

平成 30 年度 博士学位論文

マイクロフローリアクター式配糖化法を利用した

サポニン誘導体ライブラリーの構築とその性質に関する研究

**The study of saponin derivatives library construction with microflow
reactor type glycosylation method and their properties**

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略語表

Ac	acetyl
AD	aminoethyl diphenylborinate
Api	apiose
aq.	aqueous
Ara	arabinose
BF ₃ •OEt ₂	boron trifluoride ethyl ether complex
Bn	benzyl
Bz	benzoyl
Cin	cinnamoyl
Cel	cellobiose
CMC	Critical Micelle Concentration
Co., Ltd.	Company Limited
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Dig	digitoxose
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMPC	1,2 Dimyristoyl-sn-glycero-3-phosphocholine
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPH	1,6-diphenyl-1,3,5-hexatriene
DPT	Diphtheria Pertussis Tetanus
EC ₅₀	half maximal (50%) effective concentration
ELISA	Enzyme Linked Immuno Solvent Assay
eq.	equivalent
ESI	electrospray ionization
Et	ethyl

EtOAc	ethyl acetate
Fuc	fucose
Gal	galactose
Glc	glucose
GlcA	glucuronic acid
GSK	GlaxoSmithKline
h.	hour
HD ₅₀	hemolytic dose (50%)
HIV	human immunodeficiency virus
HMBC	¹ H-detected multiple-bond heteronuclear multiple quantum coherence spectrum
HMG	3-hydroxy-3-methylglutary
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectroscopy
IC ₅₀	half maximal (50%) inhibitory concentration
Inc.	Incorporated
ISCOM	Immune-Stimulating Complexes
ITAM	immunoreceptor tyrosine-based activation motif
IR	infrared absorption spectroscopy
¹ H-, ¹³ C-NMR	proton-, carbon-nuclear magnetic resonance
Lac	lactose
LDH	lactate dehydrogenase
LLC	Limited Liability Company
LR-MS	low resolution mass spectroscopy
Mal	maltose
Man	mannose
Me	methyl
Mel	mellibiose
MeOH	methanol
min	minute
MPL	monophosphoryl lipid

MS4Å	molecular sieves 4Å
Nalp3	NACHT, LRR and PYD domains-containing protein 3
nc	negative control
NHA	no hemolytic activity
NOESY	nuclear Overhauser effect spectroscopy
OD	optical density
ODt	optical density of tested saponins
OVA	ovalbumin
PBS	phosphate buffer saline
pc	positive control
Ph	phenyl
Piv	pivaloyl
PMB	<i>p</i> -methoxybenzyl
ppm	parts per million
prep.	preparative
PTFE	polytetrafluoroethylene
pyr	pyridine
QS	Quillaja Saponin
quant.	quantitative
Rha	rhamnose
sat.	saturated
r.t.	room temperature
SAR	structure-activity relationship
S _N 2	second-order Nucleophilic Substitution
<i>t</i>	tertiary
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetrabutylammonium iodide
Temp.	temperature
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate

Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TLR	Toll-like receptor
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOCSY	total correlation spectroscopy
USA	United States of America
UV	ultraviolet
Xyl	xylose

第一章 序論

第一節 サポニンの機能性

第一項 サポニンとは¹

サポニンは生薬として使用される天然の植物や一部の菌類、棘皮動物（ヒトデやナマコ）に含まれる配糖体の一種である²。アグリコンである脂溶性のトリテルペンあるいはステロイド骨格と種々の糖鎖が結合した構造に起因した両親媒性の性質を有することから、サポニンは古来より界面活性作用を活用した石鹸等に使用されてきた。サポニンの生物活性としては、鎮咳去痰、抗炎症、抗腫瘍等が報告されており、アグリコンと糖鎖構造が複雑に組み合わさる事で幅広い生物学的及び薬理学的作用を有している³。また、サポニンを含有する生薬は漢方薬に配合され、今日に至るまで服用されている。以下にサポニンを含有する生薬名と代表的なサポニンの名称を示す (Table 1)。

Table 1 サポニンを含む生薬の分類

骨格	生薬名	基原植物の学名	代表的なサポニンの名称
トリテルペン	イレイセン	<i>Clematis chinensis</i> Osbeck	clematichinenoside A,B,C
トリテルペン	オンジ	<i>Polygala tenuifolia</i> Willd.	onjisaponin A-G
トリテルペン	カンゾウ	<i>Glycyrrhiza uralensis</i> Fisch.	glycyrrhizic acid
トリテルペン	キキョウ	<i>Platycodon grandiflorum</i> A. DC.	platycodin A,C,D
トリテルペン	サイコ	<i>Bupleurum falcatum</i> Linné	saikosaponin a,c,d,e
トリテルペン	セネガ	<i>Polygala senega</i> Linné	senegin II, III, IV
トリテルペン	チクセツ ニンジン	<i>Panax japonicus</i> C. A. Mey.	chikusetsusaponin V
トリテルペン	モクツウ	<i>Akebia quinata</i> Decne. <i>Akebia trifoliata</i> Koidzumi	akeboside St _e , St _j
トリテルペン	ダイズ油	<i>Glycine max</i> Merrill.	soyasaponin I-III
ステロイド	オウギ	<i>Astragalus membranaceus</i> Bunge	astragaloside I-VII
ステロイド	サンソウニン	<i>Zizyphus jujuba</i> Mill. var. <i>spinosa</i> Hu ex H. F. Chou	jujuboside A,B,C
ステロイド	タイソウ	<i>Zizyphus jujuba</i> Mill. var. <i>inermis</i> Rehder	zizyphus saponin I-III
ステロイド	ニンジン (コウジン)	<i>Panax ginseng</i> C. A. Mey.	ginsenoside R _{b1}
ステロイド	ゴシツ	<i>Achyranthes fauriei</i> Leveille et Vaniot	achyranthoside A-D
ステロイド	コンズランゴ	<i>Marsdenia cundurango</i> Reichenbach filius	condurangoglycoside
ステロイド	ジギタリス	<i>Digitalis purpurea</i> Linné	digitoxin
ステロイド	ケジギタリス	<i>Digitalis lanata</i> Ehrh.	digoxin
ステロイド	ストロファンツス	<i>Strophanthus gratus</i> Franch	G-strophanthin
ステロイド	サンキライ	<i>Smilax glabra</i> Roxburgh	smilaxsaponin A-C
ステロイド	チモ	<i>Anemarrhena</i> <i>asphodeloides</i> Bunge	timosaponin A-I-IV B-I, II
ステロイド	バクモンドウ	<i>Ophiopogon japonicus</i> Ker-Gawler	ophiopogonin A-D
ステロイド	テンモンドウ	<i>Asparagus cochinchinensis</i> Merrill	asparasaponin 1

第二項 サポニンの生物活性

I. サポニンのアジュバント活性

サポニンの興味深い生物活性の 1 つにはアジュバント活性がある。アジュバントとは 1920 年代に Ramon によって発見され抗原と共に接種されその抗原に対する免疫応答を増強する因子の総称である⁴。欧州ではオイル・イン・ウォーターエマルジョンの MF59 や AS03 が認可されているが⁵、日本では主に皮下接種ワクチンに対し Glenney らによって開発されたアルミニウム塩アジュバント（水酸化アルミニウム、塩化アルミニウム、リン酸アルミニウムゲル: Alum）が使用されている⁶（Table 2）。

Table 2 臨床応用されているアジュバントの分類

アジュバント	成分	作用機序	免疫応答	使用ワクチン
Alum	アルミニウム塩	Nalp3, ITAM, Ag delivery	抗体、Th2	B 型肝炎、破傷風、 DT、DTP
AS04	アルミニウム塩 +MPL	TLR4	抗体、Th1	子宮頸がん サーバリックス GSK
AS03	スクアレン+ DL- α -tocopherol oil in water emulsion	Ag uptake etc.	抗体、Th1, Th2	H1N1 インフルエンザ アレパンリックス GSK
MF59	スクアレン oil in water emulsion	ASC	抗体、Th1, Th2	H1N1 インフルエンザ CELTURA ノバルティス
Imiquimod, R848	Imidazoquinolines	TLR7 TLR8	抗体、Th1	Aldara
Virosomes	-	Ag delivery	抗体、Th1, Th2, CD8	A 型肝炎 Epaxal、Inflexal

代表的なサポニンアジュバントには *Quillaja saponaria* Molina（シャボンの木の樹皮）から得られる半精製抽出物（QS-21）が知られている⁷。QS-21 は半精製抽出物を逆相 HPLC で分画し得られた 22 個の内の 21 番目の画分であり、2 つの末端糖鎖の構造が異なる QS-21A_{api} と QS-21A_{xyI} を少なくとも含んでいる。QS-21A_{api} と QS-21A_{xyI} の全合成は Gin らによって達成されており⁸（Figure 1）、グリコシルエステル結合をアミド結合に変換した安定誘導体の活性評価⁹やプローブ導入による共焦点顕微鏡を用いたメカニズム解析研究¹⁰等も行われている。現在、QS-21 は高い免疫アジュバント作用を持つことから HIV・がん・マラリア¹¹治療に優れたワクチンアジュバントの有

力候補の AS-01 (QS-21 と monophosphoryl lipid; MPL の混合物) として臨床試験が進行中である。しかし、均一な化合物としての供給は難しく、僅かな不純物由来の活性提示や溶血作用等も懸念されている。アジュバント活性発現のメカニズムは、

1) QS-21 の持つアルデヒドが T 細胞上のリジンのアミノ基と Schiff 塩基を形成し T 細胞を活性化させる¹²

2) 細胞膜に存在するレクチンを介して働く¹³

等諸説議論されており、不明な点が多い。

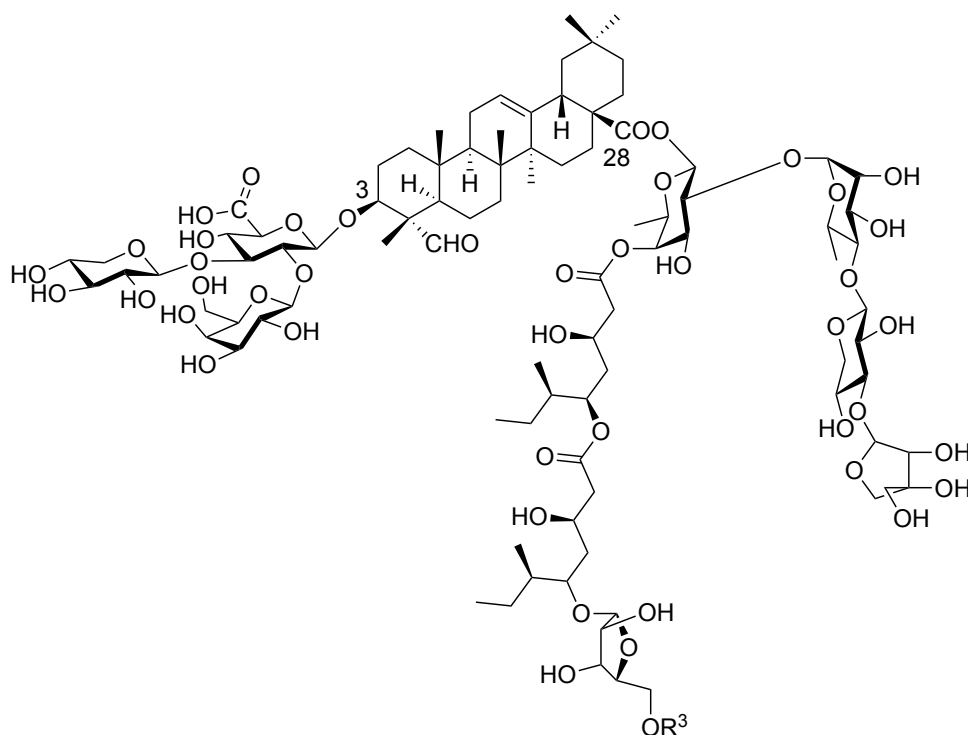


Figure 1 QS-21A_{api} の化学構造

II. サポニンの界面活性作用¹⁴

前項で示した様にサポニンは興味深い生物活性を有しているが、筆者はアジュバント活性発現のメカニズムは界面活性で説明できる報告例に注目した。

両親媒性構造を有するサポニンは水表面で脂溶性部位を外に向けて配向、あるいは水中で分散状態のモノマー分子が、脂溶性部位を内側に配向し会合体のミセルを形成して界面活性作用を発揮する (**Figure 2**)。水中でミセル形成を開始する濃度を臨界ミセル濃度 (Critical Micelle Concentration; CMC) と呼ぶ。サポニンを含む界面活性剤は CMC 以上になると石鹼に代表される洗浄力・可溶化力の増加や表面張力等の物理化学的性質が減少する¹⁵ (**Figure 3**)。

CMC あるいはミセル、界面活性作用がアジュバント活性に関与する報告は以下に示す例がある。

1) 微生物由来の界面活性剤のサーファクチン (**Figure 4**)¹⁶ は同じ投与量の場合でも接種溶液が臨界ミセル濃度以下の場合、OVA 特異的抗体価は臨界ミセル濃度以上での接種に比較して有意に低い。

2) QS-21 はコレステロール及びリン脂質とミセルを形成し、抗原提示能を示す ISCOM (Immune-Stimulating Complexes) として作用を発揮する¹⁷。

一方、CMC は毒性の溶血作用とも関連がある (**Figure 5**)¹⁸。即ち、サポニンの α -hederin は CMC 以下の濃度において脂質二重層のコレステロールとベシクルを形成し非可逆的に膜を破壊する (**Figure 5-A-C**)。CMC 以上の濃度ではサポニンのミセル構造がキャリアーの役割を果たし細胞膜を破壊する。その後、細胞膜のコレステロールやジミリストイル-ホスファチジルコリン (DMPC) と再度ミセルを形成し非可逆的に破壊する (**Figure 5-D-E**)。

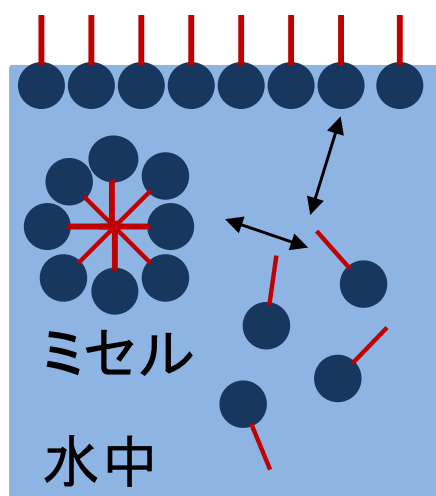


Figure 2 水中で形成されるミセル構造

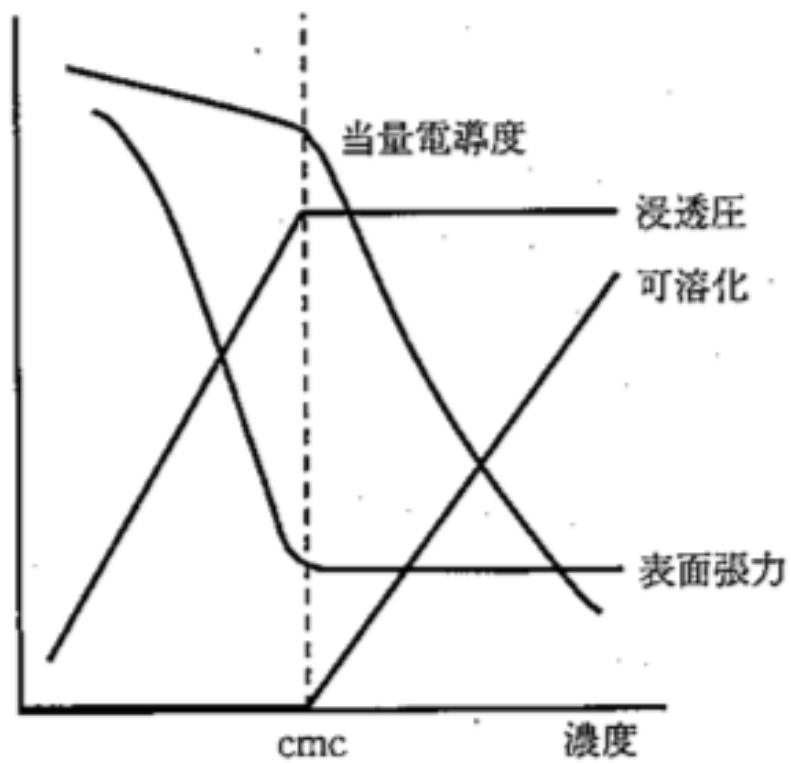


Figure 3 CMC 前後の物理化学的特性の変化

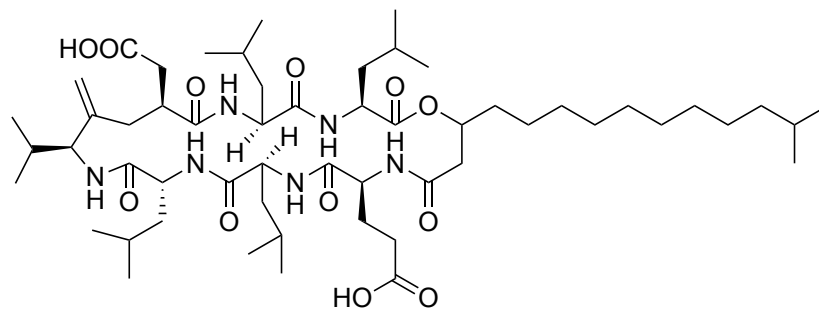


Figure 4 界面活性を有するバイオサーファクタントであるサーファクチンの構造

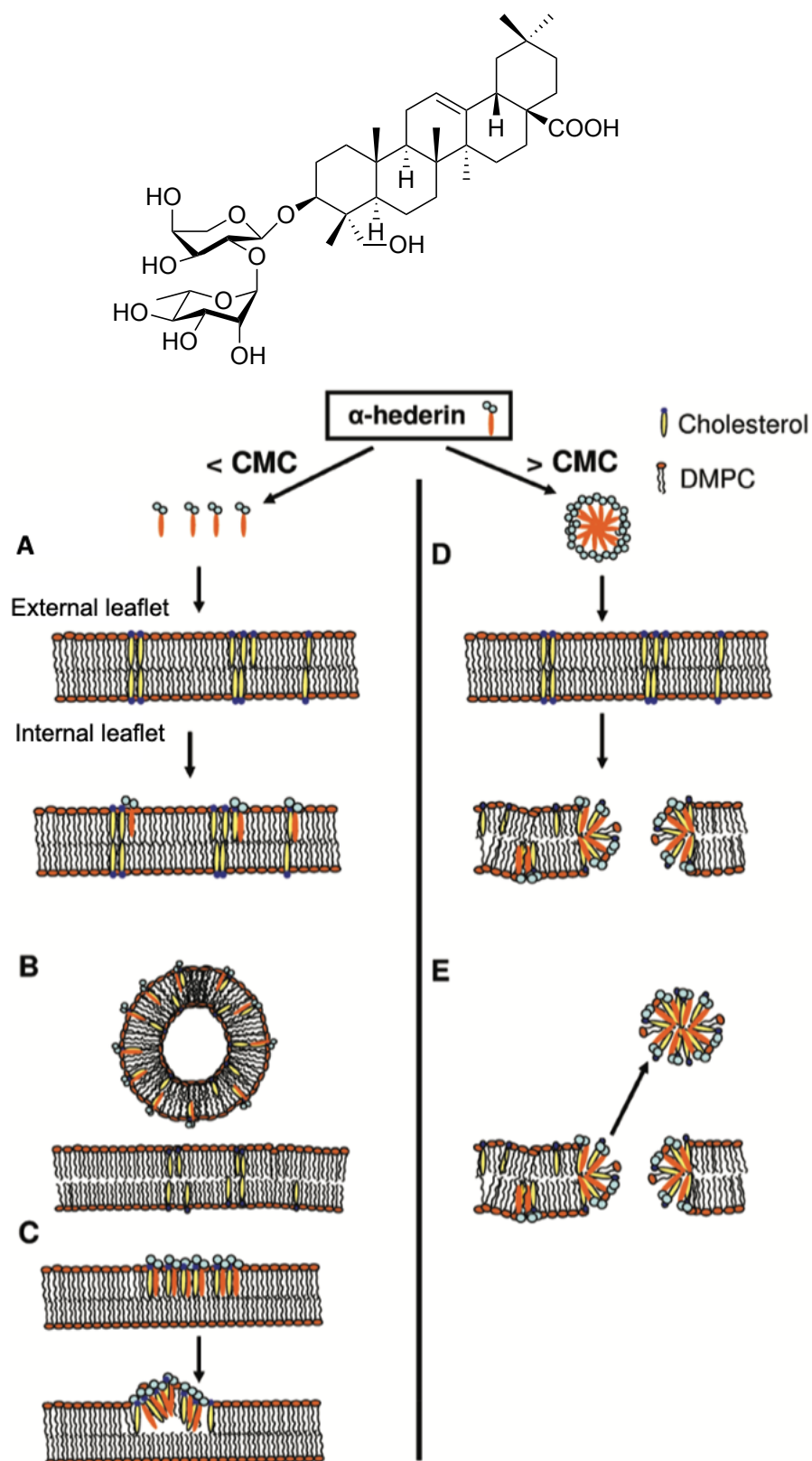


Figure 5 α-ヘデリンの構造とCMCと溶血作用の関係性

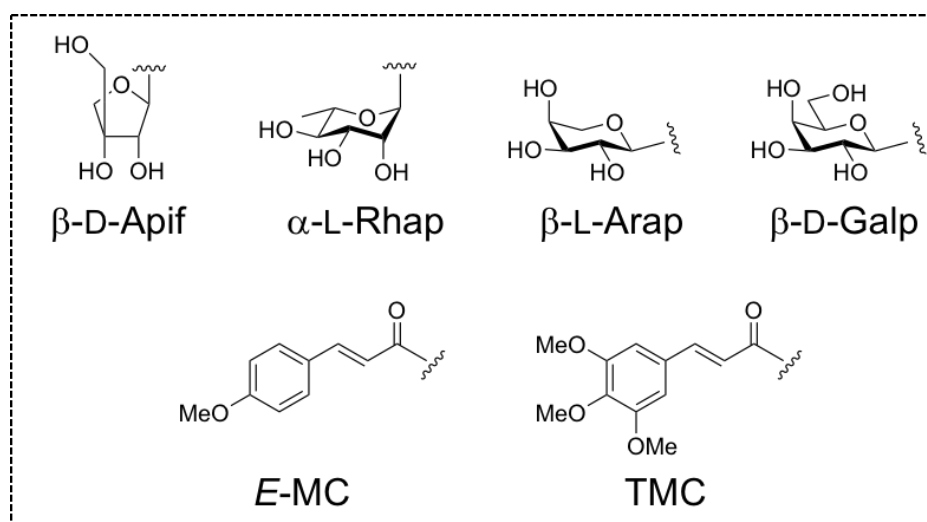
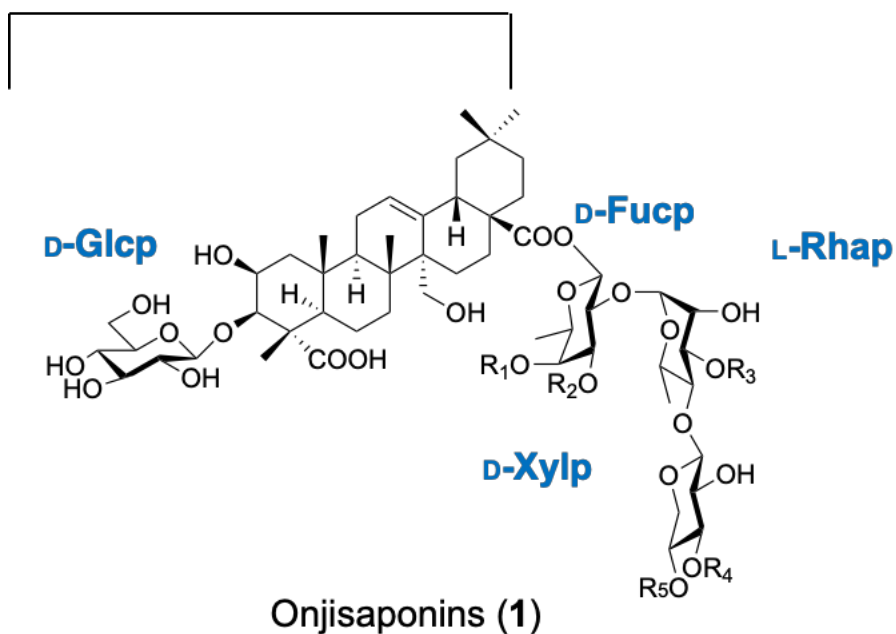
III. オンジサポニンのアジュバント活性

このような背景がある一方で、北里大学北里生命科学研究所・大学院感染制御科学府・和漢薬物学教室の山田、清原、永井らは二百数十種の生薬の熱水抽出エキスについて経鼻接種型インフルエンザスプリットワクチンと同時に接種した場合に粘膜ワクチンアジュバント活性を示す素材エキスの探索を独自に行った。その結果、生薬の「遠志（オンジ）」（イトヒメハギ *Polygala tenuifolia* Willdenow の根または根皮）の熱水抽出エキスが最も高いアジュバント活性を有し、さらにオンジ熱水抽出エキス中の有効成分を単離同定し、オンジサポニン A, E, F, G (**1Aa-d**) (**Table 3**) のアジュバント活性も見出した¹⁹。特にオンジサポニン A (**1Aa**) はコレラトキシンの B サブユニット (CTB) と同等のアジュバント活性を有しており、毒性も少ない。また、市販のオンジサポニン B (**1Ae**) はオンジサポニン E (**1Ab**) と同等の活性を有する事が明らかにされている（永井ら、未発表データ）。

オンジサポニン類はトリテルペンのオレアナン骨格であるプレセネゲニン (2 β , 3 β , 27-trihydroxyolean-12-ene-23, 28-dioic acid) をアグリコンとし、C-28 位カルボキシル基に β -D-xylopyranosyl-(1 \rightarrow 4)- α -L-rhamnopyranosyl-(1 \rightarrow 2)- β -D-fucopyranosyl 基がグリコシルエステル結合した配糖体を共通構造とする。また、C-3 位ヒドロキシ基に β -D-glucopyranosyl 基がグリコシルエーテル結合した **tenuifolin (2A)** を共通構造とする。上記構造の他に、D-フコースの 3' 位あるいは 4' 位に桂皮酸エステルを有する点が特徴的である。さらに、種々の単糖 (β -D-glucopyranosyl 基、 β -D-apiofuranosyl 基、 α -L-arabinopyranosyl 基、 β -D-galactopyranosyl 基、 α -L-rhamnopyranosyl 基) が様々な組み合わせで結合し、3-hydroxy-3-methylglutary (HMG) 基やアセチル (Ac) 基を含む構造を併せると 30 種以上のオンジサポニン類の報告がある²⁰。

Table 3 アジュバント活性を有するオンジサポニン A,E,F,G の化学構造

Tenuifolin (2A)



Onjisaponin	R ₁	R ₂	R ₃	R ₄	R ₅
A (1Aa)	<i>E</i> -MC	α -L-Rhap	β -D-Apif	H	β -D-Galp
E (1Ab)	TMC	H	H	H	β -D-Galp
F (1Ac)	TMC	H	β -D-Apif	β -L-Arap	H
G (1Ad)	TMC	H	β -D-Apif	H	H
B (1Ae)	<i>E</i> -MC	α -L-Rhap	H	H	β -D-Galp

遠志熱水抽出エキスをアルカリ処理し桂皮酸エステルやプレセネゲニン骨格の C-28 位に結合したエステル化オリゴ糖を除去した場合に活性の消失が明らかとなっている事から、C-3 位と C-28 位にそれぞれ糖が結合する bisdesmoside 構造 (糖がアグリコン上のヒドロキシ基あるいはカルボキシ基の二箇所結合した型)²¹としての性状がその活性発現に関与している事が推定された (永井ら、未発表データ)。しかし、C-28 位にエステル結合したオリゴ糖や 3' 位桂皮酸エステル結合を有するオンジサポニン類等との構造活性相関の詳細なデータは得られていない。

問題点の 1 つにはサポニンの供給方法が考えられる。サポニンの化学全合成は以下の理由で産業上の付加価値が高い医薬候補物質の合成等、コストに見合った化合物への利用に限定される²²。

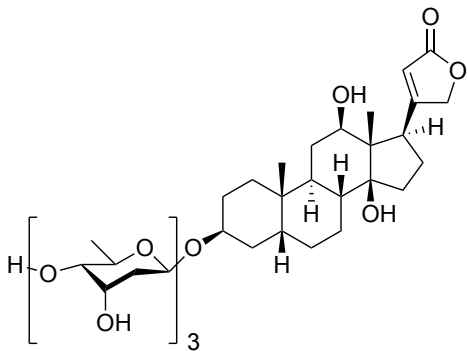
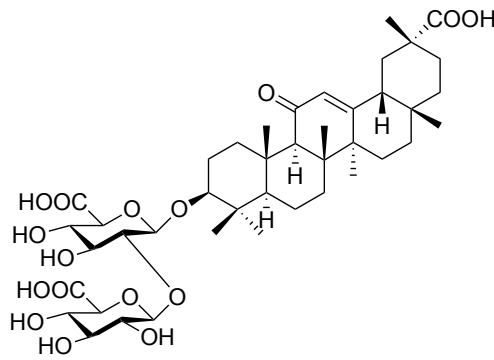
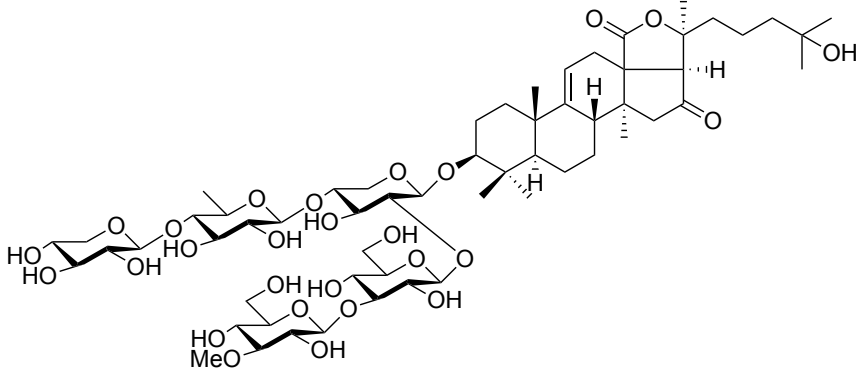
1) 半合成も含めて天然から容易に入手可能な場合を除くと、アグリコンの供給に全合成的な手法が必要²³。

2) 多数のヒドロキシ基を有する糖とアグリコンを基質とする事から、保護・配糖化・脱保護の工程が繰り返し必要²⁴。

Gin らは前述した QS-21A_{api} の全合成を達成しているが、複雑な C-3 位と C-28 位の糖鎖構造の構築に多段階合成が必要で生産性が低い問題があった²⁵。そのため、現在は単離した半精製抽出物である QS-21 が用いられている。

一方、天然のサポニン類はアグリコンと糖鎖構造の組み合わせが多岐に渡り、何十種類もの化合物が微量ずつ混在している。そのため、天然資源からの単離では個々の成分が低含量・低収率となり、生物活性の評価に必要な充分量のサポニンの確保は困難である。前述した QS-21 も単体の成分で臨床試験には用いられていない。臨床応用されている天然由来の単体のサポニンはケジギタリス (*Digitalis lanata*) の葉から十分量の抽出が可能なジゴキシンやウラルカンゾウ (*Glycyrrhiza uralensis*) の根由来のグリチルリチン製剤、マナマコ (*Stichopus japonicus*) から独自の抽出法で単離供給されるホロトキシン類²⁶等に限られている (Table 4)。

Table 4 臨床応用されているサポニンの分類

サポニンあるいは強心配糖体の構造	成分名・用途
	<p>ジゴキシン <i>Digitalis lanata</i> 由来</p> <p>うつ血性心不全薬 医療用医薬品</p>
	<p>グリチルリチン <i>Glycyrrhiza uralensis</i> 由来</p> <p>肝不全治療薬・ 抗アレルギー治療薬 医療用医薬品</p>
	<p>ホロトキシン <i>Stichopus japonicus</i> 由来</p> <p>水虫治療薬 第二類医薬品</p>

第三項 オレアノール酸サポニン誘導体のアジュバント活性

第二項に示したサポニン供給面の解決方策として、筆者らは化学合成の容易なサポニン誘導体の合成計画を立てることとした。即ち、筆者らはアジュバント活性を示すオンジサポニン類がプレセネゲニン骨格の C-28 位にグリコシルエステル結合した糖鎖や D-フコースの 4' 位にエステル結合した桂皮酸を有する共通基本構造に着目した。

初めに、筆者らはオンジサポニンの構造をアグリコン・糖鎖・桂皮酸の 3 つのパーツからなると考え、構造を簡略化した **tenuifolin** 誘導体を合成することを考えた。しかし、天然基質となる **tenuifolin (2A)** は生薬のセネガ (セネガ *Polygala senega* Linné またはヒロハセネガ *Polygala senega* Linné var. *lactifolia* et Gray の根) から単離する必要があった。また、**tenuifolin (2A)** は分子内に C-23 位と C-28 位の二箇所にカルボキシ基を有しており、天然オンジサポニンの構造に近いサポニン誘導体を合成する C-28 位選択的配糖化の方法論を検討するには **tenuifolin (2A)** の供給量に問題があった。そこで、まずは第一段階として **tenuifolin** のアグリコン上の 3 つの酸素極性官能基以外の構造が同一のオレアノール酸 (**3B**) をアグリコンとし、D-グルコースを糖基質としたサポニン誘導体を合成する方針とした (**Figure 6**)。

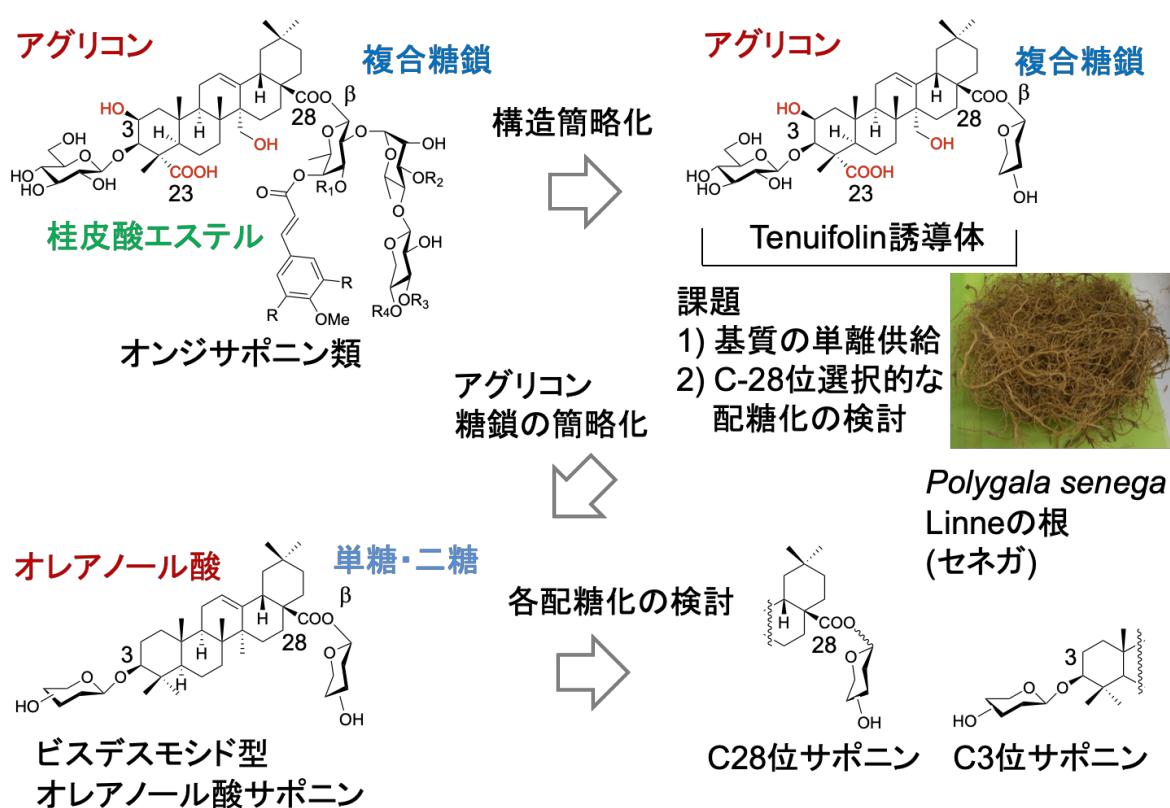


Figure 6 合成研究のコンセプト

筆者を含む研究グループは先行研究でオレアノール酸 (**3B**) をアグリコンとしたサポニン誘導体 **4Ba** とさらに D-グルコースの 4' 位にジメトキシ桂皮酸が結合したオ

レアノール酸サポニン誘導体 **4Bb** を合成し、onjisaponin A (**1Aa**) を陽性対照としてアジュバント活性を評価した (**Figure 7**)²⁷。BALB/c マウスにインフルエンザスプリットワクチン (H1N1 亜型) 及び各サポニンの混合物を 0 及び 14 日目に経鼻接種することで二次免疫を行い、初回接種後 35 日目の血清及び鼻腔洗液中の抗インフルエンザウイルス抗体価を測定した。

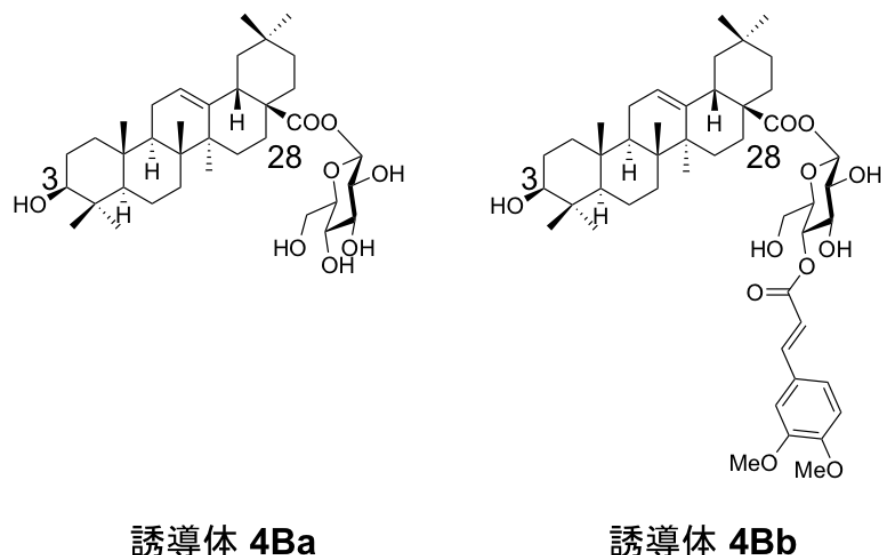


Figure 7 合成オレアノール酸 C-28 位サポニン **4Ba, b** の化学構造

その結果、誘導体 **4Bb** 接種群の血清抗インフルエンザウイルス IgG 抗体価の有意な上昇が観察された (**Figure 8-a**)。また、鼻腔洗液中の抗インフルエンザウイルス IgA 抗体価は対照群と比較して僅かであるが統計学的に有意に増加した (**Figure 8-b, c**)。一方、誘導体 **4Ba** 接種群のこれらの抗体価の変化は観察されず、逆にウイルス特異的 IgE 抗体価の上昇が引き起こされた (**Figure 8-d**)。

しかし、天然の onjisaponin A (**1Aa**) と比べ誘導体 **4Bb** の粘膜ワクチンアジュバント活性は大きく劣っていた。これらの結果から、以下に示す 3 点が示唆された。

- ①オレアノール酸とプレセネゲニンを比べると IgA 抗体価の上昇にはアグリコン上の酸素極性官能基の違いが影響を与えていること
- ②アグリコンや糖鎖構造を簡略化したオレアノール酸誘導体でも IgG や IgA 抗体価等の上昇を期待できること
- ③誘導体 **4Ba** と **4Bb** を比べると IgA 抗体価の上昇と IgE 抗体価の低減には桂皮酸エステルが必要であること

活性をさらに向上させた誘導体を供給するには、活性発現に必要な構造要件を明らかにする必要があった。

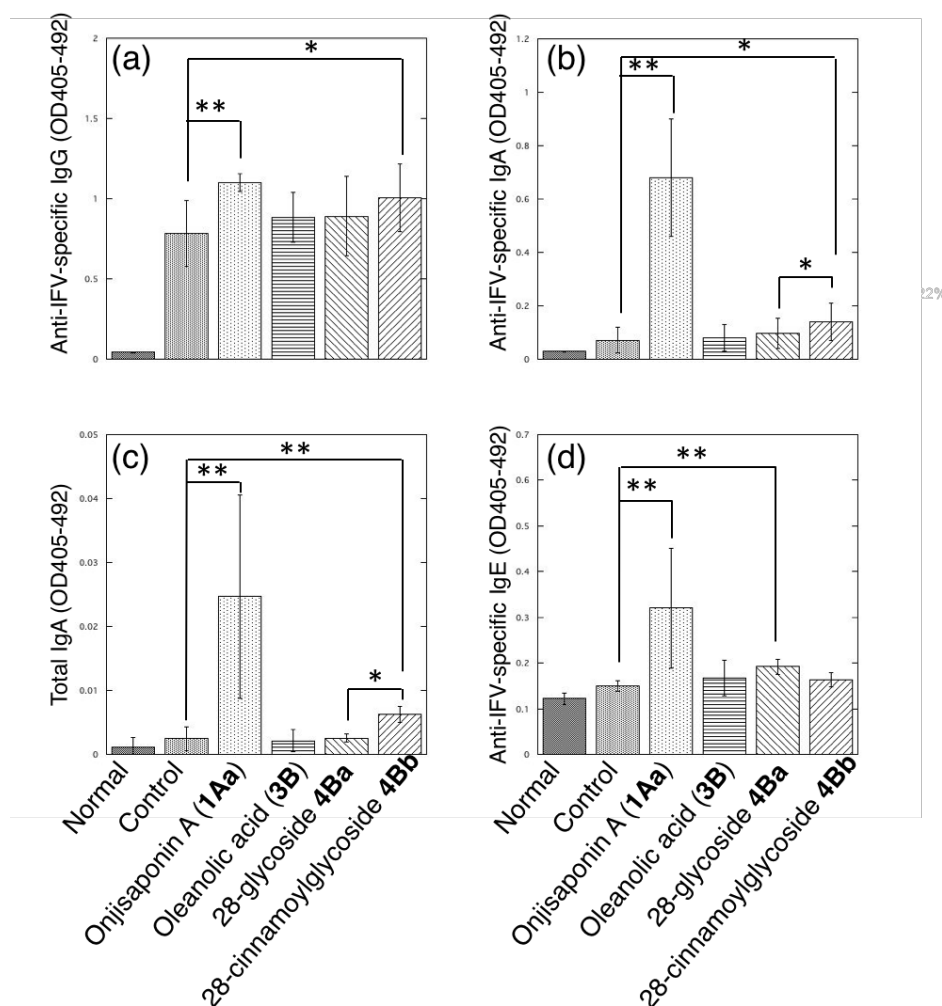


Figure 8 経鼻接種インフルエンザスプリットワクチンによる二次免疫モデルマウスでの抗原特異的抗体価及び総 IgA 抗体量に対する合成サポニン **4Ba** 及び **4Bb** のアジュバント活性

(a) 血清中の抗インフルエンザウイルス IgG 抗体価 (b) 鼻腔洗液中の抗インフルエンザウイルス IgA 抗体価 (c) 総 IgA 抗体価 (d) 血清中の抗インフルエンザウイルス IgE 抗体価

The efficiency of saponins **4Ba** and **4Bb** were assessed by vaccination of groups of BALB/c mice. Values were expressed as the mean \pm SE. Differences between groups were analyzed with one way ANOVA followed by Fischer's LSD. *P < 0.05, **P < 0.01 (n = 7).

第二節 本研究の位置付け

第一項 本研究の目的

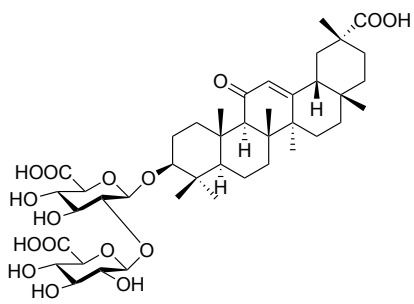
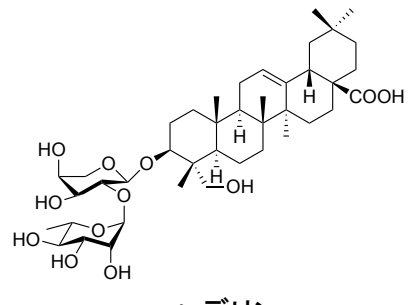
第一節第二項に示したそれぞれの報告例を基にすると、CMC以上の濃度で投与するとアジュバント活性が発現すると共に毒性である溶血作用も同時に示す可能性があった。ゆえに、優れたサポニンアジュバントの誘導体を創製するには、

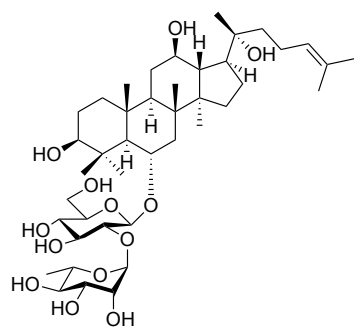
- 1) 毒性となる溶血作用の除去
- 2) アジュバント活性の保持

の2点の両立が重要となる。吉川らは47種類の天然サポニンのアジュバント活性と溶血作用間に相関関係がない報告²⁸をしており、溶血作用の発現を分離した誘導体の合成が可能であることが充分期待できると考えられた。

しかし、サポニンの物理化学的性質（表面張力）・生物活性（細胞毒性）・構造の3つに着目した先行研究例では用いたサポニン数は6種と少なく、構造的特徴も多岐に渡りその比較は困難であった²⁹ (Table 5)。

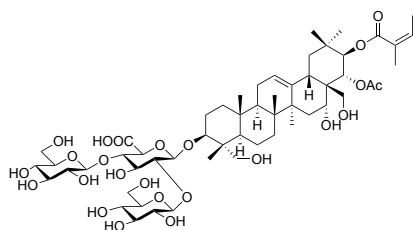
Table 5 天然サポニンのCMC・表面張力・細胞毒性の評価研究

Saponin	IC ₅₀ (μM)		EC ₅₀ (μM)	
	General cytotoxicity (DNA assay)	Membrane toxicity (LDH assay)	Reduction in surface tension	CMC (μM)
 グリチルリチン	>119	>238	128	>1429
 α-ヘデリン	35	29	4	13



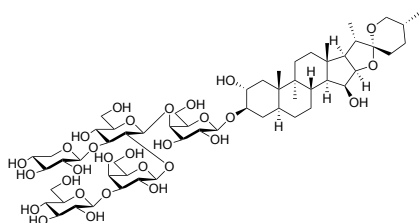
ジンセノシド Rg2

>127 783 25 >127



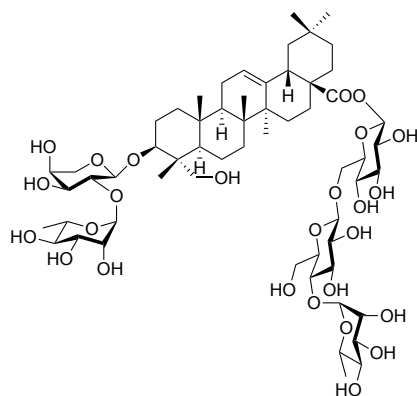
β-エスシン

52 34 7 88



ジギトニン

13 15 8 163



ヘデラコシド C

>164 >164 10 82

この理由には第一節第二項で示した供給法の課題があり、入手可能なサポニンに限定していることが原因と考えられた。

そこで、筆者らの研究グループは **tenuifolin (2A)** の単離法の確立・配糖化の研究を実施しつつ、サポニンの性質を数値化し *in vivo* アジュバント試験に用いる化合物のスクリーニング・構造活性相関の検討に役立つデータ・情報を解析することとした。本研究ではオレアノール酸サポニン誘導体合成研究方針の下、種々のアグリコンや糖鎖変換を指向したサポニン誘導体ライブラリーを構築し、界面活性作用を生じる最低濃度 (CMC) と生物活性 (赤血球溶血作用) の関連を明らかにすることを目的とし、ア

ジュバント活性試験に用いる候補化合物の選定や溶血作用を持たないサポニン誘導体アジュバントの創製等に役立つサポニンの性質データの取得を目指した (Figure 9)。

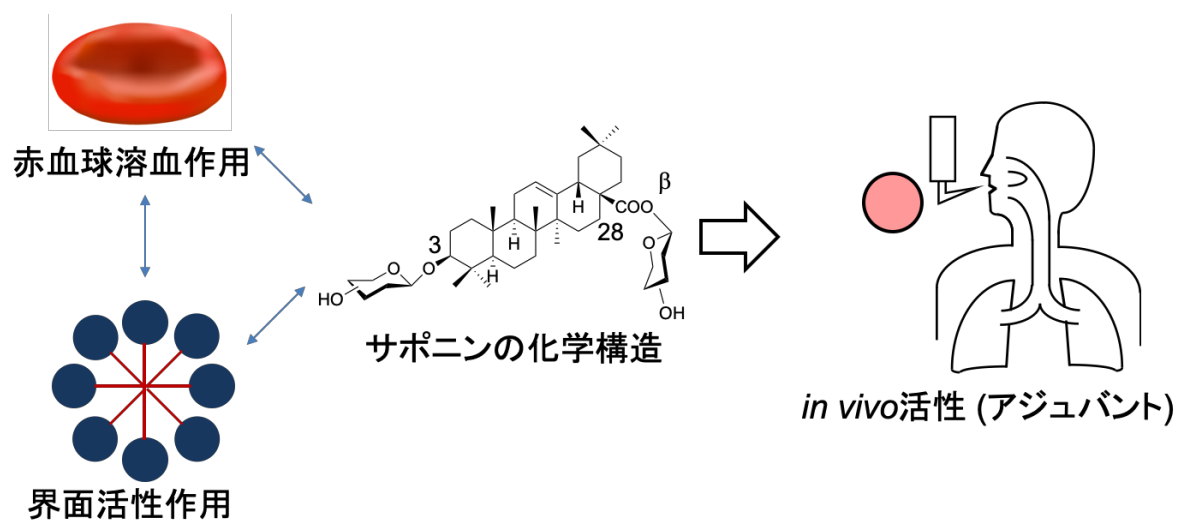
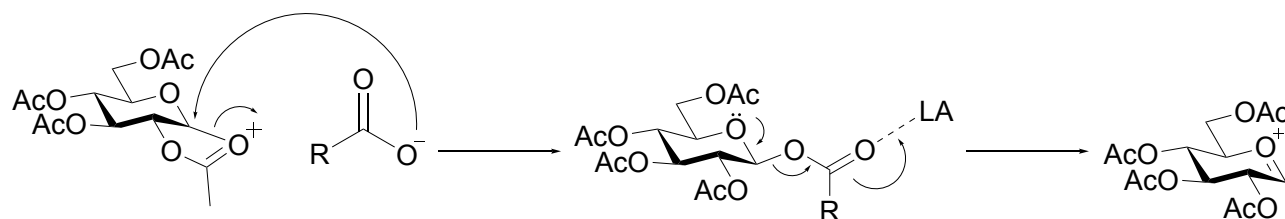


Figure 9 本研究の目的

第二項 合成上の課題

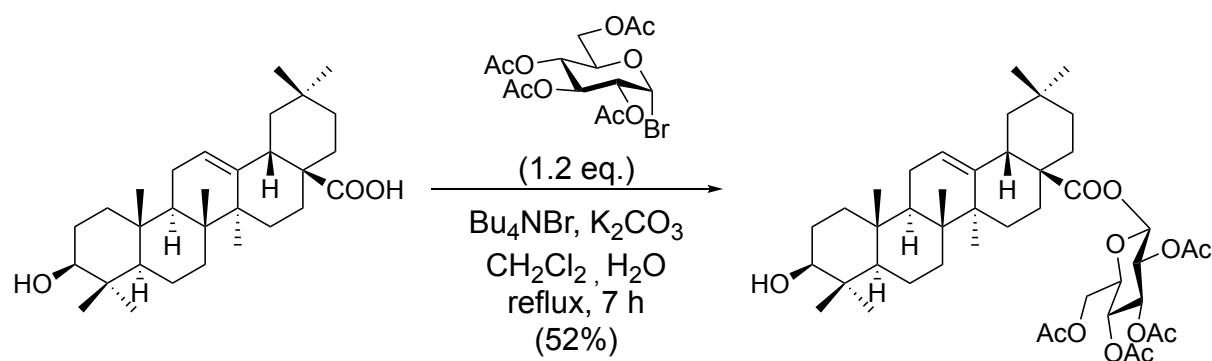
I.配糖化の方法論

サポニンは分子内エステル結合を介した糖鎖や桂皮酸構造を有しており、その合成にはエステル結合の位置及び立体選択的な付加反応の制御が重要となる。第一節第三項の二種の誘導体を合成するにあたり、鍵となる C-28 位配糖化の予備検討において、一旦形成されたグリコシルエステル結合が反応系中に残存する活性化剤による再活性化で切断が生じる過反応が観察される問題点があった (**Scheme 1**)。



Scheme 1 過反応によるグリコシルエステル結合の切断

サポニンの合成にはアグリコンと糖鎖を結合させる配糖化が鍵反応となる。トリテルペンの C-28 位カルボキシ基選択的配糖化の方法論には相関移動触媒とハロゲン化糖を用いた合成法が報告されている (**Scheme 2**)。しかし、短工程で調製可能なアセチル (Ac) 基ブロモドナーを用いた配糖化では収率が 52%と低く、反応時間も 7~24 時間必要であった³⁰。また、ハロゲン化糖は不安定で分解を受けやすく取り扱いや保存が難しい欠点があった。



Scheme 2 相関移動触媒を用いた C-28 位カルボキシ基選択的配糖化の方法論

II.解決方策: マイクロフローリアクター式合成とは

そこで、筆者はライブラリーを構築するサポニンの配糖化方法論の検討に用いる反応デバイスとしてマイクロフローリアクター式合成法に着目した。フロー式合成法³¹とは従来のフラスコで行うバッチ式合成法と比較し、反応器が管状であるので入口か

ら原料が導入され出口から生成物が放出される。物質が管の中に存在する時間を滞留時間と呼び、バッチ式反応器での反応時間に相当する。滞留時間はフロー管の長さ、断面積、流速から算出することができる (Figure 10)。このフロー式合成を可能とする反応デバイスは微細な流路を反応場とするので、主にマイクロフローリアクター、またはフローマイクロリアクター等と呼ばれる(以下、マイクロフローと称す)。

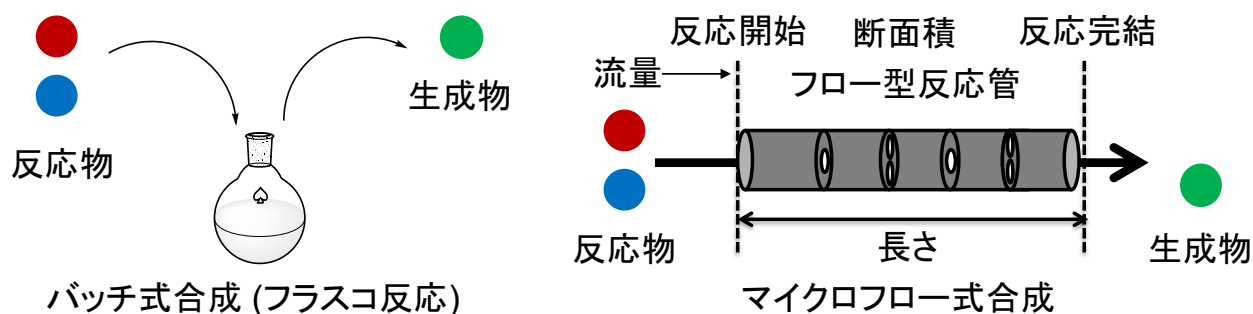


Figure 10 マイクロフローリアクター式合成の原理

III. マイクロフローの特徴

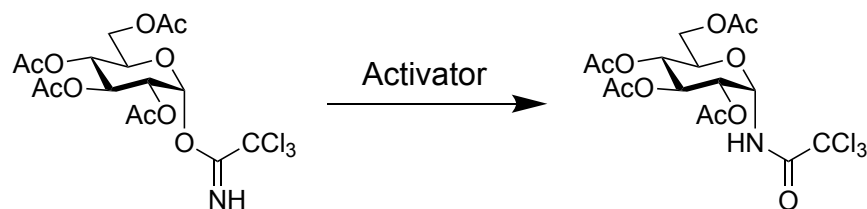
第一に、マイクロフローは微小空間を利用した反応場による短時間の混合が可能である。従って、フラスコを用いた反応場では不可能なミリ秒オーダーでの反応時間制御を行った反応を実現できる。

第二に、マイクロフローは単位容積あたりの表面積が大きく熱交換率が高い。従って、精密な温度制御や急激な加熱または冷却を必要とする反応に対し、マイクロフローを利用することで過反応や原料の分解を抑制する事ができる。

第三に、マイクロフローはフロー管の長さや内径、流速を調節する事により、滞留時間を厳密に制御できる。従って、マイクロフローを利用することで、高速な競争逐次的反応における反応選択性の向上や不安定中間体を経由した反応の実現が可能となる。近年では、吉田らによって提唱されたフロー合成法を利用したフラッシュケミストリーの概念が注目されている。フラッシュケミストリー²⁴とは、滞留時間を短く制御できるマイクロフローの特徴を利用し、短寿命活性種を活用した合成法を指す。

マイクロフローの利点は反応条件確立後の再現性の高さ、連続的な生成物の産生による容易な反応のスケールアップ、少量の液量を用いて反応を行う事のできる安全性等もある。

筆者はマイクロフロー合成を配糖化に利用する第一の理由として、イミダートドナーの転位反応³² (Scheme 3) や二糖アシルドナーの双極子モーメントの偏りによる反応性の低下³³ (Figure 11) 等の課題を解決し、配糖化に用いるドナー基質量の低減や収率の向上を期待できると考えた。



Scheme 3 イミダートドナーのチャップマン転位反応

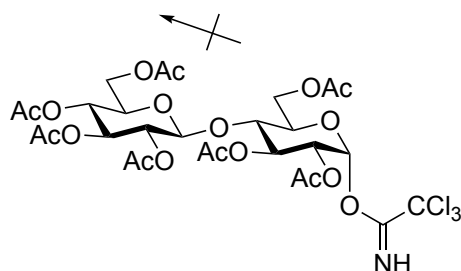


Figure 11 双極子モーメントの偏りによる二糖イミダートドナーの反応性の低下

第二の理由に、サポニンの連続反応にマイクロフローリアクターを利用できると考えた。田中らのマイクロフロー式 β マンノシル化法では、反応熱の制御をマイクロフローリアクター内で行い、フロー管の出口に連結したバッチ式反応を実施するマイクロフローリアクター・バッチ混合系システムを用いることで、バッチ式反応では収率が大幅に低下し困難であったグラムスケールの大量合成を達成している (Figure 12-A)³⁴。筆者はこの方法論に着想を得て、トリテルペンのマイクロフロー式配糖化と脱保護の連続反応を行いサポニンの精製工程数を低減させ合成できると考えた (Figure 12-B)。

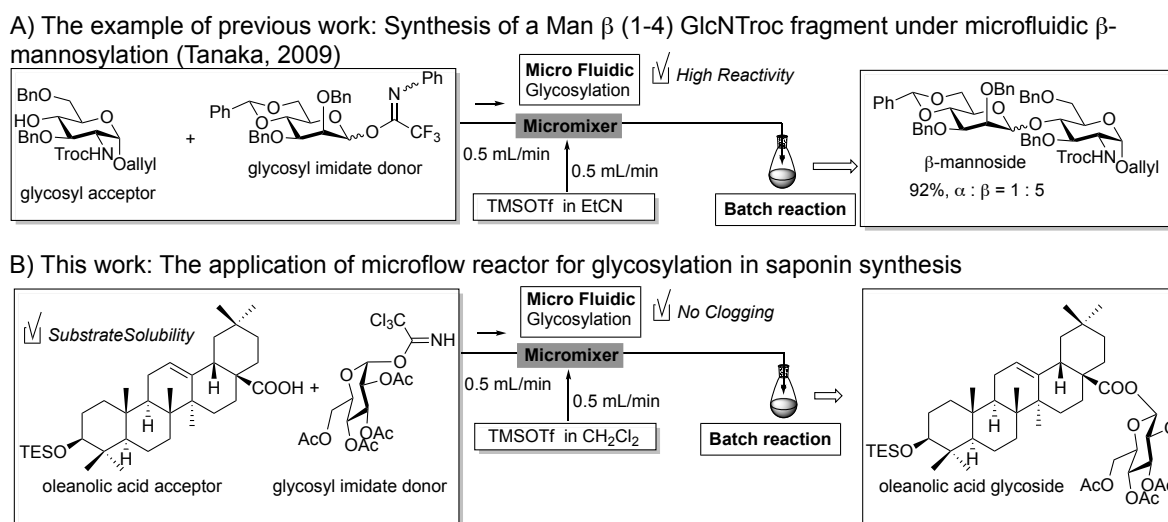


Figure 12 マイクロフローを利用したサポニン合成戦略

第三項 本研究の概要・全体像

本研究ではマイクロフロー式配糖化方法論を検討し、確立した方法論を用いて 8 種類のアグリコン・12 種類の糖鎖・2 種類の桂皮酸をそれぞれ組み合わせ、合計で 35 種類のサポニン誘導体ライブラリーの構築を行った (第一節～第六節)。

次に、合成した C-3 位サポニン、C-28 位サポニン、bisdesmoside 型サポニンライブラリーの赤血球溶血作用 (副作用) の評価、臨界ミセル濃度 (界面活性作用) の評価を実施しそれぞれの結果を示した (第七節 第一項～第三項)。

本研究の結果を基に構造・生物活性 (溶血作用)・界面活性作用 (臨界ミセル濃度; CMC) 間の関連性を考察し、今後の研究の展望: tenuifolin サポニン誘導体の合成 (第七節 第四項) をまとめたので以下順に詳述する (Figure 13)。

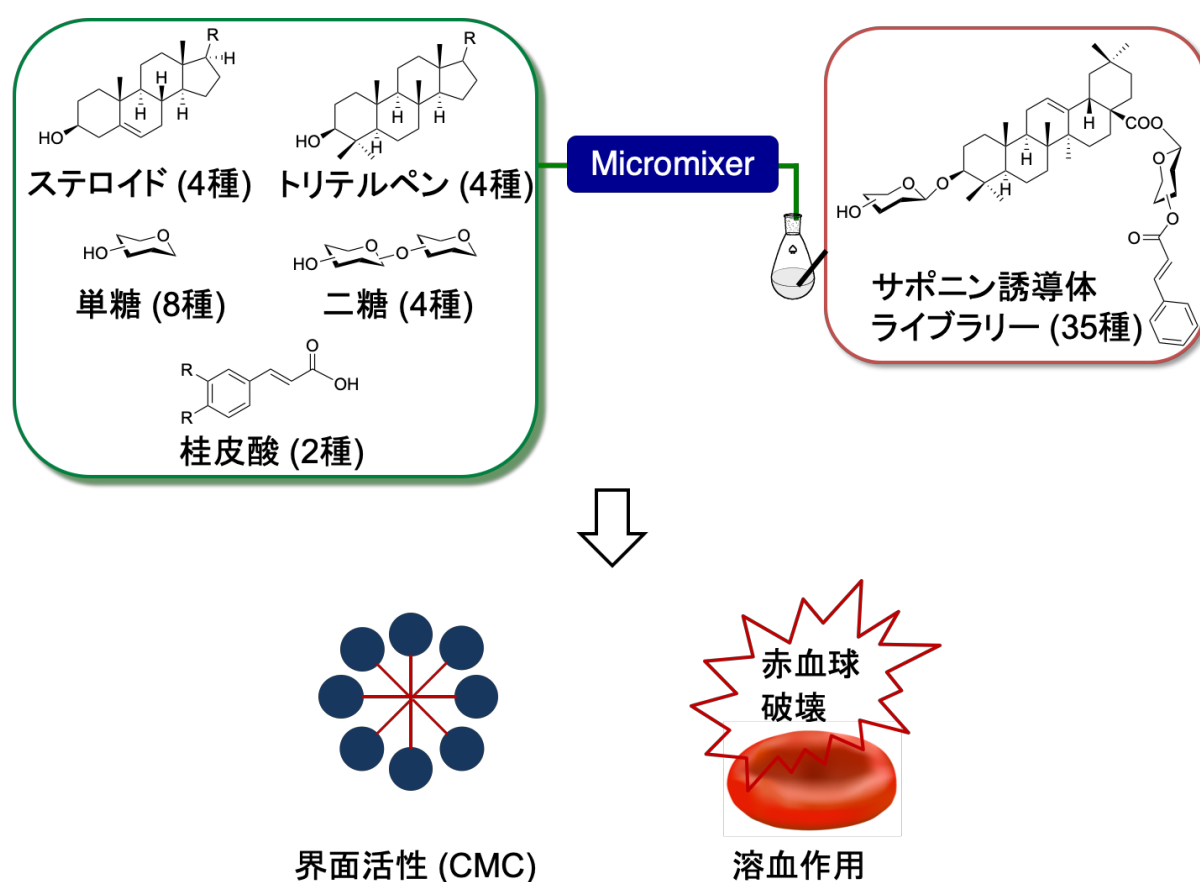


Figure 13 サポニン誘導体ライブラリーの構築とその性質評価の研究戦略

第二章 本論

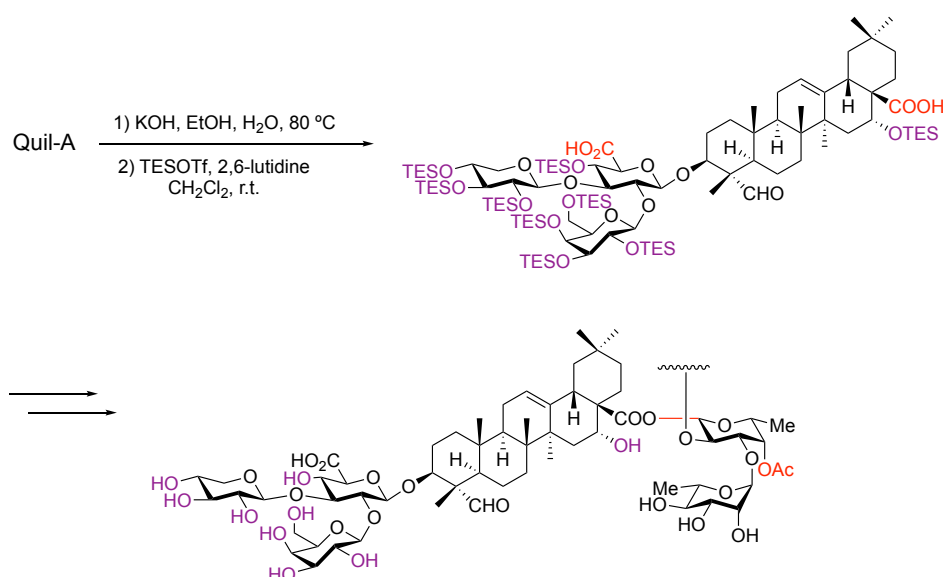
第一節 マイクロフローを利用したサポニン誘導体ライブラリーの構築

第一項 マイクロフロー式オレアノール酸 C-28 位サポニンの合成

I.オレアノール酸 (3B) を用いたグリコシルアクセプター 5B の合成

サポニンの化学合成における課題は保護基の選択である。アグリコンであるオレアノール酸 (3B) は配糖化に用いる CH_2Cl_2 に対する溶解性が低い。また、マイクロフローを用いる際には不溶物の目詰まりは致命的となるので、サポニンの合成には予め溶解性を向上させる保護基を C-3 位ヒドロキシ基あるいは C-28 位カルボキシ基に導入する必要がある。

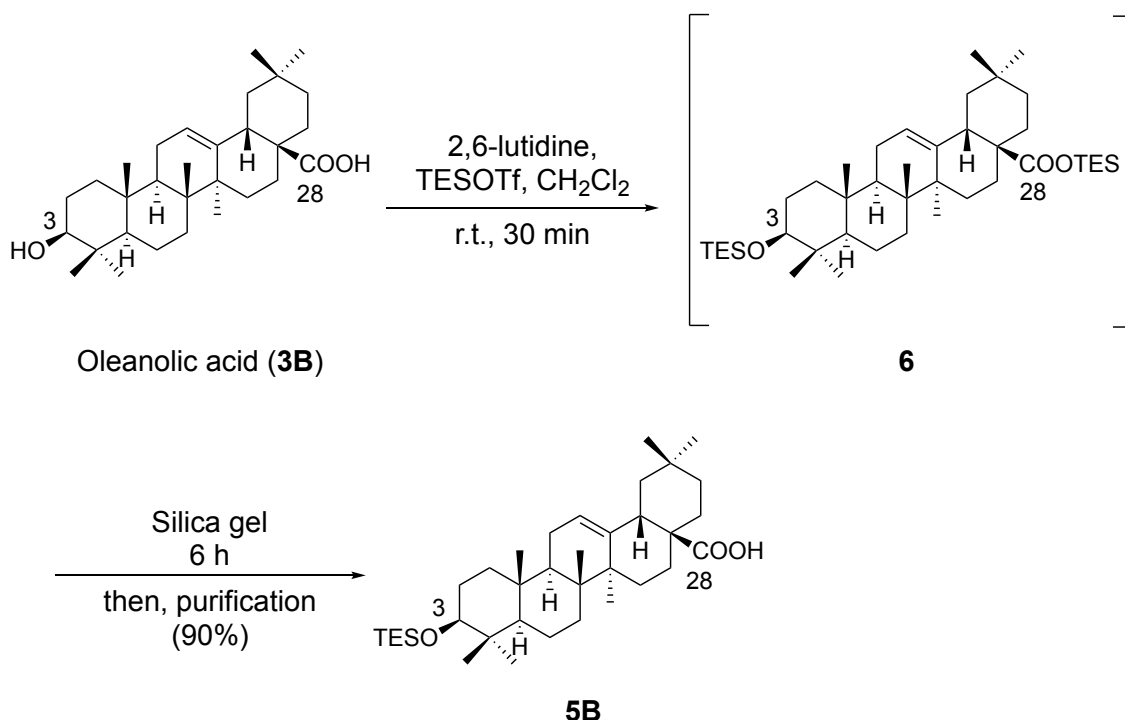
以上に点に留意して、筆者らはオレアノール酸 C-28 位選択的配糖化の方法論の確立に着手した。C-28 位のカルボキシ基に選択的に配糖化を行うにはオレアノール酸 (3B) の C-3 位の遊離ヒドロキシ基の選択的保護が必要である。また、後に C-3 位配糖化を試みる際に C-3 位選択的に脱保護可能な保護基の導入が必要である。そこで、筆者らは C-3 位のヒドロキシ基のみを保護したグリコシルアクセプターの合成に着手した。この際、用いる保護基として Gin らの報告を参考にトリエチルシリル (TES) 基を選択した。Gin らは *Quillaja saponaria* のサポニン画分である Quil-A から単離したトリテルペンである quillic acid の保護基として TES 基を選択し、配糖化と脱保護を行いヒドロキシ基のみを選択的に保護することを達成している。また、配糖化の脱保護に関してもアセチル (Ac) 基やグリコシルエステル結合、アグリコンのオレフィン構造等に対して影響を及ぼさない条件で行っている³⁵ (Scheme 4)。加えて、一般に TES 基で保護されたカルボキシ基 (TES エステル) は弱酸性条件下に不安定であり、C-3 位のヒドロキシ基のみを選択的に保護できると考えられた。



Scheme 4 TES 基を用いた QS-21 AApi の合成

市販オレアノール酸 (**3B**) を CH_2Cl_2 に溶解後 2,6-lutidine を加え、TESOTf を用いて C-3 位及び C-28 位に TES 基を導入し化合物 **6** を合成した。反応停止後に濃縮した溶液をシリカゲルクロマトグラフィーに付し、6 時間静置後に精製することで C-28 位の TES 基のみが脱保護されアクセプター **5B** を得ることができた (Scheme 5)。

なお、**5B** の構造は $^1\text{H-NMR}$ において C-3 位由来のピークの高磁場シフト 3.20 ppm (m, 1H, 3-H) 及び TES 基由来のピーク 0.95 ppm (m, 9H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$)、0.59 ppm (m, 6H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$) の出現により確認した。



Scheme 5 TES 基を用いたオレアノール酸アクセプター **5B** の合成

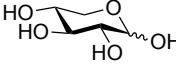
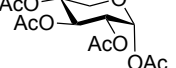
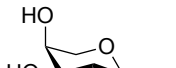
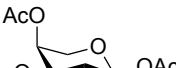


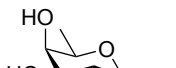
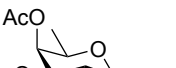
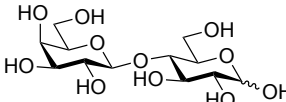
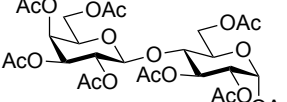
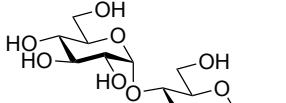
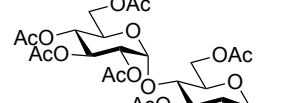
II. アセチル (Ac) 基で保護したグルコシルイミダートドナー **7a-m** の合成

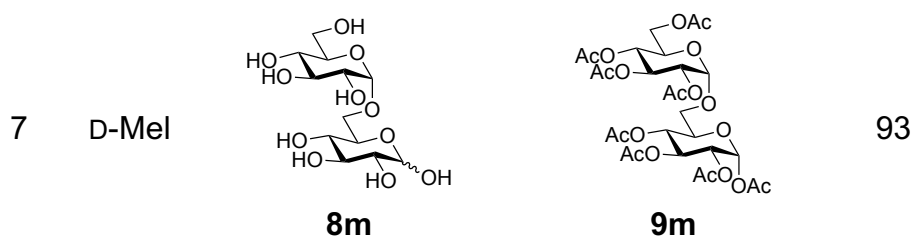
続いてアセチルグリコシルイミダートドナー **7a-m** の合成に着手した³⁶。保護基として選択したアセチル (Ac) 基は前述した Gin らを始め多くのサポニン合成においてヒドロキシ基の保護基として使用されている。さらにグリコシルドナーの C-2 位に Ac 基を導入すると隣接基関与に伴ったβ選択的な配糖化を行うことができる。アシル基には Ac 基、ピバロイル (Piv) 基、ベンゾイル (Bz) 基等があるが、最も穏和な加水分解条件等で脱保護可能な Ac 基を用いることとした。

用いる糖は単糖の D-グルコース (Glc)、D-ガラクトース (Gal)、D-マンノース (Man)、D-グルクロン酸メチル (Glc A Me)、D-キシロース (Xyl)、L-アラビノース (Ara)、L-ラムノース (Rha)、D-フコース (Fuc)、二糖の D-セロビオース (Cel)、D-ラクトース (Lac)、D-マルトース (Mal)、D-メリビオース (Mel) とした (以降対応する糖鎖の化合物番号を同様のアルファベットで示す)。

まず、原料である各種市販品の単糖あるいは二糖 (**8f-m**) を pyridine に溶解後、ジメチルアミノピリジン (DMAP) と無水酢酸 (Ac_2O) を加えアセチル化を行い化合物 **9f-m** を得た (Table 6)。 Ac_2O の当量数は単糖の場合は 8 当量、二糖の場合は 10 当量を用いた。DMAP の当量数は 0.1 当量とした。

Table 6 単糖・二糖のアセチル化

$ \begin{array}{ccc} \text{HO}-\text{Sugar} & \xrightarrow[\text{pyridine}]{\text{Ac}_2\text{O, DMAP}} & \text{AcO}-\text{Sugar} \\ \text{8f-m} & \text{r.t. over night} & \text{9f-m} \end{array} $				
Entry	Substrate of sugar		Product	
	Type	Structure	Structure	Yield (%)
1	D-Xyl	 8f	 9f (α only)	91
2	L-Ara	 8g	 9g (α only)	95
3	L-Rha	 8h	 9h (α only)	97
4	D-Fuc	 8i	 9i ($\alpha : \beta = 3 : 2$)	92
5	D-Lac	 8k	 9k	99
6	D-Mal	 8l	 9l	90

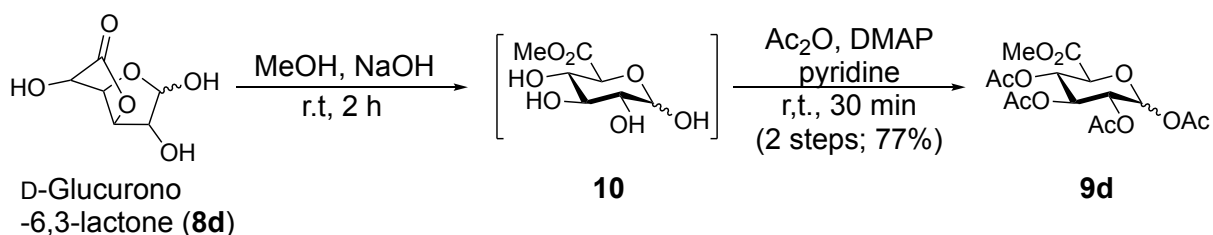


9f-m の構造は各種 Ac 基のピークの出現により確認した。また、1'-H 位のピークからアノマーの立体配置を決定した (**Table 7**)。各種カラム操作は省略し次の工程に用いた。

Table 7 化合物 **9f-m** の構造決定に関わる $^1\text{H-NMR}$

Compound	δH	
	Ac (-OCOCH ₃) (s, 3H, ppm)	1'-H (d, 1H, ppm, Hz)
9f (α only)	2.17, 2.04, 2.04, 2.01	6.25 ($J = 3.7$)
9g (α only)	2.16, 2.15, 2.06, 2.06	6.35 ($J = 3.2$)
9h (α only)	2.16, 2.15, 2.06, 2.00	6.01 ($J = 2.0$)
9i ($\alpha : \beta = 3 : 2$)	2.19, 2.18, 2.14, 2.11	6.34 ($J = 2.9$)
	2.04, 2.01, 2.00, 1.99	5.68 ($J = 8.3$)
9k	2.16, 2.11, 2.07, 2.06,	6.25 ($J = 3.7$)
	2.04, 2.01, 1.97	
9l	2.13, 2.10, 2.07, 2.03,	6.48 ($J = 3.8$)
	2.02, 2.01, 1.99	
9m	2.13, 2.09, 2.06, 2.06,	6.46 ($J = 4.0$)
	2.05, 2.04, 2.03, 1.98	

また、市販品である D-glucurono-6,3-lactone (**8d**) を MeOH に溶解後、NaOH を用いたメタノリシス反応を行い化合物 **10** を含む粗生成物を得た³⁷。続いて作業の簡略化のためにカラム精製を行わず、pyridine に溶解後 Ac₂O と DMAP を用いアセチル化を行い化合物 **9d** を得た (**Scheme 6**)。化合物 **9d** の構造は $^1\text{H-NMR}$ におけるアノマー位のピークが α 体で 6.40 ppm (d, $J = 3.7$ Hz, 1H, 1-H) と β 体で 5.77 ppm (d, $J = 7.8$ Hz, 1H, 1-H) であり、 $\alpha : \beta = 1 : 1$ であった。また α 、 β 体それぞれ 4 つの Ac 基のピークを 2.22-2.02 ppm (s, 24H, -OCOCH₃) で確認した。

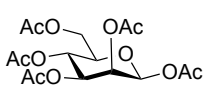
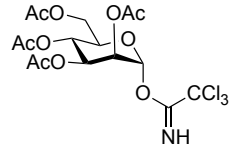
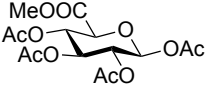
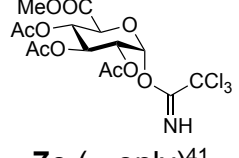
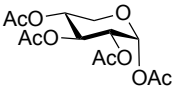
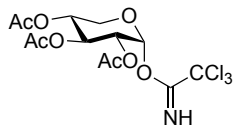
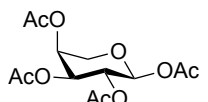
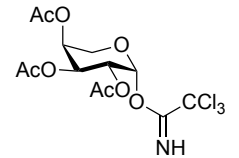
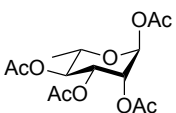
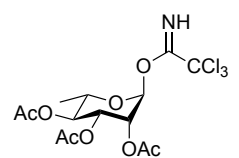
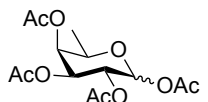
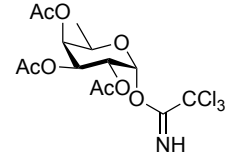
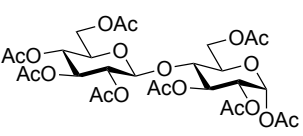
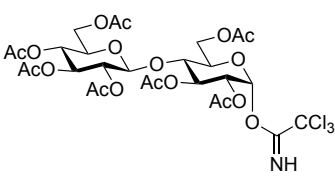
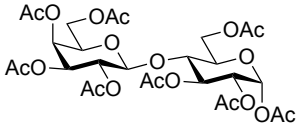
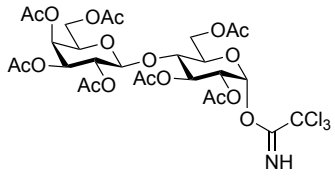


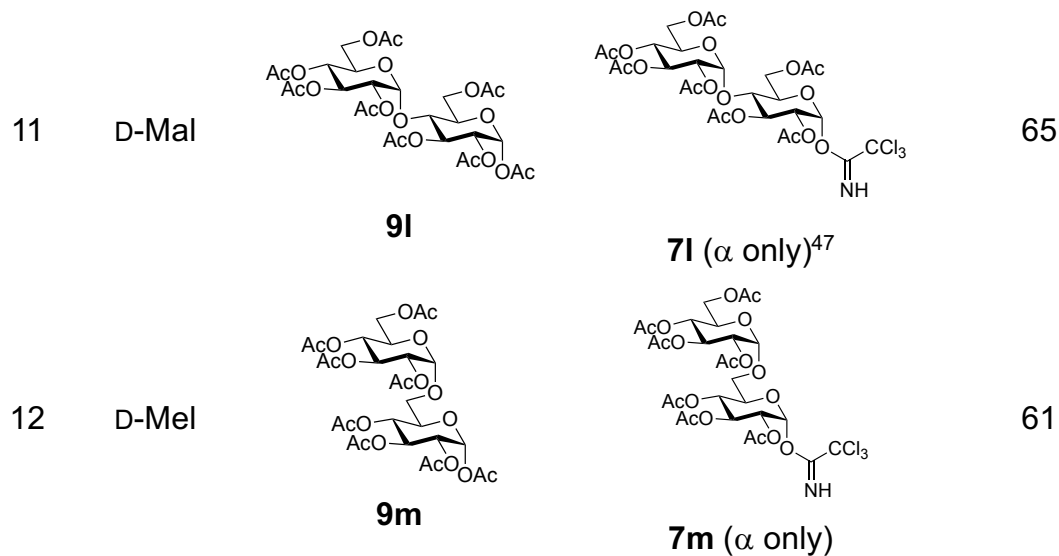
Scheme 6 化合物 **9d** の合成

続いて調製した **9f-m** と市販原料である penta-*O*-acetyl-β-D-glucopyranose (**9a**)、penta-*O*-acetyl-β-D-galactopyranose (**9c**)、penta-*O*-acetyl-β-D-mannopyranose (**9e**)、α-D-cellobiose octaacetate (**9j**) を *N,N*-ジメチルホルムアミド (DMF) に溶解後、1.4 当量の hydrazine acetate を用いてアノマー位の Ac 基を選択的に脱保護した。その後、作業の簡略化のためにカラム精製を行わずに化合物 **11a**, **11c-m** を含む粗生成物を CH₂Cl₂ に溶解後、10 当量以上のトリクロロアセトニトリル (Cl₃CCN)、触媒量の DBU を用いてイミダート化を行い目的の **7a**, **7c-m** を得た (Table 8)。

Table 8 アセチルイミダートドナー **7a-m** の合成

Substrate	
Product	
Entry	
Type	
Structure	Structure
Yield (2 steps; %)	
1	D-Glc
9a	7a (α only) ³⁸
2	D-Gal
9c	7c (α only) ³⁹

3	D-Man	 <p>9d</p>	 <p>7d⁴⁰</p>	65
4	D-Glc A	 <p>9e</p>	 <p>7e (α only)⁴¹</p>	25
5	D-Xyl	 <p>9f</p>	 <p>7f (α only)⁴²</p>	20
6	L-Ara	 <p>9g</p>	 <p>7g (β only)</p>	18
7	L-Rha	 <p>9h</p>	 <p>7h (β only)⁴³</p>	65
8	D-Fuc	 <p>9i</p>	 <p>7i (α only)⁴⁴</p>	20
9	D-Cel	 <p>9j</p>	 <p>7j (α only)⁴⁵</p>	81
10	D-Lac	 <p>9k</p>	 <p>7k (α only)⁴⁶</p>	79



7a, 7c-m の構造は $^1\text{H-NMR}$ におけるトリクロロアセトイミダートの N-H 由来のピークの出現により確認した。また、1'-H 位のピークからアノマーの立体配置を決定した (**Table 9**)。

Table 9 アセチルイミダートドナー **7a-m** の構造決定に関わる $^1\text{H-NMR}$

Compound	δH	
	-NH (s, ppm)	1'-H (d, ppm, Hz)
7a	8.69	6.56 ($J = 3.6$)
7c	8.64	6.58 ($J = 3.5$)
7d	8.79	6.28 ($J = 1.9$)
7e	8.73	6.64 ($J = 3.6$)
7f	8.66	6.48 ($J = 3.7$)
7g	8.64	6.56 ($J = 2.9$)
7h	8.72	6.20 ($J = 2.0$)
7i	8.61	6.55 ($J = 3.6$)
7j	8.65	6.49 ($J = 4.0$)
7k	8.65	6.49 ($J = 3.8$)
7l	8.67	6.48 ($J = 3.8$)
7m	8.67	6.46 ($J = 4.0$)

第二項 マイクロフロー式オレアノール酸 C-28 位配糖化の検討とサポニン合成

I. ドナー **7a** を用いたマイクロフロー式オレアノール酸 C-28 位配糖化の検討

オレアノール酸 C-28 位配糖化の方法論を確立する目的で、筆者はテクノアプリケーションズ社のマイクロフローである『コメット X-01』⁴⁸を用い条件検討を行った。『コメット X-01』は二重管接続ジョイントと充填型リアクター部から構成されている。2つの溶液が外側（A液）と内側（B液）に分かれているので、直前まで溶液同士が混合せず、B液が円柱状に内側から溶出された時にもう一方のA液が外側から円柱表面積全体にわたって包み込む形で混合する。リアクター内部は3つ穴（0.137 μL ）と1つ穴（0.55 μL マイクロ空間）のプレートが交互に10層重ねられた構造となっているため、A/B 試薬混合溶液はリアクター内部を通過する度に乱流を作り出すことができ、分散と集合が繰り返されマイクロ空間を通過する。このマイクロ空間により反応がさらに促進される（Figure 14）。混合液はテフロンチューブ（PTFE tube）を通過して排出され、テフロンチューブの滞留時間が反応時間となる。温度調節はコメット X-01 とテフロンチューブを恒温槽等に予め設置することで2つの溶液を同じ温度で調製可能である。

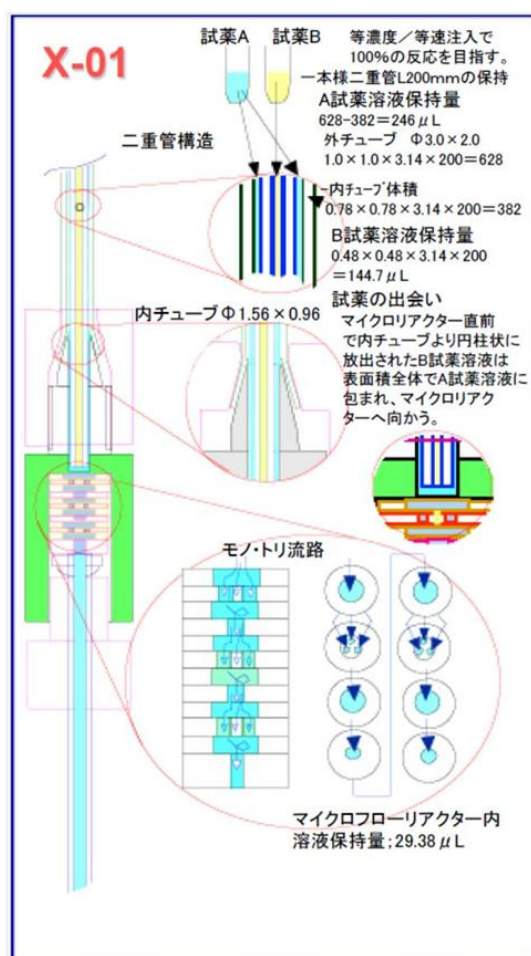
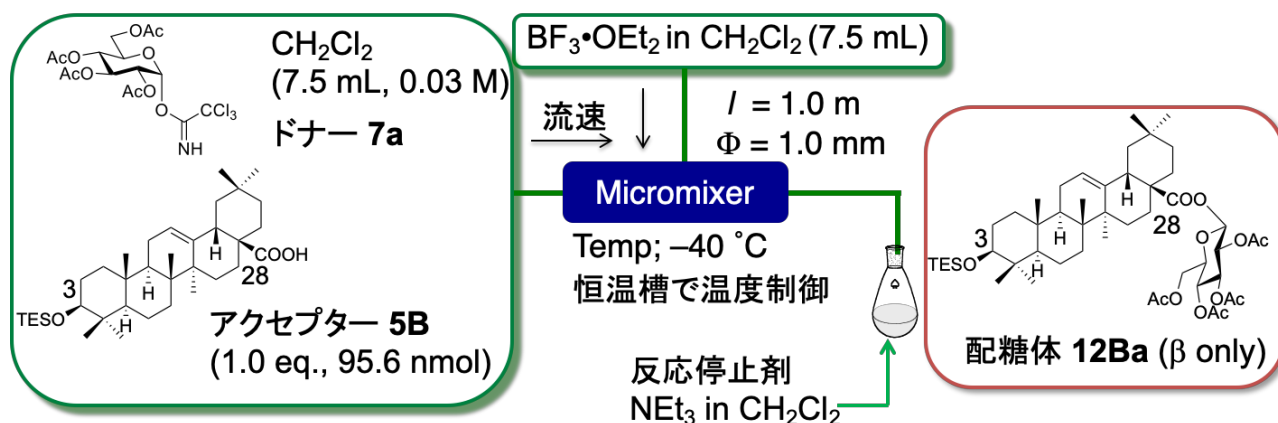


Figure 14 Comet X-01 の構造と原理⁴⁸

CH₂Cl₂に溶解させた BF₃·OEt₂ 溶液及び比較的溶解性の高いグリコシルアクセプター **5B** と既知の Ac-D-Glc グリコシルドナー **7a** の混合溶液を別途調製し、各溶液をディスポーザブルシリンジに取りマイクロフローに接続した。マイクロフロー反応部とフロー管は予め -40 °C に設定した恒温槽内に静置させた。また、フロー管の長さとお内径はそれぞれ 1.0 m と 1.0 mm とした。その後、シリンジポンプを用いて流速・流量・シリンジ内径を設定し、シリンジからテフロンチューブへと溶液を流しマイクロフロー内で C-28 位配糖化を行った (Table 10)。反応条件の最適化を、①ドナー **7a** の当量数 ②活性化剤である BF₃·OEt₂ の当量数 ③マイクロフロー内の流速 の 3 つのパラメータを変えることで試みた。反応の停止はフロー管の出口を予めトリエチルアミン (NEt₃) を加えたフラスコに接続して行った。なお、使用後のマイクロフローは CH₂Cl₂ で内部を洗浄後、窒素ガスをチューブ内に送り CH₂Cl₂ を除いた後保管した。テフロンチューブ内の残液は空のシリンジで送り出し回収した。

Table 10 マイクロフロー式オレアノール酸 C-28 位配糖化の検討



Entry	Donor 7a (eq.)	$\text{BF}_3 \cdot \text{OEt}_2$ (eq.)	Flow rate (mL/min)	Result (%)
1	1.0	0.1	0.1	no reaction
2	1.0	0.1	0.2	
3	1.0	0.1	0.3	
4	1.0	0.1	0.4	
5	1.0	0.1	0.5	
6	1.0	0.1	0.6	
7	1.0	0.1	0.7	
8	1.0	0.1	0.8	
9	1.0	0.1	0.9	
10	1.0	0.5	0.05	trace
11	1.0	0.5	0.1	trace
12	1.0	0.5	0.4	4.9
13	1.0	0.5	0.5	17
14	1.0	0.5	0.6	48
15	1.0	0.5	0.7	3.6
16	1.0	1.0	0.4	2.6
17	1.0	1.0	0.5	4.5
18	1.0	1.0	0.6	51
19	1.0	1.0	0.7	4.5
20	2.0	0.5	0.6	quant.
21	2.0	1.0	0.6	
22	2.0	0.5	0.1	quant.
23	2.0	0.5	0.5	
24	2.0	0.5	0.7	
25	2.0	0.5	0.1	
26	2.0	1.0	0.1	quant.
27	2.0	1.0	0.4	76
28	2.0	1.0	0.5	quant.
29	2.0	1.0	0.7	quant.
30	1.5	0.1	0.6	0.9
31	1.5	0.5	0.6	59
32	1.5	1.0	0.6	66
33	2.0	0.1	0.6	11
34	2.0	0.5	0.8	75

まず異なる流速 0.1 -0.9 mL/min で **7a** を 1.0 当量、BF₃·OEt₂ を 0.1 当量用いると、反応の進行は確認されなかった (Entries 1-9)。

次に BF₃·OEt₂ を 0.5 あるいは 1.0 当量用い反応を行ったところ、配糖体 **12Ba** の収率は最大で 50% 台に留まった (Entries 10-19)。TLC 上で **5B** が残存していた点と比較的遅い流速条件 (0.05~0.1 mL/min) で **12Ba** は低収率となったことから、原因は **7a** の分解に依存すると考えられた。なお、0.6 mL/min より速い流速では攪拌が不十分であること、0.6 mL/min 未満の流速では **12Ba** の分解によって収率が低下したと考えられた。

そこで **7a** の当量数を 2.0 当量に増量し検討を行った。その結果、0.5 あるいは 1.0 当量の BF₃·OEt₂ を用いると C-28 位配糖化が定量的に進行することを見出した (Entry 20-29)。

さらに **7a** の使用量を減少させる目的で追加条件を試みたが、1.5 当量の **7a** を用いると **12Ba** の収率は最大でも中程度の収率に留まった (Entries 30-32)。BF₃·OEt₂ を 0.1 当量用いた場合は **7a** を 2.0 当量に増量しても **12Ba** は低収率であった (Entry 33)。また、早い流速 (0.8 mL/min) では定量的に **12Ba** を得ることはできなかった (Entry 34)。

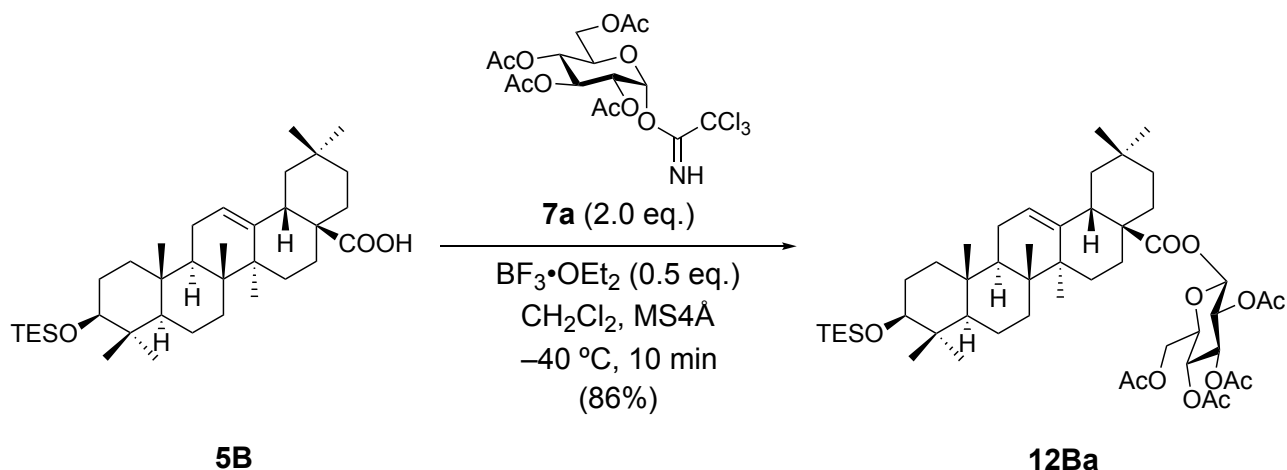
これらの結果から、完全に配糖化が進行するには十分な滞留時間 (流速 0.5~0.7 mL/min) の間で **7a** を 2.0 当量、BF₃·OEt₂ を 0.5 当量あるいは化学量論的 (1.0 当量) に用いる条件が最適であった。

通常バッチ式配糖化では一般に脱水剤として用いられるモレキュラーシーブスを加える必要がある⁴⁹。しかし、モレキュラーシーブスを用いる場合は使用前に熱で活性化させる操作と反応後の濾過操作等が必要であり実験工程数の増加を招く。また、反応前に予め原料と共に攪拌させるエージング操作による水分の除去効率は再現性に乏しく、反応の煩雑化を伴う問題もあった。ゆえにモレキュラーシーブスを用いずに本マイクロフロー式配糖化を実施できた意義は大きいと考えられた。

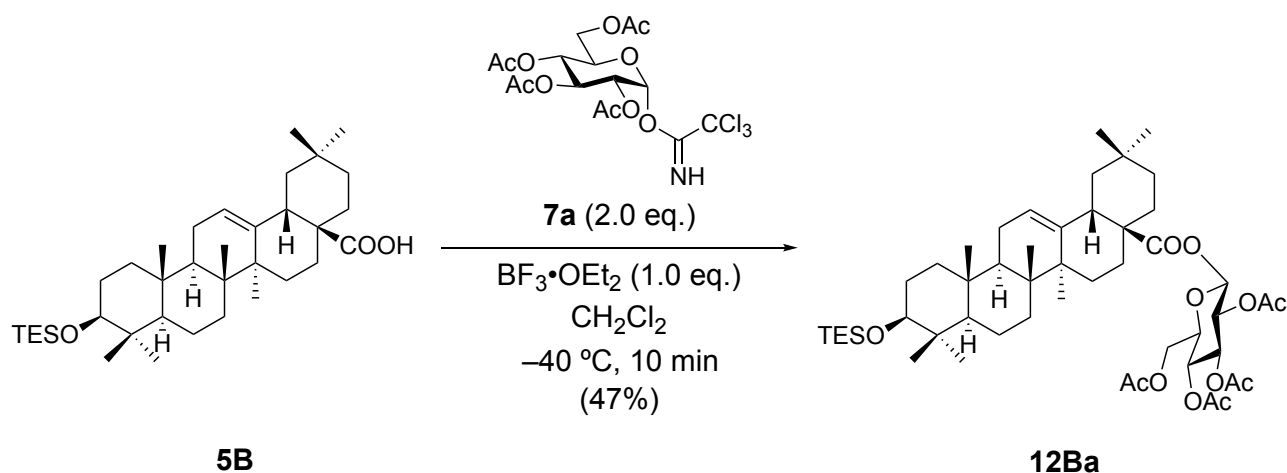
また、2.0 当量の **7a** と 0.5 当量の BF₃·OEt₂ を用いたバッチ式 C-28 位配糖化条件ではモレキュラーシーブス (MS) の有無で比較し、その収率はそれぞれ 86%、47% であった (Scheme 7, 8)。この点から、マイクロフローの微小空間の反応場を利用することで脱水条件の厳格化や熱交換率や混合効率の向上が **7a** の分解を引き起こす前に反応を完結に導いたと考えられた。また、配糖化-脱保護連続反応の検討 (詳細は後述ページ) を実施する際、一段階目の反応で副生成物の生成やアクセプター原料の残存を最小限に留めることが必須であるので、フロー法は有効であった。

今後の課題であるスケールアップは現在、所用の使用機器では 60 mL ディスポーサブルシリンジを使用した場合でも YMC 社製シリンジポンプを用いグラムスケールの合成までが可能である。

なお、**12Ba** の構造は HMBC においてアグリコンの C-28 位由来の ¹³C ピーク 175.6 ppm (C-28) と糖のアノマー位由来の ¹H ピーク 5.58 ppm (d, *J* = 8.0 Hz, 1H, 1'-H) とで相関が観測されることから、C-28 位グリコシド結合の形成を確認した。また、¹H-NMR におけるアノマー位由来のピークから所望のβ体であると確認した。



Scheme 7 バッチ式オレアノール酸 C-28 位配糖化の検討



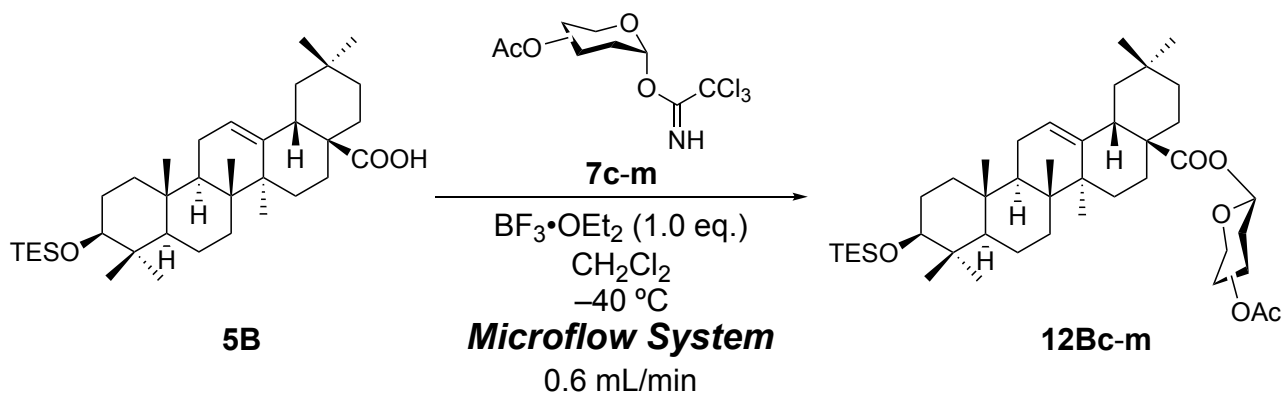
Scheme 8 モレキュラーシーブスを用いないバッチ式オレアノール酸 C-28 位配糖化の検討

II. ドナー **7c-m** を用いたマイクロフロー式オレアノール酸 C-28 位配糖化の適用

D-Glc 使用時に確立したマイクロフロー式オレアノール酸 C-28 位配糖化条件を基に、Ac イミダートドナー **7c-m** を用い糖基質一般性の検討を行った。即ち、D-Glc 以外の糖を C-28 位に導入した配糖体 **12Bc-m** の合成を試みた。

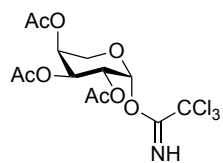
その他の単糖ドナー **7c-i** や、特にアシル基の数が多いことで双極子モーメントの偏りが生じ、アノマー位の反応性が比較し反応性が低い二糖ドナー **7j-m** を用いた場合でもそれぞれ各種配糖体 **12Bc-m** を合成できた (Table 11)。しかし、ドナー **7e** 及び **7f** の反応性が低下し中程度の収率に留まることも観測された (Entries 3, 4)。この原因は電子求引性の 5'-メチレンまたはカルボキシ部分に起因して、アノマー位である 1' 位ヒドロキシ基の求核性が減少したことにあったと考えられた。これらの場合にはドナーの当量数の検討等の再度反応条件の設定が必要と考えられた。また、2.0 当量のドナー **7c** を用いた場合、**12Bc** の収率は 66%に留まった。

Table 11 マイクロフロー式オレアノール酸 C-28 位配糖化のドナー基質一般性の検討

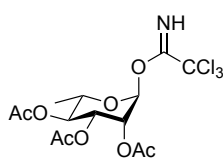


Entry	Donor type (eq.)	Glycoside	
		Structure	Yield (%)
1	 D-Gal 7c (2.5)	 12Bc (β only)	quant.
2	 D-Man 7d (2.0)	 12Bd (α only)	93
3	 D-Glc A 7e (2.0)	 12Be (β only)	74
4	 D-Xyl 7f (2.0)	 12Bf (β only)	66

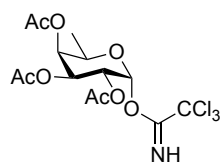
5

L-Ara **7g** (2.0)

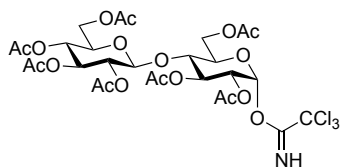
6

L-Rha **7h** (2.0)

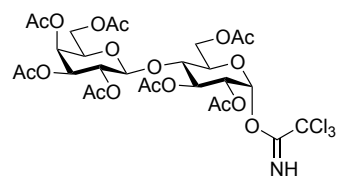
7

D-Fuc **7i** (2.0)

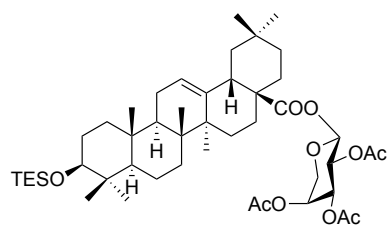
8

D-Cel **7j** (2.0)

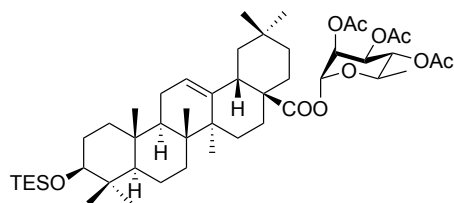
9

D-Lac **7k** (2.0)

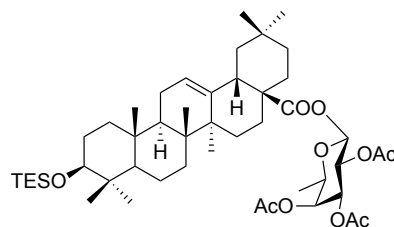
84

**12Bg** (α only)

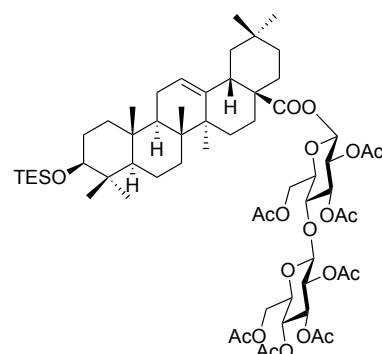
94

**12Bh** (α only)

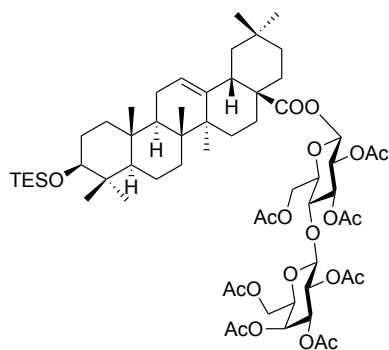
75

**12Bi** (β only)

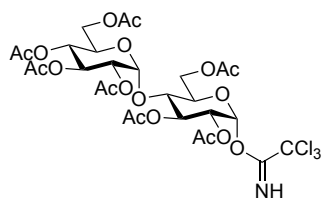
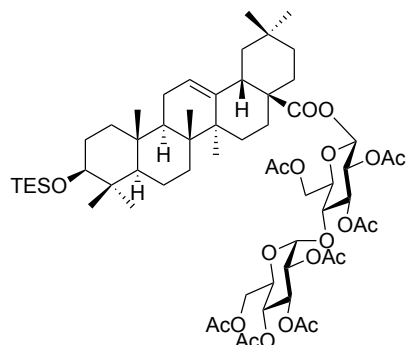
88

**12Bj** (β only)

68

**12Bk** (β only)

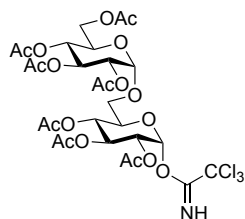
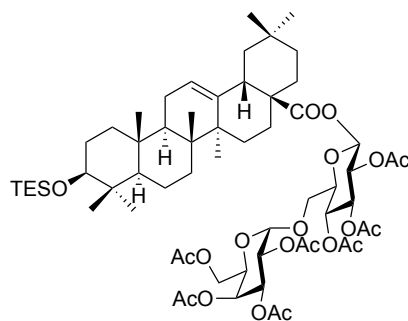
10

D-Mal **7I** (2.0)

81

12BI (β only)

11

D-Mel **7m** (2.0)

74

12Bm (β only)

なお、各種配糖体 **12Bc-m** の構造は HMBC においてアグリコンの C-28 位由来の ^{13}C ピークと糖のアノマー位由来の ^1H ピークとで相関が観測されたことから、C-28 位グリコシド結合の形成を確認した。また、 ^1H -NMR におけるアノマー位由来のピークからそれぞれ単一の α 体、 β 体であると確認した (Table 12)。アノマー位の J 値からのみでは立体を決定できない配糖体 **12Bd, g, h** に関しては脱保護したサポニンから決定することとした。

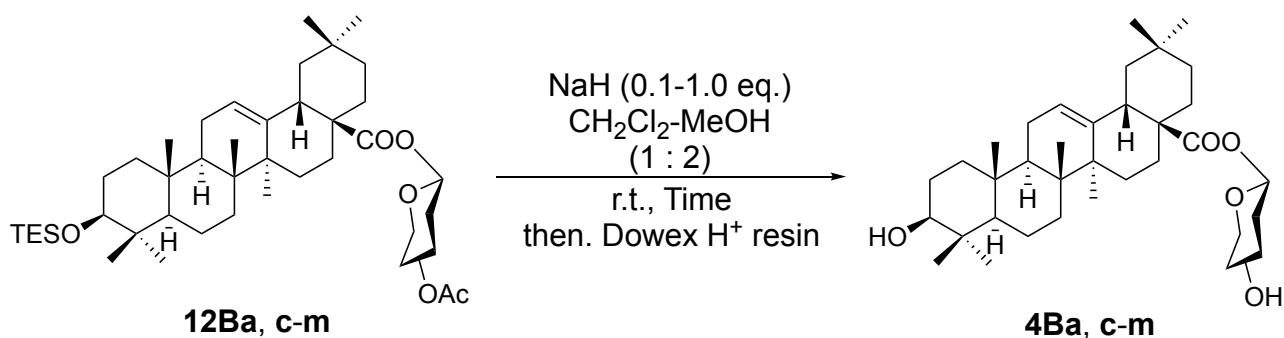
Table 12 12Bc-m の構造決定に関わる ^1H -NMR

Compound	δH	δC
	1'-H (d, ppm, Hz)	C-28 (ppm)
12Bc (β only)	5.55 ($J = 8.5$)	175.6
12Bd (α only)	6.06 ($J = 2.0$)	174.7
12Be (β only)	5.63 ($J = 8.1$)	175.5
12Bf (β only)	5.63 ($J = 6.8$)	175.6
12Bg (α only)	5.57 ($J = 6.8$)	175.5
12Bh (α only)	6.02 ($J = 2.0$)	174.7
12Bi (β only)	5.51 ($J = 8.4$)	175.7
12Bj (β only)	5.53 ($J = 8.0$)	175.5
12Bk (β only)	5.53 ($J = 8.0$)	175.5
12Bl (β only)	5.61 ($J = 8.0$)	175.4
12Bm (β only)	5.56 ($J = 8.0$)	175.4

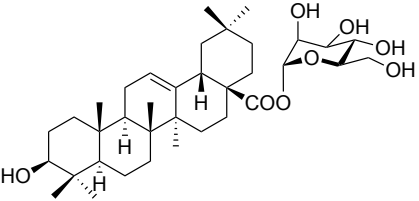
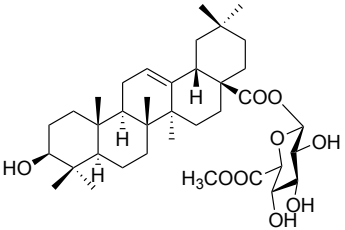
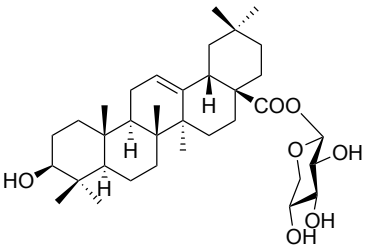
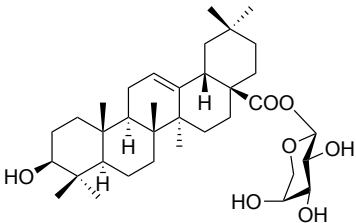
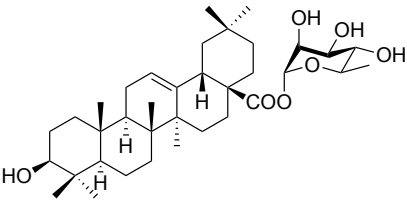
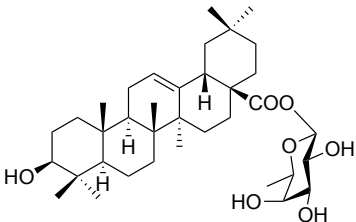
第三項 オレアノール酸 C-28 位糖結合型サポニン **4Ba, c-m** の合成

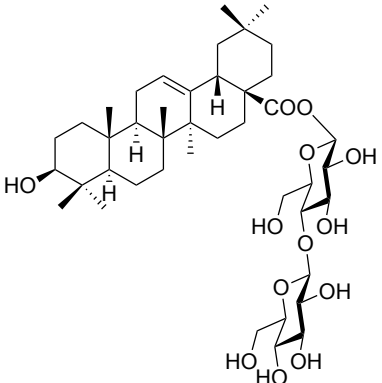
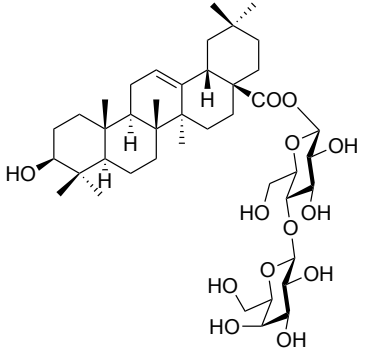
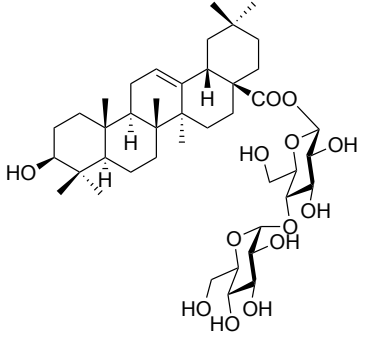
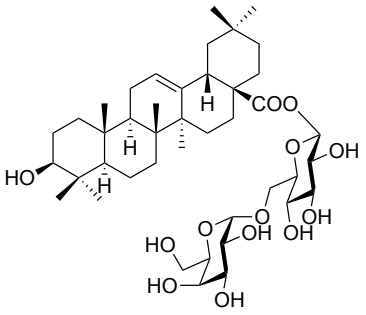
前述で合成した配糖体 **12Ba, c-m** を出発物質としオレアノール酸 C-28 位グルコース糖結合型サポニン **4Ba, c-m** を合成した。即ち、**12Ba, c-m** を MeOH-CH₂Cl₂ (2 : 1) に溶解後、NaH in oil (60% disp.) を用いたメタノリシス反応を行った。その結果、0.1-1.0 当量の NaH in oil を用いることで Ac 基の脱保護が進行し、続く陽イオン交換樹脂である Dowex H⁺ resin を用いた酸性条件下による攪拌後の後処理によって C-3 位 TES 基が脱保護されオレアノール酸 C-28 位サポニン **4Ba, c-m** を得た (Table 13)。

Table 13 オレアノール酸 C-28 位サポニン **4Ba, c-m** の合成



Entry	Glycoside Type	C-28 Saponin		Total yield of glycosylation and deprotection (%)	
		Structure	Yield (%)	Literature ^{d)}	This research
1	12Ba		4Ba (β only) ^a quant.	51 ³⁰	quant.
2	12Bc		4Bc (β only) quant.	80 ⁵⁰	quant.

3	12Bd		4Bd (α only) (新規) quant.	-	93
4	12Be		4Be (β only) 27	-	17
5	12Bf		4Bf (β only) ^b 99	74 ⁵¹	65
6	12Bg		4Bg (α only) 88	78 ⁵⁰	84
7	12Bh		4Bh (α only) quant.	78 ⁵⁰	84
8	12Bi		4Bi (β only) (新規) 93	-	68

9	12Bj		4Bj (β only) ^c 87	Data not shown	88
10	12Bk		4Bk (β only) 18	-	68
11	12Bl		4Bl (β only) 86	70 ⁵⁰	81
12	12Bm		4Bm (β only) (新規) 97	-	81

a) Isolated from *Aralia armata*.⁵² b) Isolated from *Anemone tomentosa*.⁵³

c) Isolated from *Lonicera macranthoides*.⁵⁴ d) 1-Bromo- α -D-glucose tetraacetate or tetrabenzoate of 1.2-1.3 equivalents was used.

なお、サポニン **4Bd, i, m** を新規サポニンとして合成できた。特にアセチルブロモ糖ドナー等のハロゲン化糖と相関移動触媒を用いたカルボキシ基選択的配糖化法例と比べ、配糖化と脱保護の収率は大幅に改善した。サポニン **4Be** の収率は原料が消失していたことから、C-28 位グリコシルエステル結合の切断が反応系中で起こり低下したと考えられた。サポニン **4Bk** は溶解度が悪く、濾過時点で回収量が低減して低収率であった。

各種サポニンの構造は ^1H -NMR において糖由来のピークの高磁場シフト、及び TES 基由来のピークと Ac 基由来のピークの消失から確認した。また、HMBC においてアグリコンの C-28 位由来の ^{13}C ピークと糖のアノマー位由来の ^1H ピークとで相関が観測されたことから、C-28 位グリコシド結合が切断されていないことを確認した。また、 ^1H -NMR におけるアノマー位由来のピークから **4Bd, h, g** 以外の立体構造を決定した (Table 14)。

Table 14 オレアノール酸 C-28 位サポニン **4Ba, c-m** の ^1H 及び ^{13}C -NMR

Compound	Lost signal	δH	δC
	1'-H (d, ppm, Hz)	1'-H (d, ppm, Hz)	C-28-COOH (ppm)
4Ba (β only)	0.93 (m, 9H, -Si(CH ₂ CH ₃) ₃)	6.36	176.6
	0.56 (m, 6H, -Si(CH ₂ CH ₃) ₃)	d, $J = 8.0$ Hz	
	2.06, 2.02, 2.01 (s, 3H, -OCOCH ₃ x 4)	1H, 1'-H	
	0.95 (t, $J = 7.6$ Hz, 9H, -Si(CH ₂ CH ₃) ₃)		
4Bc (β only)	0.58 (m, 6H, -Si(CH ₂ CH ₃) ₃)	6.29	176.6
	2.16, 2.03, 2.02, 1.99	d, $J = 8.2$ Hz	
	(s, 3H, -OCOCH ₃ x 4)	1H, 1'-H	
	0.97 (t, $J = 7.9$ Hz, 9H, -Si(CH ₂ CH ₃) ₃)		
4Bd (α only)	0.58 (m, 6H, -Si(CH ₂ CH ₃) ₃)	6.89	176.1
	2.14, 2.06, 2.05, 1.98	d, $J = 1.6$ Hz	
	(s, 3H, -OCOCH ₃ x 4)	1H, 1'-H	
	0.95 (t, $J = 8.0$ Hz, 9H, -Si(CH ₂ CH ₃) ₃)		
4Be (β only)	0.58 (m, 6H, -Si(CH ₂ CH ₃) ₃)	6.37	176.6
	2.03, 2.02, 2.02 (s, 3H, -OCOCH ₃ x 3)	d, $J = 7.9$ Hz	
		1H, 1'-H	
	0.93 (m, 9H, -Si(CH ₂ CH ₃) ₃)		
4Bf (β only)	0.56 (m, 6H, -Si(CH ₂ CH ₃) ₃)	6.25	176.7
	2.06, 2.05, 2.04 (s, 3H, -OCOCH ₃ x 3)	d, $J = 7.0$ Hz	
		1H, 1'-H	
	0.96 (m, 9H, -Si(CH ₂ CH ₃) ₃)		
4Bg (α only)	0.58 (m, 6H, -Si(CH ₂ CH ₃) ₃)	6.32	176.7
	2.13, 2.06, 2.05 (s, 3H, -OCOCH ₃ x 3)	d, $J = 5.8$ Hz	
		1H, 1'-H	
	0.93 (m, 9H, -Si(CH ₂ CH ₃) ₃)		
4Bh (α only)	0.56 (m, 6H, -Si(CH ₂ CH ₃) ₃)	6.83	176.0
	2.16, 2.08, 2.00 (s, 3H, -OCOCH ₃ x 3)	d, $J = 1.5$ Hz,	
		1H, 1'-H	

4Bi (β only)	0.96 (m, 9H, -Si(CH ₂ CH ₃) ₃)	6.18	
	0.58 (m, 6H, -Si(CH ₂ CH ₃) ₃)	d, <i>J</i> = 8.4 Hz	176.7
	2.18, 2.02, 2.00 (s, 3H, -OCOCH ₃ x 3)	1H, 1'-H	
4Bj (β only)	0.93 (m, 9H, -Si(CH ₂ CH ₃) ₃)	6.29	
	0.56 (m, 6H, -Si(CH ₂ CH ₃) ₃)	d, <i>J</i> = 8.0 Hz	176.6
	2.11, 2.09, 2.02, 2.02, 2.01, 2.01, 1.98 (s, 3H, -OCOCH ₃ x 7)	1H, 1'-H	
4Bk (β only)	0.93 (m, 9H, -Si(CH ₂ CH ₃) ₃)	6.28	
	0.56 (m, 6H, -Si(CH ₂ CH ₃) ₃)	d, <i>J</i> = 8.0 Hz	176.5
	2.13, 2.08, 2.05, 2.03, 2.01, 1.99, 1.97 (s, 3H, -OCOCH ₃ x 7)	1H, 1'-H	
4Bl (β only)	0.93 (m, 9H, -Si(CH ₂ CH ₃) ₃)	6.25	
	0.56 (m, 6H, -Si(CH ₂ CH ₃) ₃)	d, <i>J</i> = 8.0 Hz	176.5
	2.11, 2.10, 2.06, 2.02, 2.02, 2.00, 1.99 (s, 3H, -OCOCH ₃ x 7)	1H, 1'-H	
4Bm (β only)	0.93 (m, 9H, -Si(CH ₂ CH ₃) ₃)	6.27	
	0.56 (m, 6H, -Si(CH ₂ CH ₃) ₃)	d, <i>J</i> = 8.0 Hz	176.8
	2.14, 2.12, 2.0, 2.0, 2.01, 2.00, 1.97 (s, 3H, -OCOCH ₃ x 7)	1H, 1'-H	

なお、サポニン **4Bd, h** では2'位のプロトンがエクソリアルとなっているため、カップリング定数のみでは立体を決定することができないので、GATE-1 を用いて立体構造を決定した。一般的に、糖においてα体であれば1'位のデカップリング定数 $^1J_{C,H}$ は 170 Hz 付近、β体であれば1'位のデカップリング定数 $^1J_{C,H}$ は 160 Hz 付近であることが知られている⁵⁵。GATE-1 を測定したところ、**4Bd** の1'位デカップリング定数は $^1J_{C,H} = 175.5$ Hz (89.8 ppm, sd) であったのでα体と決定した (**Figure 15**)。 **4Bh** の1'位デカップリング定数は $^1J_{C,H} = 175.5$ Hz (89.8 ppm, sd) であったのでα体と決定した (**Figure 16**)。

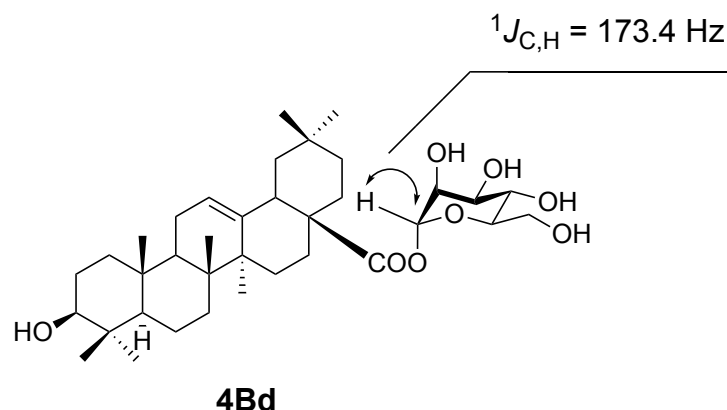


Figure 15 GATE-1 法を用いたサポニン **4Bd** の構造決定

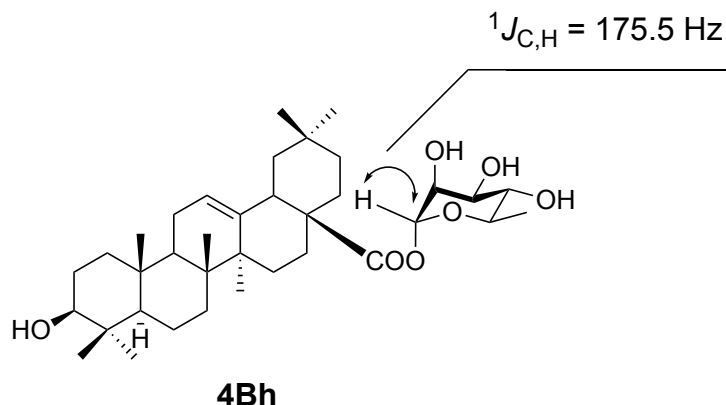


Figure 16 GATE-1 法を用いたサポニン **4Bh** の構造決定

また、L-Ara サポニン **4Bg** の立体は 2D-NOESY 法を用いて立体構造を決定した。NOESY は空間的に近い ^1H 同士の相関を確認できる方法である。アラビノース糖において $^4\text{C}_1$ 構造の場合は、1'位と 3'位と 5'位の ^1H 同士に相関があることが知られている⁵⁶ (**Figure 17**)。

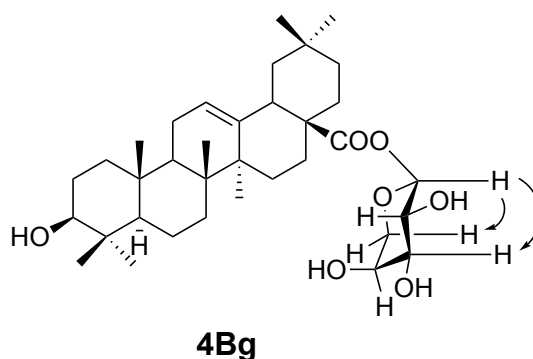
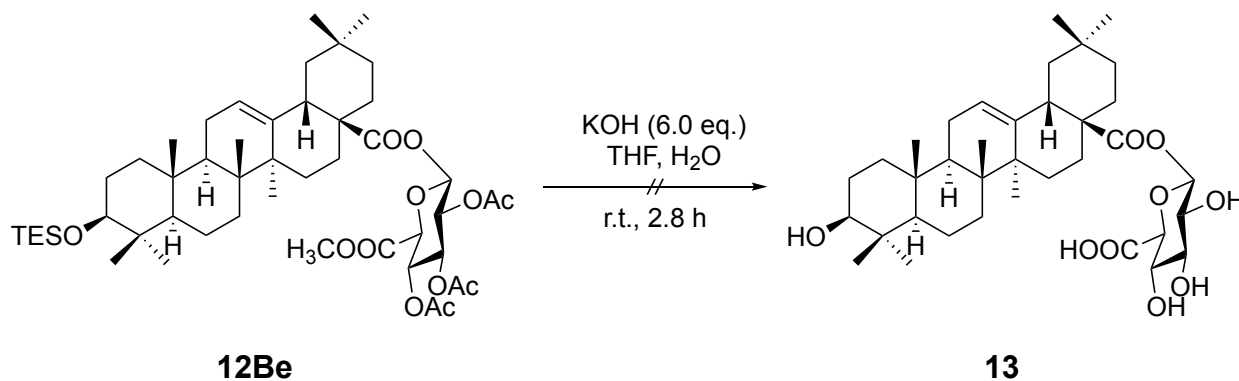


Figure 17 2D-NOESY 法を用いたサポニン **4Bg** の構造決定

なお、グルクロン酸のメチル基を脱保護したサポニン **13** は塩基性加水分解条件⁵⁷で C-28 位グリコシド結合の切断が観測されたことに起因し合成は困難であった (**Scheme 9**)。



Scheme 9 塩基性加水分解条件における **12Be** のグリコシルエステル結合の切断

サポニン **4Bj-l**における糖の ^1H 及び ^{13}C -NMR のシグナルの帰属には TOCSY 法を用いた。TOCSY は ^1H のスピン結合を介して ^1H の磁化を移動させスピン結合によって繋がっている ^1H のグループを求める方法であり、糖の帰属に有効な測定法である⁵⁸。磁化を移動させるために設定した混合時間 (mixing time) は、 $\tau_m = 150$ ms で D-Cel、D-Lac、D-Mal の 1'位から 6'位及び 1''位から 6''位までの相関が観測された (Table 15-A)。

Table 15-A TOCSY 法を用いたオレアノール酸 C-28 位二糖結合型サポニン **4Bj, k, l** の糖鎖構造の ^1H 及び ^{13}C -NMR

4Bj	β -D-Glc	δ H	δ C	β -D-Glc	δ H	δ C
	1'	6.29 (d, 8.0)	95.4	1"	5.23 (d, 8.0)	105.2
	2'	4.23 (dd, 9.0, 8.0)	73.8	2"	4.09 (t, 9.0, 8.0)	75.0
	3'	4.34 (t, 9.0)	77.3	3"	4.25 (t, 9.0)	78.4
	4'	4.46 (t, 9.0)	81.0	4"	4.18 (t, 9.0)	71.7
	5'	4.02 (dt, 9.0, 3.0, 2.0)	78.6	5"	4.04 (ddd, 9.0, 5.0, 2.0)	77.5
	6'	4.59 (dd, 12.0, 2.5) 4.40 (dd, 12.0, 2.5)	61.7	6"	4.56 (dd, 12.0, 2.0) 4.28 (dd, 12.0, 5.0)	62.6
4Bk	β -D-Glc	δ H	δ C	β -D-Gal	δ H	δ C
	1'	6.28 (d, 8.0)	95.4	1"	5.14 (d, 8.0)	106.0
	2'	4.14 (dd, 8.5, 8.0)	73.8	2"	4.53 (dd, 9.0, 8.0)	72.6
	3'	4.33 (dd, 9.0, 8.5)	77.2	3"	4.14 (dd, 9.5, 3.0)	75.3
	4'	4.43 (dd, 9.5, 9.0)	81.6	4"	4.49 (dd, 3.5)	70.2
	5'	3.99 (ddd, 9.5, 3.0, 2.5)	77.4	5"	4.15 (dd, 6.5, 5.0)	77.4
	6'	4.57 (dd, 12.0, 3.0) 4.381 (dd, 12.0, 2.5)	61.8	6"	4.46 (dd, 11.0, 6.5) 4.38 (dd, 11.0, 5.0)	62.1
4BI	β -D-Glc	δ H	δ C	α -D-Glc	δ H	δ C
	1'	6.25 (d, 8.0)	106.8	1"	5.96 (d, 4.0)	103.2
	2'	4.19 (9.0, 8.0)	75.4	2"	4.20 (dd, 9.0, 4.0)	74.5
	3'	4.40 (t, 9.0)	78.1	3"	4.59 (t, 9.0)	75.6
	4'	4.48 (t, 9.0)	81.4	4"	4.17 (t, 9.5)	72.0
	5'	3.90 (ddd, 9.0, 3.5, 2.0)	76.8	5"	4.58 (ddd, 9.0, 6.0, 2.0)	75.4
	6'	4.48 (dd, 12.0, 3.5) 4.38 (dd, 12.0, 2.0)	62.2	6"	4.58 (dd, 12.0, 2.0) 4.34 (dd, 12.0, 6.0)	62.8

サポニン **4Bm** における糖の ^1H 及び ^{13}C -NMR のシグナルの帰属には QC-TOCSY 法を用いた。磁化を移動させるために設定した混合時間 (mixing time) は、 $\tau_m = 150 \text{ ms}$ で D-Mel の 1'位から 6'位及び 1''位から 6''位までの相関が観測された (Table 15-B)。

Table 15-B TOCSY 法を用いたオレアノール酸 C-28 位二糖結合型サポニン **4Bm** の糖鎖構造の ^1H 及び ^{13}C -NMR

	$\beta\text{-D-Glc}$	δH	δC	$\beta\text{-D-Glc}$	δH	δC
	1'	6.27 (d, 8.0)	95.8	1''	5.46 (d, 3.5)	100.8
	2'	4.25 (t, 8.0)	74.0	2''	4.66 (dd, 9.0, 3.5)	70.9
	3'	4.24 (t, 8.0)	79.1	3''	4.25 (dd, 9.0, 3.5)	71.8
4Bm	4'	4.23 (t, 8.0)	71.6	4''	4.56 (d, 3.5)	71.3
	5'	4.06 (ddd, 8.0, 5.0, 2.5)	77.4	5''	4.61 (dd, 6.5, 5.5)	72.7
	6'	4.58 (dd, 10.5, 5.0)	67.8	6''	4.43 (dd, 11.0, 6.5)	62.9
		4.20 (dd, 10.5, 2.5)			4.40 (dd, 11.0, 5.5)	

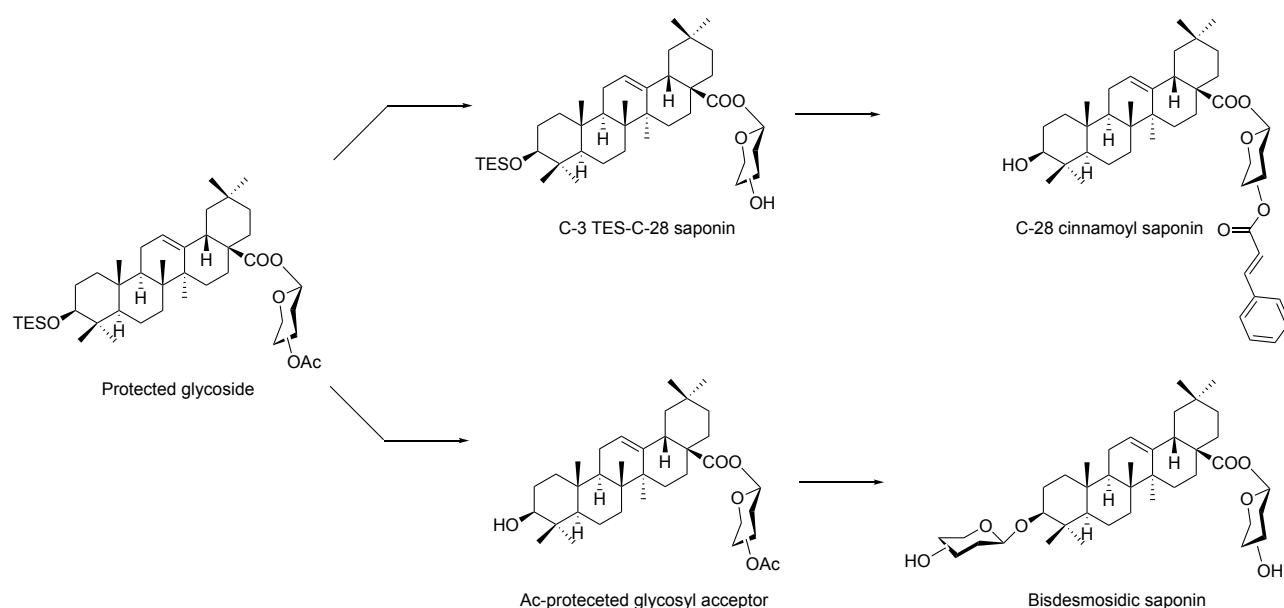
第四項 C-28 位糖含有アクセプターの合成の検討

I.C-3 位 TES 基結合型サポニン **14Ba, i** の合成

前項で示した C-28 位 D-Glc 糖結合型サポニン **4Ba, c-m** の合成法を利用し、後述の合成法の検討である、

- 1) 位置選択的桂皮酸エステル化の検討
- 2) ビスデスモシドサポニンの合成

に用いる基質である C-3 位 TES 基結合型サポニン及び C-28 位 D-Glc 結合型アクセプターの合成を試みた (**Scheme 10**)。



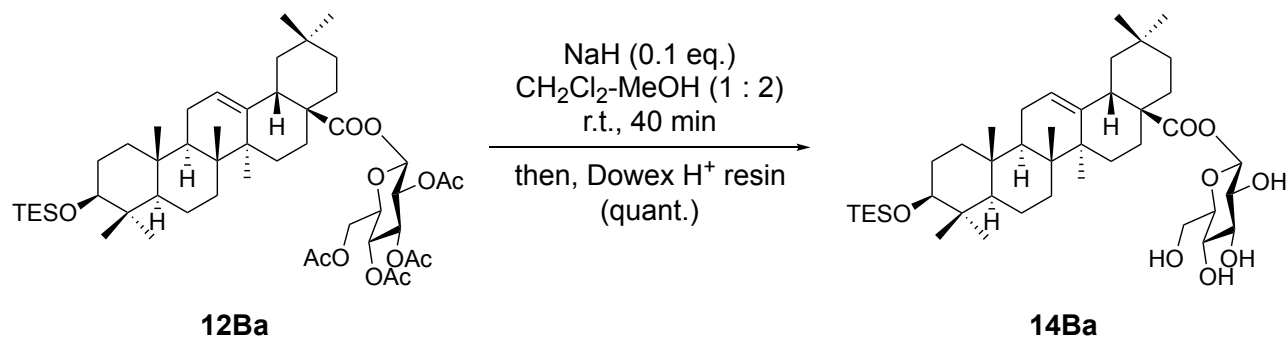
Scheme 10 TES 基及び Ac 基の選択的脱保護を用いたアクセプターの合成戦略

即ち、**12Ba** 及び **12Bi** を MeOH-CH₂Cl₂ (2 : 1) に溶解後、NaH in oil (60% disp.) を用いたメタノリシス反応を行った。その結果、0.1 当量の NaH in oil を用いることで Ac 基の脱保護が進行し、続く Dowex H⁺ resin を用いた後処理条件を中性条件下による攪拌に変えることで **14Ba, 14Bi** を得た (**Scheme 11, 12**)。

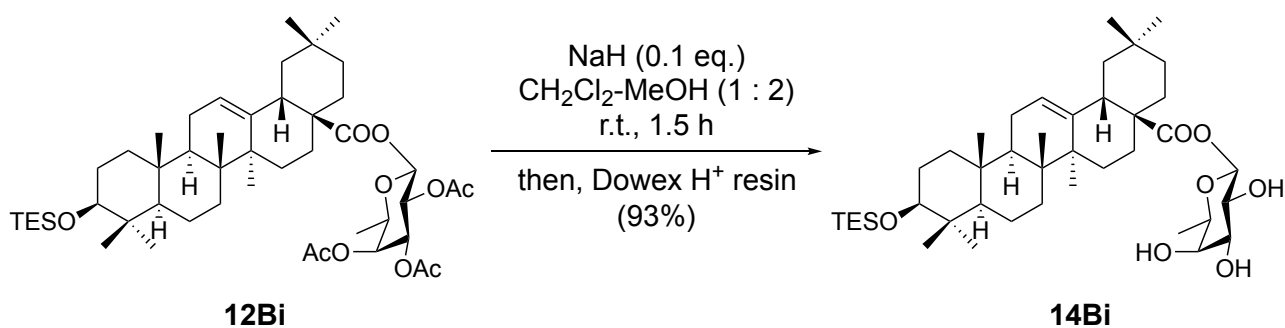
14Ba の構造は ¹H-NMR において糖由来のピークの高磁場シフト、及び Ac 基由来のピークの消失から確認した。また、HMBC においてアグリコンの C-28 位由来の ¹³C ピークと糖のアノマー位由来の ¹H ピークとで相関が観測されたことから、C-28 位グリコシド結合が切断されていないことを確認した。また、¹H-NMR におけるアノマー位由来のピークから β 体であることを決定した。

14Bi の構造は ¹H-NMR において糖由来のピークの高磁場シフト、及び Ac 基由来のピークの消失から確認した。また、HMBC においてアグリコンの C-28 位由来の ¹³C ピークと糖のアノマー位由来の ¹H ピークとで相関が観測されたことから、C-28 位グリコシド結合が

切断されていないことを確認した。また、 $^1\text{H-NMR}$ におけるアノマー位由来のピークから β 体であることを決定した。



Scheme 11 **12Ba** の Ac 基の選択的脱保護



Scheme 12 **12Bi** の Ac 基の選択的脱保護

II.C-28 位グルコース糖結合型アクセプター **15Ba** の合成の検討

次に、ビスデスモシドサポニンの合成に必要な基質となる C-28 位 D-Glc 糖結合型アクセプター **15Ba** の合成を検討した。即ち、C-3 位に導入した TES 基の選択的脱保護を検討した (Table 15)。

Table 15 **12Ba** の C-3 位 TES 基の選択的脱保護の検討

12Ba	Reaction condition	15Ba
Entry	Reaction condition	Yield (%)
1	AcOH-THF-H ₂ O (5:11:3) (0.1M), r.t., 16 h	65
2	TBAF (5.0 eq.), AcOH (5.0 eq.), THF (0.1 M) r.t., 24 h	68
3	ZnBr ₂ (5.0 eq.), H ₂ O (5.0 eq.), CH ₂ Cl ₂ (0.25 M), r.t., 16 h	97

AcOH-THF-H₂O 溶液を用いた酸性条件⁵⁹では、中程度の収率で **15Ba** を得た (Entry 1)。また、Ac 基の脱保護の抑制を考慮し THF 中 TBAF-AcOH を用いた脱保護条件⁶⁰においても収率は中程度であった (Entry 2)。そこで、臭化亜鉛 (II) を用いた脱保護条件⁶¹を用い検討を試みた。その結果、高収率で **15Ba** を得た (Entry 3)。

なお **15Ba** の構造は ¹H-NMR において TES 基由来のピーク 0.93 ppm (m, 9H, -Si(CH₂CH₃)₃)、0.56 ppm (m, 6H, -Si(CH₂CH₃)₃) の消失により確認した。また、HMBC においてアグリコンの C-28 位由来の ¹³C ピーク 175.6 ppm (C-28) と糖のアノマー位由来の ¹H ピーク 5.58 ppm (d, *J* = 8.0 Hz, 1H, 1'-H) とで相関が観測されたことから、C-28 位グリコシド結合が切断されていないことを確認した。また、¹H-NMR におけるアノマー位由来のピークから所望のβ体であると確認した。

第二節 マイクロフロー式オレアノール酸 C-28 位配糖化とバッチ式脱保護の集積化によるサポニンの連続合成の検討

第一項 マイクロフロー・バッチ式反応集積化の簡易システムの確立

続いて、サポニン合成における実験工程数の短縮を目的としたオレアノール酸 C-28 位配糖化と脱保護の連続反応の検討を行った。即ち、本マイクロフロー式 C-28 位配糖化法を利用した反応集積化を図ることで中間配糖体の単離精製の過程を省略でき、精製コストの削減や実験工程数を低減できると考えた。しかし、脱保護時におけるサポニンの物性の変化による溶解性の問題で触媒や試薬を担持したカラムを通す際に目詰まりを起こす可能性等が考えられた。目詰まりしたサポニンは H_2O や pyridine をカラム内に送液すると回収できると考えられたが、回収後の濃縮や後処理等の実験操作が煩雑化してしまう欠点があった。そこで今回の集積化法ではバッチ式脱保護を用い、溶解性や安全性を考慮し検討した。

まずマイクロフロー式配糖化・バッチ式脱保護反応集積化システムの構築を行った。即ち、窒素雰囲気下で予め加熱処理を施し無水条件とした二口フラスコに対して脱保護剤を加え、フロー管の出口に穴を空けたセプタムを介して接続し、マイクロフロー式 C-28 位配糖化と脱保護を集積化できると考えた。

なお、 $-40\text{ }^{\circ}\text{C}$ で反応を行う場合はマイクロフロー本体と反応受器を恒温槽で温度管理し、常温下で行う場合はマイクロフロー本体をクランプで固定し行った (Figure 18, 19)。

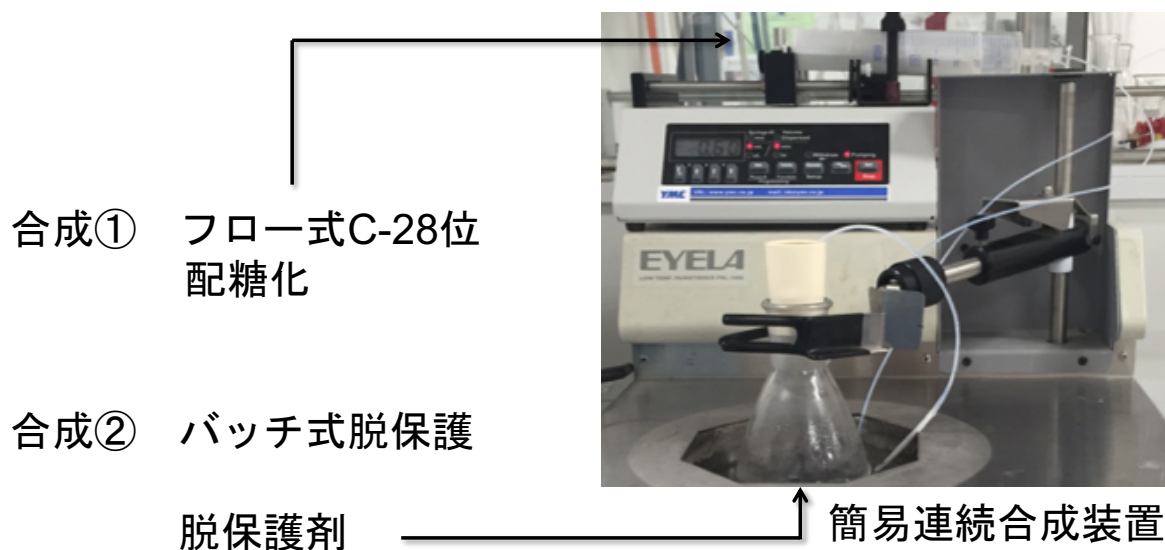


Figure 18 マイクロフロー式 C-28 位配糖化・バッチ式脱保護反応集積化の簡易システムの確立

合成① フロー式C-3位
配糖化

合成② バッチ式脱保護

脱保護剤

簡易連続合成装置

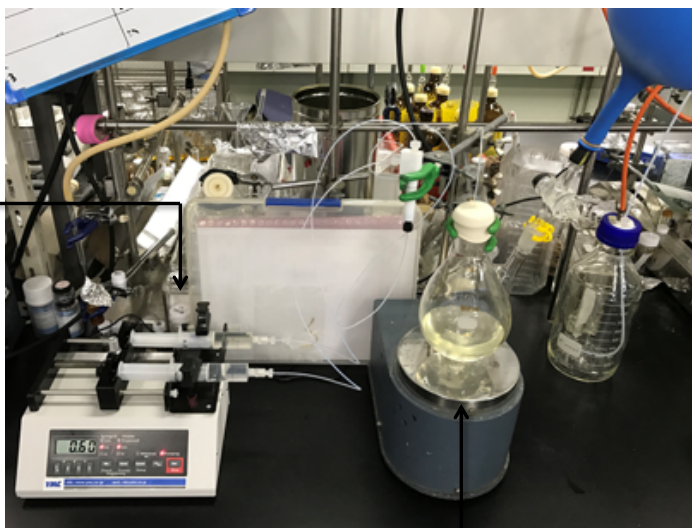


Figure 19 マイクロフロー式 C-3 位配糖化・バッチ式脱保護反応集積化の簡易システムの確立

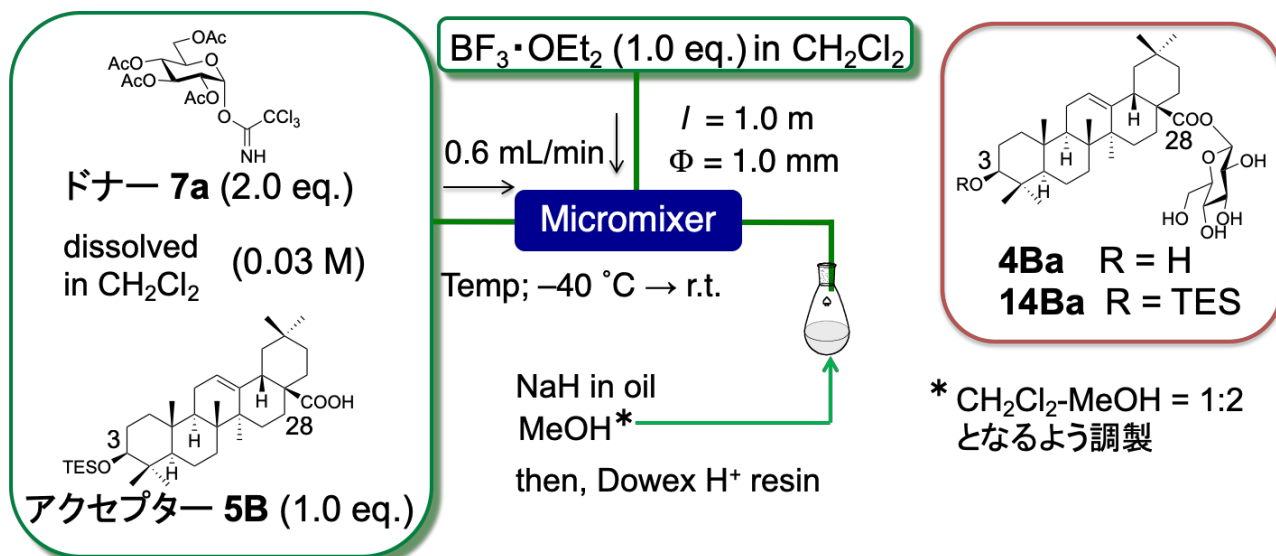
第二項 マイクロフロー式 C-28 位配糖化・バッチ式脱保護の連続反応の検討

CH₂Cl₂に溶解させた 1.0 当量の BF₃·OEt₂ 溶液及び 1.0 当量のグリコシルアクセプター **5B** と 2.0 当量のグリコシルドナー **7a** の混合溶液を別途調製し、各溶液をディスポーサブルシリンジに取りマイクロフローに接続した。このとき、マイクロフロー反応部とフロー管は予め -40 °C に設定した恒温槽内に静置させた。また、フロー管の長さ・内径はそれぞれ 1.0 m と 1.0 mm とした。その後、シリンジポンプを用いて流速 (0.6 mL/min.)・流量・シリンジ内径を設定し、シリンジからテフロンチューブへと溶液を流しマイクロフロー内で C-28 位配糖化を行った。

次に、構築したマイクロフロー・バッチ式反応集積化の簡易合成システムを用い、予め窒素雰囲気下で加熱処理を施し無水条件とした二口フラスコに NaH in oil と MeOH を加え、別途溶液を調製した。その後、フロー管の出口に穴を開けたセプタムを介して二口フラスコを接続し、脱保護を連続反応で実施した (Table 16)。

NaH in oil を 3.0 当量まで用いた場合は脱保護の進行は確認されず、配糖体 **12Ba** が定量的に得られた (Entry 1-2)。原因として、ルイス酸である BF₃·OEt₂ との中和によって NaOMe が消費され試薬活性が低下している可能性が考えられた。そこで、NaH in oil の当量数を増量させると Ac 基の脱保護は用量依存的に進行した (Entries 3-4)。最終的に 10 当量の NaH を用い、後処理の Dowex H⁺ resin の量を調節し中性条件あるいは酸性条件とすることでそれぞれ C-28 位 TES サポニン **13Ba** 及びサポニン **4Ba** をそれぞれ高収率で得た (Entries 5-6)。

Table 16 マイクロフロー式 C-28 位配糖化法・バッチ式 Ac 基脱保護連続反応を利用したサポニン **4Ba** 及び **14Ba** の合成

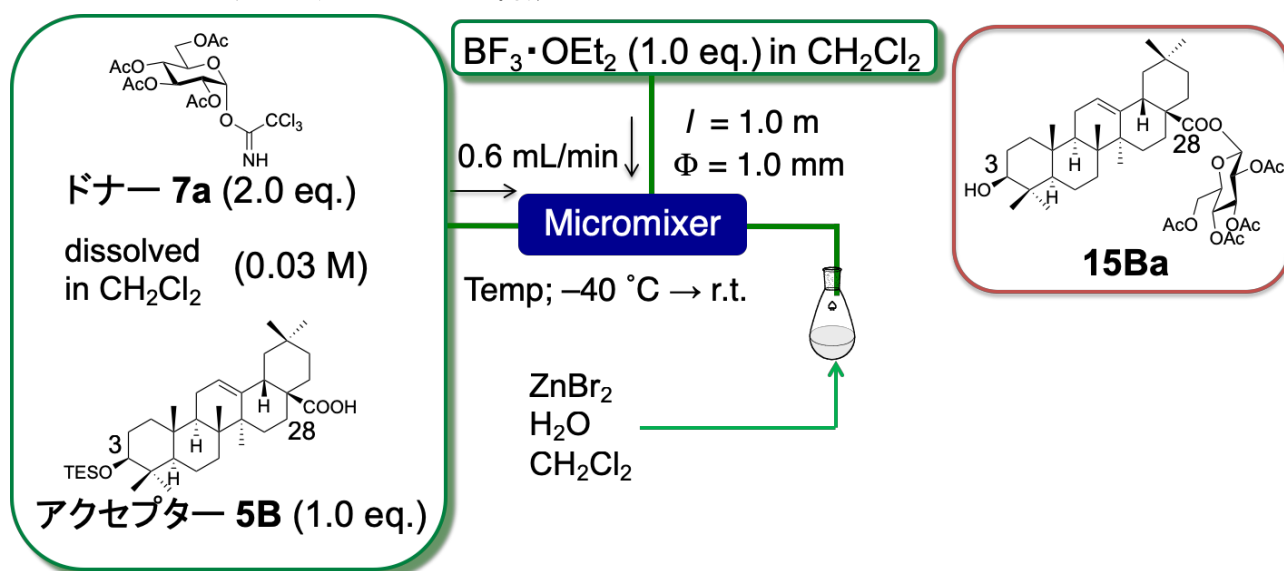


Entry	Deprotection condition	Product	
		Structure	Yield (%)
1	NaH (1.5 eq.), 1 h		quant.
2	NaH (3.0 eq.), 1 h		quant.
3	NaH (4.5 eq.), 40 min, then, neutralized to pH 7 with Dowex H^+ resin		34
4	NaH (6.0 eq.), 40 min, then, neutralized to pH 7 with Dowex H^+ resin		55
5	NaH (10 eq.), 40 min, then, neutralized to pH 7 with Dowex H^+ resin		75
6	NaH (10 eq.), 40 min, then, neutralized to pH 4 with Dowex H^+ resin		95

次に、脱保護剤を変更し脱保護連続反応を試みた (Table 17)。THF 中 AcOH と TBAF を用いた場合 2 工程収率 24% で **15Ba** が得られた (Entry 1)。配糖体 **12Ba** を精製した後、脱保護を行った検討結果と比べ収率が低下した要因として、C-28 位配糖化の際に用いる CH_2Cl_2 の影響が考えられた。

続いて、反応系中で CH_2Cl_2 を併用することのできる臭化亜鉛 (II) を用いた反応条件で脱保護を試みた。その結果、2 工程収率 55% で **15Ba** を得ることができた (Entry 2)。収率が向上しない要因としては反応溶媒である CH_2Cl_2 の濃度が考えられた。即ち、マイクロフロー式 C-28 位配糖化と脱保護の連続反応において CH_2Cl_2 の濃度はマイクロフロー式 C-28 位配糖化に用いる **5B** と **7a** を溶解させる量 (0.1 M) に依存するので、段階的な脱保護に必要とされた CH_2Cl_2 (0.25 M) と比較し薄くなる問題があった。そこで、臭化亜鉛 (II) と H_2O の当量数を 5.0 当量から 10 当量に増量させ反応を試みた。その結果、二工程収率 78% で **15Ba** を得ることに成功した (Entry 3)。

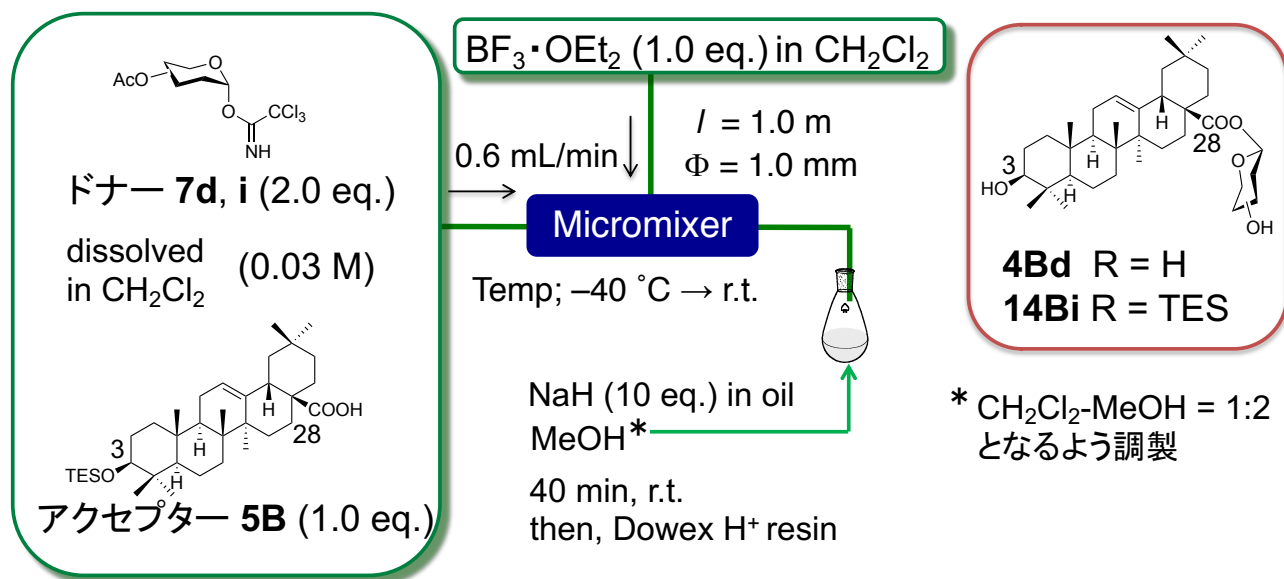
Table 17 マイクロフロー式 C-28 位配糖化法・バッチ式 C-3 位 TES 基脱保護連続反応を利用したアクセプター **15Ba** の合成



Entry	Deprotection condition	Yield (%)
1	TBAF (5.0 eq.), THF (0.1 M), AcOH (2.5 eq.), r.t., 48 h	24
2	ZnBr_2 (5.0 eq.), H_2O (10 eq.), CH_2Cl_2 (6 mL), r.t., 30 min	55
3	ZnBr_2 (10 eq.), H_2O (10 eq.), CH_2Cl_2 (6 mL), r.t., 30 min	78

また、ドナー **7d,i** を用いマイクロフロー式 C-28 位配糖化-バッチ式脱保護を行ったところ、サポニン **4Bd** 及び C-28 位 TES サポニン **14Bi** をそれぞれ高収率で合成できた (Table 18)。

Table 18 マイクロフロー式 C-28 位配糖化法・バッチ式 Ac 基脱保護連続反応を利用したサポニン **4Bd** 及び **14Bi** の合成



Entry	Donor type	pH	Product	
			Structure	Yield (%)
1	 D-Man 7d	4	 4Bd (α only)	98 ^a
2	 D-Fuc 7i	7	 14Bi (β only)	80 ^b

a) The deprotection was conducted for 10 min. b) The deprotection was conducted for 30 min.

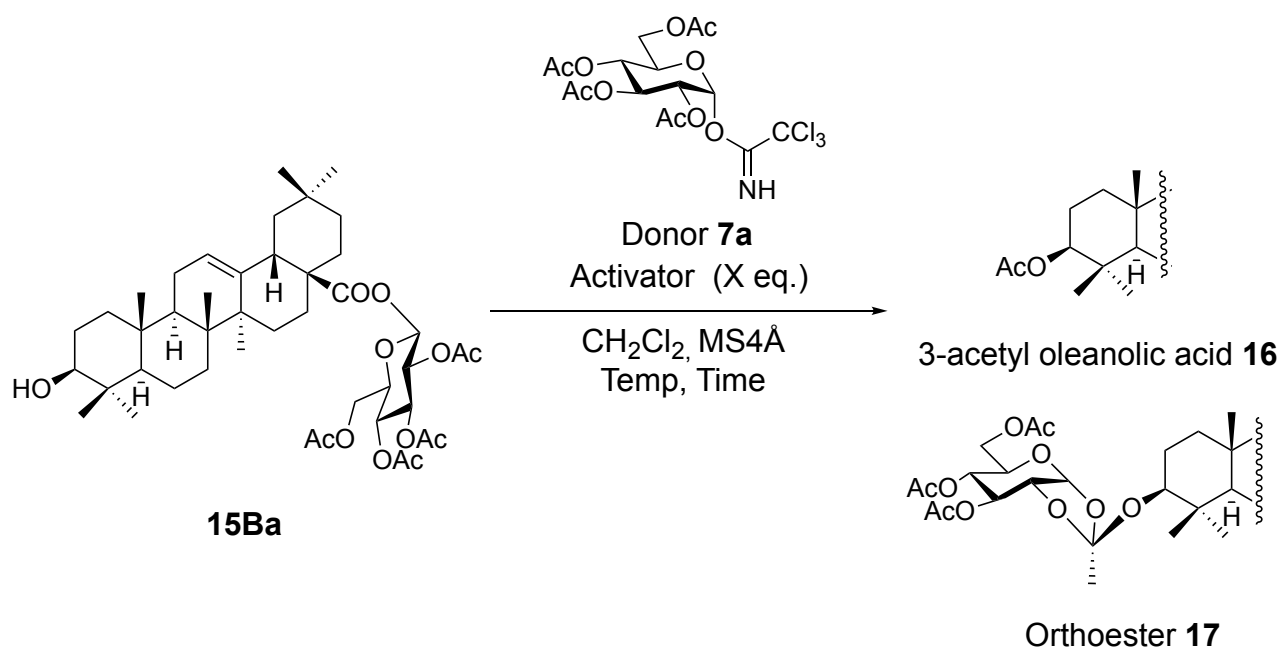
第三節 マイクロフロー式オレアノール酸 C-3 位配糖化の検討とビスデスモシドサポニンの合成

第一項 バッチ式オレアノール酸 C-3 位配糖化の検討

第二節のマイクロフロー式オレアノール酸 C-28 位配糖化の検討結果を基に、続いてマイクロフロー式オレアノール酸 C-3 位配糖化の検討を行うこととした。

まずアクセプター **15Ba** を基質としたバッチ式反応での C-3 位配糖化の検討を行った。反応条件の検討は、①アセチルドナー **7a** の当量数 ②活性化剤である $\text{BF}_3 \cdot \text{OEt}_2$ あるいは TMSOTf の当量数 ③反応温度 ④反応時間 の 4 つのパラメータを変えることで試みた (Table 19)。

Table 19 ドナー **7a** を用いたバッチ式オレアノール酸 C-3 位配糖化の検討



Entry	Donor (eq.)	Activator (eq.)	Temp (°C)	Time (min)	Product	Yield of 17 (%)
1	1	$\text{BF}_3 \cdot \text{OEt}_2$ (1.0)	-40	60	16	-
2	1	TMSOTf (1.0)	0	10	-	no reaction
3	3	TMSOTf (0.1)	-40	10	Orthoester 17	21~63
4	2	TMSOTf (0.1)	r.t	10	16	-

その結果、**7a** を基質とした条件では配糖体は得られず、副生成物である Ac 転位体 **16** あるいはオルトエステル体 **17** が得られた (Entry 1-4)。配糖化はイミダート部分が酸により活性化されオキソカルベニウムイオンを経由して、経路 A によって進行する。一方、反応するアクセプター側の構造がカルボキシ基でなくヒドロキシ基である場合には副生成物であるオルトエステル中間体⁶²が経路 B によって生成すると考えられている (Figure 20)。

なお、**17** の単離精製はシリカゲルクロマトグラフィーの弱酸性に起因し分解して困難であったので、crude NMR におけるアノマー位由来の ¹H ピーク 5.67 ppm (d, *J* = 5.2 Hz, 1H, 1'-H) の値がβグリコシド結合の値よりも小さいことから構造決定し、単一の立体異性体であることを確認した。

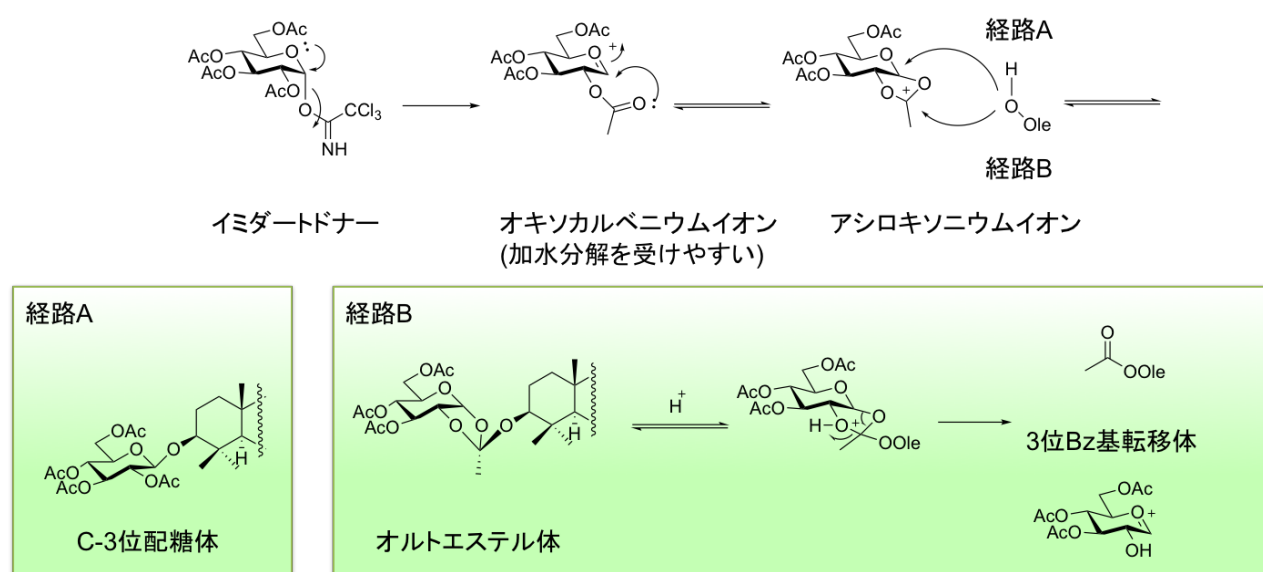
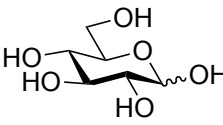
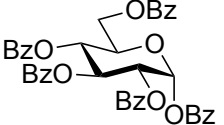
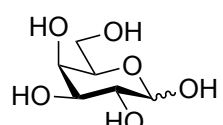
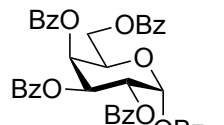
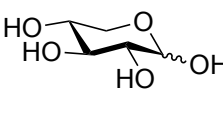
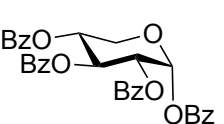


Figure 20 シュミットグリコシル化とオルトエステル体生成の反応機構

そこで、既知の Ac 基と比べ安定性・耐久性が強く嵩高い保護基である Bz 基を導入したベンゾイルグリコシルイミダートドナー **18a, c, f** の合成に着手した。原料である各種市販品の単糖 (**8a, c, f**) を pyridine に溶解後、塩化ベンゾイル (BzCl) を加えベンゾイル化を行い化合物 **19a, c, f** を得た (Table 20)。BzCl の当量数は単糖の場合は 8 当量を用いた。

Table 20 化合物 **19a, c, f** の合成

$\text{HO}-\text{Sugar} \xrightarrow[\text{pyridine}]{\text{BzCl (8.0 eq.)}} \text{BzO}-\text{Sugar}$ <p style="text-align: center;">r.t. over night</p> <p style="text-align: center;">8a, c, f 19a, c, f</p>				
Entry		Sugar		Product
	Type	Structure	Structure	Yield (%)
1	D-Glc			quant.
		8a	19a (α only)	
2	D-Gal			quant.
		8c	19c (α only)	
3	D-Xyl			quant.
		8f	19f (α only)	

19a, c, f の構造は各種 Bz 基のピークの出現により確認した。また、1'-H 位のピークからアノマーの立体配置を決定した (**Table 21**)。各種カラム操作は省略し次の工程に用いた。

Table 21 **19a, c, f** の構造決定に関わる ¹H-NMR

Compound	δH	
	Bz (Ph-H) (ppm)	1'-H (d, 1H, ppm, Hz)
19a (α only)	8.19-7.29 (m, 25H)	6.86 (<i>J</i> = 3.7)
19c (α only)	8.13-7.27 (m, 25H)	6.95 (<i>J</i> = 3.7)
19f (α only)	8.18-7.29 (m, 20H)	6.76 (<i>J</i> = 3.7)

続いて調製した **19a, c, f** を CH₂Cl₂ に溶解後、HBr/AcOH を用いてアノマー位を選択的にブromo (Br) 化し化合物 **20a, c, f** を得た後、アセトン-水 (20 : 1) 溶媒中で炭酸銀を用いアノマー位の Br 基を選択的に脱保護した化合物 **21a, c, f** を得た。その後、**21a, c, f** を含む粗生成物を CH₂Cl₂ に溶解後、10 当量以上のトリクロロアセトニトリル (Cl₃CCN)、触媒量の DBU を用いてイミダート化を行い目的の **18a, c, f** を得た (**Table 22**)。

Table 22 ベンゾイルイミダートドナー **18a, c, f** の合成

		1) 30% HBr·AcOH CH ₂ Cl ₂ , r.t., 3 h			Cl ₃ CCN, DBU CH ₂ Cl ₂ r.t.		
19a, c, f		2) Ag ₂ CO ₃ Acetone-H ₂ O (20:1) r.t., 2 h			21a, c, f		18a, c, f
		Substrate		Product			
Entry	Type	Structure	Structure	Yield (3 steps; %)			
1	D-Glc 19a			18a (α only) ⁶³ 35			
2	D-Gal 19c			18c (α only) ⁶⁴ 16			
3	D-Xyl 19f			18f (α only) ⁶⁵ 47			

18a, c, f の構造は $^1\text{H-NMR}$ におけるトリクロロアセトイミダートの N-H 由来のピークの出現により確認した (Table 23)。

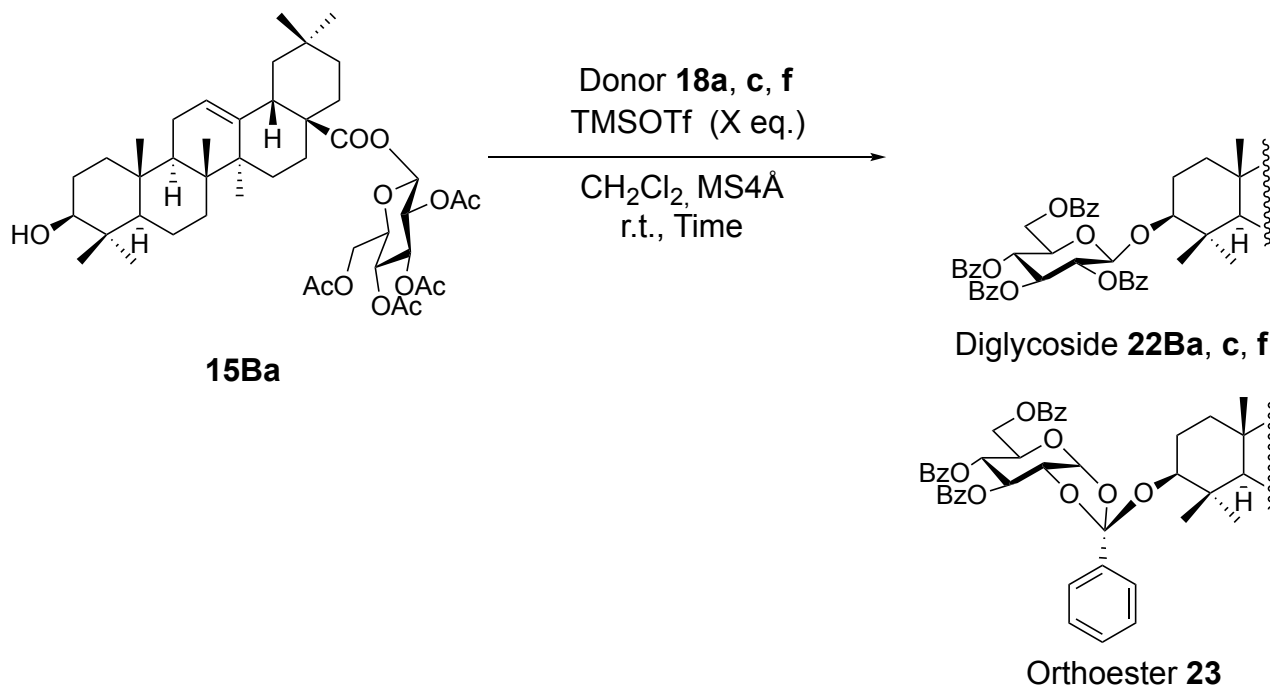
Table 23 **18a, c, f** の構造決定に関わる $^1\text{H-NMR}$

Compound	δH	
	-NH (s, ppm)	1'-H (d, ppm, Hz)
18a (α only)	8.63	6.84 ($J = 3.7$)
18c (α only)	8.64	6.92 ($J = 3.7$)
18f (α only)	8.63	6.74 ($J = 3.7$)

Bz 基を導入した 1.5 当量の **18a** を基質とした場合、触媒量の TMSOTf を用いると、配糖体 **22Ba** よりもオルトエステル体 **23** の生成が優先した (Entry 1)。**22Ba** と **23** はシリカゲルクロマトグラフィー上で分離困難であったので、収率は crude NMR におけるアノマー位の ^1H ピークの積分値から算出した。一方、1 当量の TMSOTf を用いるとオルトエステル体 **23** の生成は確認されず、配糖体 **22Ba** を中程度の収率で得ることができた (Entry 2)。**18a** の当量数を 3.0 当量に増量した場合に **22Ba** の収率は改善しなかったが、**18c, f** を用いても

それぞれ対応する配糖体 **22Bc, f** を得ることができた (Entry 3-5)。以上の結果から **22Ba, c, f** を合成するには化学量論量の TMSOTf と 1.5 当量のベンゾイルイミダートドナーが必要であった (Table 24)。

Table 24 ドナー **18a, c, f** を用いたバッチ式オレアノール酸 C-3 位配糖化の検討



Entry	eq.	Donor Structure	TMSOTf (eq.)	Time (min)	Product	Result (%)
1	1.5		0.1	50	22Ba 23	22Ba :26 23 : 43
2	1.5	18a (α only)	1.0	10	22Ba	69
3	3.0	18a (α only)	1.0	10	22Ba	70
4	3.0		1.0	20	22Bc	64
		18c (α only)				
5	3.0		1.0	20	22Bf	72
		18f (α only)				

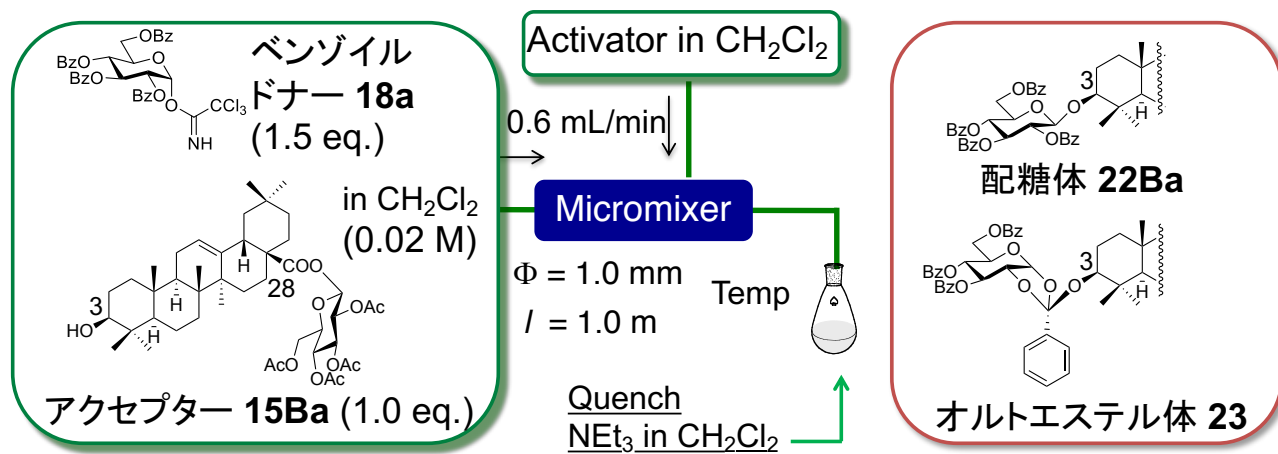
第二項 マイクロフロー式オレアノール酸 C-3 位配糖化の検討

I. マイクロフロー式オレアノール酸 C-3 位配糖化の検討

続いて、バッチ式 C-3 位配糖化の条件検討の結果を基に、マイクロフロー式オレアノール酸 C-3 位配糖化の検討を行った。

CH_2Cl_2 に溶解させた $\text{BF}_3 \cdot \text{OEt}_2$ 溶液及び比較的溶解性の高いグリコシルアクセプター **15Ba** とグリコシルドナー **18a** の混合溶液を別途調製し、各溶液をディスポーサブルシリレンジに取りマイクロフローに接続した。このとき、マイクロフロー反応部とフロー管は予めクランプで固定し静置させた。また、フロー管の長さ・内径はそれぞれ 1.0 m と 1.0 mm とした。その後、シリンジポンプを用いて流速・流量・シリンジ内径を設定し、シリンジからテフロンチューブへと溶液を流しマイクロフロー内で C-3 位配糖化を行った (Table 25)。反応条件の最適化は、①活性化剤である $\text{BF}_3 \cdot \text{OEt}_2$ あるいは TMSOTf の当量数 ③反応温度 の 2 つのパラメータを変えることで試みた。反応の停止はフロー管の出口に予めトリエチルアミン (NEt_3) を加えたフラスコを接続して行った。なお、使用後のマイクロフローは CH_2Cl_2 で内部を洗浄後、窒素ガスをチューブ内に送り CH_2Cl_2 を除いた後保管した。

Table 25 マイクロフロー式オレアノール酸 C-3 位配糖化の検討



Entry	Activator (eq.)	Temp (°C)	22Ba (%)	23 (%)
1	$\text{BF}_3 \cdot \text{OEt}_2$ (1.0)	r.t.	0	0
2	TMSOTf (0.1)	-40	20	65
3	TMSOTf (0.1)	-20	22	54
4	TMSOTf (0.1)	0	24	66
5	TMSOTf (0.1)	r.t.	27	34
6	TMSOTf (1.0)	0	47	0
7	TMSOTf (1.0)	r.t.	83	0

BF₃·OEt₂を用いた場合、反応の進行は全く確認されなかった (Entry 1)。一方、TMSOTf (0.1 eq.) に変更した場合、温度条件に関わらず配糖体 **22Ba** よりもオルトエステル体 **23** の生成が優先した (Entries 2-5)。**22Ba** と **23** はシリカゲルクロマトグラフィー上で分離困難であったので、収率は ¹H-NMR におけるアノマー位の ¹H ピークの積分値から算出した。

そこで、TMSOTf の当量数を 1.0 当量に増量し検討を試みた結果、**22Ba** を高収率で得ることができた (Entry 7)。一方、温度条件を 0 °C に低減させると **22Ba** の収率が低下した (Entry 6)。

以上の結果から、常温下で化学量論量の TMSOTf を用いる条件が最適であった。また、マイクロフロー式 C-3 位配糖化法では 1.5 当量の **18a** を用いた場合でも **22Ba** を 83% の収率で得ることができ (Table 25 Entry 7)、69% の収率であったバッチ式反応条件 (Table 24 Entry 2) に比べて **22Ba** の収率の向上と **18a** の消費の抑制を達成できた。

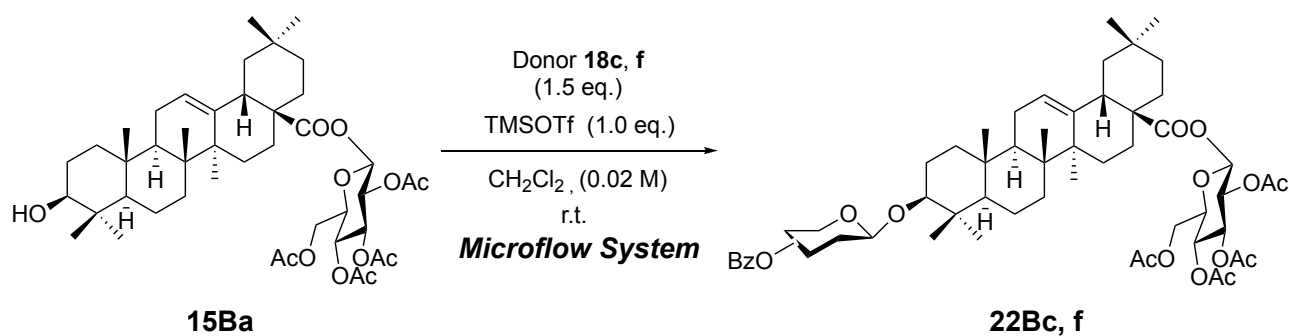
なお、**22Ba** の構造は HMBC においてアグリコンの C-28 位由来の ¹³C ピーク 175.5 ppm (C-28) と糖のアノマー位由来の ¹H ピーク 5.55 ppm (d, *J* = 8.0 Hz, 1H, 1'-H) とで相関が観測されたことから、C-28 位グリコシド結合が切断されていないことを確認した。また、アグリコンの C-3 位由来の ¹³C ピーク 90.7 ppm (C-3) と糖のアノマー位由来の ¹H ピーク 4.85 ppm (d, *J* = 8.0 Hz, 1H, 1''-H) とで相関が観測されたことから、C-3 位グリコシド結合の形成を確認した。さらに、¹H-NMR におけるそれぞれのアノマー位由来のピークからβ体と確認した。

II. ドナー **18c, f** を用いたマイクロフロー式オレアノール酸 C-3 位配糖化の適用

確立したマイクロフロー式オレアノール酸 C-3 位配糖化条件を基に、Bz イミデートドナー **18c, f** を用い D-グルコース以外の糖を C-3 位に導入した配糖体 **22Bc, f** の合成を試みた。その結果、バッチ式条件と比較し **18c, f** の消費の抑制を行いつつ **18c, f** をそれぞれ収率 71%, 81% で得ることができた (Table 26)。

22Bc, f の構造はアグリコンの C-28 位由来の ¹³C ピーク 175.5 ppm (C-28) と糖のアノマー位由来の ¹H ピーク 5.55 ppm (d, *J* = 8.0 Hz, 1H, 1'-H) とで相関が観測されたことから、C-28 位グリコシド結合が切断されていないことを確認した。また、アグリコンの C-3 位由来の ¹³C ピーク 90.7 ppm (C-3) と糖のアノマー位由来の ¹H ピーク 4.85 ppm (d, *J* = 8.0 Hz, 1H, 1''-H) とで相関が観測されたことから、C-3 位グリコシド結合の形成を確認した。さらに、¹H-NMR におけるそれぞれのアノマー位由来のピークからβ体と確認した (Table 27)。

Table 26 マイクロフロー式オレアノール酸 C-3 位配糖化を用いた **22Bc, f** の合成



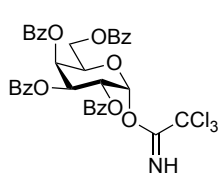
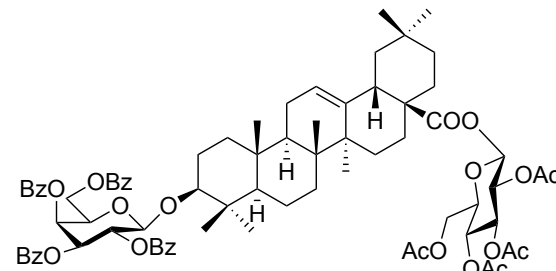
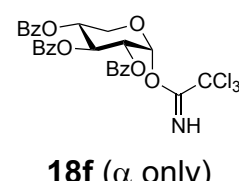
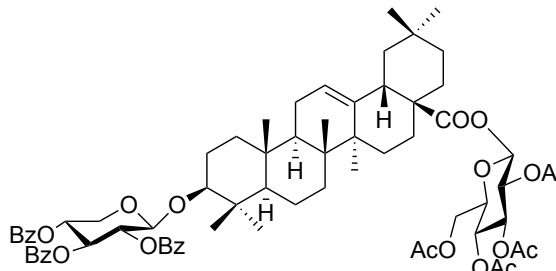
Protected bisdesmosidic glycoside			
Entry	Donor	Structure	Yield (%)
1	 <p>18c (α only)</p>	 <p>22Bc (β, β only)</p>	71
2	 <p>18f (α only)</p>	 <p>22Bf (β, β only)</p>	81

Table 27 配糖体 **22Bc, f** の構造決定に関わる ¹H 及び ¹³C-NMR

Compound	δH	δC
	Anomer-H (d, ppm, Hz)	¹³ C (ppm)
22Bc (β, β only)	5.57 (1'-H, <i>J</i> = 8.0)	175.6 (C-28)
	4.84 (1''-H, <i>J</i> = 6.1)	89.9 (C-3)
22Bf (β, β only)	5.83 (1'-H, <i>J</i> = 8.0)	175.6 (C-28)
	4.84 (1''-H, <i>J</i> = 8.0)	90.9 (C-3)

第三項 ビスデスモシドサポニン **24Ba, c, f** の合成の検討

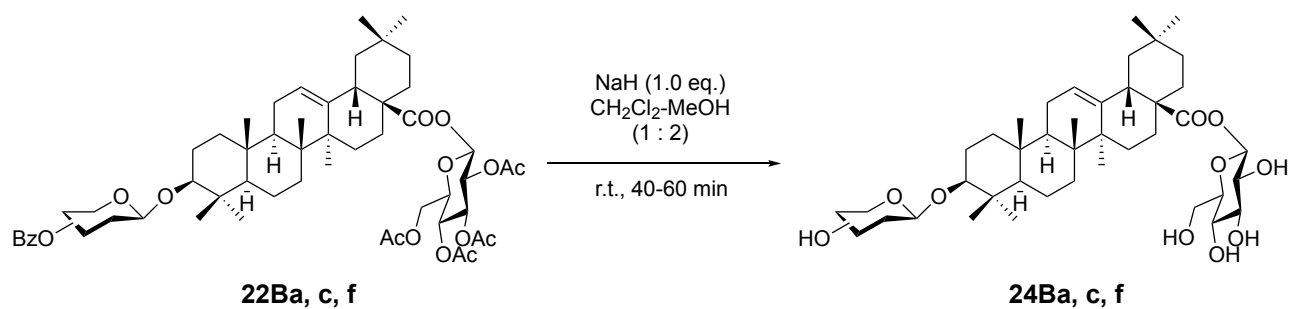
得られた配糖体 **22Ba, c, f** を用い、続いてアシル基の脱保護反応の検討を行い既知のビスデスモシドサポニン **24Ba, c, f** の合成を試みた。即ち、第一節で行った C-28 位グルコース糖結合型サポニンの合成結果を基に、MeOH - CH₂Cl₂ (2 : 1) 混合溶媒中 NaH in oil (60% disp.) を用いたメタノリシス反応を行い、Bz 基と Ac 基の脱保護を試みた。その結果、1.0 当量の NaH in oil (60% disp.) を用いた場合、高収率で天然植物に含有されるビスデスモシドサポニン **24Ba, c, f** が得られた (Table 28, 29)。

なお、糖の ¹H 及び ¹³C-NMR のシグナルの帰属には TOCSY を用いた。磁化を移動させるために設定した混合時間 (mixing time) は、τ_m = 150 ms とした。**24Ba** は D-グルコースの 1'位から 6'位及び 1''位から 6''位までの相関が確認され、**24Bc** は D-グルコースの 1'位から 6'位及び D-ガラクトースの 1''位から 6''位までの相関が確認された。また、**24Bf** は D-グルコースの 1'位から 6'位及び D-キシロースの 1''位から 5''位までの相関が確認された (Table 30)。**24Ba, c, f** の構造は ¹H-NMR において C-28 位及び C-3 位糖由来のピークの高磁場シフト、及び Bz 基由来のピークと Ac 基由来のピークの消失から確認した。また、HMBC においてアグリコンの C-28 位由来の ¹³C ピークと糖のアノマー位由来の ¹H ピークとで相関が観測されたことから、C-28 位グリコシド結合が切断されていないことを確認した。また、アグリコンの C-3 位由来の ¹³C ピークと糖のアノマー位由来の ¹H ピークとで相関が観測されたことから、C-3 位グリコシド結合が切断されていないことを確認した。さらに、¹H-NMR におけるそれぞれのアノマー位由来のピークから所望のβ体であると確認した (Table 31)。

Table 28 **24Ba, c, f** の単離報告例と合成報告例

Saponin	Imidate donor type (eq.)	Total yield		The example of isolation report
		Literature	This research	
24Ba	Bz-D-Glc (1.2)	55 ⁵¹	65	<i>Panax ginseng</i> ⁶⁶ <i>Calendula stellata</i> ⁶⁷
24Bc	Bz- D-Gal (1.2)	28 ⁵⁰	46	<i>Aralia elata</i> ⁶⁸ <i>Aralia elata</i> ⁶⁹ <i>Chenopodium</i>
24Bf	Bz- D-Xyl (1.2)	Data not shown	61	<i>berlandieri</i> ⁷⁰ <i>Patrinia scabiosaefolia</i> ⁷¹

Table 29 3 種のアノール酸ビスデスモシドサポニン **24Ba, c, f** の合成



Bisdesmosidic saponin

Entry	Substrate	Structure	Yield (%)
1	22Ba	<p style="text-align: center;">24Ba (β, β only)</p>	93 ^a
2	22Bc	<p style="text-align: center;">24Bc (β, β only)</p>	74 ^a
3	22Bf	<p style="text-align: center;">24Bf (β, β only)</p>	87 ^b

a) The reaction was conducted for 1 h. b) The reaction was conducted for 40 min.

Table 30 ビスデスモシドサポニン **24Ba, c, f** の糖鎖構造の ^1H 及び ^{13}C -NMR

	28-O- β -D-Glc			3-O- β -D-Glc		
		δH	δC		δH	δC
24 Ba	1'	6.30 (d, 8.0)	95.9	1"	4.91 (d, 8.0)	107.0
	2'	4.18 (t, 8.5)	74.2	2"	4.01 (t, 8.0)	75.9
	3'	4.26 (dd, 9.0, 8.5)	78.9	3"	4.22 (dd, 8.5, 8.0)	78.8
	4'	4.34 (dd, 9.5, 9.0)	71.2	4"	4.20 (dd, 9.0, 8.5)	71.9
	5'	4.00 (ddd, 9.5, 4.0, 2.0)	79.5	5"	3.98 (ddd, 9.0, 5.0, 2.0)	78.4
	6'	4.43 (dd, 12.0, 2.0) 4.38 (dd, 12.0, 5.0)	62.2	6"	4.56 (dd, 12.0, 2.0) 4.37 (dd, 12.0, 5.0)	63.1
24 Bc						
24 Bf						

Table 31 ビスデスモシドサポニン **24Ba, c, f** の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	Lost peak (ppm)	δC
		^{13}C (d, ppm, Hz)
24Ba (β , β only)	8.03-7.28 (m, 20H, Ar-H)	
	2.06, 2.02, 2.00, 1.99	176.6 (C-28)
	(s, 3H, $-\text{OCOCH}_3 \times 4$)	89.0 (C-3)
24Bc (β , β only)	8.12-7.34 (m, 20H, Ar-H)	
	2.06, 2.02, 2.01, 1.99	176.6 (C-28)
	(s, 3H, $-\text{OCOCH}_3 \times 4$)	88.9 (C-3)
24Bf (β , β only)	8.10-7.31 (m, 15H, Ar-H)	
	2.06, 2.02, 2.01, 2.00	176.7 (C-28)
	(s, 3H, $-\text{OCOCH}_3 \times 4$)	95.0 (C-3)

第四節 マイクロフロー式オレアノール酸 C-3 位配糖化とバッチ式アシル基脱保護の集積化によるビスデスモシドサポニンの連続合成の検討

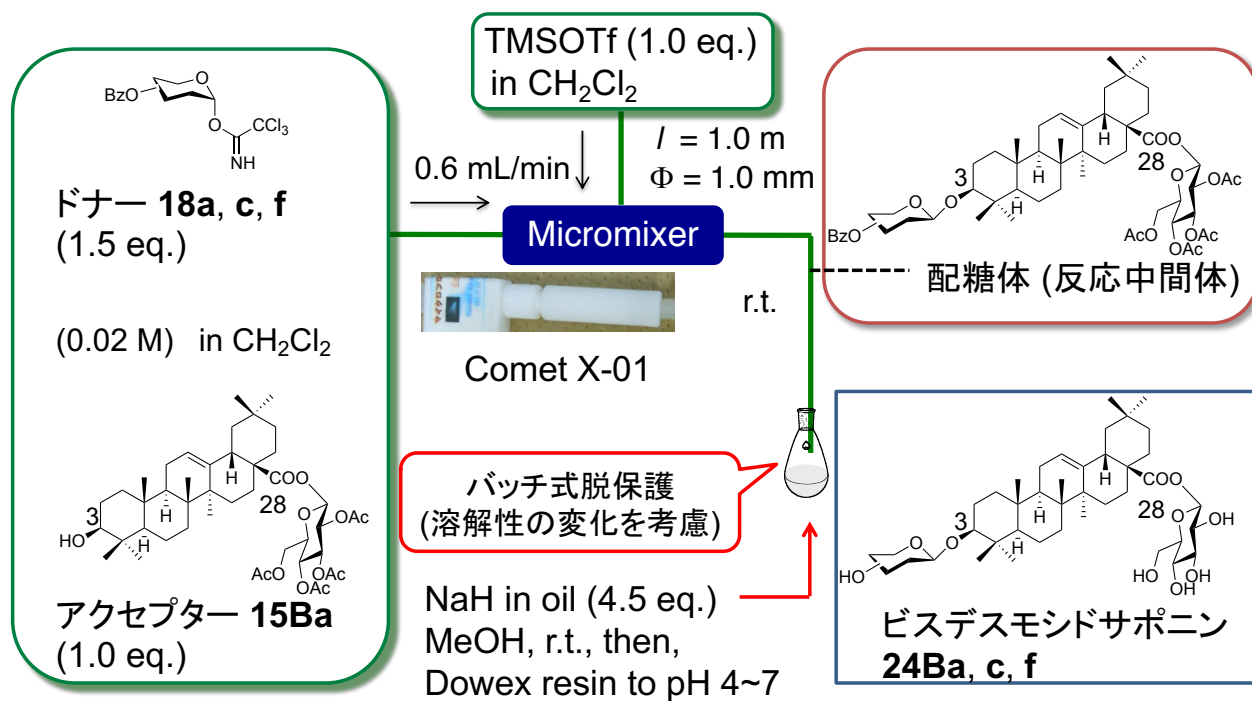
マイクロフロー式 C-28 位配糖化と NaH in oil を用いたバッチ式 Ac 基脱保護の連続反応の検討結果を利用し得られた **15Ba** を用い、続いてマイクロフロー式 C-3 位配糖化とアシル基 (Ac 基及び Bz 基) の脱保護の連続反応を検討し、ビスデスモシドサポニン **24Ba, c, f** の連続合成を試みることにした。

CH₂Cl₂に溶解させた 1.0 当量の TMSOTf 溶液及び比較的溶解性の高いグリコシルアクセプター **15Ba** と 1.5 当量のグリコシルドナー **24Ba, c, f** それぞれの混合溶液を別途調製し、各溶液をシリンジに取りマイクロフローに接続した。マイクロフロー反応部とフロー管は予めクランプに固定し常温下で静置させた。また、フロー管の長さとお内径はそれぞれ 1.0 m と 1.0 mm とした。その後、シリンジポンプを用いて流速 (0.6 mL/min)、流量 (3.0 mL)、シリンジ内径 (16 mm) を設定し、シリンジからテフロンチューブへと溶液を流しマイクロフロー内で C-3 位配糖化を行った。次に予め窒素雰囲気下で加熱処理を施し、無水条件とした二口フラスコに NaH in oil と MeOH を加え、別途溶液を調製した。その後、フロー管の出口に穴を空けたセプタムを介して接続し、アシル基脱保護を連続反応で実施した (Table 32)。

4.5 当量の NaH in oil を用いると、ビスデスモシドサポニン **24Ba, c, f** をそれぞれ二工程収率 40% 台で得ることに成功した。一方、10.0 当量の NaH を用いた場合は目的のビスデスモシドサポニンは得られず、反応系中に C-28 位グリコシドエステル結合の切断によって生じた複雑な混合物を与えた。

連続反応により合成した **24Ba, c, f** の構造は段階合成した **24Ba, c, f** の ¹H-NMR と比較し、不純物等が混入していないことを確認した。また、後述する CMC を測定する DPH 法の結果が一致したことより、無機塩類等の不純物も含まれていないことも確認した。この手法により、ビスデスモシドサポニンのカラム精製過程を短縮し迅速な供給が可能となった。

Table 32 マイクロフロー式 C-3 位配糖化・脱保護連続反応法を利用したビスデスモンドサポニン **24Ba, c, f** の合成



Entry	Donor (1.5 eq.)	Batch reaction time (min)	Bisdesmosidic saponin	Yield (%)
1	<p>18a (α only)</p>	30	<p>24Ba (β, β only)</p>	47
2	<p>18c (α only)</p>	30	<p>24Bc (β, β only)</p>	43
3	<p>18f (α only)</p>	30	<p>24Bf (β, β only)</p>	47

第五節 マイクロフロー式 C-3 位配糖化とバッチ式アシル基脱保護の集積化による C-3 位サポニンの応用

第一項 C-3 位トリテルペノイドサポニンの合成

I. トリテルペングリコシルアクセプター **25B-E** の合成

確立したマイクロフロー式 C-3 位配糖化と NaH in oil を用いたバッチ式アシル基脱保護の連続反応の方法論を利用し、続いて種々のトリテルペンを用いた C-3 位サポニンの連続合成を試みる事とした。即ち、アグリコンはトリテルペンであるオレアノール酸 (oleanolic acid, **3B**)、ウルソール酸 (ursolic acid, **3C**)、ベツリン酸 (betulinic acid, **3D**)、グリチルレチン酸 (glycyrrhetic acid, **3E**) を用い、糖はベンゾイルグルコースイミダートドナー **18a** を用いる事とした。

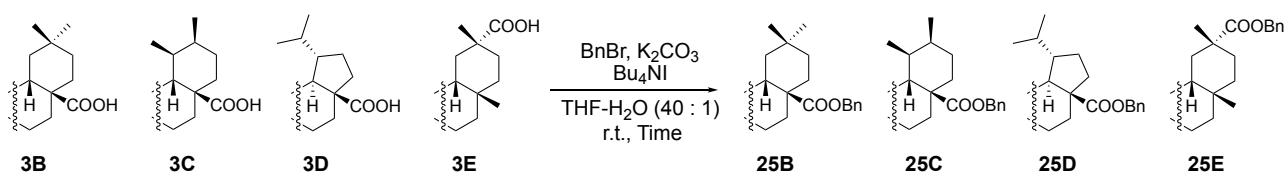
各種トリテルペンの C-3 位のヒドロキシ基に選択的に配糖化を行うには各種トリテルペンの遊離カルボキシ基の選択的保護が必要である。また、後に C-3 位配糖化を試みる際にカルボキシ基部位を選択的に脱保護可能な保護基の導入が必要である。

そこで、筆者は C-3 位のヒドロキシ基のみを保護したグリコシルアクセプターの合成に着手した。この際、用いる保護基として Bn 基を選択した。

まず、筆者は既知アクセプター **25B-E** の合成に着手した。市販品である **3B-E** を THF-H₂O (40 : 1) に溶解後、テトラブチルアンモニウムヨージド (TBAI)、炭酸カリウム (K₂CO₃)、ベンジルブロミド (BnBr) を順に加え、カルボキシ基選択的ベンジル化を行いアクセプター **25B-E** を合成した (Table 33)。

なお、各種アクセプター **25B-E** の構造は ¹³C-NMR におけるカルボキシ基由来のピークの高磁場シフト及び ¹H-NMR における Bn 基由来のピークの出現により確認した (Table 34)。

Table 33 トリテルペノイドアクセプター **25B-E** の合成



Triterpene			Product	
Entry	Type	Structure	Structure	Yield (%)
1	Oleanolic Acid (3B)			25B 92 ^a
2	Ursolic Acid (3C)			25C 88 ^b
3	Betulinic Acid (3D)			25D 94 ^c
4	Glycyrrhetic Acid (3E)			25E 59 ^c

a) The reaction was conducted for 20 h. b) The reaction was conducted for 7 h. c) The reaction was conducted for 24 h.

Table 34 アクセプター 25B-E の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	δH	δC
	Bn (ppm)	^{13}C (ppm)
25B ⁷²	7.33 (m, 5H, <u>Ph</u> CH ₂)	177.4
	5.07 (each d, $J = 12.7$ Hz, 2H, PhCH <u>2</u>)	(C-28)
25C ⁷³	7.33 (m, 5H, <u>Ph</u> CH ₂),	177.2
	5.04 (each d, $J = 12.7$ Hz, 2H, PhCH <u>2</u>)	(C-28)
25D ⁷⁴	7.37-7.31 (m, 5H, <u>Ph</u> CH ₂)	175.8
	5.11 (each d, $J = 12.3$ Hz, 2H, PhCH <u>2</u>)	(C-28)
25E ⁷⁵	7.40-7.30 (m, 5H, <u>Ph</u> CH ₂)	176.2
	5.14 (each d, $J = 12.3$ Hz, 2H, PhCH <u>2</u>)	(C-30)

II.C-28-Bn トリテルペノイドサポニン **26Ba-Ea** の連続合成

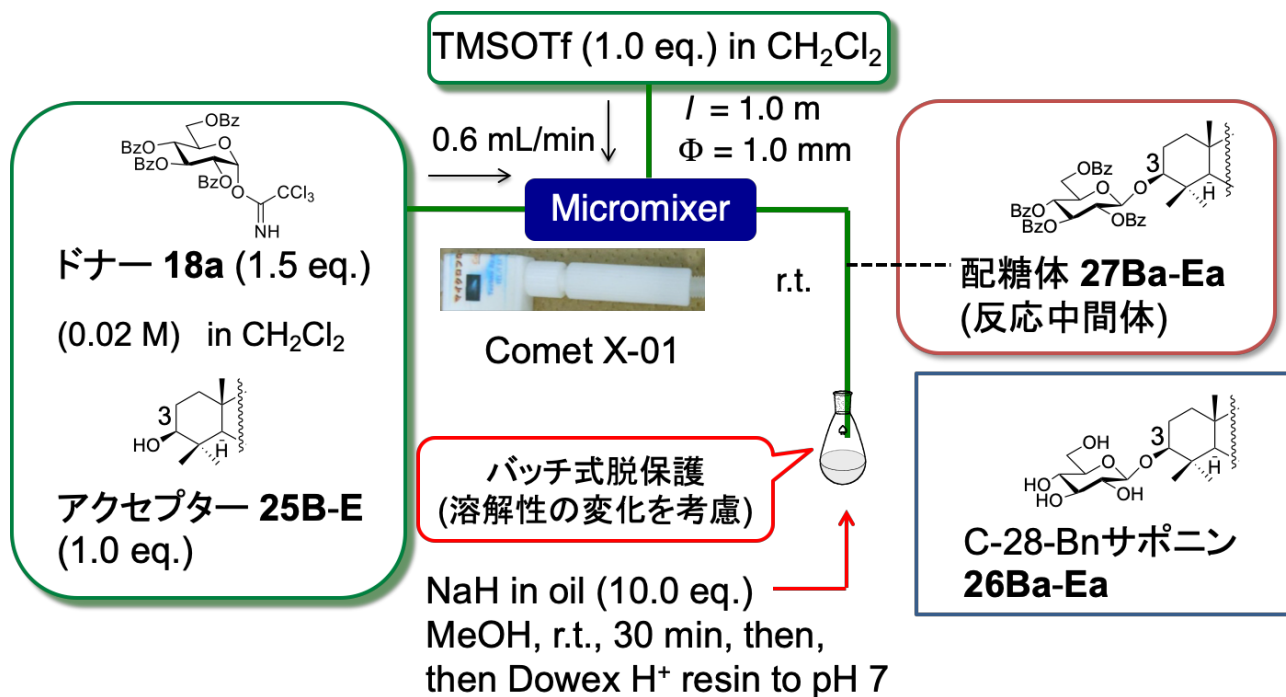
合成した各種トリテルペンアクセプター **25B-E** を用い、続いて C-28-Bn トリテルペノイドサポニン **26Ba-Ea** の連続合成を試みることにした。

まず、CH₂Cl₂ に溶解させた 1.0 当量の TMSOTf 溶液及び比較的溶解性の高いグリコシルアクセプター **25B-E** と 1.5 当量のグリコシルドナー **18a** それぞれの混合溶液を別途調製し、シリンジに取りマイクロフローに接続した。マイクロフロー反応部とフロー管は予めクランプに固定し常温下で静置させた。また、フロー管の長さ、内径はそれぞれ 1.0 m と 1.0 mm とした。その後、シリンジポンプを用いて流速 (0.6 mL/min)、流量、シリンジ内径を設定し、シリンジからテフロンチューブへと溶液を流しマイクロフロー内で C-3 位配糖化を行った。次に、予め窒素雰囲気下で加熱処理を施し無水条件とした二口フラスコに 10 当量の NaH in oil と MeOH を加え、別途溶液を調製した。その後、フロー管の出口に穴を開けたセプタムを介して接続し、アシル基脱保護を連続反応で実施した (Table 35)。その結果、配糖体 **27Ba-Ea** が生成した後 Bz 基の脱保護が円滑に進行し、**26Ba-Ea** をそれぞれ中程度以上の収率でカラム実験工程の回数を改善して得ることができた。

なお、筆者はアクセプター **25B** とドナー **18a** を用いて確立した C-3 位配糖化を行ったところ、**18a** 由来の不純物と配糖体 **27Ba** の生成には順相シリカゲルクロマトグラフィー (トルエン: 酢酸エチル系) による精製を 3 回以上繰り返さなければならなかった (Scheme 13)。連続反応を実施することでカラム工程数を低減できるだけでなく、Bn 基より先に Bz 基を脱保護することで **18a** 由来の不純物との極性の差が生じ、順相カラムクロマトグラフィー上で分離が容易になったと考えられた。

なお、**26Ba-Ea** の構造について、¹H-NMR における糖のアノマー位のピークより β 体と決定した。また、HMBC においてアグリコンの C-3 位由来の ¹³C ピークと糖のアノマー位由来の ¹H ピークとで相関が観測されたことから、C-3 位グリコシド結合の形成を確認した (Table 36)。

Table 35 マイクロフロー式 C-3 位配糖化・脱保護連続反応法を利用したベンジルサポニン **26Ba-Ea** の合成



C-28-Bn Saponin		
Entry	Acceptor	Product yield (%)
1	25B	26Ba (β only) 72
2	25C	26Ca (β only) 71
3	25D	26Da (β only) 66

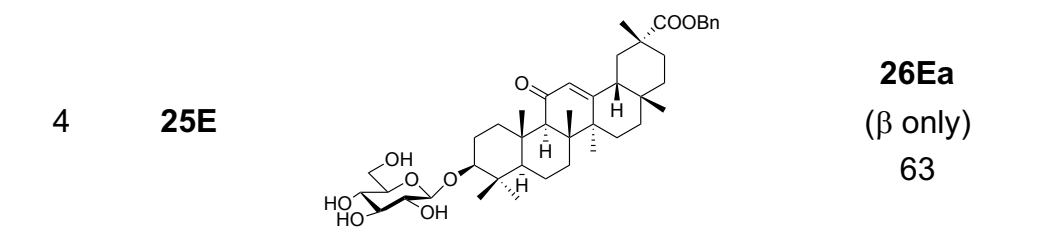
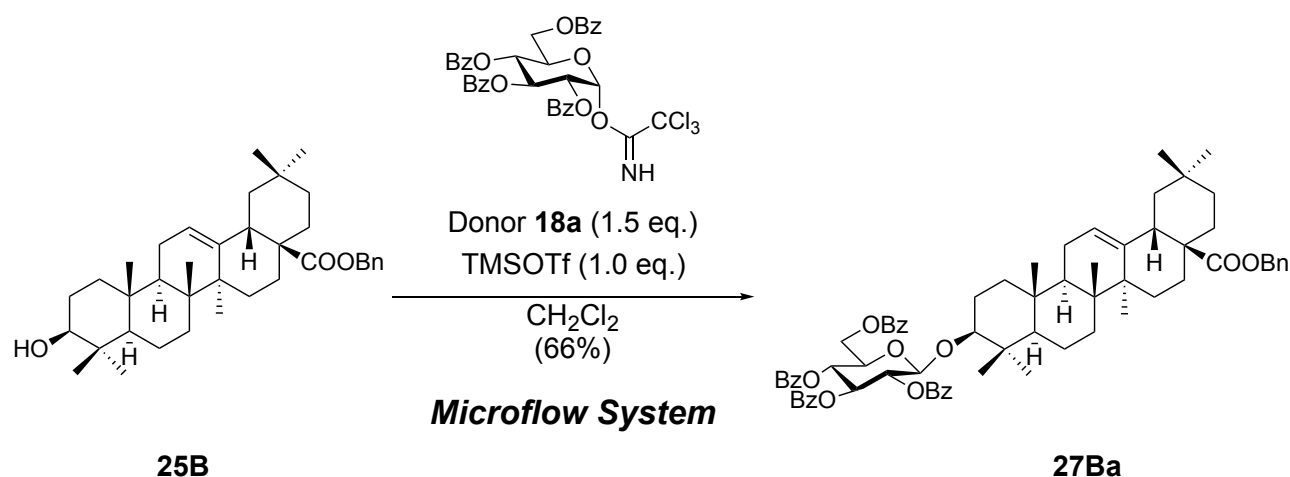


Table 36 ベンジルサポニン **26Ba-Ea** の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	δH	δC
	1'-H (d, ppm, Hz)	C-3 (ppm)
26Ba (β only)	4.96 (d, $J = 8.0$ Hz, 1H)	89.0
26Ca (β only)	4.97 (d, $J = 7.8$ Hz, 1H)	89.1
26Da (β only)	4.97 (d, $J = 7.8$ Hz, 1H)	89.0
26Ea (β only)	4.96 (d, $J = 7.8$ Hz, 1H)	88.7

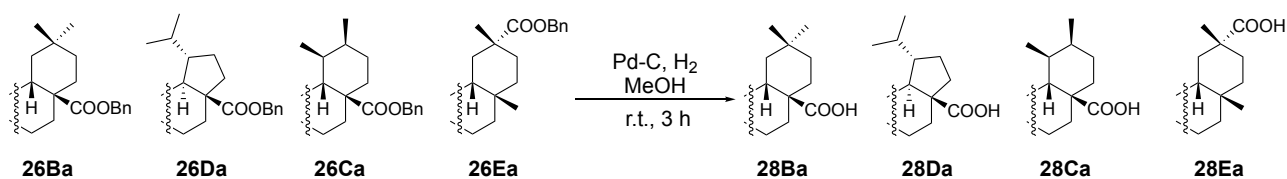


Scheme 13 マイクロフロー式 C-3 位配糖化法を用いた配糖体 **27Ba** の合成

III.C-3 位トリテルペノイドサポニン **28Ba-Ea** の合成

首尾良く得られた **26Ba-Ea** を用い、続いて C-3 位トリテルペノイドサポニン **28Ba-Ea** の合成を行った。即ち、**26Ba-Ea** を MeOH に溶解後、水素雰囲気下でパラジウム炭素 (Pd/C) 触媒を用いた接触水素化還元⁷⁶を行い 3 時間後にセライト濾過した後、順相シリカゲルカラムクロマトグラフィー (クロロホルム : メタノール系) で精製し、**28Ba-Ea** をそれぞれ高収率で得た (Table 37)。この時、エステル交換反応は確認されなかった。

Table 37 トリテルペノイド C-3 位サポニン **28Ba-Ea** の合成



		Glycoside	C-3-Saponin	
Entry	Type	Lost signal (ppm)	Structure	Yield (%)
1	26Ba	7.33 m, 5H, <u>PhCH₂</u> 5.07 each d $J = 12.7 \text{ Hz}$ 2H, <u>PhCH₂</u>	 28Ba (β only)	81
2	26Ca	7.33 m, 5H, <u>PhCH₂</u> 5.04 each d $J = 12.7 \text{ Hz}$ 2H, <u>PhCH₂</u>	 28Ca (β only)	91
3	26Da	7.37-7.31 m, 5H, <u>PhCH₂</u> 5.11 each d $J = 12.3 \text{ Hz}$ 2H, <u>PhCH₂</u>	 28Da (β only)	89
4	26Ea	7.40-7.30 m, 5H, <u>PhCH₂</u> 5.14 each d $J = 12.3 \text{ Hz}$ 2H, <u>PhCH₂</u>	 28Ea (β only)	93

なお、**28Ba-Ea** の構造について、Bn 基由来のピークの消失を確認し ^1H -NMR における糖のアノマー位のピークより β 体と決定した。また、HMBC においてアグリコンの C-3 位由来の ^{13}C ピークと糖のアノマー位由来の ^1H ピークとで相関が観測されたことから、C-3 位グリコシド結合が切断されていないことを確認した (Table 38)。

合成した各種 **28B-Ea** の合成例と単離報告例を以下の表に示す (Table 39)。

Table 38 トリテルペノイド C-3 位サポニン **28Ba-Ea** の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	δH	δC
	$1'\text{-H}$	^{13}C
	(d, ppm, Hz)	(ppm)
28Ba (β only)	4.96 (d, $J = 8.0$ Hz, 1H)	180.3 (C-28)
28Ca (β only)	4.97 (d, $J = 7.8$ Hz, 1H)	180.0 (C-28)
28Da (β only)	4.97 (d, $J = 7.8$ Hz, 1H)	179.2 (C-28)
28Ea (β only)	4.96 (d, $J = 7.8$ Hz, 1H)	179.6 (C-30)

Table 39 C-3 位サポニン **28Ba-Ea** の単離とシュミットグリコシル化を用いた合成報告例

Saponin	Donor type (eq.)	Glycosylation and deprotection yield (%)		The example of isolation report
		Literature	This research	
28Ba	Benzoylated-Glc-imidate (1.2)	72 ⁷⁶	58	<i>Calendula officinalis</i> ⁷⁷ <i>Acanthopanax nipponicus</i> ⁷⁸ <i>Tiarella polyphylla</i> ⁷⁹
28Ca	Acetylated-Glc-imidate (1.2)	29 ⁸⁰	65	<i>Lysimachia clethroides</i> ⁸¹ <i>Dryopteris wallichiana</i> ⁸² <i>Viburnum opulus</i> ⁸³
28Da	-	Not data shown	59	-
28Ea	Benzoylated-Glc-imidate (1.2)	71 ⁸⁴	59	-

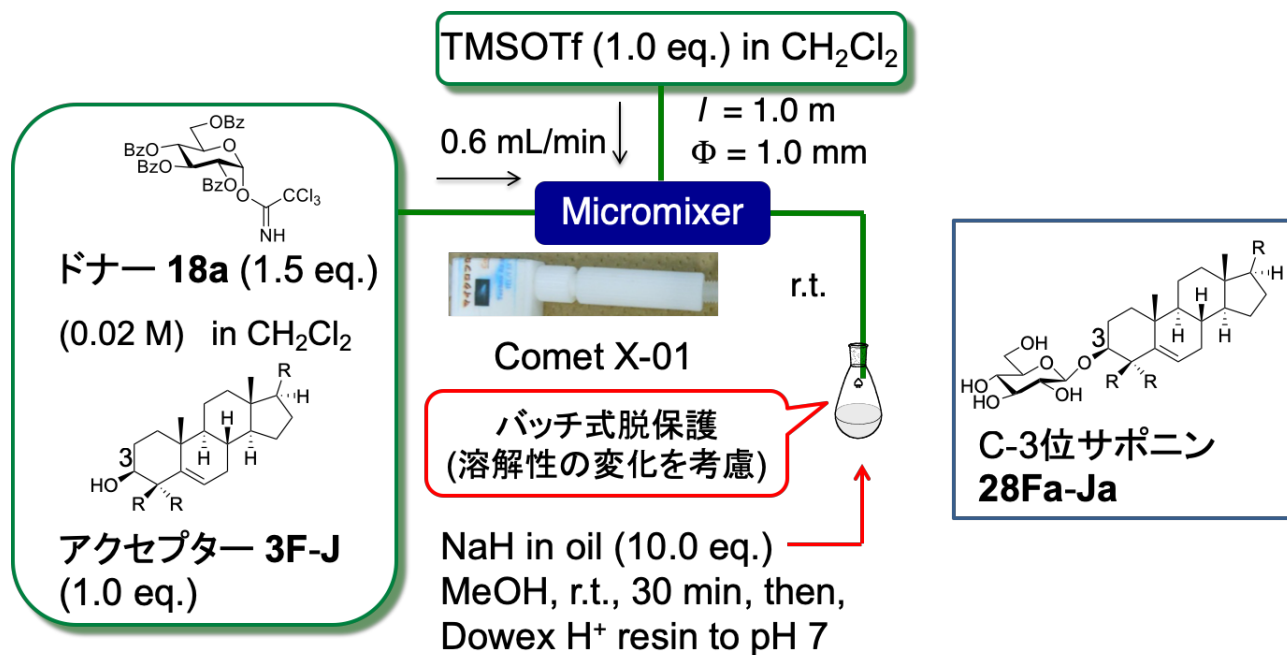
第二項 C-3 位ステロイド及び四環性トリテルペノイドサポニン **28Fa-Ja** の合成

確立したマイクロフロー式 C-3 位配糖化と NaH in oil を用いたバッチ式 Bz 基脱保護の連続反応の方法論を利用し、続いて種々のステロイドを用いた C-3 位サポニン **28Fa-Ja** の連続合成を試みることにした。即ち、アグリコンはステロイドである β -シトステロール (β -sitosterol, **3F**)、スチグマステロール (stigmasterol, **3G**)、ジオスゲニン (diosgenin, **3H**)、エルゴステロール (ergosterol, **3J**) 及び四環性トリテルペンであるラノステロール (lanosterol, **3I**) を用い、糖はベンゾイルグルコースイミダートドナー **18a** を用いることにした。

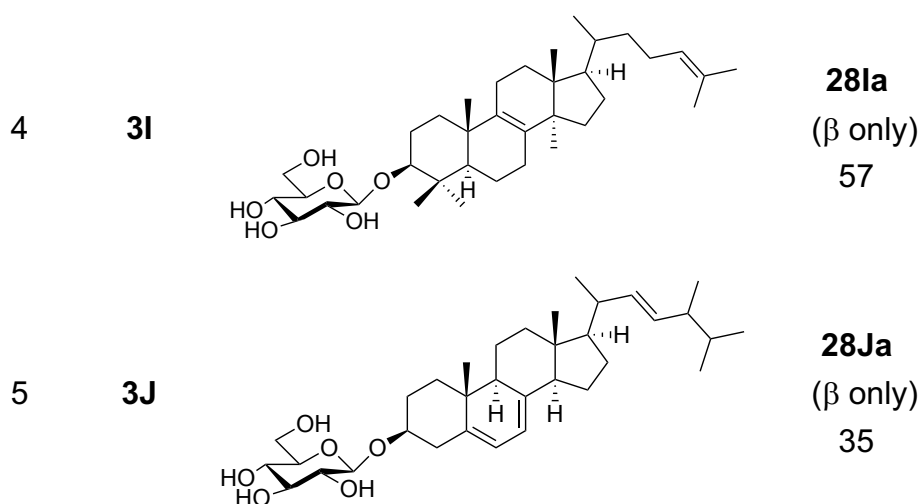
まず、CH₂Cl₂ に溶解させた 1.0 当量の TMSOTf 溶液及び比較的溶解性の高いグリコシルアクセプター **3F-3J** と 1.5 当量のグリコシルドナー **18a** からなる混合溶液を別途調製し、シリンジに取りマイクロフローに接続した。マイクロフロー反応部とフロー管は予めクランプに固定し常温下で静置させた。また、フロー管の長さと同径はそれぞれ 1.0 m と 1.0 mm とした。その後、シリンジポンプを用いて流速 (0.6 mL/min)、流量、シリンジ内径を設定し、シリンジからテフロンチューブへと溶液を流しマイクロフロー内で C-3 位配糖化を行った。次に、予め窒素雰囲気下で加熱処理を施し無水条件とした二口フラスコに 10 当量の NaH in oil と MeOH を加え、別途溶液を調製した。その後、フロー管の出口に穴を開けたセプタムを介して接続し、アシル基脱保護を連続反応で実施した (Table 40)。

その結果、中程度の収率で **28Fa, Ga, Ia** をやや低収率で **28Ha, Ja** を合成できた。各種トリテルペノイドサポニンと比べ、配糖化時の収率が低下した原因にステロイド骨格の CH₂Cl₂ に対する溶解性が低かったことが理由として考えられた。

Table 40 マイクロフロー式 C-3 位配糖化・脱保護連続反応法を利用したベンジルサポニン **28Fa-Ja** の合成



Steroid saponin			
Entry	Steroid	Structure	Yield (%)
1	3F		28Fa (β only) 52
2	3G		28Ga (β only) 60
3	3H		28Ha (β only) 39



なお、**28Fa-Ja** の構造について、 ^1H -NMR における糖のアノマー位のピークよりβ体と決定した。また、HMBC においてアグリコンの C-3 位由来の ^{13}C ピークと糖のアノマー位由来の ^1H ピークとで相関が観測されたことから、C-3 位グリコシド結合の形成を確認した (Table 41)。

合成した各種 **28Fa-Ja** の合成例と単離報告例を以下の表に示す (Table 42)。

Table 41 C-3 位サポニン **28Fa-Ja** の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	δH	δC
	1'-H (d, ppm, Hz)	C-3 (ppm)
28Fa (β only)	5.06 (d, $J = 8.0$ Hz, 1H, 1'-H)	78.3
28Ga (β only)	5.06 (d, $J = 8.0$ Hz, 1H, 1'-H)	78.3
28Ha (β only)	5.05 (d, $J = 8.0$ Hz, 1H, 1'-H)	67.0
28Ia (β only)	4.98 (d, $J = 8.0$ Hz, 1H, 1'-H)	89.1
28Ja (β only)	5.07 (d, $J = 8.0$ Hz, 1H, 1'-H)	78.8

Table 42 C-3 位サポニン **28Fa-Ja** の単離と合成報告例

Saponin	Donor type (eq.)	Glycosylation and deprotection yield (%)		The example of isolation report
		Literature	This research	
28Fa	Acetylated- Glc-Br (3.0)	65 ⁸⁵	52	<i>Eleutherococcus senticosus</i> ⁸⁶ <i>Paeonia suffruticosa</i> ⁸⁷ <i>Houttuynia cordata</i> ⁸⁸
28Ga	Benzoylated- Glc-imidate (1.1)	89 ⁸⁹	60	<i>Prunella vulgaris</i> ⁹⁰ <i>Atractylodes lancea</i> ⁹¹ <i>Cinnamomum kotoense</i> ⁹²
28Ha	Benzoylated- thiophenyl (1.2)	85 ⁹³	39	<i>Hericum erinaceus</i> ⁹⁴ <i>Catathelasma imperiale</i> ⁹⁵ <i>Chlorophyllum molybdites</i> ⁹⁶
28Ia	-	-	57	-
28Ja	Benzoylated- Glc-imidate (1.2)	79 ⁹⁷	35	<i>Borassus flabellifer</i> ⁹⁸ <i>Dioscorea zingiberensis</i> ⁹⁹

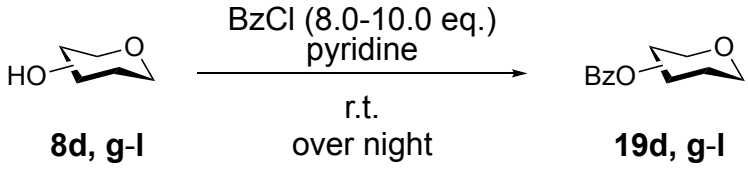
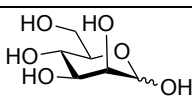
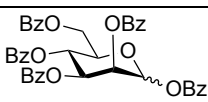
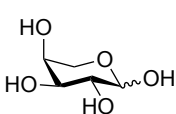
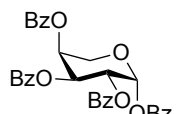
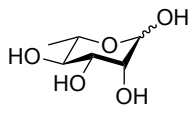
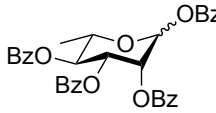
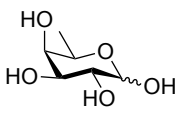
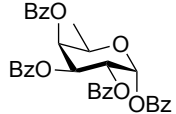
第三項 C-3 位オレアノール酸サポニン **28Bc-1** の合成

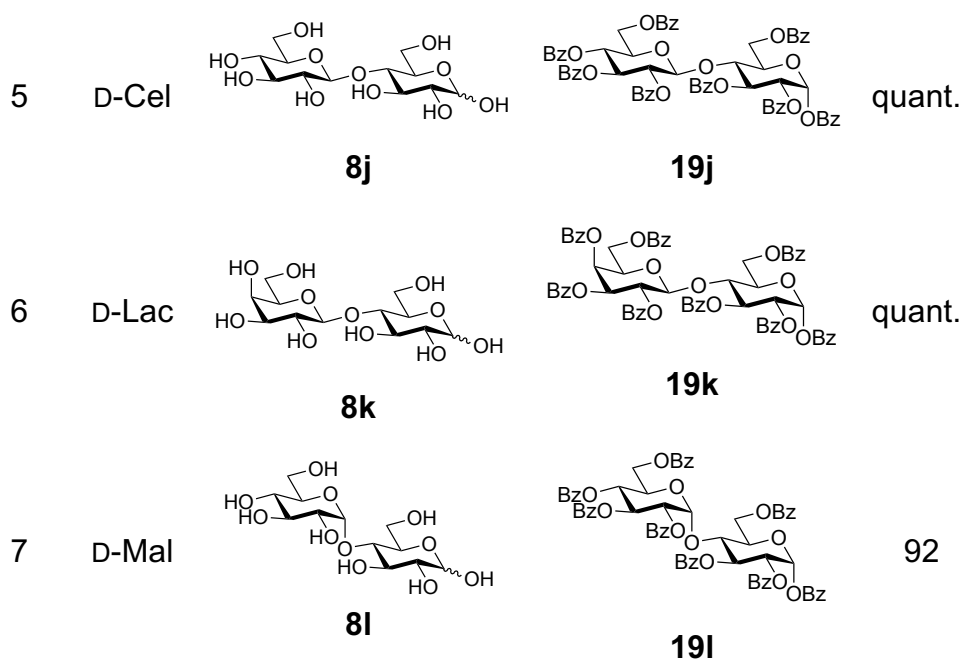
I. ベンゾイルイミダートドナー **18d, g-l** の合成

確立したマイクロフロー式 C-3 位配糖化と脱保護連続反応を用い、筆者は 9 種類の C-3 位モノグルコシドサポニン **28Ba-Ja** を合成できた。さらに、種々の糖を用いたオレアノール酸 C-3 位サポニンの連続合成を試みる事とした。即ち、アクセプターは **25B** を用い、糖は既に合成したベンゾイルイミダートドナー **18a, c, f** に加えて、**18d, g-l** を合成し用いることとした。

原料である各種市販品の単糖あるいは二糖 (**8d, 8f-l**) を pyridine に溶解後、BzCl を加えベンゾイル化を行い化合物 **19d, g-l** を得た。BzCl の当量数は単糖の場合は 8 当量、二糖の場合は 10 当量を用いた。以下の表にその構造と各種ピークを示す (Table 43)。

Table 43 化合物 **19d, g-l** の合成

<div style="text-align: center;">  </div>				
Entry		Substrate of sugar		Product
	Type	Structure	Structure	Yield (%)
1	D-Man	 8d	 19d	quant.
2	L-Ara	 8g	 19g	quant.
3	L-Rha	 8h	 19h (α only)	quant.
4	D-Fuc	 8i	 19i ($\alpha : \beta = 3 : 2$)	quant.



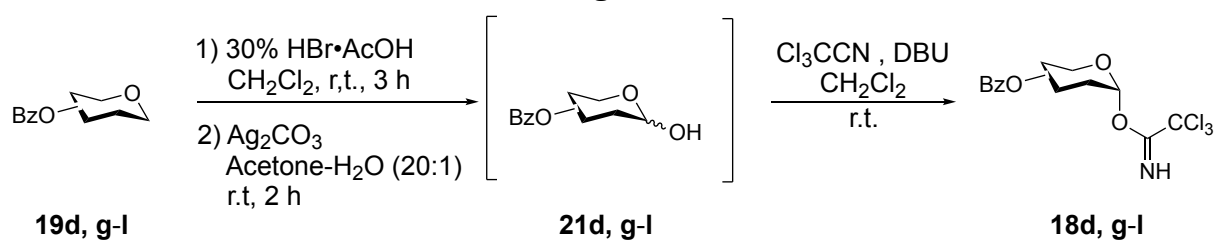
19d, g-l の構造は各種 Bz 基のピークの出現により確認した。また、1'-H 位のピークからアノマーの立体配置を決定した (Table 44)。各種カラム操作は省略し次の工程に用いた。

Table 44 化合物 **19d, g-l** の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	δH	
	Bz (Ph-H) (ppm)	1-H (d, 1H, ppm, Hz)
19d	7.69 (m, 25H, Ph-H)	6.58 (d, $J = 1.9$ Hz)
19g	8.12-7.27 (m, 20H, Ar-H)	6.82 (d, $J = 3.0$ Hz)
19h	7.68 (m, 25H, Ph-H)	6.49 (d, $J = 1.6$ Hz)
19i	8.12-7.23 (m, 15H, Ph-H)	6.83 (d, $J = 3.7$ Hz)
19j	7.62 (m, 40H, Ph-H)	6.69 (d, $J = 3.8$ Hz)
19k	8.03-7.16 (m, 40H, Ph-H)	6.71 (d, $J = 3.8$ Hz)
19l	8.09-7.19 (m, 40H, Ph-H)	6.72 (d, $J = 3.6$ Hz)

続いて調製した **19d, g-l** を CH_2Cl_2 に溶解後、 HBr/AcOH を用いてアノマー位を選択的にブromo (Br) 化した **20d, g-l** を得た後、アセトン-水 (20 : 1) 溶媒中で炭酸銀を用いアノマー位の Br 基を選択的に脱保護した化合物 **21d, g-l** を得た。その後、作業の簡略化のためにカラム精製を行わず化合物 **21d, g-l** を含む粗生成物を CH_2Cl_2 に溶解後、10 当量以上のトリクロロアセトニトリル (Cl_3CCN)、触媒量の DBU を用いてイミダート化を行い目的の **18d, g-l** を得た (Table 45)。

Table 45 ベンゾイルイミダートドナー **18d, g-l** の合成



Substrate			Product	
Entry	Type	Structure	Structure	Yield (2 steps: %)
1	D-Man 19d			18d ¹⁰⁰ 49
2	L-Ara 19g			18g ¹⁰¹ (β only) 22
3	L-Rha 19h			18h ¹⁰² (β only) 63
4	D-Fuc 19i			18i ¹⁰³ (α only) 57
5	D-Cel 19j			18j ¹⁰⁴ (α only) 71
6	D-Lac 19k			18k ¹⁰⁵ (α only) 65
7	D-Mal 19l			18l ¹⁰⁶ (α only) 61

18d, g-l の構造は ^1H -NMR におけるトリクロロアセトイミダートの N-H 由来のピークの出現により確認した (Table 46)。

Table 46 ベンゾイルイミダートドナー **18d, g-l** の構造決定に関わる ^1H 及び ^{13}C -NMR

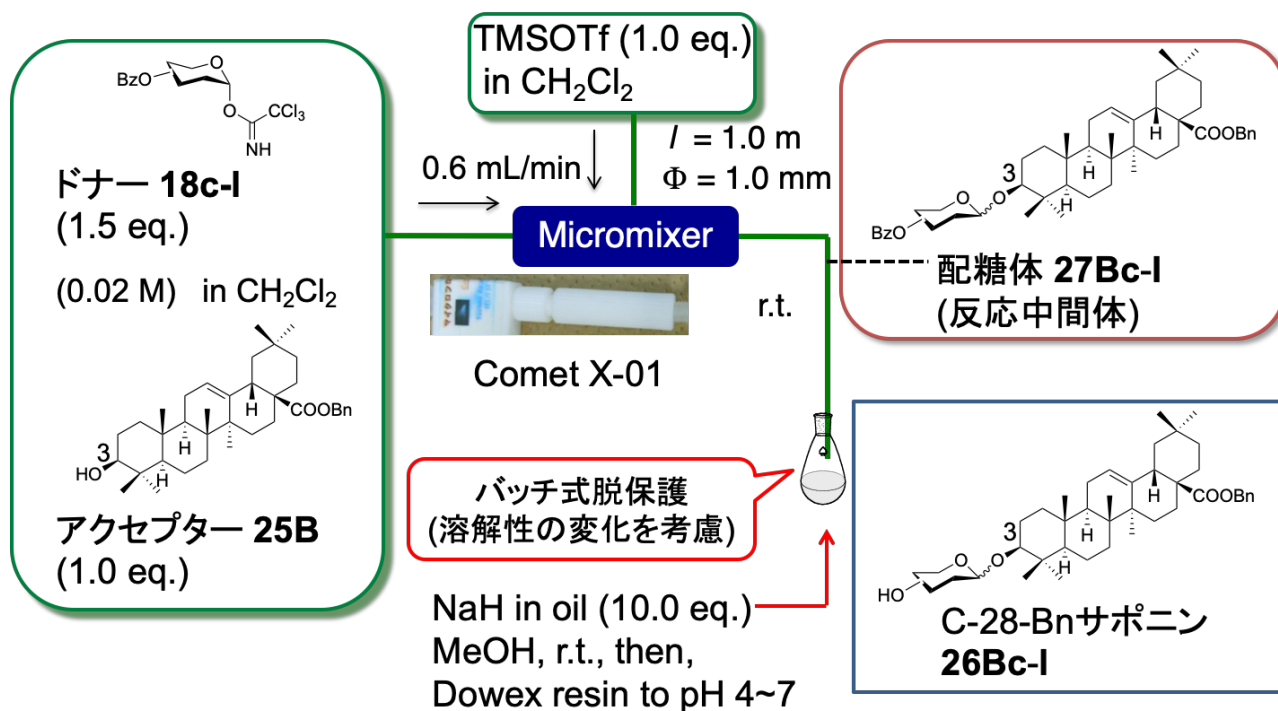
Compound	δH	
	$-\text{NH}$ (s, ppm)	$1'\text{-H}$ (d, ppm, Hz)
18d	8.86	6.58
18g (β only)	8.63	6.82
18h (β only)	8.82	6.49
18i (α only)	8.59	6.83
18j (α only)	8.54	6.69
18k (α only)	8.56	6.71
18l (α only)	8.58	6.72

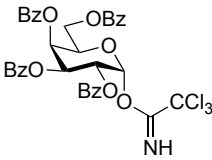
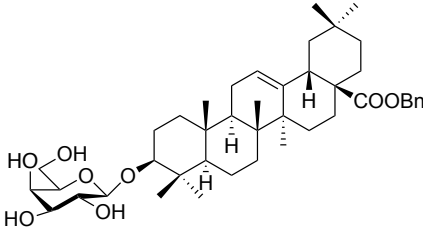
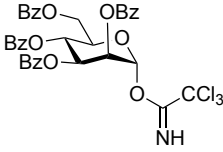
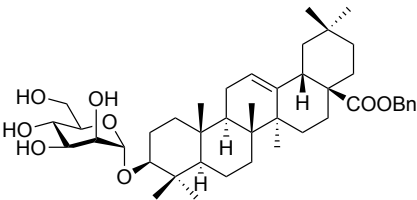
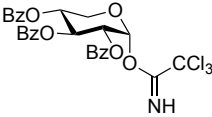
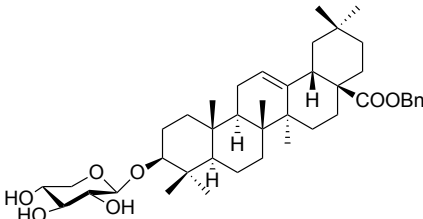
II.C-28-Bn オレアノール酸サポニン **26Bc-1** の連続合成

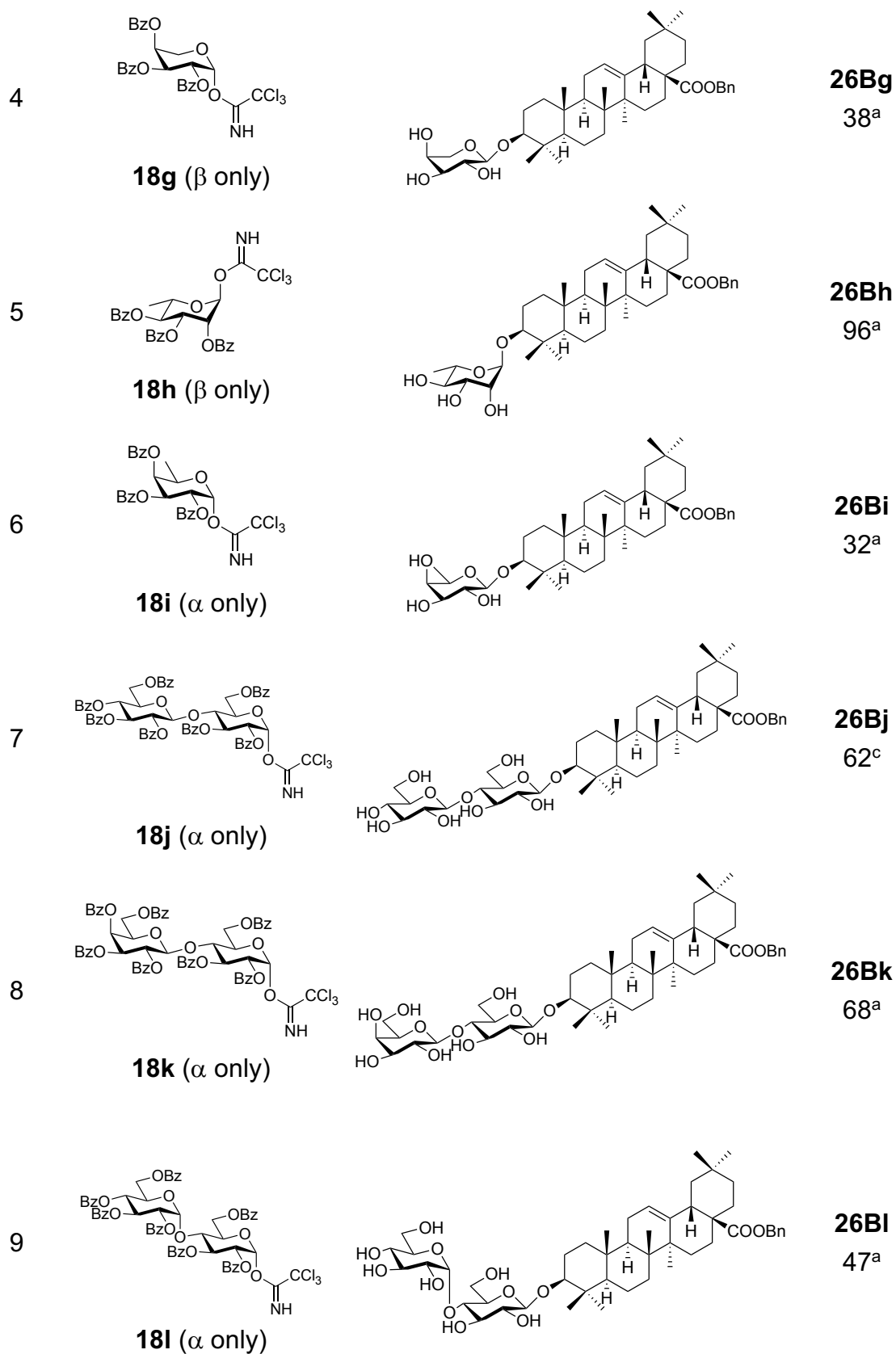
続いて、筆者はマイクロフロー式 C-3 位配糖化と NaH in oil を用いたバッチ式アシル基脱保護の連続反応を利用し C-28-Bn オレアノール酸サポニン **26Bc-1** の連続合成を試みることとした。

まず、 CH_2Cl_2 に溶解させた 1.0 当量の TMSOTf 溶液及び比較的溶解性の高いグリコシルアクセプター **25B** と 1.5 当量の既知グリコシルドナー **18d, g-l** それぞれの混合溶液を別途調製し、シリンジに取りマイクロフローに接続した。マイクロフロー反応部とフロー管は予めクランプに固定し常温下で静置させた。また、フロー管の長さと同径はそれぞれ 1.0 m と 1.0 mm とした。その後、シリンジポンプを用いて流速 (0.6 mL/min)、流量、シリンジ内径を設定し、シリンジからテフロンチューブへと溶液を流しマイクロフロー内で C-3 位配糖化を行った。次に、予め窒素雰囲気下で加熱処理を施し無水条件とした二口フラスコに 10 当量の NaH in oil と MeOH を加え、別途溶液を調製した。その後、フロー管の出口に穴を開けたセプタムを介して接続し、アシル基脱保護を連続反応で実施した (Table 47)。その結果、カラム実験工程の回数を改善し、**26Bc-1** をそれぞれ中程度の収率で得ることができた。

Table 47 マイクロフロー式 C-3 位配糖化・脱保護連続反応法を利用したベンジルサポニン **26Bc-1** の合成



C-28-Bn Oleanolic acid saponin			
Entry	Donor (1.5 eq.)	Structure	Yield (%)
1	 <p>18c (α only)</p>		26Bc 53 ^a
2	 <p>18d</p>		26Bd 57 ^b
3	 <p>18f (α only)</p>		26Bf 44 ^c



a) The reaction was conducted for 1.5 h. b) The reaction was conducted for 3 h. c) The reaction was conducted for 2 h.

なお、**26Bc-1** の構造について、 ^1H -NMR における糖のアノマー位のピークより β 体と決定した。また、HMBC においてアグリコンの C-3 位由来の ^{13}C ピークと糖のアノマー位由来の ^1H ピークとで相関が観測されたことから、C-3 位グリコシド結合の形成を確認した (Table 48)。

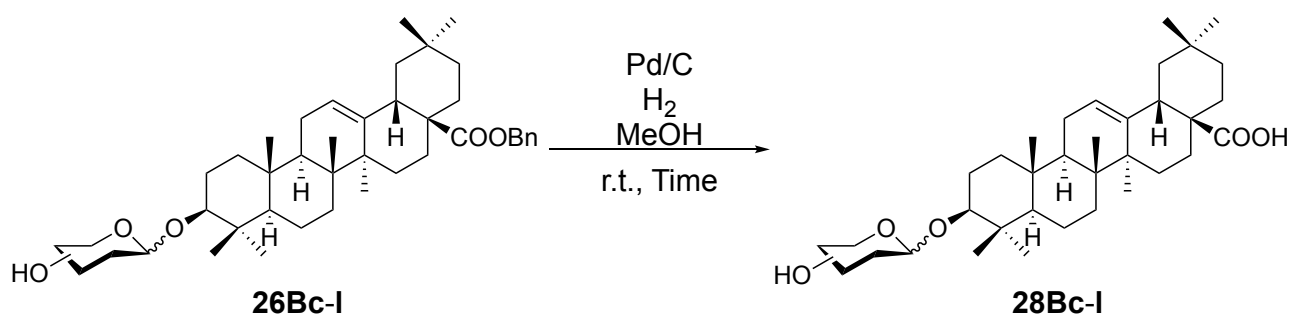
Table 48 C-28 位ベンジルサポニン **26Bc-1** の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	δH	δC
	1'-H (d, ppm, Hz)	C-3 (ppm)
26Bc	4.88 (8.0)	88.9
26Bd	5.57 (1.3)	81.9
26Bf	4.85 (8.0)	88.8
26Bg	4.80 (7.0)	88.8
26Bh	5.33 (brs)	88.6
26Bi	4.76 (7.7)	88.8
26Bj	4.89 (8.0)	89.3
26Bk	4.88 (8.0)	89.2
26Bl	4.87 (7.5)	89.2

III. オレアノール酸 C-3 位サポニン **28Bc-1** の合成

首尾良く得られた **26Bc-1** を用い、続いてオレアノール酸 C-3 位サポニン **28Bc-1** の合成を行った。即ち、**26Bc-1** を MeOH に溶解後、水素雰囲気下でパラジウム炭素 (Pd/C) 触媒を用いた接触水素化還元を行い、セライト濾過した後、順相シリカゲルカラムクロマトグラフィー (クロロホルム : メタノール系) で精製し、**28Bc-1** をそれぞれ高収率で得た (Table 49)。合成した各種 **28Bc-1** の合成例と単離報告例を以下の表に示す (Table 50)。

Table 49 オレアノール酸 C-3 位サポニン 28Bc-I の合成



C-28-Bn-Saponin				C-3-Oleanolic acid saponin	
Entry	Type	Bn (ppm)	Time (h)	Structure	Yield (%)
1	26Bc	7.45 m, 5H, <u>PhCH₂</u> 5.36, 5.29 each d $J = 12.6$ Hz 2H, <u>PhCH₂</u>	22		72
				28Bc (β only)	
2	26Bd	7.45 m, 5H, <u>PhCH₂</u> 5.36, 5.29 each d $J = 12.6$ Hz 2H, <u>PhCH₂</u>	1		88
				28Bd (α only)	
3	26Bf	7.46 m, 5H, <u>PhCH₂</u> 5.36, 5.30 each d $J = 12.6$ Hz 2H, <u>PhCH₂</u>	17		47
				28Bf (β only)	
4	26Bg	7.39 m, 5H, <u>PhCH₂</u> 5.36, 5.29 each d $J = 12.6$ Hz 2H, <u>PhCH₂</u>	9.5		73
				28Bg (α only)	

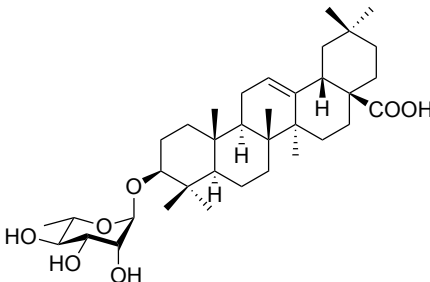
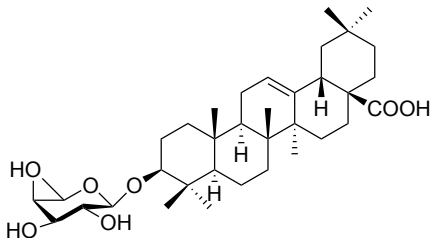
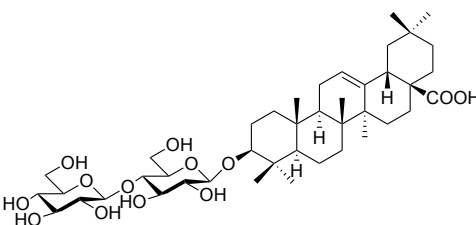
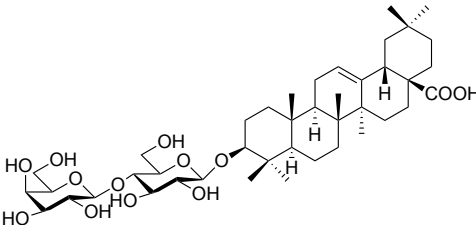
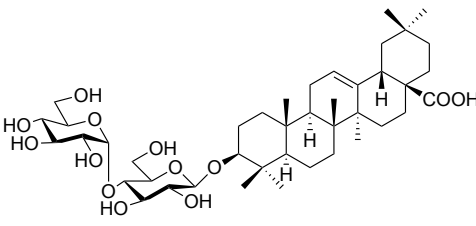
5	26Bh	7.46 m, 5H, <u>PhCH₂</u> 5.36, 5.30 each d $J = 12.6$ Hz 2H, <u>PhCH₂</u>	2		74
6	26Bi	7.47 m, 5H, <u>PhCH₂</u> 5.36, 5.30 each d $J = 12.5$ Hz 2H, <u>PhCH₂</u>	2		75
7	26Bj	7.47 m, 5H, <u>PhCH₂</u> 5.36, 5.30 each d $J = 12.5$ Hz 2H, <u>PhCH₂</u>	3.5		92
8	26Bk	7.44 m, 5H, <u>PhCH₂</u> 5.36, 5.30 each d $J = 12.5$ Hz 2H, <u>PhCH₂</u>	3.5		53
9	26Bl	7.47 m, 5H, <u>PhCH₂</u> 5.36, 5.30 each d $J = 12.5$ Hz 2H, <u>PhCH₂</u>	1		49

Table 50 オレアノール酸 C-3 位サポニン 28Bc-l の単離と合成報告例

Saponin	Donor type (eq.)	Glycosylation and deprotection yield (2 steps;%)		The example of isolation report
		Literature	This research	
28Bc	Benzoylated-imidate (1.2)	77 ⁵¹	38	<i>Lagenaria breviflora</i> ¹⁰⁷ <i>Polyscias amplifolia</i> ¹⁰⁸
28Bd	Benzoylated-imidate (1.2)	71 ⁵¹	50	-
28Bf	Benzoylated-imidate (1.2)	81 ⁵¹	21	<i>Eleutherococcus senticosus</i> ¹⁰⁹ <i>Pterocephalus hookeri</i> ¹¹⁰ <i>Anemone raddeana</i> ¹¹²
28Bg	Benzoylated-imidate (1.2)	78 ¹¹¹	28	<i>Akebia quinata</i> ¹¹³ <i>Patrinia scabiosaefolia</i> ¹¹⁴ <i>Anemone narcissiflora</i> ¹¹⁵
28Bh	Benzoylated-imidate (1.2)	79 ⁵¹	71	<i>Digitalis ciliata</i> ¹¹⁶
28Bi	-	-	24	-
28Bj	Benzoylated-imidate (1.2)	77 ⁵¹	57	<i>Calendula officinalis</i> ¹¹⁷
28Bk	Benzoylated-imidate (1.2)	77 ⁵¹	36	<i>Calendula officinalis</i> ¹¹⁸ <i>Aralia elata</i> ¹¹⁹
28Bl	Benzoylated-imidate (1.2)	70 ⁵⁰	23	-

28Bc-l の構造について、Bn 基由来のピークの消失を確認し ¹H-NMR における糖のアノマー位のピークより立体構造を決定した。また、HMBC においてアグリコンの C-3 位由来の ¹³C ピークと糖のアノマー位由来の ¹H ピークとで相関が観測されたことから、C-3 位グリコシド結合が切断されていないことを確認した (Table 51)。

なお、サポニン **28Bd, h** は 2'位のプロトンがエクソトリアルとなっているため、カップリング定数のみでは立体を決定することができないので、GATE-1 を用いて立体構造を決定した。GATE-1 を測定したところ、**28Bd** の 1'位デカップリング定数は ¹J_{C,H} = 175.5 Hz (89.82 ppm, sd) であったのでα体と決定した (Figure 21)。**28Bh** の 1'位デカップリング定数は ¹J_{C,H} = 175.5 Hz (89.82 ppm, sd) であったのでα体と決定した (Figure 22)。また、サポニン **28Bg** の立体は 2D-NOESY 法を用いて立体構造をα体と決定した (Figure 23)。

サポニン **28Bj, k, l** における糖の ¹H 及び ¹³C-NMR のシグナルの帰属には TOCSY 法を用いた。磁化を移動させるために設定した混合時間 (mixing time) は、τ_m = 150 ms で D-Cel、D-Lac、D-Mal の 1'位から 6'位及び 1''位から 6''位までの相関が観測された (Table 52)。

Table 51 オレアノール酸 C-3 位サポニン **28Bc-I** の構造決定に関わる ^1H 及び ^{13}C -NMR

Compound	δH	δC
	1'-H (d, ppm, Hz)	C-3 (ppm)
28Bc	4.88 (d, $J = 8.0$ Hz, 1H)	88.9
28Bd	5.57 (d, $J = 1.3$ Hz, 1H)	82.0
28Bf	4.85 (d, $J = 8.0$ Hz, 1H)	88.8
28Bg	4.80 (d, $J = 7.0$ Hz, 1H)	88.8
28Bh	5.33 (brs, 1H)	88.7
28Bi	4.77 (d, $J = 7.6$ Hz, 1H)	88.8
28Bj	4.89 (d, $J = 8.0$ Hz, 1H)	89.3
28Bk	4.88 (d, $J = 8.0$ Hz, 1H)	89.2
28Bl	4.87 (d, $J = 7.5$ Hz, 1H)	89.2

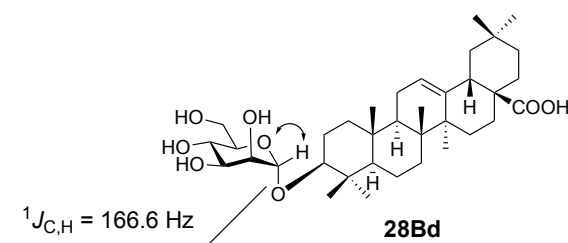


Figure 21 GATE-1 法を用いたサポニン **28Bd** の構造決定

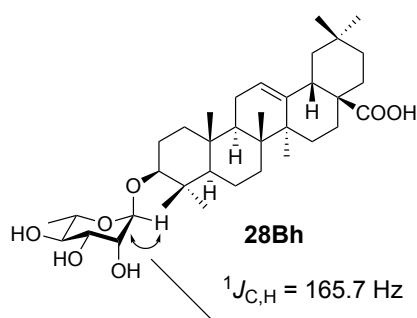


Figure 22 GATE-1 法を用いたサポニン **28Bh** の構造決定

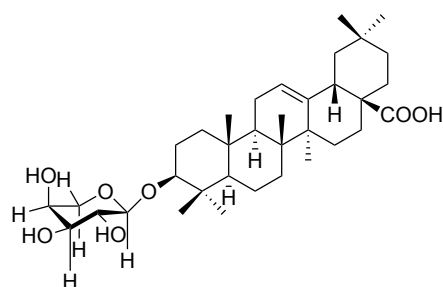


Figure 23 2D-NOESY 法を用いたサポニン 28Bg の構造決定

Table 52 TOCSY 法を用いたサポニン 28Bj, k, l の構造決定

	β -D-Glc	δ H	δ C	β -D-Glc	δ H	δ C
28 Bj	1'	4.89 (d, 8.0)	106.6	1''	5.29 (d, 8.0)	105.2
	2'	4.18 (dd, 8.5, 8.0)	75.4	2''	4.11 (dd, 8.5, 8.0)	75.0
	3'	4.34 (dd, 9.0, 8.5)	76.8	3''	4.25 (dd, 9.5, 8.5)	78.3
	4'	4.41 (t, 9.0)	81.0	4''	4.18 (dd, 9.5, 9.0)	71.5
	5'	3.96 (ddd, 9.0, 3.0, 2.0)	76.6	5''	4.01 (ddd, 9.0, 5.5, 2.0)	78.4
	6'	4.64 (dd, 12.0, 3.0) 4.50 (dd, 12.0, 2.0)	62.1	6''	4.50 (dd, 12.0, 2.0) 4.29 (dd, 12.0, 5.5)	62.1
28 Bk	β -D-Glc	δ H	δ C	β -D-Gal	δ H	δ C
	1'	4.88 (d, 8.0)	106.7	1''	5.14 (d, 8.0)	105.9
	2'	4.05 (dd, 8.5, 8.0)	75.4	2''	4.57 (dd, 9.5, 8.0)	72.6
	3'	4.30 (t, 8.5)	76.9	3''	4.20 (dd, 9.5, 3.0)	75.2
	4'	4.33 (t, 8.5)	82.1	4''	4.53 (dd, 3.0)	70.4
	5'	3.93 (ddd, 8.5, 3.0, 3.0)	76.5	5''	4.14 (dd, 5.0, 7.0)	77.2
28 Bl	β -D-Glc	δ H	δ C	α -D-Glc	δ H	δ C
	1'	4.87 (d, 7.5)	106.8	1''	5.94 (d, 3.5)	103.2
	2'	4.02 (dd, 8.5, 7.5)	75.4	2''	4.19 (dd, 9.5, 3.5)	74.5
	3'	4.35 (dd, 9.0, 8.5)	78.1	3''	4.62 (t, 9.5)	75.6
	4'	4.37 (dd, 9.0, 8.5)	81.4	4''	4.17 (d, 9.5)	72.0
	5'	3.87 (ddd, 8.5, 4.0, 2.0)	76.8	5''	4.61 (ddd, 9.5, 3.5, 2.5)	75.4
28	6'	4.52 (dd, 12.0, 4.0) 4.49 (dd, 12.0, 2.0)	62.2	6''	4.59 (dd, 12.0, 2.0) 4.33 (dd, 12.0, 3.5)	62.8

第六節 オレアノール酸桂皮酸含有サポニン **29Bia'**の合成

第一項 オレアノール酸 C-28 位 D-フコース含有サポニン **14Bi** の位置選択的シンナモイル化の検討

筆者はマイクロフローを利用したサポニン誘導体ライブラリーの構築を達成したので、続いて桂皮酸構造を有するサポニンライブラリーの構築法の確立を行った。

これまでに桂皮酸含有イミダートドナー **7b** を用いたマイクロフロー式配糖化を利用したサポニン合成を達成した。**7b** には Ac 基を用いず、電子の押し込みが強い PMB 基を用いたためドナーの反応性が向上したと考えられる。一方、脱保護時の異性化が課題であり HPLC を用いた精製工程の増加や収率の低下が問題であった。即ち、ヒドロキシ基の反応性の違いに則った保護-脱保護法を経た合成法では、保護基や脱保護反応法の選択を誤ると最終化合物を合成できない課題があった。

そこで、筆者は位置選択的アシル化法を用いた合成法に着目した。即ち、サポニン含有糖鎖に直接的に桂皮酸エステル化を行うことで、脱保護過程での異性化の制御や桂皮酸の種類を変換したライブラリー合成を達成できると考えた (**Figure 24**)。

しかし、ヒドロキシ基の反応性を区別して位置選択的アシル化を行う合成法は容易ではなく、検討するには十分なサポニン基質が必要であった。特に、オンジサポニンの C-28 位結合糖鎖である D-Fuc は他の糖鎖と比べコストが高く反応性も低いので、従来のバッチ式合成でサポニンの供給は困難であった。筆者は第二節第二項でマイクロフローを利用することでオレアノール酸 C-28 位 D-Fuc サポニン **14Bi** を充分量合成できたので、反応基質として用い位置選択的桂皮酸エステル化方法論を検討することとした。

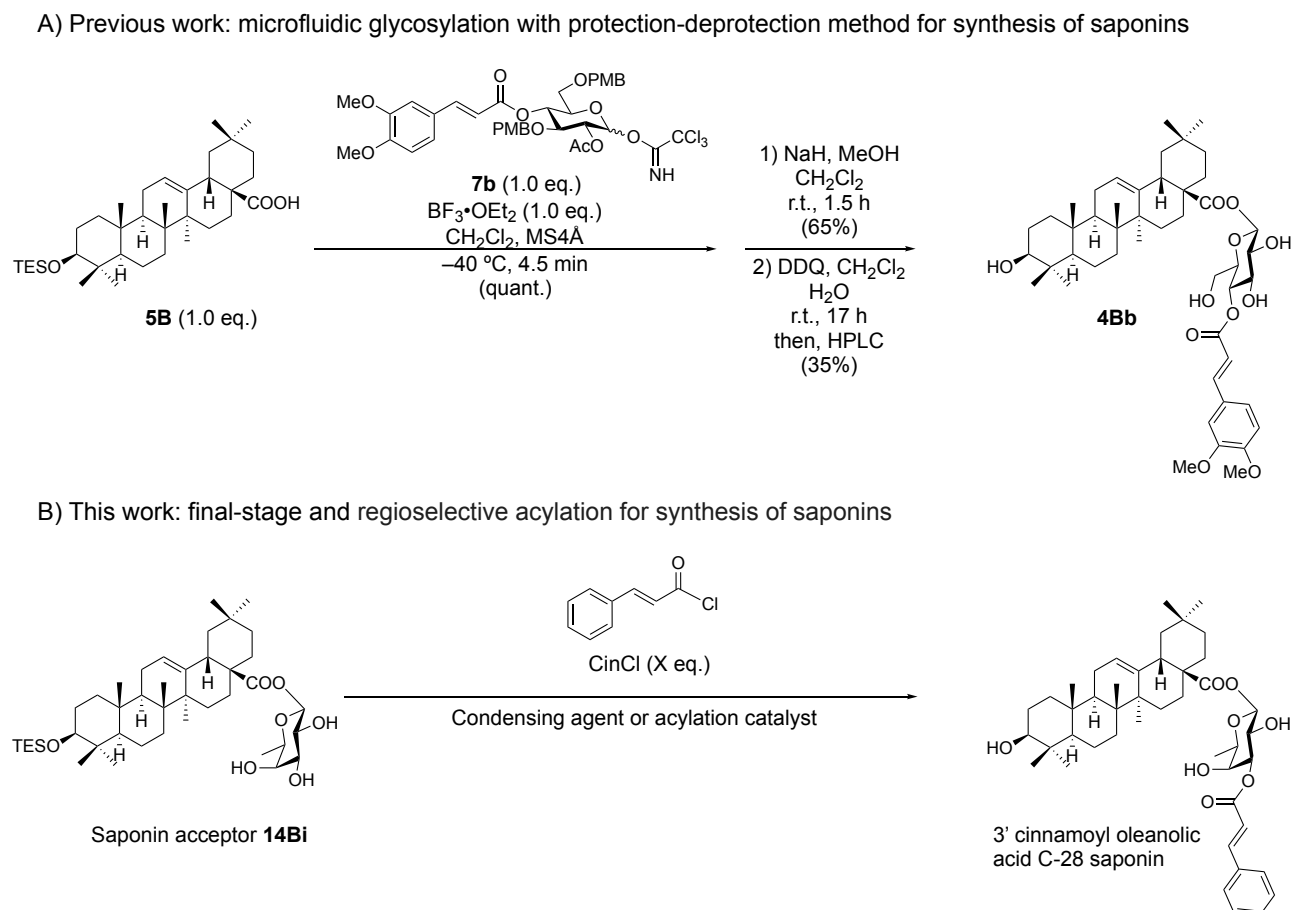
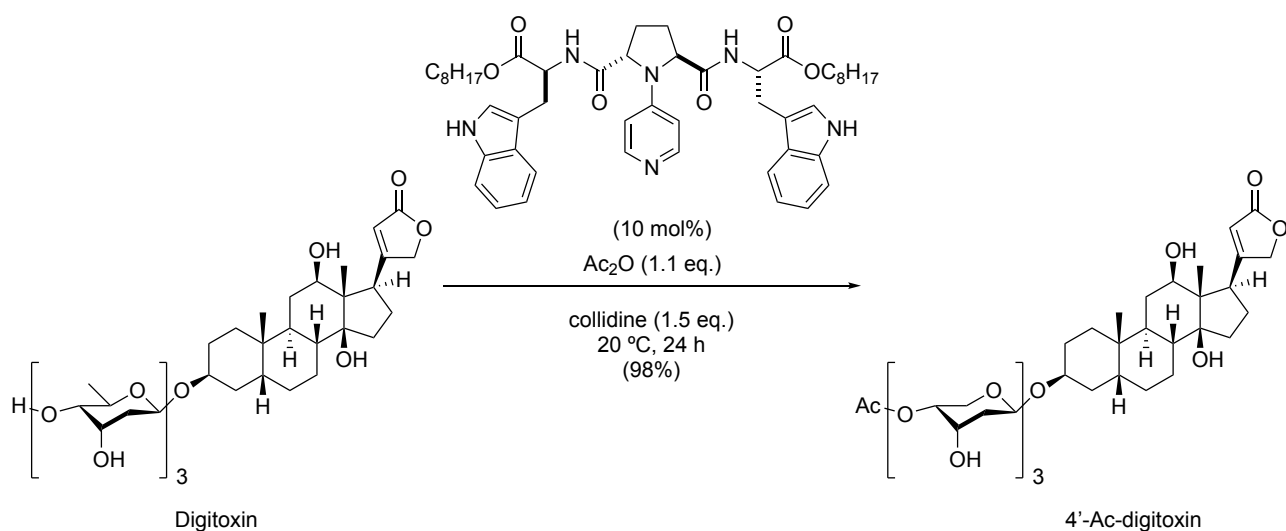


Figure 24 桂皮酸含有サポニンの合成戦略

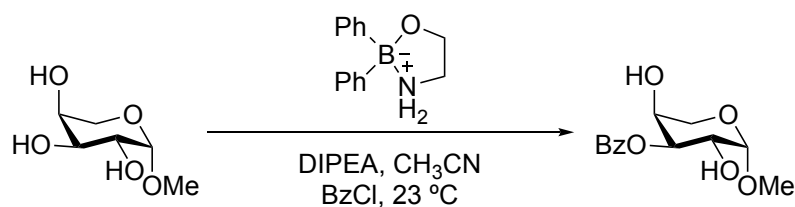
筆者は最終段階位置選択的アシル化に基づく配糖体天然物の合成報告例に着目した。川端らは開発した有機分子触媒 (川端触媒) を用いた位置選択的アシル化法を強心配糖体であるジギトキシンへ用いることで 98% の収率でジギトキソース 4' 位選択的なアシル化反応に成功している¹²⁰ (Scheme 14)。また、桂皮酸エステル化の方法論へ応用して異性化問題等を改善し、抗腫瘍活性配糖体天然物である multifidoside C 等の初の全合成を達成している¹²¹ (Figure 25-A)。

また、位置選択的アシル化方法論の先行研究例には Taylor らのボリン酸を利用した位置選択的アシル化¹²²やトシル化¹²³、配糖化を報告している¹²⁴ (Scheme 15)。

筆者はこれらの方法論を参考に、サポニンの位置選択的アシル化の検討を行うこととした。即ち、合成した C-28 位フコースサポニン 13Bi 及び TES サポニン 14Bi を基質として、有機分子触媒であるボリン酸を用いた位置選択的桂皮酸エステル化の検討を行った (Figure 25-B)。

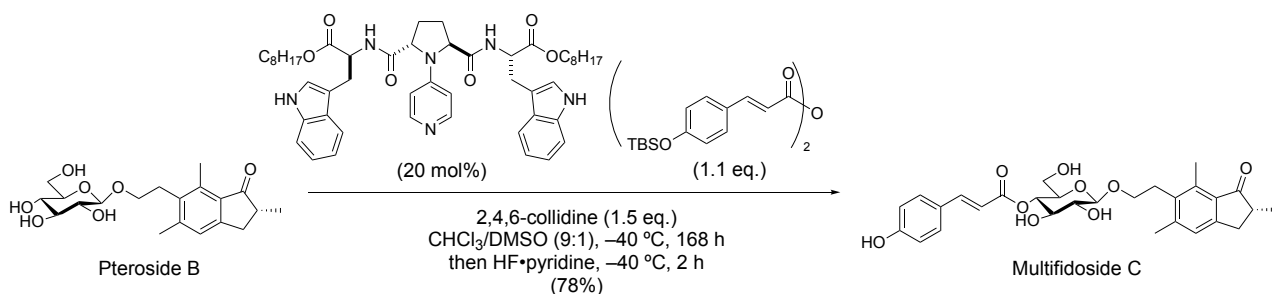


Scheme 14 川端触媒を用いたジギトキシンの 4' 位選択的アセチル化の例



Scheme 15 ボリン酸触媒を用いた D-フコース 3' 位選択的ベンゾイル化の例

A) Previous work: final-stage regioselective acylation for total synthesis of multifidoside C (Kawabata, 2015)



B) This work: final-stage and borinic acid catalyzed regioselective acylation for synthesis of saponins

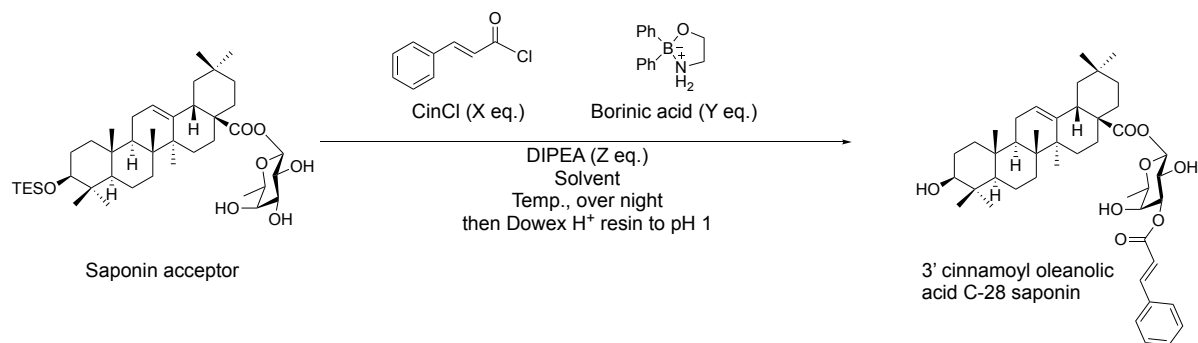


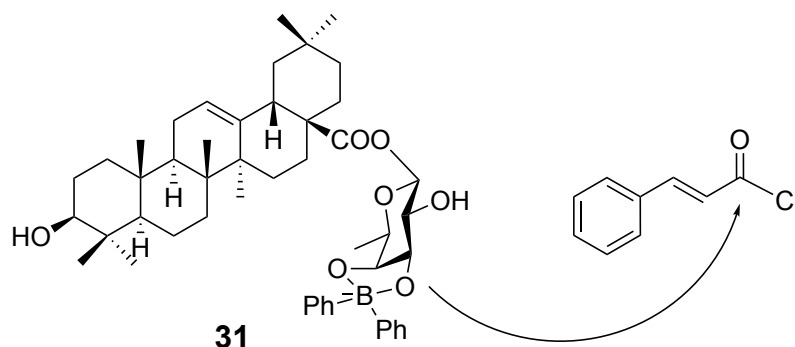
Figure 25 ボリン酸を用いた合成最終段階における位置選択的桂皮酸エステル化を応用したサポニン合成

I. ボリン酸を用いた位置選択的シンナモイル化の検討 (Table 53)

まず、通常のアシル化条件で位置選択的桂皮酸エステル化の検討を行った。**14Bi** を pyridine に溶解後、市販品である cinnamoyl chloride (CinCl) を 1.5 当量用いた場合、反応は全く進行しなかった (Entry 1)。そこで、CinCl を 3.0 当量に増量すると 1~3 当量分の桂皮酸エステル化が進行した桂皮酸含有配糖体 **30Bia'-c'** が生成し選択性は発現しなかった (Entry 2)。3 種類の配糖体を順相 prep.TLC で分離した結果、**30Bia'-c'** がそれぞれ収率 24%、26%、2% で得られ、桂皮酸エステル化が 3' 位→4' 位→2' 位の順に進行することが明らかとなった。

そこで、筆者はボリン酸触媒の 2-aminoethyl diphenylborinate (AD) を用いた直接的な C-28 位サポニン含有 D-Fuc の位置選択的桂皮酸エステル化の検討を行った。**14Bi** を pyridine に溶解後 1.0 当量の AD を用いた場合、反応は進行せず原料回収となった (Entry 3)。次に、溶媒を CH_2Cl_2 とし、*N,N*-diisopropylethylamine (DIPEA) を用いた反応条件に変更すると、僅かに反応の進行を TLC や ESI-TOF-MS 等で確認することができた (Entry 4)。一方、温度条件を常温から 40 °C に増加させると反応は全く進行しなかった (Entry 5)。

上記の結果から最適な温度条件を常温下とし、**14Bi** を CH_2Cl_2 に溶解後 0.1 当量の AD を加え攪拌し 5.0 当量の DIPEA と CinCl を用いた場合、3' 位選択的に桂皮酸エステル化が進行した桂皮酸含有配糖体 **30Bia'** が主生成物として得られた (Entry 6)。3' 位選択的桂皮酸エステル化の反応機構は、まずジフェニルボリン酸がサポニン **14Bi** の *cis*-1,2 ジオールを認識し、電子豊富な 4 配位のアート錯体 **31** を形成する。この際、酸素原子の求核性が向上し立体的に空いているエカトリアル方向の 3' 位酸素原子が $\text{S}_{\text{N}}2$ 反応し立体及び位置選択性が発現する (Scheme 16)。



Scheme 16 ボリン酸を用いた桂皮酸エステル化の作用機序

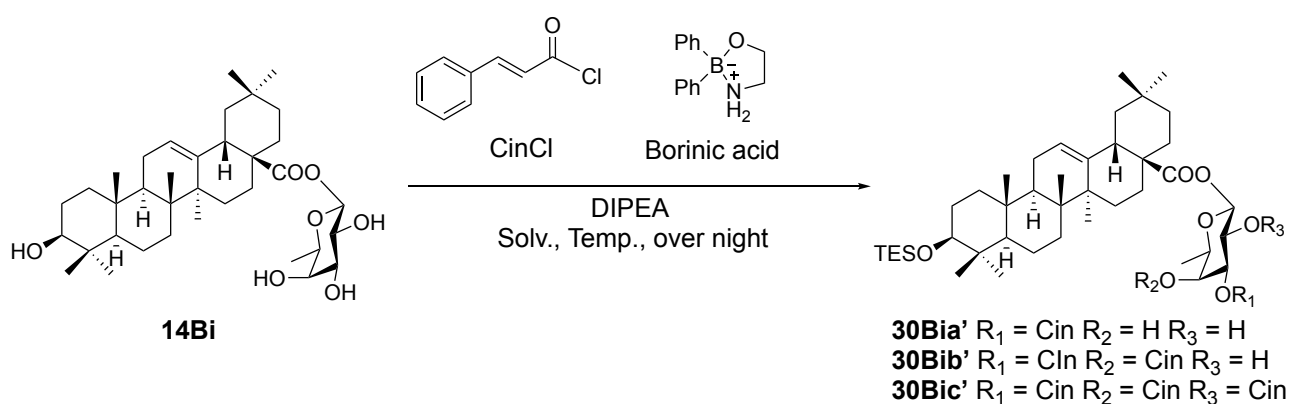
30Bia' の収率が低く留まった要因は、アシル化剤である CinCl の求電子性が高く、桂皮酸含有配糖体 **30Bib'** の生成を抑制できなかったことが考えられた。また、単体の糖を基質としたアシル化を比較し、サポニン含有 D-Fuc 糖は分子量の大きなアグリコンであるオレアノール酸を有するので、反応性に乏しいことが考えられた。

そこで、AD を触媒量から 1.0 当量に増量すると、順相カラムクロマトグラフィーによる

精製で **30Bia'** を収率 93% で得ることができた (Entry 7)。

なお、**30Bia'** の構造は $^1\text{H-NMR}$ において糖 3' 位由来のピークの低磁場シフト、及び TES 基由来のピーク 1.02 ppm (m, 9H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$)、0.63 ppm (m, 6H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$) から確認した。また、HMBC においてアグリコンの C-28 位由来の ^{13}C ピーク 176.6 ppm (C-28) と糖のアノマー位 6.34 ppm (d, $J = 8.2$ Hz, 1H, 1'-H) 由来の ^1H ピークとで相関が観測されたことと、桂皮酸エステルのカルボニル由来の ^{13}C ピークと D-フコース糖の 3' 位由来の ^1H ピークとで相関が観測されたことから、各種エステル結合を保持していることを確認した。また、 $^1\text{H-NMR}$ におけるアノマー位由来のピークから所望の β 体であることと、桂皮酸オレフィンのカップリングコンスタントから *trans* 体であることを確認した。

Table 53 ボリン酸を用いたサポニン **14Bi** の 3' 位桂皮酸エステル化の検討



Entry	CinCl (eq.)	Borinic acid (eq.)	DIPEA (eq.)	Solvent	Temp. (°C)	Product	Yield (%)
1	1.5	-	-	Pyr.	r.t.	no reaction	-
						30Bia'	24
2 ^a	3.0	-	-	Pyr.	r.t.	30Bib'	26
						30Bic'	2
3	2.0	1.0	-	Pyr.	r.t.	no reaction	-
4	2.0	1.0	2.0	CH_2Cl_2	r.t.	30Bia'	trace
5	3.0	1.0	3.0	CH_2Cl_2	40	no reaction	-
						30Bia'	48
6 ^b	5.0	0.1	5.0	CH_2Cl_2	r.t.	30Bib'	22
						30Bic'	trace
7 ^b	5.0	1.0	5.0	CH_2Cl_2	r.t.	30Bia'	93

a) Purification was conducted with prep. TLC.

b) Purification was conducted with flash column chromatography.

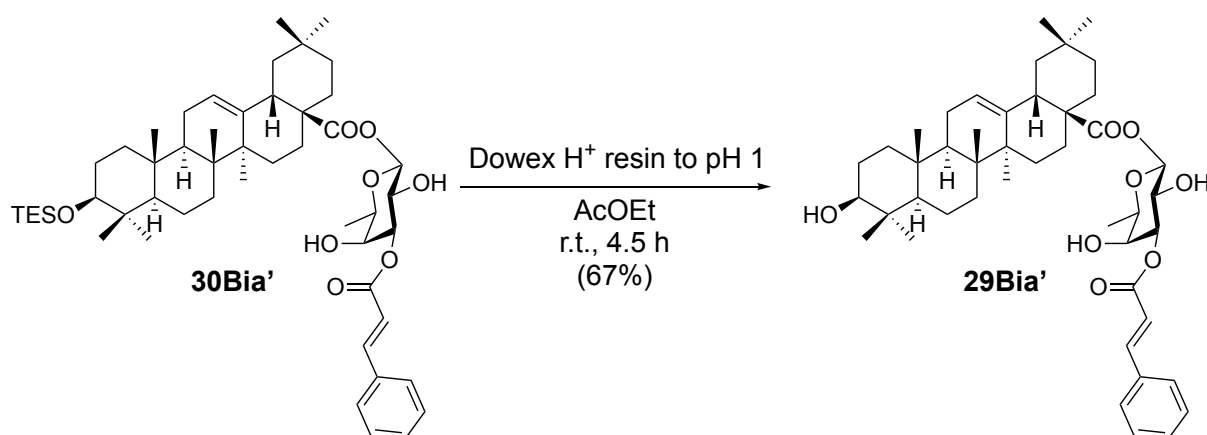
第二項 桂皮酸含有 C-28 位サポニン **29Bia'** の合成

I. 桂皮酸含有 C-28 位サポニン **29Bia'** の合成

得られた桂皮酸含有配糖体 **30Bia'** を用い、桂皮酸含有 C-28 位サポニン **29Bia'** の合成を試みた。即ち **30Bia'** を AcOEt に溶解後、Dowex resin を pH = 1 の酸性条件となるまで加え 4.5 時間攪拌し、桂皮酸含有 C-28 位サポニン **29Bia'** を収率 67% で合成できた (Scheme 17)。

桂皮酸含有 C-28 位サポニン **29Bia'** の構造は TES 基由来のピーク 1.02 ppm (m, 9H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.63 ppm (m, 6H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$) の消失から確認した。また、HMBC においてアグリコンの C-28 位由来の ^{13}C ピーク 176.6 ppm (C-28) と糖のアノマー位 6.34 ppm (d, $J = 8.2$ Hz, 1H, 1'-H) 由来の ^1H ピークとで相関が観測されたことと、桂皮酸エステルのカルボニル由来の ^{13}C ピークと D-Fuc 糖の 3' 位由来の ^1H ピークとで相関が見られたことから、各種エステル結合を保持していることを確認した。また、 ^1H -NMR におけるアノマー位由来のピークから所望の β 体であることと桂皮酸 (シンナモイル基) オレフィンのカップリングコンスタントから *trans* 体であることを確認した (Figure 26, 27)。

なお、天然には 3' 位よりも 4' 位桂皮酸が多く存在するので、その検討は今後の課題であった。



Scheme 17 オレアノール酸桂皮酸含有 C-28 位サポニン **29Bia'** の合成

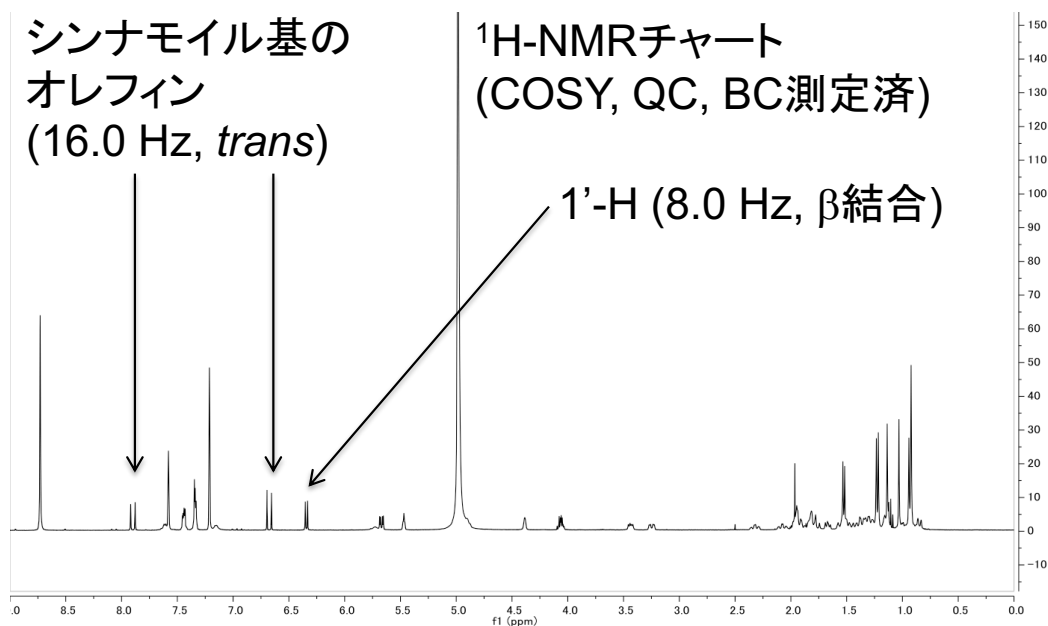


Figure 26 オレアノール酸桂皮酸含有 C-28 位サポニン **29Bia'**の ^1H -NMR

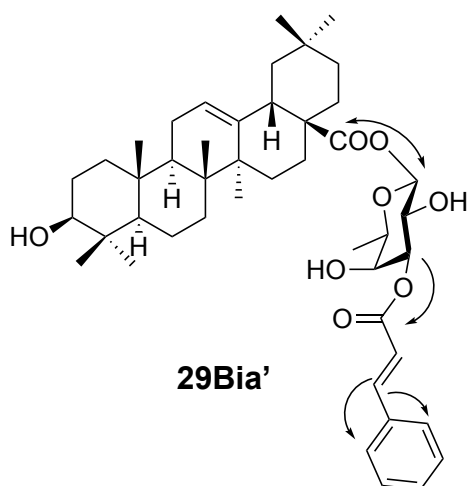
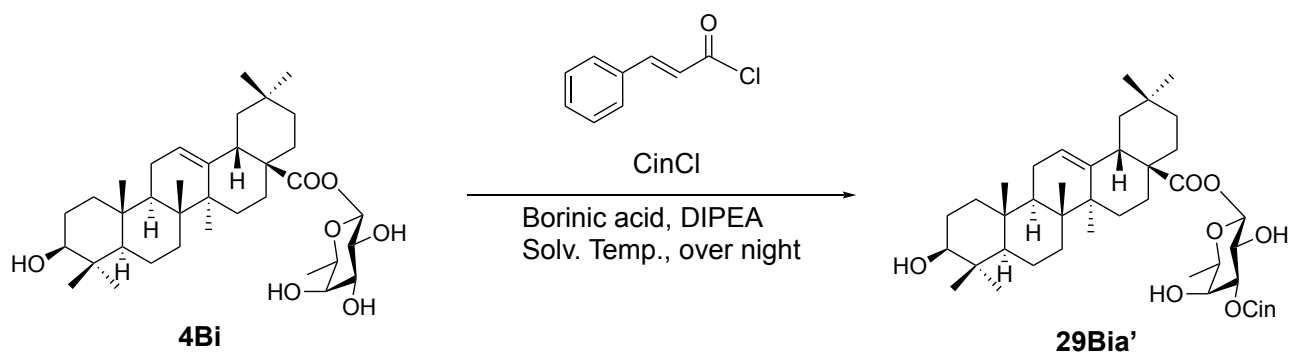


Figure 27 オレアノール酸桂皮酸含有 C-28 位サポニン **29Bia'**の HMBC 相関

II. サポニン **4Bi** を用いた **29Bia'**の合成の検討

次に、サポニン **4Bi** を基質とした **29Bia'**の合成の検討を行った (Table 54)。それぞれ 5.0 当量の桂皮酸クロリド、ボリン酸及び DIPEA を用いた条件では CH_2Cl_2 あるいは acetonitrile の両方の溶媒条件でサポニン **29Bia'**が僅かに得られた (Entry 6, 7)。その他の条件では反応の進行が確認されなかったことから、C-3 位に TES 基が導入されたサポニン **14Bi** との溶解性の違い等が収率の増減に影響したと考えられる。

Table 54 ボリン酸を用いたサポニン **4Bi** の 3'位桂皮酸エステル化の検討



Entry	CinCl (eq.)	Borinic acid (eq.)	DIPEA (eq.)	Solvent	Temp. (°C)	Product (%)
1	1.5	-	-	pyr.	r.t.	no reaction
2	2.0	1.0	2.0	CH ₃ CN	r.t.	no reaction
3	2.0	1.0	2.0	CH ₃ CN	110	no reaction
4	2.0	1.0	2.0	DMF	r.t.	no reaction
5	5.0	1.0	5.0	DMF	r.t.	no reaction
6	5.0	5.0	5.0	CH ₃ CN	r.t.	29Bia' (trace)
7	5.0	5.0	5.0	CH ₂ Cl ₂	r.t.	29Bia' (trace)

第七節 サポニン誘導体ライブラリーの生物活性・物理化学的性質の評価

第一項 サポニンの溶血作用の評価法

本研究で合成したサポニンライブラリーの溶血作用の評価を行った¹²⁵。即ち、文献法に従い調製した 10%ヒツジ赤血球 PBS 溶液 (200 μ L) と 5% DMSO-生理食塩水で調製した各種サポニン溶液 (500-7.8 μ g/mL) をそれぞれ 200 μ L 混合し、37 $^{\circ}$ C 条件で 30 分間あるいは 4 時間インキュベーションした。次に溶液を 10 分間、300 x g, 4 $^{\circ}$ C で遠心分離し、上清を 96 穴プレートに移し FlexStation 3 を用いて酸化ヘモグロビンの指標となる 570 nm の吸光度を測定した (Figure 28)。陰性対照には溶媒のみを、陽性対照にはコレステロールの定量等に用いられ文献値で高い溶血作用 (HD_{50} : 15.1 μ M) を有するステロイドサポニンのジギトニンを用いた¹²⁶ (Figure 29)。

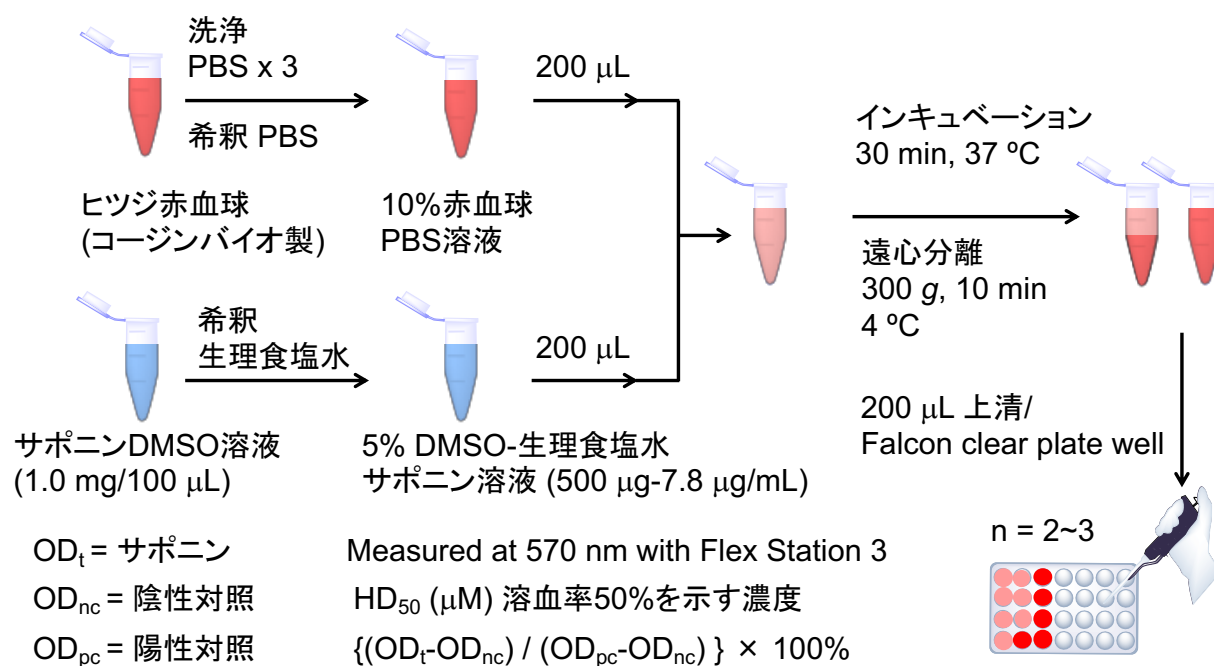


Figure 28 赤血球溶血試験の方法



第二項 サポニンの臨界ミセル濃度 (CMC) の評価法

本研究で合成したサポニンライブラリーの CMC の評価を、文献法の疎水性化合物である 1,6-ジフェニル-1,3,5-ヘキサトリエン (DPH) を溶解させる可溶化法に従った¹²⁷。調製した DPH の THF 溶液 (10 μ M, 2 μ L) と 5% DMSO-生理食塩水で調製した各種サポニン溶液 (500-7.8 μ g/mL) の 200 μ L を混合し、vortex 攪拌溶液で暗所保存し常温下 30 分間インキュベーションした。次に溶液を 96 穴プレートに移し FlexStation 3 を用いて 358-430 nm の蛍光度を測定した。陰性対照は 5% DMSO-生理食塩水溶媒のみを用いた (Figure 30)。DPH はミセルの脂溶性内部に取り込まれることで蛍光を発するので、その蛍光強度が増加傾向となる濃度を CMC と決定した。即ち、陰性対照液とサポニン溶液との蛍光強度比を縦軸に、各種サポニン溶液の濃度を横軸にしたグラフを作成し、傾きが増加する屈曲点を CMC として算出した (Figure 31)。

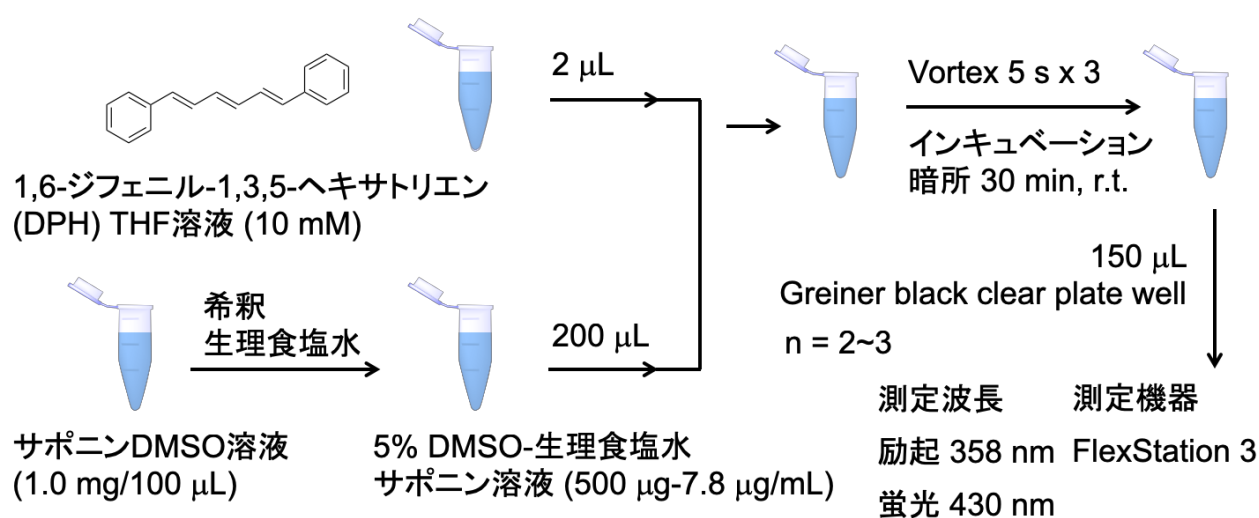


Figure 30 CMC 試験の方法

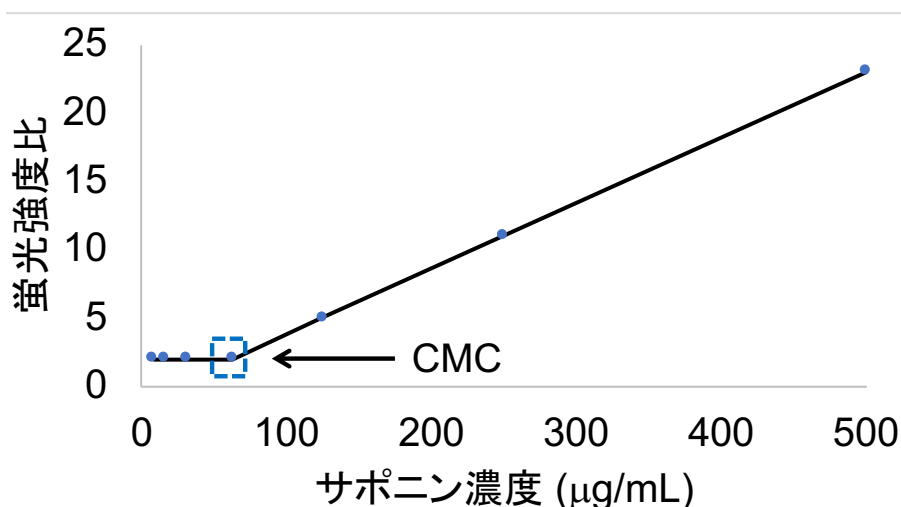


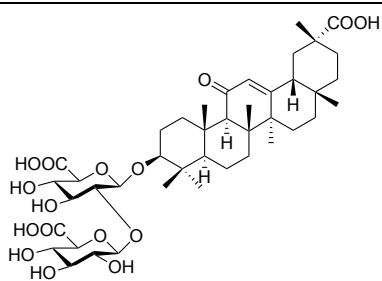
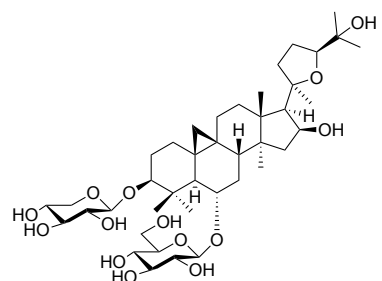
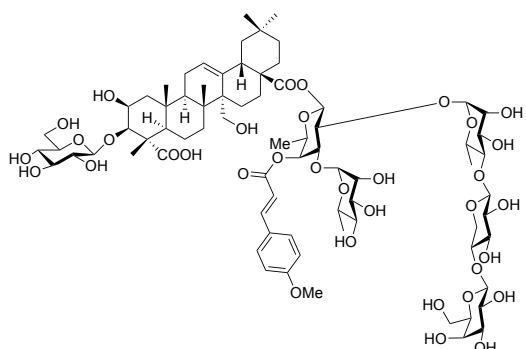
Figure 31 CMC の算出方法

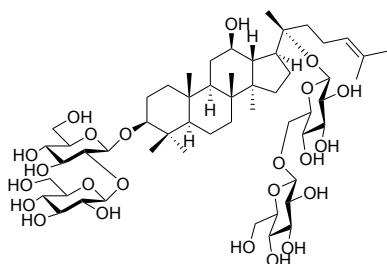
第三項 サポニンの性質評価の結果

I. 市販サポニンを用いた臨界ミセル濃度 (CMC) と溶血作用の測定の予備検討

まず、市販天然サポニンを用い臨界ミセル濃度と溶血作用を予備検討した (Table 55)。第十七改正日本薬局方で確認試験である起泡試験が規定されている生薬含有サポニンのオンジサポニン B (1Ae)、サイコサポニン A, B2, D は低い CMC を示した。一方、起泡試験が認められていない生薬含有サポニンは高い CMC を示した。ゆえに、サポニンの CMC を測定する方法として DPH 可溶化法は有効であることを確認できた。また、溶血作用の報告例があるサイコサポニン A, D¹²⁸及びジギトニン¹²⁶は本実験においても溶血作用を示し、その他の天然サポニンは溶血作用を示さなかった (No Hemolytic Activity; NHA 500-7.8 µg/mL)

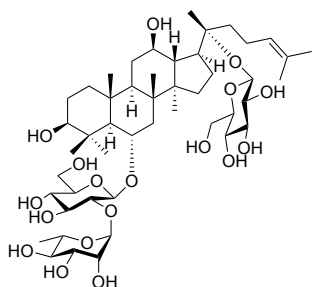
Table 55 市販天然サポニンの CMC と溶血作用の結果

Saponin	CMC (µM)	HD ₅₀ (µM)	生薬名	起泡試験
 グリチルリチン	152	NHA	カンゾウ	×
 アストラガロシド IV	156	NHA	オウギ	×
 オンジサポニン B (1Ae)	20	40	オンジ	○



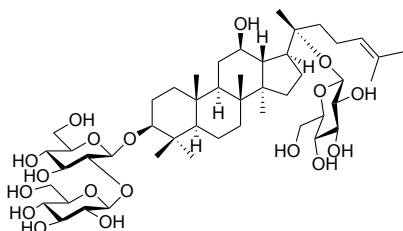
>463 NHA ニンジン ×

ジンセノシド Rc



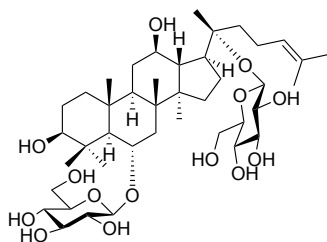
>528 NHA ニンジン ×

ジンセノシド Rd



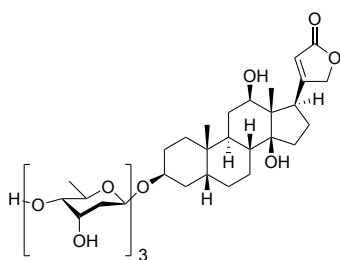
>528 NHA ニンジン ×

ジンセノシド Re



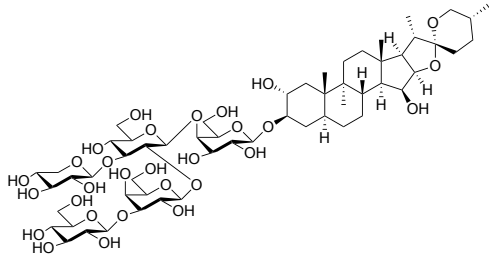
>312 NHA ニンジン ×

ジンセノシド Rg1



>640 NHA ケジギタリス ×

ジゴキシソ



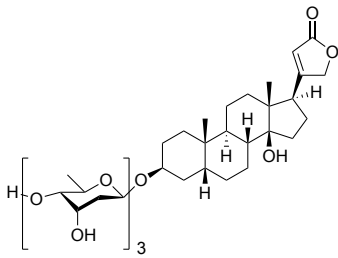
ジギトニン

12.7

12.7

ジギタリス

×



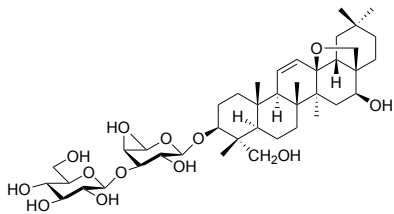
ジギトキシン

>654

NHA

ジギタリス

×



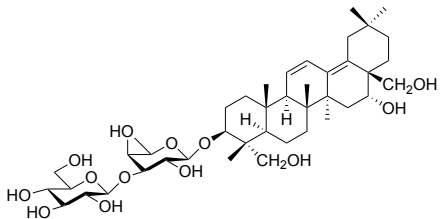
サイコサポニン A

160

10

サイコ

○



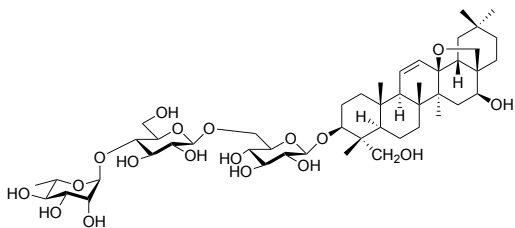
サイコサポニン B2

80

NHA

サイコ

○



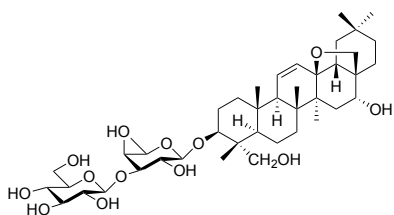
サイコサポニン C

>530

NHA

サイコ

○



サイコサポニン D

40

2.6

サイコ

○

II. サポニン誘導体の臨界ミセル濃度 (CMC) と溶血作用

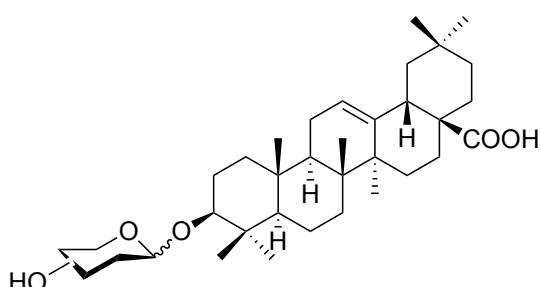
各種オレアノール酸 C-3 位サポニン **28Ba-l** は 10 μM 前後で CMC を示した後、ミセル形成に伴い溶血作用を発現した。 $\beta\text{-D-Glc}$ と $\beta\text{-D-Gal}$ を有するサポニン **28Ba, c** が最も高い溶血作用を示した (Table 56 Entry 1, 2)。一方、 $\alpha\text{-D-Man}$ と $\alpha\text{-L-Rha}$ を有するサポニン **28Bd, h** は他の糖を有するサポニンと比較し弱い溶血作用を示した (Table 56 Entry 3, 6)。ゆえに C-3 位糖鎖の種類によって溶血作用に差異があることが明らかであった。

次にビスデスモシドサポニンの CMC は 80 μM に増加し、C-3 位 C-28 位の両方に $\beta\text{-D-Glc}$ を有するサポニン **24Ba** のみが溶血作用を示した (Table 57 Entry 1)。残りの 2 種のサポニン **24Bc, f** は溶血作用を示さず、単糖のビスデスモシド構造は溶血作用の減弱傾向にあった (Table 57 Entry 2, 3)。

各種オレアノール酸 C-28 位サポニン **4Ba, c-m** 及び桂皮酸含有型サポニン **29Bia'** は CMC に関わらず、全て溶血作用を示さなかった (Table 58)。なお、桂皮酸含有サポニン **4Bb** は合成できた量が少なく、CMC と溶血作用を測定できなかった。

上記の結果から、強い溶血作用発現に関与すると考えられる $\beta\text{-D-Glc}$ を有する各種アグリコン型 C-3 位サポニン **26Ba, 28Ca-Ja** を評価した。アグリコンをウルソール酸、ジヒドロベツリン酸とする C-3 位サポニン **28Ca, Da** はオレアノール酸 C-3 位サポニン **28Ba** と比べ CMC は同程度であったが溶血作用は 8 分の 1、16 分の 1 に減弱した (Table 59 Entry 2, 3)。構造を比べると、メチル基の位置や六員環骨格が異なり、溶血作用の減弱にこれらの構造が関与していることが示唆された。一方、C-28 位カルボキシ基が共通の構造として溶血作用に関与することが文献報告例¹²⁵と一致し考えられた。CMC は同程度であったが **26Ba** は溶血作用が消失したので C-28 位カルボキシ基の溶血作用への関与は明らかであった (Table 59 Entry 1)。また、*tenuifolin* (**2A**) とグリチルレチン酸型サポニン **28Ea** は CMC が上昇し全く溶血作用を示さなかった (Table 59 Entry 4, 5)。この結果から、C-28 位カルボキシ基以外のトリテルペン上の酸素極性官能基は CMC の上昇と溶血作用の消失に関与していることが示唆された。なお、四環性トリテルペンのラノステロールや植物ステロイドの $\beta\text{-シトステロール}$ 、*stigmastanol*、*stigmasterol*、*stigmasterol*、*stigmasterol*、*stigmasterol* を骨格とする C-3 位サポニン **28Fa-Ja** は CMC に関わらず溶血作用を全く示さなかった (Table 59 Entry 6-10)。

Table 56 オレアノール酸 C-3 位サポニン誘導体の性質



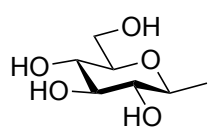
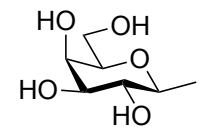
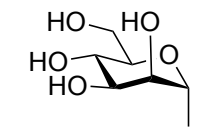
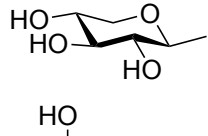
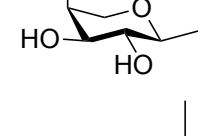
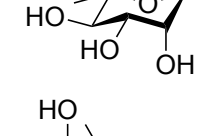
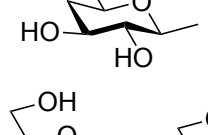
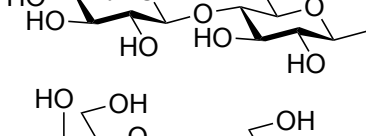
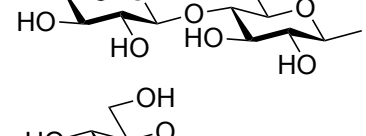
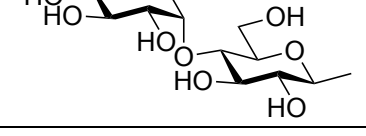
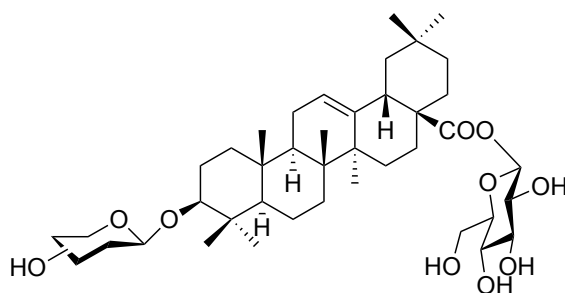
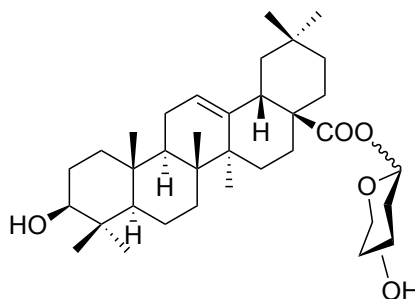
Entry	Saponin	Structure of C-3 sugar	Type	CMC (μM)	HD ₅₀ (μM)
1	28Ba		β -D-Glc	<12.6	25
2	28Bc		β -D-Gal	<12.6	25
3	28Bd		α -D-Man	<12.6	410
4	28Bf		β -D-Xyl	<13.2	53
5	28Bg		α -L-Ara	<13.2	53
6	28Bh		α -L-Rha	<12.9	207
7	28Bi		β -D-Fuc	<12.9	50
8	28Bj		β -D-Cel	<10	39
9	28Bk		β -D-Lac	<10	39
10	28Bl		β -D-Mal	<10	80

Table 57 オレアノール酸ビスデスモシドサポニン誘導体の性質



Entry	Saponin	Structure of C-3 sugar	Type	CMC (μM)	HD ₅₀ (μM)
1	24Ba		$\beta\text{-D-Glc}$	80	320
2	24Bc		$\beta\text{-D-Gal}$	80	NHA
3	24Bf		$\beta\text{-D-Xyl}$	83	NHA

Table 58 オレアノール酸 C-28 位サポニン誘導体の性質



Entry	Saponin	Structure of C-28 sugar	Type	CMC (μM)	HD ₅₀ (μM)
1	4Ba		$\beta\text{-D-Glc}$	101	NHA
2	4Bc		$\beta\text{-D-Gal}$	<12.6	NHA
3	4Bd		$\alpha\text{-D-Man}$	<12.6	NHA

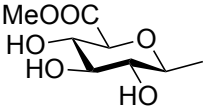

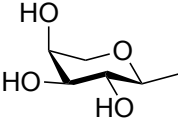
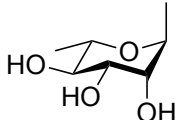
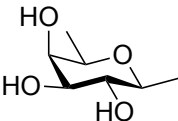
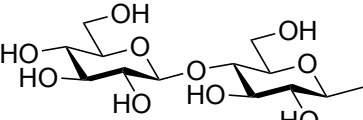
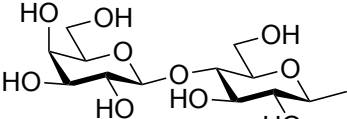
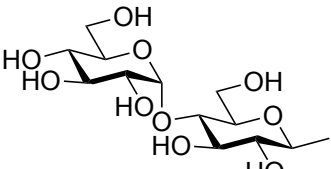
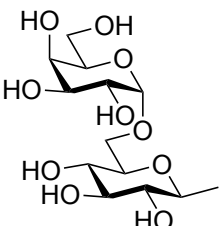
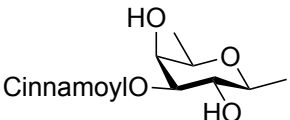
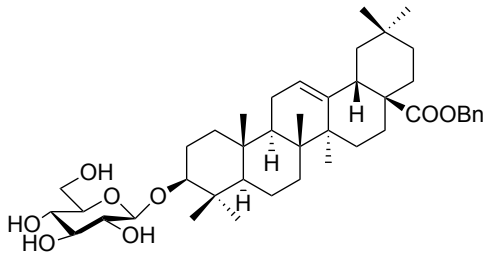
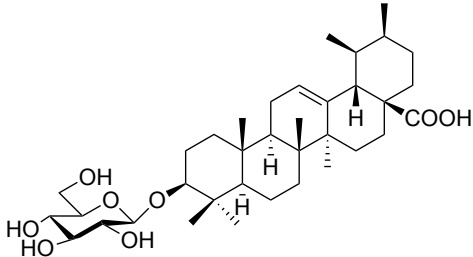
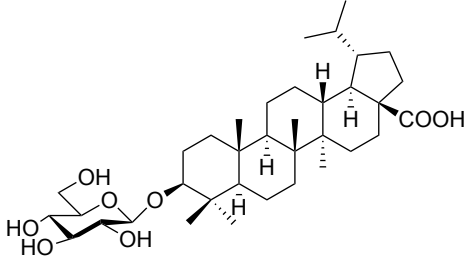
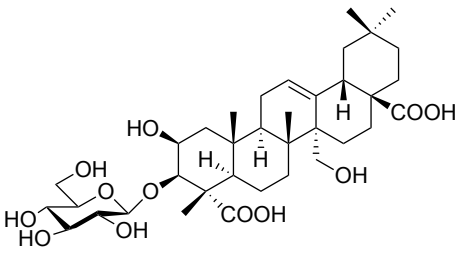
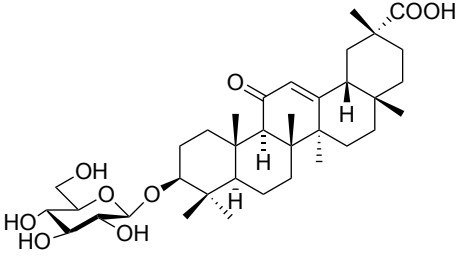
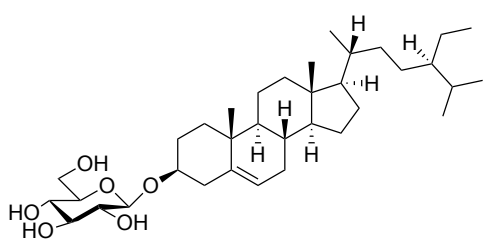
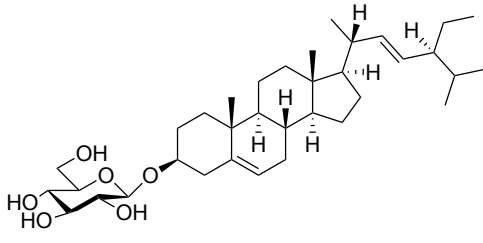
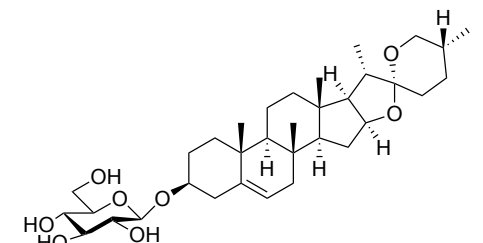
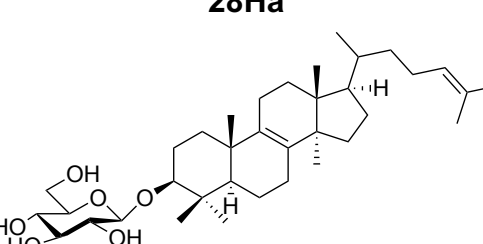
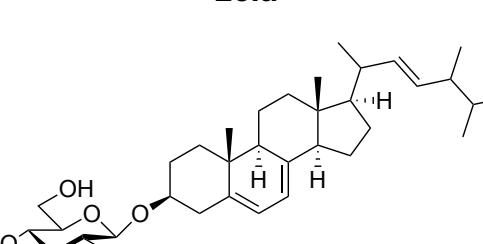
4	4Be		β -D-Glc AMe	<12.1	NHA
5	4Bf		β -D-Xyl	106	NHA
6	4Bg		α -L-Ara	<13.2	NHA
7	4Bh		α -L-Rha	13	NHA
8	4Bi		β -D-Fuc	<12.9	NHA
9	4Bj		β -D-Cel	10	NHA
10	4Bk		β -D-Lac	<10	NHA
11	4Bl		β -D-Mal	<10	NHA
12	4Bm		β -D-Mel	39.9	NHA
13	29Bia'		3'-Cinnamoyl - β -D-Fuc	<10.6	NHA

Table 59 種々の C-3 位サポニン誘導体の性質

Entry	Saponin	CMC (μM)	HD ₅₀ (μM)
1	 <p>26Ba</p>	<12.6	NHA
2	 <p>28Ca</p>	<12.6	200
3	 <p>28Da</p>	<12.6	400
4	 <p>Tenuifolin (2A)</p>	367	NHA
5	 <p>28Ea</p>	98.8	NHA

6	 <p>28Fa</p>	27	NHA
7	 <p>28Ga</p>	27.1	NHA
8	 <p>28Ha</p>	<13.5	NHA
9	 <p>28Ia</p>	26.5	NHA
10	 <p>28Ja</p>	14	NHA

第四項 考察と今後の展望

本研究で得られた結果から化学構造と CMC、溶血作用の構造活性相関 (SAR) について文献情報を基に以下に考察した。

本研究の結果から、溶血作用を発現したサポニン誘導体は単糖あるいは二糖の C-3 位糖鎖と、オレアナン (オレアノール酸)・ウルサン (ウルソール酸)・ルパン (ジヒドロベツリン酸) 骨格のトリテルペンを有していた。X 軸と Y 軸にそれぞれ CMC と HD₅₀ を示したグラフを作成すると、本研究で合成した各種サポニン誘導体は全て CMC に達した後ミセルの形成によって溶血作用を発現することが示唆された (Figure 32)。

一箇所に糖鎖を有するモノデスモシドサポニン及び二箇所に糖鎖を有するビスデスモシドサポニンの溶血作用の構造活性相関の報告例¹⁸では、赤で示す構造が溶血性の増強、青の構造が溶血性の減弱に関与すると考えられている (Figure 33)。

モノデスモシドサポニンでは、

1) R₁ には糖鎖構造が必要であり α -L-Rha-(1 \rightarrow 2)- α -L-Ara 構造が溶血作用に関わることや α -L-Rha $\rightarrow\beta$ -D-Glc (1 \rightarrow 2)、(1 \rightarrow 4)、(1 \rightarrow 6) 構造が (1 \rightarrow 3) 構造よりも溶血作用が強いこと

2) R₂ にはトリテルペンのヒドロキシ基が溶血作用の増強に、ステロイドのジオスゲニン骨格のヒドロキシ基あるいはアルカン鎖が溶血作用の減弱に関わること

3) R₃ にはトリテルペンのカルボキシ基は溶血作用の増強に関わること

と考えられている。また、ビスデスモシドサポニンでは、

1) R₁ には少なくとも糖鎖構造が 1 つ結合していること

2) R₂ にはカルボキシ基あるいは CH₂OH 基が必要であること

3) R₃ に糖鎖が 1 つ結合している場合には R₁ に糖鎖が 3 つ結合していること
と考えられている。

本研究ではオレアノール酸サポニン誘導体 **28Ba** のオレアナン骨格と比較して、以下の 3 つのトリテルペン C-3 位サポニンは溶血作用が減弱・消失し、以下の構造が異なった (Figure 33)。

1) サポニン誘導体 **28Ca** のウルサン骨格のメチル基の位置

2) サポニン誘導体 **28Da** のルパン骨格の E 環部分に該当する五員環構造

3) Tenuifolin (**2A**) のプレセネゲニン骨格の酸素官能基

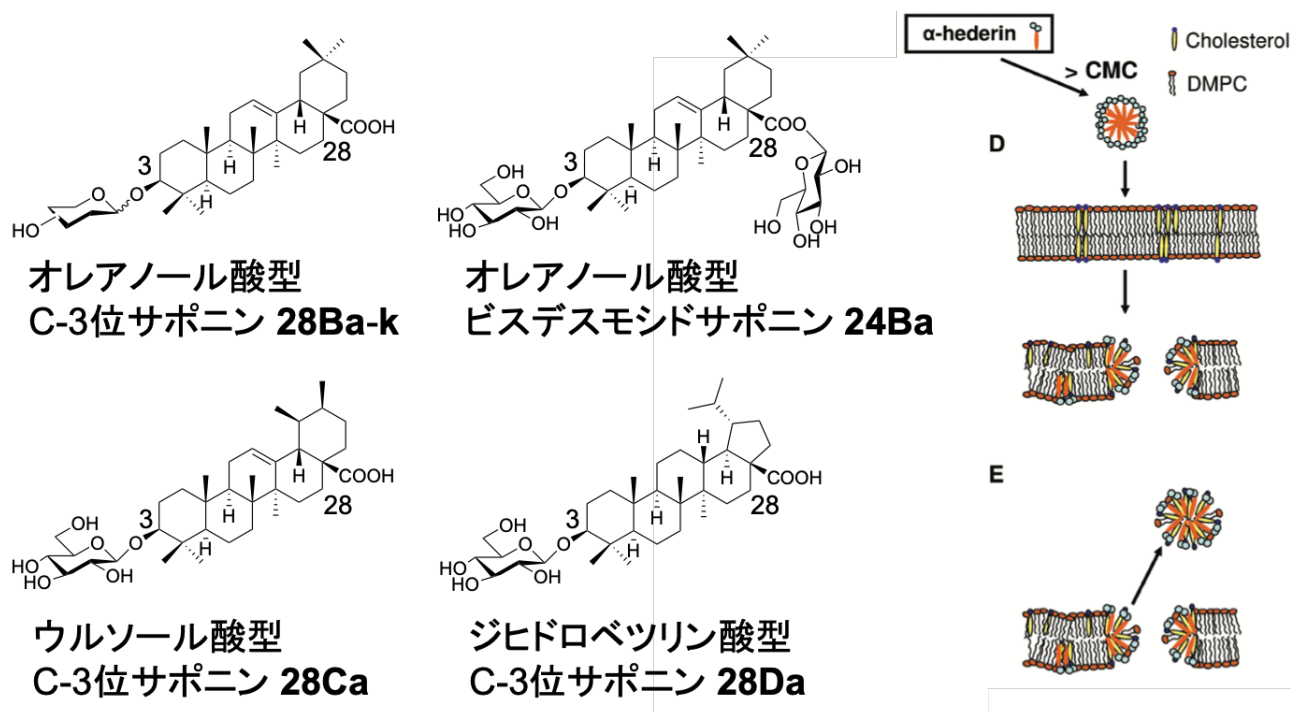
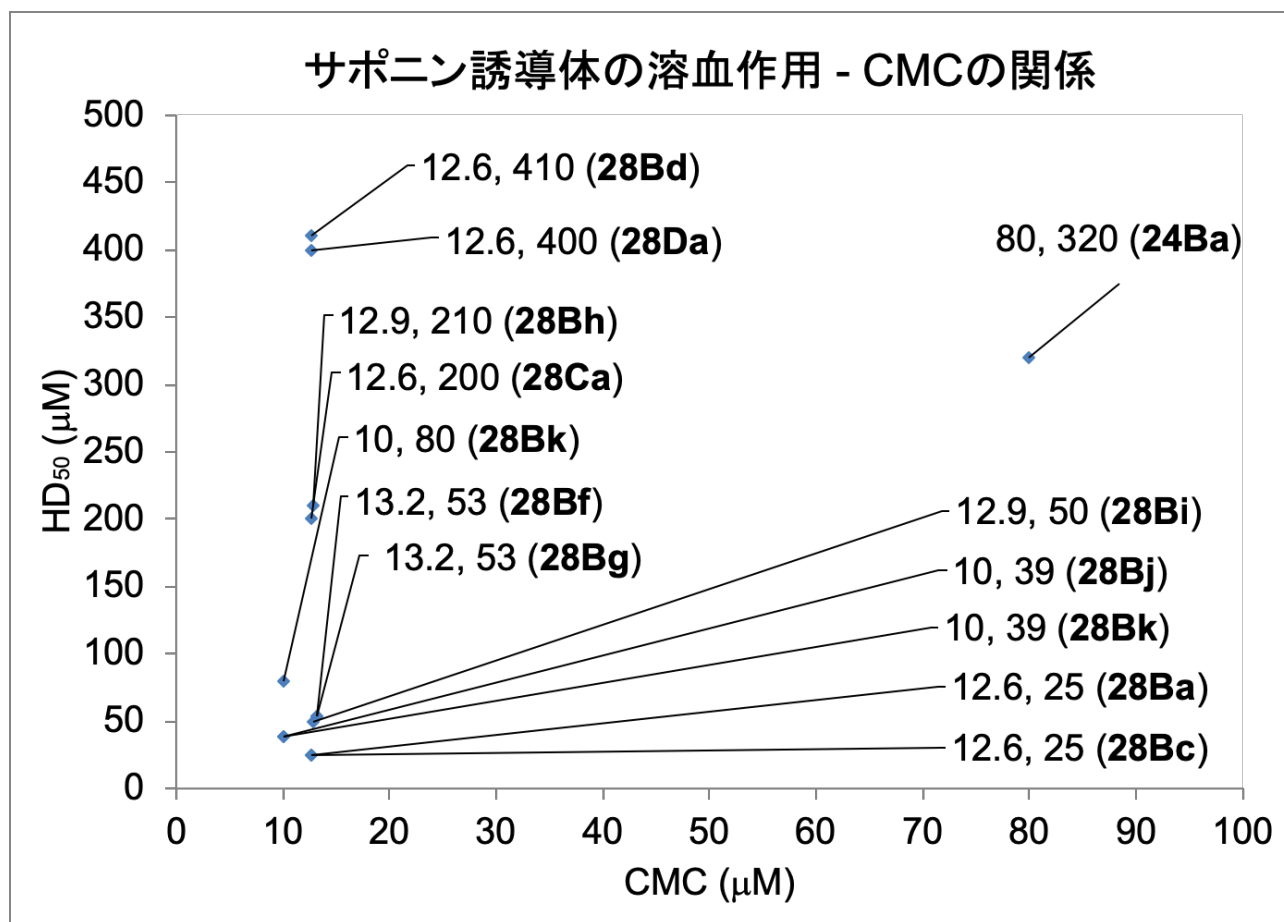
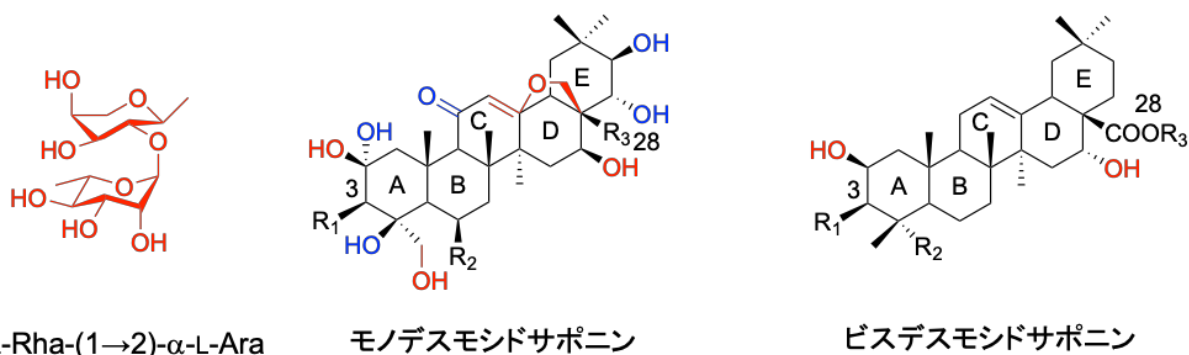


Figure 32 サポニン誘導体の CMC と溶血作用と考えられる作用機作

先行研究



本研究

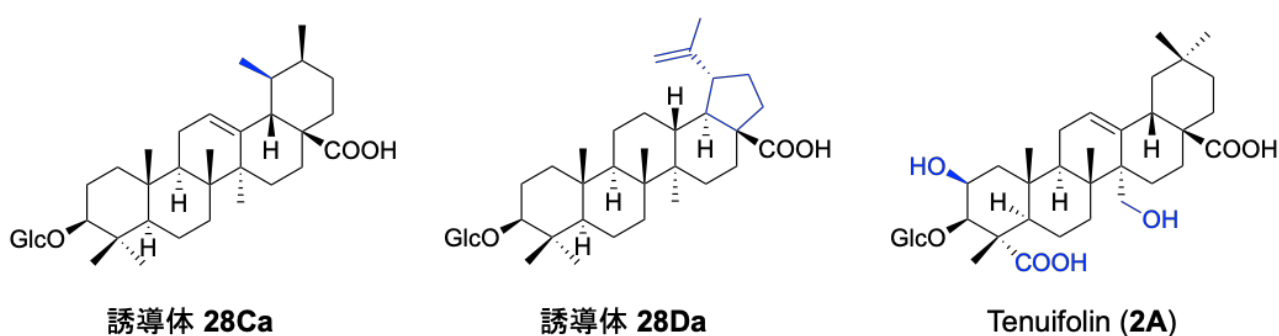


Figure 33 溶血作用の減弱に関与すると考えられるトリテルペンの構造

市販天然サポニンのサイコサポニン A, D 及びジギトニンは X 軸と Y 軸にそれぞれ CMC と HD₅₀ を示したグラフを作成すると、CMC 以下の濃度で溶血作用を発現した (Figure 34)。ステロイド骨格を有するサポニンの中で唯一溶血作用を発現し、低い CMC を示したジギトニンはコレステロールの沈殿定量法に用いられており、ジギトニドを形成することが知られている¹²⁶。この傾向から、サイコサポニン A, D もコレステロールとの親和性が高く溶血作用を発現している可能性が示唆された。

オレアノール酸 C-28 位サポニン誘導体 4Ba-m, 桂皮酸含有サポニン 29Bia', C-3 位サポニン 28Ea-Ja, ビスデスモシドサポニン 24Bc, f 及び他の市販天然サポニンの溶血作用は消失し、CMC の値は糖鎖の数の増加に従い増加する傾向にあった。溶血作用を発現しない構造要件には、

- 1) C-28 位糖鎖構造 (桂皮酸含有糖鎖を含む)
 - 2) C-28 位カルボキシ基を有さない五環性トリテルペン
 - 3) 四環性トリテルペンやステロイド
- が考えられた。

市販天然サポニンの溶血作用 - CMCの関係

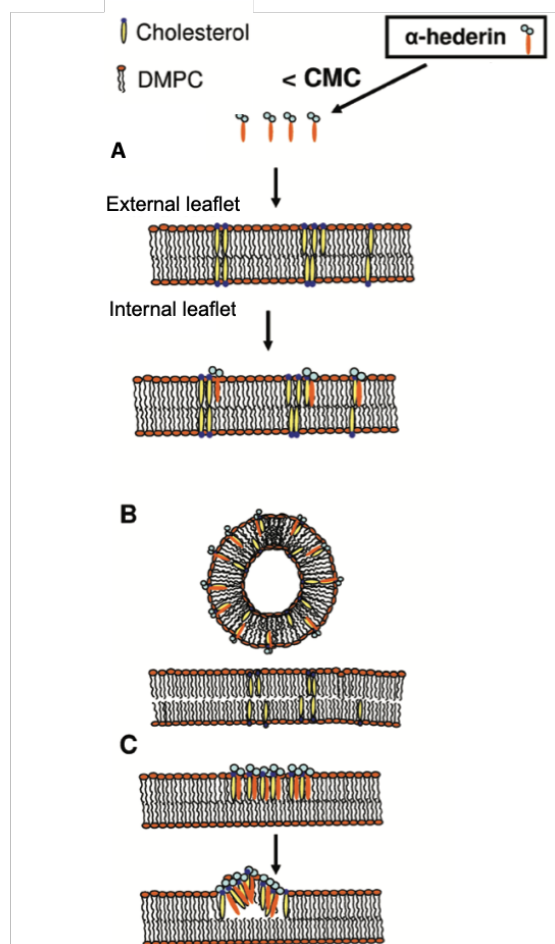
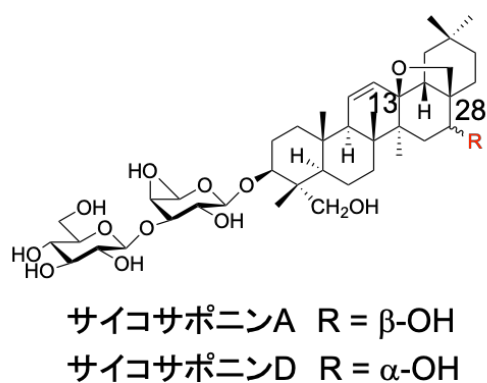
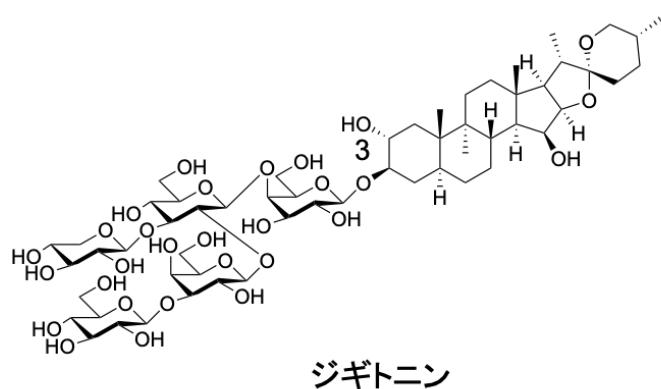
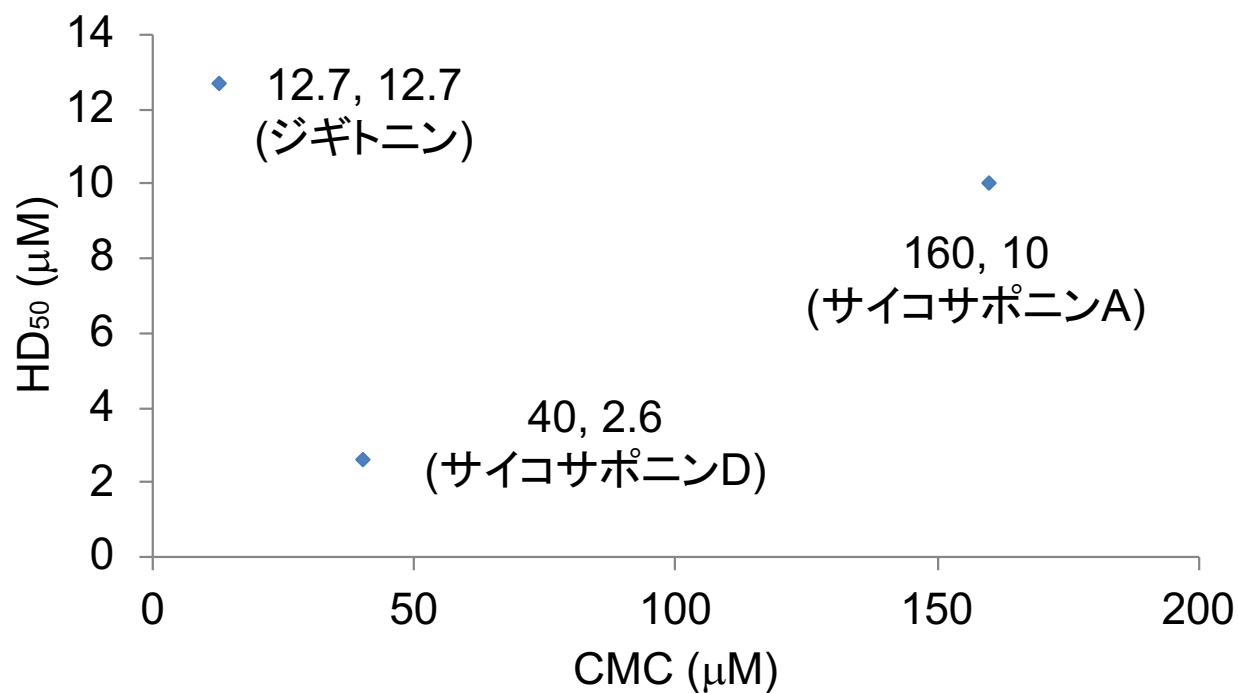


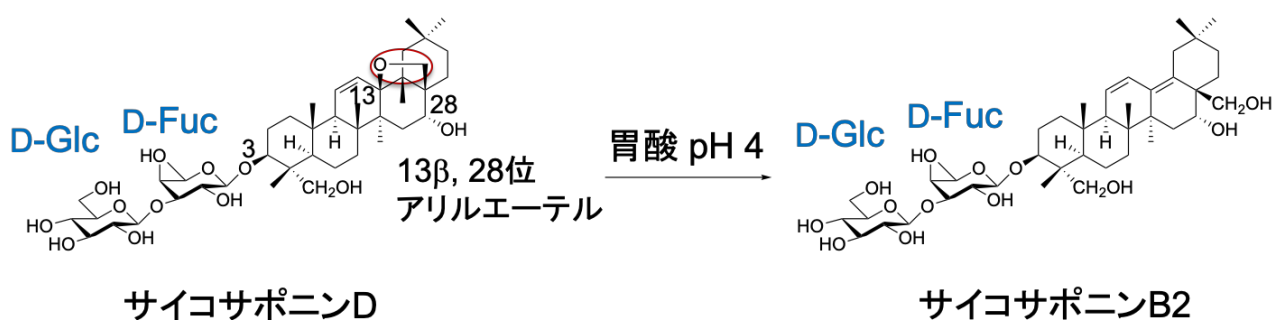
Figure 34 サイコサポニン A, D とジギトニンの CMC と溶血作用と考えられる作用機作

また、サイコサポニン A, B2, C, D を比較して CMC に達する前に溶血作用を示す鍵となる構造は以下に示す 2 つの構造が重要と考えられた。

1) 13 β , 28 位アリルエーテル構造

2) C-3 位に結合する β -D-Glc \rightarrow β -D-Fuc (1 \rightarrow 3) 糖鎖構造

なお、サイコサポニンの 13 β , 28 位アリルエーテル構造は酸性条件で速やかに分解されジエン構造になることが報告されている¹²⁹。即ち、柴胡を含む漢方薬を経口摂取した場合には胃酸によってサイコサポニン D は溶血作用を示さないサイコサポニン B2 に代謝を受け毒性が減弱している可能性が考えられた (Scheme 18)。



Scheme 18 サイコサポニンの代謝

一方、ジンセノシド類やアストラガロシド IV、グリチルリチン、強心配糖体は溶血作用を示さず、誘導体の溶血作用に関わる構造要件とも一致する傾向であった (Figure 35)。

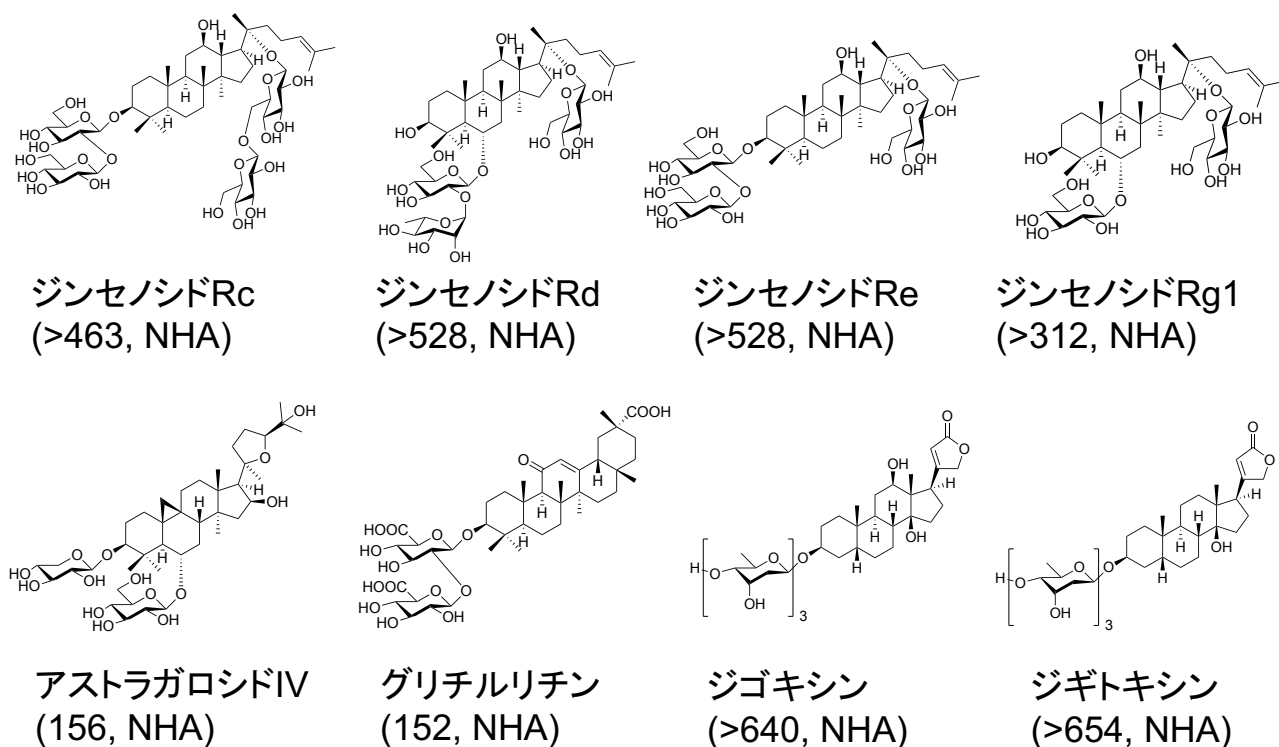


Figure 35 溶血作用を示さない市販天然サポニンの構造の特徴

第八節 総括

これまでの研究において筆者はマイクロフローリアクター式サポニン合成法を用い、合計 35 種類のサポニン誘導体ライブラリー (14 種類のオレアノール酸 C-28 位サポニン、3 種類のオレアノール酸ビスデスモシドサポニン、18 種類の C-3 位サポニン) を構築できた (Figure 36)。

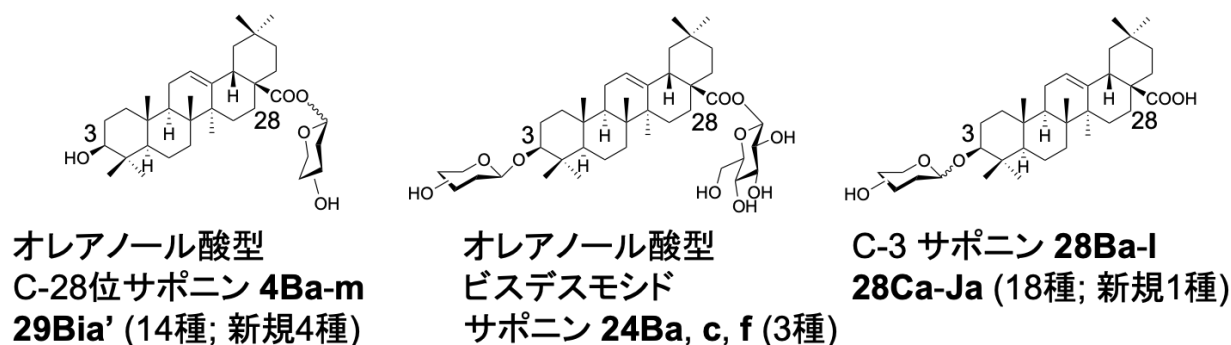


Figure 36 マイクロフローリアクター式配糖化を利用したサポニンライブラリーの構築

次にサポニンライブラリーの性質である CMC と溶血作用を評価しその関係性をグラフとして作成し考察すると A~D の 4 群に分類することができた (Figure 37)。溶血発現しないサポニンはグラフのプロットの関係上、測定範囲外の 600 μM として一律に示した。

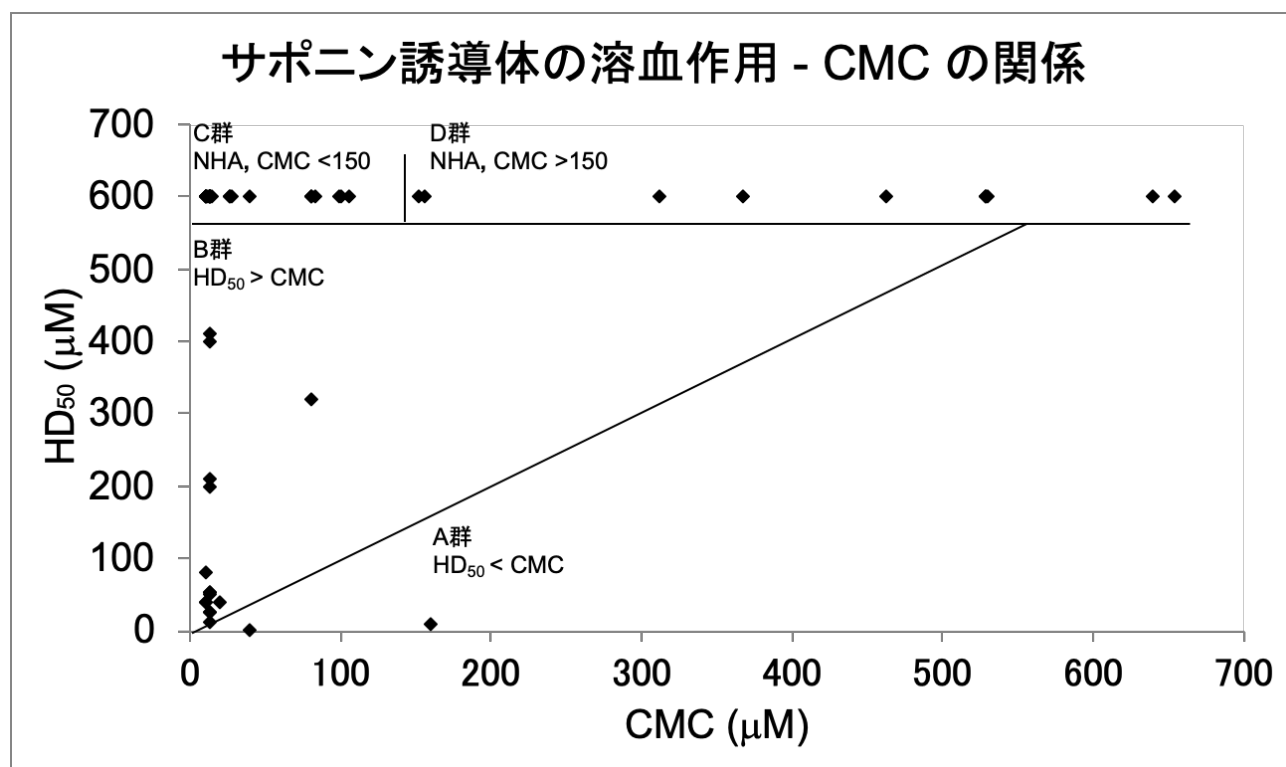


Figure 37 サポニンライブラリーの性質である CMC と溶血作用 (500-7.8 $\mu\text{g/mL}$)

A 群: ミセル形成能を示す以前に溶血作用を発現するサポニン群

A 群に該当するジギトニン、サイコサポニン A, D は CMC に達する前に溶血作用を示した ($HD_{50} < CMC$) ので、モノマー状態でコレステロール等と相互作用し溶血作用を発現するサポニン群であると考えられた。その構造の分子量は異なるものの、脂溶性のアグリコンと親水性の糖鎖の極性のバランスが類似していると考えられた (Figure 38)。

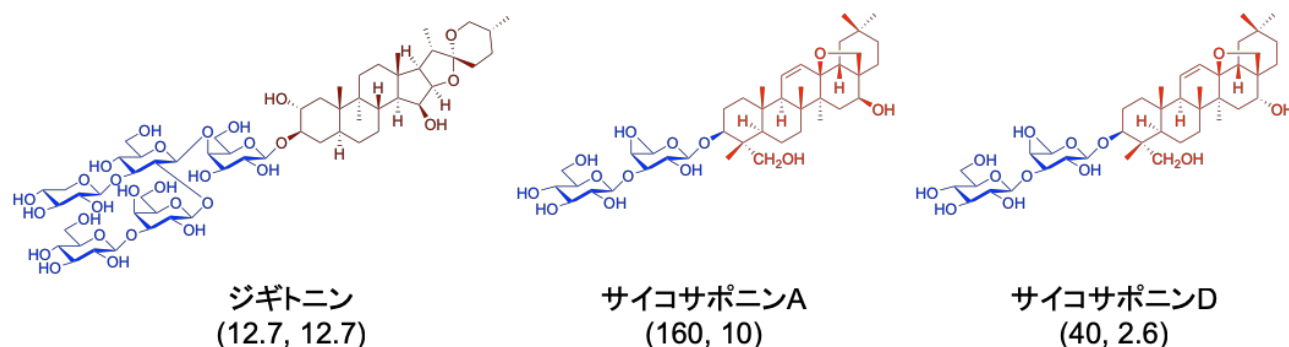


Figure 38 A 群のサポニンの構造と性質

B 群: ミセル形成能に従い溶血作用を発現するサポニン群

B 群に該当する C-3 位サポニン誘導体 **28Ba-i**, **28Ca**, **28Da** 及びオンジサポニン B (**1Ae**) は、CMC に達した後に溶血作用を示した ($CMC < HD_{50}$) ので、ミセル状態で細胞膜を破壊し溶血作用を発現するサポニン群であると考えられた (Figure 39)。その構造的特徴は、

- 1) C-28 位に直接結合するカルボキシ基
- 2) C-3 位糖鎖群
- 3) 5 環性トリテルペン

の 3 つを共通構造として有する傾向にあった。オレアノール酸 C-3 位サポニン誘導体 **28Ba-i** は全て 10 μ M 程度の CMC を示したが、溶血作用は C-3 位糖鎖やアグリコンの種類によって異なり、以下の順に従い増強した。

糖鎖: α -D-Man < α -L-Rha < β -D-Lac < β -D-Xyl, α -L-Ara < β -D-Fuc < β -D-Cel, β -D-Mal < β -D-Glc, β -D-Gal

アグリコン: ジヒドロベツリン酸 < ウルソール酸 < オレアノール酸

溶血作用を示したビスデスモシドサポニン **24Ba** は C-3 位に D-Glc を有しており、最も溶血性の強い C-3 位糖鎖であることが示唆された。例外的に、オンジサポニン (**1Ae**) は各種 C-3 位サポニン誘導体とは構造の特徴が大きく異なった。五糖を有する C-28 位複合糖鎖内に脂溶性の桂皮酸エステルを含有する複雑なビスデスモシド構造が要因と考えられた。

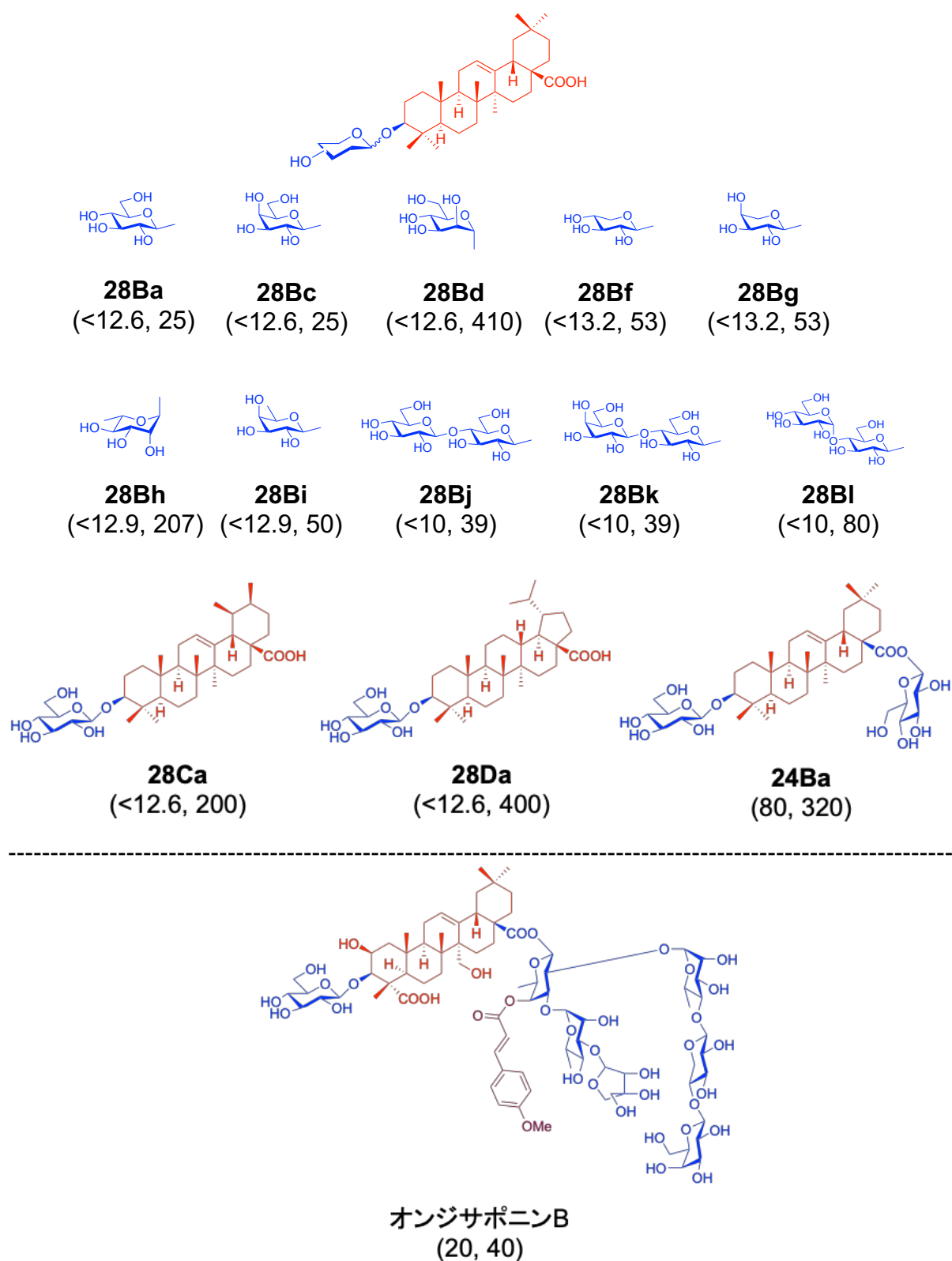


Figure 39 B 群のサポニンの構造と性質

C 群: 溶血作用を示さないミセル形成能の強いサポニン群

C 群に該当するオレアノール酸 C-28 位サポニン誘導体 **4Ba-m**, 桂皮酸含有サポニン

29Bia'、C-3 位サポニン **28Ea-Ja**、ビスデスモシドサポニン **24Bc, f**、サイコサポニン **B2** は 500-7.8 $\mu\text{g/mL}$ の測定範囲で溶血作用を発現しない CMC の低いサポニンであった (**Figure 40**)。溶血作用を発現しない構造要件には以下の 3 つの特徴が考えられた。

- 1) C-28 位糖鎖構造 (桂皮酸含有糖鎖を含む)
- 2) C-28 位カルボキシ基を有さない五環性トリテルペン
- 3) 四環性トリテルペンやステロイド

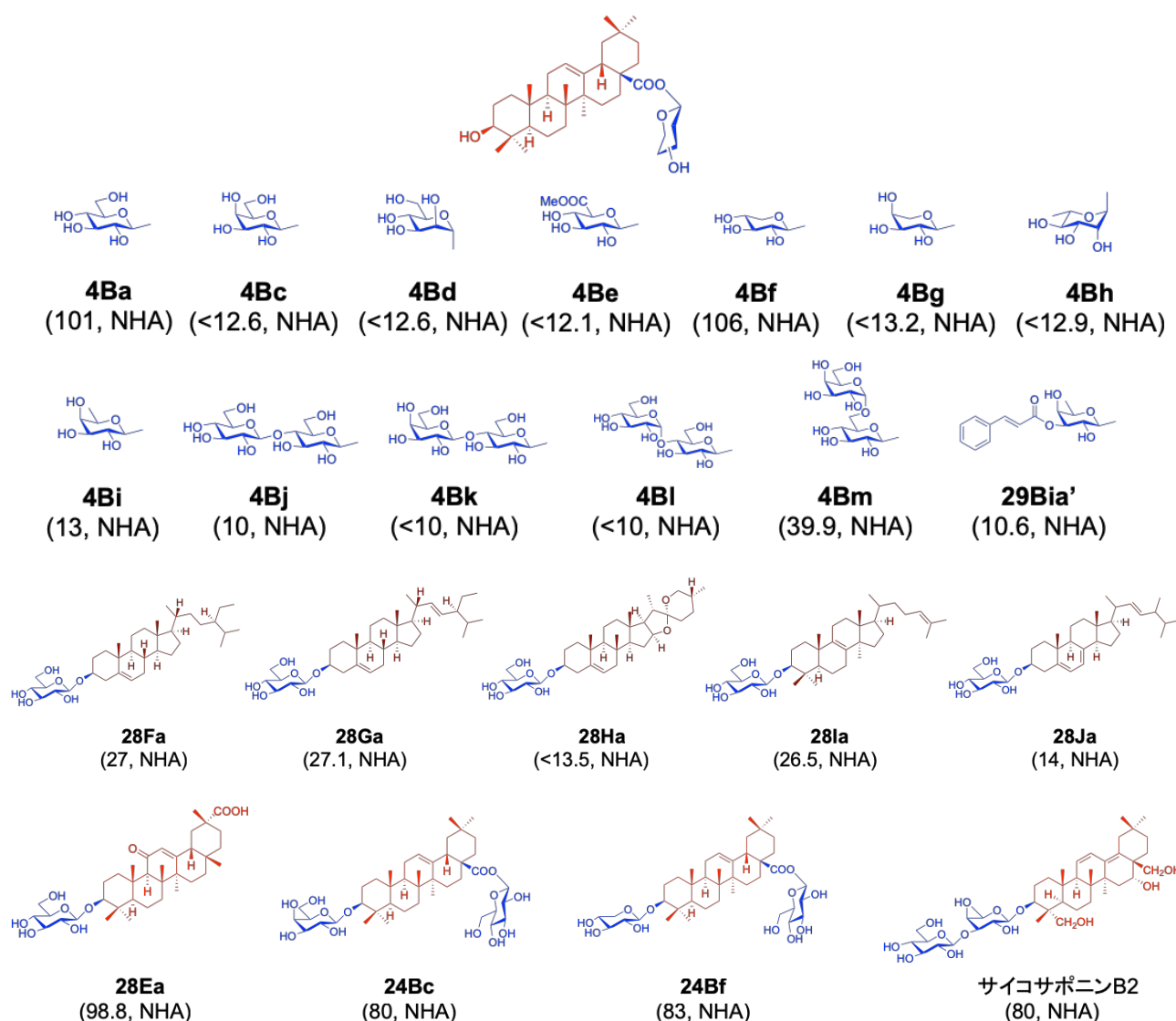


Figure 40 C 群のサポニンの構造と性質

D 群: 溶血作用を示さないミセル形成能の弱いサポニン群

D 群に該当する天然由来のサポニンであるグリチルリチン、アストラガロシド IV、ジンセノシド Rg1、Rc、Rd、Re、Tenuifolin (**2A**)、サイコサポニン C、ジゴキシシン、ジギトキシシンは 500-7.8 $\mu\text{g/mL}$ の測定範囲で溶血作用を発現しない CMC の高いサポニンであった (**Figure 41**)。CMC が高い値を示したことは水溶性の糖鎖の数が 2~4 個である点から明ら

かであり、溶血作用を発現しない構造要件はC群のサポニンと同様であることが示唆された。例外的に、オンジサポニンの共通構造である tenuifolin (2A) はC-3 位糖鎖と C-28 位カルボキシ基含有五環性トリテルペンを有するサポニンであった。

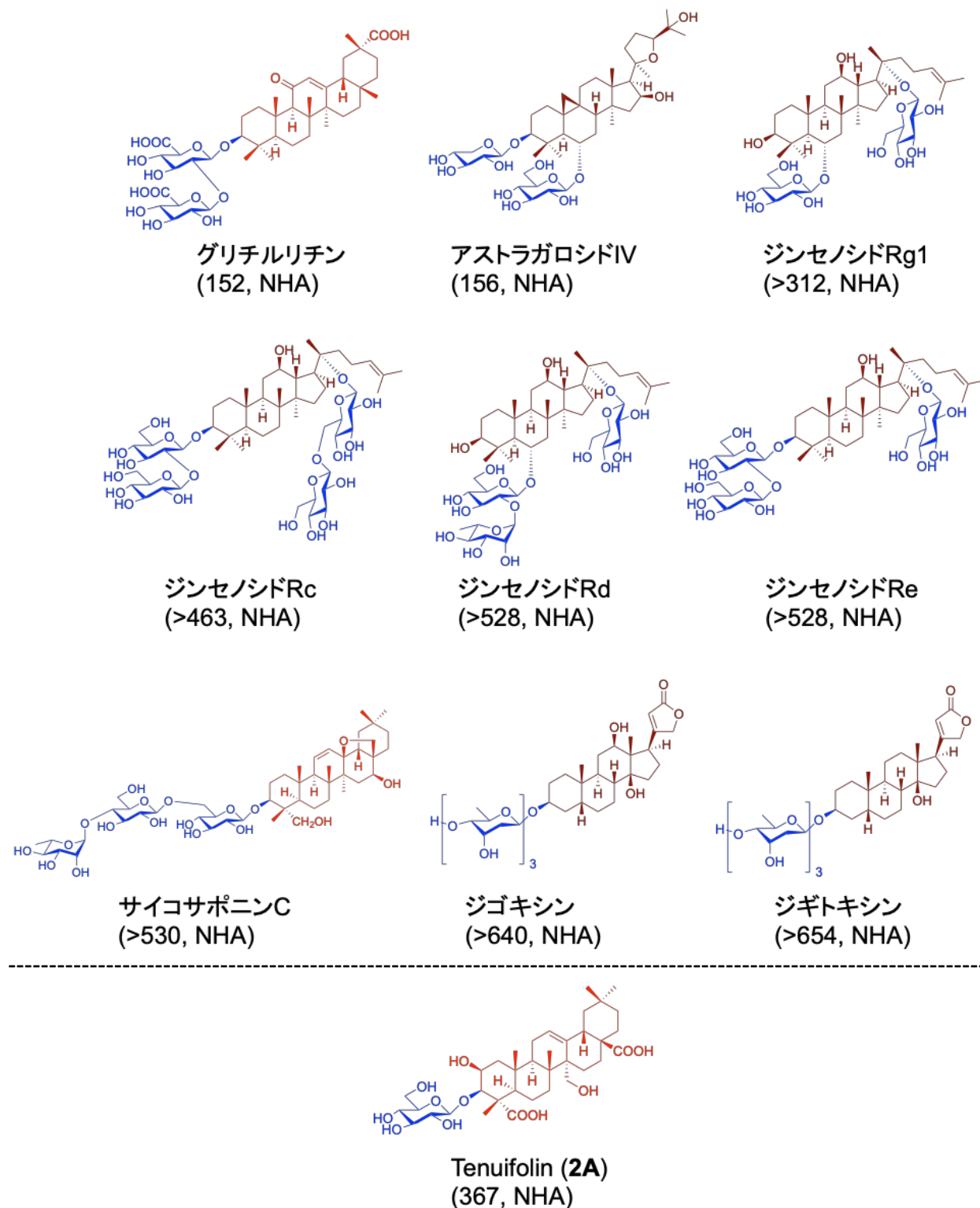


Figure 41 D 群のサポニンの構造と性質

以上の結果から、界面活性・溶血作用・化学構造間の関係は一部の例外はあるものの、サポニンを構造的な特徴から4つに分類すると溶血作用とミセル形成能の有無との関係を説明できることが明らかとなった。溶血作用を発現しないサポニン誘導体を合成するには、C群またはD群に分類される構造要件を満たす必要があり、A群とB群の構造は溶血作用発現のリスクがあった。

C群に分類されるオレアノール酸ビスデスモシドサポニン誘導体 **24Bc, f** とB群に分類されるオレアノール酸ビスデスモシドサポニン誘導体 **24Ba** の経鼻接種インフルエンザワクチンアジュバント活性を評価した。即ち、BALB/c マウスにインフルエンザスプリットワクチン (H1N1 亜型) 及び各サポニンの混合物を0及び21日目に経鼻接種することで二次免疫を行い、初回接種後35日目の血清及び鼻腔、気管支肺胞、生殖器洗液中の抗インフルエンザウイルス抗体価を測定した。その結果、**24Bf** の接種群において陽性対照の *onjisaponin B (1Ae)* には劣るが鼻腔 IgA 抗体価の上昇が認められ、溶血作用のリスクを回避したサポニン誘導体アジュバントを創製可能であることが示唆された (清原、永井ら未発表データ)。

本研究で確立したマイクロフローリアクター式配糖化法を利用し構築できたサポニン誘導体ライブラリーを用いることで、サポニンの性質を化学構造・臨界ミセル濃度 (CMC)・溶血作用間の関係を数値化しデータを取得することができた。得られたサポニンライブラリーの性質データの知見は溶血作用の消失・生物活性の賦与を指向した誘導体の設計や生物活性試験へ供給するサポニン誘導体の選定、実験計画を設定する一助になることが期待される。

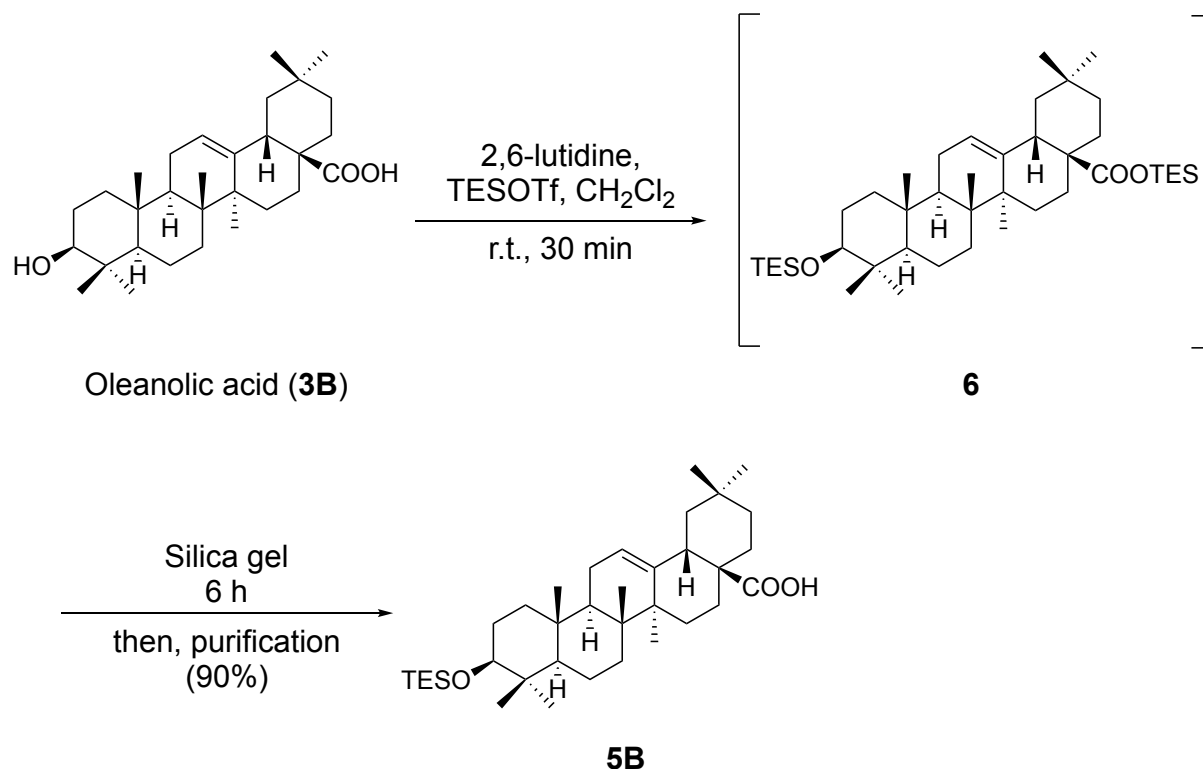
第三章 実験の部

General

- Unless otherwise noted, the water in the flask with magnet was completely removed by heat gun while reducing the pressure in the vacuum pump. Afterward, all batch-wise reactions were carried out under nitrogen atmosphere in dried glass flask.
- After purification, the desired compounds were concentrated *in vacuo* and dried under reduced pressure in the vacuum pump, unless otherwise noted.
- All reagents were purchased from Tokyo Chemical Industry Co., Ltd., Japan, Kanto Chemical Co., Inc., Japan., FUJIFILM Wako Pure Chemical Industries, Ltd., Japan, Nacalai Tesque, Inc., Japan, or Sigma- Aldrich Co., LLC., U.S.A and used without further purification, unless otherwise noted.
- Dry DMF, THF, pyridine and CH₂Cl₂ were purchased from Kanto Chemical Co., Inc., Japan.
- Activating agents (BF₃•OEt₂ and TMSOTf) were used under nitrogen atmosphere in the plastic sheet, unless otherwise noted.
- Precoated silica gel plates with a fluorescent indicator (Merck 60 F254) were used for analytical and preparative thin layer chromatography.
- Detection was carried out by staining with phosphomolybdic acid resulted in blue spots and application of UV (254 nm).
- Flash column chromatography was carried out with Kanto Chemical silica gel (Kanto Chemical Co., Inc., Japan, silica gel 60N, spherical neutral, 0.040-0.050 mm, Cat.-No. 37 563-84).
- Powdered and pre-dried molecular sieves 4Å was used for glycosylation.
- ¹H NMR spectra were recorded at 400 MHz and ¹³C NMR spectra were recorded at 100 MHz on Agilent 400-MR DD2 (400 MHz).
- The chemical shifts are expressed in ppm downfield from the internal solvent peaks for CDCl₃ (7.26 ppm, ¹H NMR), CDCl₃ (77.0 ppm, ¹³C NMR), pyridine-*d*₅ (8.73 ppm, ¹H NMR), pyridine-*d*₅ (150.0 ppm, ¹³C NMR) and J values are given in Hertz.
- The coupling patterns are denoted s (singlet), brs (broad singlet), d (doublet), dd (double doublet), dt (double triplet), ddd (double double doublet), t (triplet), td (triple doublet), q (quartet), m (multiplet).
- All infrared spectra were measured on a JASCO FT/IR-460 spectrometer.

- A solution of $\text{BF}_3 \cdot \text{OEt}_2$ or TMSOTf in CH_2Cl_2 was prepared as below; to a solution of acceptor and donor in CH_2Cl_2 (3.0 mL, 0.02 or 0.03 M) at room temperature was stirred. After the mixture was left standing for 10 min without stirring, the supernatant was used for glycosylation.
- Optical rotations ($[\alpha]_D$) were measured by using JASCO P-2200 polarimeter.
- High- and low-resolution mass spectra were measured on a JEOL JMS-T100 LP Mass Spectrometer.
- The Comet X-01 micromixing device and dual syringe pumps (Catamaran HII-10 and Catamaran Aspirate HII-10B) were obtained from Techno Applications Co., Ltd., 34-16-204 Hon, Denenchofu, Oota, Tokyo, 145-0072, Japan.
- The dual syringe pumps (YSP-202) were obtained from YMC Co., Ltd., Japan.
- Micro-flow reactor structure is alternated ten-layers of three holes (0.137 μL micro space x 3) and one hole (0.55 μL micro space plate) in the reactor. Teflon tube connected to the syringe pump was used as an inner diameter ($\phi 1$), outer diameter ($\phi 2$).
- Chemical assignments for known donors were conducted by ^1H -NMR compared with previous literatures.

3-*O*-triethylsilyl oleanolic acid (**5B**)



To a solution of commercial oleanolic acid (**3B**) (1.00 g, 2.19 mmol) in CH₂Cl₂ (15 mL) was added 2,6-lutidine (2.59 mL, 11.0 mmol) and TESOTf (2.48 mL, 11.0 mmol). After stirring for 2 h at room temperature, the reaction mixture of compound **6** was concentrated *in vacuo*, put into silica gel column chromatography and kept for 6 h. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 7:1) to afford **5B** (1.13 g, 1.97 mmol, 90%) as a white solid.

R_f = 0.47 (hexane : AcOEt = 3 : 1)

[α]_D²⁸ +47.7 (*c* 1.00, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 5.27 (m, 1H, 12-H), 3.21 (m, 1H, 3-H), 2.81 (dd, *J* = 11.2 Hz, 4.8 Hz, 1H, 18-H), 1.97 (m, 1H, 11-H), 1.86 (m, 2H, 16-H), 1.76 (m, 1H, 22-H), 1.61 (m, 3H, 11-H, 15-H, 19-H), 1.57 (m, 1H, 22-H), 1.56 (m, 1H, 1-H), 1.53 (m, 2H, 6-H), 1.52 (m, 1H, 9-H), 1.49 (m, 2H, 2-H), 1.41 (m, 1H, 7-H), 1.34 (m, 1H, 21-H), 1.27 (m, 1H, 7-H), 1.21 (m, 1H, 21-H), 1.15 (m, 1H, 19-H), 1.13 (s, 3H, 27-H), 1.07 (m, 1H, 15-H), 0.95 (m, 9H, -Si(CH₂CH₃)₃), 0.93 (s, 3H, 30-H), 0.92 (m, 1H, 1-H), 0.91 (s, 6H, 23-H, 25-H), 0.90 (s, 3H, 29-H), 0.74 (s, 6H, 24-H, 26-H), 0.69 (m, 1H, 5-H), 0.59 (m, 6H,

-Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

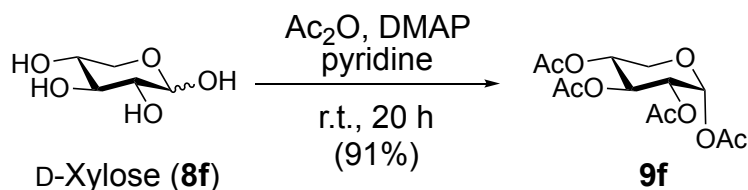
δ : 184.1 (C-28), 143.6 (C-13), 122.7 (C-12), 79.5 (C-3), 55.4 (C-5), 47.7 (C-9), 46.5 (C-17), 45.9 (C-19), 41.5 (C-14), 40.9 (C-18), 39.3 (C-8), 39.3 (C-4), 38.5 (C-1), 37.0 (C-10), 33.8 (C-21), 33.1 (C-29), 32.6 (C-7), 32.4 (C-22), 30.7 (C-20), 28.4 (C-23), 27.7 (C-15), 27.7 (C-2), 26.0 (C-27), 23.6 (C-30), 23.4 (C-16), 22.9 (C-11), 18.5 (C-6), 17.2 (C-26), 16.0 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (NaCl) cm⁻¹ ν : 3434 (-O-H), 2951 (=C-H), 1758 (-C=O), 1643 (-C=C-), 1067 (-C-O-)

HR-MS (ESI⁺)

m/z 593.4348[M+Na]⁺, Calc'd for C₃₆H₆₂O₃SiNa: 593.4366.

1, 2, 3, 4-Tetra-*O*-acetyl- α -D-xylopyrannose (9f**)**¹³⁰



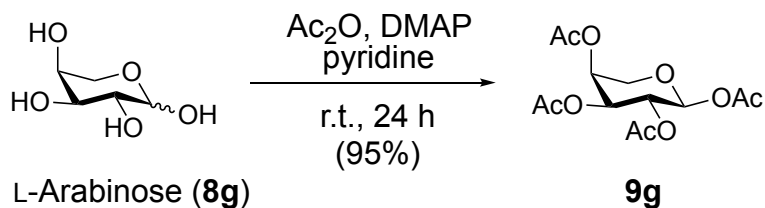
To a solution of commercial D-xylose (**8f**) (4.0 g, 26.6 mmol) in pyridine (200 mL) at 0 °C was added DMAP (325 mg, 2.66 mmol) and Ac₂O (20 mL, 213 mmol). After stirring for 20 h at room temperature, the reaction mixture was quenched with H₂O (50 mL) in ice bath. The resulting mixture was extracted with AcOEt (2 x 250 mL). The combined organic layer was washed with sat. aq. CuSO₄ (8 x 150 mL) and H₂O (3 x 150 mL), brine (300 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **9f** (α only, 7.80 g, 2.45 mmol, 91%) as a yellow oil without further purification.

R_f = 0.46 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 6.25 (d, J = 3.7 Hz, 1H, 1-H), 5.46 (t, J = 9.6 Hz, 1H, 3-H), 5.05-4.99 (m, 2H, 2-H, 4-H), 3.93 (dd, J = 11.0 Hz, 5.9 Hz, 1H, 5-H), 3.71 (t, J = 11.0 Hz, 1H, 5-H), 2.17 (s, 3H, -OCOCH₃), 2.04 (s, 3H, -OCOCH₃ x2), 2.01 (s, 3H, -OCOCH₃)

1, 2, 3, 4-Tetra-*O*-acetyl- β -L-arabinopyrannose (9g**)¹³¹**



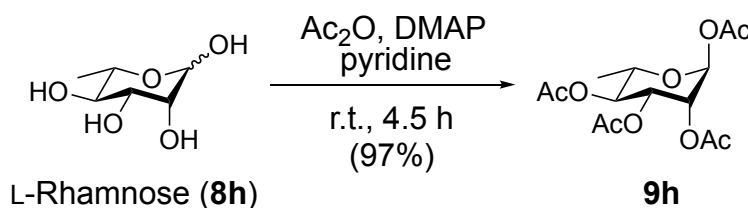
To a solution of commercial L-arabinose (**8g**) (2.0 g, 13.3 mmol) in dry pyridine (30 mL) at 0 °C was added DMAP (163 mg, 1.33 mmol) and Ac₂O (10.0 mL, 107 mmol). After stirring for 24 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (150 mL). The combined organic layer was washed with sat. aq. CuSO₄ (4 x 60 mL) and H₂O (60 mL), brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **9g** (β only, 4.03 g, 12.7 mmol, 95%) as a yellow oil without further purification.

R_f = 0.39 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

β δ : 6.35 (d, *J* = 3.2 Hz, 1H, 1-H), 5.31 (m, 3H, 2-H, 3-H, 4-H), 4.06 (dd, *J* = 13.2 Hz, 1.0 Hz, 1H, 5-H), 3.83 (dd, *J* = 13.2 Hz, 2.0 Hz, 1H, 5-H), 2.16 (s, 3H, -OCOCH₃), 2.15 (s, 3H, -OCOCH₃), 2.06 (s, 3H, -OCOCH₃ x2)

1, 2, 3, 4-Tetra-*O*-acetyl- α -L-rhamnose (9h**)**¹³²



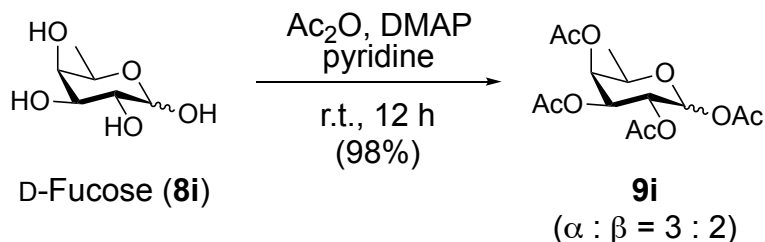
To a solution of commercial L-rhamnose (**8h**) (1.0 g, 5.49 mmol) in pyridine (50 mL) at 0 °C was added DMAP (67 mg, 0.549 mmol) and Ac₂O (4.2 mL, 43.9 mmol). After stirring for 4.5 h at room temperature, the reaction mixture was quenched with ice-cold H₂O (30 mL). The resulting mixture was extracted with AcOEt (3 x 60 mL). The combined organic layer was washed with sat. aq. CuSO₄ (5 x 60 mL) and H₂O (5 x 60 mL), brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **9h** (1.77 g, 5.33 mmol, 97%) as a colorless oil without further purification.

R_f = 0.50 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α 体 δ : 6.01 (d, J = 2.0 Hz, 1H, 1-H), 5.30 (dd, J = 10.0 Hz, 3.4 Hz, 1H, 3-H), 5.25 (dd, J = 3.4 Hz, 2.0 Hz, 1H, 2-H), 5.12 (t, J = 10.0 Hz, 1H, 4-H), 3.97 (m, 1H, 5-H), 2.16 (s, 3H, -OCOCH₃), 2.15 (s, 3H, -OCOCH₃), 2.06 (s, 3H, -OCOCH₃), 2.00 (s, 3H, -OCOCH₃), 1.23 (d, J = 6.2 Hz, 3H, -CH₃)

1, 2, 3, 4-Tetra-*O*-acetyl- α,β -D-fucopyrannose (9i**)**¹³³



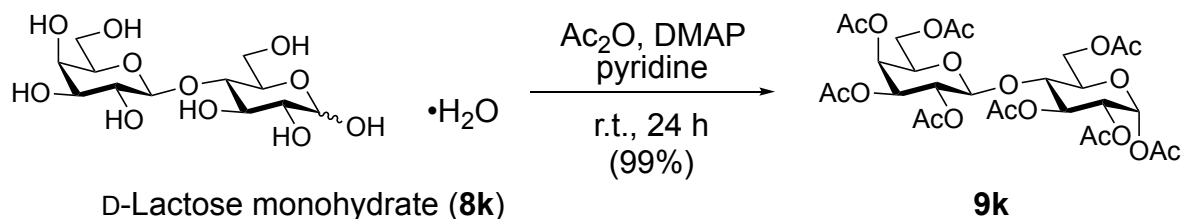
To a solution of commercial D-fucose (**8i**) (2.0 g, 12.2 mmol) in dry pyridine (50 mL) at 0 °C was added DMAP (149 mg, 1.22 mmol) and Ac₂O (9.20 mL, 97.5 mmol). After stirring for 12 h at room temperature, the reaction mixture was quenched with ice-cold H₂O (30 mL). The resulting mixture was extracted with AcOEt (150 mL). The combined organic layer was washed with sat. aq. CuSO₄ (4 x 50 mL) and H₂O (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford pure **9i** ($\alpha : \beta = 3 : 2$, 3.98 g, 12.0 mmol, 98%) as a yellow oil without further purification.

$R_f = 0.53$ (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

δ : 6.34 (d, $J = 2.9$ Hz, 1H, α -1-H), 5.68 (d, $J = 8.3$ Hz, 1H, β -1-H), 5.31 (m, 5H, α -2-H, β -2-H, α -3-H, α -4-H, β -4-H), 5.08 (dd, $J = 10.4$ Hz, 3.4 Hz, 1H, β -3-H), 4.27 (q, $J = 6.5$ Hz, 1H, α -5-H), 3.95 (q, $J = 6.5$ Hz, 1H, β -5-H), 2.19 (s, 3H, -OCOCH₃), 2.18 (s, 3H, -OCOCH₃), 2.14 (s, 3H, -OCOCH₃), 2.11 (s, 3H, -OCOCH₃), 2.04 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 2.00 (s, 3H, -OCOCH₃), 1.99 (s, 3H, -OCOCH₃), 1.23 (d, $J = 6.5$ Hz, 3H, β -6-H), 1.16 (d, $J = 6.5$ Hz, 3H, α -6-H)

α -D-Lactose octaacetate (9k**)**¹³⁴



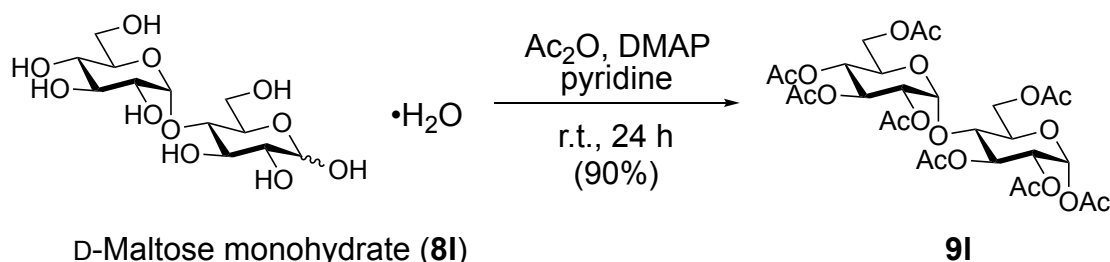
To a solution of commercial D-lactose monohydrate (**8k**) (1.0 g, 2.78 mmol) in pyridine (27 mL) at 0 °C was added DMAP (34 mg, 0.278 mmol), Ac₂O (2.61 mL, 27.8 mmol). After stirring for 24 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (100 mL). The combined organic layer was washed with sat. aq. CuSO₄ (3 x 60 mL) and H₂O (60 mL), and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **9k** (α only, 1.87 g, 2.76 mmol, 99%) as a white foamy solid without further purification.

R_f = 0.45 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ 6.25 (d, J = 3.7 Hz, 1H, 1'-H), 5.49 (dd, J = 3.6 Hz, 1.0 Hz, 1H, 4''-H), 5.46 (dd, J = 10.6 Hz, 9.3 Hz, 1H, 3'-H), 5.12 (dd, J = 10.3 Hz, 7.9 Hz, 1H, 2''-H), 5.01 (dd, J = 10.4 Hz, 3.7 Hz, 1H, 2'-H), 4.96 (dd, J = 10.3 Hz, 3.6 Hz, 1H, 3''-H), 4.63 (d, J = 7.9 Hz, 1H, 1''-H), 4.45 (dd, J = 12.4 Hz, 2.1 Hz, 1H, 6'-H), 4.12 (m, 3H, 6'-H, 6''-H, 6'''-H), 4.00 (ddd, J = 10.2 Hz, 4.4 Hz, 2.0 Hz, 1H, 5'-H), 3.84 (m, 2H, 4'-H, 5''-H), 2.18, 2.16, 2.13, 2.06, 2.06, 2.05, 2.00, 1.97 (8s, 24H, OCOCH₃)

α -D-Maltose octaacetate (9I**)**¹³⁵



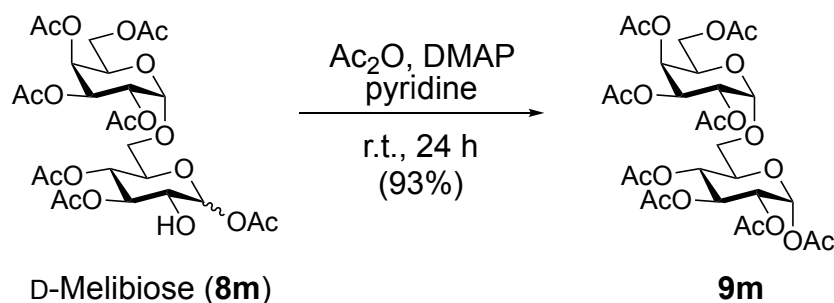
To a solution of commercial D-maltose monohydrate (**8I**) (1.0 g, 2.78 mmol) in dry pyridine (27 mL) at 0 °C was added DMAP (34 mg, 0.278 mmol) and Ac_2O (2.61 mL, 341 mmol). After stirring for 24 h at room temperature, the reaction mixture was quenched with H_2O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (100 mL). The combined organic layer was washed with sat. aq. CuSO_4 (3 x 60 mL), H_2O (60 mL) and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford pure **9I** (α only, 1.70 g, 2.51 mmol, 90%) as a white foamy solid without further purification.

$R_f = 0.43$ (hexane : $\text{AcOEt} = 1 : 1$)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

α δ 6.48 (d, $J = 3.8$ Hz, 1H, 1'-H), 5.61 (dd, $J = 10.5$ Hz, 9.0 Hz, 1H, 3'-H), 5.44 (d, $J = 4.0$ Hz, 1H, 1''-H), 5.39 (dd, $J = 10.4$ Hz, 9.6 Hz, 1H, 3''-H), 5.07 (t, $J = 9.6$ Hz, 1H, 4''-H), 5.02 (dd, $J = 10.5$ Hz, 3.8 Hz, 1H, 2'-H), 4.88 (dd, $J = 10.4$ Hz, 4.0 Hz, 1H, 2''-H), 4.50 (dd, $J = 12.4$ Hz, 2.5 Hz, 1H, 6'-H), 4.27-4.04 (m, 5H, 5'-H, 5''-H, 6'-H, 6''-H, 6''-H), 3.95 (dt, $J = 10.5$ Hz, 6.0 Hz, 1H, 4'-H), 2.13, 2.10, 2.10, 2.05, 2.02, 2.01, 2.01, 1.99 (8s, 24H, OCOCH_3)

α -D-Melibiose octaacetate (9m**)**⁴⁷



To a solution of commercial D-melibiose (**8m**) (1.0 g, 2.92 mmol) in dry pyridine (30 mL) at 0 °C was added DMAP (35.7 mg, 0.292 mmol) and Ac₂O (2.75 mL, 29.2 mmol). After stirring for 24 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (100 mL). The combined organic layer was washed with sat. aq. CuSO₄ (4 x 50 mL), H₂O (50 mL) and brine (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford pure **9m** (α only, 1.85 g, 2.73 mmol, 93%) as a white foamy solid without further purification.

$R_f = 0.43$ (hexane : AcOEt = 1 : 1)

$[\alpha]_D^{24} +141.0$ (*c* 1.105, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

α 体 δ : 6.46 (d, $J = 4.0$ Hz, 1H, 1'-H), 5.57 (t, $J = 9.8$ Hz, 1H, 3'-H), 5.45 (dd, $J = 3.5$ Hz, 1.0 Hz, 1H, 4''-H), 5.27 (dd, 10.0 Hz, 3.5 Hz, 3''-H), 5.15-5.05 (m, 4H, 2'-H, 4'-H, 1''-H, 2''-H), 4.33 (m, 1H, 5''-H), 4.15-4.06 (m, 2H, 6''-H x2), 4.19 (ddd, $J = 10.0$ Hz, 6.0 Hz, 2.0 Hz, 1H, 5'-H), 3.73 (dd, $J = 11.5$ Hz, 6.0 Hz 1H, 6'-H), 3.56 (dd, $J = 11.5$ Hz, 2.0 Hz 1H, 6'-H), 2.13, 2.09, 2.06, 2.06, 2.05, 2.04, 2.03, 1.98 (8s, 24H, OCOCH₃)

¹³C-NMR (100 MHz, CDCl₃)

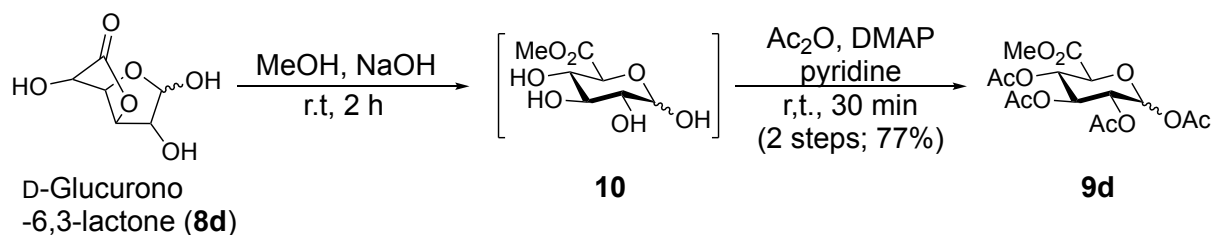
δ : 170.5 (-OCOCH₃), 170.3 (-OCOCH₃), 170.2 (-OCOCH₃), 170.1 (-OCOCH₃), 169.8 (-OCOCH₃), 169.6 (-OCOCH₃), 169.3 (-OCOCH₃), 168.8 (-OCOCH₃), 96.0 (C-1''), 88.9 (C-1'), 70.4 (C-5'), 69.8 (C-3'), 69.2 (C-2'), 68.4 (C-4'), 68.0 (C-4''), 68.0 (C-2''), 67.4 (C-3''), 66.3 (C-5''), 65.8 (C-6'), 61.6 (C-6''), 20.8 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.4 (-OCOCH₃)

IR (KBr) cm⁻¹ ν : 2969 (=C-H), 1753 (-C=O), 1041 (-C-O-)

HR-MS (ESI⁺)

m/z 701.1909[M+Na]⁺, Calc'd for C₂₈H₃₈O₁₉Na: 701.1905.

Methyl 1, 2, 3, 4-tetra-*O*-acetyl-D-glucopyranuronate (**9d**)¹³⁶



To a solution of D-glucurono-6,3-lactone (**8d**) (2 g, 11.3 mmol) in dry MeOH (20 mL) was added sodium hydroxide (10 mg, 0.25 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*.

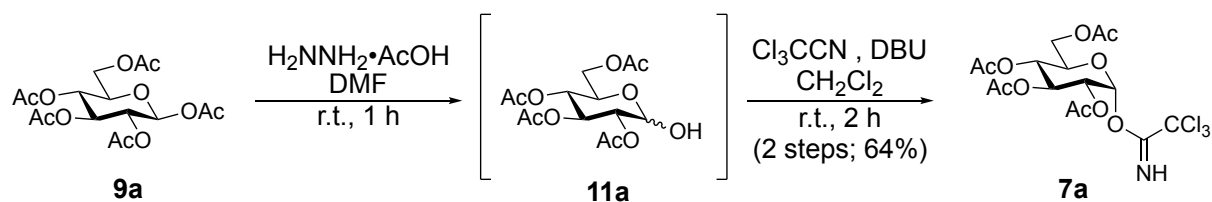
To a solution of **10** (2.36 g, 11.3 mmol) as the crude mixture of previous reaction in dry pyridine (22.6 mL) at 0 °C was added DMAP (138 mg, 1.13 mmol) and Ac₂O (8.55 mL, 90.4 mmol). After stirring at room temperature for 30 min, the reaction mixture was quenched with H₂O (20 mL) in ice bath. The resulting mixture was extracted with AcOEt (200 mL). The combined organic layer was washed with sat. aq. CuSO₄ (3 x 150 mL) and H₂O (3 x 150 mL) and brine (150 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 60 g, hexane : AcOEt = 3 : 1) to afford **9d** ($\alpha : \beta = 1 : 1$, 3.27 g, 8.69 mmol, 77%) as a pale yellow foamy solid by two steps.

R_f = 0.40 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 6.64 (d, $J = 3.6$ Hz, 1H, 1-H), 5.63 (t, $J = 10.0$ Hz, 1H, 3-H), 5.27 (dd, $J = 10.3$ Hz, 10.0 Hz, 1H, 4-H), 5.13 (dd, $J = 10.0$ Hz, 3.6 Hz, 1H, 2-H), 4.50 (d, $J = 10.3$ Hz, 1H, 5-H), 3.75 (s, 3H, -COOCH₃), 2.03 (s, 3H, -OCOCH₃), 2.03 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 1.99 (s, 3H, -OCOCH₃)

2, 3, 4, 6-Tetra-*O*-acetyl- α -D-glucopyranosyl trichloroacetimidate (7a**)**³⁸



To a solution of commercial penta-*O*-acetyl- β -D-glucopyranose (**9a**) (1.0 g, 2.56 mmol) in DMF (20 mL) at room temperature was added hydrazine acetate (330 mg, 3.59 mmol). After stirring at same temperature for 1 h, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 60 mL). The combined organic layer was washed with H₂O (5 x 60 mL) and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11a** as a mixture of colorless oil.

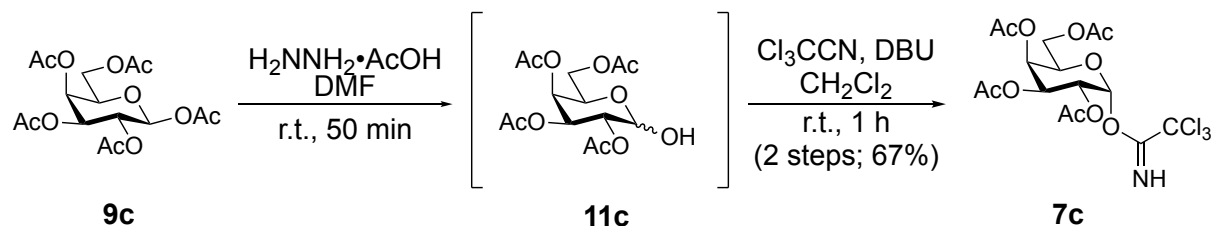
To a solution of **11a** as the crude mixture of previous reaction in CH₂Cl₂ (20 mL) was added Cl₃CCN (3.10 mL, 30.7 mmol) followed by DBU (38.1 μ L, 0.26 mmol). After stirring at room temperature for 2 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 100 g, hexane : AcOEt = 4 : 1) to afford **7a** (α only, 807 mg, 1.64 mmol, 64%) as a colorless oil by two steps.

R_f = 0.55 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.69 (s, 1H, -NH), 6.56 (d, J = 3.6 Hz, 1H, 1-H), 5.56 (t, J = 9.8 Hz, 1H, 3-H), 5.18 (t, J = 9.8 Hz, 1H, 4-H), 5.13 (dd, J = 9.8 Hz, 3.6 Hz, 1H, 2-H), 4.27 (dd, J = 12.3 Hz, 4.1 Hz, 1H, 6-H), 4.21 (ddd, J = 12.3 Hz, 4.1 Hz, 2.2 Hz, 1H, 5-H), 4.13 (dd, J = 12.3 Hz, 2.2 Hz, 1H, 6-H), 2.08 (s, 3H, -OCOCH₃), 2.05 (s, 3H, -OCOCH₃), 2.03 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃)

2, 3, 4, 6-Tetra-*O*-acetyl- α -D-galactopyranosyl trichloroacetimidate (7c**)**³⁹



To a solution of (**9c**) (2.0 g, 5.12 mmol) in DMF (51 mL) was added hydrazine acetate (661 mg, 7.17 mmol). After stirring for 50 min at room temperature, the reaction mixture was quenched with H₂O (60 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 160 mL). The combined organic layer was washed with H₂O (5 x 160 mL) and brine (160 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11c** as a mixture of white solid.

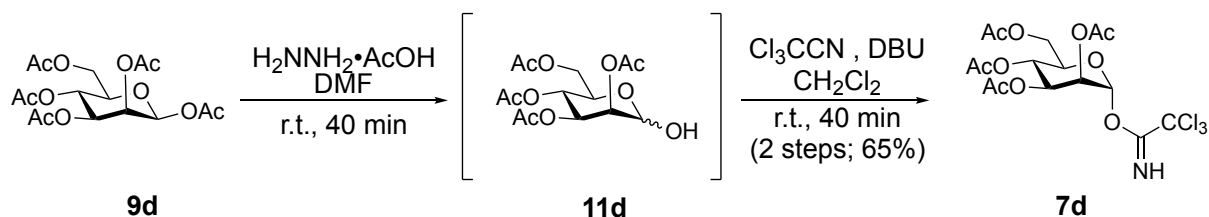
To a solution of **11c** as the crude mixture of previous reaction in CH₂Cl₂ (40 mL) was added Cl₃CCN (4.8 mL, 47.6 mmol) followed by DBU (117 μ L, 0.79 mmol). After stirring at room temperature for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 40 g, hexane : AcOEt = 4 : 1) to afford **7c** (α only, 1.68 g, 3.41 mmol, 67%) as a white solid by two steps.

R_f = 0.43 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.64 (s, 1H, -NH), 6.58 (d, *J* = 3.5 Hz, 1H, 1-H), 5.55 (dd, *J* = 3.1 Hz, 1.3 Hz, 1H, 4-H), 5.41 (dd, *J* = 10.7 Hz, 3.1 Hz, 1H, 3-H), 5.35 (dd, *J* = 10.7 Hz, 3.5 Hz, 1H, 2-H), 4.43 (ddd, *J* = 6.7 Hz, 6.7 Hz, 1.0 Hz, 1H, 5-H), 4.17 (dd, *J* = 11.3 Hz, 6.7 Hz, 1H, 6-H), 4.08 (dd, *J* = 11.3 Hz, 6.7 Hz, 1H, 6-H), 2.17 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃)

2, 3, 4, 6-Tetra-*O*-acetyl- α -D-mannnopyranosyl trichloroacetimidate (7d**)** ⁴⁰



To a solution of **9d** (1.0 g, 2.56 mmol) in DMF (25 mL) was added hydrazine acetate (330 mg, 3.59 mmol). After stirring for 40 min at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 80 mL). The combined organic layer was washed with H₂O (5 x 80 mL) and brine (80 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11d** as a mixture of colorless oil.

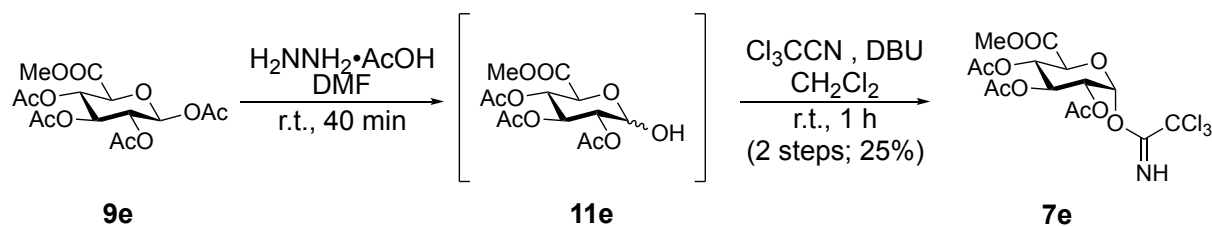
To a solution of **11d** as the crude mixture of previous reaction in CH₂Cl₂ (20 mL) was added Cl₃CCN (2.5 mL, 25.0 mmol) followed by DBU (62 μ L, 0.42 mmol). After stirring for 40 min at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 40 g, hexane : AcOEt = 4 : 1) to afford **7d** (α only, 816 mg, 1.66 mmol, 65%) as a colorless oil by two steps.

R_f = 0.35 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.79 (s, 1H, -NH), 6.28 (d, J = 1.9 Hz, 1H, 1-H), 5.47 (dd, J = 3.1 Hz, 1.9 Hz, 1H, 2-H), 5.41 (m, 1H, 3-H), 5.40 (m, 1H, 4-H), 4.28 (m, 1H, 6-H), 4.20 (m, 1H, 6-H), 4.18 (m, 1H, 5-H), 2.20 (s, 3H, -OCOCH₃), 2.08 (s, 3H, -OCOCH₃), 2.07 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃)

Methyl 2, 3, 4-tri-*O*-acetyl- α -D-glucopyranuronosyl trichloroacetimidate (7e**)**⁴¹



To a solution of **9e** (3.3 g, 8.68 mmol) in DMF (87 mL) was added hydrazine acetate (1.1 g, 12.2 mmol). After stirring for 40 min at room temperature, the reaction mixture was quenched with H₂O (100 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 100 mL). The combined organic layer was washed with H₂O (5 x 100 mL) and brine (100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and *in vacuo* to afford **11e** as a mixture of pale yellow foamy solid.

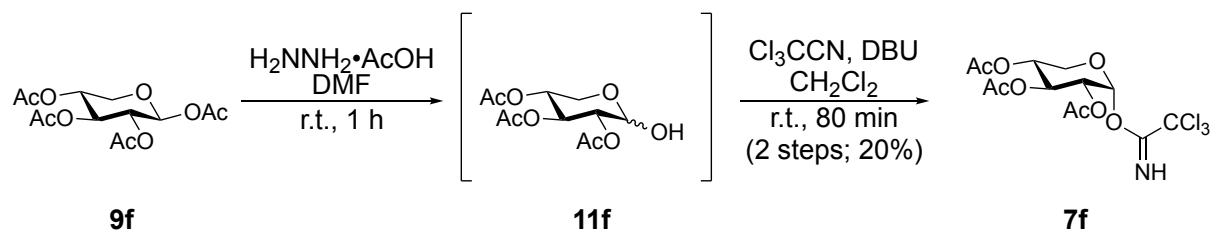
To a solution of **11e** as the crude mixture of previous reaction in CH₂Cl₂ (50.7 mL) was added Cl₃CCN (6.1 mL, 60.8 mmol) followed by DBU (151 μ L, 1.01 mmol). After stirring for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 40 g, hexane : AcOEt = 3 : 1) to afford **7e** (α only, 1.05 g, 21.9 mmol, 25%) as a pale yellow foamy solid by two steps.

R_f = 0.40 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.73 (s, 1H, -NH), 6.64 (d, J = 3.6 Hz, 1H, 1-H), 5.63 (t, J = 10.0 Hz, 1H, 3-H), 5.27 (dd, J = 10.3 Hz, 10.0 Hz, 1H, 4-H), 5.13 (dd, J = 10.0 Hz, 3.6 Hz, 1H, 2-H), 4.50 (d, J = 10.3 Hz, 1H, 5-H), 3.75 (s, 3H, -COOCH₃), 2.03 (s, 3H, -OCOCH₃), 2.03 (s, 3H, -OCOCH₃), 1.99 (s, 3H, -OCOCH₃)

2, 3, 4-Tri-*O*-acetyl- α -D-xylopyranosyl trichloroacetimidate (**7f**)⁴²



To a solution of **9f** (859 mg, 2.70 mmol) in dry DMF (20 mL) was added hydrazine acetate (348 mg, 3.78 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 60 mL). The combined organic layer was washed with H₂O (5 x 60 mL) and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11f** as a mixture oil.

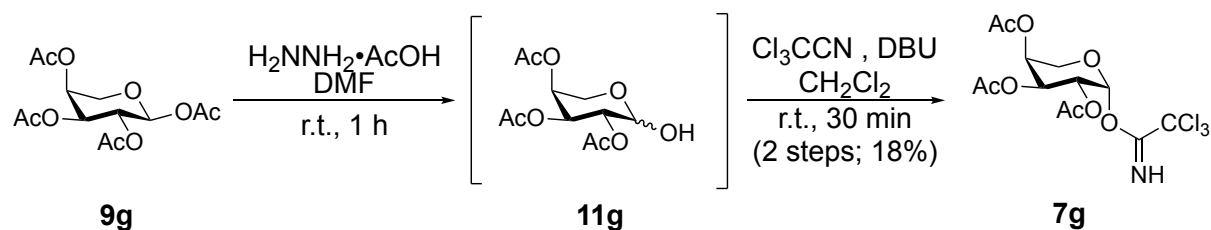
To a solution of **11f** as the crude mixture of previous reaction in dry CH₂Cl₂ (20 mL) was added Cl₃CCN (3.25 mL, 32.4 mmol) followed by DBU (40.0 μ L, 0.27 mmol). After stirring at room temperature for 80 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 35 g, hexane : AcOEt = 4 : 1) to afford **7f** (α only, 230 mg, 0.529 mmol, 20%) as a colorless oil by two steps.

R_f = 0.54 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.66 (s, 1H, -NH), 6.48 (d, J = 3.7 Hz, 1H, 1-H), 5.57 (t, J = 9.9 Hz, 1H, 3-H), 5.11-5.04 (m, 2H, 2-H, 4-H), 3.98 (dd, J = 11.0 Hz, 5.9 Hz, 1H, 5-H), 3.81 (t, J = 11.0 Hz, 1H, 5-H), 2.06 (s, 3H, -OCOCH₃), 2.05 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃)

2, 3, 4-Tri-*O*-acetyl- β -L-arabinopyranosyl trichloroacetimidate (**7g**)



To a solution of **9g** (4.0 g, 11.5 mmol) in dry DMF (30 mL) was added hydrazine acetate (1.48 mg, 16.1 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 60 mL). The combined organic layer was washed with H₂O (5 x 60 mL) and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11g** as a mixture solid.

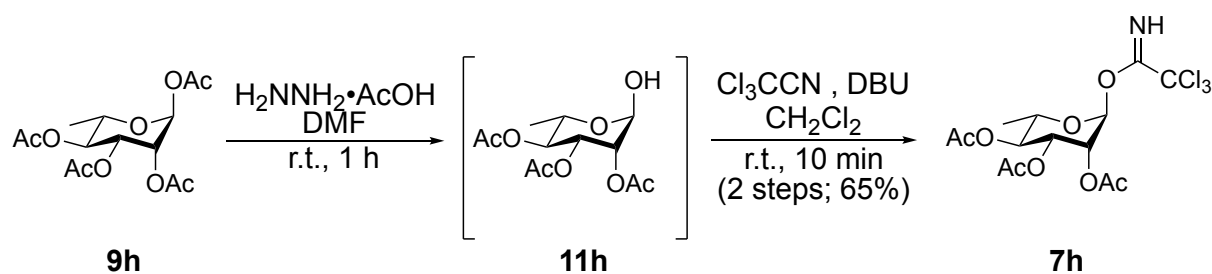
To a solution of **11g** as the crude mixture of previous reaction in dry CH₂Cl₂ (40 mL) was added Cl₃CCN (13.8 mL, 137.8 mmol) followed by DBU (342 μ L, 2.29 mmol). After stirring at room temperature for 30 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 250 g, hexane : AcOEt = 4 : 1 \rightarrow 3 : 1) to afford **7g** (β only, 887 mg, 2.11 mmol, 18% by two steps) as a white solid.

R_f = 0.42 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

β δ : 8.64 (s, 1H, -NH), 6.56 (d, J = 2.9 Hz, 1H, 1-H), 5.43 (m, 3H, 2-H, 3-H, 4-H), 4.16 (dd, J = 13.3 Hz, 0.8 Hz, 1H, 5-H), 3.88 (dd, J = 13.3 Hz, 2.0 Hz, 1H, 5-H), 2.17 (s, 3H, -OCOCH₃), 2.04 (s, 3H, -OCOCH₃), 2.03 (s, 3H, -OCOCH₃)

2, 3, 4-Tri-*O*-acetyl- α -L-rhamnopyranosyl trichloroacetimidate (7h**)**⁴³



To a solution of **9h** (1.77 g, 5.33 mmol) in dry DMF (50 mL) was added hydrazine acetate (687 mg, 7.46 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with H₂O (60 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 120 mL). The combined organic layer was washed with H₂O (5 x 120 mL) and brine (120 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11h** as a mixture oil.

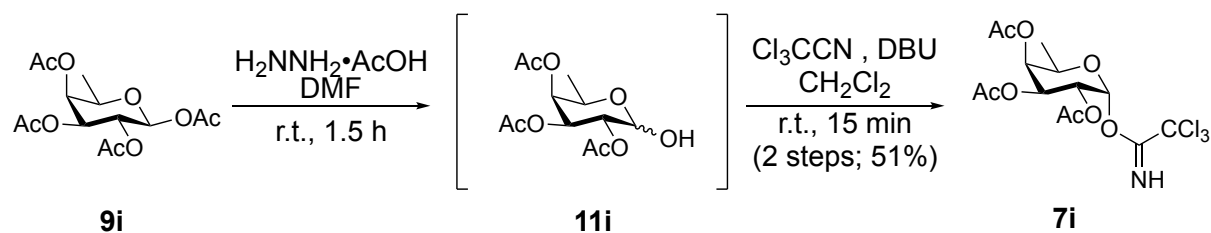
To a solution of **11h** as the crude mixture of previous reaction in dry CH₂Cl₂ (50 mL) was added Cl₃CCN (6.4 mL, 63.9 mmol) followed by DBU (158 μ L, 1.04 mmol). After stirring at room temperature for 10 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 100 g, hexane : AcOEt = 4 : 1 \rightarrow 7 : 3) to afford **7h** (α only, 1.50 g, 3.44 mmol, 65%) as a colorless oil by two steps.

R_f = 0.46 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.72 (s, 1H, -NH), 6.20 (d, J = 2.0 Hz, 1H, 1-H), 5.45 (dd, J = 3.4 Hz, 2.0 Hz, 1H, 2-H), 5.25 (dd, J = 10.0 Hz, 3.4 Hz, 1H, 3-H), 5.17 (t, J = 10.0 Hz, 1H, 4-H), 4.10 (m, 1H, 5-H), 2.18 (s, 3H, -OCOCH₃), 2.07 (s, 3H, -OCOCH₃), 2.00 (s, 3H, -OCOCH₃), 1.27 (d, J = 6.3 Hz, 3H, -CH₃)

2, 3, 4-Tri-*O*-acetyl- α -D-fucopyranosyl trichloroacetimidate (**7i**)⁴⁴



To a solution of **9i** (1.88 g, 5.66 mmol) in dry DMF (30 mL) was added hydrazine acetate (729 mg, 7.92 mmol). After stirring at room temperature for 1.5 h, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 60 mL). The combined organic layer was washed with H₂O (5 x 60 mL) and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11i** as a mixture.

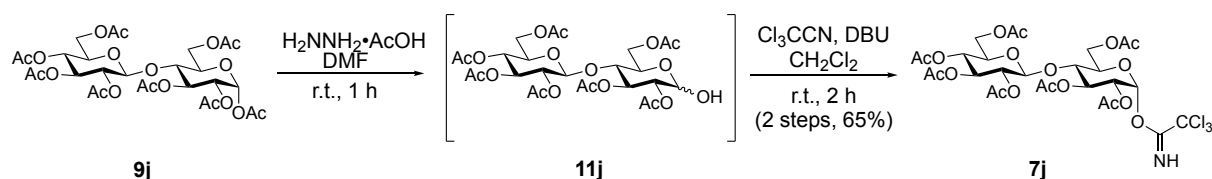
To a solution of **11i** as the crude mixture of previous reaction in dry CH₂Cl₂ (30 mL) was added Cl₃CCN (6.80 mL, 67.9 mmol) followed by DBU (167 μ L, 1.12 mmol). After stirring for 15 min at room temperature, the reaction mixture was concentrated under reduced pressure *in vacuo*. The residue was purified by flash column chromatography (silica gel 35 g, hexane : AcOEt = 4 : 1 \rightarrow 3 : 1) to afford **7i** (α only, 1.26 g, 2.90 mmol, 51% by two steps) as a colorless oil.

R_f = 0.45 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.61 (s, 1H, -NH), 6.55 (d, J = 3.6 Hz, 1H, 1-H), 5.42 (dd, J = 10.7 Hz, 3.2 Hz, 1H, 3-H), 5.40 (dd, J = 3.2 Hz, 1.2 Hz, 1H, 4-H), 5.36 (dd, J = 10.7 Hz, 3.6 Hz, 1H, 2-H), 4.37 (q, J = 6.6 Hz, 1H, 5-H), 2.18 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 1.18 (d, J = 6.6 Hz, 3H, 6-H)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-, 2,3,6-triacetate 1-(2,2,2-trichloroethanimidate) (7j**)**⁴⁵



To a solution of commercial α -D-cellobiose octaacetate (**9j**) (1.5 g, 2.21 mmol) in DMF (20 mL) was added hydrazine acetate (285 mg, 3.09 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 60 mL). The combined organic layer was washed with H₂O (5 x 60 mL) and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11j** as a mixture of white solid.

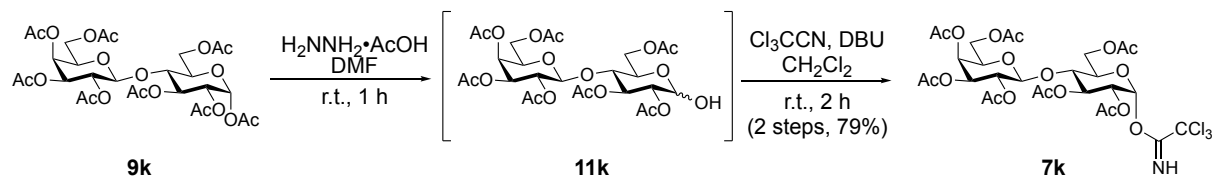
To a solution of **11j** as the crude mixture of previous reaction in CH₂Cl₂ (20 mL) was added Cl₃CCN (2.22 mL, 22.1 mmol) followed by DBU (65.5 μ L, 0.44 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 100 g, hexane : AcOEt = 3 : 1 \rightarrow 2 : 1 \rightarrow 1 : 1) to afford **7j** (1.13 g, 1.45 mmol, α only, 65%) as a white solid by two steps.

R_f = 0.28 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α 体 δ : 8.65 (s, 1H, -NH), 6.49 (d, J = 4.0 Hz, 1H, 1'-H), 5.53 (t, J = 9.8 Hz, 1H, 3'-H), 5.17 (t, J = 9.2 Hz, 1H, 3''-H), 5.09 (t, J = 9.2 Hz, 1H, 3''-H), 5.07 (dd, J = 9.8 Hz, 3.7 Hz, 1H, 2'-H), 4.93 (dd, J = 9.2 Hz, 8.0 Hz, 1H, 2''-H), 4.55 (d, J = 8.0 Hz, 1H, 1''-H), 4.51 (m, 1H, 6'-H), 4.39 (dd, J = 12.6 Hz, 4.2 Hz, 1H, 6''-H), 4.12 (dd, J = 12.8 Hz, 4.2 Hz, 1H, 6'-H), 4.20 (m, 1H, 5'-H), 4.05 (dd, J = 12.5 Hz, 2.5 Hz, 1H, 6''-H), 3.84 (t, J = 9.4 Hz, 1H, 4'-H), 3.67 (ddd, J = 9.5 Hz, 4.2 Hz, 2.2 Hz, 1H, 5'-H), 2.11, 2.09, 2.04, 2.03, 2.01, 2.00, 1.98 (7s, 21H, OCOCH₃)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-acetyl- β -D-galactopyranosyl)-, 2,3,6-triacetate 1-(2,2,2-trichloroethanimidate) (7k**)**⁴⁶



To a solution of **9k** (1.80 g, 2.65 mmol) in DMF (20 mL) was added hydrazine acetate (342 mg, 3.71 mmol). After stirring for 1 h at room temperature the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (200 mL). The combined organic layer was washed with H₂O (5 x 100 mL) and brine (100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11k** as a mixture of white foamy solid.

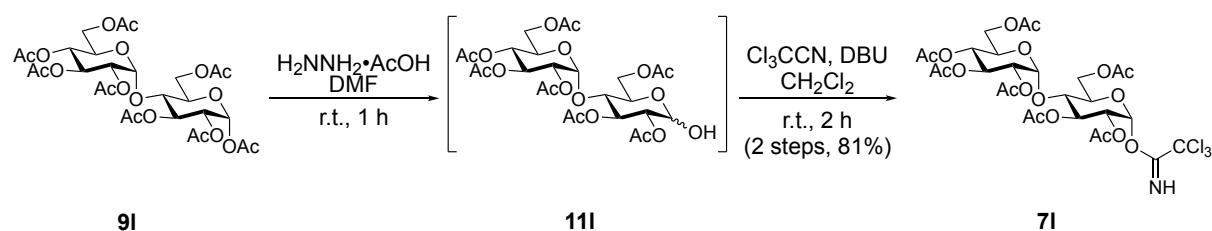
To a solution of **11k** as the crude mixture of previous reaction in CH₂Cl₂ (20 mL) was added Cl₃CCN (2.66 mL, 26.5 mmol) followed by DBU (78.9 μ L, 0.53 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 100 g, hexane : AcOEt = 3 : 1 \rightarrow 2 : 1 \rightarrow 1 : 1) to afford **7k** (1.65 g, 2.11 mmol, α only, 79%) as a white foamy solid by two steps.

R_f = 0.32 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ 8.65 (s, 1H, -NH), 6.49 (d, J = 3.8 Hz, 1H, 1'-H), 5.56 (t, J = 9.6 Hz, 1H, 3'-H), 5.35 (dd, J = 3.5 Hz, 1.0 Hz, 1H, 4''-H), 5.13 (dd, J = 10.3 Hz, 8.0 Hz, 1H, 2''-H), 5.06 (dd, J = 9.6 Hz, 3.8 Hz, 1H, 2'-H), 4.96 (dd, J = 10.3 Hz, 3.5 Hz, 1H, 3''-H), 4.52 (d, J = 8.0 Hz, 1H, 1''-H), 4.48 (dd, J = 12.4 Hz, 2.0 Hz, 1H, 6'-H), 4.18-4.06 (m, 4H, 5'-H, 6'-H, 6''-H, 6''-H), 3.90-3.85 (m, 2H, 4'-H, 5''-H), 2.16, 2.11, 2.07, 2.06, 2.04, 2.01, 1.97 (7s, 21H, OCOCH₃)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl)-, 2,3,6-triacetate 1-(2,2,2-trichloroethanimidate) (71**)**⁴⁷



To a solution of **91** (1.64 g, 2.42 mmol) in DMF (20 mL) was added hydrazine acetate (312 mg, 3.38 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (200 mL). The combined organic layer was washed with H₂O (5 x 100 mL) and brine (100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **111** as a mixture of white foamy solid.

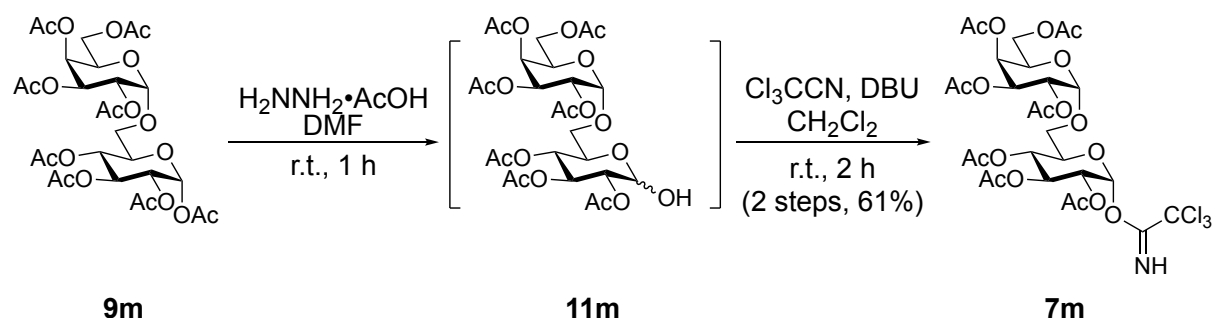
To a solution of **111** as the crude mixture of previous reaction in CH₂Cl₂ (20 mL) was added Cl₃CCN (2.43 mL, 24.2 mmol) followed by DBU (72.0 μ L, 0.48 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 100 g, hexane : AcOEt = 3 : 1 \rightarrow 2 : 1 \rightarrow 1 : 1) to afford **71** (1.53 g, 1.96 mmol, α only, 81%) as a white foamy solid by two steps.

R_f = 0.45 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ 8.67 (s, 1H, -NH), 6.48 (d, *J* = 3.8 Hz, 1H, 1'-H), 5.61 (dd, *J* = 10.5 Hz, 9.0 Hz, 1H, 3'-H), 5.44 (d, *J* = 4.0 Hz, 1H, 1''-H), 5.39 (dd, *J* = 10.4 Hz, 9.6 Hz, 1H, 3''-H), 5.07 (t, *J* = 9.6 Hz, 1H, 4''-H), 5.02 (dd, *J* = 10.5 Hz, 3.8 Hz, 1H, 2'-H), 4.88 (dd, *J* = 10.4 Hz, 4.0 Hz, 1H, 2''-H), 4.50 (dd, *J* = 12.4 Hz, 2.5 Hz, 1H, 6'-H), 4.27-4.04 (m, 5H, 5'-H, 5''-H, 6'-H, 6''-H, 6'''-H), 3.95 (dt, *J* = 10.5 Hz, 6.0 Hz, 1H, 4'-H), 2.13, 2.10, 2.07, 2.03, 2.02, 2.01, 1.99 (7s, 21H, OCOCH₃)

α -D-Glucopyranose, 6-O-(2,3,4,6-tetra-O-acetyl- α -D-galactopyranosyl)-, 2,3,6-triacetate 1-(2,2,2-trichloroethanimidate) (7m**)**



To a solution of **9m** (1.85 g, 2.73 mmol) in DMF (20 mL) was added hydrazine acetate (352 mg, 3.82 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (180 mL). The combined organic layer was washed with H₂O (5 x 60 mL) and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **11m** as a mixture of white foamy solid.

To a solution of **11m** as the crude mixture of previous reaction in CH₂Cl₂ (20 mL) was added Cl₃CCN (2.73 mL, 27.3 mmol) followed by DBU (40.6 μ L, 0.27 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 100 g, hexane : AcOEt = 4 : 1 \rightarrow 3 : 1 \rightarrow 2 : 1) to afford **7m** (1.39 g, 1.78 mmol, α only, 61%) as a white foamy solid by two steps.

R_f = 0.50 (hexane : AcOEt = 1 : 2)

[α]_D²⁶ +133.1 (*c* 1.00, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.67 (s, 1H, -NH), 6.46 (d, *J* = 4.0 Hz, 1H, 1'-H), 5.57 (t, *J* = 9.8 Hz, 1H, 3'-H), 5.45 (dd, *J* = 3.5 Hz, 1.0 Hz, 1H, 4''-H), 5.27 (dd, 10.0 Hz, 3.5 Hz, 3''-H), 5.15-5.05 (m, 4H, 2'-H, 4'-H, 1''-H, 2''-H), 4.33 (m, 1H, 5''-H), 4.15-4.06 (m, 2H, 6''-H x2), 4.19 (ddd, *J* = 10.0 Hz, 6.0 Hz, 2.0 Hz, 1H, 5'-H), 3.73 (dd, *J* = 11.5 Hz, 6.0 Hz 1H, 6'-H), 3.56 (dd, *J* = 11.5 Hz, 2.0 Hz 1H, 6'-H), 2.13, 2.09, 2.06, 2.05, 2.04, 2.03, 1.98 (7s, 21H, OCOCH₃)

¹³C-NMR (100 MHz, CDCl₃)

δ : 170.4 (-O $\overline{\text{C}}$ COCH₃), 170.3 (-O $\overline{\text{C}}$ COCH₃), 170.2 (-O $\overline{\text{C}}$ COCH₃), 169.9 (-O $\overline{\text{C}}$ COCH₃), 169.8 (-O $\overline{\text{C}}$ COCH₃), 169.8 (-O $\overline{\text{C}}$ COCH₃), 169.4 (-O $\overline{\text{C}}$ COCH₃), 160.5 ($\overline{\text{C}}$ N), 95.8 (C-1''), 92.6

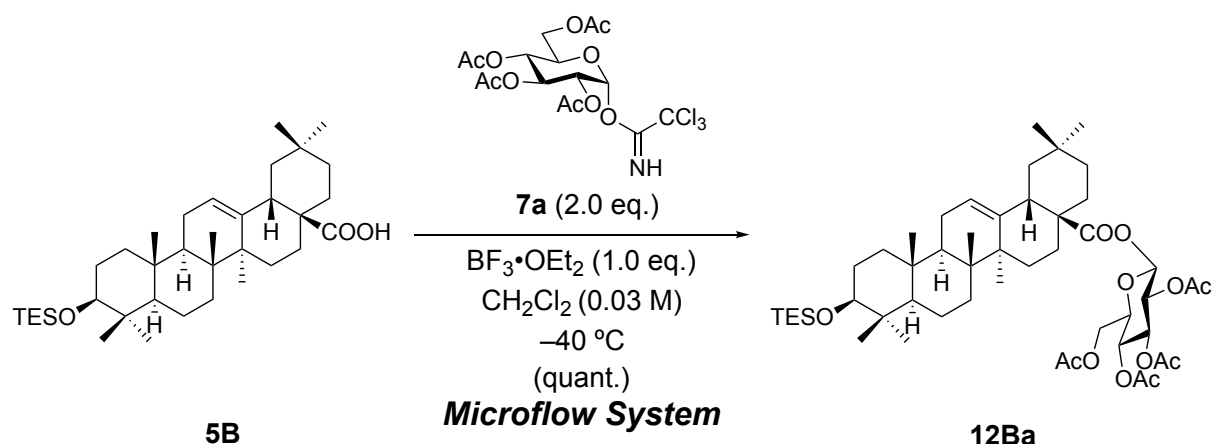
(C-1'), 90.6 (C-Cl₃), 70.6 (C-5'), 70.0 (C-3'), 69.8 (C-2'), 68.4 (C-4'), 68.2 (C-4''), 68.0 (C-2''), 67.5 (C-3''), 66.3 (C-5''), 65.4 (C-6'), 61.7 (C-6''), 20.8 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.4 (-OCOCH₃)

IR (KBr) cm⁻¹ ν : 2946 (=C-H), 1741 (-C=O)

HR-MS (ESI⁺)

m/z 802.0895[M+Na]⁺, Calc'd for C₂₈H₃₆Cl₃NO₁₈Na: 802.0896.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4, 6-Tetra-*O*-acetyl- β -D-glucopyranosyl ester (12Ba**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.0 μL , 0.096 mmol) dissolved in CH_2Cl_2 (7.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **7a** (94.2 mg, 0.191 mmol) and acceptor **5B** (54.6 mg, 0.096 mmol) dissolved in CH_2Cl_2 (7.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at -40°C . After the reaction mixture was allowed to flow at -40°C for an additional 100 sec through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was quenched with triethylamine (3.0 μL) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 20 g, hexane : $\text{AcOEt} = 6 : 1$) to afford **12Ba** (163.1 mg, 0.181 mmol, quant.) as a white foamy solid.

$R_f = 0.43$ (hexane : $\text{AcOEt} = 2 : 1$)

$[\alpha]_{\text{D}}^{26} +25.1$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.58 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.31 (dd, $J = 4.8$ Hz, 3.2 Hz, 1H, 12-H), 5.25 (dd, $J = 10.0$ Hz, 9.1 Hz, 1H, 4'-H), 5.18 (dd, $J = 9.1$ Hz, 8.0 Hz, 1H, 2'-H), 5.13 (t, $J = 9.1$ Hz, 1H, 3'-H), 4.27 (dd, $J = 12.5$ Hz, 4.3 Hz, 1H, 6'-H), 4.04 (dd, $J = 12.5$ Hz, 2.2 Hz, 1H, 6'-H), 3.79 (ddd, $J = 10.0$ Hz, 4.3 Hz, 2.2 Hz, 1H, 5'-H), 3.19 (m, 1H, 3-H), 2.78 (m, 1H, 18-H), 2.06 (s, 3H, $-\text{OCOCH}_3$), 2.02 (s, 3H, $-\text{OCOCH}_3$), 2.01 (s, 6H, $-\text{OCOCH}_3 \times 2$), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H,

21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H, -Si(CH₂CH₃)₃), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

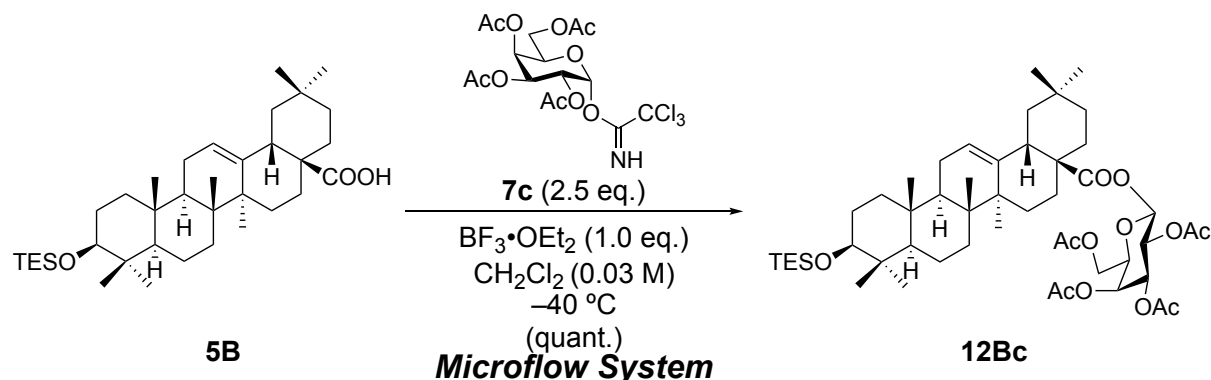
δ : 175.6 (C-28), 170.6 (-O $\overline{\text{C}}$ COCH₃), 170.2 (-O $\overline{\text{C}}$ COCH₃), 169.4 (-O $\overline{\text{C}}$ COCH₃), 169.0 (-O $\overline{\text{C}}$ COCH₃), 142.8 (C-13), 122.9 (C-12), 91.5 (C-1'), 79.4 (C-3), 72.8 (C-4'), 72.3 (C-5'), 69.8 (C-2'), 68.0 (C-3'), 61.5 (C-6'), 47.5 (C-5), 46.7 (C-9), 45.7 (C-17), 41.6 (C-19), 41.0 (C-14), 39.2 (C-18), 38.4 (C-8), 38.4 (C-4), 36.8 (C-1), 33.7 (C-10), 32.9 (C-21), 32.8 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 28.4 (C-23), 27.6 (C-15), 27.6 (C-2), 25.6 (C-27), 23.4 (C-30), 23.4 (C-16), 22.8 (C-11), 20.7 (-OCO $\overline{\text{C}}$ H₃), 20.7 (-OCO $\overline{\text{C}}$ H₃), 20.6 (-OCO $\overline{\text{C}}$ H₃), 20.6 (-OCO $\overline{\text{C}}$ H₃), 18.5 (C-6), 16.9 (C-26), 16.0 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.2 (-Si(CH₂CH₃)₃)

IR (NaCl) cm⁻¹ v : 2950 (=C-H), 1692 (-C=O), 1075 (-C-O-)

HR-MS (ESI⁺)

m/z 923.5326[M+Na]⁺, Calc'd for C₅₀H₈₀O₁₂SiNa: 923.5317.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4, 6-tetra-*O*-acetyl- β -D-galactopyranosyl ester (12Bc**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.0 μL , 0.096 mmol) dissolved in CH_2Cl_2 (7.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7c** (118 mg, 0.240 mmol) and acceptor **5B** (54.6 mg, 0.096 mmol) dissolved in CH_2Cl_2 (7.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at $-40\text{ }^\circ\text{C}$. After the reaction mixture was allowed to flow at $-40\text{ }^\circ\text{C}$ for an additional 100 sec through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the reaction mixture was quenched with triethylamine (3.0 μL) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 20 g, hexane : $\text{AcOEt} = 6 : 1$) to afford **12Bc** (163 mg, 0.181 mmol, quant.) as a white foamy solid.

$R_f = 0.40$ (hexane : $\text{AcOEt} = 2 : 1$)

$[\alpha]_{\text{D}}^{22} +44.1$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.55 (d, $J = 8.5\text{ Hz}$, 1H, 1'-H), 5.40 (dd, $J = 3.5\text{ Hz}$, 1.0 Hz, 1H, 4'-H), 5.35 (dd, $J = 10.4\text{ Hz}$, 8.4 Hz, 1H, 2'-H), 5.32 (dd, $J = 3.3\text{ Hz}$, 3.3 Hz, 1H, 12-H), 5.07 (dd, $J = 10.4\text{ Hz}$, 3.5 Hz, 1H, 3'-H), 4.10 (m, 2H, 6'-H), 4.00 (ddd, $J = 7.2\text{ Hz}$, 5.9 Hz, 1.2 Hz, 1H, 5'-H), 3.20 (dd, $J = 11.1\text{ Hz}$, 4.3 Hz, 1H, 3-H), 2.80 (dd, $J = 13.9\text{ Hz}$, 4.0 Hz, 1H, 18-H), 2.16 (s, 3H, $-\text{OCOCH}_3$), 2.03 (s, 3H, $-\text{OCOCH}_3$), 2.02 (s, 3H, $-\text{OCOCH}_3$), 1.99 (s, 3H, $-\text{OCOCH}_3$), 1.95 (m, 1H, 11-H), 1.86 (m, 2H, 16-H), 1.65 (m, 2H, 22-H), 1.61 (m, 1H, 19-H), 1.58 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.49 (m, 1H, 6-H), 1.49 (m, 2H, 9-H), 1.45 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.33 (m, 1H, 6-H), 1.30 (m, 1H, 21-H), 1.22 (m, 1H, 21-H), 1.18 (m, 1H, 7-H), 1.15 (m, 1H, 19-H), 1.12 (s, 3H, 27-H), 1.02

(m, 1H, 15-H), 0.95 (t, $J = 7.6$ Hz, 9H, -Si(CH₂CH₃)₃), 0.91 (m, 1H, 1-H), 0.90 (s, 12H, 23-H, 25-H, 29-H, 30-H), 0.74 (s, 3H, 24-H), 0.73 (s, 3H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

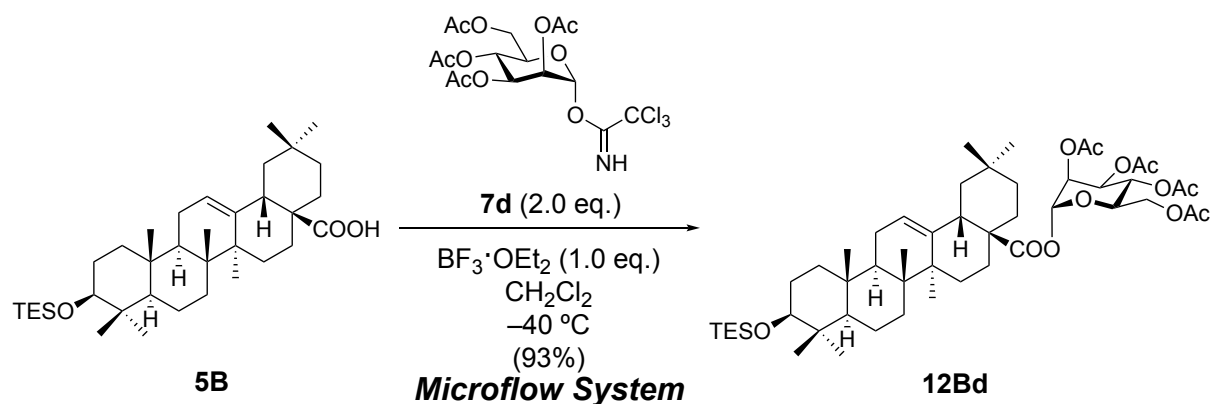
δ : 175.6 (C-28), 170.3 (-O \overline{C} COCH₃), 170.2 (-O \overline{C} COCH₃), 169.9 (-O \overline{C} COCH₃), 169.1 (-O \overline{C} COCH₃), 142.9 (C-13), 122.8 (C-12), 92.0 (C-1'), 79.4 (C-3), 71.4 (C-5'), 70.9 (C-3'), 67.5 (C-2'), 66.8 (C-4'), 60.8 (C-6'), 55.3 (C-5), 47.6 (C-9), 46.8 (C-17), 45.8 (C-19), 41.7 (C-14), 41.0 (C-18), 39.5 (C-1), 39.3 (C-8), 39.3 (C-4), 36.9 (C-10), 33.8 (C-21), 33.0 (C-7), 33.0 (C-29), 31.6 (C-22), 30.6 (C-20), 28.4 (C-23), 27.8 (C-15), 27.7 (C-2), 25.6 (C-27), 23.5 (C-11), 23.4 (C-16), 22.8 (C-30), 20.7 (-OCO \overline{C} H₃), 20.6 (-OCO \overline{C} H₃), 20.6 (-OCO \overline{C} H₃), 20.5 (-OCO \overline{C} H₃), 18.5 (C-6), 17.0 (C-26), 16.0 (C-24), 15.4 (C-25), 7.0 (-Si(CH₂ \overline{C} H₃)₃), 5.3 (-Si(\overline{C} H₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2957 (=C-H), 1752 (-C=O), 1067 (-C-O-)

HR-MS (ESI⁺)

m/z 923.5307[M+Na]⁺, Calc'd for C₅₀H₈₀O₁₂SiNa: 923.5317.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4, 6-tetra-*O*-acetyl- α -D-mannopyranosyl ester (12Bd**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (62 μL , 0.507 mmol) dissolved in CH_2Cl_2 (16.4 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7d** (500 mg, 1.01 mmol) and acceptor **5B** (290 mg, 0.507 mmol) dissolved in CH_2Cl_2 (16.4 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at $-40\text{ }^\circ\text{C}$. After the reaction mixture was allowed to flow at $-40\text{ }^\circ\text{C}$ for an additional 3 min through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the reaction mixture was quenched with triethylamine (0.26 mL, 0.1 M) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 40 g, hexane : AcOEt = 9 : 1) to afford **12Bd** (415 mg, 0.460 mmol, 93 %) as a white solid.

$R_f = 0.40$ (hexane : AcOEt = 2 : 1)

$[\alpha]_{\text{D}}^{22} +51.6$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 6.06 (d, 2.0 Hz, 1H, 1'-H), 5.36 (t, $J = 3.5\text{ Hz}$, 1H, 12-H), 5.32 (t, $J = 10.0\text{ Hz}$, 1H, 4'-H), 5.26 (dd, $J = 10.0\text{ Hz}$, 3.2 Hz, 1H, 3'-H), 5.17 (dd, $J = 3.2\text{ Hz}$, 2.0 Hz, 1H, 2'-H), 4.29 (dd, $J = 12.3\text{ Hz}$, 5.0 Hz, 1H, 6'-H), 4.07 (dd, $J = 12.3\text{ Hz}$, 2.3 Hz, 1H, 6'-H), 3.99 (ddd, $J = 10.0\text{ Hz}$, 5.0 Hz, 2.3 Hz, 1H, 5'-H), 3.18 (dd, $J = 11.0\text{ Hz}$, 4.5 Hz, 1H, 3-H), 2.83 (dd, $J = 13.8\text{ Hz}$, 4.0 Hz, 1H, 18-H), 2.14 (s, 3H, $-\text{OCOCH}_3$), 2.06 (s, 3H, $-\text{OCOCH}_3$), 2.05 (s, 3H, $-\text{OCOCH}_3$), 1.98 (s, 3H, $-\text{OCOCH}_3$), 1.93 (m, 2H, 11-H), 1.86 (m, 2H, 16-H), 1.62 (m, 1H, 19-H), 1.60 (m, 2H, 22-H), 1.57 (m, 1H, 15-H), 1.53 (m, 1H, 1-H), 1.51 (m, 1H, 9-H), 1.50 (m, 1H, 6-H), 1.47 (m, 2H, 2-H), 1.42 (m, 2H, 7-H), 1.31 (m, 1H, 21-H), 1.31 (m, 1H, 6-H), 1.20 (m, 1H, 21-H), 1.16 (m, 1H, 19-H), 1.12

(s, 3H, 27-H), 1.08 (m, 1H, 15-H), 0.97 (t, $J = 7.9$ Hz, 9H, -Si(CH₂CH₃)₃), 0.92 (s, 6H, 29-H, 30-H), 0.90 (s, 3H, 23-H), 0.90 (m, 1H, 1-H), 0.89 (s, 3H, 25-H), 0.73 (s, 3H, 24-H), 0.71 (s, 3H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

δ : 174.7 (C-28), 170.6 (-O $\overline{\text{C}}$ COCH₃), 169.8 (-O $\overline{\text{C}}$ COCH₃), 169.6 (-O $\overline{\text{C}}$ COCH₃), 169.6 (-O $\overline{\text{C}}$ COCH₃), 142.7 (C-13), 123.4 (C-12), 90.2 (C-1'), 79.5 (C-3), 71.0 (C-5'), 68.9 (C-3'), 68.3 (C-2'), 65.5 (C-4'), 62.2 (C-6'), 55.3 (C-5), 47.6 (C-9), 47.2 (C-17), 45.7 (C-19), 41.6 (C-14), 41.2 (C-18), 39.3 (C-8), 38.4 (C-1,C-4), 36.9 (C-10), 33.7 (C-21), 33.0 (C-7), 32.7 (C-29), 32.2 (C-22), 30.6 (C-20), 28.4 (C-23), 27.7 (C-15), 27.5 (C-2), 25.8 (C-27), 23.5 (C-30), 23.3 (C-16), 23.3 (C-11), 20.7 (-OCO $\overline{\text{C}}$ H₃), 20.7 (-OCO $\overline{\text{C}}$ H₃), 20.7 (-OCO $\overline{\text{C}}$ H₃), 20.6 (-OCO $\overline{\text{C}}$ H₃), 18.5 (C-6), 16.9 (C-26), 16.0 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂ $\overline{\text{C}}$ H₃)₃), 5.3 (-Si($\overline{\text{C}}$ H₂CH₃)₃)

IR (KBr) cm⁻¹ v : 2952 (=C-H), 1755 (-C=O), 1697 (-C=C-), 1057 (-C-O-)

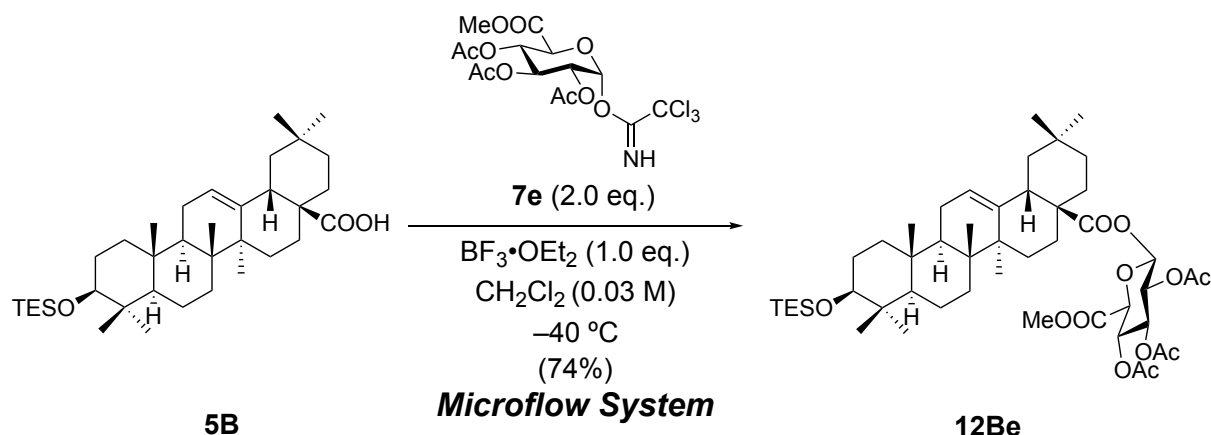
HR-MS (ESI⁺)

m/z 923.5303[M+Na]⁺, Calc'd for C₅₀H₈₀O₁₂SiNa: 923.5317.

GATE-1 (400 MHz, CDCl₃)

δ : 91.0 (s), 89.3 (s), (C-1'), ¹J_{C,H} = 177.6 Hz

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, methyl 2, 3, 4-tri-*O*-acetyl- β -D-glucopyranuronosyl ester (12Be**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (39 μL , 0.310 mmol) dissolved in CH_2Cl_2 (10.3 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7e** (297 mg, 0.619 mmol) and acceptor **5B** (177 mg, 0.310 mmol) dissolved in CH_2Cl_2 (10.3 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at $-40\text{ }^\circ\text{C}$. After the reaction mixture was allowed to flow at $-40\text{ }^\circ\text{C}$ for an additional 3 min through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the reaction mixture was quenched with triethylamine (0.17 mL, 0.1 M) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 40 g, hexane : AcOEt = 6 : 1) to afford **12Be** (204 mg, 0.230 mmol, 74%) as a white solid.

$R_f = 0.40$ (hexane : AcOEt = 2 : 1)

$[\alpha]_{\text{D}}^{24} +30.9$ (c 0.98, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.63 (d, $J = 8.1\text{ Hz}$, 1H, 1'-H), 5.31 (dt, $J = 3.7\text{ Hz}$, 1H, 12-H), 5.30 (t, $J = 9.5\text{ Hz}$, 1H, 3'-H), 5.23 (t, $J = 9.5\text{ Hz}$, 1H, 4'-H), 5.20 (dd, $J = 9.5\text{ Hz}$, 8.1 Hz, 1H, 2'-H), 4.12 (d, $J = 9.5\text{ Hz}$, 1H, 5'-H), 3.72 (s, 3H, $-\text{COOCH}_3$), 3.20 (dd, $J = 11.1\text{ Hz}$, 4.4 Hz, 1H, 3-H), 2.81 (dd, $J = 14.0\text{ Hz}$, 4.0 Hz, 1H, 18-H), 2.03 (s, 3H, $-\text{OCOCH}_3$), 2.02 (s, 3H, $-\text{OCOCH}_3$), 2.02 (s, 3H, $-\text{OCOCH}_3$), 1.96 (m, 2H, 11-H), 1.87 (m, 1H, 16-H), 1.64 (m, 2H, 22-H), 1.62 (m, 1H, 19-H), 1.60 (m, 1H, 15-H), 1.58 (m, 1H, 2-H), 1.56 (m, 1H, 1-H), 1.54 (m, 1H, 16-H), 1.52 (m, 1H, 6-H), 1.50 (m, 1H, 9-H), 1.49 (m, 1H, 2-H), 1.40 (m, 1H, 7-H), 1.35 (m, 1H, 6-H), 1.31 (m, 1H, 21-H), 1.21 (m, 1H, 21-H), 1.18 (m,

1H, 19-H), 1.12 (s, 3H, 27-H), 1.03 (m, 1H, 15-H), 0.95 (t, $J = 8.0$ Hz, 9H, -Si(CH₂CH₃)₃), 0.90 (s, 3H, 23-H), 0.90 (s, 3H, 25-H), 0.89 (m, 1H, 1-H), 0.89 (s, 3H, 29-H), 0.89 (s, 3H, 30-H), 0.74 (s, 3H, 24-H), 0.71 (s, 3H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

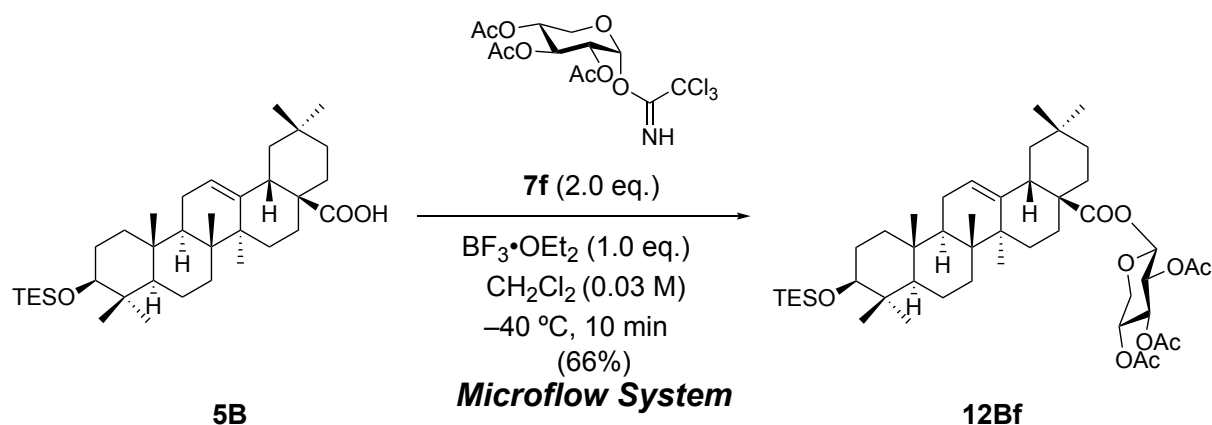
δ : 175.5 (C-28), 169.9 (-O \overline{C} COCH₃), 169.4 (-O \overline{C} COCH₃), 168.9 (-O \overline{C} COCH₃), 166.7 (C-6'), 142.7 (C-13), 123.0 (C-12), 91.2 (C-1'), 79.5 (C-3), 72.9 (C-5'), 72.0 (C-3'), 69.7 (C-2'), 69.3 (C-4'), 55.3 (C-5), 52.9 (-COO \overline{C} H₃), 47.6 (C-9), 46.8 (C-17), 45.7 (C-19), 41.7 (C-14), 41.0 (C-18), 39.3 (C-4), 39.3 (C-10), 38.5 (C-1), 36.9 (C-8), 33.7 (C-21), 33.7 (C-29), 33.0 (C-7), 31.6 (C-22), 30.6 (C-20), 28.4 (C-23), 27.7 (C-2), 27.7 (C-15), 25.7 (C-27), 23.4 (C-30), 23.4 (C-16), 22.8 (C-11), 20.6 (-OCO \overline{C} H₃), 20.6 (-OCO \overline{C} H₃), 20.4 (-OCO \overline{C} H₃), 18.5 (C-6), 16.9 (C-26), 16.4 (C-24), 15.4 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(\overline{C} H₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2952 (=C-H), 1759 (-C=O), 1698 (-C=C-), 1068 (-C-O-)

HR-MS (ESI⁺)

m/z 909.5147[M+Na]⁺, Calc'd for C₄₉H₇₈O₁₂SiNa: 909.5160.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4-tri-*O*-acetyl- β -D-xylopyranosyl ester (12Bf**)**



A solution of BF₃•OEt₂ (72.0 μ L, 0.571 mmol) dissolved in CH₂Cl₂ (18 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7f** (480 mg, 1.14 mmol) and acceptor **5B** (326 mg, 0.571 mmol) dissolved in CH₂Cl₂ (18 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at −40 °C. After the reaction mixture was allowed to flow at −40 °C for an additional 100 sec through a Teflon reactor tube (ϕ = 1.0 mm, l = 1.0 m), the reaction mixture was quenched with triethylamine (79.4 μ L) diluted in CH₂Cl₂ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 25 g, hexane : AcOEt = 6 : 1) to afford **12Bf** (312 mg, 0.094 mmol, 66%) as a white foamy solid.

R_f = 0.43 (hexane : AcOEt = 2 : 1)

$[\alpha]_D^{22}$ +28.2 (c 1.00, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 5.63 (d, J = 6.8 Hz, 1H, 1'-H), 5.31 (t, J = 3.5 Hz, 1H, 12-H), 5.20 (t, J = 8.1 Hz, 3'-H), 5.05 (dd, J = 8.1 Hz, 6.8 Hz, 1H, 2'-H), 5.13 (m, J = 9.1 Hz, 1H, 4'-H), 4.12 (m, 1H, 5'-H), 3.49 (dd, J = 13.6 Hz, 8.4 Hz, 1H, 5'-H), 3.20 (m, 1H, 3-H), 2.84 (m, 1H, 18-H), 2.06 (s, 3H, -OCOCH₃), 2.05 (s, 3H, -OCOCH₃), 2.04 (s, 3H, -OCOCH₃), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H, -Si(CH₂CH₃)₃), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H,

25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

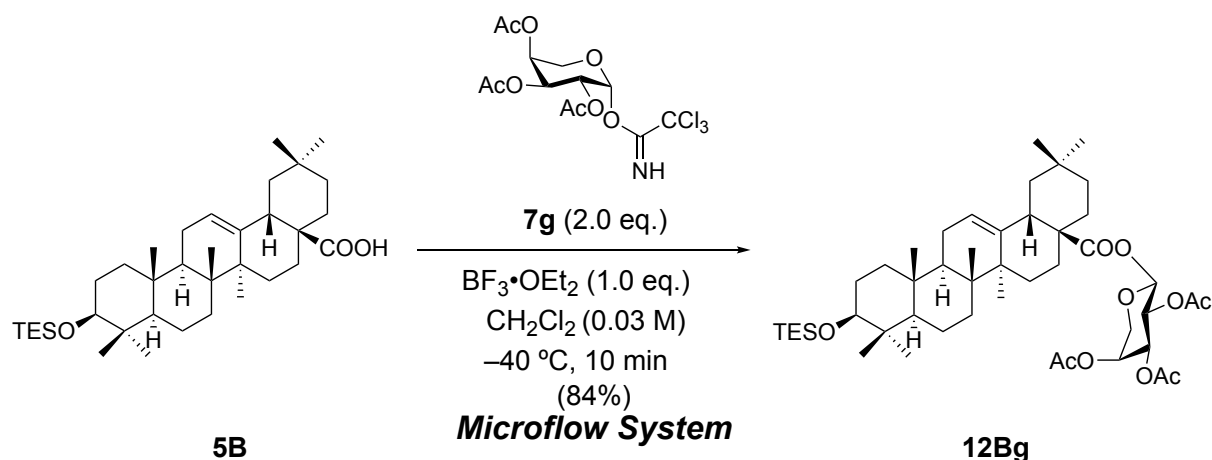
δ : 175.6 (C-28), 169.8 (-OCOCH₃ x 2), 169.0 (-OCOCH₃), 143.0 (C-13), 123.0 (C-12), 91.7 (C-1'), 79.5 (C-3), 71.0 (C-3'), 69.3 (C-2'), 68.3 (C-4'), 62.5 (C-5'), 55.2 (C-5), 47.6 (C-9), 46.8 (C-17), 45.7 (C-19), 41.7 (C-14), 39.2 (C-18), 38.7 (C-8), 38.4 (C-4), 37.0 (C-1), 33.7 (C-10), 32.9 (C-21), 32.9 (C-29), 32.8 (C-7), 31.9 (C-22), 30.6 (C-20), 28.0 (C-23), 27.7 (C-15), 27.1 (C-2), 25.6 (C-27), 23.5 (C-30), 23.4 (C-16), 22.8 (C-11), 20.7 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 18.3 (C-6), 16.9 (C-26), 15.5 (C-24), 15.3 (C-25) 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2933 (=C-H), 1760 (-C=O)

HR-MS (ESI⁺)

m/z 851.5074[M+Na]⁺, Calc'd for C₄₇H₇₆O₁₀SiNa: 851.5078.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4-tri-*O*-acetyl- α -L-arabinopyranosyl ester (12Bg**)**



A solution of BF₃•OEt₂ (65.9 μ L, 0.525 mmol) dissolved in dry CH₂Cl₂ (45 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **7g** (442 mg, 1.05 mmol) and acceptor **5B** (300 mg, 0.525 mmol) dissolved in dry CH₂Cl₂ (45 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at −40 °C. After the reaction mixture was allowed to flow at −40 °C for an additional 100 sec through a Teflon reactor tube (ϕ = 1.0 mm, l = 1.0 m), the mixture was quenched by addition of triethylamine (73.2 μ L, 0.525 mmol) diluted in CH₂Cl₂ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 23 g, hexane : AcOEt = 12 : 1 \rightarrow 10 : 1 \rightarrow 8 : 1) to afford **12Bg** (α only, 397 mg, 0.443 mmol, 84%) as a white solid.

R_f = 0.46 (hexane : AcOEt = 2 : 1)

[α]_D²⁵ +49.4 (*c* 1.01, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 5.57 (d, J = 6.8 Hz, 1H, 1'-H), 5.32 (t, J = 3.7 Hz, 1H, 12-H), 5.28 (dd, J = 9.0 Hz, 6.8 Hz, 1H, 2'-H), 5.24 (m, 1H, 4'-H), 5.13 (dd, J = 9.0 Hz, 3.6 Hz, 1H, 3'-H), 4.00 (dd, J = 13.0 Hz, 3.9 Hz, 1H, 5'-H), 3.72 (dd, J = 13.0 Hz, 2.1 Hz, 1H, 5'-H), 3.20 (dd, J = 11.3 Hz, 4.4 Hz, 1H, 3-H), 2.85 (dd, J = 14.1 Hz, 4.2 Hz, 1H, 18-H), 2.13 (s, 3H, -OCOCH₃), 2.06 (s, 3H, -OCOCH₃), 2.05 (s, 3H, -OCOCH₃), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H,

7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.13 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.96 (m, 9H, -Si(CH₂CH₃)₃), 0.91 (s, 9H, 23-H, 25-H, 30-H), 0.90 (s, 3H, 29-H), 0.89 (m, 1H, 1-H), 0.74 (s, 6H, 24-H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

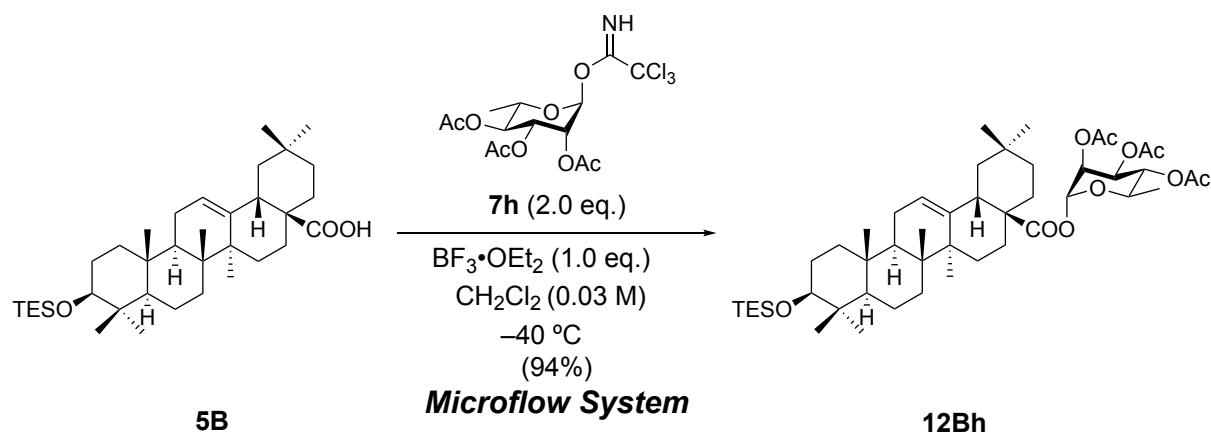
δ : 175.5 (C-28), 170.1 (-OCOCH₃), 169.8 (-OCOCH₃), 169.1 (-OCOCH₃), 142.9 (C-13), 122.9 (C-12), 91.7 (C-1'), 79.5 (C-3), 69.7 (C-3'), 68.0 (C-2'), 67.1 (C-4'), 63.4 (C-5'), 55.3 (C-5), 47.6 (C-9), 46.8 (C-17), 45.8 (C-19), 41.8 (C-14), 41.0 (C-18), 39.3 (C-8), 39.3 (C-4), 38.5 (C-1), 36.9 (C-10), 33.8 (C-21), 33.0 (C-29), 33.0 (C-7), 31.9 (C-22), 30.6 (C-20), 28.4 (C-23), 27.9 (C-15), 27.7 (C-2), 25.6 (C-27), 23.5 (C-30), 23.4 (C-16), 22.8 (C-11), 20.9 (-OCOCH₃), 20.8 (-OCOCH₃), 20.5 (-OCOCH₃), 18.5 (C-6), 16.9 (C-26), 16.1 (C-24), 15.4 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2832 (=C-H), 1715 (-C=O), 1056 (-C-O-)

HR-MS (ESI⁺)

m/z 851.5101[M+Na]⁺, Calc'd for C₄₇H₇₆O₁₀SiNa: 851.5105.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4-tri-*O*-acetyl- α -L-rhamnopyranosyl ester (12Bh**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.5 μL , 0.100 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7h** (87.1 mg, 0.200 mmol) and acceptor **5B** (57.2 mg, 0.100 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at -40°C . After the reaction mixture was allowed to flow at -40°C for an additional 100 sec through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was quenched with triethylamine (13.9 μL) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 30 g, hexane : AcOEt = 10 : 1 \rightarrow 8 : 1 \rightarrow 7 : 1 \rightarrow 5 : 1) to afford **12Bh** (79.3 mg, 0.094 mmol, 94%) as a white solid.

$R_f = 0.56$ (hexane : AcOEt = 2 : 1)

$[\alpha]_{\text{D}}^{22} +16.0$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 6.02 (d, $J = 2.0$ Hz, 1H, 1'-H), 5.32 (t, $J = 3.2$ Hz, 1H, 12-H), 5.27 (dd, $J = 10.0$ Hz, 3.3 Hz, 1H, 3'-H), 5.20 (dd, $J = 3.3$ Hz, 2.0 Hz, 1H, 2'-H), 5.13 (t, $J = 10.0$ Hz, 1H, 4'-H), 3.94 (m, 1H, 5'-H), 3.20 (m, 1H, 3-H), 2.90 (m, 1H, 18-H), 2.16 (s, 3H, -OCOCH₃), 2.08 (s, 3H, -OCOCH₃), 2.00 (s, 3H, -OCOCH₃), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.20 (d, $J = 6.2$ Hz, 3H, 6'-CH₃), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H,

15-H), 0.93 (m, 9H, -Si(CH₂CH₃)₃), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

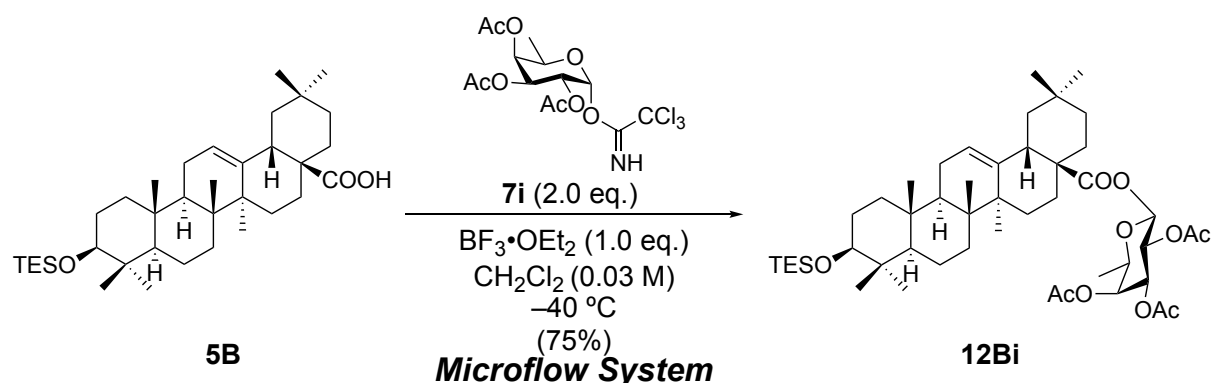
δ : 174.7 (C-28), 169.9 (-O₂CCH₃), 169.8 (-O₂CCH₃), 169.8 (-O₂CCH₃), 143.6 (C-13), 122.9 (C-12), 90.1 (C-1'), 78.9 (C-3), 70.3 (C-4'), 69.0 (C-3'), 68.9 (C-5'), 68.7 (C-2'), 55.2 (C-5), 47.5 (C-9), 47.3 (C-17), 45.6 (C-19), 41.8 (C-14), 41.7 (C-18), 39.4 (C-8), 38.7 (C-4), 38.4 (C-1), 37.0 (C-10), 33.7 (C-21), 33.0 (C-29), 32.7 (C-7), 32.5 (C-22), 30.7 (C-20), 28.1 (C-23), 27.5 (C-15), 27.1 (C-2), 25.8 (C-27), 23.5 (C-30), 23.4 (C-16), 22.9 (C-11), 20.8 (-OCOCH₃), 20.8 (-OCOCH₃), 20.6 (-OCOCH₃), 18.3 (C-6), 17.5 (6'-CH₃) 17.0 (C-26), 15.6 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2924 (=C-H), 1761 (-C=O)

HR-MS (ESI⁺)

m/z 865.5231[M+Na]⁺, Calc'd for C₄₈H₇₈O₁₀SiNa: 865.5237.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 2, 3, 4-Tri-*O*-acetyl- β -D-fucopyranosyl ester (12Bi**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.0 μL , 0.096 mmol) dissolved in CH_2Cl_2 (7.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7i** (83.0 mg, 0.191 mmol) and acceptor **5B** (54.6 mg, 0.100 mmol) dissolved in CH_2Cl_2 (7.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at -40°C . After the reaction mixture was allowed to flow at -40°C for an additional 100 sec through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was quenched with triethylamine (13.0 μL) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 50 g, hexane : $\text{AcOEt} = 12 : 1 \rightarrow 10 : 1 \rightarrow 9 : 1$) to afford **12Bi** (β only, 60.5 mg, 0.072 mmol, 75%) as a white solid.

$R_f = 0.47$ (hexane : $\text{AcOEt} = 2 : 1$)

$[\alpha]_{\text{D}}^{26} +45.2$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.51 (d, $J = 8.4$ Hz, 1H, 1'-H), 5.32 (dd, $J = 10.5$ Hz, 8.4 Hz, 1H, 2'-H), 5.32 (t, $J = 3.3$ Hz, 1H, 12-H), 5.24 (dd, $J = 3.5$ Hz, 0.8 Hz, 1H, 4'-H), 5.06 (dd, $J = 10.5$ Hz, 3.5 Hz, 1H, 3'-H), 3.90 (q, $J = 6.5$ Hz, 1H, 5'-H), 3.20 (dd, $J = 11.1$ Hz, 4.4 Hz, 1H, 3-H), 2.82 (dd, $J = 14.1$ Hz, 4.2 Hz, 1H, 18-H), 2.18 (s, 3H, $-\text{OCOCH}_3$), 2.02 (s, 3H, $-\text{OCOCH}_3$), 2.00 (s, 3H, $-\text{OCOCH}_3$), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (d, $J = 6.5$ Hz, 3H, 6'-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.13 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.96 (m, 9H,

-Si(CH₂CH₃)₃), 0.91 (s, 9H, 23-H, 25-H, 30-H), 0.90 (s, 3H, 29-H), 0.89 (m, 1H, 1-H)
0.75 (s, 6H, 24-H, 26-H), 0.68 (m, 1H, 5-H), 0.58 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

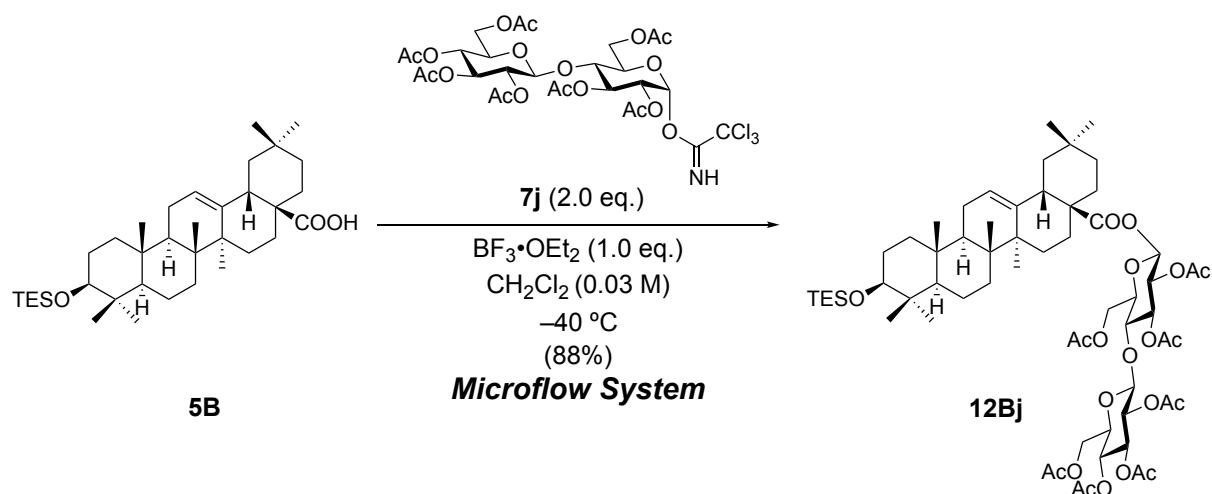
δ : 175.7 (C-28), 170.6 (-OCOCH₃), 170.0 (-OCOCH₃), 169.2 (-OCOCH₃), 142.9 (C-13), 122.8 (C-12), 92.1 (C-1'), 79.5 (C-3), 71.3 (C-3'), 70.1 (C-4'), 70.0 (C-5'), 67.6 (C-2'), 15.8 (C-6'), 47.5 (C-5), 46.7 (C-9), 45.7 (C-17), 41.6 (C-19), 41.0 (C-14), 39.2 (C-18), 38.4 (C-8), 38.4 (C-4), 36.8 (C-1), 33.7 (C-10), 32.9 (C-21), 32.8 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 28.4 (C-23), 27.6 (C-15), 27.6 (C-2), 25.6 (C-27), 23.4 (C-30), 23.4 (C-16), 22.8 (C-11), 20.8 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 18.5 (C-6), 16.9 (C-26), 16.0 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 3012 (=C-H), 1735 (-C=O), 1053 (-C-O-)

HR-MS (ESI⁺)

m/z 865.5246[M+Na]⁺, Calc'd for C₄₈H₇₈O₁₀SiNa: 865.5262.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, (2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)-, 2,3,6-tri-*O*-acetyl- β -D-glucopyranosyl ester (12Bj**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (34.3 μL , 0.273 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7j** (427 mg, 0.545 mmol) and acceptor **5B** (156 mg, 0.273 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at $-40\text{ }^\circ\text{C}$. After the reaction mixture was allowed to flow at $-40\text{ }^\circ\text{C}$ through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the reaction mixture was quenched with triethylamine (38.1 μL , 0.273 mmol) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 20 g, hexane : AcOEt = 7 : 3 \rightarrow 2 : 1) to afford **12Bj** (287 mg, 0.241 mmol, 88%) as a white foamy solid.

$R_f = 0.13$ (hexane : AcOEt = 2 : 1)

$[\alpha]_{\text{D}}^{25} +16.3$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.53 (d, $J = 8.0\text{ Hz}$, 1H, 1'-H), 5.28 (t, $J = 3.3\text{ Hz}$, 1H, 12-H), 5.22 (t, $J = 9.1\text{ Hz}$, 1H, 3''-H), 5.13 (t, $J = 9.5\text{ Hz}$, 1H, 3'-H), 5.10 (dd, $J = 9.5\text{ Hz}$, 8.0 Hz, 1H, 2'-H), 5.05 (t, $J = 9.5\text{ Hz}$, 1H, 4'-H), 4.91 (dd, $J = 9.5\text{ Hz}$, 8.0 Hz, 1H, 2'-H), 4.49 (d, $J = 8.0\text{ Hz}$, 1H, 1''-H), 4.41 (dd, $J = 12.0\text{ Hz}$, 2.0 Hz, 1H, 6''-H), 4.35 (dd, $J = 12.0\text{ Hz}$, 5.0 Hz, 1H, 6'-H), 4.12 (dd, $J = 12.0\text{ Hz}$, 5.0 Hz, 1H, 6'-H), 4.04 (dd, $J = 12.0\text{ Hz}$, 2.5 Hz, 1H, 6'-H), 3.83 (t, $J = 9.5\text{ Hz}$, 1H, 4''-H), 3.69 (ddd, $J = 10.0\text{ Hz}$, 5.0 Hz, 2.0 Hz, 1H, 5''-H), 3.64 (ddd, $J = 10.0\text{ Hz}$, 5.0 Hz, 2.5 Hz, 1H, 5'-H), 3.20 (dd, $J = 11.5\text{ Hz}$, 3.5 Hz,

1H, 3-H), 2.80 (dd, $J = 13.6$ Hz, 3.4 Hz, 1H, 18-H), 2.11 (s, 3H, -OCOCH₃), 2.09 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 1.98 (s, 3H, -OCOCH₃), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H, -Si(CH₂CH₃)₃), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

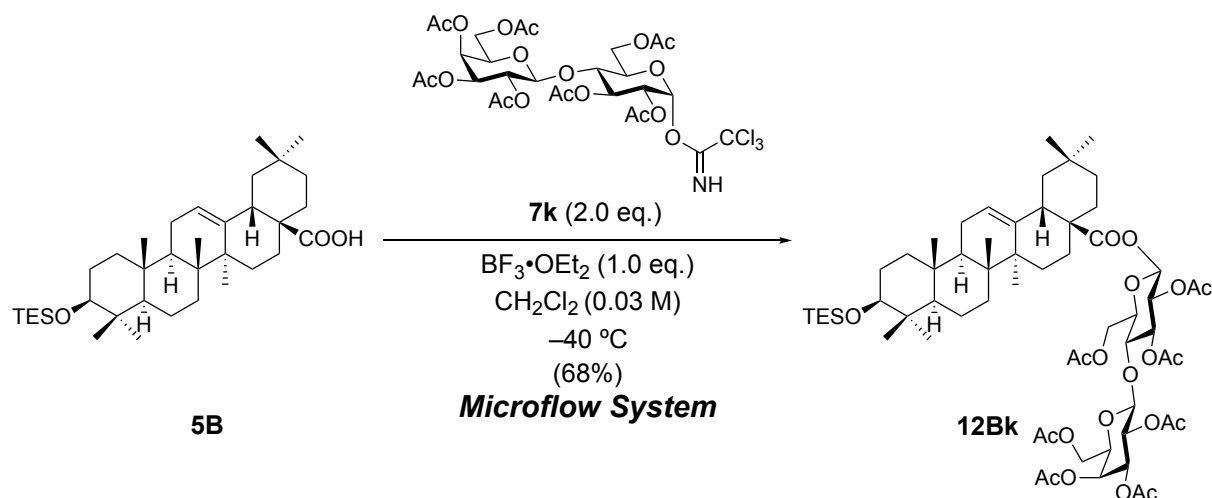
δ : 175.5 (C-28), 170.5 (-OCOCH₃), 170.2 (-OCOCH₃), 170.1 (-OCOCH₃), 169.6 (-OCOCH₃), 169.3 (-OCOCH₃), 169.2 (-OCOCH₃), 169.0 (-OCOCH₃), 142.9 (C-13), 122.9 (C-12), 100.7 (C-1''), 91.5 (C-1'), 79.5 (C-3), 76.0 (C-4''), 73.3 (C-5''), 72.9 (C-3'), 72. (C-3''), 71.5 (C-5'), 70.2 (C-2''), 67.8 (C-4'), 61.6 (C-6''), 61.6 (C-6'), 55.2 (C-5), 47.5 (C-9), 47.3 (C-17), 45.6 (C-19), 41.8 (C-14), 41.7 (C-18), 39.4 (C-8), 38.7 (C-4), 38.4 (C-1), 37.0 (C-10), 33.7 (C-21), 33.0 (C-29), 32.7 (C-7), 32.5 (C-22), 30.7 (C-20), 28.1 (C-23), 27.5 (C-15), 27.1 (C-2), 25.8 (C-27), 23.5 (C-30), 23.4 (C-16), 22.9 (C-11), 20.8 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.5 (-OCOCH₃), 20.5 (-OCOCH₃), 20.5 (-OCOCH₃), 20.5 (-OCOCH₃), 18.3 (C-6), 17.0 (C-26), 15.6 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2994 (=C-H), 1756 (-C=O), 1065 (-C-O-)

HR-MS (ESI⁺)

m/z 1211.6168[M+Na]⁺, Calc'd for C₆₂H₉₆O₂₀SiNa: 1211.6162.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, (2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)-, 2,3,6-tri-*O*-acetyl- β -D-glucopyranosyl ester (12Bk**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (33.0 μL , 0.263 mmol) dissolved in CH_2Cl_2 (22.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7k** (410 mg, 0.525 mmol) and acceptor **5B** (150 mg, 0.263 mmol) dissolved in CH_2Cl_2 (22.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at $-40\text{ }^\circ\text{C}$. After the reaction mixture was allowed to flow at $-40\text{ }^\circ\text{C}$ through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the reaction mixture was quenched with triethylamine (36.7 μL , 0.263 mmol) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 20 g, hexane : AcOEt = 3 : 1 \rightarrow 7 : 3) to afford **12Bk** (214 mg, 0.179 mmol, 68%) as a white foamy solid.

$R_f = 0.15$ (hexane : AcOEt = 2 : 1)

$[\alpha]_{\text{D}}^{26} +23.6$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.53 (d, $J = 8.0\text{ Hz}$, 1H, 1'-H), 5.33 (dd, $J = 3.5\text{ Hz}$, 1.0 Hz, 1H, 4''-H), 5.27 (t, $J = 3.5\text{ Hz}$, 1H, 12-H), 5.22 (t, $J = 9.6\text{ Hz}$, 1H, 3'-H), 5.11-5.06 (m, 2H, 2'-H, 2''-H), 4.92 (dd, $J = 10.6\text{ Hz}$, 3.4 Hz, 1H, 3''-H), 4.44 (d, $J = 8.0\text{ Hz}$, 1H, 1''-H), 4.36 (dd, $J = 12.0\text{ Hz}$, 2.0 Hz, 1H, 6''-H), 4.13-4.03 (m, 3H, 5'-H, 5''-H, 6'-H), 3.84 (dd, $J = 12.5\text{ Hz}$, 2.2 Hz, 1H, 6'-H), 3.83 (t, $J = 9.6\text{ Hz}$, 1H, 4'-H), 3.69 (ddd, $J = 10.0\text{ Hz}$, 5.0 Hz, 2.0 Hz, 1H, 5'-H), 3.18 (dd, $J = 11.2\text{ Hz}$, 3.9 Hz, 1H, 3-H), 2.78 (dd, $J = 14.0\text{ Hz}$, 4.5 Hz, 1H, 18-H), 2.13 (s, 3H, $-\text{OCOCH}_3$), 2.08 (s, 3H, $-\text{OCOCH}_3$), 2.05 (s, 3H, $-\text{OCOCH}_3$),

2.03 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 1.99 (s, 3H, -OCOCH₃), 1.97 (s, 3H, -OCOCH₃), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H, -Si(CH₂CH₃)₃), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

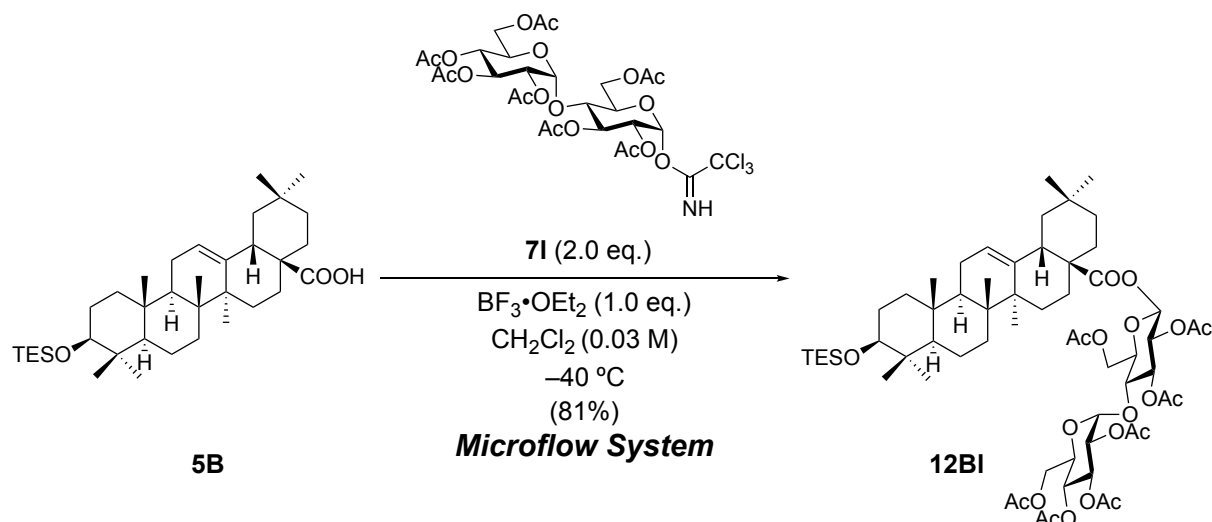
δ :175.5 (C-28), 170.3, 170.3, 170.1, 170.1, 170.0, 169.3, 169.0 (-OCOCH₃), 142.8 (C-13), 122.9 (C-12), 100.9 (C-1''), 91.4 (C-1'), 79.5 (C-3), 75.6 (C-4'), 73.2 (C-5'), 72.7 (C-3'), 70.9 (C-3''), 70.7 (C-5''), 70.2 (C-2'), 69.0 (C-2''), 66.6 (C-4''), 61.7 (C-6''), 60.8 (C-6'), 55.2 (C-5), 47.5 (C-9), 47.3 (C-17), 45.6 (C-19), 41.8 (C-14), 41.7 (C-18), 39.4 (C-8), 38.7 (C-4), 38.4 (C-1), 37.0 (C-10), 33.7 (C-21), 33.0 (C-29), 32.7 (C-7), 32.5 (C-22), 30.7 (C-20), 28.1 (C-23), 27.5 (C-15), 27.1 (C-2), 25.8 (C-27), 23.5 (C-30), 23.4 (C-16), 22.9 (C-11), 20.8 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 18.3 (C-6), 17.0 (C-26), 15.6 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2934 (=C-H), 1732 (-C=O), 1090 (-C-O-)

HR-MS (ESI⁺)

m/z 1211.6161[M+Na]⁺, Calc'd for C₆₂H₉₆O₂₀SiNa: 1211.6162.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, (2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl)-, 2,3,6-tri-*O*-acetyl- β -D-glucopyranosyl ester (12BI**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (33.0 μL , 0.263 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7I** (410 mg, 0.525 mmol) and acceptor **5B** (150 mg, 0.263 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at $-40\text{ }^\circ\text{C}$. After the reaction mixture was allowed to flow at $-40\text{ }^\circ\text{C}$ through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the reaction mixture was quenched with triethylamine (36.7 μL , 0.263 mmol) diluted in CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 20 g, hexane : $\text{AcOEt} = 3 : 1 \rightarrow 7 : 3$) to afford **12BI** (219 mg, 0.184 mmol, 81%) as a white foamy solid.

$R_f = 0.15$ (hexane : $\text{AcOEt} = 2 : 1$)

$[\alpha]_{\text{D}}^{25} +63.4$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.61 (d, $J = 8.0\text{ Hz}$, 1H, 1'-H), 5.40 (d, $J = 4.0\text{ Hz}$, 1H, 1''-H), 5.35 (t, $J = 10.0\text{ Hz}$, 1.0 Hz, 1H, 3''-H), 5.30 (t, $J = 3.5\text{ Hz}$, 1H, 12-H), 5.29 (t, $J = 10.0\text{ Hz}$, 1H, 3'-H), 5.07-5.01 (m, 2H, 2'-H, 4''-H), 4.85 (dd, $J = 10.0\text{ Hz}$, 4.0 Hz, 1H, 2''-H), 4.37 (dd, $J = 12.0\text{ Hz}$, 2.5 Hz, 1H, 6''-H), 4.26 (dd, $J = 12.0\text{ Hz}$, 4.0 Hz, 1H, 6'-H), 4.04 (dd, $J = 12.0\text{ Hz}$, 2.5 Hz, 1H, 6'-H), 4.03 (t, $J = 10.6\text{ Hz}$, 1H, 4''-H), 3.93 (ddd, $J = 10.0\text{ Hz}$, 4.3 Hz, 2.5 Hz, 1H, 5''-H), 3.78 (ddd, $J = 10.0\text{ Hz}$, 4.0 Hz, 2.5 Hz, 1H, 5'-H), 3.20 (dd, $J = 11.5\text{ Hz}$, 3.5 Hz, 1H, 3-H), 2.80 (dd, $J = 13.6\text{ Hz}$, 3.4 Hz, 1H, 18-H), 2.11 (s, 3H,

-OCOCH₃), 2.10 (s, 3H, -OCOCH₃), 2.06 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.00 (s, 3H, -OCOCH₃), 1.99 (s, 3H, -OCOCH₃), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H, -Si(CH₂CH₃)₃), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

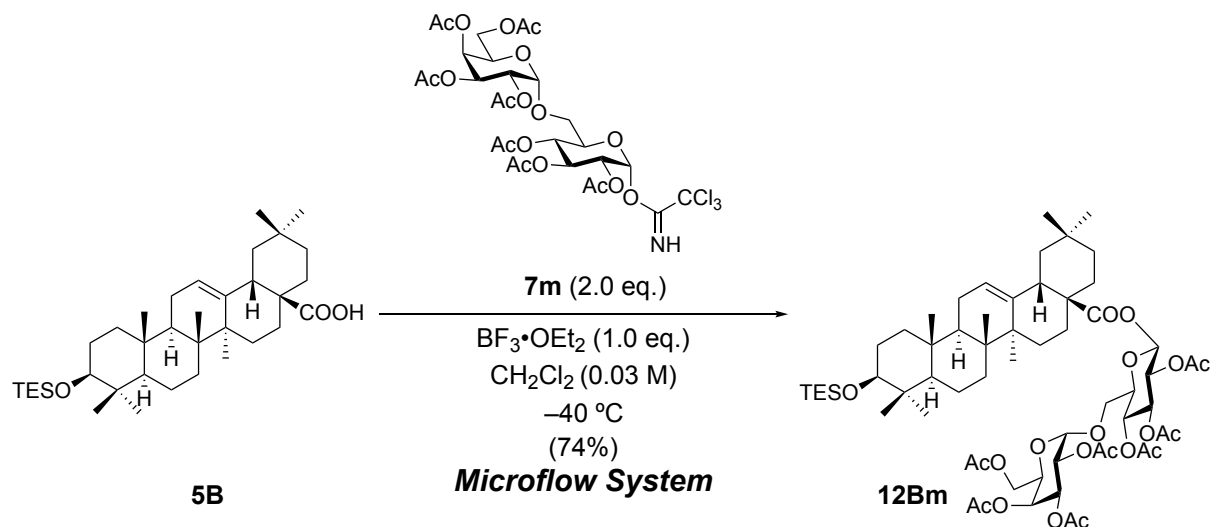
δ : 175.4 (C-28), 170.5 (-OCOCH₃), 170.5 (-OCOCH₃), 170.3 (-OCOCH₃), 170.0 (-OCOCH₃), 169.8 (-OCOCH₃), 169.4 (-OCOCH₃), 169.3 (-OCOCH₃), 142.8 (C-13), 122.9 (C-12), 95.6 (C-1''), 91.1 (C-1'), 79.5 (C-3), 75.5 (C-3'), 72.8 (C-5'), 72.6 (C-4''), 70.7 (C-2'), 70.0 (C-2''), 69.3 (C-3''), 68.5 (C-5''), 68.0 (C-4'), 62.6 (C-6''), 61.5 (C-6'), 55.2 (C-5), 47.5 (C-9), 47.3 (C-17), 45.6 (C-19), 41.8 (C-14), 41.7 (C-18), 39.4 (C-8), 38.7 (C-4), 38.4 (C-1), 37.0 (C-10), 33.7 (C-21), 33.0 (C-29), 32.7 (C-7), 32.5 (C-22), 30.7 (C-20), 28.1 (C-23), 27.5 (C-15), 27.1 (C-2), 25.8 (C-27), 23.5 (C-30), 23.4 (C-16), 22.9 (C-11), 20.8 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.5 (-OCOCH₃), 18.3 (C-6), 17.0 (C-26), 15.6 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.3 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2951 (=C-H), 1747 (-C=O), 1038 (-C-O-)

HR-MS (ESI⁺)

m/z 1211.6163[M+Na]⁺, Calc'd for C₆₂H₉₆O₂₀SiNa: 1211.6162.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, (2,3,4,6-tetra-*O*-acetyl- α -D-galactopyranosyl)-, 2,3,4-tri-*O*-acetyl- β -D-glucopyranosyl ester (12Bm**)**



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (36.3 μL , 0.289 mmol) dissolved in CH_2Cl_2 (22.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7m** (451 mg, 0.578 mmol) and acceptor **5B** (165 mg, 0.289 mmol) dissolved in CH_2Cl_2 (22.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at $-40\text{ }^\circ\text{C}$. After the reaction mixture was allowed to flow at $-40\text{ }^\circ\text{C}$ through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the reaction mixture was quenched with triethylamine (40.3 μL , 0.273 mmol) diluted in CH_2Cl_2 . The resulting mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, hexane : $\text{AcOEt} = 4 : 1 \rightarrow 3 : 1$) to afford **12Bm** (256 mg, 0.215 mmol, 74%) as a white foamy solid.

$R_f = 0.15$ (hexane : $\text{AcOEt} = 2 : 1$)

$[\alpha]_{\text{D}}^{23} +78.0$ (c 1.03, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.56 (d, $J = 8.0\text{ Hz}$, 1H, 1'-H), 5.43 (dd, $J = 3.5\text{ Hz}$, 1.0 Hz, 1H, 4''-H), 5.34-5.30 (m, 2H, 12-H, 3''-H), 5.27-5.19 (m, 2H, 4'-H, 2''-H), 5.12-5.07 (m, 3H, 2'-H, 3'-H, 1''-H), 4.16-4.00 (m, 2H, 5''-H, 6''-H), 3.74 (ddd, $J = 12.0\text{ Hz}$, 3.5 Hz, 2.5 Hz, 1H, 5'-H), 3.70 (dd, $J = 12.0\text{ Hz}$, 3.5 Hz 1H, 6'-H), 3.63 (dd, $J = 12.0\text{ Hz}$, 2.5 Hz 1H, 6'-H), 3.20 (dd, $J = 11.5\text{ Hz}$, 3.5 Hz, 1H, 3-H), 2.80 (dd, $J = 13.6\text{ Hz}$, 3.4 Hz, 1H, 18-H), 2.14 (s, 3H, $-\text{OCOCH}_3$), 2.12 (s, 3H, $-\text{OCOCH}_3$), 2.04 (s, 6H, $-\text{OCOCH}_3$), 2.04 (s, 6H,

-OCOCH₃), 2.01 (s, 6H, -OCOCH₃), 2.00 (s, 6H, -OCOCH₃), 1.97 (s, 6H, -OCOCH₃), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.93 (m, 9H, -Si(CH₂CH₃)₃), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H), 0.56 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, CDCl₃)

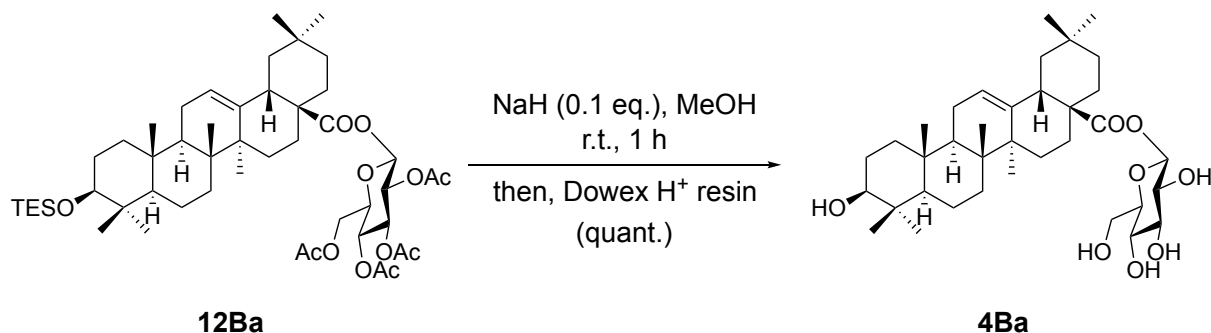
δ : 175.4 (C-28), 170.3 (-OCOCH₃), 170.3 (-OCOCH₃), 170.1 (-OCOCH₃), 170.1 (-OCOCH₃), 170.0 (-OCOCH₃), 169.2 (-OCOCH₃), 169.1 (-OCOCH₃), 142.7 (C-13), 130.0 (C-12), 96.4 (C-1''), 91.4 (C-1'), 79.4 (C-3), 73.4 (C-5'), 73.0 (C-2''), 69.8 (C-2'), 68.0 (C-4'), 67.8 (C-3'), 67.4 (C-3''), 66.4 (C-5''), 65.2 (C-6'), 61.7 (C-6''), 47.5 (C-5), 46.7 (C-9), 45.7 (C-17), 41.6 (C-19), 41.0 (C-14), 39.2 (C-18), 38.4 (C-8), 38.4 (C-4), 36.8 (C-1), 33.7 (C-10), 32.9 (C-21), 32.8 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 28.4 (C-23), 27.6 (C-15), 27.6 (C-2), 25.6 (C-27), 23.4 (C-30), 22.8 (C-11), 20.7 (-OCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 18.5 (C-6), 16.9 (C-26), 16.0 (C-24), 15.3 (C-25), 7.0 (-Si(CH₂CH₃)₃), 5.2 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 2956 (=C-H), 1751 (-C=O), 1074 (-C-O-)

HR-MS (ESI⁺)

m/z 1211.6149[M+Na]⁺, Calc'd for C₆₂H₉₆O₂₀SiNa: 1211.6162.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-glucopyranosyloxy ester (4Ba)



To a solution of **12Ba** (289 mg, 0.320 mmol) in MeOH (7.0 mL) was added NaH (1.28 mg, 0.032 mmol, 60% disp.). After stirring at room temperature for 1 h, the reaction mixture was acidified with Dowex H⁺ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* to afford the pure **4Ba** (208 mg, 0.337 mmol, quant.) as a white solid without further purification.

$R_f = 0.43$ (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{28} +33.7$ (c 1.00, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.36 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.47 (t, $J = 3.3$ Hz, 1H, 12-H), 4.48 (dd, $J = 12.0$ Hz, 2.4 Hz, 1H, 6'-H), 4.41 (dd, $J = 12.0$ Hz, 4.8 Hz, 1H, 6'-H), 4.37 (dd, $J = 9.0$ Hz, 8.2 Hz, 1H, 3'-H), 4.31 (t, 9.0 Hz, 1H, 4'-H), 4.23 (t, $J = 8.2$ Hz, 1H, 2'-H), 4.05 (ddd, $J = 12.0$ Hz, 4.8 Hz, 2.4 Hz, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.23 (dd, $J = 14.0$ Hz, 4.2 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.6 (C-28), 144.3 (C-13), 123.1 (C-12), 95.9 (C-1'), 79.5 (C-3), 79.1 (C-5'), 78.2 (C-3'), 74.3 (C-2'), 71.2 (C-4'), 62.4 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26),

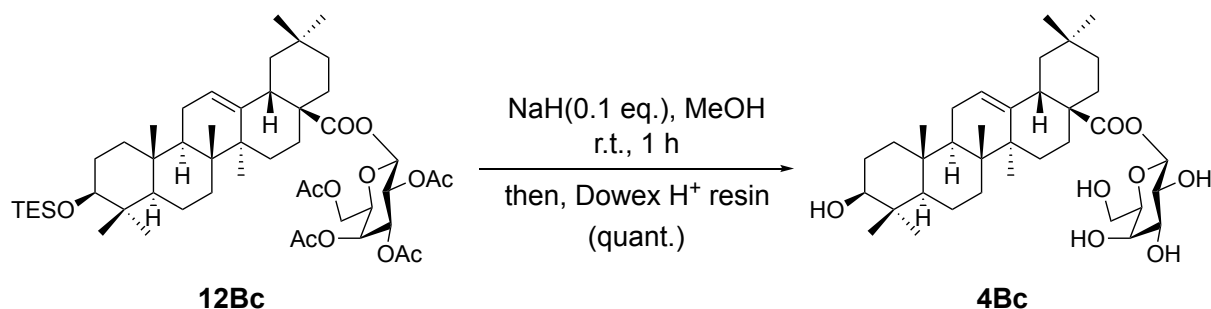
16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3420 (-O-H), 2945 (=C-H), 1753 (-C=O), 1029 (-C-O-)

HR-MS (ESI^+)

m/z 641.4002 $[\text{M}+\text{Na}]^+$, Calc'd for $\text{C}_{36}\text{H}_{58}\text{O}_8\text{Na}$: 641.4029.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-galactopyranosyl ester (4Bc)



To a solution of **12Bc** (200 mg, 0.221 mmol) in MeOH (4.4 mL) was added NaH (0.88 mg, 0.022 mmol, 60% disp.). After stirring at room temperature for 1 h, the reaction mixture was acidified with Dowex H⁺ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* to afford the pure saponin **4Bc** (144 mg, 0.233 mmol, quant.) as a white solid without further purification.

$R_f = 0.43$ (CHCl₃: MeOH = 5 : 1)

$[\alpha]_D^{22} +74.2$ (c 0.25, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.29 (d, $J = 8.2$ Hz, 1H, 1'-H), 5.46 (dd, $J = 3.4$ Hz, 3.4 Hz, 1H, 12-H), 4.68 (m, 1H, 3'-H), 4.65 (m, 1H, 2'-H), 4.51 (ddd, $J = 10.9$ Hz, 6.5 Hz, 6.5 Hz, 1H, 6'-H), 4.41 (ddd, $J = 10.8$ Hz, 5.4 Hz, 5.4 Hz, 1H, 6'-H), 4.25 (m, 1H, 4'-H), 4.21 (m, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.22 (dd, $J = 4.2$ Hz, 4.2 Hz, 1H, 18-H), 2.35 (m, 1H, 2-H), 2.06 (m, 2H, 11-H), 1.94 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.78 (m, 1H, 22-H), 1.77 (m, 1H, 19-H), 1.68 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.48 (m, 1H, 7-H), 1.40 (m, 1H, 6-H), 1.38 (m, 1H, 7-H), 1.35 (m, 1H, 21-H), 1.30 (m, 1H, 19-H), 1.24 (s, 6H, 23-H, 27-H), 1.16 (s, 3H, 26-H), 1.13 (m, 2H, 15-H), 1.09 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 0.99 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.91 (s, 3H, 29-H), 0.88 (s, 3H, 30-H), 0.85 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

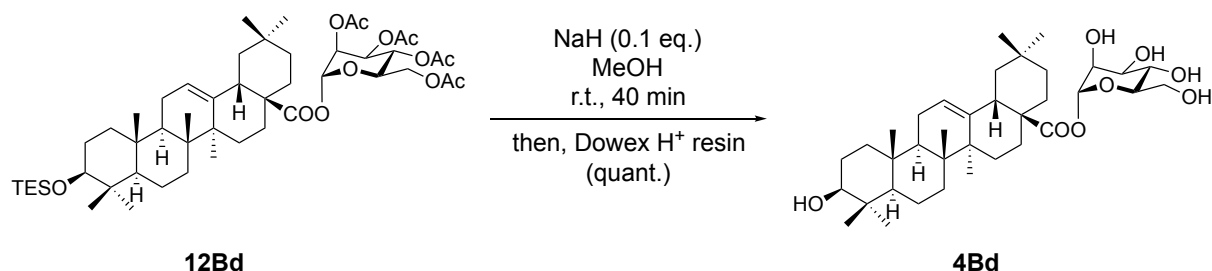
δ : 176.6 (C-28), 144.3 (C-13), 123.0 (C-12), 96.4 (C-1'), 78.2 (C-3), 77.9 (C-5'), 75.9 (C-4'), 71.6 (C-3'), 70.2 (C-2'), 62.0 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.1 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.2 (C-27), 24.0 (C-30), 23.8 (C-16), 23.5 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3435 (-O-H), 2949 (=C-H), 1736 (-C=O), 1719 (-C=C-), 1070 (-C-O-)

HR-MS (ESI^+)

m/z 641.4016 $[\text{M}+\text{Na}]^+$, Calc'd for $\text{C}_{36}\text{H}_{58}\text{O}_8\text{Na}$: 641.4029.

Olean-12-en-28-oic acid, 3-hydroxy-, α -D-mannopyranosyl ester (4Bd)



To a solution of **12Bd** (200 mg, 0.222 mmol) in dry MeOH (4.4 mL) was added sodium hydride (0.88 mg, 0.022 mmol). After stirring for 40 min at room temperature, the reaction mixture was acidified with Dowex H⁺ resin to pH 4, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* to afford the pure saponin **4Bd** (151 mg, 0.243 mmol, quant.) as a white solid without further purification.

$R_f = 0.53$ (CDCl₃: MeOH = 5 : 1)

$[\alpha]_D^{22} +67.9$ (c 0.24, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.89 (d, $J = 1.6$ Hz, 1H, 1'-H), 5.40 (t, $J = 3.5$ Hz, 1H, 12-H), 4.86 (dt, 9.5 Hz, 5.0 Hz, 1H, 4'-H), 4.68 (ddd, $J = 10.0$ Hz, 9.5 Hz, 6.5 Hz, 1H, 3'-H), 4.65 (ddd, $J = 11.5$ Hz, 6.0 Hz, 2.0 Hz, 1H, 6'-H), 4.63 (ddd, $J = 10.0$ Hz, 4.5 Hz, 1.6 Hz, 2'-H), 4.56 (ddd, $J = 11.5$ Hz, 6.5 Hz, 5.0 Hz, 1H, 6'-H), 4.51 (ddd, $J = 9.5$ Hz, 5.0 Hz, 2.0 Hz, 1H, 5'-H), 3.44 (ddd, $J = 10.9$ Hz, 5.4 Hz, 5.4 Hz, 1H, 3-H), 3.17 (dd, $J = 13.8$ Hz, 4.0 Hz, 1H, 18-H), 2.05 (m, 1H, 11-H), 2.02 (m, 2H, 2-H), 1.88 (m, 1H, 22-H), 1.85 (m, 2H, 16-H), 1.83 (m, 1H, 15-H), 1.78 (m, 1H, 11-H), 1.75 (m, 1H, 19-H), 1.64 (m, 1H, 9-H), 1.58 (m, 1H, 22-H), 1.53 (m, 1H, 1-H), 1.53 (m, 1H, 6-H), 1.47 (m, 1H, 7-H), 1.39 (m, 1H, 21-H), 1.34 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.24 (s, 3H, 23-H), 1.23 (m, 1H, 19-H), 1.21 (s, 3H, 27-H), 1.14 (m, 1H, 21-H), 1.11 (m, 1H, 15-H), 1.04 (s, 3H, 24-H), 1.00 (m, 1H, 1-H), 0.95 (s, 3H, 30-H), 0.93 (s, 3H, 26-H), 0.91 (s, 3H, 29-H), 0.86 (s, 3H, 25-H), 0.83 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.1 (C-28), 144.2 (C-13), 123.2 (C-12), 95.5 (C-1'), 78.5 (C-5'), 78.2 (C-3), 73.2 (C-3'), 71.4 (C-2'), 68.5 (C-4'), 62.8 (C-6'), 55.9 (C-5), 48.2 (C-9), 47.5 (C-17), 46.2 (C-19), 42.2 (C-14), 42.0 (C-18), 39.9 (C-8), 39.5 (C-4), 39.1 (C-1), 37.4 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.9 (C-22), 31.0 (C-20), 28.9 (C-23), 28.2 (C-15),

28.1 (C-2), 26.1 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.9 (C-6), 17.6 (C-26),
16.7 (C-24), 15.8 (C-25),

IR (KBr) cm^{-1} ν : 3382 (-O-H), 2933 (=C-H), 1697 (-C=O)

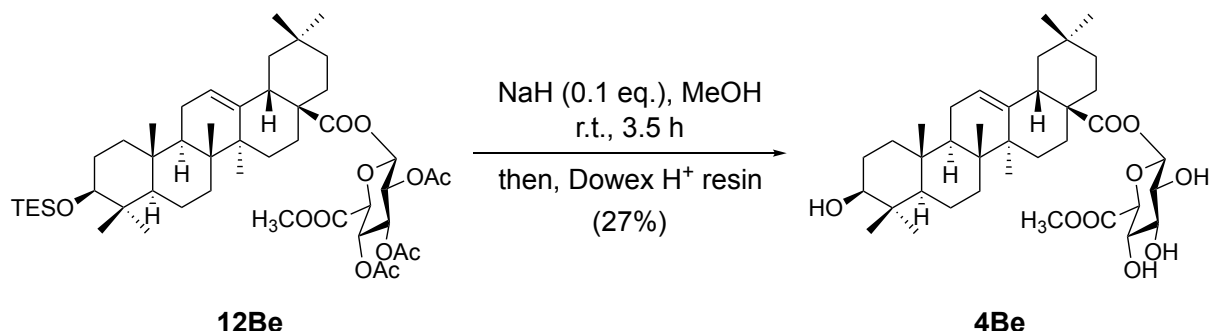
HR-MS (ESI⁺)

m/z 641.4014[M+Na]⁺, Calc'd for C₃₆H₅₈O₈Na: 641.4029

GATE-1 (400 MHz, pyridine-*d*₅)

δ : 96.3 (s), 94.6 (s), (C-1'), $^1J_{\text{C,H}} = 173.4$ Hz.

Olean-12-en-28-oic acid, 3-hydroxy-, methyl- β -D-glucopyranuronosyl ester (4Be)



To a solution of **12Be** (143 mg, 0.162 mmol) in dry MeOH (3.23 mL) was added NaH (0.53 mg, 0.016 mmol). After stirring for 3.5 h at room temperature, the reaction mixture was acidified with Dowex H⁺ resin to pH 4, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl₃ : MeOH = 20 : 1) to afford **4Be** (28.2 mg, 0.0436 mmol, 27%) as a white solid.

R_f = 0.53 (CDCl₃: MeOH = 5 : 1)

[α]_D²³ +61.1 (*c* 0.19, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.37 (d, *J* = 7.9 Hz, 1H, 1'-H), 5.45 (t, *J* = 3.5 Hz, 1H, 12-H), 4.70 (d, *J* = 9.6 Hz, 1H, 5'-H), 4.52 (dt, *J* = 9.6 Hz, 5.5 Hz, 1H, 4'-H), 4.34 (m, 1H, 3'-H), 4.28 (m, 1H, 2'-H), 3.64 (s, 3H, -COOCH₃), 3.45 (ddd, *J* = 10.0 Hz, 5.0 Hz, 5.0 Hz, 1H, 3-H), 3.21 (dd, *J* = 13.8 Hz, 4.2 Hz, 1H, 18-H), 2.32 (m, 1H, 2-H), 2.08 (m, 1H, 11-H), 1.95 (m, 1H, 11-H), 1.95 (m, 2H, 16-H), 1.89 (m, 1H, 22-H), 1.85 (m, 1H, 2-H), 1.84 (m, 1H, 15-H), 1.76 (m, 1H, 19-H), 1.76 (m, 1H, 22-H), 1.67 (dd, *J* = 10.5 Hz, 7.2 Hz, 1H, 9-H), 1.57 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.51 (m, 1H, 7-H), 1.39 (m, 1H, 6-H), 1.37 (m, 1H, 7-H), 1.34 (m, 1H, 21-H), 1.26 (m, 1H, 19-H), 1.24 (s, 3H, 23-H), 1.24 (s, 3H, 27-H), 1.17 (m, 1H, 15-H), 1.12 (s, 3H, 26-H), 1.08 (m, 1H, 21-H), 1.05 (s, 3H, 24-H), 1.00 (m, 1H, 1-H), 0.97 (s, 3H, 25-H), 0.89 (s, 3H, 29-H), 0.88 (s, 3H, 30-H), 0.85 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.6 (C-28), 170.3 (C-6'), 144.1 (C-13), 123.2 (C-12), 95.7 (C-1'), 78.2 (C-3), 78.2 (C-3'), 77.9 (C-5'), 73.8 (C-2'), 73.2 (C-4'), 55.9 (C-5), 52.2 (-COOCH₃), 48.3 (C-9), 47.2 (C-17), 46.3 (C-19), 42.2 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1

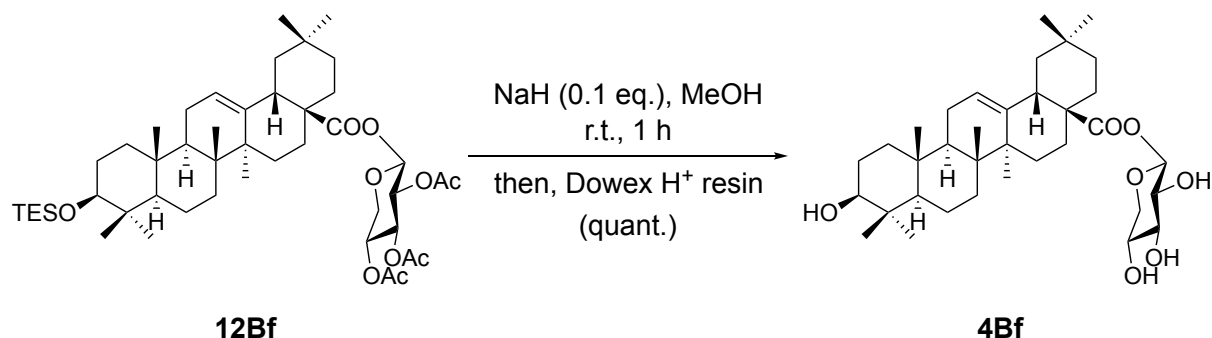
(C-1), 37.5 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.3 (C-2), 28.3 (C-15), 26.2 (C-27), 24.0 (C-30), 23.7 (C-16), 23.5 (C-11), 19.0 (C-6), 17.6 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3455 (-O-H), 2942 (=C-H), 1752 (-C=O), 1719 (-C=C-), 1090 (-C-O-)

HR-MS (ESI⁺)

m/z 669.3963[M+Na]⁺, Calc'd for C₃₇H₅₈O₉Na: 669.3979.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-xylopyranosyl ester (4Bf)



To a solution of **12Bf** (200 mg, 0.241 mmol) in MeOH (2.4 mL) was added NaH (0.96 mg, 0.024 mmol, 60% disp.). After stirring at room temperature for 1 h, the reaction mixture was acidified with Dowex H⁺ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* to afford the pure **4Bf** (141 mg, 0.239 mmol, 99%) as a white solid without further purification.

$R_f = 0.59$ (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{22} +41.7$ (c 0.31, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.25 (d, $J = 7.0$ Hz, 1H, 1'-H), 5.48 (t, $J = 3.3$ Hz, 1H, 12-H), 4.40 (dd, $J = 11.0$ Hz, 4.0 Hz, 1H, 5'-H), 4.23-4.19 (m, 3H, 2'-H, 3'-H, 4'-H), 3.85 (dd, $J = 11.0$ Hz, 10.0 Hz, 1H, 5'-H), 3.45 (dd, 10.7 Hz, 5.7 Hz, 1H, 3-H), 3.27 (dd, $J = 14.2$ Hz, 3.8 Hz, 1H, 18-H), 2.32 (m, 1H, 15-H), 2.10 (m, 2H, 16-H), 2.05 (m, 1H, 22-H), 1.97 (m, 2H, 11-H), 1.85 (m, 2H, 15-H, 22-H), 1.80 (m, 1H, 19-H), 1.68 (m, 1H, 9-H), 1.54 (m, 2H, 1-H, 6-H), 1.51 (m, 2H, 7-H), 1.37 (m, 2H, 6-H, 21-H), 1.30 (m, 1H, 19-H), 1.25 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.18 (m, 1H, 2-H), 1.15 (m, 1H, 21-H), 1.12 (s, 3H, 26-H), 1.05 (s, 3H, 24-H), 1.00 (m, 1H, 1-H), 0.95 (s, 3H, 30-H), 0.94 (s, 6H, 25-H, 29-H), 0.86 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

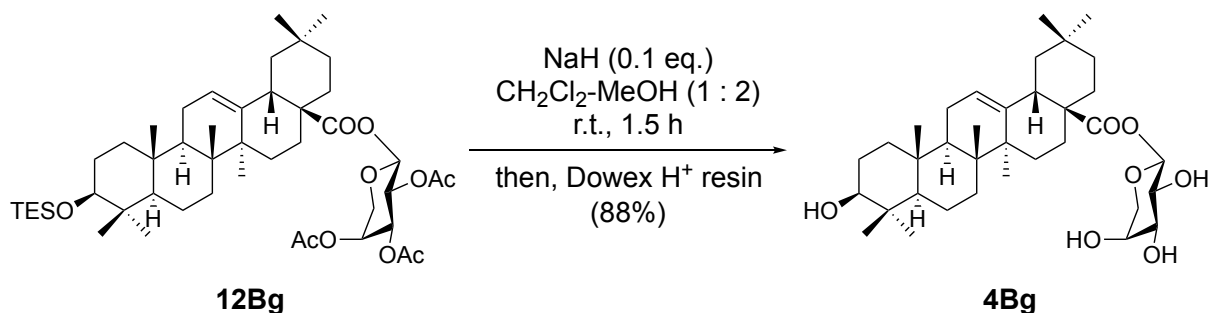
δ : 176.7 (C-28), 144.3 (C-13), 123.1 (C-12), 96.4 (C-1'), 78.4 (C-2'), 78.2 (C-3), 73.8 (C-3'), 71.0 (C-4'), 67.9 (C-5'), 56.0 (C-5), 48.3 (C-9), 47.3 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.0 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.9 (C-22), 31.0 (C-20), 29.0 (C-23), 28.4 (C-15), 28.3 (C-2), 26.2 (C-27), 24.0 (C-11), 23.8 (C-30), 23.5 (C-16), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3407 (-O-H), 2940 (=C-H), 1744 (-C=O), 1032 (-C-O-)

HR-MS (ESI⁺)

m/z 611.3908[M+Na]⁺, Calc'd for C₃₅H₅₆O₇Na: 611.3924.

Olean-12-en-28-oic acid, 3-hydroxy-, α -L-arabinopyranosyloxy ester (4Bg)



To a solution of **12Bg** (346 mg, 0.418 mmol) in dry MeOH (4.0 mL) and dry CH_2Cl_2 (2.0 mL) was added NaH (1.67 mg, 0.042 mmol, 60% disp.). After stirring for 1.5 h at room temperature, the reaction mixture was acidified with Dowex H^+ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 12 g, CHCl_3 : MeOH = 50 : 1 \rightarrow 40 : 1 \rightarrow 30 : 1 \rightarrow 20 : 1 \rightarrow 5 : 1) to afford **4Bg** (α only, 217 mg, 0.369 mmol, 88%) as a white solid.

$R_f = 0.15$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{25} +102.7$ (c 0.302, DMSO)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.32 (d, $J = 5.8$ Hz, 1H, 1'-H), 5.48 (t, $J = 3.4$ Hz, 1H, 12-H), 4.63 (t, $J = 7.3$ Hz, 1H, 2'-H), 4.48 (m, 1H, 4'-H), 4.44 (dd, $J = 11.4$ Hz, 5.0 Hz, 1H, 5'-H), 4.39 (dd, $J = 7.3$ Hz, 3.2 Hz, 1H, 3'-H), 3.95 (dd, $J = 11.4$ Hz, 2.2 Hz, 1H, 5'-H), 3.45 (dd, $J = 10.9$ Hz, 5.5 Hz, 1H, 3-H), 3.30 (dd, $J = 14.0$ Hz, 4.2 Hz, 1H, 18-H), 2.27 (m, 1H, 2-H), 2.08 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.25 (s, 6H, 23-H, 27-H), 1.12 (m, 2H, 15-H), 1.09 (s, 3H, 26-H), 1.08 (m, 1H, 21-H), 1.05 (s, 3H, 24-H), 0.97 (s, 3H, 30-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.93 (s, 3H, 29-H), 0.86 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

δ : 176.7 (C-28), 144.3 (C-13), 123.1 (C-12), 96.0 (C-1'), 78.2 (C-3), 74.1 (C-3'), 71.5 (C-2'), 68.2 (C-4'), 66.4 (C-5'), 56.0 (C-5), 48.3 (C-9), 47.3 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.0 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.9 (C-22), 31.0 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.2

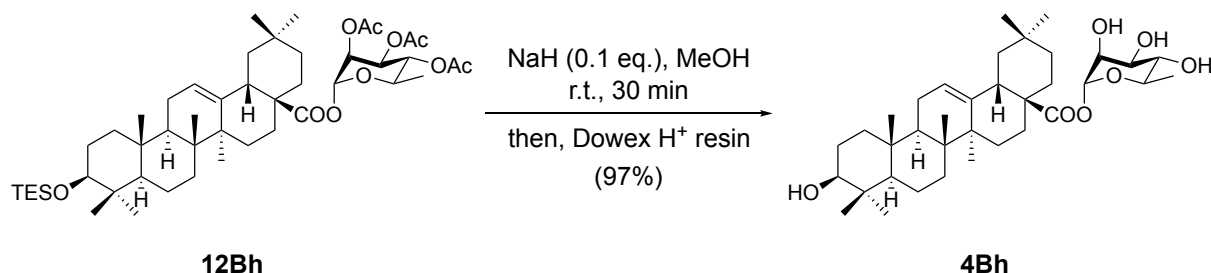
(C-27), 24.0 (C-30), 23.8 (C-16), 23.4 (C-11), 19.0 (C-6), 17.6 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3408 (-O-H), 2945 (=C-H), 1738 (-C=O), 1039 (-C-O-)

HR-MS (ESI⁺)

m/z 611.3910[M+Na]⁺, Calc'd for C₃₅H₅₆O₇Na: 611.3924.

Olean-12-en-28-oic acid, 3-hydroxy-, α -L-rhamnopyranosyloxy ester (4Bh)



To a solution of **12Bh** (200 mg, 0.237 mmol) in MeOH (2.3 mL) was added NaH (0.948 mg, 0.024 mmol, 60% disp.). After stirring at room temperature for 30 min, the reaction mixture was neutralized with Dowex H⁺ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* to give the pure **4Bh** (139 mg, 0.231 mmol, 97%) as a white solid without further purification.

$R_f = 0.57$ (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{22} +25.7$ (c 1.00, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.83 (d, $J = 1.5$ Hz, 1H, 1'-H), 5.46 (t, $J = 3.3$ Hz, 1H, 12-H), 4.61 (dd, $J = 3.3$ Hz, 1.5 Hz, 1H, 2'-H), 4.54 (dd, $J = 8.8$ Hz, 3.3 Hz, 1H, 3'-H), 4.39 (t, $J = 8.8$ Hz, 1H, 4'-H), 4.39 (m, 1H, 5'-H), 3.45 (dd, 10.7 Hz, 5.7 Hz, 1H, 3-H), 3.17 (dd, $J = 14.2$ Hz, 3.8 Hz, 1H, 18-H), 2.05 (m, 1H, 16-H), 2.01 (m, 1H, 2-H), 1.95 (m, 2H, 11-H), 1.86 (m, 2H, 2-H, 22-H), 1.75 (m, 2H, 16-H, 19-H), 1.72 (d, $J = 5.5$ Hz, 3H, 6'-CH₃), 1.64 (m, 1H, 9-H), 1.61 (m, 1H, 22-H), 1.57 (m, 2H, 1-H, 6-H), 1.46 (m, 1H, 7-H), 1.41 (m, 1H, 21-H), 1.36 (m, 1H, 6-H), 1.30 (m, 2H, 7-H, 19-H), 1.25 (s, 3H, 23-H), 1.22 (s, 3H, 27-H), 1.17 (m, 1H, 21-H), 1.12 (m, 2H, 15-H), 1.06 (s, 3H, 26-H), 1.00 (m, 1H, 1-H), 0.92 (s, 3H, 24-H), 0.92 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.89 (s, 3H, 30-H), 0.87 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.0 (C-28), 143.6 (C-13), 123.5 (C-12), 95.5 (C-1'), 78.2 (C-3), 73.6 (C-4'), 73.0 (C-3'), 72.7 (C-5'), 71.6 (C-2'), 55.9 (C-5), 48.1 (C-9), 47.5 (C-17), 46.1 (C-19), 42.2 (C-14), 42.1 (C-18), 39.9 (C-8), 39.5 (C-1), 39.0 (C-4), 37.5 (C-10), 34.1 (C-21), 33.4 (C-7), 33.2 (C-22), 33.1 (C-29), 31.0 (C-20), 29.0 (C-23), 28.2 (C-15), 28.1 (C-2), 26.1 (C-27), 24.0 (C-11), 23.7 (C-30), 23.4 (C-16), 18.9 (6'-CH₃), 18.9 (C-6), 17.2 (C-26), 16.7 (C-24), 15.7 (C-25)

IR (KBr) cm^{-1} ν : 3431 (-O-H), 2927 (=C-H), 1743 (-C=O), 1061 (-C-O-)

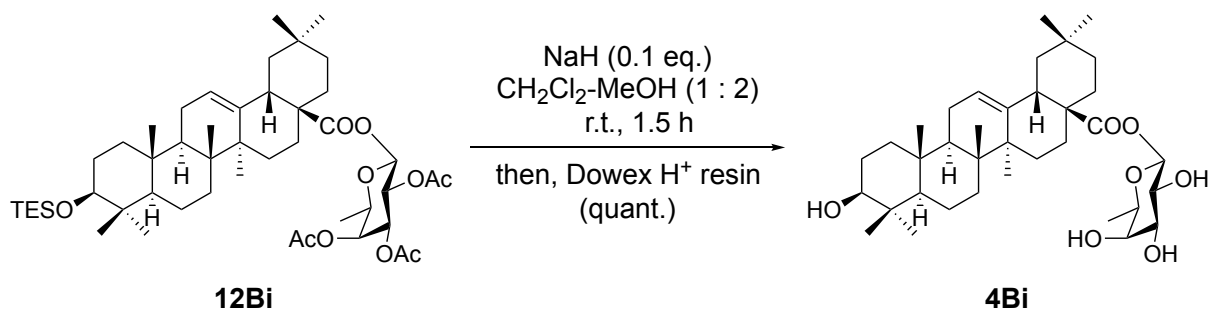
HR-MS (ESI⁺)

m/z 625.4070[M+Na]⁺, Calc'd for C₃₆H₅₈O₇Na: 625.4080.

GATEI (400 MHz, pyridine-*d*₅)

δ : 96.3 (s), 94.6 (s), (C-1'), $^1J_{\text{C,H}} = 173.0$ Hz.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-fucopyranosyloxy ester (4Bi)



To a solution of **12Bi** (677 mg, 0.803 mmol) in dry MeOH (8.0 mL) and dry CH_2Cl_2 (4.0 mL) was added NaH (3.21 mg, 0.08 mmol, 60% disp.). After stirring for 1.5 h at room temperature, the reaction mixture was acidified with Dowex H^+ resin to pH 4, filtered and rinsed with MeOH (20 mL) and pyridine (30 mL). The filtrate was three times concentrated with toluene (3 x 30 mL) as an azeotropic solvent *in vacuo*. The residue was purified by flash column chromatography (silica gel 25 g, CHCl_3 : MeOH = 10 : 1) to afford **4Bi** (β only, 487 mg, 0.808 mmol, quant.) as a white solid.

$R_f = 0.56$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{25} +57.7$ (c 0.304, DMSO)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.18 (d, $J = 8.4$ Hz, 1H, 1'-H), 5.46 (t, $J = 3.7$ Hz, 1H, 12-H), 4.57 (m, 1H, 2'-H), 4.16 (dd, $J = 9.7$ Hz, 3.3 Hz, 1H, 3'-H), 4.07 (d, $J = 3.3$ Hz, 1H, 4'-H), 3.96 (q, $J = 6.4$ Hz, 1H, 5'-H), 3.45 (dd, $J = 11.4$ Hz, 5.3 Hz, 1H, 3-H), 3.23 (dd, $J = 14.0$ Hz, 4.6 Hz, 1H, 18-H), 2.34 (m, 1H, 2-H), 2.05 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (d, $J = 6.3$ Hz, 3H, 6'-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.24 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.16 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.05 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.95 (s, 3H, 25-H), 0.91 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

δ : 176.7 (C-28), 144.4 (C-13), 123.0 (C-12), 96.1 (C-1'), 78.2 (C-3), 75.9 (C-3'), 72.8 (C-4'), 72.7 (C-5'), 71.2 (C-2'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.2

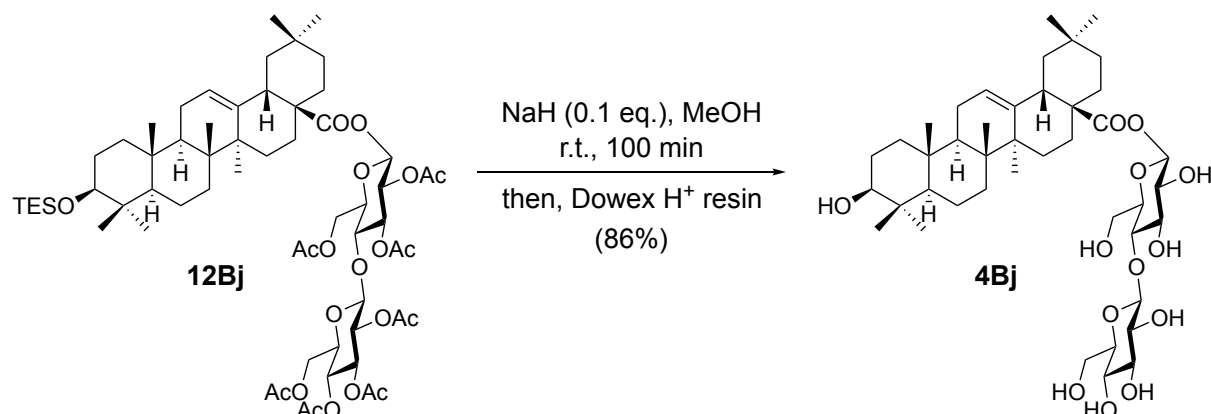
(C-27), 24.0 (C-30), 23.8 (C-16), 23.5 (C-11), 19.0 (C-6), 17.7 (C-26), 17.4 (C-6'),
16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3610 (-O-H), 2843 (=C-H), 1752 (-C=O), 1046 (-C-O-)

HR-MS (ESI⁺)

m/z 625.4076[M+Na]⁺, Calc'd for C₃₆H₅₈O₇Na: 625.4080.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-cellobiopyranosyloxy ester (4Bj)



To a solution of **12Bj** (200 mg, 0.168 mmol) in dry MeOH (5.0 mL) was added NaH (0.67 mg, 0.017 mmol, 60% disp.). After stirring for 100 min at room temperature, the reaction mixture was acidified with Dowex H⁺ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 10 : 1 → 5 : 1 → 4 : 1) to afford **4Bj** (113 mg, 0.145 mmol, 86%) as a white solid.

R_f = 0.46 (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{24}$ +25.6 (*c* 0.157, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.29 (d, J = 8.0 Hz, 1H, 1'-H), 5.47 (t, J = 3.3 Hz, 1H, 12-H), 5.23 (d, J = 8.0 Hz, 1H, 1''-H), 4.64 (dd, J = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.51 (dd, J = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.50 (dd, J = 12.0 Hz, 2.0 Hz, 1H, 6'''-H), 4.41 (t, J = 9.0 Hz, 1H, 4'-H), 4.34 (dd, J = 9.0 Hz, 8.5 Hz, 1H, 3'-H), 4.29 (dd, J = 12.0 Hz, 5.5 Hz, 1H, 6'''-H), 4.25 (dd, J = 9.5 Hz, 8.5 Hz, 1H, 3'''-H), 4.18 (dd, J = 9.5 Hz, 9.0 Hz, 1H, 4'''-H), 4.11 (dd, J = 8.5 Hz, 8.0 Hz, 1H, 2'''-H), 4.04 (dd, J = 8.5 Hz, 8.0 Hz, 1H, 2'-H), 4.02 (ddd, J = 9.0 Hz, 5.5 Hz, 2.0 Hz, 1H, 5'''-H), 3.96 (ddd, J = 9.0 Hz, 3.0 Hz, 2.0 Hz, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.23 (dd, J = 14.0 Hz, 4.2 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 144.3 (C-13), 123.1 (C-12), 105.2 (C-1''), 95.4 (C-1'), 81.0 (C-4'), 78.6 (C-3), 78.4 (C-5''), 78.3 (C-5'), 77.5 (C-3'), 77.3 (C-3''), 75.0 (C-2'), 73.8 (C-2''), 71.7 (C-4''), 62.6 (C-6''), 61.7 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm⁻¹ ν : 3421 (-O-H), 2936 (=C-H), 1752 (-C=O), 1074 (-C-O-)

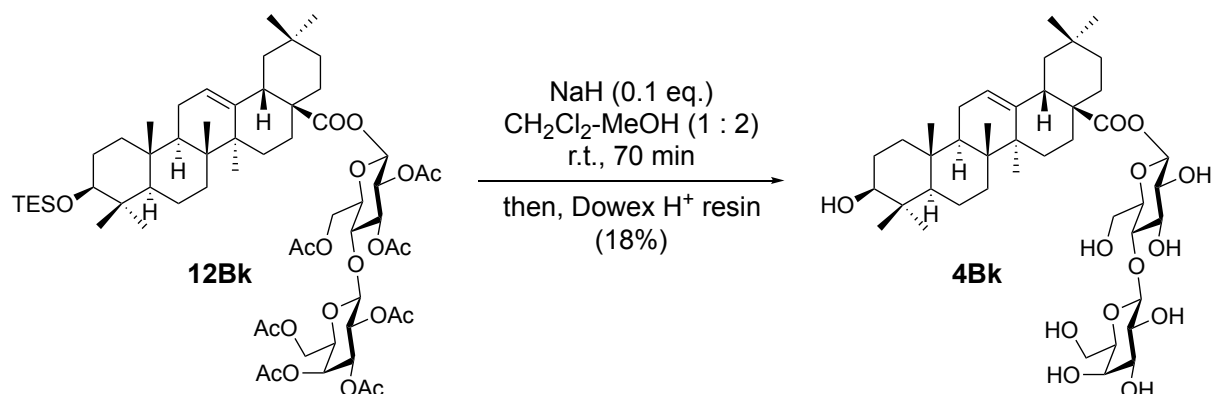
HR-MS (ESI⁺)

m/z 803.4555[M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na: 803.4558.

TOCSY (400 MHz, pyridine-*d*₅)

mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-lactopyranosyloxy ester (4Bk)



To a solution of **12Bk** (207 mg, 0.174 mmol) in dry MeOH (2.0 mL), CH_2Cl_2 (1.0 mL) was added NaH (0.696 mg, 0.017 mmol, 60% disp.). After stirring for 70 min at room temperature, the reaction mixture was acidified with Dowex H^+ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl_3 : MeOH = 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1 \rightarrow 5 : 1) to afford **4Bk** (24.8 mg, 0.032 mmol, 18%) as a white solid.

$R_f = 0.15$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{23} -180.5$ (c 1.00, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.28 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.45 (t, $J = 3.3$ Hz, 1H, 12-H), 5.14 (d, $J = 8.0$ Hz, 1H, 1''-H), 4.57 (dd, $J = 12.0$ Hz, 3.0 Hz, 1H, 6'-H), 4.53 (dd, $J = 9.0$ Hz, 8.0 Hz, 1H, 2''-H), 4.49 (d, $J = 3.5$ Hz, 1H, 4''-H), 4.46 (dd, $J = 11.0$ Hz, 6.5 Hz, 1H, 6''-H), 4.43 (dd, $J = 9.5$ Hz, 9.0 Hz, 1H, 4'-H), 4.38 (dd, $J = 12.0$ Hz, 2.5 Hz, 1H, 6'-H), 4.38 (dd, $J = 11.0$ Hz, 5.0 Hz, 1H, 6''-H), 4.33 (dd, $J = 9.0$ Hz, 8.5 Hz, 1H, 3'-H), 4.21 (dd, $J = 8.5$ Hz, 8.0 Hz, 1H, 2'-H), 4.15 (dd, $J = 6.5$ Hz, 5.0 Hz, 1H, 5''-H), 4.14 (dd, $J = 9.0$ Hz, 3.5 Hz, 1H, 3''-H), 3.99 (ddd, $J = 9.5$ Hz, 3.0 Hz, 2.5 Hz, 1H, 5'-H), 3.45 (dd, $J = 11.3$ Hz, 5.2 Hz, 1H, 3-H), 3.21 (dd, $J = 14.0$ Hz, 3.7 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.5 (C-28), 144.2 (C-13), 123.1 (C-12), 106.0 (C-1''), 95.4 (C-1'), 81.6 (C-4'), 78.2 (C-3), 77.4 (C-5''), 77.4 (C-5'), 77.2 (C-3'), 75.3 (C-3''), 73.8 (C-2'), 72.6 (C-2''), 70.2 (C-4''), 62.1 (C-6''), 61.8 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm⁻¹ ν : 3421 (-O-H), 2930 (=C-H), 1735 (-C=O), 1071 (-C-O-)

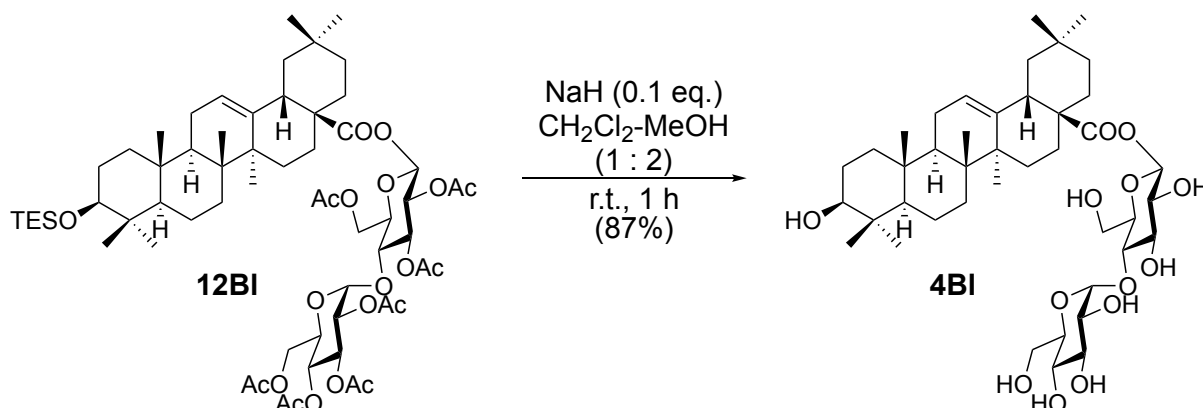
HR-MS (ESI⁺)

m/z 803.4558[M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na: 803.4558.

TOCSY (400 MHz, pyridine-*d*₅)

mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-maltopyranosyloxy ester (4BI**)**



To a solution of **12BI** (179 mg, 0.151 mmol) in dry MeOH (2.0 mL) and CH₂Cl₂ (1.0 mL) was added NaH (0.60 mg, 0.015 mmol, 60% disp.). After stirring for 1 h at room temperature, the reaction mixture was acidified with Dowex H⁺ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 20 : 1 → 15 : 1 → 10 : 1 → 5 : 1) to afford **4BI** (102 mg, 0.131 mmol, 87%) as a white solid.

R_f = 0.18 (CHCl₃ : MeOH = 5 : 1)

[α]_D²² +66.4 (*c* 0.16, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.25 (d, *J* = 8.0 Hz, 1H, 1'-H), 5.96 (d, *J* = 4.0 Hz, 1H, 1''-H), 5.46 (t, *J* = 3.4 Hz, 1H, 12-H), 4.59 (t, *J* = 9.0 Hz, 1H, 3''-H), 4.58 (ddd, *J* = 9.0 Hz, 6.0 Hz, 2.0 Hz, 1H, 5''-H), 4.58 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.48 (t, *J* = 9.0 Hz, 1H, 4'-H), 4.48 (dd, *J* = 12.0 Hz, 3.5 Hz, 1H, 6'-H), 4.40 (t, *J* = 9.0 Hz, 1H, 3'-H), 4.38 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6'-H), 4.34 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H, 6''-H), 4.20 (dd, *J* = 9.0 Hz, 4.0 Hz, 1H, 2''-H), 4.19 (dd, *J* = 9.0 Hz, 8.0 Hz, 1H, 2'-H), 4.17 (t, *J* = 9.0 Hz, 1H, 4''-H), 3.90 (ddd, *J* = 9.0 Hz, 3.5 Hz, 2.0 Hz, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.23 (dd, *J* = 14.0 Hz, 4.2 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H)

^{13}C -NMR (100 MHz, pyridine- d_5)

δ : 176.5 (C-28), 144.3 (C-13), 123.0 (C-12), 103.2 (C-1''), 95.6 (C-1'), 80.7 (C-4'), 78.4 (C-3'), 78.2 (C-3), 77.7 (C-5'), 73.7 (C-2'), 75.6 (C-3''), 75.5 (C-5''), 74.6 (C-2''), 72.1 (C-4''), 62.9 (C-6''), 61.6 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3390 (-O-H), 2929 (=C-H), 1749 (-C=O), 1069 (-C-O-)

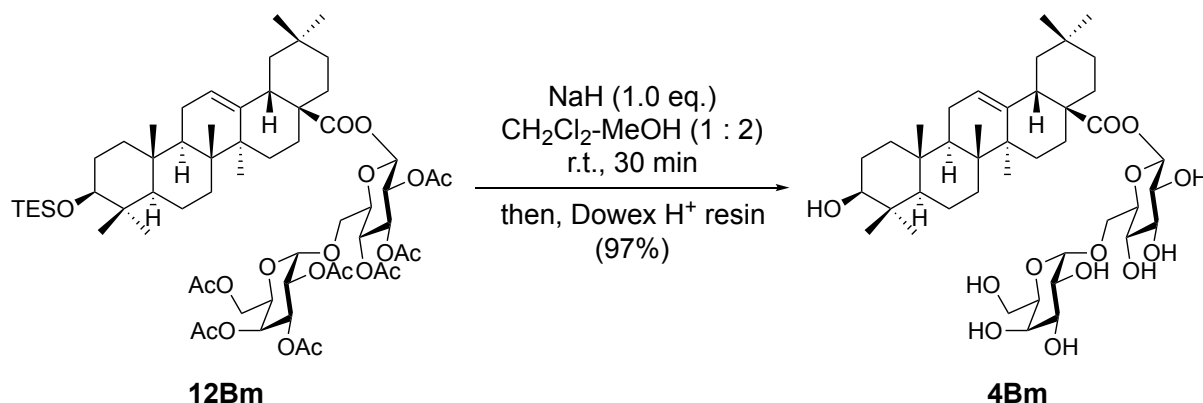
HR-MS (ESI $^{+}$)

m/z 803.4548[M+Na] $^{+}$, Calc'd for $\text{C}_{42}\text{H}_{68}\text{O}_{13}\text{Na}$: 803.4558

TOCSY (400 MHz, pyridine- d_5)

mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-melibiosyloxy ester (4Bm**)**



To a solution of **12Bm** (218 mg, 0.183 mmol) in dry MeOH (1.8 mL) and CH_2Cl_2 (0.9 mL) was added NaH (7.3 mg, 0.183 mmol, 60% disp.). After stirring for 30 min at room temperature, the reaction mixture was acidified with Dowex H^+ resin to pH 4, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl_3 : MeOH = 50 : 1 \rightarrow 40 : 1 \rightarrow 30 : 1 \rightarrow 20 : 1 \rightarrow 5 : 1) to afford **4Bm** (139 mg, 0.178 mmol, 97%) as a white solid.

$R_f = 0.17$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{24} +65.5$ (c 0.16, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.27 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.46 (d, $J = 3.5$ Hz, 1H, 1''-H), 5.45 (t, $J = 3.4$ Hz, 1H, 12-H), 4.66 (dd, $J = 9.0$ Hz, 3.5 Hz, 1H, 2''-H), 4.61 (dd, $J = 6.5$ Hz, 5.5 Hz, 1H, 5''-H), 4.58 (dd, $J = 10.5$ Hz, 5.0 Hz, 1H, 6'-H), 4.56 (d, $J = 3.5$ Hz, 1H, 4''-H), 4.53 (dd, $J = 9.0$ Hz, 3.5 Hz, 1H, 3''-H), 4.43 (dd, $J = 11.0$ Hz, 6.5 Hz, 1H, 6''-H), 4.40 (dd, $J = 11.0$ Hz, 5.5 Hz, 1H, 6''-H), 4.25 (t, $J = 8.0$ Hz, 1H, 2'-H), 4.24 (t, $J = 8.0$ Hz, 1H, 3'-H), 4.23 (t, $J = 8.0$ Hz, 1H, 4'-H), 4.20 (dd, $J = 10.5$ Hz, 2.5 Hz, 1H, 6'-H), 4.06 (ddd, $J = 8.0$ Hz, 5.0 Hz, 2.5 Hz, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.23 (dd, $J = 14.0$ Hz, 4.2 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H)

^{13}C -NMR (100 MHz, pyridine- d_5)

δ : 176.8 (C-28), 144.2 (C-13), 123.2 (C-12), 100.8 (C-1''), 95.8 (C-1'), 79.1 (C-3'), 78.3 (C-3), 77.4 (C-5'), 74.0 (C-2'), 72.7 (C-5''), 71.8 (C-3''), 71.6 (C-4'), 71.3 (C-4''), 70.9 (C-2''), 67.8 (C-6'), 62.9 (C-6''), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3480 (-O-H), 2911 (=C-H), 1747 (-C=O), 1076 (-C-O-)

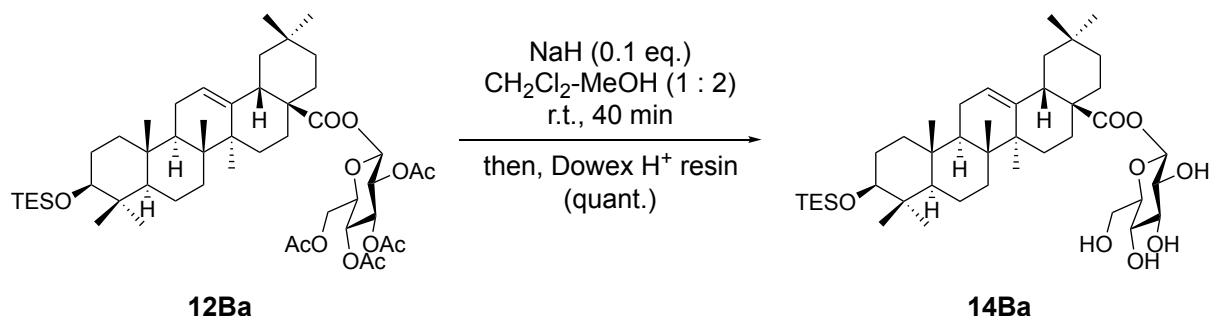
HR-MS (ESI $^{+}$)

m/z 803.4549[M+Na] $^{+}$, Calc'd for $\text{C}_{42}\text{H}_{68}\text{O}_{13}\text{Na}$: 803.4558

TOCSY (400 MHz, pyridine- d_5)

mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, β -D-glucopyranosyloxy ester (14Ba**)**



To a solution of **12Ba** (1.41 g, 1.56 mmol) in MeOH (15.0 mL) and CH₂Cl₂ (7.5 mL) was added NaH (6.26 mg, 0.156 mmol, 60% disp.). After stirring at room temperature for 40 min, the reaction mixture was neutralized with Dowex H⁺ resin to pH 7, filtered, and rinsed with MeOH (50 mL). The filtrate was concentrated *in vacuo* and to afford the pure **14Ba** (1.20 g, 1.64 mmol, quant.) as a white solid without further purification.

R_f = 0.44 (CHCl₃ : MeOH = 5 : 1)

[α]_D²⁴ +31.8 (*c* 1.00, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.36 (d, *J* = 8.0 Hz, 1H, 1'-H), 5.47 (t, *J* = 3.3 Hz, 1H, 12-H), 4.48 (dd, *J* = 12.0 Hz, 2.4 Hz, 1H, 6'-H), 4.41 (dd, *J* = 12.0 Hz, 4.8 Hz, 1H, 6'-H), 4.37 (dd, *J* = 9.0 Hz, 8.2 Hz, 1H, 3'-H), 4.31 (t, 9.0 Hz, 1H, 4'-H), 4.23 (t, *J* = 8.2 Hz, 1H, 2'-H), 4.05 (ddd, *J* = 12.0 Hz, 4.8 Hz, 2.4 Hz, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.23 (dd, *J* = 14.0 Hz, 4.2 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (m, 9H, -Si(CH₂CH₃)₃), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H), 0.65 (m, 6H, -Si(CH₂CH₃)₃)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.6 (C-28), 144.3 (C-13), 123.1 (C-12), 95.9 (C-1'), 79.5 (C-3), 79.1 (C-5'), 78.2 (C-3'), 74.3 (C-2'), 71.2 (C-4'), 62.4 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26),

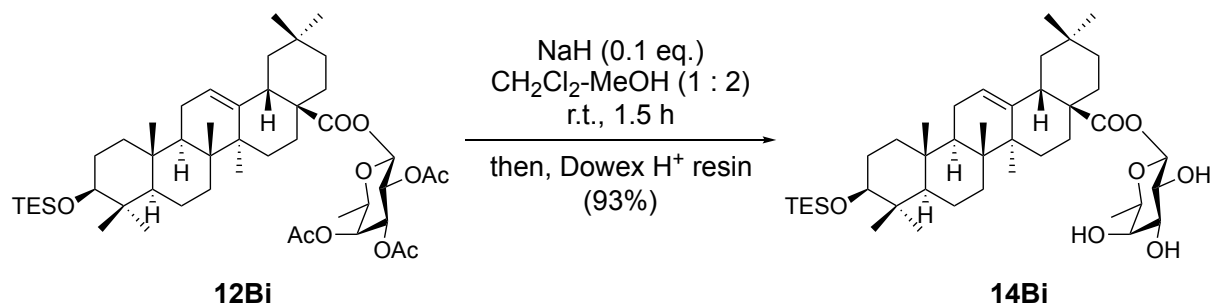
16.7 (C-24), 15.8 (C-25), 7.5 (-Si(CH₂CH₃)₃), 5.8 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 3379 (-O-H), 2953 (=C-H), 1720 (-C=O), 1080 (-C-O-)

HR-MS (ESI⁺)

m/z 755.4889[M+Na]⁺, Calc'd for C₄₂H₇₂O₈SiNa: 755.4894.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, β -D-fucopyranosyloxy ester (14Bi**)**



To a solution of **12Bi** (247 mg, 0.293 mmol) in dry MeOH (8.0 mL) and dry CH_2Cl_2 (4.0 mL) was added NaH (1.17 mg, 0.029 mmol, 60% disp.). After stirring for 1.5 h at room temperature, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 13 g, CHCl_3 : MeOH = 20 : 1) to afford **14Bi** (β only, 195 mg, 0.272 mmol, 93%) as a white solid.

$R_f = 0.61$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{24} +42.9$ (c 0.31, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.18 (d, $J = 8.2$ Hz, 1H, 1'-H), 5.47 (t, $J = 3.5$ Hz, 1H, 12-H), 4.57 (m, 1H, 2'-H), 4.15 (dd, $J = 9.5$ Hz, 3.1 Hz, 1H, 3'-H), 4.07 (br s, 1H, 4'-H), 3.96 (dd, $J = 12.5$ Hz, 4.4 Hz, 1H, 5'-H), 3.30 (dd, $J = 11.3$ Hz, 4.3 Hz, 1H, 3-H), 3.24 (dd, $J = 14.0$ Hz, 4.1 Hz, 1H, 18-H), 2.34 (m, 1H, 2-H), 2.05 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (d, $J = 6.4$ Hz, 3H, 6'-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.25 (s, 3H, 27-H), 1.16 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 23-H), 1.03 (m, 9H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$), 1.01 (m, 1H, 1-H), 0.92 (s, 3H, 25-H), 0.91 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.89 (s, 3H, 24-H), 0.86 (m, 1H, 5-H), 0.64 (m, 6H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

δ : 176.7 (C-28), 144.3 (C-13), 123.0 (C-12), 96.1 (C-1'), 79.9 (C-3), 75.9 (C-3'), 72.8 (C-5'), 72.6 (C-2'), 71.2 (C-4'), 55.7 (C-6'), 48.2 (C-5), 47.1 (C-9), 46.4 (C-17), 42.3 (C-19), 41.9 (C-14), 40.1 (C-18), 39.7 (C-8), 38.8 (C-4), 37.3 (C-1), 34.1 (C-10), 33.3 (C-21), 33.3 (C-29), 32.7 (C-7), 30.9 (C-22), 28.9 (C-20), 28.4 (C-23), 28.3 (C-15), 26.2 (C-2), 24.0 (C-27), 23.8 (C-30), 23.5 (C-16), 19.0 (C-11), 17.6 (C-6), 17.3 (C-26),

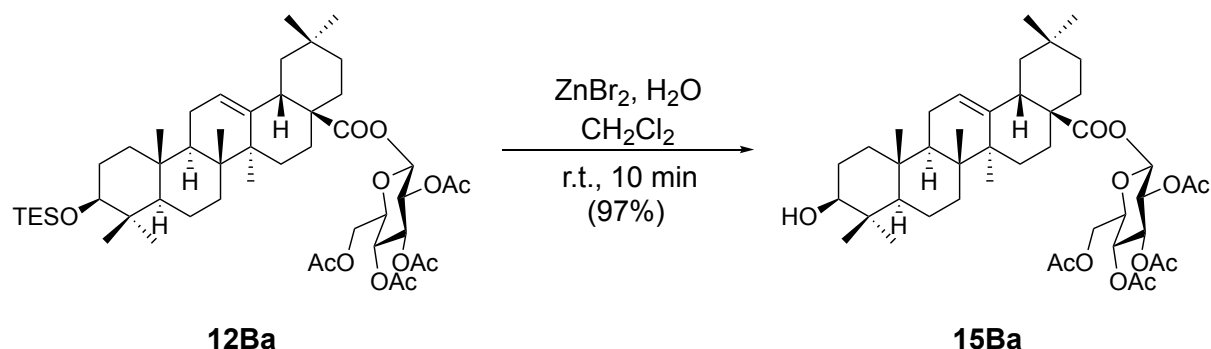
16.7 (C-24), 15.7 (C-25), 7.5 (-Si(CH₂CH₃)₃), 5.7 (-Si(CH₂CH₃)₃)

IR (KBr) cm⁻¹ ν : 3529 (-O-H), 2909 (=C-H), 1748 (-C=O), 1068 (-C-O-)

HR-MS (ESI⁺)

m/z 739.4926[M+Na]⁺, Calc'd for C₄₂H₇₂O₇SiNa: 739.4945.

Olean-12-en-28-oic acid, 3-hydroxy-, 2, 3, 4, 6-tetra-*O*-acetyl- β -D-glucopyranosyl ester (15Ba**)**



To a solution of **12Ba** (100 mg, 0.110 mmol) in dry CH_2Cl_2 (0.25 M) was added ZnBr_2 (125 mg, 0.550 mmol) followed by H_2O (9.9 μL , 0.550 mmol). After stirring at room temperature for 10 min, the reaction mixture was quenched sat. aq. NaHCO_3 (1.0 mL) in ice bath. The resulting mixture was extracted with CH_2Cl_2 (10 mL). The combined organic layer was washed with sat. aq. NaHCO_3 (5 mL), H_2O (5 x 60 mL), and, brine (5 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 10 g, hexane : AcOEt = 3 : 1 \rightarrow 2 : 1 \rightarrow 1 : 1) to afford **15Ba** (84 mg, 0.107 mmol, 97%) as a white foamy solid.

R_f = 0.40 (hexane : AcOEt = 1 : 1)

$[\alpha]_{\text{D}}^{22} +35.4$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 5.58 (d, J = 8.0 Hz, 1H, 1'-H), 5.31 (t, J = 3.5 Hz, 1H, 12-H), 5.25 (t, J = 9.3 Hz, 1H, 3'-H), 5.18 (dd, J = 9.3 Hz, 8.0 Hz, 1H, 2'-H), 5.13 (dd, J = 10.0 Hz, 9.3 Hz, 1H, 4'-H), 4.27 (dd, J = 12.5 Hz, 4.4 Hz, 1H, 6'-H), 4.05 (dd, J = 12.5 Hz, 2.4 Hz, 1H, 6'-H), 3.79 (ddd, J = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.19 (m, 1H, 3-H), 2.78 (m, 1H, 18-H), 2.06 (s, 3H, $-\text{OCOCH}_3$), 2.02 (s, 3H, $-\text{OCOCH}_3$), 2.01 (s, 6H, $-\text{OCOCH}_3$ x2), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H)

^{13}C -NMR (100 MHz, CDCl_3)

δ : 175.6 (C-28), 170.5 ($-\text{O}\text{C}\text{OCH}_3$), 170.0 ($-\text{O}\text{C}\text{OCH}_3$), 169.4 ($-\text{O}\text{C}\text{OCH}_3$), 168.9 ($-\text{O}\text{C}\text{OCH}_3$), 142.8 (C-13), 122.8 (C-12), 91.5 (C-1'), 78.8 (C-3), 72.8 (C-3'), 72.4 (C-5'), 69.9 (C-2'), 68.0 (C-4'), 61.5 (C-6'), 55.1 (C-5), 47.5 (C-9), 46.8 (C-17), 45.7 (C-19), 41.6 (C-14), 39.3 (C-18), 38.7 (C-8), 38.4 (C-4), 36.8 (C-1), 33.7 (C-10), 32.9 (C-21), 32.8 (C-29), 32.8 (C-7), 31.7 (C-22), 30.5 (C-20), 28.0 (C-23), 27.7 (C-15), 27.1 (C-2), 25.6 (C-27), 23.4 (C-30), 23.3 (C-16), 22.8 (C-11), 20.6 ($-\text{OCOCH}_3$), 20.5 ($-\text{OCOCH}_3$), 20.5 ($-\text{OCOCH}_3$), 20.5 ($-\text{OCOCH}_3$), 18.2 (C-6), 16.9 (C-26), 15.5 (C-24), 15.3 (C-25)

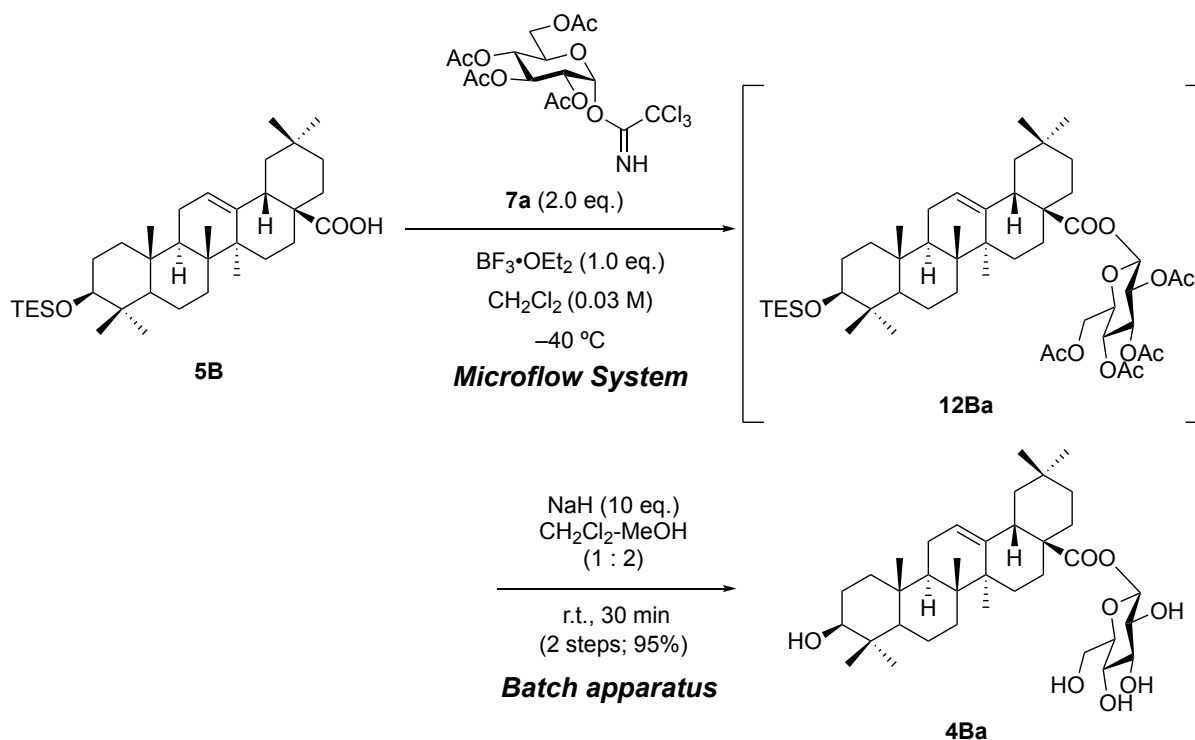
IR (KBr) cm^{-1} v : 3445 ($-\text{O}-\text{H}$), 2933 ($=\text{C}-\text{H}$), 1760 ($-\text{C}=\text{O}$), 1036 ($-\text{C}-\text{O}-$)

HR-MS (ESI^+)

m/z 809.4444 $[\text{M}+\text{Na}]^+$, Calc'd for $\text{C}_{44}\text{H}_{66}\text{O}_{12}\text{Na}$: 809.4452.

Olean-12-en-28-oic acid, 3-hydroxy-, β -D-glucopyranosyl ester (4Ba)

[Continuous flow glycosylation and batch deprotection]



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.0 μL , 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7a** (94.2 mg, 0.191 mmol) and acceptor **5B** (54.6 mg, 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **12Ba** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 10 min at room temperature in flask which was added NaH (38.2 mg, 0.956 mmol, 60% disp.) and MeOH (12.0 mL) in advance. After the reaction was completed, the reaction mixture was acidified with Dowex H^+ resin to pH 4, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 40 : 1 \rightarrow 30 : 1 \rightarrow 20 : 1 \rightarrow 10 : 1) to afford **4Ba** (56.2 mg, 0.091 mmol, 95%) as a white solid by two steps.

$R_f = 0.43$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{28} +33.7$ (*c* 1.00, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.36 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.47 (t, $J = 3.3$ Hz, 1H, 12-H), 4.48 (dd, $J = 12.0$ Hz, 2.4 Hz, 1H, 6'-H), 4.41 (dd, $J = 12.0$ Hz, 4.8 Hz, 1H, 6'-H), 4.37 (dd, $J = 9.0$ Hz, 8.2 Hz, 1H, 3'-H), 4.31 (t, 9.0 Hz, 1H, 4'-H), 4.23 (t, $J = 8.2$ Hz, 1H, 2'-H), 4.05 (ddd, $J = 12.0$ Hz, 4.8 Hz, 2.4 Hz, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.23 (dd, $J = 14.0$ Hz, 4.2 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

δ : 176.6 (C-28), 144.3 (C-13), 123.1 (C-12), 95.9 (C-1'), 79.5 (C-3), 79.1 (C-5'), 78.2 (C-3'), 74.3 (C-2'), 71.2 (C-4'), 62.4 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25)

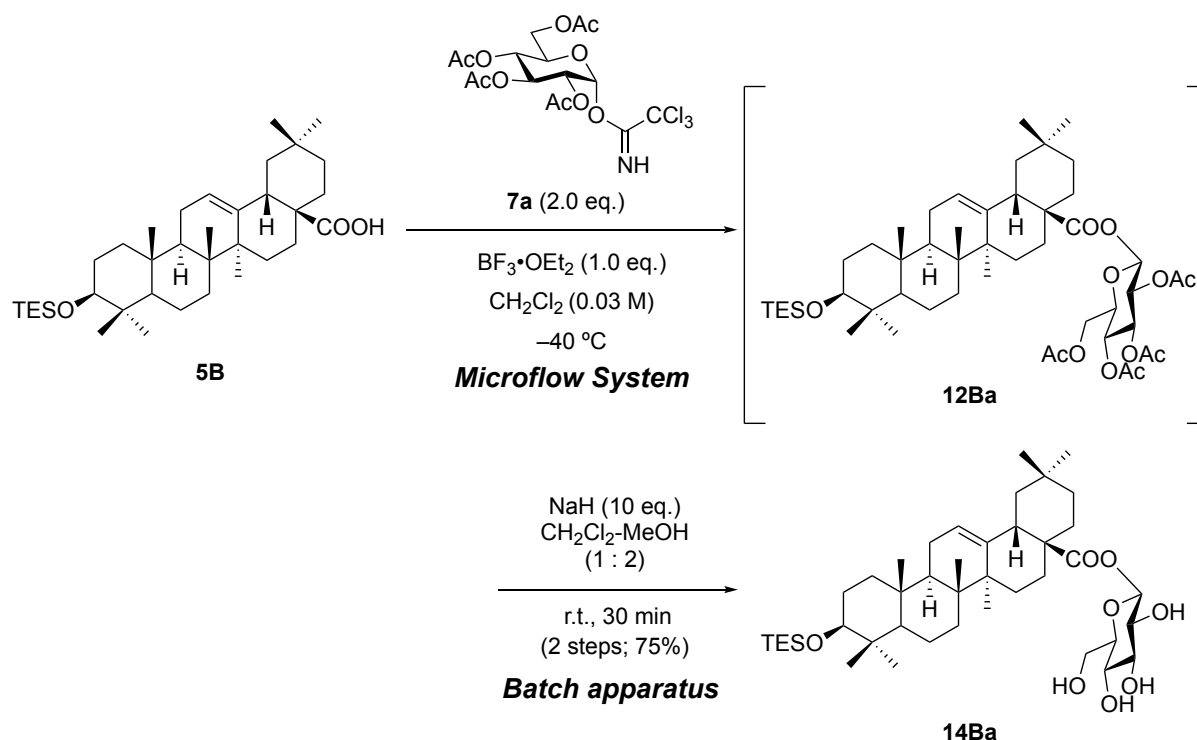
IR (KBr) cm^{-1} ν : 3420 (-O-H), 2945 (=C-H), 1753 (-C=O), 1029 (-C-O-)

HR-MS (ESI⁺)

m/z 641.4002[M+Na]⁺, Calc'd for C₃₆H₅₈O₈Na: 641.4029.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, β -D-glucopyranosyloxy ester (14Ba)

[Continuous flow glycosylation and batch deprotection]



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.0 μL , 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7a** (94.2 mg, 0.191 mmol) and acceptor **5B** (54.6 mg, 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **12Ba** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 10 min at room temperature in flask which was added NaH (38.2 mg, 0.956 mmol, 60% disp.) and MeOH (12.0 mL) in advance. After the reaction was completed, the reaction mixture was acidified with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : $\text{MeOH} = 20 : 1$) to afford **4Ba** (52.4 mg, 0.071 mmol, 75%) as a white solid by two steps.

$R_f = 0.44$ (CHCl_3 : $\text{MeOH} = 5 : 1$)

$[\alpha]_{\text{D}}^{24} +31.8$ (c 1.00, MeOH)

^1H -NMR (400 MHz, pyridine- d_5)

δ : 6.36 (d, J = 8.0 Hz, 1H, 1'-H), 5.47 (t, J = 3.3 Hz, 1H, 12-H), 4.48 (dd, J = 12.0 Hz, 2.4 Hz, 1H, 6'-H), 4.41 (dd, J = 12.0 Hz, 4.8 Hz, 1H, 6'-H), 4.37 (dd, J = 9.0 Hz, 8.2 Hz, 1H, 3'-H), 4.31 (t, 9.0 Hz, 1H, 4'-H), 4.23 (t, J = 8.2 Hz, 1H, 2'-H), 4.05 (ddd, J = 12.0 Hz, 4.8 Hz, 2.4 Hz, 1H, 5'-H), 3.45 (m, 1H, 3-H), 3.23 (dd, J = 14.0 Hz, 4.2 Hz, 1H, 18-H), 2.39 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.24 (s, 3H, 23-H), 1.15 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (m, 9H, -Si(CH₂CH₃)₃), 1.04 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (m, 1H, 5-H), 0.65 (m, 6H, -Si(CH₂CH₃)₃)

^{13}C -NMR (100 MHz, pyridine- d_5)

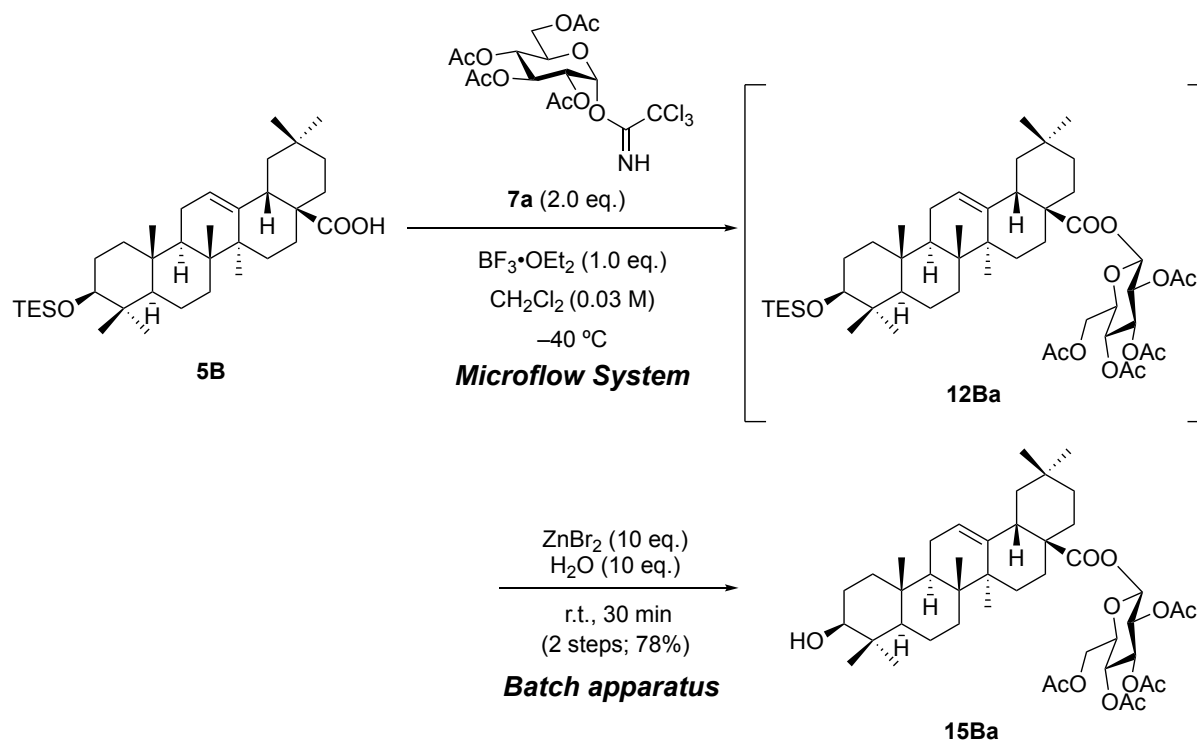
δ : 176.6 (C-28), 144.3 (C-13), 123.1 (C-12), 95.9 (C-1'), 79.5 (C-3), 79.1 (C-5'), 78.2 (C-3'), 74.3 (C-2'), 71.2 (C-4'), 62.4 (C-6'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.4 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 19.0 (C-6), 17.7 (C-26), 16.7 (C-24), 15.8 (C-25), 7.5 (-Si(CH₂CH₃)₃), 5.8 (-Si(CH₂CH₃)₃)

IR (KBr) cm^{-1} ν : 3379 (-O-H), 2953 (=C-H), 1720 (-C=O), 1080 (-C-O-)

HR-MS (ESI⁺)

m/z 755.4889[M+Na]⁺, Calc'd for C₄₂H₇₂O₈SiNa: 755.4894.

Olean-12-en-28-oic acid, 3-hydroxy-, 2, 3, 4, 6-tetra-*O*-acetyl- β -D-glucopyranosyl ester (15Ba**)** [Continuous flow glycosylation and batch deprotection]



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.0 μL , 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7a** (94.2 mg, 0.191 mmol) and acceptor **5B** (54.6 mg, 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at -40°C . After the reaction mixture was allowed to flow at -40°C through a Teflon reactor tube ($\phi = 1.0\text{ mm}$, $l = 1.0\text{ m}$), the crude mixture of **12Ba** was introduced into a flask, which was cooled to -40°C and connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which was added ZnBr_2 (216 mg, 0.956 mmol) and H_2O (17.2 μL , 0.956 mmol) in advance. After the reaction was completed, the reaction mixture was quenched with NEt_3 , filtered by celite, and rinsed with CH_2Cl_2 (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, hexane : AcOEt = 3 : 1 \rightarrow 2 : 1 \rightarrow 3 : 2) to afford **15Ba** (58.4 mg, 0.075 mmol, 78%) as a white foamy solid by two steps.

$R_f = 0.40$ (hexane : AcOEt = 1 : 1)

$[\alpha]_D^{22} + 35.4$ (*c* 1.00, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 5.58 (d, *J* = 8.0 Hz, 1H, 1'-H), 5.31 (t, *J* = 3.5 Hz, 1H, 12-H), 5.25 (t, *J* = 9.3 Hz, 1H, 3'-H), 5.18 (dd, *J* = 9.3 Hz, 8.0 Hz, 1H, 2'-H), 5.13 (dd, *J* = 10.0 Hz, 9.3 Hz, 1H, 4'-H), 4.27 (dd, *J* = 12.5 Hz, 4.4 Hz, 1H, 6'-H), 4.05 (dd, *J* = 12.5 Hz, 2.4 Hz, 1H, 6'-H), 3.79 (ddd, *J* = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.19 (m, 1H, 3-H), 2.78 (m, 1H, 18-H), 2.06 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.01 (s, 6H, -OCOCH₃ x2), 1.95 (m, 1H, 11-H), 1.84 (m, 2H, 16-H), 1.60 (m, 1H, 19-H), 1.58 (m, 2H, 22-H), 1.56 (m, 1H, 15-H), 1.54 (m, 1H, 1-H), 1.53 (m, 1H, 11-H), 1.48 (m, 2H, 6-H, 9-H), 1.44 (m, 2H, 2-H), 1.40 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.29 (m, 1H, 21-H), 1.18 (m, 1H, 21-H), 1.15 (m, 1H, 7-H), 1.14 (m, 1H, 19-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.89 (m, 1H, 1-H), 0.88 (s, 6H, 23-H, 30-H), 0.87 (s, 6H, 25-H, 29-H), 0.72 (s, 3H, 24-H), 0.69 (s, 3H, 26-H), 0.65 (m, 1H, 5-H)

¹³C-NMR (100 MHz, CDCl₃)

δ : 175.6 (C-28), 170.5 (-OCOCH₃), 170.0 (-OCOCH₃), 169.4 (-OCOCH₃), 168.9 (-OCOCH₃), 142.8 (C-13), 122.8 (C-12), 91.5 (C-1'), 78.8 (C-3), 72.8 (C-3'), 72.4 (C-5'), 69.9 (C-2'), 68.0 (C-4'), 61.5 (C-6'), 55.1 (C-5), 47.5 (C-9), 46.8 (C-17), 45.7 (C-19), 41.6 (C-14), 39.3 (C-18), 38.7 (C-8), 38.4 (C-4), 36.8 (C-1), 33.7 (C-10), 32.9 (C-21), 32.8 (C-29), 32.8 (C-7), 31.7 (C-22), 30.5 (C-20), 28.0 (C-23), 27.7 (C-15), 27.1 (C-2), 25.6 (C-27), 23.3 (C-30), 22.8 (C-11), 20.6 (-OCOCH₃), 20.5 (-OCOCH₃), 20.5 (-OCOCH₃), 20.5 (-OCOCH₃), 18.2 (C-6), 16.9 (C-26), 15.5 (C-24), 15.3 (C-25)

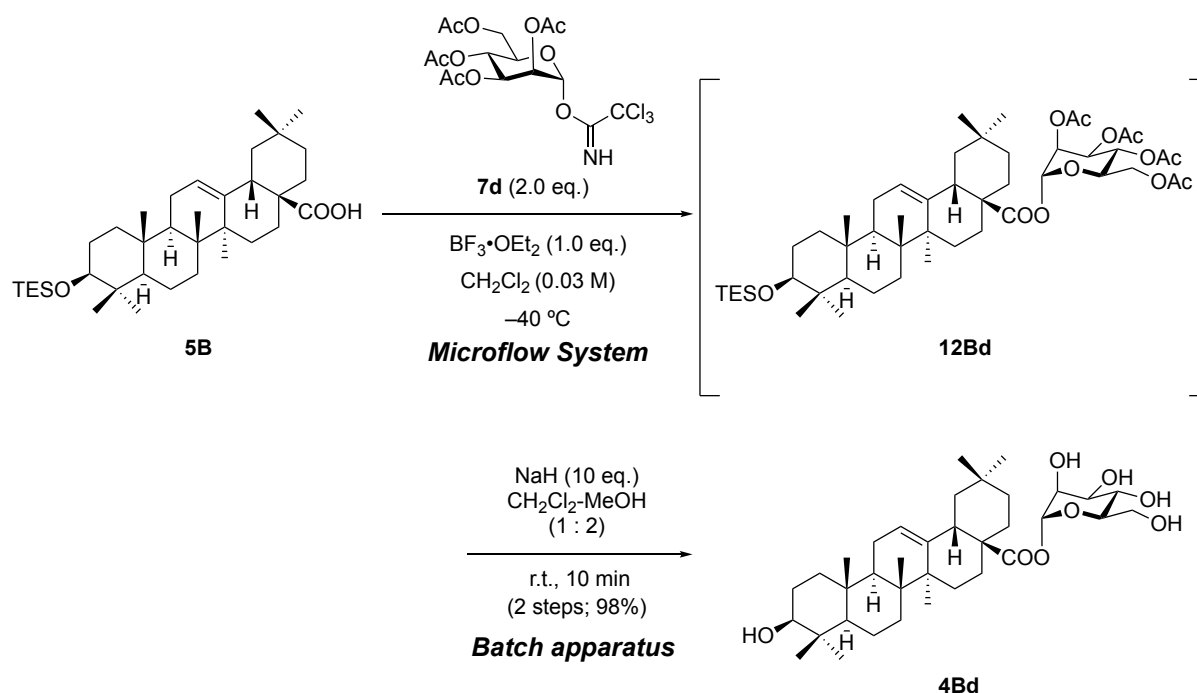
IR (KBr) cm⁻¹ ν : 3445 (-O-H), 2933 (=C-H), 1760 (-C=O), 1036 (-C-O-)

HR-MS (ESI⁺)

m/z 809.4444[M+Na]⁺, Calc'd for C₄₄H₆₆O₁₂Na: 809.4452.

Olean-12-en-28-oic acid, 3-hydroxy-, α -D-mannopyranosyl ester (**4Bd**)

[Continuous flow glycosylation and batch deprotection]



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (12.0 μL , 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7d** (94.2 mg, 0.191 mmol) and acceptor **5B** (54.6 mg, 0.096 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **12Bd** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 10 min at room temperature in flask which was added NaH (38.2 mg, 0.956 mmol, 60% disp.) and MeOH (12.0 mL) in advance. After the reaction was completed, the reaction mixture was acidified with Dowex H^+ resin to pH 4, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 25 g, CHCl_3 : MeOH = 40 : 1 \rightarrow 15 : 1) to afford **4Bd** (57.8 mg, 0.094 mmol, 98%) as a white solid by two steps.

$R_f = 0.53$ (CDCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{22} +67.9$ (c 0.24, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.89 (d, *J* = 1.6 Hz, 1H, 1'-H), 5.40 (t, *J* = 3.5 Hz, 1H, 12-H), 4.86 (dt, 9.5 Hz, 5.0 Hz, 1H, 4'-H), 4.68 (ddd, *J* = 10.0 Hz, 9.5 Hz, 6.5 Hz, 1H, 3'-H), 4.65 (ddd, *J* = 11.5 Hz, 6.0 Hz, 2.0 Hz, 1H, 6'-H), 4.63 (ddd, *J* = 10.0 Hz, 4.5 Hz, 1.6 Hz, 2'-H), 4.56 (ddd, *J* = 11.5 Hz, 6.5 Hz, 5.0 Hz, 1H, 6'-H), 4.51 (ddd, *J* = 9.5 Hz, 5.0 Hz, 2.0 Hz, 1H, 5'-H), 3.44 (ddd, *J* = 10.9 Hz, 5.4 Hz, 5.4 Hz, 1H, 3-H), 3.17 (dd, *J* = 13.8 Hz, 4.0 Hz, 1H, 18-H), 2.05 (m, 1H, 11-H), 2.02 (m, 2H, 2-H), 1.88 (m, 1H, 22-H), 1.85 (m, 2H, 16-H), 1.83 (m, 1H, 15-H), 1.78 (m, 1H, 11-H), 1.75 (m, 1H, 19-H), 1.64 (m, 1H, 9-H), 1.58 (m, 1H, 22-H), 1.53 (m, 1H, 1-H), 1.53 (m, 1H, 6-H), 1.47 (m, 1H, 7-H), 1.39 (m, 1H, 21-H), 1.34 (m, 1H, 7-H), 1.31 (m, 1H, 6-H), 1.24 (s, 3H, 23-H), 1.23 (m, 1H, 19-H), 1.21 (s, 3H, 27-H), 1.14 (m, 1H, 21-H), 1.11 (m, 1H, 15-H), 1.04 (s, 3H, 24-H), 1.00 (m, 1H, 1-H), 0.95 (s, 3H, 30-H), 0.93 (s, 3H, 26-H), 0.91 (s, 3H, 29-H), 0.86 (s, 3H, 25-H), 0.83 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.1 (C-28), 144.2 (C-13), 123.2 (C-12), 95.5 (C-1'), 78.5 (C-5'), 78.2 (C-3), 73.2 (C-3'), 71.4 (C-2'), 68.5 (C-4'), 62.8 (C-6'), 55.9 (C-5), 48.2 (C-9), 47.5 (C-17), 46.2 (C-19), 42.2 (C-14), 42.0 (C-18), 39.9 (C-8), 39.5 (C-4), 39.1 (C-1), 37.4 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.9 (C-22), 31.0 (C-20), 28.9 (C-23), 28.2 (C-15), 28.1 (C-2), 26.1 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.9 (C-6), 17.6 (C-26), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm⁻¹ ν: 3382 (-O-H), 2933 (=C-H), 1697 (-C=O)

HR-MS (ESI⁺)

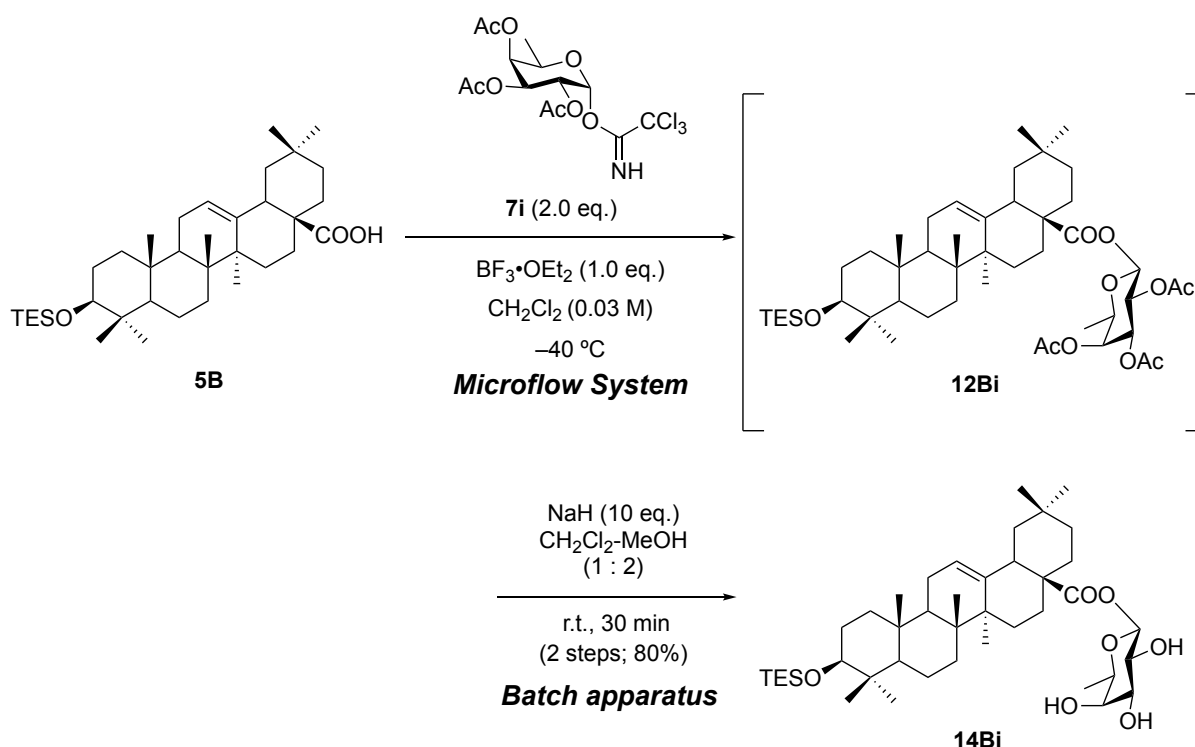
m/z 641.4014[M+Na]⁺, Calc'd for C₃₆H₅₈NaO₈: 641.4029

GATE-1 (400 MHz, pyridine-*d*₅)

δ : 96.3 (s), 94.6 (s), (C-1'), ¹*J*_{C,H} = 173.4 Hz.

Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, β -D-fucopyranosyloxy ester (14Bi**)**

[Continuous flow glycosylation and batch deprotection]



A solution of $\text{BF}_3 \cdot \text{OEt}_2$ (81.4 μL , 0.648 mmol) dissolved in CH_2Cl_2 (22.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **7i** (564 mg, 1.30 mmol) and acceptor **5B** (370 mg, 0.63 mmol) dissolved in CH_2Cl_2 (22.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in a thermostatic bath at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **12Bi** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which was added NaH (259 mg, 6.48 mmol, 60% disp.) and MeOH (88.0 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (30 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 25 g, CHCl_3 : $\text{MeOH} = 40 : 1$) to afford **14Bi** (372 mg, 0.519 mmol, 80%) as a white solid by two steps.

$R_f = 0.61$ (CHCl_3 : $\text{MeOH} = 5 : 1$)

$[\alpha]_{\text{D}}^{24} +42.9$ (*c* 0.306, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine-*d*₅)

δ : 6.18 (d, $J = 8.2$ Hz, 1H, 1'-H), 5.47 (t, $J = 3.5$ Hz, 1H, 12-H), 4.57 (m, 1H, 2'-H), 4.15 (dd, $J = 9.5$ Hz, 3.1 Hz, 1H, 3'-H), 4.07 (br s, 1H, 4'-H), 3.96 (dd, $J = 12.5$ Hz, 4.4 Hz, 1H, 5'-H), 3.30 (dd, $J = 11.3$ Hz, 4.3 Hz, 1H, 3-H), 3.24 (dd, $J = 14.0$ Hz, 4.1 Hz, 1H, 18-H), 2.34 (m, 1H, 2-H), 2.05 (m, 2H, 11-H), 1.97 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.69 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (d, $J = 6.4$ Hz, 3H, 6'-H), 1.54 (m, 1H, 6-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.25 (s, 3H, 27-H), 1.16 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.04 (s, 3H, 23-H), 1.03 (m, 9H, -Si(CH₂CH₃)₃), 1.01 (m, 1H, 1-H), 0.92 (s, 3H, 25-H), 0.91 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.89 (s, 3H, 24-H), 0.86 (m, 1H, 5-H), 0.64 (m, 6H, -Si(CH₂CH₃)₃)

$^{13}\text{C-NMR}$ (100 MHz, pyridine-*d*₅)

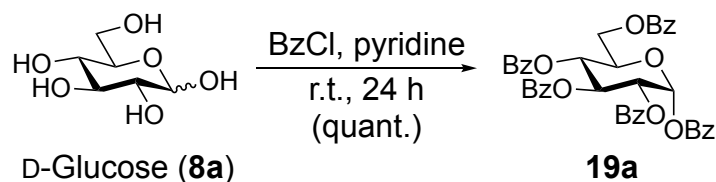
δ : 176.7 (C-28), 144.3 (C-13), 123.0 (C-12), 96.1 (C-1'), 79.9 (C-3), 75.9 (C-3'), 72.8 (C-5'), 72.6 (C-2'), 71.2 (C-4'), 55.7 (C-6'), 48.2 (C-5), 47.1 (C-9), 46.4 (C-17), 42.3 (C-19), 41.9 (C-14), 40.1 (C-18), 39.7 (C-8), 38.8 (C-4), 37.3 (C-1), 34.1 (C-10), 33.3 (C-21), 33.3 (C-29), 32.7 (C-7), 30.9 (C-22), 28.9 (C-20), 28.4 (C-23), 28.3 (C-15), 26.2 (C-2), 24.0 (C-27), 23.8 (C-30), 23.5 (C-16), 19.0 (C-11), 17.6 (C-6), 17.3 (C-26), 16.7 (C-24), 15.7 (C-25), 7.5 (-Si(CH₂CH₃)₃), 5.7 (-Si(CH₂CH₃)₃)

IR (KBr) cm^{-1} ν : 3529 (-O-H), 2909 (=C-H), 1748 (-C=O), 1068 (-C-O-)

HR-MS (ESI⁺)

m/z 739.4926[M+Na]⁺, Calc'd for C₄₂H₇₂O₇SiNa: 739.4945.

1, 2, 3, 4, 6-Penta-*O*-benzoyl- α -D-glucosyl benzoate (19a**)⁶³**



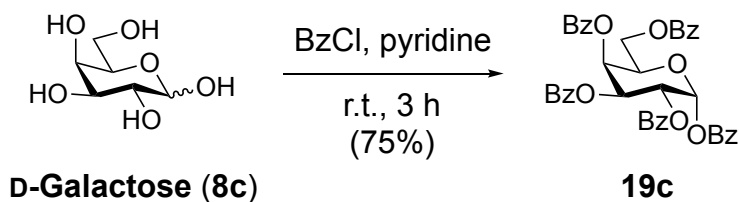
To a solution of commercial D-glucose (**8a**) (1.0 g, 5.55 mmol) in pyridine (28 mL) at 0 °C was added BzCl (4.0 mL, 33.3 mmol). After stirring for 24 h at room temperature, the reaction mixture was quenched with H₂O (10 mL) in ice bath. The resulting mixture was extracted with AcOEt (100 mL). The combined organic layer was washed with aq. CuSO₄ (3 x 50 mL) and H₂O (50 mL). The organic combined extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford pure **19a** as a white solid (α only, 4.07 g, 5.81 mmol, quant.) without further purification.

R_f = 0.57 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.19-7.29 (m, 25H, Ar-H), 6.86 (d, J = 3.7 Hz, 1H, 1-H), 6.33 (t, J = 10.0 Hz, 1H, 3-H), 5.87 (t, J = 10.0 Hz, 1H, 4-H), 5.69 (dd, J = 10.0 Hz, 3.7 Hz, 1H, 2-H), 4.65-4.60 (m, 2H, 5-H, 6-H), 4.49 (dd, J = 13.0 Hz, 4.8 Hz, 1H, 6-H)

1, 2, 3, 4, 6-Petra-*O*-benzoyl- α -D-galactosyl benzoate (19c**)**⁶³



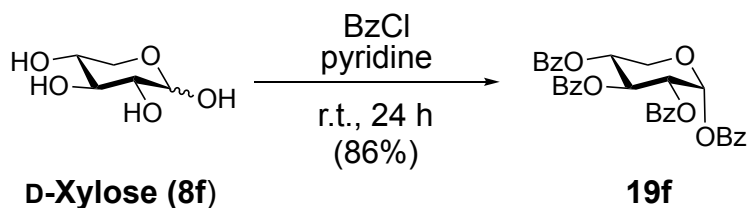
To a solution of commercial D-galactose (**8c**) (1.0 g, 5.55 mmol) in pyridine (28 mL) at 0 °C was added BzCl (4.0 mL, 33.3 mmol). After stirring for 3 h, at room temperature, the reaction mixture was quenched with sat. aq. NaHCO₃ (10 mL) in ice bath. The resulting mixture was extracted with AcOEt (100 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (2 x 50 mL), aq. CuSO₄ (3 x 50 mL) and brine (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 50 g, hexane : AcOEt = 3 : 1 → 1 : 1) to afford **19c** as a white foamy solid (α only, 2.89 g, 4.12 mmol, 75%).

$R_f = 0.57$ (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.13-7.27 (m, 25H, Ar-H), 6.95 (d, $J = 3.7$ Hz, 1H, 1-H), 6.19 (dd, $J = 3.3$ Hz, 1.3 Hz, 1H, 4-H), 6.13 (dd, $J = 10.3$ Hz, 3.3 Hz, 1H, 3-H), 6.03 (dd, $J = 10.3$ Hz, 3.7 Hz, 1H, 2-H), 4.84 (t, $J = 6.5$ Hz, 1H, 5-H), 4.63 (dd, $J = 10.8$ Hz, 6.5 Hz, 1H, 6-H), 4.43 (dd, $J = 10.8$ Hz, 7.1 Hz, 1H, 6-H)

1, 2, 3, 4-Tetra-*O*-benzoyl- α -D-xylosyl benzoate (19f**)**¹³⁷



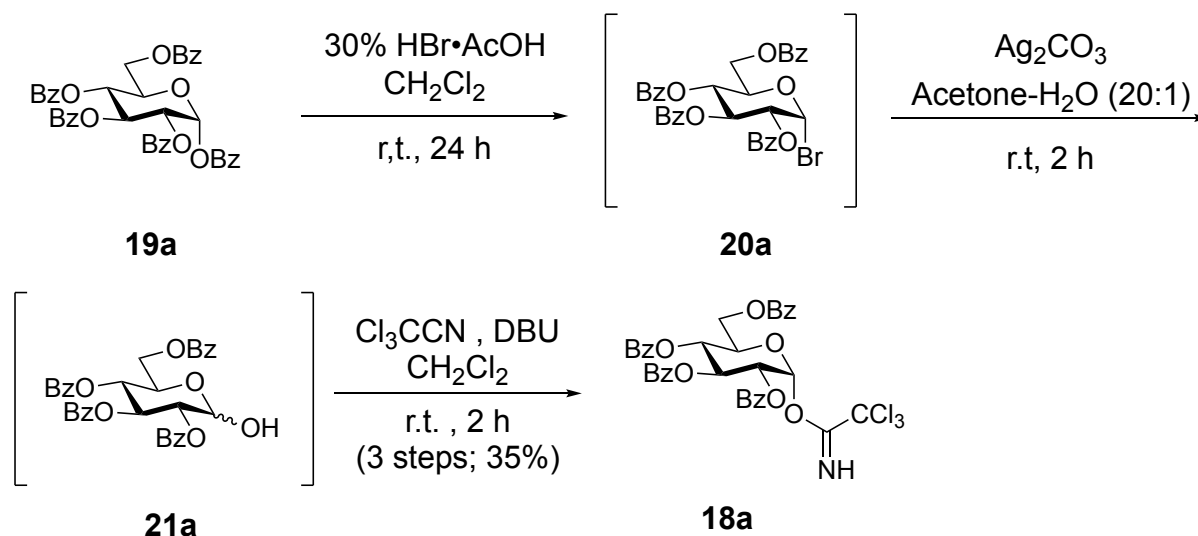
To a solution of commercial D-xylose (**8f**) (2.0 g, 13.3 mmol) in pyridine (50 mL) at 0 °C was added BzCl (12.3 mL, 107 mmol). After stirring for 24 h at room temperature, the reaction mixture was quenched with sat. aq. NaHCO₃ (50 mL) in ice bath. The resulting mixture was extracted with AcOEt (200 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (3 x 150 mL), sat. aq. CuSO₄ (3 x 150 mL), and H₂O (2 x 150 mL), brine (150 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **19f** as a pale yellow oil (α only, 6.47 g, 11.4 mmol, 86%) without further purification.

R_f = 0.42 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.18-7.29 (m, 20H, Ar-H), 6.76 (d, *J* = 3.7 Hz, 1H, 1-H), 6.28 (t, *J* = 9.9 Hz, 1H, 3-H), 5.63 (dd, *J* = 9.9 Hz, 3.7 Hz, 1H, 2-H), 5.54 (m, 1H, 4-H), 4.30 (dd, *J* = 11.0 Hz, 5.8 Hz, 1H, 5-H), 4.04 (t, *J* = 11.0 Hz, 1H, 5-H)

2, 3, 4, 6-Tetra-*O*-benzoyl- α -D-glucopyranosyl trichloroacetimidate (18a**)** ⁶³



To a solution of **19a** (3.40 g, 3.84 mmol) in dry CH₂Cl₂ (12 mL) at 0 °C was added 30% HBr/AcOH (8.0 mL). After stirring for 24 h at room temperature, the reaction mixture was quenched with H₂O (10 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (30 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (30 mL), and brine (15 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20a** as a mixture yellow oil.

To a solution of **20a** as a crude mixture of previous reaction in acetone (10.0 mL) and H₂O (0.50 mL) was added Ag₂CO₃ (700 mg, 2.54 mmol). After stirring for 2 h at room temperature, the reaction mixture was filtered by celite and rinsed with AcOEt (20 mL). The filtrate was concentrated *in vacuo* to afford **21a** as a pale yellow foamy solid.

To a solution of **21a** as a crude mixture of previous reaction in dry CH₂Cl₂ (20 mL) was added Cl₃CCN (2.30 mL, 22.79 mmol) followed by DBU (68.0 μ L, 0.456 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 20 g, hexane : AcOEt = 4 : 1 \rightarrow 3 : 1) to afford **18a** (α only, 1.01 g, 1.36 mmol, 35%) as a pale yellow foamy solid by three steps.

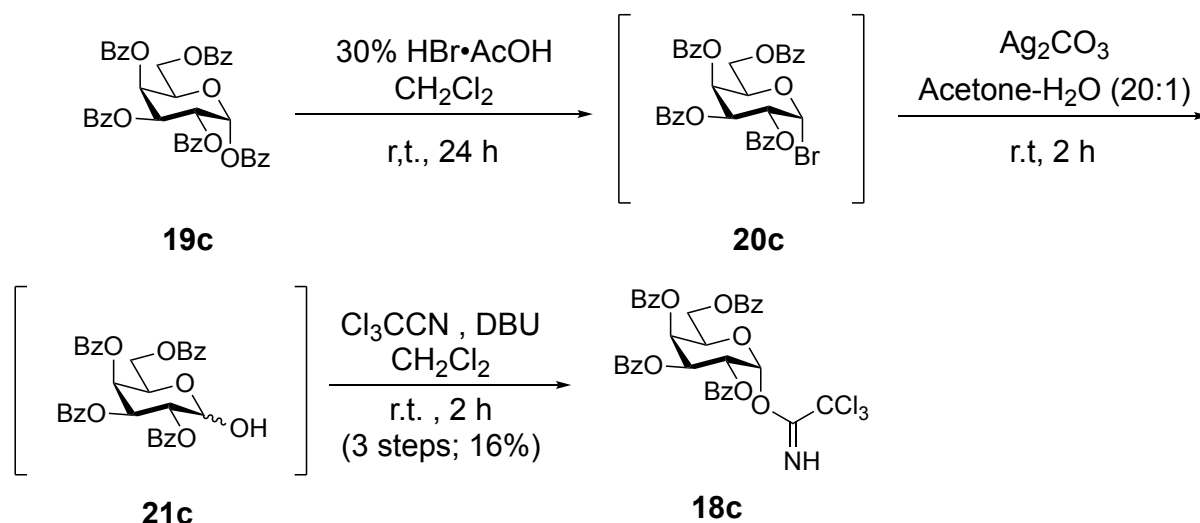
R_f = 0.58 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.63 (s, 1H, -NH), 8.05-7.30 (m, 20H, Ar-H), 6.84 (d, *J* = 3.7 Hz, 1H, 1-H), 6.28

(t, $J = 10.0$ Hz, 1H, 3-H), 5.81 (t, $J = 10.0$ Hz, 1H, 4-H), 5.62 (dd, $J = 10.0$ Hz, 3.7 Hz, 1H, 2-H), 4.67-4.62 (m, 2H, 5-H, 6-H), 4.49 (dd, $J = 12.0$ Hz, 5.5 Hz, 1H, 6-H)

2, 3, 4, 6-Tetra-*O*-benzoyl- α -D-galactopyranosyl trichloroacetimidate (18c**)**⁶⁴



To a solution of **19c** (1.84 g, 2.63 mmol) in dry CH₂Cl₂ (10 mL) at 0 °C was added 30% HBr/AcOH (9.0 mL). After stirring for 24 h at room temperature, the reaction mixture was quenched with H₂O (10 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (40 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (20 mL), and brine (20 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20c** as a mixture yellow oil.

To a solution of **20c** as a crude mixture of previous reaction in acetone (6 mL) and H₂O (0.3 mL) was added Ag₂CO₃ (383 mg, 1.39 mmol). After stirring for 2 h at room temperature, the reaction mixture was filtered by celite, and rinsed with AcOEt (20 mL). The resulting mixture was concentrated *in vacuo* to afford **21c** as a pale yellow foamy solid.

To a solution of **21c** as a crude mixture of previous reaction in dry CH₂Cl₂ (10 mL) was added Cl₃CCN (1.98 mL, 19.56 mmol) followed by DBU (72.8 μ L, 0.489 mmol). After stirring at room temperature for 2 h, the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 30 g, hexane : AcOEt = 4 : 1 \rightarrow 7 : 3) to afford **18c** (α only, 311 mg, 0.419 mmol, 16%) as a white foamy solid by three steps.

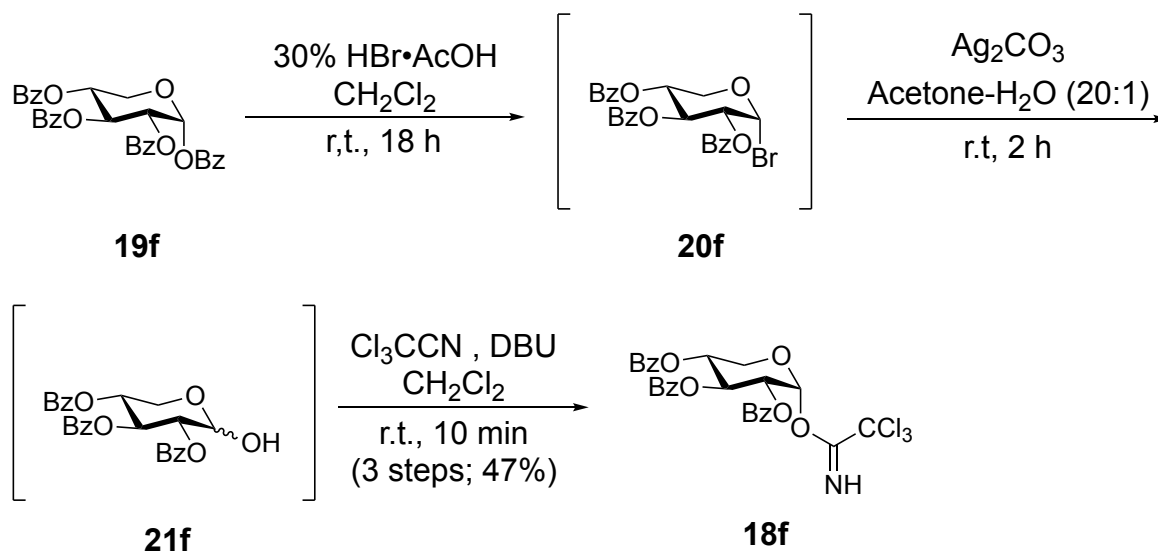
R_f = 0.58 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.64 (s, 1H, -NH), 8.11-7.34 (m, 20H, Ar-H), 6.92 (d, *J* = 3.6 Hz, 1H, 1-H), 6.16

(dd, $J = 3.3$ Hz, 1.3 Hz, 1H, 4-H), 6.08 (dd, $J = 10.3$ Hz, 3.3 Hz, 1H, 3-H), 5.96 (dd, $J = 10.3$ Hz, 3.6 Hz, 1H, 2-H), 4.87 (t, $J = 6.5$ Hz, 1H, 5-H), 4.62 (dd, $J = 10.8$ Hz, 6.5 Hz, 1H, 6-H), 4.44 (dd, $J = 12.1$ Hz, 6.1 Hz, 1H, 6-H)

2, 3, 4-Tri-*O*-benzoyl- α -D-xylopyranosyl trichloroacetimidate (18f**)** ⁶⁵



To a solution of **19f** (6.47 g, 11.4 mmol) in dry CH₂Cl₂ (50 mL) at 0 °C was added 30% HBr/AcOH (8.0 mL). After stirring for 18 h at room temperature, the reaction mixture was quenched with H₂O (50 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (100 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (3 x 100 mL), and brine (100 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20f** as a mixture yellow oil.

To a solution of **20f** as a crude mixture of previous reaction in acetone (24 mL) and H₂O (1.2 mL) was added Ag₂CO₃ (1.58 g, 5.71 mmol). After stirring for 2 h at room temperature, the reaction mixture was filtered by celite, and rinsed with AcOEt (50 mL). The filtrate was concentrated *in vacuo* to afford **21f** as a white foamy solid.

To a solution of **21f** as a crude mixture of previous reaction in dry CH₂Cl₂ (50 mL) was added Cl₃CCN (13.7 mL, 137.0 mmol) followed by DBU (510 μ L, 3.43 mmol). After stirring at room temperature for 10 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 250 g, hexane : AcOEt = 4 : 1 \rightarrow 7 : 3) to afford **18f** (α only, 3.23 g, 5.32 mmol, 47%) as a white foamy solid by three steps.

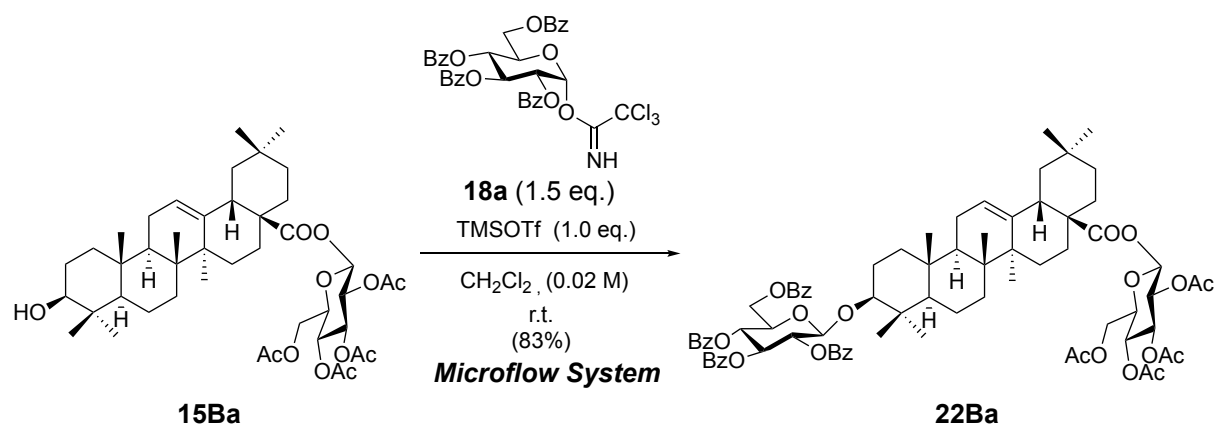
R_f = 0.47 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.63 (s, 1H, -NH), 8.16-7.31 (m, 15H, Ar-H), 6.74 (d, *J* = 3.7 Hz, 1H, 1-H), 6.25 (t, *J* = 10.0 Hz, 1H, 3-H), 5.57 (dd, *J* = 10.0 Hz, 3.7 Hz, 1H, 2-H), 5.52 (m, 1H, 4-H),

4.30 (dd, $J = 11.0$ Hz, 5.8 Hz, 1H, 5-H), 4.06 (t, $J = 11.0$ Hz, 1H, 5-H)

Olean-12-en-28-oic acid, 3-[(2, 3, 4, 6, -tetra-*O*-benzoyl- β -D-glucopyranosyl) oxy]-, 2, 3, 4, 6-tetra-*O*-acetyl- β -D-glucopyranosyl ester (22Ba**)**



A solution of TMSOTf (12.0 μ L, 0.064 mmol) dissolved in dry CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **18a** (71.0 mg, 0.094 mmol) and acceptor **15Ba** (50.0 mg, 0.064 mmol) dissolved in dry CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature for an additional 100 sec through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was quenched with triethylamine (9.0 μ L, 0.0640 mmol) diluted in CH_2Cl_2 . The resulting mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, toluene : AcOEt = 10 : 1 \rightarrow 6 : 1 \rightarrow 4 : 1) to afford **22Ba** (72.5 mg, 0.0531 mmol, 83%) as a white solid.

$R_f = 0.41$ (toluene : AcOEt = 4 : 1)

$[\alpha]_D^{22} +31.9$ (c 0.30, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 8.03-7.28 (m, 25H, Ar-H), 5.90 (t, $J = 9.5$ Hz, 1H, 3''-H), 5.58 (t, $J = 9.5$ Hz, 1H, 4''-H), 5.56 (dd, $J = 9.5$ Hz, 8.0 Hz, 1H, 2''-H), 5.55 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.32 (t, $J = 3.3$ Hz, 1H, 12-H), 5.24 (t, $J = 9.3$ Hz, 1H, 3'-H), 5.17 (dd, $J = 9.3$ Hz, 8.0 Hz, 1H, 2'-H), 5.12 (dd, $J = 10.0$ Hz, 9.3 Hz, 1H, 4'-H), 4.85 (d, $J = 8.0$ Hz, 1H, 1''-H), 4.59 (dd, $J = 12.0$ Hz, 3.6 Hz, 1H, 6''-H), 4.54 (dd, $J = 12.0$ Hz, 6.6 Hz, 1H, 6''-H), 4.27 (dd, $J = 12.5$ Hz, 4.4 Hz, 1H, 6'-H), 4.17-4.09 (m, 1H, 5''-H), 4.04 (dd, $J = 12.5$ Hz, 2.4 Hz, 1H, 6'-H), 3.78 (ddd, $J = 10.0$ Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.09 (m, 1H, 3-H), 2.82 (m, 1H, 18-H), 2.06 (s, 3H, $-\text{OCOCH}_3$), 2.02 (s, 3H, $-\text{OCOCH}_3$), 2.00 (s, 3H, $-\text{OCOCH}_3$).

-OCOCH₃), 1.99 (s, 3H, -OCOCH₃), 1.97 (m, 1H, 16-H), 1.84 (m, 2H, 2-H, 11-H), 1.82 (m, 1H, 2-H), 1.80 (m, 1H, 19-H), 1.78 (m, 2H, 22-H), 1.70 (m, 1H, 16-H), 1.42 (m, 2H, 1-H, 15-H), 1.39 (m, 1H, 9-H), 1.38 (m, 1H, 6-H), 1.33 (m, 2H, 7-H, 21-H), 1.26 (m, 1H, 6-H), 1.21 (m, 1H, 21-H), 1.16 (m, 1H, 19-H), 1.12 (m, 1H, 7-H), 1.08 (s, 3H, 27-H), 1.00 (m, 1H, 15-H), 0.91 (s, 6H, 29-H, 30-H), 0.83 (s, 3H, 25-H), 0.74 (m, 1H, 1-H), 0.68 (s, 6H, 23-H, 24-H), 0.63 (s, 3H, 26-H), 0.59 (m, 1H, 5-H)

¹³C-NMR (100 MHz, CDCl₃)

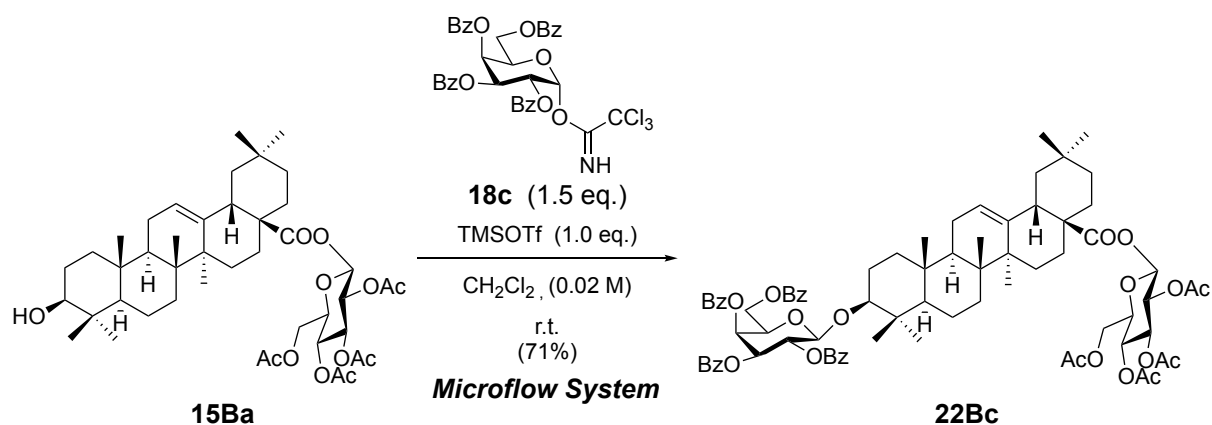
δ : 175.5 (C-28), 170.5 (-OCOCH₃), 170.0 (-OCOCH₃), 169.4 (-OCOCH₃), 168.9 (-OCOCH₃), 166.0 (-OCOPh), 165.8 (-OCOPh), 165.3 (-OCOPh), 160.0 (-OCOPh), 142.8 (C-13), 133.4, 133.2, 133.0, 133.0, 129.8, 129.7, 129.7, 129.7, 129.6, 129.4, 129.0, 128.8, 128.8, 128.4, 128.3, 128.3, 128.2, 128.2, 122.8 (C-12), 103.2 (C-1''), 91.5 (C-1'), 90.7 (C-3), 72.9 (C-3''), 72.8 (C-3'), 72.4 (C-5'), 72.1 (C-4''), 72.0 (C-5''), 70.3 (C-2''), 69.9 (C-2'), 68.0 (C-4'), 63.4 (C-6''), 61.5 (C-6'), 55.4 (C-5), 47.5 (C-9), 46.8 (C-17), 45.8 (C-19), 41.6 (C-14), 40.9 (C-18), 39.2 (C-8), 38.7 (C-1), 38.2 (C-4), 36.6 (C-10), 33.7 (C-21), 33.0 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 27.7 (C-23), 27.6 (C-15), 25.8 (C-2), 25.6 (C-27), 23.4 (C-30), 23.3 (C-16), 22.8 (C-11), 20.7 (-OCOCH₃), 20.5 (-OCOCH₃), 20.5 (-OCOCH₃), 20.5 (-OCOCH₃), 18.0 (C-6), 16.9 (C-26), 16.2 (C-24), 15.2 (C-25)

IR (KBr) cm⁻¹ ν : 2950 (=C-H), 1737 (-C=O), 1069 (-C-O-)

HR-MS (ESI⁺)

m/z 1387.6001[M+Na]⁺, Calc'd for C₇₈H₉₂O₂₁Na: 1387.6029.

Olean-12-en-28-oic acid, 3-[(2, 3, 4, 6, -tetra-*O*-benzoyl- β -D-galactopyranosyl)oxy]-, 2, 3, 4, 6-tetra-*O*-acetyl- β -D-glucopyranosyl ester (22Bc**)**



A solution of TMSOTf (35.0 μ L, 0.192 mmol) dissolved in CH₂Cl₂ (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18c** (213 mg, 0.288 mmol) and acceptor **15Ba** (150 mg, 0.192 mmol) dissolved in CH₂Cl₂ (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature for an additional 100 sec through a Teflon reactor tube (ϕ = 1.0 mm, l = 1.0 m), the reaction mixture was quenched with triethylamine (27 μ L, 0.1922 mmol) diluted in CH₂Cl₂ (1.0 mL). The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, toluene : AcOEt = 20 : 1 \rightarrow 18 : 1 \rightarrow 17 : 1) to afford **22Bc** (185 mg, 0.1355 mmol, 71%) as a white solid.

R_f = 0.54 (toluene : AcOEt = 4 : 1)

$[\alpha]_D^{23}$ +74.2 (c 0.35, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 8.12-7.34 (m, 25H, Ar-H), 5.95 (dd, J = 3.4 Hz, 1.0 Hz 1H, 4''-H), 5.83 (dd, J = 10.0 Hz, 8.0 Hz, 1H, 2''-H), 5.60 (dd, J = 10.0 Hz, 3.4 Hz, 1H, 3''-H), 5.57 (d, J = 8.0 Hz, 1H, 1'-H), 5.33 (t, J = 3.3 Hz, 1H, 12-H), 5.24 (t, J = 9.2 Hz, 1H, 3'-H), 5.17 (dd, J = 9.2 Hz, 8.0 Hz, 1H, 2'-H), 5.12 (dd, J = 10.0 Hz, 9.2 Hz, 1H, 4'-H), 4.82 (d, J = 8.0 Hz, 1H, 1''-H), 4.66 (dd, J = 11.6 Hz, 7.4 Hz, 1H, 6''-H), 4.43 (dd, J = 11.6 Hz, 6.0 Hz, 1H, 6''-H), 4.30 (ddd, J = 7.4 Hz, 6.0 Hz, 1.0 Hz, 1H, 5''-H), 4.27 (dd, J = 12.5 Hz, 4.4 Hz, 1H, 6'-H), 4.04 (dd, J = 12.5 Hz, 2.4 Hz, 1H, 6'-H), 3.78 (ddd, J = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.13 (m, 1H, 3-H), 2.82 (m, 1H, 18-H), 2.06 (s, 3H, -OCOCH₃),

2.02 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 1.99 (s, 3H, -OCOCH₃), 1.97 (m, 1H, 16-H), 1.86 (m, 1H, 2-H), 1.80 (m, 2H, 11-H), 1.76 (m, 1H, 2-H), 1.63 (m, 1H, 19-H), 1.62 (m, 2H, 22-H), 1.53 (m, 1H, 16-H), 1.42 (m, 1H, 1-H), 1.38 (m, 2H, 9-H, 15-H), 1.34 (m, 2H, 6-H, 7-H), 1.26 (m, 1H, 6-H), 1.18 (m, 2H, 21-H), 1.14 (m, 1H, 19-H), 1.12 (m, 1H, 7-H), 1.10 (s, 3H, 27-H), 1.01 (m, 1H, 15-H), 0.92 (s, 6H, 29-H, 30-H), 0.85 (s, 3H, 25-H), 0.76 (m, 1H, 1-H), 0.70 (s, 3H, 23-H), 0.69 (s, 3H, 26-H), 0.66 (s, 3H, 24-H), 0.62 (m, 1H, 5-H)

¹³C-NMR (100 MHz, CDCl₃)

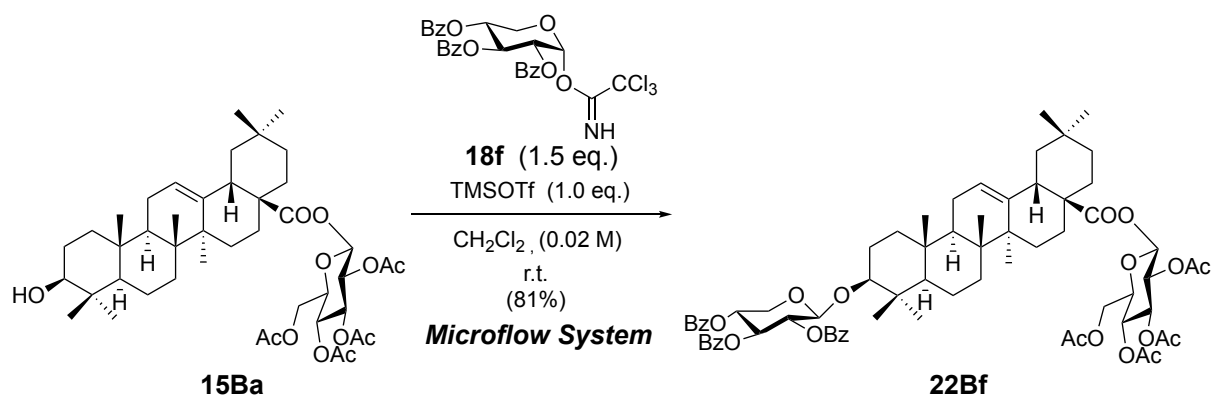
δ : 175.6 (C-28), 170.6 (-OCOCH₃), 170.1 (-OCOCH₃), 169.4 (-OCOCH₃), 168.9 (-OCOCH₃), 166.0 (-OCOPh), 165.7 (-OCOPh), 165.6 (-OCOPh), 165.2 (-OCOPh), 142.8 (C-13), 133.5, 133.2, 133.2, 133.0, 133.0, 129.7, 129.7, 129.5, 129.5, 129.0, 129.0, 128.9, 128.7, 128.5, 128.5, 128.4, 128.2, 122.8 (C-12), 103.8 (C-1''), 91.5 (C-1'), 90.9 (C-3), 72.8 (C-3'), 72.4 (C-5'), 71.8 (C-3''), 71.2 (C-5''), 71.0 (C-2''), 69.9 (C-2'), 68.2 (C-4''), 68.0 (C-4'), 62.1 (C-6''), 61.5 (C-6'), 55.4 (C-5), 47.5 (C-9), 46.8 (C-17), 45.8 (C-19), 41.6 (C-14), 39.3 (C-18), 38.7 (C-8), 38.3 (C-4), 36.6 (C-1), 33.7 (C-10), 33.0 (C-21), 32.8 (C-29), 31.7 (C-7), 30.6 (C-22), 29.7 (C-20), 27.7 (C-23), 27.7 (C-15), 25.9 (C-2), 25.6 (C-27), 23.4 (C-30), 23.3 (C-16), 22.8 (C-11), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 20.6 (-OCOCH₃), 18.0 (C-6), 16.9 (C-26), 16.2 (C-24), 15.2 (C-25)

IR (KBr) cm⁻¹ ν : 2952 (=C-H), 1735 (-C=O), 1069 (-C-O-)

HR-MS (ESI⁺)

m/z 1387.6019[M+Na]⁺, Calc'd for C₇₈H₉₂O₂₁Na: 1387.6029.

Olean-12-en-28-oic acid, 3-[(2, 3, 4, -tri-*O*-benzoyl- β -D-xylopyranosyl) oxy]-, 2, 3, 4, 6-tetra-*O*-acetyl- β -D-glucopyranosyl ester (22Bf**)**



A solution of TMSOTf (35.0 μ L, 0.192 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18f** (175 mg, 0.288 mmol) and acceptor **15Ba** (150 mg, 0.1922 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature for an additional 100 sec through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was quenched with triethylamine (27 μ L, 0.1922 mmol) diluted in CH_2Cl_2 (1.0 mL). The resulting mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, toluene : AcOEt = 20 : 1 \rightarrow 18 : 1 \rightarrow 17 : 1) to afford **22Bf** (193 mg, 0.157 mmol, 81%) as a white solid.

$R_f = 0.54$ (toluene : AcOEt = 4 : 1)

$[\alpha]_D^{23} +17.5$ (c 0.30, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 8.10-7.31 (m, 25H, Ar-H), 5.78 (t, $J = 8.0$ Hz, 1H, 3''-H), 5.57 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.44 (dd, $J = 8.0$ Hz, 6.1 Hz, 1H, 2'-H), 5.33 (t, $J = 3.3$ Hz, 1H, 12-H), 5.24 (t, $J = 9.3$ Hz, 1H, 3'-H), 5.17 (dd, $J = 9.3$ Hz, 8.0 Hz, 1H, 2'-H), 5.12 (dd, $J = 10.0$ Hz, 9.2 Hz, 1H, 4'-H), 4.84 (d, $J = 6.1$ Hz, 1H, 1''-H), 4.43 (dd, $J = 12.0$ Hz, 4.6 Hz, 1H, 5''-H), 4.27 (dd, $J = 12.5$ Hz, 4.4 Hz, 1H, 6'-H), 4.04 (dd, $J = 12.5$ Hz, 2.4 Hz, 1H, 6'-H), 3.78 (ddd, $J = 10.0$ Hz, 4.4 Hz, 2.4 Hz, 1H, 5'-H), 3.63 (dd, $J = 12.0$ Hz, 8.0 Hz, 1H, 5''-H), 3.13 (dd, $J = 11.5$ Hz, 4.8 Hz, 1H, 3-H), 2.81 (m, 1H, 18-H), 2.06 (s, 3H, -OCOCH₃), 2.02 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 2.00 (s, 3H, -OCOCH₃),

1.94 (m, 1H, 16-H), 1.86 (m, 2H, 11-H), 1.79 (m, 2H, 2-H), 1.64 (m, 2H, 1-H, 19-H), 1.61 (m, 2H, 22-H), 1.51 (m, 1H, 16-H), 1.48 (m, 1H, 9-H), 1.42 (m, 1H, 15-H), 1.39 (m, 2H, 6-H, 7-H), 1.26 (m, 2H, 6-H, 21-H), 1.22 (m, 1H, 21-H), 1.18 (m, 1H, 19-H), 1.14 (m, 1H, 7-H), 1.10 (s, 3H, 27-H), 1.03 (m, 1H, 15-H), 0.98 (m, 1H, 1-H), 0.90 (s, 6H, 29-H, 30-H), 0.89 (s, 3H, 25-H), 0.77 (s, 3H, 23-H), 0.70 (s, 3H, 26-H), 0.69 (m, 1H, 5-H), 0.65 (s, 3H, 24-H)

^{13}C -NMR (100 MHz, CDCl_3)

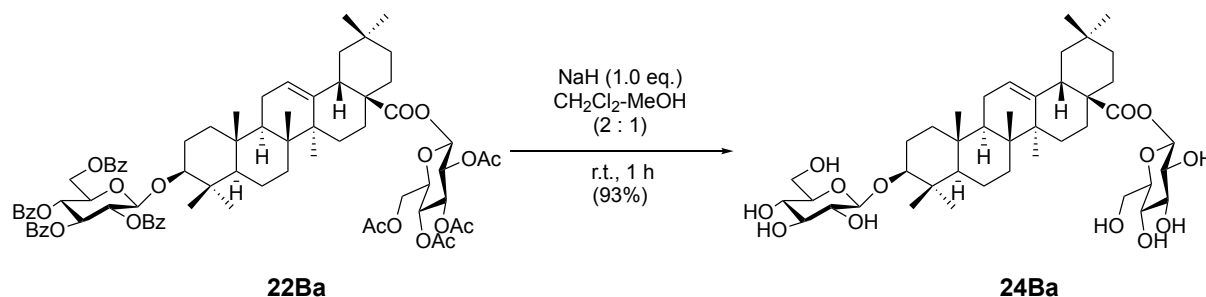
δ : 175.6 (C-28), 170.6 ($-\text{O}\text{C}\text{OCH}_3$), 170.0 ($-\text{O}\text{C}\text{OCH}_3$), 169.4 ($-\text{O}\text{C}\text{OCH}_3$), 168.9 ($-\text{O}\text{C}\text{OCH}_3$), 165.5 ($-\text{O}\text{C}\text{OPh}$), 165.5 ($-\text{O}\text{C}\text{OPh}$), 165.0 ($-\text{O}\text{C}\text{OPh}$), 142.8 (C-13), 135.8, 133.5, 133.3, 133.2, 133.0, 130.1, 129.8, 129.8, 129.4, 129.2, 129.1, 128.9, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 122.9 (C-12), 102.7 (C-1''), 91.5 (C-1'), 89.9 (C-3), 72.8 (C-3'), 72.4 (C-5'), 71.0 (C-2''), 69.9 (C-2'), 69.5 (C-4''), 68.0 (C-4'), 61.6 (C-5''), 61.5 (C-6'), 55.4 (C-5), 47.5 (C-9), 46.8 (C-17), 45.7 (C-19), 41.6 (C-14), 41.0 (C-18), 39.3 (C-8), 38.9 (C-4), 38.4 (C-1), 36.7 (C-10), 33.7 (C-21), 33.0 (C-29), 32.8 (C-7), 31.7 (C-22), 30.6 (C-20), 27.7 (C-23), 27.7 (C-15), 25.8 (C-2), 25.6 (C-27), 23.4 (C-30), 23.4 (C-16), 22.8 (C-11), 20.7 ($-\text{OCOCH}_3$), 20.6 ($-\text{OCOCH}_3$), 20.6 ($-\text{OCOCH}_3$), 20.5 ($-\text{OCOCH}_3$), 18.1 (C-6), 16.9 (C-26), 16.2 (C-24), 15.3 (C-25)

IR (KBr) cm^{-1} ν : 2946 (=C-H), 1759 (C=O), 1070 (C-O-)

HR-MS (ESI $^{+}$)

m/z 1253.5649[M+Na] $^{+}$, Calc'd for $\text{C}_{70}\text{H}_{86}\text{O}_{19}\text{Na}$: 1253.5661.

Olean-12-en-28-oic acid, 3-(β -D-glucopyranosyloxy)-, β -D-glucopyranosyl ester (24Ba)



To a solution of **22Ba** (100 mg, 0.073 mmol) in dry MeOH (1.4 mL) and CH₂Cl₂ (0.7 mL) was added NaH (3.0 mg, 0.073 mmol 60% disp.). After stirring for 1 h at room temperature, the reaction mixture was neutralized with Dowex H⁺ resin to pH 7, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl₃ : MeOH = 5 : 1 → 4 : 1 → 3 : 1) to afford **24Ba** (53 mg, 0.068 mmol, 93%) as a white solid.

R_f = 0.08 (CHCl₃ : MeOH = 5 : 1)

[α]_D²⁴ +18.4 (*c* 1.00, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.30 (d, *J* = 8.0 Hz, 1H, 1'-H), 5.40 (t, *J* = 3.3 Hz, 1H, 12-H), 4.91 (d, *J* = 8.0 Hz, 1H, 1''-H), 4.56 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.43 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6'-H), 4.38 (dd, *J* = 12.0 Hz, 5.0 Hz, 1H, 6'-H), 4.37 (dd, *J* = 12.0 Hz, 5.0 Hz, 1H, 6''-H), 4.34 (dd, *J* = 9.5 Hz, 9.0 Hz, 1H, 4'-H), 4.26 (dd, *J* = 9.0 Hz, 8.5 Hz, 1H, 3'-H), 4.22 (dd, *J* = 8.5 Hz, 8.0 Hz, 1H, 3''-H), 4.20 (dd, *J* = 9.0 Hz, 8.5 Hz, 1H, 4''-H), 4.18 (t, *J* = 8.5 Hz, 1H, 2'-H), 4.01 (t, *J* = 8.0 Hz, 1H, 2''-H), 4.00 (ddd, *J* = 9.5 Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 3.98 (ddd, *J* = 9.0 Hz, 5.0 Hz, 2.0 Hz, 1H, 5''-H), 3.39 (dd, *J* = 14.0 Hz, 4.2 Hz, 1H, 3-H), 3.21 (dd, *J* = 14.0 Hz, 3.9 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.32 (s, 3H, 23-H), 1.28 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.11 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 3H, 24-H), 0.96 (m, 1H, 1-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.6 (C-28), 144.3 (C-13), 123.2 (C-12), 107.0 (C-1''), 95.9 (C-1'), 89.0 (C-3), 79.5 (C-5'), 78.9 (C-3'), 78.8 (C-3''), 78.4 (C-5''), 75.9 (C-2''), 74.2 (C-2'), 71.9 (C-4''), 71.2 (C-4'), 63.1 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.4 (C-23), 28.4 (C-15), 26.7 (C-2), 26.3 (C-27), 23.9 (C-30), 23.8 (C-16), 23.5 (C-11), 18.7 (C-6), 17.6 (C-26), 17.1 (C-24), 15.7 (C-25)

IR (KBr) cm^{-1} ν : 3441 (-O-H), 2939 (=C-H), 1735 (-C=O), 1069 (-C-O-)

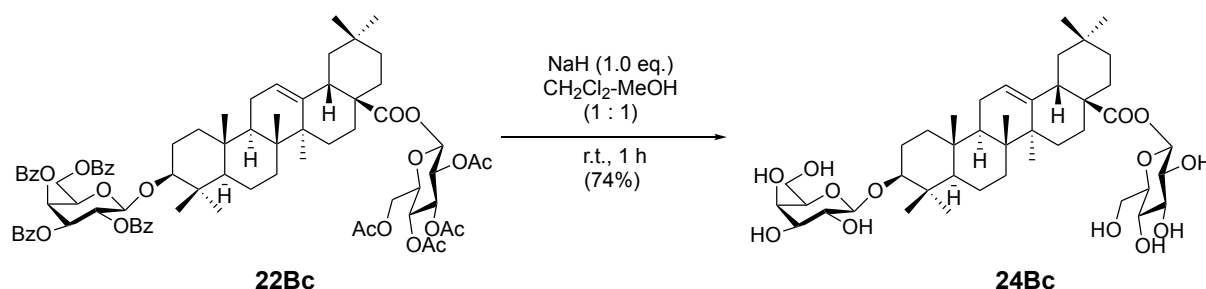
HR-MS (ESI⁺)

m/z 803.4558[M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na: 803.4558

TOCSY (400 MHz, pyridine-*d*₅)

mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-(β-D-galactopyranosyloxy)-, β-D-glucopyranosyl ester (24Bc)



To a solution of **22Bc** (137 mg, 0.1003 mmol) in dry MeOH (1.0 mL) and CH₂Cl₂ (1.0 mL) was added NaH (4.0 mg, 0.1003 mmol 60% disp.). After stirring at room temperature for 1 h, the reaction mixture was neutralized with Dowex H⁺ resin to pH 7, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 20 g, CHCl₃ : MeOH = 5 : 1 → 4 : 1 → 3 : 1) to afford **24Bc** (58 mg, 0.0743 mmol, 74%) as a white solid.

R_f = 0.36 (CHCl₃ : MeOH = 3 : 1)

[α]_D²⁴ +24.2 (c 1.00, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.33 (d, *J* = 8.0 Hz, 1H, 1'-H), 5.43 (t, *J* = 3.3 Hz, 1H, 12-H), 4.87 (d, *J* = 8.0 Hz, 1H, 1''-H), 4.60 (dd, *J* = 3.0 Hz, 1.0 Hz, 1H, 4''-H), 4.50 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H, 6''-H), 4.48 (dd, *J* = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.46 (dd, *J* = 9.0 Hz, 8.0 Hz, 1H, 2''-H), 4.45 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H, 6''-H), 4.41 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H, 6'-H), 4.37 (dd, *J* = 9.5 Hz, 9.0 Hz, 1H, 4'-H), 4.30 (dd, *J* = 9.0 Hz, 8.5 Hz, 1H, 3'-H), 4.22 (dd, *J* = 8.5 Hz, 8.0 Hz, 1H, 2'-H), 4.19 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H, 3''-H), 4.13 (td, *J* = 6.0 Hz, 1.0 Hz, 1H, 5''-H), 4.04 (ddd, *J* = 9.5 Hz, 4.0 Hz, 3.0 Hz, 1H, 5'-H), 3.37 (dd, *J* = 12.0 Hz, 4.5 Hz, 1H, 3-H), 3.19 (dd, *J* = 14.0 Hz, 3.9 Hz, 1H, 18-H), 2.35 (m, 1H, 15-H), 2.26 (m, 1H, 2-H), 2.08 (m, 2H, 11-H), 1.95 (m, 2H, 16-H), 1.81 (m, 1H, 2-H), 1.76 (m, 2H, 22-H), 1.72 (m, 1H, 19-H), 1.61 (m, 1H, 9-H), 1.40 (m, 2H, 1-H, 6-H), 1.43 (m, 1H, 7-H), 1.34 (m, 2H, 21-H), 1.31 (m, 1H, 6-H), 1.29 (s, 3H, 23-H), 1.26 (s, 3H, 27-H), 1.23 (m, 1H, 19-H), 1.17 (m, 1H, 15-H), 1.09 (s, 3H, 26-H), 1.04 (m, 1H, 7-H), 0.96 (s, 3H, 24-H), 0.93 (m, 1H, 1-H), 0.90 (s, 3H, 29-H), 0.88 (s, 3H, 30-H), 0.82 (s, 3H, 25-H), 0.77 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.6 (C-28), 144.3 (C-13), 123.2 (C-12), 107.0 (C-1''), 95.9 (C-1'), 88.9 (C-3), 79.5 (C-5'), 78.9 (C-3'), 76.9 (C-5''), 75.5 (C-3''), 74.2 (C-2'), 73.2 (C-2''), 71.1 (C-4'), 70.3 (C-4''), 62.5 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.2 (C-21), 33.3 (C-29), 33.3 (C-7), 32.7 (C-22), 31.0 (C-20), 28.4 (C-23), 28.4 (C-15), 26.8 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.7 (C-6), 17.6 (C-26), 17.2 (C-24), 15.7 (C-25)

IR (KBr) cm^{-1} ν : 3398 (-O-H), 2948 (=C-H), 1735 (-C=O), 1074 (-C-O-)

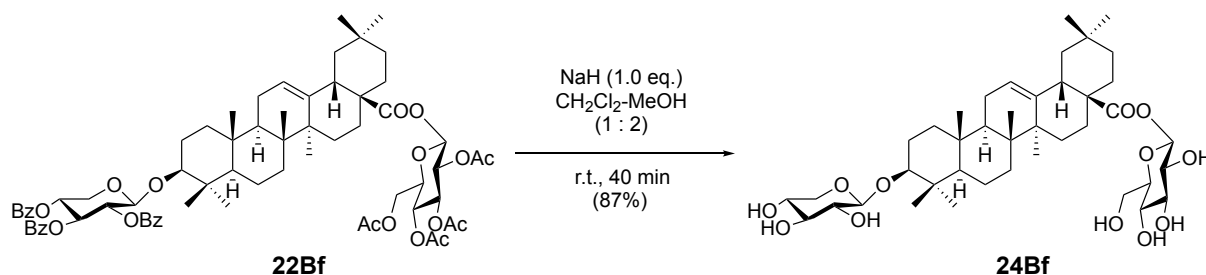
HR-MS (ESI⁺)

m/z 803.4551[M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na: 803.4558

TOCSY (400 MHz, pyridine-*d*₅)

mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-(β -D-xylopyranosyloxy)-, β -D-glucopyranosyl ester (24Bf)



To a solution of **22Bf** (163 mg, 0.1003 mmol) in dry MeOH (2.6 mL) and CH₂Cl₂ (1.3 mL) was added NaH (10.6 mg, 0.1003 mmol, 60% disp.). After stirring for 40 min at room temperature, the reaction mixture was neutralized with Dowex H⁺ resin to pH 7, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl₃ : MeOH = 10 : 1) to afford **24Bf** (77.9 mg, 0.1037 mmol, 87%) as a white solid.

R_f = 0.48 (CHCl₃ : MeOH = 3 : 1)

[α]_D²⁴ +20.6 (*c* 1.00, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.33 (d, *J* = 8.5 Hz, 1H, 1'-H), 5.44 (t, *J* = 3.3 Hz, 1H, 12-H), 4.84 (d, *J* = 7.5 Hz, 1H, 1''-H), 4.47 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6'-H), 4.41 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H, 6''-H), 4.39 (dd, *J* = 11.0 Hz, 5.0 Hz, 1H, 5''-H), 4.38 (dd, *J* = 9.5 Hz, 9.0 Hz, 1H, 4'-H), 4.30 (t, *J* = 9.0 Hz, 1H, 3'-H), 4.24 (ddd, *J* = 10.0 Hz, 8.5 Hz, 5.0 Hz, 1H, 4''-H), 4.21 (dd, *J* = 9.0 Hz, 8.5 Hz, 1H, 2'-H), 4.18 (t, *J* = 8.5 Hz, 1H, 3''-H), 4.04 (ddd, *J* = 9.5 Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 4.03 (dd, *J* = 8.5 Hz, 7.5 Hz, 1H, 2''-H), 3.79 (dd, *J* = 11.0 Hz, 5.0 Hz, 1H, 5''-H), 3.36 (dd, *J* = 12.0 Hz, 4.5 Hz, 1H, 3-H), 3.21 (dd, *J* = 14.0 Hz, 3.9 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.20 (m, 1H, 2-H), 2.13 (m, 2H, 11-H), 2.00 (m, 2H, 16-H), 1.94 (m, 1H, 2-H), 1.92 (m, 2H, 22-H), 1.77 (m, 1H, 19-H), 1.66 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.47 (m, 2H, 6-H, 7-H), 1.37 (m, 2H, 21-H), 1.31 (s, 3H, 23-H), 1.29 (m, 1H, 6-H), 1.27 (s, 3H, 27-H), 1.25 (m, 1H, 19-H), 1.19 (m, 1H, 15-H), 1.12 (s, 3H, 26-H), 1.08 (m, 1H, 7-H), 1.00 (s, 3H, 24-H), 0.98 (m, 1H, 1-H), 0.93 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.88 (s, 3H, 25-H), 0.83 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.7 (C-28), 144.3 (C-13), 123.1 (C-12), 107.8 (C-1'), 95.9 (C-1'), 88.8 (C-3),

79.5 (C-5'), 78.9 (C-3'), 78.7 (C-3''), 75.6 (C-2''), 74.2 (C-2'), 71.2 (C-4''), 71.1 (C-4'), 67.3 (C-5''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 39.0 (C-1), 37.2 (C-10), 34.2 (C-21), 33.3 (C-29), 33.3 (C-7), 32.7 (C-22), 31.0 (C-20), 28.4 (C-23), 28.4 (C-15), 26.9 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.7 (C-6), 17.6 (C-26), 17.1 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3390 (-O-H), 2959 (=C-H), 1730 (-C=O), 1075 (-C-O-)

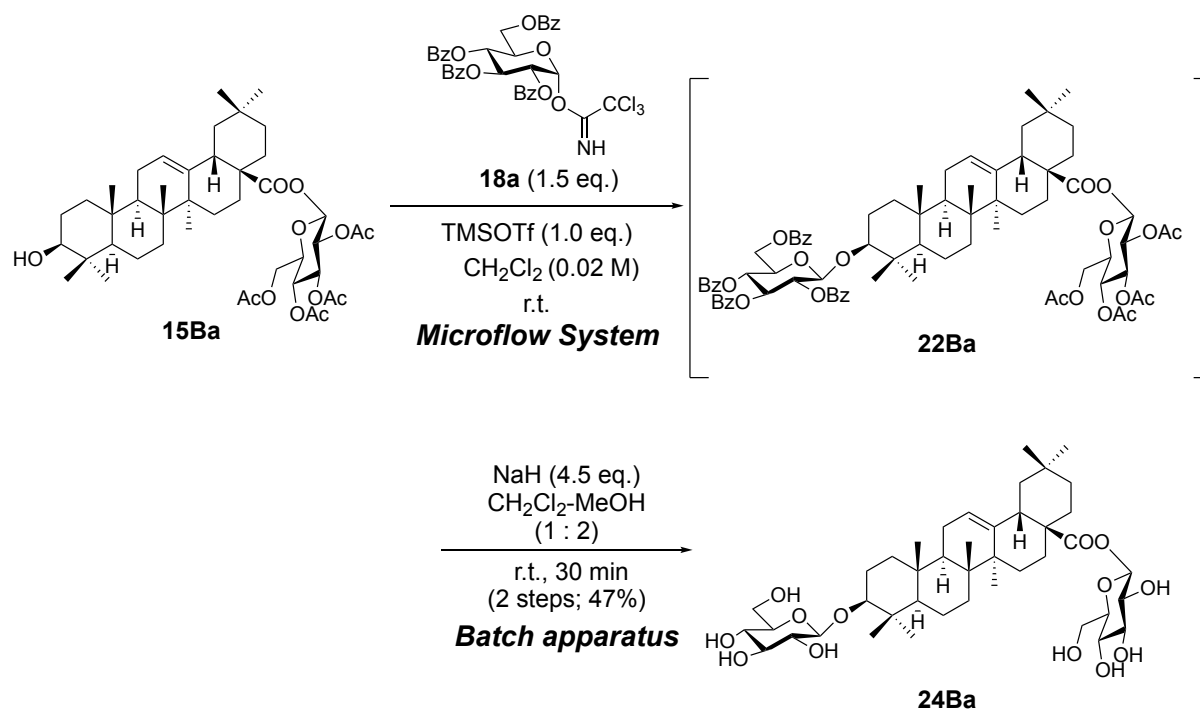
HR-MS (ESI⁺)

m/z 773.4455[M+Na]⁺, Calc'd for C₄₁H₆₆O₁₂Na: 773.4452

TOCSY (400 MHz, pyridine-*d*₅)

mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-(β -D-glucopyranosyloxy)-, β -D-glucopyranosyl ester (24Ba)



A solution of TMSOTf (11.5 μL , 0.064 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (71.0 mg, 0.095 mmol) and acceptor **15Ba** (50.0 mg, 0.064 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **22Ba** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (11.5 mg, 0.286 mmol, 60% disp.) and MeOH (12 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 10 : 1 \rightarrow 8 : 1 \rightarrow 6 : 1) to afford **24Ba** (23.3 mg, 0.030 mmol, 47%) as a white solid by two steps.

$R_f = 0.08$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_D^{24} + 18.4$ (c 1.00, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.30 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.40 (t, $J = 3.3$ Hz, 1H, 12-H), 4.91 (d, $J = 8.0$ Hz, 1H, 1''-H), 4.56 (dd, $J = 12.0$ Hz, 2.0 Hz, 1H, 6''-H), 4.43 (dd, $J = 12.0$ Hz, 2.0 Hz, 1H, 6'-H), 4.38 (dd, $J = 12.0$ Hz, 5.0 Hz, 1H, 6'-H), 4.37 (dd, $J = 12.0$ Hz, 5.0 Hz, 1H, 6''-H), 4.34 (dd, $J = 9.5$ Hz, 9.0 Hz, 1H, 4'-H), 4.26 (dd, $J = 9.0$ Hz, 8.5 Hz, 1H, 3'-H), 4.22 (dd, $J = 8.5$ Hz, 8.0 Hz, 1H, 3''-H), 4.20 (dd, $J = 9.0$ Hz, 8.5 Hz, 1H, 4''-H), 4.18 (t, $J = 8.5$ Hz, 1H, 2'-H), 4.01 (t, $J = 8.0$ Hz, 1H, 2''-H), 4.00 (ddd, $J = 9.5$ Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 3.98 (ddd, $J = 9.0$ Hz, 5.0 Hz, 2.0 Hz, 1H, 5''-H), 3.39 (dd, $J = 14.0$ Hz, 4.2 Hz, 1H, 3-H), 3.21 (dd, $J = 14.0$ Hz, 3.9 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.32 (s, 3H, 23-H), 1.28 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.11 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 3H, 24-H), 0.96 (m, 1H, 1-H), 0.92 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

δ : 176.6 (C-28), 144.3 (C-13), 123.2 (C-12), 107.0 (C-1'), 95.9 (C-1'), 89.0 (C-3), 79.5 (C-5'), 78.9 (C-3'), 78.8 (C-3''), 78.4 (C-5''), 75.9 (C-2''), 74.2 (C-2'), 71.9 (C-4''), 71.2 (C-4'), 63.1 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.7 (C-22), 30.9 (C-20), 28.4 (C-23), 28.4 (C-15), 26.7 (C-2), 26.3 (C-27), 23.9 (C-30), 23.8 (C-16), 23.5 (C-11), 18.7 (C-6), 17.6 (C-26), 17.1 (C-24), 15.7 (C-25)

IR (KBr) cm^{-1} ν : 3441 (-O-H), 2939 (=C-H), 1735 (-C=O), 1069 (-C-O-)

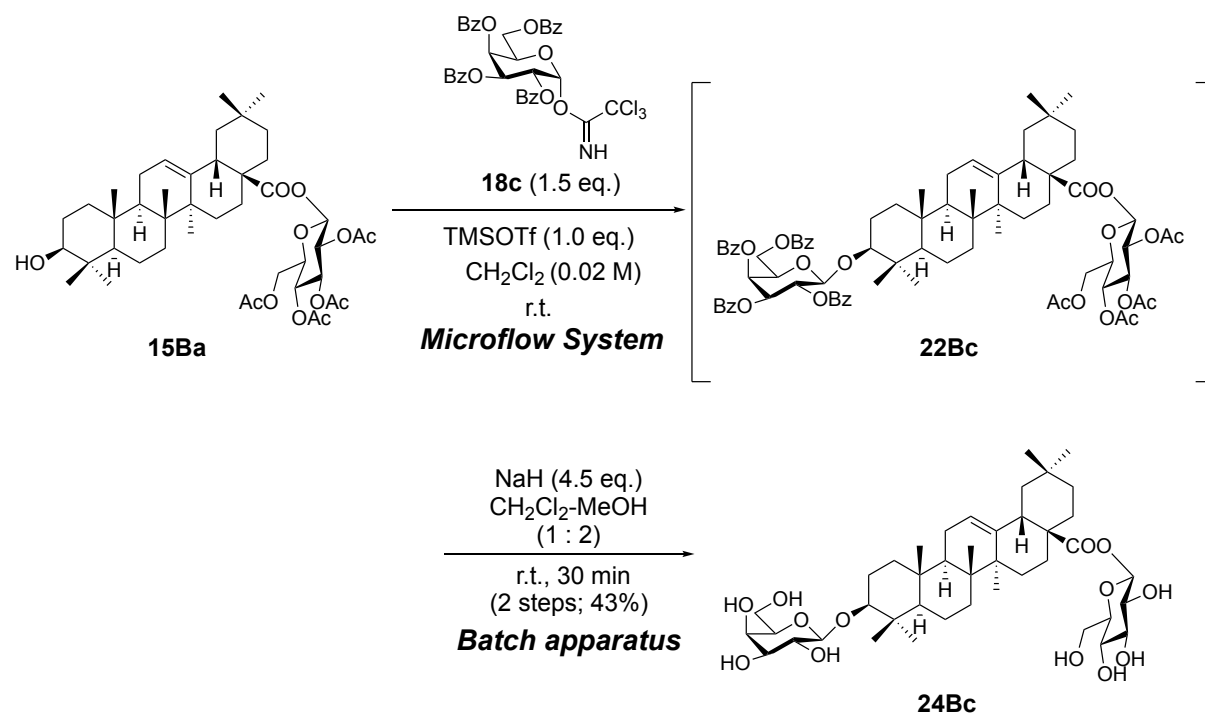
HR-MS (ESI⁺)

m/z 803.4558[M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na: 803.4558

TOCSY (400 MHz, pyridine- d_5)

mixing time $\tau_m = 150$ ms.

Olean-2-en-28-oic acid, 3-(β -D-galactopyranosyloxy)-, β -D-glucopyranosyl ester (24Bc)



A solution of TMSOTf (11.5 μL , 0.064 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18c** (71.0 mg, 0.095 mmol) and acceptor **15Bc** (50.0 mg, 0.064 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed in at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **22Bc** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (11.5 mg, 0.286 mmol, 60% disp.) and MeOH (12 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 10 : 1 \rightarrow 8 : 1 \rightarrow 6 : 1) to afford **24Bc** (21.5 mg, 0.028 mmol, 43%) as a white solid by two steps.

$R_f = 0.36$ (CHCl_3 : MeOH = 3 : 1)

$[\alpha]_{\text{D}}^{24} + 24.2$ (*c* 1.00, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 6.33 (d, $J = 8.0$ Hz, 1H, 1'-H), 5.43 (t, $J = 3.3$ Hz, 1H, 12-H), 4.87 (d, $J = 8.0$ Hz, 1H, 1''-H), 4.60 (dd, $J = 3.0$ Hz, 1.0 Hz, 1H, 4''-H), 4.50 (dd, $J = 12.0$ Hz, 6.0 Hz, 1H, 6''-H), 4.48 (dd, $J = 12.0$ Hz, 3.0 Hz, 1H, 6'-H), 4.46 (dd, $J = 9.0$ Hz, 8.0 Hz, 1H, 2''-H), 4.45 (dd, $J = 12.0$ Hz, 6.0 Hz, 1H, 6''-H), 4.41 (dd, $J = 12.0$ Hz, 4.0 Hz, 1H, 6'-H), 4.37 (dd, $J = 9.5$ Hz, 9.0 Hz, 1H, 4'-H), 4.30 (dd, $J = 9.0$ Hz, 8.5 Hz, 1H, 3'-H), 4.22 (dd, $J = 8.5$ Hz, 8.0 Hz, 1H, 2'-H), 4.19 (dd, $J = 9.0$ Hz, 3.0 Hz, 1H, 3''-H), 4.13 (td, $J = 6.0$ Hz, 1.0 Hz, 1H, 5''-H), 4.04 (ddd, $J = 9.5$ Hz, 4.0 Hz, 3.0 Hz, 1H, 5'-H), 3.37 (dd, $J = 12.0$ Hz, 4.5 Hz, 1H, 3-H), 3.19 (dd, $J = 14.0$ Hz, 3.9 Hz, 1H, 18-H), 2.35 (m, 1H, 15-H), 2.26 (m, 1H, 2-H), 2.08 (m, 2H, 11-H), 1.95 (m, 2H, 16-H), 1.81 (m, 1H, 2-H), 1.76 (m, 2H, 22-H), 1.72 (m, 1H, 19-H), 1.61 (m, 1H, 9-H), 1.40 (m, 2H, 1-H, 6-H), 1.43 (m, 1H, 7-H), 1.34 (m, 2H, 21-H), 1.31 (m, 1H, 6-H), 1.29 (s, 3H, 23-H), 1.26 (s, 3H, 27-H), 1.23 (m, 1H, 19-H), 1.17 (m, 1H, 15-H), 1.09 (s, 3H, 26-H), 1.04 (m, 1H, 7-H), 0.96 (s, 3H, 24-H), 0.93 (m, 1H, 1-H), 0.90 (s, 3H, 29-H), 0.88 (s, 3H, 30-H), 0.82 (s, 3H, 25-H), 0.77 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

δ : 176.6 (C-28), 144.3 (C-13), 123.2 (C-12), 107.0 (C-1'), 95.9 (C-1'), 88.9 (C-3), 79.5 (C-5'), 78.9 (C-3'), 76.9 (C-5''), 75.5 (C-3''), 74.2 (C-2'), 73.2 (C-2''), 71.1 (C-4'), 70.3 (C-4''), 62.5 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.2 (C-21), 33.3 (C-29), 33.3 (C-7), 32.7 (C-22), 31.0 (C-20), 28.4 (C-23), 28.4 (C-15), 26.8 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.7 (C-6), 17.6 (C-26), 17.2 (C-24), 15.7 (C-25)

IR (KBr) cm^{-1} ν : 3398 (-O-H), 2948 (=C-H), 1735 (-C=O), 1074 (-C-O-)

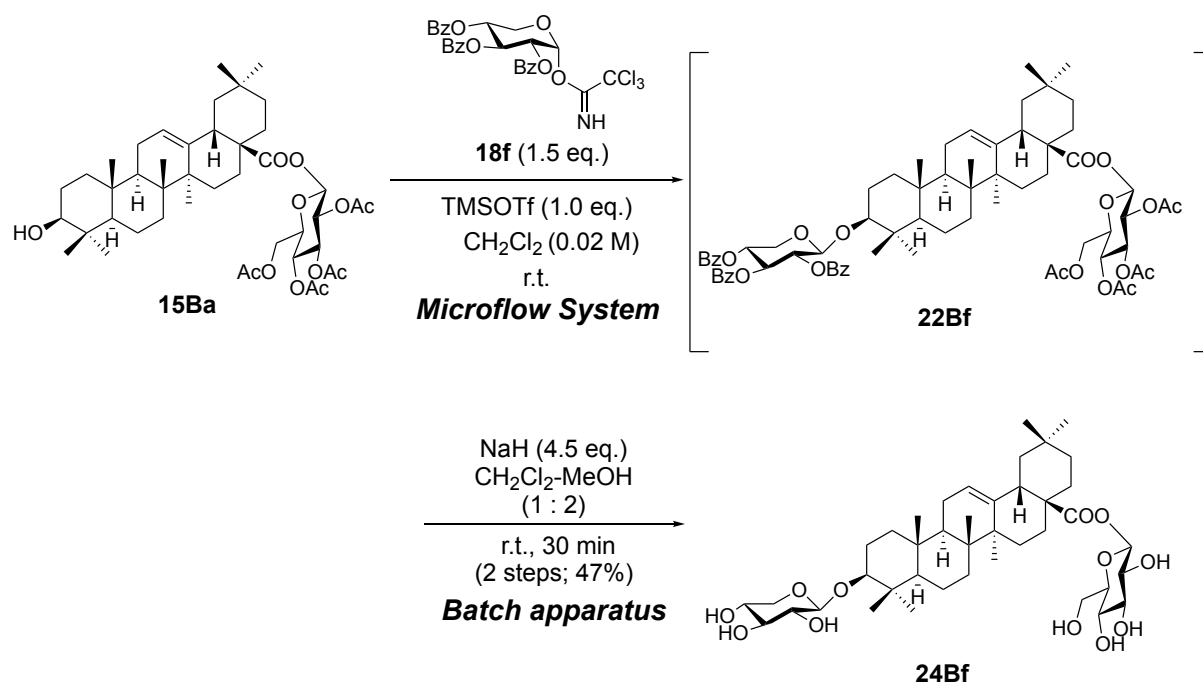
HR-MS (ESI⁺)

m/z 803.4551 [M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na: 803.4558

TOCSY (400 MHz, pyridine- d_5)

mixing time $\tau_m = 150$ ms.

Olean-12-en-28-oic acid, 3-(β -D-xylopyranosyloxy)-, β -D-glucopyranosyl ester (24Bf)



A solution of TMSOTf (11.5 μL , 0.064 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **18f** (71.0 mg, 0.095 mmol) and acceptor **15Ba** (50.0 mg, 0.064 mmol) dissolved in CH_2Cl_2 (3.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **22Bf** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube.

The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (11.5 mg, 0.286 mmol, 60% disp.) and MeOH (12 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 10 : 1 \rightarrow 9 : 1) to afford **24Bf** (22.5 mg, 0.030 mmol, 47%) as a white solid by two steps.

$R_f = 0.48$ (CHCl_3 : MeOH = 3 : 1)

$[\alpha]_{\text{D}}^{24} +20.6$ (c 1.00, MeOH)

^1H -NMR (400 MHz, pyridine- d_5)

δ : 6.33 (d, J = 8.5 Hz, 1H, 1'-H), 5.44 (t, J = 3.3 Hz, 1H, 12-H), 4.84 (d, J = 7.5 Hz, 1H, 1''-H), 4.47 (dd, J = 12.0 Hz, 2.0 Hz, 1H, 6'-H), 4.41 (dd, J = 12.0 Hz, 4.0 Hz, 1H, 6''-H), 4.39 (dd, J = 11.0 Hz, 5.0 Hz, 1H, 5''-H), 4.38 (dd, J = 9.5 Hz, 9.0 Hz, 1H, 4'-H), 4.30 (t, J = 9.0 Hz, 1H, 3'-H), 4.24 (ddd, J = 10.0 Hz, 8.5 Hz, 5.0 Hz, 1H, 4''-H), 4.21 (dd, J = 9.0 Hz, 8.5 Hz, 1H, 2'-H), 4.18 (t, J = 8.5 Hz, 1H, 3''-H), 4.04 (ddd, J = 9.5 Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 4.03 (dd, J = 8.5 Hz, 7.5 Hz, 1H, 2''-H), 3.79 (dd, J = 11.0 Hz, 5.0 Hz, 1H, 5''-H), 3.36 (dd, J = 12.0 Hz, 4.5 Hz, 1H, 3-H), 3.21 (dd, J = 14.0 Hz, 3.9 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.20 (m, 1H, 2-H), 2.13 (m, 2H, 11-H), 2.00 (m, 2H, 16-H), 1.94 (m, 1H, 2-H), 1.92 (m, 2H, 22-H), 1.77 (m, 1H, 19-H), 1.66 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.47 (m, 2H, 6-H, 7-H), 1.37 (m, 2H, 21-H), 1.31 (s, 3H, 23-H), 1.29 (m, 1H, 6-H), 1.27 (s, 3H, 27-H), 1.25 (m, 1H, 19-H), 1.19 (m, 1H, 15-H), 1.12 (s, 3H, 26-H), 1.08 (m, 1H, 7-H), 1.00 (s, 3H, 24-H), 0.98 (m, 1H, 1-H), 0.93 (s, 3H, 29-H), 0.90 (s, 3H, 30-H), 0.88 (s, 3H, 25-H), 0.83 (m, 1H, 5-H)

^{13}C -NMR (100 MHz, pyridine- d_5)

δ : 176.7 (C-28), 144.3 (C-13), 123.1 (C-12), 107.8 (C-1'), 95.9 (C-1'), 88.8 (C-3), 79.5 (C-5'), 78.9 (C-3'), 78.7 (C-3''), 75.6 (C-2''), 74.2 (C-2'), 71.2 (C-4''), 71.1 (C-4'), 67.3 (C-5''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.7 (C-4), 39.0 (C-1), 37.2 (C-10), 34.2 (C-21), 33.3 (C-29), 33.3 (C-7), 32.7 (C-22), 31.0 (C-20), 28.4 (C-23), 28.4 (C-15), 26.9 (C-2), 26.3 (C-27), 24.0 (C-30), 23.8 (C-16), 23.6 (C-11), 18.7 (C-6), 17.6 (C-26), 17.1 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} v : 3390 (-O-H), 2959 (=C-H), 1730 (-C=O), 1075 (-C-O-)

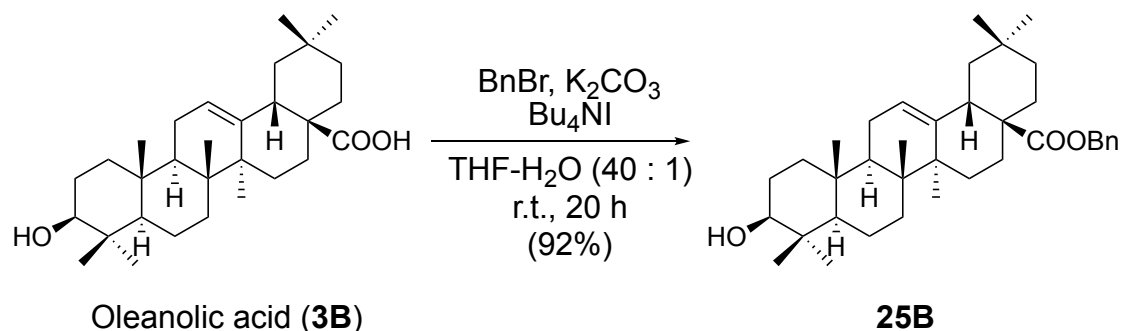
HR-MS (ESI $^+$)

m/z 773.4455[M+Na] $^+$, Calc'd for $\text{C}_{41}\text{H}_{66}\text{O}_{12}\text{Na}$: 773.4452

TOCSY (400 MHz, pyridine- d_5)

mixing time τ_m = 150 ms.

28-benzyl oleanolic acid (**25B**)



To a solution of commercial oleanolic acid (**3B**) (5.0 g, 10.9 mmol) in THF-H₂O (41 mL 40 : 1) was added K₂CO₃ (3.0 g, 21.8 mmol), Bu₄NI (403 mg, 1.09 mmol), and BnBr (2.1 mL, 17.5 mmol). After stirring for 20 h at room temperature, the reaction mixture was filtered by celite, and rinsed with AcOEt (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 250 g, hexane : AcOEt = 8 : 1) to afford **25B** (5.51 g, 10.1 mmol, 92%) as a white solid.

$R_f = 0.35$ (hexane : AcOEt = 3 : 1)

$[\alpha]_D^{23} +60.4$ (c 1.00, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 7.33 (m, 5H, PhCH₂), 5.29 (t, $J = 3.5$ Hz, 1H, 12-H), 5.07 (each d, $J = 12.7$ Hz, 2H, PhCH₂), 3.21 (m, 1H, 3-H), 2.90 (dd, $J = 14.0$ Hz, 4.8 Hz, 1H, 18-H), 1.97 (m, 1H, 11-H), 1.86 (m, 2H, 16-H), 1.76 (m, 1H, 22-H), 1.61 (m, 3H, 11-H, 15-H, 19-H), 1.57 (m, 1H, 22-H), 1.56 (m, 1H, 1-H), 1.53 (m, 2H, 6-H), 1.52 (m, 1H, 9-H), 1.49 (m, 2H, 2-H), 1.41 (m, 1H, 7-H), 1.34 (m, 1H, 21-H), 1.27 (m, 1H, 7-H), 1.21 (m, 1H, 21-H), 1.15 (m, 1H, 19-H), 1.12 (s, 3H, 27-H), 1.07 (m, 1H, 15-H), 0.98 (s, 3H, 30-H), 0.92 (m, 1H, 1-H), 0.92 (s, 3H, 23-H), 0.89 (s, 3H, 25-H), 0.88 (s, 3H, 29-H), 0.77 (s, 3H, 24-H), 0.61 (s, 3H, 26-H), 0.69 (m, 1H, 5-H)

¹³C-NMR (100 MHz, CDCl₃)

δ : 177.4 (C-28), 143.7 (C-13), 136.4, 128.4, 127.9, 127.9 (-CH₂Ph), 122.5 (C-12), 79.0 (C-3), 65.9 (-CH₂Ph), 55.2 (C-5), 47.6 (C-9), 46.7 (C-17), 46.0 (C-19), 41.7 (C-14), 41.4 (C-18), 39.3 (C-8), 38.7 (C-4), 38.4 (C-1), 37.0 (C-10), 33.9 (C-21), 33.1 (C-29), 32.7 (C-7), 32.4 (C-22), 30.7 (C-20), 28.1 (C-23), 27.6 (C-15), 27.2 (C-2), 25.9 (C-27), 23.6 (C-30), 23.4 (C-16), 23.0 (C-11), 18.3 (C-6), 16.9 (C-26), 15.6 (C-24),

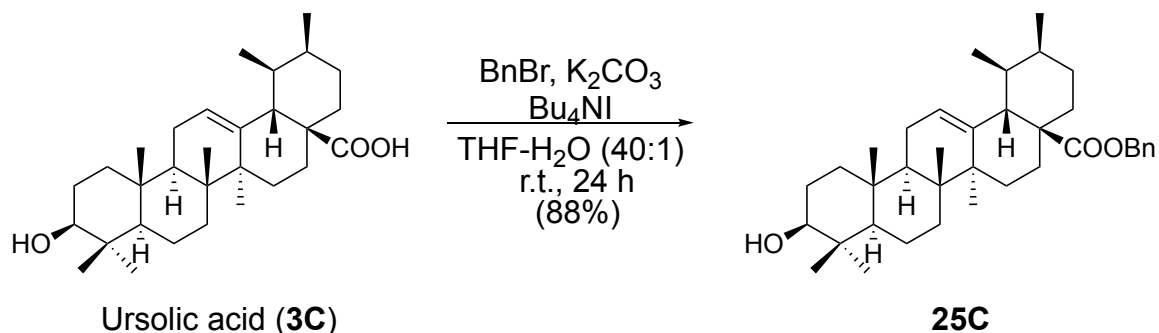
15.3 (C-25)

IR (KBr) cm^{-1} ν : 3583 (-O-H), 2938 (=C-H), 1726 (-C=O)

HR-MS (ESI⁺)

m/z 569.3952[M+Na]⁺, Calc'd for C₃₇H₅₄O₃Na:569.3971.

28-benzyl ursolic acid (**25C**)



To a solution of commercial ursolic acid (**3C**) (300 mg, 0.657 mmol) in THF- H_2O (6.5 mL 40 : 1) was added K_2CO_3 (182 mg, 1.31 mmol), Bu_4NI (24.3 mg, 0.066 mmol), and BnBr (124 μL , 1.05 mmol). After stirring for 24 h at room temperature, the reaction mixture was filtered by celite, rinsed with AcOEt (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, hexane : AcOEt = 8 : 1 \rightarrow 3 : 1) to afford **25C** (316 mg, 0.578 mmol, 88%) as a white solid.

R_f = 0.35 (hexane : AcOEt = 3 : 1)

$[\alpha]_{\text{D}}^{24} +49.5$ (c 1.00, CHCl_3)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 7.33 (m, 5H, PhCH_2), 5.23 (t, J = 3.6 Hz, 1H, 12-H), 5.04 (each d, J = 12.7 Hz, 2H, PhCH_2), 3.21 (dd, J = 11.1 Hz, 4.8 Hz, 1H, 3-H), 2.26 (d, J = 11.6 Hz, 1H, 18-H), 2.04 (m, 1H, 15-H), 1.99 (dd, J = 13.2 Hz, 4.6 Hz, 2H, 22-H), 1.89-1.78 (m, 2H, 6-H, 16-H), 1.75-1.57 (m, 4H, 1-H, 15-H, 16-H, 21-H), 1.56-1.40 (m, 4H, 6-H, 7-H, 9-H, 21-H), 1.37-1.24 (m, 4H, 2-H, 7-H, 19-H), 1.07 (s, 3H, 27-H), 1.05-1.01 (m, 1H, 20-H), 0.98 (s, 3H, 23-H), 0.97 (m, 1H, 11-H), 0.93 (d, J = 6.4 Hz, 3H, 29-H), 0.89 (s, 3H, 26-H), 0.85 (d, J = 6.4 Hz, 3H, 30-H), 0.78 (s, 3H, 24-H), 0.72-0.69 (m, 2H, 1-H, 5-H), 0.64 (s, 3H, 25-H)

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3)

δ : 177.2 (C-28), 138.1 (C-13), 136.3, 128.4, 128.1, 127.9 ($-\text{CH}_2\text{Ph}$), 125.7 (C-12), 79.0 (C-3), 65.9 ($-\text{CH}_2\text{Ph}$), 55.2 (C-5), 52.9 (C-18), 48.1 (C-17), 47.5 (C-9), 42.0 (C-14), 39.5 (C-20), 39.1 (C-19), 38.8 (C-4), 38.7 (C-1), 38.6 (C-8), 36.9 (C-22), 36.6 (C-10), 33.0 (C-7), 30.6 (C-21), 28.1 (C-23), 27.9 (C-2), 27.2 (C-15), 24.2 (C-16), 23.5 (C-27), 23.2 (C-11), 21.1 (C-30), 18.3 (C-6), 17.0 (C-29), 16.9 (C-24), 15.6 (C-26),

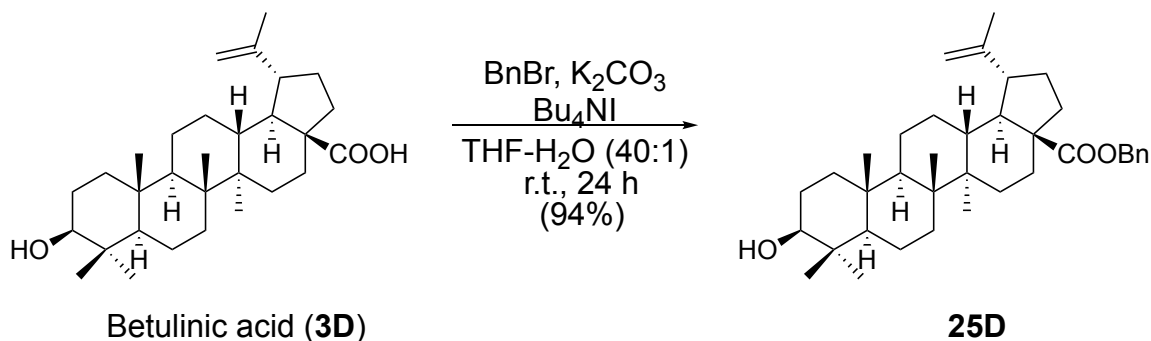
15.4 (C-25)

IR (KBr) cm^{-1} ν : 3449 (-O-H), 2926 (=C-H), 1722 (-C=O), 1138 (-C-O-)

HR-MS (ESI⁺)

m/z 569.3964[M+Na]⁺, Calc'd for C₃₇H₅₄O₃Na:569.3971.

28-benzyl betulinic acid (**25D**)



To a solution of commercial betulinic acid (**3D**) (300 mg, 0.657 mmol) in THF-H₂O (6.5 mL 40 : 1) was added K₂CO₃ (182 mg, 1.31 mmol), Bu₄NI (24.3 mg, 0.066 mmol), and BnBr (124 μ L, 1.05 mmol). After stirring for 24 h at room temperature, the reaction mixture was filtered by celite, rinsed with AcOEt (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, hexane : AcOEt = 8 : 1) to afford **25D** (338 mg, 0.618 mmol, 94%) as a white solid.

R_f = 0.30 (hexane : AcOEt = 3 : 1)

$[\alpha]_D^{24} +12.9$ (c 1.00, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 7.37-7.31 (m, 5H, PhCH₂), 5.11 (each d, J = 12.7 Hz, 2H, PhCH2), 3.20-3.15 (m, 1H, 3-H), 3.05-0.64 (m, other aliphatic ring protons), 0.96, 0.94, 0.80, 0.76, 0.75 (each s, 3H, 23-H, 24-H, 25-H, 26-H, 27-H)

¹³C-NMR (100 MHz, CDCl₃)

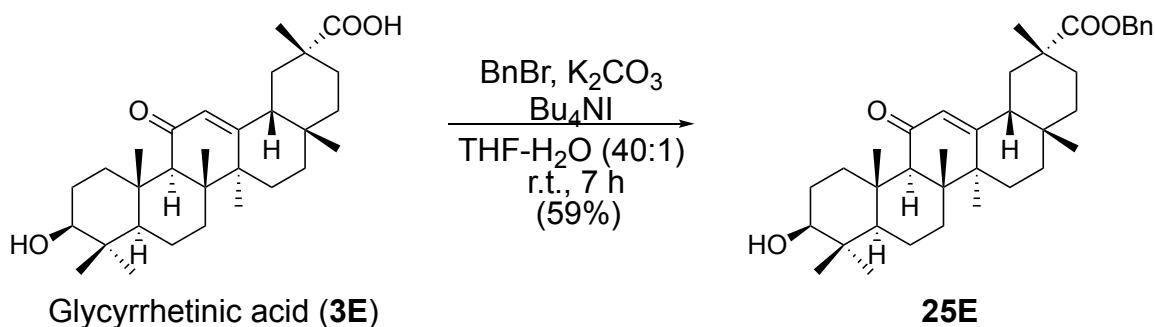
δ : 175.8 (C-28), 150.5 (C-20), 128.5, 128.1, 128.2, 128.0 (-CH₂Ph), 109.5 (C-29), 78.9 (C-3), 65.7 (-CH₂Ph), 56.5 (C-17), 55.3 (C-5), 50.5 (C-9), 49.4 (C-18), 46.9 (C-19), 42.3 (C-14), 40.6 (C-8), 38.8 (C-4), 38.7 (C-1), 38.1 (C-13), 37.1 (C-10), 36.9 (C-22), 32.1 (C-7), 34.3 (C-16), 30.6 (C-21), 29.6 (C-23), 28.0 (C-2), 27.4 (C-15), 25.5 (C-12), 20.9 (C-11), 19.4 (C-30), 18.3 (C-6), 16.1 (C-26), 15.8 (C-25), 15.3 (C-24), 14.7 (C-27)

IR (KBr) cm⁻¹ ν : 3558 (-O-H), 2942 (=C-H), 1694 (-C=O), 1074 (-C-O-)

HR-MS (ESI⁺)

m/z 569.3957[M+Na]⁺, Calc'd for C₃₇H₅₄O₃Na:569.3971.

30-benzyl glycyrrhetic acid (**25E**)



To a solution of commercial glycyrrhetic acid (**3E**) (1.0 g, 2.12 mmol) in THF-H₂O (20 mL, 40 : 1) was added K₂CO₃ (586 mg, 4.25 mmol), Bu₄NI (78.3 mg, 0.212 mmol), and BnBr (403 μ L, 3.40 mmol). After stirring for 7 h at room temperature, the reaction mixture was filtered by celite, rinsed with AcOEt (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 50 g, hexane : AcOEt = 8 : 1 \rightarrow 7 : 1 \rightarrow 6 : 1) to afford **25E** (698 mg, 1.24 mmol, 59%) as a pale yellow solid.

$R_f = 0.45$ (hexane : AcOEt = 3 : 1)

$[\alpha]_D^{23} +145.9$ (c 1.00, CHCl₃)

¹H-NMR (400 MHz, CDCl₃)

δ : 7.40-7.30 (m, 5H, PhCH₂), 5.55 (s, 1H, 12-H), 5.14 (each d, $J = 12.3$ Hz, 2H, PhCH₂), 3.22 (m, 1H, 3-H), 2.79 (dt, $J = 13.6$ Hz, 3.6 Hz, 1H, 1-H), 2.32 (s, 1H, 9-H), 2.05 (m, 1H, 18-H), 1.99 (m, 2H, 15-H, 21-H), 1.81 (m, 1H, 19-H), 1.67 (m, 1H, 7-H), 1.63 (m, 2H, 2-H, 19-H), 1.57 (m, 1H, 6-H), 1.41 (m, 1H, 6-H), 1.38 (m, 1H, 7-H), 1.35 (s, 3H, 27-H), 1.32 (m, 1H, 22-H), 1.30 (m, 1H, 21-H), 1.28 (m, 1H, 16-H), 1.28 (m, 1H, 22-H), 1.25 (m, 1H, 15-H), 1.18 (m, 1H, 15-H), 1.16 (s, 3H, 28-H), 1.13 (s, 3H, 25-H), 1.11 (s, 3H, 26-H), 1.00 (s, 3H, 23-H), 0.95 (m, 1H, 1-H), 0.80 (s, 3H, 24-H), 0.73 (s, 3H, 29-H), 0.69 (m, 1H, 5-H)

¹³C-NMR (100 MHz, CDCl₃)

δ : 200.1 (C-11), 176.2 (C-30), 168.9 (C-13), 136.1, 128.6, 128.6 (-CH₂Ph), 128.5 (C-12), 128.3, 128.2, 128.2, 78.7 (C-3), 66.2 (-CH₂Ph), 61.8 (C-9), 54.9 (C-5), 48.2 (C-18), 45.3 (C-8), 44.0 (C-20), 43.1 (C-14), 41.0 (C-19), 39.1 (C-1), 39.1 (C-4), 37.6 (C-22), 37.0 (C-10), 32.7 (C-7), 31.7 (C-17), 31.1 (C-21), 28.4 (C-29), 28.3 (C-23), 28.1 (C-28), 27.3 (C-2), 26.4 (C-16), 26.4 (C-15), 23.3 (C-27), 18.6 (C-26), 17.5 (C-6),

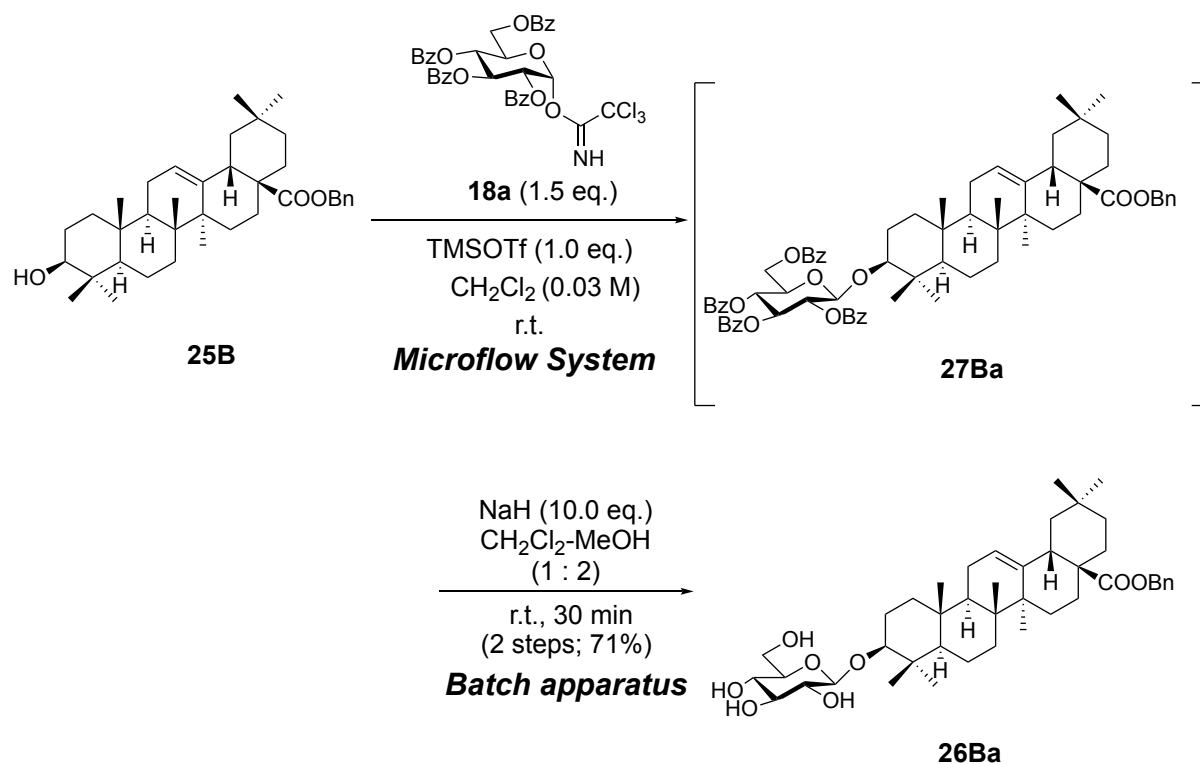
16.3 (C-25), 15.6 (C-24)

IR (KBr) cm^{-1} ν : 3450 (-O-H), 2946 (=C-H), 1729 (-C=O), 1151 (-C-O-)

HR-MS (ESI^+)

m/z 583.3753 $[\text{M}+\text{Na}]^+$, Calc'd for $\text{C}_{37}\text{H}_{52}\text{O}_4\text{Na}$:583.3763.

Olean-12-en-28-oic acid, 3-O-(β-D-glucopyranosyloxy)-, phenylmethyl ester (26Ba)



A solution of TMSOTf (39.6 μ L, 0.219 mmol) dissolved in CH₂Cl₂ (7.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (244 mg, 0.329 mmol) and acceptor **25B** (120 mg, 0.219 mmol) dissolved in CH₂Cl₂ (7.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube (ϕ = 1.0 mm, l = 1.0 m), the reaction mixture of **27Ba** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (88 mg, 2.19 mmol, 60% disp.) and MeOH (28 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H⁺ resin to pH 7, filtered, and rinsed with MeOH (30 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 20 : 1) to afford **26Ba** (111 mg, 0.157 mmol, 71%) as a white solid by two steps.

R_f = 0.39 (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{23} +27.2$ (*c* 0.30, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine-*d*₅)

δ : 7.45 (m, 5H, PhCH₂), 5.41 (t, *J* = 3.4 Hz, 1H, 12-H), 5.35, 5.29 (each d, *J* = 12.6 Hz, 2H, PhCH₂), 4.96 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.61 (dd, *J* = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.43 (dd, *J* = 12.0 Hz, 5.5 Hz, 1H, 6'-H), 4.28 (t, *J* = 8.0 Hz, 1H, 3'-H), 4.25 (t, *J* = 8.0 Hz, 1H, 4'-H), 4.06 (t, *J* = 8.0 Hz, 1H, 2'-H), 4.03 (ddd, *J* = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.41 (dd, *J* = 11.8 Hz, 4.4 Hz, 1H, 3-H), 3.31 (dd, *J* = 14.0 Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine-*d*₅)

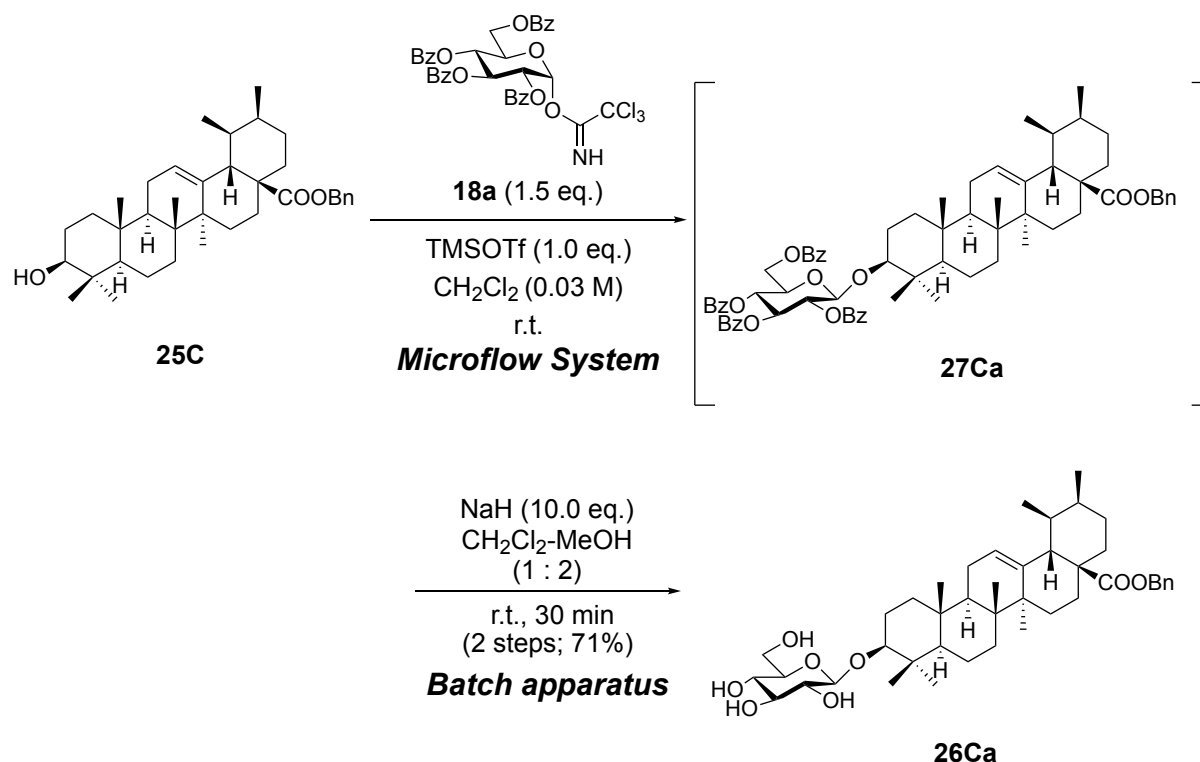
δ : 177.3 (C-28), 144.1 (C-13), 137.4, 129.0, 128.6, 128.5 (PhCH₂), 123.1 (C-12), 107.0 (C-1'), 89.0 (C-3), 78.9 (C-3'), 78.4 (C-5'), 76.0 (C-2'), 72.0 (C-4'), 66.3 (PhCH₂), 63.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 3434 (-O-H), 2945 (=C-H), 1726 (-C=O), 1078 (-C-O-)

HR-MS (ESI⁺)

m/z 731.4498[M+Na]⁺, Calc'd for C₄₃H₆₄O₈Na:731.4499.

Urso-12-en-28-oic acid, 3-*O*-(β-D-glucopyranosyloxy)-, phenylmethyl ester (26Ca)



A solution of TMSOTf (41.6 μ L, 0.230 mmol) dissolved in CH₂Cl₂ (7.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (256 mg, 0.346 mmol) and acceptor **5C** (126 mg, 0.230 mmol) dissolved in CH₂Cl₂ (7.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube (ϕ = 1.0 mm, l = 1.0 m), the reaction mixture of **27Ca** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (92 mg, 2.30 mmol, 60% disp.) and MeOH (28 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H⁺ resin to pH 7, filtered, and rinsed with MeOH (30 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 15 g, CHCl₃ : MeOH = 40 : 1 \rightarrow 5 : 1) to afford **26Ca** (116 mg, 0.163 mmol, 71%) as a white solid by two steps.

R_f = 0.56 (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{23}$ +17.7 (c 0.31, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 7.45 (m, 5H, PhCH₂), 5.49 (t, J = 3.2 Hz, 1H, 12-H), 5.35, 5.29 (each d, J = 12.6 Hz, 2H, PhCH₂), 4.97 (d, J = 7.8 Hz, 1H, 1'-H), 4.62 (dd, J = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.43 (dd, J = 12.0 Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, J = 8.0 Hz, 1H, 3'-H), 4.25 (t, J = 8.0 Hz, 1H, 4'-H), 4.06 (t, J = 8.0 Hz, 1H, 2'-H), 4.03 (ddd, J = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.43 (dd, J = 11.9 Hz, 4.3 Hz, 1H, 3-H), 2.65 (d, J = 11.4 Hz, 1H, 18-H), 2.36 (m, 1H, 15-H), 2.25 (m, 1H, 2-H), 2.07 (m, 2H, 16-H), 1.92 (m, 2H, 11-H), 1.83 (m, 1H, 2-H), 1.63 (m, 1H, 9-H), 1.53 (m, 2H, 1-H, 6-H), 1.50 (m, 1H, 7-H), 1.50 (m, 2H, 19-H, 21-H), 1.43 (m, 1H, 21-H), 1.34 (s, 3H, 23-H), 1.32 (m, 2H, 6-H, 7-H), 1.27 (s, 3H, 27-H), 1.20 (m, 1H, 15-H), 1.03 (s, 3H, 24-H), 1.02 (m, 1H, 20-H), 1.01 (s, 3H, 26-H), 1.01 (d, J = 3.4 Hz, 3H, 29-H), 0.97 (d, J = 6.0 Hz, 3H, 30-H), 0.90 (m, 1H, 1-H), 0.83 (s, 3H, 25-H), 0.80 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

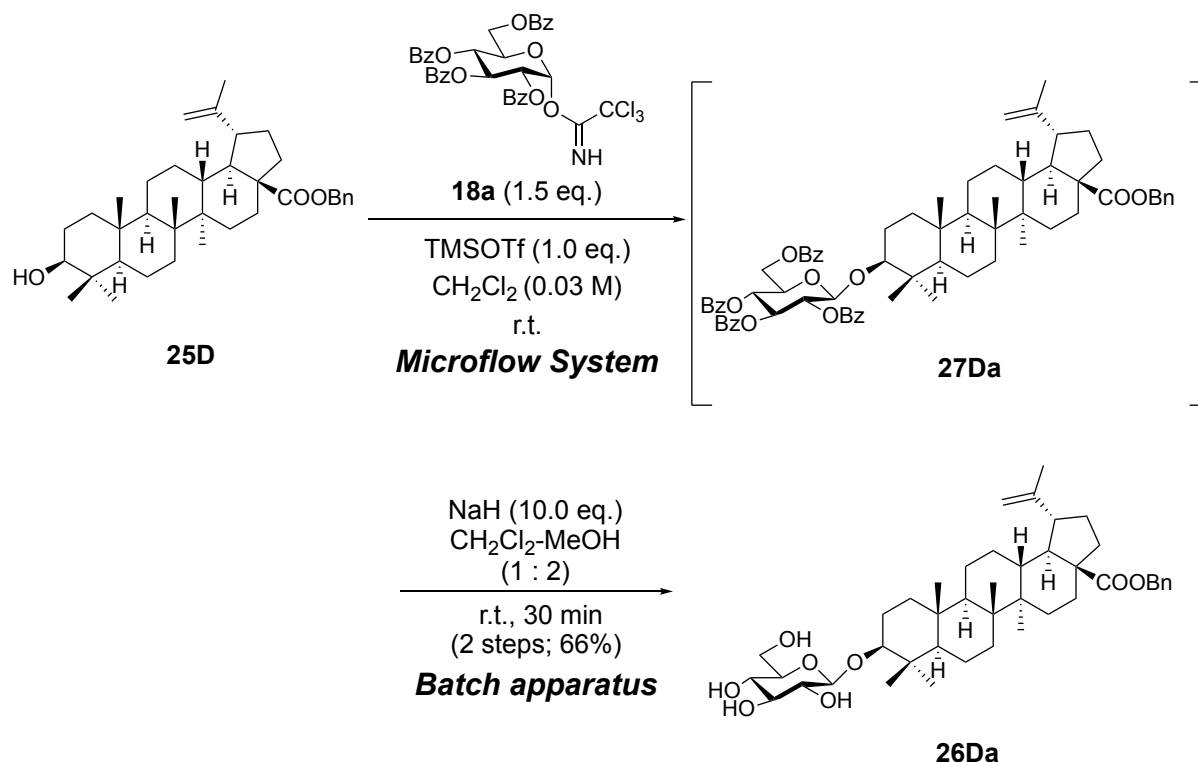
δ : 177.1 (C-28), 139.4 (C-13), 136.0, 135.7, 135.4, 129.0, 128.7, 128.5 (PhCH₂), 126.2 (C-12), 107.1 (C-1'), 89.1 (C-3), 78.9 (C-3'), 78.5 (C-5'), 75.9 (C-2'), 72.0 (C-4'), 66.3 (PhCH₂), 63.2 (C-6'), 56.0 (C-5), 53.7 (C-18), 48.2 (C-9), 48.1 (C-17), 42.7 (C-14), 40.1 (C-8), 39.7 (C-4), 39.7 (C-1), 39.6 (C-20), 39.0 (C-19), 37.6 (C-22), 37.1 (C-10), 33.7 (C-7), 31.3 (C-21), 28.8 (C-15), 28.5 (C-23), 26.8 (C-2), 25.1 (C-16), 24.1 (C-27), 23.8 (C-11), 21.6 (C-30), 18.6 (C-6), 17.7 (C-29), 17.6 (C-26), 17.2 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3423 (-O-H), 2926 (=C-H), 1723 (-C=O), 1077 (-C-O-)

HR-MS (ESI⁺)

m/z 731.4495[M+Na]⁺, Calc'd for C₄₃H₆₄O₈Na:731.4499.

Lup-20(29)-en-28-oic acid, 3-*O*-(β-D-glucopyranosyloxy)-, phenylmethyl ester (26Da)



A solution of TMSOTf (41.6 μL , 0.230 mmol) dissolved in CH_2Cl_2 (7.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (256 mg, 0.346 mmol) and acceptor **5D** (126 mg, 0.230 mmol) dissolved in CH_2Cl_2 (7.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture of **27Da** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (92 mg, 2.30 mmol, 60% disp.) and MeOH (28 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (30 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 15 g, CHCl_3 : MeOH = 30 : 1 \rightarrow 5 : 1) to afford **26Da** (108 mg, 0.152 mmol, 66%) as a white solid by two steps.

$R_f = 0.57$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{23} + 3.37$ (c 0.31, MeOH)

^1H -NMR (400 MHz, pyridine- d_5)

δ : 7.58-7.34 (m, 5H, PhCH₂), 5.33 (each d, J = 12.7 Hz, 2H, PhCH₂), 4.97 (d, J = 7.8 Hz, 1H, 1'-H), 4.61 (dd, J = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.43 (dd, J = 12.0 Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, J = 8.0 Hz, 1H, 3'-H), 4.25 (t, J = 8.0 Hz, 1H, 4'-H), 4.06 (t, J = 8.0 Hz, 1H, 2'-H), 4.03 (ddd, J = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.43 (dd, J = 13.0 Hz, 4.5 Hz, 1H, 3-H), 3.36-0.76 (m, other aliphatic ring protons), 1.32, 1.04, 1.00, 0.89, 0.77 (each s, 3H, 23-H, 24-H, 25-H, 26-H, 27-H)

^{13}C -NMR (100 MHz, pyridine- d_5)

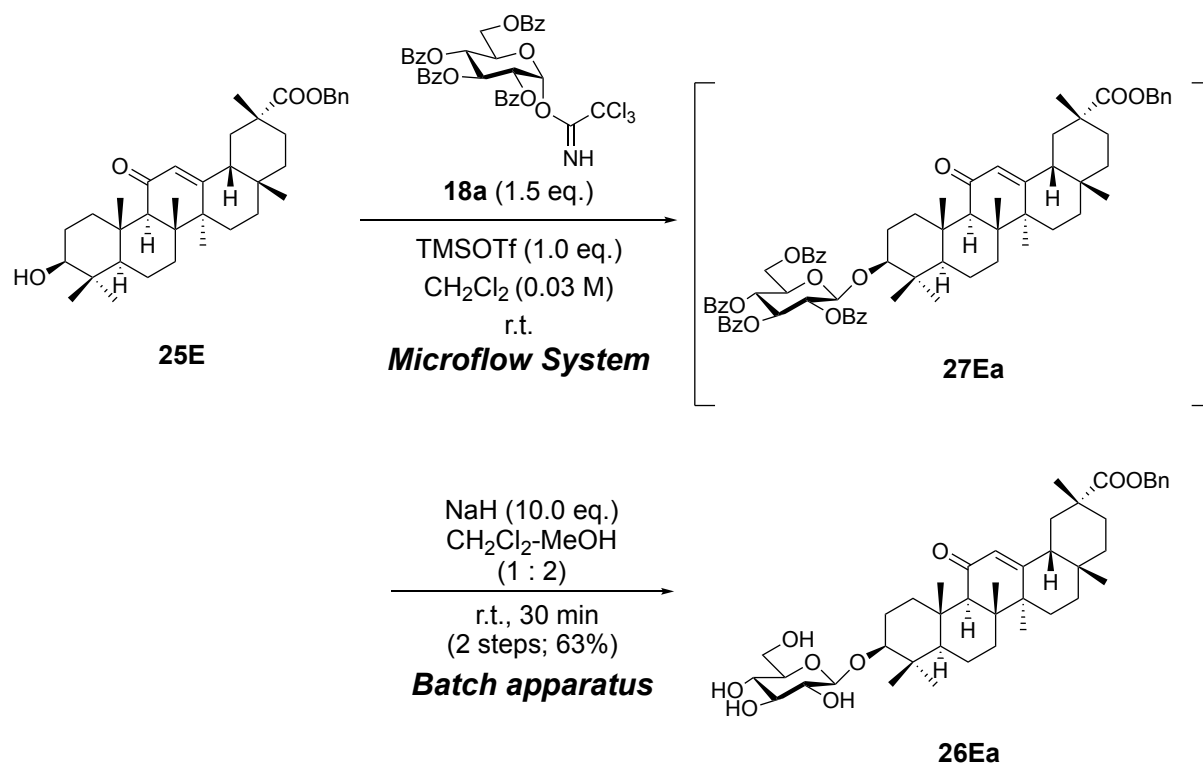
δ : 179.2 (C-28), 151.4 (C-20), 137.5, 130.1, 129.1, 128.9, 128.8, 128.6 (PhCH₂), 110.3 (C-29), 107.0 (C-1'), 89.0 (C-3), 78.9 (C-3'), 78.4 (C-5'), 76.0 (C-2'), 72.0 (C-4'), 66.1 (PhCH₂), 63.2 (C-6'), 57.2 (C-17), 56.1 (C-5), 50.7 (C-9), 49.4 (C-18), 45.0 (C-19), 43.1 (C-14), 40.0 (C-8), 39.2 (C-4), 38.5 (C-1), 38.1 (C-13), 37.2 (C-10), 35.1 (C-22), 33.0 (C-7), 30.4 (C-16), 30.3 (C-21), 28.3 (C-23), 27.6 (C-2), 27.0 (C-15), 23.6 (C-12), 23.5 (C-11), 21.4 (C-30), 18.5 (C-6), 17.0 (C-26), 16.6 (C-25), 16.5 (C-24), 15.1 (C-27)

IR (KBr) cm^{-1} ν : 3421 (-O-H), 2944 (=C-H), 1726 (-C=O), 1078 (-C-O-)

HR-MS (ESI⁺)

m/z 731.4506[M+Na]⁺, Calc'd for C₄₃H₆₄O₈Na:731.4499.

**Olean-12-en-29-oic acid, 3-O-(β -D-glucopyranosyloxy)-
11-oxo-, phenylmethyl ester (26Ea)**



A solution of TMSOTf (41.6 μL , 0.230 mmol) dissolved in CH_2Cl_2 (7.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. Also, a solution of donor **18a** (256 mg, 0.346 mmol) and acceptor **5E** (129 mg, 0.230 mmol) dissolved in CH_2Cl_2 (7.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at ambient temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the crude mixture of **27Ea** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (92 mg, 2.30 mmol, 60% disp.) and MeOH (28 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (30 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 15 g, CHCl_3 : MeOH = 30 : 1 \rightarrow 25 : 1) to afford **26Ea** (105 mg, 0.145 mmol, 63%) as a pale yellow solid by two steps.

$R_f = 0.59$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{22} +100.7$ (*c* 0.30, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine-*d*₅)

δ : 7.59-7.22 (m, 5H, PhCH₂), 6.00 (s, 1H, 12-H), 5.36, 5.29 (each d, *J* = 12.6 Hz, 2H, PhCH₂), 4.96 (d, *J* = 7.8 Hz, 1H, 1'-H), 4.58 (dd, *J* = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.42 (dd, *J* = 12.0 Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, *J* = 8.0 Hz, 1H, 3'-H), 4.25 (t, *J* = 8.0 Hz, 1H, 4'-H), 4.06 (t, *J* = 8.0 Hz, 1H, 2'-H), 4.01 (ddd, *J* = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.46 (dd, *J* = 11.5 Hz, 4.5 Hz, 1H, 3-H), 3.10 (dt, *J* = 13.6 Hz, 3.6 Hz, 1H, 1-H), 2.59-2.54 (m, 1H, 18-H), 2.51 (s, 1H, 9-H), 2.33-2.28 (m, 2H, 15-H, 21-H), 2.18-2.10 (m, 1H, 19-H), 2.08-1.96 (m, 1H, 16-H), 1.80-1.70 (m, 4H, 2-H, 15-H, 19-H, 22-H), 1.59 (m, 1H, 7-H), 1.54 (m, 1H, 6-H), 1.51 (m, 1H, 21-H), 1.48 (m, 1H, 22-H), 1.45 (s, 3H, 27-H), 1.40 (m, 1H, 6-H), 1.37 (s, 3H, 23-H), 1.37 (s, 3H, 28-H), 1.36 (m, 1H, 7-H), 1.33 (m, 1H, 1-H), 1.28 (s, 3H, 24-H), 1.11 (s, 3H, 26-H), 1.07 (s, 3H, 25-H), 0.96 (m, 1H, 15-H), 0.89-0.84 (m, 1H, 5-H), 0.81 (s, 3H, 29-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine-*d*₅)

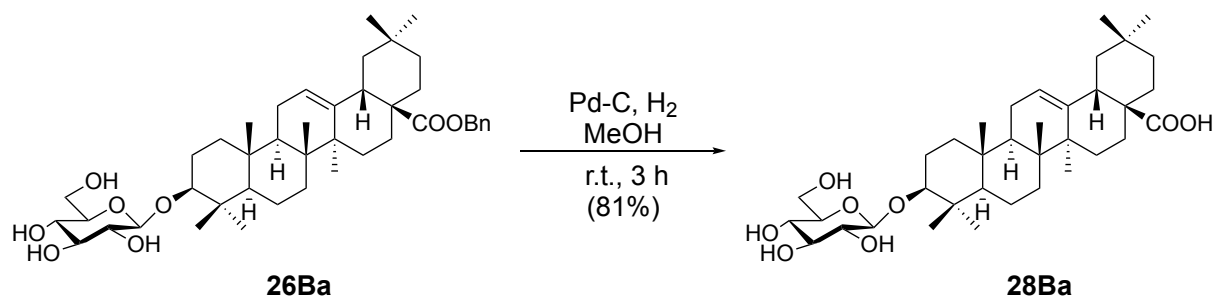
δ : 199.6 (C-11), 176.3 (C-30), 169.0 (C-13), 137.2, 135.9, 135.7, 135.4, 129.1, 128.9 (PhCH₂), 128.8 (C-12), 107.0 (C-1'), 88.7 (C-3), 78.9 (C-3'), 78.4 (C-5'), 75.9 (C-2'), 71.9 (C-4'), 66.5 (PhCH₂), 63.1 (C-6'), 62.2 (C-9), 55.5 (C-5), 48.7 (C-18), 45.6 (C-8), 44.3 (C-20), 43.5 (C-14), 41.4 (C-19), 40.0 (C-1), 39.7 (C-4), 38.1 (C-22), 37.4 (C-10), 33.0 (C-7), 32.1 (C-17), 31.5 (C-21), 28.7 (C-29), 28.4 (C-23), 28.3 (C-28), 26.9 (C-2), 26.8 (C-16), 26.6 (C-15), 23.5 (C-27), 18.9 (C-26), 17.8 (C-6), 17.2 (C-25), 16.9 (C-24)

IR (KBr) cm^{-1} ν : 3423 (-O-H), 2947 (=C-H), 1656 (-C=O), 1082 (-C-O-)

HR-MS (ESI⁺)

m/z 745.4298[M+Na]⁺, Calc'd for C₄₃H₆₂O₉Na:745.4292.

3-O- β -D-glucopyranosyl oleanolic acid (**28Ba**)



To a solution of **26Ba** (47.6 mg, 0.067 mmol) in MeOH (6.7 mL) was added 10% Pd-C (50 mg). and purged with H₂ atmosphere at room temperature. After stirring for 3 h at room temperature, the reaction mixture was filtered by celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 30 : 1 \rightarrow 5 : 1) to afford **28Ba** (33.4 mg, 0.054 mmol, 81%) as a white solid.

R_f = 0.29 (CHCl₃ : MeOH = 5 : 1)

[α]_D²³ -144.4 (*c* 0.10, DMSO)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.49 (t, *J* = 3.4 Hz, 1H, 12-H), 4.96 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.61 (dd, *J* = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.43 (dd, *J* = 12.0 Hz, 5.5 Hz, 1H, 6'-H), 4.28 (t, *J* = 8.0 Hz, 1H, 3'-H), 4.25 (t, *J* = 8.0 Hz, 1H, 4'-H), 4.06 (t, *J* = 8.0 Hz, 1H, 2'-H), 4.03 (ddd, *J* = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.41 (dd, *J* = 11.8 Hz, 4.4 Hz, 1H, 3-H), 3.31 (dd, *J* = 14.0 Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 180.3 (C-28), 145.0 (C-13), 122.7 (C-12), 107.0 (C-1'), 89.0 (C-3), 78.9 (C-3'), 78.4 (C-5'), 76.0 (C-2'), 72.0 (C-4'), 63.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6

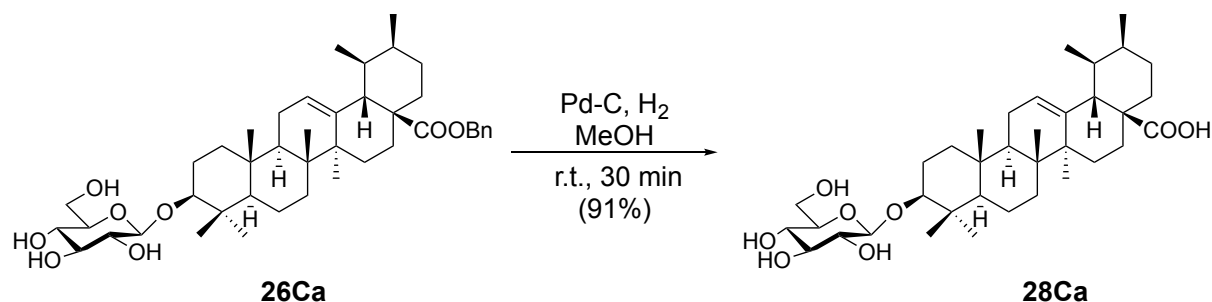
(C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 3435 (-O-H), 2945 (=C-H), 1698 (-C=O), 1031 (-C-O-)

HR-MS (ESI^+)

m/z 641.4029 $[\text{M}+\text{Na}]^+$, Calc'd for $\text{C}_{36}\text{H}_{58}\text{O}_8\text{Na}$:641.4029.

3-*O*-β-D-glucopyranosyl ursolic acid (**28Ca**)



To a solution of **26Ca** (113 mg, 0.160 mmol) in MeOH (16 mL) was added 10% Pd-C (113 mg). and purged with H₂ atmosphere. After stirring for 30 min at room temperature, the reaction mixture was filtered by celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 20 : 1 → 5 : 1) to afford **28Ca** (89.7 mg, 0.145 mmol, 91%) as a white solid.

R_f = 0.35 (CHCl₃ : MeOH = 5 : 1)

[α]_D²³ +26.2 (*c* 0.33, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.49 (t, *J* = 3.2 Hz, 1H, 12-H), 4.97 (d, *J* = 7.8 Hz, 1H, 1'-H), 4.62 (dd, *J* = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.43 (dd, *J* = 12.0 Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, *J* = 8.0 Hz, 1H, 3'-H), 4.25 (t, *J* = 8.0 Hz, 1H, 4'-H), 4.06 (t, *J* = 8.0 Hz, 1H, 2'-H), 4.03 (ddd, *J* = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.43 (dd, *J* = 11.9 Hz, 4.3 Hz, 1H, 3-H), 2.65 (d, *J* = 11.4 Hz, 1H, 18-H), 2.36 (m, 1H, 15-H), 2.25 (m, 1H, 2-H), 2.07 (m, 2H, 16-H), 1.92 (m, 2H, 11-H), 1.83 (m, 1H, 2-H), 1.63 (m, 1H, 9-H), 1.53 (m, 2H, 1-H, 6-H), 1.50 (m, 1H, 7-H), 1.50 (m, 2H, 19-H, 21-H), 1.43 (m, 1H, 21-H), 1.34 (s, 3H, 23-H), 1.32 (m, 2H, 6-H, 7-H), 1.27 (s, 3H, 27-H), 1.20 (m, 1H, 15-H), 1.03 (s, 3H, 24-H), 1.02 (m, 1H, 20-H), 1.01 (s, 3H, 26-H), 1.01 (d, *J* = 3.4 Hz, 3H, 29-H), 0.97 (d, *J* = 6.0 Hz, 3H, 30-H), 0.90 (m, 1H, 1-H), 0.83 (s, 3H, 25-H), 0.80 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 180.0 (C-28), 139.4 (C-13), 125.8 (C-12), 107.1 (C-1'), 89.1 (C-3), 78.9 (C-3'), 78.5 (C-5'), 75.9 (C-2'), 72.0 (C-4'), 63.2 (C-6'), 56.0 (C-5), 53.7 (C-18), 48.2 (C-9), 48.1 (C-17), 42.7 (C-14), 40.1 (C-8), 39.7 (C-4), 39.7 (C-1), 39.6 (C-20), 39.0 (C-19), 37.6 (C-22), 37.1 (C-10), 33.7 (C-7), 31.3 (C-21), 28.8 (C-15), 28.5 (C-23), 26.8 (C-2), 25.1 (C-16), 24.1 (C-27), 23.8 (C-11), 21.6 (C-30), 18.6 (C-6), 17.7 (C-29), 17.6

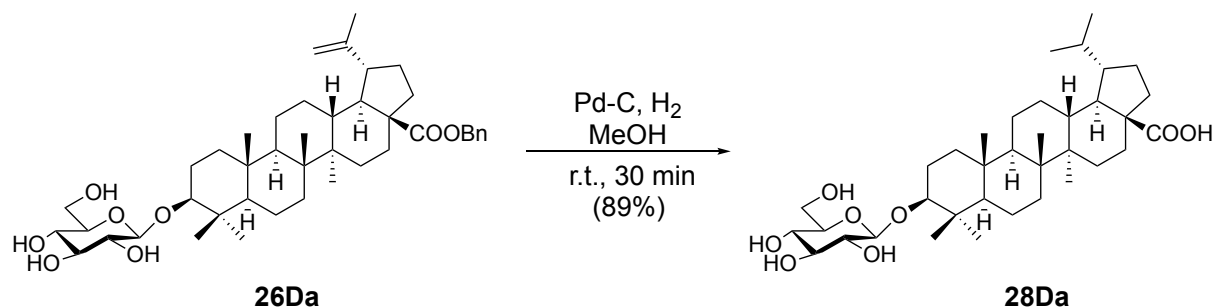
(C-26), 17.2 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} ν : 3432 (-O-H), 2926 (=C-H), 1694 (-C=O), 1079 (-C-O-)

HR-MS (ESI^+)

m/z 641.40258 $[\text{M}+\text{Na}]^+$, Calc'd for $\text{C}_{36}\text{H}_{58}\text{O}_8\text{Na}$:641.40294.

3-*O*- β -D-glucopyranosyl dihydrobetulinic acid (**28Da**)



To a solution of **26Da** (105 mg, 0.148 mmol) in MeOH (15 mL) was added 10% Pd-C (105 mg) and purged up with H₂ atmosphere. After stirring for 30 min at room temperature, the reaction mixture was filtered by celite. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 20 g, CHCl₃ : MeOH = 10 : 1 \rightarrow 5 : 1) to afford **28Da** (82.0 mg, 0.132 mmol, 89%) as a white solid.

R_f = 0.28 (CHCl₃ : MeOH = 5 : 1)

[α]_D²² -18.1 (*c* 0.31, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.49 (t, *J* = 3.2 Hz, 1H, 12-H), 4.97 (d, *J* = 7.8 Hz, 1H, 1'-H), 4.61 (dd, *J* = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.43 (dd, *J* = 12.0 Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, *J* = 8.0 Hz, 1H, 3'-H), 4.25 (t, *J* = 8.0 Hz, 1H, 4'-H), 4.06 (t, *J* = 8.0 Hz, 1H, 2'-H), 4.03 (ddd, *J* = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.43 (dd, *J* = 13.0 Hz, 4.5 Hz, 1H, 3-H), 3.36-0.76 (m, other aliphatic ring protons), 1.33, 1.09, 1.03, 1.00, 0.78 (each s, 3H, 23-H, 24-H, 25-H, 26-H, 27-H), 0.93 (d, *J* = 7.5 Hz, 1H, 29-H), 0.85 (d, *J* = 7.5 Hz, 1H, 30-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

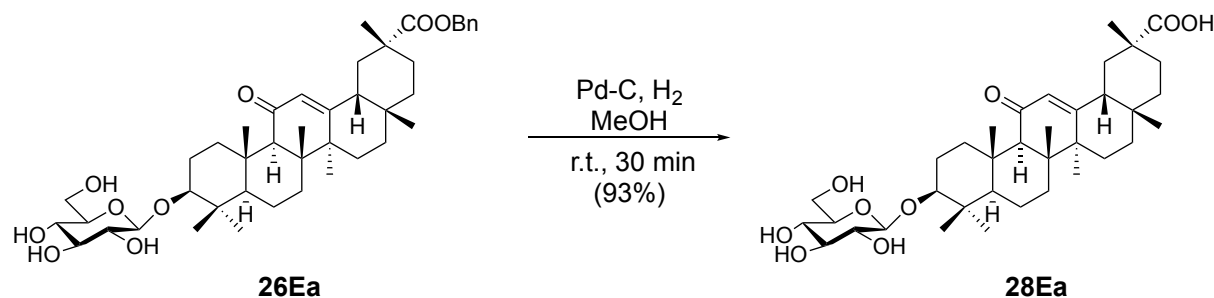
δ : 179.2 (C-28), 151.4 (C-20), 107.0 (C-1'), 89.0 (C-3), 78.9 (C-3'), 78.4 (C-5'), 76.0 (C-2'), 72.0 (C-4'), 63.2 (C-6'), 57.2 (C-17), 56.1 (C-5), 50.7 (C-9), 49.4 (C-18), 45.0 (C-19), 43.1 (C-14), 40.0 (C-8), 39.2 (C-4), 38.5 (C-1), 38.1 (C-13), 37.2 (C-10), 35.1 (C-22), 33.0 (C-7), 30.4 (C-16), 30.3 (C-21), 28.3 (C-23), 27.6 (C-2), 27.0 (C-15), 23.6 (C-12), 23.5 (C-11), 21.4 (C-30), 18.5 (C-6), 17.0 (C-26), 16.6 (C-25), 16.5 (C-24), 15.1 (C-27), 15.0 (C-29)

IR (KBr) cm⁻¹ ν : 3395 (-O-H), 2940 (=C-H), 1687 (-C=O), 1078 (-C-O-)

HR-MS (ESI⁺)

m/z 643.4170[M+Na]⁺, Calc'd for C₃₆H₆₀O₈Na:643.4186.

3-*O*-β-D-glucopyranosyl glycyrrhetic acid (**28Ea**)



To a solution of **26Ea** (73.8 mg, 0.102 mmol) in MeOH (10 mL) was added 10% Pd–C (105 mg) and purged with H₂ atmosphere. After stirring for 30 min at room temperature, the reaction mixture was filtered by celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 20 : 1 → 5 : 1) to afford **28Ea** (60.4 mg, 0.095 mmol, 93%) as a white solid.

R_f = 0.22 (CHCl₃ : MeOH = 5 : 1)

[α]_D²³ +91.0 (*c* 0.32, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 6.00 (s, 1H, 12-H), 4.96 (d, *J* = 7.8 Hz, 1H, 1'-H), 4.58 (dd, *J* = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.42 (dd, *J* = 12.0 Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, *J* = 8.0 Hz, 1H, 3'-H), 4.25 (t, *J* = 8.0 Hz, 1H, 4'-H), 4.06 (t, *J* = 8.0 Hz, 1H, 2'-H), 4.01 (ddd, *J* = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.46 (dd, *J* = 11.5 Hz, 4.5 Hz, 1H, 3-H), 3.10 (dt, *J* = 13.6 Hz, 3.6 Hz, 1H, 1-H), 2.59-2.54 (m, 1H, 18-H), 2.51 (s, 1H, 9-H), 2.33-2.28 (m, 2H, 15-H, 21-H), 2.18-2.10 (m, 1H, 19-H), 2.08-1.96 (m, 1H, 16-H), 1.80-1.70 (m, 4H, 2-H, 15-H, 19-H, 22-H), 1.59 (m, 1H, 7-H), 1.54 (m, 1H, 6-H), 1.51 (m, 1H, 21-H), 1.48 (m, 1H, 22-H), 1.45 (s, 3H, 27-H), 1.40 (m, 1H, 6-H), 1.37 (s, 3H, 23-H), 1.37 (s, 3H, 28-H), 1.36 (m, 1H, 7-H), 1.33 (m, 1H, 1-H), 1.28 (s, 3H, 24-H), 1.11 (s, 3H, 26-H), 1.07 (s, 3H, 25-H), 0.96 (m, 1H, 15-H), 0.89-0.84 (m, 1H, 5-H), 0.81 (s, 3H, 29-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 199.8 (C-11), 179.6 (C-30), 170.0 (C-13), 128.8 (C-12), 107.0 (C-1'), 88.8 (C-3), 78.9 (C-3'), 78.4 (C-5'), 75.9 (C-2'), 72.0 (C-4'), 63.1 (C-6'), 62.3 (C-9), 55.6 (C-5), 48.9 (C-18), 45.8 (C-8), 44.4 (C-20), 43.7 (C-14), 42.0 (C-19), 40.1 (C-1), 39.8 (C-4), 38.7 (C-22), 37.5 (C-10), 33.1 (C-7), 32.4 (C-17), 31.8 (C-21), 29.0 (C-29), 28.9 (C-23), 28.9 (C-28), 28.4 (C-2), 27.0 (C-16), 26.9 (C-15), 23.8 (C-27), 19.0 (C-26),

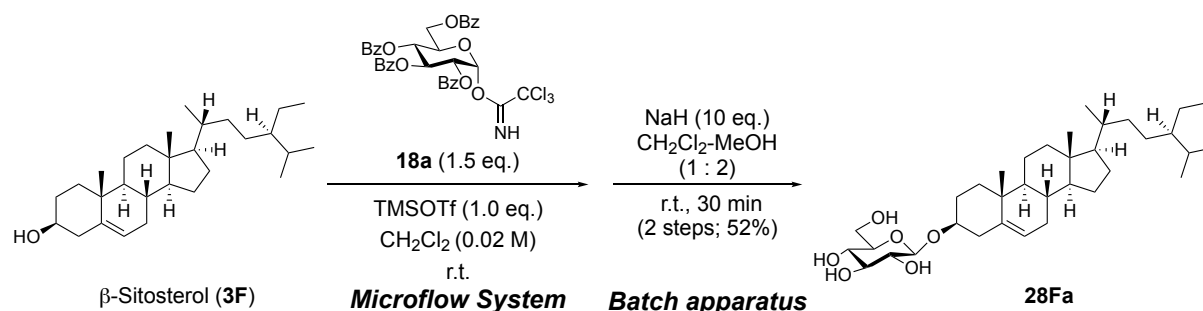
17.9 (C-6), 17.3 (C-25), 17.0 (C-24)

IR (KBr) cm^{-1} ν : 3415 (-O-H), 2948 (=C-H), 1656 (-C=O), 1077 (-C-O-)

HR-MS (ESI^+)

m/z 655.3803 $[\text{M}+\text{Na}]^+$, Calc'd for $\text{C}_{36}\text{H}_{56}\text{O}_9\text{Na}$:655.3822.

3-*O*-β-*D*-glucopyranosyl β-sitosterol (**28Fa**)



A solution of TMSOTf (41.6 μL , 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (268 mg, 0.362 mmol) and commercial β -sitosterol (**3F**) (100 mg, 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture of **7a** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (96.4 mg, 2.41 mmol, 60% disp.) and MeOH (40 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (40 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 50 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1) to afford **28Fa** (72.1 mg, 0.125 mmol, 52%) as a white solid by two steps.

$R_f = 0.41$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_D^{23} -42.2$ (c 0.10, DMSO)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 5.36 (t, $J = 2.5$ Hz, 1H, 6-H), 5.24 (dd, $J = 15.5$ Hz, 8.8 Hz, 1H, 22-H), 5.24 (dd, $J = 15.5$ Hz, 8.8 Hz, 1H, 22-H), 5.09 (dd, $J = 15.5$ Hz, 8.8 Hz, 1H, 23-H), 5.06 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.58 (dd, $J = 12.0$ Hz, 2.5 Hz, 1H, 6'-H), 4.42 (dd, $J = 12.0$ Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, $J = 8.0$ Hz, 1H, 3'-H), 4.25 (t, $J = 8.0$ Hz, 1H, 4'-H), 4.06 (t, $J = 8.0$ Hz, 1H, 2'-H), 4.01 (ddd, $J = 8.0$ Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 2.74 (m, 1H, 4-H), 2.48 (m, 1H, 4-H), 2.13 (m, 2H, 7-H), 2.07 (m, 1H, 20-H), 1.97 (m, 1H, 12-H), 1.95-1.88 (m, 2H, 2-H), 1.81-1.72 (m, 2H, 1-H, 16-H), 1.62 (m, 1H, 9-H), 1.58-1.51

(m, 2H, 2-H, 28-H), 1.48-1.42 (m, 2H, 11-H, 15-H), 1.41-1.34 (m, 2H, 8-H, 16-H), 1.31 (m, 1H, 15-H), 1.21-1.14 (m, 2H, 12-H, 17-H), 1.10 (d, $J = 6.6$ Hz, 1H, 21-H), 1.07-0.99 (m, 4H, 1-H, 11-H, 16-H, 24-H), 0.96 (s, 1H, 19-H), 0.92 (t, $J = 6.6$ Hz, 1H, 29-H), 0.90 (d, $J = 7.0$ Hz, 1H, 27-H), 0.88 (d, $J = 6.6$ Hz, 1H, 26-H), 0.70 (s, 1H, 18-H)

^{13}C -NMR (100 MHz, pyridine- d_5)

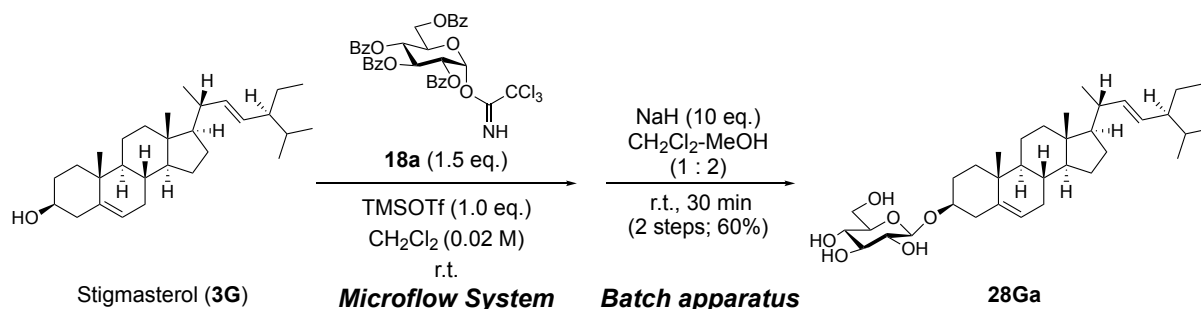
δ : 141.0 (C-5), 122.1 (C-6), 102.7 (C-1'), 78.7 (C-3'), 78.6 (C-5'), 78.3 (C-3), 75.5 (C-2'), 71.8 (C-4'), 63.0 (C-6'), 57.1 (C-14), 56.2 (C-17), 51.6 (C-9), 50.5 (C-24), 42.5 (C-13), 40.9 (C-20), 40.0 (C-12), 39.5 (C-4), 37.6 (C-10), 37.1 (C-1), 32.3 (C-25), 32.3 (C-8), 32.2 (C-2), 30.4 (C-7), 29.5 (C-16), 25.9 (C-15), 24.7 (C-28), 21.6 (C-21), 21.5 (C-27), 21.4 (C-11), 19.6 (C-19), 19.4 (C-26), 15.5 (C-23), 12.7 (C-29), 12.3 (C-18), 12.1 (C-22)

IR (KBr) cm^{-1} ν : 3421 (-O-H), 2934 (=C-H), 1073 (-C-O-)

HR-MS (ESI $^+$)

m/z 599.4278[M+Na] $^+$, Calc'd for $\text{C}_{35}\text{H}_{60}\text{O}_6\text{Na}$:599.4288.

3-O-β-D-glucopyranosyl stigmasterol (28Ga)



A solution of TMSOTf (43.6 μL , 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (268 mg, 0.362 mmol) and commercial stigmasterol (**3G**) (99.5 mg, 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 20 min at room temperature in flask which added NaH (96.4 mg, 2.41 mmol, 60% disp.) and MeOH (30 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (40 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 50 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1) to afford **28Ga** (83.2 mg, 0.145 mmol, 60%) as a white solid by two steps.

$R_f = 0.37$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_D^{23} -770.1$ (c 0.10, DMSO)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 5.36 (t, $J = 2.5$ Hz, 1H, 6-H), 5.24 (dd, $J = 15.5$ Hz, 8.8 Hz, 1H, 22-H), 5.09 (dd, $J = 15.5$ Hz, 8.8 Hz, 1H, 23-H), 5.06 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.58 (dd, $J = 12.0$ Hz, 2.5 Hz, 1H, 6'-H), 4.42 (dd, $J = 12.0$ Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, $J = 8.0$ Hz, 1H, 3'-H), 4.25 (t, $J = 8.0$ Hz, 1H, 4'-H), 4.06 (t, $J = 8.0$ Hz, 1H, 2'-H), 4.01 (ddd, $J = 8.0$ Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 2.74 (m, 1H, 4-H), 2.48 (m, 1H, 4-H), 2.13 (m, 2H, 7-H), 2.07 (m, 1H, 20-H), 1.97 (m, 1H, 12-H), 1.95-1.88 (m, 2H, 2-H), 1.81-1.72 (m, 2H, 1-H, 16-H), 1.62 (m, 1H, 9-H), 1.58-1.51 (m, 2H, 2-H, 28-H), 1.48-1.42 (m, 2H, 11-H,

15-H), 1.41-1.34 (m, 2H, 8-H, 16-H), 1.31 (m, 1H, 15-H), 1.21-1.14 (m, 2H, 12-H, 17-H), 1.10 (d, $J = 6.6$ Hz, 1H, 21-H), 1.07-0.99 (m, 4H, 1-H, 11-H, 16-H, 24-H), 0.96 (s, 1H, 19-H), 0.92 (t, $J = 6.6$ Hz, 1H, 29-H), 0.90 (d, $J = 7.0$ Hz, 1H, 27-H), 0.88 (d, $J = 6.6$ Hz, 1H, 26-H), 0.70 (s, 1H, 18-H)

^{13}C -NMR (100 MHz, pyridine- d_5)

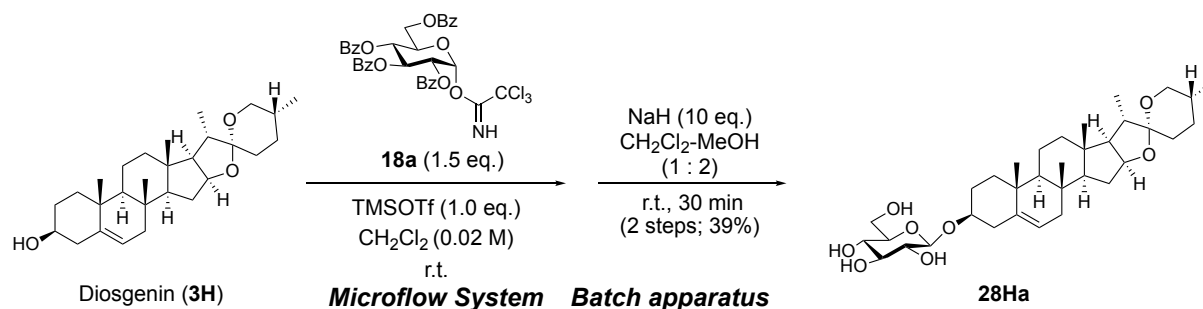
δ : 141.1 (C-5), 139.0 (C-22), 129.0 (C-23), 122.0 (C-6), 102.7 (C-1'), 78.7 (C-3'), 78.6 (C-5'), 78.3 (C-3), 75.5 (C-2'), 71.8 (C-4'), 63.0 (C-6'), 57.1 (C-14), 56.2 (C-17), 51.6 (C-9), 50.5 (C-24), 42.5 (C-13), 40.9 (C-20), 40.0 (C-12), 39.5 (C-4), 37.6 (C-10), 37.1 (C-1), 32.3 (C-25), 32.3 (C-8), 32.2 (C-2), 30.4 (C-7), 29.5 (C-16), 25.9 (C-15), 24.7 (C-28), 21.6 (C-21), 21.5 (C-27), 21.4 (C-11), 19.6 (C-19), 19.4 (C-26), 12.7 (C-29), 12.3 (C-18)

IR (KBr) cm^{-1} ν : 3421 (-O-H), 2934 (=C-H), 1726 (-C=O), 1024 (-C-O-)

HR-MS (ESI $^{+}$)

m/z 597.4124[M+Na] $^{+}$, Calc'd for $\text{C}_{35}\text{H}_{58}\text{O}_6\text{Na}$:597.4131.

3-O- β -D-glucopyranosyl diosgenin (**28Ha**)



A solution of TMSOTf (43.6 μL , 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (268 mg, 0.362 mmol) and commercial diosgenin (**3H**) (100 mg, 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (96.4 mg, 2.41 mmol, 60% disp.) and MeOH (30 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (40 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 15 g, CHCl_3 : MeOH = 50 : 1 \rightarrow 45 : 1 \rightarrow 40 : 1 \rightarrow 35 : 1 \rightarrow 30 : 1 \rightarrow 20 : 1) to afford **28Ha** (53.6 mg, 0.093 mmol, 39%) as a white solid by two steps.

$R_f = 0.41$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{23} -210.1$ (c 0.10, DMSO)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 5.32 (d, $J = 4.8$ Hz, 1H, 6-H), 5.05 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.57 (dd, $J = 12.0$ Hz, 2.5 Hz, 1H, 6'-H), 4.57-4.52 (m, 1H, 16-H), 4.41 (dd, $J = 12.0$ Hz, 5.4 Hz, 1H, 6'-H), 4.28 (t, $J = 8.0$ Hz, 1H, 3'-H), 4.25 (t, $J = 8.0$ Hz, 1H, 4'-H), 4.05 (t, $J = 8.0$ Hz, 1H, 2'-H), 4.01 (ddd, $J = 8.0$ Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.61-0.69 (m, other aliphatic ring protons), 1.15 (d, $J = 7.0$ Hz, 1H, 21-H), 0.92 (s, 1H, 19-H), 0.84 (s, 1H, 18-H), 0.71 (d, $J = 5.8$ Hz, 1H, 27-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

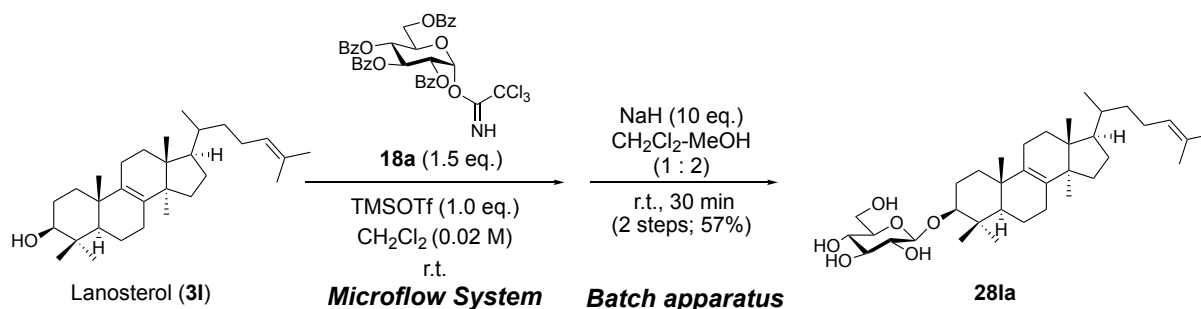
δ : 141.0 (C-5), 121.8 (C-6), 109.4 (C-22), 102.7 (C-1'), 81.2 (C-16), 78.6 (C-3'), 78.2 (C-5'), 75.5 (C-2'), 71.8 (C-4'), 67.0 (C-3), 63.0 (C-6'), 56.8, 50.4, 42.2, 40.6, 40.6, 40.0, 39.5, 37.6, 37.2, 37.2, 32.4, 32.3, 32.0, 31.8, 30.7, 30.4, 29.4, 21.3, 19.6, 17.5, 16.5, 15.2

IR (KBr) cm^{-1} ν : 3464 (-O-H), 2939 (=C-H), 1027 (-C-O-)

HR-MS (ESI⁺)

m/z 599.3564[M+Na]⁺, Calc'd for C₃₃H₅₂O₈Na:599.3560.

3-O- β -D-glucopyranosyl lanosterol (**28Ia**)



A solution of TMSOTf (43.6 μL , 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (268 mg, 0.362 mmol) and commercial lanosterol (**3I**) (103 mg, 0.241 mmol) dissolved in CH_2Cl_2 (10.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (96.4 mg, 2.41 mmol, 60% disp.) and MeOH (30 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (40 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 15 g, CHCl_3 : MeOH = 50 : 1 \rightarrow 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1) to afford **28Ia** (81.1 mg, 0.138 mmol, 57%) as a white solid by two steps.

$R_f = 0.46$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{23} -116.7$ (c 0.10, DMSO)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 5.26 (t, $J = 7.0$ Hz, 1H, 24-H), 4.98 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.62 (dd, $J = 12.0$ Hz, 2.5 Hz, 1H, 6'-H), 4.45 (dd, $J = 12.0$ Hz, 5.4 Hz, 1H, 6'-H), 4.30-4.23 (m, 2H, 3-H, 3'-H), 4.25 (t, $J = 8.0$ Hz, 1H, 4'-H), 4.07 (t, $J = 8.0$ Hz, 1H, 2'-H), 4.01 (ddd, $J = 8.0$ Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 3.45-0.70 (m, other aliphatic ring protons)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

δ : 134.5, 131.0, 130.4, 125.9, 107.2 (C-1'), 89.1 (C-3), 78.9 (C-3'), 78.5 (C-4'), 75.9 (C-2'), 72.0 (C-5'), 63.2 (C-6'), 50.2, 44.9, 40.0, 37.1, 36.0, 31.4, 31.3, 28.7, 28.4,

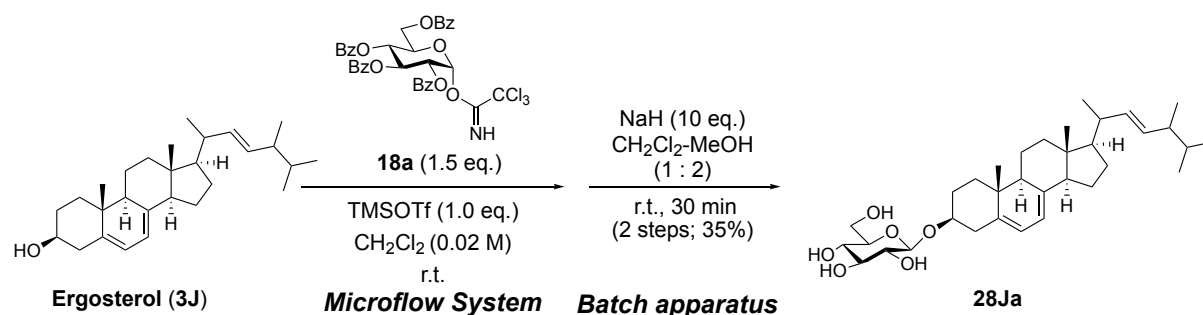
28.3, 27.4, 26.9, 26.0, 25.4, 24.6, 23.1, 22.9, 21.4, 19.5, 19.2, 19.0, 18.6, 17.9, 17.0, 16.2

IR (KBr) cm^{-1} ν : 3422 (-O-H), 2951 (=C-H), 1726 (-C=O), 1074 (-C-O-)

HR-MS (ESI⁺)

m/z 611.4284[M+Na]⁺, Calc'd for C₃₆H₆₀O₆Na:611.4288.

3-*O*-β-*D*-glucopyranosyl ergosterol (**28Ja**)



A solution of TMSOTf (43.6 μ L, 0.241 mmol) dissolved in CH₂Cl₂ (10.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18a** (268 mg, 0.362 mmol) and commercial ergosterol (**3J**) (95.6 mg, 0.241 mmol) dissolved in CH₂Cl₂ (10.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube (ϕ = 1.0 mm, *l* = 1.0 m), the reaction mixture of **18a** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 30 min at room temperature in flask which added NaH (96.4 mg, 2.41 mmol, 60% disp.) and MeOH (30 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H⁺ resin to pH 7, filtered and rinsed with MeOH (40 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 20 g, CHCl₃ : MeOH = 35 : 1 \rightarrow 30 : 1 \rightarrow 25 : 1 \rightarrow 15 : 1) to afford **28Ja** (47.8 mg, 0.086 mmol, 35%) as a white solid by two steps.

*R*_f = 0.39 (CHCl₃ : MeOH = 5 : 1)

[α]_D²² -9.91 (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.46 (brs, 1H, 6-H), 5.38-5.26 (m, 3H, 7-H, 22-H, 23-H), 5.07 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.62 (dd, *J* = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.44 (dd, *J* = 12.0 Hz, 5.4 Hz, 1H, 6'-H), 4.28 (m, 2H, 3-H, 3'-H), 4.25 (t, *J* = 8.0 Hz, 1H, 4'-H), 4.05 (t, *J* = 8.0 Hz, 1H, 2'-H), 4.01 (ddd, *J* = 8.0 Hz, 5.5 Hz, 2.5 Hz, 1H, 5'-H), 2.38-0.87 (m, other aliphatic ring protons), 0.64 (s, 1H, 18-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 151.4 (C-8), 141.3 (C-5), 132.4 (C-22), 130.4 (C-23), 128.9 (C-6), 118.0 (C-7),

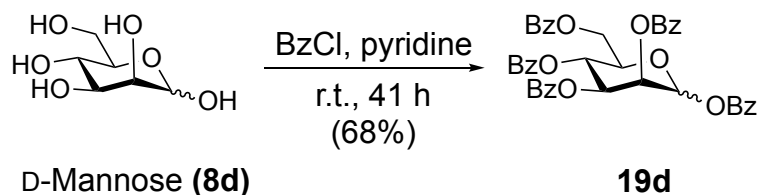
102.5 (C-1'), 78.8 (C-3), 78.6 (C-3'), 77.2 (C-4'), 75.5 (C-2'), 71.9 (C-5'), 63.1 (C-6'), 57.6 (C-17), 56.3 (C-14), 45.2 (C-9), 43.2 (C-13), 41.1 (C-24), 39.4 (C-20), 37.3 (C-12), 37.1 (C-4), 35.7 (C-1), 35.2 (C-25), 33.5 (C-2), 30.4 (C-10), 27.1 (C-16), 25.8 (C-15), 22.2 (C-26), 21.4 (C-11), 20.3 (C-21), 20.0 (C-27), 18.5 (C-28), 18.0 (C-19), 16.3 (C-18)

IR (KBr) cm^{-1} ν : 3406 (-O-H), 2933 (=C-H), 1726 (-C=O), 1077 (-C-O-)

HR-MS (ESI⁺)

m/z 581.3799[M+Na]⁺, Calc'd for C₃₄H₅₄O₆Na:581.3818.

1, 2, 3, 4, 6-Penta-*O*-benzoyl-D-mannose (19d**)**¹³⁸



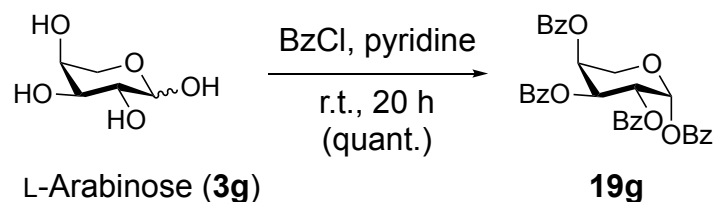
To a solution of commercial D-mannose **8d** (1.0 g, 5.55 mmol) in pyridine (28 mL) at 0 °C was added BzCl (4.0 mL, 33.5 mmol). After stirring for 41 h at room temperature, the reaction mixture was quenched with H₂O (10 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 50 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (2 x 150 mL), aq. CuSO₄ (2 x 150 mL) and H₂O (150 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford pure **19d** as a pale yellow foamy solid (α only, 2.64 g, 3.77 mmol, 68%) without further purification.

$R_f = 0.55$ (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 7.69 (m, 25H, Ph-H), 6.58 (d, $J = 1.9$ Hz, 1H, 1-H), 6.23 (t, $J = 10.2$ Hz, 1H, 4-H), 5.98 (dd, $J = 10.2$ Hz, 3.4 Hz, 1H, 3-H), 5.94 (dd, $J = 3.4$ Hz, 1.9 Hz, 1H, 2-H), 4.73 (dd, $J = 12.2$ Hz, 2.5 Hz, 1H, 6-H), 4.63 (ddd, $J = 10.2$ Hz, 4.2 Hz, 2.5 Hz, 1H, 5-H), 4.50 (dd, $J = 12.2$ Hz, 4.2 Hz, 1H, 6-H)

1, 2, 3, 4-Tetra-*O*-benzoyl- β -L-arabinosyl benzoate (19g**)**¹³⁹



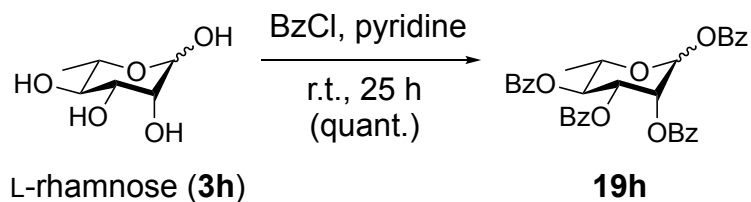
To a solution of commercial L-arabinose (**3g**) (1.0 g, 6.66 mmol) in pyridine (30 mL) at 0 °C was added BzCl (6.2 mL, 53.3 mmol). After stirring for 20 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 60 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (2 x 80 mL), aq. CuSO₄ (5 x 120 mL) and brine (120 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **19g** as a pale yellow solid (α only, 4.01 g, 7.08 mmol, quant.) without further purification.

R_f = 0.61 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.12-7.27 (m, 20H, Ar-H), 6.82 (d, J = 3.0 Hz, 1H, 1-H), 6.06-5.88 (m, 3H, 2-H, 3-H, 4-H), 4.42 (dd, J = 13.5 Hz, 1.0 Hz, 1H, 5-H), 4.18 (dd, J = 13.5 Hz, 2.0 Hz, 1H, 5-H)

1, 2, 3, 4 -Tetra-*O*-benzoyl-L-rhamnose (19h**)** ¹⁴⁰



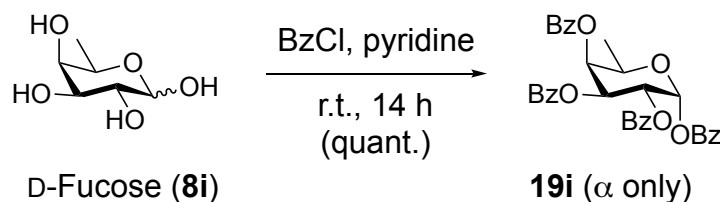
To a solution of commercial L-rhamnose (**3h**) (2 g, 11.0 mmol) in pyridine (55 mL) at 0 °C was added BzCl (10.1 mL, 87.8 mmol). After stirring for 25 h at room temperature, the reaction mixture was quenched with H₂O (20 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 100 mL). The combined organic layer was washed with aq. CuSO₄ (2 x 300 mL) and H₂O (150 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **19h** (6.46 g, 11.1 mmol, quant.) as a pale yellow foamy solid.

R_f = 0.53 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

δ : 7.68 (m, 25H, Ph-H), 6.49 (d, *J* = 1.6 Hz, 1H, 1-H), 5.90 (m, 1H, 2-H), 5.77 (ddd, *J* = 11.8 Hz, 9.8 Hz, 1.5 Hz, 1H, 3-H), 4.42 (dd, *J* = 9.8 Hz, 6.3 Hz, 1H, 4-H), 4.39 (dd, *J* = 9.8 Hz, 6.3 Hz, 1H, 5-H), 1.42 (d, *J* = 6.3 Hz, 1H, 6-H)

1, 2, 3, 4-Tetra-*O*-benzoyl- α -D-fucosyl benzoate (19i**)**¹⁰³



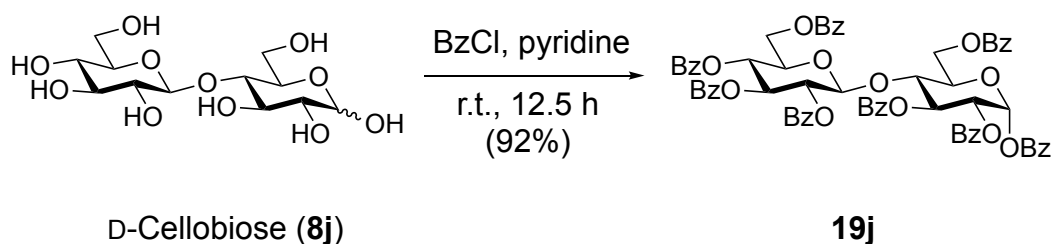
To a solution of commercial D-fucose (**8i**) (500 mg, 3.05 mmol) in pyridine (15 mL) at 0 °C was added BzCl (2.30 mL, 24.4 mmol). After stirring for 14 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (50 mL). The combined organic layer was washed with sat. aq. CuSO₄ (4 x 50 mL) and H₂O (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **19i** (3.40 g, 2.89 mmol, quant.) as a colorless oil without further purification.

$R_f = 0.53$ (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.12-7.23 (m, 15H, Ph-H), 6.83 (d, $J = 3.7$ Hz, 1H, 1-H), 6.05 (dd, $J = 10.8$ Hz, 3.7 Hz, 1H, 3-H), 5.92 (dd, $J = 10.8$ Hz, 3.7 Hz, 1H, 4-H), 5.88 (dd, $J = 3.7$ Hz, 1.0 Hz, 1H, 2-H), 4.65 (m, 1H, 5-H)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-, 1,2,3,6-tetrabenzoate (19j**)**¹⁴¹



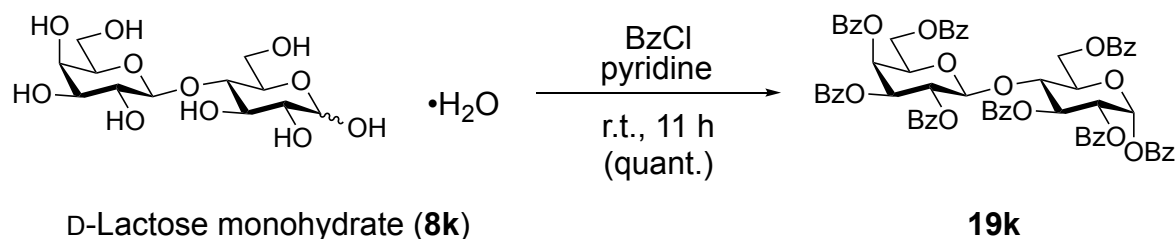
To a solution of commercial D-cellobiose (**8j**) (1.0 g, 2.92 mmol) in pyridine (28 mL) at 0 °C was added BzCl (4.0 mL, 35.1 mmol). After stirring for 12.5 h at room temperature, the reaction mixture was quenched with H₂O (10 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 50 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (2 x 150 mL), aq. CuSO₄ (2 x 150 mL) and H₂O (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **19j** (3.12 g, 2.65 mmol, 92%) as a pale yellow foamy solid without further purification.

R_f = 0.43 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 7.62 (m, 40H, Ph-H), 6.69 (d, J = 3.8 Hz, 1H, 1'-H), 6.14 (ddd, J = 10.1 Hz, 6.9 Hz, 1.7 Hz, 1H, 3'-H), 5.75 (t, J = 9.6 Hz, 1H, 3''-H), 5.52 (dd, J = 9.6 Hz, 7.9 Hz, 1H, 2''-H), 5.47 (dd, J = 10.1 Hz, 3.8 Hz, 1H, 2'-H), 5.42 (t, J = 9.6 Hz, 1H, 4''-H), 5.01 (d, J = 7.9 Hz, 1H, 1''-H), 4.59 (dd, J = 12.3 Hz, 1.3 Hz, 1H, 6'-H), 4.49 (dd, J = 12.3 Hz, 3.3 Hz, 1H, 6'-H), 4.33 (m, 2H, 4'-H, 5'-H), 4.07 (dd, J = 11.8 Hz, 3.3 Hz, 1H, 6''-H), 3.87 (dd, J = 11.8 Hz, 5.1 Hz, 1H, 6''-H), 3.83 (ddd, J = 9.6 Hz, 4.8 Hz, 3.3 Hz, 1H, 5''-H)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-benzoyl- α -D-glucopyranosyl)-, 1,2,3,6-tetrabenzoate (19k**)**¹⁰⁵



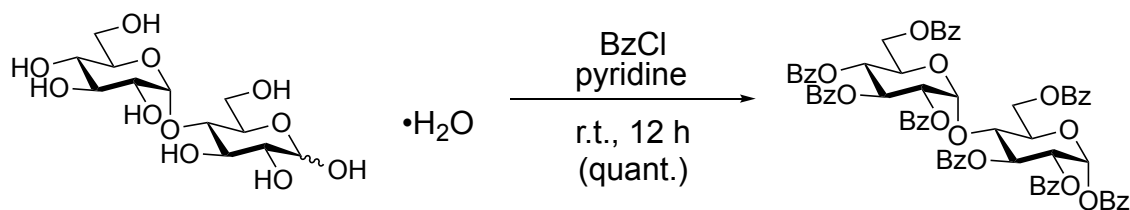
To a solution of commercial D-lactose monohydrate (**8k**) (1.0 g, 2.78 mmol) in pyridine (20 mL) at 0 °C was added BzCl (5.12 mL, 27.8 mmol). After stirring for 11 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 50 mL). The combined organic layer was washed with sat. aq. CuSO₄ (4 x 50 mL) and H₂O (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **19k** (3.49 g, 2.97 mmol, quant.) as a white foamy solid without further purification.

$R_f = 0.39$ (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.03-7.16 (m, 40H, Ph-H), 6.71 (d, $J = 3.8$ Hz, 1H, 1-H), 6.16 (t, 1H, $J = 9.9$ Hz, 3-H), 5.76-5.72 (m, 2H, 2'-H, 4'-H), 5.54 (dd, $J = 10.5$ Hz, 3.8 Hz, 1H, 2-H), 5.39 (dd, $J = 10.5$ Hz, 3.8 Hz, 1H, 3-H), 4.94 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.59-4.50 (m, 2H, 6-H), 4.36-4.32 (m, 2H, 4-H, 5-H), 3.92- 3.71 (m, 3H, 5'-H, 6'-H)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-benzoyl- α -D-glucopyranosyl)-, 1,2,3,6-tetrabenzoate (19I**)**¹⁴¹



D-Maltose monohydrate (**8I**)

19I

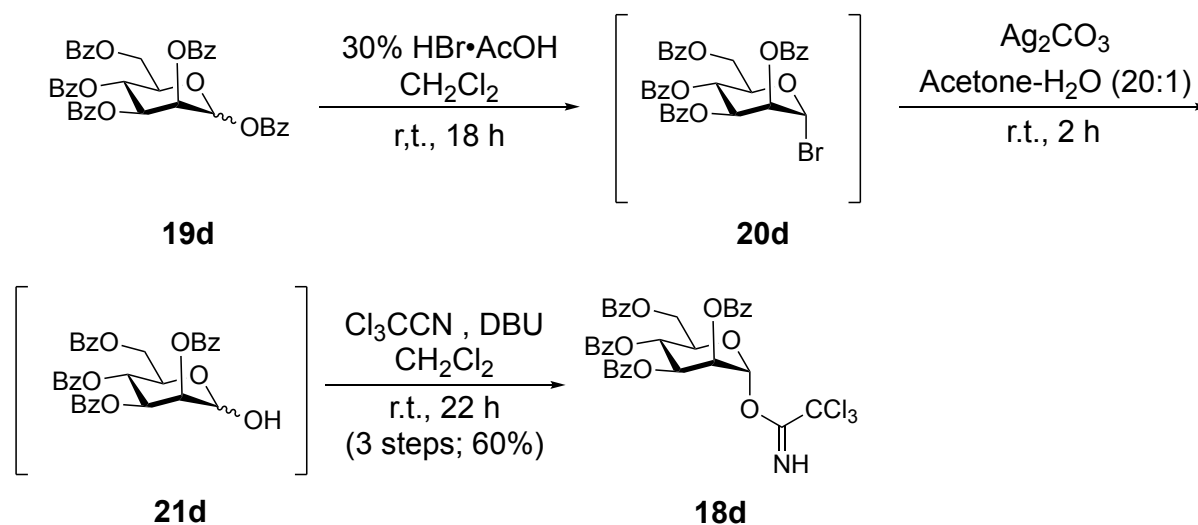
To a solution of commercial D-maltose monohydrate (**8I**) (1 g, 2.78 mmol) in pyridine (20 mL) at 0 °C was added BzCl (5.12 mL, 44.4 mmol). After stirring for 12 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with AcOEt (3 x 50 mL). The combined organic layer was washed with sat. aq. CuSO₄ (4 x 50 mL) and H₂O (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford the pure **19I** (3.40 g, 2.89 mmol, quant.) as a colorless oil without further purification.

R_f = 0.34 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.09-7.19 (m, 40H, Ph-H), 6.72 (d, J = 3.6 Hz, 1H, 1'-H), 6.15 (t, 1H, J = 10.0 Hz, 3-H), 6.10 (t, 1H, J = 10.0 Hz, 3'-H), 5.80 (d, J = 3.6 Hz, 1H, 1'-H), 5.66 (t, 1H, J = 10.0 Hz, 4'-H), 5.39 (dd, J = 10.0 Hz, 3.6 Hz, 1H, 2-H), 5.30 (dd, J = 10.0 Hz, 3.6 Hz, 1H, 2'-H), 5.39 (dd, J = 10.5 Hz, 3.8 Hz, 1H, 3-H), 4.94 (d, J = 8.0 Hz, 1H, 1'-H), 4.89-4.75 (m, 2H, 6-H), 4.57-4.55 (m, 2H, 4-H, 5-H), 4.48-4.44 (m, 1H, 5'-H), 4.41 (dd, J = 12.0 Hz, 2.5 Hz, 1H, 6'-H), 4.28 (dd, J = 12.0 Hz, 3.6 Hz, 1H, 6'-H)

2, 3, 4, 6-Tetra-*O*-benzoyl-D-mannopyranosyl trichloroacetimidate (18d**)**¹⁰⁰



To a solution of **19d** (2.64 g, 3.77 mmol) in dry CH₂Cl₂ (20 mL) at 0 °C was added 30% HBr/AcOH (13.0 mL). After stirring for 18 h at room temperature, the reaction mixture was quenched with H₂O (20 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (60 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (40 mL), and brine (40 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20d** as a mixture yellow oil.

To a solution of **20d** as a crude mixture of previous reaction in acetone (20 mL) and H₂O (1.0 mL) was added Ag₂CO₃ (520 mg, 1.89 mmol). After stirring for 2 h at room temperature, the reaction mixture was filtered by celite, and rinsed with AcOEt (20 mL). The resulting mixture was concentrated *in vacuo* to afford **21d** as a pale yellow foamy solid.

To a solution of **21d** as a crude mixture of previous reaction in dry CH₂Cl₂ (10 mL) was added Cl₃CCN (3.78 mL, 37.7 mmol) followed by DBU (56.1 μL, 0.377 mmol). After stirring at room temperature for 22 h, the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 120 g, hexane : AcOEt = 4 : 1 → 7 : 3) to afford **18d** (α only, 1.68 g, 2.26 mmol, 60%) as a white foamy solid by three steps.

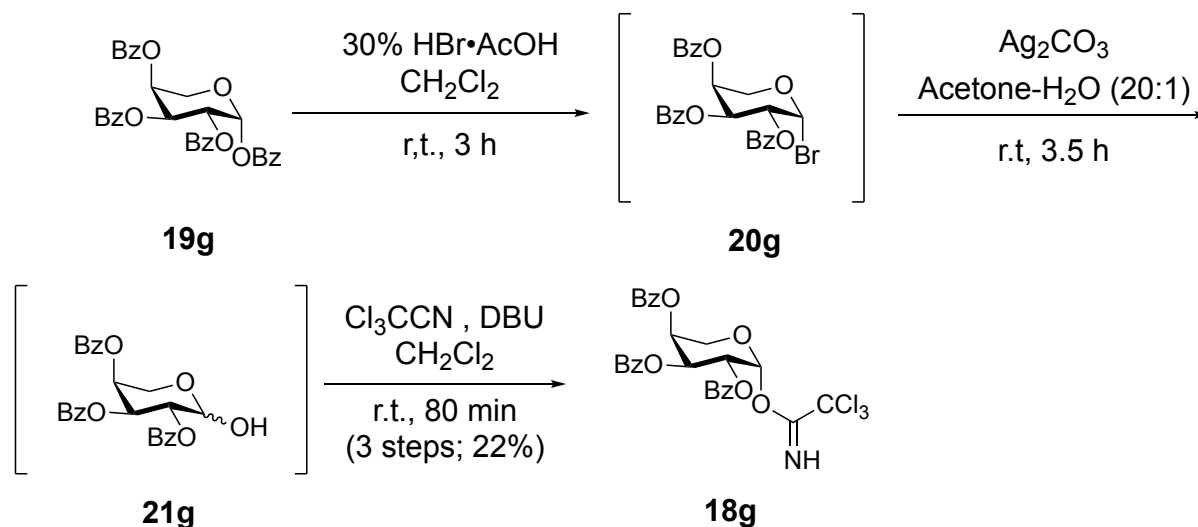
R_f = 0.61 (hexane : AcOEt = 1 : 1)

¹H-NMR (300 MHz, CDCl₃)

δ : 8.86 (s, 1H, -NH), 7.69 (m, 20H, Ph-H), 6.58 (d, *J* = 1.9 Hz, 1H, 1-H), 6.23 (t, *J* =

10.2 Hz, 1H, 4-H), 5.98 (dd, $J = 10.2$ Hz, 3.4Hz, 1H, 3-H), 5.94 (dd, $J = 3.4$ Hz, 1.9 Hz, 1H, 2-H), 4.73 (dd, $J = 12.2$ Hz, 2.5 Hz, 1H, 6-H), 4.63 (ddd, $J = 10.2$ Hz, 4.2 Hz, 2.5Hz, 1H, 5-H), 4.50 (dd, $J = 12.2$ Hz, 4.2 Hz, 1H, 6-H)

2, 3, 4-Tri-*O*-benzoyl- β -L-arabinopyranosyl trichloroacetimidate (18g**)**¹⁰¹



To a solution of **19g** (4.01 g, 7.08 mmol) in dry CH₂Cl₂ (30 mL) at 0 °C was added 30% HBr/AcOH (9.0 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (60 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (2 x 60 mL), and brine (60 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20g** as a mixture pale yellow solid.

To a solution of **20g** as the crude mixture of previous reaction in acetone (20.0 mL) and H₂O (1.0 mL) was added Ag₂CO₃ (976 mg, 3.54 mmol). After stirring for 3.5 h at room temperature, the reaction mixture was filtered by celite and rinsed with acetone (20 mL). The resulting mixture was concentrated *in vacuo* to afford **21g** as a pale yellow foamy solid.

To a solution of **21g** as the crude mixture in dry CH₂Cl₂ (50 mL) was added Cl₃CCN (8.5 mL, 84.96 mmol) followed by DBU (105 μ L, 0.708 mmol). After stirring for 80 min at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 150 g, hexane : AcOEt = 4 : 1) to afford **18g** (β only, 966 mg, 1.59 mmol, 22%) as a pale yellow foamy solid by three steps.

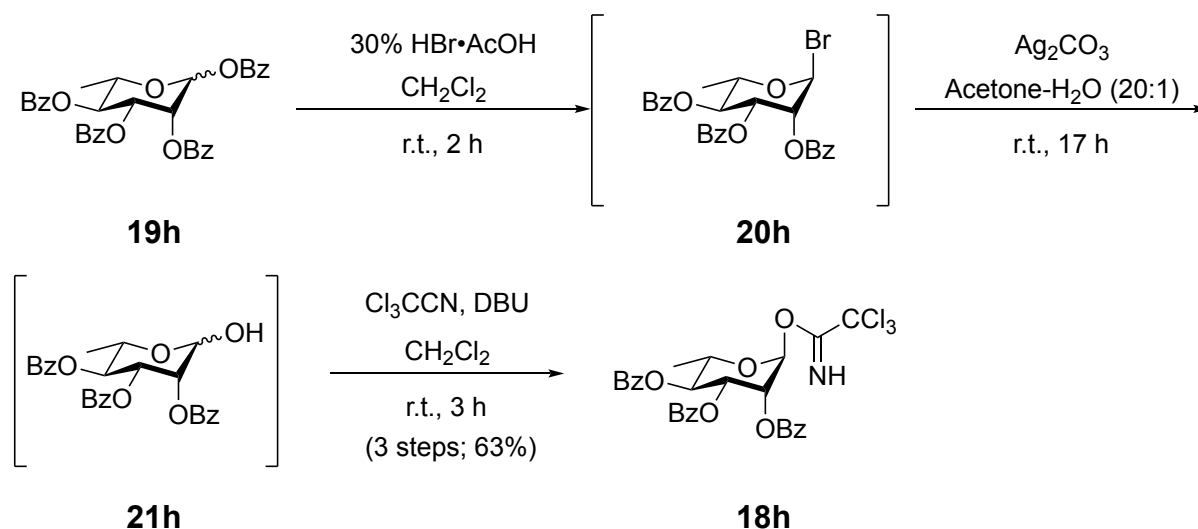
R_f = 0.62 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

β δ : 8.63 (s, 1H, -NH), 8.12-7.27 (m, 15H, Ar-H), 6.82 (d, *J* = 3.0 Hz, 1H, 1-H),

6.06-5.88 (m, 3H, 2-H, 3-H, 4-H), 4.42 (dd, $J = 13.5$ Hz, 1.0 Hz, 1H, 5-H), 4.18 (dd, $J = 13.5$ Hz, 2.0 Hz, 1H, 5-H)

2, 3, 4 -Tri-*O*-benzoyl-L-rhamnopyranosyl trichloroacetimidate (18h**)**¹⁰²



To a solution of **19h** (1.00 g, 1.72 mmol) in CH_2Cl_2 (18 mL) was added 30% HBr/AcOH (8 mL). After stirring for 2 h at room temperature, the reaction mixture was quenched with H_2O (20 mL) in ice bath. The resulting mixture was extracted with CH_2Cl_2 (20 mL). The combined organic layer was washed with sat. aq. NaHCO_3 (3 x 20 mL), and brine (20 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20h** as a mixture pale yellow foamy solid.

To a solution of **20h** as the crude mixture of previous reaction in acetone (17 mL) and H_2O (1.0 mL) was added Ag_2CO_3 (238 mg, 0.86 mmol). After stirring for 17 h at room temperature, the reaction mixture was filtered by celite and rinsed with acetone (30 mL). The resulting mixture was concentrated *in vacuo* to afford **21h** as a white foamy solid.

To a solution of **21h** as the crude mixture of previous reaction in dry CH_2Cl_2 (18 mL) was added Cl_3CCN (2.0 mL, 20.67 mmol) followed by DBU (128.3 μL , 0.86 mmol). After stirring for 3 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 50 g, hexane : AcOEt = 4 : 1) to afford **18h** (α only, 669.3 mg, 1.08 mmol, 63% by three steps) as a white foamy solid.

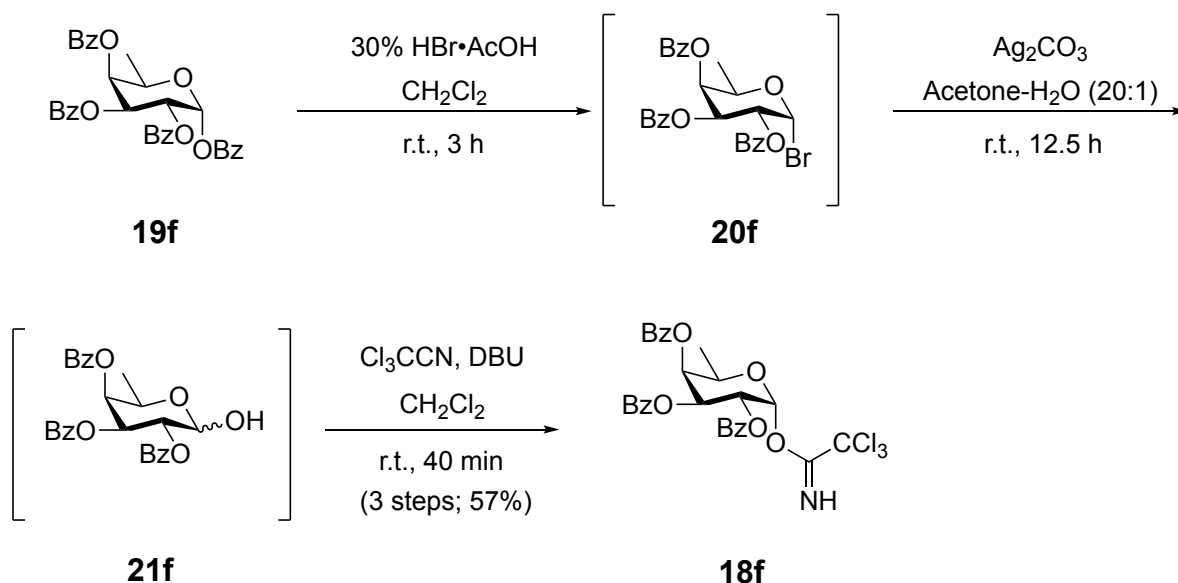
$R_f = 0.60$ (hexane : AcOEt = 1 : 1)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

δ : 8.82 (s, 1H, -NH), 7.68 (m, 20H, Ph-H), 6.49 (d, $J = 1.6$ Hz, 1H, 1-H), 5.90 (m, 1H,

2-H), 5.77 (ddd, $J = 11.8$ Hz, 9.8 Hz, 1.5 Hz, 1H, 3-H), 4.42 (dd, $J = 9.8$ Hz, 6.3 Hz, 1H, 4-H), 4.39 (dd, $J = 9.8$ Hz, 6.3 Hz, 1H, 5-H), 1.42 (d, $J = 6.3$ Hz, 1H, 6-H)

2, 3, 4-Tri-*O*-benzoyl- α -D-fucopyranosyl trichloroacetimidate (**18f**)¹⁰³



To a solution of **19f** (1.91 g, 3.29 mmol) in dry CH₂Cl₂ (30 mL) at 0 °C was added 30% HBr/AcOH (12.0 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (50 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (2 x 50 mL), and brine (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20f** as a white foamy solid.

To a solution of **20f** as the crude mixture of previous reaction in acetone (40 mL) and H₂O (2.0 mL) was added Ag₂CO₃ (454 mg, 1.65 mmol). After stirring for 12.5 h at room temperature, the reaction mixture filtered by celite, and rinsed with acetone (30 mL). The filtrate was concentrated *in vacuo* to afford **21f** as a white foamy solid.

To a solution of **21f** as the crude mixture of previous reaction in dry CH₂Cl₂ (30 mL) was added Cl₃CCN (3.30 mL, 32.9 mmol) followed by DBU (246 μ L, 1.65 mmol). After stirring for 40 min at room temperature, the reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 100 g, hexane : AcOEt = 4 : 1) to afford **18f** (α only, 1.16 g, 1.86 mmol, 57%) as a white foamy solid by three steps.

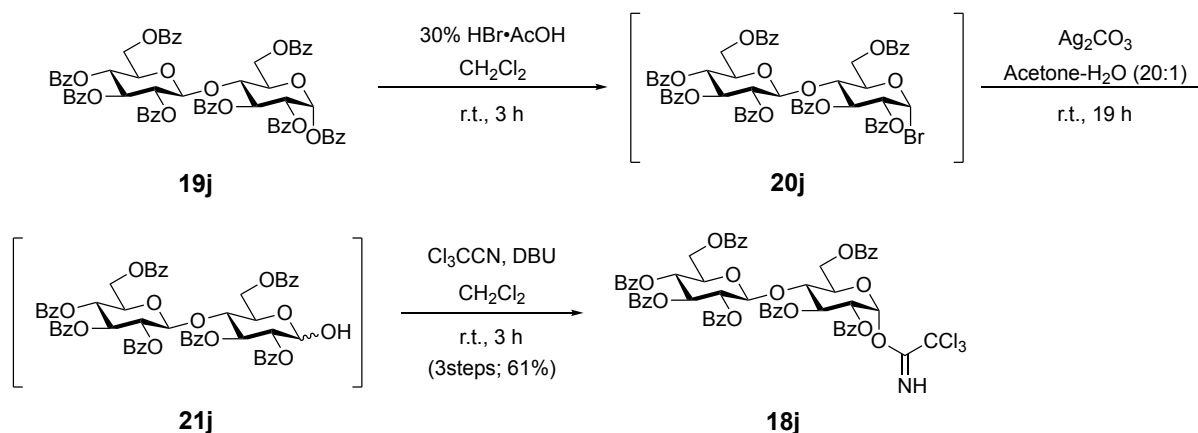
R_f = 0.49 (hexane : AcOEt = 2 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.59 (s, 1H, -NH), 8.12-7.23 (m, 15H, Ph-H), 6.83 (d, *J* = 3.7 Hz, 1H, 1-H), 6.05 (dd, *J* = 10.8 Hz, 3.7 Hz, 1H, 3-H), 5.92 (dd, *J* = 10.8 Hz, 3.7 Hz, 1H, 4-H), 5.88 (dd, *J*

= 3.7 Hz, 1.0 Hz, 1H, 2-H), 4.65 (m, 1H, 5-H)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-benzoyl- β -D-glucopyranosyl)-, 2,3,6-tribenzoate 1-(2,2,2-trichloroethanimidate) (18j**)**¹⁰⁴



To a solution of **19j** (1.0 g, 0.85 mmol) in CH_2Cl_2 (8.5 mL) was added 30% HBr/AcOH (19 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched with H_2O (40 mL) in ice bath. The resulting mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was washed with sat. aq. NaHCO_3 (4 x 10 mL), and brine (20 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20j** as a mixture pale yellow foamy solid.

To a solution of **20j** as the crude mixture of previous reaction in acetone (32 mL) and H_2O (1.6 mL) was added Ag_2CO_3 (117.3 mg, 0.43 mmol). After stirring for 19 h at room temperature, the reaction mixture was filtered by celite and rinsed with acetone (30 mL). The resulting mixture was concentrated *in vacuo* to afford **21j** as a pale yellow foamy solid.

To a solution of **21j** as the crude mixture of previous reaction in dry CH_2Cl_2 (8.5 mL) was added Cl_3CCN (1.0 mL, 10.21 mmol) followed by DBU (12.7 μL , 0.09 mmol). After stirring for 3 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 50 g, hexane : AcOEt = 4 : 1 \rightarrow 3 : 1) to afford **18j** (α only, 629.6 mg, 0.52 mmol, 61% by three steps) as a pale yellow foamy solid.

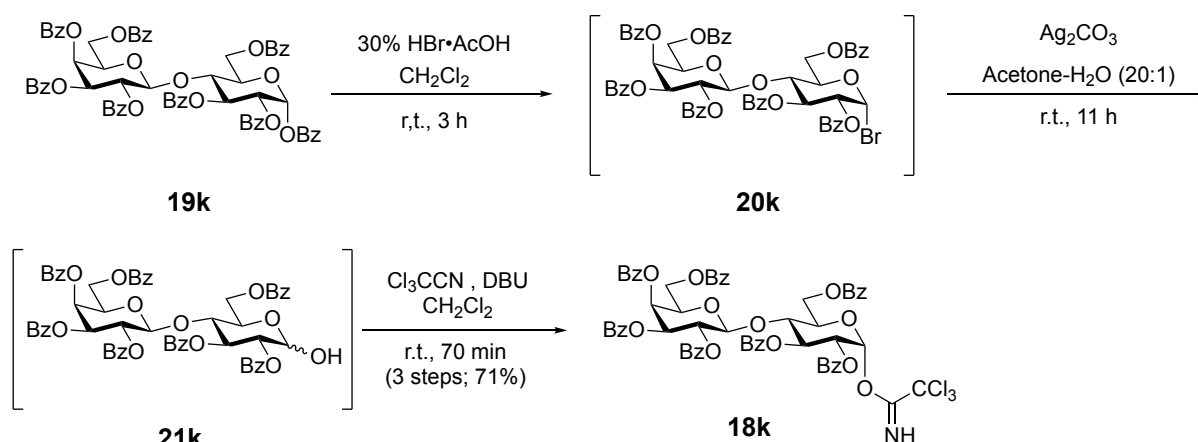
R_f = 0.39 (hexane : AcOEt = 1 : 1)

$^1\text{H-NMR}$ (400 MHz, CDCl_3)

α δ : 8.54 (s, 1H, -NH), 7.62 (m, 35H, Ph-H), 6.69 (d, J = 3.8 Hz, 1H, 1'-H), 6.14 (ddd, J = 10.1 Hz, 6.9 Hz, 1.7 Hz, 1H, 3'-H), 5.75 (t, J = 9.6 Hz, 1H, 3''-H), 5.52 (dd, J =

9.6 Hz, 7.9 Hz, 1H, 2''-H), 5.47 (dd, $J = 10.1$ Hz, 3.8 Hz, 1H, 2'-H), 5.42 (t, $J = 9.6$ Hz, 1H, 4''-H), 5.01 (d, $J = 7.9$ Hz, 1H, 1''-H), 4.59 (dd, $J = 12.3$ Hz, 1.3 Hz, 1H, 6'-H), 4.49 (dd, $J = 12.3$ Hz, 3.3 Hz, 1H, 6'-H), 4.33 (m, 2H, 4'-H, 5'-H), 4.07 (dd, $J = 11.8$ Hz, 3.3 Hz, 1H, 6''-H), 3.87 (dd, $J = 11.8$ Hz, 5.1 Hz, 1H, 6''-H), 3.83 (ddd, $J = 9.6$ Hz, 4.8 Hz, 3.3 Hz, 1H, 5''-H)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-benzoyl- β -D-galactopyranosyl)-, 2,3,6-tribenzoate 1-(2,2,2-trichloroethanimidate) (18k**)**¹⁰⁵



To a solution of **19k** (3.49 g, 2.97 mmol) in dry CH₂Cl₂ (30 mL) at 0 °C was added 30% HBr/AcOH (13.0 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (80 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (2 x 50 mL), and brine (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20k** as a white formy solid.

To a solution of **20k** as the crude mixture of previous reaction in acetone (20 mL) and H₂O (1.0 mL) was added Ag₂CO₃ (409 mg, 1.49 mmol). After stirring for 11 h at room temperature, the reaction mixture was filtered by celite, and rinsed with acetone (40 mL). The resulting mixture was concentrated *in vacuo* to afford **21k** as a white foamy solid.

To a solution of **21k** as the crude mixture of previous reaction in dry CH₂Cl₂ (30 mL) was added Cl₃CCN (2.98 mL, 29.7 mmol) followed by DBU (221 μ L, 1.49 mmol). After stirring for 70 min at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 150 g, hexane : AcOEt = 7 : 3 \rightarrow 3 : 2) to afford **18k** (α only, 2.58 g, 2.12 mmol, 71%) as a white foamy solid by three steps.

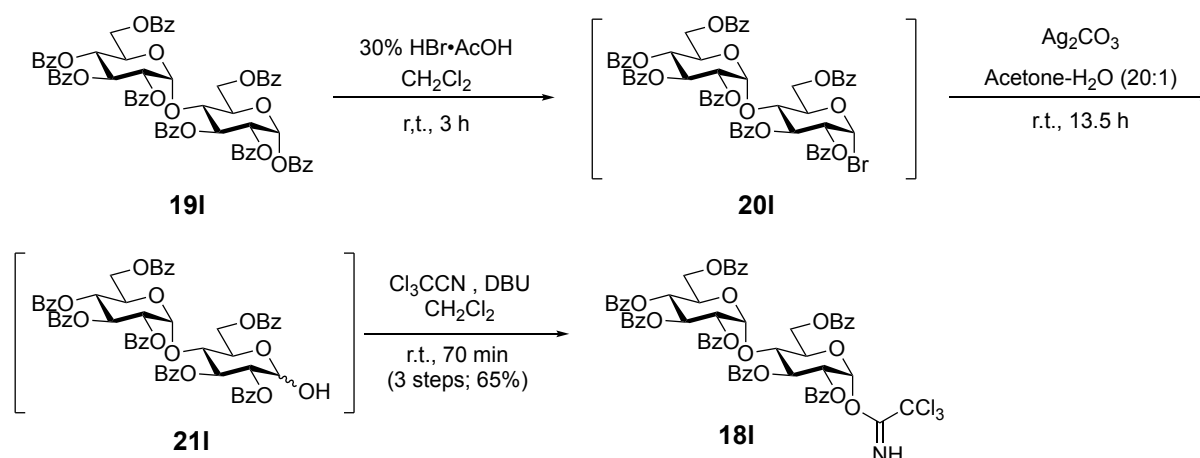
R_f = 0.42 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.56 (s, 1H, -NH), 8.03-7.16 (m, 35H, Ph-H), 6.71 (d, *J* = 3.8 Hz, 1H, 1-H), 6.16

(t, 1H, $J = 9.9$ Hz, 3-H), 5.76-5.72 (m, 2H, 2'-H, 4'-H), 5.54 (dd, $J = 10.5$ Hz, 3.8 Hz, 1H, 2-H), 5.39 (dd, $J = 10.5$ Hz, 3.8 Hz, 1H, 3'-H), 4.94 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.59-4.50 (m, 2H, 6-H), 4.36-4.32 (m, 2H, 4-H, 5-H), 3.92-3.71 (m, 3H, 5'-H, 6'-H)

α -D-Glucopyranose, 4-O-(2,3,4,6-tetra-O-benzoyl- α -D-glucopyranosyl)-, 2,3,6-tribenzoate 1-(2,2,2-trichloroethanimidate) (18I**)**¹⁰⁶



To a solution of **19I** (3.26 g, 2.78 mmol) in dry CH₂Cl₂ (30 mL) at 0 °C was added 30% HBr/AcOH (13.0 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched with H₂O (30 mL) in ice bath. The resulting mixture was extracted with CH₂Cl₂ (80 mL). The combined organic layer was washed with sat. aq. NaHCO₃ (3 x 50 mL), and brine (50 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to afford **20I** as a white foamy solid.

To a solution of **20I** as the crude mixture of previous reaction in acetone (20 mL) and H₂O (1.0 mL) was added Ag₂CO₃ (383 mg, 1.39 mmol). After stirring for 13.5 h at room temperature, the reaction mixture was filtered by celite, and rinsed with Acetone (40 mL). The resulting mixture was concentrated *in vacuo* to afford **21I** as a white foamy solid.

To a solution of **21I** as the crude mixture of previous reaction in dry CH₂Cl₂ (30 mL) was added Cl₃CCN (2.78 mL, 27.8 mmol) followed by DBU (207 μ L, 1.39 mmol). After stirring for 70 min at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel 250 g, hexane : AcOEt = 7 : 3 \rightarrow 3 : 2) to afford **18I** (α only, 2.39 g, 1.97 mmol, 65%) as a white foamy solid by three steps.

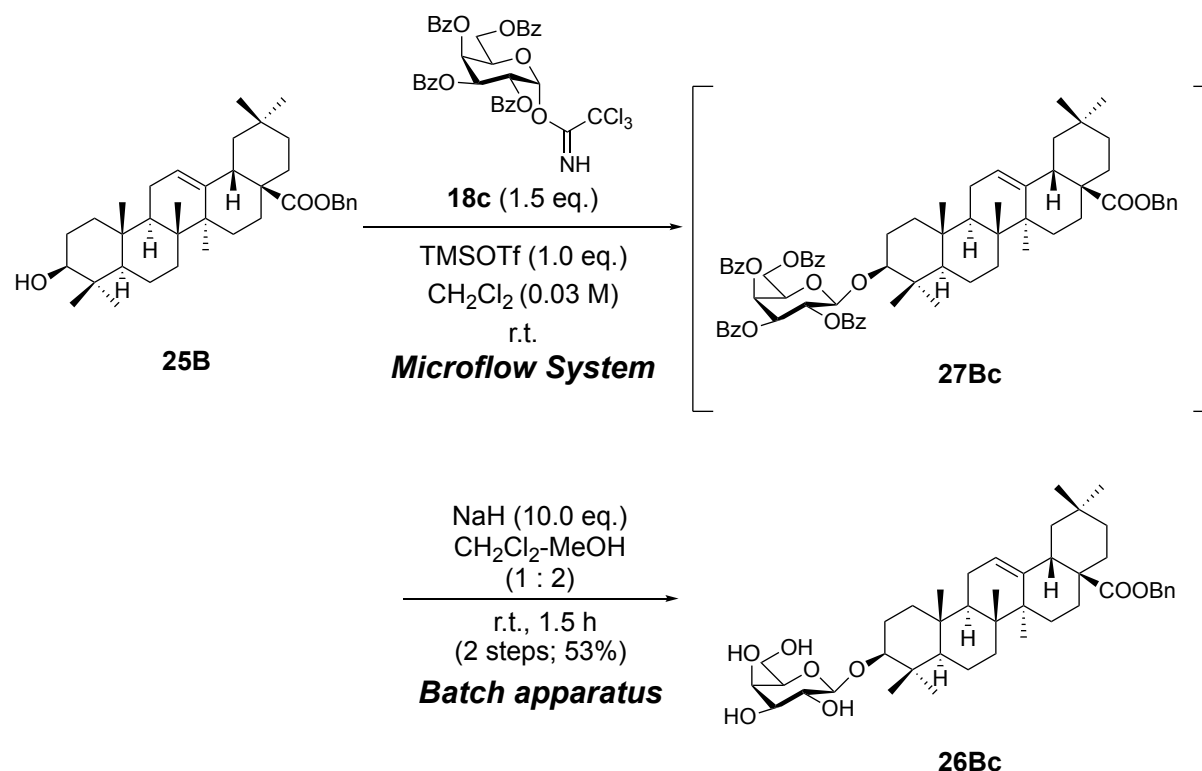
R_f = 0.57 (hexane : AcOEt = 1 : 1)

¹H-NMR (400 MHz, CDCl₃)

α δ : 8.58 (s, 1H, -NH), 8.09-7.19 (m, 35H, Ph-H), 6.72 (d, *J* = 3.6 Hz, 1H, 1'-H), 6.15 (t, 1H, *J* = 10.0 Hz, 3-H), 6.10 (t, 1H, *J* = 10.0 Hz, 3'-H), 5.80 (d, *J* = 3.6 Hz, 1H,

1'-H), 5.66 (t, 1H, $J = 10.0$ Hz, 4'-H), 5.39 (dd, $J = 10.0$ Hz, 3.6 Hz, 1H, 2-H), 5.30 (dd, $J = 10.0$ Hz, 3.6 Hz, 1H, 2'-H), 5.39 (dd, $J = 10.5$ Hz, 3.8 Hz, 1H, 3-H), 4.94 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.89-4.75 (m, 2H, 6-H), 4.57-4.55 (m, 2H, 4-H, 5-H), 4.48-4.44 (m, 1H, 5'-H), 4.41 (dd, $J = 12.0$ Hz, 2.5 Hz, 1H, 6'-H), 4.28 (dd, $J = 12.0$ Hz, 3.6 Hz, 1H, 6'-H)

Olean-12-en-28-oic acid, 3-O-(β -D-galactopyranosyloxy)-, phenylmethyl ester (26Bc)



A solution of TMSOTf (49 μL , 0.274 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18c** (305 mg, 0.412 mmol) and acceptor **25B** (150 mg, 0.274 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture of **27Bc** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 1.5 h at room temperature in flask which added NaH (109.7 mg, 2.743 mmol, 60% disp.) and dry MeOH (36 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (100 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl_3 : MeOH = 50 : 1 \rightarrow 45 : 1) to afford **26Bc** (102 mg, 0.144 mmol, 53%) as a white solid by two steps.

$R_f = 0.29$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{22} + 27.6$ (c 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 7.45 (m, 5H, PhCH₂), 5.42 (t, *J* = 3.0 Hz, 1H, 12-H), 5.36, 5.29 (each d, *J* = 12.6 Hz, 2H, PhCH₂), 4.88 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.61 (d, *J* = 3.4 Hz, 1H, 5'-H), 4.48 (dd, *J* = 8.0 Hz, 6.0 Hz, 1H, 2'-H), 4.48 (m, 2H, 6'-H), 4.26 (t, *J* = 6.0 Hz, 1H, 3'-H), 4.19 (dd, *J* = 9.5 Hz, 3.4 Hz, 1H, 4'-H), 3.40 (dd, *J* = 11.8 Hz, 4.4 Hz, 1H, 3-H), 3.16 (dd, *J* = 14.0 Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

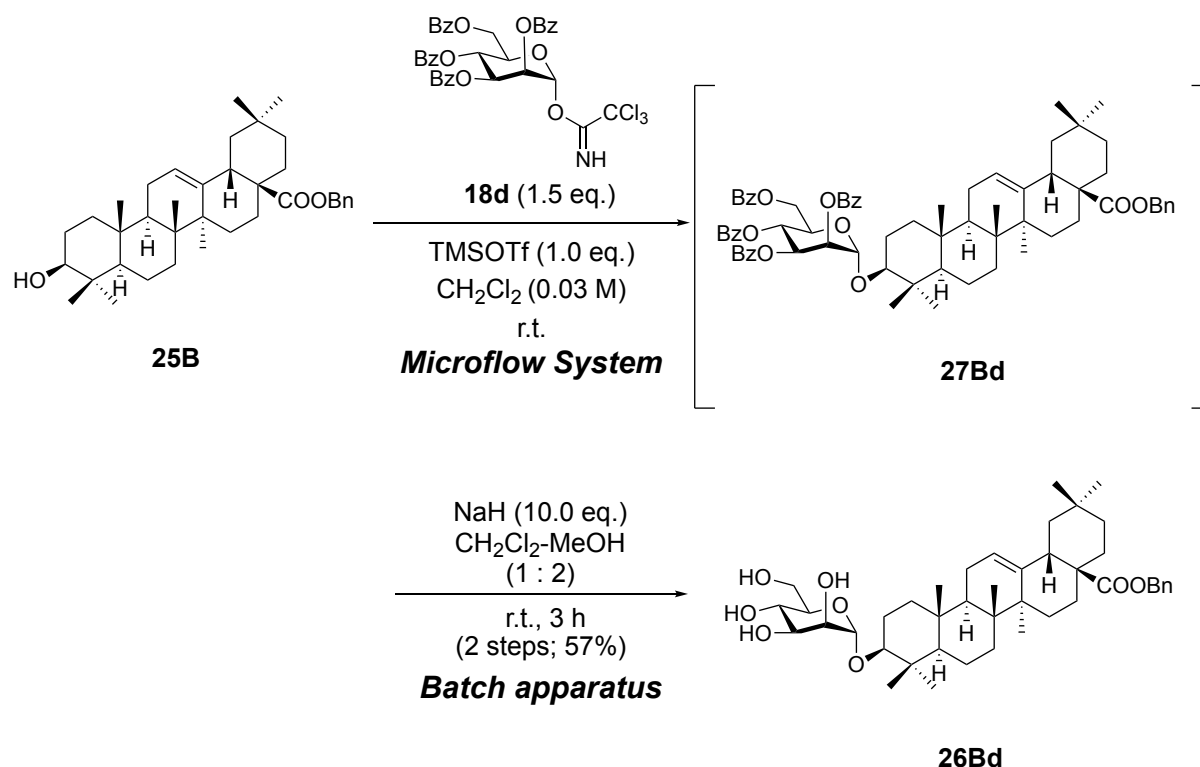
δ : 177.5 (C-28), 144.2 (C-13), 137.5, 129.1, 128.6 (PhCH₂), 123.2 (C-12), 107.7 (C-1'), 88.9 (C-3), 76.9 (C-3'), 75.5 (C-4'), 73.2 (C-2'), 70.3 (C-5'), 66.4 (PhCH₂), 62.5 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm⁻¹ ν : 3422 (-O-H), 2945 (=C-H), 1726 (-C=O), 1063 (-C-O-)

HR-MS (ESI⁺)

m/z 731.4482[M+Na]⁺, Calc'd for C₄₃H₆₄O₈Na:731.4499.

Olean-12-en-28-oic acid, 3-*O*-(α -D-mannopyranosyl oxy)-, phenylmethyl ester (26Bd)



A solution of TMSOTf (49 μL , 0.274 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18d** (305 mg, 0.412 mmol) and acceptor **25B** (150 mg, 0.274 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture of **27Bd** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 3 h at room temperature in flask which added NaH (110 mg, 2.74 mmol, 60% disp.) and dry MeOH (36 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (100 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 100 : 1 \rightarrow 90 : 1 \rightarrow 85 : 1 \rightarrow 80 : 1 \rightarrow 75 : 1 \rightarrow 70 : 1 \rightarrow 60 : 1 \rightarrow 50 : 1 \rightarrow 40 : 1 \rightarrow 35 : 1 \rightarrow 30 : 1 \rightarrow 25 : 1 \rightarrow 15 : 1) to afford **26Bd** (111 mg, 0.157 mmol, 57%) as a white solid by two steps.

$R_f = 0.68$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{23} +88.0$ (*c* 0.30, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 7.45 (m, 5H, PhCH_2), 5.57 (d, $J = 1.3$ Hz, 1H, 1'-H), 5.42 (t, $J = 3.0$ Hz, 1H, 12-H), 5.36, 5.29 (each d, $J = 12.6$ Hz, 2H, PhCH_2), 4.73 (t, $J = 9.5$ Hz, 1H, 4'-H), 4.63 (m, 1H, 6'-H), 4.60 (dd, $J = 9.5$ Hz, 3.5 Hz, 1H, 3'-H), 4.55 (dd, $J = 3.5$ Hz, 1.3 Hz, 1H, 2'-H), 4.49-4.42 (m, 2H, 5'-H, 6'-H), 3.40 (dd, $J = 11.8$ Hz, 4.4 Hz, 1H, 3-H), 3.16 (dd, $J = 14.0$ Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

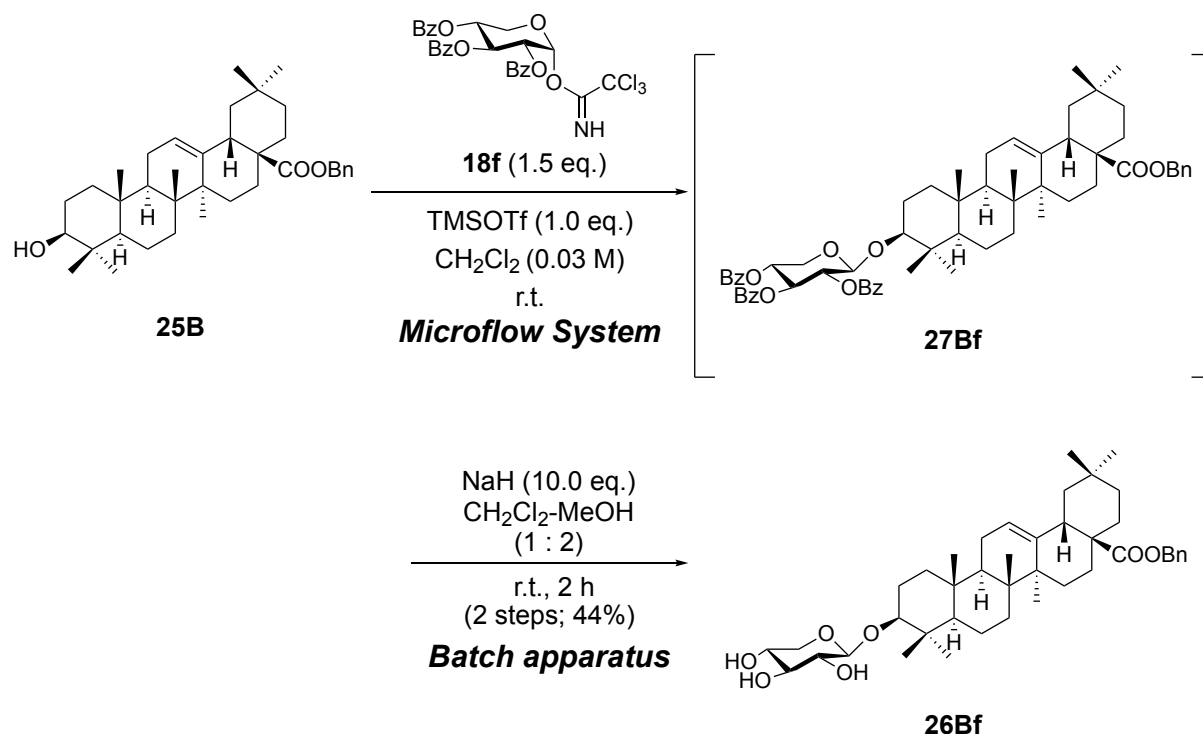
δ : 177.4 (C-28), 144.3 (C-13), 137.5, 129.1, 128.6 (PhCH_2), 123.1 (C-12), 97.9 (C-1'), 81.9 (C-3), 76.1 (C-5'), 73.3 (C-3'), 73.1 (C-2'), 69.2 (C-4'), 66.2 (PhCH_2), 63.4 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 3422 (-O-H), 2944 (=C-H), 1726 (-C=O), 1059 (-C-O-)

HR-MS (ESI⁺)

m/z 731.4484[M+Na]⁺, Calc'd for $\text{C}_{43}\text{H}_{64}\text{O}_8\text{Na}$:731.4499.

Olean-12-en-28-oic acid, 3-*O*-(β -D-xylopyranosyloxy)-, phenylmethyl ester (26Bf**)**



A solution of TMSOTf (49 μL , 0.274 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18f** (250 mg, 0.412 mmol) and acceptor **25B** (150 mg, 0.274 mmol) dissolved in CH_2Cl_2 (9.0 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture of **27Bf** was stirred for 2 h at room temperature in flask which added NaH (110 mg, 2.74 mmol, 60% disp.) and dry MeOH (36 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (100 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 20 g, CHCl_3 : MeOH = 95 : 1 \rightarrow 90 : 1 \rightarrow 85 : 1) to afford **26Bf** (81.8 mg, 0.121 mmol, 44%) as a white solid by two steps.

$R_f = 0.39$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{23} +29.1$ (c 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 7.46 (m, 5H, PhCH₂), 5.42 (t, *J* = 3.2 Hz, 1H, 12-H), 5.36, 5.30 (each d, *J* = 12.6 Hz, 2H, PhCH₂), 4.85 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.40 (dd, *J* = 11.0 Hz, 5.0 Hz, 1H, 5'-H), 4.25 (m, 1H, 4'-H), 4.18 (t, *J* = 8.0 Hz, 1H, 3'-H), 4.04 (t, *J* = 8.0 Hz, 1H, 2'-H), 3.80 (t, *J* = 11.0 Hz, 1H, 5'-H), 3.37 (dd, *J* = 11.8 Hz, 4.3 Hz, 1H, 3-H), 3.16 (dd, *J* = 13.9 Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

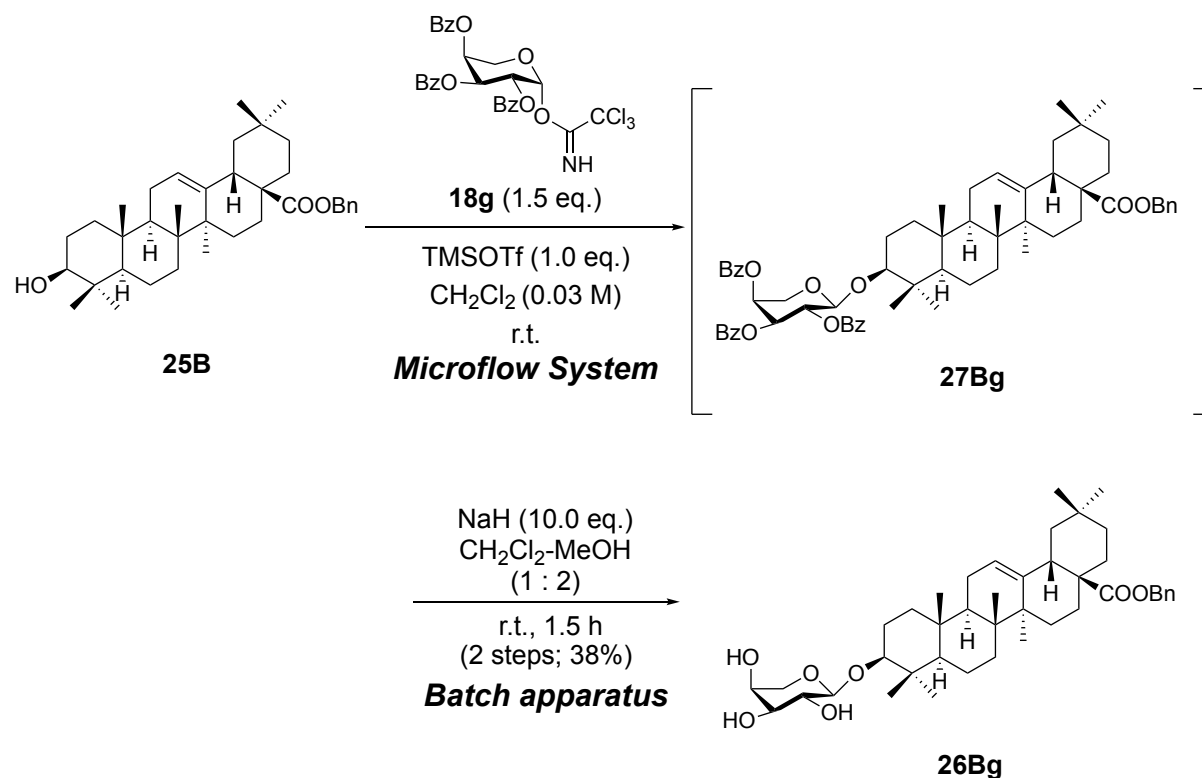
δ : 177.4 (C-28), 144.2 (C-13), 129.1, 128.6, 128.5 (PhCH₂), 123.2 (C-12), 107.8 (C-1'), 88.8 (C-3), 78.6 (C-3'), 75.6 (C-2'), 71.3 (C-4'), 67.2 (C-5'), 66.3 (PhCH₂), 60.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm⁻¹ ν : 3423 (-O-H), 2946 (=C-H), 1726 (-C=O), 1043 (-C-O-)

HR-MS (ESI⁺)

m/z 701.4384[M+Na]⁺, Calc'd for C₄₂H₆₂O₇Na:701.4393.

Olean-12-en-28-oic acid, 3-O-(α -L-arabinopyranosyl oxy)-, phenylmethyl ester (26Bg)



A solution of TMSOTf (59.8 μL , 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18g** (301 mg, 0.496 mmol) and acceptor **25B** (181 mg, 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture of **27Bg** was stirred for 1.5 h at room temperature in flask which added NaH (132 mg, 3.31 mmol, 60% disp.) and dry MeOH (44 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (100 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 30 g, CHCl_3 : MeOH = 100 : 1 \rightarrow 95 : 1 \rightarrow 90 : 1 \rightarrow 85 : 1 \rightarrow 70 : 1 \rightarrow 60 : 1) to afford **26Bg** (38.2 mg, 0.056 mmol, 38%) as a white solid by two steps.

$R_f = 0.50$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{26} + 38.1$ (*c* 0.30, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 7.39 (m, 5H, PhCH₂), 5.42 (t, J = 3.5 Hz, 1H, 12-H), 5.36, 5.29 (each d, J = 12.6 Hz, 2H, PhCH₂), 4.79 (d, J = 7.0 Hz, 1H, 1'-H), 4.45 (dd, J = 9.3 Hz, 7.4 Hz, 1H, 2'-H), 4.34 (m, 2H, 4'-H, 5'-H), 4.18 (dd, J = 8.9 Hz, 3.4 Hz, 1H, 3'-H), 4.06 (dd, J = 14.6 Hz, 7.2 Hz, 1H, 5'-H), 3.36 (dd, J = 11.8 Hz, 4.4 Hz, 1H, 3-H), 3.16 (dd, J = 14.1 Hz, 4.1 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

$^{13}\text{C-NMR}$ (100 MHz, pyridine- d_5)

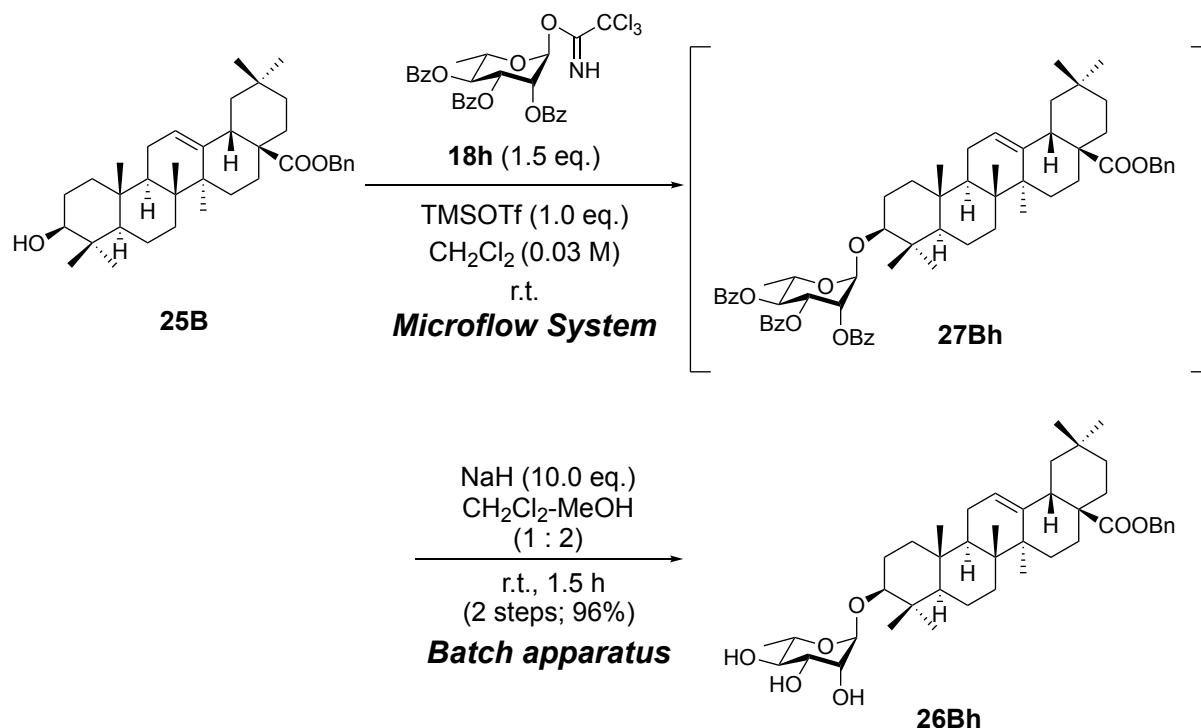
δ : 177.3 (C-28), 144.1 (C-13), 129.0, 128.6, 128.5 (PhCH₂), 123.1 (C-12), 107.7 (C-1'), 88.8 (C-3), 74.8 (C-3'), 73.1 (C-2'), 69.7 (C-4'), 66.3 (C-5'), 66.3 (PhCH₂), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 2997 (-O-H), 1722 (=C-H)

HR-MS (ESI⁺)

m/z 701.4393 $[\text{M}+\text{Na}]^+$, Calc'd for C₄₂H₆₂O₇Na: 715.4393.

Olean-12-en-28-oic acid, 3-*O*-(α -L-rhamnopyranosyloxy)-, phenylmethyl ester (26Bh)



A solution of TMSOTf (59.8 μL , 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18h** (308 mg, 0.496 mmol) and acceptor **25B** (181 mg, 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture of **27Bh** was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture was stirred for 1.5 h at room temperature in flask which added NaH (132 mg, 3.31 mmol, 60% disp.) and dry MeOH (44 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (100 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 50 g, CHCl_3 : MeOH = 30 : 1 \rightarrow 25 : 1) to afford **26Bh** (219 mg, 0.317 mmol, 96%) as a white solid by two steps.

$R_f = 0.46$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{26} +8.06$ (c 0.30, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

7.46 (m, 5H, PhCH₂), 5.42 (t, $J = 3.3$ Hz, 1H, 12-H), 5.36, 5.30 (each d, $J = 12.6$ Hz, 2H, PhCH₂), 5.33 (brs, 1H, 1'-H), 4.58 (dd, $J = 3.0$ Hz, 1.7 Hz, 1H, 2'-H), 4.49 (dd, $J = 8.0$ Hz, 3.0 Hz, 1H, 3'-H), 4.33 (dd, $J = 9.0$ Hz, 8.0 Hz, 1H, 4'-H), 4.30 (dt, $J = 9.0$ Hz, 5.0 Hz, 1H, 5'-H), 3.38 (dd, $J = 12.0$ Hz, 4.3 Hz, 1H, 3-H), 3.16 (dd, $J = 14.0$ Hz, 3.7 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.69 (d, $J = 5.0$ Hz, 3H, 6'-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

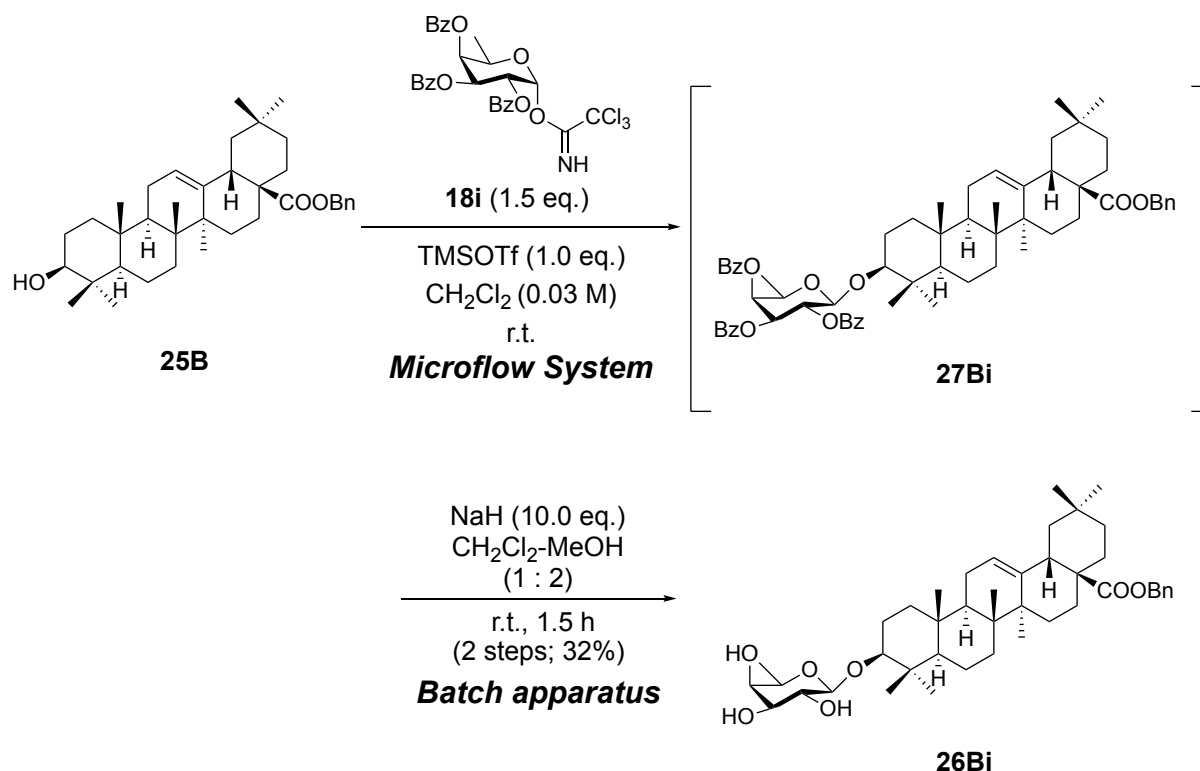
δ : 177.4 (C-28), 144.2 (C-13), 129.1, 128.6, 128.5 (PhCH₂), 123.1 (C-12), 104.5 (C-1'), 88.6 (C-3), 74.2 (C-5'), 73.0 (C-3'), 72.5 (C-2'), 70.0 (C-4'), 66.3 (PhCH₂), 55.7 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.7 (C-6'), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm⁻¹ ν : 3423 (-O-H), 2943 (=C-H), 1726 (-C=O), 1053 (-C-O-)

HR-MS (ESI⁺)

m/z 715.4548[M+Na]⁺, Calc'd for C₄₃H₆₄O₇Na:715.4550.

Olean-12-en-28-oic acid, 3-O-(β -D-fucopyranosyloxy)-, phenylmethyl ester (26Bi**)**



A solution of TMSOTf (59.8 μL , 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18i** (308 mg, 0.496 mmol) and acceptor **25B** (181 mg, 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture of was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture of **27Bi** was stirred for 1.5 h at room temperature in flask which added NaH (132 mg, 3.31 mmol, 60% disp.) and dry MeOH (44 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered, and rinsed with MeOH (100 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 50 g, CHCl_3 : MeOH = 30: 1) to afford **26Bi** (73.5 mg, 0.106 mmol, 32%) as a white solid by two steps.

$R_f = 0.54$ (CHCl_3 : MeOH = 5 : 1)

$[\alpha]_{\text{D}}^{26} +8.18$ (c 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 7.47 (m, 5H, PhCH₂), 5.43 (t, *J* = 3.4 Hz, 1H, 12-H), 5.36, 5.30 (each d, *J* = 12.5 Hz, 2H, PhCH₂), 4.76 (d, *J* = 7.7 Hz, 1H, 1'-H), 4.37 (dd, *J* = 9.0 Hz, 7.7 Hz, 1H, 2'-H), 4.11 (dd, *J* = 9.0 Hz, 3.6 Hz, 1H, 3'-H), 4.08 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H, 4'-H), 3.89 (ddd, *J* = 14.3 Hz, 6.5 Hz, 0.8 Hz, 1H, 5'-H), 3.38 (dd, *J* = 12.0 Hz, 4.3 Hz, 1H, 3-H), 3.16 (dd, *J* = 14.0 Hz, 3.7 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.60 (d, *J* = 6.5 Hz, 3H, 6'-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

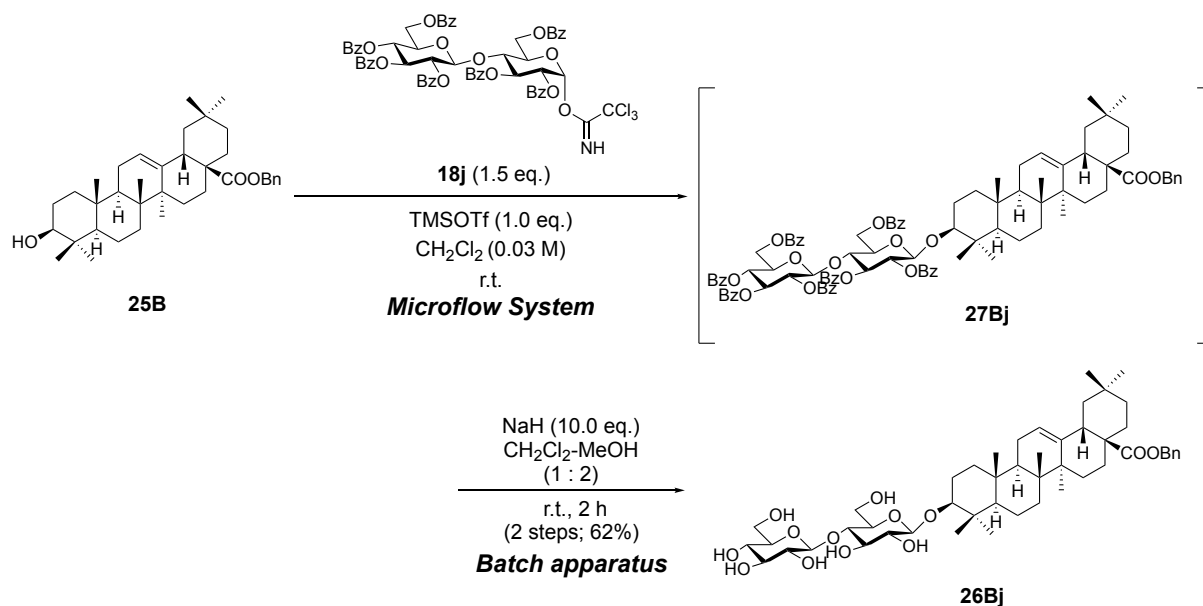
δ : 177.4 (C-28), 144.2 (C-13), 137.5, 129.1, 128.6 (PhCH₂), 123.2 (C-12), 107.4 (C-1'), 88.8 (C-3), 75.5 (C-3'), 73.0 (C-4'), 72.8 (C-2'), 71.4 (C-5'), 66.3 (PhCH₂), 56.1 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.7 (C-6'), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm⁻¹ ν : 3449 (-O-H), 2945 (=C-H), 1726 (-C=O), 1071 (-C-O-)

HR-MS (ESI⁺)

m/z 715.4544[M+Na]⁺, Calc'd for C₄₃H₆₄O₇Na:715.4550.

Olean-12-en-28-oic acid, 3-[(4-*O*- β -D-glucopyranosyl- β -D-glucopyranosyl)oxy]-, phenylmethyl ester (26Bj**)**



A solution of TMSOTf (59.8 μL , 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18j** (603 mg, 0.496 mmol) and acceptor **25B** (181 mg, 0.331 mmol) dissolved in CH_2Cl_2 (11 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture of **27Bj** was stirred for 2 h at room temperature in flask which added NaH (132 mg, 3.31 mmol, 60% disp.) and dry MeOH (44 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (100 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 50 g, CHCl_3 : MeOH = 30 : 1 \rightarrow 25 : 1 \rightarrow 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1) to afford **26Bj** (180 mg, 0.207 mmol, 62%) as a pale yellow solid by two steps.

$R_f = 0.33$ (CHCl_3 : MeOH = 3 : 1)

$[\alpha]_{\text{D}}^{26} + 8.18$ (c 0.30, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 7.47 (m, 5H, PhCH₂), 5.46 (t, J = 1.8 Hz, 1H, 12-H), 5.36, 5.30 (each d, J = 12.5 Hz, 2H, PhCH₂), 5.29 (d, J = 8.0 Hz, 1H, 1''-H), 4.89 (d, J = 8.0 Hz, 1H, 1'-H), 4.64 (dd, J = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.51 (dd, J = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.50 (dd, J = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.41 (t, J = 9.0 Hz, 1H, 4'-H), 4.34 (dd, J = 9.0 Hz, 8.5 Hz, 1H, 3'-H), 4.29 (dd, J = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.25 (dd, J = 9.5 Hz, 8.5 Hz, 1H, 3''-H), 4.18 (dd, J = 9.5 Hz, 9.0 Hz, 1H, 4''-H), 4.11 (dd, J = 8.5 Hz, 8.0 Hz, 1H, 2''-H), 4.04 (dd, J = 8.5 Hz, 8.0 Hz, 1H, 2'-H), 4.02 (ddd, J = 9.0 Hz, 5.5 Hz, 2.0 Hz, 1H, 5''-H), 3.96 (ddd, J = 9.0 Hz, 3.0 Hz, 2.0 Hz, 1H, 5'-H), 3.34 (dd, J = 12.0 Hz, 4.3 Hz, 1H, 3-H), 3.16 (dd, J = 14.0 Hz, 3.7 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

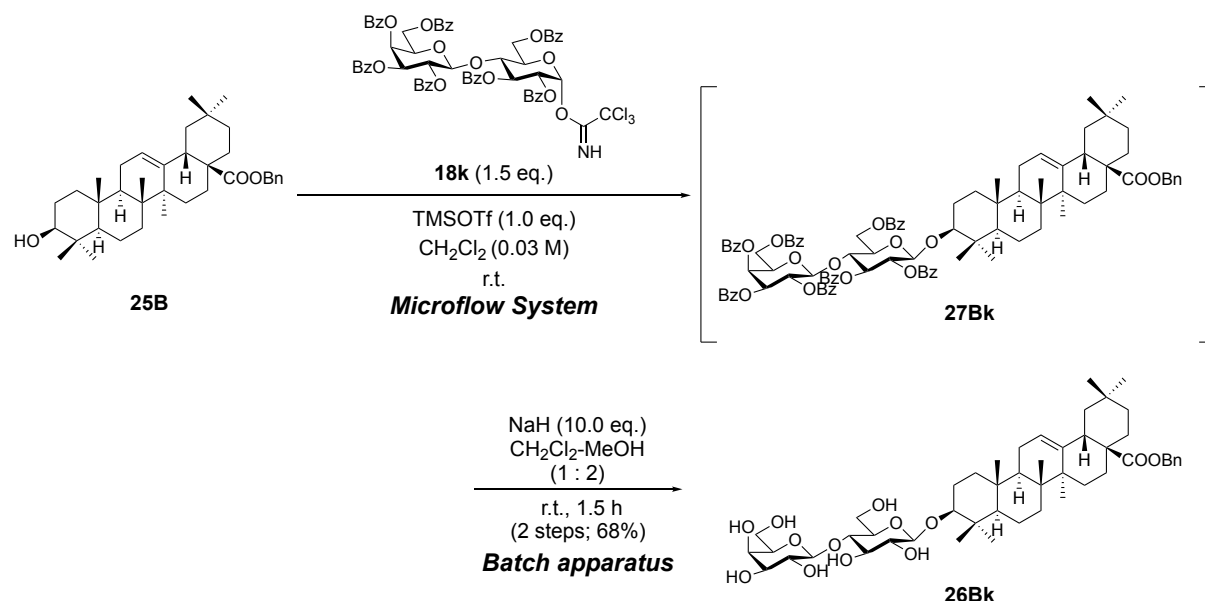
δ : 177.4 (C-28), 144.3 (C-13), 129.1, 128.6 (PhCH₂), 123.1 (C-12), 106.6 (C-1'), 105.2 (C-1''), 89.3 (C-3), 81.0 (C-4'), 78.4 (C-5''), 78.3 (C-3''), 76.8 (C-3'), 76.6 (C-5'), 75.4 (C-2'), 75.0 (C-2''), 71.5 (C-4'') 66.3 (PhCH₂), 62.1 (C-6'), 62.1 (C-6''), 55.9 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm⁻¹ ν : 3422 (-O-H), 2947 (=C-H), 1638 (-C=O), 1033 (-C-O-)

HR-MS (ESI⁺)

m/z 893.5034[M+Na]⁺, Calc'd for C₄₉H₇₄O₁₃Na:893.5027.

Olean-12-en-28-oic acid, 3-[(4-O- β -D-galactopyranosyl- β -D-glucopyranosyl)oxy], phenylmethyl ester (26Bk**)**



A solution of TMSOTf (89.7 μL , 0.496 mmol) dissolved in CH_2Cl_2 (16.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18k** (905 mg, 0.744 mmol) and acceptor **25B** (271 mg, 0.496 mmol) dissolved in CH_2Cl_2 (16.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture of **27Bk** was stirred for 1.5 h at room temperature in flask which added NaH (199 mg, 4.96 mmol, 60% disp.) and dry MeOH (66 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (100 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 70 g, CHCl_3 : MeOH = 30 : 1 \rightarrow 25 : 1 \rightarrow 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1 \rightarrow 8 : 1 \rightarrow 5 : 1) to afford **26Bk** (295 mg, 0.338 mmol, 68%) as a pale yellow solid by two steps.

$R_f = 0.69$ (CHCl_3 : MeOH = 3 : 1)

$[\alpha]_{\text{D}}^{24} +10.7$ (c 0.335, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 7.44 (m, 5H, PhCH₂), 5.49 (t, J = 3.0 Hz, 1H, 12-H), 5.36, 5.30 (each d, J = 12.5 Hz, 2H, PhCH₂), 5.14 (d, J = 8.0 Hz, 1H, 1''-H), 4.88 (d, J = 8.0 Hz, 1H, 1'-H), 4.57 (dd, J = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.57 (dd, J = 9.5 Hz, 8.0 Hz, 1H, 2''-H), 4.53 (d, J = 3.0 Hz, 1H, 4''-H), 4.51 (dd, J = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.44 (dd, J = 11.0 Hz, 7.0 Hz, 1H, 6''-H), 4.36 (dd, J = 11.0 Hz, 5.0 Hz, 1H, 6''-H), 4.33 (t, J = 8.5 Hz, 1H, 4'-H), 4.30 (t, J = 8.5 Hz, 1H, 3'-H), 4.20 (dd, J = 9.5 Hz, 3.0 Hz, 1H, 3''-H), 4.14 (dd, J = 7.0 Hz, 5.0 Hz, 1H, 5''-H), 4.05 (dd, J = 8.5 Hz, 8.0 Hz, 1H, 2'-H), 3.93 (ddd, J = 8.5 Hz, 3.0 Hz, 3.0 Hz, 1H, 5'-H), 3.32 (m, 2H, 3-H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

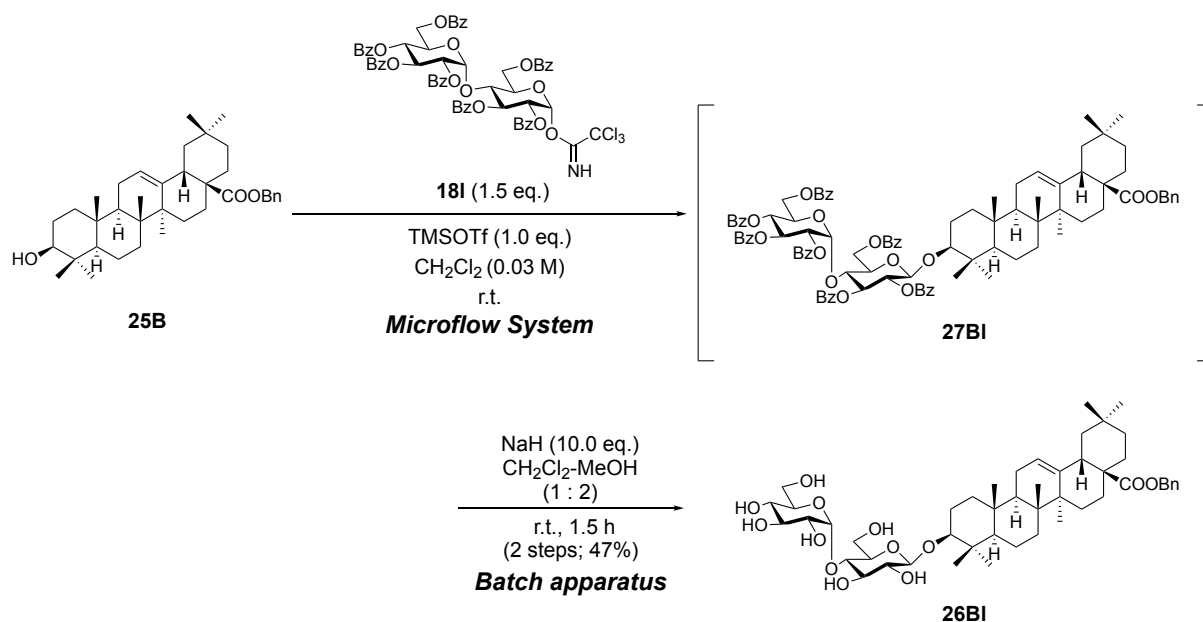
δ : 177.4 (C-28), 144.4 (C-13), 129.2, 128.7 (PhCH₂), 120.5 (C-12), 106.7 (C-1'), 105.9 (C-1''), 89.2 (C-3), 82.1 (C-4'), 77.2 (C-5''), 76.9 (C-3'), 76.5 (C-5'), 75.4 (C-2'), 75.2 (C-3''), 72.6 (C-2''), 70.4 (C-4''), 66.5 (PhCH₂), 62.4 (C-6'), 62.2 (C-6''), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm⁻¹ ν : 3420 (-O-H), 2948 (=C-H), 1677 (-C=O), 1037 (-C-O-)

HR-MS (ESI⁺)

m/z 893.5009[M+Na]⁺, Calc'd for C₄₉H₇₄O₁₃Na:893.5027.

Olean-12-en-28-oic acid, 3-[(4-*O*- α -D-glucopyranosyl- β -D-glucopyranosyl)oxy]-, phenylmethyl ester (26BI**)**



A solution of TMSOTf (89.7 μL , 0.496 mmol) dissolved in CH_2Cl_2 (16.5 mL) was injected to the micromixer by using the syringe pump at the flow rate of 0.6 mL/min. A solution of donor **18I** (905 mg, 0.744 mmol) and acceptor **25B** (271 mg, 0.496 mmol) dissolved in CH_2Cl_2 (16.5 mL) was injected to the micromixer by the same syringe pump at the flow rate of 0.6 mL/min and mixed at room temperature. After the reaction mixture was allowed to flow at room temperature through a Teflon reactor tube ($\phi = 1.0$ mm, $l = 1.0$ m), the reaction mixture of was introduced into a flask, which was connected to the outlet of a Teflon reactor tube. The reaction mixture of **27BI** was stirred for 1.5 h at room temperature in flask which added NaH (199 mg, 4.96 mmol, 60% disp.) and dry MeOH (66 mL) in advance. After the reaction was completed, the reaction mixture was neutralized with Dowex H^+ resin to pH 7, filtered and rinsed with MeOH (100 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 70 g, CHCl_3 : MeOH = 30 : 1 \rightarrow 25 : 1 \rightarrow 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1 \rightarrow 5 : 1) to afford **26BI** (203 mg, 0.233 mmol, 47%) as a pale yellow solid by two steps.

$R_f = 0.36$ (CHCl_3 : MeOH = 3 : 1)

$[\alpha]_{\text{D}}^{22} +30.1$ (c 0.311, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 7.47 (m, 5H, PhCH₂), 5.94 (d, J = 3.5 Hz, 1H, 1''-H), 5.49 (t, J = 3.0 Hz, 1H, 12-H), 5.36, 5.30 (each d, J = 12.5 Hz, 2H, PhCH₂), 4.87 (d, J = 7.5 Hz, 1H, 1'-H), 4.62 (t, J = 9.5 Hz, 1H, 3''-H), 4.61 (ddd, J = 9.5 Hz, 3.5 Hz, 2.0 Hz, 1H, 5''-H), 4.59 (dd, J = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.52 (dd, J = 12.0 Hz, 4.0 Hz, 1H, 6'-H), 4.49 (dd, J = 12.0 Hz, 2.0 Hz, 1H, 6'-H), 4.37 (dd, J = 9.0 Hz, 8.5 Hz, 1H, 4'-H), 4.35 (dd, J = 9.0 Hz, 8.5 Hz, 1H, 3'-H), 4.33 (dd, J = 12.0 Hz, 3.5 Hz, 1H, 6''-H), 4.19 (dd, J = 9.5 Hz, 3.5 Hz, 1H, 2''-H), 4.17 (d, J = 9.5 Hz, 1H, 4''-H), 4.02 (dd, J = 8.5 Hz, 7.5 Hz, 1H, 2'-H), 3.87 (ddd, J = 8.5 Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 3.32 (m, 2H, 3-H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

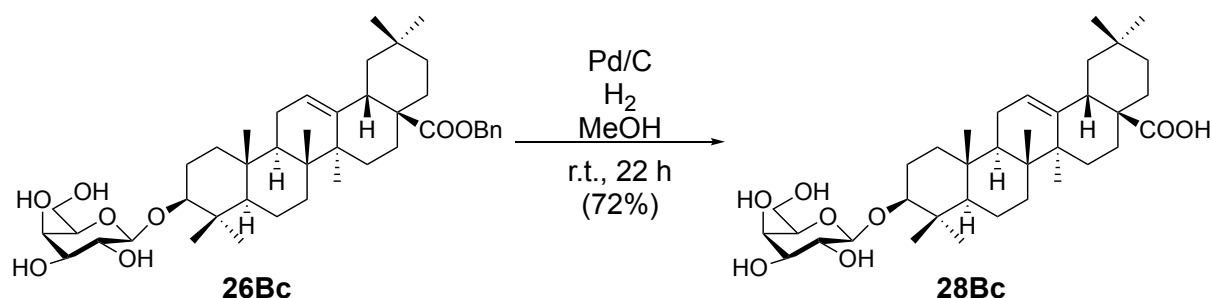
δ : 177.4 (C-28), 144.3 (C-13), 129.2, 128.7 (PhCH₂), 120.5 (C-12), 106.8 (C-1'), 103.2 (C-1''), 89.2 (C-3), 81.4 (C-4'), 78.1 (C-3'), 76.8 (C-5'), 75.6 (C-3''), 75.4 (C-5''), 75.4 (C-2'), 74.5 (C-2''), 72.0 (C-4''), 66.3 (PhCH₂), 62.8 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm⁻¹ ν : 3423 (-O-H), 2949 (=C-H), 1648 (-C=O), 1035 (-C-O-)

HR-MS (ESI⁺)

m/z 893.5006[M+Na]⁺, Calc'd for C₄₉H₇₄O₁₃Na:893.5027.

3-O- β -D-galactopyranosyl oleanolic acid (**28Bc**)



To a solution of **26Bc** (63.7 mg, 0.090 mmol) in MeOH (3.5 mL) was added 10% Pd–C (63.7 mg) and purged up with H₂ atmosphere. After stirring for 22 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 5 g, CHCl₃ : MeOH = 50 : 1 \rightarrow 20 : 1 \rightarrow 10 : 1 \rightarrow 7 : 1 \rightarrow 5 : 1) to afford **28Bc** (36.8 mg, 0.060 mmol, 72%) as a white solid.

R_f = 0.35 (CHCl₃ : MeOH = 5 : 1)

[α]_D²⁶ +35.0 (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.50 (t, *J* = 3.4 Hz, 1H, 12-H), 4.88 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.61 (d, *J* = 3.4 Hz, 1H, 5'-H), 4.48 (dd, *J* = 8.0 Hz, 6.0 Hz, 1H, 2'-H), 4.48 (m, 2H, 6'-H), 4.26 (t, *J* = 6.0 Hz, 1H, 3'-H), 4.20 (dd, *J* = 9.5 Hz, 3.4 Hz, 1H, 4'-H), 3.41 (dd, *J* = 11.8 Hz, 4.4 Hz, 1H, 3-H), 3.31 (dd, *J* = 14.0 Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

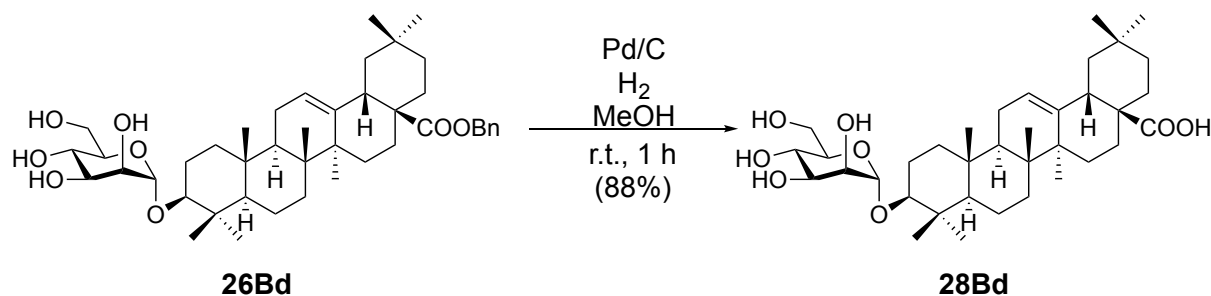
δ : 180.4 (C-28), 145.0 (C-13), 122.7 (C-12), 107.7 (C-1'), 88.9 (C-3), 76.9 (C-3'), 75.6 (C-4'), 73.3 (C-2'), 70.4 (C-5'), 62.6 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 3442 (-O-H), 2944 (=C-H), 1702 (-C=O), 1056 (-C-O-)

HR-MS (ESI⁺)

m/z 641.4020[M+Na]⁺, Calc'd for C₃₆H₅₈O₈Na:641.4029.

3-*O*- α -D-mannopyranosyl oleanolic acid (**28Bd**)



To a solution of **26Bd** (76.5 mg, 0.108 mmol) in MeOH (1.5 mL) was added 10% Pd–C (76.5 mg) and purged with H₂ atmosphere. After stirring for 1 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 5 g, CHCl₃ : MeOH = 50 : 1 \rightarrow 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1 \rightarrow 7 : 1 \rightarrow 5 : 1) to afford **28Bd** (58.7 mg, 0.095 mmol, 88%) as a white solid.

R_f = 0.23 (CHCl₃ : MeOH = 5 : 1)

[α]_D²³ +98.1 (c 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.57 (d, *J* = 1.3 Hz, 1H, 1'-H), 5.42 (t, *J* = 3.0 Hz, 1H, 12-H), 4.73 (t, *J* = 9.5 Hz, 1H, 4'-H), 4.63 (m, 1H, 6'-H), 4.60 (dd, *J* = 9.5 Hz, 3.5 Hz, 1H, 3'-H), 4.55 (dd, *J* = 3.5 Hz, 1.3 Hz, 1H, 2'-H), 4.49-4.42 (m, 2H, 5'-H, 6'-H), 3.40 (dd, *J* = 11.8 Hz, 4.4 Hz, 1H, 3-H), 3.16 (dd, *J* = 14.0 Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 180.4 (C-28), 145.0 (C-13), 122.7 (C-12), 97.9 (C-1'), 82.0 (C-3), 76.1 (C-5'), 73.3 (C-3'), 73.1 (C-2'), 69.2 (C-4'), 63.5 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26),

17.2 (C-24), 15.6 (C-25)

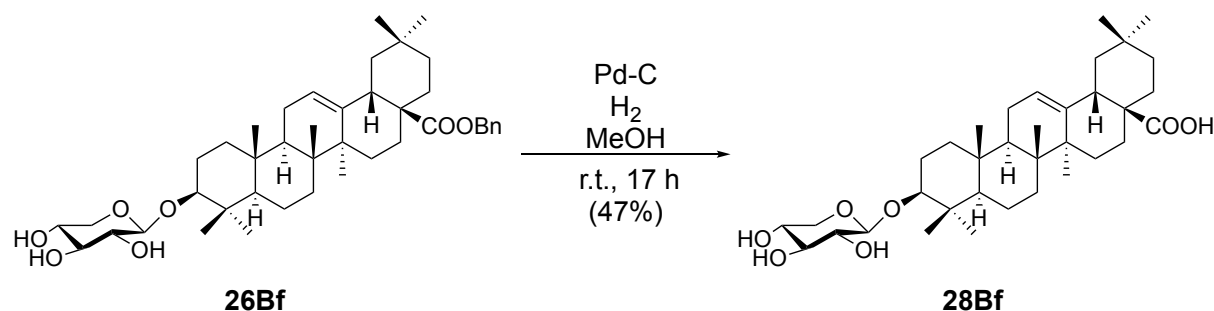
IR (KBr) cm^{-1} ν : 3387 (-O-H), 2942 (=C-H), 1700 (-C=O), 1057 (-C-O-)

HR-MS (ESI⁺)

m/z 641.4017[M+Na]⁺, Calc'd for C₃₆H₅₈O₈Na:641.4029

GATEI (400 MHz, pyridine-*d*₅) δ : 98.7 (s), 97.1 (s), (C-1'), $^1J_{\text{C,H}} = 166.6$ Hz.

3-*O*- β -D-xylopyranosyl oleanolic acid (**28Bf**)



To a solution of **26Bf** (75.5 mg, 0.111 mmol) stirring in MeOH (1.5 mL) was added 10% Pd-C (75.5 mg) and purged up with H₂ atmosphere. After stirring for 17 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 5 g, CHCl₃ : MeOH = 50 : 1 \rightarrow 45 : 1 \rightarrow 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1 \rightarrow 7 : 1 \rightarrow 5 : 1) to afford **28Bf** (31.0 mg, 0.053 mmol, 47%) as a white solid.

$R_f = 0.46$ (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{23} +32.5$ (c 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.49 (t, $J = 3.4$ Hz, 1H, 12-H), 4.85 (d, $J = 8.0$ Hz, 1H, 1'-H), 4.40 (dd, $J = 11.0$ Hz, 5.0 Hz, 1H, 5'-H), 4.25 (m, 1H, 4'-H), 4.18 (t, $J = 8.0$ Hz, 1H, 3'-H), 4.03 (t, $J = 8.0$ Hz, 1H, 2'-H), 3.80 (t, $J = 11.0$ Hz, 1H, 5'-H), 3.37 (dd, $J = 11.8$ Hz, 4.3 Hz, 1H, 3-H), 3.31 (dd, $J = 14.0$ Hz, 4.0 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 180.3 (C-28), 144.9 (C-13), 122.7 (C-12), 107.8 (C-1'), 88.8 (C-3), 78.6 (C-3'), 75.6 (C-2'), 71.3 (C-4'), 67.2 (C-5'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2),

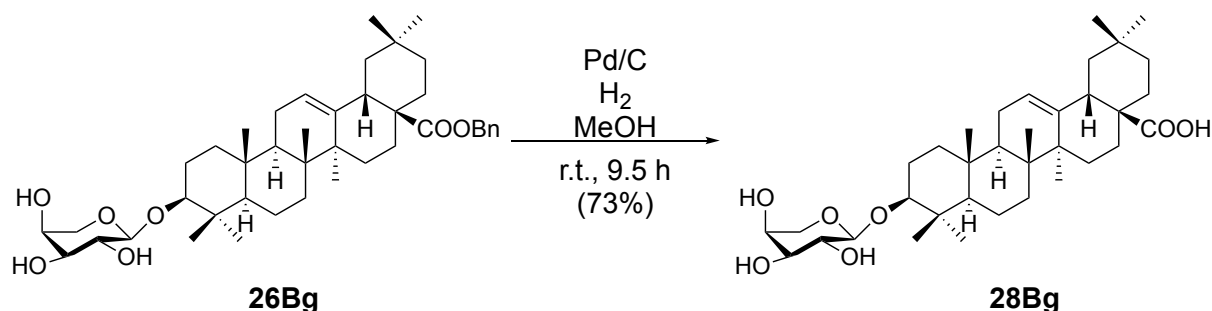
26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 3484 (-O-H), 2947 (=C-H), 1708 (-C=O), 1047 (-C-O-)

HR-MS (ESI⁺)

m/z 611.3913[M+Na]⁺, Calc'd for C₃₅H₅₆O₇Na:611.3924.

3-*O*- α -L-arabinopyranosyl oleanolic acid (**28Bg**)



To a solution of **26Bg** (100.0 mg, 0.170 mmol) in MeOH (2.0 mL) was added 10% Pd–C (100 mg) and purged with H₂ atmosphere. After stirring for 9.5 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (30 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 5 g, CHCl₃ : MeOH = 50 : 1 \rightarrow 20 : 1 \rightarrow 10 : 1 \rightarrow 7 : 1) to afford **28Bg** (72.5 mg, 0.123 mmol, 73%) as a white solid.

R_f = 0.40 (CHCl₃ : MeOH = 5 : 1)

[α]_D²³ +36.7 (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.49 (t, *J* = 3.4 Hz, 1H, 12-H), 4.80 (d, *J* = 7.0 Hz, 1H, 1'-H), 4.45 (dd, *J* = 8.9 Hz, 7.0 Hz, 1H, 2'-H), 4.34 (m, 2H, 4'-H, 5'-H), 4.20 (dd, *J* = 8.9 Hz, 3.3 Hz, 1H, 3'-H), 3.86 (dd, *J* = 14.2 Hz, 2.1 Hz, 1H, 5'-H), 3.36 (dd, *J* = 11.9 Hz, 4.4 Hz, 1H, 3-H), 3.31 (dd, *J* = 14.6 Hz, 4.1 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 180.3 (C-28), 150.0 (C-13), 122.7 (C-12), 107.7 (C-1'), 88.8 (C-3), 74.7 (C-3'), 73.0 (C-2'), 69.6 (C-4'), 66.9 (C-5'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2

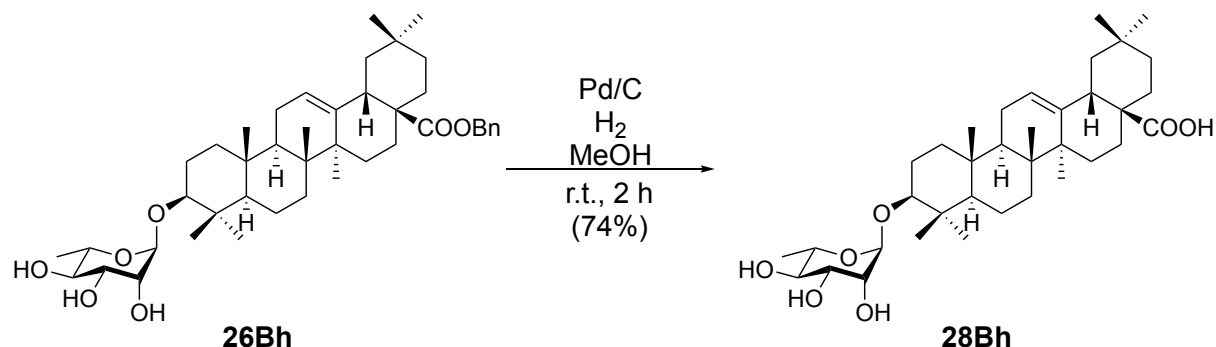
(C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 3422 (-O-H), 2942 (=C-H), 1670 (-C=O), 1086 (-C-O-)

HR-MS (ESI⁺)

m/z 625.4067[M+Na]⁺, Calc'd for C₃₆H₅₈O₇Na:625.4080.

3-*O*- α -L-rhamnopyranosyl oleanolic acid (**28Bh**)



To a solution of **26Bh** (184 mg, 0.26 mmol) stirring in MeOH (4.0 mL) was added 10% Pd–C (184 mg) and purged with H₂ atmosphere. After stirring for 2 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (30 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 5 g, CHCl₃ : MeOH = 50 : 1 → 20 : 1 → 10 : 1 → 7 : 1) to afford **28Bh** (118 mg, 0.196 mmol, 74%) as a white solid.

$R_f = 0.43$ (CHCl₃ : MeOH = 5 : 1)

$[\alpha]_D^{26} +13.4$ (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.42 (t, $J = 3.3$ Hz, 1H, 12-H), 5.33 (brs, 1H, 1'-H), 4.58 (dd, $J = 3.0$ Hz, 1.7 Hz, 1H, 2'-H), 4.49 (dd, $J = 8.0$ Hz, 3.0 Hz, 1H, 3'-H), 4.33 (dd, $J = 9.0$ Hz, 8.0 Hz, 1H, 4'-H), 4.30 (dt, $J = 9.0$ Hz, 5.0 Hz, 1H, 5'-H), 3.30 (dd, $J = 13.4$ Hz, 3.6 Hz, 1H, 3-H), 3.16 (dd, $J = 12.2$ Hz, 4.2 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.69 (d, $J = 5.0$ Hz, 3H, 6'-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 180.3 (C-28), 150.0 (C-13), 122.7 (C-12), 104.5 (C-1'), 88.7 (C-3), 74.2 (C-5'), 73.0 (C-3'), 72.6 (C-2'), 70.0 (C-4'), 55.8 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2),

26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.7 (C-6'), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

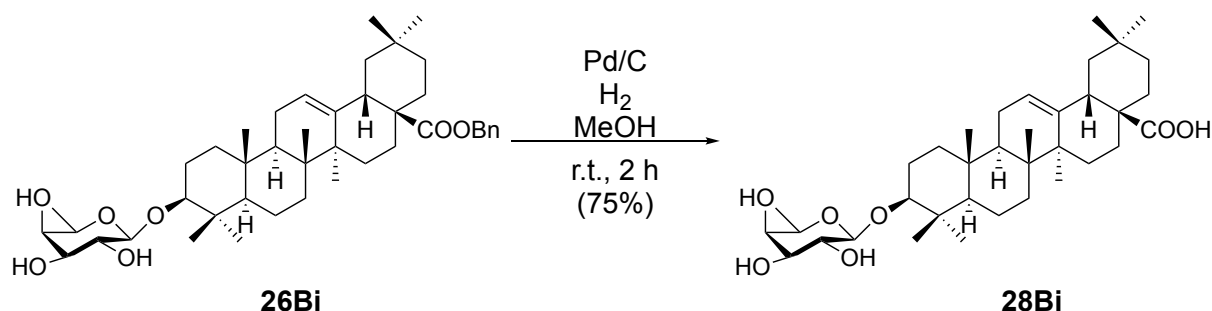
IR (KBr) cm^{-1} ν : 3423 (-O-H), 2944 (=C-H), 1687 (-C=O), 1054 (-C-O-)

HR-MS (ESI⁺)

m/z 625.4070[M+Na]⁺, Calc'd for C₃₆H₅₈O₇Na:625.4080

GATEI (400 MHz, pyridine-*d*₅) δ : 105.4 (s), 103.8 (s), (C-1'), ¹*J*_{C,H} = 165.7 Hz.

3-*O*- β -D-fucopyranosyl oleanolic acid (**28Bi**)



To a solution of **26Bi** (42.9 mg, 0.060 mmol) in MeOH (1.0 mL) was added 10% Pd–C (42.9 mg) and purged up with H₂ atmosphere. After stirring for 2 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (20 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 5 g, CHCl₃ : MeOH = 50 : 1 \rightarrow 20 : 1 \rightarrow 15 : 1 \rightarrow 10 : 1 \rightarrow 7 : 1) to afford **28Bi** (28.1 mg, 0.047 mmol, 75%) as a white solid.

R_f = 0.48 (CHCl₃ : MeOH = 5 : 1)

[α]_D²⁶ +37.3 (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.50 (t, *J* = 3.2 Hz, 1H, 12-H), 4.77 (d, *J* = 7.6 Hz, 1H, 1'-H), 4.36 (dt, *J* = 7.6 Hz, 1.7 Hz, 1H, 2'-H), 4.10 (ddd, *J* = 9.0 Hz, 3.6 Hz, 1.7 Hz, 1H, 3'-H), 4.08 (dd, *J* = 3.6 Hz, 0.8 Hz, 1H, 4'-H), 3.89 (ddd, *J* = 14.3 Hz, 6.5 Hz, 0.8 Hz, 1H, 5'-H), 3.38 (dd, *J* = 12.0 Hz, 4.3 Hz, 1H, 3-H), 3.16 (dd, *J* = 14.0 Hz, 3.7 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.60 (d, *J* = 6.5 Hz, 3H, 6'-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 180.3 (C-28), 150.0 (C-13), 122.7 (C-12), 107.4 (C-1'), 88.8 (C-3), 75.5 (C-3'), 73.0 (C-4'), 72.8 (C-2'), 71.3 (C-5'), 56.1 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.7 (C-6'), 17.6

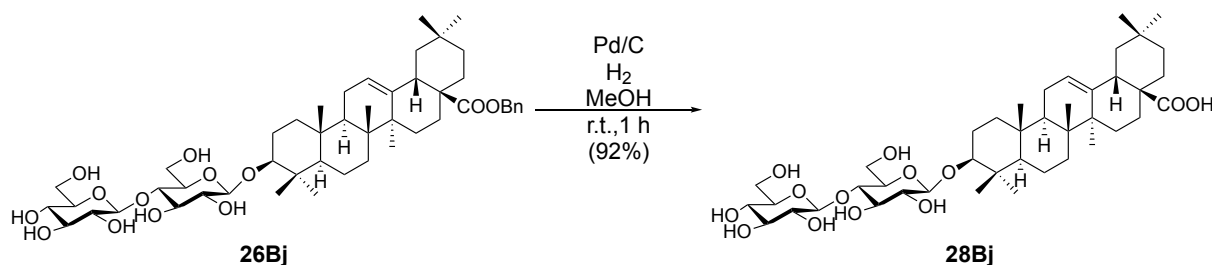
(C-26), 17.2 (C-24), 15.6 (C-25)

IR (KBr) cm^{-1} ν : 3422 (-O-H), 2945 (=C-H), 1688 (-C=O), 1073 (-C-O-)

HR-MS (ESI⁺)

m/z 625.4067[M+Na]⁺, Calc'd for C₃₆H₅₈O₇Na:625.4080.

Olean-12-en-28-oic acid, 3-[(4-O- β -D-glucopyranosyl- β -D-glucopyranosyl)oxy] (28Bj)



To a solution of **26Bj** (132 mg, 0.15 mmol) in MeOH (2.5 mL) was added 10% Pd–C (132 mg) and purged up with H₂ atmosphere. After stirring for 1 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (20 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 50 : 1 → 20 : 1 → 10 : 1 → 7 : 1 → 5 : 1) to afford **28Bj** (109 mg, 0.140 mmol, 92%) as a white solid.

R_f = 0.54 (CHCl₃ : MeOH = 3 : 1)

[α]_D²⁶ +10.5 (c 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.46 (t, *J* = 1.8 Hz, 1H, 12-H), 5.29 (d, *J* = 8.0 Hz, 1H, 1''-H), 4.89 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.64 (dd, *J* = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.51 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6'-H), 4.50 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.41 (t, *J* = 9.0 Hz, 1H, 4'-H), 4.34 (dd, *J* = 9.0 Hz, 8.5 Hz, 1H, 3'-H), 4.29 (dd, *J* = 12.0 Hz, 5.5 Hz, 1H, 6''-H), 4.25 (dd, *J* = 9.5 Hz, 8.5 Hz, 1H, 3''-H), 4.18 (dd, *J* = 9.5 Hz, 9.0 Hz, 1H, 4''-H), 4.11 (dd, *J* = 8.5 Hz, 8.0 Hz, 1H, 2''-H), 4.04 (dd, *J* = 8.5 Hz, 8.0 Hz, 1H, 2'-H), 4.02 (ddd, *J* = 9.0 Hz, 5.5 Hz, 2.0 Hz, 1H, 5''-H), 3.96 (ddd, *J* = 9.0 Hz, 3.0 Hz, 2.0 Hz, 1H, 5'-H), 3.34 (dd, *J* = 12.0 Hz, 4.3 Hz, 1H, 3-H), 3.16 (dd, *J* = 14.0 Hz, 3.7 Hz, 1H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 177.4 (C-28), 145.4 (C-13), 120.8 (C-12), 106.6 (C-1'), 105.2 (C-1''), 89.3 (C-3),

81.0 (C-4'), 78.4 (C-5''), 78.3 (C-3''), 76.8 (C-3'), 76.6 (C-5'), 75.4 (C-2'), 75.0 (C-2''), 71.5 (C-4''), 62.1(C-6'), 62.1(C-6''), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

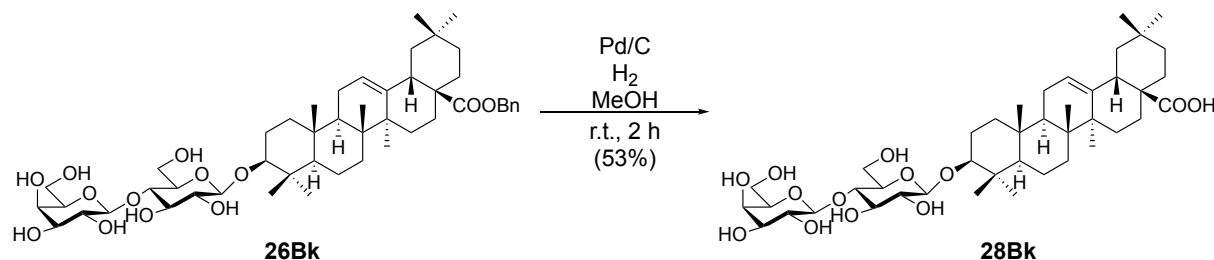
IR (KBr) cm^{-1} v : 3448(-O-H), 2945 (=C-H), 1691 (-C=O), 1034 (-C-O-)

HR-MS (ESI⁺)

m/z 803.4550[M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na:803.4558

TOCSY (400 MHz, pyridine-*d*₅) mixing time τ_m = 150 ms.

**Olean-12-en-28-oic acid, 3-[(4-O-β-D-galactopyranosyl-β-D-glucopyranosyl)oxy]
(28Bk)**



To a solution of **26Bk** (132.4 mg, 0.15 mmol) in MeOH (2.5 mL) was added 10% Pd–C (132 mg) and purged up with H₂ atmosphere. After stirring for 2 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 10 g, CHCl₃ : MeOH = 50 : 1 → 30 : 1 → 20 : 1 → 15 : 1 → 10 : 1 → 5 : 1) to afford **28Bk** (62.9 mg, 0.081 mmol, 53%) as a white solid.

R_f = 0.27 (CHCl₃ : MeOH = 3 : 1)

[α]_D²⁶ +15.5 (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.48 (t, *J* = 3.0 Hz, 1H, 12-H), 5.14 (d, *J* = 8.0 Hz, 1H, 1''-H), 4.88 (d, *J* = 8.0 Hz, 1H, 1'-H), 4.57 (dd, *J* = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.57 (dd, *J* = 9.5 Hz, 8.0 Hz, 1H, 2''-H), 4.53 (d, *J* = 3.0 Hz, 1H, 4''-H), 4.51 (dd, *J* = 12.0 Hz, 3.0 Hz, 1H, 6'-H), 4.44 (dd, *J* = 11.0 Hz, 7.0 Hz, 1H, 6''-H), 4.36 (dd, *J* = 11.0 Hz, 5.0 Hz, 1H, 6''-H), 4.33 (t, *J* = 8.5 Hz, 1H, 4'-H), 4.30 (t, *J* = 8.5 Hz, 1H, 3'-H), 4.20 (dd, *J* = 9.5 Hz, 3.0 Hz, 1H, 3''-H), 4.14 (dd, *J* = 7.0 Hz, 5.0 Hz, 1H, 5''-H), 4.05 (dd, *J* = 8.5 Hz, 8.0 Hz, 1H, 2'-H), 3.93 (ddd, *J* = 8.5 Hz, 3.0 Hz, 3.0 Hz, 1H, 5'-H), 3.32 (m, 2H, 3-H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 181.2 (C-28), 145.2 (C-13), 122.6 (C-12), 106.7 (C-1'), 105.9 (C-1''), 89.2 (C-3), 82.1 (C-4'), 77.2 (C-5''), 76.9 (C-3'), 76.5 (C-5'), 75.4 (C-2'), 75.2 (C-3''), 72.6 (C-2''), 70.4 (C-4''), 62.4 (C-6'), 62.2 (C-6''), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17),

46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

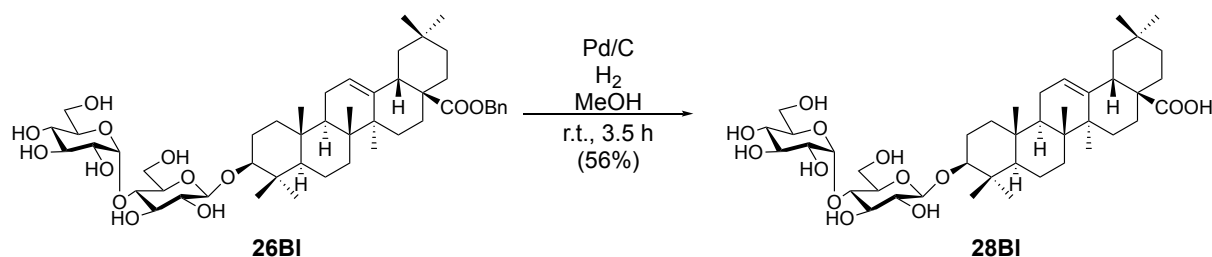
IR (KBr) cm^{-1} ν : 3435 (-O-H), 2944 (=C-H), 1691 (-C=O), 1033 (-C-O-)

HR-MS (ESI⁻)

m/z 779.4578[M-H]⁻, Calc'd for C₄₂H₆₇O₁₃:779.4582

TOCSY (400 MHz, pyridine-*d*₅) mixing time τ_m = 150 ms.

Olean-12-en-28-oic acid, 3-[(4-*O*- α -D-glucopyranosyl- β -D-glucopyranosyl)oxy] (28BI**)**



To a solution of **26BI** (100 mg, 0.11 mmol) in MeOH (2.5 mL) was added 10% Pd–C (100 mg) and purged up with H₂ atmosphere. After stirring for 3.5 h at room temperature, the reaction mixture was filtered by celite and rinsed with MeOH (20 mL). The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (silica gel 5 g, CHCl₃ : MeOH = 30 : 1 → 25 : 1 → 20 : 1 → 15 : 1 → 10 : 1 → 3 : 1) to afford **28BI** (50.1 mg, 0.064 mmol, 56%) as a white solid.

R_f = 0.51 (CHCl₃ : MeOH = 3 : 1)

[α]_D²⁶ +46.3 (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 5.94 (d, *J* = 3.5 Hz, 1H, 1''-H), 5.49 (t, *J* = 3.0 Hz, 1H, 12-H), 4.87 (d, *J* = 7.5 Hz, 1H, 1'-H), 4.62 (t, *J* = 9.5 Hz, 1H, 3''-H), 4.61 (ddd, *J* = 9.5 Hz, 3.5 Hz, 2.0 Hz, 1H, 5''-H), 4.59 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6''-H), 4.52 (dd, *J* = 12.0 Hz, 4.0 Hz, 1H, 6'-H), 4.49 (dd, *J* = 12.0 Hz, 2.0 Hz, 1H, 6'-H), 4.37 (dd, *J* = 9.0 Hz, 8.5 Hz, 1H, 4'-H), 4.35 (dd, *J* = 9.0 Hz, 8.5 Hz, 1H, 3'-H), 4.33 (dd, *J* = 12.0 Hz, 3.5 Hz, 1H, 6''-H), 4.19 (dd, *J* = 9.5 Hz, 3.5 Hz, 1H, 2''-H), 4.17 (d, *J* = 9.5 Hz, 1H, 4''-H), 4.02 (dd, *J* = 8.5 Hz, 7.5 Hz, 1H, 2'-H), 3.87 (ddd, *J* = 8.5 Hz, 4.0 Hz, 2.0 Hz, 1H, 5'-H), 3.32 (m, 2H, 3-H, 18-H), 2.37 (m, 1H, 15-H), 2.24 (m, 1H, 2-H), 2.10 (m, 2H, 11-H), 1.99 (m, 2H, 16-H), 1.90 (m, 1H, 2-H), 1.85 (m, 2H, 22-H), 1.78 (m, 1H, 19-H), 1.63 (m, 1H, 9-H), 1.49 (m, 2H, 1-H, 6-H), 1.45 (m, 1H, 7-H), 1.41 (m, 2H, 21-H), 1.36 (m, 1H, 6-H), 1.34 (s, 3H, 23-H), 1.32 (s, 3H, 27-H), 1.21 (m, 1H, 19-H), 1.18 (m, 1H, 15-H), 1.02 (s, 3H, 26-H), 1.07 (m, 1H, 7-H), 1.01 (s, 6H, 24-H, 29-H), 0.96 (m, 1H, 1-H), 0.97 (s, 3H, 29-H), 0.83 (s, 3H, 30-H), 0.86 (s, 3H, 25-H), 0.79 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 181.0 (C-28), 145.2 (C-13), 122.6 (C-12), 106.8 (C-1'), 103.2 (C-1''), 89.2 (C-3), 81.4 (C-4'), 78.1 (C-3'), 76.8 (C-5'), 75.6 (C-3''), 75.4 (C-5''), 75.4 (C-2'), 74.5

(C-2''), 72.0 (C-4''), 62.8 (C-6''), 62.2 (C-6'), 56.0 (C-5), 48.2 (C-9), 46.8 (C-17), 46.6 (C-19), 42.3 (C-14), 42.1 (C-18), 39.9 (C-8), 39.7 (C-4), 38.9 (C-1), 37.1 (C-10), 34.4 (C-21), 33.5 (C-7), 33.4 (C-29), 31.1 (C-22), 31.1 (C-20), 28.5 (C-23), 28.4 (C-15), 26.7 (C-2), 26.4 (C-27), 23.9 (C-30), 23.9 (C-16), 23.9 (C-11), 18.6 (C-6), 17.6 (C-26), 17.2 (C-24), 15.6 (C-25)

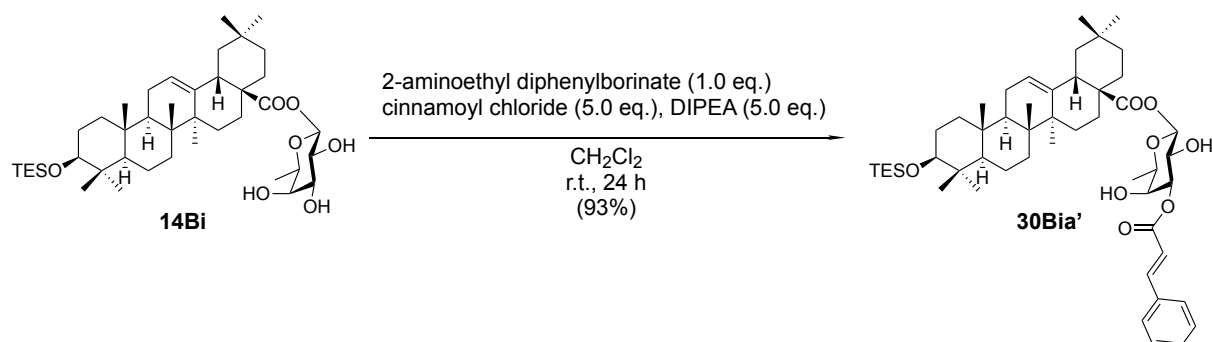
IR (KBr) cm^{-1} ν : 3423 (-O-H), 2943 (=C-H), 1691 (-C=O), 1031 (-C-O-)

HR-MS (ESI⁺)

m/z 803.4531[M+Na]⁺, Calc'd for C₄₂H₆₈O₁₃Na:803.4558

TOCSY (400 MHz, pyridine-*d*₅) mixing time τ_m = 150 ms.

**Olean-12-en-28-oic acid, 3-*O*-triethylsilyl-, 3-*O*-[(*E*)-cinnamoyl]-
β-D-fucopyranosyloxy ester (**30Bia'**)**



To a solution of **14Bi** (50 mg, 0.070 mmol) in dry CH_2Cl_2 (1.0 mL) was added 2-aminoethyl diphenylborinate (15.6 mg, 0.070 mmol). The reaction mixture was stirred for 10 min at room temperature. To a solution of the mixture was added DIPEA (59.2 μL , 0.349 mmol) and cinnamoyl chloride (58.0 mg, 0.349 mmol). After stirring for 24 h at room temperature, the reaction mixture was quenched with MeOH (14.1 μL , 0.349 mmol). The resulting mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 7 g, hexane : AcOEt = 10 : 1 \rightarrow 9 : 1) to afford **30Bia'** (β only, *E* only, 55.1 mg, 0.065 mmol, 93%) as a white solid.

$R_f = 0.27$ (hexane : AcOEt = 3 : 1)

$[\alpha]_{\text{D}}^{27} +67.7$ (c 0.27, MeOH)

$^1\text{H-NMR}$ (400 MHz, pyridine- d_5)

δ : 7.89 (d, $J = 16.0$ Hz, 1H, PhCH=CH), 7.44 (m, 2H, Ph-H), 7.35 (m, 3H, Ph-H), 6.67 (d, $J = 16.0$ Hz, 1H, PhCH=CH), 6.34 (d, $J = 8.2$ Hz, 1H, 1'-H), 5.66 (dd, $J = 10.1$ Hz, 3.3 Hz, 1H, 3'-H), 5.48 (t, $J = 3.5$ Hz, 1H, 12-H), 4.90 (dd, $J = 10.1$ Hz, 8.2 Hz, 1H, 2'-H), 4.38 (d, 1H, $J = 3.3$ Hz, 4'-H), 4.06 (m, 1H, 5'-H), 3.29 (dd, $J = 11.6$ Hz, 4.2 Hz, 1H, 3-H), 3.25 (dd, $J = 14.9$ Hz, 4.2 Hz, 1H, 18-H), 2.33 (m, 1H, 2-H), 2.08 (m, 2H, 11-H), 1.96 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.67 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (m, 1H, 6-H), 1.53 (d, $J = 6.4$ Hz, 3H, 6'-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.26 (s, 3H, 27-H), 1.13 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.01 (s, 3H, 23-H), 1.01 (m, 1H, 1-H), 1.02 (m, 9H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.92 (s, 6H, 29-H, 30-H), 0.92 (s, 3H, 25-H), 0.87 (s, 3H, 24-H), 0.82 (m, 1H, 5-H), 0.63 (m, 6H, $-\text{Si}(\text{CH}_2\text{CH}_3)_3$)

^{13}C -NMR (100 MHz, pyridine- d_5)

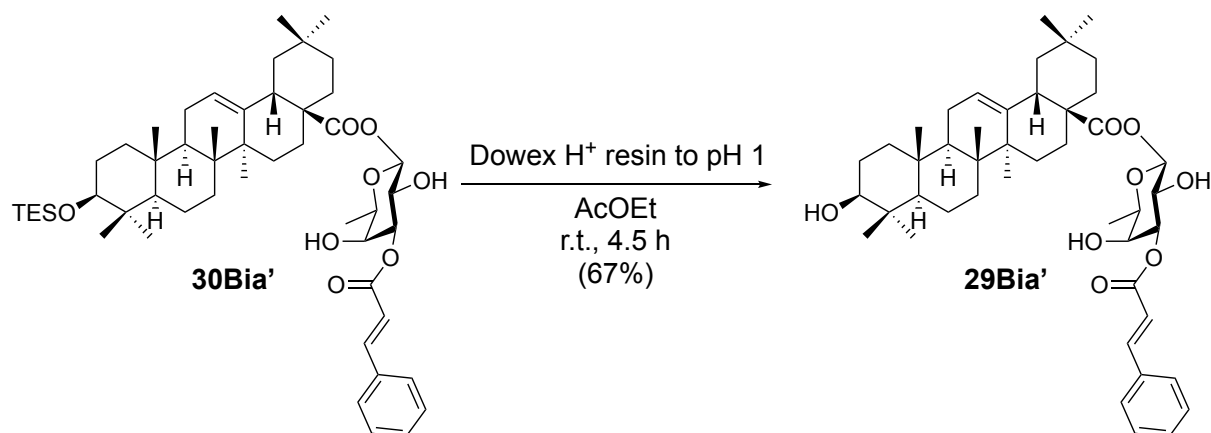
δ : 176.6 (C-28), 166.9 (3'-OCO-), 145.1 (PhCH=CH), 144.2 (C-13), 134.9, 130.8, 130.4, 129.4, 129.4, 128.6, 123.1 (C-12), 119.1 (PhCH=CH), 95.9 (C-1'), 80.0 (C-3'), 78.5 (C-3), 72.5 (C-5'), 70.2 (C-4'), 68.4 (C-2'), 55.7 (C-5), 48.2 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.0 (C-8), 39.7 (C-4), 38.8 (C-1), 37.3 (C-10), 34.1 (C-21), 33.3 (C-7), 33.3 (C-29), 32.8 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.3 (C-2), 26.2 (C-27), 24.0 (C-30), 23.8 (C-16), 23.5 (C-11), 19.0 (C-6), 17.7 (C-26), 17.1 (C-6'), 16.6 (C-24), 15.7 (C-25), 7.5 (-Si(CH₂CH₃)₃), 5.7 (-Si(CH₂CH₃)₃)

IR (KBr) cm^{-1} ν : 3498 (-O-H), 2922 (=C-H), 1718 (-C=O), 1631 (-C=O), 1158 (-C-O-), 1066 (-C-O-)

HR-MS (ESI⁺)

m/z 869.5363[M+Na]⁺, Calc'd for C₅₁H₇₈O₈SiNa: 869.5364.

**Olean-12-en-28-oic acid, 3-*O*-hydroxy-, 3-*O*-[(*E*)-cinnamoyl]-
β-D-fucopyranosyloxy ester (**29Bia'**)**



To a solution of **30Bia'** (40 mg, 0.047 mmol) in AcOEt (2.0 mL) was added Dowex H⁺ resin to pH 1. After stirring for 4.5 h at room temperature, the reaction mixture was filtered and rinsed with AcOEt (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel 7 g, hexane : AcOEt = 8 : 1 → 6 : 1 → 4 : 1 → 2 : 1) to afford **29Bia'** (β only, *E* only, 23.2 mg, 0.032 mmol, 67%) as a white solid.

R_f = 0.47 (hexane : AcOEt = 1 : 1)

[α]_D²⁷ +104.026 (*c* 0.30, MeOH)

¹H-NMR (400 MHz, pyridine-*d*₅)

δ : 7.90 (d, *J* = 16.0 Hz, 1H, PhCH=CH), 7.44 (m, 2H, Ph-H), 7.34 (m, 3H, Ph-H), 6.68 (d, *J* = 16.0 Hz, 1H, PhCH=CH), 6.34 (d, *J* = 8.2 Hz, 1H, 1'-H), 5.67 (dd, *J* = 10.1 Hz, 3.3 Hz, 1H, 3'-H), 5.47 (t, *J* = 3.5 Hz, 1H, 12-H), 4.90 (m, 1H, 2'-H), 4.39 (br s, 1H, 4'-H), 4.07 (m, 1H, 5'-H), 3.44 (dd, *J* = 10.1 Hz, 5.6 Hz, 1H, 3-H), 3.25 (dd, *J* = 14.3 Hz, 4.4 Hz, 1H, 18-H), 2.32 (m, 1H, 2-H), 2.08 (m, 2H, 11-H), 1.96 (m, 2H, 16-H), 1.83 (m, 2H, 2-H, 22-H), 1.82 (m, 1H, 22-H), 1.75 (m, 1H, 19-H), 1.67 (m, 1H, 9-H), 1.58 (m, 1H, 1-H), 1.54 (d, 3H, 6'-H), 1.54 (m, 1H, 6-H), 1.53 (d, *J* = 6.4 Hz, 3H, 6'-H), 1.40 (m, 1H, 7-H), 1.37 (m, 1H, 6-H), 1.34 (m, 1H, 7-H), 1.33 (m, 1H, 21-H), 1.31 (m, 1H, 19-H), 1.23 (s, 3H, 27-H), 1.22 (s, 3H, 23-H), 1.14 (s, 3H, 26-H), 1.12 (m, 2H, 15-H), 1.08 (m, 1H, 21-H), 1.03 (s, 3H, 24-H), 1.01 (m, 1H, 1-H), 0.94 (s, 3H, 25-H), 0.92 (s, 6H, 29-H, 30-H), 0.86 (m, 1H, 5-H)

¹³C-NMR (100 MHz, pyridine-*d*₅)

δ : 176.6 (C-28), 166.9 (3'-OCO-), 145.1 (PhCH=CH), 144.2 (C-13), 134.9, 130.8, 129.4, 129.4, 128.6, 128.6, 123.2 (C-12), 119.1 (PhCH=CH), 95.9 (C-1'), 78.5 (C-3'), 78.3 (C-3), 72.5 (C-5'), 70.2 (C-4'), 68.4 (C-2'), 56.0 (C-5), 48.3 (C-9), 47.2 (C-17), 46.4 (C-19), 42.3 (C-14), 41.9 (C-18), 40.1 (C-8), 39.5 (C-4), 39.1 (C-1), 37.5 (C-10), 34.2 (C-21), 33.3 (C-7), 33.3 (C-29), 32.8 (C-22), 30.9 (C-20), 28.9 (C-23), 28.4 (C-15), 28.2 (C-2), 26.2 (C-27), 24.0 (C-30), 23.8 (C-16), 23.5 (C-11), 19.0 (C-6), 17.7 (C-26), 17.1 (C-6'), 16.7 (C-24), 15.8 (C-25)

IR (KBr) cm^{-1} v : 3424 (-O-H), 2939 (=C-H), 1719 (-C=O), 1638 (-C=O), 1158 (-C-O-), 1066 (-C-O-)

HR-MS (ESI⁺)

m/z 755.4509[M+Na]⁺, Calc'd for C₄₅H₆₄O₈Na: 755.4500.

Hemolytic Assay

Preserved sheep's blood (diluted 1:1 in Alsever's solution) was purchased hemolytic activities of pure from Kohjin Bio (Japan). The blood was centrifuged at 300×g for 5 min at 4 °C by using KUBOTA 6930 high-speed cooled centrifuge (KUBOTA Corp., Japan). The plasma (supernatant) was discarded, and aliquots of the pellet were washed three times with sterile PBS (pH 7.4, Gibco) by centrifugation at 300×g for 5 min at 4 °C. The erythrocytes were diluted with PBS to obtain a 10% suspension.

All tested saponin solutions (1 mg/mL) dissolved in DMSO (FUJIFILM Wako Pure Chemical Corp.) were prepared and then prepared saline was added to dilute the solution to the testing concentrations ranging from 500 to 7.8 µg/mL and stirred by VORTEX-GENIE 2 mixer (M&S Instruments Inc., Japan). The final volume of the derivative solution was 200 µL. The erythrocyte suspension (200 µL) was added to 200 µL of the suspension to be tested, and the samples were rapidly incubated at 37 °C with periodic stirring during a 30 min incubation period by using a PERSONAL-11 water bath shaker (TAITEC Corp., Japan). The solution was then centrifuged 232×g for 10 min at 20 °C. Absorbance of the supernatant was transferred to 96-well clear microplate measured at 570 nm using a FlexStation 3 multimode microplate reader (Molecular devices Corp., USA). The hemolytic % was calculated by comparison with the 100% hemolytic activity caused by commercial digitonin as maximal hemolytic positive control. The hemolytic % developed by the 5% DMSO-saline solution as negative control was subtracted from all groups. Each experiment was performed in triplicate at all concentrations used.

The hemolytic % was calculated with the formula

$$\text{Hemolytic\%} = (\text{ODt} - \text{ODnc}) / (\text{ODpc} - \text{ODnc}) \times 100\%$$

where ODt is the absorbance of tested saponins, ODpc is the absorbance of positive control, and ODnc is the absorbance of negative control. The concentration inducing 50% of the maximum hemolytic activity is the HD₅₀.

CMC dye solubilization method

2 μL of 1,6-diphenyl-1,3,5-hexatriene (DPH), in THF (0.01 M) was added to 200 μL of tested saponin. All tested saponin solutions (1 mg/mL) dissolved in DMSO (FUJIFILM Wako Pure Chemical Corp.) were prepared and then prepared saline was added to dilute the solution to the testing concentrations ranging from 500 to 7.8 $\mu\text{g/mL}$ and stirred by VORTEX-GENIE 2 mixer (M&S Instruments Inc., Japan). The final volume of the derivative solution was 200 μL . The DPH solution (2 μL) was added to 200 μL of the suspension to be tested, and the samples were incubated at room temperature in the dark for a 30 min incubation period. Fluorescence of the solutions was transferred to 96-well clear microplate and measured with an excitation wave-length of 358 nm and an emission of 430 nm using a FlexStation 3 multimode microplate reader (Molecular devices Corp., USA). Signal/background ratio was plotted as a function of dye solubilization. The CMC (Critical micelle Concentration) was determined by the point where absorbance starts increasing.

学位論文目録

主論文

“Synthesis of bisdesmosidic oleanolic acid saponins via a glycosylation-deprotection sequence under continuous microfluidic/batch conditions”

Naruki Konishi, Tatsuya Shirahata, Masaki Yokoyama, Tatsuya Katsumi, Yoshikazu Ito, Nozomu Hirata, Takashi Nishino, Kazuishi Makino, Noriko Sato, Takayuki Nagai, Hiroaki Kiyohara, Haruki Yamada, Eisuke Kaji, Yoshinori Kobayashi

The Journal of Organic Chemistry, American Chemical Society, 82, 6703-6719, (2017)

Impact factor 4.805

(本論 第一節・第二節・第三節)

参考論文

“Syntheses and mucosal adjuvant activity of simplified oleanolic acid saponins possessing cinnamoyl ester”

Tatsuya Shirahata, Takayuki Nagai, Nozomu Hirata, Masaki Yokoyama, Tatsuya Katsumi, Naruki Konishi, Takashi Nishino, Kazuishi Makino, Haruki Yamada, Eisuke Kaji, Hiroaki Kiyohara, Yoshinori Kobayashi

Bioorganic & Medicinal Chemistry, ELSEVIER, 25, 1747-1755, (2017)

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