(*1E*)-3,3-dimethyl-4-[(2-methyl-1-oxopropan-2-yl)amino]-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-4-(propan-2-yl)phenyl}-D-glucitol (90d)

Compound **88d** (510 mg, 0.708 mmol) was used as starting materials and synthesized in the same manner as compound **89a** and **90a** to give the titled compound (215 mg, 38% for 3 steps) as a pale orange amorphous. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.13 (m, 6H), 1.32 (s, 6H), 1.39 (s, 6H), 1.77 (s, 3H), 1.99 (s, 3H), 2.04 (m, 6H), 2.33 (s, 3H), 2.42 (s, 6H), 2.79 - 2.99 (m, 3H), 3.76 - 3.90 (m, 3H), 4.06 - 4.26 (m, 4H),4.75 - 4.88 (m, 1H), 5.11 - 5.42 (m, 3H), 6.13 (s, 1H), 6.26 - 6.36 (m, 1H), 6.48 - 6.56 (m, 1H), 6.66 (d, J = 7.93 Hz, 1H), 6.83 (s, 1H), 6.98 (s, 1H), 7.10 (dd, J = 7.85, 1.63 Hz, 1H), 7.25 (s, 1H), 9.34 (s, 1H); MS (ESI/APCI Dual) *m/z*: 823$[M+H]^+$.

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(2-Amino-2-oxoethyl)amino]-2-methylpropan-2-yl}amino)-3,3-

dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (92a)

Compound **90a** (300 mg, 0.39 mmol) was used as starting materials and synthesized in the same manner as compound **82a** to give the titled compound (41 mg, 16% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.12 - 1.17 (m, 6 H), 1.30 (s, 6 H), 1.35 (s, 6 H), 2.32 (s, 3 H), 2.66 (s, 2 H), 2.99 (s, 1 H), 3.18 (s, 2 H), 3.34 (d, J = 2.3 Hz, 2 H), 3.43 - 3.48 (m, 1 H), 3.49 - 3.53 (m, 1 H), 3.59 - 3.64 (m, 1 H), 3.80 - 3.84 (m, 1 H), 3.84 (s, 3 H), 3.92 (s, 2 H), 4.59 - 4.63 (m, 1 H), 6.35 - 6.39 (m, 1 H), 6.48 - 6.52 (m, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 6.92 (s, 1 H), 7.07 (s, 1 H), 7.09 - 7.12 (m, 1 H), 7.24 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.00, 24.05, 24.19, 25.30, 25.92, 30.73, 36.36, 46.57, 53.24, 54.69, 56.52, 59.61, 63.43, 72.31, 75.75, 76.96, 80.29, 82.54, 109.64, 125.00, 126.26, 129.16, 130.18, 130.20, 130.58, 131.75, 134.99, 136.31, 137.61, 140.64, 149.79, 158.61, 177.21, 178.81,; HR-MS ESI/APCI Dual *m/z*: 656.3951 $[M+H]^+$ (calcd for $C_{36}H_{53}N_3O_8$: 656.3905).

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(2-Amino-2-oxoethyl)amino]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-ethoxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (92b)

Compound **90b** (175 mg, 0.224 mmol) was used as starting materials and synthesized in the same manner as compound **82g** to give the titled compound (80 mg, 56% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.10 - 1.16 (m, 6 H), 1.30 (s, 6 H), 1.35 (s, 6 H), 1.41 (t, J = 6.9 Hz, 3 H), 2.32 (s, 3 H), 2.66 (s, 2 H), 2.95 - 3.02 (m, 1 H), 3.18 (s, 2 H), 3.33 - 3.38 (m, 2 H), 3.45 (t, J = 8.7 Hz, 1 H), 3.55 - 3.64 (m, 2 H), 3.83 (dd, J = 11.9, 1.8 Hz, 1 H), 3.92 (s, 2 H), 4.05 - 4.13 (m, 2 H), 4.59 (d, J = 9.6 Hz, 1 H), 6.37 (d, J = 16.5 Hz, 1 H), 6.50 (d, J = 16.5 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.91 (s, 1 H), 7.05 (s, 1 H), 7.11 (d, J = 7.8 Hz, 1 H), 7.24 (s, 1 H); ^{13}C NMR

(126 MHz, CD_3OD) δ ppm 15.49, 19.99, 24.06, 24.18, 25.30, 25.92, 30.66, 36.36, 46.57, 53.24, 54.69, 59.60, 63.46, 65.80, 72.30, 75.36, 77.36, 80.33, 82.51, 111.13, 125.00, 126.42, 129.16, 130.21, 130.24, 130.57, 131.88, 134.99, 136.31, 137.62, 140.61, 149.76, 158.05, 177.22, 178.79,; HR-MS ESI/APCI Dual *m/z*: 670.4090 $[M+H]^+$ (calcd for $C_{37}H_{55}N_3O_8$: 670.4062).

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(2-Amino-2-oxoethyl)amino]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-(2-hydroxyethoxy)-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (92c)

Compound **90c** (120 mg, 0.143 mmol) was used as starting materials and synthesized in the same manner as compound **82g** to give the titled compound (30 mg, 30% for 2 steps) as a colorless amorphous. ^1H NMR (600 MHz, CD_3OD) δ ppm 1.13 (d, J = 6.9 Hz, 3 H), 1.14 (d, J = 6.9 Hz, 3 H), 1.30 (s, 6 H), 1.34 (s, 6 H), 2.32 (s, 3 H), 2.66 (s, 2 H), 2.98 (m, 1 H), 3.17 (s, 2 H), 3.34 (s, 2 H), 3.37 - 3.40 (m, 1 H), 3.45 - 3.51 (m, 2 H), 3.60 - 3.65 (m, 1 H), 3.81 - 3.90 (m, 3 H), 3.91 (s, 2 H), 4.08 - 4.15 (m, 2 H), 4.68 (d, J = 9.2 Hz, 1 H), 6.37 (d, J = 16.5 Hz, 1 H), 6.50 (d, J = 16.5 Hz, 1 H), 6.73 (d, J = 7.8 Hz, 1 H), 6.93 (s, 1 H), 7.07 - 7.12 (m, 2 H), 7.24 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.00, 24.04, 24.20, 25.30, 25.92, 30.68, 36.38, 46.57, 53.24, 54.69, 59.60, 62.07, 63.39, 72.00, 72.27, 76.17, 77.04, 80.28, 82.47, 111.41, 125.00, 127.04, 129.15, 130.18, 130.56, 130.70, 131.75, 135.00, 136.32, 137.61, 140.58, 149.75, 157.77, 177.23, 178.78,; HR-MS ESI/APCI Dual *m/z*: 686.3997 $[M+H]^+$ (calcd for $C_{37}H_{55}N_3O_9$: 686.4011).

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(2-Amino-2-oxoethyl)amino]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-[2-(dimethylamino)ethoxy]-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (92d)

Compound **90c** (120 mg, 0.146 mmol) was used as starting materials and synthesized in the same

manner as compound **82b** to give the titled compound (35 mg, 27% for 2 steps) as a colorless amorphous. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.14 (dd, J = 6.50, 5.35 Hz, 6H), 1.30 (s, 6H), 1.35 (s, 6H), 2.32 (s, 3H), 2.40 (s, 6H), 2.66 (s, 2H), 2.74 - 2.82 (m, 1H), 2.85-2.92 (m, 1H), 2.95 - 3.06 (m, 1H), 3.17 (s, 2H), 3.32 - 3.39 (m, 2H), 3.42 - 3.49 (m, 2H), 3.58 - 3.65 (m, 1H), 3.82 (dd, J = 11.85, 1.91 Hz, 1H), 3.92 (s, 2H), 4.08 - 4.23 (m, 2H), 4.60 - 4.67 (m, 1H), 6.33 - 6.41 (m, 1H), 6.47 - 6.55 (m, 1H), 6.73 (d, J = 8.03 Hz, 1H), 6.93 (s, 1H), 7.05 - 7.13 (m, 2H), 7.24 (d, J = 1.15 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.00, 24.04, 24.18, 25.30, 25.92, 30.70, 36.37, 46.07, 46.57, 53.24, 54.69, 59.59, 63.44, 67.75, 72.37, 76.03, 77.09, 80.41, 82.59, 111.02, 125.00, 126.80, 129.16, 130.18, 130.56, 130.70, 131.77, 135.00, 136.32, 137.60, 140.57, 149.78, 157.67, 177.22, 178.78,; HR-MS ESI/APCI Dual *m/z*: 713.4498 $[M+H]^+$ (calcd for $C_{39}H_{60}N_4O_8$: 713.4484).

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(4-Amino-4-oxobutyl)amino]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (94b)

Compound **90a** (360 mg, 0.470 mmol) and 4-aminobutanamide (57 mg, 0.558 mmol) was used as starting materials and synthesized in the same manner as compound **82a** to give the titled compound (151 mg, 47% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.14 (d, J = 6.7 Hz, 3 H), 1.15 (d, J = 6.7 Hz, 3 H), 1.29 - 1.32 (m, 6 H), 1.33 - 1.36 (m, 6 H), 1.61 - 1.70 (m, 2 H), 2.11 (t, J = 7.3 Hz, 2 H), 2.31 - 2.35 (m, 3 H), 2.61 (t, J = 6.9 Hz, 2 H), 2.72 (br. s., 2 H), 2.93 - 3.02 (m, 1 H), 3.37 - 3.42 (m, 2 H), 3.44 - 3.49 (m, 1 H), 3.50 - 3.55 (m, 1 H), 3.60 - 3.65 (m, 1 H), 3.79 - 3.86 (m, 4 H), 3.92 (s, 2 H), 4.62 (d, J = 9.6 Hz, 1 H), 6.36 (d, J = 16.0 Hz, 1 H), 6.50 (d, J = 16.0 Hz, 1 H), 6.73 (d, J = 7.8 Hz, 1 H), 6.92 (s, 1 H), 7.08 - 7.12 (m, 2 H), 7.24 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.03, 24.05, 24.21, 25.37, 25.87, 30.74, 34.27, 36.37, 46.54, 50.72, 54.31, 56.52, 59.44, 63.40, 72.29, 75.72, 76.99, 80.28, 82.54, 109.65, 125.02, 126.24, 129.18, 130.13, 130.16,

130.68, 131.83, 134.69, 136.23, 137.59, 140.69, 149.82, 158.62, 178.68, 179.14,; HR-MS ESI/APCI Dual *m/z*: 684.4246 $[M+H]^+$ (calcd for $C_{38}H_{57}N_3O_8$: 684.4218).

(*1S*)-1-[5-({4-[(*1E*)-4-({1-[(6-Amino-6-oxohexyl)amino]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-1,5-anhydro-D-glucitol (94c)

Compound **90a** (300 mg, 0.392 mmol) and 5-aminopentanamide (76.5 mg, 0.588 mmol) was used as starting materials and synthesized in the same manner as compound **82b** to give the titled compound (141 mg, 52% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.14 (t, J = 6.9 Hz, 6 H), 1.17 - 1.24 (m, 2 H), 1.26 - 1.37 (m, 14 H), 1.45 - 1.53 (m, 2 H), 2.12 (t, J = 7.6 Hz, 2 H), 2.33 (s, 3 H), 2.49 (t, J = 7.3 Hz, 2 H), 2.61 (s, 2 H), 2.92 - 3.00 (m, 1 H), 3.33 - 3.38 (m, 2 H), 3.46 (t, J = 8.5 Hz, 1 H), 3.51 - 3.56 (m, 1 H), 3.62 (dd, J = 11.9, 5.0 Hz, 1 H), 3.79 - 3.87 (m, 4 H), 3.92 (s, 2 H), 4.62 (d, J = 9.6 Hz, 1 H), 6.34 (d, J = 16.0 Hz, 1 H), 6.49 (d, J = 16.0 Hz, 1 H), 6.73 (d, J = 8.3 Hz, 1 H), 6.92 (s, 1 H), 7.06 - 7.12 (m, 2 H), 7.24 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.08, 24.08, 24.22, 25.42, 25.90, 26.80, 28.06, 30.51, 30.74, 36.44, 36.56, 46.55, 51.37, 54.39, 56.52, 59.90, 63.42, 72.29, 75.73, 76.99, 80.30, 82.54, 109.66, 125.05, 126.25, 129.15, 130.07, 130.15, 130.64, 131.90, 134.76, 136.25, 137.53, 140.70, 149.83, 158.63, 178.79, 179.18,; HR-MS ESI/APCI Dual *m/z*: 712.4554 $[M+H]^+$ (calcd for $C_{40}H_{61}N_3O_8$: 712.4531).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[2-(dimethylamino)ethyl]amino}-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (94d)

Compound **90a** (150 mg, 0.196 mmol) and N^1,N^1-dimethylethane-1,2-diamine (26.0 mg, 0.294 mmol) was used as starting materials and synthesized in the same manner as compound **82b** to give

the titled compound (77.1 mg, 61% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, c 1.15 (d, *J* = 6.4 Hz, 6 H), 1.30 (s, 6 H), 1.33 (s, 6 H), 2.10 (s, 6 H), 2.20 (t, *J* = 6.4 Hz, 2 H), 2.34 (s, 3 H), 2.58 - 2.63 (m, 4 H), 2.94 - 3.02 (m, 1 H), 3.34 - 3.39 (m, 2 H), 3.43 - 3.49 (m, 1 H), 3.48 - 3.54 (m, 1 H), 3.59 - 3.66 (m, 1 H), 3.80 - 3.88 (m, 4 H), 3.92 (s, 2 H), 4.61 (d, *J* = 9.6 Hz, 1 H), 6.35 (d, *J* = 16.0 Hz, 1 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 6.73 (d, *J* = 7.8 Hz, 1 H), 6.93 (s, 1 H), 7.08 (s, 1 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 7.26 (s, 1 H); ^{13}C NMR (126 MHz, v 20.07, 24.08, 24.24, 25.28, 25.87, 30.75, 36.39, 45.74, 46.60, 54.29, 56.52, 60.01, 60.26, 63.45, 72.33, 75.83, 76.93, 80.28, 82.55, 109.62, 125.08, 126.37, 129.18, 130.01, 130.08, 130.70, 131.84, 134.71, 136.28, 137.55, 140.70, 149.76, 158.63, 178.65,; HR-MS ESI/APCI Dual *m/z*: 670.4437 $[M+H]^+$ (calcd for $C_{38}H_{59}N_3O_7$: 670.4426).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[3-(dimethylamino)propyl]amino}-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (94e)

Compound **90a** (350 mg, 0.457 mmol) and N^1,N^1-dimethylpropane-1,3-diamine (56 mg, 0.548 mmol) was used as starting materials and synthesized in the same manner as compound **82a** to give the titled compound (100 mg, 32% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.14 (d, *J* = 6.4 Hz, 3 H), 1.15 (d, *J* = 6.4 Hz, 3 H), 1.30 (s, 6 H), 1.33 (s, 6 H), 1.46 - 1.56 (m, 2 H), 2.12 (s, 6 H), 2.17 - 2.24 (m, 2 H), 2.33 (s, 3 H), 2.51 (t, *J* = 7.1 Hz, 2 H), 2.60 (s, 2 H), 2.93 - 3.03 (m, 1 H), 3.37 - 3.42 (m, 2 H), 3.43 - 3.48 (m, 1 H), 3.48 - 3.55 (m, 1 H), 3.57 - 3.65 (m, 1 H), 3.80 - 3.87 (m, 4 H), 3.92 (s, 2 H), 4.61 (d, *J* = 9.2 Hz, 1 H), 6.31 - 6.37 (m, 1 H), 6.49 (d, *J* = 16.5 Hz, 1 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 6.92 (s, 1 H), 7.07 - 7.12 (m, 2 H), 7.24 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.06, 24.08, 24.24, 25.34, 25.92, 28.49, 30.75, 36.41, 45.57, 46.58, 48.64, 49.76, 54.40, 56.52, 58.72, 60.06, 63.46, 72.34, 75.82, 76.95, 80.30, 82.57, 109.64, 125.03, 126.36, 129.21, 130.07, 130.11, 130.54, 131.83, 134.92, 136.32, 137.55, 140.65, 149.77, 158.64, 178.67,; HR-MS

ESI/APCI Dual *m/z*: 684.4611[M+H]$^+$ (calcd for $C_{39}H_{61}N_3O_7$: 684.4582).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[4-(dimethylamino)butyl]amino}-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (94f)

Compound **90a** (500 mg, 0.653 mmol) and N^1,N^1-dimethylbutane-1,4-diamine dihydrochloride (184 mg, 0.979 mmol) was used as starting materials and synthesized in the same manner as compound **82b** to give the titled compound (66.6 mg, 38% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.11 - 1.17 (m, 6 H), 1.29 - 1.41 (m, 16 H), 2.16 - 2.23 (m, 8 H), 2.33 (s, 3 H), 2.51 (t, *J* = 7.3 Hz, 2 H), 2.62 (s, 2 H), 2.94 - 3.02 (m, 1 H), 3.33 - 3.38 (m, 2 H), 3.43 - 3.48 (m, 1 H), 3.48 - 3.54 (m, 1 H), 3.61 (dd, *J* = 12.2, 5.7 Hz, 1 H), 3.79 - 3.87 (m, 4 H), 3.92 (s, 2 H), 4.61 (d, *J* = 9.6 Hz, 1 H), 6.34 (d, *J* = 16.0 Hz, 1 H), 6.49 (d, *J* = 16.0 Hz, 1 H), 6.74 (d, *J* = 7.8 Hz, 1 H), 6.92 (s, 1 H), 7.08 (s, 1 H), 7.10 (d, *J* = 7.8 Hz, 1 H), 7.24 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.09, 24.07, 24.22, 25.40, 25.90, 26.08, 28.81, 30.74, 36.45, 45.53, 46.56, 51.36, 54.40, 56.52, 59.91, 60.64, 63.47, 72.34, 75.79, 76.97, 80.28, 82.56, 109.65, 125.05, 126.33, 129.20, 130.07, 130.15, 130.58, 131.76, 134.87, 136.32, 137.51, 140.59, 149.75, 158.63, 178.71,; HR-MS ESI/APCI Dual *m/z*: 698.4783 [M+H]$^+$ (calcd for $C_{40}H_{63}N_3O_7$: 698.4739).

(*1S*)-1,5-Anhydro-1-{5-[(4-{(*1E*)-4-[(1-{[4-(dimethylamino)butyl](methyl)amino}-2-methylpropan-2-yl)amino]-3,3-dimethyl-4-oxobut-1-en-1-yl}-2-methylphenyl)methyl]-2-methoxy-4-(propan-2-yl)phenyl}-D-glucitol (94g)

Sodium triacetoxyborohydride (554 mg, 2.61 mmol) and N^1,N^1-dimethylbutane-1,4-diamine dihydrochloride (184 mg, 0.979 mmol) were added to a *N*,*N*-dimethylformamide (6 mL) solution of compound **90a** (500 mg, 0.653 mmol) in a nitrogen atmosphere, and the mixture was stirred for 16

hours at room temperature. An aqueous sodium hydrogen carbonate solution was added to the reaction liquid, and after extracting the mixture with chloroform, the organic layer was washed with 10% brine and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified by performing silica gel column chromatography (chloroform: methanol = 10: 0 to 9: 1) to obtain the intermediate (262 mg). To a solution of the intermediate (156 mg), 37% formaldehyde solution (73 mg, 0.90 mmol) and sodium triacetoxyborohydride (153 mg, 0.720 mmol) were added, and stirred for 6 hours at room temperature. An aqueous sodium hydrogen carbonate solution was added to the reaction liquid, and after extracting the mixture with chloroform, the organic layer was washed with 10% brine and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified by performing silica gel column chromatography (chloroform: methanol = 10: 0 to 9: 1) to obtain the intermediate (141 mg). The crude intermediate (141 mg) in methanol: triethylamine: water (5: 1: 1) solution (2.5 mL) was stirred at the room temperature for 16 hours, the solvent was distilled off under reduced pressure. The resulting residue was purified by performing neutral silica gel column chromatography (ethyl acetate: ethanol: water = 30: 2: 1) to give the titled compound (76mg, 27% in 3 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.14 (d, J = 6.4 Hz, 6 H), 1.25 - 1.37 (m, 16 H), 2.14 - 2.21 (m, 11 H), 2.30 - 2.36 (m, 5 H), 2.41 (s, 2 H), 2.93 - 3.00 (m, 1 H), 3.34 - 3.38 (m, 2 H), 3.46 (t, J=8.7 Hz, 1 H), 3.49 - 3.55 (m, 1 H), 3.62 (dd, J = 11.9, 6.0 Hz, 1 H), 3.81 - 3.86 (m, 4 H), 3.93 (s, 2 H), 4.61 (d, J = 9.6 Hz, 1 H), 6.34 (d, J = 16.5 Hz, 1 H), 6.51 (d, J = 16.5 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 6.92 (s, 1 H), 7.08 - 7.13 (m, 2 H), 7.25 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.12, 24.09, 24.25, 25.91, 26.13, 26.37, 26.79, 30.75, 36.47, 45.19, 45.57, 46.68, 54.50, 56.52, 60.73, 61.17, 63.47, 68.43, 72.34, 75.79, 77.00, 80.29, 82.57, 109.66, 125.05, 126.35, 129.23, 130.06, 130.12, 130.79, 131.86, 134.70, 136.20, 137.52, 140.74, 149.75, 158.65, 178.40,; HR-MS ESI/APCI Dual *m/z*: 712.4916

$[M+H]^+$ (calcd for $C_{41}H_{65}N_3O_7$: 712.4895).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-4-({1-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (94h)

Compound **90a** (300 mg, 0.392 mmol) and 1-piperazine ethanol (76 mg, 0.588 mmol) was used as starting materials and synthesized in the same manner as compound **82b** to give the titled compound (68.6 mg, 25% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 1.16 (d, J = 6.9 Hz, 6 H), 1.30 (s, 6 H), 1.33 (s, 6 H), 2.05 - 2.22 (m, 6 H), 2.33 (s, 2 H), 2.35 - 2.38 (m, 3 H), 2.47 (br. s., 4 H), 2.97 - 3.05 (m, 1 H), 3.34 - 3.39 (m, 2 H), 3.43 - 3.54 (m, 4 H), 3.63 (dd, J = 12.2, 5.3 Hz, 1 H), 3.80 - 3.87 (m, 4 H), 3.93 (s, 2 H), 4.62 (d, J = 9.2 Hz, 1 H), 6.38 (d, J = 16.0 Hz, 1 H), 6.53 (d, J = 16.0 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.93 (s, 1 H), 7.11 (s, 1 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.28 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.12, 24.08, 24.32, 26.02, 30.77, 36.28, 46.72, 54.58, 54.71, 55.93, 56.50, 59.75, 61.21, 63.34, 68.64, 72.23, 75.75, 76.95, 80.30, 82.62, 109.60, 125.15, 126.32, 129.49, 130.01, 130.24, 130.87, 131.83, 134.41, 136.07, 137.72, 141.03, 149.79, 158.64, 178.47,; HR-MS ESI/APCI Dual *m/z*: 712.4561 $[M+H]^+$ (calcd for $C_{40}H_{61}N_3O_8$: 712.4531).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-4-{[1-(4-carbamoylpiperidin-1-yl)-2-methylpropan-2-yl]amino}-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (94i)

Compound **90a** (150 mg, 0.196 mmol) and piperidine-4-carboxamide (38.0 mg, 0.294 mmol) was used as starting materials and synthesized in the same manner as compound **82b** to give the titled compound (32 mg, 23% for 2 steps) as a colorless amorphous. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.09 - 1.21 (m, 6 H), 1.29 (s, 6 H), 1.34 (s, 6 H), 1.43 - 1.59 (m, 4 H), 1.98 - 2.13 (m, 1 H), 2.15 - 2.28

(m, 2 H), 2.33 (s, 3 H), 2.41 (s, 2 H), 2.73 - 2.86 (m, 2 H), 2.89 - 3.02 (m, 1 H), 3.33 - 3.67 (m, 5 H), 3.78 - 3.86 (m, 4 H), 3.91 (s, 2 H), 4.62 (d, *J* = 9.5 Hz, 1 H), 6.35 (d, *J* = 16.2 Hz, 1 H), 6.50 (d, *J* = 16.2 Hz, 1 H), 6.67 - 6.76 (m, 1 H), 6.92 (s, 1 H), 7.08 - 7.16 (m, 2 H), 7.25 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.01, 24.09, 24.21, 25.81, 25.84, 25.87, 30.28, 30.73, 36.40, 43.09, 46.63, 55.04, 56.52, 56.70, 56.72, 63.39, 68.25, 72.30, 75.65, 76.96, 80.29, 82.57, 109.66, 125.03, 126.21, 129.22, 130.13, 130.16, 130.77, 131.87, 134.52, 136.01, 137.65, 140.79, 149.84, 158.63, 178.66, 180.83,; HR-MS ESI/APCI Dual *m/z*: 710.4399 $[M+H]^+$ (calcd for $C_{40}H_{59}N_3O_8$: 710.4375).

(*1S*)-1,5-Anhydro-1-[5-({4-[(*1E*)-4-({1-[4-(dimethylamino)piperidin-1-yl]-2-methylpropan-2-yl}amino)-3,3-dimethyl-4-oxobut-1-en-1-yl]-2-methylphenyl}methyl)-2-methoxy-4-(propan-2-yl)phenyl]-D-glucitol (94j)

Sodium triacetoxyborohydride (166 mg, 0.784 mmol) and *N*,*N*-dimethylpiperidin-4-amine (37.7 mg, 0.294 mmol) were added to a chloroform (2 mL) solution of compound **90a** (150 mg, 0.196 mmol) in a nitrogen atmosphere, and the mixture was stirred for 16 hours at room temperature. An aqueous sodium hydrogen carbonate solution was added to the reaction liquid, and after extracting the mixture with chloroform, the organic layer was washed with 10% brine and then dried over anhydrous magnesium sulfate. The desiccant was filtered out, and the solvent was distilled off under reduced pressure. The resulting residue was purified by performing silica gel column chromatography (chloroform: methanol = 10: 0 to 9: 1) to obtain the intermediate (97.6 mg). The crude intermediate (97 mg) in methanol: triethylamine: water (5: 1: 1) solution (2.5 mL) was stirred at the room temperature for 16 hours, and after stirring the reaction mixture for 16 hours at room temperature, the solvent was distilled off under reduced pressure. The resulting residue was purified by performing neutral silica gel column chromatography (ethyl acetate: ethanol: water = 30: 2: 1) to give the titled compound (56 mg, 41% for 2 steps) as a colorless amorphous. ^{1}H NMR (600 MHz, CD_3OD) δ ppm

1.13 (d, *J* = 6.4 Hz, 3 H), 1.14 (d, *J* = 6.4 Hz, 3 H), 1.19 - 1.27 (m, 2 H), 1.29 (s, 6 H), 1.33 (s, 6 H), 1.47 - 1.54 (m, 2 H), 1.98 - 2.05 (m, 1 H), 2.14 (s, 6 H), 2.34 (m, 5H), 2.76 - 2.82 (m, 2 H), 2.96 (t, *J* = 6.7 Hz, 1 H), 3.35 - 3.38 (m, 2 H), 3.44 - 3.48 (m, 1 H), 3.48 - 3.54 (m, 1 H), 3.62 (dd, *J* = 11.9, 6.0 Hz, 1 H), 3.80 - 3.87 (m, 4 H), 3.91 (s, 2 H), 4.62 (d, *J* = 9.6 Hz, 1 H), 6.37 (d, *J* = 16.5 Hz, 1 H), 6.53 (d, *J* = 16.5 Hz, 1 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 6.93 (s, 1 H), 7.09 (s, 1 H), 7.14 (d, *J* = 7.8 Hz, 1 H), 7.26 (s, 1 H); ^{13}C NMR (126 MHz, CD_3OD) δ ppm 20.08, 24.10, 24.24, 25.79, 25.85, 29.55, 29.65, 30.77, 36.41, 41.68, 46.68, 55.06, 56.52, 56.65, 63.25, 63.47, 68.00, 72.35, 75.83, 76.93, 80.29, 82.57, 109.64, 124.90, 126.39, 130.02, 131.88, 134.64, 136.13, 137.61, 140.82, 149.76, 158.65, 178.40; IR (KBr) $\tilde{\nu}$ = 3388, 2963, 2928, 1669, 1505, 1451, 1379, 1364, 1278, 1207, 1090, 1055, 1040 cm^{-1}; HR-MS ESI/APCI Dual *m/z*: 710.4767 $[M+H]^+$ (calcd for $C_{41}H_{63}N_3O_7$: 710.4739); $[\alpha]_D^{25}$= +3 (*c* = 0.10, MeOH).

薬理試験及び動態試験に関する実験

Glucose uptake inhibition assay

Chinese hamster ovary-K1 cells stably expressing human SGLT2 (NM_003041) or human SGLT1 (NM_000343) were used for the sodium-dependent glucose transport inhibition test. Cells were incubated in 200 μL of pretreatment buffer solution (140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES/5 mM Tris, pH7.4) for 20 min. The pretreatment buffer was removed, and 75 μL of uptake buffer containing the test compound (methyl-α-D-glucopyranoside containing [^{14}C] methyl-α-D-glucopyranoside [0.1 mM for SGLT1 inhibition, 1 mM for SGLT2 inhibition], 140 mM NaCl, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES/5mM Tris, pH7.4) were added. The uptake reaction was performed at 37˚C for 30 min (SGLT1) or 1 h (SGLT2). After the reaction, the cells were washed twice with 200 μL of washing buffer (10 mM methyl-α-D-glucopyranoside, 140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES/5 mM Tris, pH7.4) and dissolved in 75 μL of 0.25 M NaOH. Opti phase Super Mix (Perkin-Elmer Corporation) was added and mixed well with the sample; the radioactivity was then measured using a Micro Beta Trilux counter (Perkin-Elmer Corporation). An uptake buffer that did not contain the test compound was used as a control. Another uptake buffer containing choline chloride instead of NaCl was also prepared as a background control. To determine the IC_{50} values, each test compound was tested at six suitable concentrations. The concentration at which glucose uptake was inhibited by 50% (IC_{50} value) compared with the glucose uptake in the control (100%) was then calculated.

Pharmacokinetic evaluation

The permeability measurement and the data analysis of the test compound were performed using PAMPA Evolution™ (pION Inc.). A 96-well PAMPA sandwich plate (pION Inc.) was used for the

permeability measurement. The “sandwich” filters were coated with 4 μL of GIT-0 Lipid (pION Inc.). The donor plate was filled with 200 μL of the test compound dissolved in the PRISMA HT Universal Buffer (pION Inc.).

The plasma and kidney concentration-time profiles of the test compounds were investigated in fasted male SD rats. After a single intravenous administration of the test compounds, blood was obtained from the tail vein at each sampling time point and then centrifuged to prepare the plasma samples. After a single intravenous administration of the test compounds, the animal were euthanized at each sampling time point and the kidneys were harvested and homogenized in purified water. The cumulative excretion of unaltered drug in the urine and bile was investigated in bile duct-cannulated SD rats. After a single intravenous administration of the test compounds, urine and bile samples were collected for a 24-hour time period. The quantitative analysis of the target analyte in each sample was performed using liquid chromatography-tandem mass spectrometry. The pharmacokinetic parameters were calculated using a non-compartmental analysis with Phoenix WinNonlin (version 6.2, Certara).

Plasma glucose level after glucose administration in normal rats

After overnight fasting, SD rats were orally administered the vehicle (0.5 w/v% Carboxymethyl Cellulose) or the compound **30b** solution and a glucose (2 g/kg) solution. Blood was collected from the orbital venous sinus of the rats under ether anesthesia. The plasma glucose concentration was measured using a Glucose CII test Wako kit (Wako Pure Chemical Industries Ltd., Osaka Japan). The difference from the baseline plasma glucose levels over the study period was calculated to determine the delta area under the curve (ΔGlucose AUC).

Plasma glucose level after sucrose administration in normal rats

After overnight fasting, SD rats were orally administered the vehicle (water for injection) or a **62d**

solution and a sucrose (2.5 g/kg) solution. Blood was collected from the tail vein. The plasma glucose concentration was measured using the Glucose CII test Wako kit (Wako Pure Chemical Industries Ltd., Osaka Japan). The difference from the baseline plasma glucose level throughout the study period was calculated as the delta area under the curve (ΔGlucose AUC).

引用文献

1. International Diabetes Federation, *IDF diabetes atlas 8th edition,* http://www.diabetesatlas.org/.
2. World Health Organization, *Global report on diabetes,* https://www.who.int/publications/i/item/9789241565257.
3. Ohkubo Y., Kishikawa H., Araki E., Miyata T., Isami S., Motoyoshi S., Kojima Y., Furuyoshi N., Shichiri M., , Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*., **28**,103–117 (1995).
4. Oishi M., Yamazaki K., Okuguchi F., Sugimoto H., Kanatsuka A., Kashiwagi A., Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). *J Diabetes Investig.,* **5**, 581–587 (2014).
5. Ahrén B., Avoiding hypoglycemia: a key to success for glucose-lowering therapy in type 2 diabetes. *Vasc Health Risk Manag.,* **9**, 155–163 (2013).
6. Rossetti L., Shulman G. I., Zawalich W., Defronzo R. A., Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatectomized rats. *J. Clin. Invest*., **87**, 1037–1044 (1987).
7. Rossetti L. Smith D., Shulman G. I., Papachristou D., Defronzo R. A., Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. *J. Clin. Invest*., **79**, 1510–1515 (1987).
8. Wright E.M., Loo D.D., Hirayama B.A., Biology of human sodium glucose transporters. .*Physiol Rev.*, **91**, 733–94 (2011).
9. Vallon V., The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. *Annu Rev Med.,* **66**, 255–70 (2015).
10. Gallo L. A., Wright E. M., Vallon V., Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res.*, **12**, 78–89 (2015).

11. Meng W., Ellsworth B. A., Nirschl A. A., McCann P.J., Patel M., Girotra R. N., Wu G., Sher P. M., Morrison E. P., Biller S. A., Zahler R., Deshpande P. P., Pullockaran A., Hagan D. L., Morgan N., Taylor J. R., Obermeier M. T., Humphreys W. G., Khanna A., Discenza L., Robertson J. G., Wang A., Han S., Wetterau J. R., Janovitz E. B., Flint O. P., Whaley J. M., Washburn W. N., Diabetes. Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. *J. Med. Chem.*, **51**, 1145−1149 (2008).
12. Nomura S., Sakamaki S., Hongu M., Kawanishi E., Koga Y., Sakamoto T., Yamamoto Y., Ueta K., Kimata H., Nakayama K., Tsuda-Tsukimoto M., Discovery of Canagliflozin, a Novel *C*-Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus. *J. Med. Chem.*, **53**, 6355−6360 (2010).
13. Eckhardt M., Himmelsbach F., Wang X-J., Sun X., Zhang L., Tang W., Krishnamurthy D., Senanayake C. H., Han Z., Processes for preparing of glucopyranosyl-substituted benzyl-benzene derivatives and intermediates therein. PCT Int. Appl. WO 2006120208, (2006).
14. Imamura M., Nakanishi K., Suzuki T., Ikegai K., Shiraki R., Ogiyama T., Murakami T., Kurosaki E., Noda A., Kobayashi Y., Yokota M., Koide T., Kosakai K., Ohkura Y., Takeuchi M., Tomiyama H., Ohta M., Discovery of ipragliflozin (ASP1941): A novel *C*-glucoside with benzothiophene structure as a potent and selective sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes mellitus. *Bioorg. Med. Chem.*, **20**, 3263−3279 (2012).
15. Kakinuma H., Oi T., Hashimoto-Tsuchiya Y., Arai M., Kawakita Y., Fukusawa Y., Iida I., Hagima N., Takeuchi H., Chino Y., Asami J., Okumura-Kitajima L., Io F., Yamamoto D., Miyata N., Takahashi T., Uchida S., Yamamoto K., (*1S*)-1,5-Anhydro-1-[5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl]-1-thio-D-glucitol (TS-071) is a Potent, Selective Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for Type 2 Diabetes Treatment. *J. Med. Chem.*, **53**, 3247–3261

(2010).

16. Ohtake Y., Sato T., Kobayashi T., Nishimoto M., Taka N., Takano K., Yamamoto K., Ohmori M., Yamaguchi M., Takami K., Yeu S. Y., Ahn K. H., Matsuoka H., Morikawa K., Suzuki M., Hagita H., Ozawa K., Yamaguchi K., Kato M., Ikeda S., Discovery of Tofogliflozin, a Novel C-Arylglucoside with an *O*-Spiroketal Ring System, as a Highly Selective Sodium Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes. *J. Med.Chem.*, **55**, 7828−7840 (2012).
17. Bernard Z., Christoph W., John M. L., David F., Erich B., Stefan H., Michaela M., Dipl B., Theresa D., Odd E. J., Hans J. W., Uli C. B., Silvio E. I., Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N. Engl. J. Med*., **373**, 2117–2128 (2015).
18. Bruce N., Vlado P., Kenneth W. M., Dick de Z., Greg F., Ngozi E., Wayne S., Gordon L., Mehul D., David R. M., Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N. Engl. J. Med*., **377**, 644–657 (2017).
19. Stephen D. W., Itamar R., Marc P. B., Ofri M., Eri T. K., Avvit C., Michael G. S., Thomas A. Z., Julia F. K., Sabina A. M., Deepak L. B., Lawrence A.L., Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med*., **380**, 347–357 (2019).
20. Haneda M., Seino Y., Inagaki N., Kaku K., Sasaki T., Fukatsu A., Kakiuchi H., Sakai S., Samukawa Y., Influence of Renal Function on the 52-Week Efficacy and Safety of the Sodium Glucose Cotransporter 2 Inhibitor Luseogliflozin in Japanese Patients with Type 2 Diabetes Mellitus. Clin. Ther., **38**, 66–88 (2016).
21. Dyer J., Garner A., Wood I. S., Sharma A. K., Chandranath I., Shirazi-Beechey S. P., Changes in the levels of intestinal Na /glucose co-transporter (SGLT1) in experimental diabetes. *Biochem Soc Trans.,* **25**, 479S (1997).
22. Ertl P, Rohde B, Selzer P., Fast Calculation of Molecular Polar Surface Area as a Sum of

Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties. *J. Med. Chem*., **43**, 3714-3717 (2000).

23. Tian S., Li Y., Wang J., Zhang J., Hou T., ADME Evaluation in Drug Discovery. 9. Prediction of Oral Bioavailability in Humans Based on Molecular Properties and Structural Fingerprints. *Mol. Pharmaceutics*., **8**, 841–851 (2011).
24. Zhou L., Cryan E. V., D'Andrea M. R., belkowski S., Conway B. R., Demarest K. T., Human cardiomyocytes express high level of Na+/glucose cotransporter 1 (SGLT1). *J. Cell. Biochem.*, **90**, 339–46 (2003).
25. Banerjee S. K., Mcgaffin K. R., Pator-Soler N. M., Ahmad F., SGLT1 is a novel cardiac glucose transporter that is perturbed in disease states. *Cardiovasc Res.*, **84**, 111–118 (2009).
26. Hirose M., Matsushita N., Ishid N., Ibi M., Saito M., Roles of Sodium-Glucose Cotransporter 1 (SGLT1) in the Induction of Cardiac Remodeling. *YAKUGAKU ZASSHI*, **138**, 939–943 (2018).
27. Kashiwagi Y., Nagoshi T., Yoshino T., Tanaka T., Ito K., Harada T., Takahashi H., Ikegami M., Anzawa R., Yoshimura M., Expression of SGLT1 in Human Hearts and Impairment of Cardiac Glucose Uptake by Phlorizin during Ischemia-Reperfusion Injury in Mice. *Plos One*, **10**, 6(2015).
28. Fushimi N., Fujikura H., Shiohara H., Teranishi H., Shimizu K., Yonekubo S., Ohno K., Miyagi T., Itoh F., Shibazaki K., Tomoe M., Ishikawa-Takemura Y., Nakabayashi T., Kamada N., Ozawa T., Kobayashi S., isaji M., Structure–activity relationship studies of 4-benzyl-1H-pyrazol-3-yl *β*-D-glucopyranoside derivatives as potent and selective sodium glucose co-transporter 1 (SGLT1) inhibitors with therapeutic activity on postprandial hyperglycemia. *Bioorg. Med. Chem.*, **20**, 6598–6612 (2012).
29. Fushimi N., Teranishi H., Shimizu K., Yonekubo S., Ohno K., Miyagi T., Itoh F., Shibazaki K., Tomoe M., Ishikawa-Takemura Y., Nakabayashi T., Kamada N., Yamauchi Y., Kobayashi S., isaji M., Design, synthesis, and structure–activity relationships of a series of 4-benzyl-5-isopropyl-1H-

pyrazol-3-yl *β*-D-glycopyranosides substituted with novel hydrophilic groups as highly potent inhibitors of sodium glucose co-transporter 1 (SGLT1). *Bioorg. Med. Chem.*, **21**, 748–765 (2013).

30. Goodwin N. C., Ding Z., Harrison B. A, Stobel E. D., Harris A. L., Smith M., Thompson A. Y., Xiong W., Mseeh F., Bruce D. J., Diaz D., Gopinathan S., Li L., O'Neill E., Thiel M., Wilson A. G. E., Carson K. G., Powell D. R., Rawlins D. B., Discovery of LX2761, a Sodium-Dependent Glucose Cotransporter 1 (SGLT1) Inhibitor Restricted to the Intestinal Lumen, for the Treatment of Diabetes. *J. Med. Chem.,* **60**, 710−721 (2017).
31. Lapuerta P., Zambrowicz B., Strumph, P., Sands A., Development of Sotagliflozin, a Dual Sodium-dependent Glucose Transporter 1/2 Inhibitor. *Diabetes Vasc. Dis. Res*., **12**, 101−110 (2015).
32. Zambrowicz B. P., Ogbaa I., Frazier K. S., Banks P., Turnage A., Freiman J., Boehm K. A., Ruff D., Powell D. R., Sands A., Effects of LX4211, a Dual Sodium-Dependent Glucose Cotransporters 1 and 2 Inhibitor, on Postprandial Glucose, Insulin, Glucagon-like Peptide 1, and Peptide Tyrosine Tyrosine in a Dose-Timing Study in Healthy Subjects. *Clin. Ther*., 35, 1162−1773 (2013).
33. Zambrowicz B. P., Ding Z. M., Ogbaa I., Frazier K., Banks P., Turnage A., Freiman J., Smith M., Ruff D., Sands A. T., Powell D. R., Effects of LX4211, a Dual SGLT1/SGLT2 Inhibitor, Plus Sitagliptan on Postprandial Active GLP-1 and Glycemic Control in Type 2 Diabetes. *Clin. Ther.,* **35**, 273−285 (2013).
34. Yamamoto K., Uchid S., Kitano k., Fukuhara N., Okumura-Kitajima L., Gunji E., Kozakai A., Tomoike H., Kojima N., Asami J., Toyada H., Arai M., Takahashi T., Takahashi K., TS-071 is a novel, potent and selective renal sodium-glucose cotransporter 2 (SGLT2) inhibitor with anti-hyperglycaemic activity. *Br. J. Phamacol*., **164**, 181−191 (2011).
35. ManFred K. Frank S. Klaus G., Physicochemical High Throughput Screening: Parallel Artificial Membrane Permeation Assay in the Description of Passive Absorption Processes. *J. Med. Chem*.,

41, 1007−1010 (1998).

36. Veber D. F., Johnson S. R., Cheng H., Smith B. R., Ward K. W., Kopple K. D., Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.*, **45**, 2615-2623 (2002).
37. Deshpande P. P., Ellsworth B. A., Buono F. G., Pullockaran A., Singh J., Kissick T. P., Huang M-H., Lobinger H., Denzel T., Mueller R. H., Remarkable β-1-*C*-Arylglucosides: Stereoselective Reduction of Acetyl-Protected Methyl 1-*C*-Arylglucosides without Acetoxy-Group Participation., *J. Org. Chem.*, **72**, 9746−9749 (2007).
38. Mizoroki T., Mori K., Ozaki A., Arylation of Olefin with Aryl Iodide Catalyzed By Palladium. *Bull. Chem. Soc. Jpn*., **44**, 581 (1971).
39. Heck R. F., Nolley J.P., Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem*., **37**, 2320−2322 (1972).
40. Mohun R., Ravi K. S., Stephen D., So J. L., David W., Xue Y. H., Ferhaan A., Transgenic knockdown of cardiac sodium/glucose cotransporter 1 (SGLT1) attenuates PRKAG2 cardiomyopathy, whereas transgenic overexpression of cardiac SGLT1 causes pathologic hypertrophy and dysfunction in mice. *J. Am. Heart. Assoc*., **3**, e000899 (2014).
41. Matsushita N., Ishida N., Ibi M., Saito M., Sanbe A., Shimojo H., Suzuki S., Hermann K., Takeishi Y., Morino Y., Taira E., Sawa Y., Hirose M., Chronic Pressure Overload Induces Cardiac Hypertrophy and Fibrosis via Increases in SGLT1 and IL-18 Gene Expression in Mice. *Int. Heart. J*., **59**, 1123−1133 (2018).
42. Vicor S., Directed ortho metalation. Tertiary amide and O-carbamate directors in synthetic strategies for polysubstituted aromatics. *Chem. Rev*., **90**, 879−933 (1990).

Dess D. B., Martin J. C., Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem*., **48**, 4155−4156 (1983).