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Deactivating Influence of 3-*O*-Glycosyl Substituent on Anomeric Reactivity of Thiomannoside Observed in Oligomannoside Synthesis

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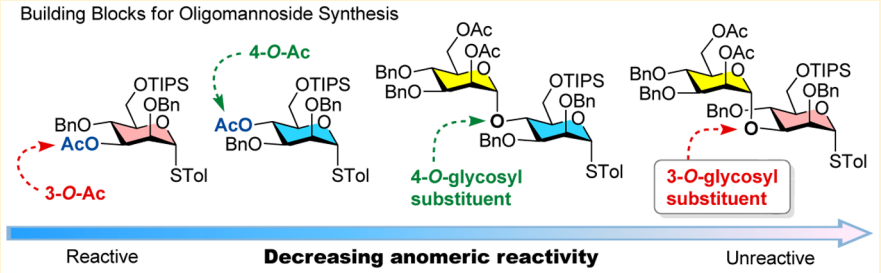
Supporting Information



ABSTRACT: It has been long recognized that, in chemical glycosylation, the anomeric reactivity of glycosyl donor can be influenced greatly by protecting groups. As opposed to the effects of protecting groups, we report herein a finding on how *O*-glycosyl substituent can affect the reactivity of oligosaccharyl donor, which in turn should have impact on convergent assembly of oligosaccharide. During our synthetic efforts toward *Pichia holstii* oligomannoside, a type of α-1,3-linked dimannosyl thioglycosides was found to exhibit unexpected low reactivity toward the activation of NIS/TMSOTf. This observation prompted us to perform a series of comparative reactivity studies, which attributed the donor deactivation to the presence of 3-*O*-glycosyl substituent, by comparison with *O*-acetyl group and *O*-glycosidic linkages at C-4/C-6 positions. To rationalize the unusual phenomenon, we hypothesize that *O*-glycosyl moiety at C-3 could destabilize the oxocarbenium ion intermediate by additionally increasing the O2−C2−C3−O3 torsional strain, which was further supported by DFT calculation of the hypothetical $^4H_3$-like oxocarbeniums. The observed deactivating influence provides a basis for estimation of donor reactivity and logical selection of synthetic strategy in oligosaccharide synthesis. Following this finding, we opted to use an iterative strategy for the synthesis of targeted pentamannoside **1** by using monomeric thiomannosides that ensured sufficient reactivity.

INTRODUCTION

Mammalian and microbial cell surfaces are decorated prominently with carbohydrate structures, which play a pivotal role in regulating various pathological processes, such as tumor angiogenesis and metastasis, virus binding and entry, and bacterial infections.[1] Understanding these processes by means of homogeneous synthetic oligosaccharides could facilitate carbohydrate-based drug and vaccine discovery.[2] However, as distinct from peptides and oligonucleotides that can be routinely synthesized through automated protocols,[3] chemical synthesis of oligosaccharide still remains a unique category in synthetic chemistry with widely acknowledged challenges,[4] despite tremendous advances in new methodology development.[5]

The most prominent difficulties encountered in oligosaccharide synthesis are definitely imparted by the complex and elusive nature of chemical glycosylation, a central reaction forming glycosidic bond. With regard to the mechanism,[6] conventional glycosylations proceed via *trapping of transient intermediate*,[7] an oxacarbenium ion or a covalent adduct derived from the activation of glycosyl donor, by a nucleophilic glycosyl acceptor. As such, chemoselective, regio-, and stereochemical control in a glycosylation often suffers from the exceedingly instable character of the transient intermediate. In particular, failure to catch the highly energized intermediate with an acceptor can result in an array of side reactions, such as elimination, hydrolysis, and aglycon migration.[8] This may turn into a major problem when the anomeric reactivity of glycosyl donor mismatches with the acceptor,[9] making a glycosylation unpredictable in chemoselective outcome. As a result, estimation and tuning of anomeric reactivity by elaborate selection of compatible glycosyl donors emerges to be decisive to the success of glycosylation.

In addition, chemical glycosylations are also challenged by the elusiveness that reactivity, regio-, and stereoselectivity are heavily dependent on the structure of both coupling partners.[10,11] Even a slight structural change in either donor or acceptor may give rise to great difference in reaction outcome, making each glycosylation a unique reaction that needs to be explored. Therefore, oligosaccharide synthesis relies mainly on elaborate design and optimization, custom-tailored

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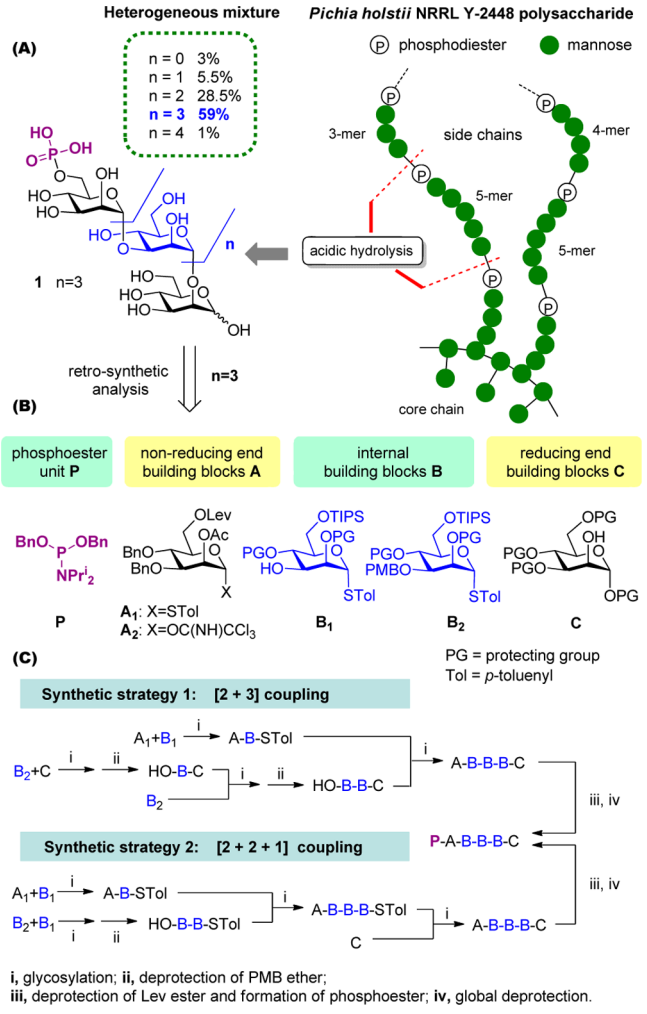
approach, and in particular our deepening insights into how structure can influence the glycosylation outcome.

Over the years, a number of studies have indicated that donor anomeric reactivity is greatly affected by hydroxyl orientation and protecting groups.[11−17] Fraser-Reid first introduced the definition of *armed-disarmed* to describe the phenomenon that 2-*O*-esters can observably reduce donor reactivity by disarming electronic effect, in contrast with electron-donating 2-*O*-ethers.[13] In terms of donor reactivity tuning, Ley developed a set of diacetal groups that confer intermediate reactivity levels by disarming torsional effect and first had relative reactivities expressed in numerical values.[14] As an extensive advancement, Wong's group quantified relative reactivity values (RRVs) to cover a broad range of thioglycosides, allowing for anomeric reactivity-based one-pot glycosylation.[15] The further elevation of donor reactivity levels by neighboring and conformational superarming, as reported by Demchenko[16] and Bols,[17] respectively, have extended beyond the conventional reactivity spectrum and enhanced the flexibility of oligosaccharide assembly. The significance of arming-disarming is also demonstrated in Crich's direct approach to β-mannoside,[18] wherein the stereochemical control originates, in a large part, from the combined electronic and torsional disarming effect of 4,6-*O*-benzylidene group.[19]

As for the synthesis of oligosaccharide by convergent coupling, the glycosyl donors are often oligosaccharide building blocks instead of monomeric ones. Thus, it is a general belief that the donor reactivity involved should be impacted by the *O*-glycosyl moiety appended onto the first sugar residue at reducing end, considering the electron-withdrawing feature of glycosidic linkage. However, in comparison to the extensively studied protecting-group effects, much less attention has been directed toward the one arising from *O*-glycosyl substituent,[15a] as for the widely used oligosaccharyl donors. In our synthetic study of *Pichia holstii* oligomannoside, it was demonstrated that 3-*O*-glycosyl substituent can result in a considerable decrease in anomeric reactivity of thiomannoside due to torsional effect, compared to *O*-acetyl group and glycosidic linkages at C-4/C-6 positions. Herein, we present the studies in details.

Scheme 1. (A) Structure of *Pichia holstii* Y-2448 Polysaccharide and Its Hydrolysates; (B) Building Blocks for the Synthesis of Pentasaccharide 1; (C) Synthetic Strategies for Convergent Assembly of 1



RESULTS AND DISCUSSION

Oligomannoside structures are incorporated in various biologically relevant glycoconjugates, such as high-mannose type *N*-glycans, glycosylphosphatidylinisotol (GPI) anchors, and phosphatidylinositol mannosides (PIMs).[20] Nonetheless, the most abundant source of oligomannoside is the yeast cell wall polysaccharides. As the prime constituent of extracellular polysaccharide from *Pichia holstii* NRRL Y-2448, the side chain domain consists of α-1,2/1,3-oligomannan repeating subunits that are connected via phosphodiester linkages (Scheme 1A).[21] Owing to the microheterogeneity in subunit length (2- to 6-mer), the mild acidic digestion by cleaving the phosphodiester bonds was reported to provide a heterogeneous mixture of phosphorylated oligomannans, ranging from di- to hexasaccharide, with pentasaccharide **1** as the major component (59%).[22] However, isolation of pure pentasaccharide **1** from the complex mixture has not been achieved by size-exclusive chromatography (SEC), and in actual fact, direct sulfation of this oligomannan mixture was utilized to produce a promising antiangiogenic agent PI-88, which remains heterogeneous in both chain length and sulfation patterns.[23] Because of the biological importance of mannose-6-phosphate[24] (M6P) moiety and the pharmaceutical significance of PI-88, we became interested in acquiring phosphorylated pentamannoside **1** in a pure form, by chemical synthesis, for uncovering its potential biological functions.

The phosphorylated and neutral oligomannosides consisting of α-1,2/1,3-linkages are conventionally synthesized by glycosylation with mannosyl imidates, which are sufficiently reactive but lack of shelf-stability, and early stage introduction of *O*-aryl phosphoester that leads to problematic global deprotection.[25] Therefore, it is desirable to synthesize pentasaccharide **1** by mannosyl thioglycosides[26] in combination with late-stage incorporation of dibenzyl phosphoester unit.[27] The upcoming difficulties can be anticipated with the integrated low reactive nature of both mannoside and thioglycoside,[11,20b] which could, however, be overcome by the use of arming protecting groups and strong activation conditions.[28]

Despite different plausible strategies for assembly, e.g., convergent and linear assembly, we envisioned that three common types of monomers could be the starting points: nonreducing end **A**, internal **B**, and reducing end **C**, with appropriate protecting groups (Scheme 1B). Herein, 6-OH of **A** is protected as levulinoyl (Lev) ester that can be selectively removed over acetyl (Ac) groups for late-stage introduction of phosphoester, while 3-OH of **B** can be either free or protected

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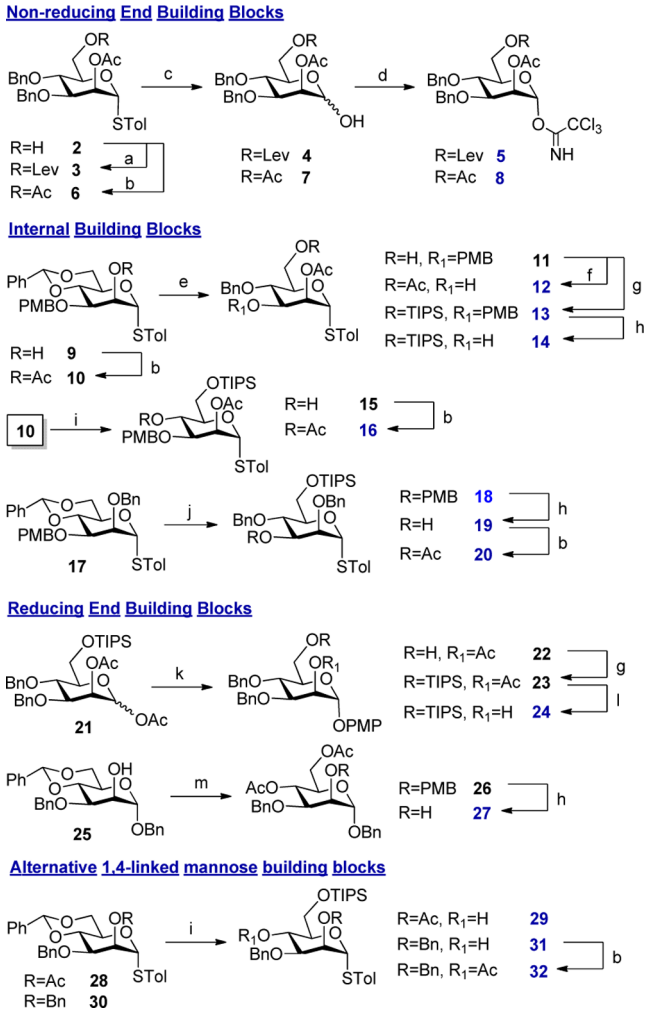
as 4-methoxybenzyl (PMB) ether that serves as a potential elongation position. To enhance the anomeric reactivity, 6-OH of **B** is decorated with an arming triisopropylsilyl (TIPS) ether group.[15d] Accordingly, a set of orthogonally protected monosaccharide building blocks **3**, **5**, **6**, **8**, **12**−**14**, **16**, **18**−**20**, **24**, **27**, **29**, **31**, and **32** were prepared in a conventional manner and the details are outlined in Scheme 2.

Considering the synthetic efficiency, we initially planned to assemble **1** in a convergent fashion by either [2 + 3] or [2 + 2 + 1] strategy (Scheme 1C). The latter could be achieved by reactivity-based[15] or preactivation-based[5c,d] one-pot glycosylation, wherein a disaccharyl thioglycoside can be directly coupled with a 1-thio disaccharide acceptor. To explore the convergent [2 + 3] strategy through a model [2 + 2] coupling, we first synthesized dimannosyl thioglycoside donor **33** and dimeric acceptor **35** (Scheme 3). Thus, the glycosylation of monohydroxy thioglycoside **12** by trichloroacetimidate **5** under the activation of trimethylsilyl triflate (TMSOTf) afforded donor **33** (85%). Disaccharide acceptor **35** was synthesized by the union of thioglycoside **13** with acceptor **24** in the presence of NIS/TMSOTf (79%) and subsequent deprotection of PMB group using DDQ (72%). With these building blocks in hand, we moved forward to the [2 + 2] coupling to probe the anomeric reactivity of **33** (Scheme 3). Unfortunately, thioglycoside **33** was not activated in the presence of NIS/TMSOTf at −10 °C, and therefore no desired tetrasaccharide could be detected. The failure was not surprising at first as we considered that the low reactivity is ascribed to the electronic disarming ability of multiple acetyl (Ac) groups, as evidenced by a productive chemoselective glycosylation of **12** with **18** (86%), wherein the more reactive thioglycoside **18** can be activated over the multiacetylated less reactive thioglycoside **12**. This led to the question if donor reactivity could be elevated by installing a set of electron-rich protective groups. In view of this, we synthesized disaccharyl thioglycoside **36** equipped with benzyl (Bn) and triisopropylsilyl (TIPS) groups,[15d] of which the reactivity was then assessed using NIS/TMSOTf in the presence of 1-thio disaccharide acceptor **38** that is electronically disarmed, giving a basis for the reactivity-based [2 + 2 + 1] assembly. To our surprise, donor **36** emerged to be much less reactive than expected on the basis of arming capacities of Bn and TIPS ether groups, affording tetrasaccharide **39** in a disappointing yield (21%), together with large amount of donor **36** recovered (72%). We became curious whether the anomeric reactivity of **36** was principally governed by *O*-glycosyl substituent situated at C-3^{I} position, rather than protecting groups at other positions.

Hence, we decided to investigate the anomeric reactivity of a range of dimannosyl thioglycoside donors featuring α-1,3-, 1,4-, and 1,6-linkages, respectively. Accordingly, dimeric donors **40**−**46** (Scheme 4) being representative in oligomannoside synthesis were prepared analogously to the synthesis of **33**. The anomeric reactivities were evaluated using the standard NIS/TMSOTf activation system, while monomeric acceptors **52**−**54**[29] (Table 1, chart) were employed to trap the generated oxacarbenium ions. The structures of donors, acceptors, and their coupling products, as well as the results of glycosylations, are summarized in Table 1. To explore the coupling between oligosaccharide fragments, we also synthesized a 3,6-branched Man_3 acceptor **51** as a representative. In details, regioselective ring-opening of dibenzylidine mannoside **47**[29d] by the combination of BH_3·THF/$Cu(OTf)_2$ afforded 3,6-diol **48** (45%).[30] The regiochemistry of resulting *O*-benzyl groups at

Scheme 2. Synthesis of Monomeric Mannose Building Blocks[a]



[a]Reagents and conditions: (a) LevOH, EDCI, DMAP, CH_2Cl_2, 4 Å MS, rt, 12 h; 90% for **3**; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; 91% for **6**; 87% for **10**; 97% for **16**; 94% for **20**; 97% for **32**; (c) NIS, AgOTf, TTBP, CH_2Cl_2, H_2O, 0 °C; 1 h, 71% for **4**; 30 min, 85% for **7**; (d) Cl_3CCN, K_2CO_3, CH_2Cl_2, rt; 8 h, 78% for **5**; 4 h, 62% for **8**; (e) cyanuric chloride, $NaBH_4$, CH_3CN, 0 °C, 20 min, then rt, 9 h; 84% for **11**; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 30 min; DDQ, CH_2Cl_2, pH 7.0 phosphate buffer, 0 °C, 30 min, then rt 2 h; 81% for **12**; (g) TIPSCl, imidazole, CH_2Cl_2, rt, 12 h; 87% for **13**; 95% for **23**; (h) DDQ, CH_2Cl_2, pH 7.0 phosphate buffer, 0 °C, 30 min, then rt 2 h; 83% for **14**; 66% for **19**; 89% for **27**; (i) TsOH, CH_3OH, rt, 12 h; then TIPSCl, imidazole, CH_2Cl_2, rt, 5 h; 85% for **15**; 76% for **29**; 97% for **31**; (j) TsOH, CH_3OH, rt, 12 h; TIPSCl, imidazole, CH_2Cl_2, rt, 8 h; BnBr, NaH, TBAI, THF, rt, 12 h; 96% for **18**; (k) *p*-methoxyphenol, BF_3·OEt_2, CH_2Cl_2, rt, 12 h; 35% for **22** and 37% for **23**; (l) MeONa, CH_3OH, rt; 93% for **24**; (m) PMBCl, NaH, THF, rt, 12 h; 80% HOAc, 50 °C, 4 h; then Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 12 h; 98% for **26**. Abbreviation: EDCI: 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride; DMAP: 4-dimethylaminopyridine; NIS: N-iodosuccinimide; AgOTf: silver triflate; TTBP: 2,4,6-tri-*tert*-butylpyrimidine; DDQ: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; MS: molecular sieves; TsOH: 4-toluenesulfonic acid; PMP: 4-methoxyphenyl.

C-2/C-4 was confirmed by three-bond C−H correlations ($^3J_{C-H}$) observed in HMBC spectrum. Next, mannosyl thioglycosides **3** and **18** were sequentially coupled onto C-6

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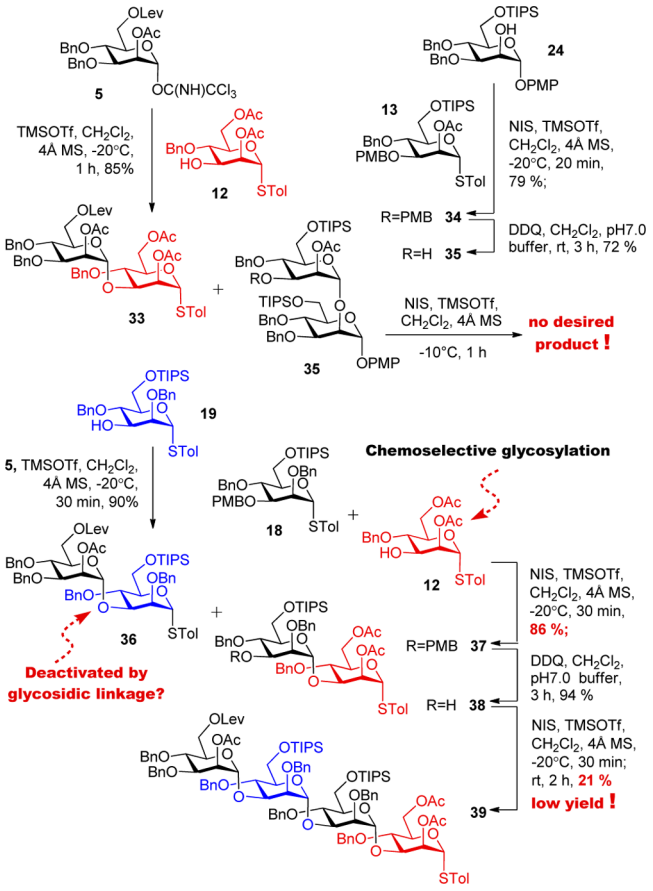
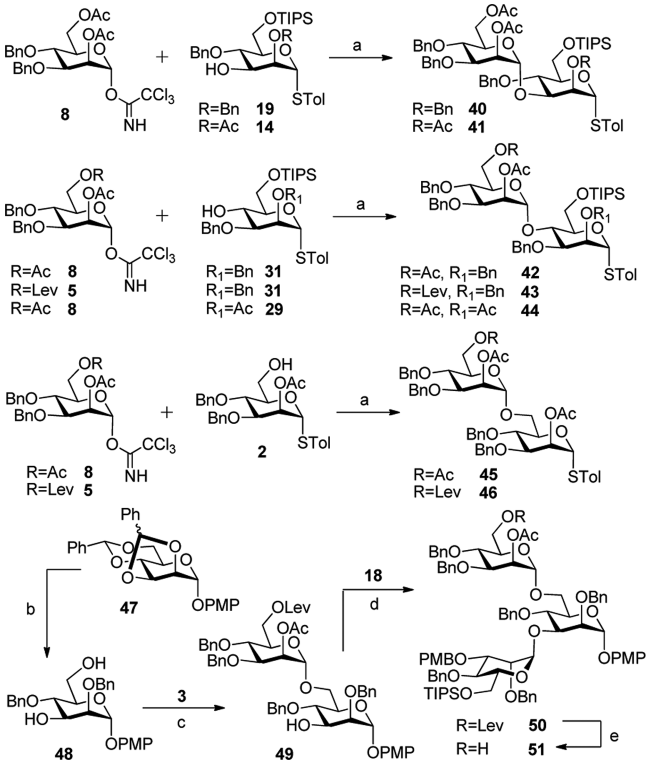
Scheme 3. Investigation of [2 + 2] Coupling and the Problematic Glycosylations with 3-*O*-Glycosylated Thiomannosides



Scheme 4. Synthesis of Disaccharyl Thioglycosides and Acceptor 51[a]



[a]Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 4 Å MS, −20 °C, 30 min; then −20 to 0 °C, 30 min; 89% for **40**; 78% for **41**; 87% for **42**; 73% for **43**; 83% for **44**; 64% for **45**; 77% for **46**; (b) BH_3·THF, $Cu(OTf)_2$, CH_2Cl_2, 0 °C, 30 min; rt, 1h; 45%; (c) NIS, TMSOTf, CH_2Cl_2, 4 Å MS, −20 °C, 20 min; then 0 °C, 10 min; 57%; (d) NIS, TMSOTf, CH_2Cl_2, 4 Å MS, −15 °C, 20 min; 87%; (e) N_2H_4·HOAc (1 M in CH_3OH), CH_2Cl_2, CH_3OH, rt, 2 h; 89%.

and C-3 hydroxyl groups of **48** in a regioselective fashion, giving 3,6-branched trisaccharide **50** in good overall yield. The *O*-Lev ester group on the C-6 branch was then cleaved by N_2H_4·HOAc to deliver acceptor **51** (89%).

The reactivity of thiomannosides having *O*-benzyl group at C-2 position was first examined. When conducting the glycosylation of acceptor **52** with α-1,3-linked disaccharide donor **40** at −15 °C for a duration of 1 h, as anticipated, only 29% yield of trisaccharide **55** was obtained with 58% of donor **40** recovered (Table 1, entry 1). In a great contrast, α-1,4-linked disaccharide donor **42**, decorated by an identical set of protective groups, exhibited a significantly higher reactivity under the same conditions, affording trisaccharide **56** in 92% yield (Table 1, entry 2). Donor **43** behaved similarly in the coupling with acceptor **53**, giving trisaccharide **57** in 72% yield (Table 1, entry 3). These model reactions indicated an obvious difference in the reactivity between α-1,3- and 1,4-linked dimannosyl thioglycosides.

Replacing the *O*-Bn group at C-2 position with electron-withdrawing acetyl (Ac) group was shown to relatively reduce the reactivity. Herein, 2-*O*-benzylated donors **42** and **43** can be activated readily at −15 °C, whereas the activation of 2-OAc counterpart **44** proceeded slowly even at elevated temperatures. Thus, the coupling of α-1,4-linked disaccharide donor **44** and acceptor **54** at room temperature for 10 h provided trisaccharide **58** in a moderate yield of 61% (Table 1, entry 4). Under the same conditions, however, the glycosylation of **54** with α-1,3-linked analogue **41** afforded trisaccharide **59** in only 22% yield, with large majority of donor **41** recovered (80%) (Table 1, entry 5).

The glycosylations using α-1,6-linked disaccharide donors **45** and **46** delivered trisaccharide **60** and branched Man_5 pentasaccharide **61**, respectively, in acceptable yields (Table 1, entry 6−7), indicating that α-1,6-linked dimannosyl thioglycoside was not significantly disarmed and it is therefore compatible for convergent synthesis of oligomannoside. As the reference donor substrates, monomeric thioglycosides **20** and **32**, possessing an acetyl group at O-3 and O-4 position, respectively, were found to be the most reactive in this series, since the rapid activation produced coupling products **62** and **63** in nearly quantitative yields (Table 1, entry 8−9). In addition, most of the glycosylations were highly α-selective including those with 2-*O*-benzylated mannosyl donors, and the newly formed α-mannosidic linkages were confirmed by anomeric C−H coupling constants ($^1J_{C-H}$) (see Experimental Section).

In order to obtain a deep insight into the low reactivity bestowed by 3-*O*-glycosidic linkage, we set out to establish the relative reactivity of **40** with respect to α-1,4-linked counterpart **42** and corresponding 3-OAc/4-OAc substituted monomers **20** and **32** (Table 2). The competition experiments between two glycosyl donors (1.0 eq, each) were performed at −15 °C with the use of limited amount of NIS (1.0 equiv) and catalytic TMSOTf (0.1 equiv) in the presence of excess acceptor **52** (3.0

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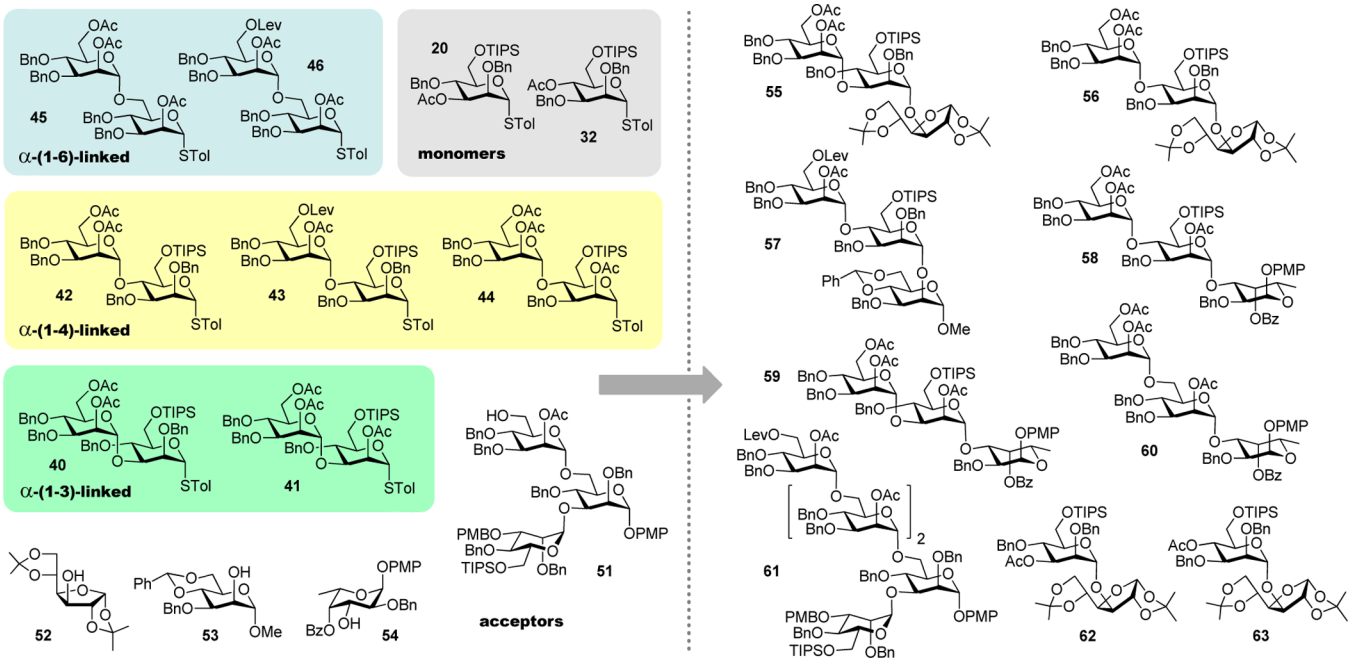
Table 1. Investigation of Glycosylating Properties of Glycosyl Donors 40−46, 20, and 32



entry	donor	acceptor	product	condition	yield (%)[e]	α/β ratio[f]
1	1,3-linked **40**	**52**	**55**	A[a]	29[c]	>20:1
2	1,4-linked **42**	**52**	**56**	A	92	>20:1
3	1,4-linked **43**	**53**	**57**	A	72	7:1
4	1,4-linked **44**	**54**	**58**	B[b]	61	α only
5	1,3-linked **41**	**54**	**59**	B	22[d]	α only
6	1,6-linked **45**	**54**	**60**	A	54	α only
7	1,6-linked **46**	**51**	**61**	A	65	α only
8	monomer **20**	**52**	**62**	A	97	>20:1
9	monomer **32**	**52**	**63**	A	95	>20:1

[a]Glycosylation condition A: Donor (1.2 equiv), acceptor (1.0 equiv), NIS (1.3 equiv), TMSOTf (0.1 equiv), CH_2Cl_2 (9.4 μM for acceptor), 4 Å MS, −15 to 0 °C, 1h. [b]Glycosylation condition B: Donor (1.2 equiv), acceptor (1.0 equiv), NIS (1.3 equiv), TMSOTf (0.1 equiv), CH_2Cl_2 (9.4 μM for acceptor), 4 Å MS, rt, 10 h. [c]58% of donor was recovered. [d]80% of donor was recovered. [e]Isolated yields of pure major anomers. [f]Anomeric ratios were determined by crude ^{1}H NMR or preparative isolation.

equiv).[31,12,14,16,17] The reaction results are summarized in Table 2, wherein the product ratios can reflect the relative reactivity between the two donors surveyed, although the virtual differences might be even larger due to concentration changing during the reactions. α-(1−3)-linked **40** was found to be the least reactive, and the reactivities of the donors surveyed followed the order of **20** > **32** > **42** > **40**. As compared to the corresponding *O*-acetylated monomers, α-1,4-linkage caused only a slight reactivity decrease by a factor of 61/39 (Table 2, entry 2), while α-1,3-linkage showed a larger magnitude of disarming effect with a factor of 87/13 (Table 2, entry 4). Moreover, electron-withdrawing acetyl substituent at C-3 was found to have less deactivating power than the one at C-4 (Table 2, entry 3), being consistent with the trend observed in mannose series by Ley,[14] whereas the *O*-glycosyl substituent at C-3 has more disarming capacity than α-1,4-linkage (Table 2, entry 1). This unusual observation was the first indication that the effect of *O*-glycosidic linkage on donor reactivity may not be limited to electronics.

On the basis of the observations above, we hypothesize that the low reactivity results from the disarming torsional effect of 3-*O*-glycosdic linkage, which can be explained by considering the O2−C2−C3−O3 torsional interaction during donor activation for mannose system.[32] As a general mechanism, the activation of thiomannoside using NIS/TMSOTf initiates with iodination of anomeric sulfide to form iodonium sulfide[33] intermediate **A** without altering $^4C_1$ conformation (Scheme 5), followed by dissociation of C−S bond to access oxacarbenium ion intermediate **B** in a $^4H_3$ conformation,[34] with the latter step being rate-determining for the glycosylation.[6b] In the course of dissociation, the O2−C2−C3−O3 torsional angle is forced to be compressed from 60° to 45° due to required conformational change, leading to the increase of torsional interaction between O2−C2 and O3−C3 bonds. When the thiomannoside is 3-*O*-glycosylated as for a disaccharyl donor, the 3-*O*-glycosyl substituent should be much more sterically hindered than a simple protecting group and could thereby additionally enhance the torsional strain. As such, the resulting oxacarbenium ion intermediate and the related transition state would be relatively destabilized, thus slowing down the donor activation step.

To further rationalize the mechanistic proposal, we assessed the stabilities of putative oxacarbenium ion intermediates by computational studies. Thus, the geometries of two representative oxacarbenium ions **E** and **F** (Scheme 5), adopting a preferred $^4H_3$-like conformation, were optimized using DFT calculations. The 3-*O*-glycosylated oxacarbenium ion **E** was

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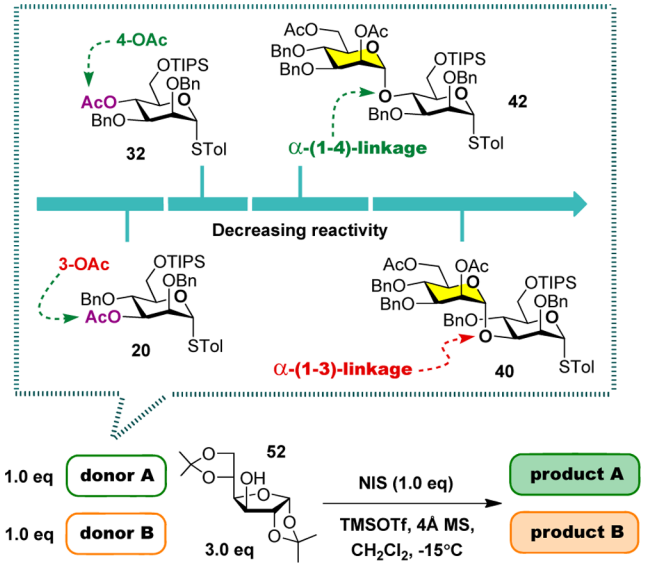
Table 2. Competition Experiments in Glycosylation of Acceptor 52



entry	donor A	donor B	product ratio[c] (for A/B)	yield[d] (%)
1[a]	**42**	**40**	69/31	87
2[b]	**32**	**42**	61/39	70
3[b]	**20**	**32**	61/39	73
4[b]	**20**	**40**	87/13	67

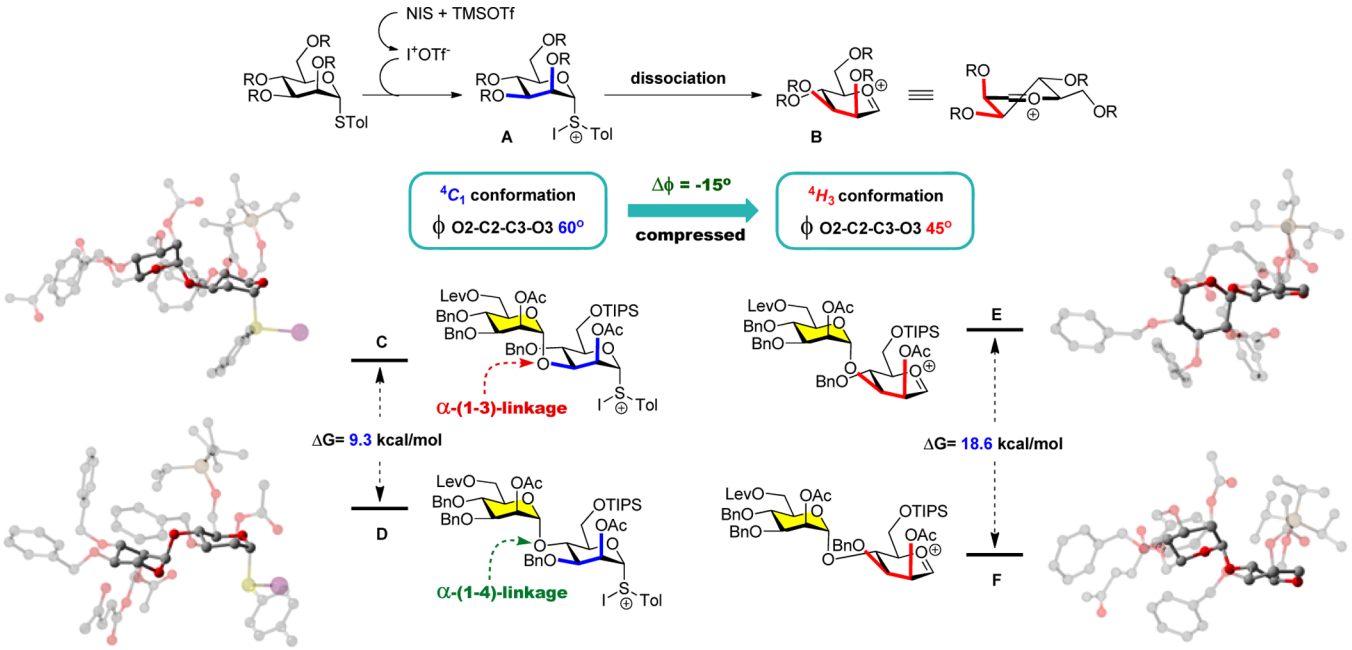
[a]Competition reaction condition: donor A (1.0 equiv), donor B (1.0 equiv), acceptor (3.0 equiv), NIS (1.0 equiv), TMSOTf (0.1 equiv), CH_2Cl_2 (9.4 μM for one donor), 4 Å MS, −15 °C, 2 h. [b]Reaction time: 1 h. [c]Product ratios were determined by ^{1}H NMR of crude reaction mixture. [d]Combined yields of two coupling products were determined by ^{1}H NMR of reaction mixture.

found to be energetically higher (18.6 kcal/mol in CH_2Cl_2) than the 4-*O*-glycosylated counterpart **F**. As a reference, the energy difference between the corresponding iodonium sulfides **C** and **D** was also calculated, and it was apparently smaller (9.3 kcal/mol in CH_2Cl_2). In principle, the results of theoretical studies supported the mechanistic proposal pertaining to the disarming torsional effect.

Having established an understanding of how anomeric reactivity of thiomannoside is affected by 3-*O*-glycosidic linkage, we retrospected a number of synthetic achievements of mannoside-containing glycans, most of which are constructed by linear assembly using more reactive mannosyl imidates.[35] In some cases of convergent assembly, thioglycoside that serves, at the early stage, as anomeric protection for an oligomannan fragment has to be converted into an imidate donor for higher reactivity.[36] The limited glycosylating capacity of oligomannosyl thioglycoside may result from the inherent low reactivity level of both mannoside and thioglycoside structures as mentioned above.[11,20b] Herein, the observed deactivating influence of 3-*O*-glycosyl substituent on thiomannosides would provide more insights into qualitative estimation of donor reactivity and logical selection of donors and synthetic strategies, in the hope of achieving optimal synthesis of oligosaccharide.

Although the unreactive problem could be eliminated by using harsh conditions and specific strong promoters,[28] it is still preferable to utilize general and facile approaches, especially when a pharmaceutically valuable oligosaccharide is targeted. In consideration of the unreactive 3-*O*-glycosylated thiomannoside, we opted to an iterative coupling strategy for the synthesis of pentasaccharide **1** (Scheme 6), wherein chain elongation could be initiated at reducing end acceptor **27** by the glycosylation with monomeric thioglycoside **13** or alternative **16**, followed by nonreducing end donor **3**, ensuring donor reactivity and efficiency for each glycosylation. Next, the

Scheme 5. Mechanistic Hypothesis and Results of DFT Calculations[a]



[a]3D structures of **C**, **D**, **E**, and **F** were obtained by DFT geometrical optimization. For the sake of clarity, hydrogen atoms have been omitted and pyranosyl rings are highlighted. Gibbs free energy differences (ΔG) are calculated in consideration of solvation in CH_2Cl_2.

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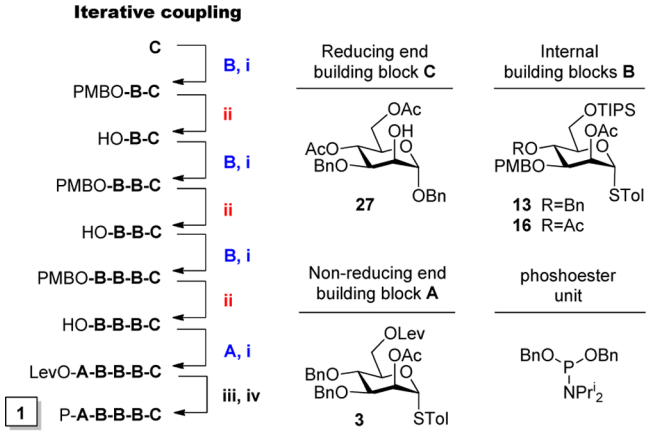
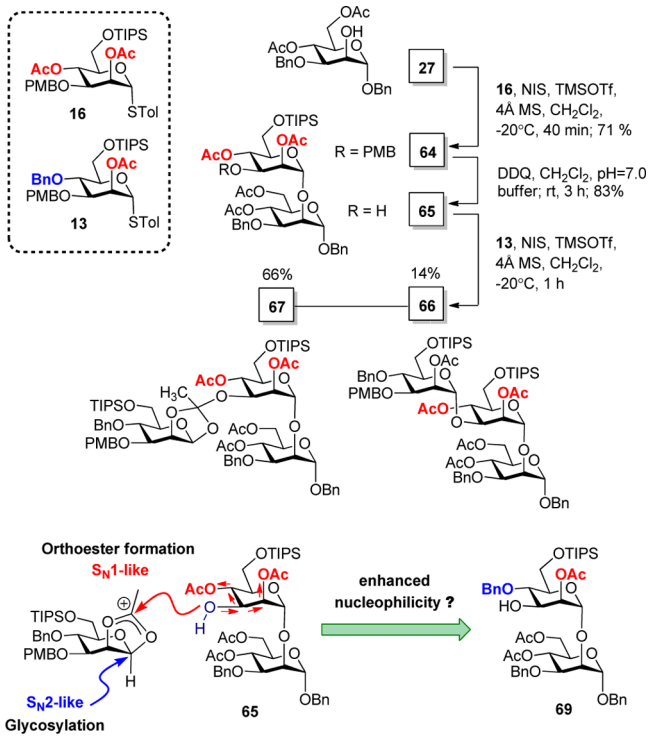
Scheme 6. Iterative Strategy for the Synthesis of 1



resulting pentamannoside can be capped by phosphoester unit before global deprotection. Since the pentasaccharide **1** consists of internal repeating [→3)-α-D-mannose-(1→] units, the elongation could be achieved by three iterations of a unified glycosylation-deprotection procedure. In addition, the linear assembly approach could be a basis for the solid-phase synthesis[5f] and would enable the divergent synthesis of the congeners, e.g., hexa-, tetra-, tri, and disaccharide, by altering the number of iterations. Also, late-stage introduction of phosphoester unit provides flexibility for the synthesis of both phosphorylated and neutral oligomannosides.

Thus, the synthetic study of pentasaccharide **1** was continued, commencing with the glycosylation of reducing end acceptor **27** by thioglycoside **16** (Scheme 7). The reaction

Scheme 7. Orthoester Formation Side Reaction



proceeded in the presence of NIS/TMSOTf at −20 °C to provide disaccharide **64** (71%). Then, PMB ether group was removed by DDQ oxidation to give disaccharide acceptor **65** (83%). When the alternative donor **13** was coupled onto disaccharide acceptor **65** under the activation of NIS/TMSOTf at −20 °C, the major adduct obtained was found to be orthoester **67** (66%),[37] as confirmed by an upfield-shifting CH_3 at 1.69 ppm in ^{1}H NMR, along with the desired trisaccharide **66** as a minor product (14%). Raising the amount of TMSOTf was not able to promote rearrangement of orthoester to trisaccharide, resulting in degradation instead. Herein, the undesired orthoester formation may be originated from the poor nucleophilicity of C-3^{II} hydroxyl group, in acceptor **65**, caused by adjacent electron-withdrawing acetyl groups. In general, a poor nucleophile preferentially undergoes S_N1-like orthoester formation, while the desired glycosylation via S_N2-like process demands a more nucleophilic acceptor. To suppress this side reaction, *O*-acetyl group at C-4^{II} was switched to *O*-benzyl group, as in the use of disaccharide acceptor **69** (Scheme 8), and the modification has proven able to give desired trisaccharide **70** in 72% yield.

As an optimal internal building block, thiomannoside **13** was eventually selected for the synthesis of **1** (Scheme 8). Starting from reducing end monomer **27**, the first iteration was achieved through glycosylation with **13** (92%) under standard condition **A** and subsequent deprotection of PMB ether group (81%) by standard condition **B**, providing disaccharide acceptor **69**. After the second and third iteration of the unified glycosylation-deprotection procedure, the resulting tetrasaccharide acceptor **73** was glycosylated by nonreducing end donor **3** to afford fully protected pentasaccharide **74** (72%) in high overall yield with exclusive formation of all α-glycosidic bonds, which was confirmed by the anomeric C−H coupling constants ($^1J_{C-H}$) with values between 173.6 and 175.8 Hz, acquired from coupled-HSQC spectra.[38]

Finally, selective removal of *O*-Lev ester group at C-6^V position of **74** by treatment with N_2H_4·HOAc provided corresponding alcohol **75** (90%). Next, phosphitylation of **75** by dibenzyl *N*,*N*-diisopropylphosphoramidite and subsequent *m*-CPBA oxidation,[27] in one-port, afforded 6^V-*O*-phosphoester **76** (98%, 2 steps), which was subjected to cleavage of acetyl ester groups under Zemplén condition,[39] followed by deprotection of TIPS ether groups in the presence of TBAF and HOAc, providing nona-alcohol **77** (95%, 2 steps). As for final benzyl deprotection, we interestingly found that hydrogenolysis of **77** over $Pd(OH)_2/C$ in CH_3OH/H_2O proceeded with partial over-reduction of the reducing end hemiacetal to mannitol **78**,[40] as indicated by a $[M - H]^-$ ion at *m*/*z* 909.2443 in HRESIMS analysis. Using greater excess amount of $Pd(OH)_2/C$ in conjuction with extended reaction time provided a quantitative yield of mannitol **78**, of which the structure was confirmed by the loss of one anomeric $^1J_{C-H}$ correlation in HSQC spectrum. Finally, global debenzylation of **77** was performed using Pd/C as catalyst without over-reduction, and subsequent SEC purification on a Sephadex G-25 column afforded the targeted pentamannoside **1** in a quantitative yield.

The chemical structure of **1** was unambiguously determined on the basis of 2D-NMR techniques, including gCOSY, multiplicity edited-HSQC, HMBC, HSQC-TOCSY, coupled-HSQC, and ROESY.[41] In addition, the major reducing end α-anomer of **1** was found to coexist in equilibrium with the minor β-anomer in an approximate ratio of 7:1 (in D_2O). As

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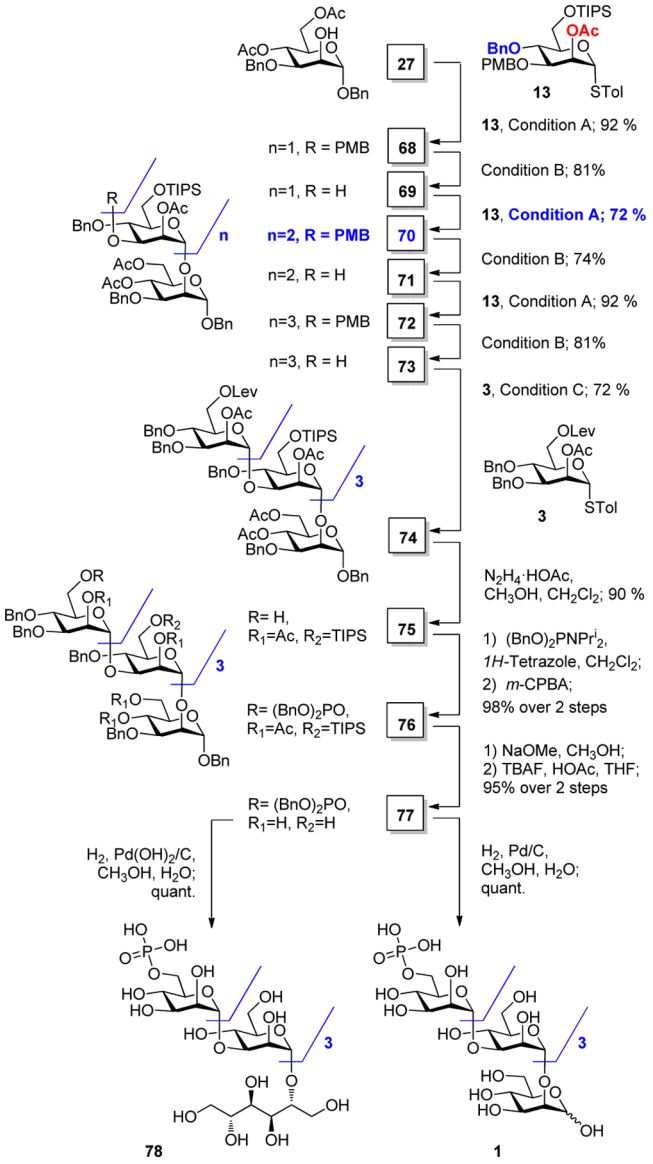
Scheme 8. Synthesis of Pentasaccharide 1[a]



[a]Condition A: NIS, TMSOTf, CH_2Cl_2, 4 Å MS, −20 °C, 40 min. Condition B: DDQ, CH_2Cl_2, pH 7.0 phosphate buffer, 0 °C, 30 min, then rt 3 h. Condition C: NIS, TMSOTf, CH_2Cl_2, 4 Å MS, −20 °C, 1 h; then 0 °C, 20 min. Abbreviation: TBAF: tetra-*n*-butylammonium fluoride; *m*-CPBA: meta-chloroperoxybenzoic acid.

illustrated in Figure 1B, HSQC clearly exhibited five anomeric signals for the major all-α-configured pentasaccharide, along with a weak cross peak corresponding to the minor β-anomer at the reducing end. Stereochemistry of the β-anomer was assigned by a characteristic $^1J_{C-H}$ value (160.7 Hz) from coupled-HSQC spectrum (Figure 1A), while all α-mannosidic bonds gave rise to larger $^1J_{C-H}$ values ranging from 173.3 to 175.0 Hz.

In conclusion, it has been demonstrated that the presence of 3-*O*-glycosyl substituent can reduce the anomeric reactivity of thiomannoside donor in NIS/TMSOTf-promoted glycosylation, in comparison with electron-withdrawing *O*-acetyl group and *O*-glycosyl substituents situated at C-4/C-6 positions by means of comparative glycosylations and competition experiments. Thus, we hypothesize that 3-*O*-glycosyl substituent could relatively disfavor the formation of oxocarbenium ion by

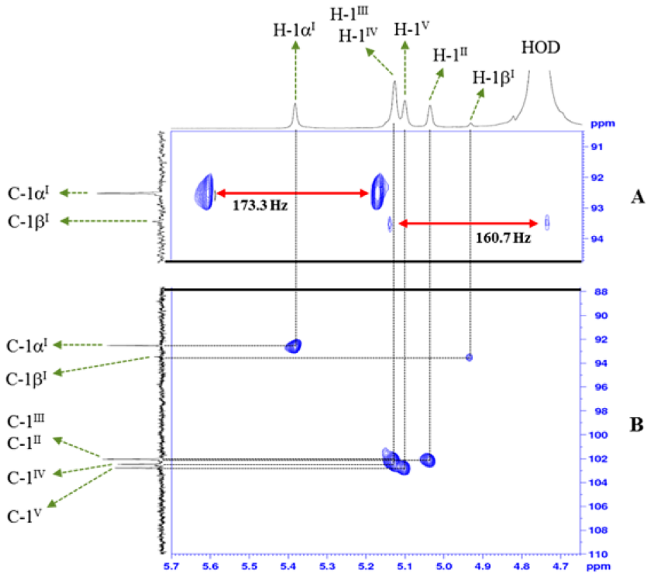


Figure 1. Anomeric region expansion of coupled-HSQC (A) and HSQC (B) spectra for pentasaccharide **1** in D_2O (300 K). To designate resonances, sugar residues were numbered with Roman numerals I, II, III, etc. beginning at the reducing end.

additionally increasing the O2−C2−C3−O3 torsional interaction during donor activation, thereby deactivating the corresponding thioglycoside donors. To verify the mechanistic discussion, DFT calculations of the hypothetical oxocarbenium ion intermediates were performed, indicating the increase in energy by virtue of 3-*O*-glycosyl substituent. This deactivating influence would be a basis for preliminary estimation of donor reactivity and logical selection of donor and synthetic strategy in oligosaccharide synthesis. Herein, we also report the chemical synthesis of phosphorylated pentamannoside **1** from *Pichia holstii* extracellular polysaccharide. In view of the low glycosylating capacity of 3-*O*-glycosylated thiomannoside donors, we opted to use an iterative strategy to access the targeted pentamannoside **1** efficiently in a good overall yield.

EXPERIMENTAL SECTION

General Information. ^1H, ^{13}C, and 2D NMR spectra were recorded on a 400 MHz spectrometer with operating frequencies of 400 MHz for ^1H and 100 MHz for ^{13}C, while probe temperature was kept at 300 K during all experiments. Chemical shifts are reported in ppm and calibrated using tetramethylsilane (0.00 ppm for ^1H in $CDCl_3$), HOD (4.76 ppm for ^1H in D_2O at 300 K), and $CDCl_3$ (77.0 ppm for ^{13}C) as standards. Coupling constants (J) were obtained from analysis of 1D-spectra and reported in hertz (Hz). The multiplicities are reported using abbreviations: singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), quartet of doublet (qd), multiplet (m), and quartet of AB system (ABq). The chemical shifts for ^1H and ^{13}C resonances that are either missing or overlapping were determined on the basis of edited-HSQC and HMBC spectra. The anomeric C−H coupling constants ($J_{C1/H1}$) were measured by coupled-HSQC experiments, or alternatively using standard pulse programs, including HMBCGPND (hmbcgpndqf) and HSQC-HECADE[42] (hsqcdietgpjcndsisp).

*p-Tolyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-1-thio-α-D-mannopyranoside (**3**).* To a solution of known **2**[36g] (403 mg, 0.79 mmol) in CH_2Cl_2 (10 mL) were added 4 Å MS (500 mg), EDCI (304 mg, 1.58 mmol), DMAP (97 mg, 0.79 mmol) and LevOH (184 mg, 1.58 mmol) under nitrogen at room temperature. After stirring for 12 h, the mixture was filtered and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash

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chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/5/1−1/3/1) provided **3** (431 mg, 90%) as a syrup. $[\alpha]_D^{25}$ + 96.1 (*c* 0.22, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 12H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.59 (dd, *J* = 3.2, 1.7 Hz, 1H), 5.40 (d, *J* = 1.6 Hz, 1H), 4.92 and 4.58 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.72 and 4.56 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.42−4.35 (m, 2H), 4.30 (dd, *J* = 14.2, 4.9 Hz, 1H), 3.95 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.78 (dd, *J* = 9.2, 9.2 Hz, 1H), 2.78−2.67 (m, 2H), 2.59−2.52 (m, 2H), 2.32 (s, 3H), 2.16 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 172.5, 170.2, 138.2, 138.0, 137.5, 132.5, 129.9, 129.5, 128.51, 128.46, 128.2, 128.1, 128.0, 127.9, 86.4, 78.4, 75.3, 74.4, 71.9, 70.6, 70.1, 63.5, 37.9, 29.8, 27.8, 21.11, 21.03. HRMS (ESI-TOF) *m*/*z* calcd for $C_{34}H_{38}O_8NaS$ $[M + Na]^+$ 629.2185, found 629.2162.

*2-O-Acetyl-3,4-di-O-benzyl-6-O-levulinoyl-D-mannopyranose (**4**).* To a solution of **3** (325 mg, 0.54 mmol) in wet CH_2Cl_2 (7 mL) was added TTBP (266 mg, 1.07 mmol), and the mixture was stirred for 30 min at 0 °C. NIS (717 mg, 3.19 mmol) and AgOTf (82 mg, 0.32 mmol) were added and the reaction was kept at 0 °C for 1 h. The reaction was quenched with $NaHCO_3$ (sat. aq.) and $Na_2S_2O_3$ (sat. aq.) and then diluted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/4/1−1/1/1) provided compound **4** (190 mg, 71%, anomeric mixture, α/β = 6/1) as a syrup. $[\alpha]_D^{25}$ + 44.4 (*c* 0.334, CH_2Cl_2). HRMS (ESI-TOF) *m*/*z* calcd for $C_{27}H_{32}O_9Na$ $[M + Na]^+$ 523.1944, found 523.1945. Data for **4α**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 10H), 5.40 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.20 (dd, *J* = 2.6, 2.0 Hz, 1H), 4.91 and 4.57 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.71 and 4.54 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.43 (dd, *J* = 11.6, 2.1 Hz, 1H), 4.25 (dd, *J* = 11.7, 6.4 Hz, 1H), 4.10 (ddd, *J* = 9.8, 6.4, 2.0 Hz, 1H), 4.06 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.69 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.43 (d, *J* = 3.3 Hz, 1H), 2.79−2.74 (m, 2H), 2.63−2.55 (m, 2H), 2.18 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 172.5, 170.5, 138.1, 137.8, 128.4, 128.12, 128.07, 127.8, 92.5, 77.6, 75.1, 74.4, 71.8, 69.6, 69.0, 63.7, 38.1, 29.9, 28.0, 21.1. HMBCGPND anomeric C−H correlation (400 MHz, $CDCl_3$) δ 5.20/92.5 ($J_{C1/H1}$ = 172.1 Hz).

*2-O-Acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl trichloroacetimidate (**5**).* To a solution of **4** (181 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (5 mL) were added Cl_3CCN (0.109 mL, 1.1 mmol) and K_2CO_3 (100 mg, 0.72 mmol) at room temperature. After stirring for 8 h, the mixture was filtered and concentrated in vacuo. Flash chromatography on triethylamine-deactivated silica gel (EtOAc/hexanes/CH_2Cl_2, 1/5/1−1/3/1, 1% Et_3N) afforded **5** (181 mg, 78%) as a syrup. ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.38−7.27 (m, 10H), 6.24 (d, *J* = 1.9 Hz, 1H), 5.49 (dd, *J* = 3.2, 2.1 Hz, 1H), 4.92 and 4.59 (ABq, J_{AB} = 10.6 Hz, 2H, CH_2Ar), 4.75 and 4.59 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.40−4.29 (m, 2H), 4.04 (dd, *J* = 9.4, 3.2 Hz, 1H), 4.01 (dd, *J* = 4.1, 2.5 Hz, 1H), 3.85 (dd, *J* = 9.7, 9.7 Hz, 1H), 2.79−2.71 (m, 2H), 2.62−2.56 (m, 2H), 2.21 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 172.4, 170.0, 159.9, 137.7, 137.3, 128.5, 128.4, 128.3, 128.1, 95.0, 90.7, 77.3, 75.5, 73.4, 72.4, 72.0, 67.2, 63.0, 37.9, 29.9, 27.8, 21.0. Coupled-HSQC anomeric correlation (400 MHz, $CDCl_3$) δ 6.24/95.0 ($J_{C1/H1}$ = 178.3 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{29}H_{32}Cl_3NO_9Na$ $[M + Na]^+$ 666.1040, found 666.1014.

*p-Tolyl 2,6-O-diacetyl-3,4-di-O-benzyl-1-thio-α-D-mannopyranoside (**6**).* To a solution of **2** (912 mg, 1.80 mmol), Et_3N (8.6 mL, 62 mmol) and DMAP (126 mg, 1.04 mmol) in CH_2Cl_2 (15 mL) was added Ac_2O (1.96 mL, 20.7 mmol) dropwise under nitrogen at room temperature. After stirring for 1 h, the mixture was treated with $NaHCO_3$ (sat. aq.). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/30/1−1/4/1) provided **6** (893 mg, 91%) as a syrup. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 12H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.59 (dd, *J* = 3.2, 1.7 Hz, 1H), 5.40 (d, *J* = 1.5 Hz, 1H), 4.92 and 4.57 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.73 and 4.56 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.44−4.37 (m, 1H), 4.35 (dd, *J* = 11.6, 5.5 Hz, 1H), 4.30 (dd, *J* = 11.6, 2.1 Hz, 1H), 3.96 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.78 (dd, *J* = 9.4, 9.4 Hz, 1H), 2.32 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.7, 170.2, 138.2, 137.9, 137.4, 132.6, 129.9, 129.4, 128.53, 128.48, 128.2, 128.1, 128.0, 127.9, 86.4, 78.4, 75.3, 74.4, 71.9, 70.6, 70.0, 63.4, 21.1, 21.0, 20.8. HRMS (ESI-TOF) *m*/*z* calcd for $C_{31}H_{34}O_7NaS$ $[M + Na]^+$ 573.1923, found 573.1951.

*2,6-O-Diacetyl-3,4-di-O-benzyl-D-mannopyranose (**7**).* To a solution of **6** (877 mg, 1.59 mmol) and TTBP (396 mg, 1.59 mmol) in CH_2Cl_2/H_2O (v/v 20/1, 10 mL) at 0 °C were added NIS (717 mg, 3.19 mmol) and then AgOTf (82 mg, 0.32 mmol). After stirring at 0 °C for 30 min, the mixture was quenched with $NaHCO_3$ (sat. aq.)/$Na_2S_2O_3$ (sat. aq.). The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/2/1) provided compound **7** (604 mg, 85%, anomeric mixture, α/β = 10/1) as a syrup. Data of **7α**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 10H), 5.38 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.21 (dd, *J* = 3.9, 1.8 Hz, 1H), 4.91 and 4.57 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.71 and 4.55 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.36 (dd, *J* = 11.9, 2.3 Hz, 1H), 4.29 (dd, *J* = 11.9, 5.0 Hz, 1H), 4.11−4.04 (m, 1H), 4.07 (dd, *J* = 9.3, 3.4 Hz, 1H), 3.74 (dd, *J* = 9.6 Hz, 1H), 3.14 (d, *J* = 4.0 Hz, 1H), 2.15 (s, 3H), 2.06 (s, 3H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 138.0, 137.7, 128.46, 128.45, 128.13, 128.05, 127.9, 92.5, 77.5, 75.2, 74.1, 71.8, 69.8, 68.9, 63.5, 21.1, 20.9. Coupled-HSQC anomeric C−H correlation (400 MHz, $CDCl_3$) δ 5.21/92.5 ($J_{C1/H1}$ = 174.5 Hz). The analytical data were in agreement with the reported spectra.[43]

*2,6-O-Diacetyl-3,4-di-O-benzyl-α-D-mannopyranosyl trichloroacetimidate (**8**).* To a solution of hemiacetal **7** (300 mg, 0.67 mmol) in anhydrous CH_2Cl_2 (5 mL) were added Cl_3CCN (0.21 mL, 2.0 mmol) and K_2CO_3 (187 mg, 1.3 mmol) at room temperature. After stirring for 4 h, the mixture was filtered and concentrated. Flash chromatography on triethylamine deactivated silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/6/1, with 1% Et_3N) afforded **8** (245 mg, 62%) as a syrup. ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.39−7.27 (m, 10H), 6.25 (d, *J* = 1.9 Hz, 1H), 5.50 (dd, *J* = 3.3, 2.1 Hz, 1H), 4.92 and 4.58 (ABq, J_{AB} = 10.7 Hz, 2H, CH_2Ar), 4.74 and 4.58 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.35 (dd, *J* = 12.1, 2.4 Hz, 1H), 4.30 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.05 (dd, *J* = 9.4, 3.3 Hz, 1H), 4.05−3.99 (m, 1H), 3.85 (dd, *J* = 9.7, 9.7 Hz, 1H), 2.20 (s, 3H), 2.04 (s, 3H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 170.7, 170.0, 159.9, 137.7, 137.3, 128.5, 128.4, 128.3, 128.1, 95.0, 90.7, 77.3, 75.5, 73.4, 72.4, 72.1, 67.1, 62.9, 20.9, 20.8. Coupled-HSQC anomeric C−H correlation (400 MHz, $CDCl_3$) δ 6.25/95.0 ($J_{C1/H1}$ = 182.5 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{28}NO_8NaCl_3$ $[M + Na]^+$ 610.0778, found 610.0771.

*p-Tolyl 2-O-acetyl-4,6-O-benzylidene-3-O-(4-methoxylbenzyl)-1-thio-α-D-mannopyranoside (**10**).* To a solution of known **9**[44] (1.314 g, 2.66 mmol), Et_3N (4.4 mL, 32 mmol) and DMAP (32 mg, 0.27 mmol) in CH_2Cl_2 (15 mL) was added Ac_2O (1.26 mL, 13.3 mmol) dropwise at room temperature. After stirring for 1 h, the mixture was treated with $NaHCO_3$ (sat. aq.) and diluted with DCM. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) provided **10** (1.24 g, 87%) as a syrup. $[\alpha]_D^{25}$ + 69.9 (*c* 0.102, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.47 (m, 2H), 7.43−7.36 (m, 3H), 7.36−7.32 (m, 2H), 7.31−7.26 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.91−6.78 (m, 2H), 5.63 (s, 1H), 5.59 (dd, *J* = 3.4, 1.4 Hz, 1H), 5.37 (d, *J* = 1.2 Hz, 1H), 4.66 and 4.60 (ABq, J_{AB} = 11.6 Hz, 2H, CH_2Ar), 4.36 (ddd, *J* = 9.8, 9.8, 4.8 Hz, 1H), 4.22 (dd, *J* = 10.3, 4.8 Hz, 1H), 4.11 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.99 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.84 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.80 (s, 3H), 2.33 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 159.4, 138.4, 137.4, 132.7, 130.0, 129.7, 129.5, 129.2, 129.0, 128.2, 126.1, 113.8, 101.6, 87.5, 78.5, 73.6, 72.0, 71.3, 68.4, 65.1, 55.3, 21.2, 21.0. HRMS (ESI-TOF) *m*/*z* calcd for $C_{30}H_{32}O_7NaS$ $[M + Na]^+$ 559.1766, found 559.1738.

*p-Tolyl 2-O-acetyl-4-O-benzyl-3-O-(4-methoxybenzyl)-1-thio-α-D-mannopyranoside (**11**).* To a solution of compound **10** (1.22 g, 2.27 mmol) in CH_3CN (22 mL) at 0 °C were added $NaBH_4$ (859 mg, 22.7 mmol) and then cyanuric chloride (3.35 g, 18.2 mmol). The reaction mixture was kept at 0 °C for 20 min and then stirred at room temperature for another 9 h. The mixture was diluted with EtOAc,

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filtered through a pad of Celite, and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/2−1/3/1) afforded **11** (1.03 g, 84%) as a syrup. $[\alpha]_D^{25}$ + 55.8 (*c* 0.44, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 9H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.90−6.82 (m, 2H), 5.58 (dd, *J* = 3.1, 1.6 Hz, 1H), 5.37 (d, *J* = 1.4 Hz, 1H), 4.92 and 4.62 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.66 and 4.49 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.19 (ddd, *J* = 7.2, 4.0, 3.2 Hz, 1H), 3.94 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.88−3.77 (m, 6H), 2.32 (s, 3H), 2.13 (s, 3H), 1.74 (t, *J* = 6.5 Hz, 1H, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.4, 138.34, 138.25, 132.8, 130.0, 129.9, 129.7, 129.4, 128.5, 128.0, 127.8, 113.9, 86.7, 77.9, 75.3, 74.3, 72.9, 71.5, 70.3, 62.1, 55.3, 21.14, 21.06. HRMS (ESI-TOF) *m*/*z* calcd for $C_{30}H_{34}O_7NaS$ [M + Na]$^+$ 561.1923, found 561.1915.

*p-Tolyl 2,6-O-acetyl-4-O-benzyl-1-thio-α-D-mannopyranoside (**12**).* To a solution of compound **11** (300 mg, 0.722 mmol), Et_3N (1.2 mL, 8.686 mmol) and DMAP (9 mg, 0.073 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (0.34 mL, 3.61 mmol) dropwise at room temperature. After stirring for 30 min, the mixture was treated with $NaHCO_3$ (sat. aq.) and diluted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give an oily residue. To a solution of resulting residue in a mixed solvent (CH_2Cl_2/pH 7.0 phosphate buffer, v/v 20/1, 5 mL) at 0 °C was added DDQ (193 mg, 0.942 mmol). After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and kept for 2 h. The reaction was then quenched by $NaHCO_3$ (sat. aq.) and diluted with CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes, 1/2) afforded **12** (197 mg, 81%, over 2 steps) as a syrup. $[\alpha]_D^{25}$ + 148.1 (*c* 0.144, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m, 7H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.41 (d, *J* = 1.3 Hz, 1H), 5.35 (dd, *J* = 3.5, 1.5 Hz, 1H), 4.85 and 4.68 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.41 (ddd, *J* = 9.5, 4.9, 3.1 Hz, 1H), 4.35 (s, 1H), 4.34 (d, *J* = 2.3 Hz, 1H), 4.16 (ddd, *J* = 8.9, 5.1, 3.6 Hz, 1H), 3.68 (dd, *J* = 9.5, 9.5 Hz, 1H), 2.32 (s, 3H), 2.24 (d, *J* = 5.2 Hz, 1H, O*H*), 2.15 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 138.2, 137.7, 132.7, 129.9, 129.4, 128.7, 128.2, 128.0, 86.2, 76.2, 75.1, 73.9, 71.13 70.3, 63.4, 21.1, 21.0, 20.8. HRMS (ESI-TOF) *m*/*z* calcd for $C_{24}H_{28}O_7NaS$ [M + Na]$^+$ 483.1453, found 483.1434.

*p-Tolyl 2-O-acetyl-4-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**13**).* To a solution of compound **11** (496 mg, 0.92 mmol) and 1*H*-imidazole (188 mg, 2.76 mmol) in CH_2Cl_2 (10 mL) at room temperature was added TIPSCl (0.34 mL, 1.56 mmol). After stirring overnight, the reaction was quenched with water and extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/40/1−1/20/1) provided **13** (559 mg, 87%) as a syrup. $[\alpha]_D^{25}$ + 64.2 (*c* 0.334, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.25 (m, 9H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.88−6.82 (m, 2H), 5.54 (dd, *J* = 3.0, 1.7 Hz, 1H), 5.39 (d, *J* = 1.5 Hz, 1H), 4.90 and 4.65 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.65 and 4.50 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.11 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.04 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.99 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.95−3.87 (m, 2H), 3.80 (s, 3H), 2.31 (s, 3H), 2.09 (s, 3H), 1.15−0.97 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.4, 138.6, 137.6, 131.9, 130.6, 129.90, 129.87, 129.7, 128.4, 128.0, 127.7, 113.9, 86.4, 78.1, 75.3, 74.2, 74.0, 71.6, 70.7, 62.6, 55.3, 21.1, 21.0, 18.0, 17.9, 12.1. HRMS (ESI-TOF) *m*/*z* calcd for $C_{39}H_{54}O_7NaSiS$ [M + Na]$^+$ 717.3257, found 717.3247.

*p-Tolyl 2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**14**).* DDQ (193 mg, 0.94 mmol) was added to a solution of compound **13** (400 mg, 0.72 mmol) in a mixed solvent (CH_2Cl_2/pH 7.0 phosphate buffer, v/v 20/1, 10 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and kept for 2 h. The reaction was then quenched by $NaHCO_3$ (sat. aq.) and CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) afforded **14** (277 mg, 83%) as a syrup. $[\alpha]_D^{25}$ + 125.2 (*c* 0.404, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 7H, ArH), 7.08 (d, *J* = 7.9 Hz, 2H, ArH), 5.42 (d, *J* = 1.6 Hz, 1H, H-1), 5.32 (dd, *J* = 3.3, 1.6 Hz, 1H, H-2), 4.82 and 4.79 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.15−4.02 (m, 3H, H-3, H-4, H-6$_a$), 4.01−3.89 (m, 2H, H-5, H-6$_b$), 2.31 (s, 3H, CH_3Ar), 2.17 (d, *J* = 4.8 Hz, 1H, O*H*), 2.09 (s, 3H, COCH_3), 1.18−0.98 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.6, 138.4, 137.5, 131.9, 131.8, 130.5, 128.6, 127.97, 127.95, 86.1, 75.7, 75.0, 74.1, 73.6, 70.8, 62.4, 21.1, 20.9, 18.0, 17.9, 12.1. HRMS (ESI-TOF) *m*/*z* calcd for $C_{31}H_{46}O_6NaSiS$ [M + Na]$^+$ 597.2682, found 597.2716.

*p-Tolyl 2-O-acetyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**15**).* To a solution of compound **10** (2.62 g, 4.88 mmol) in MeOH (30 mL) was added *p*-toluenesulfonic acid monohydrate (93 mg, 0.49 mmol) at room temparature. After stirring for 12 h, Et_3N (5 mL) was added to quench the reaction, and the mixture was concentrated to give a residue. To a solution of resulting residue and imidazole (930 mg, 13.66 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added TIPSCl (1.15 mL, 5.37 mmol) dropwise. After stirring at 0 °C for 10 min, the mixture was warmed to room temperature and kept for 5 h. The reaction was quenched by adding H_2O and diluted with EtOAc. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1:40:1−1:5:1) afforded **15** (2.49 g, 85%, over 2 steps) as a syrup. $[\alpha]_D^{25}$ + 39.9 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.34 (m, 2H), 7.31−7.26 (m, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.93−6.85 (m, 2H), 5.55 (dd, *J* = 3.1, 1.7 Hz, 1H), 5.39 (d, *J* = 1.4 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.15 (ddd, *J* = 9.2,4.4, 4.4 Hz, 1H), 4.02 (d, *J* = 9.5 Hz, 1H), 4.00−3.94 (m, 2H), 3.81 (s, 3H), 3.74 (dd, *J* = 9.4, 3.1 Hz, 1H), 2.80 (s, 1H), 2.32 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.5, 137.9, 132.3, 130.1, 129.9, 129.8, 129.6, 114.0, 86.7, 77.3, 73.0, 71.4, 69.7, 68.2, 64.1, 55.3, 21.1, 20.9, 17.96, 17.94, 11.9. HRMS (ESI-TOF) *m*/*z* calcd for $C_{32}H_{48}O_7NaSiS$ [M + Na]$^+$ 627.2788, found 627.2762.

*p-Tolyl 2,4-O-diacetyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**16**).* Compound **16** (2.56 g, 97%) was synthesized from **15** (2.48 g, 4.1 mmol) according to the standard procedure for compound **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.35 (m, 2H), 7.24−7.17 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.91−6.84 (m, 2H), 5.54 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.39 (d, *J* = 1.6 Hz, 1H), 5.22 (dd, *J* = 9.8, 9.8 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 4.38 (d, *J* = 11.9 Hz, 1H), 4.25 (ddd, *J* = 9.9, 5.8, 2.3 Hz, 1H), 3.85−3.80 (m, 4H), 3.80−3.77 (m, 1H), 3.77−3.70 (m, 1H), 2.32 (s, 3H), 2.10 (s, 3H), 2.01 (s, 3H), 1.14−0.90 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.7, 159.4, 138.0, 132.5, 132.4, 130.0, 129.8, 129.6, 113.9, 86.9, 74.9, 73.1, 70.9, 69.9, 68.1, 63.2, 55.3, 21.1, 21.00, 20.89, 17.93, 17.92, 11.9. HRMS (ESI-TOF) *m*/*z* calcd for $C_{34}H_{50}O_8NaSiS$ [M + Na]$^+$ 669.2893, found 669.2888.

*p-Tolyl 2,4-di-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**18**).* A solution of known compound **17**[44] (2.23 g, 3.81 mmol) in CH_3OH (25 mL) was treated with *p*-toluenesulfonic acid monohydrate (73 mg, 0.38 mmol). After stirring for 12 h at room temperature, the mixture was neutralized by triethylamine (0.5 mL) and concentrated. The residue was dissolved in DMF (15 mL), and then treated with 1*H*-imidazole (600 mg, 8.77 mmol) and TIPSCl (0.9 mL, 4.20 mmol) at 0 °C. After stirring for 8 h at room temperature, the reaction was quenched with water and extracted with EtOAc. The organic phase was washed with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in THF (30 mL), and then treated with BnBr (0.91 mL, 7.9 mmol) and TBAI (141 mg, 0.38 mmol) at 0 °C followed by adding NaH (198 mg, 60%, 4.94 mmol). After stirring at room temperature for 12 h, the reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/50/1−1/30/1) afforded **18** (2.73 g, 96%, 3 steps) as a syrup. $[\alpha]_D^{25}$ + 77.4 (*c* 0.146, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 14H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.88−6.83 (m, 2H), 5.48 (d, *J* = 1.5 Hz, 1H), 4.92 (A of ABq, J_{AB} = 10.9 Hz, 1H), 4.69−4.59 (m, 3H, benzylic), 4.56 (s, 2H, CH_2Ar), 4.09 (ddd, *J* = 9.7, 4.4, 1.8 Hz, 1H), 4.03−3.90 (m,

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4H), 3.84 (dd, J = 9.2, 3.1 Hz, 1H), 3.81 (s, 3H), 2.31 (s, 3H), 1.09−1.00 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 138.8, 138.2, 137.2, 131.7, 131.3, 130.5, 129.6, 129.5, 128.32, 128.26, 128.0, 127.8, 127.6, 127.5, 113.8, 85.9, 79.9, 76.7, 75.2, 74.9, 74.4, 71.8, 71.8, 63.0, 55.3, 21.1, 18.02, 17.97, 12.03. HRMS (ESI-TOF) m/z calcd for $C_{44}H_{58}O_6NaSiS$ $[M + Na]^+$ 765.3621, found 765.3643.

*p-Tolyl 2,4-di-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**19**).* Compound **19** (83 mg, 66%) was synthesized from **18** (160 mg, 0.22 mmol) according to the standard procedure for compound **14**. $[\alpha]_D^{25}$ + 73.7 (c 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 12H), 7.08 (d, J = 7.9 Hz, 2H), 5.58 (s, 1H), 4.90 and 4.68 (ABq, J_{AB} = 11.1 Hz, 2H, ArCH_2), 4.71 and 4.50 (ABq, J_{AB} = 11.6 Hz, 2H, ArCH_2), 4.10 (ddd, J = 9.5, 4.2, 1.7 Hz, 1H), 4.03−3.92 (m, 4H), 3.83−3.76 (m, 1H), 2.42 (d, J = 8.9 Hz, 1H, OH), 2.32 (s, 3H), 1.14−0.98 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 137.5, 137.3, 131.7, 131.0, 129.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 85.1, 80.0, 76.6, 75.0, 73.6, 72.3, 72.0, 62.8, 21.1, 18.03, 17.97, 12.0. HRMS (ESI-TOF) m/z calcd for $C_{36}H_{50}O_5NaSiS$ $[M + Na]^+$ 645.3046, found 645.3015.

*p-Tolyl 3-O-acetyl-2,4-di-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**20**).* Compound **20** (159 mg, 94%) was synthesized from **19** (158 mg, 0.25 mmol) according to the standard procedure for compound **6**. $[\alpha]_D^{25}$ + 67.0 (c 0.21, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 12H, ArH), 7.11−7.05 (m, 2H, ArH), 5.47 (d, J = 2.1 Hz, 1H, H-1), 5.21 (dd, J = 8.9, 3.2 Hz, 1H, H-3), 4.73 and 4.67 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.63 and 4.48 (ABq, J_{AB} = 12.1 Hz, 2H, CH_2Ar), 4.18−4.09 (m, 2H, H-4, H-5), 4.08 (dd, J = 3.2, 2.1 Hz, 1H, H-2), 3.99 (dd, J = 11.2, 3.8 Hz, 1H, H-6_a), 3.91 (dd, J = 11.2, 1.4 Hz, 1H, H-6_b), 2.32 (s, 3H, ArCH_3), 1.98 (s, 3H, COCH_3), 1.17−0.95 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.2, 138.4, 137.9, 137.3, 131.9, 131.8, 131.0, 129.7, 128.4, 128.3, 127.74, 127.71, 127.68, 127.66, 85.5, 77.4, 74.7, 74.0, 73.8, 73.4, 72.1, 62.7, 21.09, 21.05, 18.00, 17.95, 12.0. HRMS (ESI-TOF) m/z calcd for $C_{38}H_{52}O_6NaSiS$ $[M + Na]^+$ 687.3152, found 687.3112.

*p-Methoxyphenyl 2-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranoside (**22**) and p-Methoxyphenyl 2-O-acetyl-3,4-di-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranoside (**23**).* To a solution of known compound **21**[45] (876 mg, 1.46 mmol) and p-methoxyphenol (217 mg, 1.75 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (370 μL, 2.92 mmol) dropwise under nitrogen at 0 °C. The mixture was allowed to warm to room temperature, stirred until completion, and quenched with $NaHCO_3$ (sat. aq.). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (EtOAc/hexanes, 1/2) provided **22** (261 mg, 35%) and **23** (272 mg, 37%) as syrup. The resulting compound **22** was then sialylated to give **23** in 95% yield according to the standard procedure for compound **13**. Data for **22**: $[\alpha]_D^{25}$ + 45.0 (c 0.222, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 10H), 6.98−6.91 (m, 2H), 6.85−6.77 (m, 2H), 5.55 (dd, J = 3.3, 1.9 Hz, 1H), 5.40 (d, J = 1.8 Hz, 1H), 4.94 and 4.66 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.77 and 4.62 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.19 (dd, J = 9.2, 3.4 Hz, 1H), 3.92 (dd, J = 9.5, 9.5 Hz, 1H), 3.87−3.81 (m, 1H), 3.81−3.77 (m, 2H), 3.76 (s, 3H), 2.18 (s, 3H), 1.77 (brs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 155.3, 149.8, 138.2, 137.9, 128.48, 128.46, 128.07, 128.03, 127.87, 127.84, 117.9, 114.7, 97.1, 77.9, 75.3, 73.8, 72.5, 72.0, 68.7, 61.9, 55.6, 21.1. HRMS (ESI-TOF) m/z calcd for $C_{29}H_{32}O_8Na$ $[M + Na]^+$ 531.1995, found 531.1998. Data for **23**: $[\alpha]_D^{25}$ + 42.4° (c 0.202, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.27 (m, 10H), 7.00−6.91 (m, 2H), 6.82−6.72 (m, 2H), 5.49 (dd, J = 3.2, 2.0 Hz, 1H), 5.38 (d, J = 1.8 Hz, 1H), 4.92 and 4.68 (ABq, J_{AB} = 10.7 Hz, 2H, ArCH_2), 4.77 and 4.63 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.18 (dd, J = 9.5, 3.3 Hz, 1H), 4.04 (dd, J = 9.7, 9.7 Hz, 1H), 3.99 (dd, J = 11.3, 3.8 Hz, 1H), 3.89 (dd, J = 11.2, 1.5 Hz, 1H), 3.78 (ddd, J = 9.8, 3.8, 1.4 Hz, 1H), 3.76 (s, 3H), 2.14 (s, 3H), 1.15−0.99 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.0, 150.2, 138.6, 138.0, 128.43, 128.39, 128.1, 128.0, 127.8, 127.7, 117.7, 114.5, 96.7, 78.0, 75.3, 73.9, 73.4, 72.0, 68.9, 62.5, 55.6, 21.0, 18.0, 17.9, 12.0. HRMS (ESI-TOF) m/z calcd for $C_{38}H_{52}O_8NaSi$ $[M + Na]^+$ 687.3329, found 687.3337.

*p-Methoxyphenyl 3,4-di-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranoside (**24**).* A solution of **23** (337 mg, 0.507 mmol) in methanol (5 mL) was treated with MeONa (2.8 mg, 0.051 mol) and then stirred for 12 h at room temperature. Dowex 50WX8 acidic resin was added to neutralize MeONa and then removed. The solution was concentrated in vacuo to provide **24** (292 mg, 93%) as a syrup. $[\alpha]_D^{25}$ + 66.1 (c 0.182, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.20 (m, 10H), 6.95−6.89 (m, 2H), 6.75−6.69 (m, 2H), 5.37 (d, J = 1.5 Hz, 1H), 4.82 and 4.61 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.69 (s, 2H, CH_2Ar), 4.12 (dd, J = 3.2, 1.8 Hz, 1H), 4.00 (dd, J = 9.1, 3.3 Hz, 1H), 3.87−3.83 (m, 1H), 3.83−3.80 (m, 2H), 3.71 (ddd, J = 9.9, 3.9, 2.3 Hz, 1H), 3.68 (s, 3H), 2.48 (brs, 1H, OH), 1.05−0.90 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 150.4, 138.5, 138.0, 128.6, 128.4, 128.0, 127.9, 127.7, 117.8, 117.87, 114.6, 98.2, 80.1, 75.2, 74.1, 73.1, 72.2, 68.5, 62.7, 55.6, 18.00, 17.96, 12.0. HRMS (ESI-TOF) m/z calcd for $C_{36}H_{50}O_7NaSi$ $[M + Na]^+$ 645.3224, found 645.3248.

*Benzyl 4,6-O-diacetyl-3-O-benzyl-2-O-(4-methoxybenzyl)-α-D-mannopyranoside (**26**).* To a solution of 25[46] (201 mg, 0.67 mmol) in DMF (5 mL) at 0 °C was added NaH (60%, 54 mg, 1.34 mmol) in portions. After stirring at 0 °C for 20 min, PMBCl (182 μL, 1.34 mmol) was added to the mixture. The reaction was allowed to warm to room temperature and kept for 12 h. Then H_2O was added slowly to quench the reaction and the aqueous phase was extracted with EtOAc. The organic phase was washed consecutively with H_2O and brine, dried over $MgSO_4$, filtered and concentrated to give a residue. A solution of the resulting PMB ether in AcOH/H_2O (4:1, 10 mL) was heated at 50 °C for 4 h and then cooled to room temperature. The mixture was diluted with EtOAc, and the organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated to a residue. To a solution of resulting residue in CH_2Cl_2 (5 mL) at 0 °C was added Et_3N (4.4 mL, 32.2 mmol), DMAP (16 mg, 0.134 mmol), and Ac_2O (1.26 mL, 13.4 mmol). After stirring at room temperature for 12 h, the reaction was quenched with $NaHCO_3$ (sat. aq.) and extracted with EtOAc. The organic phase was washed brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) afforded **26** (369 mg, 98%, over 3 steps) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 10H), 7.24−7.18 (m, 2H), 6.85−6.74 (m, 2H), 5.42 (dd, J = 9.9, 9.9 Hz, 1H), 4.91 (d, J = 1.8 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.0 Hz, 2H), 4.45 (d, J = 12.1 Hz, 1H), 4.22 (dd, J = 12.1, 5.5 Hz, 1H), 4.09 (dd, J = 12.1, 2.4 Hz, 1H), 3.86 (dd, J = 9.7, 3.1 Hz, 1H), 3.85 (ddd, J = 9.7, 5.6, 2.5 Hz, 1H), 3.82−3.78 (m, 1H), 3.78 (s, 3H), 2.09 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.7, 159.2, 138.2, 137.0, 130.1, 129.5, 128.5, 128.3, 128.0, 127.9, 127.6, 127.4, 113.7, 97.6, 77.2, 73.6, 72.4, 71.9, 69.4, 69.3, 68.1, 63.1, 55.3, 20.91, 20.85. HRMS (ESI-TOF) m/z calcd for $C_{32}H_{36}O_9Na$ $[M + Na]^+$ 587.2257, found 587.2243.

*Benzyl 4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**27**).* Compound **27** (253 mg, 89%) was synthesized from **26** (361 mg, 0.64 mmol) according to the standard procedure for compound **14**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.19 (m, 10H), 5.29 (t, J = 9.8 Hz, 1H), 5.00 (d, J = 1.5 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.66 (d, J = 11.9 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.53 (d, J = 11.8 Hz, 1H), 4.24 (dd, J = 12.2, 5.2 Hz, 1H), 4.09−4.03 (m, 2H), 3.90 (ddd, J = 10.2, 5.1, 2.3 Hz, 1H), 3.84 (dd, J = 9.5, 3.4 Hz, 1H), 2.55 (d, J = 1.5 Hz, 1H), 2.09 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.8, 137.5, 136.8, 128.6, 128.2, 128.1, 128.0, 127.7, 98.4, 77.1, 72.0, 69.5, 68.6, 68.3, 67.3, 62.7, 20.9, 20.8. HRMS (ESI-TOF) m/z Calcd for $C_{24}H_{28}O_8Na$ $[M + Na]^+$ 467.1682, found 467.1675.

*p-Tolyl 2-O-acetyl-3-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**29**).* A solution of the known intermediate **28**[47] (206 mg, 0.41 mmol) in methanol (10 mL) was treated with p-toluenesulfonic acid (8 mg, 0.04 mmol). After stirring at room temperature for 6 h, the mixture was neutralized by triethylamine (2 mL) and concentrated. The crude diol was dissolved in CH_2Cl_2 (5 mL), and then treated with 1H-imidazole (78 mg, 1.14 mmol) and TIPSCl (0.096 mL, 0.45 mmol). After stirring at room temperature for 9 h, the reaction was quenched with water and extracted with EtOAc. The organic phase was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on

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silica gel (EtOAc/hexanes/CH_2Cl_2, 1/40/1−1/8/1) provided **29** (177 mg, 76%, 2 steps) as a syrup. $[\alpha]_D^{25}$ + 58.6 (*c* 0.46, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 7H, ArH), 7.09 (d, *J* = 7.9 Hz, 2H, ArH), 5.55 (dd, *J* = 3.1, 1.7 Hz, 1H, H-2), 5.39 (d, *J* = 1.4 Hz, 1H, H-1), 4.73 and 4.55 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.19−4.12 (m, 1H, H-5), 4.04 (td, *J* = 9.7, 2.1 Hz, 1H, H-4), 3.99 (dd, *J* = 10.7, 4.6 Hz, 1H, H-6_a), 3.95 (dd, *J* = 10.6, 4.5 Hz, 1H, H-6_b), 3.77 (dd, *J* = 9.3, 3.2 Hz, 1H, H-3), 2.83 (d, *J* = 1.8 Hz, 1H, O*H*), 2.32 (s, 3H, ArCH_3), 2.07 (s, 3H, COCH_3), 1.18−0.93 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.2, 137.9, 137.6, 132.3, 130.1, 129.8, 128.6, 128.2, 128.0, 86.7, 77.7, 72.9, 71.8, 69.8, 68.4, 64.2, 21.1, 20.9, 18.0, 17.9, 11.9. HRMS (ESI-TOF) *m*/*z* calcd for $C_{31}H_{46}O_6NaSiS$ [M + Na]$^+$ 597.2682, found 597.2716.

*p-Tolyl 2,3-di-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**31**).* Compound **31** (310 mg, 97%) was synthesized from the known **30**[12b] (285 mg, 0.51 mmol) according to the standard procedure for compound **15**. $[\alpha]_D^{25}$ + 58.3 (*c* 0.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.25 (m, 12H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.48 (d, *J* = 1.6 Hz, 1H), 4.64 and 4.55 (ABq, J_{AB} = 12.2 Hz, 2H, CH_2Ar), 4.63 and 4.60 (ABq, J_{AB} = 11.9 Hz, 2H, CH_2Ar), 4.18−4.07 (m, 2H), 4.04−3.89 (m, 3H), 3.75−3.68 (m, 1H), 2.97 (brs, 1H, O*H*), 2.32 (d, *J* = 5.0 Hz, 3H), 1.13−1.01 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 138.0, 137.6, 132.1, 130.8, 129.8, 128.5, 128.3, 127.92, 127.86, 127.8, 127.7, 86.3, 79.5, 76.0, 73.0, 72.1, 72.0, 69.4, 65.0, 21.1, 18.0, 11.9. HRMS (ESI-TOF) *m*/*z* calcd for $C_{36}H_{50}O_5NaSiS$ [M + Na]$^+$ 645.3046, found 645.3015.

*p-Tolyl 4-O-acetyl-2,3-di-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**32**).* Compound **32** (310 mg, 97%) was synthesized from **31** (300 mg, 0.48 mmol) according to the standard procedure for compound **6**. $[\alpha]_D^{25}$ + 46.3 (*c* 0.178, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.23 (m, 12H, ArH), 7.07 (d, *J* = 7.9 Hz, 2H, ArH), 5.47 (d, *J* = 1.8 Hz, 1H, H-1), 5.32 (dd, *J* = 9.7, 9.7 Hz, 1H, H-4), 4.66 and 4.60 (ABq, J_{AB} = 12.5 Hz, 2H, CH_2Ar), 4.57 and 4.47 (ABq, J_{AB} = 12.2 Hz, 2H, CH_2Ar), 4.27−4.17 (m, 1H, H-5), 3.97 (dd, *J* = 2.8, 2.1 Hz, 1H, H-2), 3.84 (dd, *J* = 11.2, 6.6 Hz, 1H, H-6_a), 3.79−3.73 (m, 2H, H-3, H-6_b), 2.32 (s, 3H, ArCH_3), 2.02 (s, 3H, COCH_3), 1.19−0.86 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 169.8, 138.0, 137.9, 137.6, 132.2, 130.6, 129.7, 128.4, 128.3, 127.9, 127.71, 127.67, 127.6, 86.2, 77.2, 75.9, 73.5, 72.0, 71.6, 68.9, 63.6, 21.1, 21.0, 18.0, 11.9. HRMS (ESI-TOF) *m*/*z* calcd for $C_{38}H_{52}O_6NaSiS$ [M + Na]$^+$ 687.3152, found 687.3112.

*p-Tolyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→3)-2,6-O-diacetyl-4-O-benzyl-1-thio-α-D-mannopyranoside (**33**).* Donor **5** (167 mg, 0.259 mmol) and acceptor **12** (107 mg, 0.233 mmol) were dissolved in anhydrous CH_2Cl_2 (7 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −20 °C, and TMSOTf (5 μL, 0.026 mmol) was added dropwise. After stirring at −20 °C for 1h, the mixture was allowed to warm to room temperature and monitored by TLC. After completion, the reaction was treated with Et_3N, diluted with CH_2Cl_2, filtered through a pad of Celite and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/7/1−1/3/1) afforded **33** (187 mg, 85%) as a syrup. $[\alpha]_D^{25}$ + 81.6 (*c* 0.430, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.17 (m, 17H), 7.02 (d, *J* = 7.9 Hz, 2H), 5.38 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.34 (d, *J* = 1.4 Hz, 1H), 5.29 (dd, *J* = 3.2, 1.7 Hz, 1H), 5.07 (d, *J* = 1.6 Hz, 1H), 4.82 and 4.50 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.74 and 4.47 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.58 and 4.42 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.32 (ddd, *J* = 9.1, 4.3, 2.6 Hz, 1H), 4.29−4.25 (m, 1H), 4.24−4.17 (m, 3H), 4.07 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.85 (dd, *J* = 9.2, 3.3 Hz, 1H), 3.83−3.78 (m, 1H), 3.73 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.63 (dd, *J* = 9.5, 9.5 Hz, 1H), 2.74−2.66 (m, 2H), 2.66−2.60 (m, 2H), 2.24 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 206.5, 172.7, 170.6, 170.0, 169.9, 138.2, 137.9, 137.6, 137.2, 132.6, 129.8, 129.1, 128.6, 128.4, 128.13, 128.10, 127.99, 127.9, 127.8, 99.9, 85.9, 77.7 (2C), 75.4, 75.08, 75.06, 74.0, 73.4, 71.8, 70.8, 70.6, 68.62, 63.58, 63.1, 37.9, 29.8, 27.8, 21.1, 21.0, 20.9, 20.8. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.34/85.9 ($J_{C1/H1}$ = 171.8 Hz), 5.07/99.9 ($J_{C1/H1}$ = 173.1 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{51}H_{58}O_{15}SNa$ [M + Na]$^+$ 965.3394, found 965.3384.

*p-Methoxyphenyl 2-O-acetyl-4-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-3,4-O-dibenzyl-6-O-triisopropylsilyl-α-D-mannopyranoside (**34**).* Donor **13** (139 mg, 0.243 mmol) and acceptor **24** (136 mg, 0.235 mmol) were dissolved in anhydrous CH_2Cl_2 (7 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −20 °C, and treated successively with NIS (66 mg, 0.293 mmol) and TMSOTf (4.4 μL, 0.024 mmol). After stirring at −20 °C for 20 min, the mixture was allowed to warm to room temperature and monitored by TLC. After completion, the reaction was treated with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes, 1/50−1/15) afforded **34** (174 mg, 79%) as a syrup. $[\alpha]_D^{25}$ + 33.7 (*c* 0.366, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.37 (m, 2H), 7.37−7.27 (m, 15H), 6.97−6.91 (m, 2H), 6.87−6.82 (m, 2H), 6.81−6.75 (m, 2H), 5.53 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.43 (d, *J* = 1.7 Hz, 1H), 5.19 (d, *J* = 1.5 Hz, 1H), 4.91 and 4.69 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.88 and 4.63 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.77 and 4.73 (ABq, J_{AB} = 11.7 Hz, 2H, CH_2Ar), 4.70 and 4.46 (ABq, J_{AB} = 10.5 Hz, 2H, CH_2Ar), 4.26−4.20 (m, 1H), 4.11 (dd, *J* = 9.5, 3.0 Hz, 1H), 4.04−3.97 (m, 3H), 3.96−3.84 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 3.75−3.68 (m, 2H), 2.08 (s, 3H), 1.11−0.97 (m, 42H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 170.3, 159.4, 154.9, 150.4, 139.0, 138.8, 138.5, 130.6, 129.9, 128.54, 128.48, 128.4, 128.2, 128.1, 127.9, 127.74, 127.72, 127.66, 117.7, 114.7, 113.9, 99.1, 97.8, 80.0, 78.2, 75.2, 75.2, 74.2, 74.0, 73.6, 73.5, 73.2, 72.1, 71.8, 68.9, 62.6 (2C, C-6^I, C-6^{II}), 55.7, 55.2, 21.2, 18.2, 18.2, 18.14, 18.08, 12.2, 12.1. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.43/97.8 ($J_{C1/H1}$ = 173.1 Hz), 5.19/99.1 ($J_{C1/H1}$ = 174.0 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{68}H_{96}O_{14}NaSi_2$ [M + Na]$^+$ 1215.6236, found 1215.6190.

*p-Methoxyphenyl 2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-3,4-O-dibenzyl-6-O-triisopropylsilyl-α-D-mannopyranoside (**35**).* DDQ (13 mg, 0.056 mmol) was added to a solution of compound **34** (27 mg, 0.024 mmol) in a mixed solvent (CH_2Cl_2/pH 7.0 phosphate buffer, v/v 20/1, 5 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction was warmed to room temperature and kept for 3 h. The reaction was quenched by adding $NaHCO_3$ (sat. aq.) and CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes, 1/10−1/5) afforded **35** (18 mg, 72%) as a syrup. $[\alpha]_D^{25}$ + 53.6 (*c* 0.074, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.20 (m, 15H), 6.89−6.81 (m, 2H), 6.74−6.67 (m, 2H), 5.35 (d, *J* = 1.7 Hz, 1H), 5.19 (dd, *J* = 3.3, 1.7 Hz, 1H), 5.08 (d, *J* = 1.3 Hz, 1H), 4.82 and 4.59 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.75 and 4.68 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.67−4.64 (m, 2H, CH_2Ar), 4.12 (dd, *J* = 9.6, 3.4 Hz, 1H), 4.09−4.08 (m, 1H), 4.02 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.96−3.90 (m, 2H), 3.87−3.75 (m, 4H), 3.69 (s, 3H), 3.66−3.60 (m, 2H), 2.02 (s, 3H), 1.03−0.91 (m, 42H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 170.7, 154.8, 150.3, 138.6, 138.6, 138.3, 128.5, 128.40, 128.35, 128.0, 127.9, 127.78, 127.76, 127.65, 127.60, 117.5, 114.2, 98.9, 97.7, 79.7, 75.4, 75.3, 75.0, 74.13, 74.07, 73.6, 73.1, 72.5, 72.1, 70.1, 62.6, 62.5, 55.7, 21.0, 18.02, 17.99, 17.98, 17.9, 12.1, 11.9. HRMS (ESI-TOF) *m*/*z* calcd for $C_{60}H_{88}O_{13}NaSi_2$ [M + Na]$^+$ 1095.5661, found 1095.5653.

Procedure for the Glycosylation Coupling of 33 and 35. Donor **33** (99 mg, 0.086 mmol) and acceptor **35** (77 mg, 0.071 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −10 °C, and treated successively with NIS (21 mg, 0.093 mmol) and TMSOTf (1.3 μL, 0.0071 mmol). After stirring at −10 °C for 60 min, the reaction was treated with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$,

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filtered and concentrated. Flash chromatography on silica gel recovered the starting materials.

*p-Tolyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→3)-2,4-O-dibenzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**36**).* Donor **5** (152 mg, 0.236 mmol) and acceptor **19** (134 mg, 0.214 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −20 °C, and TMSOTf (4 μL, 0.021 mol) was added dropwise. After stirring for 30 min, the mixture was allowed to warm to room temperature and monitored by TLC. After completion, the reaction was treated with Et_3N, diluted with CH_2Cl_2 and filtered through a pad of Celite and the organic layer was concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/30/1−1/4/1) afforded **36** (213 mg, 90%) as a syrup. $[\alpha]_D^{25}$ + 33.3 (*c* 0.03, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 18H), 7.25−7.17 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.54 (d, *J* = 1.1 Hz, 1H), 5.51 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.18 (d, *J* = 1.2 Hz, 1H), 4.91 and 4.54 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.77 and 4.65 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.68 and 4.52 (ABq, J_{AB} = 11.4 Hz, 2H, CH_2Ar), 4.68 and 4.49 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.26 (dd, *J* = 11.8, 5.7 Hz, 1H), 4.22 (dd, *J* = 11.8, 2.3 Hz, 1H), 4.11−4.04 (m, 3H), 4.03−3.95 (m, 3H), 3.93−3.84 (m, 2H), 3.67 (dd, *J* = 9.6, 9.6 Hz, 1H), 2.76−2.69 (m, 2H), 2.68−2.62 (m, 2H), 2.32 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 1.11−1.01 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 206.4, 172.7, 170.0, 138.3, 138.1, 137.7, 137.6, 137.4, 131.6, 131.0, 129.7, 128.5, 128.41, 128.35, 128.2, 128.1, 128.0, 127.81, 127.77, 127.72, 127.70, 127.68, 99.6, 85.2, 79.0, 78.6, 78.0, 75.3, 75.12, 75.08, 74.3, 74.2, 71.9, 71.4, 70.2, 68.6, 63.8, 62.6, 37.9, 29.9, 27.9, 21.1, 21.0, 18.03, 17.97, 12.0. HRMS (ESI-TOF) *m*/*z* calcd for $C_{63}H_{80}O_{13}NaSiS$ $[M + Na]^+$ 1127.4987, found 1127.4969.

*p-Tolyl 2,4-di-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2,6-O-diacetyl-4-O-benzyl-1-thio-α-D-mannopyranoside (**37**).* Donor **18** (143 mg, 0.192 mmol) and acceptor **12** (68 mg, 0.147 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −20 °C, and treated successively with NIS (40 mg, 0.177 mmol) and TMSOTf (3 μL, 0.015 mmol). After stirring at −20 °C for 30 min, the reaction was treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) afforded **37** (131 mg, 86%) as a syrup. $[\alpha]_D^{25}$ + 71.5 (*c* 0.372, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.19 (m, 19H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.81−6.74 (m, 2H), 5.39 (d, *J* = 1.6 Hz, 1H), 5.32 (dd, *J* = 3.0, 1.8 Hz, 1H), 5.09 (d, *J* = 1.4 Hz, 1H), 4.89 and 4.71 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.66 and 4.46 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.60 and 4.49 (ABq, J_{AB} = 12.3 Hz, 2H, CH_2Ar), 4.58 and 4.51 (ABq, J_{AB} = 11.5 Hz, 2H, CH_2Ar), 4.37 (ddd, *J* = 9.7, 3.8, 3.8 Hz, 1H), 4.24 (d, *J* = 3.9 Hz, 2H), 4.18 (dd, *J* = 9.5, 9.5 Hz, 1H), 4.06 (dd, *J* = 9.3, 3.1 Hz, 1H), 4.02 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.86 (dd, *J* = 11.3, 1.3 Hz, 1H), 3.82 (ddd, *J* = 12.5, 6.1, 3.1 Hz, 1H), 3.75−3.67 (m, 5H), 3.57−3.51 (m, 1H), 2.31 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.16−1.01 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 170.7, 169.9, 159.1, 138.9, 138.4, 138.1, 137.6, 132.6, 130.8, 129.8, 129.5, 129.2, 128.6, 128.3, 128.2, 128.0, 127.58, 127.55, 127.4, 113.7, 100.5, 85.9, 79.3, 78.4, 76.0, 75.0, 74.9, 74.5, 74.2, 74.1, 73.6, 72.4, 72.0, 70.5, 63.3, 62.1, 55.2, 21.1, 21.1, 20.8, 18.1, 18.0, 12.1. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.39/85.9 ($J_{C1/H1}$ = 172.3 Hz), 5.09/100.5 ($J_{C1/H1}$ = 170.5 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{61}H_{78}O_{13}NaSiS$ $[M + Na]^+$ 1101.4830, found 1101.4801.

*p-Tolyl 2,4-di-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2,6-O-diacetyl-4-O-benzyl-1-thio-α-D-mannopyranoside (**38**).* According to the standard procedure for **14**, compound **37** (112 mg, 0.11 mmol) was converted into **38** (93 mg, 94%) as a syrup. $[\alpha]_D^{25}$ + 72.4 (*c* 0.362, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 15H), 7.20 (dd, *J* = 7.4, 1.7 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.39 (d, *J* = 1.4 Hz, 1H), 5.32 (dd, *J* = 3.0, 1.7 Hz, 1H), 5.15 (s, 1H), 4.83 and 4.73 (ABq, J_{AB} = 11.5 Hz, 2H, CH_2Ar), 4.80 and 4.62 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.46−4.38 (m, 2H), 4.34−4.25 (m, 3H), 4.11 (dd, *J* = 9.4, 3.2 Hz, 1H), 4.04 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.96−3.86 (m, 3H), 3.79 (dd, *J* = 9.6 Hz, 1H), 3.72−3.65 (m, 1H), 3.56−3.48 (m, 1H), 2.32 (s, 3H), 2.27 (brs, 1H, O*H*), 2.09 (s, 3H), 2.04 (s, 3H), 1.21−1.03 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 170.7, 170.0, 138.8, 138.2, 137.8, 137.7, 132.6, 129.9, 129.4, 128.6, 128.4, 128.3, 128.0, 127.71, 127.66, 127.4, 127.3, 99.8, 86.0, 78.9, 78.2, 75.5, 75.0, 74.9, 74.8, 73.6, 73.3, 72.5, 71.5, 70.6, 63.3, 62.0, 21.1, 21.0, 20.8, 18.1, 18.0, 12.1. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.39/86.0 ($J_{C1/H1}$ = 171.5 Hz), 5.15/99.8 ($J_{C1/H1}$ = 170.7 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{53}H_{70}O_{12}NaSiS$ $[M + Na]^+$ 981.4255, found 981.4274.

*p-Tolyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→3)-2,4-O-dibenzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2,4-di-O-benzyl-3-O-(4-methoxybenzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2,6-O-diacetyl-4-O-benzyl-1-thio-α-D-mannopyranoside (**39**).* Donor **36** (115 mg, 0.104 mmol) and acceptor **38** (73 mg, 0.080 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −20 °C, and treated successively with NIS (22 mg, 0.096 mmol) and TMSOTf (3 μL, 0.016 mmol). After stirring at −20 °C for 30 min, the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) afforded **39** (33 mg, 21%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.07 (m, 39H), 5.45 (dd, *J* = 2.9, 2.0 Hz, 1H), 5.40 (d, *J* = 1.4 Hz, 1H), 5.37−5.31 (m, 1H), 5.22 (s, 1H), 5.16 (d, *J* = 1.4 Hz, 1H), 5.14 (s, 1H), 4.85 and 4.63 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.80−4.69 (m, 4H, benzylic), 4.57 (A of ABq, J_{AB} = 11.1 Hz, 1H), 4.54−4.43 (m, 4H, benzylic), 4.42−4.34 (m, 2H, benzylic ×1, pyranosyl ×1), 4.32−4.22 (m, 4H, benzylic ×1, pyranosyl ×3), 4.22−4.08 (m, 5H, benzylic ×1, pyranosyl ×4), 4.09−4.00 (m, 2H), 3.99−3.86 (m, 4H), 3.80−3.69 (m, 5H), 3.61−3.49 (m, 3H), 2.61−2.55 (m, 2H), 2.53−2.48 (m, 2H), 2.31 (s, 3H), 2.10 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.12−1.04 (m, 21H), 1.01−0.94 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$, HSQC) δ 205.2, 171.4, 169.6, 169.0, 168.9, 137.6, 137.3, 137.2, 137.1, 136.81, 136.76, 136.3, 131.5, 129.0, 128.8, 128.7, 128.4, 127.6, 127.4, 127.33, 127.30, 127.28, 127.2, 127.13, 127.08, 127.05, 126.9, 126.7, 126.61, 126.55, 126.46, 126.2, 126.1, 126.0, 125.7, 100.3, 99.6, 98.8 (missing), 85.9, 79.4 (missing), 78.4, 78.2, 78.0 (2C), 77.4 (missing), 75.2, 74.9 (3C), 74.8, 74.2 (missing, 2C), 74.0, 73.9, 73.7, 73.4, 72.2, 71.7, 71.6, 70.5, 70.1, 68.7, 63.3, 63.2, 62.3, 62.0, 37.7, 29.8, 27.8, 21.1, 21.02, 21.01, 20.8, 18.1, 18.03, 18.00, 17.95, 12.1, 12.0. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.39/85.9 ($J_{C1/H1}$ = 171.9 Hz), 5.22/98.8 ($J_{C1/H1}$ = 171.5 Hz), 5.16/100.3 ($J_{C1/H1}$ = 172.2 Hz), 5.14/99.6 ($J_{C1/H1}$ = 172.8 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{109}H_{142}O_{25}NaSi_2S$ $[M + Na]^+$ 1961.8997, found 1961.9050.

*p-Tolyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→3)-2,4-O-dibenzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**40**).* Trichloroacetimidate donor **8** (332 mg, 0.564 mmol) and acceptor **19** (320 mg, 0.513 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (800 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −20 °C and TMSOTf (9.3 μL, 0.051 mmol) was added dropwise. After stirring at −20 °C for 30 min, the mixture was allowed to warm to 0 °C during 0.5 h. The mixture was treated with Et_3N (2 mL), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/30/1−1/8/1) afforded disaccharide **40** (432 mg, 89%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.15 (m, 22H), 7.07 (d, *J* = 7.9

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Hz, 2H), 5.54 (d, J = 1.4 Hz, 1H), 5.50 (dd, J = 3.2, 1.8 Hz, 1H), 5.19 (d, J = 1.4 Hz, 1H), 4.91 and 4.54 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.78 and 4.65 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.682 and 4.49 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.677 and 4.53 (ABq, J_{AB} = 11.8 Hz, 2H, CH_2Ar), 4.23 (d, J = 4.3 Hz, 2H), 4.06 (dd, J = 9.9, 7.1 Hz, 3H), 4.04−3.95 (m, 3H), 3.94−3.85 (m, 2H), 3.66 (dd, J = 9.6 Hz, 1H), 2.32 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.17−0.90 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.9, 169.9, 138.23, 138.15, 137.8, 137.7, 137.4, 131.7, 131.6, 131.1, 129.7, 128.43, 128.41, 128.36, 128.2, 128.0, 127.9, 127.8, 127.74, 127.70, 127.67, 99.6, 85.3, 79.1, 78.5, 78.1, 75.24, 75.15, 75.1, 74.4, 74.2, 71.9, 71.4, 70.2, 68.6, 63.8, 62.7, 21.1, 21.02, 20.95, 18.02, 17.96, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.54/85.3 ($J_{C1/H1}$ = 170.5 Hz), 5.19/99.6 ($J_{C1/H1}$ = 176.0 Hz). HRMS (ESI-TOF) m/z calcd for $C_{60}H_{76}O_{12}NaSiS$ [M + Na]$^+$ 1071.4724, found 1071.4734.

*p-Tolyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**41**).* According to the procedure for **40**, the coupling of donor **8** (115 mg, 0.195 mmol) and acceptor **14** (97 mg, 0.170 mmol) was performed to give disaccharide **41** (131 mg, 78%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.25 (m, 17H), 7.07 (d, J = 8.0 Hz, 2H), 5.47 (dd, J = 3.2, 1.8 Hz, 1H), 5.42 (d, J = 1.6 Hz, 1H), 5.36 (dd, J = 3.0, 1.7 Hz, 1H), 5.16 (d, J = 1.5 Hz, 1H), 4.88 and 4.56 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.78 and 4.70 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.67 and 4.49 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.29 (d, J = 4.2 Hz, 2H), 4.17−3.97 (m, 4H), 3.97−3.83 (m, 3H), 3.67 (dd, J = 9.6, 9.6 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 1.15−0.96 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 171.0, 170.1, 170.0, 138.02, 138.00, 137.7, 137.6, 131.84, 131.75, 130.3, 129.7, 128.5, 128.412, 128.406, 128.1, 128.0, 127.9, 127.83, 127.81, 99.8, 85.9, 77.8, 77.2, 75.4, 75.0, 74.7, 74.1, 73.9, 73.8, 71.9, 70.6, 68.6, 63.6, 62.2, 21.1, 21.0, 20.94, 20.91, 18.0, 17.9, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.42/85.9 ($J_{C1/H1}$ = 171.8 Hz), 5.16/99.8 ($J_{C1/H1}$ = 174.8 Hz). HRMS (ESI-TOF) m/z calcd for $C_{55}H_{72}O_{13}NaSiS$ [M + Na]$^+$ 1023.4361, found 1023.4323.

*p-Tolyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→4)-2,3-O-dibenzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**42**).* According to the procedure for **40**, the coupling of donor **8** (105 mg, 0.178 mmol) and acceptor **31** (92 mg, 0.148 mmol) was performed to give disaccharide **42** (135 mg, 87%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.1 Hz, 2H), 7.35−7.21 (m, 20H), 7.07 (d, J = 7.9 Hz, 2H), 5.54−5.43 (m, 3H), 4.88 and 4.53 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.70 and 4.45 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.60 and 4.47 (ABq, J_{AB} = 12.1 Hz, 2H, CH_2Ar), 4.52 (s, 2H, CH_2Ar), 4.37 (dd, J = 11.8, 4.8 Hz, 1H), 4.24 (dd, J = 11.8, 1.9 Hz, 1H), 4.17−4.08 (m, 2H), 4.04−3.86 (m, 5H), 3.84−3.76 (m, 1H), 3.71 (dd, J = 9.6, 9.6 Hz, 1H), 2.32 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.19−0.89 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.8, 169.8, 138.4, 137.91, 137.85, 137.6, 137.5, 131.8, 131.1, 129.7, 128.41, 128.39, 128.31, 128.27, 128.2, 128.1, 127.8, 127.73, 127.68, 127.67, 127.6, 98.8, 85.9, 80.3, 78.3, 75.7, 74.9, 73.8, 73.8, 72.3, 71.84, 71.80, 71.3, 70.6, 68.4, 63.7, 63.5, 21.1, 21.0, 20.8, 18.0, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.49/85.9 ($^1J_{C1/H1}$ = 169.8 Hz), 5.47/98.8 ($J_{C1/H1}$ = 177.9 Hz). HRMS (ESI-TOF) m/z calcd for $C_{60}H_{76}O_{12}NaSiS$ [M + Na]$^+$ 1071.4724, found 1071.4734.

*p-Tolyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→4)-2,3-O-dibenzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**43**).* According to the procedure for **40**, the coupling of donor **5** (68 mg, 0.106 mmol) and acceptor **31** (60 mg, 0.096 mmol) provided was performed to give disaccharide **43** (90 mg, 73%) as a syrup. $[\alpha]_D^{25}$ + 73.7 (c 0.062, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 9.3, 4.8 Hz, 2H), 7.34−7.23 (m, 20H), 7.13−7.04 (m, 2H), 5.54−5.42 (m, 3H), 4.88 (A of ABq, J_{AB} = 11.0 Hz, 1H), 4.70 and 4.46 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.60 and 4.47 (ABq, J_{AB} = 12.1 Hz, 2H, CH_2Ar), 4.56−4.51 (m, 3H, benzylic), 4.41 (dd, J = 11.8, 4.3 Hz, 1H), 4.23 (dd, J = 11.8, 1.9 Hz, 1H), 4.14−4.08 (m, 2H), 4.02−3.87 (m, 5H), 3.84−3.78 (m, 1H), 3.77−3.69 (m, 1H), 2.78−2.62 (m, 2H), 2.62−2.52 (m, 2H), 2.32 (s, 3H), 2.14 (s, 3H), 2.05 (s, 3H), 1.11−0.93 (m, 21H). ^{13}C NMR and DEPT135(100 MHz, $CDCl_3$) δ 206.4, 172.5, 169.9, 138.4, 137.9, 137.8, 137.6, 137.5, 131.8, 131.0, 129.7, 128.42, 128.38, 128.32, 128.25, 128.2, 128.1, 127.8, 127.73, 127.70, 127.68, 127.5, 98.8, 85.9, 80.3, 78.3, 75.7, 74.9, 73.7, 73.7, 72.2, 71.8, 71.8, 71.3, 70.6, 68.4, 63.6, 63.4, 37.9, 29.8, 27.9, 21.1, 21.0, 18.0, 12.0. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.48/85.9 ($J_{C1/H1}$ = 169.5 Hz), 5.46/98.8 ($J_{C1/H1}$ = 176.4 Hz). HRMS (ESI-TOF) m/z calcd for $C_{63}H_{80}O_{13}NaSiS$ [M + Na]$^+$ 1127.4987, found 1127.5011.

*p-Tolyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→4)-2-O-acetyl-3-O-benzyl-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**44**).* According to the procedure for **40**, the coupling of donor **8** (121 mg, 0.205 mmol) and acceptor **29** (103 mg, 0.179 mmol) was performed to give disaccharide **44** (148 mg, 83%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.21 (m, 17H), 7.08 (d, J = 7.9 Hz, 2H), 5.56 (dd, J = 3.0, 1.7 Hz, 1H), 5.50 (dd, J = 3.0, 2.0 Hz, 1H), 5.46 (d, J = 1.8 Hz, 1H), 5.37 (d, J = 1.5 Hz, 1H), 4.88 and 4.54 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.71 and 4.45 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.65 and 4.49 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.36 (dd, J = 11.9, 4.1 Hz, 1H), 4.26 (dd, J = 11.9, 2.0 Hz, 1H), 4.17−4.03 (m, 2H), 4.01−3.81 (m, 5H), 3.73 (dd, J = 9.6 Hz, 1H), 2.32 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.17−0.89 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.7, 170.2, 169.9, 138.3, 137.9, 137.8, 137.0, 132.0, 130.2, 129.8, 128.53, 128.45, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 98.7, 86.4, 78.4, 78.2, 75.0, 73.6, 73.3, 71.8, 71.4, 71.2, 70.7, 69.6, 68.3, 63.3, 63.1, 21.1, 21.0, 20.9, 20.8, 18.0, 17.9, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.46/98.7 ($J_{C1/H1}$ = 177.4 Hz), 5.37/86.4 ($J_{C1/H1}$ = 170.8 Hz). HRMS (ESI-TOF) m/z calcd for $C_{55}H_{72}O_{13}NaSiS$ [M + Na]$^+$ 1023.4361, found 1023.4323.

*p-Tolyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→6)-2-O-acetyl-3,4-O-dibenzyl-1-thio-α-D-mannopyranoside (**45**).* According to the procedure for **40**, the coupling of donor **8** (96 mg, 0.163 mmol) and acceptor **2** (72 mg, 0.142 mmol) was performed to give **45** (85 mg, 64%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.19 (m, 22H), 7.08 (d, J = 7.9 Hz, 2H), 5.60 (dd, J = 3.2, 1.7 Hz, 1H), 5.44 (dd, J = 3.2, 1.9 Hz, 1H), 5.38 (d, J = 1.5 Hz, 1H), 4.92 and 4.50 (ABq, J_{AB} = 11.8 Hz, 2H, CH_2Ar), 4.91 (s, 1H), 4.90 and 4.54 (ABq, J_{AB} = 10.7 Hz, 2H, CH_2Ar), 4.73 and 4.55 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.67 and 4.47 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.34−4.20 (m, 3H), 3.97 (dd, J = 9.3, 3.5 Hz, 1H), 3.94 (dd, J = 9.5, 3.3 Hz, 1H), 3.94−3.87 (m, 1H), 3.86−3.78 (m, 2H), 3.73 (dd, J = 9.4, 9.4 Hz, 1H), 3.69 (dd, J = 11.7, 1.6 Hz, 1H), 2.21 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 2.01 (s, 3H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.7, 170.3, 170.1, 138.2, 137.9, 137.6, 137.5, 131.9, 130.0, 130.0, 128.51, 128.49, 128.41, 128.38, 128.3, 128.2, 128.01, 127.97, 127.9, 127.78, 127.76, 127.7, 98.0, 86.6, 78.5, 77.8, 75.2, 75.2, 74.3, 74.0, 72.1, 71.9, 71.7, 70.2, 69.8, 68.2, 66.2, 63.3, 21.04, 21.01(2C), 20.8. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ5.38/86.6 ($J_{C1/H1}$ = 170.4 Hz), 4.91/98.0 ($J_{C1/H1}$ = 175.0 Hz). HRMS (ESI-TOF) m/z calcd for $C_{53}H_{58}O_{13}NaS$ [M + Na]$^+$ 957.3496, found 957.3444.

*p-Tolyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→6)-2-O-acetyl-3-O-dibenzyl-1-thio-α-D-mannopyranoside (**46**).* According to the procedure for **40**, the coupling of donor **5** (103 mg, 0.157 mmol) and acceptor **2** (73 mg, 0.143 mmol) was performed to give disaccharide **46** (108 mg, 77%) as a syrup. $[\alpha]_D^{25}$ + 65.1 (c 0.312, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.19 (m, 22H), 7.08 (d, J = 7.9 Hz, 2H), 5.60 (dd, J = 3.2, 1.7 Hz, 1H), 5.44 (dd, J = 3.2, 1.9 Hz, 1H), 5.38 (d, J = 1.5 Hz, 1H), 4.92 and 4.50 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.899 and 4.545 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.896 (d, J = 1.9 Hz, 1H), 4.73 and 4.554 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.67 and 4.47 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.31 (dd, J = 11.8, 4.4 Hz, 1H), 4.30−4.26 (m, 1H), 4.23 (dd, J = 11.9, 2.0 Hz, 1H), 4.00−3.88 (m, 3H), 3.86−3.78 (m, 2H), 3.76−3.71 (m, 1H), 3.69 (dd, J = 11.5, 1.6 Hz, 1H), 2.75−2.64 (m, 2H), 2.59−2.51 (m, 2H), 2.21 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$, HSQC) δ 206.2, 172.5, 170.3, 170.1, 138.3, 138.2, 138.0, 137.7, 137.6, 132.0, 130.1, 130.0, 128.52, 128.50, 128.42, 128.37, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.74, 127.70, 98.0, 86.7, 78.5, 77.8, 75.3, 75.2, 74.3, 74.0, 72.1, 71.9, 71.6, 70.2, 69.9, 68.2, 66.2, 63.4, 37.9, 29.8, 27.8, 21.1, 21.03 (2C).

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HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.38/86.7 ($J_{C1/H1}$ = 171.1 Hz), 4.896/98.0 ($J_{C1/H1}$ = 174.7 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{56}H_{62}O_{14}NaS$ $[M + Na]^+$ 1013.3758, found 1013.3718.

*p-Methoxyphenyl 2,4-di-O-benzyl-α-D-mannopyranoside (**48**).* To a solution of known compound **47**[29d] (349 mg, 0.753 mmol) in CH_2Cl_2 (6 mL) at 0 °C were added BH_3·THF (5 mL, 1 M in THF, 5 mmol) and then $Cu(OTf)_2$ (82 mg, 0.23 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 1h. After completion, the mixture was quenched with Et_3N (1 mL) and MeOH, and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/10/1−1/3/1) provided **48** (157 mg, 45%) as a syrup. $[\alpha]_D^{25}$ + 6.0 (*c* 0.294, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.26 (m, 10H), 6.96−6.88 (m, 2H), 6.86−6.77 (m, 2H), 5.45 (d, *J* = 1.5 Hz, 1H), 4.92 and 4.70 (ABq, J_{AB} = 11.1 Hz, 2H, C*H*$_2$Ar), 4.76 and 4.67 (ABq, J_{AB} = 11.6 Hz, 2H, C*H*$_2$Ar), 4.19 (ddd, *J* = 8.5, 8.5, 3.8 Hz, 1H), 3.93 (dd, *J* = 3.7, 1.7 Hz, 1H), 3.87−3.67 (m, 7H), 2.39 (d, *J* = 8.9 Hz, 1H, O*H*), 1.91 (brs, 1H, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.0, 138.3, 137.5, 128.7, 128.5, 128.2, 128.1, 128.0, 127.9, 117.7, 114.7, 96.4, 78.3, 76.1, 75.0, 73.4, 72.1, 71.6, 62.0, 55.7. HRMS (ESI-TOF) m/z calcd for $C_{50}H_{66}O_{11}NaSi$ $[M + Na]^+$ 893.4272, found 893.4246.

*p-Methoxyphenyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→6)-2,4-O-dibenzyl-α-D-mannopyranoside (**49**).* Thioglycoside donor **3** (150 mg, 0.247 mmol) and acceptor **48** (110 mg, 0.235 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −20 °C, and treated successively with NIS (61 mg, 0.270 mmol) and TMSOTf (4.3 μL, 0.0235 mmol). After stirring at −20 °C for 20 min, the mixture was allowed to warm to 0 °C and stirred for 10 min. The mixture was treated with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/10/1−1/3/1) afforded **49** (126 mg, 57%) as a syrup. $[\alpha]_D^{25}$ + 34.5 (*c* 0.506, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.35 (m, 4H), 7.34−7.24 (m, 16H), 6.98−6.90 (m, 2H), 6.82−6.75 (m, 2H), 5.49 (d, *J* = 1.5 Hz, 1H), 5.37 (dd, *J* = 3.1, 1.9 Hz, 1H), 4.91 and 4.52 (ABq, J_{AB} = 11.3 Hz, 2H, C*H*$_2$Ar), 4.91 and 4.57 (ABq, J_{AB} = 10.9 Hz, 2H, C*H*$_2$Ar), 4.85 (d, *J* = 1.6 Hz, 1H), 4.81 and 4.63 (ABq, J_{AB} = 11.7 Hz, 2H, C*H*$_2$Ar), 4.60 and 4.38 (ABq, J_{AB} = 11.1 Hz, 2H, C*H*$_2$Ar), 4.31 (dd, *J* = 11.9, 4.5 Hz, 1H), 4.26 (dd, *J* = 11.8, 2.2 Hz, 1H), 4.23−4.14 (m, 1H), 3.92 (dd, *J* = 3.7, 1.6 Hz, 1H), 3.90−3.80 (m, 4H), 3.73 (dd, *J* = 9.6 Hz, 1H), 3.68−3.58 (m, 5H), 2.74−2.64 (m, 2H), 2.61−2.52 (m, 2H), 2.44 (d, *J* = 7.8 Hz, 1H, O*H*), 2.14 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 172.5, 170.1, 154.9, 150.2, 138.3, 138.2, 137.8, 137.5, 128.7, 128.44, 128.38, 128.37, 128.2, 128.1, 128.04, 128.02, 127.8, 127.7, 117.4, 114.7, 97.7, 95.6, 78.4, 77.9, 76.3, 75.2, 74.8, 74.0, 73.2, 71.8, 71.5, 70.8, 69.8, 68.3, 66.5, 63.4, 55.5, 37.9, 29.8, 27.9, 21.1. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.49/95.6 ($J_{C1/H1}$ = 171.1 Hz), 4.85/97.7 ($J_{C1/H1}$ = 173.6 Hz). HRMS (ESI-TOF) m/z calcd for $C_{54}H_{60}O_{15}Na$ $[M + Na]^+$ 971.3830, found 971.3836.

*p-Methoxyphenyl 2,4-O-dibenzyl-3-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-[2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→6)]-2,4-di-O-benzyl-α-D-mannopyranoside (**50**).* Thioglycoside donor **18** (101 mg, 0.136 mmol) and acceptor **49** (100 mg, 0.105 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −15 °C, and treated successively with NIS (31 mg, 0.136 mmol) and TMSOTf (2 μL, 0.011 mmol). After stirring at −15 °C for 20 min, the mixture was allowed to warm to 0 °C. The mixture was treated with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/10/1−1/3/1) afforded **50** (142 mg, 87%) as a syrup. $[\alpha]_D^{25}$ + 35.4 (*c* 0.112, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.33−7.17 (m, 30H), 6.98−6.89 (m, 2H), 6.81−6.73 (m, 4H), 5.45 (d, *J* = 1.5 Hz, 1H), 5.36 (dd, 1H), 5.23 (s, 1H), 4.94 (A of ABq, J_{AB} = 11.3 Hz, 1H), 4.90 (A of ABq, J_{AB} = 10.8 Hz, 1H), 4.82 (d, *J* = 1.5 Hz, 1H), 4.76 (s, 2H, benzylic), 4.66−4.39 (m, 9H, benzylic), 4.35 (B of ABq, J_{AB} = 11.1 Hz, 1H), 4.32−4.23 (m, 3H), 4.08−4.04 (m, 1H), 3.99 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.96−3.79 (m, 8H), 3.78−3.67 (m, 6H), 3.60 (s, 3H), 3.58−3.53 (m, 1H), 2.73−2.60 (m, 2H), 2.59−2.47 (m, 2H), 2.13 (s, 3H), 2.12 (s, 3H), 1.13−0.92 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 206.3, 172.5, 170.1, 159.1, 154.8, 150.1, 139.1, 138.5, 138.3, 138.2, 138.1, 137.8, 130.8, 129.3, 128.5, 128.39, 128.37, 128.3, 128.23, 128.15, 128.1, 127.74, 127.71, 127.68, 127.4, 127.3, 127.0, 117.4, 114.6, 113.7, 100.2, 97.8, 95.9, 79.8, 78.7 (missing), 78.0, 77.8, 76.0, 75.3, 75.0, 74.9, 74.8, 74.7, 74.3, 74.0, 72.8, 72.4, 72.1, 71.6, 71.4, 69.8, 68.3, 66.5, 63.4 (2C), 55.5, 55.2, 37.9, 29.8, 27.9, 21.1, 18.04, 18.02, 12.0. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.45/95.9 ($J_{C1/H1}$ = 171.2 Hz), 5.23/100.2 ($J_{C1/H1}$ = 169.9 Hz), 4.82/97.8 ($J_{C1/H1}$ = 172.5 Hz). HRMS (ESI-TOF) m/z calcd for $C_{91}H_{110}O_{21}NaSi$ $[M + Na]^+$ 1589.7207, found 1589.7234.

*p-Methoxyphenyl 2,4-O-dibenzyl-3-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-[2-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→6)]-2,4-di-O-benzyl-α-D-mannopyranoside (**51**).* N_2H_4·HOAc (1 M in MeOH, 0.18 mL, 0.18 mmol) was added to a solution of compound **50** (140 mg, 0.089 mmol) in a mixed solvent (CH_2Cl_2/MeOH, v/v 12.5/1, 5.4 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was then quenched by acetone and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/10/1−1/3/1) afforded **51** (116 mg, 89%) as a syrup. $[\alpha]_D^{25}$ + 42.9 (*c* 0.056, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H), 7.35−7.17 (m, 30H), 6.96−6.90 (m, 2H), 6.83−6.75 (m, 4H), 5.43 (d, *J* = 1.8 Hz, 1H), 5.36 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.22 (s, 1H), 4.94 (A of ABq, J_{AB} = 11.3 Hz, 1H), 4.91 (A of ABq, J_{AB} = 11.1 Hz, 1H), 4.79 (d, *J* = 1.7 Hz, 1H), 4.76 and 4.73 (ABq, J_{AB} = 11.9 Hz, 2H, C*H*$_2$Ar), 4.67−4.38 (m, 9H, benzylic), 4.36 (B of ABq, J_{AB} = 11.1 Hz, 1H), 4.28 (dd, *J* = 9.0, 3.2 Hz, 1H), 4.05 (dd, *J* = 3.0, 2.0 Hz, 1H), 3.99 (dd, *J* = 9.2, 2.9 Hz, 1H), 3.96−3.78 (m, 7H), 3.78−3.70 (m, 5H), 3.69 (s, 3H), 3.68−3.63 (m, 1H), 3.62 (s, 3H), 3.55 (d, *J* = 10.8 Hz, 1H), 2.11 (s, 3H), 1.07−0.97 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$, HSQC) δ 170.1, 159.1, 154.8, 150.1, 139.1, 138.52, 138.48, 138.1, 138.0, 130.7, 129.3, 128.5, 128.38, 128.36, 128.22, 128.20, 128.15, 128.08, 128.05, 128.0, 127.73, 127.70, 127.6, 127.38, 127.36, 127.3, 127.0, 117.4, 114.6, 113.7, 100.2, 97.9, 96.0, 79.8, 78.7 (missing), 77.9, 77.7, 76.0, 75.3, 75.0, 74.9, 74.8, 74.7, 74.3, 74.1, 72.7, 72.4, 72.1, 71.9, 71.51, 71.45, 68.4, 66.5, 63.4, 62.1, 55.5, 55.2, 21.1, 18.03, 18.00, 12.0. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.43/96.0 ($J_{C1/H1}$ = 171.8 Hz), 5.22/100.2 ($J_{C1/H1}$ = 171.1 Hz), 4.79/97.9 ($J_{C1/H1}$ = 173.1 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{86}H_{104}O_{19}NaSi$ $[M + Na]^+$ 1491.6839, found 1491.6852.

General Glycosylation Method A. Thioglycoside donor (1.2 equiv) and acceptor (1.0 equiv) were dissolved in anhydrous CH_2Cl_2 (9.4 μM for acceptor). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −15 °C, and treated successively with NIS (1.3 equiv) and TMSOTf (0.1 equiv). The reaction was allowed to warm to 0 °C within 1 h, and then quenched with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.). The mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel afforded the product.

General Glycosylation Method B. Thioglycoside donor (1.2 equiv) and acceptor (1.0 equiv) were dissolved in anhydrous CH_2Cl_2 (9.4 μM for acceptor). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −15 °C, and treated successively with NIS (1.3 equiv) and TMSOTf (0.1 equiv). The reaction was allowed to warm to room temperature and stirred for

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10 h. The mixture was treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel afforded the products.

General Procedure for Competing Reaction. Thioglycoside donor A (1 equiv), thioglycoside donor B (1.0 equiv) and acceptor (3.0 equiv) were dissolved in anhydrous CH_2Cl_2 (9.4 μM for donor). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −15 °C, and treated successively with NIS (1.0 equiv) and TMSOTf (0.1 equiv). The reaction was kept at −15 °C for a period of time (1 or 2 h), and then treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.). The mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with water and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a residue. The ratio of two coupling products was determined by crude ^{1}H NMR. Flash chromatography on silica gel afforded the products.

*2,6-O-Acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→3)-2,4-O-dibenzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-1,2:4,6-di-O-isopropylidene glucofuranose (**55**).* According to the general method A, donor **40** (57.7 mg, 0.057 mmol) and acceptor **52** (11.9 mg, 0.048 mmol) were subjected to glycosylation to produce **55** (15.7 mg, 29%) with **40** (33.5 mg, 58%) recovered. Data for **55**: $[\alpha]_D^{25}$ + 21.4 (*c* 0.26, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.14 (m, 20H), 5.79 (d, *J* = 3.5 Hz, 1H), 5.47 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.23 (d, *J* = 1.4 Hz, 1H), 5.15 (d, *J* = 1.4 Hz, 1H), 4.89 (A of ABq, J_{AB} = 10.9 Hz, 1H), 4.77 and 4.60 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.66 (A of ABq, J_{AB} = 11.8 Hz, 1H), 4.64 and 4.46 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.56−4.49 (m, 3H, benzylic ×2, pyranosyl ×1), 4.27 (d, *J* = 2.6 Hz, 1H), 4.23 (dd, *J* = 11.9, 4.9 Hz, 1H), 4.16−4.06 (m, 3H), 4.06−3.94 (m, 5H), 3.95−3.86 (m, 3H), 3.76 (dd, *J* = 2.7, 2.0 Hz, 1H), 3.71 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.61 (ddd, *J* = 9.3, 3.2, 3.2 Hz, 1H), 2.10 (s, 3H), 2.00 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.17−0.92 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$, HSQC) δ 170.6, 169.9, 138.2, 138.0, 137.8, 137.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.82, 127.80, 127.74, 127.65, 127.4, 111.9, 109.3, 105.2, 99.6, 97.7, 84.1, 81.5, 79.8, 77.9, 78.6 (missing), 77.4 (missing), 75.2, 75.1, 74.8, 74.2, 74.1, 72.5, 71.9, 71.8, 70.1, 68.7, 67.8, 63.4, 62.9, 26.9(2C), 26.2, 25.5, 21.0, 20.8, 18.04, 17.99, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.79/105.2 ($J_{C1/H1}$ = 187.0 Hz), 5.23/97.7 ($J_{C1/H1}$ = 173.1 Hz), 5.15/99.6 ($J_{C1/H1}$ = 175.6 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{65}H_{88}O_{18}NaSi$ $[M + Na]^+$ 1207.5638, found 1207.5696.

*2,6-O-Acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→4)-2,3-O-dibenzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-1,2:4,6-di-O-isopropylidene glucofuranose (**56**).* According to the general method A, donor **42** (60 mg, 0.057 mmol) and acceptor **52** (12.4 mg, 0.048 mmol) were subjected to glycosylation to produce **56** (52.5 mg, 92%) as a syrup. $[\alpha]_D^{25}$ + 19.6 (*c* 0.354, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 20H), 5.87 (d, *J* = 3.5 Hz, 1H), 5.49 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.45 (d, *J* = 1.6 Hz, 1H), 5.18 (d, *J* = 1.7 Hz, 1H), 4.88 (A of ABq, J_{AB} = 11.0 Hz, 1H), 4.70 (A of ABq, J_{AB} = 10.9 Hz, 1H), 4.64−4.57 (m, 2H, benzylic ×1, anomeric ×1), 4.55−4.42 (m, 5H, benzylic), 4.36 (dd, *J* = 11.8, 4.9 Hz, 1H), 4.26 (dd, *J* = 6.7, 1.9 Hz, 2H), 4.24 (dd, *J* = 11.8, 2.0 Hz, 1H), 4.16−4.10 (m, 1H), 4.09−3.97 (m, 5H), 3.94−3.88 (m, 2H), 3.86 (dd, *J* = 10.8, 6.9 Hz, 1H), 3.79 (dd, *J* = 9.2, 2.9 Hz, 1H), 3.73−3.60 (m, 4H), 2.03 (s, 3H), 2.02 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.09−0.98 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.8, 169.8, 138.3, 138.0, 137.9, 137.8, 128.4, 128.34, 128.30, 128.27, 128.02, 127.97, 127.71, 127.66, 127.61, 127.58, 112.1, 109.3, 105.3, 98.8, 98.5, 83.9, 81.6, 80.6, 79.6, 78.4, 74.9, 74.0, 73.89, 73.85, 72.6, 72.3, 72.2, 71.8, 71.3, 70.6, 68.3, 67.9, 64.1, 63.4, 27.0, 26.9, 26.3, 25.6, 20.9, 20.8, 18.02, 18.00, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.87/105.3 ($J_{C1/H1}$ = 185.2 Hz), 5.45/98.8 ($J_{C1/H1}$ = 178.2 Hz), 5.18/98.5 ($J_{C1/H1}$ = 173.8 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{65}H_{88}O_{18}NaSi$ $[M + Na]^+$ 1207.5638, found 1207.5696.

*Methyl 2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→4)-2,3-O-dibenzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-3-O-benzyl-4,6-O-benzylidene mannopyranoside (**57**).* According to the general method A, donor **43** (44 mg, 0.039 mmol) and known acceptor **53** (12.2 mg, 0.033 mmol) were subjected to glycosylation to produce **57** (32 mg, 72%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.43−7.36 (m, 3H), 7.34−7.25 (m, 18H), 7.25−7.15 (m, 7H), 5.67 (s, 1H), 5.49 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.46 (d, *J* = 1.7 Hz, 1H), 5.31 (d, *J* = 1.6 Hz, 1H), 4.88 (A of ABq, J_{AB} = 11.0 Hz, 1H), 4.81 and 4.64 (ABq, J_{AB} = 11.5 Hz, 2H, CH_2Ar), 4.73 (d, *J* = 1.5 Hz, 1H), 4.72 and 4.47 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.57−4.50 (m, 3H, benzylic), 4.40 (dd, *J* = 12.1, 4.1 Hz, 1H), 4.38 (d, *J* = 12.4 Hz, 1H), 4.30 (d, *J* = 12.1 Hz, 1H), 4.28 (dd, *J* = 9.7, 4.2 Hz, 1H), 4.21 (dd, *J* = 11.8, 1.9 Hz, 1H), 4.18 (dd, *J* = 2.7, 1.7 Hz, 1H), 4.04−3.94 (m, 4H), 3.92−3.78 (m, 7H), 3.74−3.70 (m, 1H), 3.69−3.61 (m, 1H), 3.34 (s, 3H), 2.75−2.65 (m, 2H), 2.60−2.53 (m, 2H), 2.13 (s, 3H), 2.03 (s, 3H), 1.09−0.97 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 206.3, 172.5, 169.8, 138.43, 138.37, 138.3, 138.0, 137.9, 137.6, 129.0, 128.39, 128.37, 128.32, 128.25, 128.2, 128.12, 128.10, 128.07, 127. 8, 127.70, 127.68, 127.6, 127.5, 127.4, 126.1, 101.6, 101.2, 98.80, 98.76, 79.4, 79.29, 78.34, 76.4, 74.9, 74.6, 74.3, 73.8, 73.6, 73.5, 72.3, 72.1, 71.8, 70.9, 70.6, 68.9, 68.3, 64.2, 63.8, 63.4, 54.6, 37.9, 29.8, 27.9, 21.0, 18.02, 18.00, 12.0. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.46/98.80 ($J_{C1/H1}$ = 177.0 Hz), 5.31/98.76 ($J_{C1/H1}$ = 174.2 Hz), 4.73/101.2 ($J_{C1/H1}$ = 172.7 Hz). HRMS (ESI-TOF) *m*/*z* Calcd for $C_{77}H_{96}O_{19}NaSi$ $[M + Na]^+$ 1375.6213, found 1375.6171.

*p-Methoxyphenyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→4)-2-O-acetyl-3-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-4-O-benzoyl-2-O-benzyl-α-L-fucopyranoside (**58**).* According to the general method B, donor **44** (75 mg, 0.080 mmol) and acceptor **54** (31 mg, 0.067 mmol) were subjected to glycosylation to produce **58** (51.9 mg, 61%) as a syrup. $[\alpha]_D^{25}$ −29.0 (*c* 0.248, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.05 (m, 2H), 7.65−7.57 (m, 1H), 7.54−7.45 (m, 2H), 7.37−7.23 (m, 15H), 7.21−7.16 (m, 3H), 7.10−7.05 (m, 2H), 7.04−6.97 (m, 2H), 6.88−6.81 (m, 2H), 5.54 (dd, *J* = 3.5, 0.9 Hz, 1H), 5.51 (dd, *J* = 3.1, 2.0 Hz, 1H), 5.46 (d, *J* = 3.4 Hz, 1H), 5.39 (d, *J* = 1.7 Hz, 1H), 5.26 (d, *J* = 1.6 Hz, 1H), 5.21 (dd, *J* = 3.0, 1.9 Hz, 1H), 4.88 (A of ABq, J_{AB} = 11.0 Hz, 1H), 4.78 (A of ABq, J_{AB} = 10.7 Hz, 1H), 4.69 and 4.60 (ABq, J_{AB} = 11.9 Hz, 2H, CH_2Ar), 4.56−4.48 (m, 3H, benzylic ×2, pyranosyl ×1), 4.36 (dd, *J* = 11.9, 4.3 Hz, 1H), 4.32−4.23 (m, 3H), 4.07−3.99 (m, 3H), 4.00−3.86 (m, 5H), 3.79 (s, 3H), 3.70 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.62 (dd, *J* = 9.0, 3.1 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 6H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.13−1.00 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$, HSQC) δ 170.8, 170.0, 169.9, 166.1, 155.0, 151.1, 138.4, 137.9, 137.7, 137.4, 133.3, 130.1, 129.8, 128.7, 128.5, 128.41, 128.35, 128.31, 128.25, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 117.9, 114.6, 98.4, 98.2, 96.3, 78.5, 78.4, 76.2, 74.9, 73.8, 73.6, 73.1, 72.6, 72.0, 71.4 (missing), 71.3, 71.2 (missing), 70.6, 68.4, 68.1, 65.7, 63.6, 63.4, 55.7, 21.0, 20.9, 20.8, 18.03, 18.01, 16.0, 12.1. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ5.46/96.3 ($J_{C1/H1}$ = 173.0 Hz), 5.39/98.4 ($J_{C1/H1}$ = 177.3 Hz), 5.26/98.2 ($J_{C1/H1}$ = 178.1 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{75}H_{92}O_{20}NaSi$ $[M + Na]^+$ 1363.5849, found 1363.5864.

*p-Methoxyphenyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-4-O-benzoyl-2-O-benzyl-α-L-fucopyranoside (**59**).* According to the general method B, donor **41** (55.1 mg, 0.059 mmol) and acceptor **54** (22.8 mg, 0.049 mmol) were subjected to glycosylation to produce **59** (14.1 mg, 22%) with **41** (43.9 mg, 80%) recovered. Data for **59**: $[\alpha]_D^{25}$ −24.4 (*c* 0.176, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.00 (m, 2H), 7.60−7.53 (m, 1H), 7.48−7.43 (m, 2H), 7.38−7.22 (m, 20H), 7.00−6.92 (m, 2H), 6.88−6.77 (m, 2H), 5.48 (d, *J* = 2.8 Hz, 1H), 5.35 (dd, *J* = 2.9, 2.0 Hz, 1H), 5.32 (d, *J* = 3.5 Hz, 1H), 5.27 (d, *J* = 1.6 Hz, 1H), 5.17 (dd, *J* = 2.8, 1.9 Hz, 1H), 4.83 and 4.49 (ABq, J_{AB} = 10.7 Hz, 2H, CH_2Ar), 4.82 and 4.57 (ABq, J_{AB} = 12.2 Hz, 2H, CH_2Ar), 4.772 (d, *J* = 1.7 Hz, 1H), 4.765 and 4.66 (ABq, J_{AB} = 11.5 Hz, 2H, CH_2Ar), 4.51 and 4.32 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.47 (dd, *J* = 10.2, 3.4 Hz, 1H), 4.32−4.23 (m, 2H), 4.00−3.84 (m, 8H), 3.81 (ddd, *J* = 10.0, 4.3, 1.9 Hz, 1H), 3.78 (s, 3H),

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3.65 (dd, J = 9.6, 9.6 Hz, 1H), 2.09 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H), 1.11 (d, J = 5.9 Hz, 3H), 1.10−1.03 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.6, 169.8, 169.7, 166.1, 155.0, 151.1, 138.6, 138.01, 137.95, 137.7, 133.1, 129.9, 129.8, 128.5, 128.5, 128.40, 128.37, 128.3, 128.2, 128.1, 127.9, 127.83, 127.75, 127.5, 127.4, 117.9, 114.5, 99.9, 98.2, 96.8, 78.1, 77.9, 76.3, 75.1, 74.4, 73.9, 73.7, 73.5, 73.4, 73.28, 72.25, 71.8, 71.5, 70.4, 68.4, 65.8, 63.1, 62.6, 55.7, 21.0, 20.9, 20.7, 18.1, 18.0, 16.1, 12.1. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ5.32/96.8 ($J_{C1/H1}$ = 172.8 Hz), 5.27/98.2 ($J_{C1/H1}$ = 178.5 Hz), 4.77/99.9 ($J_{C1/H1}$ = 172.8 Hz). HRMS (ESI-TOF) m/z calcd for $C_{75}H_{92}O_{20}NaSi$ $[M + Na]^+$ 1363.5849, found 1363.5864.

*p-Methoxyphenyl 2,6-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→6)-2-O-acetyl-3,4-di-O-benzyl-α-D-mannopyranosyl-(1→3)-4-O-benzoyl-2-O-benzyl-α-L-fucopyranoside (**60**).* According to the general method A, donor **45** (64 mg, 0.068 mmol) and acceptor **54** (26.4 mg, 0.057 mmol) were subjected to glycosylation to produce **60** (39 mg, 54%) as a syrup. $[\alpha]_D^{25}$ −31.6 (c 0.178, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.00 (m, 2H), 7.63−7.54 (m, 1H), 7.50−7.41 (m, 2H), 7.36−7.17 (m, 23H), 7.16−7.10 (m, 2H), 7.05−6.98 (m, 2H), 6.86−6.74 (m, 2H), 5.51−5.47 (m, 2H), 5.42 (d, J = 3.5 Hz, 1H), 5.32 (dd, J = 3.1, 1.8 Hz, 1H), 5.24 (d, J = 1.5 Hz, 1H), 5.03 (d, J = 1.7 Hz, 1H), 4.86 and 4.52 (ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.84 and 4.48 (ABq, J_{AB} = 11.6 Hz, 2H, CH_2Ar), 4.72 and 4.59 (ABq, J_{AB} = 11.8 Hz, 2H, CH_2Ar), 4.67 and 4.43(ABq, J_{AB} = 10.9 Hz, 2H, CH_2Ar), 4.48−4.44 (m, 1H), 4.40 and 4.14 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.32 (qd, J = 6.2, 0.7 Hz, 1H), 4.24 (d, J = 3.4 Hz, 2H), 4.07−4.00 (m, 2H), 3.97 (dd, J = 9.2, 3.3 Hz, 1H), 3.87 (dd, J = 11.9, 3.8 Hz, 1H), 3.84−3.74 (m, 6H), 3.73−3.66 (m, 2H), 2.13 (s, 3H), 2.11 (s, 3H), 2.00 (s, 3H), 1.13 (d, J = 6.5 Hz, 3H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.8, 170.2, 170.0, 166.2, 155.1, 151.2, 138.8, 138.2, 137.9, 137.7, 137.6, 133.2, 129.93, 129.86, 128.53, 128.48, 128.4, 128.3, 128.31, 128.26, 128.25, 128.2, 128.03, 127.96, 127.8, 127.7, 127.6, 127.31, 127.25, 118.0, 114.6, 99.2, 98.0, 96.6, 78.1, 77.9, 76.1, 75.1, 74.1, 73.9, 73.7, 73.6, 72.84, 72.80, 71.9, 71.8, 71.6, 69.8, 68.7, 68.1, 65.82, 65.75, 63.4, 55.6, 21.1, 20.9, 20.8, 16.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ5.42/96.6 ($J_{C1/H1}$ = 172.6 Hz), 5.24/99.2 ($J_{C1/H1}$ = 178.4 Hz), 5.03/98.0 ($J_{C1/H1}$ = 175.3 Hz). HRMS (ESI-TOF) m/z calcd for $C_{73}H_{78}O_{20}Na$ $[M + Na]^+$ 1297.4984, found 1297.4929.

*p-Methoxyphenyl 2,4-O-dibenzyl-3-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-[2-O-acetyl-3,4-di-O-benzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→6)-(2-O-acetyl-3,4-O-dibenzyl-α-D-mannopyranosyl-(1→6)-2-O-acetyl-3,4-O-dibenzyl-α-D-mannopyranosyl-(1→6)]-2,4-O-dibenzyl-α-D-mannopyranoside (**61**).* According to the general method A, donor **46** (92 mg, 0.093 mmol) and acceptor **51** (114 mg, 0.078 mmol) were subjected to glycosylation to produce **61** (119 mg, 65%) as a syrup. $[\alpha]_D^{25}$ + 55.4 (c 0.13, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 2H), 7.34−7.11 (m, 50H), 6.95−6.90 (m, 2H), 6.81−6.73 (m, 4H), 5.48−5.44 (m, 2H), 5.44 (d, J = 1.4 Hz, 1H), 5.40−5.35 (m, 1H), 5.23 (s, 1H), 4.96−4.84 (m, 6H, benzylic ×4, anomeric ×2), 4.80 (d, J = 1.4 Hz, 1H), 4.75 (s, 2H, CH_2Ar), 4.69−4.37 (m, 15H, benzylic), 4.33 (B of ABq, J_{AB} = 11.0 Hz, 1H), 4.28 (dd, J = 8.9, 2.9 Hz, 1H), 4.23 (dd, J = 11.7, 3.3 Hz, 1H), 4.15 (d, J = 11.1 Hz, 1H), 4.06−4.03 (m, 1H), 3.99 (dd, J = 9.3, 2.8 Hz, 1H), 3.96−3.65 (m, 21H), 3.63−3.57 (m, 4H), 3.57−3.49 (m, 3H), 2.74−2.61 (m, 2H), 2.58−2.46 (m, 2H), 2.15 (s, 6H), 2.14 (s, 3H), 2.13 (s, 3H), 1.11−0.90 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$, HSQC) δ 206.2, 172.5, 170.3, 170.2, 170.0, 159.1, 154.8, 150.2, 139.1, 138.7, 138.6, 138.5, 138.23, 138.19, 138.18, 137.9, 137.7, 137.6, 130.8, 129.3, 128.52, 128.49, 128.42, 128.39, 128.36, 128.31, 128.27, 128.24, 128.16, 128.1, 127.92, 127.89, 127.8, 127.7, 127.51, 127.45, 127.4, 127.3, 127.0, 117.5, 114.6, 113.8, 100.2, 98.1, 98.03, 97.99, 96.0, 79.9, 78.7, 78.0, 77.73, 77.69, 77.5, 76.0, 75.2, 74.99 (2C), 74.96, 74.9, 74.8, 74.6, 74.3, 73.9, 73.8, 73.7, 72.7, 72.4, 72.1, 71.8, 71.4 (2C), 71.3, 71.2, 71.1, 69.8, 68.2, 68.1 (2C), 66.57, 65.62, 65.43, 63.39, 63.3, 55.5, 55.2, 37.9, 29.9, 27.8, 21.09 (2C), 21.06, 18.1, 18.0, 17.7, 12.1. HSQC-HECADE anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.44/96.0 ($J_{C1/H1}$ = 170.8 Hz), 5.23/100.2 ($J_{C1/H1}$ = 170.4 Hz), 4.93/98.1 ($J_{C1/H1}$ = 172.9 Hz), 4.89/98.03 ($J_{C1/H1}$ = 173.3 Hz), 4.80/97.99 ($J_{C1/H1}$ = 172.7 Hz). HRMS (ESI-TOF) m/z Calcd for $C_{135}H_{158}O_{33}NaSi$ $[M + Na]^+$ 2358.0352, found 2358.0339.

*3-O-Acetyl-2,4-di-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-1,2:4,6-di-O-isopropylidene glucofuranose (**62**).* According to the general method A, donor **20** (50 mg, 0.075 mmol) and acceptor **52** (16.3 mg, 0.063 mmol) were subjected to glycosylation to produce **62** (48.7 mg, 97%) as a syrup. $[\alpha]_D^{25}$ + 7.7 (c 0.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 10H), 5.83 (d, J = 3.5 Hz, 1H), 5.20 (dd, J = 9.4, 3.3 Hz, 1H), 5.16 (d, J = 1.9 Hz, 1H), 4.70 and 4.63 (ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.63 and 4.51(ABq, J_{AB} = 11.2 Hz, 2H, CH_2Ar), 4.57 (d, J = 3.5 Hz, 1H), 4.27 (d, J = 2.8 Hz, 1H), 4.21−4.14 (m, 1H), 4.13 (dd, J = 8.4, 6.0 Hz, 1H), 4.06 (dd, J = 8.5, 2.8 Hz, 1H), 4.03−3.97 (m, 2H), 3.95 (d, J = 3.2 Hz, 2H), 3.86 (dd, J = 3.3, 2.0 Hz, 1H), 3.71 (ddd, J = 9.7, 3.2, 3.2 Hz, 1H), 1.98 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.16−1.01 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.2, 138.2, 138.0, 128.4, 128.3, 127.80, 127.77, 127.7, 127.5, 111.9, 109.2, 105.3, 98.6, 84.1, 81.6, 80.4, 75.9, 74.9, 74.0, 73.43, 73.37, 72.6, 72.5, 67.8, 63.0, 27.0, 26.9, 26.3, 25.5, 21.1, 18.03, 17.99, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.83/105.3 ($J_{C1/H1}$ = 185.4 Hz), 5.16/98.6 ($J_{C1/H1}$ = 173.7 Hz). HRMS (ESI-TOF) m/z calcd for $C_{43}H_{64}O_{12}NaSi$ $[M + Na]^+$ 823.4065, found 823.4097.

*4-O-Acetyl-2,3-di-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-1,2:4,6-di-O-isopropylidene glucofuranose (**63**).* According to the general method A, donor **32** (50 mg, 0.075 mmol) and acceptor **52** (16.3 mg, 0.063 mmol) were subjected to glycosylation to produce **63** (47.5 mg, 95%) as a syrup. $[\alpha]_D^{25}$ + 9.9 (c 0.258, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 10H), 5.85 (d, J = 3.5 Hz, 1H), 5.26 (dd, J = 9.4 Hz, 1H), 5.17 (d, J = 1.7 Hz, 1H), 4.66 (s, 2H, CH_2Ar), 4.61 (d, J = 3.5 Hz, 1H), 4.53 and 4.46 (ABq, J_{AB} = 12.2 Hz, 2H, CH_2Ar), 4.26 (s, 1H), 4.13−3.96 (m, 4H), 3.86−3.78 (m, 1H), 3.78−3.69 (m, 4H), 2.01 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H), 1.11−1.01 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 169.8, 138.2, 138.1, 128.33, 128.28, 127.7, 127.6, 127.5, 112.1, 109.3, 105.3, 99.1, 83.8, 81.4, 80.9, 76.8, 74.2, 73.7, 72.6, 72.5, 71.8, 68.9, 67.8, 65.0, 27.0, 26.9, 26.3, 25.5, 21.0, 18.0, 11.9. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.85/105.3 ($J_{C1/H1}$ = 183.0 Hz), 5.17/99.1 ($J_{C1/H1}$ = 173.6 Hz). HRMS (ESI-TOF) m/z calcd for $C_{43}H_{64}O_{12}NaSi$ $[M + Na]^+$ 823.4065, found 823.4097.

*Benzyl 2,4-O-diacetyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**64**).* Donor **16** (260 mg, 0.402 mmol) and acceptor **27** (149 mg, 0.335 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (600 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −20 °C, and treated successively with NIS (91 mg, 0.402 mmol) and TMSOTf (6 μL, 0.034 mmol). After stirring at −20 °C for 40 min, the mixture was allowed to warm to room temperature and stirred until the reaction is complete. The mixture was treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) to afford **64** (229 mg, 71%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 12H), 6.91−6.84 (m, 2H), 5.43 (dd, J = 3.0, 2.2 Hz, 1H), 5.28 (dd, J = 9.9, 9.9 Hz, 1H), 5.13 (dd, J = 9.8, 9.8 Hz, 1H), 5.02 (d, J = 1.8 Hz, 1H), 4.98 (d, J = 1.9 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.36 (d, J = 11.9 Hz, 1H), 4.13−4.08 (m, 2H), 4.02 (dd, J = 2.8, 2.2 Hz, 1H), 3.93−3.77 (m, 7H), 3.72 (dd, J = 11.1, 6.0 Hz, 1H), 3.63 (dd, J = 11.1, 2.0 Hz, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.10−0.96 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.0, 169.7, 169.6, 159.3, 138.0, 137.0, 129.9, 129.8, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 113.8, 99.4, 98.4, 76.3, 75.1, 73.6, 72.7, 72.2, 70.7, 69.5, 69.1, 68.03, 68.02, 67.7, 63.3, 63.1, 55.2, 21.0, 20.9, 20.7, 18.0, 12.0. HRMS (ESI-TOF) m/z calcd for $C_{51}H_{70}O_{16}NaSi$ $[M + Na]^+$ 989.4331, found 989.4343.

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*Benzyl 2,4-O-diacetyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**65**).* DDQ (70 mg, 0.310 mmol) was added to a solution of compound **64** (222 mg, 0.230 mmol) in a mixed solvent (CH_2Cl_2/pH 7.0 phosphate buffer, v/v 20/1, 5 mL) at 0 °C. After stirring at 0 °C for 60 min, the mixture was warmed to room temperature and kept for 3 h. The reaction was then quenched by $NaHCO_3$ (sat. aq.) and CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/10/1−1/0/1) to afford **65** (162 mg, 83%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.16 (m, 10H), 5.27 (dd, J = 9.8, 9.8 Hz, 1H), 5.21−5.14 (m, 2H), 5.04 (d, J = 1.7 Hz, 1H), 5.02 (d, J = 1.8 Hz, 1H), 4.68 (d, J = 12.2 Hz, 1H), 4.65 (d, J = 12.5 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.19−4.12 (m, 2H), 4.08 (dd, J = 12.2, 2.5 Hz, 1H), 3.98 (dd, J = 2.8, 2.1 Hz, 1H), 3.90 (dd, J = 9.6, 3.0 Hz, 1H), 3.88−3.80 (m, 2H), 3.77 (dd, J = 11.2, 4.7 Hz, 1H), 3.65 (dd, J = 11.2, 1.8 Hz, 1H), 2.36 (d, J = 7.5 Hz, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H), 1.11−0.97 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.8, 170.3, 169.7, 138.0, 136.9, 128.5, 128.4, 128.0, 127.8, 127.73, 127.66, 98.9, 98.1, 76.0, 75.4, 72.5, 72.1, 71.8, 69.48, 69.46, 69.1, 68.6, 67.8, 62.9, 62.6, 21.1, 20.9, 20.82, 20.77, 17.94, 17.91, 12.0. HRMS (ESI-TOF) m/z calcd for $C_{43}H_{62}O_{15}NaSi$ $[M + Na]^+$ 869.3756, found 869.3724.

*Benzyl 2-O-acetyl-4-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2,4-O-diacetyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**66**) and Corresponding Orthoester (**67**).* Donor **13** (169 mg, 0.243 mmol) and acceptor **65** (159 mg, 0.187 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (600 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −20 °C, and treated successively with NIS (55 mg, 0.243 mmol) and TMSOTf (4 μL, 0.019 mmol). After stirring at −20 °C for 1 h, the mixture was allowed to warm to room temperature and stirred until the reaction is complete. The mixture was treated with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/1/1) to afford orthoester **67** (175 mg, 66%) and trisaccharide **66** (37 mg, 14%) as syrup. Data for **67**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.17 (m, 15H), 7.13−7.07 (m, 2H), 6.82−6.76 (m, 1H), 5.71 (d, J = 2.3 Hz, 1H), 5.38 (dd, J = 10.1, 10.1 Hz, 1H), 5.32 (dd, J = 2.7, 2.1 Hz, 1H), 5.26 (dd, J = 10.0, 10.0 Hz, 1H), 5.11 (d, J = 1.7 Hz, 1H), 4.97 (d, J = 1.8 Hz, 1H), 4.86−4.77 (m, 2H), 4.63 (d, J = 3.3 Hz, 1H), 4.61 (d, J = 1.4 Hz, 1H), 4.52 (dd, J = 10.0, 2.9 Hz, 1H), 4.43 (d, J = 0.9 Hz, 1H), 4.40 (d, J = 2.6 Hz, 1H), 4.33 (d, J = 12.8 Hz, 1H), 4.28 (d, J = 12.7 Hz, 1H), 4.16 (dd, J = 12.2, 2.3 Hz, 1H), 4.07−3.83 (m, 8H), 3.79−3.72 (m, 5H), 3.67−3.60 (m, 2H), 3.40 (ddd, J = 9.4, 3.0, 1.8 Hz, 1H), 2.19 (s, 3H), 2.15 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.69 (s, 3H), 1.12−0.98 (m, 42H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.5, 169.63, 169.59, 159.2, 138.9, 137.7, 137.1, 130.7, 130.4, 128.5, 128.4, 128.24, 128.20, 128.15, 128.0, 127.9, 127.5, 127.2, 124.7, 113.7, 99.3, 98.2, 98.1, 80.4, 78.2, 77.0, 75.3, 75.1, 74.3, 73.5, 72.7, 72.5, 72.0, 71.0, 69.5, 68.9, 67.4, 66.7 (2C), 63.4, 62.4, 62.0, 55.2, 26.7, 21.1, 21.0, 20.9, 20.8, 18.1, 18.04, 17.96, 17.9, 12.0. HRMS (ESI-TOF) m/z calcd for $C_{75}H_{108}O_{22}NaSi_2$ $[M + Na]^+$ 1439.6768, found 1439.6826. Data for **66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.18 (m, 17H), 6.88−6.78 (m, 2H), 5.25−5.17 (m, 3H), 5.12 (dd, J = 3.0, 1.9 Hz, 1H), 5.03 (d, J = 1.9 Hz, 1H), 5.02 (d, J = 2.0 Hz, 1H), 4.93 (d, J = 1.5 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.67 (2 overlapping d, J = 12.2 Hz, 2H), 4.63 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 10.9 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.43 (d, J = 10.9 Hz, 1H), 4.16−3.99 (m, 6H), 3.92−3.80 (m, 5H), 3.78 (s, 3H), 3.76−3.70 (m, 1H), 3.65 (dd, J = 11.2, 2.2 Hz, 1H), 3.59 (d, J = 9.5 Hz, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.12−0.98 (m, 42H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.5, 169.8, 169.7, 169.3, 159.2, 139.2, 138.0, 137.0, 130.3, 129.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.73, 127.71, 127.64, 127.55, 127.4, 127.3, 113.8, 113.8, 99.5, 98.5, 98.3, 77.2, 76.0, 75.7, 74.9, 74.8, 73.5, 73.4, 72.3, 72.0, 71.4, 71.2, 69.4, 69.2 (2C), 68.1, 67.8, 63.3, 63.1, 61.8, 55.2, 20.94, 20.85, 20.81, 20.79, 20.7, 18.02, 17.96, 17.95, 17.9, 12.03, 11.97. HRMS (ESI-TOF) m/z calcd for $C_{75}H_{108}O_{22}NaSi_2$ $[M + Na]^+$ 1439.6768, found 1439.6749.

*Benzyl 2-O-acetyl-4-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**68**).* Donor **13** (469 mg, 0.675 mmol) and acceptor **27** (250 mg, 0.562 mmol) were dissolved in anhydrous CH_2Cl_2 (9 mL). Freshly activated 4 Å molecular sieves (1.1 g) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −20 °C, and treated successively with NIS (152 mg, 0.675 mmol) and TMSOTf (12.5 μL, 0.068 mmol). After stirring at −20 °C for 40 min, the reaction was quenched with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) to afford **68** (482 mg, 84%) as a syrup. $[\alpha]_D^{25}$ + 29.7 (c 0.046, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 17H), 6.90−6.81 (m, 2H), 5.43 (dd, J = 3.0, 2.0 Hz, 1H), 5.29 (dd, J = 9.8, 9.8 Hz, 1H), 4.96 (d, J = 1.7 Hz, 1H), 4.94 (d, J = 1.8 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.67 (d, J = 10.6 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.65 (d, J = 10.8 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.44 (d, J = 12.2 Hz, 1H), 4.09 (d, J = 3.9 Hz, 2H), 4.03−3.97 (m, 2H), 3.94−3.85 (m, 3H), 3.84−3.78 (m, 1H), 3.77 (s, 1H), 3.74 (dd, J = 11.2, 1.3 Hz, 1H), 3.70−3.62 (m, 1H), 2.06 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.13−0.99 (m, 21H). ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 170.9, 170.0, 169.7, 159.3, 138.7, 138.1, 136.9, 130.2, 130.0, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 113.9, 99.3, 98.1, 77.4, 76.4, 75.2, 74.4, 73.8, 73.5, 71.9, 71.5, 69.3, 69.1, 68.7, 68.0, 62.9, 62.6, 55.2, 21.0, 20.9, 20.7, 18.1, 18.0, 12.1. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 4.96/99.3 ($J_{C1/H1}$ = 174.5 Hz), 4.94/98.1 ($J_{C1/H1}$ = 173.0 Hz). HRMS (ESI-TOF) m/z calcd for $C_{56}H_{74}O_{15}NaSi$ $[M + Na]^+$ 1037.4695, found 1037.4685.

*Benzyl 2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**69**).* DDQ (151 mg, 0.665 mmol) was added to a solution of compound **68** (479 mg, 0.475 mmol) in a mixed solvent (CH_2Cl_2/pH 7.0 phosphate buffer, v/v 20/1, 6 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and kept for 3 h. The reaction was then quenched by $NaHCO_3$ (sat. aq.) and CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/2/1) to afford **69** (329 mg, 78%). $[\alpha]_D^{25}$ + 32.4 (c 0.072, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 15H), 5.26 (dd, J = 9.8, 9.8 Hz, 1H), 5.20 (dd, J = 3.3, 1.8 Hz, 1H), 4.97 (d, J = 1.7 Hz, 1H), 4.96 (d, J = 1.9 Hz, 1H), 4.83 (d, J = 11.1 Hz, 1H), 4.70 (d, J = 11.1 Hz, 1H), 4.66 (d, J = 11.8 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.22 (ddd, J = 9.3, 4.4, 3.5 Hz, 1H), 4.13−4.04 (m, 2H), 3.97 (dd, J = 2.9, 2.0 Hz, 1H), 3.94 (dd, J = 11.4, 3.7 Hz, 1H), 3.91−3.83 (m, 2H), 3.82−3.78 (m, 1H), 3.76 (dd, J = 11.3, 1.1 Hz, 1H), 3.67 (ddd, J = 9.7, 3.3, 1.3 Hz, 1H), 2.16 (d, J = 4.7 Hz, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.14−1.01 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 171.0, 170.6, 169.6, 138.5, 138.0, 136.9, 128.49, 128.45, 128.4, 128.01, 127.95, 127.83, 127.79, 127.7, 127.6, 99.0, 98.0, 76.3, 75.3, 75.0, 74.7, 73.2, 72.5, 71.9, 70.2, 69.3, 69.1, 67.8, 62.7, 62.5, 20.9, 20.83, 20.76, 18.04, 17.95, 12.1. HRMS (ESI-TOF) m/z calcd for $C_{48}H_{66}O_{14}NaSi$ $[M + Na]^+$ 917.4120, found 917.4074.

*Benzyl 2-O-acetyl-4-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**70**).* Donor **13** (332 mg, 0.478 mmol) and acceptor **69** (329 mg, 0.368 mmol) were dissolved in anhydrous CH_2Cl_2 (8 mL). Freshly activated 4 Å molecular sieves (900 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −20 °C, and treated successively

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with NIS (108 mg, 0.478 mmol) and TMSOTf (6.7 μL, 0.037 mmol). After stirring at −20 °C for 40 min, the mixture was treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/30/1−1/6/1) to afford **70** (419 mg, 78%) as a syrup. $[\alpha]_D^{25}$ + 21.3 (*c* 0.23, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 20H), 7.22−7.16 (m, 2H), 6.80−6.74 (m, 2H), 5.43 (dd, *J* = 3.0, 1.9 Hz, 1H), 5.24−5.17 (m, 2H), 5.09 (d, *J* = 1.4 Hz, 1H), 4.97 (d, *J* = 1.8 Hz, 1H), 4.94 (d, *J* = 1.9 Hz, 1H), 4.86 (d, *J* = 10.7 Hz, 1H), 4.77 (d, *J* = 10.8 Hz, 1H), 4.71 (d, *J* = 10.7 Hz, 1H), 4.64 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 12.3 Hz, 1H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 4.51 (d, *J* = 12.3 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.19−4.12 (m, 2H), 4.10−4.05 (m, 3H), 3.96−3.76 (m, 7H), 3.72 (s, 3H), 3.71−3.62 (m, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.12−0.99 (m, 42H). ^{13}C-APT NMR (100 MHz, $CDCl_3$, HSQC) δ 170.9, 170.2, 169.8, 169.3, 159.2, 139.1, 138.2, 138.2, 137.0, 130.3, 129.7, 128.47, 128.45, 128.4, 128.3, 127.96, 127.95, 127.81, 127.77, 127.59, 127.58, 127.5, 113.7, 99.5, 98.5, 97.9, 77.6, 77.6, 75.9, 75.2 (2C, $ArCH_2$), 75.0, 73.9, 73.6, 73.5, 73.1, 71.81, 71.79, 71.4, 69.3, 69.2, 69.0, 68.0, 62.9, 62.3, 61.7, 55.2, 21.0, 20.9, 20.8, 20.7, 18.1, 18.04, 17.97, 17.9, 12.0. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.09/99.5 ($J_{C1/H1}$ = 172.3 Hz), 4.97/98.5 ($J_{C1/H1}$ = 174.4 Hz), 4.94/97.9 ($J_{C1/H1}$ = 173.7 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{80}H_{112}O_{21}NaSi_2$ $[M + Na]^+$ 1487.7132, found 1487.7081.

*Benzyl 2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**71**).* DDQ (28 mg, 0.122 mmol) was added to a solution of compound **70** (149 mg, 0.101 mmol) in a mixed solvent (CH_2Cl_2/pH 7.0 phosphate buffer, v/v 20/1, 5 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and kept for 3 h. The reaction was then quenched by $NaHCO_3$ (sat. aq.) and CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/20/1−1/5/1) to afford **71** (106 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.24 (m, 20H), 5.24−5.15 (m, 3H), 5.10 (d, *J* = 1.3 Hz, 1H), 4.95 (d, *J* = 1.9 Hz, 1H), 4.93 (d, *J* = 1.9 Hz, 1H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 1H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.60 (d, *J* = 10.7 Hz, 1H), 4.52 (d, *J* = 12.2 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.15 (dd, *J* = 9.3, 3.2 Hz, 1H), 4.12−4.01 (m, 5H), 3.97−3.84 (m, 5H), 3.80 (ddd, *J* = 9.7, 5.1, 2.9 Hz, 1H), 3.72−3.61 (m, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.15−0.97 (m, 42H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 169.9, 169.3, 138.8, 138.21, 138.17, 136.9, 128.52, 128.47, 128.39, 128.37, 128.2, 128.0, 127.83, 127.81, 127.7, 127.6, 127.5, 99.2, 98.5, 97.9, 76.6, 76.0, 75.2, 74.9, 74.7, 74.6, 74.3, 73.3, 73.2, 72.4, 71.9, 71.8, 69.7, 69.3, 69.2, 68.1, 63.1, 62.3, 61.8, 20.9, 20.8 (2C), 20.7, 18.04, 18.03, 17.95, 17.9, 12.1. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.10/99.2 ($J_{C1/H1}$ = 173.7 Hz), 4.95/98.5 ($J_{C1/H1}$ = 174.6 Hz), 4.93/97.9 ($J_{C1/H1}$ = 172.8 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{72}H_{104}O_{20}NaSi_2$ $[M + Na]^+$ 1367.6557, found 1367.6591.

*Benzyl 2-O-acetyl-4-O-benzyl-3-O-(4-methoxybenzyl)-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**72**).* Donor **13** (71 mg, 0.102 mmol) and acceptor **71** (106 mg, 0.079 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −20 °C, and treated successively with NIS (23 mg, 0.102 mmol) and TMSOTf (2 μL, 0.0118 mmol). After stirring at −20 °C for 40 min, the mixture was treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/30/1−1/8/1) to afford **72** (139 mg, 92%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 27H), 6.83−6.74 (m, 2H), 5.42 (dd, *J* = 2.9, 1.9 Hz, 1H), 5.26 (dd, *J* = 2.6, 1.8 Hz, 1H), 5.21−5.14 (m, 2H), 5.09 (d, *J* = 1.1 Hz, 1H), 5.08 (d, *J* = 1.4 Hz, 1H), 4.94 (d, *J* = 1.5 Hz, 1H), 4.91 (d, *J* = 1.8 Hz, 1H), 4.84 (d, *J* = 10.1 Hz, 1H), 4.83 (d, *J* = 10.8 Hz, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.632 (d, *J* = 10.8 Hz, 1H), 4.628 (d, *J* = 12.3 Hz, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 10.7 Hz, 1H), 4.54−4.49 (m, 2H), 4.41 (d, *J* = 10.8 Hz, 1H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.22−4.09 (m, 4H), 4.08−4.00 (m, 3H), 3.98−3.80 (m, 7H), 3.80−3.75 (m, 1H), 3.74 (s, 3H), 3.67−3.61 (m, 2H), 3.61−3.54 (m, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H), 1.15−1.01 (m, 42H), 0.99−0.88 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 171.0, 170.2, 170.1, 169.9, 169.2, 159.2, 139.1, 138.6, 138.2, 138.0, 136.9, 130.3, 129.7, 128.7, 128.5, 128.40, 128.35, 128.2, 127.99, 127.95, 127.9, 127.8, 127.7, 127.63, 127.57, 127.54, 127.52, 127.4, 113.7, 99.9, 99.8, 98.5, 97.8, 78.5, 77.6, 77.0, 75.9, 75.68, 75.2, 75.0, 74.9, 73.9 (2C), 73.5, 73.39, 73.37, 73.1, 72.2, 72.1, 71.8, 71.5, 69.24, 69.17, 69.13, 68.07, 63.0, 62.2, 61.8, 61.5, 55.2, 21.0, 20.9, 20.81, 20.80, 20.6, 18.07, 18.06, 18.0, 17.94, 17.91, 17.8, 12.1, 12.03, 11.96. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.09/99.8 ($J_{C1/H1}$ = 173.7 Hz), 5.08/99.9 ($J_{C1/H1}$ = 175.5 Hz), 4.94/98.5 ($J_{C1/H1}$ = 174.2 Hz), 4.91/97.7 ($J_{C1/H1}$ = 173.5 Hz). HRMS (ESI-TOF) *m*/*z* calcd for $C_{104}H_{150}O_{27}NaSi_3$ $[M + Na]^+$ 1937.9570, found 1937.9478.

*Benzyl 2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**73**).* DDQ (49 mg, 0.213 mmol) was added to a solution of compound **72** (314 mg, 0.164 mmol) in a mixed solvent (CH_2Cl_2/pH 7.0 phosphate buffer, v/v 20/1, 5 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and kept for 3 h. The reaction was then quenched by $NaHCO_3$ (sat. aq.) and CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/15/1−1/3/1) to afford **73** (238 mg, 81%). $[\alpha]_D^{25}$ + 33.3 (*c* 0.076, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 20H), 5.27 (dd, *J* = 3.0, 1.8 Hz, 1H), 5.23−5.13 (m, 3H), 5.09 (d, *J* = 1.6 Hz, 1H), 5.08 (d, *J* = 1.3 Hz, 1H), 4.94 (d, *J* = 1.6 Hz, 1H), 4.91 (d, *J* = 1.8 Hz, 1H), 4.83 (d, *J* = 10.0 Hz, 1H), 4.79 (d, *J* = 10.7 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 12.3 Hz, 1H), 4.52 (d, *J* = 12.4 Hz, 1H), 4.51 (d, *J* = 10.0 Hz, 1H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.23−4.08 (m, 3H), 4.09−3.91 (m, 6H), 3.92−3.81 (m, 4H), 3.81−3.72 (m, 2H), 3.70−3.50 (m, 5H), 2.07 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.92 (s, 3H), 1.16−1.00 (m, 42H), 1.00−0.88 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$, HSQC) δ 171.0, 170.5, 170.1, 170.0, 169.3, 138.8, 138.6, 138.2, 138.0, 136.9, 128.7, 128.49, 128.46, 128.4, 128.1, 128.0, 127.9, 127.83, 127.77, 127.6, 127.53, 127.51, 100.0, 99.5, 98.5, 97.7, 78.7, 76.5, 75.8, 75.7, 75.2, 75.1, 74.8, 74.4, 74.1, 73.9, 73.5, 73.1, 73.0, 72.4, 72.1 (2C), 71.8, 69.6, 69.2, 69.1, 68.1, 63.0, 62.2, 61.8, 61.5, 21.0, 20.84, 20.80, 20.77, 20.6, 18.1, 18.04, 17.97, 17.93, 17.89, 17.8, 12.05, 12.03, 11.96. HRMS (ESI-TOF) *m*/*z* calcd for $C_{96}H_{142}O_{26}NaSi_3$ $[M + Na]^+$ 1817.8995, found 1817.8987.

*Benzyl 2-O-acetyl-3,4-O-dibenzyl-6-O-levulinoyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**74**).* Donor **3** (121 mg, 0.199 mmol) and acceptor **73** (238 mg, 0.133 mmol) were dissolved in anhydrous CH_2Cl_2 (6 mL). Freshly activated 4 Å molecular sieves (650 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −20 °C, and treated successively with NIS (46 mg, 0.205 mmol) and TMSOTf (6 μL, 0.033 mmol). After stirring at −20 °C for 1 h, the reaction was allowed to warm to 0 °C and stirred until the reaction is complete. The mixture was treated with $NaHCO_3/Na_2S_2O_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered. The organic layer

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was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/15/1−1/3/1) to afford **74** (218 mg, 72%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 35H), 5.43 (dd, J = 3.0, 1.9 Hz, 1H), 5.28−5.22 (m, 2H), 5.20−5.14 (m, 2H), 5.12 (d, J = 1.4 Hz, 1H), 5.11 (d, J = 1.6 Hz, 1H), 5.08 (d, J = 0.8 Hz, 1H), 4.93 (d, J = 1.6 Hz, 1H), 4.90 (d, J = 1.8 Hz, 1H), 4.88−4.79 (m, 3H), 4.74−4.66 (m, 3H), 4.66−4.58 (m, 3H), 4.56−4.47 (m, 3H), 4.45−4.35 (m, 3H), 4.21−4.10 (m, 5H), 4.09−4.00 (m, 4H), 3.97−3.91 (m, 2H), 3.90−3.71 (m, 8H), 3.66−3.59 (m, 2H), 3.60−3.51 (m, 3H), 2.73−2.57 (m, 2H), 2.57−2.49 (m, 2H), 2.11 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.92 (s, 3H), 1.13−1.02 (m, 42H), 1.00−0.90 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$, HSQC) δ 206.3, 172.4, 171.0, 170.09, 170.07, 170.0 (2C), 169.2, 138.6, 138.5, 138.2 (2C), 138.0, 137.8, 136.9, 128.7, 128.5, 128.37, 128.35, 128.2, 128.1, 128.04, 127.95, 127.9, 127.8, 127.7, 127.60, 127.57, 127.5, 100.1, 99.8, 99.2, 98.4, 97.8, 78.5, 78.0, 77.9, 77.1, 75.9, 75.7, 75.4, 75.1, 75.01, 74.96, 74.04, 73.95, 73.6, 73.5 (2C), 73.3, 73.1, 72.14 (2C), 72.10, 71.8, 71.7, 70.6, 69.2, 69.1, 68.7, 68.1, 63.0 (2C), 62.2, 61.6, 61.5, 37.8, 29.79, 27.76, 21.0, 20.94, 20.90, 20.8 (2C), 20.6, 18.1, 18.0, 17.92, 17.85, 12.0, 11.9. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ 5.12/99.2 ($J_{C1/H1}$ = 174.4 Hz), 5.11/100.1 ($J_{C1/H1}$ = 173.6 Hz), 5.08/99.8 ($J_{C1/H1}$ = 174.4 Hz), 4.93/98.4 ($J_{C1/H1}$ = 175.8 Hz), 4.90/97.8 ($J_{C1/H1}$ = 175.1 Hz). HRMS (ESI-TOF) m/z calcd for $C_{123}H_{172}O_{34}NaSi_3$ [M + Na]$^+$2300.0936, found 2300.0989.

*Benzyl 2-O-acetyl-3,4-O-dibenzyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**75**).* To a solution of compound **74** (107 mg, 0.051 mmol) in a mixed solvent (CH_2Cl_2/MeOH, v/v 12.5/1 5.4 mL) at 0 °C was added a solution of N_2H_4·HOAc (1 M in MeOH, 0.33 mL, 0.33 mmol). The mixture was allowed to warm to room temperature and stirred for 10 h. The reaction was then quenched by acetone and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2, 1/6/1−1/3/1) afforded **75** (92 mg, 90%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.18 (m, 35H), 5.43 (dd, J = 3.1, 1.9 Hz, 1H), 5.25 (dd, J = 2.8, 1.7 Hz, 1H), 5.24−5.21 (m, 1H), 5.20−5.12 (m, 2H), 5.09−5.07 (m, 2H), 5.06 (d, J = 1.6 Hz, 1H), 4.94 (d, J = 1.6 Hz, 1H), 4.91 (d, J = 1.6 Hz, 1H), 4.88−4.79 (m, 3H), 4.74−4.65 (m, 3H), 4.65−4.56 (m, 4H), 4.55−4.48 (m, 2H), 4.43 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 11.9 Hz, 1H), 4.21−4.09 (m, 5H), 4.08−3.99 (m, 3H), 3.97−3.73 (m, 9H), 3.71−3.52 (m, 8H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.92 (s, 3H), 1.11−1.01 (m, 42H), 0.99−0.90 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$, HSQC) δ 171.0, 170.3, 170.1 (2C), 170.0, 169.3, 138.6, 138.5, 138.4, 138.2, 138.1, 138.0, 136.9, 128.7, 128.5, 128.39, 128.37, 128.35, 128.3, 128.04, 127.99, 127.97, 127.94, 127.87, 127.8, 127.73, 127.70, 127.66, 127.61, 127.58, 127.55, 127.5, 100.0, 99.8, 99.2, 98.5, 97.8, 78.5, 77.8, 77.33, 77.26, 75.8, 75.7, 75.3, 75.08, 75.06, 75.0, 73.9 (2C), 73.8, 73.6, 73.44, 73.40, 73.1, 72.8, 72.10, 72.06, 72.0, 71.8, 71.7, 69.2, 69.1, 68.9, 68.1, 63.0, 62.2, 61.8, 61.6, 61.5, 20.97, 20.95, 20.87, 20.85, 20.8, 20.6, 18.1, 18.0, 17.91, 17.85, 12.05, 12.03, 11.9. HRMS (ESI-TOF) m/z calcd for $C_{118}H_{166}O_{32}NaSi_3$ [M + Na]$^+$ 2202.0568, found 2202.0613.

*Benzyl 2-O-acetyl-3,4-O-dibenzyl-6-O-dibenzyloxyphosphoryl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→3)-2-O-acetyl-4-O-benzyl-6-O-triisopropylsilyl-α-D-mannopyranosyl-(1→2)-4,6-O-diacetyl-3-O-benzyl-α-D-mannopyranoside (**76**).* Compound **75** (88 mg, 0.0407 mmol) and 1*H*-tetrazole (15 mg, 0.203 mmol) were dissolved in anhydrous CH_2Cl_2 (4 mL). Freshly activated 4 Å molecular sieves (400 mg) were added, and the mixture was stirred at room temperature for 30 min. The mixture was treated with dibenzyl *N,N*-diisopropylphosphoramidite (54 μL, 0.163 mmol) and stirred for 2 h until the reaction is complete by TLC. The mixture was cooled to −20 °C, and treated with *m*-CPBA (36 mg, 77%, 0.163 mmol). After stirring at −20 °C for 1 h, the reaction was quenched by adding $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with EA and filtered. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_2Cl_2, 1/10/1−1/3/1) to afford **76** (96 mg, 98% over 2 steps) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 45H), 5.41 (s, 1H), 5.29−5.26 (m, 1H), 5.26 (dd, J = 2.8, 1.6 Hz, 1H), 5.20−5.13 (m, 2H), 5.12 (d, J = 1.3 Hz, 1H), 5.10−5.05 (m, 2H), 5.03−4.89 (m, 6H), 4.86−4.78 (m, 3H), 4.72 (d, J = 10.6 Hz, 1H), 4.69−4.65 (m, 2H), 4.65−4.57 (m, 4H), 4.55−4.46 (m, 2H), 4.40 (2 overlapping d, J = 11.1 Hz, 2H), 4.32 (ddd, J = 10.8, 5.8, 1.7 Hz, 1H), 4.22−4.01 (m, 9H), 3.96−3.81 (m, 7H), 3.81−3.73 (m, 3H), 3.63 (d, J = 10.1 Hz, 2H), 3.60−3.50 (m, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H), 1.92 (s, 3H), 1.12−1.01 (m, 42H), 0.99−0.92 (m, 21H). ^{13}C-APT NMR (100 MHz, $CDCl_3$, HSQC) δ 171.0, 170.13, 170.06, 170.0, 169.9, 169.3, 138.48, 138.46, 138.4, 138.2, 138.0, 137.9, 136.9, 135.9, 135.8, 128.7, 128.51, 128.49, 128.47, 128.46, 128.41, 128.35, 128.34, 128.33, 128.29, 128.15, 128.0, 127.94, 127.90, 127.87, 127.8, 127.7, 127.63, 127.58, 127.51, 127.50, 99.9, 99.7, 99.5, 98.4, 97.8, 78.6, 77.7, 77.3, 77.0, 75.8, 75.7, 75.3, 75.04, 75.02, 74.9, 74.0, 73.9, 73.7, 73.5, 73.2, 73.11, 73.05, 72.2, 72.1, 71.84, 71.80, 71.6, 71.3 (d, J = 8.0 Hz), 69.27−69.22 (2C, benzyl phosphate and ether), 69.2 (d, J = 2.5 Hz), 69.1, 68.6, 68.1, 66.0(d, J = 5.8 Hz), 63.0, 62.2, 61.6, 61.5, 20.94, 20.90, 20.83, 20.80, 20.76, 20.6, 18.1, 18.0, 17.92, 17.85, 12.1, 12.0. ^{31}P NMR (162 MHz, $CDCl_3$) δ −0.93. Coupled-HSQC anomeric C−H correlations (400 MHz, $CDCl_3$) δ5.12/99.7 ($J_{C1/H1}$ = 174.8 Hz), 5.09/99.5 ($J_{C1/H1}$ = 174.2 Hz), 5.08/99.9 ($J_{C1/H1}$ = 175.4 Hz), 4.93/98.4 ($J_{C1/H1}$ = 177.0 Hz), 4.91/97.8 ($J_{C1/H1}$ = 175.5 Hz). HRMS (ESI-TOF) m/z calcd for $C_{132}H_{179}O_{35}NaPSi_3$ [M + Na]$^+$ 2462.1170, found 2462.1118.

*Benzyl 3,4-O-dibenzyl-6-O-dibenzyloxyphosphoryl-α-D-mannopyranosyl-(1→3)-4-O-benzyl-α-D-mannopyranosyl-(1→3)-4-O-benzyl-α-D-mannopyranosyl-(1→3)-4-O-benzyl-α-D-mannopyranosyl-(1→2)-3-O-benzyl-α-D-mannopyranoside (**77**).* A solution of **76** (96 mg, 0.039 mmol) in methanol (5 mL) was treated with MeONa (11.6 mg, 0.205 mmol) and then stirred for 12 h at room temperature. Dowex 50WX8 acidic resin was added to neutralize MeONa and then removed. The solution was concentrated in vacuo to provide crude hexa-alcohol: HRMS (ESI-TOF) m/z calcd for $C_{120}H_{167}O_{29}NaPSi_3$ [M + Na]$^+$ 2210.0536, found 2210.0562. To a solution of crude hexa-alcohol in anhydrous THF (3 mL) at room temperature was added TBAF solution (1 M in THF, 0.24 mL, 0.24 mmol) and acetic acid (2.4 mmol, 14 μL). The mixture was stirred at room temperature for 20 h and then concentrated in vacuo. The crude product was purified by silica gel flash chromatography (EtOAc/hexanes/CH_3OH, 1:10:0−1:0:0.03) to afford **77** (64 mg, 95%) as a syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.12 (m, 45H), 5.15−5.11 (m, 2H), 5.09 (s, 1H), 5.03 (s, 1H), 4.92−4.84 (m, 4H), 4.83−4.77 (m, 2H), 4.71 (d, J = 10.9 Hz, 1H), 4.67−4.34 (m, 12H), 4.24−4.01 (m, 9H), 4.00−3.84 (m, 7H), 3.82−3.73 (m, 3H), 3.71−3.51 (m, 10H), 3.46 (d, J = 9.6 Hz, 1H), 3.29 (brs, 1H), 2.70 (m, 5H). ^{13}C-APT NMR (100 MHz, $CDCl_3$) δ 138.00, 137.95, 137.93, 137.86, 137.7, 137.2, 135.7 (d, J = 2.6 Hz), 135.6 (d, J = 2.1 Hz), 130.0, 129.94, 129.91, 129.8, 128.6, 128.54, 128.52, 128.50, 128.44, 128.43, 128.38, 128.1, 127.98, 127.96, 127.89, 127.85, 127.83, 127.79, 127.6, 101.5, 101.0, 100.91, 100.88, 98.4, 80.3, 79.6, 79.3, 79.1, 78.3, 75.4, 75.2, 75.1, 74.9, 74.7, 74.6, 74.1, 74.0, 73.7, 73.20, 73.18, 72.9, 72.7, 72.5, 72.0, 71.1 (d, J = 5.2 Hz), 70.4, 70.2, 69.7, 69.51 (d, J = 1.9 Hz), 69.46 (d, J = 1.7 Hz), 69.1, 68.7, 67.6 (d, J = 6.3 Hz), 65.8, 62.2, 62.0, 61.5, 61.3. ^{31}P NMR (162 MHz, $CDCl_3$) δ −1.35. HRMS (ESI-TOF) m/z calcd for $C_{93}H_{107}O_{29}NaP$ [M + Na]$^+$ 1741.6533, found 1741.6511.

*6-O-Phosphate-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→2)-D-mannitol (**78**).* A solution of compound **77** (23 mg, 0.0135 mmol) in a mixed solvent (MeOH/H_2O, v/v 4/1, 5 mL) containing 20% $Pd(OH)_2$/C (230 mg) was degassed and equipped with a hydrogen balloon. After stirring at room temperature for 36 h, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was subjected to size-exclusion chromatography on a Sephadex G-25 column eluted with H_2O. The appropriate fractions were lyophilized to provide compound **78** (12.3 mg, 100%) as a white fluffy solid. ^{1}H NMR (400 MHz, D_2O, 300 K) δ 5.14 (d, J =

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1.1 Hz, 1H), 5.10 (d, J = 1.5 Hz, 1H), 5.08 (d, J = 1.1 Hz, 1H), 4.98 (d, J = 1.3 Hz, 1H), 4.38 (dd, J = 3.0, 1.8 Hz, 1H), 4.21 (dd, J = 3.0, 1.8 Hz, 1H), 4.14 (dd, J = 2.9, 1.9 Hz, 1H), 4.13−4.09 (m, 1H), 4.08 (dd, J = 3.4, 1.5 Hz, 1H), 4.03 (dd, J = 8.7, 0.8 Hz, 1H), 4.01−3.70 (m, 24H), 3.70−3.64 (m, 2H). ^{13}C-APT NMR (100 MHz, D_2O, 300 K, HSQC) δ 102.9, 102.6, 102.2, 101.4, 79.5, 79.4, 78.3, 78.2, 73.7, 73.44, 73.36, 72.7 (d, J = 6.2 Hz), 70.9, 70.3, 70.1, 70.0, 69.8, 69.32, 69.25, 67.3, 66.8, 66.0, 65.9, 65.8, 63.4 (d, J = 3.0 Hz), 63.2, 61.1 (2C), 61.0, 60.8. HRMS (ESI-TOF) m/z calcd for $C_{30}H_{54}O_{29}P$ $[M - H]^-$ 909.2488, found 909.2443.

6-O-Phosphate-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→2)-D-mannopyranose (1). A solution of compound 77 (30.4 mg, 0.0177 mmol) in a mixed solvent (MeOH/H_2O, v/v 4/1, 5 mL) containing 10% Pd/C (43 mg) was degassed and equipped with a hydrogen balloon. After stirring at room temperature for 20 h, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was subjected to size-exclusion chromatography on a Sephadex G-25 column eluted with H_2O. The appropriate fractions were lyophilized to provide compound **1** (16.1 mg, 100%) as a white fluffy solid. ^{1}H NMR (400 MHz, D_2O, 300 K, HSQC, α-anomer) δ 5.38 (s, 1H, H-1α^{I}), 5.15−5.12 (m, 2H, H-1^{III}, H-1^{IV}), 5.10 (s, 1H, H-1^{V}), 5.04 (s, 1H, H-1^{II}), 4.33 (s, 1H, H-2^{IV}), 4.25−4.20 (m, 3H, H-2^{II}, H-2^{III}, H-2^{IV}), 4.09 (s, 1H, H-6a^{V}), 4.05−3.64 (m, 25H). ^{13}C-APT NMR (100 MHz, D_2O, 300 K, HSQC, α-anomer) δ 102.8 (C-1^{V}), 102.5 (C-1^{IV}), 102.05 (C-1^{II}), 102.02 (C-1^{III}), 92.5 (C-1α^{I}), 79.2 (C-3^{IV}), 79.1 (C-2^{I}), 78.3 (C-3^{III}), 77.9 (C-3^{II}), 73.6 (C-5^{II}), 73.5 (C-5^{IV}), 73.4 (C-5^{III}), 72.5 (C-5^{I}), 72.4 (d, J_{C-P} = 6.6 Hz, C-5^{V}), 70.3 (C-3^{V}), 70.02 (C-2^{V}), 69.98 (C-3^{I}), 69.8 (C-2^{III}), 69.6 (C-2^{II}), 69.5 (C-2^{IV}), 67.0 (C-4^{I}), 66.7 (C-4^{V}), 66.2 (C-4^{II}), 65.9 (2C, C-4^{III}, C-4^{IV}), 64.4 (C-6^{V}), 61.1 (C-6^{IV}), 61.0 (3C, C-6^{I}, C-6^{II}, C-6^{III}). ^{31}P NMR (162 MHz, D_2O, 300 K) δ 1.31. Coupled-HSQC anomeric C−H correlations (400 MHz, D_2O, 300 K) δ 5.38/92.5 ($J_{C1/H1}$ = 173.3 Hz, I), 5.14/102.02 ($J_{C1/H1}$ = 175.0 Hz, residue III), 5.13/102.5 ($J_{C1/H1}$ = 175.0 Hz, residue IV), 5.10/102.8 ($J_{C1/H1}$ = 174.0 Hz, residue V), 5.04/102.05 ($J_{C1/H1}$ = 174.0 Hz, residue II). HRMS (ESI-TOF) m/z calcd for $C_{30}H_{52}O_{29}P$ $[M - H]^-$ 907.2332, found 907.2347.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03017.

1D/2D NMR spectra for all new compounds and details in computational studies (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Yi, W.; Liu, X.; Li, Y.; Li, J.; Xia, C.; Zhou, G.; Zhang, W.; Zhao, W.; Chen, X.; Wang, P. G. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 4207−4212. (b) Gamblin, D. P.; Scanlan, E. M.; Davis, B. G. *Chem. Rev.* **2009**, *109*, 131−163. (c) Linhardt, R. J.; Toida, T. *Acc. Chem. Res.* **2004**, *37*, 431−438. (d) Werz, D. B.; Ranzinger, R.; Herget, S.; Adibekian, A.; von der Lieth, C.-W.; Seeberger, P. H. *ACS Chem. Biol.* **2007**, *2*, 685−691. (e) Aussedat, B.; Vohra, Y.; Park, P. K.; Fernández-Tejada, A.; Alam, S. M.; Dennison, S. M.; Jaeger, F. H.; Anasti, K.; Stewart, S.; Blinn, J. H.; Liao, H.-X.; Sodroski, J. G.; Haynes, B. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 13113−13120. (f) Boltje, T. J.; Zhong, W.; Park, J.; Wolfert, M. A.; Chen, W.; Boons, G.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14255−14262. (g) Yang, Y.; Oishi, S.; Martin, C. E.; Seeberger, P. H. *J. Am. Chem. Soc.* **2013**, *135*, 6262−6271.

(2) (a) Stallforth, P.; Lepenies, B.; Adibekian, A.; Seeberger, P. H. *J. Med. Chem.* **2009**, *52*, 5561−5577. (b) Krasnova, L.; Wong, C.-H. *Mol. Aspects Med.* **2016**, *51*, 125−143. (c) Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046−1051. (d) Danishefsky, S. J.; Shue, Y.-K.; Chang, M. N.; Wong, C.-H. *Acc. Chem. Res.* **2015**, *48*, 643−652. (e) Buskas, T.; Thompson, P.; Boons, G.-J. *Chem. Commun.* **2009**, 5335−5349. (f) Wilson, R. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 14462−14472.

(3) (a) Palomo, J. M. *RSC Adv.* **2014**, *4*, 32658−32672. (b) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557−6602. (c) Roy, B.; Depaix, A.; Périgaud, C.; Peyrottes, S. *Chem. Rev.* **2016**, *116*, 7854−7897.

(4) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nat. Chem.* **2009**, *1*, 611−622.

(5) (a) Yu, B.; Sun, J.; Yang, X. *Acc. Chem. Res.* **2012**, *45*, 1227−1236. (b) Yang, Y.; Zhang, X.; Yu, B. *Nat. Prod. Rep.* **2015**, *32*, 1331−1355. (c) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221−5224. (d) Yang, L.; Qin, Q.; Ye, X.-S. *Asian J. Org. Chem.* **2013**, *2*, 30−49. (e) Fang, T.; Mo, K.-F.; Boons, G.-J. *J. Am. Chem. Soc.* **2012**, *134*, 7545−7552. (f) Seeberger, P. H. *Acc. Chem. Res.* **2015**, *48*, 1450−1463. (g) Lowary, T. L. *Acc. Chem. Res.* **2016**, *49*, 1379−1388. (h) McKay, M. J.; Nguyen, H. M. *ACS Catal.* **2012**, *2*, 1563−1595. (i) Li, X.; Zhu, J. *Eur. J. Org. Chem.* **2016**, *2016*, 4724−4767.

(6) (a) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900−1934. (b) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497−510. (c) Mulani, S. K.; Hung, W.-C.; Ingle, A. B.; Shiau, K.-S.; Mong, K.-K. T. *Org. Biomol. Chem.* **2014**, *12*, 1184−1197. (d) Das, R.; Mukhopadhyay, B. *ChemistryOpen* **2016**, *5*, 401−433.

(7) (a) Martin, A.; Arda, A.; Désiré, J.; Martin-Mingot, A.; Probst, N.; Sinaÿ, P.; Jiménez-Barbero, J.; Thibaudeau, S.; Blériot, Y. *Nat. Chem.* **2016**, *8*, 186−191. (b) Frihed, T. G.; Bols, M.; Pedersen, C. M. *Chem. Rev.* **2015**, *115*, 4963−5013. (c) Bohé, L.; Crich, D. *Carbohydr. Res.* **2014**, *14*, 3−16. (d) Hosoya, T.; Takano, T.; Kosma, P.; Rosenau, T. *J. Org. Chem.* **2014**, *79*, 7889−7894.

(8) (a) Li, Z.; Gildersleeve, J. C. *J. Am. Chem. Soc.* **2006**, *128*, 11612−11619. (b) Christensen, H. M.; Oscarson, S.; Jensen, H. H. *Carbohydr. Res.* **2015**, *408*, 51−95.

(9) (a) Bohé, L.; Crich, D. *Trends Glycosci. Glycotechnol.* **2010**, *22*, 1−15. (b) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952−7962. (c) Fraser-Reid, B.; López, J. C.; Gómez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, *2004*, 1387−1395. (d) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155−173.

(10) (a) Dharuman, S.; Crich, D. *Chem. - Eur. J.* **2016**, *22*, 4535−4542. (b) Schumann, B.; Parameswarappa, S. G.; Lisboa, M. P.; Kottari, N.; Guidetti, F.; Pereira, C. L.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 14431−14434. (c) Guo, J.; Ye, X.-S. *Molecules* **2010**, *15*, 7235−7265. (d) Zhang, Q.; van Rijssel, E. R.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Eur. J. Org. Chem.* **2016**, *2016*, 2393−2397. (e) van der Vorm, S.; Hansen, T.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Chem. Sci.* **2017**, DOI: 10.1039/C6SC04638J. (f) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687−2704. (g) Fraser-Reid, B.; Lopez, J. C.; Radhakrishnan, K. V.; Mach, M.; Schlueter, U.; Gomez, A. M.; Uriel, C. *J. Am. Chem. Soc.* **2002**, *124*, 3198−3199. (h) Baek, J. Y.; Lee, B.-Y.; Jo, M. G.; Kim, K. S. *J. Am. Chem. Soc.* **2009**, *131*, 17705−17713.

DOI: 10.1021/acs.joc.6b03017
J. Org. Chem. 2017, 82, 2599−2621

(11) Hsu, C.-H.; Hung, S.-C.; Wu, C.-Y.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 11872−11923.
(12) (a) de Jong, A.-R.; Hagen, B.; van der Ark, V.; Overkleeft, H. S.; Codée, J. D. C.; Van der Marel, G. A. *J. Org. Chem.* **2012**, *77*, 108−125. (b) Walvoort, M. T. C.; de Witte, W.; van Dijk, J.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Org. Lett.* **2011**, *13*, 4360−4363. (c) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2011**, *13*, 5956−5959. (d) Heuckendorff, M.; Bendix, J.; Pedersen, C. M.; Bols, M. *Org. Lett.* **2014**, *16*, 1116−1119. (e) Gervay-Hague, J. *Acc. Chem. Res.* **2016**, *49*, 35−47. (f) Liang, X.-Y.; Bin, H.-C.; Yang, J.-S. *Org. Lett.* **2013**, *15*, 2834−2837. (g) Wang, S.; Meng, X.; Huang, W.; Yang, J.-S. *J. Org. Chem.* **2014**, *79*, 10203−10217. (h) Heuckendorff, M.; Poulsen, L. T.; Jensen, H. H. *J. Org. Chem.* **2016**, *81*, 4988−5006.
(13) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584.
(14) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−65.
(15) (a) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (b) Ye, X.-S.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 2410−2431. (c) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465−4494. (d) Hsu, Y.; Lu, X.-A.; Zulueta, M. M. L.; Tsai, C.-M.; Lin, K.-I.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 4549−4552. (e) Wong, C.-H.; Ye, X.-S.; Zhang, Z. *J. Am. Chem. Soc.* **1998**, *120*, 7137−7138. (f) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344−2350.
(16) (a) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215−3218. (b) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2103−2106. (c) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2107−2110. (d) Premathilake, H. D.; Mydock, L. K.; Demchenko, A. V. *J. Org. Chem.* **2010**, *75*, 1095−1100.
(17) (a) Jensen, H. H.; Pedersen, C. M.; Bols, M. *Chem. - Eur. J.* **2007**, *13*, 7577−7582. (b) Pedersen, C. M.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222−9235. (c) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Chem. Commun.* **2008**, 2465−2467. (d) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *J. Org. Chem.* **2012**, *77*, 5559−5568. (e) Heuckendorff, M.; Premathilake, H. D.; Pornsuriyasak, P.; Madsen, A. Ø.; Pedersen, C. M.; Bols, M.; Demchenko, A. V. *Org. Lett.* **2013**, *15*, 4904−4907. (f) Bandara, M. D.; Yasomanee, J. P.; Rath, N. P.; Pedersen, C. M.; Bols, M.; Demchenko, A. V. *Org. Biomol. Chem.* **2017**, *15*, 559−563.
(18) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506−4507. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199. (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223. (d) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435−436. (e) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.
(19) (a) Jensen, H. H.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213. (b) Crich, D.; Banerjee, A. *J. Am. Chem. Soc.* **2006**, *128*, 8078−8086. (c) Crich, D.; Li, L. *J. Org. Chem.* **2009**, *74*, 773−781. (d) Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M. *J. Org. Chem.* **2013**, *78*, 2191−2205. (e) Moumé-Pymbock, M.; Furukawa, T.; Mondal, S.; Crich, D. *J. Am. Chem. Soc.* **2013**, *135*, 14249−14255.
(20) (a) Patil, P. S.; Lee, C.-C.; Huang, Y.-W.; Zuluetaa, M. M. L.; Hung, S.-C. *Org. Biomol. Chem.* **2013**, *11*, 2605−2612. (b) Lee, H.-K.; Scanlan, C. N.; Huang, C.-Y.; Chang, A. Y.; Calarese, D. A.; Dwek, R. A.; Rudd, P. M.; Burton, D. R.; Wilson, I. A.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1000−1003. (c) Mandal, M.; Dudkin, V. Y.; Geng, X.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2557−2561. (d) Tsai, Y.-H.; Götze, S.; Vilotijevic, I.; Grube, M.; Silva, D. V.; Seeberger, P. H. *Chem. Sci.* **2013**, *4*, 468−481. (e) Tsai, Y.-H.; Liu, X.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 11438−11456. (f) Boonyarattanakalin, S.; Liu, X.; Michieletti, M.; Lepenies, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 16791−16799.
(21) (a) Parolis, L. A. S.; Duus, J. Ø.; Parolis, H.; Meldal, M.; Bock, K. *Carbohydr. Res.* **1996**, *293*, 101−117. (b) Parolis, L. A.S.; Parolis, H.; Kenne, L.; Meldalc, M.; Bock, K. *Carbohydr. Res.* **1998**, *309*, 77−87.
(22) (a) Ferro, V.; Fewings, K.; Palermo, M. C.; Li, C. *Carbohydr. Res.* **2001**, *332*, 183−189. (b) Ferro, V.; Li, C.; Fewings, K.; Palermo, M. C.; Linhardt, R. J.; Toida, T. *Carbohydr. Res.* **2002**, *337*, 139−146.
(23) (a) Yu, G.; Gunay, N. S.; Linhardt, R. J.; Toida, T.; Fareed, J.; Hoppensteadt, D. A.; Shadid, H.; Ferro, V.; Li, C.; Fewings, K.; Palermo, M. C.; Podger, D. *Eur. J. Med. Chem.* **2002**, *37*, 783−791. (b) Cochran, S.; Li, C.; Fairweather, J. K.; Kett, W. C.; Coombe, D. R.; Ferro, V. *J. Med. Chem.* **2003**, *46*, 4601−4608. (c) Karoli, T.; Liu, L.; Fairweather, J. K.; Hammond, E.; Li, C. P.; Cochran, S.; Bergefall, K.; Trybala, E.; Addison, R. S.; Ferro, V. *J. Med. Chem.* **2005**, *48*, 8229−8236. (d) Johnstone, K. D.; Karoli, T.; Liu, L.; Dredge, K.; Copeman, E.; Li, C. P.; Davis, K.; Hammond, E.; Bytheway, I.; Kostewicz, E.; Chiu, F. C. K.; Shackleford, D. M.; Charman, S. A.; Charman, W. N.; Harenberg, J.; Gonda, T. J.; Ferro, V. *J. Med. Chem.* **2010**, *53*, 1686−1699. (e) Ferro, V.; Liu, L.; Johnstone, K. D.; Wimmer, N.; Karoli, T.; Handley, P.; Rowley, J.; Dredge, K.; Li, C. P.; Hammond, E.; Davis, K.; Sarimaa, L.; Harenberg, J.; Bytheway, I. *J. Med. Chem.* **2012**, *55*, 3804−3813.
(24) (a) Yoshida-Moriguchi, T.; Yu, L.; Stalnaker, S. H.; Davis, S.; Kunz, S.; Madson, M.; Oldstone, M. B. A.; Schachter, H.; Wells, L.; Campbell, K. P. *Science* **2010**, *327*, 88−92. (b) Tiels, P.; Baranova, E.; Piens, K.; Visscher, C. D.; Pynaert, G.; Nerinckx, W.; Stout, J.; Fudalej, F.; Hulpiau, P.; Tännler, S.; Geysens, S.; Hecke, A. V.; Valevska, A.; Vervecken, W.; Remaut, H.; Callewaert, N. *Nat. Biotechnol.* **2012**, *30*, 1225−1234. (c) Magali, G.-B.; Philippe, N.; Audrey, J.; Alain, M.; Marcel, G. *Curr. Med. Chem.* **2007**, *14*, 2945−2953. (d) Coutinho, M. F.; Prata, M. J.; Alves, S. *Mol. Genet. Metab.* **2012**, *105*, 542−550. (e) Sleat, D. E.; Valle, M. C. D.; Zheng, H.; Moore, D. F.; Lobel, P. *J. Proteome Res.* **2008**, *7*, 3010−3021. (f) Yamaguchi, T.; Amin, M. N.; Toonstra, C.; Wang, L.-X. *J. Am. Chem. Soc.* **2016**, *138*, 12472−12485.
(25) (a) Fairweather, J. K.; Karoli, T.; Ferro, V. *Bioorg. Med. Chem.* **2004**, *12*, 6063−6075. (b) Fairweather, J. K.; Hammond, E.; Johnstone, K. D.; Ferro, V. *Bioorg. Med. Chem.* **2008**, *16*, 699−709. (c) Gu, G.; Wei, G.; Du, Y. *Carbohydr. Res.* **2004**, *339*, 1155−1162. (d) Valerio, S.; Pastore, A.; Adinolfi, M.; Iadonisi, A. *J. Org. Chem.* **2008**, *73*, 4496−4503. (e) Mong, K.-K. T.; Shiau, K.-S.; Lin, Y. H.; Cheng, K.-C.; Lin, C.-H. *Org. Biomol. Chem.* **2015**, *13*, 11550−11560.
(26) (a) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769−782. (b) Lian, G.; Zhang, X.; Yu, B. *Carbohydr. Res.* **2015**, *403*, 13−22.
(27) (a) Priyanka, P.; Parsons, T. B.; Miller, A.; Platt, F. M.; Fairbanks, A. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 5058−5061. (b) Liu, Y.; Chen, G. *J. Org. Chem.* **2011**, *76*, 8682−8689. (c) Liu, Y.; Marshall, J.; Li, Q.; Edwards, N.; Chen, G. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2328−2331.
(28) (a) Tatai, J.; Fügedi, P. *Org. Lett.* **2007**, *9*, 4647−4650. (b) Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522.
(29) (a) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2003**, *68*, 4531−4534. (b) Volbeda, A. G.; Kistemaker, H. A. V.; Overkleeft, H. S.; van der Marel, G. A.; Filippov, D. V.; Codée, J. D. C. *J. Org. Chem.* **2015**, *80*, 8796−8806. (c) Zhou, J.; Yang, L.; Hu, W. *J. Org. Chem.* **2014**, *79*, 4718−4726. (d) Worm-Leonhard, K.; Larsen, K.; Jensen, K. J. *J. Carbohydr. Chem.* **2007**, *26*, 349−368.
(30) Shie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665−1668.
(31) (a) Ritter, T. K.; Mong, K. K. T.; Liu, H. T.; Nakatani, T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4657−4660. (b) Lee, J.-C.; Greenberg, W. A.; Wong, C.-H. *Nat. Protoc.* **2006**, *1*, 3143−3152.
(32) (a) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144−1153. (b) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930. (c) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2006**, *71*, 8473−8480. (d) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681−1690. (e) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193−9209.
(33) Kartha, K. P. R.; Cura, P.; Aloui, M.; Readman, S. K.; Rutherford, T. J.; Field, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 581−593.

DOI: 10.1021/acs.joc.6b03017
J. Org. Chem. 2017, 82, 2599−2621

(34) (a) Hashimoto, Y.; Tanikawa, S.; Saito, R.; Sasaki, K. *J. Am. Chem. Soc.* **2016**, *138*, 14840−14843. (b) Codée, J. D. C.; van den Bos, L. J.; de Jong, A.-R.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 38−47. (c) Dinkelaar, J.; de Jong, A.-R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982−4991. (d) Hosoya, T.; Kosma, P.; Rosenau, T. *Carbohydr. Res.* **2015**, *401*, 127−131.

(35) (a) Tsai, Y.-H.; Götze, S.; Azzouz, N.; Hahm, H. S.; Seeberger, P. H.; Silva, D. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 9961−9964. (b) Liu, X.; Kwon, Y.-U.; Seeberger, P. H. *J. Am. Chem. Soc.* **2005**, *127*, 5004−5005. (c) Liu, X.; Stocker, B. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2006**, *128*, 3638−3648. (d) Hölemann, A.; Stocker, B. L.; Seeberger, P. H. *J. Org. Chem.* **2006**, *71*, 8071−8088. (e) Seeberger, P. H.; Soucy, R. L.; Kwon, Y.-U.; Snyder, D. A.; Kanemitsu, T. *Chem. Commun.* **2004**, 1706−1707. (f) Xue, J.; Guo, Z. *J. Am. Chem. Soc.* **2003**, *125*, 16334−16339. (g) Hou, D.; Skogman, F.; Lowary, T. L. *Carbohydr. Res.* **2008**, *343*, 1778−1789.

(36) (a) Patil, P. S.; Cheng, T.-J. R.; Zulueta, M. M. L.; Yang, S.-T.; Lico, L. S.; Hung, S.-C. *Nat. Commun.* **2015**, *6*, 7239. (b) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731−732. (c) Wu, Z.; Guo, X.; Wang, Q.; Swarts, B. M.; Guo, Z. *J. Am. Chem. Soc.* **2010**, *132*, 1567−1571. (d) Swarts, B. M.; Guo, Z. *J. Am. Chem. Soc.* **2010**, *132*, 6648−6650. (e) Wu, X.; Guo, Z. *Org. Lett.* **2007**, *9*, 4311−4313. (f) Gao, J.; Liao, G.; Wang, L.; Guo, Z. *Org. Lett.* **2014**, *16*, 988−991. (g) Gao, J.; Guo, Z. *J. Org. Chem.* **2013**, *78*, 12717−12725.

(37) (a) Fraser-Reid, B.; Grimme, S.; Piacenza, M.; Mach, M.; Schlueter, U. *Chem. - Eur. J.* **2003**, *9*, 4687−4692. (b) Rele, S. M.; Iyer, S. S.; Baskaran, S.; Chaikof, E. L. *J. Org. Chem.* **2004**, *69*, 9159−9170.

(38) (a) Podlasek, C. A.; Wu, J.; Stripe, W. A.; Bondo, P. B.; Serianni, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 8635−8644. (b) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *J. Org. Chem.* **2004**, *69*, 1174−1179.

(39) Ren, B.; Wang, M.; Liu, J.; Ge, J.; Zhang, X.; Dong, H. *Green Chem.* **2015**, *17*, 1390−1394.

(40) Ohara, K.; Lin, C.-C.; Yang, P.-J.; Hung, W.-T.; Yang, W.-B.; Cheng, T.-J. R.; Fang, J.-M.; Wong, C.-H. *J. Org. Chem.* **2013**, *78*, 6390−6411.

(41) (a) Duus, J. Ø.; Gotfredsen, C. H.; Bock, K. *Chem. Rev.* **2000**, *100*, 4589−4614. (b) Breton, R. C.; Reynolds, W. F. *Nat. Prod. Rep.* **2013**, *30*, 501−524.

(42) (a) Kozminski, W.; Nanz, D. *J. Magn. Reson.* **1997**, *124*, 383−392. (b) Kozminski, W.; Nanz, D. *J. Magn. Reson.* **2000**, *142*, 294−299. (c) Palermo, G.; Riccio, R.; Bifulco, G. *J. Org. Chem.* **2010**, *75*, 1982−1991. (d) Nilewski, C.; Geisser, R. W.; Ebert, M.-O.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 15866−15876. (e) Morinaka, B. I.; Molinski, T. F. *Org. Lett.* **2011**, *13*, 6338−6341.

(43) Zhu, X.-X.; Ding, P.; Cai, M.-S. *Tetrahedron: Asymmetry* **1996**, *7*, 2833−2838.

(44) Sun, B.; Srinivasan, B.; Huang, X. *Chem. - Eur. J.* **2008**, *14*, 7072−7081.

(45) John, F.; Hendrickson, T. L. *Org. Lett.* **2010**, *12*, 2080−2083.

(46) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647−5656.

(47) Tam, P.-H.; Lowary, T. L. *Carbohydr. Res.* **2007**, *342*, 1741−1772.

DOI: 10.1021/acs.joc.6b03017
J. Org. Chem. 2017, 82, 2599−2621