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Regioselective and stereoselective benzylidene installation and one-pot protection of D-mannose†

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Oligosaccharide syntheses are an important source of well-defined sugar constructs particularly needed for the evaluation of structure–activity relationships. The chemical assembly of oligosaccharides requires several building blocks, that is, glycosyl donors and acceptors, which are prepared in multistep processes and in a generally tedious and time-consuming manner. Having developed one-pot procedures meant to minimise the effort in sugar building block preparation, we tackled herein the one-pot preparation of fully protected and 2-, 3-, 4-, and 6-alcohol derivatives of D-mannose, a widely distributed monosaccharide. As a consequence of the hydroxyl group pattern of D-mannose, regioselective and stereoselective benzylidenations were developed and later seamlessly utilised as the first transformation in the one-pot procedure.

Introduction

Carbohydrates are involved in numerous biological processes.[1] The physiological roles of these complex molecules are attributed to their elaborate structures, which, in turn, are the results of simple-looking yet diversified multihydroxy monosaccharide residues. Among the widely distributed monosaccharides, D-mannose is an integral component of several biologically significant molecules, such as *N*-glycans (**1**),[1b] glycosylphosphatidylinositol (GPI) anchors (**2**),[2] bacterial cell wall phosphatidylinositol mannosides (PIMs, **3**),[3] lipomannan (LM),[4] lipoarabinomannan (LAM)[4] and the yeast cell surface oligomannosides[5] (Fig. 1). Additionally, mannopyranosyl derivatives form useful chiral pools for the synthesis of enantiomerically pure natural products,[6] preparation of various amino sugars[7] and mannosidase inhibitors.[8]

Access to structurally defined oligosaccharides and glycoconjugates is essential to understand their function. However, these natural compounds typically exist in heterogeneous mixtures, which make their isolation and purification a forbidding effort. Chemical synthesis has, therefore, become necessary to sustain high demands of pure materials for biological studies.[9] Moreover, it also offers essential routes toward the preparation of natural and non-natural conjugates with exceptional flexibility, enabling the preparation of carbohydrate-based vaccines[10] and antibiotics.[11]

A typical bottleneck in sugar synthesis is the acquisition of suitably protected monosaccharide building blocks. Conventional methods follow some thoughtfully laid-out multistep protection–deprotection protocols to ultimately differentiate the various hydroxyl groups of an unprotected

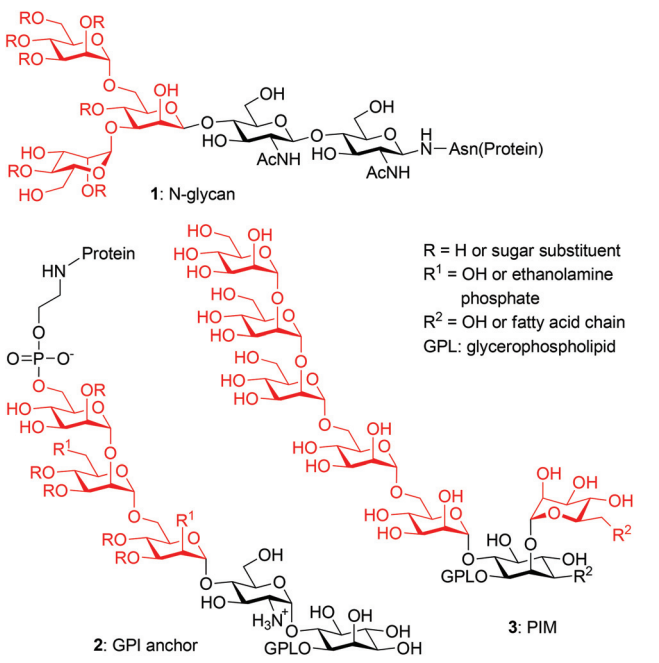

Fig. 1 Some D-mannose-containing natural compounds.

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monosaccharide. Cumbersome work-up and purifications often punctuate these step-by-step schemes, rendering the synthetic effort hectic and time-consuming. To tackle these challenges and efficiently create a library of suitably protected monosaccharide derivatives, streamlining functional group manipulations is essential. Our contribution to such an endeavour involved the combinatorial and highly regioselective trimethylsilyl triflate (TMSOTf)-catalysed one-pot protection strategy, facilitating the efficient accumulation of hundreds of building blocks.[12]

Our research group strives toward the efficient synthesis of biologically significant oligosaccharides through one-pot protection and glycosylation strategies.[12a,d,13] As we tackle the synthesis of various D-mannose-containing constructs, particularly the mycobacterial cell-surface carbohydrates,[14] we recognised the necessity of efficient one-pot methods for the preparation of differentially protected D-mannosyl derivatives. Extending our parallel combinatorial one-pot protection strategy, we disclose herein the synthesis of several D-mannose-derived building blocks. The distinct hydroxylation pattern of D-mannose required us to initially establish conditions for regioselective and stereoselective benzylidenations, a common first step in our established one-pot protocol. This step was later integrated in the one-pot synthesis of fully protected derivatives and 2-, 3-, 4- and 6-alcohols.

Results and discussion

Cyclic acetals are frequently used in simultaneous protection of 1,2- and 1,3-diols.[15] In carbohydrates, isopropylidene is usually employed for the protection of C-1/C-2 and C-5/C-6 hydroxyls of furanoses, whereas arylmethylidenes, especially benzylidenes, are most commonly used for the regioselective 4,6-*O* protection of multi-hydroxy pyranoses. Generally, the 4,6-*O*-benzylidene formation leads to either *cis*- or *trans*-fused 1,3-dioxane rings of only the thermodynamically more stable isomer, where the phenyl group is equatorial. In addition, tolerance to a diverse set of nucleophilic and basic reagents and the opportunities for regioselective reductive or oxidative ring opening to afford the desired 4- or 6-alcohol amplify the synthetic interest for the arylmethylidene protecting groups. The same benzylidene ring at the 4,6-*O* position of D-mannose provides rigidity to the sugar structure that augments stereoselectivity in β-glycosidic bond formation at the anomeric centre.[16] Because the synthetic utilities of arylmethylidene protecting groups are well-recognised in carbohydrate chemistry, the protocol for their introduction is now generalised for most sugars.

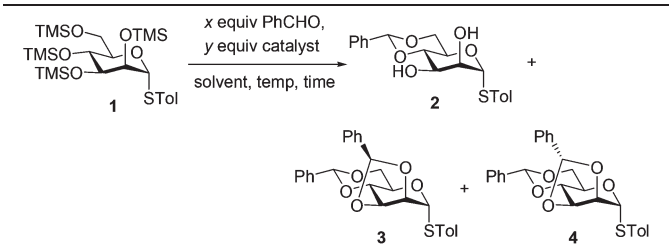
For D-mannose, however, the targeted acetalation is still an issue to be resolved. The most familiar setback in 4,6-*O*-benzylidenation is the often unwanted 2,3-*O*-benzylidene formation. Owing to the *cis*-orientation of the 2- and 3-hydroxyls of D-mannose, acetalation at C-2/C-3 occurs concurrent to the more preferred C-4/C-6 acetalation. In addition, 2,3-*O*-benzylidenation often leads to a mixture of *exo*- and *endo*-isomers complicating purification and the succeeding reactions. For instance, the outcome of the reductive ring opening of such 1,3-dioxolane rings is very much dependent on the orientation of the phenyl group.[17] A variety of catalysts such as copper triflate,[18] vanadyl triflate,[19] $HClO_4$ on silica,[20] $FeCl_3$[21] and $HBF_4{\cdot}Et_2O$[22] have been reported for the regioselective 4,6-*O*-benzylidenation of D-mannose with varying efficiencies and success in curbing 2,3-*O*-benzylidenation. Numerous efforts have also been dedicated in the past to carry out the dibenzylidenation of D-mannose. However, the stereoselectivity in the orientation of the phenyl group (*exo* or *endo*) could not be achieved. The common approach involves treatment of the mannosyl substrate with benzaldehyde dimethyl acetal and camphorsulfonic acid (CSA) or *p*-toluenesulfonic acid in CH_3CN or dimethylformamide at elevated temperatures and even pressures only to generate mixtures of *exo*- and *endo*-isomers in various ratios.[23] Furthermore, the commonly studied substrates are alkyl or aryl mannosides, whereas the dibenzylidenation of thiomannosides, which are convenient intermediates in carbohydrate synthesis because of their dual roles as glycosyl acceptors and donors, is rarely visited.

To prepare variously protected D-mannosyl building blocks in a one-pot manner, a clear-cut method for the regioselective and stereoselective benzylidene installation that blends effectively with our established protocol is desirable. In the D-glucose case, we have shown that the per-trimethylsilylated substrate not only provides a chance for testing various polar and nonpolar organic solvents by increasing the solubility of the corresponding tetraols, but the silyl groups also offer thermodynamic and steric leverage during protecting group installation.[12a,13b] Thus, 4-methylphenyl 1-thio-α-D-mannopyranoside[24] was subjected to trimethylsilyl (TMS) chloride and Et_3N to acquire the per-*O*-trimethylsilyl thiomannoside **1** in 96% yield. Compound **1** was then treated with benzaldehyde under various acid-catalysed conditions (Table 1). In most of these cases, tetra-*n*-butylammonium fluoride (TBAF) was added to the reaction mixture after the stated reaction period to quench the acid catalyst and cleave any remaining TMS groups. When **1** was exposed to 2.1 equiv. of benzaldehyde and 0.5 equiv. of CSA in CH_2Cl_2 at room temperature, monobenzylidenation occurred favourably with compound **2** isolated in 87% yield (entry 1). The dibenzylidene compounds **3** (4%) and **4** (3%) were obtained as minor products.

The stereochemistries of the *exo*- and *endo*-isomers **3** and **4** were confirmed using ^1H–^1H NOESY. For the *exo*-compound **3**, the acetal proton of the five-membered benzylidene ring is facing 4-H. As a consequence of their close proximity, this acetal proton shows spatial coupling with 4-H (Fig. 2). Such a relationship should not be found for the *endo*-isomer **4**. Instead, the corresponding acetal proton of **4** possesses NOE correlation with 2-H as both protons are projected on the same face.

To force dibenzylidenation, the quantities of benzaldehyde and CSA were increased to 4 equiv. and 1 equiv., respectively. Although the yields of compounds **3** (30%) and **4** (23%) increased in this case, the *exo*-/*endo*-stereoselectivity was poor.

Table 1 Benzylidenation of the per-trimethylsilylated thiomannoside **1**



						Yield[b] (%)		
Entry	*x*	*y*[a]	Solvent	Temp	Time (h)	**2**	**3**	**4**
1	2.1	0.5	CH_2Cl_2	rt	5	87	4	3
2	4.0	1.0	CH_2Cl_2	rt	5	23	30	23
3	2.1	0.5	CH_3NO_2	rt	5	77	7	3
4	2.1	0.5	Et_2O	rt	5	77	7	10
5	2.1	0.5	CH_3CN	rt	7	89	5	1
6	4.0	1.0	CH_3CN	rt	16	73	0	0
7	1.05	0.05	CH_2Cl_2	−78 °C	1.5	92	0	0
8	1.05	0.05	CH_2Cl_2	−78 °C	2.5	72	0	0
9	2.1	0.1	CH_2Cl_2	−78 °C	2	0	27	73
10	2.1	0.1	CH_2Cl_2	rt	5	17	23	19
11	2.1	0.1	CH_3CN	rt	1.5	0	83	7
12	2.1	0.1	CH_3CN	rt	3	14	67	8
13	2.1	0.1	CH_3CN	rt	5	24	35	7
14	2.1	0.1	CH_3CN	0 °C	0.5	0	91	0

[a] CSA was used as a catalyst for entries 1–6; TMSOTf is the catalyst in entries 7–14. [b] The values for compound **2** are isolated yields; compounds **3** and **4** were recovered together to get the combined yield, and the yields of each compound were determined using ^{1}H NMR.

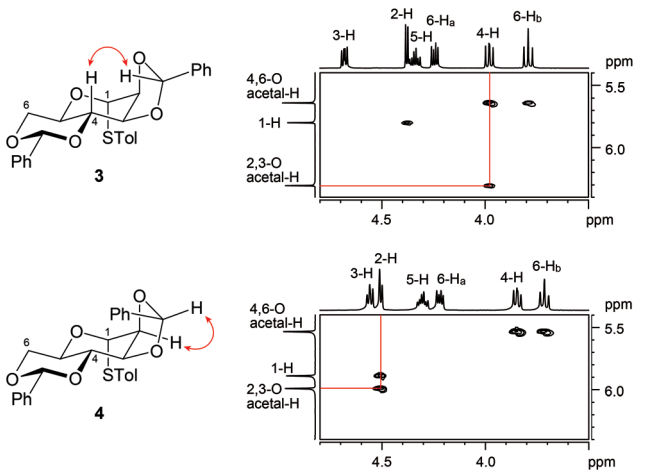


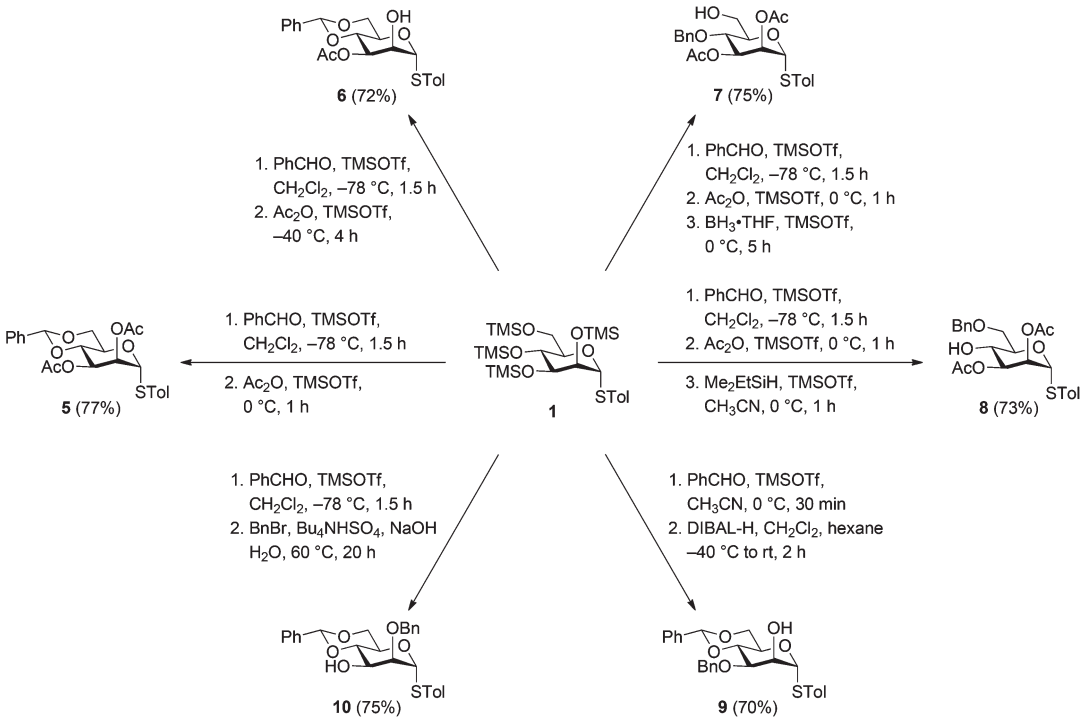
Fig. 2 NOE correlations confirming the relevant stereochemistry of compounds **3** and **4**.

We, then, turned our focus to other more polar solvents. With CH_3NO_2, Et_2O and CH_3CN, comparable preferences toward monobenzylidation similar to CH_2Cl_2 (entries 3–5) were noted, with CH_3CN providing the best yield for diol **2** at 89%. The *exo*-isomer **3** also appears as the favoured dibenzylidenation product when CH_3CN is used as solvent. On trying to boost the yield for dibenzylidenation, compound **1** was treated with 4 equiv. of benzaldehyde and 1 equiv. of CSA (entry 6). Despite the prolonged conditions, only the monobenzylidene **2** (73%) was obtained, indicating the vulnerability of the five-membered ring on protracted reaction time.

Based on our previous experience, the Lewis acid TMSOTf catalyses the benzylidenation of per-trimethylsilylated monosaccharides even at sub-zero temperatures,[12a,d,13c] enabling the evaluation of mono- and dibenzylidenation under such conditions. Initially, monobenzylidenation was tested by treating compound **1** with 1.05 equiv. of benzaldehyde and 5 mol% TMSOTf in CH_2Cl_2 at −78 °C. We observed that 1.5 h of reaction led to the exclusive formation of the monobenzylidene **2** in an excellent 92% yield (entry 7), but some product degradation occurred when the reaction was kept longer (entry 8). The feasibility of TMSOTf for dibenzylidenation was tested by using 2.1 equiv. of benzaldehyde at −78 °C (entry 9), which offered the *endo*-isomer **4** (73%) as the major product, along with the *exo*-isomer **3** (27%). However, when carried out at room temperature for 5 h (entry 10), the yield and selectivity became poor, and, surprisingly, the *exo* and *endo* preference was reversed.

A change of solvent to CH_3CN furnished the *exo*-compound **3** as the major product in 83% yield (*exo*/*endo* = 12.5/1) when the reaction was carried out for 1.5 h at room temperature (entry 11). It should be mentioned that compound **3** has low solubility in CH_3CN and crystallises out of solution during the course of the reaction. Here, no monobenzylidene product was recovered. Allowing the reaction system to stir for extended periods (entries 12 and 13) only decreased the yield of **3**, with a minor increase in yield for **2** as well as the formation of minor amounts of **4**. These results corroborate our earlier observation that the reaction time is a critical factor in this transformation. If the reaction was left for a longer time period, the five membered benzylidene ring may undergo hydrolysis to produce the diol **2**, and isomerization occurs, to some extent, to the *endo*-product **4**. Once the benzylidene compound was hydrolysed to diol **2**, further benzylidenation is unlikely under these conditions, even after longer reaction time because of the unfavourable entropy effect. To minimise the unwanted transformations, we performed the reaction in CH_3CN at 0 °C for only 30 min (entry 14). Delightfully, exclusive generation of the *exo*-compound **3** was noted in an excellent yield of 91%. By this result, we reckoned that the lower temperature led to greater chances of precipitation for compound **3**, forcing the reaction to favour its formation. To our knowledge, this is the first time such completely stereoselective dibenzylidenation of D-mannose is achieved and is a vital advantage offered by the use of per-trimethylsilylated mannoside as a substrate.

With suitable methods for regioselective monobenzylidenation and stereoselective dibenzylidenation, their further application in one-pot protection to afford the fully protected and 2-, 3-, 4- and 6-alcohol derivatives of D-mannose commenced (Scheme 1). We expected that the fully protected derivative **5** could be prepared by regioselective 4,6-*O*-benzylidenation followed by acetylation at the 2-*O* and 3-*O* positions. Then, subsequent regioselective reductive ring opening of the



Scheme 1 One-pot synthesis of several thiomannoside derivatives.

benzylidene acetal should be sufficient to supply the 6-alcohol **7** and 4-alcohol **8**. Thus, the solution of tetrasilylated thiomannoside **1** in CH_2Cl_2 was treated with 1.05 equiv. of benzaldehyde and TMSOTf at −78 °C to selectively install the 4,6-*O*-benzylidene. After 1.5 h, 3 equiv. of acetic anhydride (Ac_2O) and TMSOTf were added at −78 °C to the same flask, and the reaction temperature was gradually raised to 0 °C over a period of 1 h. However, to our surprise, only the 3-acetate **6** was generated in 62% yield along with the diol **2** (32%). With this development, we attempted to increase the yield of compound **6**. After benzylidenation, Ac_2O and TMSOTf were added to the reaction flask, and the reaction was stirred at −40 °C for 4 h. After quenching with TBAF, the desired product **6** was obtained in an improved 72% yield. Failure to generate the diacetate **5**, even in the presence of an excess of Ac_2O, could be attributed to the low reactivity of the axially oriented 2-OTMS at lower temperature and the cleavage of the TMS-group on extended reaction time. Acquainted with these observations, we transferred the reaction flask to an ice–water bath after completion of benzylidene formation, and then added Ac_2O and the catalyst. Consequently, compound **5** was finally afforded in a satisfactory 77% yield.

As envisioned, the 6-alcohol **7** and 4-alcohol **8** were obtained by regioselective 4,6-*O*-benzylidene ring opening at 6-*O* and 4-*O*, respectively, after the consecutive TMSOTf-catalysed monobenzylidenation and diacylation. Generally, the control of regioselectivity in these transformations rests on the applied reducing agent.[25] For our purposes, a borane–tetrahydrofuran (BH_3·THF) complex and TMSOTf readily facilitated the exclusive 6-*O*-ring opening of the benzylidene acetal, successfully generating compound **7** (75%) in the process. The reverse *O*-4 ring opening was accomplished, on the other hand, by using dimethylethylsilane (Me_2EtSiH) and TMSOTf, supplying compound **8** in 73% yield.

While regioselectivity in the reductive ring opening of 4,6-*O*-benzylidene can be achieved with an appropriate choice of reducing agent, the ring-opening of the more labile 5-membered 2,3-*O*-benzylidene does not follow such convention. In general, the *exo*-isomer gives axial hydroxyl (*i.e.*, the 3*x* rule of thumb)[17] regardless of the reducing agent. Accordingly, we planned to prepare the 2-alcohol **9** by dibenzylidenation towards the *exo*-product **3** followed by the regioselective 2-*O* ring opening. For the regioselective five-membered ring opening of dibenzylidene derivatives, the combination of $LiAlH_4$ and $AlCl_3$[23f] or diisobutylaluminum hydride (DIBAL-H) in toluene[23b] was reported. In our hands, we found that the DIBAL-H in hexane works remarkably well. Thus, after treatment with 2.1 equiv. of benzaldehyde and TMSOTf in CH_3CN for 30 min, Et_3N was added followed by solvent removal *in vacuo*. Then, CH_2Cl_2 and DIBAL-H in hexane were successively added to the same flask producing the 2-alcohol **9** in 70% yield, without generating its 3-alcohol counterpart. This result further strengthens the significance of developing completely stereoselective benzylidenation at 2-*O* and 3-*O* positions.

The 3-alcohol **10** was prepared by regioselective 4,6-*O*-benzylidenation followed by regioselective benzylation at the 2-*O* position. Others have shown that tetra-*n*-butylammonium sulfate (Bu_4NHSO_4) under phase-transfer conditions effectively facilitates the introduction of a benzyl-type protecting group preferentially on the axial hydroxyl of D-mannose.[26] Thus, after

the completion of 4,6-benzylidenation, the reaction mixture was treated with Bu_4NHSO_4 and benzyl bromide under basic conditions to afford 3-alcohol **10** in 75% yield.

Conclusions

We have successfully demonstrated the efficient preparation of various D-mannose-derived building blocks in a one-pot manner. Regio- and stereoselective monobenzylidenation and dibenzylidenation were effectively achieved and incorporated into the one-pot process, enabling the generation of several derivatives containing acetyl and benzyl groups. These methods and the insights gained here would benefit the quest for the expeditious chemical synthesis of D-mannose-containing constructs.

Experimental

General procedures

CH_2Cl_2 and CH_3CN were purified and dried using a safe purification system filled with anhydrous Al_2O_3. All other reagents were obtained from commercial sources and used without further purification. Water was either distilled or Milli-Q-purified. Flash column chromatography was carried out on Silica Gel 60 (230–400 mesh, E. Merck). TLC was performed on glass plates pre-coated with Silica Gel 60 F254 (0.25 mm, E. Merck); detection was executed by spraying with a solution of $Ce(NH4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$, and H_2SO_4 in water followed by subsequent heating on a hot plate. Specific rotations were taken under ambient conditions and reported in 10^{-1} deg cm^2 g^{-1}; the sample concentrations are in g dL^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on 400, 500 and 600 MHz spectrometers. Proton peaks were assigned with the aid of 2D NMR techniques (^{1}H–^{1}H COSY, HMQC and NOESY). The chemical shifts and coupling constants are provided in ppm and Hz, respectively. The hydrogen multiplicities of carbon peaks were determined using DEPT-90 and DEPT-135 experiments.

4-Methylphenyl 2,3,4,6-tetra-*O*-trimethylsilyl-1-thio-α-D-mannopyranoside (1). A mixture of 4-methylphenyl-1-thio-α-D-mannopyranoside (4.42 g, 15.5 mmol) and Et_3N (25.8 mL, 185 mmol) in CH_2Cl_2 (44.0 mL) was stirred at 0 °C under an N_2 atmosphere. TMSCl (11.7 mL, 92.7 mmol) was added to the solution, and the mixture was gradually warmed up to room temperature for 16 h. The solvent was evaporated under reduced pressure, the residue was diluted with hexane, and the resulting mixture was filtered through Celite. The filtrate was concentrated *in vacuo* to obtain compound **1** (8.3 g, 96%). $[\alpha]_D^{24}$ +115.7 (*c* 3.51 in $CHCl_3$) (lit.,[27] +116.6); IR (thin film) ν/cm^{-1} 2955, 2896, 1492, 1246, 1121, 1100, 838; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41 (2 H, d, *J* 8.0, Ar-H), 7.08 (2 H, d, *J* 8.0, Ar-H), 5.18 (1 H, d, *J* 2.1, 1-H), 4.01 (t, *J* = 2.1 Hz, 1 H, 2-H), 3.96–4.00 (1 H, m, 5-H), 3.87 (1 H, t, *J* 8.9, 4-H), 3.81 (1 H, dd, *J* 11.2, 2.1, 6-H$_a$), 3.74 (1 H, dd, *J* 11.2, 5.9, 6-H$_b$), 3.71 (1 H, dd, *J* 8.9, 2.1, 3-H), 2.31 (3 H, s, CH_3), 0.18 (9 H, s, $Si(CH_3)_3$), 0.14 (9 H, s, $Si(CH_3)_3$), 0.10 (18 H, s, $Si(CH_3)_3$ × 2), 0.10 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (C), 132.1 (CH × 2), 131.3 (C), 129.6 (CH × 2), 89.8 (CH), 75.4 (CH), 74.8 (CH), 73.3 (CH), 68.5 (CH), 62.3 (CH_2), 21.1 (CH_3), 0.7 (CH_3), 0.6 (CH_3), 0.4 (CH_3), −0.2 (CH_3); HRMS (ESI, $[M + Na]^+$) *m*/*z* calcd for $C_{25}H_{50}O_5NaSSi_4$ 597.2354, found 597.2346.

4-Methylphenyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (2). TMSOTf (7 μL, 0.04 mmol) was added to a solution of compound **1** (230 mg, 0.40 mmol) and PhCHO (41 μL, 0.41 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C under an N_2 atmosphere. After stirring for 1.5 h, TBAF was added to the mixture and the reaction flask was gradually warmed up to room temperature. The whole mixture was diluted with saturated $NaHCO_{3(aq)}$ (10 mL). The desired material was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate–hexanes = 1/2) to afford the 2,3-diol **2** (138 mg, 92%). $[\alpha]_D^{24}$ +295.5 (*c* 0.44 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3358, 3229, 2918, 2849, 1502, 1450, 1378, 1079, 806, 747, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (2 H, m, Ar-H), 7.49–7.34 (5 H, m, Ar-H), 7.12 (2 H, d, *J* 8.0, Ar-H), 5.56 (1 H, s, C*H*Ph), 5.50 (1 H, s, 1-H), 4.34 (1 H, dt, *J* 10.4, 4.8, 5-H), 4.30–4.29 (1 H, m, 2-H), 4.21 (1 H, dd, *J* 10.4, 4.8, 6-H$_a$), 4.11 (1 H, dd, *J* 10.4, 3.6, 3-H), 3.98 (1 H, t, *J* 10.4, 4-H), 3.81 (1 H, t, *J* 10.4, 6-H$_b$), 2.81 (2 H, br s, 2-OH, 3-OH), 2.32 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (C), 137.1 (C), 132.4 (CH), 130.0 (CH), 129.5 (C), 129.3 (CH), 128.4 (CH), 126.3 (CH), 102.3 (CH), 88.4 (CH), 79.1 (CH), 72.3 (CH), 69.1 (CH), 68.5 (CH_2), 64.1 (CH), 21.1 (CH_3); HRMS (FAB, $[M + H]^+$) *m*/*z* calcd for $C_{20}H_{23}O_5S$ 375.1266, found 375.1262.

4-Methylphenyl 2,3;4,6-di-*O*-[(*R*)-benzylidene]-1-thio-α-D-mannopyranoside (3). A solution of compound **1** (70 mg, 0.12 mmol) and PhCHO (26 μL, 0.26 mmol) in CH_3CN (1.0 mL) was stirred at 0 °C under an N_2 atmosphere. TMSOTf (2.2 μL, 0.012 mmol) was added to the solution, and the mixture was kept stirring at 0 °C for 30 min. The reaction mixture was then quenched with one drop of Et_3N, and the resulting mixture was filtered through a filter paper. The solids were washed with CH_3CN (0.5 mL) and then with hexane (1 mL) to get the pure *exo*-compound **3** (51 mg, 91%). $[\alpha]_D^{24}$ +155.3 (*c* 0.98 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3037, 2968, 1450, 1383, 1101, 822, 748, 691; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (2 H, dd, *J* 7.8, 2.0, Ar-H), 7.47 (2 H, dd, *J* 7.8, 2.0, Ar-H), 7.43–7.32 (8 H, m, Ar-H), 7.14 (1 H, d, *J* 7.9, Ar-H), 6.31 (1 H, s, C*H*Ph), 5.80 (1 H, s, 1-H), 5.64 (1 H, s, C*H*Ph), 4.68 (1 H, dd, *J* 9.5, 5.3, 3-H), 4.38 (1 H, d, *J* 5.3, 2-H), 4.37–4.30 (1 H, m, 5-H), 4.24 (1 H, dd, *J* 10.3, 5.2, 6-H$_a$), 3.98 (1 H, dd, *J* 9.5, 8.3, 4-H), 3.79 (1 H, t, *J* 10.3, 6-H$_b$), 2.34 (3 H, s, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6 (C), 138.4 (C), 137.0 (C), 133.2 (CH), 130.0 (CH), 129.2 (CH), 129.2 (CH), 128.6 (C), 128.4 (CH), 128.3 (CH), 126.3 (CH), 126.0 (CH), 103.0 (CH), 102.0 (CH), 84.9 (CH), 77.7 (CH), 75.8 (CH), 75.3 (CH), 68.6 (CH_2), 61.5 (CH), 21.2 (CH_3); HRMS (FAB, $[M + H]^+$) *m*/*z* calcd for $C_{27}H_{27}O_5S$ 463.1579, found 463.1585.

4-Methylphenyl 4,6-*O*-[(*R*)-benzylidene]-2,3-*O*-[(*S*)-benzylidene]-1-thio-α-D-mannopyranoside (4). The filtrate obtained after the

separation of the crystallised *exo*-isomer **3** in Table 1 was concentrated under reduced pressure. The residue was subjected to flash column chromatography (ethyl acetate–hexanes = 1/15) to obtain the pure *endo*-isomer **4** that was used to acquire characterisation data. $[\alpha]_D^{24}$ +169.4 (*c* 0.59 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3044, 2948, 1500, 1448, 1373, 1106, 1105, 823, 749, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.47 (4 H, m, Ar-H), 7.41–7.31 (8 H, m, Ar-H), 7.13 (2 H, d, *J* 7.9, Ar-H), 5.97 (1 H, s, C*H*Ph), 5.84 (1 H, d, *J* 0.5 Hz, 1-H), 5.50 (1 H, s, C*H*Ph), 4.52 (1 H, dd, *J* 7.5, 6.2, 3-H), 4.48 (1 H, dd, *J* 6.2, 0.5, 2-H), 4.30–4.21 (1 H, m, 5-H), 4.17 (1 H, dd, *J* 10.3, 5.2, 6-H_a), 3.79 (1 H, dd, *J* 9.9, 7.5, 4-H), 3.68 (1 H, t, *J* 10.3, 6-H_b), 2.33 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 138.4 (C), 137.1 (C), 136.9 (C), 133.1 (CH), 129.9 (CH), 129.4 (CH), 129.0 (CH), 128.6 (C), 128.4 (CH), 128.1 (CH), 126.4 (CH), 126.2 (CH), 104.0 (CH), 101.7 (CH), 84.4 (CH), 80.7 (CH), 78.5 (CH), 73.9 (CH), 68.5 (CH_2), 61.6 (CH), 21.1 (CH_3); HRMS (FAB, $[M + Na]^+$) *m*/*z* calcd for $C_{27}H_{26}O_5NaS$ 485.1399, found 485.1400.

4-Methylphenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (5). A mixture of compound **1** (200 mg, 0.35 mmol), PhCHO (37 μL, 0.37 mmol) and freshly dried 3 Å molecular sieves (200 mg) in CH_2Cl_2 (2.0 mL) was stirred at −78 °C under an N_2 atmosphere. TMSOTf (6.3 μL, 0.035 mmol) was added to the solution, and the mixture was kept stirring at the same temperature for 1.5 h. Then, Ac_2O (79 μL, 0.84 mmol) and TMSOTf (18.9 μL, 0.104 mmol) were sequentially added to the reaction mixture, and the reaction bottle was shifted to an ice-bath. The reaction mixture was stirred for 1 h at 0 °C, quenched with MeOH and filtered through Celite. The filtrate was concentrated under reduced pressure to get a residue, which was purified by flash column chromatography (ethyl acetate–hexanes = 1/3) to obtain the diacetate **5** (123 mg, 77%). $[\alpha]_D^{24}$ +158.9 (*c* 3.2 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3036, 2933, 1750, 1493, 1371, 1237, 1101, 966; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (2 H, m, Ar-H), 7.38–7.34 (5 H, m, Ar-H), 7.12 (2 H, d, *J* 8, Ar-H), 5.59–5.58 (2 H, m, 1-H, C*H*Ph), 5.40 (1 H, dd, *J* 9.6, 3.6, 3-H), 5.34 (1 H, d, *J* 1.2, 2-H), 4.45 (1 H, ddd, *J* 9.6, 5.2, 4.8, 5-H), 4.24 (1 H, dd, *J* 10.4, 4.8, 6-H_a), 4.10 (1 H, t, *J* 9.6, 4-H), 3.85 (1 H, t, *J* 10.4, 6-H_b), 2.32 (3 H, s, Ar-CH_3), 2.14 (3 H, s, $COCH_3$), 2.02 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C × 2), 138.5 (C), 137.0 (C), 132.9 (CH × 2), 130.0 (CH × 2), 129.2 (CH), 128.9 (C), 128.3 (CH × 2), 126.3 (CH × 2), 102.0 (CH), 87.2 (CH), 76.3 (CH), 71.5 (CH), 68.5 (CH), 68.4 (CH_2), 65.1 (CH), 21.2 (CH_3), 20.9 (CH_3), 20.8 (CH_3); HRMS (ESI, $[M + Na]^+$) *m*/*z* calcd for $C_{24}H_{26}O_7SNa$ 481.1297, found 481.1290.

4-Methylphenyl 3-*O*-acetyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (6). A mixture of compound **1** (515 mg, 0.90 mmol), PhCHO (37 μL, 0.37 mmol) and freshly dried 3 Å molecular sieves (515 mg) in CH_2Cl_2 (10.0 mL) was stirred at −78 °C under an N_2 atmosphere. TMSOTf (16 μL, 0.09 mmol) was added to the solution, and the mixture was kept stirring at the same temperature for 1.5 h. Ac_2O (102 μL, 1.08 mmol) and TMSOTf (180 μL, 0.18 mmol) were sequentially added to the reaction solution, and the stirring continued with gradually warming up the reaction temperature to −40 °C. After stirring at −40 °C for 4 h, the reaction mixture was quenched with TBAF (1 M solution in THF, 1 mL) and immediately filtered through Celite. The filtrate was washed successively with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate–hexanes = 1/2) to furnish 2-alcohol **6** (272 mg, 72%). $[\alpha]_D^{23}$ +230.4 (*c* 3.60 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3460, 3021, 2924, 1732, 1493, 1372, 1234, 1098, 1028, 755; ^1H NMR (600 MHz, $CDCl_3$) δ 7.46 (2 H, d, *J* 7.9, Ar-H), 7.37–7.34 (5 H, m, Ar-H), 7.11 (2 H, d, *J* = 7.9 Hz, Ar-H), 5.54 (1 H, s, C*H*Ph), 5.45 (1 H, s, 1-H), 5.34 (1 H, dd, *J* 10.2, 3.2, 3-H), 4.45 (ddd, *J* 10.0, 10.0, 4.8, 5-H), 4.39 (1 H, d, *J* 1.8, 2-H), 4.22 (1 H, dd, *J* 4.8, 10.2, 4-H), 4.16 (1 H, t, *J* = 10.0 Hz, 6-H_a), 3.84 (1 H, t, *J* 10.0, 6-H_b), 2.66 (1 H, br s, 2-OH), 2.32 (3 H, s, Ar-CH_3), 2.12 (3 H, s, $COCH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9 (C), 138.1 (C), 137.1 (C), 132.7 (CH), 132.4 (CH), 129.9 (CH), 129.3 (C), 129.1 (CH), 128.4 (CH), 128.2 (CH), 126.2 (CH), 101.9 (CH), 88.7 (CH), 76.2 (CH), 71.0 (CH), 70.7 (CH), 68.4 (CH_2), 65.0 (CH), 21.1 (CH_3), 21.0 (CH_3); HRMS (ESI, $[M + Na]^+$) *m*/*z* calcd for $C_{22}H_{24}O_6SNa$ 439.1191, found 439.1187.

4-Methylphenyl 2,3-di-*O*-acetyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (7). A mixture of compound **1** (250 mg, 0.44 mmol), PhCHO (46 μL, 0.46 mmol) and freshly dried 3 Å molecular sieves (250 mg) in CH_2Cl_2 (2.5 mL) was stirred at −78 °C under an N_2 atmosphere. TMSOTf (8 μL, 0.044 mmol) was added to the solution, and the mixture was kept stirring at the same temperature for 1.5 h. Ac_2O (99 μL, 1.05 mmol) and TMSOTf (24 μL, 0.13 mmol) were sequentially added to the reaction solution, and the resulting mixture was stirred for another 1 h at 0 °C. BH_3·THF (1 M solution in THF, 1.3 mL, 1.3 mmol) was added to the reaction mixture, followed by addition of TMSOTf (39.4 μL, 0.22 mmol), and the solution was kept stirring for another 5 h at 0 °C. Et_3N was added, followed by slow addition of MeOH at 0 °C. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was partitioned in ethyl acetate and water and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified by flash column chromatography (ethyl acetate–hexanes = 1/2) to acquire the 6-alcohol **7** (110 mg, 75%). $[\alpha]_D^{26}$ +63.7 (*c* 1.4 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3491, 2919, 2850, 1749, 1239, 1088; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (7 H, m, Ar-H), 7.10 (2 H, d, *J* 7.6, Ar-H), 5.48 (1 H, dd, *J* 3.4, 2.0, 2-H), 5.34–5.31 (2 H, m, 3-H, 1-H), 4.71 (1 H, d, *J* 11.6, CH_2Ph), 4.65 (1 H, d, *J* 11.6, CH_2Ph), 4.25 (1 H, dt, *J* 9.6, 3.2, 5-H), 3.97 (1 H, t, *J* 9.6, 4-H), 3.81 (2 H, br s, 6-H × 2), 2.31 (3 H, s, Ar-CH_3), 2.10 (3 H, s, 3 H, $COCH_3$), 1.97 (3 H, s, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C), 169.8 (C), 138.4 (C), 137.9 (C), 132.9 (CH), 130.0 (CH), 129.1 (C), 128.5 (CH), 127.9 (CH), 127.7 (CH), 86.2 (CH), 75.0 (CH_2), 72.9 (CH × 2), 72.0 (CH), 71.4 (CH), 61.6 (CH_2), 21.1 (CH_3), 20.8 (CH_3 × 2); HRMS (FAB, M^+) *m*/*z* calcd for $C_{17}H_{21}O_7$ 422.1729, found 422.1721.

4-Methylphenyl 2,3-di-*O*-acetyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (8). A mixture of compound **1** (200 mg, 0.35 mmol), PhCHO (37 μL, 0.37 mmol) and freshly dried 3 Å

molecular sieves (200 mg) in CH_2Cl_2 (2.0 mL) was stirred at −78 °C under an N_2 atmosphere. TMSOTf (6.3 μL, 0.035 mmol) was added, and the mixture was kept stirring at the same temperature for 1.5 h. Ac_2O (79 μL, 0.84 mmol) and TMSOTf (18.9 μL, 0.104 mmol) were sequentially added, and the mixture was stirred for 1 h at 0 °C. CH_3CN (6 mL), Me_2EtSiH (92 μL, 0.70 mmol) and TMSOTf (12.6 μL, 0.070 mmol) were successively added to the reaction solution at 0 °C, and the mixture was kept stirring for 1 h. The reaction mixture was filtered through Celite, and the filtrate was carefully quenched with saturated $NaHCO_{3(aq)}$. The desired material was extracted with ethyl acetate, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue through flash column chromatography (ethyl acetate–hexanes = 1/2) provided the 4-alcohol **8** (85 mg, 73%). $[\alpha]_D^{24}$ +83.7 (*c* 2.8 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3473, 2920, 2851, 1749, 1372, 1240, 1085; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (7 H, m, Ar-H), 7.03 (2 H, d, *J* 8.0, Ar-H), 5.46 (1 H, dd, *J* 3.2, 1.2, 2-H), 5.37 (1 H, d, *J* 1.2, 1-H), 5.18 (1 H, dd, *J* 9.6, 3.2, 3-H), 4.62 (1 H, d, *J* 11.8, C*H*$_2$Ph), 4.52 (1 H, d, *J* 11.8, C*H*$_2$Ph), 4.40–4.35 (1 H, m, 5-H), 4.06 (1 H, t, *J* 9.6, 4-H), 3.85–3.79 (2 H, m, 6-H × 2), 2.90 (1 H, br s, 4-OH), 2.28 (3 H, s, Ar-CH_3), 2.08 (3 H, s, $COCH_3$), 2.06 (3 H, s, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (C), 169.9 (C), 138.1 (C), 137.8 (C), 132.5 (CH), 129.8 (CH), 129.3 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 86.2 (CH), 73.6 (CH_2), 72.1 (CH), 72.0 (CH), 71.1 (CH), 69.9 (CH_2), 67.3 (CH), 21.1 (CH_3), 20.8 (CH_3 × 2); HRMS (FAB, M^+) *m*/*z* calcd for $C_{17}H_{21}O_7$ 422.1729, found 422.1721.

4-Methylphenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (9). TMSOTf (1.6 μL, 0.01 mmol) was added to a solution of compound **1** (200 mg, 0.35 mmol) and PhCHO (75 μL, 0.73 mmol) in CH_3CN (0.2 mL) at room temperature under an N_2 atmosphere. After stirring for 30 min, Et_3N (25 μL, 0.18 mmol) was added, and the mixture was concentrated *in vacuo* for 1 h. The residue was dissolved in CH_2Cl_2 (3.2 mL) at room temperature under an N_2 atmosphere, the reaction flask was cooled down to −40 °C, and 1 M DIBAL-H solution in hexane (1.7 mL, 1.7 mmol) was added to the mixture. Then, the reaction solution was gradually warmed up to room temperature, and the mixture was kept stirring for another 2 h. H_2O (0.2 mL), 3 N $NaOH_{(aq)}$ (0.2 mL) and H_2O (0.6 mL) were sequentially added to the solution, the mixture was filtered, and the solid was ground into a powder followed by reconstitution with CH_2Cl_2. After several filtration and reconstitution, the combined filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (ethyl acetate–hexanes = 1/4) to furnish the 2-alcohol **9** (110 g, 70%). $[\alpha]_D^{24}$ +216.1 (*c* 5.05 in $CHCl_3$); IR (thin film) ν/cm^{-1} 3031, 2913, 2865, 1449, 1100, 750, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.46 (2 H, m, Ar-H), 7.41–7.29 (10 H, m, Ar-H), 7.11 (2 H, d, *J* 8.0, Ar-H), 5.60 (1 H, s, C*H*Ph), 5.50 (1 H, d, *J* 1.0, 1-H), 4.88, 4.73 (2 H, ABq, *J* 11.8, C*H*$_2$Ph), 4.37–4.29 (1 H, m, 5-H), 4.26 (1 H, dd, *J* 3.4, 1.0, 2-H), 4.19 (1 H, dd, *J* 10.3, 4.9, 6-H_a), 4.16 (1 H, t, *J* 9.5, 4-H), 3.95 (1 H, dd, *J* 9.5, 3.4, 3-H), 3.83 (1 H, t, *J* 10.3, 6-H_b), 2.83 (1 H, br s, 2-OH), 2.31 (3 H, s, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (C), 137.7 (C), 137.4 (C), 132.4 (CH), 129.9 (CH), 129.3 (C), 129.0 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 126.1 (CH), 101.6 (CH), 88.1 (CH), 79.0 (CH), 75.7 (CH), 73.2 (CH_2), 71.3 (CH), 68.6 (CH_2), 64.5 (CH), 21.1 (CH_3); HRMS (FAB, $[M + H]^+$) *m*/*z* calcd for $C_{27}H_{29}O_5S$ 465.1736, found 465.1741.

4-Methylphenyl 2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (10). TMSOTf (8.0 μL, 0.045 mmol) was added to a solution of compound **1** (256 mg, 0.45 mmol), PhCHO (47 μL, 0.47 mmol) and freshly dried 3 Å molecular sieves (256 mg) in CH_2Cl_2 (2.6 mL) at −78 °C under an N_2 atmosphere. After stirring at the same temperature for 1.5 h, 1 M $NaOH_{(aq)}$ (3.2 mL), CH_2Cl_2 (7 mL), Bu_4NHSO_4 (30 mg, 0.089 mmol) and BnBr (64 μL, 0.53 mmol) were sequentially added to the solution, and the mixture was continuously stirred for another 20 h at 60 °C. The mixture was filtered through Celite, and saturated $NaHCO_{3(aq)}$ was added to the filtrate. The desired material was extracted with ethyl acetate, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of this residue *via* flash column chromatography (ethyl acetate–hexanes = 1/4) yielded the 3-alcohol **10** (114 mg, 75%). $[\alpha]_D^{24}$ +128.8 (*c* 6.37 in $CHCl_3$); mp 136–137 °C; IR (thin film) ν/cm^{-1} 3481, 2920, 2867, 1493, 1456, 1099, 1090; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (2 H, m, Ar-H), 7.40–7.33 (10 H, m, Ar-H), 7.15–7.13 (2 H, m, Ar-H), 5.58 (1 H, s, PhCH), 5.52 (1 H, s, 1-H), 4.73 (1 H, d, *J* 11.6, C*H*$_2$Ph), 4.63 (1 H, d, *J* 11.6, C*H*$_2$Ph), 4.33 (1 H, dt, *J* 10.0, 4.8, 5-H), 4.23 (1 H, dd, *J* 10.0, 4.8, 6-H_a), 4.13–4.08 (2 H, m, 3-H, 2-H), 3.99 (1 H, t, *J* 10.0, 4-H), 3.83 (1 H, t, *J* 10.0, 6-H_b), 2.56 (1 H, d, *J* 6.8, 3-OH), 2.35 (3 H, s, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (C), 137.2 (C), 132.4 (CH), 130.0 (CH), 129.7 (C), 129.1 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 128.1 (C), 128.0 (CH), 126.3 (CH), 102.1 (CH), 86.5 (CH), 79.9 (CH), 79.5 (CH), 73.0 (CH_2), 68.9 (CH), 68.4 (CH_2), 64.6 (CH), 21.1 (CH_3); HRMS (FAB, M^+) *m*/*z* calcd for $C_{20}H_{21}O_5$ 422.1729, found 422.1721.

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