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Unique Reactivity of the Mukaiyama Glycosidation Catalyst ($SnCl_3ClO_4$) Toward β-Mannopyranosides

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: Glycosidation of a mannosyl donor in the presence of the Mukaiyama catalyst was found to give exceptionally high α/β selectivity. A systematic study was conducted to reveal that selective β-to-α anomerization accounts for the observed high α/β stereoselectivity. Furthermore, the Mukaiyama catalyst was shown to exhibit an unusual level of substrate and anomer selectivity for the anomerization. On the basis of the combined anomeric and Δ2 effects, a mechanistic rationale was proposed, thereby suggesting the minimum structural moiety essential for the anomerization in question. With this analysis, β-talo-, β-altro-, and β-idopyranosides are predicted to exhibit a reactivity profile similar to β-mannopyranosides, but all other pyranosides should not. This prediction was verified by using β- and α-talopyranosides as an example.

Keywords: anomeric effect · anomerization · delta2 effect · glycosidation · glycosides

Introduction

Fatty acid (FA) biosynthesis in *Mycobacterium smegmatis* is known to show a bimodal product distribution, with palmitic and tetracosanoic acids being the two dominant products.[1] Bloch and co-workers discovered that two endogenous *M. smegmatis* polysaccharides, 3-*O*-methyl-D-mannose-containing polysaccharides (*n*MMPs) and 6-*O*-methyl-D-glucose-containing lipopolysaccharides (*n*MGLPs)/6-*O*-methyl-D-glucose-containing polysaccharides (*n*MGPs) (Scheme 1),[2] have profound effects on FA biosynthesis catalyzed by *M. smegmatis* fatty acid synthase I (FAS I), most noticeably on product distribution and stimulation. We are interested in gaining mechanistic insight into the intriguing biological role(s) of *n*MMP and *n*MG(L)P. However, we felt that naturally occurring *n*MMPs and *n*MG(L)Ps are not necessarily ideal substrates for our study, as they were isolated as complex mixtures of closely related polysaccharides. Thus, we designed and used synthetic polysaccharides structurally related to natural MMPs and MG(L)Ps for two reasons: 1) synthetic polysaccharides can be available as structurally well-defined and chemically homogeneous materials, and 2) synthetic polysaccharides can be structurally tunable for the needs of our systematic investigation. Clearly, the most unique structural feature of *n*MMPs and *n*MG(L)Ps is the polymeric form of 3-*O*-methylmannose and 6-*O*-methylglucose, respectively. Therefore, we incorporated this structural feature in the synthetic polysaccharides, that is, synthetic 3-*O*-methyl-D-mannose-containing polysaccharides (*s*MMPs) and synthetic 6-*O*-methyl-D-glucose-containing polysaccharides (*s*MGPs) (Scheme 1).[3]

We recently reported an iterative synthesis of *s*MMPs (Scheme 2).[3a] The key step of this synthesis was the highly stereoselective α glycosidation in the presence of the Mukaiyama catalyst ($SnCl_3ClO_4$);[4] for example, the glycosidation of **1** and **2** gave the α-disaccharide **3-α** with excellent stereoselectivity. A time-course study revealed that the α/β selectivity was only 3:1 after 1 h, but improved to 5:1, 9:1, and 20:1 after 8, 22, and 30 h, respectively, thereby suggesting that the β-disaccharide **3-β** anomerized into the α-disaccharide **3-α** under the glycosidation conditions. Indeed, in the presence of 10 mol% Mukaiyama catalyst, the β-disaccharide **3-β** was found to anomerize and furnish α-glycoside **3-α** (78%), along with two monosaccharides. Interestingly, the corresponding α-disaccharide **3-α** was found not to anomerize to the β-disaccharide **3-β** under the same conditions. Thus, the observed high α/β stereoselectivity was at-

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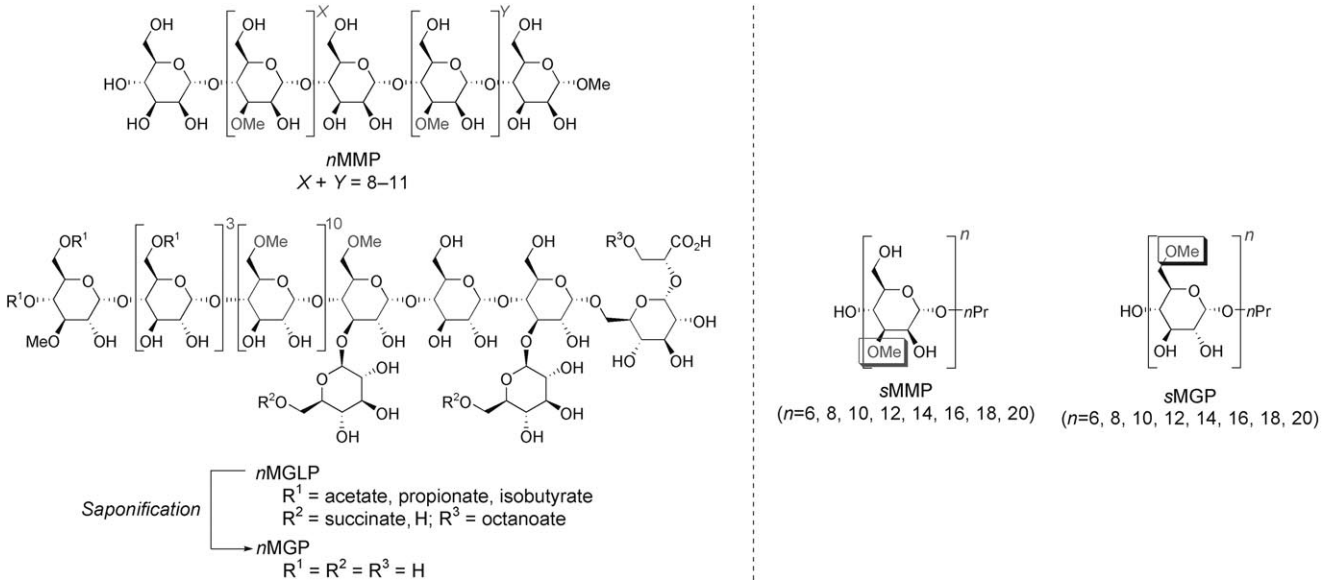
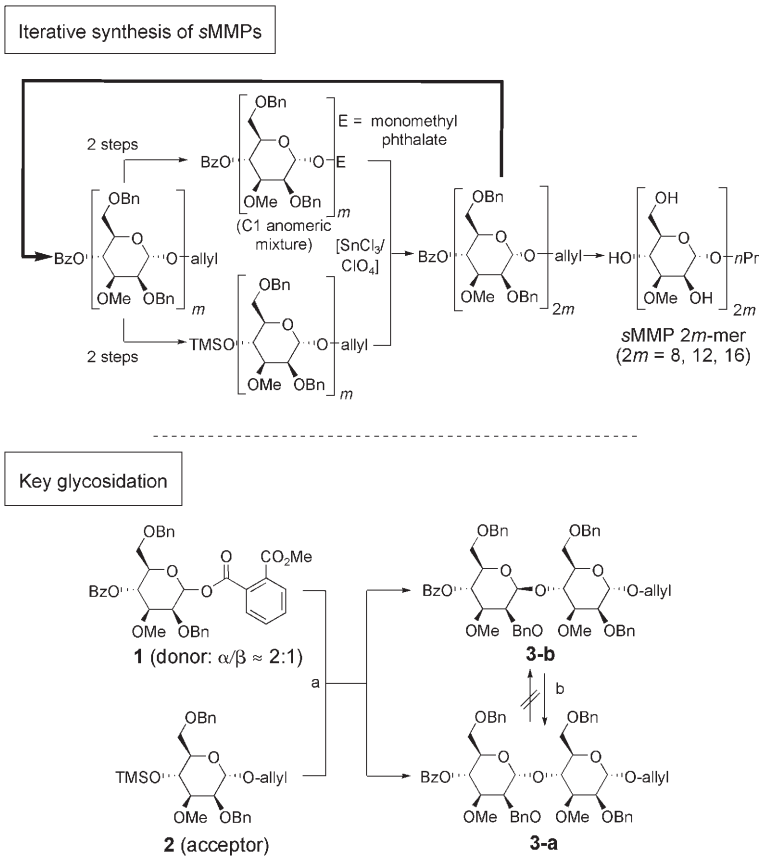


Scheme 1. Structure of *n*MMPs, *n*MG(L)Ps, *s*MMPs, and *s*MGPs.

tributed to the selective anomerization from the β anomer to the α anomer.

Since the pioneering work by Lemieux,[5] the anomerization of glycosidic bonds has been a subject of extensive research.[6] It is now widely recognized that glycosidic linkages anomerize in the presence of various acids, typically Lewis acids such as $BF_3{\cdot}Et_2O$ and $TiCl_4$, to yield equilibrium mixtures of α- and β-pyranosides. However, it is worth noting that the Mukaiyama catalyst exhibits an unusual level of substrate and anomer selectivity; this catalyst was found 1) to promote the β-to-α, but not the α-to-β, anomerization in the mannopyranoside series, and 2) not to promote either the β-to-α or the α-to-β anomerization in the glucopyranoside series. In this respect alone, the Mukaiyama glycosidation catalyst is unique. Herein, we report a systematic study to gain insight into the observed selective β-to-α anomerization in the presence of the Mukaiyama catalyst.



Scheme 2. Iterative synthesis of *s*MMPs and key glycosidation. Reagents and conditions: a) **1** (1.0 equiv), **2** (1.2 equiv), 10 mol% $SnCl_3ClO_4$ (prepared in situ from $SnCl_4$ and $AgClO_4$), Et_2O, 0 °C; b) **3-β** or **3-α**, 10 mol% $SnCl_3ClO_4$, Et_2O, 0 °C. Bn = benzyl, Bz = benzoyl, TMS = trimethylsilyl.

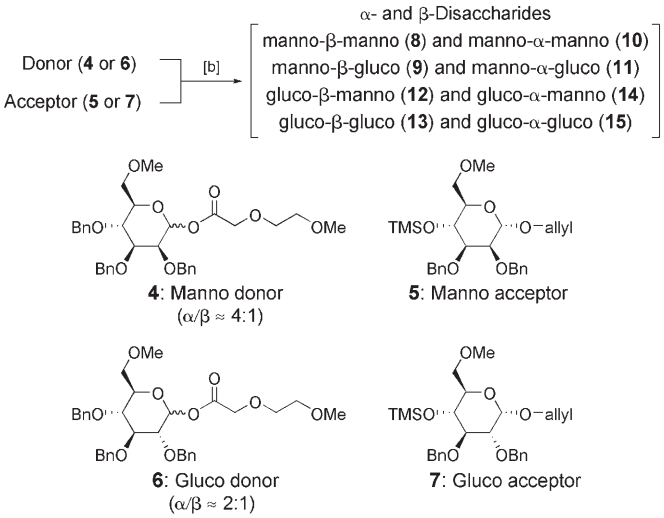
Results and Discussion

To establish whether the observed phenomena are specific to the mannosyl donor and/or acceptor, we synthesized donors and acceptors belonging to the mannose and glucose series and conducted the time-course study on glycosidation of the four possible

combinations in the presence of the Mukaiyama catalyst. For these studies, we purposely chose the second-generation Mukaiyama leaving group,[4c] instead of monomethyl phthalate,[3a] with the consideration that the results of our current work could be compared with those in the literature. Furthermore, in connection with our interest in *s*MGPs,[3b,g] we decided to place a methyl ether group at C6.

As summarized in Table 1, the α/β selectivity for the glycosidation between the mannosyl donor **4** and the acceptor **5** or **7** improved with the reaction time, whereas that between the glucosyl donor **6** and the acceptor **5** or **7** remained virtually constant throughout the reaction. This time-course study showed that the unique profile in the glycosidation relates to the structural moiety of the mannosyl donor, but not of the glucosyl donor or the mannosyl and glucosyl acceptors.

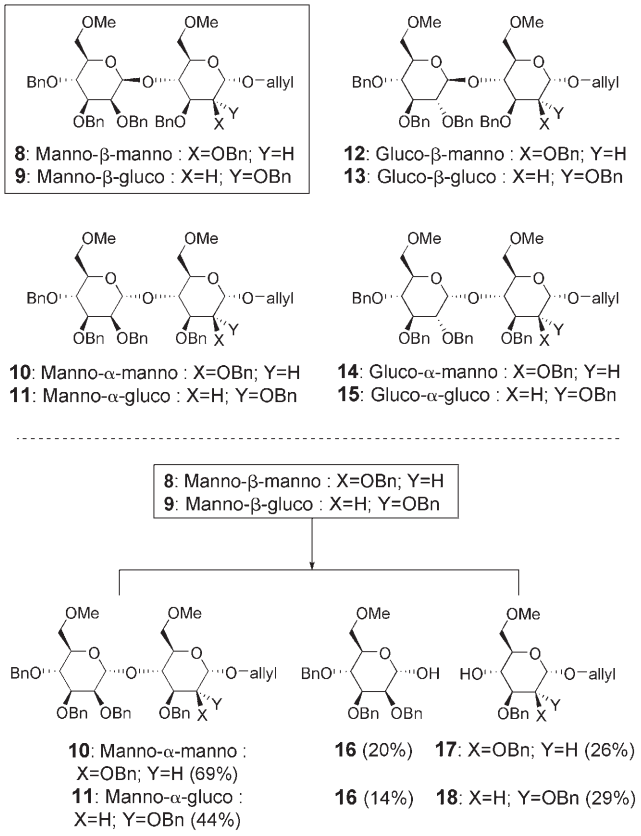
Table 1. Ratio of α to β anomers formed as a function of reaction time.[a,b]



Donor	Acceptor	1/3 h	1 h	2 h	3 h	7 h	20 h
4	**5**	13.2	–	17.0	–	18.5	20.5
4	**7**	13.5	17.8	–	18.0	18.7	23.7
6	**5**	6.7	–	6.8	–	6.7	6.4
6	**7**	–	6.4	–	6.8	6.4	6.9

[a] For the structures of the disaccharides, see Scheme 3. [b] Glycosidation was carried out under the Mukaiyama conditions (donor (1.0 equiv), acceptor (1.2 equiv), 10 mol% $SnCl_3ClO_4$, prepared in situ from $SnCl_4$ and $AgClO_4$, Et_2O, 0°C) and the α/β ratio was estimated from the ^1H NMR spectra of the crude products obtained from an aliquot taken from the glycosidation at a given time. The combined material recovery, that is, the α- and β-disaccharides and the monosaccharides, was virtually quantitative for all the cases studied.

To verify the conclusion derived from the time-course study of glycosidation, eight disaccharides **8**–**15** were synthesized and subjected to anomerization under the Mukaiyama glycosidation conditions (Scheme 3). As anticipated, all the α- and β-disaccharides, except for β-disaccharides **8** and **9** derived from the mannosyl donor, were stable under the glycosidation conditions. However, under the same conditions, **8** and **9** were found to yield a mixture of three products, anomerized α-disaccharide **10** (69%) or **11** (44%), and two monosaccharides **16** (20 and 14%) and **17** (26%) or **18** (29%), besides the starting disaccharides (**8**: 5%; **9**:14%).



Scheme 3. Disaccharides derived from glucose and mannose and their reactivity toward the Mukaiyama glycosidation catalyst. Reagents and conditions: Disaccharide, 10 mol% $SnCl_3ClO_4$, Et_2O, 0°C; the analysis was conducted with the reaction time 46 and 38 h for **8** and **9**, respectively.

Figure 1 shows the time course for the anomerization of **8**. This experiment showed that: 1) the α/β ratio changed

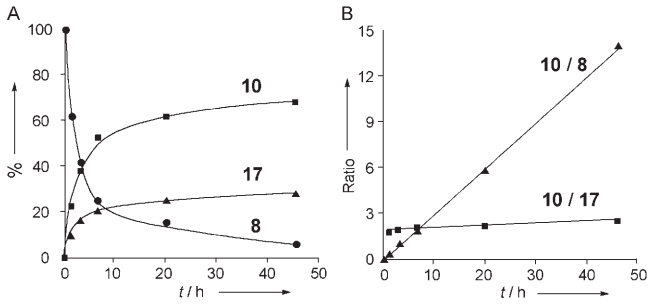
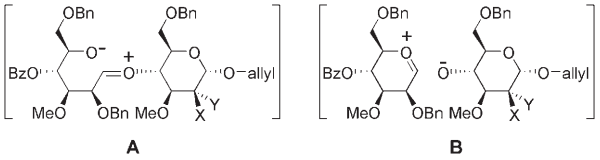


Figure 1. A) Anomerization product distribution and B) product ratio as a function of time under the Mukaiyama conditions (**8**, 10 mol% $SnCl_3ClO_4$, Et_2O, 0°C). The amounts of **8**, **10**, and **17** were estimated from the MeO peak intensities (**8**: $\delta = 3.23$ and 3.22 ppm; **10**: $\delta = 3.39$ and 3.38 ppm; **17**: $\delta = 3.41$ ppm) in the ^1H NMR spectrum ($CDCl_3$) of the crude product obtained from an aliquot taken from the reaction mixture at a given time. This NMR spectroscopic method was not suitable for estimating the amount of **16**. However, formation of **16** was confirmed through its isolation and characterization from the same anomerization experiment.

with the reaction time (**10/8** line, Figure 1B), but 2) the ratio of anomerized α-disaccharide **10** and cleaved monosaccharide **17** was almost constant throughout the anomerization (**10/17** line, Figure 1B), thereby indicating that **17** is derived from β-disaccharide **8**.

These experiments establish that the exceptionally high α/β selectivity of glycosidation is due to the selective β-to-α anomerization in the mannosyl-donor series.[7–9] As mentioned above, the Mukaiyama catalyst promotes only the β-to-α anomerization in the mannopyranoside series, whereas $TiCl_4$ and $BF_3{\cdot}Et_2O$ promote both β-to-α and α-to-β anomerization, not only for the mannopyranosides, but also in the glucopyranoside series.[3a,b,10] To the best of our knowledge, anomerization with the observed level of substrate and anomer selectivity is exceptional.[11]

Mechanistically, the anomerization can take place through the acyclic oxonium ion **A** or the cyclic oxonium ion **B** (Scheme 4).[12,13] The fact that the β-disaccharides **8** and **9**

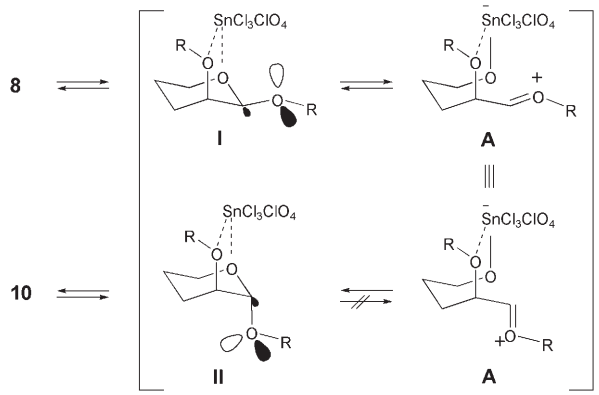


Scheme 4. Structure of oxonium ions **A** and **B**.

gave the α-disaccharides **10** and **11**, along with a smaller amount of the monosaccharides **16** and **17** or **18**, suggests that the anomerization is more likely to proceed through the acyclic oxonium ion **A**. Two questions then remain: 1) why is **A**, or **B**, formed from a β-mannopyranoside, but not from a β-glucopyranoside, and 2) why is **A**, or **B**, formed from a β-mannopyranoside, but not from an α-mannopyranoside?

Owing to the so-called anomeric effect,[14] α-pyranosides are known to be more stable than the corresponding β-pyranosides. Thus, the activation energy required for formation of the oxonium ion from a β-pyranoside is smaller than that from an α-pyranoside. Owing to the so-called Δ2 effect,[15,16] the relative stability of an α-mannopyranoside over a β-mannopyranoside is expected to be more pronounced than that of an α-glucopyranoside over a β-glucopyranoside. Taking both anomeric and Δ2 effects into account, we can predict that 1) the activation energy for the formation of oxonium ion from a β-mannopyranoside is significantly smaller than that from a β-glucopyranoside, and 2) the activation energy for the formation of oxonium ion from a β-mannopyranoside is significantly smaller than that from both β- and α-glucopyranosides. Therefore, on the balance of the reactivity of the substrates and the glycosidation catalyst, we envision the case whereby only a β-mannopyranoside anomerizes to the corresponding α-mannopyranoside.

Inspection of the three-dimensional structures of β- and α-mannopyranosides may shed further light on the unique anomerization. A β-mannopyranoside appears to present a good coordination site to the Mukaiyama glycosidation catalyst (**I**; Scheme 5). The complexation on this site would result in 1) weakening of the C1/ring–oxygen bond and, therefore, facilitating of the formation of oxonium ion **A**,

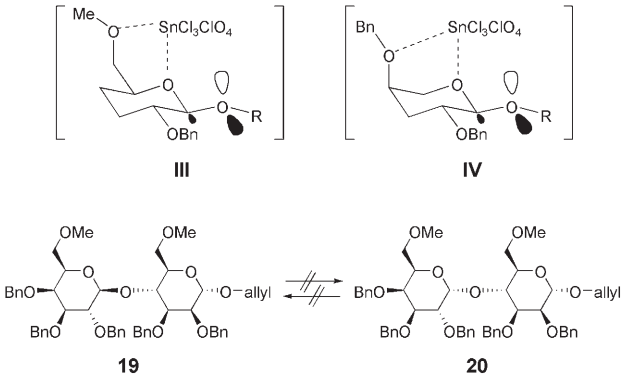


Scheme 5. Possible steps involved in the anomerization of **8** to **10**. The pair of orbitals in solid black indicates an $n\rightarrow\sigma^*$ interaction from one of the exocyclic oxygen lone-pair electrons to the antibonding σ orbital of the polarized C1/ring–oxygen bond.

and 2) an increase in the polarization of the C1/ring–oxygen bond and, consequently, an increase in the double-bond character of the C1/exocyclic oxygen atom, owing to a greater degree of stereoelectronic stabilization, that is, a greater $n\rightarrow\sigma^*$ interaction from one of the lone-pair electrons of the exocyclic oxygen atom to the more polarized C1/ring–oxygen bond.[13] These considerations present the case for favoring the acyclic oxonium ion **A** over the cyclic oxonium ion **B**.

An α-mannopyranoside contains the same spatial arrangement of the lone-pair orbitals of the ring and C2 oxygen atoms, which should present a good coordination site for the Mukaiyama catalysis (**II**; Scheme 5). This complexation should also result in the two effects mentioned above. However, due to the combined anomeric and Δ2 effects, an α-mannopyranoside is significantly more stable than the corresponding β-mannopyranoside; therefore, the activation energy from the α-mannopyranoside to the oxonium ion is too large for the **II**→**A** process to take place. Overall, the anomerization is likely to proceed through the steps depicted in Scheme 5.

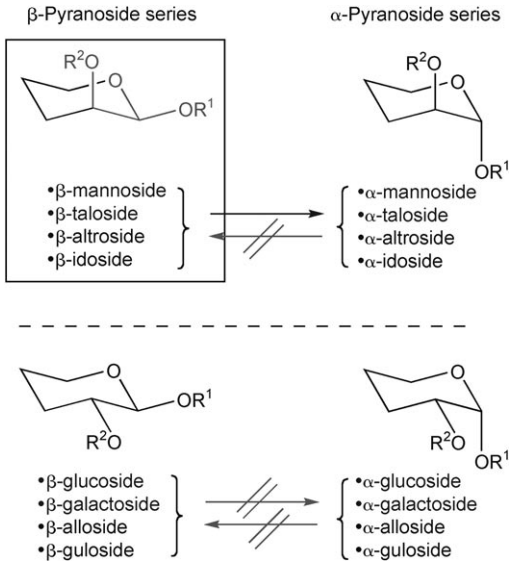
Along with the C6 oxygen atom, the β-glucopyranoside can provide the Mukaiyama catalyst with a similar coordination site (**III**; Scheme 6), but the β-glucopyranoside did not anomerize. The difference in reactivity between the β-manno- and β-glucopyranoside series may be attributed to one or both of two probable factors. First, due to the lack of the Δ2 effect, the activation energy to the oxonium ion in the β-glucopyranoside series is simply too large for the anomerization to take place. Second, due to the conformational flexibility, the coordination site involving the C6 oxygen atom is not potent enough. In this connection, we studied the chemical behavior of the β-disaccharide **19**, be-



Scheme 6. Possible sites of complexation and attempted anomerization of **19** and **20** in the presence of the Mukaiyama catalyst ($SnCl_3ClO_4$).

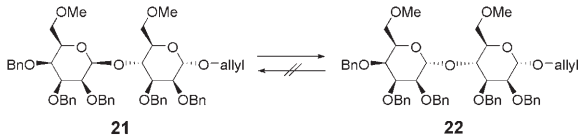
cause it should provide a coordination site closer to the one proposed for the β-mannopyranoside (**IV** vs. **I**). Under the Mukaiyama glycosidation conditions, **19** remained unchanged, thereby suggesting that the presence or absence of the Δ2 effect is the primary determining factor (Scheme 6).

Overall, the experimental results discussed above demonstrate that the unique properties observed in the mannosyl donor series are due to the structural moiety present in the C1–C2 portion of β-mannopyranoside, that is, the structural portion in gray in the boxed structure in Scheme 7. On the basis of this analysis, we predicted similar reactivity profiles for the donors derived from altrose, idose, and talose, for which both anomeric and Δ2 effects are present (Scheme 7). However, because of the lack of the Δ2 effect, we did not anticipate the unique reactivity profile for the donors derived from galactose, allose, and gulose.



Scheme 7. Four subgroups of pyranosides. The minimum structural moiety required for the selective anomerization is in gray in the boxed structure. It is predicted that, among the four subgroups, only β-pyranosides in the box exhibit the unique profile of reactivity. The chemical behavior of the pyranosides highlighted in gray were experimentally confirmed.

To verify the prediction, we studied the chemical behavior of α- and β-talopyranosides **21** and **22**. To our delight, their chemical behavior was found to be identical with, or at least very close to, the unique properties observed for α- and β-mannopyranosides; namely, the α/β stereoselectivity improved with glycosidation time, and only β-disaccharide **21** anomerized to α-disaccharide **22** in the presence of the Mukaiyama glycosidation catalyst (Scheme 8).[17]



Scheme 8. α- and β-Talopyranosides **21** and **22** exhibited chemical behavior similar to α- and β-mannopyranosides **8** and **10**, respectively, in the presence of 10 mol% $SnCl_3ClO_4$ in Et_2O for 3 h at 0 °C. In the β→α anomerization, the β anomer **21** smoothly anomerized to give the α anomer **22** in 60% yield (α/β = 20:1), along with the cleaved monosaccharides. In the attempted α→β anomerization, the α anomer **22** was recovered intact.

Conclusions

Glycosidation of a mannosyl donor in the presence of the Mukaiyama catalyst ($SnCl_3ClO_4$) was found to give exceptionally high α/β selectivity. A systematic study was conducted to reveal that the selective β-to-α anomerization accounts for the observed high α/β stereoselectivity. Furthermore, the Mukaiyama catalyst was shown to exhibit an unusual level of substrate and anomer selectivity for the anomerization. Taking both anomeric and Δ2 effects into account, we proposed a mechanistic rationale, thereby suggesting the minimum structural moiety essential for the anomerization. With this analysis, β-talo-, β-altro-, and β-idopyranosides were predicted to exhibit a reactivity profile similar to that of β-mannopyranosides, but all other pyranosides should not. This prediction was verified by using β- and α-talopyranosides as an example.

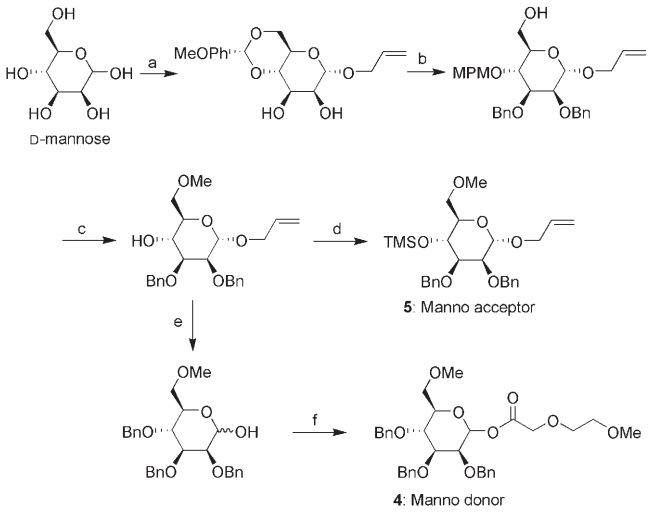
Experimental Section

The general experimental procedure is given in the Supporting Information of reference [3a,b].

General procedure for time-course study of glycosidation: Tin tetrachloride (0.1 equiv) in toluene (0.3 M) was added to a solution of silver perchlorate (0.1 equiv) in diethyl ether (0.005 M) at room temperature. The mixture was stirred in the dark for 1 h, and then a solution of donor (1.0 equiv) and acceptor (1.2 equiv) in diethyl ether (0.075 M) was added at 0 °C. An aliquot was taken from the reaction mixture, and the reaction was quenched with aqueous $NaHCO_3$. After standard workup, the crude products were subject to ^1H NMR spectroscopic analysis.

General procedure for anomerization of disaccharides: The procedure is the same as that for the time-course study of glycosidation, except that a solution of the disaccharide (1 equiv) in diethyl ether (0.075 M) was added to a solution of the catalyst at 0 °C. The anomerization was followed by ^1H NMR spectroscopy; the minor anomer was clearly detected with as low as 5% content (1:20) until its signal became ambiguous owing to the baseline of the spectrum.

Manno donor **4** and acceptor **5** were synthesized as summarized in Scheme 9. The experimental procedures reported in reference [3a,b] were adopted to carry out this synthesis, except for step b2, which was done with the protocol in the literature.[18]



Scheme 9. Synthesis of manno donor **4** and manno acceptor **5**. Reagents, conditions, and yield: a) 1) Allyl alcohol, $Sc(OTf)_3$, reflux, 74%; 2) *p*-$MeOPhCH(OMe)_2$, HBF_4, DMF, room temperature, 42% (α anomer); b) 1) BnBr, NaH, THF/DMF (4:1), room temperature, 92%; 2) LAH, $AlCl_3$, Et_2O/CH_2Cl_2 (3:1), −78 °C→room temperature, 92%; c) 1) NaH, MeI, THF/DMF (4:1), room temperature, 91%; 2) DDQ, CH_2Cl_2/H_2O (19:1), room temperature, 91%; d) TMSOTf, Et_3N, CH_2Cl_2, room temperature, 94%; e) 1) BnBr, NaH, THF/DMF (4:1), room temperature, 97%; 2) $(Ph_3P)_3RhCl$, DABCO, EtOH/toluene/H_2O (6:3:1), 90 °C, followed by treatment with 1 N HCl/acetone (9:1), 90 °C, 93%; f) 2-(2-methoxyethoxy)acetic acid, EDCI, DMAP, CH_2Cl_2, room temperature, 93% (α/β = 4:1). DABCO = 1,4-diazabicyclo[2.2.2]octane, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, LAH = lithium aluminum hydride, MPM = 4-methoxyphenylmethyl, Tf = trifluoromethanesulfonyl.

4: ^1H NMR ($CDCl_3$): Characteristic resonances for α anomer: $\delta = 3.36$ (s, 3H, methoxy), 3.38 (s, 3H, methoxy), 6.28 ppm (d, $J = 2$ Hz, 1H, anomeric); characteristic resonances for β anomer: $\delta = 3.35$ (s, 3H, methoxy), 3.38 (s, 3H, methoxy), 5.65 ppm (s, 1H, anomeric).

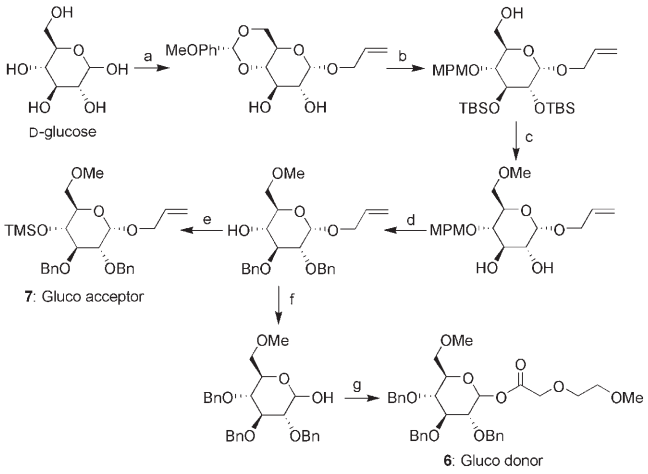
5: ^1H NMR ($CDCl_3$): $\delta = 0.11$ (s, 9H), 3.39 (s, 3H), 3.54–3.62 (m, 2H), 3.66–3.69 (m, 2H), 3.74 (m, 1H), 3.90–3.94 (m, 1H), 4.08 (t, $J = 9$ Hz, 1H), 4.13–4.17 (m, 1H), 4.57 (s, 2H), 4.66 (dd, $J = 12.5$, 21 Hz, 2H), 4.87 (d, $J = 1.5$ Hz, 1H), 5.13–5.24 (m, 2H), 5.80–5.89 (m, 1H), 7.24–7.34 ppm (m, 10H).

Gluco donor **6** and acceptor **7** were synthesized as summarized in Scheme 10. The experimental procedures reported in reference [3a,b] were adopted to carry out this synthesis, except for step b2, which was done with the protocol in the literature.[18]

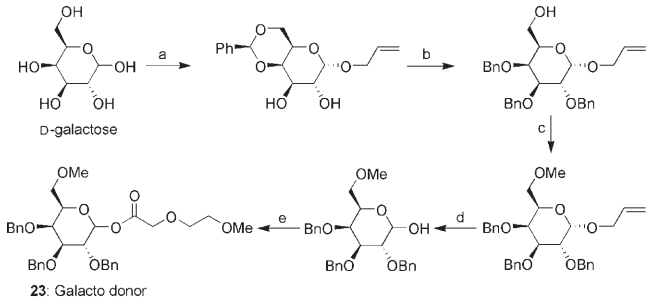
6: ^1H NMR ($CDCl_3$; α/β = 2:1): Characteristic resonances for α anomer: $\delta = 3.33$ (s, 3H, methoxy), 3.38 (s, 3H, methoxy), 6.42 ppm (d, $J = 3.5$ Hz, 1H, anomeric); characteristic resonances for β anomer: $\delta = 3.34$ (s, 3H, methoxy), 3.36 (s, 3H, methoxy), 5.65 ppm (d, $J = 8.5$ Hz, 1H, anomeric).

7: ^1H NMR ($CDCl_3$): $\delta = 0.01$ (s, 9H), 3.37 (s, 3H), 3.45–3.53 (m, 2H), 3.58–3.60 (m, 1H), 3.69–3.78 (m, 3H), 3.97–4.01 (m, 1H), 4.13–4.17 (m, 1H), 4.56 (d, $J = 12$ Hz, 1H), 4.68 (d, $J = 11.5$ Hz, 1H), 4.74 (d, $J = 11.5$ Hz, 1H), 4.78 (d, $J = 4$ Hz, 1H), 5.01 (d, $J = 11.5$ Hz, 1H), 5.20–5.34 (m, 2H), 5.88–5.97 (m, 1H), 7.25–7.36 ppm (m, 10H).

Galacto donor **23**, which was used for the preparation of **19** (Scheme 6), was synthesized as summarized in Scheme 11. The experimental procedures reported in reference [3a,b] were adopted to carry out this synthesis, except for step b2, which was done with the protocol in the literature.[18]



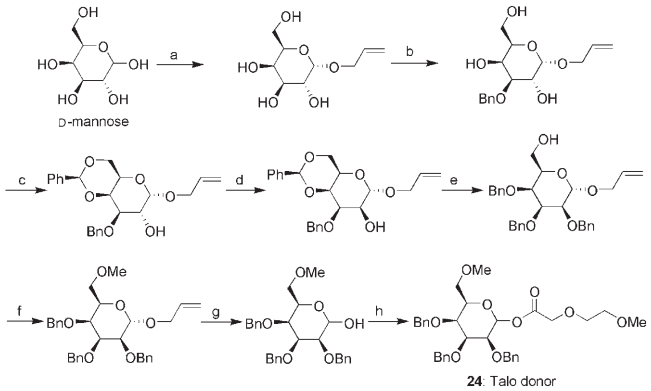
Scheme 10. Synthesis of gluco donor **6** and gluco acceptor **7**. Reagents, conditions, and yield: a) 1) Allyl alcohol, $Sc(OTf)_3$, reflux, 71%; 2) *p*-$MeOPhCH(OMe)_2$, HBF_4, DMF, room temperature, 58% (α anomer); b) 1) TBSCl, imidazole, DMF, room temperature, 100%; 2) LAH, $AlCl_3$, Et_2O/CH_2Cl_2 (3:1), −78 °C→room temperature, 86%; c) 1) NaH, MeI, THF/DMF (4:1), room temperature, 88%; 2) TBAF, THF, room temperature, 82%; d) 1) BnBr, NaH, THF/DMF (4:1), 65 °C, 100%; 2) DDQ, CH_2Cl_2/H_2O (18:1), room temperature, 99%; e) TMSOTf, Et_3N, CH_2Cl_2, room temperature, 95%; f) 1) BnBr, NaH, THF/DMF (4:1), room temperature, 100%; 2) $[(Ph_3P)_3RhCl]$, DABCO, EtOH/toluene/H_2O (6:3:1), 80 °C, followed by treatment with 1 N HCl/acetone (9:1), 80 °C, 73%; g) 2-(2-methoxyethoxy)acetic acid, EDCI, DMAP, CH_2Cl_2, room temperature, 98% (α/β = 2:1). TBAF = tetra-*n*-butylammonium fluoride, TBS = *tert*-butyldimethylsilyl.



Scheme 11. Synthesis of galacto donor **23**. Reagents, conditions, and yield: a) 1) Allyl alcohol, $Sc(OTf)_3$, reflux, 61%; 2) *p*-$PhCH(OMe)_2$, amberlyst-15, $CHCl_3$, reflux, 86% (α anomer); b) 1) BnBr, NaH, THF/DMF (4:1), room temperature, 86%; 2) LAH, $AlCl_3$, Et_2O/CH_2Cl_2 (3:1), −78 °C→reflux, 81% (along with 11% of the 6-*O*-benzyl isomer); c) NaH, MeI, THF/DMF (4:1), room temperature, 90%; d) $[(Ph_3P)_3RhCl]$, DABCO, EtOH/toluene/H_2O (6:3:1), 90 °C, followed by treatment with 1 N HCl/acetone (9:1), 90 °C, 93%; e) 2-(2-methoxyethoxy)acetic acid, EDCI, DMAP, CH_2Cl_2, room temperature, 89% (α/β = 1.1:1).

23: ^1H NMR ($CDCl_3$): Characteristic resonances for α anomer: $\delta = 3.27$ (s, 3H, methoxy), 3.34 (s, 3H, methoxy), 6.48 ppm (d, $J = 3.7$ Hz, 1H, anomeric); characteristic resonances for β anomer: $\delta = 3.26$ (s, 3H, methoxy), 3.35 (s, 3H, methoxy), 5.63 ppm (d, $J = 8.1$ Hz, 1H, anomeric).

Talo donor **24** was synthesized as summarized in Scheme 12. The experimental procedures reported in reference [3a,b] were adopted to carry out



Scheme 12. Synthesis of talo donor **24**. Reagents, conditions, and yield: a) 1) Allyl alcohol, $Sc(OTf)_3$, reflux, 74%; b) 1) Bu_2SnO, MeOH, reflux. 2. BnBr, TBAI, toluene, room temperature, 62% over 2 steps; c) *p*-$PhCH(OMe)_2$, amberlyst-15, $CHCl_3$, reflux, 72% (α anomer); d) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; 2) LAH, Et_2O, 0°C, 50% over 2 steps; e) 1) BnBr, NaH, THF/DMF (4:1), room temperature, 83%; 2) LAH, $AlCl_3$, Et_2O/CH_2Cl_2 (3:1), −78°C→reflux, 74% (along with 18% of the 6-*O*-benzyl isomer); f) NaH, MeI, THF/DMF (4:1), room temperature, 77%; g) $[(Ph_3P)_3RhCl]$, DABCO, EtOH/toluene/H_2O (6:3:1), 90°C, followed by treatment with 1N HCl/acetone (9:1), 90°C, 93%; h) 2-(2-methoxyethoxy)acetic acid, EDCI, DMAP, CH_2Cl_2, room temperature, 89% (α/β = 4:1). DMSO = dimethyl sulfoxide, TBAI = tetra-*n*-butylammonium iodide.

this synthesis, except for steps b and e2, which were done with the protocols in the literature.[18,19]

24: ^{1}H NMR ($CDCl_3$): α anomer: $\delta = 3.34$ (s, 3H, methoxy), 3.35 (s, 3H, methoxy), 6.14 ppm (d, $J = 2$ Hz, 1H, anomeric); β anomer: 3.35 (s, 3H, methoxy), 3.35 (s, 3H, methoxy), 5.80 ppm (s, 1H, anomeric).

β-Disaccharides **8**, **9**, **12**, **13**, **19**, and **21** and α-disaccharides **10**, **11**, **14**, **15**, **20**, and **22** were synthesized by glycosidation according to the procedure reported by Mukaiyama and co-workers,[4] that is, 20 mol% $SiCl_4$/$2AgClO_4$, CH_3CN, −10°C for β anomer, 10 mol% $SnCl_4/AgClO_4$, Et_2O, 0°C for α anomer.

8: ^{1}H NMR ($CDCl_3$): $\delta = 3.18$–3.22 (m, 1H), 3.22 (s, 3H), 3.23 (s, 3H), 3.39–3.42 (m, 1H), 3.45–3.47 (m, 4H), 3.67–3.72 (m, 2H), 3.78 (d, $J =$ 3 Hz, 1H), 3.82–3.92 (m, 3H), 4.08–4.13 (m, 2H), 4.76 (s, 1H), 4.51–4.56 (m, 4H), 4.62 (m, 2H), 4.82–4.86 (m, 5H), 5.12–5.22 (m, 2H), 5.78–5.86 (m, 1H), 7.18–7.29 (m, 24H), 7.38 ppm (d, $J = 7.5$, 1H).

10: ^{1}H NMR ($CDCl_3$): $\delta = 3.39$ (s, 3H), 3.40 (s, 3H), 3.61–3.68 (m, 5H), 3.73 (m, 1H), 3.76–3.82 (m, 3H), 3.83–3.86 (m, 1H), 3.93–3.99 (m, 2H), 4.06 (t, $J = 9$ Hz, 1H), 4.18–4.35 (m, 4H), 4.51–4.68(m, 6H), 4.91 (d, $J =$ 11 Hz, 1H), 4.94 (s, 1H), 5.19–5.29 (m, 2H), 5.31 (d, $J = 1.5$ Hz, 1H), 5.84–5.92 (m, 1H), 7.18–7.33 ppm (m, 25H).

9: ^{1}H NMR ($CDCl_3$): $\delta = 3.21$ (s, 3H), 3.25 (s, 3H), 3.25–3.29 (m, 1H), 3.32–3.36 (m, 1H), 3.40–3.44 (m, 2H), 3.48–3.53 (m, 3H), 3.67–3.73 (m, 1H), 3.77 (d, $J = 3$ Hz, 1H), 3.83 (t, $J = 10$ Hz, 1H), 3.92–3.96 (m, 2H), 3.97–4.03 (m, 1H), 4.15 (dd, $J = 4.5$, 12.5 Hz, 1H), 4.44 (s, 1H), 4.58–4.62 (m, 4H), 4.73–4.79 (m, 3H), 5.15 (d, $J = 11$ Hz, 1H), 5.24 (d, $J = 10$, 1H), 5.33 (d, $J = 17.5$ Hz, 1H), 5.90–5.99 (m, 1H), 7.24–7.32 (m, 23H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.43 ppm (d, $J = 7.5$ Hz, 1H).

11: ^{1}H NMR ($CDCl_3$): $\delta = 3.37$ (s, 3H), 3.37 (s, 3H), 3.54–3.79 (m, 9H), 3.84–3.89 (m, 2H), 3.93–4.03 (m, 2H), 4.16–4.29 (m, 3H), 4.52–4.65 (m, 6H), 4.81 (d, $J = 3.5$ Hz, 1H), 4.90 (d, $J = 11$ Hz, 1H), 5.11 (d, $J = 11.5$ Hz, 1H), 5.24–5.36 (m, 3H), 5.90–5.99 (m, 1H), 7.14–7.33 ppm (m, 25H).

12: ^{1}H NMR ($CDCl_3$): $\delta = 3.26$ (s, 3H), 3.28 (s, 3H), 3.31–3.35 (m, 1H), 3.42 (t, $J = 9$ Hz, 1H), 3.49 (dd, $J = 4.5$, 11.5 Hz, 1H), 3.55–3.73 (m, 6H), 3.76–3.80 (m, 1H), 3.90 (dd, $J = 8$, 3.5 Hz, 1H), 3.95–3.99 (m, 1H), 4.16–4.20 (m, 1H), 5.17–5.28 (m, 2H), 5.84–5.92 (m, 1H), 7.25–7.34 (m, 24H), 7.40 ppm (d, $J = 7.5$ Hz, 1H).

14: ^{1}H NMR ($CDCl_3$): $\delta = 3.35$ (s, 3H), 3.35 (s, 3H), 3.48 (dd, $J = 3.5$ Hz, $J = 9.5$ Hz, 1H), 3.53–3.59 (m, 1H), 3.60–3.67 (m, 4H), 3.75 (dd, $J = 4.0$, 7.5 Hz, 1H), 3.84–3.91 (m, 3H), 3.95–3.99 (m, 1H), 4.06 (dd, $J = 3$, 8.5 Hz, 1H), 4.16–4.19 (m, 1H), 4.37–4.69 (m, 8H), 4.77–4.85 (m, 2H), 4.92–4.96 (m, 2H), 5.17–5.29 (m, 2H), 5.81 (d, $J = 3.5$ Hz, 1H), 5.84–5.92 (m, 1H), 7.03–7.31 ppm (m, 25H).

13: ^{1}H NMR ($CDCl_3$): $\delta = 3.23$ (s, 3H), 3.26 (s, 3H), 3.33–3.43 (m, 3H), 3.49–3.52 (m, 3H), 3.58–3.68 (m, 4H), 3.72–3.76 (m, 1H), 3.84–3.88 (m, 3H), 3.98–4.02 (m, 1H), 4.13–4.16 (m, 1H), 4.40 (d, $J = 8$ Hz, 1H), 4.52–4.67 (m, 1H), 4.73–4.85 (m, 7H), 4.92 (d, $J = 11$ Hz, 1H), 5.10 (d, $J =$ 11 Hz, 1H), 5.22 (d, $J = 10$ Hz, 1H), 5.33 (d, $J = 17.5$ Hz, 1H), 5.90–5.98 (m, 1H), 7.23–7.33 (m, 24H), 7.44 ppm (d, $J = 7.5$ Hz, 1H).

15: ^{1}H NMR ($CDCl_3$): $\delta = 3.30$ (s, 3H), 3.33 (s, 3H), 3.31–3.37 (m, 1H), 3.50 (dd, $J = 4$, 10 Hz, 1H), 3.55–3.67 (m, 5H), 3.73–3.78 (m, 1H), 3.85–3.89 (m, 1H), 3.93 (t, $J = 9.5$ Hz, 1H), 3.86–4.17 (m, 4H), 4.52–4.67 (m, 5H), 4.77–4.91 (m, 5H), 5.09 (d, $J = 12$ Hz, 1H), 5.24 (d, $J = 11$ Hz, 1H), 5.33 (d, $J = 17$ Hz, 1H), 5.78 (d, $J = 4$ Hz, 1H), 5.90–5.98 (m, 1H), 7.61–7.31 ppm (m, 25H).

19: ^{1}H NMR ($CDCl_3$): $\delta = 3.17$ (s, 3H), 3.24 (s, 3H), 3.22–3.28 (m, 1H), 3.38–3.45 (m, 2H), 3.54 (dd, $J = 2.9$, 9. 7 Hz, 1H), 3.58–3.62 (m, 1H), 3.73–3.78 (m, 1H), 3.80–3.83 (m, 2H), 3.89–3.92 (m, 2H), 3.95–4.00 (m, 1H), 4.15–4.22 (m, 2H), 4.50 (d, $J = 7.8$ Hz, 1H), 4.61 (d, $J = 11.7$ Hz, 1H), 4.71 (d, $J = 12.2$ Hz, 2H), 4.74 (d, $J = 12.2$ Hz, 2H), 4.82–4.92 (m, 4H), 4.97 (d, $J = 11.7$ Hz, 1H), 5.19 (d, $J = 10.3$ Hz, 1H), 5.27 (dd, $J =$ 1.5 Hz, $J = 17.1$ Hz, 1H), 5.85–5.94 (m, 1H), 7.22–7.38 ppm (m, 25H).

20: ^{1}H NMR ($CDCl_3$): $\delta = 3.29$ (s, 3H), 3.41 (s, 3H), 3.44–3.48 (m, 1H), 3.52 (t, $J = 8.3$ Hz, 1H), 3.58–3.62 (m, 1H), 3.73 (dd, $J = 4.9$, 10. 7 Hz, 1H), 3.82 (br s, 1H), 3.86–3.95 (m, 3H), 3.96–4.02 (m, 2H), 4.02–4.06 (m, 2H), 4.20 (dd, $J = 4.9$, 11.7 Hz, 1H), 4.35 (t, $J = 9.3$ Hz, 1H) 4.48 (d, $J =$ 9.3 Hz, 1H), 4.53 (br s, 2H), 4.55 (d, $J = 11.7$ Hz, 1H), 4.61 (d, $J =$ 11.7 Hz, 1H), 4.63 (d, $J = 11.7$ Hz, 1H), 4.66 (d, $J = 11.7$ Hz, 1H), 4.74 (d, $J = 11.6$ Hz, 1H), 4.80 (d, $J = 11.6$ Hz, 1H), 4.82 (d, $J = 11.7$ Hz, 1H), 4.96 (d, $J = 1$ Hz, 1H), 5.22 (d, $J = 10.2$ Hz, 1H), 5.28 (dd, $J = 1.0$, 7.1 Hz, 1H), 5.81 (d, $J = 3.4$ Hz, 1H), 5.81–5.94 (m, 1H), 7.18–7.38 ppm (m, 25H).

21: ^{1}H NMR ($CDCl_3$): $\delta = 3.19$ (s, 3H), 3.30 (s, 3H), 3.30–3.44 (m, 3H), 3.55–3.60 (m, 2H), 3.60–3.70 (m, 1H), 3.77–3.82 (m, 3H), 3.84–3.88 (m, 1H), 3.82 (dd, $J = 3.4$, 9.3 Hz, 1H), 3.95–4.40 (m, 2H), 4.12 (t, $J = 8.5$ Hz, 1H), 4.19 (dd, $J = 5.0$, 13 Hz, 1H), 4.51–4.60 (m, 5H), 4.69 (s, 2H), 4.70 (d, $J = 18$ Hz, 1H), 4.86 (d, $J = 4.5$ Hz, 1H), 4.88 (d, $J = 4.5$ Hz, 1H), 4.90 (d, $J = 3.5$ Hz,1H), 4.96 (t, $J = 13.5$ Hz, 2H), 5.19 (d, $J = 10.3$ Hz, 1H), 5.27 (dd, $J = 1.5$ Hz, 17.1 Hz, 1H), 5.85–5.94 (m, 1H), 7.20–7.45 ppm (m, 25H)

22: ^{1}H NMR ($CDCl_3$): $\delta = 3.35$ (s, 3H), 3.42 (s, 3H), 3.62 (dd, $J = 6.3$, 9.8 Hz, 1H), 3.65–3.72 (m, 4H), 3.72–3.74 (m, 1H), 3. 77 (br s, 1H), 3.79–3.81 (m, 1H), 3.92 (br s, 1H), 3.96–4.03 (m, 2H), 4.12 (t, $J = 8.7$ Hz, 1H), 4.19–4.24 (m, 1H), 4.39 (d, $J = 12.7$ Hz, 1H), 4.45–4.52 (m, 3H). 4.53–4.58 (m, 2H), 4.65 (d, $J = 12.7$ Hz, 1H), 4.68 (d, $J = 12.7$ Hz, 1H), 4.76 (d, $J =$ 11.7 Hz, 1H), 4.95 (d, $J = 1.5$ Hz, 1H), 4.97 (d, $J = 11.7$ Hz, 1H), 5.21 (dd, $J = 1.5$, 10.7 Hz, 1H), 5.28 (dd, $J = 1.5$,17 Hz, 1H), 5.47 (s, 1H), 5.86–5.95 ppm (m, 1H), 7.25–7.36 (m, 25H).

Acknowledgements

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[7] In the work on *s*MMP,[3a] the experimental observations made suggested that the β-to-α anomerization is virtually kinetically controlled for the reaction within 10 h. However, with longer reaction times, the scrambled products were observed at least in the octasaccharide series, thereby implying that formation of oxonium ion(s) from the α anomer is feasible, although very sluggish.

[8] It is generally recognized that β-mannosides are prone to facile anomerization.[6]

[9] Masubara and Mukaiyama reported anomerization of a 2-amino-2-deoxy-β-glucopyranoside in the presence of $SnCl_3ClO_4$: K. Masubara, T. Mukaiyama, *Chem. Lett.* **1993**, 2145: to our knowledge, however, no anomerization of a 2-oxypyranoside was reported under the Mukaiyama conditions.

[10] A facile α-to-β anomerization was observed for α-mannopyranosides, including mano-α-mano disaccharide **10**, in the presence of $TiCl_4$ (20 mol%); for example, allyl 3-*O*-methyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside[3a] gave an approximately 94:6 mixture of α and β anomers at room temperature in 5 min in both CH_2Cl_2 and Et_2O.

[11] Among numerous examples known in literature, the example reported by Lee and co-workers is most relevant to the current case: C. K. Lee, E. J. Kim, I.-S. H. Lee, *Carbohydr. Res.* **1993**, *240*, 197.

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[17] Extrapolating the subgroup analysis in Scheme 7, we noticed the possibility that the Mukaiyama glycosidation catalyst might be developed as a selective cleavage reagent of a β-glycosidic linkage present in a permethylated polysaccharide.

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