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# Selective 4,6-O-benzylidene formation of methyl α-D-mannopyranoside using 2,6-dimethylbenzaldehyde

Louis J. Liotta*, Jennifer F. Chalmers, Jessica N. Falco Marshall, Timothy E. Ferreira, Hannah E. Mullen, Nicholas J. Pace

*Stonehill College, 320 Washington Street, Easton, MA 02357*

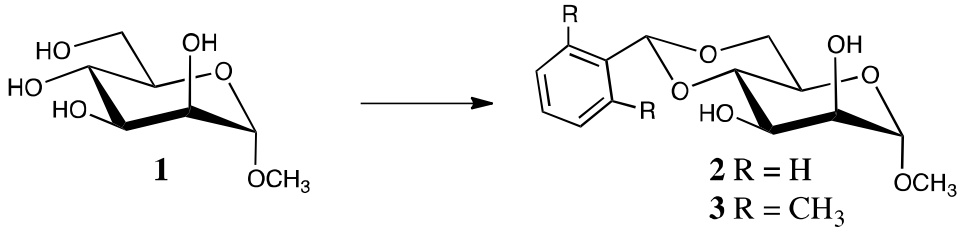
*Phone: 1-508-565-1043 Fax: 1-508-565-1469 Email: lliotta@stonehill.edu*

ABSTRACT

While methyl α-D-glucopyranosides and α-D-galactopyranosides selectively form 4,6-O-benzylidenes when reacted with excess benzaldehyde in the presence of acid catalyst methyl α-D-mannopyranosides does not exhibit the same selectivity because of the *cis*-arrangement of the C2 and C3 hydroxyl groups. The selectivity for the 4,6-O-benzylidene is restored by using 2,6-dimethylbenzaldehyde instead of benzaldehyde. In addition the excess 2,6-dimethylbenzaldehyde is easily recovered from the reaction by extraction with petroleum ether and can be reused without further purification. The 2,6-dimethylbenzylidene exhibits properties similar to the unsubstituted benzylidene with regards to chemical synthesis.

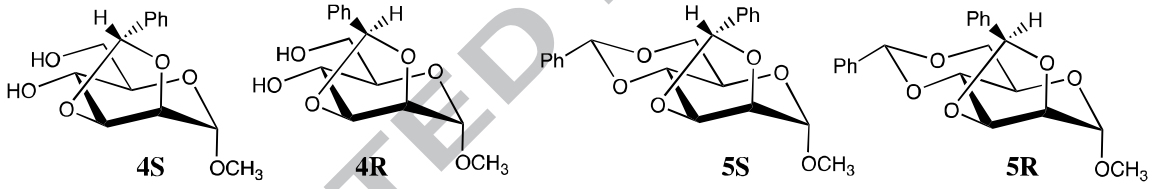
## 1. Introduction

As we developed a general synthesis of all the possible stereoisomers of polyhydroxylated pyrrolidines, pyrrolizidines and indolizidines, we require the 4,6-O-benzylidene protected methyl pyranosides of different sugars including D- and L-glucose, D-galactose, D- and L-mannose, D- and L-allose and D-altrose.[1] The 4,6-benzylidenes of both glucose isomers and the D-galactose were directly prepared in high yields from the




**Scheme 1**. 4,6-O-Benzylidene formation of methyl α-D-mannopyranoside

corresponding methyl pyranosides of these sugars. Both allose isomers and the altrose are easily prepared from the corresponding isomers of the methyl pyranoside of glucose.[2,3] Preparing the 4,6-O-benzylidene of both the D- and L-isomers methyl mannopyranosides in high yield has been particularly challenging due to the formation of both the 2,3-O-benzylidene (**4S** and **4R**) and the 2,3,4,6-di-O-benzylidene (**5S** and **5R**) byproducts. Our solution to this problem has been to prepare the 2,6-dimethylbenzylidene of the methyl mannopyranosides instead of the unsubstituted benzylidenes (Scheme 1).




## 2. Results and discussion

A number of methods are reported to give reasonable yields of the desired 4,6-O-benzylidene **2** of methyl α-D-mannopyranoside.[4-14] We tried a number of the reported methods utilizing both benzaldehyde **6** and benzaldehyde dimethyl acetal **7** as the benzylidene forming reagent. Reacting methyl α-D-mannopyranoside **1** with a 1:1 mixture of redistilled, anhydrous benzaldehyde **6** and 98+% formic acid for two minutes at room temperature followed by quenching with a $K_2CO_3$ solution resulted in 4,6-O-benzylidene **2** in 32% yield and the

appreciable yields of the 2,3-O-benzylidene **4** (10%) and the 2,3,4,6-di-O-benzylidene **5** (25%) (Table 1, entry 1).[4] The methyl α-D-mannopyranoside **1** was next reacted with benzaldehyde **6** (12.5 equiv.) in DMF containing pTsOH (0.13 equiv.) at 50˚ C for one hour.[5] Analysis of the crude product after evaporation of the DMF indicated the mixture contained a 42% yield of 4,6-O-benzylidene **2**, a 6% yield of 2,3-O-benzylidene **4** and a 48% yield of 2,3,4,6-di-O-benzylidene **5** (entry 2). Quenching of the reaction with a solution of $K_2CO_3$ before evaporating the DMF resulted in a 52% yield of the 4,6-O-benzylidene, a 17% yield of the 2,3-O-benzylidene and a 18% yield of the 2,3,4,6-di-O-benzylidene (entry 3).

Reacting the methyl α-D-mannopyranoside **1** with benzaldehyde dimethyl acetal **7** (2 equiv.) in the ionic liquid 3-butyl-1-methylimidazolium tetrafluoroborate containing pTsOH (0.1 equiv.) at 80˚ C for two hours before quenching with $Na_2CO_3$ resulted in a mixture of the 4,6-O-benzylidene **2** (29%), the 2,3-O-benzylidene **4** (1%), and the 2,3,4,6-di-O-benzylidene **5** (38%) (Table 1, entry 4).[6] Using DMF as the solvent and pTsOH (0.10 equiv.) as the catalyst with benzaldehyde dimethyl acetal **7** (1.01 equiv.) at 60˚ C under reduced pressure to remove methanol for 2 hours and quenching with $K_2CO_3$ produced a mixture of the 4,6-O-benzylidene **2** (47%), the 2,3-O-benzylidene **4** (15%), and the 2,3,4,6-di-O-benzylidene **5** (24%) (entry 5).[7-10] Yields of the 4,6-O-benzylidene **2** of about 50% were not as high as some of those reported in the literature[7] but similar to reports by Leino *et. al* in which they indicated that the 2,3-O-benzylidene compounds were the major byproducts.[8-10] Our results are also similar to the results reported in a paper by Patroni *et. al.*, in which they investigated a number of methods to synthesize the desired 4,6-O-benzylidene of methyl α-D-mannopyranoside.[15] When using benzaldehyde dimethyl acetal **7** in DMF with pTsOH as the catalyst they obtained a 53:8:8:16:15 mixture of the 4,6-O-benzylidene **2**, the (S)-2,3-O-benzylidenes **4S**, the (R)-2,3-O-benzylidene

**4R**, the (S)-2,3,4,6-di-O-benzylidene **5S** and the (R)-2,3,4,6-di-O-benzylidene **5R**. In order to improve the yield of the desired 4,6-O-benzylidene **2** we tried a number of ways to selectively cleave the 2,3-O-benzylidene of the 2,3,4,6-di-O-benzylidene **5**.[16,17] The methods we investigated were not synthetically viable.

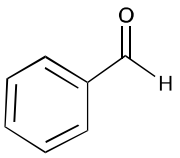
It should be noted that two promising methods to selectively prepare the 4,6-O-benzylidene of mannopyranosides in high yields have appeared in the literature while this work was being completed. The one method used an acid-free organic catalyst with benzaldehyde dimethyl acetal and reported the selective formation of the 4,6-O-benzylidene in 86% yield.[18] The second method reacted the fully silylated mannopyranoside with benzaldehyde and TMS-OTf at -78˚ C in $CH_2Cl_2$ and resulted in a 92% yield of the 4,6-benzylidene.[19] We did not attempt either of these methods.

Since both in our investigation and that of Patroni it appeared that the 4,6-O-benzylidene formed much faster than the 2,3-O-benzylidene and that the 2,3,4,6-di-O-benzylidene product was mostly being formed from the 4,6-O-benzylidene,[15] we speculated that substituted benzaldehydes may be more selective due to steric hindrance. Molecular models and MM2 calculations indicated that methyl substitution at the 2- and 6- positions of the benzene ring would experience very little interference in the 4,6-O-benzylidene but would experience interference from the C2 and C3 hydrogens when forming the R isomer of the 2,3-O-benzylidene and from the C4 hydrogen when forming the S isomer (Figure 1). This steric interference is more pronounced when the pyranoside ring is made more ridged by first forming the 4,6-O-benzylidene. Thus, we would predict a small amount of the 2,3-O-benzylidene may still be observed but the formation of the 2,3,4,6-di-O-benzylidene should be substantially reduced. The calculated streric energy of the 2,3,4,6-di-O-benzylidene using the 2,6-dimethylbenzaldehyde

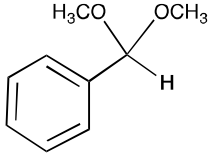
was calculated to be 52.9 kcal/mole for the R-isomer and 51.4 kcal/mole for the S-isomer. This compared to 44.5 kcal/mole and 43.7 kcal/mole for the R- and S-isomers respectively when using unsubstituted benzaldehyde. The calculated energies for the 4,6-O-benzylidenes were 30.4 kcal/mole for the unsubstituted benzaldehyde and 33.8 kcal/mole for the 2,6-dimethylbenzaldehyde.

In practice using 2,6-dimethylbenaldehyde **9** to prepare the 4,6-O-benzylidene of methyl α-D-mannopyranoside was much more selective, giving no dibenzylidene when the reaction was conducted and fully quenched at 50˚ C. In addition, the reaction is more environmentally friendly than using benzaldehyde because the unreacted 2,6-dimethylbenzaldehyde can easily be recovered by extraction with petroleum ether and reused without any purification, giving comparable if not better yields than the new 2,6-dimethylbenzaldehyde. A similar recovery of benzaldehyde was not possible both because benzaldehyde was more volatile and thus evaporated during DMF removal and because benzaldehyde is more susceptible to air oxidation forming benzoic acid.

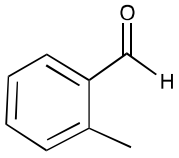
Initially both 2-methylbenzaldehyde **8** and the 2,6-dimethylbenzyaldehyde **9** were investigated as to their usefulness in selectively providing the 4,6-O-benzylidene of methyl α-D-mannopyranoside. It quickly became evident that the mono-methylated benzyaldehyde provided more selectivity than benzaldehyde but the 2,3,4,6-di-O-benzylidene product was still formed in an appreciable yield (Table 1, entry 6). Consequently, further experimentation was continued only with the 2,6-dimethylbenzaldehyde **9** (entries 7-15). The use of formic acid as



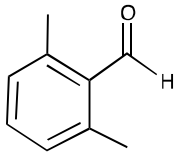

**6**




**7**




**8**




**9**

**Table 1**

Reaction Conditions for Benzylidene Formation of Methyl α-D-Mannopyranoside

| Entry | Mannoside Conc.[a] | Benzaldehyde (mole eq.) | Catalyst (mole eq.) | Solvent | Temp. | Time | Acid Quench[c] | Yield of Benzylidene[b] | | | Recovered Aldehyde |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 4,6- | 2,3- | 2,3,4,6- | |
| 1. | 1.60 | **6** (6.1) | HCOOH (16.5) | HCOOH | rt | 2 min | (b) | 32% | 10% | 25% | 0% |
| 2. | 0.629 | **6** (12.5) | *p*TsOH (0.13) | DMF | 50˚ C | 1 hr | (a) | 42% | 6% | 48% | 0% |
| 3. | 0.665 | **6** (12.5) | *p*TsOH (0.13) | DMF | 50˚ C | 1 hr | (b) | 52% | 17% | 18% | 0% |
| 4. | 0.515 | **7** (2.0) | *p*TsOH (0.01) | [bmim]$BF_4$ | 80˚ C | 2 hrs | (d) | 29% | 1% | 38% | --- |
| 5. | 0.443 | **7** (1.01) | *p*TsOH (0.10) | DMF | 60˚ C | 2 hrs | (b) | 47% | 15% | 24% | --- |
| 6. | 0.632 | **8** (11.4) | *p*TsOH (0.13) | DMF | 50˚ C | 1 hr | (b) | 64% | 16% | 17% | --- |
| 7. | 1.03 | **9** (8.7) | HCOOH | HCOOH | rt | 6 hrs | (b) | 29% | 0% | 0% | --- |
| 8. | 1.03 | **9** (8.7) | HCOOH | HCOOH | rt | 16 hrs | (b) | 0% | 0% | 0% | --- |
| 9. | 0.644 | **9** (9.1) | *p*TsOH (0.13) | DMF | 50˚ C | 2 hrs | (a) | 49% | 0% | 50% | 82% |
| 10. | 0.648 | **9** (9.7) | *p*TsOH (0.13) | DMF | 50˚ C | 1 hr | (c) | 60% | 4% | 5% | 71% |
| 11. | 0.667 | **9** (9.4) | *p*TsOH (0.13) | DMF | 50˚ C | 23 hrs | (c) | 60% | 5% | 4% | 59% |
| 12. | 0.658 | **9** (9.5) | *p*TsOH (0.13) | DMF/ sieves | 50˚ C | 4 hrs | (c) | 29% | 9% | 0% | 73% |
| 13. | 0.672 | **9** (8.8) | *p*TsOH (0.13) | DMF | 50˚ C | 1 hr | (b) | 67% (64%) | 4% (4%) | 0% | 82% |
| 14. | 0.336 | **9** (28.4) | *p*TsOH (0.26) | DMF | 50˚ C | 1 hr | (b) | 67% (66%) | 5% (4%) | 0% | 75% |
| 15. | 0.681 | **9** (9.2) | *p*TsOH (0.13) | DMF | 80˚ C | 1 hr | (b) | 47% | 6% | 0% | 69% |

[a] mmoles of methyl α-D-mannopyranoside per milliliter of solvent, [b]yields of individual compounds in mixture determined by NMR isolated yield in parentheses, [c]acid quenching conditions: (a) none, (b) $K_2CO_3$ solution, (c) $K_2CO_3$ solid, (d) $Na_2CO_3$ solution.

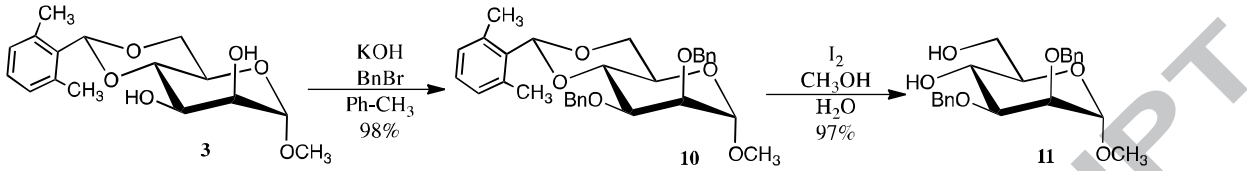
both the catalyst and the solvent under various conditions displayed the expected selectivity for the 4,6-O-benzylidene over the 2,3,4,6-di-O-benzylidenes but yields of the desired 4,6-O-benzylidene were relatively low (entry 7). The desired 4,6-O-benzylidene also appeared to be unstable under the reaction conditions since after 6 hours the amount of 4,6-benzylidene produced decreased, being unobservable after 16 hours (entry 8). Consequently, conditions were sought in which a catalytic amount of acid would be used in a solvent capable of solubilizing the

starting mannopyranoside and the 2,6-dimethylbenzaldehyde as opposed to having a very large excess of acid as was the case when using formic acid as both the solvent and the catalyst.

The common benzylidene forming conditions of pTsOH as the catalyst in DMF met these conditions and proved to be both selective and much higher yielding. Proper quenching of the reaction before proceeding to the workup appears to be critical. Removing most of the DMF under vacuum at 80˚ C before neutralizing the acid catalyst resulted in a large amount of the 2,3,4,6-di-O-benzylidene product (entry 9). Neutralizing the acid with dry $K_2CO_3$ before evaporating off the DMF resulted in a 4-5% yield of the 2,3,4,6-di-O-benzylidene (entries 10-11) while neutralizing the acid with a $K_2CO_3$ solution resulted in complete elimination of the dibenzylidene (entries 12-15). Increasing the reaction time did not affect the yield of the 4,6-O-benzylidene (entry 10 versus 11). Likewise a higher concentration of aldehyde starting material did not affect the yield of the desired benzylidene (entry 13 versus 14). An attempt to drive the reaction by conducting the it at a higher temperature (80˚ C) or by removing water with molecular sieves actually resulted in less of the desired 4,6-O-benzylidene product and more the 2,3-O-benzylidene byproduct (entries 15 and 12).

The best results were obtained with using 8.8 mole equivalents of the 2,6-dimethylbenzyaldehyde and 0.13 mole equivalents of *p*-toluenesulfonic acid in DMF at 50˚ C for one hour and quenching with a solution of $K_2CO_3$ (entry 13). After evaporating off most of the DMF the reaction mixture is partitioned between petroleum ether and water. The unreacted 2,6-dimethylbenzyaldehyde is recovered in pure form simply be evaporating off the petroleum ether. This recovered aldehyde gave identical if not better yields when used in the reaction than the original commercial aldehyde. The methyl 4,6-O-(2,6-dimethylbenzylidene)-α-D-

mannopyranoside **3** was extracted from the aqueous layer with dichloromethane and purified by chromatography in 64% yield.

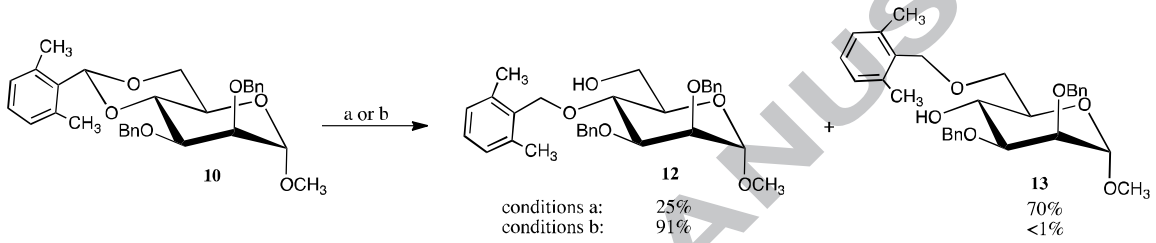



**Scheme 2**. Utility of 2,6-dimethylbenzylidene as a protecting group

The 2,6-dimethylbenzylidene exhibited chemistry identical to the unsubstituted benzylidene when the methyl 4,6-O-(2,6-dimethylbenzylidene)-α-D-mannopyranoside **3** was substituted for the methyl 4,6-O-benzylidene-α-D-glucopyranoside in our synthetic scheme developed for synthesizing polyhydroxylated pyrrolizidines.[1] Thus the C2 and C3 hydroxyl groups were readily protected as benzyl ethers by treating with KOH and benzyl bromide in toluene,[20] yielding the desired fully protected mannopyranoside **10** in 98% yield (Scheme 2). This compared to a 91% yield for the corresponding reaction for the unsubstituted 4,6-O-benzylidene of the glucopyranoside.[1] The 2,6-dimethylbenzylidene group was then readily hydrolyzed by treating with iodine in wet methanol.[20] The desired 4,6-deprotected mannopyranoside **11** was isolated in 97% yield (Scheme 2) as compared to 100% yield for the hydrolysis of unsubstituted benzylidene of glucopyranoside.[1]

One of the most useful aspects of 4,6-benzylidene protected pyranosides is that they can be opened regioselectively under different reduction conditions to give a free hydroxyl group at either the C4 or C6 position.[8,21-29] To further investigate the utility of the 2,6-dimethylbenzylidene protecting group, the benzyl protected 4,6-O-(2,6-dimethylbenzylidene)-α-D-mannopyranoside **10** was subjected to two different reductive ring opening conditions, one selective for the C4 hydroxyl ($NaBH_3CN$, HCl)[21] and one for the C6 hydroxyl ($BH_3$•THF, TMS-

OTf)[22] (Scheme 3). Under these two different conditions the 2,6-dimethylbenzylidene exhibited reactivity similar to the unsubstituted benzylidene. With the $NaBH_3CN$ and HCl, the mannopyranoside with the C4 hydroxyl group **13** was isolated in 70% yield. This compares to reported yields when starting with the unsubstituted benzylidene of 83%. With $BH_3$•THF, TMS-OTf the mannopyranoside with the C6 hydroxyl group **12** was isolated in 91% yield. This compares to a reported yield of the C6 hydroxyl compound of 85% when starting with the unsubstituted benzylidene.




**Scheme 3**. Regioselective opening of 2,6-dimethylbenzylidene: (a) $NaBH_3CN$, HCl, 0° C, 1.5 hrs; (b) $BH_3$•THF, TMS-OTf, rt, 1.5 hrs.

A more selective and environmentally friendly way to prepare the 4,6-O-benzylidene of methyl α-D-mannopyranoside in good yield was developed using 2,6-dimethylbenzaldehyde as opposed to benzaldehyde. Notably, this method gave no dibenzylidene byproduct, which is a major problem typically encountered when using the unsubstituted benzaldehyde. An additional advantage of our method is that the conditions allowed for recovery and reuse of the unreacted 2,6-dimethylbenzaldehyde, which was used in excess. The 2,6-dimethylbenzylidene exhibits similar reactivity towards hydrolysis and selective reduction as the unsubstituted benzylidene.

## 3. Experimental

### 3.1 General methods

Thin layer chromatography was performed using Merck silica gel 60 $F_{254}$ plates. Plates were visualized using 20% ethanolic phosphomolybdic acid. Flash column chromatography was performed using Biotage SNAP KP-Sil columns. Crude and purified products were allowed to dry on a vacuum line attached to a Welch 1400 DuoDeal vacuum pump overnight to ensure complete dryness. All NMR spectra was collected using the Bruker Avance 300 MHz Spectrometer in $CDCl_3$ containing 0.03% TMS as in internal standard. Infrared spectroscopy was performed on a ThermoNicolet Avatar 370 FT-IR spectrophotometer. Optical rotations were collected using a Jasco P-1010 polarimeter. The exact mass measurements were performed using JEOL AccuTOF DART mass spectrometer (Boston College 2609 Beacon Street Chestnut Hill MA, USA). 2,6-Dimethylbenzyaldehyde was from Combi-Blocks Inc. Toluene was acquired from the mBraun solvent purification system. DMF from Acros was classified as extra dry and stored over molecular sieves. All other chemicals were from either Fisher Scientific or Sigma-Aldrich.

### 3.2 Experimental Procedures

**3.2.1 Methyl 4,6-O-(2,6-dimethylbenzylidene)-α-D-mannopyranoside (3)** Methyl α-D-mannopyranoside **1** (1.043 g, 5.38 mmol) and *p*-TsOH•$H_2O$ (0.133 g, 0.699 mmol) were dried over night in a vacuum oven at 60˚ C. After removing from the oven, the methyl α-D-mannopyranoside **1** was suspended in DMF (8 mL) while stirring under $N_2$. The 2,6-dimethylbenzaldehyde (6.38 mL, 47.6mmol) was added followed by the dried *p*-TsOH. The reaction was heated to 50˚ C while stirring under $N_2$ for 1 h. After cooling to rt, the reaction was quenched by adding $K_2CO_3$ (0.080 mg, 0.58 mmol) as a solution in $H_2O$ (2 mL). The DMF was mostly evaporated off under vacuum at 80˚ C. The resulting mixture was mixed with petroleum

ether (75 mL) and $H_2O$ (50 mL). After vigorous mixing the aqueous layer was removed and the petroleum ether extracted with $H_2O$ (2 x 50 mL). The petroleum ether was dried over $Na_2SO_4$, decanted and evaporated *in vacuo* to yield pure 2,6-dimethybenzaldehyde (4.830 g, 36.04 mmol, 82%). The combined aqueous layers were extracted with $CH_2Cl_2$ (3 x 75 mL). The $CH_2Cl_2$ extracts were combined, dried over $Na_2SO_4$, decanted and evaporated to an oil. The crude product was chromatographed through silica gel first using pure $CH_2Cl_2$ followed by 40:1 $CH_2Cl_2/CH_3OH$ and then 20:1 $CH_2Cl_2/CH_3OH$. Fractions were analyzed by TLC in 20:1 $CH_2Cl_2/CH_3OH$. This procedure resulted in the isolation of pure **3** as a clear oil ($R_f$=0.14, 1.065 g, 3.44 mmol, 64%). $[\alpha]^{23}_D$ 70.4 (*c* 1.53, $CH_2Cl_2$). $^1$H-NMR (300 MHz, $CDCl_3$): (m, 3 H, Ar-H), 5.92 (s, 1 H, benzylidene-H), 4.67 (d, 1 H, J=1.3 Hz, C1-H), 4.27 (m, 1 H, C6-H), 3.95 (m, 1 H, C3-H), 3.91 (m, 1 H, C2-H), 3.86-3.76 (m, 3 H, C5-H, C4-H, C6-H), 3.39 (s, 3 H, $OCH_3$), 3.00 (br, 1 H, C3-OH), 2.91 (br, 1 H, C2-OH), 2.47 (s, 6 H, Ar-C$H_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 136.93 (C, Ar), 132.74 (C, Ar), 129.14 (CH, Ar), 128.95 (CH, Ar), 101.43 (CH, C1) 101.31 (CH, $ArCHO_2$), 79.32 (CH, C4), 70.80 (CH, C2), 69.23 ($CH_2$, C6), 68.61 (CH, C3), 62.92 (CH, C5), 55.24 ($CH_3$, $OCH_3$) 20.53 ($CH_3$, Ar-$CH_3$). IR: 3415 (m, br), 2930 (m), 1597 (w), 1468 (w), 1444 (m), 1377 (w), 1349 (w), 1276 (w), 1201 (m), 1132 (s), 1106 (s), 1087 (s), 1067 (s), 1033 (s), 997 (m), 977 (s), 962 (s), 914 (w), 862 (w), 801 (w), 774 (m), 736 (m), 684 (m), 651 (w), 628 (w) $cm^{-1}$. HRMS calculated for $C_{16}H_{23}O_6$ ($M^+$ + H) 311.14946, found 311.14971.

**3.2.2 Methyl 2,3-di-O-benzyl-4,6-(2,6-dimethylbenzylidene)-α-D-mannoopyranoside (10)**

Methyl 4,6-O-(2,6-dimethylbenzylidene)-α-D-mannopyranoside **3** (1.05 g, 3.39 mmol), KOH (3.35g, 59.8 mmol), and benzyl bromide (3.4 mL, 28.5 mmol) were suspended in toluene (140 mL) and the reaction was heated to reflux under nitrogen. The reaction was monitored by TLC

(5:1:1 hexane/EtOAc/$CH_2Cl_2$) for disappearance of **3** ($R_f$=0.09) and the appearance of 6 ($R_f$=0.64) at which point (approx. 6 h) the reaction was allowed to cool to rt. Toluene (400 mL) was added to the reaction mixture and the mixture was washed with water (2 x 500 mL). The toluene was dried with $Na_2SO_4$, decanted and evaporated to an oil. The crude product was chromatographed through silica gel using hexane/EtOAc/$CH_2Cl_2$ first at an 20:1:1 ratio, then a 10:1:1 ratio. Fractions were analyzed by TLC in 10:1:1 hexane/EtOAc/$CH_2Cl_2$. This procedure resulted in the isolation of pure **10** as a clear oil ($R_f$=0.42, 1.63 g, 3.33 mmol, 98%). $[\alpha]^{23}_D$ 9.2 (*c* 3.60, $CH_2Cl_2$). $^1$H-NMR (300 MHz, $CDCl_3$): 7.39-6.96 (m, 13 H, Ar-H), 5.94 (s, 1 H, benzylidene-H), 4.79 (d, 1 H, J=12.3 Hz, C*H*HPh), 4.72-4.67 (m, 3 H, C1-H, C$H_2$Ph), 4.57 (d, 1 H, J=12.6 Hz, C*H*HPh), 4.20 (m, 2 H, C4-H, C6-H), 3.89 (dd, 1 H, J=3.2, 9.9 Hz, C3-H), 3.81-3.78 (m, 3 H, C6-H, C5-H, C2-H), 3.29 (s, 3 H, $OCH_3$), 2.47 (s, 6 H, Ar-C$H_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 138.80 (C, Ar), 138.30 (C, Ar), 137.03(C, Ar), 133.53 (C, Ar), 129.09 (CH, Ar), 128.68 (CH, Ar), 128.52 (CH, Ar), 128.35 (CH, Ar), 128.16 (CH, Ar), 127.89 (CH, Ar), 127.56 (CH, Ar), 127.51 (CH, Ar), 101.29 (CH, Ar$CHO_2$), 100.65 (CH, C1), 79.70 (CH, C4), 76.58 (CH, C2), 76.17 (CH, C3), 73.69 ($CH_2$, OBn), 72.95 ($CH_2$, OBn), 69.35 ($CH_2$, C6), 64.25 (CH, C5), 55.11 ($CH_3$, $OCH_3$) 20.78 ($CH_3$, Ar-$CH_3$). IR: 3087 (m), 3063 (s), 3029 (s), 2905 (s), 2734 (w), 1952 (w), 1597 (m), 1589 (m), 1497 (s), 1454 (s), 1373 (s), 1318 (s), 1279 (s), 1200 (s), 1170 (s), 1054 (s), 998 (s), 958 (s), 910 (s), 875 (m), 855 (m), 798 (s), 773 (s), 736 (s), 698 (s), 680 (s), 651 (w), 630 (w) $cm^{-1}$. HRMS calculated for $C_{30}H_{35}O_6$ ($M^+$ + H) 491.24336, found 491.24270.

**3.2.3 Methyl 2,3-di-O-benzyl-α-D-mannopyranoside (11)** Methyl 2,3-di-O-benzyl-4,6-(2,6-dimethylbenzylidene)-α-D-mannoopyranoside **10** (1.29 g, 2.63 mmol), $I_2$ (0.51 g, 1.99 mmol) and $H_2O$ (0.5 g, 27.8 mmol) were dissolved in methanol (190 mL) and the reaction was heated to

reflux. The reaction was monitored by TLC (10:1:1 hexane/EtOAc/$CH_2Cl_2$) for the disappearance of **6** ($R_f$ = 0.42). When the reaction was complete (approximately 3.5 h), it was cooled to rt. Ten percent $Na_2S_2O_3$ was added (32 mL), and the solution was evaporated to an oil which was subsequently dissolved in water (225 mL) and extracted with $CH_2Cl_2$ (2 x 225 mL). The organic layers were combined, dried with $Na_2SO_4$, decanted and evaporated to dryness to result in pure **11** as a clear oil (0.953 g, 2.55 mmol, 97% yield). $[\alpha]^{23}_D$ -9.48 (*c* 1.69, $CH_2Cl_2$). $^1$H-NMR (300 MHz, $CDCl_3$): □ 7.36-7.23 (m, 10 H, Ar-H), 4.73 (d, 1 H, J=1.5 Hz, C1-H), 4.65 (s, 2 H, C*H*$_2$Ph), 4.58 (d, 1 H, J=11.8 Hz, C*H*HPh), 4.47 (d, 1 H, J=11.8 Hz, C*H*HPh), 4.02 (td, 1 H, J=2.4, 9.6 Hz, C4-H), 4.06-3.99 (m, 2 H, C6-$CH_2$), 3.77 (dd, 1 H, J=1.6, 2.9 Hz, C2-H), 3.69 (dd, 1 H, J=3.0, 9.5 Hz, C3-H), 3.58 (dt, 1 H, J=4.4, 9.2 Hz, C5-H), 3.31 (s, 3 H, $OCH_3$), 2.81 (br, 1 H, C4-OH), 2.49 (br, 1 H, C6-OH). $^{13}$C NMR (75 MHz, $CDCl_3$): 138.10 (C, Ar), 138.07(C, Ar), 128.53 (CH, Ar), 128.42 (CH, Ar), 127.91 (CH, Ar), 127.86 (CH, Ar), 127.79 (CH, Ar), 127.75 (CH, Ar), 99.37 (CH, C1), 79.73 (CH, C3), 73.90 (CH, C2), 72.84 ($CH_2$, OBn), 72.24 (CH, C5), 71.78 ($CH_2$, OBn), 67.27 (CH, C4), 62.80 ($CH_2$, C6), 54.90 ($CH_3$, $OCH_3$). IR: 3439 (s,br), 3088 (m), 3063 (m), 3030 (m), 2913 (s), 2834 (m), 1605 (w), 1586 (w), 1497 (s), 1454 (s), 1367 (s), 1323 (m), 1251 (m), 1198 (s), 1053 (s), 968 (s), 910 (m), 804 (m), 737 (s), 699 (s) cm$^{-1}$. HRMS calculated for $C_{21}H_{30}NO_6$ ($M^+$ + $NH_4$) 392.20731, found 392.20853.

**3.2.5 Methyl 2,3-di-O-benzyl-4-O-(2,6-dimethylbenzyl)-α-D-mannopyranoside (12)** Methyl 2,3-di-O-benzyl-4,6-(2,6-dimethylbenzylidene)-α-D-mannoopyranoside **10** (0.134 g, 0.274 mmol) was dissolved in $CH_2Cl_2$ (3 mL) followed by the addition of a 1 M solution of $BH_3$ in THF (0.55 mL, 0.55 mmol). The resulting solution was stirred at room temperature under $N_2$ while TMS-OTf (0.005 mL, 0.026 mmol) was added. The reaction was monitored by TLC (10:3:1 hexane/EtOAc/$CH_2Cl_2$) for the disappearance of **10** ($R_f$ = 0.57). When the reaction was

complete (approximately 1.5 h) it was quenched by the addition of $Et_3N$ (0.150 mL, 1.08 mmol) followed by the careful addition of $CH_3OH$ until $H_2$ was no longer evolved. The solution was concentrated under vacuum. To assist in evaporating the excess $Et_3N$, the resulting residue was three times dissolved in $CH_3OH$ (5 mL) and evaporated under vacuum. The crude product was chromatographed through silica gel first using 10:3:1 hexane/EtOAc/$CH_2Cl_2$ and then 10:4:1 hexane/EtOAc/$CH_2Cl_2$. Fractions were analyzed by TLC in 10:3:1 hexane/EtOAc/$CH_2Cl_2$. This procedure resulted in the isolation of pure **12** as a clear oil ($R_f$=0.13, 0.123 g, 0.263 mmol, 91%). $[\alpha]^{23.5}_D$ 14.2 (*c* 4.32, $CH_2Cl_2$). $^1$H-NMR (300 MHz, $CDCl_3$): 7.39-7.24 (m, 10 H, Ar-H), 7.10-6.97 (m, 3 H, $(CH_3)_2$Ar-*H*), 5.00 (d, 1 H, J=10.3 Hz, C*H*HPh), 4.74-4.58 (m, 6 H, C1-H, C*H*HPh, C$H_2$Ph, C$H_2$Ph), 3.98-3.92 (m, 2 H, C3-H, C4-H), 3.82 (t, 1 H, J=2.4 Hz, C2-H), 3.81-3.70 (m, 2 H, C6-H, C6-H), 3.56 (m, 1 H, C5-H), 3.30 (s, 3 H, $OCH_3$), 2.34 (s, 6 H, Ar-C$H_3$), 1.94 (s, 1 H, C6-OH). $^{13}$C NMR (75 MHz, $CDCl_3$): 138.43 (C, Ar), 138.27 (C, Ar), 138.01(C, Ar), 134.52 (C, Ar), 128.34 (CH, Ar), 128.33 (CH, Ar), 128.21 (CH, Ar), 128.10 (CH, Ar), 127.74 (CH, Ar), 127.69 (CH, Ar), 127.49 (CH, Ar), 127.39 (CH, Ar), 99.17 (CH, C1), 80.69 (CH, C3), 74.22 (CH, C4), 74.19 (CH, C2), 72.86 ($CH_2$, OBn), 71.94 (CH, C5), 71.54 ($CH_2$, OBn), 69.17 ($CH_2$, OBn), 62.56 ($CH_2$, C6), 54.79 ($CH_3$, $OCH_3$) 19.72 ($CH_3$, Ar-$CH_3$). IR: 3484 (m,br), 3064 (w), 3030 (m), 2914 (s), 1589 (w), 1497 (m), 1469 (m), 1454 (s), 1396 (m), 1363 (s), 1321 (m), 1267 (m), 1197 (m), 1072 (s), 970 (s), 907 (w), 846 (w), 827 (w), 803 (w), 773 (m), 737 (s), 698 (s), 600 (m), 485 (m), 471 (w), 462 (m), 426 (w), 417 (w), 408 (w), 401 (w) $cm^{-1}$. HRMS calculated for $C_{32}H_{40}NO_6$ ($M^+ + NH_4$) 510.28556, found 510.28447.

**3.2.5 Methyl 2,3-di-O-benzyl-6-O-(2,6-dimethylbenzyl)-α-D-mannopyranoside (13)** Methyl 2,3-di-O-benzyl-4,6-(2,6-dimethylbenzylidene)-α-D-mannoopyranoside **10** (0.107 g, .219 mmol) was dissolved in a 1.0 M solution of $NaBH_3CN$ in THF. A few grains of methyl orange

were added to the solution. The yellow solution was cooled on ice while stirring under $N_2$ for 15 min. A saturated solution of HCl in ether was slowly added to the reaction until the color of the solution remained pink for five minutes (about 9 mL). The mixture was stirred at 0˚ C for 10 min and then diluted with an equal volume of $CH_2Cl_2$. After filtering through Celite, the solution was washed sequentially with saturated $NaHCO_3$, brine, and water. The organic layer was dried over anhydrous $Na_2SO_4$, decanted, and evaporated under reduced pressure to a clear oil. The crude product was chromatographed through silica gel first using 10:2:1 hexane/EtOAc/$CH_2Cl_2$ and then 10:3:1 hexane/EtOAc/$CH_2Cl_2$. Fractions were analyzed by TLC in 10:3:1 hexane/EtOAc/$CH_2Cl_2$. This procedure resulted in the isolation of pure **13** as a clear oil ($R_f$=0.26, 0.0753 g, 0.153 mmol, 70%). $[\alpha]^{23.5}_D$ -4.8 (*c* 2.51, $CH_2Cl_2$). $^1$H-NMR (300 MHz, $CDCl_3$): 7.32-7.21 (m, 10 H, Ar-H), 7.09-6.97 (m, 3 H, Ar-H), 4.74 (d, 1 H, J=1.5 Hz, C1-H), 4.70-4.48 (m, 6 H, C*H*$_2$Ph, C*H*$_2$Ph, C*H*$_2$Ph), 4.20 (td, 1 H, J=9.39, 1.53 Hz, C4-H), 3.82-3.74 m, 3 H, C6-H, C6-H, C2-H), 3.73-3.65 (m, 2 H, C3-H, C5-H), 3.32 (s, 3 H, $OCH_3$), 2.59 (d, 1 H, J=1.8 Hz, C4-OH), 2.38 (s, 6 H, Ar-C*H*$_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 138.35 (C, Ar), 138.29 (C, Ar), 138.04(C, Ar), 134.17 (C, Ar), 128.49 (CH, Ar), 128.37 (CH, Ar), 128.16 (CH, Ar), 127.98 (CH, Ar), 127.90 (CH, Ar), 127.74 (CH, Ar), 127.69 (CH, Ar), 99.27 (CH, C1), 79.69 (CH, C3), 74.04 (CH, C2), 72.75 ($CH_2$, OBn), 71.92 ($CH_2$, OBn), 71.47 (CH, C5), 70.82 ($CH_2$, C6), 68.31 (CH, C4), 68.03 ($CH_2$, OBn), 54.91 ($CH_3$, $OCH_3$) 19.77 ($CH_3$, Ar-$CH_3$). IR: 3466 (m,br), 3063 (w), 3029 (m), 2910 (s), 1496 (m), 1468 (m), 1454 (m), 1362 (m), 1324 (m), 1284 (m), 1197 (m), 1058 (s), 967 (m), 908 (w), 804 (w), 772 (m), 737 (s), 698 (s), 598 (m), 500 (m), 488 (m), 479 (m), 466 (s), 455 (m), 450 (m), 429 (w), 418 (m), 401 (m) $cm^{-1}$. HRMS calculated for $C_{32}H_{40}NO_6$ ($M^+ + NH_4$) 510.28556, found 510.28659.

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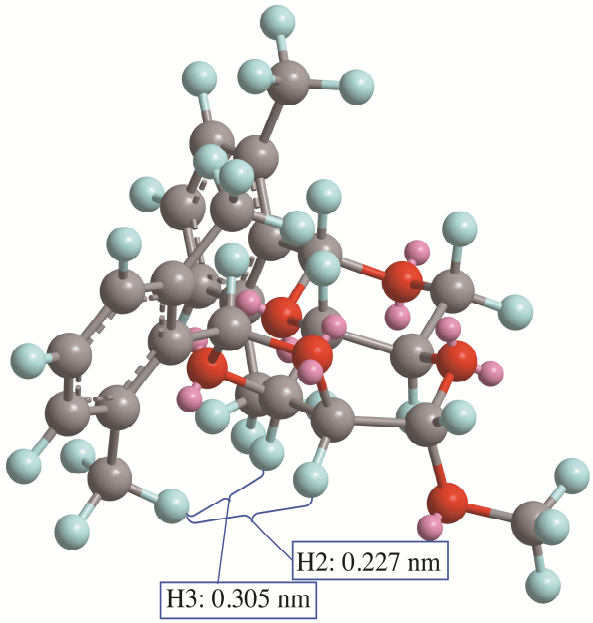
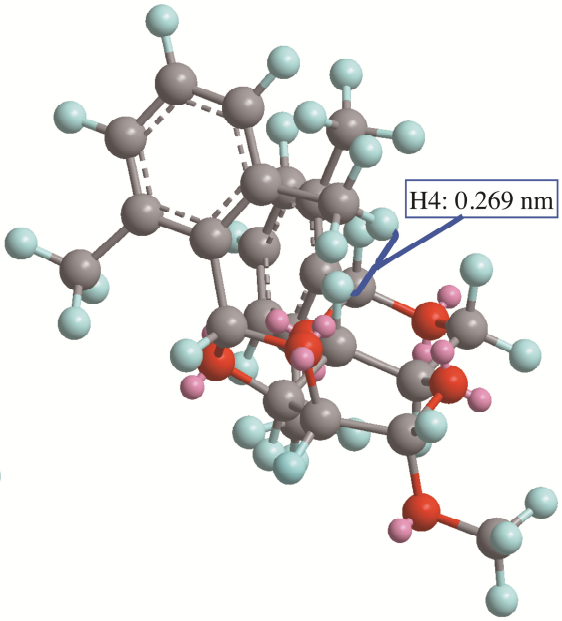
**Figure 1:** Steric hindrance in 2,3,4,6-di-O-benzylidene of methyl α-D-mannopyranoside resulting from methyl groups on the benzene.

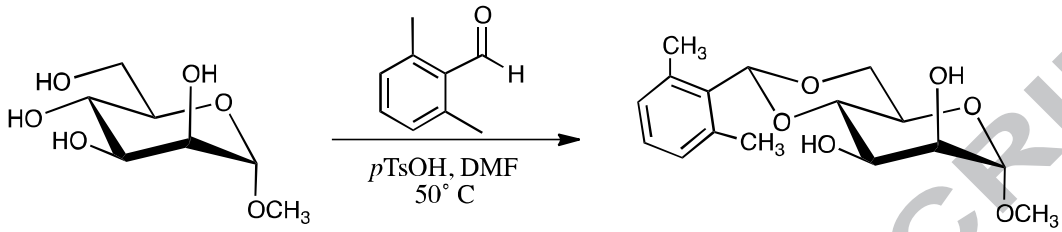



R-Isomer of 2,3,4,6-Dibenzylidene **5R**




S-Isomer of 2,3,4,6-Dibenzylidene **5S**

Graphical abstract



Highlights

- A method to protect the C4 and C6 hydroxyls of α-mannopyranoside is provided.
- The use of 2,6-dimethylbenzaldehyde in benzylidene formation is investigated.
- Formation of benzylidenes using 2,6-dimethylbenzaldehyde is more selective.
- 2,6-dimethylbenzaldehyde is compared to benzaldehyde for benzylidene formation.