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Catalytic Stereoselective Glycosidation with Glycosyl Diphenyl Phosphates: Rapid Construction of 1,2-*cis*-α-Glycosidic Linkages

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Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract: A commercially available 0.1 M solution of $HClO_4$ in dioxane has been shown to catalyze the glycosidation of glycosyl diphenyl phosphates. The per-*O*-benzyl-protected glucosyl and galactosyl donors and the 3,4,6-tri-*O*-acetyl-2-azido-2-deoxygalactosyl donor each react with a range of acceptor alcohols in the presence of 0.05–0.2 equiv of $HClO_4$ in dioxane/Et_2O (1:1) to afford glycosides in good yields with good to excellent α selectivities. The synthetic utility of this glycosidation method was demonstrated by a stereoselective synthesis of the α-galactosylceramide KRN7000, an activator of natural killer (NK) T cells through CD1d molecules.

Keywords: carbohydrates · glycosylation · perchloric acid · phosphates · stereoselectivity

Introduction

The development of a general stereoselective glycosidation reaction has been an enduring problem in carbohydrate chemistry for nearly 30 years.[1] Since the 1,2-*cis*-α-glycoside is one of the most important structural units and is ubiquitously found in natural oligosaccharides and glycoconjugates, considerable effort has been devoted to the stereocontrolled construction of this linkage.[2] While 1,2-*trans*-β-glycosides can be prepared with the use of anchimeric assistance of a neighboring participating group, the formation of 1,2-*cis*-α-glycosides usually requires donors with a non-assisting functionality at C-2,[3,4] leading to a mixture of anomers despite the favorable stereoelectronic preference. One approach involves the use of the in situ anomerization concept introduced by Lemieux,[5] wherein stable α-glycosyl halides are equilibrated via ion-pair intermediates to reactive β counterparts, which, upon S_N2-like displacement by acceptor alcohols, predominantly afford α-glycosides. In most cases, observed selectivities are good to excellent, but the reaction requires very reactive glycosyl halides and relatively long reaction times. Another approach has focused on the use of beneficial α-directing effects of ethereal solvents.[6,7] Ether, THF, and dioxane have been utilized for this purpose. In particular, promoters possessing the perchlorate counterion have been successfully employed in combination with these solvents.[8,9] In addition to these approaches, an intramolecular glycosidation strategy,[10,11] the use of a donor with a bulky protecting group at O-6[12] or the use of an acceptor alcohol in a $^1C_4$ conformation,[13] and the remote group participation strategy[9f,h,14] have been reported.

Over the last two decades, we have been concerned with the development of novel stereocontrolled glycosidation reactions capitalizing on phosphorus-containing leaving groups.[15–21] For stereoselective construction of 1,2-*cis*-α-glycosidic linkages, we developed *S*-(2-*O*-benzyl-β-glycosyl)-*N*,*N*,*N*′,*N*′-tetramethyl-*N*′′-phenylphosphorodiamidimidothioates as donors, which provided glycosides in good yields with excellent α selectivities (α/β = 91:9–>99:1) upon activation with 2,6-lutidinium *p*-toluenesulfonate (LPTS) in the presence of Bu_4NI.[17] We also demonstrated that glycosidations with glycosyl diethyl phosphites, when treated with 2,6-di-*tert*-butylpyridinium iodide (DTBPI) in the presence of Bu_4NI, predominantly gave α-glycosides.[19e] Independent of our studies, Waldmann and Schmid reported that exposure of α-glucosyl phosphates to a 1 M solution of $LiClO_4$ in CH_2Cl_2 in the presence of LiI resulted in formation of the

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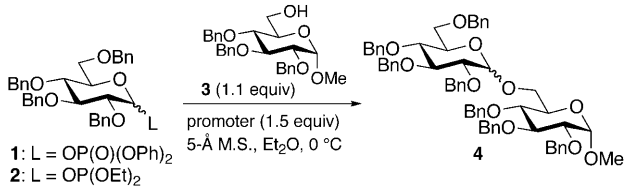
corresponding glycosyl iodides, which reacted with glycoside alcohols to afford di- and trisaccharides in modest yields with good to excellent α selectivities.[22] It is noteworthy that all of these methods are based on Lemieux's in situ anomerization concept and glycosyl iodides[23] are formed as common reactive intermediates. Compared to glycosyl bromides originally employed by Lemieux and co-workers,[5] the corresponding β-glycosyl iodide intermediates exhibit high reactivities toward S_N2-like displacement; however, long times (3–72 h) are required for completion of the reaction. In contrast to the in situ anomerization-based methods, documentation of the α-directing effect of ethereal solvents, especially in glycosidations with glycosyl phosphates,[24] is limited. Herein, we report a rapid, high-yielding and stereoselective synthesis of 1,2-*cis*-α-glycosides by $HClO_4$-catalyzed glycosidation with glycosyl diphenyl phosphates in dioxane/Et_2O (1:1) or dioxane.

Results and Discussion

Reaction Optimization

At the outset of this work, we speculated that an enhanced α selectivity would be obtained by the use of less-reactive acceptor alcohols such as 4-*O*-unprotected glycosides owing to the kinetic anomeric effect (KAE).[25] Therefore, highly reactive 6-*O*-unprotected glucoside **3** was chosen as an acceptor alcohol, and glucosyl diphenyl phosphate **1** (α/β = 98:2) and glucosyl diethyl phosphite **2** (α/β = 80:20) were evaluated as glycosyl donors. Addition of 1.5 equiv of a promoter to a mixture of donor **1** or **2**, 1.1 equiv of acceptor **3**, and 5 Å molecular sieves (M.S.) in Et_2O afforded disaccharide **4**, the α/β ratio of which was assayed by HPLC (Zorbax Sil column). Several promoters were screened in the reaction, and the results are compiled in Table 1. All of the reactions proceeded to full conversion within 30 min at 0 °C. Initial experiments revealed that trimethylsilyl triflate (TMSOTf) promoted glycosidation of phosphate **1** with alcohol **3** in Et_2O to afford disaccharide **4** in 93% yield with good α selectivity (α/β = 79:21), whereas a 56:44 mixture was obtained from phosphite **2** (Table 1, entries 1 vs 2). Of various metal triflates screened, $Cu(OTf)_2$ and $Sn(OTf)_2$ were found to activate both phosphate **1** and phosphite **2**, providing disaccharide **4** in modest yields, albeit in lower

Table 1. Effects of promoters in the glycosidation of per-*O*-benzyl-protected glucosyl donors **1** and **2** with alcohol **3**.



1: L = OP(O)(OPh)$_2$
2: L = OP(OEt)$_2$

Entry	Donor[a]	Promoter	*t* [min]	Yield [%]	α/β[b]
1	**1**	TMSOTf	5	93	79:21
2	**2**	TMSOTf	5	91	56:44
3	**1**	$Cu(OTf)_2$	10	70	71:29
4	**2**	$Cu(OTf)_2$	5	76	60:40
5	**1**	$Sn(OTf)_2$	30	59	48:52
6	**2**	$Sn(OTf)_2$	5	58	58:42
7	**1**	$TMSClO_4$[c]	5	95	83:17
8	**2**	$TMSClO_4$[c]	5	94	76:24
9	**1**	$HClO_4$[d]	5	91	84:16
10	**2**	$HClO_4$[d]	5	93	78:22

[a] Anomeric ratio of the donors: **1**, 98:2; **2**, 80:20. [b] The ratio was determined by HPLC (column, Zorbax Sil, 4.6×250 mm; eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}). [c] Prepared from TMSCl and $AgClO_4$. [d] Prepared from *t*BuCl and $AgClO_4$. Bn = benzyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

α selectivities (Table 1, entries 3–6). As expected from the precedents, the use of a 0.5 M solution of $TMSClO_4$ in toluene, prepared from TMSCl and $AgClO_4$,[26] for the activation of phosphate **1** resulted in the formation of disaccharide **4** with improved α selectivity (α/β = 83:17, Table 1, entry 7). Interestingly, lower α selectivity (α/β = 76:24) was obtained using phosphite **2** as a donor under identical conditions (Table 1, entry 8). These results suggest that, for inexplicable reasons, the leaving group plays an important role in reaction selectivity. In addition to Lewis acids, some Brønsted acids have been shown to activate glycosyl phosphites.[27] The beneficial effect of perchlorate counterion is evident from the result using perchloric acid ($HClO_4$), prepared from *t*BuCl and $AgClO_4$ in toluene,[9l] as a promoter for the glycosidation of phosphite **2**, whereby an α selectivity (α/β = 76:24) comparable to that with $TMSClO_4$ was obtained (Table 1, entries 10 vs 8). To our surprise, $HClO_4$ also activated phosphate **1** in Et_2O at 0 °C, providing an 84:16 mixture in favor of α-disaccharide **4**α in 91% combined yield (Table 1, entry 9). Owing to the advantage of phosphate **1** over phosphite **2** as a donor, phosphate **1** was employed for optimization of the glycosidation parameters. Although a 0.1 M solution of anhydrous $HClO_4$ in dioxane can be purchased from Kishida Chemical Co., Ltd., its low concentration has precluded its use in our investigation. Accordingly, both $TMSClO_4$ and $HClO_4$ should be prepared prior to use. Therefore, our initial efforts focused on the use of the more conveniently handled 0.5 M solution of $TMSClO_4$ in toluene.

To evaluate the beneficial effect of ethereal solvents, we next undertook a solvent survey in the $TMSClO_4$-promoted glycosidation of phosphate **1** with alcohol **3** at 0 °C (Table 2). As expected, employment of solvents such as CH_2Cl_2 and toluene led to a significant decline in stereose-

Abstract in Japanese:

ジフェニルホスファートを脱離基として組み込んだ糖供与体によるグリコシル化反応が、市販されている過塩素酸の 0.1 M ジオキサン溶液を触媒量用いることで進行することを見出した。ベンジル基で保護したグルコースおよびガラクトース糖供与体、アセチル基で保護した 2-アジド-2-デオキシ糖供与体を用いた場合、ジオキサン/エーテル（1:1）混合溶媒中 0.05–0.2 当量の過塩素酸存在下で種々の受容体アルコールのグリコシル化反応を行うと、良好な収率かつ α-選択性で対応するグリコシドが得られた。本法を利用することで、ナチュラルキラー（NK）T 細胞の活性化により抗腫瘍活性を発現する α-ガラクトシルセラミド（KRN7000）を簡便に合成することができた。

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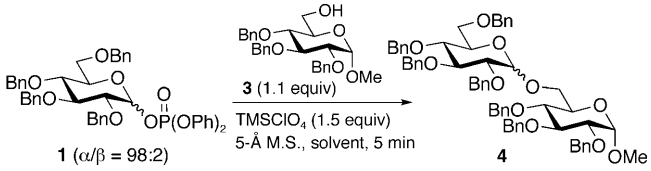
Table 2. Effects of solvents on stereoselectivity.



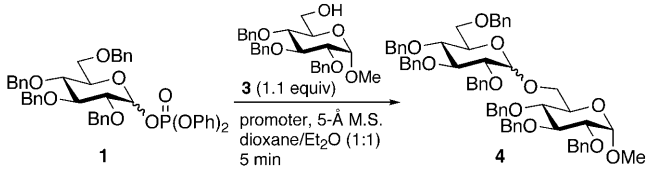
Entry	Solvent	T [°C]	Yield [%]	α/β[a]
1	Et_2O	0	95	83:17
2	CH_2Cl_2	0	89	62:38
3	toluene	0	87	66:34
4	THF	0	91	62:38
5	*t*BuOMe	0	82	82:18
6	dioxane	25	87	88:12
7	dioxane/Et_2O 1:1	0	97	88:12

[a] The ratio was determined by HPLC (column, Zorbax Sil, 4.6× 250 mm; eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}).

lectivity (Table 2, entries 2 and 3). In contrast, with the lone exception of THF (Table 2, entry 4), good to high α selectivities were obtained in ethereal solvents, with dioxane being the optimal solvent, although the high melting point of dioxane precluded a direct comparison (Table 2, entries 1, 5, and 6).[28] Since the use of Et_2O as a cosolvent had no effect on reaction selectivity (Table 2, entry 7), the mixed solvent system, which allowed the glycosidation to be run at lower temperatures, was chosen for further development.

An examination of the temperature profile of the reaction in dioxane/Et_2O (1:1) demonstrated that a decrease in the reaction temperature to −20 °C was accompanied by a decrease in α selectivity (Table 3, entries 1 vs 2 and 3). Since the α selectivity and yield obtained at 0 °C were comparable to those at 25 °C (Table 3, entries 2 vs 3), further optimization was performed at 0 °C. To date, glycosylations of alcohols with glycosyl phosphates have not been rendered catalytic.[29] Despite the lack of precedent, the foregoing finding that phosphate **1** can be activated by $HClO_4$ prompted us to investigate the glycosidation under catalytic conditions in anticipation that $HClO_4$, released upon glycosidation (see below), could function as a promoter. Gratifyingly, in the presence of 0.2 equiv of $TMSClO_4$, alcohol **3** underwent reaction with glycosyl phosphate **1** at 0 °C to provide the disaccharide **4** with high α selectivity (α/β = 90:10, Table 3, entry 4). Finally, complete conversion to disaccharide **4** within 5 min was realized by employing only 0.05 equiv of $TMSClO_4$; no change in stereoselectivity (α/β = 91:9) or chemical yield (94 %) was observed at this loading (Table 3, entry 5). As previously discussed, $HClO_4$ was comparable to $TMSClO_4$ when used in the reaction of phosphate **1** with alcohol **3** in Et_2O at 0 °C (Table 1, entry 7 vs 9). The catalytic potency of $HClO_4$, in conjunction with the use of dioxane as an optimal solvent, led us to explore the glycosidation under catalytic conditions using a commercially available $HClO_4$ solution. Fortunately, the $HClO_4$-catalyzed glycosidation of phosphate **1** with alcohol **3** reached completion in less than 5 min, giving virtually the same result as that obtained with $TMSClO_4$ (Table 3, entry 6).[30] The use of commercially available $HClO_4$ solution in place of $TMSClO_4$ obviated the need to prepare the promoter from explosive $AgClO_4$ for every reaction. It is well documented that thermodynamically less-stable β-phosphates anomerize to the corresponding α-phosphates in the presence of acids.[31] On the basis of precedent, it is speculated that the stereoselectivities are independent of the anomeric composition of the phosphate donor when glycosidations are performed under acidic conditions.[32] Surprisingly, the use of phosphate **1** (α/β = 5:95)[33] gave disaccharide **4** with minor erosion in α selectivity (α/β = 88:12, Table 3, entry 7). While the reason for the decreased α selectivity is not clear at present, we postulated that alcohol **3** is so reactive that the β-phosphate **1**β could not completely anomerize to the α-phosphate **1**α prior to glycosidation.[34] Indeed, a permuted order of addition improved the stereoselectivity of the glycosidation using phosphate **1** of α/β ratio 5:95 (Table 3, entry 8). Since a synthetically useful level of stereoselection was possible using the β-phosphate, stereoselective preparation of α-phosphates is not a requirement for the construction of 1,2-*cis*-α-glycosidic linkages. However, caution should be exercised when performing glycosylations of reactive alcohols such as **3** using reactive donors containing a substantial amount of β anomer.

Table 3. Effects of temperature, amount of promoter and anomeric composition of the donor on stereoselectivity.



Entry[a]	Donor **1** α/β	Promoter (equiv)	T [°C]	Yield [%]	α/β[b]
1	98:2	$TMSClO_4$ (1.5)	−20	92	80:20
2	98:2	$TMSClO_4$ (1.5)	0	97	88:12
3	98:2	$TMSClO_4$ (1.5)	25	92	89:11
4	98:2	$TMSClO_4$ (0.2)	0	93	90:10
5	98:2	$TMSClO_4$ (0.05)	0	94	91:9
6	98:2	$HClO_4$ (0.05)	0	90	91:9
7	5:95	$HClO_4$ (0.05)	0	92	88:12
8[c]	5:95	$HClO_4$ (0.05)	0	79	90:10

[a] A promoter was added to a mixture of donor **1**, alcohol **3**, and 5-Å M.S. in dioxane/Et_2O (1:1). [b] The ratio was determined by HPLC (column, Zorbax Sil, 4.6×250 mm; eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}). [c] After stirring a mixture of donor **1** and $HClO_4$ in dioxane/Et_2O (1:1) at 0 °C for 30 min, a solution of alcohol **3** in dioxane/Et_2O (1:1) was added at 0 °C.

Reaction Scope

Having optimized the reaction conditions, the scope of the $HClO_4$-catalyzed glycosidation was explored. Results of experiments for probing the scope of the alcohol component (Figure 1) with glucosyl phosphate **1** (α/β = 98:2) are summarized in Table 4. $HClO_4$-catalyzed glycosidations of **1** in dioxane/Et_2O (1:1) in the presence of 5-Å M.S. at 0 °C provided rapid and high-yielding access to a broad range of 1,2-

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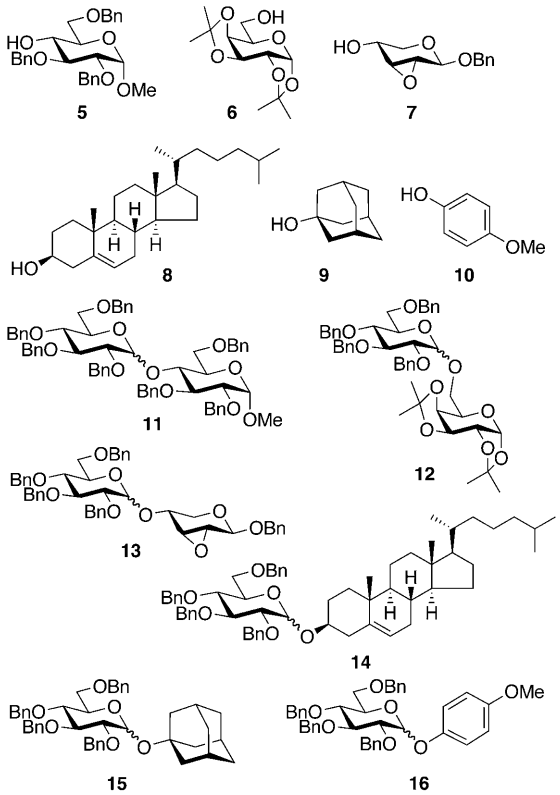
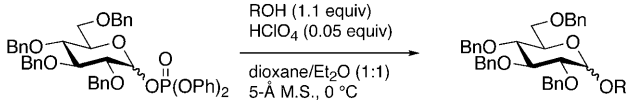


Figure 1. Acceptor alcohols and products in Table 4.

Table 4. $HClO_4$-catalyzed glycosidation of per-*O*-benzyl-protected glucosyl diphenyl phosphate **1** with acceptor alcohols.



1 (α/β = 98:2) → **11**–**16**

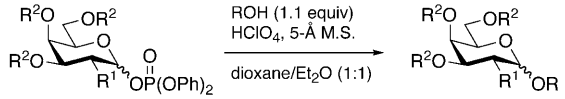
Entry	ROH	*t* [min]	Glycoside	Yield [%]	α/β[a]
1	**5**	20	**11**	80	91:9
2	**6**	5	**12**	95	89:11
3	**7**	10	**13**	85	86:14
4	**8**	20	**14**	94	89:11
5	**9**	30	**15**	86	87:13
6	**10**	20	**16**	85	85:15

[a] The ratio for the glycoside was determined by HPLC (column, Zorbax Sil, 4.6×250 mm; eluent, hexane/THF 6:1 or hexane/AcOEt 10:1–20:1; flow rate, 1.0–1.5 mL min^{-1}).

cis-α-glycosides; reaction times were typically 5–30 min and α selectivities ranged from 85:15 to 91:9. We previously reported that a limitation of DTBPI-promoted glycosidation was encountered with the less-reactive 4-*O*-unprotected glucoside **5**, which, upon reaction with diethyl phosphite **2** in the presence of Bu_4NI for 48 h, afforded disaccharide **11** in 59% yield, albeit with excellent α selectivity (α/β = 95:5).[19e] Under the optimized conditions, the alcohol **5** underwent glycosylation with donor **1** within 20 min to provide the disaccharide **11** in 80% yield with a slightly lower stereoselectivity (α/β = 91:9, Table 4, entry 1). It is noteworthy that alcohols **6** and **7** bearing acid-sensitive acetal or epoxy groups were safely glycosylated under these conditions with good α selectivities (Table 4, entries 2 and 3). A steroidal alcohol (cholesterol, **8**) and a *tert*-alcohol (1-adamantanol, **9**) were also successfully utilized in this reaction, and α-glycosides **14**α and **15**α were preferentially formed (Table 4, entries 4 and 5). It has been demonstrated that Lewis acid promoted glycosidations with phenols are accompanied by *O*→*C* glycoside rearrangements, resulting in the formation of *C*-aryl glycosides.[35] The advantage of employing a Brønsted acid ($HClO_4$) as a promoter becomes evident for the stereoselective synthesis of aryl glycosides, as the present method delivered *p*-methoxyphenyl (PMP) glucoside **16** free from contamination by rearranged products (Table 4, entry 6).

In an effort to expand the scope of the glycosidation method, we next examined the reaction of diphenyl phosphates **17** (α/β = 98:2) and **18** (α/β = 33:67) in the D-galacto series (Table 5, Figure 2). Consistent with the general trend,[36] per-*O*-benzyl-protected galactosyl donor **17** afforded better reactivity relative to the glucosyl donor **1**, thereby allowing the glycosidation to reach completion within 5 min even with the less-reactive alcohol **5** (Table 5, entry 2). While galactosides were obtained in good to high yields in all cases, the selectivities were not as favorable as those obtained with **1** (Table 5, entries 1–4). Selectivities appeared to depend on the reactivity of the acceptor alcohols: High α selectivities were observed in the reaction with less-reactive 4-*O*-unprotected glycosides **5** and **19**, but the primary alcohol **3** leads to poor α selectivity (α/β = 75:25).

Table 5. $HClO_4$-catalyzed glycosidation of galactosyl diphenyl phosphates **17** and **18**.



17: R^1 = OBn, R^2 = Bn
18: R^1 = N_3, R^2 = Ac
→ **23**–**28**

Entry	Donor[a]	ROH	Equiv $HClO_4$	*T* [°C]	*t* [min]	Glycoside	Yield [%]	α/β[b]
1	**17**	**3**	0.05	0	5	**23**	88	75:25
2	**17**	**5**	0.05	0	5	**24**	77	90:10
3	**17**	**19**	0.05	0	5	**25**	82	87:13
4	**17**	**20**	0.05	0	5	**26**	91	87:13
5	**18**	**21**	0.2	25	120	**27**	82	91:9
6	**18**	**22**	0.2	25	360	**28**	78	92:8

[a] Anomeric ratio of the donors: **17**, 98:2; **18**, 33:67. [b] The ratio for the glycoside was determined by HPLC (column, Zorbax Sil, 4.6×250 mm; eluent, hexane/THF 4:1–6:1 or hexane/AcOEt 5:1; flow rate, 0.5–1.5 mL min^{-1}). Ac = acetyl.

The scope of the $HClO_4$-catalyzed glycosidation is not limited to the use of per-*O*-benzyl-protected donors. When 3,4,6-tri-*O*-acetyl-2-azido-2-deoxygalactosyl diphenyl phosphate (**18**, α/β = 33:67) was used as a donor, 0.2 equiv of $HClO_4$, an elevated temperature (25 °C), and longer reaction

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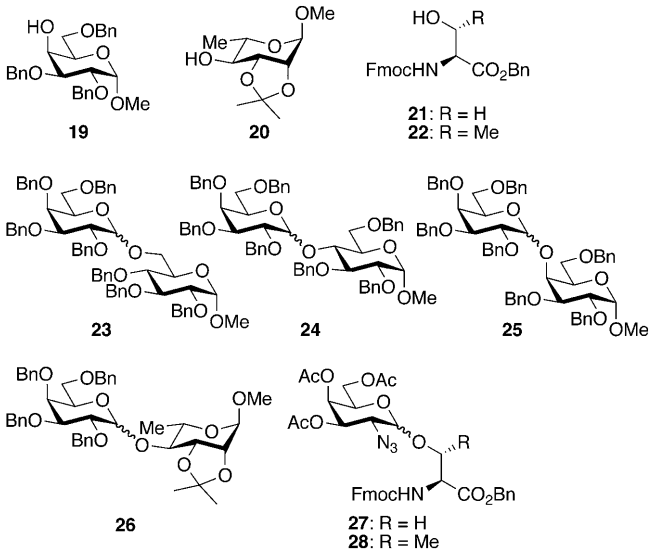
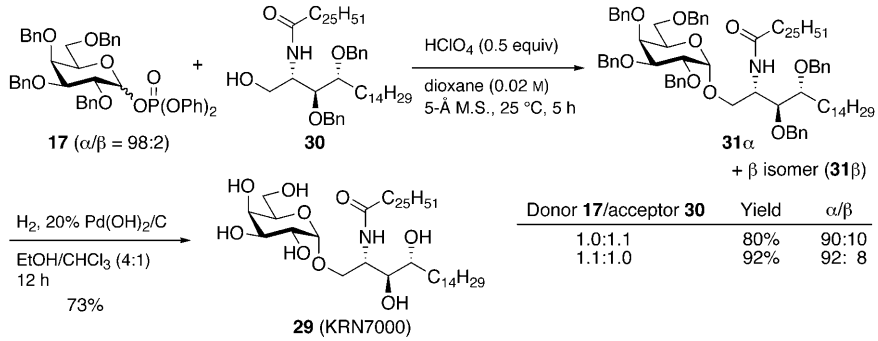


Figure 2. Acceptor alcohols and products in Table 5. Fmoc = 9-fluorenylmethoxycarbonyl.

times were required to effect complete conversion owing to the attenuated reactivity of the donor.[37] Excellent stereocontrol was realized for serine and threonine derivatives **21** and **22**, leading to predominant formation of α-glycosides **27**α and **28**α, which correspond to constituents of *O*-linked glycoproteins (Table 5, entries 5 and 6).



Scheme 1. Synthesis of KRN7000.

Synthesis of α-Galactosylceramide KRN7000 (29)

In 1993, a research group of Kirin Brewery Co., Ltd. reported the isolation and characterization of agelasphins, the first glycosylceramides found as α-linked galactosides.[38] Owing to their significant antitumor activities in mice, these molecules hold promise as new lead structures for the development of antitumor therapeutics. Therefore, the Kirin group synthesized various analogues and concluded on the basis of their structure–activity relationships that (2*S*,3*S*,4*R*)-1-*O*-(α-D-galactopyranosyl)-2-(*N*-hexacosanoylamino)-1,3,4-octadecanetriol (**29**), named KRN7000, was the compound of choice for clinical trials.[39] With regard to the mechanism of action, KRN7000 was shown to act as a ligand for the CD1d receptor on antigen-presenting cells to form a complex which binds to natural killer (NK) T cells, leading to the stimulation of a cascade of cytokines.[40,41] Not surprisingly, the potent biological properties have aroused considerable interest in KRN7000 within the medicinal and synthetic chemistry communities, and routes to KRN7000 have been reported by 12 groups to date.[42] We then considered that a synthesis of KRN7000 would provide a stringent test for the glycosidation method presented herein, since glycosidations employing ceramides as acceptor alcohols frequently suffer from poor reactivity presumably owing to hydrogen-bond donation from the amide N–H group.[43]

Ceramide **30** was readily prepared from D-galactose according to literature procedures (Scheme 1).[44] At this stage, we noticed that the insolubility of **30** in Et_2O precluded the use of a solvent mixture of dioxane/Et_2O. Since ceramide **30** is sparingly soluble in dioxane, we opted to run the reaction in dioxane at a low concentration (0.02 M) at room temperature. Our initial attempt to couple galactosyl diphenyl phosphate **17** (α/β = 98:2) and alcohol **30** under the optimized conditions resulted in the formation of a trace amount of glycoside **31** with complete recovery of unreacted starting materials. We surmised that the result is attributed to both the low concentration and the presence of the amide moiety that would buffer the acidity of the promoter. After considerable experimentation, we found that the use of 0.5 equiv of $HClO_4$ was sufficient for the reaction to proceed to completion, providing glycoside **31** in 80% yield with an α/β ratio of 90:10. Examination of the amount of donor used in the glycosidation revealed that a slight excess of diphenyl phosphate **17** (1.1 equiv) was beneficial to both chemical yield (92%) and diastereoselectivity (α/β = 92:8). As compared to the precedents wherein an excess amount of donors (at least 1.5 equiv) was utilized for the glycosylation of ceramide derivatives to give α-galactosides in good yields (53–74%),[42a–c,f,j,k] the method presented herein offers the advantage of high product yield when using approximately equimolar proportions of glycosyl donor **17** and acceptor **30**. After chromatographic separation of the anomers, the α anomer **31**α was subjected to hydrogenolysis in the presence of 20% $Pd(OH)_2/C$ to give KRN7000, whose data were identical in all respects with those previously reported.

Mechanistic Considerations

A control experiment established that the anomeric ratio of glycoside **4** (α/β = 2:98) did not change upon exposure to a stoichiometric amount of $HClO_4$ in the presence of 5-Å M.S. in dioxane/Et_2O (1:1) even under reflux for 5 h, imply-

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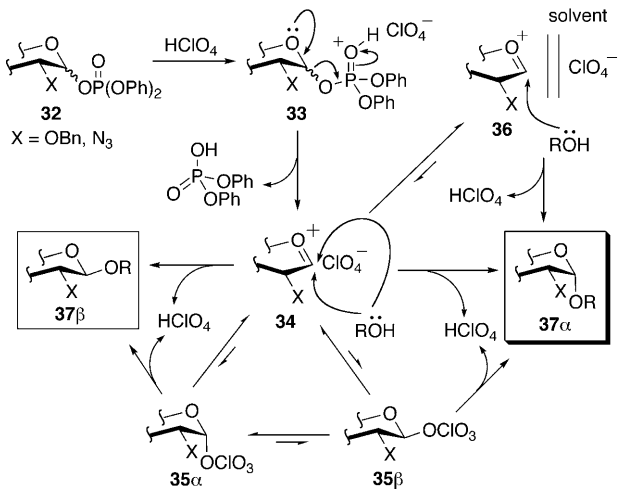
ing that the observed α selectivity is the result of kinetic control. On the basis of this result, we propose the reaction pathway for $HClO_4$-catalyzed glycosidation using glycosyl diphenyl phosphates as glycosyl donors (Scheme 2). Diphenyl phosphate **32** is activated by protonation at the phosphoryl oxygen atom,[45] resulting in cleavage of the phosphate group to provide an equilibrium mixture of contact ion pair (CIP) **34** and glycosyl perchlorates[8] **35**α and **35**β, along with diphenyl phosphate. Since it is speculated, in analogy to most organic perchlorates, that glycosyl perchlorates **35**α and **35**β are unstable, the equilibration between **34**, **35**α, and **35**β would lie toward CIP **34**, especially at high temperatures. In addition, ethereal solvents are capable of stabilization of CIP **34** and facilitate the formation of solvent-separated ion pair (SSIP) **36**. Axial attack of acceptor alcohols from the α face of CIP **34** or SSIP **36** is favored owing to KAE, leading to the preferential formation of α-glycosides and the regeneration of $HClO_4$. The trend for α selectivity to increase with increasing temperature (Table 3, entry 1 vs 2) provides strong support for the proposed mechanism because of a large equilibrium preference for CIP **34** at a higher temperature. The reason for the enhanced α selectivity in dioxane is unclear;[46] however, low donicity of dioxane would avoid formation of oxonium ions by solvent participation,[47] thus promoting the glycosidation through CIP **34** and SSIP **36**. The rationale for the difference in stereoselectivity between phosphate **1** and phosphite **2** is not fully understood at this time, and further studies to address this issue will be forthcoming.



Scheme 2. Plausible mechanism of the $HClO_4$-catalyzed glycosidation with glycosyl diphenyl phosphates.

Conclusions

This study documents the stereoselective glycosylation of alcohols with glycosyl diphenyl phosphates in the presence of an acid catalyst. Commercially available 0.1 M solution of $HClO_4$ has been found to be an excellent catalyst for the transformation, providing glycosides in high yields with high α selectivities. A wide range of glycosyl acceptors, including steroidal alcohols, *tert*-alcohols, and phenols as well as glycoside alcohols bearing acid-sensitive acetal or epoxy groups, can be employed in this coupling. The glycosyl donor is not confined to highly reactive benzyl-protected glucosyl and galactosyl diphenyl phosphates, and the scope of this reaction is extended to include less-reactive 3,4,6-tri-*O*-acetyl-2-azido-2-deoxygalactosyl diphenyl phosphate as a donor. Of particular note is the development of a simple reaction protocol that employs a commercially available promoter, low catalyst loading (as little as 5 mol% catalyst), and moderate temperature (0–25 °C), conditions that render this glycosidation particularly attractive from a preparative standpoint. We have also demonstrated that this method was successfully utilized in the synthesis of KRN7000.

With regard to the activation of glycosyl phosphates, stoichiometric amounts of Lewis acids such as TMSOTf,[15] $BF_3{\cdot}OEt_2$,[48] and $LiClO_4$[22] have been employed as promoters, and protic acids have been reported to be ineffective for this purpose.[29] Therefore, the method present herein is the first example of the use of a protic acid as a promoter in the glycosidation with glycosyl phosphates. Seeberger and coworkers proposed that a driving force of silyl triflate promoted glycosidation using glycosyl phosphates is the formation of a stoichiometric amount of silyl phosphate as a byproduct.[29] On the basis of this speculation, they developed a catalytic method employing a TMS ether as an acceptor and TfOH as a catalyst.[29] However, direct catalytic glycosylation of alcohol acceptors does not appear to have been precedented prior to the present study. This is also the first example of direct catalytic glycosidation of glycosyl phosphates with alcohols.

To date, there is no generally applicable direct method for the construction of 1,2-*cis*-α-glycosides from glycosyl phosphates because, even without a participating group at C-2, 1,2-*trans*-β-glycosidic linkages are readily formed with these donors. Thus, we have now developed a stereoselective entry to either 1,2-*cis*-α-glycosides or 1,2-*trans*-β-glycosides using glycosyl phosphates as common glycosyl donors by appropriate choice of the reaction conditions. This method complements glycosidations based on the in situ anomerization concept and should find wide application in organic synthesis.

Experimental Section

General

Melting points were measured on a Büchi 535 digital melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO P-1030 digital polarimeter with a sodium lamp (589 nm). Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JEOL JNM-AL400 (400 MHz), JNM-ECX400P (400 MHz), JNM-ECA500 (500 MHz), or Bruker ARX500 (500 MHz) spectrometer with tetrame-

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thylsilane ($\delta_H = 0.00$ ppm), $CHCl_3$ ($\delta_H = 7.26$ ppm), or pyridine ($\delta_H = 8.73$ ppm) as an internal standard. Coupling constants (J) are reported in hertz (Hz). Abbreviations of multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data are presented as follows: chemical shift, multiplicity, coupling constants, integration, and assignment. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-AL400 (100 MHz) or Bruker ARX500 (126 MHz) spectrometer with $CDCl_3$ ($\delta_C = 77.0$ ppm) or [D_5]pyridine ($\delta_C = 149.9$ ppm) as an internal standard. Phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded on a JEOL EX270 (109 MHz) spectrometer with H_3PO_4 ($\delta_P = 0.00$ ppm) as an external standard. Fast atom bombardment (FAB) mass spectra were obtained on a JEOL JMS-HX110 spectrometer by the Center for Instrumental Analysis, Hokkaido University.

Column chromatography was carried out on Kanto silica gel 60 N (40–50 μm or 63–210 μm) or Wakogel C-200 (75–150 μm). Analytical and preparative thin layer chromatography (TLC) was carried out on 0.25 mm Merck Kieselgel 60 F_{254} plates. Visualization was accomplished with ultraviolet light and anisaldehyde or phosphomolybdic acid stain, followed by heating. Analytical high-performance liquid chromatography (HPLC) was performed on a JASCO PU-980 and UV-970 (detector, $\lambda = 254$ nm). Retention times (t_R) and peak ratios were determined with a Shimadzu Chromatopac C-R6A. Hexane was HPLC grade, and was filtered and degassed prior to use.

Reagents and solvents were purified by standard means or used as received unless otherwise noted. Dehydrated CH_2Cl_2, THF (stabilizer free), and toluene were purchased from Kanto Chemical Co., Inc. Dioxane was distilled from sodium metal/benzophenone ketyl prior to use. 5-Å molecular sieves were finely ground in a mortar and heated in vacuo at 200 °C for 12 h.

All reactions were conducted under an argon atmosphere. 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl diphenyl phosphate (**18**)[15c] and 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetimidate[49] were prepared according to literature procedures.

Preparation of Glycosyl Donors

Typical procedure for preparation of glycosyl diphenyl phosphates: 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl diphenyl phosphate (**1**; α/β = 98:2) was prepared using a slight modification of the literature procedure.[50] Diphenyl chlorophosphate (0.70 mL, 3.34 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1.5 g, 2.78 mmol) and DMAP (1.02 g, 8.34 mmol) in CH_2Cl_2 (18 mL) at 0 °C. After stirring for 30 min, the reaction was quenched with crushed ice, followed by stirring for 10 min. The mixture was poured into a two-layer mixture of AcOEt (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), and the whole mixture was extracted with AcOEt (50 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (2.37 g), which was purified by column chromatography (silica gel 40 g, hexane/AcOEt 3:1 with 3% Et_3N) to give diphenyl phosphate **1**[50] (1.54 g, 75%, α/β = 98:2) as a white solid. The anomeric α/β ratio of the product was determined by ^{31}P NMR. Data for α anomer **1**α: $R_f = 0.49$ (hexane/AcOEt 2:1); $[\alpha]_D^{21} = +62.1$ ($c = 1.00$ in $CHCl_3$) [lit.: $[\alpha]_D^{25} = +61.9 \pm 0.7$ ($c = 2.80$ in $CHCl_3$)];[50] IR (film): $\tilde{\nu} = 3421, 3062, 3032, 2925, 2878, 1948, 1877, 1811, 1747, 1589, 1490, 1454, 1368, 1291, 1187, 1071, 1008, 954\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.35$ (dd, $J = 1.6$, 11.0 Hz, 1H; H-6a), 3.61–3.64 (m, 2H; H-2, H-6b), 3.72 (t, $J = 9.9$ Hz, 1H; H-4), 3.77 (dd, $J = 1.6$, 9.9 Hz, 1H; H-5), 3.88 (t, $J = 9.9$ Hz, 1H; H-3), 4.41 (d, $J = 12.2$ Hz, 1H; OC*H*Ph), 4.48 (d, $J = 10.9$ Hz, 1H; OC*H*Ph), 4.53 (d, $J = 12.2$ Hz, 1H; OC*H*Ph), 4.63 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 4.74 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 4.76 (d, $J = 10.9$ Hz, 1H; OC*H*Ph), 4.80 (d, $J = 10.9$ Hz, 1H; OC*H*Ph), 4.89 (d, $J = 10.9$ Hz, 1H; OC*H*Ph), 6.06 (dd, $J = 3.2$, 6.5 ($J_{H\text{-}P}$) Hz, 1H; H-1), 7.23–7.31 ppm (m, 30H; aromatic); ^{31}P NMR (109 MHz, $CDCl_3$): $\delta = -12.67$ (α), −12.86 ppm (β).

17: The reaction was performed according to the typical procedure (7 mL CH_2Cl_2, 0 °C, 30 min) employing 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (500 mg, 0.93 mmol), diphenyl chlorophosphate (0.25 mL, 1.20 mmol), and DMAP (361 mg, 2.96 mmol). The crude product (869 mg) was purified by column chromatography (silica gel 18 g, hexane/AcOEt 5:2 with 3% Et_3N) to give 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl diphenyl phosphate[50] (**17**; 459 mg, 60%, α/β = 98:2) as a colorless oil. The anomeric α/β ratio of the product was determined by ^{31}P NMR. Data for α anomer **17**α: $R_f = 0.51$ (hexane/AcOEt 2:1); $[\alpha]_D^{23} = +56.7$ ($c = 1.01$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3063, 3031, 2919, 2871, 1952, 1590, 1490, 1454, 1358, 1291, 1190, 1110, 957\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.28$ (dd, $J = 5.2$, 8.4 Hz, 1H; H-6a), 3.52 (t, $J = 8.4$, 1H; H-6b), 3.83 (dd, $J = 3.2$, 10.0 Hz, 1H; H-3), 3.97–4.00 (m, 2H; H-4, H-5), 4.12 (dt, $J = 10.0$, 3.2, 1H; H-2), 4.35 (d, $J = 12.0$ Hz, 1H; OC*H*Ph), 4.38 (d, $J = 12.0$ Hz, 1H; OC*H*Ph), 4.55 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 4.68 (d, $J = 12.0$ Hz, 1H; OC*H*Ph), 4.71 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 4.76 (d, $J = 12.0$ Hz, 1H; OC*H*Ph), 4.77 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 4.93 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 6.07 (dd, $J = 3.2$, 6.3 ($J_{H\text{-}P}$) Hz, 1H; H-1), 7.05–7.37 ppm (m, 30H; aromatic); ^{31}P NMR (109 MHz, $CDCl_3$): $\delta = -12.95$ (α), −17.42 ppm (β).

2: Diethyl chlorophosphite (0.16 mL, 1.11 mmol) was added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (500 mg, 0.93 mmol, α/β = 80:20) and Et_3N (0.32 mL, 2.31 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After 30 min, the reaction was quenched with crushed ice, followed by stirring at 0 °C for 15 min. The whole mixture was partitioned between AcOEt (30 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with brine (2×15 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (765 mg), which was purified by column chromatography (silica gel 30 g, hexane/AcOEt 7:1 with 2% Et_3N) to give 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl diethyl phosphite (**2**; 544 mg, 89%, α/β = 80:20) as a colorless oil. The anomeric α/β ratio of the product was determined by ^{31}P NMR. $R_f = 0.67$ (hexane/AcOEt 2:1); $[\alpha]_D^{23} = +47.4$ ($c = 1.02$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3063, 3030, 2978, 2924, 1952, 1873, 1811, 1605, 1497, 1454, 1362, 1028, 916\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$) (data for α anomer): $\delta = 1.210$ (t, $J = 6.9$ Hz, 3H; OCH_2CH_3), 1.213 (t, $J = 7.2$ Hz, 3H; OCH_2CH_3), 3.60 (dd, $J = 3.4$, 9.7 Hz, 1H; H-2), 3.62 (dd, $J = 1.7$, 10.3 Hz, 1H; H-6a), 3.69 (t, $J = 9.7$ Hz, 1H; H-4), 3.75 (dd, $J = 3.4$, 10.3 Hz, 1H; H-6b), 3.84–3.95 (m, 4H; $2\times OCH_2CH_3$), 3.98 (m, 1H; H-5), 3.99 (t, $J = 9.7$ Hz, 1H; H-3), 4.46 (d, $J = 12.1$ Hz, 1H; OC*H*Ph), 4.49 (d, $J = 10.8$ Hz, 1H; OC*H*Ph), 4.59 (d, $J = 12.1$ Hz, 1H; OC*H*Ph), 4.68 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 4.71 (d, $J = 11.5$ Hz, 1H; OC*H*Ph), 4.81 (d, $J = 10.8$ Hz, 1H; OC*H*Ph), 4.84 (d, $J = 10.8$ Hz, 1H; OC*H*Ph), 4.94 (d, $J = 10.8$ Hz, 1H; OC*H*Ph), 5.57 (dd, $J = 3.4$, 8.5 ($J_{H\text{-}P}$) Hz, 1H; H-1), 7.16–7.35 ppm (m, 20H; aromatic); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 91.4$ (d, $J = 17.6$ Hz; C-1α), 96.9 ppm (d, $J = 15.7$ Hz; C-1β); ^{31}P NMR (109 MHz, $CDCl_3$): $\delta = 140.05$ (α), 140.71 ppm (β); FAB-HRMS: m/z calcd for $C_{38}H_{46}O_8P$ $[M+H]^+$: 661.2930, found: 661.2927.

Preparation of Promoters

0.5 M $TMSClO_4$ in toluene: TMSCl (0.095 mL, 0.75 mmol) was added to a stirred solution of $AgClO_4$ (155.9 mg, 0.75 mmol) in toluene (1.5 mL), and the mixture was stirred for 30 min. After standing for 10 min without stirring, the supernatant was used for glycosidation as a promoter.[26]

0.5 M $HClO_4$ in toluene: *t*BuCl (0.090 mL, 0.83 mmol) was added to a stirred solution of $AgClO_4$ (155.9 mg, 0.75 mmol) in toluene (1.5 mL), and the mixture was stirred for 30 min. After standing for 10 min without stirring, the supernatant was used for glycosidation as a promoter.[9l]

Glycosidation

Typical procedure for $HClO_4$-catalyzed glycosidation: $HClO_4$ in dioxane (0.1 M, 0.05 mL, 0.005 mmol) was added to a stirred mixture of diphenyl phosphate **1** (77.3 mg, 0.10 mmol), alcohol **3** (51.1 mg, 0.11 mmol), and pulverized 5-Å M.S. (50 mg) in dioxane/Et_2O (1:1, 1 mL) at 0 °C. After stirring for 5 min, the reaction was quenched with Et_3N (0.1 mL), and the mixture was filtrated through a celite pad. The filtrate was poured into a two-layer mixture of AcOEt (3 mL) and saturated aqueous $NaHCO_3$ (6 mL), and the whole mixture was extracted with AcOEt (30 mL). The organic extract was successively washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (105.8 mg), from

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which an anomeric mixture of methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside[9] (**4**; 88.8 mg, 90%, α/β=91:9) was obtained as a white solid after column chromatography (silica gel 10 g, hexane/AcOEt 5:1). The anomeric α/β ratio of disaccharide **4** was determined by HPLC analysis [column, Zorbax Sil, 4.6×250 mm; eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (β anomer)=15.8 min, t_R (α anomer)=16.4 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 20:20:1). Data for α anomer **4**α: R_f=0.62 (hexane/AcOEt 2:1), 0.29 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{21}$=+54.4 (c=1.01 in $CHCl_3$) [lit.: $[\alpha]_D^{24}$=+53 (c=0.57 in $CHCl_3$)];[9] IR (film): $\tilde{\nu}$=3031, 2927, 1496, 1455, 1361, 1071, 1028, 909 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.35 (s, 3H; OCH_3), 3.44 (dd, J=3.6, 9.6 Hz, 1H; H-2), 3.52–3.55 (m, 2H; H-6a, H-2′), 3.59–3.66 (m, 3H; H-4, H-4′, H-6′a), 3.70 (br d, J=10.3 Hz, 1H; H-6b), 3.75–3.83 (m, 3H; H-5, H-5′, H-6′b), 3.95 (dd, J=9.2, 9.6 Hz, 1H; H-3′), 3.97 (dd, J=9.2, 9.6 Hz, 1H; H-3), 4.41 (d, J=12.1 Hz, 1H; OC*H*Ph), 4.44 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.54 (d, J=3.6 Hz, 1H; H-1), 4.56 (d, J=12.1 Hz, 1H; OC*H*Ph), 4.57 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.62–4.69 (m, 3H; 3×OC*H*Ph), 4.70 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.76 (d, J=11.0 Hz, 1H; OC*H*Ph), 4.80 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.81 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.91 (d, J=11.0 Hz, 1H; OC*H*Ph), 4.93 (d, J=11.0 Hz, 1H; OC*H*Ph), 4.95 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.96 (d, J=3.4 Hz, 1H; H-1′), 7.10–7.33 ppm (m, 35H; aromatic). Data for β anomer **4**β: R_f=0.62 (hexane/AcOEt 2:1), 0.21 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{20}$=19.2 (c=0.83 in $CHCl_3$) [lit.: $[\alpha]_D^{24}$=+19 (c=1.0 in $CHCl_3$)];[9] IR (film): $\tilde{\nu}$=3031, 2913, 1496, 1455, 1360, 1069, 1028, 795 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.32 (s, 3H; OCH_3), 3.43 (m, 1H; H-5′), 3.46–3.53 (m, 3H; H-2, H-4, H-2′), 3.56 (dd, J=8.8, 9.4 Hz, 1H; H-4′), 3.62 (dd, J=8.8, 9.0 Hz, 1H; H-3′), 3.64–3.73 (m, 3H; H-6a, H-6′ab), 3.82 (m, 1H; H-5), 3.98 (t, J=9.2 Hz, 1H; H-3), 4.17 (dd, J=1.9, 10.7 Hz, 1H; H-6b), 4.34 (d, J=7.7 Hz, 1H; H-1′), 4.50 (d, J=11.0 Hz, 1H; OC*H*Ph), 4.51–4.53 (m, 2H; 2×OC*H*Ph), 4.55 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.60 (d, J=3.3 Hz, 1H; H-1), 4.65 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.71 (d, J=11.1 Hz, 1H; OC*H*Ph), 4.74 (d, J=11.1 Hz, 1H; CH_2Ph), 4.76–4.81 (m, 4H; 4×OC*H*Ph), 4.90 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.96 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.97 (d, J=11.1 Hz, 1H; OC*H*Ph), 7.10–7.33 ppm (m, 35H; aromatic).

11: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0°C, 20 min) employing diphenyl phosphate **1** (77.3 mg, 0.10 mmol), alcohol **5** (51.1 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside[51] (**11**; 79.1 mg, 80%, α/β=91:9) was obtained as a colorless oil from the crude product (105.8 mg) after column chromatography (silica gel 10 g, hexane/AcOEt 5:1). The anomeric α/β ratio of disaccharide **11** was determined by HPLC analysis [eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (β anomer)=15.2 min, t_R (α anomer)=16.9 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 20:20:1). Data for α anomer **11**α: R_f=0.56 (hexane/AcOEt 2:1), 0.45 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}$=+39.2 (c=0.95 in $CHCl_3$) [lit.: $[\alpha]_D^{20}$=+40 (c=1.1 in $CHCl_3$)];[51] IR (film): $\tilde{\nu}$=3062, 3030, 2925, 2865, 1730, 1605, 1496, 1454, 1361, 1208, 1157, 1096, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.37 (s, 3H; OCH_3), 3.38 (m, 1H; H-6′a), 3.47–3.50 (m, 2H; H-2′, H-6′b), 3.59 (dd, J=3.4, 9.2 Hz, 1H; H-2), 3.62–3.66 (m, 2H; H-6a, H-4′), 3.70 (m, 1H; H-5′), 3.81–3.86 (m, 2H; H-5, H-6b), 3.90 (dd, J=8.6 Hz, 1H; H-3′), 4.04 (dd, J=9.2 Hz, 1H; H-4), 4.09 (t, J=9.2 Hz, 1H; H-3), 4.27 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.41 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.49–4.58 (m, 6H; 6×OC*H*Ph), 4.60 (d, J=4.0 Hz, 1H; H-1), 4.70 (d, J=12.6 Hz, 1H; OC*H*Ph), 4.77 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.78 (d, J=10.3 Hz, 1H; OC*H*Ph), 4.80 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.88 (d, J=10.3 Hz, 1H; OC*H*Ph), 5.03 (d, J=11.5 Hz, 1H; OC*H*Ph), 5.69 (d, J=3.4 Hz, 1H; H-1′), 7.08–7.28 ppm (m, 35H; aromatic). Data for β anomer **11**β: R_f=0.56 (hexane/AcOEt 2:1), 0.36 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{22}$=+19.6 (c=1.01 in $CHCl_3$) [lit.: $[\alpha]_D^{20}$=+20 (c=1.0 in $CHCl_3$)];[51] IR (film): $\tilde{\nu}$=3062, 3030, 2904, 1952, 1874, 1809, 1730, 1605, 1586, 1496, 1453, 1360, 1044, 911 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.29 (m, 1H; H-5′), 3.35 (m, 1H; H-2′), 3.36 (s, 3H; OCH_3), 3.44–3.49 (m, 3H; H-2, H-6a, H-3′), 3.54 (dd, J=4.6, 11.5 Hz, 1H; H-6′a), 3.58 (m, 1H; H-5), 3.60 (t, J=9.7 Hz, 1H; H-4′), 3.71 (dd, J=1.7, 11.5 Hz, 1H; H-6′b), 3.61 (dd, J=3.4, 10.9 Hz, 1H; H-6b), 3.84 (t, J=9.7 Hz, 1H; H-3), 3.96 (t, J=9.7 Hz, 1H; H-4), 4.36–4.39 (m, 3H; H-1′, 2×OC*H*Ph), 4.43 (d, J=12.6 Hz, 1H; OC*H*Ph), 4.55 (d, J=10.3 Hz, 1H; OC*H*Ph), 4.56 (d, J=3.4 Hz, 1H; H-1), 4.57 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.60 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.73–4.81 (m, 6H; 6×OC*H*Ph), 4.86 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.09 (d, J=11.5 Hz, 1H; OC*H*Ph), 7.17–7.42 ppm (m, 35H; aromatic).

12: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0°C, 5 min) employing diphenyl phosphate **1** (77.3 mg, 0.10 mmol), alcohol **6** (28.6 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of 1,2:3,4-di-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-galactopyranoside[52] (**12**; 77.0 mg, 95%, α/β=89:11) was obtained as a colorless oil from the crude product (89.3 mg) after column chromatography (silica gel 10 g, hexane/AcOEt 5:1). The anomeric α/β ratio of disaccharide **12** was determined by HPLC analysis [eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (α anomer)=11.3 min, t_R (β anomer)=12.5 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 20:20:1). Data for α anomer **12**α: R_f=0.59 (hexane/AcOEt 2:1), 0.27 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}$=+12.9 (c=1.41 in $CHCl_3$) [lit.: $[\alpha]_D^{20}$=+11 (c=0.87 in $CHCl_3$)];[52a] IR (film): $\tilde{\nu}$=3063, 3030, 2987, 2931, 1496, 1454, 1382, 1371, 1255, 1211, 1165, 1071, 1001, 919 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.32 (s, 6H; 2×CCH_3), 1.46 (s, 3H; CCH_3), 1.54 (s, 3H; CCH_3), 3.59 (dd, J=4.0, 9.7 Hz, 1H; H-2′), 3.65 (dd, J=1.7, 10.3 Hz, 1H; H-6′a), 3.69 (t, J=9.7 Hz, 1H; H-4′), 3.73–3.80 (m, 3H; H-6ab, H-6′b), 3.83 (m, 1H; H-5′), 3.99 (t, J=9.7 Hz, 1H; H-3′), 4.05 (m, 1H; H-5), 4.32 (dd, J=2.3, 5.2 Hz, 1H; H-2), 4.36 (dd, J=2.3, 8.0 Hz, 1H; H-4), 4.47 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.48 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.60 (dd, J=2.3, 8.0 Hz, 1H; H-3), 4.63 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.70 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.75 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.80 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.83 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.98 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.00 (d, J=4.0 Hz, 1H; H-1′), 5.52 (d, J=5.2 Hz, 1H; H-1), 7.13–7.38 ppm (m, 20H; aromatic). Data for β anomer **12**β: R_f=0.59 (hexane/AcOEt 2:1), 0.15 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}$=−34.2 (c=0.22 in $CHCl_3$) [lit.: $[\alpha]_D^{24}$=−32.5 (c=0.85 in $CHCl_3$)];[52b] IR (film): $\tilde{\nu}$=3090, 3031, 3010, 2911, 2867, 1717, 1603, 1496, 1454, 1384, 1257, 1069, 1008 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.31 (s, 6H; 2×CCH_3), 1.45 (s, 3H; CCH_3), 1.50 (s, 3H; CCH_3), 3.44–3.48 (m, 2H; H-2′, H-5′), 3.59–3.65 (m, 2H; H-3′, H-4′), 3.67–3.75 (m, 3H; H-6a, H-6′ab), 4.09 (m, 1H; H-5), 4.16 (dd, J=3.4, 10.3 Hz, 1H; H-6b), 4.24 (dd, J=2.3, 8.0 Hz, 1H; H-4), 4.32 (dd, J=2.3, 5.2 Hz, 1H; H-2), 4.45 (d, J=8.0 Hz, 1H; H-1′), 4.50 (d, J=10.3 Hz, 1H; OC*H*Ph), 4.53 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.59 (dd, J=2.3, 8.0 Hz, 1H; H-3), 4.61 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.72 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.77 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.81 (d, J=10.3 Hz, 1H; OC*H*Ph), 4.96 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.05 (d, J=11.5 Hz, 1H; OC*H*Ph), 5.57 (d, J=5.2 Hz, 1H; H-1), 7.12–7.43 ppm (m, 20H; aromatic).

13: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0°C, 10 min) employing diphenyl phosphate **1** (77.3 mg, 0.10 mmol), alcohol **7** (24.4 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of benzyl 2,3-anhydro-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-β-D-ribopyranoside[53] (**13**; 62.8 mg, 85%, α/β=86:14) was obtained as a colorless oil from the crude product (79.3 mg) after column chromatography (silica gel 10 g, hexane/AcOEt 5:1). The anomeric α/β ratio of glucoside **13** was determined by HPLC analysis [eluent, hexane/AcOEt 20:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (β anomer)=6.5 min, t_R (α anomer)=14.9 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 10:10:1). Data for α anomer **13**α: R_f=0.56 (hexane/AcOEt 2:1), 0.20 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}$=+44.3 (c=0.36 in $CHCl_3$) [lit.: $[\alpha]_D^{25}$=+48 (c=1.2 in $CHCl_3$)];[53] IR ($CHCl_3$): $\tilde{\nu}$=3130, 2926, 2868, 1496, 1454, 1362, 1140, 1088, 1069, 1027 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.28 (d, J=4.0 Hz, 1H; H-2), 3.48–3.51 (m, 2H; H-3, H-5a), 3.58–3.65 (m, 3H; H-2′, H-4′, H-6′a), 3.70 (dd, J=3.4, 10.9 Hz, 1H; H-6′b), 3.78 (m, 1H; H-5′), 3.83 (dd, J=4.6, 12.0 Hz, 1H;

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H-5b), 4.00–4.06 (m, 2H; H-4, H-3′), 4.45 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.46 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.58 (d, J=11.2 Hz, 1H; OC*H*Ph), 4.59 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.72 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.77–4.85 (m, 4H; 4×OC*H*Ph), 5.011 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.014 (s, 1H; H-1), 5.11 (d, J=3.4 Hz, 1H; H-1′), 7.12–7.41 ppm (m, 25H; aromatic). Data for β anomer **13**β: R_f=0.56 (hexane/AcOEt 2:1), 0.19 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{22}$=+6.0 (c=0.91 in $CHCl_3$) [lit.: $[\alpha]_D^{25}$=+6 (c=1.0 in $CHCl_3$)];[53] IR ($CHCl_3$): $\tilde{\nu}$=3089, 3066, 3032, 3012, 2914, 2870, 1952, 1731, 1496, 1454, 1360, 1069, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=3.25 (d, J=4.0 Hz, 1H; H-2), 3.50 (m, 1H; H-5′), 3.53–3.58 (m, 3H; H-5a, H-2′, H-3′), 3.60 (t, J=4.0 Hz, 1H; H-3), 3.63–3.67 (m, 2H; H-4′, H-6′a), 3.72 (dd, J=1.7, 10.9 Hz, 1H; H-6′b), 3.84 (dd, J=4.6, 12.0 Hz, 1H; H-5b), 4.07 (m, 1H; H-4), 4.52 (d, J=8.0 Hz, 1H; H-1′), 4.54 (d, J=12.7 Hz, 1H; OC*H*Ph), 4.55 (d, J=10.7 Hz, 1H; OC*H*Ph), 4.58 (d, J=12.7 Hz, 1H; OC*H*Ph), 4.59 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.73 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.79 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.81–4.83 (m, 2H; 2×OC*H*Ph), 4.93 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.96 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.02 (s, 1H; H-1), 7.17–7.38 ppm (m, 25H; aromatic).

14: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0°C, 20 min) employing diphenyl phosphate **1** (77.3 mg, 0.10 mmol), cholesterol (**8**; 42.5 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of cholesteryl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside[54] (**14**; 85.6 mg, 94%, α/β=89:11) was obtained as a white solid from the crude product (101.6 mg) after column chromatography (silica gel 10 g, CH_2Cl_2/hexane 5:1). The anomeric α/β ratio of glucoside **14** was determined by HPLC analysis [eluent, hexane/AcOEt 20:1; flow rate, 1.0 mL min^{-1}; detection, 254 nm; t_R (β anomer)=26.7 min, t_R (α anomer)=41.1 min]. The α- and β-glycosides were separated by flash column chromatography with CH_2Cl_2/hexane (4:1). Data for α anomer **14**α: R_f=0.40 (CH_2Cl_2/hexane 5:1); $[\alpha]_D^{20}$=+45.4 (c=1.00 in $CHCl_3$) [lit.: $[\alpha]_D^{20}$=+46.0 (c=1.5 in $CHCl_3$)];[54b] IR (KBr): $\tilde{\nu}$=3027, 2932, 2866, 1496, 1454, 1375, 1165, 1052, 753, 732, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.68 (s, 3H; H-18), 0.86–1.60 (m, 33H), 1.79–1.88 (m, 3H), 1.95 (m, 1H), 2.02 (m, 1H), 2.27 (m, 1H; H-4a), 2.43 (m, 1H; H-4b), 3.48 (m, 1H; H-3), 3.55 (dd, J=4.0, 9.2 Hz, 1H; H-2′), 3.62–3.66 (m, 2H; H-4′, H-6′a), 3.74 (dd, J=3.4, 10.9 Hz, 1H; H-6′b), 3.86–3.89 (m, 1H; H-5′), 4.00 (t, J=9.2 Hz, 1H, H-3′), 4.45 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.46 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.61 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.65 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.77 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.82 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.83 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.93 (d, J=4.0 Hz, 1H; H-1′), 5.01 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.29 (m, 1H; H-6), 7.12–7.37 ppm (m, 20H; aromatic). Data for β anomer **14**β: R_f=0.22 (CH_2Cl_2/hexane 5:1); $[\alpha]_D^{21}$=+1.6 (c=0.33 in $CHCl_3$) [lit.: $[\alpha]_D^{20}$=+0.2 (c=1.6 in $CHCl_3$)];[54b] IR ($CHCl_3$): $\tilde{\nu}$=3032, 2942, 2868, 1490, 1455, 1362, 1292, 1068, 1011, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.68 (s, 3H; H-18), 0.86–1.71 (m, 33H), 1.79–1.87 (m, 2H), 1.96–2.03 (m, 3H), 2.34 (m, 1H; H-4a), 2.41 (m, 1H; H-4b), 3.43–3.47 (m, 2H; H-2′, H-6′a), 3.54 (t, J=9.2 Hz, 1H; H-3′), 3.57–3.66 (m, 3H; H-3, H-4′, H-5′), 3.73 (dd, J=1.7, 10.9 Hz, 1H; H-6′b), 4.50 (d, J=8.1 Hz, 1H; H-1′), 4.53 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.55 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.60 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.72 (d, J=10.8 Hz, 1H; OC*H*Ph), 4.78 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.81 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.92 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.97 (d, J=10.8 Hz, 1H; OC*H*Ph), 5.35 (m, 1H; H-6), 7.16–7.36 ppm (m, 20H; aromatic).

15: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0°C, 30 min) employing diphenyl phosphate **1** (77.3 mg, 0.10 mmol), 1-adamantanol (**9**; 16.7 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of 1-adamantyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside[55] (**15**; 58.3 mg, 86%, α/β=87:13) was obtained as a colorless oil from the crude product (103.7 mg) after column chromatography (silica gel 10 g, hexane/AcOEt 5:1). The anomeric α/β ratio of glucoside **15** was determined by HPLC analysis [eluent, hexane/THF 6:1; flow rate, 1.0 mL min^{-1}; detection, 254 nm; t_R (β anomer)=6.41 min, t_R (α anomer)=6.97 min]. The α- and β-glycosides were separated by flash column chromatography with CH_2Cl_2/hexane (20:1). Data for α anomer **15**α: R_f=0.60 (hexane/AcOEt 2:1), 0.37 (CH_2Cl_2); $[\alpha]_D^{23}$=+45.3 (c=0.98 in $CHCl_3$); IR (film): $\tilde{\nu}$=3063, 3006, 2852, 1869, 1728, 1586, 1453, 1315, 1268, 1186, 1073, 983, 908, 814, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.57–1.64 (m, 6H; 3×CH_2), 1.79–1.85 (m, 6H; 3×CH_2), 2.10–2.16 (m, 3H; 3×C*H*), 3.53 (dd, J=3.4, 9.7 Hz, 1H; H-2), 3.61 (dd, J=1.7, 10.3 Hz, 1H; H-5), 3.65 (dd, J=1.7, 9.2 Hz, 1H; H-6a), 3.76 (dd, J=3.4, 10.3 Hz, 1H; H-4), 3.99–4.03 (m, 2H; H-3, H-6b), 4.45 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.46 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.62–4.71 (m, 3H; 3×OC*H*Ph), 4.80 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.83 (d, J=10.3 Hz, 1H; OC*H*Ph), 4.99 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.27 (d, J=3.4 Hz, 1H; H-1), 7.12–7.36 ppm (20H, m, aromatic). Data for β anomer **15**β: R_f=0.53 (hexane/AcOEt 2:1), 0.18 (CH_2Cl_2); $[\alpha]_D^{23}$=+14.2 (c=0.96 in $CHCl_3$) [lit.: $[\alpha]_D^{20}$=+14.1 (c=6.1 in $CHCl_3$)];[55a] IR (film): $\tilde{\nu}$=3088, 3026, 2830, 2807, 1947, 1817, 1604, 1454, 1363, 1318, 1278, 1239, 1209, 1165, 1032, 940, 907, 841, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.60–1.66 (m, 6H; 3×CH_2), 1.82–1.95 (m, 6H; 3×CH_2), 2.12–2.18 (m, 3H; 3×C*H*), 3.43 (dd, J=5.7, 8.6 Hz, 1H; H-2), 3.47 (m, 1H; H-5), 3.50 (dd, J=5.2, 9.7 Hz, 1H; H-4), 3.60 (m, 1H; H-6a), 3.64 (dd, J=5.2, 8.6 Hz, 1H; H-3), 3.73 (br d, J=10.9 Hz, 1H; H-6b), 4.53–4.60 (m, 3H; 3×OC*H*Ph), 4.69 (d, J=5.7 Hz, 1H; H-1), 4.71 (d, J=9.2 Hz, 1H; OC*H*Ph), 4.77 (d, J=10.8 Hz, 1H; OC*H*Ph), 4.82 (d, J=10.8 Hz, 1H; OC*H*Ph), 4.91 (d, J=10.8 Hz, 1H; OC*H*Ph), 5.01 (d, J=10.8 Hz, 1H; OC*H*Ph), 7.18–7.36 ppm (20H, m, aromatic).

16: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0°C, 20 min) employing diphenyl phosphate **1** (77.3 mg, 0.10 mmol), 4-methoxyphenol (**10**; 13.7 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of 4-methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside[56] (**16**; 55.1 mg, 85%, α/β=85:15) was obtained as a colorless oil from the crude product (69.0 mg) after column chromatography (silica gel 10 g, hexane/AcOEt 6:1). The anomeric α/β ratio of glucoside **16** was determined by HPLC analysis [eluent, hexane/AcOEt 10:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (β anomer)=17.7 min, t_R (α anomer)=19.9 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 20:20:1). Data for α anomer **16**α: R_f=0.69 (hexane/AcOEt 2:1), 0.63 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}$=+91.3 (c=1.35 in $CHCl_3$) [lit.: $[\alpha]_D^{23}$=+92 (c=1.0 in $CHCl_3$)];[56b] IR (film): $\tilde{\nu}$=3062, 3030, 2928, 2865, 1588, 1507, 1453, 1361, 1214, 1073, 1031, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=3.59 (dd, J=1.7, 10.9 Hz, 1H; H-6a), 3.67–3.77 (m, 3H; H-2, H-4, H-6b), 3.77 (s, 3H; OCH_3), 3.92 (m, 1H; H-5), 4.18 (t, J=9.2 Hz, 1H; H-3), 4.41 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.49 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.59 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.69 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.80 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.86 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.88 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.05 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.36 (d, J=3.4 Hz, 1H; H-1), 6.78–6.82 (m, 2H; aromatic), 7.00–7.03 (m, 2H; aromatic), 7.13–7.39 ppm (m, 20H; aromatic). Data for β anomer **16**β: R_f=0.69 (hexane/AcOEt 2:1), 0.56 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}$=−5.1 (c=0.41 in $CHCl_3$) [lit.: $[\alpha]_D^{23}$=−4 (c=1.0 in $CHCl_3$)];[56a] IR (film): $\tilde{\nu}$=3033, 3011, 2911, 2868, 1507, 1454, 1360, 1211, 1068, 1029, 828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=3.58 (m, 1H; H-5), 3.64–3.73 (m, 4H; H-2, H-3, H-4, H-6a), 3.78 (s, 3H; OCH_3), 3.79 (m, 1H; H-6b), 4.54 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.57 (d, J=10.9 Hz, 1H; OC*H*Ph), 4.60 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.81–4.86 (m, 3H; 3×OC*H*Ph), 4.88 (dd, J=2.3, 5.7 Hz, 1H; H-1), 4.95 (d, J=10.9 Hz, 1H; OC*H*Ph), 5.05 (d, J=10.9 Hz, 1H; OC*H*Ph), 6.79–6.83 (m, 2H; aromatic), 7.02–7.05 (m, 2H; aromatic), 7.18–7.47 ppm (m, 20H; aromatic).

23: The glycosidation was performed according to the typical procedure (0.5 mL dioxane/Et_2O 1:1, 0°C, 5 min) employing galactosyl diphenyl phosphate **17** (38.6 mg, 0.05 mmol), alcohol **3** (25.6 mg, 0.055 mmol), $HClO_4$ (0.1 M in dioxane, 0.025 mL, 0.0025 mmol), and pulverized 5-Å M.S. (25 mg). An anomeric mixture of methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside[9] (**23**; 43.6 mg, 88%, α/β=75:25) was obtained as a colorless oil from the crude product (60.1 mg) after column chromatography (silica gel 8 g, hexane/AcOEt 5:1). The anomeric α/β ratio of disaccharide **23** was determined by HPLC analysis [eluent, hexane/THF 4:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (α anomer)=14.5 min, t_R (β anomer)=16.7 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 20:20:1). Data for α anomer **23**α: R_f=

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0.53 (hexane/AcOEt 2:1), 0.38 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}=+51.9$ ($c=1.04$ in $CHCl_3$) [lit.: $[\alpha]_D^{23}=+51$ ($c=1.3$ in $CHCl_3$)];[9] IR (film): $\tilde{\nu}=3011$, 2927, 1724, 1496, 1454, 1360, 1160, 1095, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.25$ (s, 3H; OCH_3), 3.41 (dd, $J=3.2$, 9.5 Hz, 1H; H-2), 3.46–3.53 (m, 2H; H-6′ab), 3.58 (t, $J=9.5$ Hz, 1H; H-4), 3.71–3.81 (m, 3H; H-5, H-6ab), 3.89–3.99 (m, 4H; H-3, H-3′, H-4′, H-5′), 4.03 (dd, $J=3.2$, 9.5 Hz, 1H; H-2′), 4.36 (d, $J=11.8$ Hz, 1H; OC*H*Ph), 4.43 (d, $J=11.8$ Hz, 1H; OC*H*Ph), 4.52 (d, $J=3.2$ Hz, 1H; H-1), 4.54–4.59 (m, 3H; 3×OC*H*Ph), 4.67–4.75 (m, 4H; 4×OC*H*Ph), 4.79 (d, $J=12.2$ Hz, 1H; OC*H*Ph), 4.80 (d, $J=10.9$ Hz, 1H; OC*H*Ph), 4.85 (d, $J=10.9$ Hz, 1H; OC*H*Ph), 4.94 (d, $J=11.3$ Hz, 1H; OC*H*Ph), 4.96 (d, $J=10.9$ Hz, 1H; OC*H*Ph), 4.99 (d, $J=3.2$ Hz, 1H; H-1′), 7.13–7.28 ppm (m, 35H; aromatic). Data for β anomer **23**β: $R_f=0.53$ (hexane/AcOEt 2:1), 0.30 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}=+12.6$ ($c=0.46$ in $CHCl_3$) [lit.: $[\alpha]_D^{21}=+12$ ($c=1.0$ in $CHCl_3$)];[9] IR (film): $\tilde{\nu}=3011$, 2930, 1720, 1496, 1454, 1360, 1281, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.29$ (s, 3H; OCH_3), 3.46 (t, $J=9.5$ Hz, 1H; H-4), 3.47–3.62 (m, 6H; H-2, H-6a, H-3′, H-5′, H-6′ab), 3.81 (m, 1H; H-5), 3.84 (t, $J=7.7$ Hz, 1H; H-2′), 3.97 (t, $J=9.5$ Hz, 1H; H-3), 4.14 (dd, $J=1.8$, 10.4 Hz, 1H; H-6b), 4.30 (d, $J=7.7$ Hz, 1H; H-1′), 4.39 (d, $J=11.8$ Hz, 1H; OC*H*Ph), 4.43 (d, $J=11.8$ Hz, 1H; OC*H*Ph), 4.50 (d, $J=11.3$ Hz, 1H; OC*H*Ph), 4.56 (d, $J=11.8$ Hz, 1H; OC*H*Ph), 4.57 (d, $J=3.2$ Hz, 1H; H-1), 4.64 (d, $J=12.2$ Hz, 1H; OC*H*Ph), 4.69–4.72 (m, 3H; 3×OC*H*Ph), 4.76–4.79 (m, 3H; 3×OC*H*Ph), 4.91–4.97 (m, 3H; 3×OC*H*Ph), 7.15–7.35 ppm (m, 35H; aromatic).

24: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0 °C, 5 min) employing diphenyl phosphate **17** (77.3 mg, 0.10 mmol), alcohol **5** (51.1 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside[9,57] (**24**; 75.6 mg, 77%, α/β=90:10) was obtained as a colorless oil from the crude product (136.1 mg) after column chromatography (silica gel 10 g, hexane/AcOEt 5:1). The anomeric α/β ratio of disaccharide **24** was determined by HPLC analysis [eluent, hexane/THF 6:1; flow rate, 0.5 mL min^{-1}; detection, 254 nm; t_R (β anomer)=50.9 min, t_R (α anomer)=52.4 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 20:20:1). Data for α anomer **24**α: $R_f=0.53$ (hexane/AcOEt 2:1), 0.42 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}=+37.0$ ($c=0.52$ in $CHCl_3$) [lit.: $[\alpha]_D^{23}=+33$ ($c=1.3$ in $CHCl_3$)];[9] IR (film): $\tilde{\nu}=3132$, 3010, 2928, 1722, 1496, 1454, 1360, 1279, 1095, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=3.37$ (s, 1H; OCH_3), 3.39–3.49 (m, 2H; H-6ab), 3.55 (dd, $J=3.2$, 9.5 Hz, 1H; H-2), 3.64 (dd, $J=2.3$, 10.9 Hz, 1H; H-6′a), 3.70 (dd, $J=4.1$, 10.9 Hz, 1H; H-6′b), 3.81 (dd, $J=2.3$, 10.0 Hz, 1H; H-3′), 3.84–3.88 (m, 2H; H-5, H-5′), 3.93 (m, 1H; H-4′), 3.96–4.00 (m, 2H; H-4, H-2′), 4.07 (t, $J=9.5$ Hz, 1H; H-3), 4.22 (d, $J=11.3$ Hz, 1H; OC*H*Ph), 4.29 (d, $J=11.3$ Hz, 1H; OC*H*Ph), 4.41 (d, $J=12.2$ Hz, 1H; OC*H*Ph), 4.51–4.57 (m, 4H; H-1, 3×OC*H*Ph), 4.60 (d, $J=12.2$ Hz, 1H; OC*H*Ph), 4.65–4.71 (m, 4H; 4×OC*H*Ph), 4.81 (d, $J=11.8$ Hz, 1H; OC*H*Ph), 4.86 (d, $J=11.3$ Hz, 1H; OC*H*Ph), 4.97 (d, $J=11.8$ Hz, 1H; OC*H*Ph), 5.76 (d, $J=3.6$ Hz, 1H; H-1′), 7.17–7.31 ppm (m, 35H; aromatic). Data for β anomer **24**β: $R_f=0.53$ (hexane/AcOEt 2:1), 0.36 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{22}=+10.5$ ($c=0.75$ in $CHCl_3$) [lit.: $[\alpha]_D^{20\pm2}=+10$ ($c=1$ in $CHCl_3$)];[57] IR (film): $\tilde{\nu}=3062$, 3030, 2918, 2867, 1953, 1875, 1811, 1605, 1496, 1454, 1363, 1097, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=3.29$–3.36 (m, 3H; H-3′, H-5′, H-6′a), 3.36 (s, 1H; OCH_3), 3.46 (dd, $J=3.4$, 9.7 Hz, 1H; H-2), 3.49 (m, 1H; H-6a), 3.53 (t, $J=8.6$ Hz, 1H; H-6′), 3.59 (m, 1H; H-5), 3.73 (dd, $J=7.4$, 9.7 Hz, 1H; H-2′), 3.79–3.83 (m, 2H; H-3, H-6), 3.88–3.91 (m, 2H; H-4, H-4′), 4.23 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.29 (d, $J=7.4$ Hz, 1H; H-1′), 4.32 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.35 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.52 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.54 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 4.55 (d, $J=3.4$ Hz, 1H; H-1), 4.63 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.66–4.73 (m, 3H; 3×OC*H*Ph), 4.75 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 4.80 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 4.81 (d, $J=11.3$ Hz, 1H; OC*H*Ph), 4.96 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 5.03 (d, $J=10.3$ Hz, 1H; OC*H*Ph), 7.17–7.37 ppm (m, 35H; aromatic).

25: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0 °C, 5 min) employing galactosyl diphenyl phosphate **17** (77.3 mg, 0.10 mmol), alcohol **19** (51.1 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-galactopyranoside (**25**; 80.8 mg, 82%, α/β=87:13) was obtained as a colorless oil from the crude product (101.6 mg) after column chromatography (silica gel 10 g, hexane/AcOEt 5:1). The anomeric α/β ratio of disaccharide **25** was determined by HPLC analysis [eluent, hexane/AcOEt 5:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (α anomer)=17.6 min, t_R (β anomer)=19.6 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (hexane/CH_2Cl_2/acetone 20:20:1). Data for α anomer **25**α: $R_f=0.53$ (hexane/AcOEt 2:1), 0.38 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{22}=+38.8$ ($c=1.00$ in $CHCl_3$); IR (film): $\tilde{\nu}=3062$, 3030, 2925, 1724, 1604, 1496, 1454, 1360, 1207, 1100, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=3.21$ (dd, $J=5.2$, 8.6 Hz, 1H; H-6a), 3.36 (s, 3H; OCH_3), 3.49 (dd, $J=6.3$, 9.7 Hz, 1H; H-4′), 3.54 (t, $J=8.6$ Hz, 1H; H-5), 3.81–3.86 (m, 2H; H-3, H-5′), 3.89–3.93 (m, 3H; H-2, H-3′, H-6′), 4.05 (dd, $J=2.3$ Hz, 1H; H-4), 4.07–4.13 (m, 2H; H-2′, H-6′), 4.20 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.23 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.40 (dd, $J=5.2$, 8.6 Hz, 1H; H-6), 4.54 (d, $J=10.9$ Hz, 1H; OC*H*Ph), 4.60 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.69–4.76 (m, 5H; H-1, 4×OC*H*Ph), 4.80 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.84–4.87 (m, 2H; 2×OC*H*Ph), 4.89 (d, $J=10.9$ Hz, 1H; OC*H*Ph), 4.98 (d, $J=4.0$ Hz, 1H; H-1′), 7.16–7.42 ppm (m, 35H; aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=67.8$, 68.1, 69.2, 69.5, 72.2, 72.6, 72.9, 73.1, 73.3, 74.1, 74.6, 74.9, 75.0, 76.2, 76.5, 77.2, 78.0, 79.5, 98.8, 100.3, 127.2, 127.31, 127.34, 127.39, 127.44, 127.47, 127.52, 127.55, 127.62, 127.8, 128.0, 128.08, 128.11, 128.2, 128.27, 128.32, 138.1, 138.2, 138.6, 138.8, 139.0 ppm; FAB-LRMS: *m/z*: 988 $[M+H]^+$; FAB-HRMS: *m/z* calcd for $C_{62}H_{67}O_{11}$ $[M+H]^+$: 987.4683, found: 987.4692. Data for β anomer **25**β: $R_f=0.53$ (hexane/AcOEt 2:1), 0.30 (hexane/$CHCl_3$/acetone 20:20:1); $[\alpha]_D^{23}=+19.4$ ($c=0.40$ in $CHCl_3$); IR (film): $\tilde{\nu}=3062$, 3030, 2919, 2868, 1725, 1604, 1496, 1454, 1360, 1099, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=3.37$ (s, 3H; OCH_3), 3.40–3.43 (m, 2H; H-6′ab), 3.46 (dd, $J=2.9$, 9.7 Hz, 1H; H-3′), 3.52 (t, $J=9.2$ Hz, 1H; H-5′), 3.64 (dd, $J=6.3$, 10.3 Hz, 1H; H-6a), 3.69 (dd, $J=4.6$, 10.3 Hz, 1H; H-6b), 3.76 (dd, $J=7.4$, 9.7 Hz, 1H; H-2′), 3.85 (d, $J=2.9$ Hz, 1H; H-4′), 3.87–3.93 (m, 3H; H-2, H-3, H-5), 4.27 (m, 1H; H-4), 4.32–4.35 (m, 3H; 3×OC*H*Ph), 4.48 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.55–4.59 (m, 3H; 3×OC*H*Ph), 4.65 (d, $J=3.4$ Hz, 1H; H-1), 4.68–4.70 (m, 2H; 2×OC*H*Ph), 4.73 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 4.74 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.79 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.90 (d, $J=7.4$ Hz, 1H; H-1′), 4.97 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 5.05 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 7.12–7.38 ppm (m, 35H; aromatic); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=68.6$, 69.6, 70.2, 72.1, 73.0, 73.3, 73.4, 73.7, 74.0, 74.49, 74.53, 77.2, 78.7, 79.8, 81.8, 98.7, 102.8, 127.1, 127.28, 127.31, 127.34, 127.36, 127.40, 127.44, 127.5, 127.7, 127.8, 128.07, 128.14, 128.2, 128.3, 128.4, 137.9, 138.56, 138.58, 138.7, 138.9, 139.0, 139.3 ppm; FAB-LRMS: *m/z*: 988 $[M+H]^+$; FAB-HRMS: *m/z* calcd for $C_{62}H_{67}O_{11}$ $[M+H]^+$: 987.4683, found: 987.4675.

26: The glycosidation was performed according to the typical procedure (1 mL dioxane/Et_2O 1:1, 0 °C, 5 min) employing galactosyl diphenyl phosphate **17** (77.3 mg, 0.10 mmol), alcohol **20** (24.0 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.05 mL, 0.005 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of methyl 2,3-*O*-isopropylidene-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-L-rhamnopyranoside[58] (**26**; 67.1 mg, 91%, α/β=87:13) was obtained as a colorless oil from the crude product (169.2 mg) after column chromatography (silica gel 12 g, hexane/AcOEt 5:1). The anomeric α/β ratio of disaccharide **26** was determined by HPLC analysis [eluent, hexane/THF 6:1; flow rate, 0.5 mL min^{-1}; detection, 254 nm; t_R (α anomer)=19.5 min, t_R (β anomer)=20.7 min]. The α- and β-glycosides were separated by flash column chromatography with CH_2Cl_2/AcOEt (50:1). Data for α anomer **26**α: $R_f=0.46$ (hexane/AcOEt 2:1), 0.30 (CH_2Cl_2/AcOEt 30:1); $[\alpha]_D^{21}=+33.3$ ($c=1.06$ in $CHCl_3$); IR (film): $\tilde{\nu}=3064$, 3030, 2986, 2934, 1497, 1454, 1382, 1370, 1243, 1220, 1140, 1094, 1049, 1025, 861, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=1.24$ (s, 3H; CCH_3), 1.29 (d, $J=6.9$ Hz, 3H; H-6), 1.36 (s, 3H; CCH_3), 3.31 (dd, $J=7.4$, 10.3 Hz, 1H; H-4), 3.32 (s, 3H; OCH_3), 3.49 (dd, $J=4.6$, 8.0 Hz, 1H; H-5′), 3.65 (dd, $J=8.0$, 9.2 Hz, 1H; H-6′a), 3.73 (dd, $J=6.9$, 10.3 Hz, 1H; H-5), 3.96 (dd, $J=2.9$, 10.3 Hz, 1H; H-3′), 4.05–4.08 (m, 2H; H-2, H-2′), 4.13 (m, 2H; H-3, H-4′), 4.24 (dd, $J=4.6$, 9.2 Hz, 1H; H-6′b), 4.39 (d, $J=12.0$ Hz, 1H; OC*H*Ph), 4.48 (d, $J=11.5$ Hz, 1H; OC*H*Ph), 4.58 (d, $J=10.9$ Hz, 1H; OC*H*Ph), 4.72 (m, 3H; 3×OC*H*Ph),

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4.82 (s, 1H; H-1), 4.84 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.94–4.96 (m, 2H; H-1′, OC*H*Ph), 7.24–7.38 ppm (m, 20H; aromatic). Data for β anomer **26**β: R_f=0.50 (hexane/AcOEt 2:1), 0.44 (CH_2Cl_2/AcOEt 30:1); $[\alpha]_D^{22}$=−13.1 (c=1.08 in $CHCl_3$); IR (film): $\tilde{\nu}$=3065, 3030, 2983, 2933, 2871, 1496, 1454, 1382, 1369, 1242, 1220, 1138, 1092, 1065, 1022, 861, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.24–1.37 (m, 6H; CCH_3, H-6), 1.44 (s, 3H; CCH_3), 3.37 (s, 3H; OCH_3), 3.51–3.55 (m, 3H; H-3, H-3′, H-6′a), 3.59–3.63 (m, 3H; H-4, H-5, H-4′), 3.73 (dd, J=7.4, 9.7 Hz, 1H; H-2), 3.88 (m, 1H; H-5′), 4.07 (d, J=5.2 Hz, 1H; H-1′), 4.21 (m, 1H; H-2′), 4.38–4.50 (m, 2H; H-6′b, OC*H*Ph), 4.61 (d, J=12.0 Hz, 1H; OC*H*Ph), 4.68–4.76 (m, 3H; 3×OC*H*Ph), 4.81–4.84 (m, 2H; H-1, OC*H*Ph), 4.91 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.94 (d, J=11.5 Hz, 1H; OC*H*Ph), 7.26–7.40 ppm (m, 20H; aromatic).

27: The glycosidation was performed according to the typical procedure (0.5 mL dioxane/Et_2O 1:1, 25 °C, 2 h) employing 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl diphenyl phosphate (**18**; 56.3 mg, 0.10 mmol), alcohol **21** (45.9 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.2 mL, 0.02 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of *N*-(9-fluorenylmethoxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl)-L-serine benzyl ester[59] (**27**; 60.1 mg, 82%, α/β=91:9) was obtained as a colorless oil from the crude product (86.3 mg) after column chromatography (silica gel 10 g, CH_2Cl_2/acetone 20:1). The anomeric α/β ratio of glycoside **27** was determined by HPLC analysis [eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (α anomer)=39.8 min, t_R (β anomer)=76.8 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (toluene/AcOEt 3:1). Data for α anomer **27**α: R_f=0.44 (CH_2Cl_2/acetone 20:1), 0.46 (toluene/AcOEt 3:1); $[\alpha]_D^{22}$=+82.8 (c=1.50 in $CHCl_3$) [lit.: $[\alpha]_D^{21}$=+84 (c=1.0 in $CHCl_3$)];[59c] IR (film): $\tilde{\nu}$=3360, 3032, 2951, 2112, 1751, 1521, 1450, 1371, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.94 (s, 3H; CH_3CO), 2.05 (s, 3H; CH_3CO), 2.13 (s, 3H; CH_3CO), 3.58 (dd, J=3.2, 11.1 Hz, 1H; H-2), 3.96–4.08 (m, 4H; H-5, H-6ab, OC*H*), 4.14 (dd, J=2.8, 11.2 Hz, 1H; OC*H*), 4.22 (br t, J=7.0 Hz, 1H; Fmoc-C*H*), 4.40 (d, J=7.0 Hz, 2H; Fmoc-CH_2), 4.61 (m, 1H; NC*H*), 4.86 (d, J=3.2 Hz, 1H; H-1), 5.21 (d, J=12.1 Hz, 1H; CO_2C*H*Ph), 5.24 (d, J=12.1 Hz, 1H; CO_2C*H*Ph), 5.27 (dd, J=2.6, 11.1 Hz, 1H; H-3), 5.38 (br s, 1H; H-4), 5.95 (d, J=8.0 Hz, 1H; N*H*), 7.28–7.40 (m, 9H; aromatic), 7.61 (m, 2H; aromatic), 7.74 ppm (d, J=7.5 Hz, 2H; aromatic). Data for β anomer **27**β: R_f=0.42 (CH_2Cl_2/acetone 20:1), 0.42 (toluene/AcOEt 3:1); $[\alpha]_D^{21}$=−9.3 (c=0.40 in $CHCl_3$) [lit.: $[\alpha]_D^{22}$=−7.1 (c=1 in $CHCl_3$)];[59a] IR (film): $\tilde{\nu}$=3360, 2951, 2110, 1751, 1521, 1450, 1371, 1228 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.02 (s, 3H; CH_3CO), 2.06 (s, 3H; CH_3CO), 2.16 (s, 3H; CH_3CO), 3.66 (dd, J=8.2, 10.8 Hz, 1H; H-2), 3.76 (dd, J=6.5, 7.0 Hz, 1H; H-5), 3.93 (dd, J=2.9, 10.1 Hz, 1H; OC*H*), 4.09 (dd, J=6.5, 11.1 Hz, 1H; H-6a), 4.12 (dd, J=7.0, 11.1 Hz, 1H; H-6b), 4.23 (dd, J=6.7, 7.4 Hz, 1H; Fmoc-C*H*), 4.32 (d, J=8.2 Hz, 1H; H-1), 4.37 (dd, J=7.4, 10.5 Hz, 1H; Fmoc-C*H*), 4.41–4.44 (m, 2H; OC*H*, Fmoc-C*H*), 4.63 (m, 1H; NC*H*), 4.76 (dd, J=3.2, 10.8 Hz, 1H; H-3), 5.23 (d, J=12.3 Hz, 1H; CO_2C*H*Ph), 5.27 (d, J=12.3 Hz, 1H; CO_2C*H*Ph), 5.32 (d, J=3.2 Hz, 1H; H-4), 5.84 (d, J=8.2 Hz, 1H; N*H*), 7.29–7.41 (m, 9H; aromatic), 7.61 (m, 2H; aromatic), 7.77 ppm (d, J=7.6 Hz, 2H; aromatic).

28: The glycosidation was performed according to the typical procedure (0.5 mL dioxane/Et_2O 1:1, 25 °C, 6 h) employing diphenyl phosphate **18** (56.3 mg, 0.10 mmol), alcohol **22** (47.5 mg, 0.11 mmol), $HClO_4$ (0.1 M in dioxane, 0.2 mL, 0.02 mmol), and pulverized 5-Å M.S. (50 mg). An anomeric mixture of *N*-(9-fluorenylmethoxycarbonyl)-*O*-(3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl)-L-threonine benzyl ester[59a,b] (**28**; 58.2 mg, 78%, α/β=92:8) was obtained as a colorless oil from the crude product (105.6 mg) after column chromatography (silica gel 10 g, CH_2Cl_2/acetone 20:1). The anomeric α/β ratio of glycoside **28** was determined by HPLC analysis [eluent, hexane/THF 6:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (α anomer)=39.7 min, t_R (β anomer)=51.2 min]. The α- and β-glycosides were separated by preparative thin layer chromatography (toluene/AcOEt 3:1). Data for α anomer **28**α: R_f=0.44 (CH_2Cl_2/acetone 20:1), 0.46 (toluene/AcOEt 3:1); $[\alpha]_D^{20}$=+65.1 (c=1.00 in $CHCl_3$) [lit.: $[\alpha]_D^{22}$=+63 (c=1 in $CHCl_3$)];[59a] IR (film): $\tilde{\nu}$=3356, 3032, 2951, 2112, 1751, 1518, 1450, 1371, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.33 (d, J=6.4 Hz, 3H; OCHCH_3), 2.00 (s, 3H; CH_3CO), 2.05 (s, 3H; CH_3CO), 2.12 (s, 3H; CH_3CO), 3.58 (dd, J=3.7, 11.2 Hz, 1H; H-2), 4.06 (d, J=6.5 Hz, 2H; H-6ab), 4.22 (br t, J=6.5 Hz, 1H; H-5), 4.23 (t, J=7.5 Hz, 1H; Fmoc-C*H*), 4.34 (dd, J=7.5, 10.5 Hz, 1H; Fmoc-C*H*), 4.42 (dd, J=7.5, 10.5 Hz, 1H; Fmoc-C*H*), 4.45 (dq, J=1.5, 6.4 Hz, 1H; OC*H*CH_3), 4.49 (dd, J=1.5, 9.5 Hz, 1H; NC*H*), 4.89 (d, J=3.7 Hz, 1H; H-1), 5.18 (d, J=12.2 Hz, 1H; CO_2C*H*Ph), 5.25 (d, J=12.2 Hz, 1H; CO_2C*H*Ph), 5.28 (dd, J=3.1, 11.2 Hz, 1H; H-3), 5.44 (d, J=3.1 Hz, 1H; H-4), 5.74 (d, J=9.5 Hz, 1H; N*H*), 7.27–7.39 (m, 9H; aromatic), 7.61 (d, J=7.4 Hz, 2H; aromatic), 7.74 ppm (d, J=7.6 Hz, 2H; aromatic). Data for β anomer **28**β: R_f=0.43 (CH_2Cl_2/acetone 20:1), 0.43 (toluene/AcOEt 3:1); $[\alpha]_D^{20}$=−17.0 (c=0.68 in $CHCl_3$) [lit.: $[\alpha]_D^{22}$=−14 (c=1 in $CHCl_3$)];[59a] IR (film): $\tilde{\nu}$=3358, 3032, 2951, 2110, 1751, 1518, 1450, 1373, 1230, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.35 (d, J=6.3 Hz, 3H; OCHCH_3), 2.02 (s, 3H; CH_3CO), 2.05 (s, 3H; CH_3CO), 2.13 (s, 3H; CH_3CO), 3.59 (dd, J=6.2, 7.5 Hz, 1H; H-5), 3.63 (dd, J=8.0, 10.9 Hz, 1H; H-2), 4.01 (dd, J=6.2, 11.0 Hz, 1H; H-6a), 4.09 (dd, J=7.5, 11.0 Hz, 1H; H-6b), 4.25 (d, J=7.3 Hz, 1H; Fmoc-C*H*), 4.29 (d, J=8.0 Hz, 1H; H-1), 4.38 (dd, J=7.3, 10.5 Hz, 1H; Fmoc-C*H*), 4.41 (dd, J=7.3, 10.5 Hz, 1H; Fmoc-C*H*), 4.51 (dd, J=1.2, 9.5 Hz, 1H; NC*H*), 4.59 (dq, J=1.2, 6.3 Hz, 1H; OC*H*CH_3), 4.67 (dd, J=3.2, 10.9 Hz, 1H; H-3), 5.19 (d, J=12.3 Hz, 1H; OC*H*Ph), 5.23 (d, J=12.3 Hz, 1H; OC*H*Ph), 5.26 (d, J=3.2 Hz, 1H; H-4), 5.66 (d, J=9.5 Hz, 1H; N*H*), 7.28–7.41 (m, 9H; aromatic), 7.61 (m, 2H; aromatic), 7.76 ppm (d, J=7.7 Hz, 2H; aromatic).

*Synthesis of KRN7000 (**29**)*

31: The glycosidation was performed according to the typical procedure (1 mL dioxane, 25 °C, 5 min) employing diphenyl phosphate **17** (16.2 mg, 0.022 mmol), ceramide **30** (17.5 mg, 0.02 mmol), $HClO_4$ (0.1 M in dioxane, 0.1 mL, 0.01 mmol), and pulverized 5-Å M.S. (20 mg). An anomeric mixture of (2*S*,3*S*,4*R*)-3,4-di-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-2-*N*-hexanoylamino-1,3,4-octadecenetriol[42b] (**31**; 25.0 mg, 92%, α/β=92:8) was obtained as a white solid from the crude product (33.1 mg) after column chromatography (silica gel 6 g, hexane/AcOEt 6:1). The anomeric α/β ratio of galactoside **31** was determined by HPLC analysis [eluent, hexane/AcOEt 5:1; flow rate, 1.5 mL min^{-1}; detection, 254 nm; t_R (α anomer)=8.3 min, t_R (β anomer)=19.8 min]. The α- and β-glycosides were separated flash column chromatography with hexane/AcOEt (7:1). Data for α anomer **31**α: R_f=0.50 (hexane/AcOEt 4:1); m.p. 75.5–76.0 °C [lit.: m.p. 74–75 °C];[42b] $[\alpha]_D^{21}$=+19.1 (c=1.00 in $CHCl_3$) [lit.: $[\alpha]_D^{24}$=+18.8 (c=0.9 in $CHCl_3$)];[42b] IR (KBr): $\tilde{\nu}$=3330, 2920, 2850, 1647, 1532, 1496, 1469, 1454, 1348, 1117, 1060, 736, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.9 Hz, 6H; 2×CH_3), 1.22–1.70 (m, 72H; 36×CH_2), 1.87–2.00 (m, 2H; H-2′ab), 3.39 (dd, J=6.2, 9.0 Hz, 1H; H-6″a), 3.47–3.50 (m, 2H; H-4, H-6″b), 3.72 (dd, J=3.8, 10.9 Hz, 1H; H-1a), 3.85–3.93 (m, 4H; H-3, H-3″, H-4″, H-5″), 3.99–4.05 (m, 2H; H-1b, H-2″), 4.12–4.18 (m, 1H; H-2), 4.35 (d, J=11.8 Hz, 1H; OC*H*Ph), 4.41 (d, J=11.7 Hz, 1H; OC*H*Ph), 4.47 (d, J=11.8 Hz, 1H; OC*H*Ph), 4.51 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.56 (d, J=11.5 Hz, 1H; OC*H*Ph), 4.58 (d, J=11.7 Hz, 1H; OC*H*Ph), 4.63 (d, J=11.7 Hz, 1H; OC*H*Ph), 4.71–4.80 (m, 4H; 4×OC*H*Ph), 4.84 (d, J=3.6 Hz, 1H; H-1″), 4.91 (d, J=11.5 Hz, 1H; OC*H*Ph), 6.18 (d, J=8.3 Hz, 1H; N*H*CO), 7.21–7.37 ppm (m, 30H; aromatic). Data for β anomer **31**β: R_f=0.37 (hexane/AcOEt 4:1); m.p. 53.5–54.5 °C [lit.: m.p. 54–56 °C];[42b] $[\alpha]_D^{21}$=−1.7 (c=0.74 in $CHCl_3$) [lit.: $[\alpha]_D^{22}$=−0.4 (c=1.0 in $CHCl_3$)];[42b] IR (KBr): $\tilde{\nu}$=3433, 3325, 3031, 2919, 1646, 1536, 1468, 1454, 1111, 1072, 733, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.9 Hz, 6H; 2×CH_3), 1.22–1.70 (m, 72H; 36×CH_2), 1.87–2.00 (m, 2H; H-2′ab), 3.41–3.43 (m, 1H; H-4), 3.51–3.53 (m, 3H; H-3″, H-5″, H-6″a), 3.58–3.61 (m, 1H; H-6″b), 3.65 (dd, J=3.2, 10.1 Hz, 1H; H-1a), 3.78–3.84 (m, 2H; H-3, H-2″), 3.94 (d, J=2.4 Hz, 1H; H-4″), 4.14–4.26 (m, 2H; H-1b, H-2), 4.30 (d, J=9.7 Hz, 1H; H-1″), 4.36–4.43 (m, 3H; 3×OC*H*Ph), 4.53–4.62 (m, 3H; 3×OC*H*Ph), 4.69–4.85 (m, 5H; 5×OC*H*Ph), 4.58 (d, J=11.5 Hz, 1H; OC*H*Ph), 5.89 (d, J=8.3 Hz, 1H; N*H*CO), 7.21–7.33 ppm (m, 30H; aromatic).

29 (KRN7000): $Pd(OH)_2$ on carbon (20%, 10 mg) was added to a stirred solution of galactosylceramide **31**α (28.0 mg, 0.02 mmol) in CH_2Cl_2/EtOH (1:3, 3 mL), and the mixture was vigorously stirred under 1 atm of hydrogen for 12 h. The catalyst was filtered through a celite pad, and the filtrate was evaporation in vacuo. Purification by recrystallization (EtOH/H_2O 10:1) afforded (2*S*,3*S*,4*R*)-1-*O*-(α-D-galactopyranosyl)-2-*N*-hexanoyl-

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amino-3,4-octadecenediol[39,42] (KRN7000, **29**; 13.4 mg, 73 %) as a white solid: $R_f = 0.27$ (CH_2Cl_2/MeOH 9:1); m.p. 192–193 °C [lit.: m.p. 189.5–190.5 °C];[39b] $[\alpha]_D^{17} = +43.6$ ($c = 1.04$ in pyridine) [lit.: $[\alpha]_D^{23} = +43.6$ ($c = 1.0$ in pyridine),[39a,b] $[\alpha]_D^{23} = +42.2$ ($c = 0.54$ in pyridine)];[42c] IR (KBr): $\tilde{\nu} =$ 3337, 2919, 2850, 1663, 1539, 1464, 1077 cm^{-1}; ^1H NMR (400 MHz, [D_5]pyridine): $\delta = 0.87$ (t, $J = 6.7$ Hz, 6H; $2 \times CH_3$), 1.25–1.49 (m, 66H; $33 \times CH_2$), 1.66–1.74 (m, 1H; H-6a), 1.77–1.86 (m, 2H; H-3′), 1.87–1.98 (m, 2H; H-5a, H-6b), 2.26–2.24 (m, 1H; H-5b), 2.45 (t, $J = 7.5$ Hz, 2H; H-2′), 4.33–4.35 (m, 2H; H-3, H-4), 4.38–4.47 (m, 4H; H-1a, H-3″, H-5″, H-6″a), 4.52–4.55 (m, 1H; H-6″b), 4.56–4.57 (m, 1H; H-4″), 4.65–4.71 (m, 2H; H-1b, H-2″), 5.29 (m, 1H; H-2), 5.60 (d, $J = 3.9$ Hz, 1H; H-1″), 8.53 ppm (d, $J = 8.4$ Hz, 1H; N*H*CO); ^{13}C NMR (100 MHz, [D_5]pyridine): $\delta = 14.8$, 23.5, 26.9, 27.0, 30.10, 30.13, 30.25, 30.32, 30.37, 30.41, 30.47, 30.50, 30.54, 30.7, 30.9, 32.6, 34.8, 37.3, 51.8, 63.0, 69.0, 70.6, 71.3, 71.9, 72.8, 73.4, 77.0, 101.8 (C1′), 173.2 ppm (NHC=O).

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