環状 polyol を基盤とした gallotannin 誘導体の合成と抗酸化活性及び α-glucosidase 阻害活性評価

日本大学大学院薬学研究科

生物有機化学研究室

町田　翔太

目次

序論 4
本論 9
第一章 環状 polyol 類の合成 9
第 1 節 1,5-anhydroalditol 類の合成 9
第 2 節 アミノ基を有する anhydroalditol 類の合成 15
第 3 節 1,4-Anhydro-L-arabinitol の合成 16
第 4 節 Anhydroalditol を有する二糖類の合成 17
第 5 節 1-Deoxy-D-glucuronic acid の合成 19
第二章 環状 polyol をコアにもつ gallotannin 及びその誘導体の合成 21
第 1 節 1,5-AG をコアにもつ gallotannin 類の網羅的合成 21
第 2 節 異なるフェノール酸ユニットを有する誘導体の合成 24
第 3 節 Ellagitannin 誘導体の合成 25
第 4 節 多様な polyol をコアにもつ gallotannin 誘導体の合成 26
第三章 環状 polyol をコアにもつ gallotannin 及びその誘導体の抗酸化活性と α-glucosidase 阻害活性評価 29
第 1 節 抗酸化活性の評価 29
第 2 節 α-Glucosidase 阻害活性の評価 33
結語 41
実験の部 42
参考文献 75

略語一覧

Ac	Acetyl
AIBN	2,2'-Azobis(isobutyronitrile)
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
2-CMPI	2-Chloromethylpyridinium iodide
CSA	(±)-10-Camphorsulfonic acid
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl Azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DPPA	Diphenylphosphoryl azide
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride
Et	Ethyl
HHDP	Hexahydroxydiphenoyl
Me	Methyl
Ph	Phenyl
Pr	Propyl
Py	Pyridine
TBA	Tetra-*n*-butylammonium
TBDPS	*tert*-Butyldiphenylsilyl
TEA	Triethylamine
TES	Triethylsilane
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl

序論

タンニン（tannin）とは自然界に広く分布しているポリフェノール構造を有する化合物の一群を指し、縮合型タンニンと加水分解型タンニンに分類される[1]。本研究において着目した加水分解型タンニンは双子葉植物により産生され、加水分解を受け gallic acid などのフェノール酸を遊離する。加水分解型タンニンは、さらに gallotannin と ellagitannin に分類される。Gallotannin は D-glucose などの polyol コアと、polyol コアに結合する gallic acid（galloyl 基）から成り立ち、代表的な化合物に 1,6-di-*O*-galloyl-glucose や 1,4,6-tri-*O*-galloyl-D-glucose、pentagalloyl glucose（PGG）、tannic acid などがある（Figure 1）。一方、ellagitannin は、polyol コアの gallic acid が酸化的にカップリングした hexahydroxydiphenoyl（HHDP）基と呼ばれる特徴的なマクロラクトン構造を有する天然物群で、代表的な化合物に tellimagrandin I や strictinin などがある。これらタンニン類は、polyol コア上の gallic acid の結合位置、結合数、酸化状態などの違いにより、非常に多くの類縁体が存在する[2,3]。

また、gallotannin 類は、galloyl 基による多様性に加え、polyol コアの多様性もみられる。Gallotannin の polyol コアは一般的に D-glucose であるが、植物によって、個性的なコアを持つ gallotannin も存在する。例えば、hamamelose をコアにもつ hamamelitannin[4] や 1,5-anhydroalditol の一種である 1,5-anhydro-D-glucitol（1,5-AG）をコアに有する acertannin （**1**）などが知られている。本研究において合成化合物には化合物番号を付してある。

Gallotannin や ellagitannin は多彩な生物活性を有することが知られており、polyol に結合する galloyl 基の数や結合位置などによって生物活性が異なる。例えば、lipase 阻害作用は galloyl 基の数や HHDP 基が阻害活性向上に寄与することが報告されている[5]。また、1,2,3,6-tetra-*O*-galloyl-β-D-glucose および PGG は、peroxisome proliferator-activated receptor（PPAR）α/βの発現を増加させ、さらに 1,2,3,6-tetra-*O*-galloyl-β- D-glucose には、glucose の細胞内取り込みを促進させる作用があることが報告されている[6]。Gallotannin 類による生物活性の報告は天然物間を比較したものが多いが、合成された非天然型 gallotannin 類を交えて検討を行なっている例もある。Y. Ren らは、様々な polyol をコアにもつ gallotannin 誘導体の合成を行ない、6-chloro-6-deoxy-1,2,3,4-tetra-*O*-galloyl-α-D-glucose がα-PGG などと比較し強く glucose 取り込みを促進することを明らかにしている[7]。また T. Sylla らは、depside 結合を有する gallotannin 類を合成し、α-glucogallin およびβ-hexagalloyl glucose が強い amyloid β-peptide の凝集抑制作用を示すことを報告している[8]。

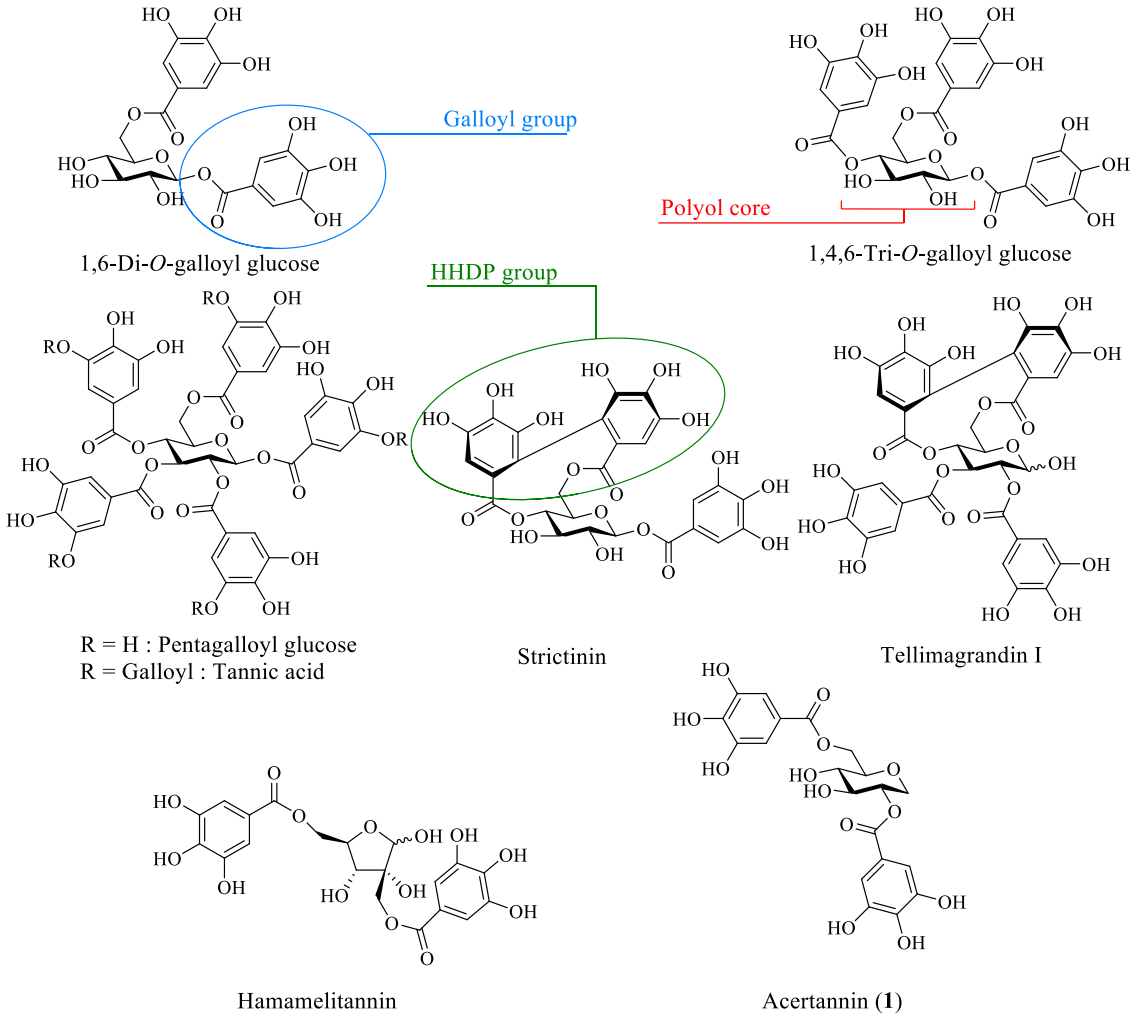


Figure 1.　タンニンの構造

1,5-AG は、glucitol（sorbitol）の 1 位と 5 位のヒドロキシ基が脱水した環状 polyol で、D-glucopyranose の 1 位のヒドロキシ基を欠いた構造を有しており、ヘミアセタール性ヒドロキシ基を持たないためアノマー異性体が存在せず、化学的にも安定であり取り扱いやすい

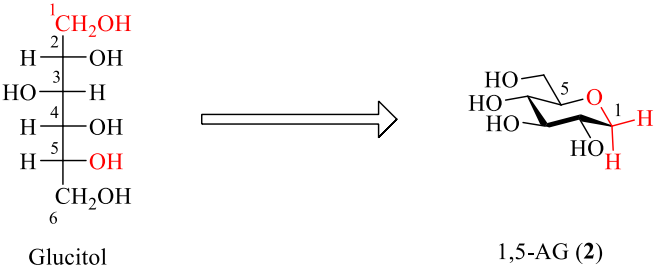


Figure 2.　1,5-AG の構造

といった特徴を持つ（Figure 2）。1,5-AG は、1860 年に初めてセネガなどヒメハギ科（*Polygalaceae*）の植物から単離され、構造が不明であったことから植物の名前をとって polygalitol と命名された [9]。また、acer 属の植物から得られるタンニンを加水分解することで同一な化合物が得られていたため、aceritol とも呼ばれている [10,11]。存在量は少ないが 1,5-AG だけではなく、その epimer である 1,5-anhydro-D-mannitol（1,5-AMan）もエゴノキ科のハクウンボク（*Styrax obassia*）から単離されており、styracitol と呼ばれている [12]。1,5-AG はデンプンなどα-1,4-glucoside 結合をもつマルトオリゴ糖から産生される。マルトオリゴ糖が、lyase によって分解されると 1,5-anhydro-D-fructose（1,5-AFru）が遊離し、この 1,5-AFru が還元されることで 1,5-AG が生成すると考えられている（Figure 3）[13]。

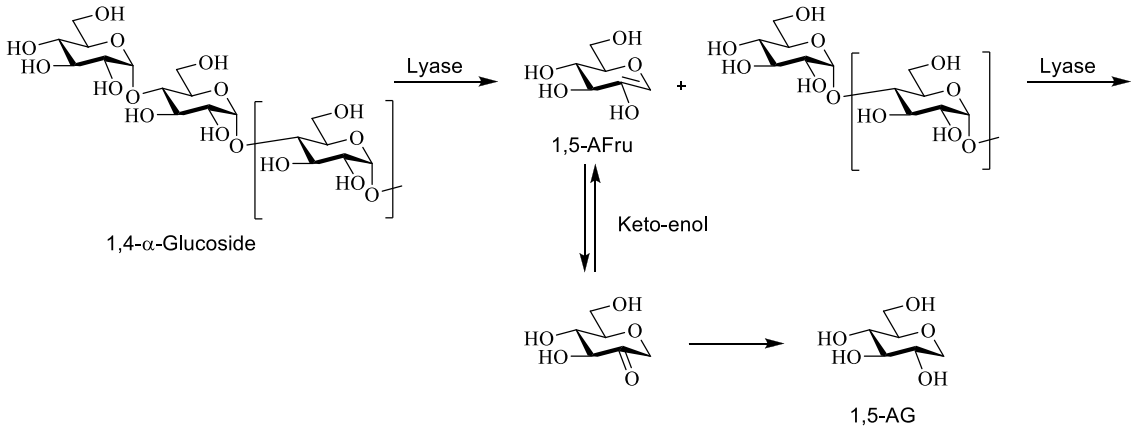


Figure 3.　1,5-AG の生合成経路

興味深いことに、1,5-AG はヒトの血液中にも存在しており、一部肝臓などで glycogen からの産生が示唆されているが、ほとんどが食事由来によるものである [14–16]。1,5-AG は、D-glucose と構造が類似しているため、生体内では D-glucose と同じような挙動を示し、SGLT1（SLC5A1）、SGLT4（SLC5A9）、SGTL5（SLC5A10）、SWEET1（SLC50A1）などのトランスポーターが吸収に関与していると考えられている [17]。1,5-AG は、尿細管にて SGLT4（SLC5A9）を介し 99.9%再吸収され、14–40 μg/mL 程度の血中濃度を保っているが、食事や服薬などの外的要因で変動する [18]。例えば、オンジを含む漢方薬である帰脾湯、人参養栄湯には 1,5-AG が多く含まれるため、これらを服用すると血中 1,5-AG 濃度は高くなる [19,20]。一方、低 glycemic index（GI）の食事や、acarbose、SGLT2 阻害薬の服用により血中 1,5-AG 濃度は低下する [21–23]。また、高血糖状態に陥ると、排出される多量の D-glucose により尿細管での 1,5-AG の再吸収が妨げられ、血中の 1,5-AG 濃度が低下するため、1,5-AG は約 1 週間前の短期的な血糖変動を知るバイオマーカーとして用いられている [24,25]。1,5-AG は日常的

に摂取している化合物であるため、毒性が低いと考えられている。また、1,5-AG は腸管から glucose の吸収を抑制することが報告され、生物活性を示す可能性が示唆されている[26]。1,5-AG の生物学的影響は未だでも未解明な部分が多く、現在も精力的に研究がなされている。

現在まで、1,5-AG をコアにもつ gallotannin は、*acer* 属の植物からしか単離されていない。1,5-AG をコアにもつ gallotannin は、1922 年に A. G. Perkin らによりカラコギカエデ（*acer ginnala*）の葉から初めて単離され、acertannin と命名された[10,27]。1,5-AG をコアにもつ gallotannin は現在までに、ginnalin B、C[28]、maplexin A–I[29,30]、depside 結合をもつ 2,6-bis-*O*-digalloyl-1,5-AG[31] などが単離されている（Figure 4）。これらの gallotannin や gallotannin を含む植物エキスは、抗酸化作用[32–40]および高血糖抑制作用[41–43]、高脂肪食による肥満抑制作用[44]、melanin 形成抑制作用[45]、elastase 阻害作用[46]、collagen 分解抑制および合成促進作用[47]、皮膚代謝促進作用[48]、glutathione 産生促進作用[49]、抗腫瘍作用[50–55]、好中球 apoptosis の誘導[56]、amyloid β-peptide 凝集抑制作用[57] などの生物活性を有していることが報告されている。H. Ma らは、1,5-AG を polyol コアに有する gallotannin のα-glucosidase 阻害作用に着目し galloyl 基の数が活性発現に重要であることを報告している[58]。A. Kamori らは、天然には存在しない 1,5-AG を polyol コアに有する誘導体を合成し、ceramidase 阻害および ceramide 合成促進作用を評価した[59]。その結果、maplexin E、F が最もよく ceramidase を阻害する一方、ginnalin B が最も良く ceramide 合成を促進することを明らかにしている。Gallotannin を始めとする polyphenol は多様な生物活性を示すため健康に寄与する可能性が示唆されている。しかし、polyphenol は数千種類の分子を含む巨大な化合物群であり、なかには生物活性を示す化合物もあれば示さない化合物もあるはずである。また、比較的天然に多く存在する化合物は注目され盛んに研究がなされているが、天然からの入手が難しい希少な化合物を交えた検討は少ない。さらに天然に存在しない polyphenol 誘導体を加えた網羅的な構造活性相関の検討の例は少なく、あるターゲット分子に対し、どのような構造が最も良い活性を示すのか十分に検討されていないのが現状である。本研究は、polyphenol のクラスの 1 つである gallotannin に着目し、環状 polyol をコアに有する gallotannin 誘導体の化学構造の特徴と生物活性の関係を明らかにすることを目的としている。本論文では、網羅的化学合成により得られた非天然型 gallotannin 誘導体を含む gallotannin 類の化合物ライブラリーの構築法、ならびに抗酸化活性と α-glucosidase の構造活性相関について詳述する。

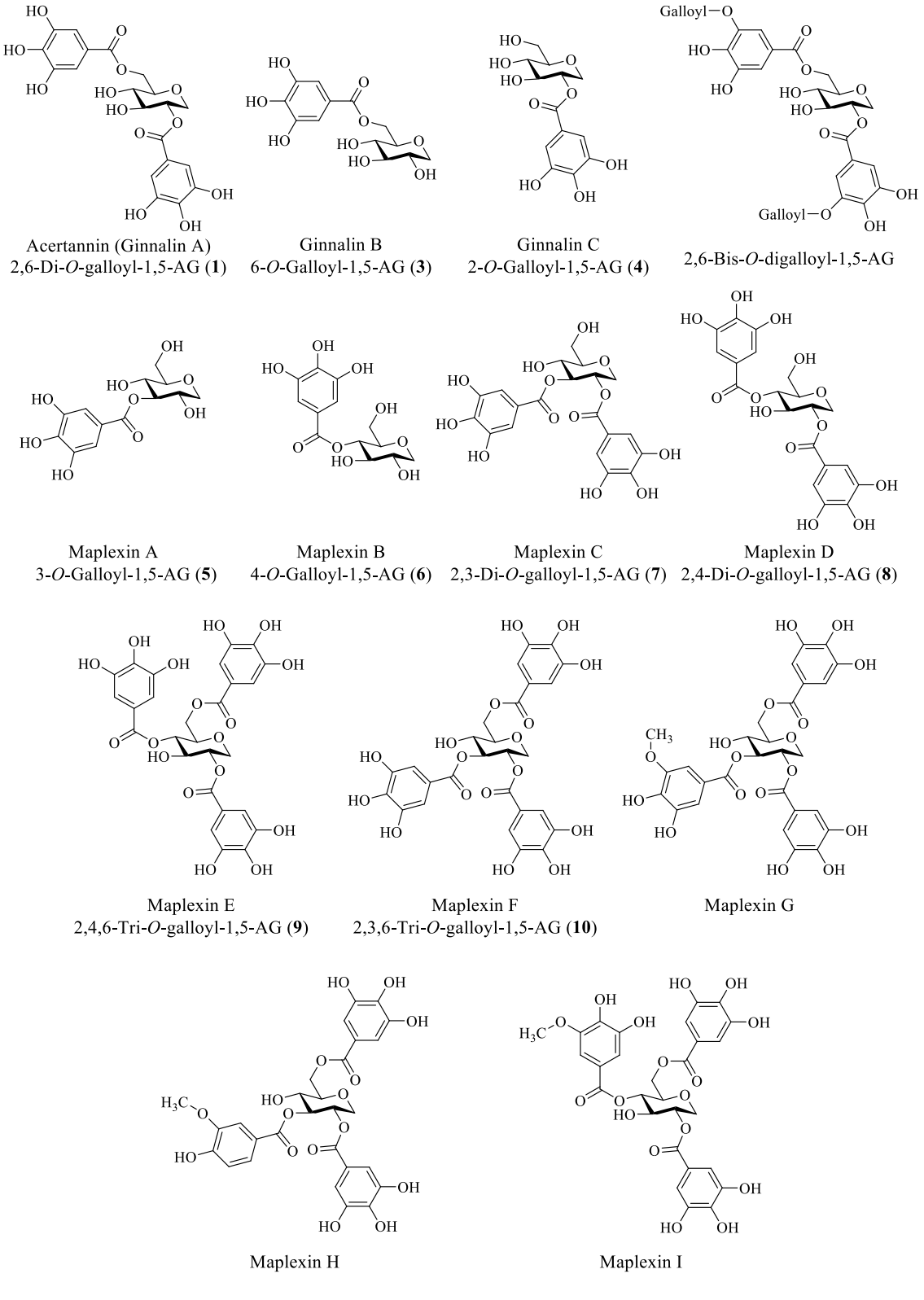


Figure 3.　1,5-AG を polyol コアに有する gallotannin の構造

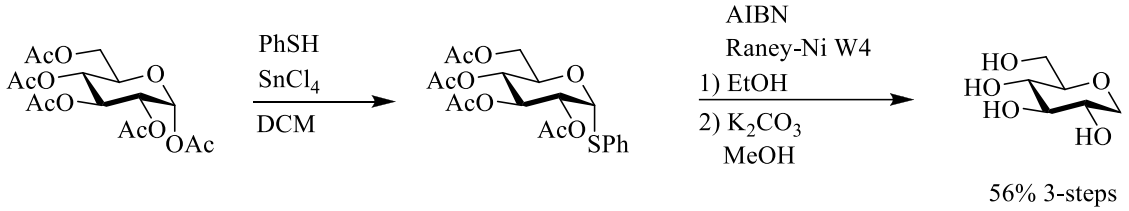
本論

第一章 環状 polyol 類の合成

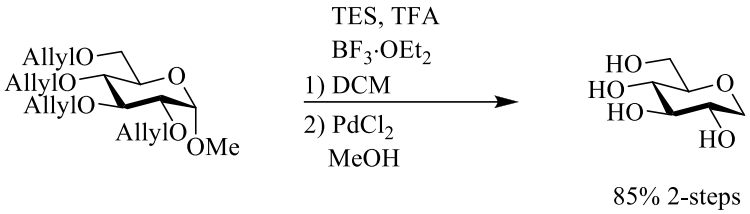
第1節　1,5-anhydroalditol 類の合成

1,5-AG は植物を中心に天然に広く分布する環状 polyol であるが、植物中の含有量としてはさほど多くない。また、1,5-AG 以外の 1,5-anhydroalditol 類は天然にほとんど存在しないため、これらを大量に得るためには人工的に作り出す必要がある。今日までに、化学的に合成する方法[60–74]や化学合成に頼らず微生物を用いる方法[62]、1,5-AG を豊富に含む植物であるオンジから抽出する方法[75]などさまざまな 1,5-anhydroalditol の入手法が報告されている。以下には合成法の例を示す。

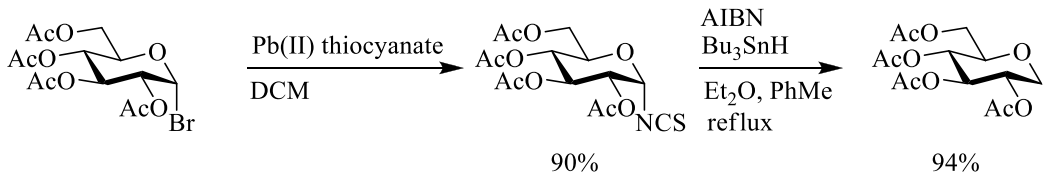
1) Thioglycoside を Raney Ni を用いて還元する方法[76]



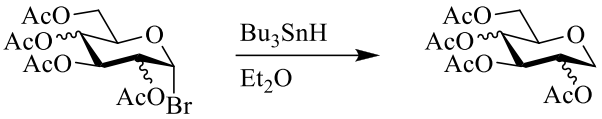
2) TES を用いてアルコキシ基を還元する方法[73]



3) Isotiocyanate へ活性化し、AIBN、Bu_3SnH によって還元する方法[77,78]

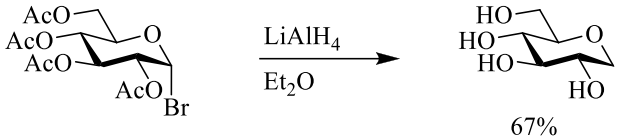


4) Glycosyl bromide を Bu_3SnH で還元する方法 [79,80]



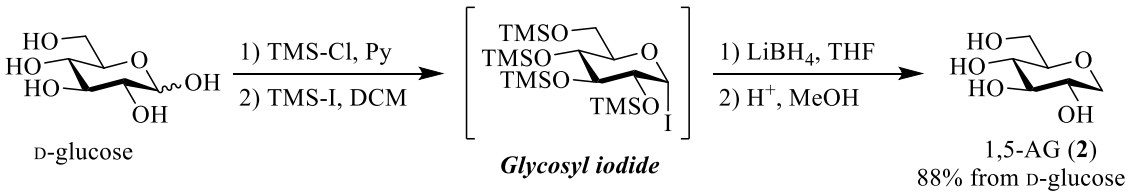
63-86%

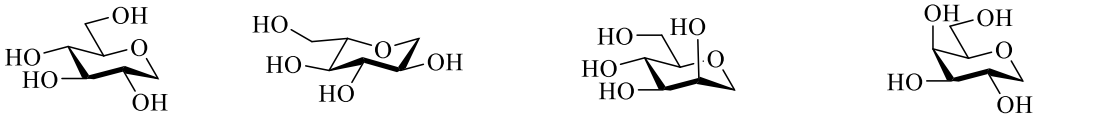
5) Glycosyl bromide を、LAH を用いて還元する方法 [81]

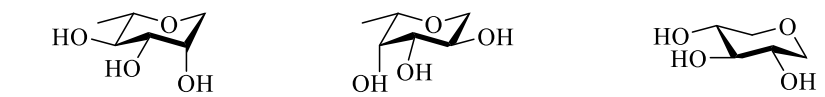


67%

これら従来の合成法には、トリブチルスズや高価な試薬を必要とすること、中間体の合成が数ステップにわたること、精製が煩雑であるなどの課題がある。当研究室ではこれまで、per-*O*-TMS 保護をした alditol を TMS-I を用いて glycosyl iodide へと活性化し、$LiBH_4$ で還元、酸で脱保護をすることで、対応する 1,5-anhydroalditol をグラムスケールで得られることを報告しており、環境毒性のあるスズ化合物を用いない点や、脱保護が容易な点、精製が容易な点で優れている（Scheme 1）[82]。







Scheme 1.　Glycosyl iodide を経由した 1,5-anhudroalditol 類の合成.

本反応の活性中間体である glycosyl iodide は反応性が極めて高く、単離できない。そこで、per-*O*-TMS-glycosyl iodide の生成を ^{1}H NMR 測定（600 MHz）により確認を行なった。モレキュラーシーブス 3A にて乾燥した $CDCl_3$ に各種 per-*O*-TMS-sugar（glucose、mannose、galactose、rhamnose、fucose、xylose）を溶解し、そこに 20~25℃で TMS-I （1.5 eq.）を加え、直ちに ^{1}H NMR を測定した。得られた NMR スペクトルを（Figure 4A–F）に示す。いずれの化合物も anomeric-H 由来のシグナルが 6.7~6.8 ppm 付近へ低磁場シフトした（Figure 5 下段）ことから、glycosyl iodide が概ね 5 分以内に生成していたことが推察された。

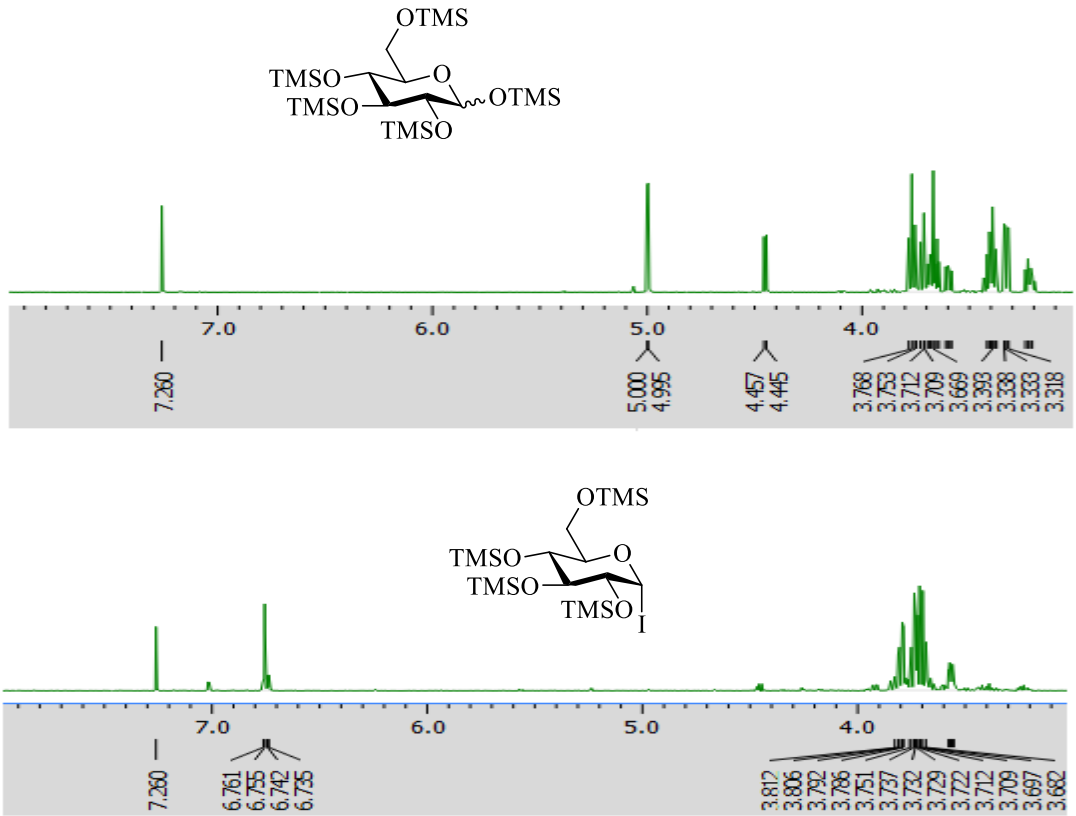


Figure 4A.　^{1}H NMR Spectra of Per-*O*-TMS-glucose and its iodide.

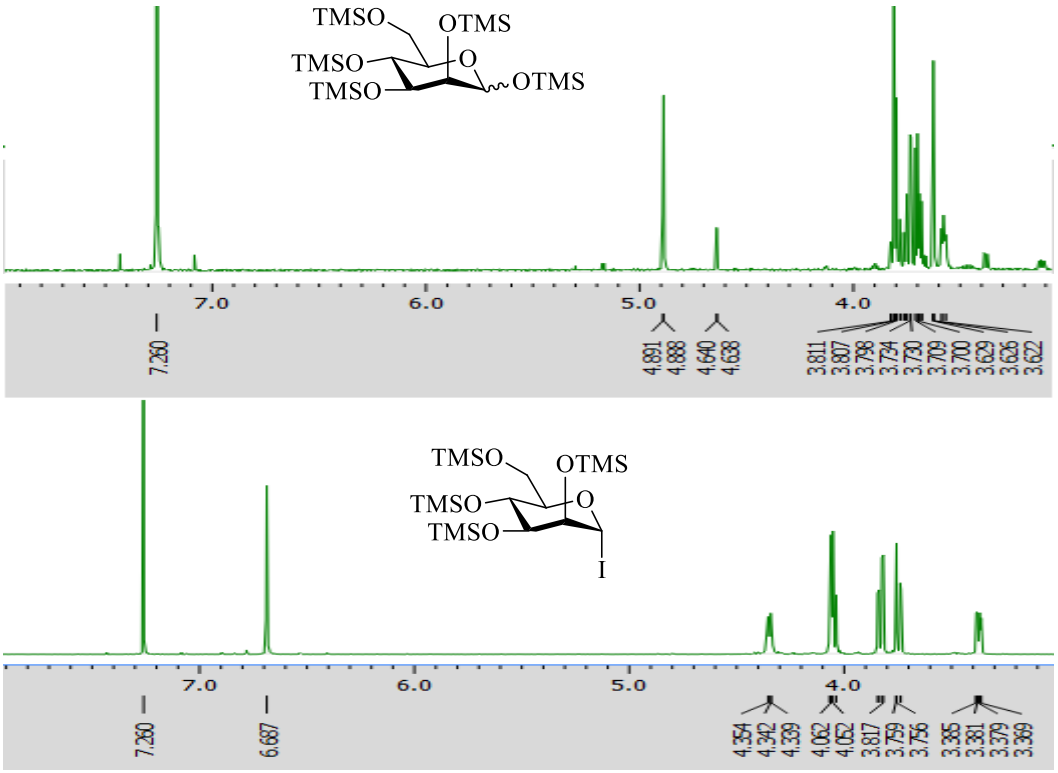


Figure 4B. ^{1}H NMR Spectra of Per-*O*-TMS-mannose and its iodide.

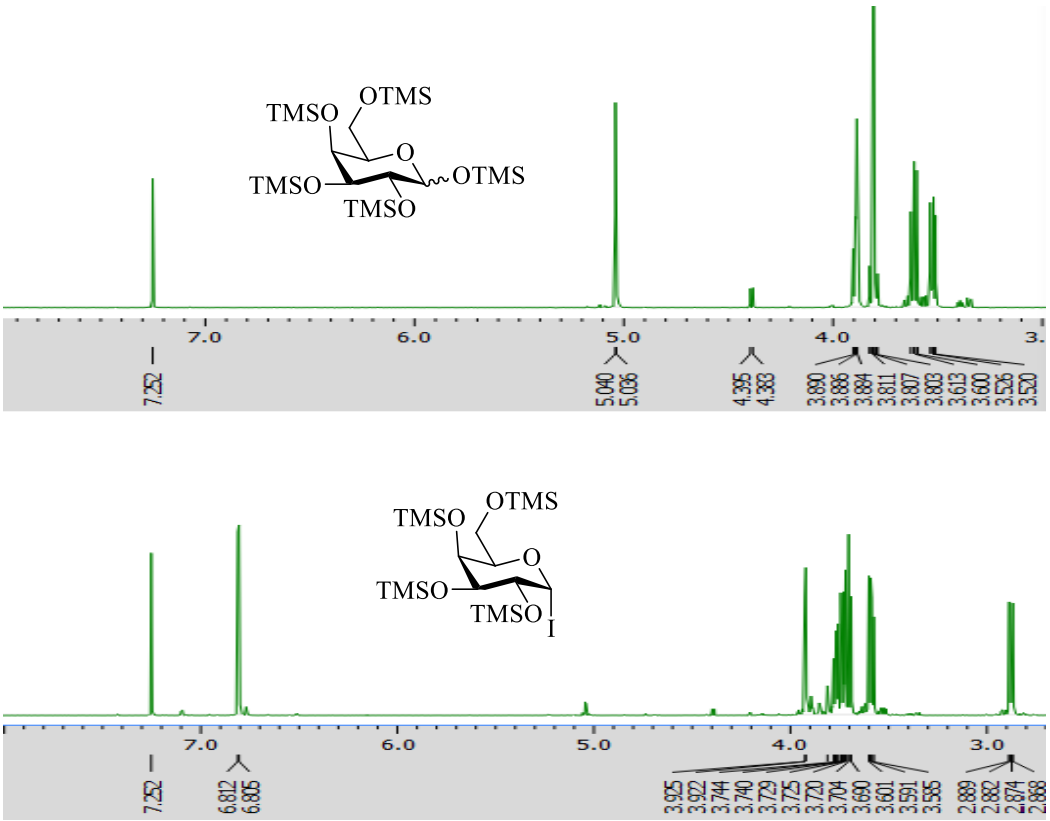


Figure 4C. ^{1}H NMR Spectra of Per-*O*-TMS-galactose and its iodide.

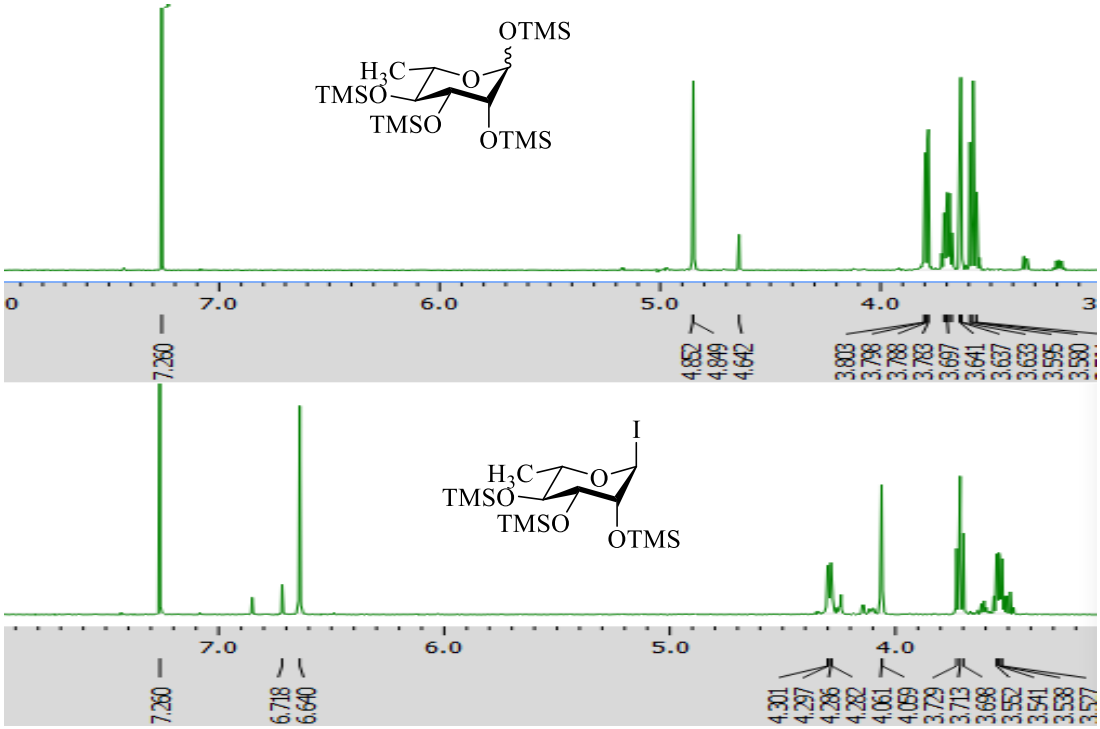


Figure 4D. ^{1}H NMR Spectra of Per-*O*-TMS-rhamnose and its iodide.

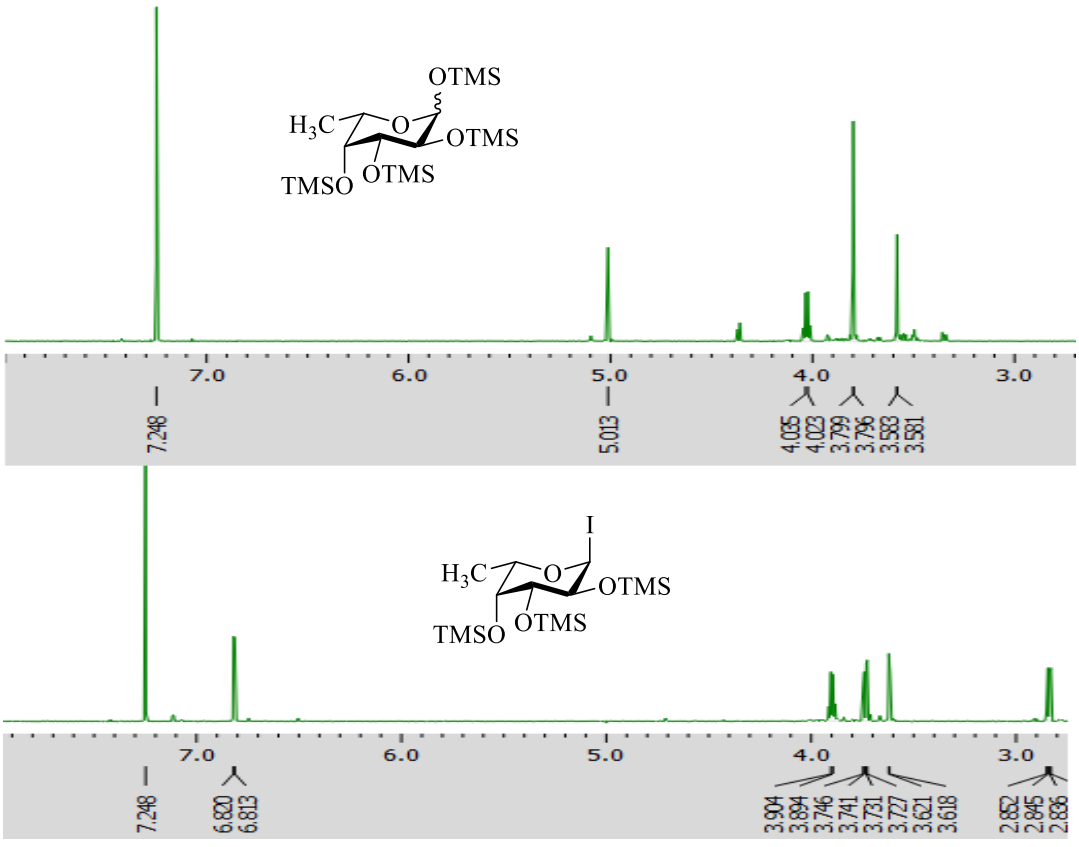


Figure 4E. ^{1}H NMR Spectra of Per-*O*-TMS-fucose and its iodide.

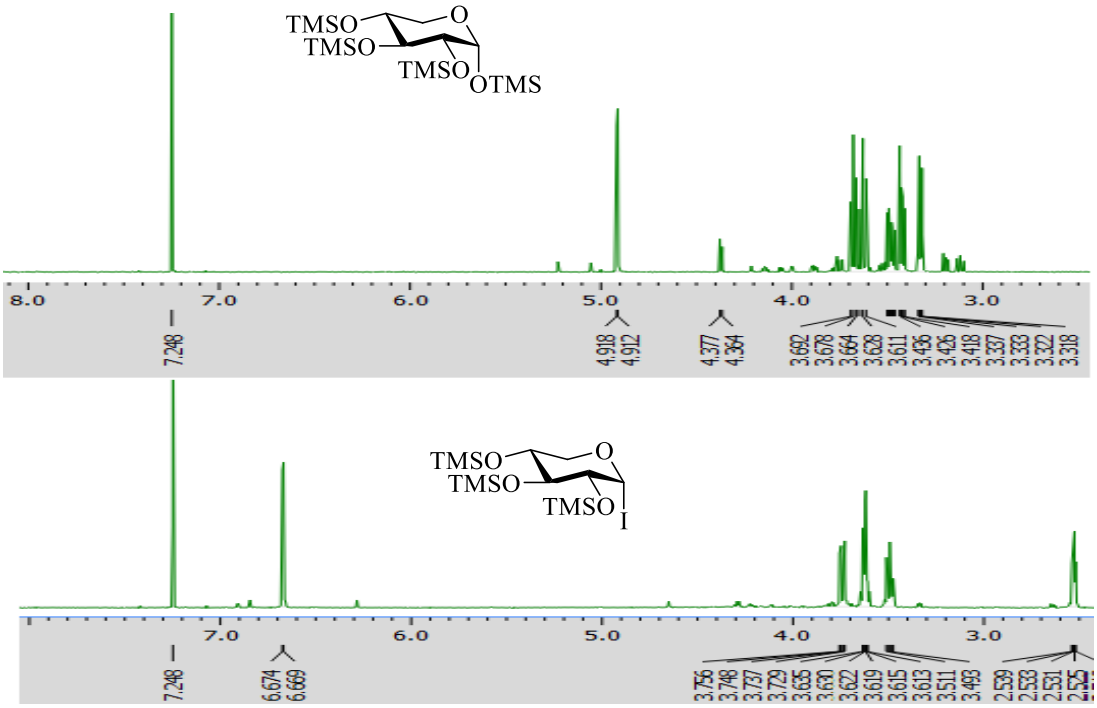
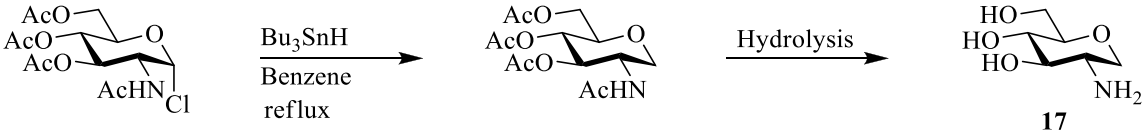


Figure 4F. ^{1}**H NMR Spectra of Per-*O*-TMS-xylose and its iodide.**

第2節　アミノ基を有する anhydroalditol 類の合成

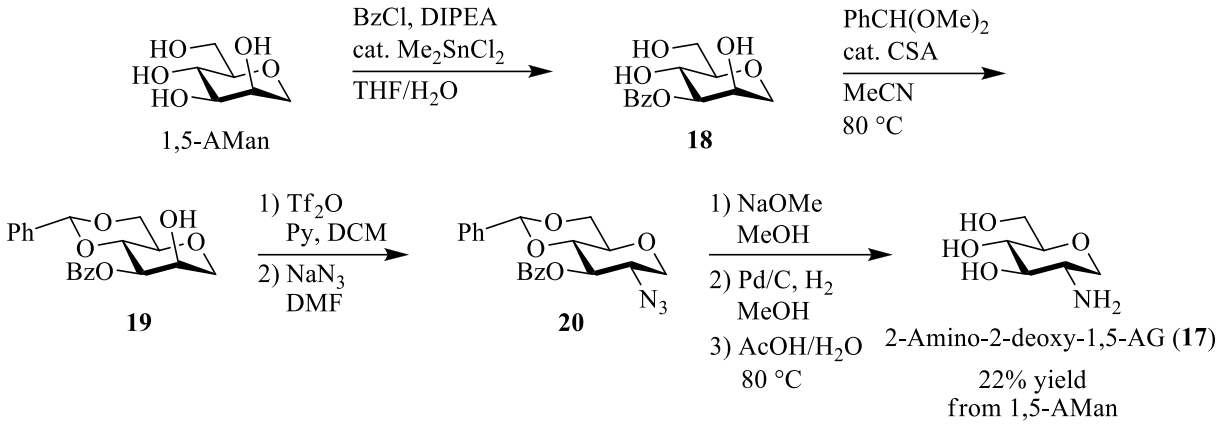
アミノ基を有する環状 polyol は、hexosamine biosynthesis pathway を阻害する生物活性物質[83]や不斉 aldol 反応の有機分子触媒[84]など機能性分子の building block として用いられている。Glucosamine（$GlcNH_2$）は容易に入手可能な化合物であるが、$GlcNH_2$ のもつ 2 位のアミノ基は、1 位の活性化をしばし困難にする[85]。既報[86]では、*N*-acetyl-glucosamine（NAcGlc）を出発物質に、glucosaminyl chloride へと活性化し、トリブチルスズを用いて還元することで 2-amino-2-deoxy-1,5-AG を合成している（Scheme 2）。しかし、トリブチルスズを用いなくてはならない点や*N*-Ac 基の加水分解後に得られる目的物の精製がしばし困難となる点に課題がある[87]。



17

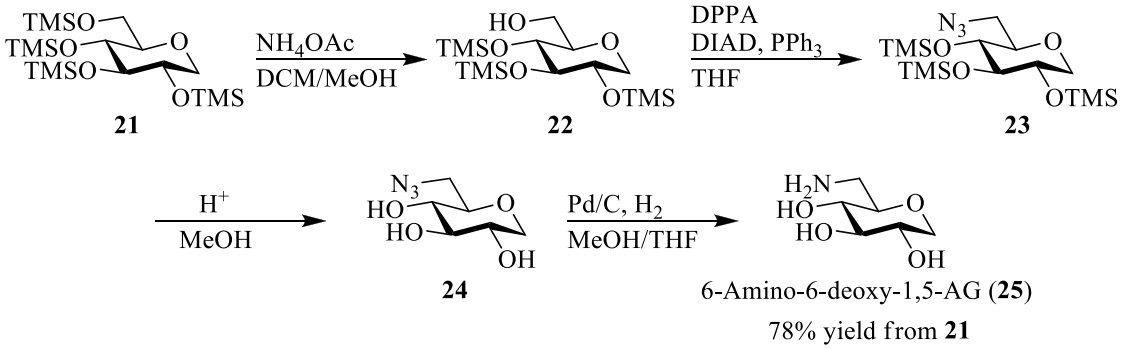
Scheme 2.　トリブチルスズを用いた 1-deoxy-glucosamin（17）の合成

そこで本研究では、1,5-AG を出発物質としてトリブチルスズを用いず、かつ *N*-Ac 体を経由しない新規 2-amino-2-deoxy-1,5-AG 合成法の確立を試みた。すなわち、アジド基の還元により目的とするアミノ基を有する anhydroalditol 類を得るという合成法を立案した。アジド基は後処理が容易な Pd/C, H_2 を用いて還元することで変換が可能である点に加え、アジド基を有する化合物は click ケミストリーの基質としての利用も期待される[88,89]。また、アジド基は 1,5-anhydroalditol 類のヒドロキシ基を官能基変換により導入することとした。立体反転によるアジド基導入を試みるため、出発物質として 2 位に axial-OH を有する 1,5-AMan を用いた。Y. Demizu らによって報告された Me_2SnCl_2 を用いた 3 位選択的 benzoyl 化を行なった（Scheme 3）[90]。本反応機構は、糖の 1,2-*cis*-diol に対して Sn が配位した後、立体的に空いているヒドロキシ基へ優先的に benzoyl 化が進行するものとされているが、1-deoxy 糖への適用は本研究が初めての試みである。予想どおり、3 位選択的に benzoyl 化が進行し 89%の収率で **18** を得た。続いて 4,6-*O*-benzylidene 保護を行ない、2 位のヒドロキシ基を triflate 化することで活性化、NaN_3 を用いる S_N2 反応によりアジド基を導入し **20** を得た。最後に脱保護および還元を行なうことで、目的とする 2-amino-2-deoxy-1,5-AG（**17**）を総収率 22%で得た。



Scheme 3. 2-Amino-2-deoxy-1,5-AG（17）の合成

次に、6 位にアミノ基を有する 1,5-AG 誘導体の合成を行なった（Scheme 4）。Silyl 化糖 **21** の 6 位選択的脱 silyl 化反応[91]により 6-OH 誘導体 **22** を得た。さらに、遊離したヒドロキシ基を、光延反応を用いてアジド基へと変換し、silyl 基を酸で脱保護することでアジド糖 **24** を得た。最後に、Pd/C、H_2 を用いてアジド基を還元することで、6-amino-6-deoxy-1,5-AG (**25**) を総収率 78%で得た。



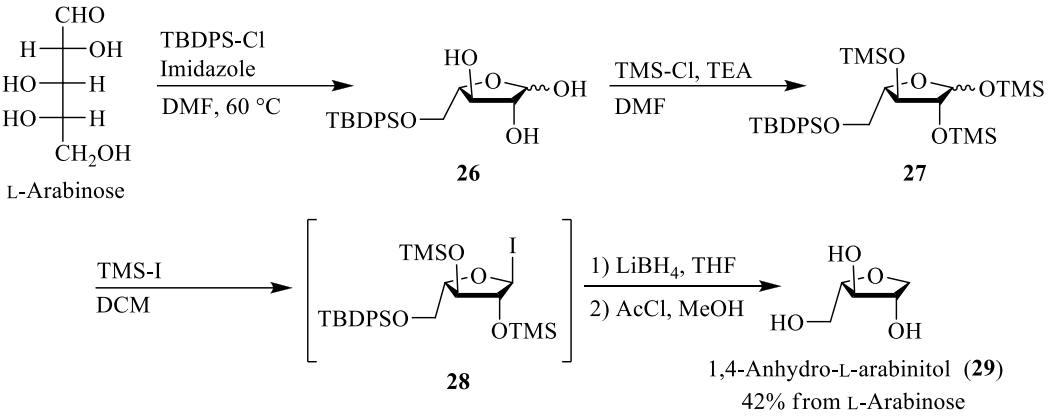
Scheme 4.　6-Amino-6-deoxy-1,5-AG（25）の合成

第3節　1,4-Anhydro-L-arabinitol の合成

五員環構造をもつ polyol は非天然型 gallotannin の polyol コアとして大変興味深い化合物である[92]。そこで、1 位ヘミアセタール性ヒドロキシ基をもたない furanose 型環状 polyol である anhydroalditol、すなわち 1,4-anhydroalditol の合成を試みた。L-Arabinose を pyridine 中 TMS-Cl を用いて *O*-TMS 保護を行なうと、pyranose 型を含む混合物が得られてしまうことから、まず、furanose 型のみに存在する 1 級のヒドロキシ基をかさ高いシリル基による選択的保護を行ない、furanose 型誘導体 **26** を得た（Scheme 5）。続いて残りのヒドロキシ基を

TMS 化した後、TMS-I を用いて L-arabinofranosyl iodide（**28**）へ活性化した。この活性中間体である L-arabinofranosyl iodide（**28**）の存在は、反応を ^{1}H NMR にて追跡することで生成していることが確認された（Figure 5）。最後に **28** を、$LiBH_4$ を用いて還元し、酸性条件下で *O*-TMS 基を脱保護することで、目的とする 1,4-anhydro-L-arabinitol（**29**）を総収率 42%で得た。

第4節　Anhydroalditol を有する二糖類の合成



Scheme 5. 1,4-Anhydroalabinitol の合成

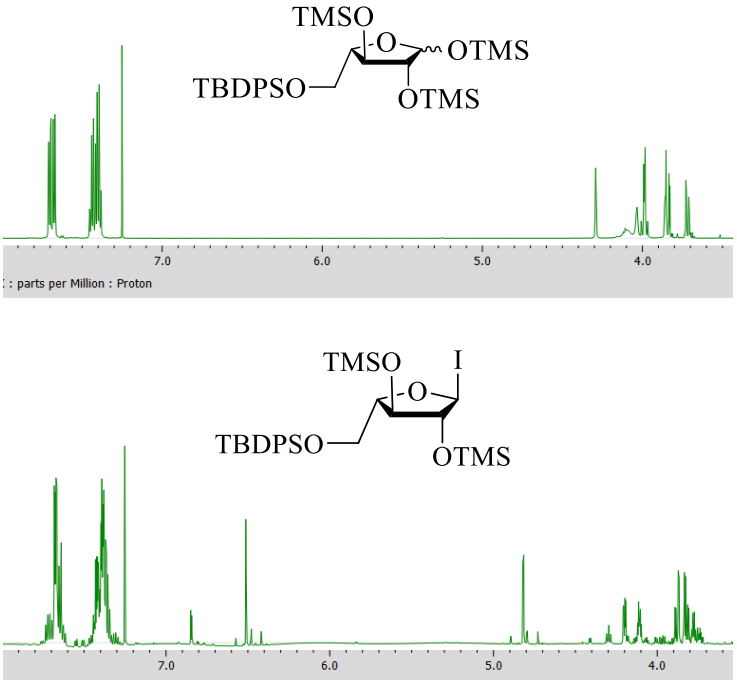
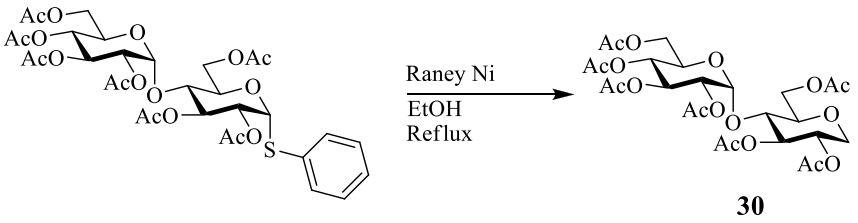


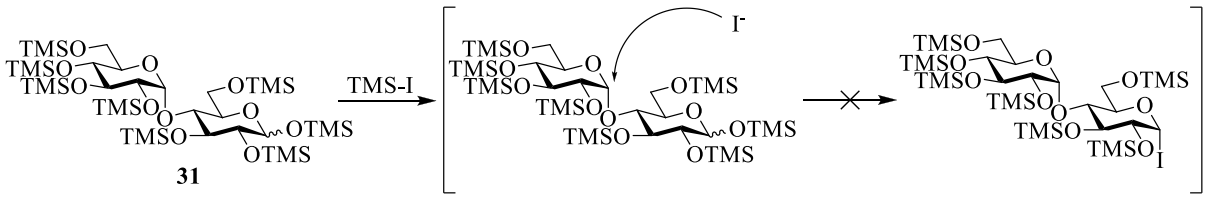
Figure 4.　L-Arabinofuranosyl iodide（28）の ^{1}H NMR スペクトル

Anhydroalditol を含むオリゴ糖は、1974 年に K. Takiura らによってセネガ（*polygala senega*）の根から発見されている [93,94]。また 2006 年には M-C. Cheng らによって、類似したオリゴ糖 polygalatenoside A と B がイトヒメハギ（*Polygala tenuifolia*）の根より単離されており [95]、2008 年に C-M. Huang らによって全合成がなされている [96]。Polygalatenoside は、Noradrenalin トランスポーターを阻害することで、抗抑うつ作用を持つ可能性が示唆されている [95]。単糖の 1,5-anhydro 糖類と比較し、二糖類以上の anhydro 糖類が合成された例は少ない。G. Li らは、glycosyl dithiocarbamate をラジカル還元することで、lactose、melibiose、chitobiose の 1-deoxy 体を得ている [78]。また、H. G. Fletcher らは、phenyl-thio glycoside を Raney-Ni を用いて還元することで、1,5-anhydrolactitol と 1-deoxy-maltose を得ているが、1-deoxy-maltose は精製が困難であったため詳細な物理データは提示されていない [97]。



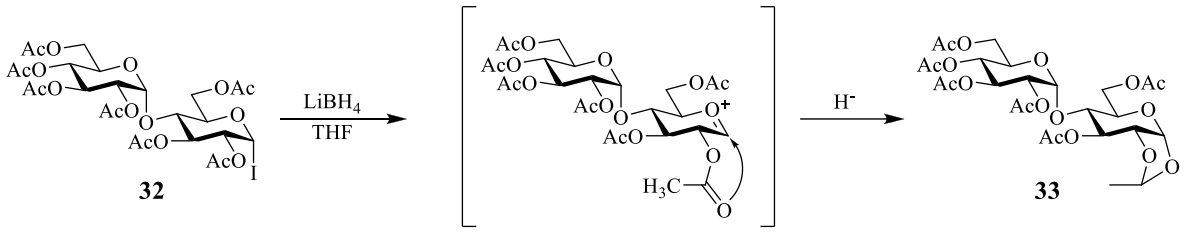
Scheme 6. H. G. Fletcher らによる maltose の 1-deoxy 化

Glycosyl halide は安価かつ容易に合成可能であるため、glycosyl halide を中間体として用いるオリゴ糖類の 1-deoxy 化法の確立は、1-deoxy オリゴ糖類の簡便入手に繋がる。そこで、単糖類と同様に *O*-TMS 保護をした D-maltose（**31**）を、TMS-I で活性化する方法を用いて検討したが、glucose 由来の分解物が得られ、目的物は得られなかった（Scheme 7）。ベンジル保護をされたα-glycoside 結合をもつ多糖類は、TMS-I によって非還元末端側の glycoside 結合が開裂してしまうことが知られている。同様な反応が起きたと考え、保護基を acetyl 基に変えて検討を行なった。



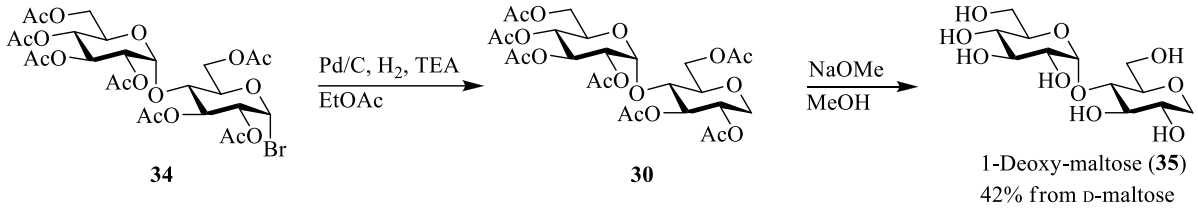
Scheme 7.　TMS-I による非還元末端グリコシド結合の開裂

容易に合成可能な per-*O*-Ac-maltosyl iodide（**32**）を、$LiBH_4$ を用いて還元を行ったところ、オルトエステルの還元体 **33** と思われる化合物が主生成物として得られた（Scheme 8）。より反応性が低い per-O-Ac-maltosyl bromide[98]（**34**）に変更して検討を行なったが、同様の生成物が得られたため、還元剤の再検討を行なった。



Scheme 8.　隣接基関与に伴うオルトエステル形成の推定機構

Pd/C、H_2 を用いた接触水素化による anhydroalditol の合成は少ないが、1956 年に Z. L. Zioudrou は per-*O*-Ac-cellobiosyl bromide を接触水素化することで対応する 1-deoxy 体を得ている [99]。重金属である Pd を用いなくてはならないが、水素源として水素ガスを用いることが出来る点や触媒で還元が行える点で優れているため、本方法を用いて検討を行なった（Scheme 9）。



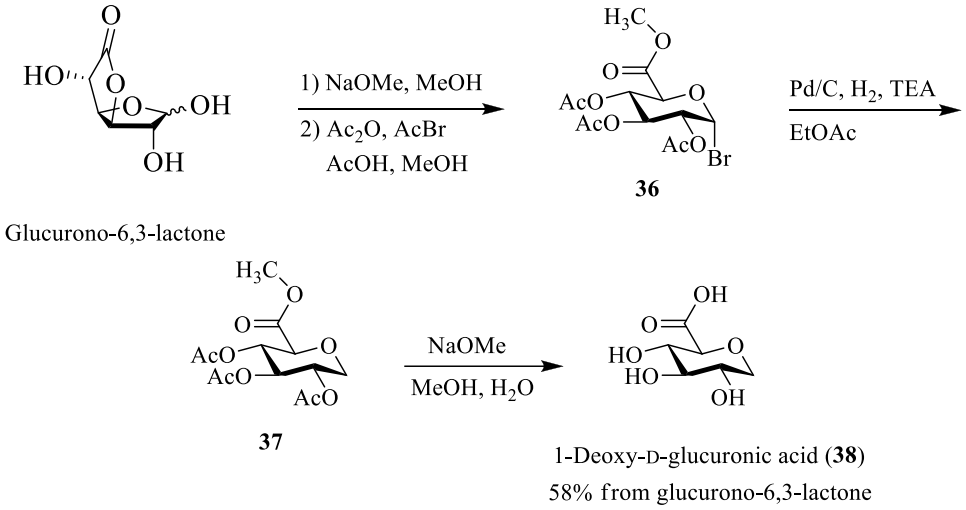
Scheme 9.　Pd/C，H_2 を用いた 1-deoxy-maltose の合成

Per-*O*-Ac-maltosyl bromide（**34**）を、TEA 存在下 Pd/C, H_2 を用いて接触水素化を行なうと、脱ハロゲン体 **30** が得られた。得られた **30** の Ac 基を加水分解することで、目的とする 1-deoxy-maltose（**35**）を総収率 42%で得た。

第5節　1-Deoxy-D-glucuronic acid の合成

1-Deoxy-D-glucronic acid（2,6-anhydro-L-gluconic acid）の合成は 1998 年に M. Dromowicz らによって、D-xylofranosyl nitromethane を原料に Nef reaction と類似したニトロ基の加水分解を行なうことで達成している [100]。今回は新たな合成法として、容易に合成可能な glycosyl halide を中間体とした合成法の確立を試みた。

初めに、D-glucuronic acid を原料に、per-*O*-TMS 化を行ない、TMS-I を用いて glycosyl iodide への活性化を試みたが、TMS-ester の分解が確認された。また、glycosyl halide を還元する際、$LiBH_4$ などを用いると 6 位のカルボキシ基も還元してしまう恐れがあるため、Pd/C、H_2 を用いた接触水素化による脱ハロゲン化を行なった（Scheme 10）。D-Glucurono-6,3-lactone より合成可能な glucuronyl bromide（**36**）を TEA 存在下、Pd/C, H_2 により脱ハロゲン化することで **37** を得た。脱ハロゲン化反応は、maltose での検討とは異なり副生成物はほとんど生じず良好に進行した。最後に得られた **38** を加水分解することで目的とする 1-deoxy-D-glucronic acid を総収率 58%で得た。



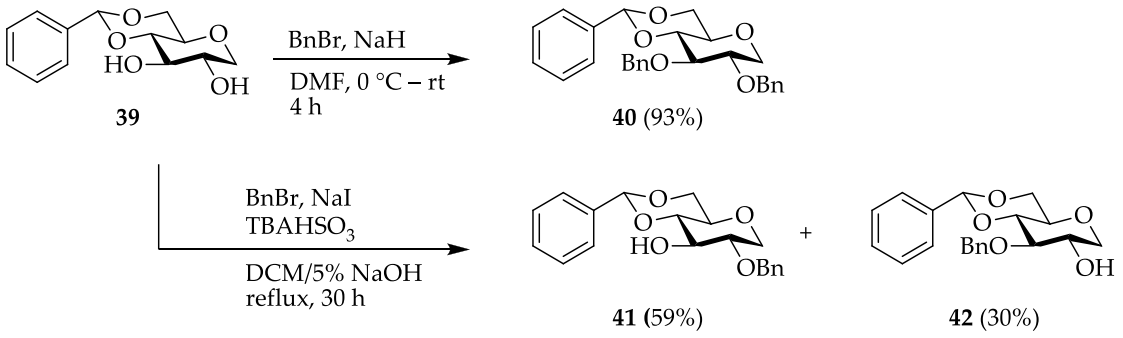
Scheme 10.　Pd/C を用いた 1-deoxy-glucuronic acid の合成

第二章 環状 polyol をコアにもつ gallotannin 及びその誘導体の合成

第1節　1,5-AG をコアにもつ gallotannin 類の網羅的合成

1,5-AG を polyol コアに有する gallotannin には、polyol コアに縮合する galloyl 基の数や位置が異なる類縁体が多く存在する。1,5-AG には 4 つのヒドロキシ基が存在し、そこに galloyl 基が 1〜4 個縮合する組み合わせは計 15 通り存在する。現在まで、9 種類の gallotannin（ginnalin A–C、Maplexin A–F）が発見されているが、3,4-di-*O*-galloyl-1,5-AG や 3,4,6-tri-*O*-galloyl-1,5-AG など、残りの 6 種類については天然より単離された報告は未だない。そこで、より詳細な構造活性相関の検討を行うため、1,5-AG を基盤とした天然・非天然を含むすべての組合せの gallotannin 類の網羅的合成法の確立を試みた。Gallotannin 類は、シリカゲル等への吸着力が強くカラム等で精製が困難であり、最終的な脱保護反応は高収率かつ後処理が容易である必要がある。そのためヒドロキシ基の保護基として、後処理が容易な Pd(OH)/C, H_2 を用いた接触水素化により除去可能な benzyl 基を選択した。また、糖のヒドロキシ基に結合したアシル基は、容易に隣接するヒドロキシ基へ転移する（acyl migration）ことが知られている。フェノール酸ユニットにおいても、長期保存下において同様な転移が起こる可能性を考え、polyol コア上の遊離のヒドロキシ基を benzyl 基等で保護することとした。すなわち、benzyl 基による保護を軸に polyol コアの位置選択的保護を行ない、カルボン酸ユニットを縮合させた後、Pd(OH)/C, H_2 を用いた benzyl 基の脱保護により目的物を得るという合成計画をデザインした。

まず、4,6-*O*-benzylidene-1,5-AG（**39**）を出発物質に、NaH、BnBr により benzyl 化することで化合物 di-*O*-benzyl 体 **40** を得た。次に、DCM/5%NaOH の 2 層系溶媒中で 1 当量の BnBr を反応させることで、2-*O*-Bn 体 **41** および 3-*O*-Bn 体 **42** をそれぞれ 59、30%で得た（Scheme 11）。

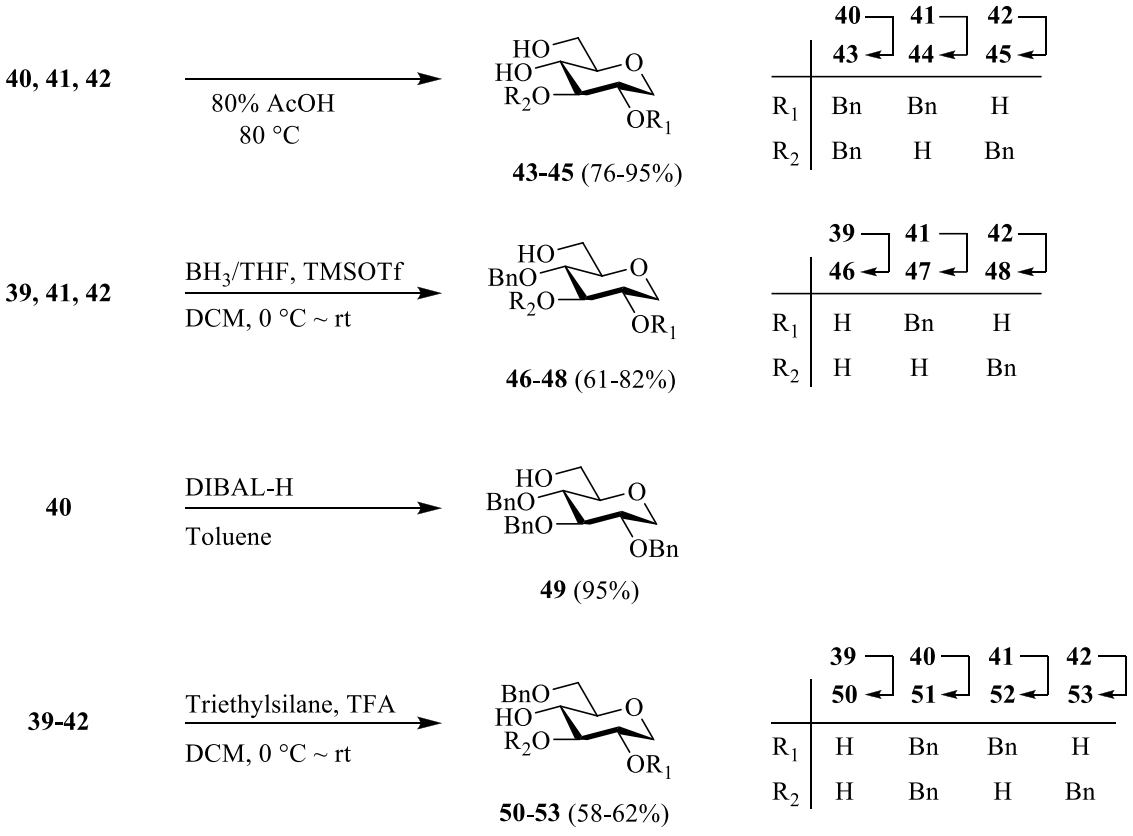


39　**40** (93%)　**41** (59%)　**42** (30%)

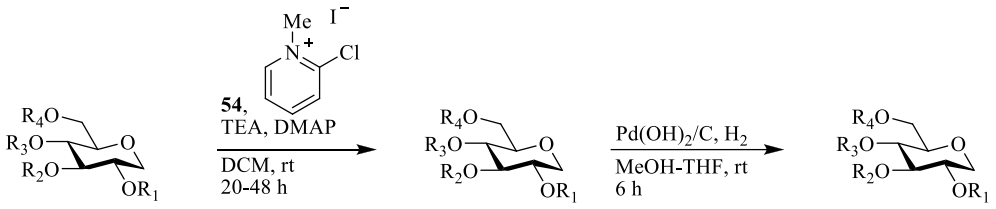
Scheme 11.　1,5-AG 上 2 位、3 位ヒドロキシ基の保護

続いて、**39–42** の選択的 benzylidene acetal の開裂反応を行なった（Scheme 12）。初めに、**40–42** を、80%AcOH を用いて 4,6-*O*-benzylidene の脱保護を行ない、4,6-diol 体 **43–45** を 76–95%で得た。また、**39**、**41**、**42** を TMSOTf 存在下、BH_3・THF、を用いて還元することで、6-OH 体 **46–48** を 61–82%で得た。一方、**40** を DIBAL-H を用いて還元することで、6-OH 体 **49** を 95%の収率で得た。さらに、**39–42** を TFA 存在下、TES を用いて還元することで、4-OH 体 **50–53** を 58–62%で得た。

得られた各中間体を benzyl 保護された gallic acid 誘導体 **54** と縮合させることで gallotannin 前駆体 **55–68** を得た。最後に、$Pd(OH)_2$/C、H_2 を用いて脱 benzyl 化を行なうことで、1,5-AG を polyol コアに有する、galloyl 基の結合位置、結合数が異なる 14 種類の組合せすべての gallotannin 類の網羅的合成を達成した（Scheme 13）。



Scheme 12.　4,6-*O*-Benzylidene の選択的開裂



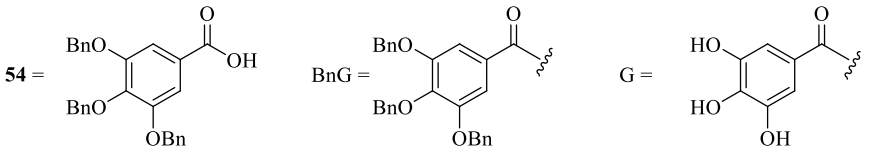
55-68 (41-92%)

1, 4-10, 69-73 (95-100%)

	R_1	R_2	R_3	R_4
42	H	Bn	Benzylidene	
41	Bn	H	Benzylidene	
51	Bn	Bn	H	Bn
49	Bn	Bn	Bn	H
39	H	H	Benzylidene	
53	H	Bn	H	Bn
48	H	Bn	Bn	H
52	Bn	H	H	Bn
47	Bn	H	Bn	H
43	Bn	Bn	H	H
50	H	H	H	Bn
46	H	H	Bn	H
45	H	Bn	H	H
44	Bn	H	H	H

	R_1	R_2	R_3	R_4
55	BnG	Bn	Benzylidene	
56	Bn	BnG	Benzylidene	
57	Bn	Bn	BnG	Bn
58	Bn	Bn	Bn	BnG
59	BnG	BnG	Benzylidene	
60	BnG	Bn	BnG	Bn
61	BnG	Bn	Bn	BnG
62	Bn	BnG	BnG	Bn
63	Bn	BnG	Bn	BnG
64	Bn	Bn	BnG	BnG
65	BnG	BnG	BnG	Bn
66	BnG	BnG	Bn	BnG
67	BnG	Bn	BnG	BnG
68	Bn	BnG	BnG	BnG

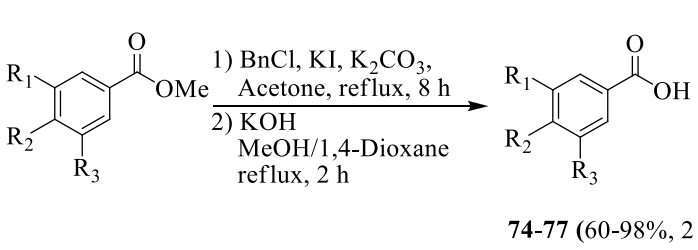
	R_1	R_2	R_3	R_4
4	G	H	H	H
5	H	G	H	H
6	H	H	G	H
3	H	H	H	G
7	G	G	H	H
8	G	H	G	H
1	G	H	H	G
69	H	G	G	H
70	H	G	H	G
71	H	H	G	G
72	G	G	G	H
10	G	G	H	G
9	G	H	G	G
73	H	G	G	G



Scheme 13.　1,5-AG を polyol コアに有する gallotannin 類の合成

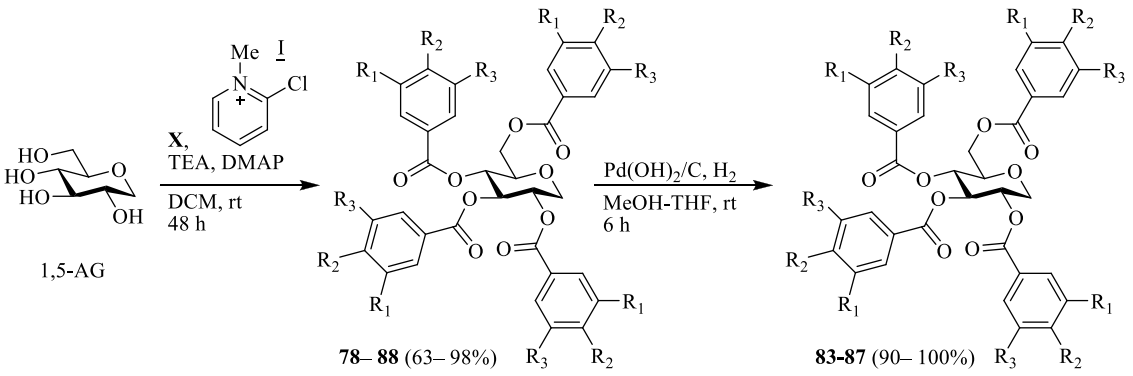
第2節　**異**なるフェノール酸ユニットを有する誘導体の合成

フェノール性ヒドロキシ基の位置や数などが生物活性に与える影響は flavonoid などを中心に盛んに研究が行われており[101]、gallotannin に含まれる gallic acid は連続する 3 つのフェノール性ヒドロキシ基を有していることから、その数や位置の異なる化合物が活性に与える影響については興味のもたれるところである。実際に、maplexin F と vanillic acid が縮合した maplexin I で大きく生物活性が異なることが報告されている[29]。そこで、本研究ではフェノール性ヒドロキシ基の違いが生物活性に与える影響を検討するため、gallic acid とフェノール性ヒドロキシ基の位置や数が異なる誘導体の合成に取り組んだ。まず、methyl protocatechuate、methyl resorcylate、methyl 3-hydrozybenzoate、methyl 4-hydrozybenzoate をそれぞれ原料に、benzyl 保護および加水分解することで、フェノール酸誘導体 **74**–**77** を得た（Scheme 14）。得られた誘導体を 1,5-AG と縮合した後、脱 benzyl 化することで目的とするフェノール性ヒドロキシ基の位置や数が異なる誘導体 **83**–**87** を得た（Scheme 15）。



	R_1	R_2	R_3
74	OBn	OBn	H
75	OBn	H	OBn
76	OBn	H	H
77	H	OBn	H

Scheme 14.　フェノール酸誘導体の合成



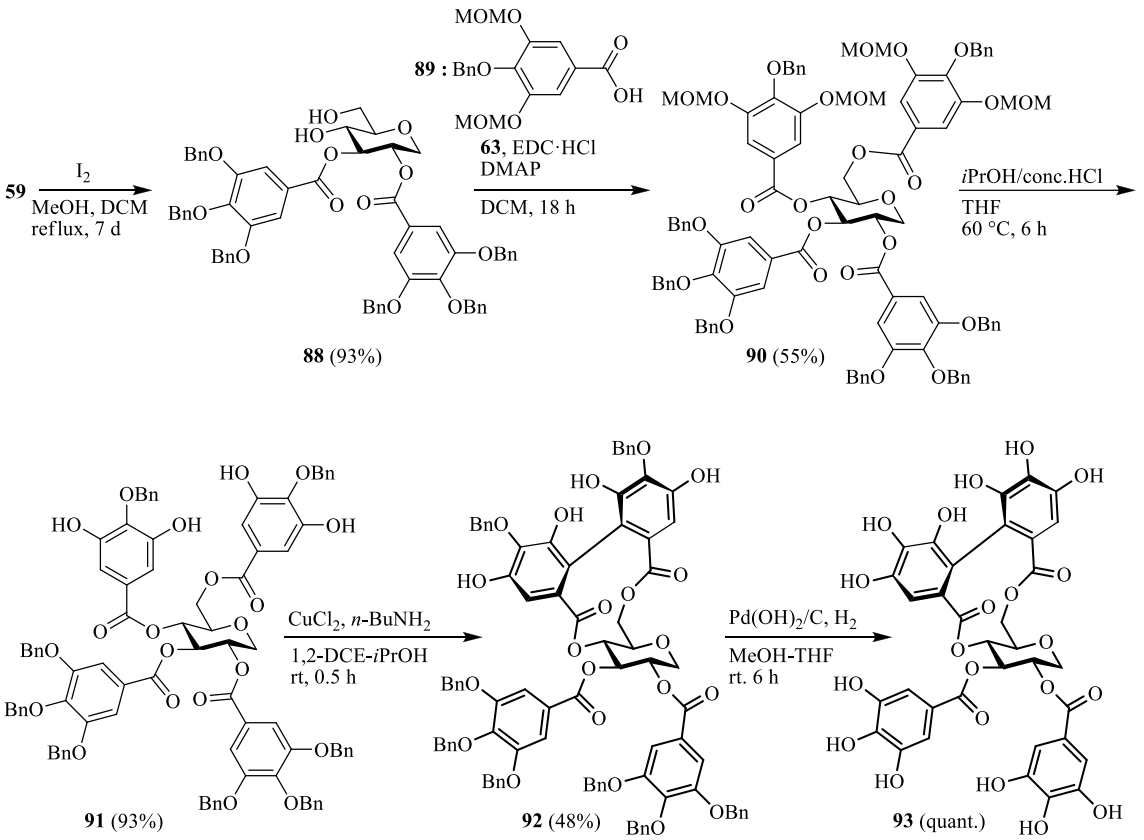
	X	R_1	R_2	R_3
78	**54**	OBn	OBn	OBn
79	**74**	OBn	OBn	H
80	**75**	OBn	H	OBn
81	**76**	OBn	H	H
82	**77**	H	OBn	H

	R_1	R_2	R_3
83	OH	OH	OH
84	OH	OH	H
85	OH	H	OH
86	OH	H	H
87	H	OH	H

Scheme 15.　フェノール性ヒドロキシ基の位置や数が異なる gallotannin 誘導体の合成

第3節　Ellagitannin 誘導体の合成

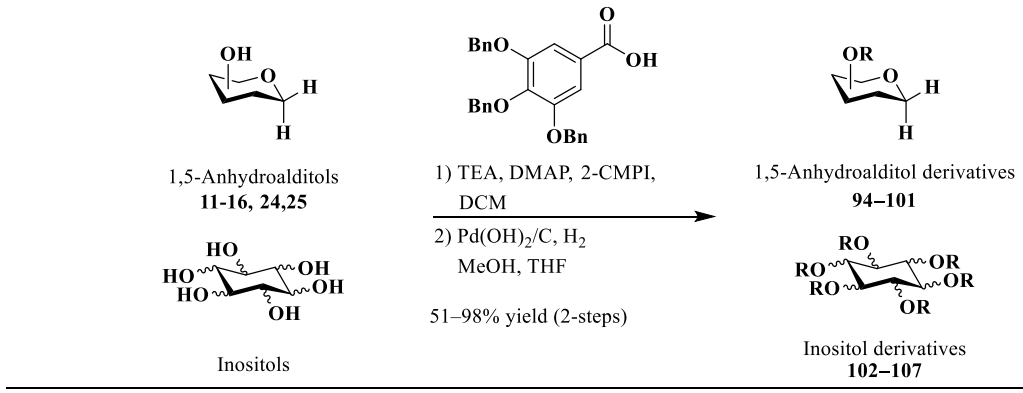
Ellagitannin は HHDP と呼ばれる特徴的なマクロラクトン構造を分子内に有しており、HHDP 基は生物活性発現に重要な官能基として着目されている[102,103]。HHDP 基の化学的構築法は K. S. Feldman や H. Yamada らによって開発され、多くの ellagitannin の全合成を達成している[104–107]。そこで本研究では、D-glucose を polyol コアにもつ ellagitannin の一種である tellimagrandin I に着目し、1,5-AG を出発原料として用いることで 1 位ヘミアセタール性ヒドロキシ基を欠いた 1-deoxy-tellimagrandin I の合成を試みた。先に得た gallotannin 前駆体 **59** を MeOH 中、I_2 を用いて 4,6-*O*-benzylidene を脱保護し 4,6-diol 体 **88** を得た。続いて gallic acid 誘導体 **89** を縮合させ、MOM 基を酸性条件下で脱保護し **91** を得た。**91** を H. Yamada らによる $CuCl_2$, *n*$BuNH_2$ を用いた酸化的カップリング反応により、HHDP 基の構築を行なった。最後に、$Pd(OH)_2/C$, H_2 による脱 benzyl 化を行なうことで、1,5-anhydroalditol を polyol コアに有する新規 ellagitannin 誘導体 **93** の合成に成功した（Scheme 16）。

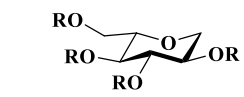


Scheme 16.　1,5-AG を polyol コアに有する ellagitannin 誘導体の合成

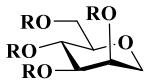
第4節　多様な polyol をコアにもつ gallotannin 誘導体の合成

Gallotannin は、polyol コア由来の立体配置によっても生物活性が異なることが報告されている。例えば、E. G. Doyagüez らは、galactofuranose や trehalose などを polyol コアに有する gallotannin 誘導体を合成し、per-*O*-galloyl-β-mannopyranose が PGG など他の誘導体よりも強力に capillary morphogenesis gene-2 protein に結合し、血管新生抑制を示すことを明らかにした[92]。また Feldman らは、化学的に合成された天然には存在しない hexa-*O*-galloyl-*myo*-inositol が PGG や tellimagrandin I などの gallotannin と比べ、より強く bovine serum albumin と複合体を形成することを報告している[108]。本研究では、1,5-AG 以外の 1,5-anhydroalditol 類（*ent*-1,5-AG、1,5-AMan、1,5-AGal、1,5-AXyl、1,5-ARha、1,5-AFuc）、窒素原子を有する 6-azido-6-deoxy-1,5-AG および 6-amino-6-deoxy-1,5-AG、さらに glucopyranose や 1,5-AG と同様に 6 員環構造を有する inositol 類（*allo*-、D-*chiro*-、L-*chiro*-、*epi*-、*scyllo*-、*muco*-、*myo*-）を polyol コアに有する gallotannin 誘導体の合成を行なった（Scheme 17）。各種 polyol を DCM 中、gallic acid 誘導体 **54** と 2-CMPI を用いて縮合させた。*scyllo*-Inositol においては、他の inositol 類と同様に DCM を溶媒に用いて縮合を行なうと収率が著しく低かった（20% yield）。さらに、カラムよる精製が困難であったため、反応溶媒を DMF に変え、さらに対応する gallic acid 誘導体 **54** の量を検討することで収率の改善を図ることができた（Scheme 18）。最後に $Pd(OH)_2/C$, H_2 にて脱 benzyl 化を行なうことで、目的とする各種 gallotannin 誘導体、すなわち、1,5-AG と立体配置の異なる誘導体 **94**–**96**、galloyl 基を 3 つ有する糖誘導体 **97**–**99**、6 位に amino 基を有する誘導体 **100**、amide 結合を有する誘導体 **101**、galloyl 基を 6 個有する inositol 誘導体 **102–108** を良好な総収率（51–98%）で得ることができた。

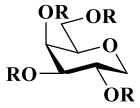




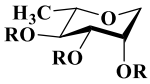
Per-*O*-galloyl-*ent*-1,5-AG (**94**)



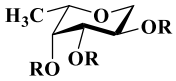
Per-*O*-galloyl-1,5-AMan (**95**)



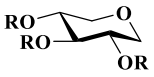
Per-*O*-galloyl-1,5-AGal (**96**)



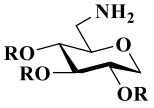
Per-*O*-galloyl-1,5-ARha (**97**)



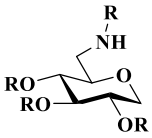
Per-*O*-galloyl-1,5-AFuc (**98**)



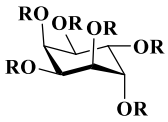
Per-*O*-galloyl-1,5-AXyl (**99**)



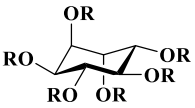
6-Amino-2,3,4-*O*-galloyl-1,5-AG (**100**)



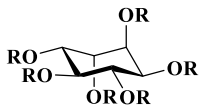
6-*N*-Galloyl-2,3,4-*O*-galloyl-1,5-AG (**101**)



Per-*O*-galloyl-*allo*-inositol (**102**)

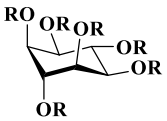


Per-*O*-galloyl-D-*chilo*-inositol (**103**)

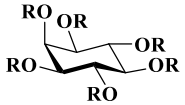


Per-*O*-galloyl-L-*chilo*-inositol (**104**)

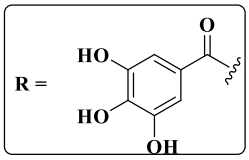
Per-*O*-galloyl-*epi*-inositol (**105**)



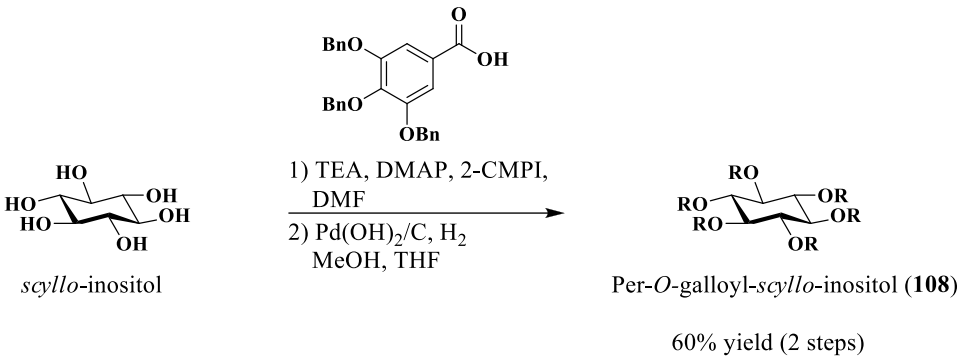
Per-*O*-galloyl-*muco*-inositol (**106**)



Per-*O*-galloyl-*myo*-inositol (**107**)



Scheme 17.　Polyol コアの構造が異なる gallotannin 誘導体の合成



scyllo-inositol

Per-*O*-galloyl-*scyllo*-inositol (**108**)

60% yield (2 steps)

Scheme 18.　*syllo*-Inositol 誘導体の合成

第三章 環状 polyol をコアにもつ gallotannin 及びその誘導体の抗酸化活性と α-glucosidase 阻害活性評価

第1節　抗酸化活性の評価

Gallic acid のアルキルエステルは酸化防止剤として広く用いられている。Gallotannin も同様に gallic acid のエステルであり、gallotannin 類の有する優れた抗酸化活性がどのような構造に基づくものなのかを明らかにすることができれば、新しい抗酸化剤の開発が期待できる。そこで、本研究において構築した gallotanninn 類の化合物ライブラリーを用いて、網羅的に抗酸化活性の評価を行なった。抗酸化活性は広く用いられている DPPH ラジカル消去能を用いて評価した[109–111]。

3.1.1.　方法

96-well マイクロプレートに 50%EtOH で調製した試料（0.1–1000 μg/mL）および control として trolox（40–160 μg/mL）溶液 100 mL、MES 緩衝液（200 mM、pH 6.0）50 mL、EtOH で調製した DPPH（800 mM）溶液 50 mL を加え、遮光下 20 分間振盪した。Blank は、DPPH を 50%EtOH に置き換えたものを用いた。試験は n = 3、triplicate で行なった。反応終了後、520 nm の吸光度を測定した。さらに、x 軸に sample の濃度、y 軸に 520 nm の吸光度をとり、回帰直線を求め、EC_{50} を以下の式を用いて算出した（式 1）。

$$\text{Effective percentages (\%)} = 1 - \frac{\text{As}}{\text{Ab}} \times 100$$

・・・（式 1）

As は、sample の吸光度、Ab は blank の吸光度を表す。

また、得られた回帰曲線の傾きと Trolox の回帰曲線の傾きから Trolox-equivalent（TE）を算出した（式 2）。

$$\text{Trolox-equivalent (mol-trolox/mol-sample)} = \frac{\text{Ss}}{\text{St}}$$

・・・（式 2）

Ss は sample の傾き、St は trolox の傾きを表す。TE は、trolox の何倍強い抗酸化活性を示したかを表す。

Table 1. Results of Antioxidative activities.

Sample	EC_{50} (μM)	TE	Sample	EC_{50}(μM)	TE
Methyl gallate	19.6 ± 0.1	2.42 ± 0.27	Per-*O*-galloyl-1,5-AG (**83**)	6.81 ± 0.17	6.87 ± 0.55
Methyl protocatechuate	21.1 ± 1.1	2.20 ± 0.05	Per-*O*-galloyl-*ent*-1,5-AG (**94**)	7.12 ± 0.80	5.62 ± 0.72
Methyl resorcylate	nd	-	Per-*O*-(3-hydroxybenzoyl)-1,5-AG (**86**)	78<	-
Methyl 3-hydroxybenzoate	nd	-	Per-*O*-(4-hydroxybenzoyl)-1,5-AG (**87**)	78<	-
Methyl 4-hydroxybenzoate	nd	-	Per-*O*-protocatechuyl-1,5-AG (**84**)	6.99 ± 0.11	6.54 ± 0.15
2-*O*-Galloyl-1,5-AG (**4**)	19.4 ± 1.02	2.04 ± 0.08	Per-*O*-resorcylyl-1,5-AG (**85**)	70<	-
3-*O*-Galloyl-1,5-AG (**5**)	20.5 ± 2.05	2.38 ± 0.24	2,3,4,6-Tetra-*O*-galloyl-Glc	5.60 ± 0.28	8.33 ± 0.49
4-*O*-Galloyl-1,5-AG (**6**)	20.8 ± 1.54	2.09 ± 0.19	1-Deoxy-tellimagrandin I (**93**)	6.79 ± 0.21	6.44 ± 0.24
6-*O*-Galloyl-1,5-AG (**3**)	22.9 ± 1.61	2.13 ± 0.12	Tellimagrandin I	6.31 ± 0.27	7.04 ± 0.37
2,3-Di-*O*-galloyl-1,5-AG (**7**)	11.3 ± 1.0	4.29 ± 0.23	2,3,4-*O*-6-*N*-Galloyl-1,5-AG (**101**)	5.46 ± 0.68	8.15 ± 0.42
2,4-Di-*O*-galloyl-1,5-AG (**8**)	14.3 ± 0.3	3.36 ± 0.13	Per-*O*-galloyl-1,5-AMan (**95**)	6.99 ± 0.06	7.57 ± 0.45
2,6-Di-*O*-galloyl-1,5-AG (**1**)	15.2 ± 0.5	3.32 ± 0.37	Per-*O*-galloyl-1,5-AGal (**96**)	7.16 ± 0.10	7.01 ± 0.57
3,4-Di-*O*-galloyl-1,5-AG (**69**)	14.8 ± 0.6	3.55 ± 0.42	PGG	5.90 ± 0.51	8.07 ± 0.44
3,6-Di-*O*-galloyl-1,5-AG (**70**)	11.9 ± 0.7	3.67 ± 0.19	Casarictin	4.55 ± 0.09	10.0 ± 0.8
4,6-Di-*O*-galloyl-1,5-AG (**71**)	13.0 ± 1.1	3.78 ± 0.33	Eugeniin	4.58 ± 0.11	9.78 ± 1.04
2,3,4-Tri-*O*-galloyl-1,5-AG (**72**)	7.94 ± 0.39	5.59 ± 0.26	Per-*O*-galloyl-*allo*-inositol (**102**)	5.12 ± 0.15	9.53 ± 1.03
2,3,6-Tri-*O*-galloyl-1,5-AG (**10**)	8.09 ± 0.41	5.75 ± 0.18	Per-*O*-galloyl-D-*chiro*-inositol (**103**)	5.37 ± 0.43	8.09 ± 0.04
2,4,6-Tri-*O*-galloyl-1,5-AG (**9**)	10.3 ± 0.8	4.31 ± 0.35	Per-*O*-galloyl-L-*chiro*-inositol (**104**)	5.12 ± 0.54	8.91 ± 0.54
3,4,6-Tri-*O*-galloyl-1,5-AG (**79**)	8.48 ± 0.21	5.36 ± 0.20	Per-*O*-galloyl-*epi*-inositol (**105**)	6.00 ± 0.49	7.22 ± 0.16
2,3,4-Tri-*O*-galloyl-6-amino-1,5-AG (**100**)	8.16 ± 0.32	5.34 ± 0.31	Per-*O*-galloyl-*scyllo*-inositol (**108**)	4.24 ± 0.27	10.1 ± 0.4
Per-*O*-galloyl-1,5-ARha (**97**)	9.06 ± 0.58	5.88 ± 0.31	Per-*O*-galloyl-*muco*-inositol (**106**)	5.46 ± 0.19	8.89 ± 0.92
Per-*O*-galloyl-1,5-AFuc (**98**)	9.88 ± 0.42	4.96 ± 0.30	Per-*O*-galloyl-*myo*-inositol (**107**)	6.80 ± 0.82	7.20 ± 0.83
Per-*O*-galloyl-1,5-AXyl (**99**)	10.0 ± 0.4	4.93 ± 0.54	Tannin acid	2.84 ± 0.05	16.2 ± 1.7
Strictinin	11.6 ± 0.6	4.10 ± 0.32	Trolox	51.08 ± 2.26	-

[a] IC_{50} data represents mean ± S.D. of n = 3.

3.1.2.　結果

抗酸化活性を比較すると、galloyl ユニットの数に比例して、強い抗酸化活性を示す結果が得られた。フェノール酸の methyl ester 類を比較すると、methyl gallate と methyl protocatechuate は同程度の抗酸化活性（EC_{50} = 19.6、21.1 μM、TE = 2.42、2.20）を示したが、methyl resorcylate 及び methyl hydroxybenzoate は抗酸化活性を示さなかった。また、galloyl 基を 1 つ有する誘導体 **3**–**6** も methyl gallate と同程度の抗酸化活性（19.4–22.9 μM、TE = 2.04–2.38）を示し、galloyl 基を 2 つ有する誘導体 **1**, **7**, **8**, **69**–**71** は、galloyl 基を 1 つもつ誘導体より 1.5–1.8 倍近い活性（EC_{50} = 11.3–15.2 μM、TE = 3.32–4.29）を示した。次いで galloyl 基を 3 つ有する誘導体 **9**, **10**, **72**, **97**–**100**（EC_{50} = 7.94–10.3 μM、TE = 4.31–5.88）、galloyl 基を 4 つ有する誘導体 **83**, **94**–**96**（EC_{50} = 6.81–7.16 μM、TE = 5.62–7.57）と galloyl 基の数の増加に伴い抗酸化活性は強くなった。フェノール性ヒドロキシ基 1 つしか持たない誘導体 **86**, **87** および resorcylyl 誘導体 **85** はメチルエステル同様抗酸化活性を示さなかったが、protocatechuyl 誘導体 **84** は、**83** と同程度の抗酸化活性を示した（EC_{50} = 6.99 μM、TE = 6.54）。このことから抗酸化活性を示すには、隣接したフェノール性ヒドロキシ基が必要であることが示された。HHDP 基をもつ tellimagrandin I、**93** と HHDP 基を持たない 2,3,4,6-tetra-*O*-galloyl-glucose、**83** を比較すると 2,3,4,6-tetra-*O*-galloyl-glucose がやや強い活性を示した（EC_{50} = 6.31–6.81 μM、TE = 6.44–6.87 *vs* EC_{50} = 5.60 μM、TE = 8.33）。また、6 位にアミド結合をもつ誘導体も活性が高く、galloyl 基を 5 個有する PGG と同程度であった（EC_{50} = 5.46 μM、TE = 8.15 *vs* EC_{50} = 5.90 μM、TE = 8.07）。さらに、PGG と HHDP 基をもつ casuarictin、eugeniin を比較すると、HHDP 基をもつものがより強い活性を示した（EC_{50} = 5.90 μM、TE = 8.07 *vs* EC_{50} = 4.55, 4.88 μM、TE = 10.0, 9.78）。一方、galloyl 基を 5 個有する化合物と 6 個有する inositol 誘導体 **102**–**108** の間では、抗酸化活性に差が見られなくなった（EC_{50} = 4.24–6.80 μM、TE = 7.20–10.1）。総合的には、galloyl 基を 10 個有する tannic acid が最も強い活性（EC_{50} = 2.84 μM、TE = 16.2）を示した。一方で、polyol コアに galloyl 基が縮合するにつれ galloyl 基 1 つあたりの抗酸化活性は低下した。すなわち、methyl gallate もしくは mono-galloyl 誘導体 **3**–**6** が最も効率的な抗酸化活性を示した。また、その galloyl 基の結合位置による活性の差はみられなかった。Galloyl 基が 2 つになっても、抗酸化活性は mono-galloyl 誘導体 **3**–**6** の 2 倍にはならず 1.5–1.8 倍程度であり、同様に、tannic acid においても 7–8 倍程度の抗酸化活性示した。

今回評価を行なった化合物は高い水溶性が特徴である。効率のよい抗酸化作用を示した mono-galloyl 誘導体の polyol コア上には 3 つの遊離のヒドロキシ基が存在する。そこに脂肪酸などを付加することで脂溶性の向上など、さらなる機能性の付与が可能と考えられる。ま

た、anhydroalditol 類はアルデヒド基を持たないことから褐変現象などを起こさず安定である。これら gallotannin 類は新規抗酸化剤の素材として、さらなる研究の発展が期待される。

第2節　α-Glucosidase 阻害活性の評価

食後高血糖は、食後に現れる持続した血糖値の上昇のこと指し、インスリン分泌や感受性の低下が原因とされ、脳梗塞や心血管イベントに繋がる。食事は 1 日に複数回、毎日繰り返されるため食後高血糖の予防は重要である。食後高血糖を抑制する医療用医薬品として miglitol や voglibose、acarbose などのα-glucosidase 阻害薬が用いられている。また、医薬品以外にも 1-deoxy-nojirimycin を含有するエキス（桑の葉エキス）や重合タンニンを含有するグァバ茶エキスなどが食後の血糖値の上昇を抑える機能性表示食品や特定保健用食品に用いられている。

α-Glucosidase 阻害活性評価は、yeast 由来のα-glucosidase を用いる場合、*p*-nitrophenyl glucoside（pNPG）を基質に酵素反応を行なう方法が一般的である。一方、ヒトと同じく哺乳類に分類される rat 小腸由来の酵素を用いた報告も多く、酵素の起源の違いにより活性が異なることが知られているため、他の研究との比較および構造活性相関の評価が困難となっているのが現状である。そこで本研究では、よりヒトに近い rat 由来のα-glucosidase を用いて検討を行ない、活性を示した化合物については yeast 由来のα-glucosidase を用いても検討を行ない、併せて評価することとした。

3.2.1.　α-Glucosidase 阻害活性の測定

Rat 由来のα-glucosidase を用いた検討は購入可能な kit を用いて測定した。2.0 mL エッペンドルフチューブに各濃度の sample（0.5–1000 μg/mL in water）25 μL、D-maltose 溶液（18.5 mM in 100 mM maleic anhydride solution、pH 6.0）50 μL を加え、37 ℃ で 3 分間加温浸透する。続いて、α-glucosidase 酵素液 25 μL を加え正確に 37 ℃ で 30 分間加温振盪した。反応終了後、直ちに水 400 μL を加え沸騰水で 3 分間煮沸した。冷後、96-well に反応液 100 μL および、LabAssay^{TM} glucose 溶液 150 μL を加え、37 ℃ で 10 分間反応させた（triplicate）。反応終了後、直ちにマイクロプレートリーダーで 505 nm の吸光度を測定した。対照化合物として acarbose（0.5–8.0 μL/mL）を用いた。酵素液を加えた後、直ちに煮沸を行なったものを blank、sample 溶液を水に置き換え試験したものを control とした。得られた吸光度から算出した D-glucose 量を y 軸に、sample の各濃度を x 軸にプロットし、回帰曲線を得た。得られた回帰曲線から以下の式を用いて IC_{50} を算出した（式 3）。

$$\text{Inhibition percentage (\%)} = 1 - \frac{\text{As} - \text{Ab}}{\text{Ac}} \times 100$$

・・・（式 3）

ここで As は sample の吸光度、Ab は blank の吸光度、Ac は control の吸光度を表す。

96-well に、各濃度の sample 溶液（1000–0.5 μg/mL in 0.1 M phosphate buffer、pH 6.8）50 μL および α-glucosidase 溶液（0.1 U/mL in 0.1 M phosphate buffer, pH 6.8）100 μL を加え、25 °C で 6 分間振盪させた。次に pNPG 溶液（5 mM in 0.1 M phosphate buffer, pH 6.8）50 μL を加え、25 °C で 10 分間振盪させた。反応終了後、直ちにマイクロプレートリーダーで 405 nm の吸光度を測定した。対象化合物として acarbose（100–5000 μg/mL）を用いた。Sample 溶液を 0.1 M phosphate buffer に置き換え、試験したものを control とした。また、x 軸に sample の濃度、y 軸に 405 nm の吸光度をプロットし、回帰曲線を求めた。得られた回帰曲線より、以下の式を用いて IC_{50} を算出した（式 3）。

$$\text{Inhibition percentage}\ (\%) = \frac{\text{Ac} - \text{As}}{\text{Ac}} \times 100$$

・・・（式 4）

Ac は control、As は sample の吸光度を表す。

Table 2. Results of α-glucosidase inhibitory activities. IC_{50} (μM)

Sample	Rat[a]	Yeast[b]	Sample	Rat[a]	Yeast[b]
Methyl gallate	90.5 ± 7.0	-	Per-*O*-galloyl-1,5-AG (**83**)	2.59 ± 0.03	1.06 ± 0.04
Methyl protocatechuate	300<<		Per-*O*-galloyl-*ent*-1,5-AG (**94**)	2.30 ± 0.10	1.17 ± 0.15
Methyl resorcylate	300<<		Per-*O*-(3-hydroxybenzoyl)-1,5-AG (**86**)	nd	-
Methyl 3-hydroxybenzoate	660<<		Per-*O*-(4-hydroxybenzoyl)-1,5-AG (**87**)	nd	-
Methyl 4-hydroxybenzoate	660<<		Per-*O*-protocatechuyl-1,5-AG (**84**)	3.28 ± 0.16	-
2-*O*-Galloyl-1,5-AG (**4**)	95.1 ± 0.2	-	Per-*O*-resorcylyl-1,5-AG (**85**)	9.34 ± 0.02	-
3-*O*-Galloyl-1,5-AG (**5**)	137 ± 1	-	2,3,4,6-Tetra-*O*-galloyl-Glc	1.68 ± 0.21	-
4-*O*-Galloyl-1,5-AG (**6**)	143 ± 1	-	1-Deoxy-tellimagrandin I (**93**)	3.22 ± 0.51	-
6-*O*-Galloyl-1,5-AG (**3**)	127 ± 1	-	Tellimagrandin I	3.37 ± 0.04	-
2,3-Di-*O*-galloyl-1,5-AG (**7**)	20.5 ± 0.5	-	2,3,4-*O*-6-*N*-Galloyl-1,5-AG (**101**)	4.41 ± 0.79	0.557 ± 0.101
2,4-Di-*O*-galloyl-1,5-AG (**8**)	48.3 ± 1.3	-	Per-*O*-galloyl-1,5-AMan (**95**)	5.19 ± 1.21	0.626 ± 0.011
2,6-Di-*O*-galloyl-1,5-AG (**1**)	35.6 ± 2.6	-	Per-*O*-galloyl-1,5-AGal (**96**)	2.88 ± 0.28	1.67 ± 0.05
3,4-Di-*O*-galloyl-1,5-AG (**69**)	91.4 ± 6.6	-	PGG	0.336 ± 0.040	0.211 ± 0.033
3,6-Di-*O*-galloyl-1,5-AG (**70**)	55.0 ± 8.8	-	Casarictin	10.1 ± 0.2	0.226 ± 0.004
4,6-Di-*O*-galloyl-1,5-AG (**71**)	26.6 ± 2.4	-	Eugeniin	1.04 ± 0.21	0.245 ± 0.072
2,3,4-Tri-*O*-galloyl-1,5-AG (**72**)	6.72 ± 0.21	-	Per-*O*-galloyl-*allo*-inositol (**102**)	0.811 ± 0.178	0.166 ± 0.006
2,3,6-Tri-*O*-galloyl-1,5-AG (**10**)	5.34 ± 0.55	-	Per-*O*-galloyl-D-*chiro*-inositol (**103**)	0.659 ± 0.216	0.137 ± 0.003
2,4,6-Tri-*O*-galloyl-1,5-AG (**9**)	9.34 ± 0.99	-	Per-*O*-galloyl-L-*chiro*-inositol (**104**)	1.75 ± 0.09	0.137 ± 0.002
3,4,6-Tri-*O*-galloyl-1,5-AG (**79**)	12.6 ± 0.6	-	Per-*O*-galloyl-*epi*-inositol (**105**)	1.20 ± 0.21	0.149 ± 0.003
2,3,4-Tri-*O*-galloyl-6-amino-1,5-AG (**100**)	5.76 ± 0.39	2.89 ± 0.413	Per-*O*-galloyl-*muco*-inositol (**106**)	0.921 ± 0.045	0.121 ± 0.016
Per-*O*-galloyl-1,5-ARha (**97**)	4.53 ± 0.10	7.20 ± 0.90	Per-*O*-galloyl-*myo*-inositol (**107**)	1.20 ± 0.03	0.110 ± 0.016
Per-*O*-galloyl-1,5-AFuc (**98**)	20.3 ± 0.5	4.06 ± 0.52	Tannin acid	0.866 ± 0.176	0.183 ± 0.013
Strictinin	72.6 ± 18.0	1.74 ± 0.81	Acarbose	0.113 ± 0.030	312.1 ± 9.8

[a]IC_{50} data represents mean ± S.D. of n = 2. [b]IC_{50} data represents mean ± S.D. of n = 3.

3.2.1.　結果

Rat 由来α-glucosidase 阻害活性では、galloyl 基の数が増えるにつれ、α-glucosidase 阻害活性が強くなる傾向がみられたが、galloyl 基の数以外にも、polyol コアの立体などによりさらに阻害活性が変化した（Table 2）。

まず、フェノール酸メチルエステル類のα-glucosidase 阻害活性を比較すると、興味深いことに methyl gallate のみが rat 由来α-glucosidase 阻害活性を示し（IC_{50} = 90.5 μM）、methyl hydroxybenzoate や methyl resorcylate、抗酸化活性を示した methyl protocatechuate は阻害活性を示さなかった。Galloyl 基を 1 つ有する誘導体 **3**–**6** はいずれも methyl gallate よりも弱い活性を示した（IC_{50} = 95.1–143 μM *vs* IC_{50} = 90.5 μM）。*In vivo* でα-glucosidase 阻害活性による高血糖抑制効果が示唆されている acertannin（**1**）を含む galloyl 基を 2 個有する誘導体 **7**, **8**, **69**–**71** を比較すると、3,4-di-galloyl 誘導体 **69** は、methyl gallate 程度の阻害活性であった（IC_{50} = 91.4 μM）。一方、2,3-di-galloyl 誘導体 **7**（IC_{50} = 20.5 μM）と 4,6-di-galloyl 体 **71**（IC_{50} = 26.6 μM）は methyl gallate よりも 4 倍以上の阻害活性を示し、**1**（IC_{50} = 35.6 μM）よりも強力であった。Galloyl 基を 3 つ有する誘導体 **9**, **10**, **72**, **79** はさらに強く、methyl gallate の 10 倍以上強い活性を示すものもあった（IC_{50} = 5.34–12.6 μM vs 90.5 μM））。また、2 位、3 位に galloyl 基を有する誘導体 **7**, **10**, **72** が持たない誘導体と比べ、阻害活性が強い傾向が見られた。

Polyol コアの構造が異なる tri-galloyl 誘導体 **97**, **98**, **100** を比較すると、6-amino 誘導体 **100** は、1,5-AG コアの誘導体と同程度の活性（IC_{50} = 5.76 μM）を示した。6 位に methyl 基をもち 2 位が axial の配置を有する 1,5-ARha 誘導体 **97** も、**10** などの tri-galloyl 誘導体と比べ若干強い活性を示したが、4 位が axial の 1,5-AFuc 誘導体 **98** は活性が低下し（IC_{50} = 20.3 μM）、di-galloyl 誘導体 **7** 程度の阻害活性を示した。また、D-glucose を polyol コアにもち、ellagitannin の 1 種である strictinin は著しく阻害活性が低下し（IC_{50} = 72.6 μM）、mono、di-galloyl 誘導体相応の阻害活性を示した。

Galloyl 基を 4 個有する誘導体を比較すると、per-*O*-galloyl-1,5-AG **83** は、tri-*O*-galloyl 誘導体 **9**, **10**, **72**, **79** より強い阻害活性（IC_{50} = 2.59 μM）を示した。生物活性物質は、enantiomer 間に大きな活性の違いが見られることがあるが、**83** の enantiomer である **94** は同程度の活性（IC_{50} = 2.30 μM）を示した。1,5-AG をコアに有する ellagitannin 誘導体 **93** は、HHDP 基を持たない **83** より弱い阻害活性を示した（IC_{50} = 20.5 μM *vs* 2.59 μM）。Polyol コアとして D-glucose をもち、1 位に遊離のヘミアセタール性ヒドロキシ基をもつ 2,3,4,6-tetra-*O*-galloyl-glucose は、**83** より強い阻害活性を示した（IC_{50} = 1.68 μM *vs* 2.59 μM）。一方、2,3,4,6-tetra-*O*-galloyl-glucose の 4 位と 6 位の galloyl 基が酸化的カップリングした ellagitannin である tellimagrandin I の阻害活性は、**83** より弱いものであった（IC_{50} = 3.37 μM vs 2.59 μM）。6 位

にアミド結合をもつ誘導体 **101** および 1,5-AMan 誘導体 **95** は rat 由来のα-glucosidase 阻害活性が低下し、galloyl 基を 3 つしか持たない 1,5-ARha 誘導体 **97** 程度の阻害活性であった（IC_{50} = 4.41、5.19 μM *vs* 4.53 μM）。また、1,5-AGal 誘導体 **96** は、 **83** と同程度の阻害活性を示した（IC_{50} = 2.88 μM）。

異なる phenol ユニットをもつ誘導体 **84**–**87** では、抗酸化活性同様 hydroxybenzoyl 誘導体 **86**、**87** はα-glucosidase 阻害活性を示さなかった。Methyl protocatechuate は阻害活性をほとんど示さなかったが、polyol コアに縮合することで活性を示し、protocatechuyl 誘導体 **84** は **83** に匹敵する活性を示した（IC_{50} = 3.28 μM）。さらに、抗酸化活性も示さなかった resorcylyl 誘導体 **85** も同様に polyol コアに縮合することで、阻害活性を示すようになったが（IC_{50} = 9.34 μM）、**84** よりは弱かった。

Galloyl 基を 5 個有する PGG と、PGG の 4,6-HDDP 体である eugeniin、2,3-,4,6-di-HDDP 体である casuarictin を比較すると、PGG が最も強い活性を示した（IC_{50} = 0.336 μM）。HHDP 基を 1 つ有する eugeniin はやや阻害活性が低下したが galloyl 基を 4 つ有する誘導体よりも高い活性（IC_{50} = 1.04 μM）を示した。興味深いことに HHDP 基を 2 つ持つ casuarictin は著しく阻害活性が低下した（IC_{50} = 10.1 μM）。同様に HHDP 基を有する strictinin や tellimagrandin I ならびに **93** においても、HHDP 基をもたない化合物に比して阻害活性が低下していることから、HHDP 基は、α-glucosidase 阻害活性を減弱させることが示唆された。

Galloyl 基を 6 個有する inositol 誘導体 **102–107** の阻害活性を比較すると、*chiro*-D-inositol 誘導体 **103** が最も強い活性を示す一方、*chiro*-L-inositol 誘導体 **104** は最も弱い活性を示し、enantiomer 間で差が見られた（IC_{50} = 0.659 μM *vs* 1.75 μM）。他の誘導体 **102**, **105–107** は、PGG 以下の阻害活性を示し、eugeniin と同程度であった（IC_{50} = 8.11–1.20 μM）。最も強い抗酸化活性を示した tannic acid は、galloyl 基の数から想像されるほど活性は強くなく、*allo*-inositol 誘導体 **102** と同程度の活性を示した（IC_{50} = 0.866 μM）。

1,5-AXyl 誘導体 **99** および *scyllo*-inositol 誘導体 **108** は、分子内対称性を有しており水に対する溶解度が非常に小さいため、10%DMSO に溶解したものをサンプルとして用いて評価を行なった（Table 3）。DMSO を用いて検討を行なうと、水のみを用いて行なった検討と比較しIC_{50}値はやや大きい値を示した（**83**；rat IC_{50} = 2.74 μM vs 2.59 μM、yeast IC_{50} = 1.53 μM vs 1.06 μM）。1,5-AXyl 誘導体 **99** および *scyllo*-inositol 誘導体 **108** 共に、3 個もしくは 6 個 galloyl 基を有する誘導体と同程度の活性を示した（IC_{50} = 4.89 μM, 2.82 μM））。

Table 3. Results of α-glucosidase inhibitory activities. IC_{50} (μM)

Sample[a]	Rat[b]	Yeast[c]
Per-*O*-galloyl-1,5-AXyl (**99**)	4.89 ± 0.29	4.72 ± 0.48
Per-*O*-galloyl-*scyllo*-inositol (**108**)	2.82 ± 0.43	0.200 ± 0.011
Per-*O*-galloyl-1,5-AG (**83**)	2.74 ± 0.08	1.53 ± 0.04
Acarbose	0.163 ± 0.010	455.2 ± 3.9

[a]Dissolved in 10% DMSO. [b]IC_{50} data represents mean ± S.D. of n = 2. [c]IC_{50} data represents mean ± S.D. of n = 3.

Gallotannin 類の rat 由来α-glucosidase 阻害における構造活性相関の検討より以下の点が示唆された。①フェノール性ヒドロキシ基を 1 つしか持たない誘導体は阻害活性を示さなかったことから、少なくとも 2 つのフェノール性ヒドロキシ基が活性発現に必要である。②1,5-AG より、D-glucose を polyol コアに有する誘導体が強い活性を示し、糖コア上の 1 位の存在が活性発現に寄与する可能性が示唆された。③同様に Inositol より、D-glucose を polyol コアに有する誘導体が比較的強い活性を示し、polyol 環の酸素原子の存在が重要であることが示唆された。また、6 個以上の galloyl 基は活性向上に寄与しない可能性が示唆された。④Amide 結合や HHDP 基など、分子構造を堅くする構造があると活性が低下する傾向が見られ、分子挙動の自由度が活性向上に重要である。

次に、yeast 由来の酵素を用いて行なったα-glucosidase 阻害活性について比較すると、rat 由来の酵素を用いた場合と同様に galloyl 基の数が増えるにつれ、活性が向上した。しかし、rat 由来のα-glucosidase を最も強く阻害した PGG は、yeast 由来のα-glucosidase を用いると inositol 誘導体より低い阻害活性を示した（IC_{50} = 0.211 μM vs 0.110–0.166 μM）。一方、tannic acid は PGG よりやや低い阻害活性を示した（IC_{50} = 0.183 μM）。

Polyol コアによる違いを比較すると、rat 由来のα-glucosidase を用いた場合とは異なる結果が得られた。Galloyl 基を 4 つ有する誘導体では、アミド結合をもつ誘導体 **101** が最も強い阻害活性を示した。また、enantiomer である **83**、**94** の間には差は無く（IC_{50} = 1.06、1.17 μM）、1,5-AMan 誘導体 **95** は他の tetra-galloyl 誘導体より強い阻害活性を示し（IC_{50} = 0.626 μM）、1,5-AGal 誘導体 **96** は **95** の半分以下の阻害活性を示した（IC_{50} = 1.67 μM）。また、1,5-ARha 誘導体 **97** は、1,5-AFuc 誘導体 **98** より活性が低下した（IC_{50} = 7.20 μM *vs* 4.06 μM）。

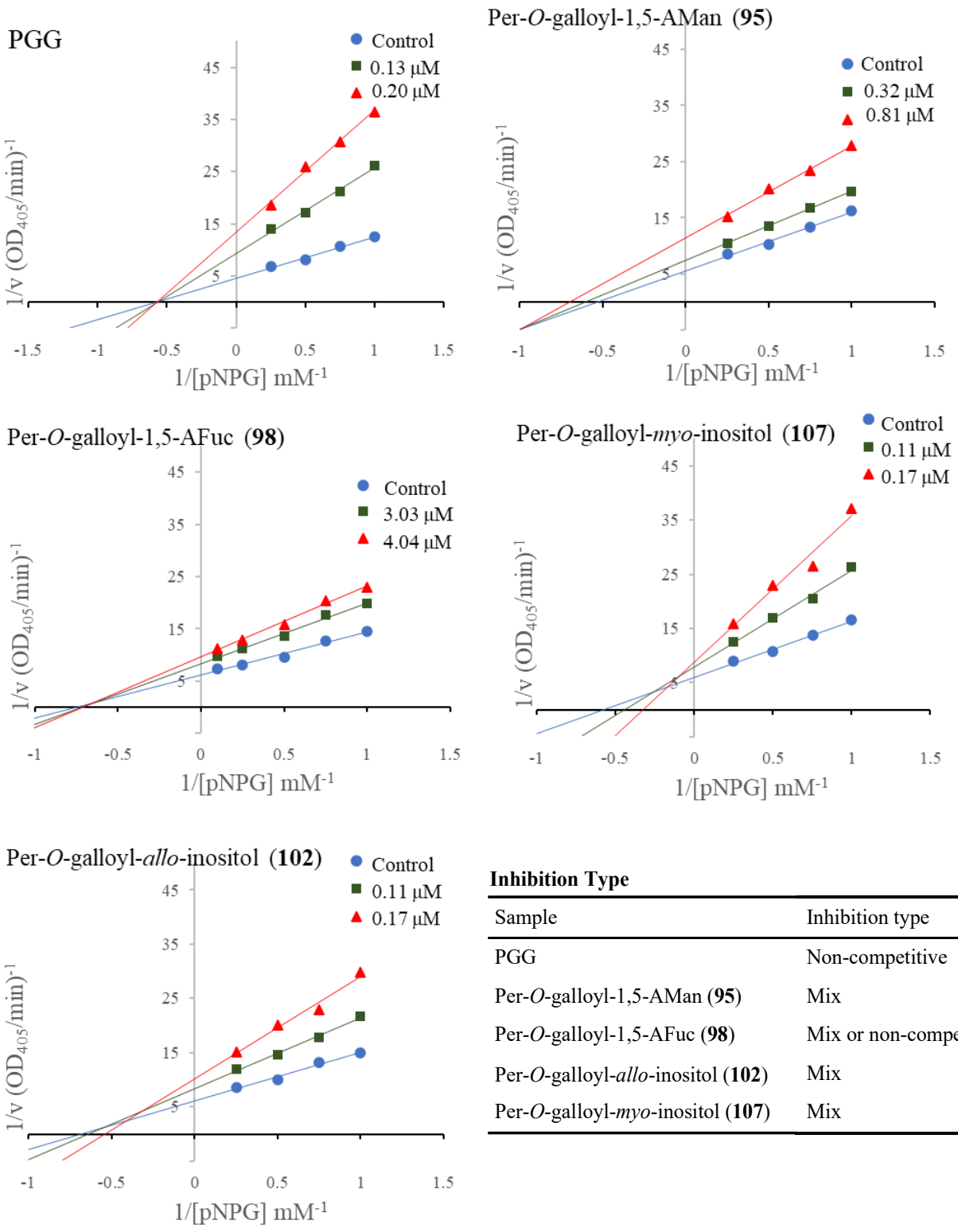
Rat 由来のα-glucosidase を用いた検討では、HHDP 基の有無により阻害活性に大きな差が

見られたが、yeast 由来のα-glucosidase においては、阻害活性に差は見られなかった。Galloyl 基を 3 つ有する化合物の中では、strictinin が最も強い阻害活性（IC_{50} = 1.74 μM）を示し、PGG、casuarictin、eugeniin とも全て同程度の阻害活性を示した（IC_{50} = 0.211–0.245 μM）。

Inositol 誘導体 **102–108** を比較すると、polyol コアの構造の違いにより阻害活性に僅かに差が見られたものの、1,5-anhydroalditol 誘導体に見られたような大きな差は見られなかった。Tannic acid は inositol 誘導体と同程度以下の阻害活性を示した（IC_{50} = 0.183 μM）。今回検討を行なった gallotannin 類の中では、*myo*-inositol 誘導体が最も強い阻害活性（IC_{50} = 0.110 μM）を示した。

Yeast 由来のα-glucosidase を用いた検討から得られた結果をまとめると、以下の点が示唆された。①Galloyl 基の数が増えるにつれ阻害活性は強くなったが、inositol 誘導体と tannic acid の間に大きな差は見られなかった。②1,5-anhydroalditol 誘導体では polyol コアにより差が見られ、阻害活性の強弱は rat 由来のα-glucosidase を用いた場合とは大きく異なった。③HHDP 基や amide 基などの分子を堅くする構造があっても活性は低下しなかった。G. Cao らは PGG と tannic acid を含む gallotannin の *Saccharomyces cerevisiae*（yeast）由来のα-glucosidase を用いた *in vitro* 試験、およびマウスを用いた *in vivo* 試験を行ない、興味深い結果を報告している [112]。*In vitro* 試験結果では、本研究による結果と同様に PGG と tannic acid が同程度の活性を示しているが、マウスを用いた *in vivo* 試験では、PGG が他の gallotannin の中で最も強い活性を示しており、本検討の rat 由来のα-glucosidase 用いた阻害活性結果と類似していた。

最後に、yeast 由来のα-glucosidase、基質に pNPG を用いて、Lineweaver-Burk plot を作成し阻害様式の検討を行った。PGG は非競合型阻害を、**83** は混合型阻害を示すことが報告されており、基質結合部位ではなくアロステリック部位に結合すると考えられている [58]。検討の結果、1,5-AFuc 誘導体 **98** を除き、x 軸、y 軸で交点を作らない混合型のグラフを与え、**83** と同様の混合型阻害を示した（Figure 6）。



Inhibition Type

Sample	Inhibition type
PGG	Non-competitive
Per-*O*-galloyl-1,5-AMan (**95**)	Mix
Per-*O*-galloyl-1,5-AFuc (**98**)	Mix or non-competitive
Per-*O*-galloyl-*allo*-inositol (**102**)	Mix
Per-*O*-galloyl-*myo*-inositol (**107**)	Mix

Figure 5.　本検討で用いた gallotannin 類の阻害様式の検討

結語

本論文は、新規 gallotannin 誘導体を網羅的に合成し、gallotannin 類の構造多様性が抗酸化活性およびα-glucosidase 阻害活性に与える影響を比較検討したものである。

第一章では、環状ポリオール類として着目した各種 1,5-anhydroalditol 類やアミノ基を有する 1,5-AG 誘導体、五員環構造を有する 1,4-anhydro-L-arabinitol、anhydroalditol を含む二糖、および 1-deoxy-D-glucuronic acid の合成法について詳述した。

第二章では、第一章において合成された環状ポリオール類を基盤とした新規化合物 20 種を含む計 36 種類の gallotannin 類のデザインと合成法および化合物ライブラリーについて詳述した。

第三章では、天然由来 gallotannin や ellagitannin を含む計 47 種類の化合物ライブラリー化合を用いて、抗酸化活性およびα-glucosidase 阻害活性を評価し、構造と活性の相関を明らかにした。

本研究における鍵化合物である 1,5-anhydroalditol 類は、豊富な立体配置を有する化合物群とみなすこともできることから、生物活性物質のみならず機能性分子、有機分子触媒などへの開発研究が期待される。本研究ではその応用研究として gallotannin 類に着目し、合成化学的手法を用いて化合物ライブラリーの構築を試み、抗酸化活性及びα-glucosidase 阻害活性を評価した。本研究により得られた合成 gallotannin 類の化合物ライブラリーおよび構造活性相関の知見は、機能性分子としての利用を目指した gallotannin に関する研究の発展に寄与できるものと考える。

実験の部

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-ECA600 spectrometer. Chemical shifts are reported relative to the internal standard (tetramethylsilane: δ H 0.00 or $CHCl_3$: δ H 7.26). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-ECA600 (150 MHz) spectrometer. The following internal references were used: tetramethylsilane: δ 0.00; $CDCl_3$: δ 77.0; acetone-d_6: δ 29.8; CD_3OD: δ 49.0. Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). Electron ionization (EI) mass analyses and fast atom bombardment (FAB) mass analyses were carried out with a JEOL JMS-GCMATE. High-resolution mass spectra (HRMS) was recorded on Waters Xevo G2-QTof spectrometer under electro spray ionization (ESI) mode. Column chromatography was carried out on Kanto Silica gel 60N spherical (63–210 mesh). Analytical thin-layer chromatography (TLC) was carried out using Merck Kieselgel 60 F254 plates with visualization by ultraviolet light or stained by 8% H_2SO_4/EtOH solution on a hot plate. Acarbose was purchased from Fujifilm Wako Pure Chemical Corporation (Osaka, Japan). Trolox was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). PGG and DPPH were purchased from Sigma-Aldrich Japan (Tokyo, Japan).

Synthesis procedure of anhydroalditols **2**, **11**–**17**, **29**, **35**, **38**.

1,5-Anhydroalditols 2, 11–16

1,5-Anhydroalditols **2**, **11**–**16** was synthesized according to previous literature[82]

3-*O*-Benzoyl-1,5-AMan (18)

To the solution of 1,5-AMan (820 mg, 5 mmol) in 40 mL of THF/water (19/1) was added $MeSnCl_2$ (55 mg, 0.25 mmol) and DIPEA (630 μL, 10 mmol) was stirred at rt. After the 5 min, BnCl was added to the solution and stirred for 2.5 h. The reaction solution was quenched by addition of 20 mL of 3% HCl and the mixture was stirred for 5 min. The mixture was diluted by 40 mL of EtOAc, organic phase was washed with $NaHCO_3$ and water. The combined aqueous phase was back extracted with EtOAc (20 mL×3). The combined organic phase was washed with brine. The aqueous phase was with EtOAc (20 mL×3). The combined organic phase was dried over Na_2SO_4, and concentrated. The crude product was purified by C.C (Hex/EtOAc = 1/4) to obtain the desired product **18** as a white solid (1.2 g, 89%

yield). $[\alpha]_D^{20}$ = −53.6 (c 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 8.12 (m, 2H), 7.60 (m, 2H), 7.48 (m, 1H), 4.99 (dd, J = 10.0, 3.5 Hz, 1H), 4.15 (m, 1H), 3.99 (t, J = 10.0 Hz, 1H) 3.95 (dd, J = 12.5, 2.0 Hz, 1H), 3.89 (dd, J = 11.5, 6.0 Hz, 1H), 3.73 (dd, J = 11.5, 6.0 Hz, 1H), 3.69 (dd, J = 12.5, 1.0 Hz, 1H), 3.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.91, 134.26, 131.58, 130.87, 129.45, 82.90, 79.15, 71.34, 68.75, 66.36, 63.01; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{13}H_{16}O_6Na]^+$: 291.0845; found 291.0845.

3-*O*-Benzoyl-4,6-*O*-benzylidene-1,5-AMan (19)

The solution of **18** (1.19 g, 4.4 mmol), CSA (232 mg, 1.0 mmol), benzaldehyde dimethyl acetal (720 μL, 4.8 mmol) in 21 mL of MeCN was stirred for 10 min at rt. The reaction mixture was quenched by TEA (140 μL, 1 mmol), diluted by 50 mL of EtOAc and water. The EtOAc phase was washed with water (30 4), brine, dried over Na_2SO_4, and concentrated. The crude product was dissolved in $CHCl_3$ 100 mL at 40 °C and Hex was slowly added to generate precipitate. The precipitate was filtered to obtained **19** as a white solid (1.24 g, 3.48 mmol, 79% yield). $[\alpha]_D^{20}$ = −120.9 (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 8.08 (dd, J = 8.5, 1.5 Hz, 2H), 7.58 (t, J = 8.5 Hz, 1H), 7.46 (m, 2H), 7.35 (dd, J = 7.5, 2.0 Hz, 2H), 7.31 (m, 3H), 5.62 (s, 1H), 5.35 (dd, J = 10.0, 3.5 Hz, 1H), 4.35 (dd, J = 10.0, 5.0 Hz, 1H), 4.32 (m, 1H), 4.27 (t, J = 10.0 Hz, 1H), 4.12 (dd, J = 12.5, 2.0 Hz, 1H) 3.87 (t, J = 10.0 Hz, 1H), 3.80 (d, J = 12.5 Hz, 1H) 3.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.78, 137.15, 133.43, 129.84, 129.57, 129.01, 129.00, 128.21, 126.07, 101.72, 76.30, 73.68, 72.37, 70.76, 68.58, 68.33; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{21}H_{28}O_4NaSi]^+$: 379.1158; found 379.1159.

2-Deoxy-2-azido-3-*O*-benzoyl-4,6-*O*-benzylidene-1,5-AG (20)

To the stirred solution of **19** (356 mg, 1 mmol) in 10 mL of $CHCl_3$ was added Tf_2O (328 μL, 2 mmol) at 0 °C. After 2 min, the reaction solution was added pyridine (170 μL, 2 mmol) and stirred for 10 min. The reaction mixture was diluted with 30 mL DCM and washed with $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. The concentrate was dissolved 4 mL of DMF, added NaN_3 (130 mg), and stirred for 1 h at rt. The reaction mixture was diluted 20 mL of Hex and EtOAc, and washed with water, dried over Na_2SO_4, and concentrated. The crude was purified by C.C (Hex/EtOAc = 5/1) to obtain desired product **20** (268 mg, 70 % yield) as a white solid. $[\alpha]_D^{20}$ = +14.8 (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 8.09 (dd, J = 8.0, 1.5 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.45 (m, 2H), 7.39 (dd, J = 8.0, 2.0 Hz, 2H), 7.29 (m, 3H), 5.52 (t, *J* = 9.5 Hz, 1H), 5.50 (s, 1H), 4.36 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.16 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.74 (t, *J* = 10.5 Hz, 1H), 3.53 (m, 1H), 3.45 (t, *J* = 11.5 Hz, 1H),;

HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{20}H_{19}N_3O_5Na]^+$: 404.1222; found 404.1222.

1-Deoxy-D-glucosamine (17)

The solution of **20** (200 mg, 0.52 mmol), 28% NaOMe in MeOH (200 μL) was stirred for 2.5 h. The reaction solution was neutralized by acidic resin, filtrated, and concentrated. The crude was purified by C.C (Hex/EtOAc = 10/1) to obtain 2-deoxy-2-azido-4,6-*O*-benzylidene-1,5-AG (92 mg, 64% yield) as a white solid. Pd/C (50 mg) was added to the solution of 2-deoxy-2-azido-4,6-*O*-benzylidene-1,5-AG (75 mg, 0.27 mmol) in 25 mL of MeOH and stirred for 14 h at rt under the H_2 atmosphere. After the removal of Pd/C by filtrated, the solution was concentrated. The crude was dissolved in 20 mL of 70%AcOH and stirred for 2 h at 80 °C. After the removal solvents, crude product was purified by C.C ($CHCl_3$/MeOH/25%aq. NH_3 = 6/4/0.5) to obtain the desired product **17** (30.2 mg, 68%) as a yellow oil. $[\alpha]_D^{20}$ = +25.8 (c 2.1, CD_3OD); ^1H NMR (CD_3OD, 600 MHz) δ 3.90 (dd, J = 11.0, 5.0 Hz, 1H), 3.82 (dd, J = 12.0, 2.5 Hz, 1H), 3.62 (dd, J = 12.0, 6.0 Hz, 1H), 3.23 (dd, J = 10.0, 9.0 Hz, 1H), 3.17 (overlapped, 2H), 3.16 (t, J = 11.0 Hz, 1H), 2.72 (m, 1H); ^{13}C NMR (CD_3OD, 150 MHz) δ 82.80, 80.04, 72.14, 71.15, 63.12, 54.23; HRMS (ESI, *m/z*): $[M-H]^-$, calcd for $[C_6H_{14}NO_4]^-$: 164.0923; found 164.0927.

2,3,4-*O*-TMS-1,5-AG (21)

The solution of per-*O*-TMS-1,5-AG[82] (2.65 g, 5.9 mmol) and NaOAc (0.9 g, 11.8 mmol) in 25 mL of dry MeOH and 25 mL of dry DCM was stirred for 17 h at rt under the Ar atmosphere. After the removal solvent, crude was dissolved Hex and washed with ice water. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by C.C. to obtain **21** (1.9 g, 85% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 600 MHz) δ 3.87 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.79 (m, 1H), 3.60 (m, 1H), 3.50 (m, 1H), 3.40 (m, 2H), 3.19 (m, 2H), 2.08 (t, J = 6.6 Hz, 1H), 0.17–0.,14 (s, 9H).

6-Deoxy-6-azido-1,5-AG[113] (24)

To the stirred solution of PPh_3 (1.3 g, 5.1 mmol) in 20 mL of THF was dropwise added DIAD (2.7 mL, 5.1 mmol) at -20 °C. After the 10 min, a solution of **21** (965 mg, 2.5 mmol) in 10 mL of THF was added to the reaction solution and the mixture was warmed to 0 °C. After 30 min, to the reaction solution was added DPPA (1.1 mL, 5.1 mmol) and stirred for 2.5 h. The reaction mixture was diluted by THF to generate precipitate of triphenylphosphine oxide, filtrated and concentrated. The crude **23**

was dissolved MeOH and added acidic resin, the mixture was stirred for 30 min. After removal resin and solvent, the crude was purified by C.C. ($CHCl_3$/MeOH = 5/1) to obtain **24** (453 mg, 95% yield) as a white solid. ^{1}H NMR (CD_3OD, 600 MHz) δ 3.93 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.50 (dd, *J* = 13.0, 2.0 Hz), 3.46 (m, 1H), 3.34 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.28 (m, 1H), 3.23 (t, *J* = 9.0 Hz, 1H), 3.20 (*J* = 10.2 Hz, 1H), 3.17 (t, *J* = 10.8 Hz, 1H); HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_6H_{11}N_3O_4Na]^+$: 212.0648; found 212.0647.

6-Deoxy-6-amino-1,5-AG (25)

25 was synthesized according to previously literature[113]. (160 mg, 98%, Yellow oil)

1,4-Anhydro-L-arabinose[114] (29)

To the solution of L-arabinose and imidazole in 10 mL of dry DMF was added the solution of TBDPS-Cl in 40 mL of dry DMF and the mixture was stirred for 7 h at 60 °C. After the reaction solution cooling to rt, TEA and TMS-Cl was slowly added at 0 °C and the mixture was stirred for 4 h. The reaction mixture was diluted by 200 mL of Hex and washed by water, brine, dried over the Na_2SO_4, and concentrated. The obtained oil was dissolved in 50 mL of dry DCM followed slowly added TMS-I (1.4 mL, 10 mmol) at rt. After 1 h, $LiBH_4$ was added to the reaction solution at 0 °C and the mixture was stirred for 3 h. The reaction solution was diluted by 200 mL of Hex and washed with 200 mL of NH_4Cl (aq.), water, brine, dried over Na_2SO_4, and concentrated. The crude was dissolved by MeOH and added small amount of acidic resin. The reaction suspension was monitored by TLC, after the complete reaction, filtrated and concentrated. The crude was purified C.C (Hex/EtOAc = 3/1 – 1/1) to obtain 5-*O*-TBDPS-1,4-anhydro-L-arabinose (1.7 g 46%) as a colorless oil. $[\alpha]_D^{20}$ = -23.8 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.72–7.67 (m 4H), 7.46–7.34 (m, 6H), 4.31 (s, br, 1H), 4.04–4.00 (overlapped, 3H), 3.87–3.84 (overlapped, 2H), 3.78 (dd, *J* = 10.8, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 135.65, 1355.58, 132.23, 132.00, 130.07, 130.00, 127.91, 127.90, 86.00, 79.37, 77.58, 74.47, 64.66, 26.70, 19.04; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{21}H_{28}O_4NaSi]^+$: 395.1655; found 395.1656.

The solution of 5-*O*-TBDPS-1,4-anhydro-L-arabinose (1.3 g, 3.3 mmol), AcCl (36 μL, 0.5 mmol) in 10 mL of dry MeOH was stirred at rt under the Ar atmosphere. The reaction was monitored by TLC. After the completed reaction, to the solution was added alkalic resin, filtrated, and concentrated. The crude was purified by C.C (DCM/MeOH = 4/1) to obtain desired product **29** (405 mg, 92%) as a colorless oil. ^{1}H NMR (CD_3OD, 600 MHz) δ 4.05 (m, 1H), 3.96–3.94 (overlapped, 2H), 3.79–3.75

(m, 2H), 3.68–3.63 (overlapped, 2H); ^{13}C NMR (CD_3OD, 150 MHz) δ 87.71, 79.76, 78.72, 74.58, 63.50; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_5H_{10}O_4Na]^+$: 157.0477; found 157.0482.

Per-*O*-Ac-1-deoxy-D-maltose (30)

The suspension of **34**[98] (1.5 g, 2.5 mmol), Pd/C (10%, 120 mg) and TEA (700 μL, 5 mmol) in 50 mL of EtOAc was stirred for 12 h at rt under the H_2 atmosphere. The suspension was filtrated and concentrated. The crude was purified by C.C (Hex/EtOAc = 2/1 – 1/1) to obtain **30** (1.2 g, 79%) as a white solid. $[\alpha]_D^{20}$ = +83.4 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.43 (d, *J* = 4.1 Hz, 1H), 5.37 (dd, *J* = 10.7, 9.6 Hz, 1H), 5.25 (t, *J* = 8.9 Hz, 1H), 5.06 (t, *J* = 10.0 Hz, 1H), 4.96–4.83 (overlapped, 2H), 4.50 (dd, *J* = 12.2, 2.6 Hz, 1H), 4.26 (dd, *J* = 12.7, 3.8 Hz, 1H), 4.18 (dd, *J* = 12.2, 4.6 Hz, 1H), 4.09–4.02 (overlapped, 2H), 3.97 (m, 1H), 3.93 (t, *J* = 9.1 Hz, 1H), 3.59 (m, 1H), 3.37 (t, *J* = 10.8 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 2.03 (overlapped, 6H), 2.01 (overlapped, 6H), ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.57, 170.53, 170.28, 169.97, 169.93, 169.44, 95.73, 76.28, 72.75, 69.96, 69.49, 64.39, 68.53, 67.98, 66.57, 62.99, 61.45, 21.00, 20.84, 20.69, 20.60; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{26}H_{36}O_{17}Na]^+$: 643.1850; found 643.1851.

1-Deoxy-D-maltose (35)

To the solution of **30** (1.2 g, 2.0 mmol) in 20 mL of MeOH was added catalytic amount of NaOMe. The reaction was monitored by TLC. After the completed reaction, acidic resin was added, filtrated, and concentrated. The crude was purified by C.C (DCM/MeOH = 6/1–2/1) to obtain **35** (480 mg, 74%) as a colorless syrup. $[\alpha]_D^{20}$ = +97.4 (c , CH_3OH); ^{1}H NMR (CD_3OD, 600 MHz) δ 5.14 (d, *J* = 3.8 Hz, 1H), 3.88 (q, *J* = 5.4 Hz, 1H), 3.87–3.79 (overlapped, 2H), 3.75 (dd, *J* = 12.2, 5.0 Hz, 1H), 3.70–3.58 (overlapped, 4H), 3.57–3.43 (overlapped, 4H), 3.29–3.23 (overlapped, 2H), 3.16 (dd, *J* = 11.0, 10.3 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz) δ 103.03, 81.78, 81.00, 79.76, 75.03, 74.73, 74.22, 71.43, 71.00, 70.79, 62.68, 62.45; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{12}H_{22}O_{10}Na]^+$: 349.1111; found 349.1111.

1-Deoxy-2,3,4-*O*-Ac-methyl-D-glucuronate[115] **(37)**

The suspension of **36**[116] (1.0 g, 2.5 mmol), Pd/C (10%, 100 mg) and TEA (700 μL, 5 mmol) in 50 mL of EtOAc was stirred for 12 h at rt under the H_2 atmosphere. The suspension was filtrated and concentrated. The crude was used for next step without purification. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.25 (t, *J* = 8.8 Hz, 1H), 5.16 (t, *J* = 8.8 Hz 1H), 5.00 (td, *J* = 9.0, 5.3 Hz, 1H), 4.26 (dd, *J* = 11.7, 5.2

Hz, 1H), 4.02 (d, *J* = 8.9 Hz, 1H), 3.42 (dd, *J* = 11.5, 9.5 Hz, 1H), 2.05 (s, 9H); HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{13}H_{18}O_9Na]^+$: 341.0849; found 341.0849.

1-Deoxy-glucuronic acid[100] **(38)**

The solution of **37** (165 mg, 0.52 mmol) and excess NaOMe in 5 mL of MeOH and water was stirred at rt for 1 d. The reaction solution was concentrated, and acidic resin was added to adjust pH to 2. The resin was filtration and filtrate concentrated. The crude was purified by C.C. (Diol silica-gel, DCM/MeOH = 6/1–2/1) to obtain **38** (67 mg, 73%) as a white solid. ^{1}H NMR (CD_3OD, 600 MHz) δ 3.86 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.50 (m, 2H), 3.36–3.32 (overlapped, 2H), 3.16 (t, *J* = 11.0 Hz, 1H); HRMS (ESI, *m/z*): $[M-H]^-$, calcd for $[C_6H_9O_6]^-$: 177.0396; found 177.0399.

Synthesis procedure of 1,5-AG-based gallotannin derivatives **1, 4–10, 69–73, 83–87, 93.**

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1,5-anhy1dro-D-glucitol (40)

Compound **40** was synthesized from **39** according to previous literature[59].

2-*O*-Benzyl-4,6-*O*-benzylidene-1,5-anhydro-D-glucitol (41) and

3-*O*-Benzyl-4,6-*O*-benzylidene-1,5-anhydro-D-glucitol (42)

Compound **39** (2.5 g, 10 mmol) and $TBAHSO_4$ (68 mg, 0.20 mmol) in 160 mL of DCM and 14 mL of 5% NaOH was stirred at rt. Then, BnBr (0.21 mL, 1.7 mmol) was slowly added, and the mixture was refluxed for 30 h. After the addition 50 mL of water, the mixture was extracted with DCM (3× 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was separated by C.C (Hex/EtOAc = 4/1) to obtain 2-*O*-Bn compound **41** (2.0 g, 59%) as a colorless needle crystal and 3-*O*-Bn compound **42** (1.0 g, 30% yield) as a white solid. Compound **41**: m.p. 163 °C; $[\alpha]_D^{20}$ = –3.16 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.49–7.47 (m, 2H), 7.38–7.29 (m, 8H), 5.50 (s, 1H), 4.76, 4.67 (ABq, *J* = 11.7 Hz, 2H), 4.30 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.01 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.84 (m, 1H), 3.65 (t, *J* = 10.3 Hz, 1H), 3.59–3.55 (m, 1H), 3.45 (t, *J* = 9.3 Hz, 1H), 3.35 (m, 1H), 3.30 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.02, 137.05, 129.23, 128.56, 128.33, 128.03, 127.89, 126.29, 101.88, 81.05, 77.74, 74.81, 73.43, 70.91, 68.79, 68.45. Compound **42**: m.p. 137 °C; $[\alpha]_D^{20}$ = +5.3 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.50–7.48 (m, 2H), 7.41–7.29 (m, 8H), 5.58 (s, 1H), 5.03, 4.72 (ABq, *J* = 11.3 Hz, 2H), 4.34 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.06 (dd, *J* = 11.2, 5.7 Hz, 1H), 3.80–3.76 (m, 1H), 3.72 (t, *J* = 10.3 Hz, 1H), 3.66 (t, *J* = 9.1 Hz, 1H), 3.58 (t, *J* = 8.8 Hz, 1H), 3.44–3.40 (m, 1H), 3.34 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.30, 137.32, 129.00, 128.61, 128.30, 128.13, 128.01, 125.98, 101.21, 82.66, 82.13, 74.71, 71.53, 69.91, 69.79, 68.88.

2,3-Di-*O*-benzyl-1,5-anhydro-D-glucitol (43)

Compound **40** (0.86 g, 2.0 mmol) in 10 mL of 80% AcOH solution was stirred at 80 °C for 5 h. After removed the solvent, the crude was purified by recrystallization (EtOAc/Hex) to obtain **43** (0.65 g, 95%) as a colorless needle crystal. m.p. 129 °C; $[\alpha]_D^{20}$ = −10.4 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.43–7.29 (m, 10H), 5.03, 4.70 (ABq, *J* = 11.7 Hz, 2H), 4.64, 4.03 (ABq, *J* = 11.3, 2H), 3.86–3.82 (m, 1H), 3.72–3.68 (m, 1H), 3.63–3.59 (m, 1H), 3.50–3.44 (m, 2H), 3.28–3.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.54, 137.97, 128.67, 128.53, 127.98, 127.93, 127.83, 85.30, 79.53, 78.29, 75.10, 73.07, 70.45, 67.94, 62.89.

1,5-Anhydro-2-*O*-benzyl-D-glucitol (44)

Compound **41** (860 mg, 2.5 mmol) in 10 mL of 80% AcOH solution was stirred at 80 °C for 5 h. According to the same procedure described for previously **43** preparation, **44** (503 mg, 76%) was obtained as a colorless needle crystal. m.p. 131 °C; $[\alpha]_D^{20}$ = +8.4 (c 1.00, MeOH); ^1H NMR (CD_3OD, 600 MHz); δ 7.40–7.36 (m, 2H), 7.33–7.31 (m, 2H), 7.28–7.25 (m, 1H), 4.75, 4.64 (ABq, *J* = 11.7 Hz, 2H), 3.96 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.81 (dd, *J* = 11.9, 2.2 Hz, 1H), 3.59 (dd, *J* = 11.9, 6.0 Hz, 1H), 3.43 (t, *J* = 8.9 Hz, 1H), 3.39–3.35 (m, 1H), 3.26–3.22 (m, 1H), 3.15–3.11 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz); δ 140.09, 129.37, 129.05, 128.76, 82.42, 79.31, 79.27, 74.14, 71.92, 68.95, 63.07.

1,5-Anhydro-3-*O*-benzyl-D-glucitol (45)

Compound **45** (680 mg, 2.0 mmol) in 10 mL of 80% AcOH solution was stirred at 80 °C for 5 h. According to the same procedure described for previously **43** preparation to obtain **45** (410 mg, 80%) as a colorless needle crystal. m.p. 153 °C; $[\alpha]_D^{20}$ = +28.6 (c 1.00, MeOH); ^1H NMR (CD_3OD, 600 MHz); δ 7.44 (m, 2H), 7.32–7.30 (m, 2H), 7.26–7.23 (m, 1H), 4.90 (overlap, 2H), 3.89 (dd, *J* = 11.3, 5.5 Hz, *1*H), 3.83 (dd, *J* = 11.9, 2.2 Hz, 1H), 3.62–3.57 (m, 2H), 3.37 (dd, *J* = 18.0, 8.7 Hz, 1H), 3.31–3.28 (overlap, 1H), 3.22–3.16 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz); δ 140.53, 129.20, 129.09, 128.49, 88.20, 82.68, 76.10, 71.67, 71.54, 71.09, 63.05.

1,5-Anhydro-4-*O*-benzyl-D-glucitol (46)

Compound **39** (0.76 g, 3.0 mmol) in 15 mL of DCM was stirred at 0 °C. Then, 15 mL of borane-THF (ca. 1M THF solution) and TMSOTf (0.11 mL, 0.60 mmol) were successively added to the mixture. The mixture was allowed to stir for 4 h and added MeOH carefully to the mixture. After the addition 1 mL of saturated aq.$NaHCO_3$, the reaction solution was extracted with DCM (5 × 40 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by C.C. ($CHCl_3$/MeOH = 8/1) to obtain **46** (0.64 g, 74%) as a white solid. $[\alpha]_D^{20}$ = +27.7 (c 0.45, $CHCl_3$); ^1H NMR (CD_3OD, 600 MHz) δ 7.38–7.25 (m, 5H), 4.94,

4.64 (ABq, J = 11.0 Hz, 2H), 3.89 (dd, J = 13.3, 5.4 Hz, 1H), 3.78 (dd, J = 12.0, 2.1 Hz, 1H), 3.60 (dd, 1H, J = 11.4, 5.73 Hz,), 3.49–3.46 (m, 2H), 3.33–3.30 (overlap, 1H), 3.20 (ddd, J = 9.7, 5.2, 2.1 Hz, 1H), 3.14 (t, J = 10.7 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz); δ 140.09, 129.33, 129.14, 128.70, 81.75, 80.43, 79.50, 75.90, 71.77, 70.93, 62.72.

2,4-Di-*O*-benzyl-1,5-anhydro-D-glucitol (47)

Compound **41** (1.0 g, 3.0 mmol) in 15 mL of DCM was successively added 15 mL of borane-THF (ca. 1M THF solution) and TMSOTf (0.11 mL, 0.6 mmol) at 0 °C. The mixture was allowed to stir at rt for 10 h and added 1 mL of MeOH carefully. After the addition 1 mL of saturated aq. Na_2HCO_3, the mixture was extracted with DCM (3 × 40 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by recrystallization (Hex/EtOAc) to obtain **47** (820 mg, 82%) as a colorless needle crystal. m.p. 112 °C; $[\alpha]_D^{20}$ = +34.6 (c 1.00, $CHCl_3$); NMR ($CDCl_3$, 600 MHz) δ 7.37–7.28 (m, 10H), 4.86, 4.70 (ABq, J = 11.3 Hz, 2H), 4.65 (s, 2H), 3.99 (dd, J = 11.3, 5.2 Hz, 1H), 3.84 (ddd, J = 11.8, 5.8, 2.7 Hz, 1H), 3.74 (td, J = 8.9, 2.1 Hz, 1H), 3.68–3.64 (m, 1H), 3.45–3.41 (m, 1H), 3.41 (t, J = 9.2 Hz, 1H), 3.26 (ddd, J = 9.6, 4.5, 2.7 Hz, 1H), 3.19 (t, J = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.18, 138.00, 128.60, 128.56, 128.09, 127.98, 127.85, 79.34, 78.18, 77.97, 77.39, 74.74, 73.05, 67.44, 62.27.

3,4-Di-*O*-benzyl-1,5-anhydro-D-glucitol (48)

Compound **42** (850 g, 2.5 mmol) in 15 mL of DCM was successively added 12.5 mL of borane-THF (ca. 1M THF solution) and TMSOTf (90 μL, 0.5 mmol) at 0 °C. The mixture was allowed to stir at rt for 7 h and added 5 mL of MeOH carefully. After the addition 1 mL of saturated aq. Na_2HCO_3, the mixture was extracted with DCM (3 × 40 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by recrystallization (Hex/EtOAc) to obtain **48** (523 mg, 61%) as a colorless needle crystal. m.p. 99 °C; $[\alpha]_D^{20}$ = +48.3 (c 1.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.38–7.30 (m, 10H), 4.97, 4.77 (ABq, J = 11.3 Hz, 2H), 4.86, 4.68 (ABq, J = 11.0 Hz, 2H), 3.98 (dd, J = 11.2, 5.3 Hz, 1H), 3.84 (ddd, J = 11.9, 5.5, 2.6 Hz, 1H), 3.71–3.65 (m, 2H), 3.52 (t, J = 9.1 Hz, 1H), 3.47 (t, J = 8.8 Hz, 1H), 3.32–3.29 (m, 1H), 3.23 (t, J = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.45, 137.84, 128.71, 128.56, 128.02, 127.86, 86.73, 79.92, 77.79, 75.25, 74.95, 70.16, 69.30, 61.99.

2,3,4-Tri-*O*-benzyl-1,5-anhydro-D-glucitol (49)

Compound **40** (860 mg, 2.0 mmol) in 10 mL of toluene was stirred at rt. DIBAL-H (ca. 1M toluene solution, 6 mL) was added to the reaction solution and stirred at rt for 20 h. The reaction solution was slowly added 4.2 mL of MeOH and 7.2 mL of 30% Rochelle salt aqueous solution and stirred for 1 h. After the addition 20 mL of EtOAc, the mixture was extracted with 30% Rochelle salt aqueous solution

(3 × 15 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by C.C. (Hex/EtOAc = 4/1 – 2/1) to obtain **49** (760 mg, 90% yield) as a colorless needle crystal. m.p. 83 °C; $[\alpha]_D^{20}$ = +8.9 (c 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.37–7.28 (m, 15H), 4.98–4.64 (m, 6H), 3.99 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.84–3.81 (m, 1H), 3.67–3.58 (m, 3H), 3.48 (t, *J* = 9.3 Hz, 1H), 3.29–3.25 (m, 1H), 3.23 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.61, 138.09, 138.01, 128.48, 128.41, 128.05, 127.89, 127.83, 127.64, 86.17, 79.69, 78.55, 77.57, 75.55, 75.13, 73.34, 67.96, 62.25.

1,5-Anhydro-6-*O*-benzyl-D-glucitol (50)

Compound **39** (760 mg, 3.0 mmol) in 15 mL of DCM was added triethylsilane (2.4 mL, 15 mmol) and trifluoracetic acid (1.2 mL, 15 mmol) at 0 °C. The reaction solution was stirred at rt for 8 h. After the addition 10 mL of saturated aq.$NaHCO_3$, the mixture was extracted with DCM (5 × 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by C.C ($CHCl_3$/MeOH = 100/1 – 10/1) to obtain **50** (471 mg, 62%) as a colorless oil. $[\alpha]_D^{20}$ = +8.9 (c 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.35–7.25 (m, 5H), 4.55 (d, *J* = 2.1 Hz, 2H), 3.88 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.77 (dd, *J* = 10.8, 1.9 Hz, 1H), 3.60 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.48–3.42 (m, 1H), 3.32–3.24 (overlap, 3H), 3.15 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 139.57, 129.34, 128.90, 128.67, 81.38, 79.95, 74.48, 71.85, 71.31, 71.19, 70.95.

2,3,6-Tri-*O*-benzyl-1,5-anhydro-D-glucitol (51)

Compound **40** (860 mg, 2.0 mmol) in 10 mL of DCM was added triethylsilane (1.6 mL, 10 mmol) and tifluoroacetic acid (0.8 mL, 10 mmol) at 0 °C. The reaction solution was stirred at rt for 15 h. After the addition 5 mL of saturated aq.$NaHCO_3$, the mixture was extracted with DCM (3 × 30 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by C.C. (Hex/EtOAc = 4/1) to obtain **51** (505 mg, 59%) as a colorless oil. $[\alpha]_D^{20}$ = –7.0 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.37–7.25 (m, 15H), 5.00, 4.76 (ABq, *J* = 11.5 Hz, 2H), 4.69, 4.63 (ABq, *J* = 11.7 Hz, 2H), 4.58, 4.54 (ABq, *J* = 12.2 Hz, 2H), 4.04 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.70 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.64–3.60 (m, 2H), 3.54 (td, *J* = 9.2, 2.1 Hz, 1H), 3.44 (t, *J* = 8.9 Hz, 1H), 3.37–3.34 (m, 1H), 3.23 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.64, 138.05, 137.84, 128.58, 128.48, 128.39, 127.95, 127.90, 127.87, 127.83, 127.77, 127.70, 85.40, 78.75, 78.04, 75.10, 73.65, 73.05, 70.87, 69.98, 68.06.

2,6-Di-*O*-benzyl-1,5-anhydro-D-glucitol (52)

Compound **41** (860 mg, 2.5 mmol) in 15 mL of DCM was added triethylsilane (2.0 mL, 12.5 mmol) and tifluoroacetic acid (1.0 mL, 12.5 mmol) at 0 °C. The reaction solution was stirred at rt for 8 h. After the addition 10 mL of saturated aq.$NaHCO_3$, the mixture was extracted with DCM (3 × 40 mL).

The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by C.C. ($CHCl_3$/MeOH = 8/1) to obtain **52** (500 mg, 58%) as a white solid. $[\alpha]_D^{20}$ = +17.4 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.36–7.27 (m, 10H), 4.64 (s, 2H), 4.59, 4.54 (ABq, *J* = 12.0 Hz, 2H), 4.02 (dd, *J* = 11.2, 5.0 Hz, 1H), 3.69 (dd, *J* = 10.5, 3.6 Hz, 1H), 3.65 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.55 (td, *J* = 8.8, 2.1 Hz, 1H), 3.50 (td, *J* = 9.0, 2.6 Hz, 1H), 3.47–3.43 (m, 1H), 3.37–3.34 (m, 1H), 3.19 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 137.96, 137.71, 128.59, 128.46, 128.07, 127.90, 127.81, 78.31, 77.74, 77.41, 73.68, 72.95, 71.34, 70.01, 67.70.

1,5-Anhydro-3,6-di-*O*-benzyl-D-glucitol (53)

Compound **42** (680 mg, 2.0 mmol) in 15 mL of DCM was added triethylsilane (1.6 mL, 10 mmol) and trifluoroacetic acid (0.80 mL, 10 mmol) at 0 °C. The reaction solution was stirred at rt for 4 h. After the addition 10 mL of saturated aq.$NaHCO_3$, the mixture was extracted with DCM (3 × 40 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by C.C. ($CHCl_3$/MeOH = 8/1) to obtain **53** (420 mg, 62%) as a white solid. $[\alpha]_D^{20}$ = +22.7 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.39–7.27 (m, 10H), 4.91, 4.83 (ABq, *J* = 11.7 Hz, 2H), 4.59, 4.54 (ABq, *J* = 12.2 Hz, 2H), 3.96 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.72–3.66 (m, 3H), 3.61 (dt, *J* = 9.1, 2.6 Hz, 1H), 3.39–3.36 (m, 1H), 3.31 (t, *J* = 8.8 Hz, 1H), 3.21 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.60, 137.61, 128.70, 128.47, 128.02, 127.93, 127.86, 127.82, 86.47, 78.47, 74.87, 73.74, 72.11, 70.38, 69.79, 69.57.

1,5-Anhydro-2-*O*-(3',4',5'-tribenzyloxybenzoyl)-3-*O*-benzyl-4,6-*O*-benzylidene-D-glucitol (55)

Compound **41** (340 mg, 1.0 mmol), compound **54** (650 mg, 1.5 mmol), 2-chloro-1-methylpyridinium iodide (380 mg, 1.5 mmol), DMAP (37 mg, 0.30 mmol), TEA (416 μL, 3.0 mmol) in 15 mL of DCM was stirred at rt for 20 h. After the addition 100 mL of saturated aq. NH_4Cl, the reaction solution was extracted with DCM (3 × 60 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by C.C. (DCM/MeOH = 500/1 – 200/1) to obtain **55** (350 mg, 41%) as a colorless amorphous. $[\alpha]_D^{20}$ = +8.4 (c 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.53–7.11 (m, 29H), 5.61 (s, 1H), 5.27–5.20 (m, 1H), 5.15 (s, 2H), 5.09 (s, 4H), 4.86, 4.71 (ABq, *J* = 12.0 Hz, 2H), 4.36 (dd, *J* = 10.3, 4.8 Hz, 1H), 4.19 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.87 (t, *J* = 9.1 Hz, 1H), 3.79–3.74 (m, 2H), 3.45 (td, *J* = 9.7, 4.9 Hz, 1H), 3.36 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.06, 152.55, 142.74, 138.10, 137.31, 137.28, 136.56, 129.03, 128.57, 128.30, 128.25, 128.22, 128.07, 128.02, 127.89, 127.58, 127.47, 126.02, 124.50, 109.41, 101.32, 81.96, 79.12, 75.14, 74.33, 71.50, 71.30, 68.76, 67.68; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{48}H_{44}O_9Na]^+$: 787.2883; found 787.2881.

1,5-Anhydro-2-*O*-benzyl-3-*O*-(3',4',5'-tribenzyloxybenzoyl)-4,6-*O*-benzylidene-D-glucitol (56)

Compound **41** (0.51 g, 1.5 mmol), compound **54** (1.0 g, 2.3 mmol), 2-chloro-1-methylpyridinium iodide (0.59 g, 2.3 mmol), DMAP (28 mg, 0.23 mmol), TEA (0.62 mL, 4.5 mmol) in 20 mL of DCM was stirred at rt for 20 h. According to the same procedure described for previously **55** preparation, **56** (0.87 g, 68%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = –45.6 (c 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.24–7.44 (m, 24H), 7.20–7.14 (m, 5H), 5.53 (t, *J* = 9.3 Hz, 1H), 5.46 (s, 1H), 5.15–5.10 (m, 6H), 4.55, 4.46 (ABq, *J* = 12.4 Hz, 2H), 4.35 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.13 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.76–3.72 (m, 1H), 3.70 (t, *J* = 10.3 Hz, 1H), 3.65 (t, *J* = 9.5 Hz, 1H), 3.51 (td, *J* = 9.7, 4.8 Hz, 1H), 3.48 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.16, 152.47, 142.58, 137.53, 137.39, 136.69, 128.95, 128.54, 128.38, 128.21, 128.16, 128.02, 127.98, 127.87, 127.53, 126.14, 125.05, 109.55, 101.35, 79.18, 75.62, 75.15, 74.94, 72.97, 71.48, 71.33, 68.80, 68.74; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{48}H_{44}O_9Na]^+$: 787.2883; found 787.2882.

1,5-Anhydro-2,3,6-tris-*O*-benzyl-4-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (57)

Compound **51** (340 mg, 0.78 mmol), compound **54** (530 mg, 1.2 mmol), 2-chloro-1-methylpyridinium iodide (307 mg, 1.2 mmol), DMAP (95 mg, 0.78 mmol), TEA (315 μL, 2.3 mmol) in 15 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **54** preparation, **57** (607 mg, 91%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = –32.0 (c 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.44–7.26 (m, 20H), 7.23–7.15 (m, 7H), 7.11–7.03 (m, 5H), 5.18–5.15 (m, 3H), 5.13–5.07 (m, 4H), 4.76, 4.54 (ABq, *J* = 11.3 Hz, 2H), 4.74, 4.65 (ABq, *J* = 11.7 Hz, 1H), 4.45 (s, 2H), 4.08 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.75–3.71 (m, 1H), 3.65 (t, *J* = 9.1 Hz, 1H), 3.59–3.56 (m, 1H), 3.50 (dd, *J* = 10.8, 2.6 Hz, 1H), 3.45 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.29 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.83, 152.41, 142.58, 138.03, 137.58, 137.37, 136.62, 128.57, 128.50, 128.23, 128.14, 128.06, 128.01, 127.94, 127.86, 127.83, 127.58, 127.49, 127.45, 124.67, 109.34, 83.08, 78.18, 78.08, 75.13, 74.94, 73.67, 73.40, 71.24, 69.47, 68.23; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{55}H_{52}O_9Na]^+$: 879.3509; found 879.3511.

1,5-Anhydro-2,3,4-tris-*O*-benzyl-6-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (58)

Compound **49** (0.43 g, 1.0 mmol), compound **54** (0.66 g, 1.5 mmol), 2-chloro-1-methylpyridinium iodide (0.38 g, 1.5 mmol), DMAP (0.18 g, 1.5 mmol), TEA (0.42 mL, 3.0 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **58** (0.50 g, 58%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +27.9 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.43–7.18 (m, 32H), 5.14–5.10 (m, 6H), 5.03, 4.88 (ABq, *J* = 10.7 Hz, 2H), 4,85, 4.53 (ABq, *J* = 11.8 Hz, 2H), 4.74, 4.67 (ABq, *J* = 11.7 Hz, 2H), 4.52 (dd, *J* = 12.0, 2.1 Hz, 1H), 4.37 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.03 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.69 (t, *J* = 8.8 Hz, 1H), 3.66–3.62 (m, 1H), 3.52–3.49 (m, 1H), 3.46 (t, *J* = 8.9 Hz, 1H), 3.23 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150

MHz) δ 165.82, 152.41, 142.46, 138.55, 138.04, 137.69, 137.37, 136.65, 128.59, 128.53, 128.48, 128.46, 128.20, 128.08, 128.01, 127.96, 127.93, 127.85, 127.76, 127.45, 124.91, 109.30, 86.33, 78.48, 77.83, 77.57, 75.73, 75.23, 75.09, 73.29, 71.17, 68.12, 63.86; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{55}H_{52}O_9Na]^+$: 879.3509; found 879.3509.

1,5-Anhydro-2,3-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-4,6-*O*-benzylidene-D-glucitol (59)

Compound **39** (380 mg, 1.5 mmol), compound **54** (2.0 g, 4.5 mmol), 2-chloro-1-methylpyridinium iodide (1.2 g, 4.5 mmol), DMAP (0.55 g, 4.5 mmol), TEA (1.3 mL, 9.0 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **59** (1.6 g, 88 %) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +46.4 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.44–7.42 (m, 6H), 7.34–7.31 (m, 26H), 7.25–7.22 (m, 4H), 5.80 (t, *J* = 9.5 Hz, 1H), 5.56 (s, 1H), 5.27–5.23 (m, 1H), 5.11–4.93 (m, 12H), 4.45–4.41 (m, 2H), 3.87 (t, *J* = 16.0 Hz, 1H), 3.82 (t, *J* = 17.0 Hz, 1H), 3.65–3.62 (m, 1H), 3.55 (t, *J* = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.6, 165.4, 152.6, 142.9, 142.8, 137.4, 136.8, 136.5, 129.1, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.5, 126.2, 109.3, 109.1, 101.6, 78.8, 75.1, 73.0, 71.9, 71.2, 71.2, 71.1, 68.7, 67.7; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{48}H_{44}O_9Na]^+$: 1119.3932; found 1119.3901.

1,5-Anhydro-2,4-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-3,6-bis-*O*-benzyl-D-glucitol (60)

Compound **53** (0.30 mg, 0.87 mmol), compound **54** (1.3 g, 3.0 mmol), 2-chloro-1-methylpyridinium iodide (0.77 g, 3.0 mmol), DMAP (0.37 g, 3.0 mmol), TEA (0.83 mL, 6.0 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **60** (0.93 g, 77%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +7.87 (c 1.00, $CHCl_3$); 1H-NMR ^1H NMR ($CDCl_3$, 600 MHz) δ 7.58–7.14 (m, 45H), 7.08–6.95 (m, 5H), 5.32–5.25 (m, 2H), 5.19–5.08 (m, 13H), 4.61–4.45 (m, 4H), 4.29 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.94 (t, *J* = 9.1 Hz, 1H), 3.72–3.68 (m, 1H), 3.58–3.53 (m, 2H), 3.39 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 164.87, 164.71, 152.61, 152.51, 142.88, 142.79, 137.54, 137.52, 137.32, 137.27, 136.56, 136.49, 128.59, 128.57, 128.55, 128.28, 128.24, 128.22, 128.16, 128.10, 128.05, 128.02, 127.85, 127.76, 127.65, 127.53, 127.49, 124.51, 109.43, 80.72, 78.29, 75.16, 74.16, 73.72, 72.12, 71.35, 71.32, 69.44, 67.03; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{76}H_{68}O_{13}Na]^+$: 1211.4558; found 1211.4554.

1,5-Anhydro-2,6-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-3,4-bis-*O*-benzyl-D-glucitol (61)

Compound **48** (0.45 g, 1.3 mmol), compound **54** (1.8 g, 4.0 mmol), 2-chloro-1-methylpyridinium iodide (1.0 g, 4.0 mmol), DMAP (0.49 g, 4.0 mmol), TEA (1.1 mL, 8.0 mmol) in 30 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **61** (1.4 g, 92%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +51.2 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.43–7.18 (m, 44H), 5.27–5.21 (m, 1H), 5.17–5.07 (m, 12H), 4.82, 4.52 (ABq, *J* = 11.0

Hz, 2H), 4.77, 4.70 (ABq, J = 11.3 Hz, 2H), 4.56 (m, 1H), 4.42–4.39 (m, 1H), 4.19 (dd, J = 11.2, 5.7 Hz, 1H), 3.85–3.82 (m, 1H), 3.60–3.56 (m, 2H), 3.31 (t, J = 10.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.80, 165.05, 152.56, 152.43, 142.76, 142.47, 137.88, 137.49, 137.37, 137.28, 136.66, 136.53, 128.62, 128.60, 128.57, 128.51, 128.39, 128.21, 128.12, 128.06, 128.01, 127.88, 127.80, 127.40, 127.37, 124.80, 124.49, 109.32, 109.25, 84.32, 77.91, 77.42, 75.45, 75.26, 75.13, 75.09, 72.22, 71.26, 71.15, 67.11, 63.52; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{76}H_{68}O_{13}Na]^+$: 1211.4558; found 1211.4550.

1,5-Anhydro-2,6-bis-*O*-benzyl-3,4-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (62)

Compound **52** (380 mg, 1.1 mmol), compound **54** (1.5 g, 3.3 mmol), 2-chloro-1-methylpyridinium iodide (0.84 g, 3.3 mmol), DMAP (0.91 g, 3.3 mmol), TEA (0.91 mL, 6.6 mmol) in 30 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **62** (1.2 g, 92%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = −80.8 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.41–7.14 (m, 44H), 5.58 (t, J = 9.5 Hz, 1H), 5.31 (t, J = 9.8 Hz, 1H), 5.09–5.00 (m, 12H), 4.54, 4.48 (ABq, J = 12.2 Hz, 2H), 4.52, 4.47 (ABq, J = 12.0 Hz, 2H), 4.19 (dd, J = 11.5, 5.3 Hz, 1H), 3.79 (td, J = 9.9, 5.2 Hz, 1H), 3.73 (m, 1H), 3.59 (dd, J = 10.7, 2.4 Hz, 1H), 3.51 (dd, J = 10.8, 5.3 Hz, 1H), 3.46 (t, J = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.62, 165.18, 152.43, 142.67, 142.53, 137.56, 137.48, 137.43, 137.39, 136.57, 136.56, 128.49, 128.41, 128.38, 128.36, 128.27, 128.16, 127.98, 127.89, 127.87, 127.84, 127.65, 127.55, 124.67, 124.20, 109.15, 77.99, 76.35, 75.22, 75.10, 75.08, 73.70, 72.96, 71.12, 70.07, 69.06, 68.30; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{76}H_{68}O_{13}Na]^+$: 1211.4558; found 1211.4558.

1,5-Anhydro-2,4-bis-*O*-benzyl-3,6-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (63)

Compound **47** (0.52 g, 1.5 mmol), compound **54** (2.0 g, 4.5 mmol), 2-chloro-1-methylpyridinium iodide (1.2 g, 4.5 mmol), DMAP (0.55 g, 4.5 mmol), TEA (1.2 mL, 9.0 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **63** (1.6 g, 91%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +16.1 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.43–7.24 (m, 34H), 7.18–7.05 (m, 10H), 5.50 (t, J = 9.3 Hz, 1H), 5.19–5.08 (m, 12H), 4.56, 4.43 (ABq, J = 12.4 Hz, 2H), 4.55 (dd, J = 12.0 Hz, 2.0 Hz, 1H), 4.45 (dd, J = 12.0, 5.5 Hz, 1H) 4.41 (s, 2H), 4.11 (dd, J = 11.3, 5.2 Hz, 1H), 3.67–3.62 (m, 2H), 3.54 (t, J = 9.5 Hz, 1H), 3.36 (t, J = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.84, 165.22, 152.49, 142.66, 137.65, 137.31, 136.99, 136.59, 128.56, 128.36, 128.22, 128.16, 128.05, 127.94, 127.83, 127.52, 127.47, 124.96, 124.88, 109.54, 109.51, 78.19, 77.87, 76.42, 75.26, 75.13, 74.68, 72.63, 71.32, 67.97, 63.91; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{76}H_{68}O_{13}Na]^+$: 1211.4558; found 1211.4557.

1,5-Anhydro-2,3-bis-*O*-benzyl-4,6-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (64)

Compound **43** (0.34 g, 1.0 mmol), compound **54** (1.3 g, 3.0 mmol), 2-chloro-1-methylpyridinium iodide (0.77 g, 3.0 mmol), DMAP (0.37 g, 3.0 mmol), TEA (0.83 mL, 6.0 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **64** (1.0 g, 87%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +13.7 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.45–7.21 (m, 39H), 7.12–7.03 (m, 5H), 5.32 (t, *J* = 9.5 Hz, 1H), 5.15–5.08 (m, 8H), 5.03–5.01 (m, 4H), 4.79, 4.58 (ABq, *J* = 11.5, 2H), 4.76, 4.66 (ABq, *J* = 11.5 Hz, 2H), 4.63 (dd, *J* = 12.0, 2.8 Hz, 1H), 4.12 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.07 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.70–3.68 (m, 2H), 3.70 (t, *J* = 8.9 Hz, 1H), 3.30 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.80, 164.76, 152.48, 152.44, 142.77, 142.42, 137.98, 137.91, 137.47, 137.37, 136.73, 136.56, 128.53, 128.50, 128.47, 128.20, 128.17, 128.07, 128.03, 128.01, 127.94, 127.84, 127.60, 127.53, 124.75, 124.54, 109.40, 109.14, 82.95, 78.22, 76.56, 75.15, 75.08, 73.47, 71.24, 71.06, 70.96, 68.32, 63.44; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{76}H_{68}O_{13}Na]^+$: 1211.4558; found 1211.4553.

1,5-Anhydro-2,3,4-tris-*O*-(3',4',5'-tribenzyloxybenzoyl)-6-*O*-benzyl-D-glucitol (65)

Compound **50** (180 mg, 0.70 mmol), compound **54** (1.4 g, 3.2 mmol), 2-chloro-1-methylpyridinium iodide (0.82 g, 3.2 mmol), DMAP (0.39 g, 3.2 mmol), TEA (0.89 mL, 6.4 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **65** (0.94 g, 91%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = –4.9 (c 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.43–7.16 (m, 56H), 5.82 (t, *J* = 9.6 Hz, 1H), 5.55 (t, *J* = 10.0 Hz, 1H), 5.29 (td, *J* = 10.0, 5.5 Hz, 1H), 5.13–4.96 (m, 14H), 4.90 (s, 4H), 4.58, 4.53 (ABq, *J* = 12.0, 2H), (dd, *J* = 10.2, 5.6 Hz, 1H), 3.88–3.84 (m, 1H), 3.67 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.61 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.57 (t, *J* = 10.8 Hz, 1H) ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.92, 165.17, 165.02, 152.54, 152.50, 142.88, 142.82, 142.71, 137.44, 137.34, 136.49, 136.45, 136.36, 128.55, 128.51, 128.39, 128.32, 128.27, 128.17, 128.15, 128.10, 128.06, 128.02, 127.95, 127.92, 127.89, 127.81, 127.72, 127.56, 127.52, 124.08, 124.03, 109.20, 109.11, 109.02, 78.36, 75.12, 75.09, 75.07, 74.65, 73.77, 71.18, 71.10, 71.02, 70.75, 69.71, 69.00, 67.26; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{97}H_{84}O_{17}Na]^+$: 1543.5606; found 1543.5601.

1,5-Anhydro-2,3,6-tris-*O*-(3',4',5'-tribenzyloxybenzoyl)-4-*O*-benzyl-D-glucitol (66)

Compound **46** (0.38 g, 1.5 mmol), compound **54** (3.0 g, mmol), 2-chloro-1-methylpyridinium iodide (1.8 g, 7.0 mmol), DMAP (0.12 g, 1.0 mmol), TEA (1.9 mL, 14 mmol) in 30 mL of DCM was stirred at rt for 1 d. According to the same procedure described for previously **55** preparation, **66** (1.0 g, 45% yield) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +47.2 (c 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.47–7.19 (m, 51H), 7.11–7.05 (m, 5H), 5.75 (t, *J* = 9.1 Hz, 1H), 5.19–5.03 (m, 15H), 5.00, 4.92 (ABq, *J* = 11.7 Hz, 4H), 4.60–4.53 (m, 2H), 4.45 (s, 2H), 4.41 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.75–3.70 (m, 2H), 3.46 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.84, 165.51, 165.41,

152.59, 152.54, 142.94, 142.75, 142.65, 137.35, 137.32, 137.27, 136.86, 136.62, 136.51, 136.39, 128.60, 128.54, 128.46, 128.44, 128.38, 128.22, 128.18, 128.14, 128.08, 128.06, 128.01, 127.97, 127.90, 127.61, 127.50, 127.43, 124.81, 124.40, 124.05, 109.54, 109.29, 109.03, 78.11, 76.54, 76.04, 75.14, 75.11, 75.09, 74.96, 71.34, 71.20, 71.06, 70.81, 67.07, 63.58; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{97}H_{84}O_{17}Na]^+$: 1543.5606; found 1543.5604.

1,5-Anhydro-2,4,6-tris-*O*-(3',4',5'-tribenzyloxybenzoyl)-3-*O*-benzyl-D-glucitol (67)

Compound **45** (0.33 g, 1.3 mmol), compound **54** (2.6 g, 6.0 mmol), 2-chloro-1-methylpyridinium iodide (1.5 g, 6.0 mmol), DMAP (0.73 g, 6.0 mmol), TEA (1.7 mL, 12 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **67** (1.3 g, 65% yield) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +26.7 (c 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.46–7.21 (m, 49H), 7.07–6.96 (m, 5H), 5.48 (t, *J* = 9.5 Hz, 1H), 5.34–5.29 (m, 1H), 5.17–5.07 (m, 14H), 5.04 (s, 4H), 4.68 (dd, *J* = 12.0, 3.1 Hz, 1H), 4.62, 4.54 (ABq, *J* = 11.7 Hz, 2H), 4.30 (dd, *J* = 11.2, 5.7 Hz, 1H), 4.22 (dd, *J* = 12.2, 5.0 Hz, 1H), 3.99 (t, *J* = 9.1 Hz, 1H), 3.90–3.87 (m, 1H), 3.42 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.81, 164.83, 164.61, 152.63, 152.55, 152.46, 142.94, 142.49, 137.46, 137.41, 137.33, 137.24, 136.67, 136.50, 136.46, 128.57, 128.53, 128.51, 128.46, 128.21, 128.19, 128.14, 128.10, 128.06, 128.02, 127.95, 127.85, 127.80, 127.62, 127.56, 127.47, 124.64, 124.41, 124.38, 109.47, 109.44, 109.13, 80.62, 76.53, 75.16, 75.08, 74.34, 72.02, 71.35, 71.30, 71.05, 70.98, 67.05, 63.33; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{97}H_{84}O_{17}Na]^+$: 1543.5606; found 1543.5599.

1,5-Anhydro-2-*O*-benzyl-3,4,6-tris-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (68)

Compound **44** (0.38 g, 1.5 mmol), compound **54** (3.0 g, 6.8 mmol), 2-chloro-1-methylpyridinium iodide (1.7 g, 6.8 mmol), DMAP (0.83 g, 6.8 mmol), TEA (2.0 mL, 14 mmol) in 30 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, **68** (2.0 g, 89% yield) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = −36.2 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.42–7.14 (m, 54H), 5.67 (t, *J* = 9.6 Hz, 1H), 5.41 (t, *J* = 9.8 Hz, 1H), 5.13–4.94 (m, 18H), 4.69 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.59, 4.51 (ABq, *J* = 12.4 Hz, 2H), 4.23 (dd, *J* = 12.4, 5.5 Hz, 1H), 4.19 (dd, *J* = 11.5, 5.3 Hz, 1H) 3.92 (m, 1H), 3.83 (td, *J* = 9.8, 5.3 Hz, 1H), 3.48 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.68, 165.65, 165.29, 152.51, 152.48, 152.40, 142.87, 142.66, 142.53, 137.54, 137.43, 137.38, 136.63, 136.46, 128.51, 128.46, 128.43, 128.38, 128.29, 128.15, 128.11, 127.98, 127.92, 127.89, 127.87, 127.80, 127.78, 127.57, 127.52, 124.65, 124.53, 123.97, 109.18, 76.69, 76.16, 75.17, 75.08, 72.95, 71.13, 71.03, 70.20, 68.38, 63.54; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{97}H_{84}O_{17}Na]^+$: 1543.5606; found 1543.5607.

1,5-Anhydro-2-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (4)

$Pd(OH)_2$ on C (20 wt.%, 20 mg) was added to a solution of **55** (270 mg, 0.35 mmol) in 10 mL of MeOH and 10 mL of THF under the argon. After the replaced argon atmosphere to hydrogen gas, the suspension was stirred at rt for 6 h. The reaction mixture was filtered and concentrated under reduced pressure to obtain purple amorphous. The purple amorphous was dissolved by 2 mL acetone and filtered through a whatman™ puradisc 0.1 μM TF and concentrated under reduced pressure. In addition, the purple amorphous dissolved with 2 mL of MeOH and added acidic resin until becoming a clear solution. After the filtered through the whatman™ puradisc 0.1 μM TF, the solution was concentrated under reduced pressure to give **4** (106 mg, 96%) as pale yellow amorphous. $[\alpha]_D^{20}$ = +58.5 (c 0.70, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 7.08 (d, *J* = 5.5 Hz, 2H), 4.87–4.83 (overlap, 1H), 4.08 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.86 (dd, *J* = 11.9, 2.2 Hz, 1H), 3.66– 3.63 (m, 2H), 3.36 (t, *J* = 9.5 Hz, 1H), 3.29 (t, *J* = 10.7 Hz, 1H), 3.24 (ddd, *J* = 9.7, 5.9, 2.3 Hz, 1H). ^{13}C NMR (CD_3OD, 150 MHz) δ 167.80, 146.42, 139.92, 121.14, 110.25, 82.56, 77.06, 73.28, 71.97, 67.84, 62.93; HRMS (ESI^-, *m*/*z*): $[M-H]^-$, calcd for $[C_{13}H_{15}O_9]^-$: 315.0716; found 315.0718.

1,5-Anhydro-3-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (5)

$Pd(OH)_2$ on C (20 wt.%, 20 mg) was added to a solution of compound **56** (270 mg, 0.35 mmol) in 10 mL of MeOH and 10 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **5** (110 mg, quant.) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +24.8 (c 1.0 MeOH); ^{1}H NMR CD_3OD, 600 MHz) δ 7.13 (s, 2H), 5.04 (t, *J* = 9.3 Hz, 1H), 3.97 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.85 (dd, *J* = 11.9, 2.2 Hz, 1H), 3.73–3.69 (m, 1H), 3.66 (dd, *J* = 12.0, 5.8 Hz, 1H), 3.51 (t, *J* = 9.5 Hz, 1H), 3.31–3.27 (overlap, 2H). ^{13}C NMR (CD_3OD, 150 MHz) δ 168.50, 146.39, 139.64, 121.88, 110.34, 82.51, 81.20, 70.95, 69.98, 69.89, 62.75; HRMS (ESI^-, *m*/*z*): $[M-H]^-$, calcd for $[C_{13}H_{15}O_9]^-$: 315.0716; found 315.0721.

1,5-Anhydro-4-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (6)

$Pd(OH)_2$ on C (20 wt.%, 20 mg) was added to a solution of compound **57** (280 mg, 0.33 mmol) in 10 mL of MeOH and 10 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **6** (100 mg, 96%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = –5.7 (c 0.90, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ 7.14 (s, 2H), 4.88 (t, *J* = 9.3 Hz, 1H), 3.94 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.68 (t, *J* = 8.9 Hz, 1H), 3.64–3.60 (m, 1H), 3.57 (dd, *J* = 12.0, 2.1 Hz, 1H), 3.51–3.44 (m, 2H), 3.25 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.59, 145.90, 138.86, 121.46, 110.07, 80.56, 77.44, 72.70, 71.38, 70.45, 62.54; HRMS (ESI^-, *m*/*z*): $[M-H]^-$, calcd for $[C_{13}H_{15}O_9]^-$: 315.0716; found 315.0718.

1,5-Anhydro-6-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (3)

$Pd(OH)_2$ on C (20 wt.%, 20 mg) was added to a solution of compound **58** (210 mg, 0.25 mmol) in 10

mL of MeOH and 10 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **55** (74 mg, 96%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +30.3 (c 1.00, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 7.09 (s, 2H), 4.54 (dd, *J* = 11.9, 1.9 Hz, 1H), 4.35 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.93 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.51–3.55 (m, 1H), 3.48–3.45 (m, 1H), 3.40 (t, *J* = 8.6 Hz, 1H), 3.37 (t, *J* = 8.6 Hz, 1H), 3.23 (t, *J* = 10.8 Hz, 1H). ^{13}C NMR (CD_3OD, 150 MHz) δ 168.32, 146.36, 139.71, 121.26, 110.09, 79.91, 79.63, 71.59, 71.20, 70.86, 65.02; HRMS (ESI$^-$, *m*/*z*): $[M-H]^-$, calcd for $[C_{13}H_{15}O_9]^-$: 315.0716; found 315.0718.

1,5-Anhydro-2,3-bis-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (7)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **59** (210 mg, 0.25 mmol) in 10 mL of MeOH and 10 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **7** (113 mg, quant.) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +139.7 (c 1.00, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) *δ* 7.05 (s, 2H), 6.96 (s, 2H), 5.41 (t, *J* = 9.5 Hz, 1H), 5.08 (td, *J* = 10.1, 5.3 Hz, 1H), 4.20 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.90 (dd, *J* = 11.9, 2.2 Hz, 1H), 3.74–3.69 (m, 2H), 3.45 (t, *J* = 10.8 Hz, 1H), 3.40 (ddd, *J* = 9.6, 5.5, 2.1 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz) δ 168.18, 167.38, 146.38, 146.34, 140.08, 139.85, 121.29, 120.55, 110.30, 110.25, 82.65, 77.91, 71.39, 69.83, 67.81, 62.57; HRMS (ESI$^-$, *m*/*z*): $[M-H]^-$, calcd for $[C_{20}H_{19}O_{13}]^-$: 467.0826; found 467.0831.

1,5-Anhydro-2,4-bis-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (8)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **60** (680 mg, 0.57 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **8** (267 mg, quant.) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +11.3 (c 0.70, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ 7.17 (s, 2H), 7.14 (dd, *J* = 9.8, 4.0 Hz, 2H), 5.04 (t, *J* = 9.5 Hz, 1H), 5.01–4.97 (m, 1H), 4.15–4.11 (m, 2H), 3.63–3.54 (m, 3H), 3.41 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.39, 166.21, 146.00, 145.98, 138.99, 138.94, 121.43, 121.38, 110.15, 110.09, 80.72, 74.30, 73.19, 72.73, 67.38, 62.49; HRMS (ESI$^-$, *m*/*z*): $[M-H]^-$, calcd for $[C_{20}H_{19}O_{13}]^-$: 467.0826; found 467.0827.

1,5-Anhydro-2,6-bis-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (1)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **61** (440 mg, 0.37 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **1** (170 mg, quant.) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = +19.4 (c 1.00 in MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ 7.16 (s, 2H), 7.14 (s, 2H), 4.92–4.88 (m, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.41–4.35 (m, 1H), 4.07 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.83–3.78 (m, 1H), 3.61–3.57 (m, 2H), 3.37 (t, *J* = 10.7 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ

166.63, 166.30, 146.02, 145.96, 138.89, 138.77, 121.74, 121.46, 110.07, 109.85, 79.47, 76.57, 72.94, 71.60, 67.45, 64.54; HRMS (ESI^-, *m/z*): $[M-H]^-$, calcd for $[C_{20}H_{19}O_{13}]^-$: 467.0826; found 467.0831.

1,5-Anhydro-3,4-bis-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (69)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **62** (710 mg, 0.60 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **69** (280 mg, quant.) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = –78.2 (c 1.00, MeOH); ^1H NMR (Acetone-d_6, 600 MHz) δ 7.06 (s, 2H), 7.04 (s, 2H), 5.40 (t, *J* = 9.5 Hz, 1H), 5.16 (t, *J* = 9.6 Hz, 1H), 4.06 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.98–3.93 (m, 1H), 3.71–3.64 (m, 2H), 3.58 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.45 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.41, 166.12, 145.83, 145.72, 139.04, 138.66, 121.52, 120.78, 110.05, 110.01, 80.29, 78.04, 70.50, 70.17, 69.50, 62.25; HRMS (ESI^-, *m/z*): $[M-H]^-$, calcd for $[C_{20}H_{19}O_{13}]^-$: 467.0826; found 467.0829.

1,5-Anhydro-3,6-bis-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (70)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **63** (800 mg, 0.67 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **70** (310 mg, quant.) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = +28.7 (c 0.60, MeOH); ^1H NMR (Acetone-d_6, 600 MHz) δ 7.17 (s, 2H), 7.16 (s, 2H), 5.11 (t, J = 9.1 Hz, 1H), 4.57 (dd, J = 11.9, 1.9 Hz, 1H), 4.40 (dd, J = 11.9, 5.3 Hz, 1H), 3.99 (dd, J = 11.0, 5.5 Hz, 1H), 3.84–3.79 (m, 1H), 3.72 (t, J = 9.5 Hz, 1H), 3.65–3.63 (m, 1H), 3.38 (t, J = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.90, 166.63, 145.97, 145.82, 138.71, 138.52, 122.16, 121.76, 110.10, 109.85, 81.10, 79.61, 70.73, 69.66, 69.46, 64.54; HRMS (ESI^-, *m/z*): $[M-H]^-$, calcd for $[C_{20}H_{19}O_{13}]^-$: 467.0826; found 467.0828.

1,5-Anhydro-4,6-bis-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (71)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **64** (430 mg, 0.36 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **71** (160 mg, 95%) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = +41.7 (c 0.60, MeOH); ^1H NMR (Acetone-d_6, 600 MHz) δ 7.15 (s, 2H), 7.14 (s, 2H), 5.09 (t, *J* = 9.5 Hz, 1H), 4.41 (dd, *J* = 12.0, 2.1 Hz, 1H), 4.13 (dd, *J* = 12.0, 5.8 Hz, 1H), 3.97 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.82–3.79 (m, 1H), 3.75 (t, *J* = 9.1 Hz, 1H), 3.71–3.66 (m, 1H), 3.33 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.47, 166.13, 145.92, 138.90, 138.77, 121.53, 121.38, 110.12, 109.91, 77.56, 77.42, 72.24, 71.28, 70.51, 69.79, 63.98, 55.32; HRMS (ESI^-, *m/z*): $[M-H]^-$, calcd for $[C_{20}H_{19}O_{13}]^-$: 467.0826; found 467.0829.

1,5-Anhydro-2,3,4-tris-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (72)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **65** (520 mg, 0.34 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **72** (210 mg, quant.) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = –4.8 (c 1.00, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ 7.07 (d, J = 3.8 Hz, 4H), 7.01 (d, J = 3.8 Hz, 2H), 5.77 (t, J = 9.6 Hz, 1H), 5.36 (t, J = 9.8 Hz, 1H), 5.23 (td, J = 10.1, 5.4 Hz, 1H), 4.28 (dd, J = 11.2, 5.7 Hz, 1H), 3.83–3.80 (m, 1H), 3.72 (dd, J = 12.4, 2.1 Hz, 1H), 3.62-3.65 (m, 2H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.12, 165.91, 165.89, 145.80, 145.65, 139.00, 138.76, 120.93, 120.70, 120.62, 110.03, 109.96, 109.91, 80.37, 74.46, 70.83, 69.96, 67.27, 61.99; HRMS (ESI$^-$, m/z): $[M - H]^-$, calcd for $[C_{27}H_{23}O_{17}]^-$: 619.0935; found 619.0934.

1,5-Anhydro-2,3,6-tris-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (10)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **66** (410 mg, 0.27 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **10** (170 mg, quant.) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = +80.9 (c 0.70, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ 7.19 (s, 2H), 7.10 (s, 2H), 7.04 (s, 2H), 5.50 (t, J = 9.5 Hz, 1H), 5.13–5.09 (m, 1H), 4.60 (dd, J = 11.9, 1.9 Hz, 1H), 4.47 (dd, J = 12.0, 4.8 Hz, 1H), 4.20 (dd, J = 11.0, 5.5 Hz, 1H), 3.93 (t, J = 9.5 Hz, 1H), 3.79–3.77 (m, 1H), 3.56 (t, J = 10.8 Hz, 1H) ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.60, 166.39, 166.03, 146.05, 145.96, 145.87, 139.15, 138.86, 138.81, 121.64, 121.56, 120.75, 110.06, 110.00, 109.89, 79.67, 77.07, 70.84, 69.60, 67.44, 64.23; HRMS (ESI$^-$, m/z): $[M - H]^-$, calcd for $[C_{27}H_{23}O_{17}]^-$: 619.0935; found 619.0931.

1,5-Anhydro-2,4,6-tris-O-(3',4',5'-trihydroxybenzoyl)-D-glucitol (**9**) [18]; $Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **67** (480 mg, 0.32 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **9** (200 mg, quant.) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = +36.3 (c 1.00, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ 7.17 (s, 2H), 7.16 (s, 2H), 7.15 (s, 2H), 5.25 (dd, J = 10.0, 9.3 Hz, 1H), 5.07–5.03 (m, 1H), 4.46 (dd, J = 12.2, 1.9 Hz, 1H), 4.20–4.16 (m, 3H), 3.95–3.92 (m, 1H), 3.50 (t, J = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.44, 166.19, 165.95, 145.98, 138.98, 138.83, 121.56, 121.35, 121.31, 110.20, 110.11, 109.96, 77.63, 74.27, 72.96, 72.22, 67.45, 63.76; HRMS (ESI$^-$, m/z): $[M - H]^-$, calcd for $[C_{27}H_{23}O_{17}]^-$: 619.0935; found 619.0934.

1,5-Anhydro-3,4,6-tris-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (73)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **68** (765 mg, 0.50 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for

previously **4** preparation, desired compound **73** (310 mg, quant.) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = –6.12 (c 0.80, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz) δ 7.20 (s, 2H), 7.07 (s, 2H), 7.06 (s, 2H), 5.46 (t, *J* = 9.5 Hz, 1H), 5.34 (t, *J* = 9.8 Hz, 1H), 4.47 (dd, *J* = 12.4, 2.1 Hz, 1H), 4.27 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.12 (dd, *J* = 11.3, 5.5 Hz, 1H), 4.04–4.00 (m, 2H), 3.55 (t, *J* = 10.8 Hz, 1H) ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.39, 166.35, 165.72, 145.83, 145.73, 145.66, 138.98, 138.74, 138.64, 121.44, 121.38, 120.67, 110.05, 109.97, 109.94, 77.86, 77.41, 70.54, 69.73, 69.41, 63.52; HRMS (ESI$^-$, *m*/*z*): $[M-H]^-$, calcd for $[C_{27}H_{23}O_{17}]^-$: 619.0935; found 619.0941.

3,4-bis(benzyloxy)benzoic acid (74)

Methyl 3,4-dihydroxybenzoate (2.5 g, 15 mmol) and K_2CO_3 (8.2 g, 60 mmol) and KI (2.0 g, 12 mmol) in 100 mL of acetone was stirred at rt. The reaction suspension was slowly added BnCl (4.2 mL, 36 mmol) and refluxed for 7 h. TLC indicated full conversion of the start material, added MeOH and stirred 1 h. The reaction mixture was filtered by celite and filtrate was evaporated under reduced pressure. The residue was purified by recrystallization with hexane, and the mother liquid was purified by C.C (Hex/EtOAc = 100/1 – 4/1) to afford methyl ester of **74** (total 5.0 g, 97%) as a white solid. Further on, methyl ester of **74** (3.0 g, 9.0 mmol), KOH (5.0 g, 90 mmol) in 90 mL of 1,4-dioxane and 30 mL of MeOH was stirred at 85 °C for 2 h. TLC indicated full conversion of the start material, the reaction mixture was cooled to 0 °C and slowly added 6 M HCl until pH = 1. The precipitating muddy suspension was filtrated, and the white residue was washed by water and MeOH until pH = 7. The white solid was dried *in vacuo*, purified by recrystallizing with MeOH to obtain desired compound **74** (2.4 g, 79%) as colorless needle crystal. m.p. 211 °C; ^{1}H NMR (DMSO-*d*6, 600 MHz) δ 7.56–7.15 (m, 13H), 5.22 (s, 2H), 5.18 (s, 2H); ^{13}C NMR (DMSO-*d*6, 150 MHz) δ 166.88, 151.94, 147.50, 136.93, 136.62, 128.36, 128.30, 127.82, 127.71, 127.46, 127.34, 123.36, 123.22, 114.43, 112.97, 69.87, 69.73.

3,5-bis(benzyloxy)benzoic acid (75)

Methyl 3,5-dihydroxybenzoate (2.5 g, 15 mmol) and K_2CO_3 (8.2 g, 60 mmol) and KI (2.0 g, 12 mmol) in 100 mL of acetone was stirred at rt. The reaction suspension was slowly added BnCl (4.2 mL, 36 mmol) and refluxed for 9 h. According to the same procedure described for previously **74** preparation, methyl ester of **75** (5.2 g, quant.) was obtained as a white solid. Further on, methyl ester of **75** (3.0 g, 9.0 mmol), KOH (5.0 g, 90 mmol) in 90 mL of 1,4-dioxane and 30 mL of MeOH was stirred at 85 °C for 2 h. According to the same procedure described for previously **74** preparation, desire compound **75** (2.5 g, 81%) was obtained as a colorless needle crystal. m.p. 185 °C; ^{1}H NMR (DMSO-*d*6, 600 MHz) δ 7.46–7.30 (m, 11H), 7.19–7.16 (m, 2H), 6.93–6.93 (m, 1H), 5.15 (s, 4H); ^{13}C NMR (DMSO-*d*6, 150 MHz) *δ* 166.80, 159.30, 136.64, 132.80, 128.36, 127.79, 127.58, 107.87, 106.43, 69.38.

3-(benzyloxy)benzoic acid (76)

Methyl 3-hydroxybenzoate (2.3g, 15 mmol) and K_2CO_3 (4.2 g, 30 mmol) and KI (1.0 g, 6.0 mmol) in 100 mL of acetone was stirred at rt. The reaction suspension was slowly added BnCl (2.1 mL, 18 mmol) and refluxed for 10 h. According to the same procedure described for previously **74** preparation, methyl ester of **76** (3.7 g, 95%) was obtained as a white solid. Further on, methyl ester of **76** (1.9 g, 7.4 mmol), KOH (4.2 g, 74 mmol) in 90 mL of 1,4-dioxane and 30 mL of MeOH was stirred at 85 °C for 2 h. According to the same procedure described for previously **74** preparation, desire compound **76** (1.4 g, 85%) was obtained as a colorless needle crystal. m.p. 136 °C; ^{1}H NMR (600 MHz, DMSO-*d*6) δ 7.57–7.53 (m, 2H), 7.48–7.39 (m, 5H), 7.35–7.32 (m, 1H), 7.28–7.26 (m, 1H), 5.17 (s, 2H); ^{13}C-NMR (150 MHz, DMSO-*d*6) δ 167.12, 158.34, 136.84, 132.23, 129.79, 128.50, 127.92, 127.70, 121.82, 119.77, 114.89, 69.35.

4-(benzyloxy)benzoic acid (77)

Methyl 4-hydroxybenzoate (2.3g, 15 mmol) and K_2CO_3 (4.2 g, 30 mmol) and KI (1.0 g, 6.0 mmol) in 100 mL of acetone was stirred at rt. The reaction suspension was slowly added BnCl (2.1 mL, 18 mmol) and refluxed for 9 h. According to the same procedure described for previously **74** preparation, methyl ester of **77** (3.6 g, quant.) was obtained as a white solid. Further on, methyl ester of **77** (2.3 g, 9.0 mmol), KOH (5.0 g, 90 mmol) in 90 mL of 1,4-dioxane and 30 mL of MeOH was stirred at 85 °C for 2 h. According to the same procedure described for previously **74** preparation, desired compound **77** (1.4 g, 85%) was obtained as a colorless needle crystal. m.p. 192 °C; ^{1}H NMR (600 MHz, DMSO-*d*6) δ 7.95–7.90 (m, 2H), 7.48–7.46 (m, 2H), 7.42–7.40 (m, 2H), 7.36–7.34 (m, 1H), 7.12–7.09 (m, 2H), 5.19 (s, 2H); ^{13}C-NMR (150 MHz, DMSO-*d*6) δ 166.90, 161.83, 136.43, 131.27, 128.40, 127.92, 127.73, 123.09, 114.50, 69.35.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (78)

1,5-AG (82 mg, 0.50 mmol), compound **54** (1.1 g, 2.4 mmol), 2-chloro-1-methylpyridinium iodide (0.61 g, 2.4 mmol), DMAP (0.29 g, 2.4 mmol), TEA (0.67 mL, 4.8 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, desire compound **78** (0.86 g, 92%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +7.0 (c 1.00, $CHCl_3$); 1H-NMR (600 MHz, $CDCl_3$) δ 7.56–7.07 (m, 68H), 5.89 (t, *J* = 9.8 Hz, 1H), 5.63 (t, *J* = 9.8 Hz, 1H), 5.35–5.31 (m, 1H), 5.18–4.94 (m, 22H), 4.88–4.84 (m, 4H), 4.76 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.52 (dd, *J* = 11.3, 5.5 Hz, 1H), 4.30 (dd, *J* = 12.4, 5.2 Hz, 1H), 4.06–4.03 (m, 1H), 3.60 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.91, 165.71, 165.14, 165.10, 152.54, 152.43, 143.06, 142.93, 142.79, 142.62, 137.41, 137.31, 136.59, 136.44, 136.35, 136.25, 128.54, 128.45, 128.44, 128.37, 128.27, 128.23, 128.14, 128.11, 128.08, 128.02, 128.00, 127.95, 127.90, 127.87, 127.81, 127.55, 127.52,

124.56, 123.95, 123.79, 109.22, 109.14, 109.03, 75.10, 75.06, 74.53, 71.18, 71.11, 71.05, 70.51, 69.78, 67.31, 63.36 HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{118}H_{100}O_{21}Na]^+$: 1875.6644; found 1875.6653.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(3',4'-dibenzyloxybenzoyl)-D-glucitol (79)

1,5-AG (0.12 g, 0.7 mmol), compound **74** (1.4 g, 4.2 mmol), 2-chloro-1-methylpyridinium iodide (1.1 g, 4.2 mmol), DMAP (0.52 g, 4.2 mmol), TEA (1.1 mL, 8.0 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, desired compound **79** (0.61 g, 72%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +18.8 (c 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.65–7.23 (m, 48H), 6.89–6.86 (m, 2H), 6.82–6.80 (m, 1H), 6.77–6.75 (m, 1H), 5.81 (t, *J* = 9.8 Hz, 1H), 5.56 (t, *J* = 9.6 Hz, 1H), 5.29 (td, *J* = 10.1, 5.5 Hz, 1H), 5.22–5.03 (m, 14H), 4.99 (s, 2H), 4.63 (dd, *J* = 12.4, 2.7 Hz, 1H), 4.43 (dd, *J* = 11.3, 5.5 Hz, 1H), 4.29 (dd, *J* = 12.4, 5.2 Hz, 1H), 3.97–3.94 (m, 1H), 3.53 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.83, 165.69, 165.17, 164.91, 153.26, 153.14, 152.96, 148.27, 148.17, 136.87, 136.68, 136.51, 136.38, 128.57, 128.53, 128.46, 128.40, 127.94, 127.86, 127.46, 127.41, 127.09, 127.01, 126.98, 124.36, 124.25, 121.79, 115.37, 115.20, 113.01, 76.91, 73.90, 71.07, 71.04, 70.95, 70.70, 70.64, 70.16, 69.38, 67.29, 63.16; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{62}H_{56}O_{13}Na]^+$: 1451.4980; found 1451.4977.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(3',5'-dibenzyloxybenzoyl)-D-glucitol (80)

1,5-AG (0.15 g, 0.9 mmol), compound **75** (1.8 g, 5.4 mmol), 2-chloro-1-methylpyridinium iodide (1.3 g, 5.4 mmol), DMAP (0.66 g, 5.4 mmol), TEA (1.5 mL, 10.8 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, desired compound **80** (0.69 g, 63%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +8.3 (c 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.45–7.18 (m, 48H), 6.79–6.76 (m, 2H), 6.72–6.69 (m, 2H), 5.89 (t, *J* = 9.6 Hz, 1H), 5.62 (t, *J* = 9.8 Hz, 1H), 5.37 (td, *J* = 10.1, 5.6 Hz, 1H), 5.06–4.98 (m, 8H), 4.95–4.84 (m, 8H), 4.66 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.49 (dd, *J* = 11.3, 5.5 Hz, 1H), 4.40 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.04–4.01 (m, 1H), 3.58 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.84, 165.80, 165.20, 165.06, 159.76, 159.75, 159.70, 136.44, 136.31, 136.26, 136.22, 131.45, 130.91, 130.87, 130.71, 128.60, 128.57, 128.51, 128.09, 128.06, 127.59, 127.57, 108.53, 108.49, 108.41, 108.11, 107.74, 107.70, 107.51, 74.28, 70.41, 70.23, 70.19, 69.73, 67.21, 63.51; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{62}H_{56}O_{13}Na]^+$: 1451.4980; found 1451.4980.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(3'-benzyloxybenzoyl)-D-glucitol (81)

1,5-AG (0.10 g, 0.6 mmol), compound **76** (0.82 g, 3.6 mmol), 2-chloro-1-methylpyridinium iodide (0.81 g, 3.6 mmol), DMAP (0.44 g, 3.6 mmol), TEA (1.0 mL, 7.2 mmol) in 20 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, desire compound **81** (0.56 g, 92%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +22.7 (c 1.00,

$CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 7.68–7.05 (m, 36H), 5.90 (t, *J* = 9.6 Hz, 1H), 5.65 (t, *J* = 9.8 Hz, 1H), 5.40 (td, *J* = 10.1, 5.6 Hz, 1H), 5.02–5.13 (m, 4H), 5.00 (s, 2H), 4.96 (s, 2H), 4.65 (dd, *J* = 12.0, 2.7 Hz, 1H), 4.48 (dd, *J* = 11.2, 5.7 Hz, 1H), 4.42 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.02–4.05 (m, 1H), 3.59 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.03, 165.85, 165.34, 165.11, 158.66, 136.57, 136.37, 130.91, 130.30, 130.12, 129.56, 129.49, 128.61, 128.56, 128.13, 127.62, 127.58, 122.52, 121.12, 120.85, 120.71, 120.53, 115.16, 115.12, 115.00, 114.84, 76.89, 74.07, 70.27, 70.12, 69.50, 67.21, 63.31; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{62}H_{56}O_{13}Na]^+$: 1027.3306; found 1027.3301.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(4'-benzyloxybenzoyl)-D-glucitol (88)

1,5-AG (0.16 g, 1.0 mmol), compound **77** (1.4 g, 6.1 mmol), 2-chloro-1-methylpyridinium iodide (1.4 g, 6.0 mmol), DMAP (0.73 g, 6.0 mmol), TEA (1.7 mL, 12 mmol) in 30 mL of DCM was stirred at rt for 2 d. According to the same procedure described for previously **55** preparation, desire compound **88** (0.99 g, 98%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +38.2 (c 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 8.06–7.96 (m, 2H), 7.92–7.86 (m, 6H), 7.44–7.17 (m, 20H), 6.93–6.78 (m, 8H), 5.89 (t, *J* = 9.5 Hz, 1H), 5.63 (t, *J* = 9.8 Hz, 1H), 5.40 (td, *J* = 10.0, 5.7 Hz, 1H), 5.02–4.85 (m, 8H), 4.61–4.59 (m, 1H), 4.41 (td, *J* = 12.5, 5.4 Hz, 2H), 3.99–3.96 (m, 1H), 3.54 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.83, 165.55, 165.15, 164.86, 162.78, 162.62, 162.57, 136.22, 136.07, 131.93, 131.86, 128.63, 128.61, 128.17, 127.46, 127.41, 127.19, 122.30, 121.65, 121.59, 121.46, 114.52, 114.47, 114.43, 114.38, 73.69, 69.96, 69.90, 69.24, 67.23, 63.05; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{62}H_{56}O_{13}Na]^+$: 1027.3306; found 1027.3304.

2,3,4,6-tetrakis-*O*-(3',4',5'-trihydroxybenzoyl)-D-glucitol (83)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **78** (860 mg, 0.46 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **54** (321 mg, 90%) was obtained as a yellow amorphous. $[\alpha]_D^{20}$ = +58.0 (c 1.04, MeOH); ^1H NMR (Acetone-d_6, 600 MHz) δ 7.19 (s, 2H), 7.06 (s, 2H)×2, 6.99 (s, 2H), 5.81 (t, *J* = 9.6 Hz, 1H), 5.50 (t, *J* = 9.8 Hz, 1H), 5.28–5.24 (m, 1H), 4.49 (dd, *J* = 12.4, 2.1 Hz, 1H), 4.33–4.29 (m, 2H), 4.17–4.15 (m, 1H), 3.72 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.36, 166.05, 165.90, 165.63, 146.00, 145.97, 145.92, 145.80, 139.22, 138.97, 138.90, 121.50, 120.90, 120.63, 110.17, 110.08, 110.01, 109.98, 77.57, 74.31, 70.74, 69.61, 67.44, 63.32; HRMS-ESI (*m/z*): $[M+Na]^+$, calcd for $[C_{34}H_{28}O_{21}Na]^+$: 795.1021; found 795.1019.

***1,5-Anhydro-2,3,4,6-tetrakis-O-(3',4'-dihydroxybenzoyl)-D-glucitol* (84)**

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **79** (365 mg, 0.30 mmol) in 10 mL of MeOH and 10 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **55** (196 mg, 92%) was obtained as a colorless amorphous.

$[\alpha]_D^{20}$ = +48.3 (c 0.65, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz); δ 7.56 (d, J = 2.1 Hz, 1H), 7.49 (dd, J = 8.4, 1.9 Hz, 1H), 7.43–7.33 (m, 6H), 6.90 (d, J = 8.2 Hz, 1H), 6.84 (dd, J = 11.3, 8.2 Hz, 2H), 6.76 (d, J = 8.2 Hz, 1H), 5.85 (t, J = 9.6 Hz, 1H), 5.55 (t, J = 9.8 Hz, 1H), 5.30 (td, J = 10.1, 5.4 Hz, 1H), 4.52 (dd, J = 12.0, 2.4 Hz, 1H), 4.37–4.32 (m, 2H), 4.20–4.17 (m, 1H), 3.75 (t, J = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.22, 166.00, 165.76, 165.56, 151.21, 151.01, 145.55, 145.39, 123.78, 123.71, 123.62, 122.53, 121.96, 121.74, 117.41, 117.29, 117.19, 117.09, 115.74, 115.68, 77.53, 74.40, 70.78, 69.87, 67.48, 63.52; HRMS (ESI$^-$, m/z): [M − H]$^-$, calcd for $[C_{34}H_{27}O_{17}]^-$: 707.1248; found 707.1255.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(3,5-dihydroxybenzoyl)-D-glucitol (85)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **80** (365 mg, 0.30 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **85** (210 mg, quant.) was obtained as a colorless amorphous.$[\alpha]_D^{20}$ = +39.1 (c 0.50, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz); δ 7.09 (s, 2H), 6.95 (d, J = 1.4 Hz, 4H), 6.89 (d, J = 1.7 Hz, 2H), 6.63–6.49 (m, 4H), 5.90 (t, J = 9.6 Hz, 1H), 5.59 (t, J = 9.6 Hz, 1H), 5.37 (td, J = 10.0, 5.6 Hz, 1H), 4.55 (d, J = 12.4 Hz, 1H), 4.43 (dd, J = 12.2, 4.6 Hz, 1H), 4.37 (dd, J = 11.3, 5.5 Hz, 1H), 4.25 (dd, J = 9.8, 4.3 Hz, 1H), 3.80 (t, J = 10.8 Hz, 1H) ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.33, 166.13, 165.82, 165.67, 159.36, 159.31, 159.24, 132.73, 132.10, 131.91, 129.67, 128.96, 108.81, 108.74, 108.65, 108.39, 108.24, 108.08, 77.25, 74.65, 70.85, 69.79, 67.25, 63.45; HRMS (ESI$^-$, m/z): [M − H]$^-$, calcd for $[C_{34}H_{27}O_{17}]^-$: 707.1248; found 707.1255.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(3-hydroxybenzoyl)-D-glucitol (86)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **81** (300 mg, 0.30 mmol) in 20 mL of MeOH and 20 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **86** (181 mg, 94%) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +36.4 (c 0.70, MeOH); ^{1}HNMR(Acetone-d_6, 600 MHz); δ 7.55–6.97 (m, 20H), 5.94 (t, J = 9.5 Hz, 1H), 5.65 (t, J = 9.6 Hz, 1H), 5.41 (td, J = 10.1, 5.4 Hz, 1H), 4.57 (dd, J = 12.2, 2.6 Hz, 1H), 4.47 (dd, J = 12.4, 4.8 Hz, 1H), 4.39 (dd, J = 11.2, 5.7 Hz, 1H), 4.29–4.26 (m, 1H), 3.83 (t, J = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.38, 166.23, 165.90, 165.82, 158.46, 158.25, 132.14, 131.57, 131.43, 130.49, 130.44, 130.40, 129.72, 129.00, 126.08, 121.43, 121.39, 121.21, 121.08, 117.04, 116.93, 116.88, 116.73, 77.23, 74.83, 70.96, 70.23, 67.33, 63.83; HRMS (ESI$^-$, m/z): [M − H]$^-$, calcd for $[C_{34}H_{27}O_{13}]^-$: 643.1452; found 643.1459.

1,5-Anhydro-2,3,4,6-tetrakis-*O*-(4-hydroxybenzoyl)-D-glucitol (87)

$Pd(OH)_2$ on C (20 wt.%, 50 mg) was added to a solution of compound **88** (288 mg, 0.29 mmol) in 15

mL of MeOH and 15 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **87** (190 mg, quant.) was obtained as a colorless amorphous. $[\alpha]_D^{20}$ = +45.3 (c 0.50, MeOH); ^{1}H NMR (Acetone-d_6, 600 MHz); δ 7.93–7.76 (m, 8H), 6.92–6.77 (m, 8H), 5.89 (t, *J* = 9.6 Hz, 1H), 5.61 (t, *J* = 9.8 Hz, 1H), 5.34 (td, *J* = 10.0, 5.3 Hz, 1H), 4.55 (dd, *J* = 12.4, 2.7 Hz, 1H), 4.41–4.35 (m, 2H), 4.23–4.20 (m, 1H), 3.77 (t, *J* = 10.8 Hz, 1H); ^{13}C NMR (Acetone-d_6, 150 MHz) δ 166.17, 165.99, 165.69, 165.54, 163.17, 163.13, 162.88, 162.82, 132.75, 132.68, 132.61, 132.58, 121.99, 121.44, 121.21, 121.19, 116.09, 116.05, 116.00, 115.94, 77.45, 74.47, 70.76, 70.05, 67.50, 63.65; HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{34}H_{27}O_{13}]^-$: 643.1452; found 643.1459.

Synthesis Procedure of 1-Deoxy-tellimagrandin I

1,5-Anhydro-2,3-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-D-glucitol (88)

Compound **59** (3.5 g, 3.2 mmol), iodine (0.71 g, 5.6 mmol) in 100 mL of DCM and 50 mL of MeOH was stirred at 70 °C for 7 days. The reaction mixture was washed with sodium thiosulfate solution and brine. The crude product was purified by C.C (DCM/MeOH = 4/1) to obtain desired compound **88** (3.0 g, 93%) as a white solid. $[\alpha]_D^{20}$ = +80.3 (c 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.38–7.21 (m, 32H), 5.34 (t, *J* = 9.0 Hz, 1H), 5.28–5.26 (m, 1H), 5.07–4.97 (m, 12H), 4.35–4.32 (m, 1H), 4.00–3.99 (m, 1H), 3.91–3.88 (m, 2H), 3.51–3.48 (m, 2H), 3.07 (d, *J* = 4.0 Hz, 1H), 2.01 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.2, 165.3, 152.6, 143.1, 142.9, 137.3, 136.5, 136.4, 128.5, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 109.3, 109.1, 80.4, 78.5, 75.1, 71.1, 67.0, 69.8, 66.9, 62.4; HRMS-ESI (*m/z*): $[M+Na]^+$, calcd for $[C_{62}H_{56}O_{13}Na]^+$: 1031.3612; found 1031.3619.

1,5-Anhydro-2,3-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-4,6-bis-*O*-(3',5'-dimetoxymetoxy-4'-benzyloxybenzoyl)-D-glucitol (90)

Compound **88** (2.5 g, 2.5 mmol), **89** (2.5 g, 6.2 mmol), EDC·HCl (1.4 g, 7.2 mmol), DMAP (0.15 g, 1.2 mmol) in 15 mL of DCM was stirred at rt for 18 h. After the addition 30 mL of water, the reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by C.C ($CHCl_3$/acetone = 100/1) to obtain **90** (2.3 g, 55% yield) as a colorless amorphous. $[\alpha]_D^{20}$ = +24.7 (c 2.15 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.58 (s, 2H), 7.46–7.25 (m, 50H), 5.85 (t, *J* = 10 Hz, 1H), 5.61 (t, *J* = 10.0Hz, 1H), 5.28–5.26 (m, 1H), 5.22–4.93 (m, 24H), 4.73–4.71 (m, 1H), 4.50–4.47 (m, 1H), 4.35–4.32 (m, 1H), 4.06–4.03 (m, 1H), 3.56 (t, *J* = 11.0 Hz, 1H), 3.48 (s, 6H), 3.42(s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.7, 165.5, 165.1, 164.8, 152.5, 150.9, 150.8, 143.7, 143.4, 142.8, 142.7, 137.4, 137.3, 137.2, 136.5, 136.4, 132.4, 130.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 125.1, 124.2, 124.1, 124.0, 112.4, 112.3, 109.1, 109.0, 95.4, 75.2, 75.1, 75.0, 74.4, 71.1, 71.0, 70.6, 69.3, 68.1, 67.1, 63.3, 56.4; HRMS-ESI (*m/z*): $[M+Na]^+$, calcd for

$[C_{98}H_{92}O_{25}Na]^+$: 1691.5824; found 1691.5825.

1,5-Anhydro-2,3-bis-*O*-(3',4',5'-tribenzyloxybenzoyl)-4,6-bis-*O*-(3',5'-dihydroxy-4'-benzyloxybenzoyl)-D-glucitol (91)

Compound **90** (2.0 g, 1.2 mmol) in 8 mL of THF solution was added 8.8 mL of 2-propanol and 0.2 mL of conc. HCl solution, and the mixture was stirred at 60 °C for 6 h. After the addition 3 mL of $NaHCO_3$, the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by C.C ($CHCl_3$/MeOH = 1000/1 – 500/1) to obtain **91** (1.7 g, 93% yield) as a white amorphous. $[\alpha]_D^{20}$ = +26.8 (c 2.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.43–7.14 (m, 48H), 6.00 (s, 4H), 5.82 (t, *J* = 9.5 Hz, 1H), 5.59 (t, *J* = 9.5 Hz, 1H), 5.37–5.30 (m, 1H), 5.10–4.82 (m, 16H), 4.70–4.68 (m, 1H), 4.54–4.52 (m, 1H), 4.45–4.42 (m, 1H), 3.97–3.95 (m, 1H), 3.57 (t, *J* = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.2, 165.8, 165.5, 165.2, 152.5, 149.0, 148.9, 142.8, 142.7, 138.2, 137.8, 137.3, 137.2, 136.6, 136.4, 136.2,128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 124.5, 123.9, 123.8, 109.9, 109.8, 109.1, 108.9, 77.6, 75.2, 75.1, 75.0, 74.3, 71.1, 71.0, 70.7, 69.7, 68.6, 67.3, 62.6; HRMS-ESI (*m/z*): $[M+Na]^+$, calcd for $[C_{90}H_{76}O_{21}Na]^+$: 1515.4775; found 1515.4777.

Benzyl protected 1-deoxy-tellimagrandin I (92)

To a solution of $CuCl_2$ (135 mg, 1.0 mmol) in 10 mL of MeOH was added *n*-butylamine (400 μL, 4.0 mmol). After the stirred at rt for 1.5 h, the mixture was added to solution of compound **91** (500 mg, 0.34 mmol) in 20 mL of 1,2-dichloroethane (DCE) and stirred at rt for 30 min. The reaction mixture was diluted with 50 mL of diethyl ether, and 50 mL of 5M aq. HCl and 50 mL of diethyl ether were added. The separating organic layer washed with water, $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by C.C (DCM/MeOH = 250/1) and HPLC (column, FNED01048, 250 × 20 mm, SG80–5 μm, eluant DCM/MeOH = 200/1) to afford **92** (237 mg, 48%) as a peal yellow amorphous. $[\alpha]_D^{20}$ = +69.5 (c 1.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.43-7.23 (m, 50H), 6.75 (s, 1H), 6.67 (s, 1H), 5.67 (t, *J* = 10.0 Hz, 1H), 5.37–5.34 (m, 1H), 5.29 (t, *J* = 10.0 Hz, 1H), 5.25–5.24 (m, 1H), 5.13–4.85 (m, 16H), 4.47–4.45 (m, 1H), 3.98 (d, *J* = 12.5 Hz, 1H), 3.96–3.94 (m. 1H), 3.46 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.1, 166.6, 165.8, 165.2, 152.5, 149.0, 147.0, 142.8, 137.4, 137.3, 136.5, 136.4, 136.3, 136.2, 135.7, 135.5, 130.3, 129.6, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 123.9, 113.7, 113.2, 109.2, 108.4, 107.9, 75.6, 75.1, 75.0, 74.4, 71.1, 71.0, 70.8, 70.1, 67.7, 63.6; HRMS-ESI (*m/z*): $[M+Na]^+$, calcd for $[C_{90}H_{74}O_{21}Na]^+$: 1513.4619; found 1513.4620.

1-Deoxy-tellimagrandin I (**93**)

$Pd(OH)_2$ on C (20 wt.%, 20 mg) was added to a solution of compound **92** (60 mg, 0.40 mmol) in 2 mL of MeOH and 2 mL of THF under the argon. According to the same procedure described for previously **4** preparation, desired compound **93** (32 mg, quant.) was obtained as a peal yellow amorphous. $[\alpha]_D^{20}$ = +113.3 (c 0.29, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 7.00 (s, 2H), 6.95 (s, 2H), 6.60 (s, 1H), 6.40 (s, 1H), 5.61 (t, *J* = 9.5 Hz, 1H), 5.27–5.19 (m, 2H), 5.03 (t, *J* = 10.0 Hz, 1H), 4.25–4.22 (m, 1H), 4.08–4.07 (m, 1H), 3.80 (t, *J* = 13.0 Hz, 1H), 3.54 (t, *J* = 11.0 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz); 171.1, 170.7, 168.8, 168.3, 150.6, 147.6, 147.1, 144.6, 143.5, 141.8, 139.7, 126.8, 126.7, 126.3, 120.7, 120.3, 120.1, 119.4, 111.1, 110.8, 108.3, 107.7, 78.7, 78.5, 76.2, 72.1, 72.0, 71.8, 71.4, 71.3, 69.4, 68.7, 64.7; HRMS (ESI, *m/z*): $[M+Na]^+$, calcd for $[C_{34}H_{26}O_{21}Na]^+$: 793.0864; found 793.0865.

Synthesis Procedure of polyol derivatives **94–107.**

General Synthetic Procedure of 1,5-Anhydroalditol Derivatives

A suspension of 1,5-anhydro-L-glucitol (49 mg, 0.30 mmol), gallic acid derivative **54** (650 mg, 1.44 mmol), 2-chloro-1-methylpyridinium iodide (367 mg, 1.44 mmol), triethylamine (400 μL, 2.88 mmol), and *N,N*-dimethyl-4-aminopyridine (176 mg, 1.44 mmol) in 10 mL of dry DCM was stirred for 2 days under argon atmosphere. The reaction mixture was diluted by 20 mL of DCM and 50 mL of ammonium chloride (aq.) was added. The separated solution was extracted with DCM (2×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM/MeOH = 500/1) to obtain the desired benzyl-protected analog (440 mg, 0.24 mmol, 80% yield) as a white solid.

$Pd(OH)_2$ on activated carbon (20 wt.%, 50 mg) was added to the solution of the benzyl-protected analog (150 mg, 0.081 mmol) in 15 mL of MeOH and 15 mL of THF under argon atmosphere. After replacing the argon with hydrogen gas, the suspension was stirred at rt for 5 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to obtain a purple amorphous. The purple amorphous was dissolved in 2 mL acetone, filtered through a Whatman™ puradisc 0.1 μM TF and concentrated under reduced pressure. The amorphous was dissolved in 2 mL of MeOH again and acidic resin (Dowex™ 50×8, 50–100 mesh) was added until the solution became clear. After filtering through the Whatman™ puradisc 0.1 μm TF, the solution was concentrated under reduced pressure to obtain the desired product as a pale-yellow amorphous (61 mg, 0.079 mmol, 97% yield).

General Synthetic Procedure of Inositol Derivatives

A suspension of *myo*-inositol (180 mg, 1.0 mmol), gallic acid derivative **54** (3.17 g, 7.2 mmol), 2-chloro-1-methylpyridinium iodide (1.84 g, 7.2 mmol), triethylamine (2.0 mL, 14.4 mmol), and *N,N*-dimethyl-4-aminopyridine (880 mg, 7.2 mmol) in 30 mL of dry DCM was stirred for 2 days under argon atmosphere. The reaction mixture was diluted by 30 mL of DCM and 100 mL of ammonium chloride (aq.) was added. The separated solution was extracted with DCM (2×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (Hex/DCM = 2/1–DCM/MeOH = 500/1) to obtain the desired benzyl-protected analog (2.66 g, 0.98 mmol, 98% yield) as a white solid.

$Pd(OH)_2$ on activated carbon (20 wt.%, 50 mg) was added to the solution of the benzyl-protected analog (300 mg, 0.11 mmol) in 20 mL of THF under argon atmosphere. After replacing argon with

hydrogen gas, the suspension was stirred at rt for 5 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to obtain a purple amorphous. The purple amorphous was dissolved in 10 mL acetone, filtered through a Whatman™ puradisc 0.1 μM TF and concentrated under reduced pressure. The amorphous was dissolved in 10 mL of MeOH again and acidic resin (Dowex™ 50×8, 50–100 mesh) was added until the solution became clear. After filtering through the Whatman™ puradisc 0.1 μm TF, the solution was concentrated under reduced pressure.

The obtained pale-yellow oil was purified using Chromatorex (DIOL MB100-40/75, Fuji Silysia Chemical, Ltd.) column chromatography (DCM/MeOH = 6/1–1/1) to obtain the desired product as a colorless amorphous (120 mg, 0.11 mmol, quant.).

Synthetic Procedure for the Condensation of *scyllo*-Inositol

A suspension of *scyllo*-inositol (18 mg, 0.1 mmol), gallic acid derivative **54** (270 mg, 0.6 mmol), 2-chloro-1-methylpyridinium iodide (153 mg, 0.6 mmol), triethylamine (166 μL, 1.2 mmol), and *N,N*-dimethyl-4-aminopyridine (73 mg, 0.6 mmol) in 5 mL of dry DMF was stirred for 2 days under argon atmosphere. The reaction mixture was added to 30 mL of ice water, followed by the addition of 30 mL of DCM. The suspension was extracted by DCM (2×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (Hex/DCM = 1/3) to obtain the desired benzyl-protected analog (164 mg, 0.06 mmol, 60% yield) as a white solid.

2,3,4,6-Tetra-*O*-galloyl-1,5-anhydro-L-glucitol (94)

Pale-yellow amorphous. 78% yield from 1,5-anhydro-L-glucitol. $[\alpha]_D^{20} = -56.8$ (c 1.00, Acetone); ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.19 (s, 2H), 7.05 (s, 2H)×2, 6.99 (s, 2H), 5.81 (t, *J* = 9.6 Hz, 1H), 5.49 (t, *J* = 9.8 Hz, 1H), 5.26 (m, 1H), 4.48 (dd, *J* = 12.4, 2.1 Hz, 1H), 4.32–4.29 (overlap, 2H), 4.16 (m, 1H), 3.72 (t, *J* = 11.0 Hz, 1H); HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{34}H_{27}O_{21}]^-$: 771.1045; found 771.1046.

2,3,4,6-Tetra-*O*-galloyl-1,5-anhydro-D-mannitol (95)

Pale-yellow amorphous. 83% yield from 1,5-anhydro-D-mannitol. $[\alpha]_D^{20} = -173.1$ (c 1.00, Acetone); ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.21 (s, 2H), 7.17 (s, 2H), 7.08 (s, 2H), 6.97 (s, 2H), 5.71 (t, *J* = 10.0 Hz, 1H), 5.65 (m, 1H), 5.58 (dd, *J* = 3.5, 10.0 Hz, 1H), 4.47 (dd, *J* = 1.7, 12.0 Hz, 1H), 4.37 (dd, *J* = 7.2, 12.0 Hz, 1H), 4.21–4.17 (overlap, 2H), 4.11 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 166.5, 166.11, 166.02, 165.95, 146.01, 145.87, 139.30, 139.21, 139.08, 139.12, 121.51,

121.37, 120.86, 120.72, 110.20, 110.17, 110.10, 110.01, 77.83, 73.20, 70.35, 68.69, 67.97, 64.61; HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{34}H_{27}O_{21}]^-$: 771.1045; found 771.1045.

2,3,4,6-Tetra-*O*-galloyl-1,5-anhydro-D-galactitol (96)

Pale-yellow amorphous. 81% yield from 1,5-anhydro-D-galactitol. $[\alpha]_D^{20}$ = +147.3 (c 1.00, Acetone); ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.19 (s, 2H), 7.12 (s, 2H), 7.06 (s, 2H), 6.97 (s, 2H), 5.91 (dd, *J* = 1.1, 3.1 Hz, 1H), 5.63 (dd, *J* = 6.9, 10.0 Hz, 1H), 5.59 (m, 1H), 4.44 (dd, *J* = 6.9, 11.0 Hz, 1H), 4.40–4.36 (overlap, 2H), 4.21 (dd, *J* = 5.8, 11.0 Hz, 1H), 3.74 (t, *J* = 10.0 Hz, 1H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 166.29, 166.06, 165.96, 165.82, 146.10, 145.97, 145.82, 139.23, 139.17, 139.01, 121.16, 120.85, 120.81, 120.68, 110.07, 109.94, 76.14, 72.83, 69.33, 68.01, 67.74, 63.01; HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{34}H_{27}O_{21}]^-$: 771.1045; found 771.1044.

2,3,4-Tri-*O*-galloyl-1,5-anhydro-L-rhamnitol (97)

Colorless amorphous. 86% yield from 1,5-anhydro-L-rhamnitol. $[\alpha]_D^{20}$ = +316.2 (c 1.00, Acetone); ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.20 (s, 2H), 7.08 (s, 2H), 6.96 (s, 2H), 5.60 (m, 1H), 5.49 (t, *J* = 9.3 Hz, 1H), 5.55 (dd, *J* = 3.8, 10.0 Hz, 1H), 4.10 (dd, *J* = 2.1, 13.1 Hz, 1H), 3.99 (d, *J* = 12.3 Hz, 1H), 3.82 (m, 1H), 1.28 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 166.11, 166.03, 165.94, 146.04, 145.97, 145.79, 139.05, 138.98, 121.41, 120.99, 120.91, 110.02, 109.95, 75.66, 73.14, 72.33, 70.60, 68.49, 18.37; HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{27}H_{23}O_{16}]^-$: 603.0986; found 603.0988.

2,3,4-Tri-*O*-galloyl-1,5-anhydro-L-fucitol (98)

Colorless amorphous. 94% yield from 1,5-anhydro-L-fucitol. $[\alpha]_D^{20} = -257.1$ (c 1.00, Acetone); ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.19 (s, 2H), 7.05 (s, 2H), 6.96 (s, 2H), 5.62 (d, *J* = 1.7 Hz, 1H), 5.53–5.50 (overlap, 2H), 4.25 (m, 1H), 4.10 (dd, *J* = 5.8, 12.4 Hz, 1H), 3.16 (m, 1H), 1.18 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 166.13, 165.98, 146.08, 145.97, 145.81, 139.07, 138.96, 121.09, 120.98, 120.81, 110.01, 109.92, 74.41, 73.25, 72.04, 68.04, 67.72, 16.88; HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{27}H_{23}O_{16}]^-$: 603.0986; found 603.0988.

2,3,4-Tri-*O*-galloyl-1,5-anhydroxylitol (99)

Colorless amorphous. 84% yield from 1,5-anhydroxylitol. ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.07 (s, 4H), 7.06 (s, 2H), 5.73 (t, *J* = 9.3 Hz, 1H), 5.23 (m, 2H), 4.22 (dd, *J* = 5.5, 11.4 Hz, 2H), 3.57

(t, J = 10.3 Hz, 2H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 166.12, 165.92, 145.97, 145.88, 139.21, 139.04, 120.94, 120.66, 110.06, 110.00, 73.45, 70.52, 68.08; HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{26}H_{21}O_{16}]^-$: 589.0830; found 589.0832.

2,3,4-Tri-*O*-galloyl-6-amino-6-deoxy-1,5-AG (100)

Pale yellow amorphous. 90% yield from 6-azido-6-deoxy-1,5-AG. $[\alpha]_D^{20} = -2.6$ (c 0.7, Methanol); ^{1}H NMR (600 MHz, Methanol-d_4): δ 7.01 (s, 2H), 6.98 (s, 2H), 6.92 (s, 2H), 5.81 (t, J = 9.6 Hz, 1H), 5.31-5.23 (m, 2H), 4.37 (q, J = 5.5 Hz, 1H), 3.97-3.94 (m, 1H), 3.68-3.58 (m, 1H), 3.17 (dd, J = 13.6, 2.6 Hz, 1H), 3.10-3.05 (m, 1H); ^{13}C NMR (150 MHz, Methanol-d_4) δ 167.6, 167.5, 167.2, 146.6, 146.5, 146.4, 140.7, 140.4, 140.2, 120.5, 120.2, 119.7, 110.6, 110.4, 76.2, 74.3, 71.7, 70.8, 68.0, 49.9 ; $[M+Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 642.0071; found 642.0071.

2,3,4-Tri-*O*-, *N*-galloyl-6-amino-6-deoxy-1,5-AG (101)

Colorless amorphous. 68% yield from 6-amino-6-deoxy-1,5-AG. $[\alpha]_D^{20} = -2.9$ (c 1.0, Methanol); ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.01 (s, 2H), 6.96 (s, 2H), 6.92 (s, 2H), 6.85 (s, 2H), 5.71 (t, J = 9.6 Hz, 1H), 5.27-5.21 (overlapped, 2H), 4.29 (q, J = 5.5 Hz, 1H), 3.89–3.85 (m, 1H), 3.79 (dd, J = 14.1, 2.4 Hz, 1H), 3.61–3.55 (m, 1H), 3.32 (overlapped, 1H); ^{13}C NMR (150 MHz, Methanol-d_4): δ167.6, 167.5, 167.2, 146.6, 146.5, 146.4, 140.7, 140.4, 140.2, 120.5, 120.2, 119.7, 110.6, 110.4, 76.2, 74.3, 71.7, 70.8, 68.0, 49.9, 41.8; HRMS (ESI$^-$, *m/z*): $[M-H]^-$, calcd for $[C_{48}H_{35}O_{30}]^-$: 770.1283; found 770.1283.

1,2,3,4,5,6-Hexa-*O*-galloyl-*allo*-inositol (102)

Colorless amorphous. 55% yield from *allo*-inositol. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.16–6.75 (m, br, 12H), 6.20–5.66 (m, br, 6H); ^{13}C NMR (150 MHz, Methanol-d_4): δ 167.36, 146.43, 140.55, 120.58, 120.38, 120.24, 111.04, 110.45, 70.67; HRMS (ESI$^+$, *m/z*): $[M+Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 1115.1189; found 1115.1189.

1,2,3,4,5,6-Hexa-*O*-galloyl-D-*chiro*-inositol (103)

Colorless amorphous. 51% yield from D-*chiro*-inositol. $[\alpha]_D^{20} = +92.7$ (c 1.00, Acetone): ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.31 (s, 4H), 7.04 (s, 4H), 6.98 (s, 4H), 6.22 (m, 2H), 5.95 (m, 2H), 5.87 (m, 2H); HRMS (ESI$^+$, *m/z*): $[M+Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 1115.1189; found 1115.1188.

1,2,3,4,5,6-Hexa-*O*-galloyl-L-*chiro*-inositol (104)

Colorless amorphous. 52% yield from L-*chiro*-inositol. $[\alpha]_D^{20} = -90.2$ (c 1.00, Acetone); ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.31 (s, 4H), 7.03 (s, 4H), 6.98 (s, 4H), 6.22 (m, 2H), 5.94 (m, 2H), 5.87 (m, 2H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 165.90×2, 165.18, 146.33, 145.92, 145.89, 139.68, 139.22, 139.07, 120.61, 120.43, 120.31, 110.40, 110.15×2, 70.94, 70.43, 68.91; HRMS (ESI$^+$, *m/z*): $[M + Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 1115.1189; found 1115.1191.

1,2,3,4,5,6-Hexa-*O*-galloyl-*epi*-inositol (105)

Colorless amorphous. 55% yield from *epi*-inositol. ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.32 (s, 4H), 7.02 (s, 2H)×2, 6.98 (s, 4H), 6.57 (t, *J* = 10.7 Hz, 1H), 6.29 (t, *J* = 3.4 Hz, 2H), 5.98 (t, *J* = 3.8 Hz, 1H), 5.89 (dd, *J* = 10.3, 3.4 Hz, 2H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 166.69, 166.18, 165.84, 165.63, 145.86, 145.80, 139.45, 139.27, 139.17, 139.06, 121.23, 121.01, 120.83, 120.64, 110.85, 110.37, 110.14, 110.02, 70.82, 70.19, 68.36, 67.78; HRMS (ESI$^+$, *m/z*): $[M + Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 1115.1189; found 1115.1189.

1,2,3,4,5,6-Hexa-*O*-galloyl-*muco*-inositol (107)

Colorless amorphous. 45% yield from *muco*-inositol. ^{1}H NMR (600 MHz, Methanol-d_4): δ 7.03 (m, 12H), 5.812 (m, 6H); ^{13}C NMR (150 MHz, Methanol-d_4): δ 167.28, 146.47, 146.43, 140.58, 140.48, 120.32, 110.73, 110.50, 71.20, 69.36; HRMS (ESI$^+$, *m/z*): $[M + Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 1115.1189; found 1115.1189.

1,2,3,4,5,6-Hexa-*O*-galloyl-*myo*-inositol (107)

Colorless amorphous. 98% yield from *myo*-inositol. ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.25 (s, 2H), 7.01 (s, 2H), 7.00 (s, 4H), 6.97 (s, 4H), 6.26 (t, *J* = 3.1 Hz, 1H), 6.22 (t, *J* = 10.0 Hz, 2H), 6.13 (t, *J* = 10.0 Hz, 1H), 5.90 (dd, *J* = 10.3, 2.7 Hz, 2H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 165.96, 165.87, 165.78, 165.69, 146.19, 145.86, 145.82, 139.47, 139.26, 139.12, 139.10, 120.66, 120.62, 120.39, 110.15, 110.08, 110.05, 110.03, 71.36, 70.67, 70.63, 69.43; HRMS (ESI$^+$, *m/z*): $[M + Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 1115.1189; found 1115.1189.

1,2,3,4,5,6-Hexa-*O*-galloyl-*scyllo*-inositol (108)

Colorless amorphous. 60% yield from *scyllo*-inositol. ^{1}H NMR (600 MHz, Acetone-d_6): δ 6.95 (s, 12H), 6.05 (s, 6H); ^{13}C NMR (150 MHz, Acetone-d_6): δ 165.78, 145.79, 139.04, 120.76, 110.15,

71.45; HRMS (ESI$^+$, *m/z*): $[M + Na]^+$, calcd for $[C_{48}H_{36}O_{30}Na]^+$: 1115.1189; found 1115.1188.

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