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H-Bonding Activation in Highly Regioselective Acetylation of Diols

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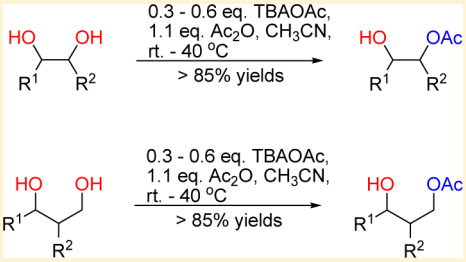
Supporting Information

ABSTRACT: H-bonding activation in the regioselective acetylation of vicinal and 1,3-diols is presented. Herein, the acetylation of the hydroxyl group with acetic anhydride can be activated by the formation of H-bonds between the hydroxyl group and anions. The reaction exhibits high regioselectivity when a catalytic amount of tetrabutylammonium acetate is employed. Mechanistic studies indicated that acetate anion forms dual H-bonding complexes with the diol, which facilitates the subsequent regioselective monoacetylation.

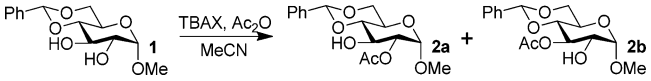


Regioselective protection of carbohydrates under mild and environmentally sustainable conditions is necessary in order to meet the requirements for preparation of value-added intermediates and building blocks in efficient protecting group strategies, and it remains a prominent challenge in synthetic carbohydrate chemistry.[1,2] Several protection methods have been developed to this end by making use of certain reagents to enlarge small differences in reactivity of hydroxyl groups for diols and polyols. For example, methods employing organotin,[3−8] organoboron,[9−11] organosilicon,[12−15] and metal salts,[16−18] organo-catalytic methods,[19−21] and enzymatic methods[22−24] have been exemplified, all with their respective advantages and shortcomings. In the present study, we report on the application of H-bonding activation principles in a highly regioselective carbohydrate acetylation. Herein, a catalytic amount of tetrabutylammonium acetate was employed to promote the regioselective acylation of diols by acetic anhydride under mild conditions without the assistance of any other reagents. Different from the general pyridine-catalyzed acylation,[25−30] our mechanistic studies suggest that the catalytic acetylation owes its increased reactivity to hydroxyl groups engaged in H-bonding.

In our earlier studies, we found that new and improved reaction routes may be found by the application of intermolecular non-covalent forces.[31−33] For example, in intramolecular acetyl group migration with anions in aprotic solvents under mild conditions, which was recently reported by us, the leading cause for this process was found to be the formation of hydrogen bonds between the neighboring hydroxyl group and anions.[33] The catalytic effect of anions follows the corresponding H-bond formation tendencies, where more basic anions lead to faster migration. These results inspired us to think that H-bonds between hydroxyl groups and anions might also be able to activate the acylation of hydroxyl groups. We have found this H-bond activation principle to be supported by experiments and preliminary quantum-chemical studies.

First, acetylation of the diol methyl 4,6-*O*-benzylidene-α-D-glucoside (**1**) by the addition of anions was examined using 1.1 equiv of acetic anhydride (Table 1). Without the addition of anions, the acetylation of **1** did not proceed, even at 80 °C. With the addition of 0.6 equiv of tetrabutylammonium bromide (TBAB), the acetylation of **1** was very slow at 80 °C. However, when 0.6 equiv of tetrabutylammonium acetate (TBAOAc) was used, the reaction proceeded at room temperature, and the 2-hydroxyl group of diol **1** was regioselectively acetylated after 12 h, leading to a 90% isolated yield of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucoside (**2a**). There no acetyl group migration occurred, since compound **2b** is the migration product. The reason must be that only a catalytic amount of TBAOAc was used in this case. The reaction showed higher

Table 1. Acetylation of Methyl 4,6-*O*-Benzylidene-α-D-glucoside (1) upon the Addition of Anions[a]



entry	reagent	T (°C)	conversion
1	–	80	no reaction
2	HOAc	80	no reaction
3	TBAB	80	low conversion
4	TBAOAc	r.t.	**2a** (90%)[b]
5	TBAF	r.t.	**2a**/**2b** (68/32)[c]

[a]Reaction conditions: reactant (100 mg), Ac_2O (1.1 equiv), TBAX (0.3−0.6 equiv), 8−12 h. [b]Isolated yield. [c]NMR ratio.

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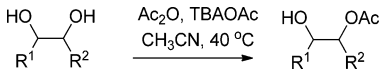
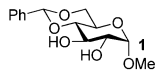
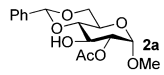
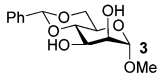
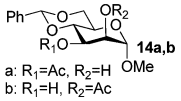
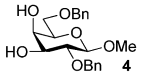
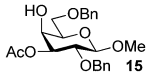
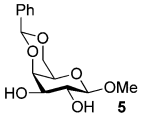
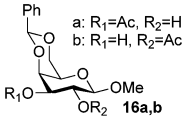
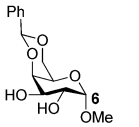
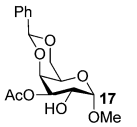
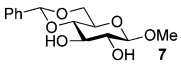
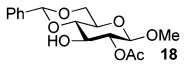
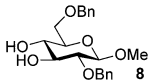
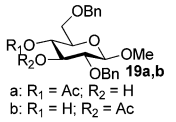
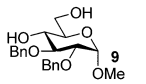
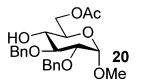
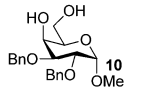
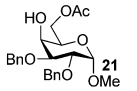
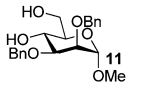
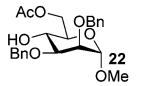
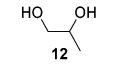
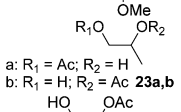
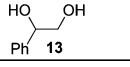
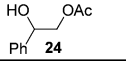
reactivity but lower selectivity with 0.3 equiv of tetrabutylammonium fluoride (TBAF). The results indicate that H-bonds between hydroxyl groups and anions are indeed able to activate the acylation of hydroxyl groups, and the catalytic effect of anions followed the corresponding H-bond formation tendencies. However, high regioselectivities were obtained when acetate anion was employed as the catalyst.

In light of these results, TBAOAc was chosen and tested together with a range of diols (cf. Table 2): methyl 4,6-*O*-benzylidene-*α*-D-mannoside (**3**) and methyl 2,6-di-*O*-benzyl-*β*-D-galactoside (**4**), two *cis*-diols; methyl 4,6-*O*-benzylidene-*β*-D-galactoside (**5**), a *trans*-diol where one of the substituents adjacent to the hydroxyl group is equatorial and the other is axial; methyl 4,6-*O*-benzylidene-*α*-D-galactoside (**6**) and -*β*-D-glucoside (**7**), *trans*-diols where both substituents adjacent to the hydroxyl group are equatorial or axial; methyl 2,6-di-*O*-benzyl-*β*-D-glucoside (**8**), a *trans*-diol; methyl 2,3-di-*O*-benzyl-*α*-D-glucoside (**9**), -galactoside (**10**), and -mannoside (**11**), three 1,3-diols with one primary (1°) hydroxyl group; and 1,2-propanediol (**12**) and 1-phenyl-1,2-ethanediol (**13**), two 1,2-diols with one 1° hydroxyl group. These compounds were allowed to react with 1.1 equiv of Ac_2O in the presence of 0.6 equiv of TBAOAc in acetonitrile at 40 °C for 8 h. The results (cf. Table 2) show high regioselectivities in most cases and excellent isolated yields (85−93%). However, when the reactions were performed at room temperature, a longer reaction time (24−48 h) was necessary to reach the same isolated yields. For acetylation of compounds **3**, **5**, and **8** at lower temperatue, no noticeably improved selectivities were observed.

Table 2. Acetate-Promoted Regioselective Acetylation of 1,2- and 1,3-Diols[a]



Entry	Reactant	Product	Condition	Yield (%)[b]
1	 **1**	 **2a**	A	88
			B	85
2	 **3**	 a: R_1=Ac, R_2=H b: R_1=H, R_2=Ac **14a,b**	A	a/b (50/50)[c]
3	 **4**	 **15**	A	90
			B	86
4	 **5**	 a: R_1=Ac, R_2=H b: R_1=H, R_2=Ac **16a,b**	A	No reaction
			C	a/b (46/30)[d]
5	 **6**	 **17**	A	90
6	 **7**	 **18**	A	85
7	 **8**	 a: R_1 = Ac; R_2 = H b: R_1 = H; R_2 = Ac **19a,b**	A	a/b (48/42)
8	 **9**	 **20**	A	91
			B	88
9	 **10**	 **21**	A	93
			B	90
10	 **11**	 **22**	A	91
11	 **12**	 a: R_1 = Ac; R_2 = H b: R_1 = H; R_2 = Ac **23a,b**	A	a/b (83/17)[c]
12	 **13**	 **24**	A	90

[a]Reaction conditions: (A) reactant (100 mg), Ac_2O (1.1 equiv), TBAOAc (0.6 equiv), 40 °C, 8−12 h; (B) reactant (100 mg), Ac_2O (1.1 equiv), TBAOAc (0.3 equiv), 40 °C, 16−24 h; (C) reactant (100 mg), Ac_2O (1.1 equiv), TBAOAc (0.6 equiv), 80 °C, 48 h. [b]Isolated yields. [c]NMR ratio; raw materials could hardly be observed. [d]NMR ratio; 24% of the raw material was observed.

Comparisons with the outcomes from organosilicon-, organotin-, and Ag_2O-mediated methods are shown in Table S1 in the Supporting Information (SI). The di-OAc products did not form in any of the reactions, even for the acetylations of compounds **3** and **8** in which poor selectivities were observed. This suggests that acetylation of one of the hydroxyl groups dramatically decreases the reactivity of its neighbors. Thus, overacetylation should not be of concern. Our method showed selectivities for compounds **1** and **4** and diols with one 1° hydroxyl group similar to those reported for organotin/organosilicon-mediated methods (Table S1). Interestingly, in contrast to the poor selectivities usually observed in organotin/organosilicon-mediated methods, our method showed very good selectivities for *trans*-diols **6** and **7** (Table 2, entries 5 and 6).[4,15] In comparison with the Ag_2O-mediated method,[16] our method enabled the reversed protection pattern of compounds **1**, **6**, and **7**. When 0.3 equiv of TBAOAc was employed, a longer reaction time was necessary to reach the same isolated yield. The acetylation of compound **5** appears to be a special case, as no reaction occurred at 40 °C and 24% of the starting material remained even after 48 h at 80 °C (Table 2, entry 4).

All of these experimental results support our hypothesis that anions enable regioselective acetylation of hydroxyl groups by H-bonding. The ^{1}H NMR spectra of the protons involved in H-bonding (see the SI) further support this. For example, the resonances of the protons on the 3- and 4-hydroxyl groups of **4** shifted from 2.57 and 2.47 ppm in $CDCl_3$ to 3.27 and 3.02 ppm in CD_3CN and to 4.91 and 4.64 ppm in DMSO-d_6 as a result of the formation of hydrogen bonds between the hydroxyl groups and the solvent molecules. Anions form stronger hydrogen bonds with hydroxyl groups than these solvent molecules, leading to greater downfield chemical shifts of the protons.[33] For example, the addition of 0.6 equiv of TBAB into the solution of **4** in CD_3CN caused the chemical shifts of the protons on the 3- and 4-hydroxyl groups to change from 3.27 and 3.02 ppm to 3.40 and 3.15 ppm, respectively (see the SI). We found that the hydroxyl groups with greatest downfield chemical shift were preferentially acetylated (compounds **1**, **4**, **6**, and **7** in CD_3CN; see the SI). When the acetate anion was used, the proton signals originating from the hydroxyl groups disappeared because of rapid proton interchange in all solvents. However, the H-bonding effect was observable by proton chemical shifts on carbons adjacent to the hydroxyl groups.

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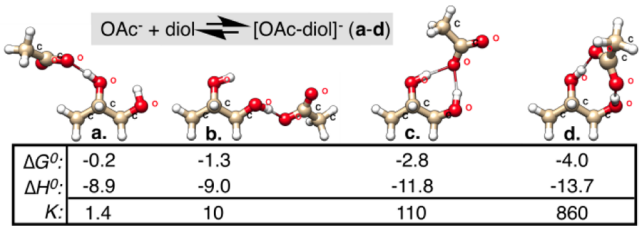
These chemical shifts also moved downfield. We performed a preliminary quantum-chemical study (see the SI and Figure 1),



	a.	b.	c.	d.
ΔG^0:	-0.2	-1.3	-2.8	-4.0
ΔH^0:	-8.9	-9.0	-11.8	-13.7
K:	1.4	10	110	860

Figure 1. Four investigated possibilities (**a**–**d**) for binding of 1,2-propanediol to an acetate anion. SMD-PCM-M06-2X/aug-cc-pVTZ energies relative to the free species in acetonitrile solution (1 M, 298 K) are shown.

which demonstrated that the formation of dual H-bonding between the acetate anion and the diols is favorable by ~4 kcal/mol relative to separate solvated species in 1 M acetonitrile solution at 298 K. This corresponds to an equilibrium constant of ca. 900. Thus, in contrast to the cases of catalysis using bromide and fluoride anions, the high selectivity when using the acetate anion for catalysis might be attributed to the specific dual H-bonding prereaction complex between the diol reagent and the acetate catalyst.

Different from the DMAP-catalyzed regioselective acetylation mechanism,[26−28] a suggested mechanism for the regioselective acetylation of diols catalyzed by acetate anions is shown in Figure 2. For the acetylation of diols with one primary hydroxyl

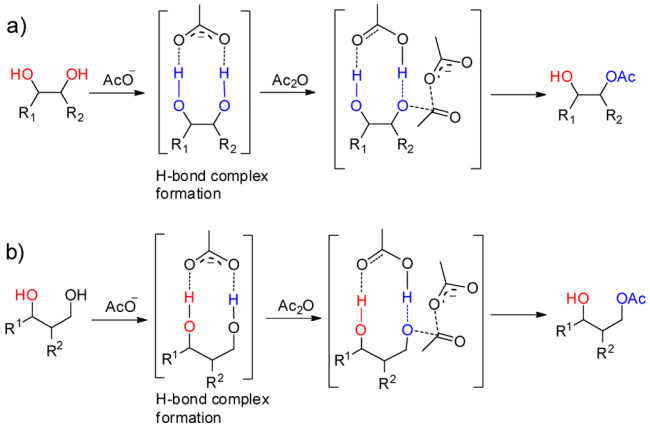


Figure 2. Highly regioselective acetylation of diols activated by dual H-bonding.

group (compounds **9**–**13**), the regioselectivity might be more dependent on steric effects. The poor selectivities for compounds **3**, **5**, and **8** might arise because two hydroxyl groups in each compound are in similar steric and stereoelectronic situations. Further support for the dual H-bonding mechanism was found when the diols were coreacted with their corresponding monohydric alcohols in competitive acetylation of 1.1 equiv of acetic anhydride (see Table 3). The conversion rates for acetylation of these diols were 3−4 times higher than those of the corresponding monohydric alcohols. Especially for the case in entry 2, the secondary hydroxyl group in compound **7** was preferentially acetylated as a result of dual H-bonding. Usually the primary hydroxyl group is preferentially acetylated because of the small steric effects. Thus, different from the two-step reaction approaches in organotin, organoboron, and organosilicon methods, this straightforward one-step reaction proceeds efficiently with all reactants tested, producing the predicted monoacylated products in all cases. Anhydrous conditions are not necessary when using in this method, since moisture does not noticeably disrupt the formation of the H-bonds.

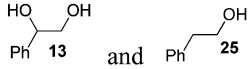
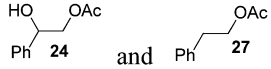
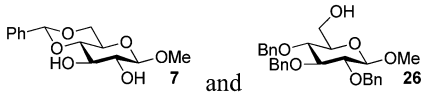
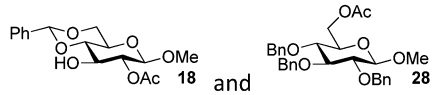
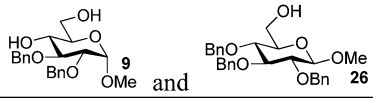
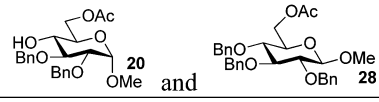
In conclusion, we propose that H-bonding plays an important role in the acylation of alcohols, in which hydroxyl groups are first bound to anions through the formation of H-bonds. On the basis of this principle, a highly regioselective acetylation of diols in which acetylation is enabled by a catalytic amount of acetate was developed. The roles of the acetate anion have been disclosed by mechanistic studies involving ^{1}H NMR experiments and preliminary quantum-chemical calculations. The larger scope of this methodology is currently under investigation, as regioselective acetylations of polyols and benzyolations are being tested and the mechanism is being explored by theoretical calculations and kinetic isotope effect measurements.

EXPERIMENTAL SECTION

General Method for Regioselective Acylation of Diols. The 1,2- or 1,3-diol reactant (100 mg) was allowed to react with acetic anhydride (1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8−12 h in the presence of tetrabutylammonium acetate (0.3−0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexanes/EtOAc = 5:1 to 1:2), affording the pure selectively protected derivatives.

General Method for Obtaining the ^{1}H NMR Ratio of Products. The 1,2- or 1,3-diol reactant (100 mg) was allowed to react with acetic anhydride (1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8−12 h in the presence of tetrabutylammonium acetate (0.3 equiv). A 0.2 mL sample of the reaction mixture was taken and dried in vacuum. The dried mixture was directly tested by ^{1}H NMR analysis.

Table 3. Competitive Acetylation of Hydroxyl Groups[a]

Entry	Reactants	Products	Conversion ratio
1			**13**:**25** (3:1)
2			**7**:**26** (2.5:1)
3			**9**:**26** (4:1)

[a]Conditions: reactants (1:1 mixture), Ac_2O (1.1 equiv), TBAOAc (0.3 equiv), 40 °C, 16−24 h.

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General Method for Testing the Formation of H-Bonds between Glycosides and Anions. The anion salt (0.3 equiv of TBAB or 0.6 equiv of TBAOAc) was added to a solution of methyl 2,6-OBn-β-D-galactopyranoside (10 mg) in dry CD_3CN (0.5 mL), and then an ^1H NMR test was performed.

General Method for Testing the Formation of H-Bonds between Glycosides and Solvents. The 1,2-diol reactant (10 mg) was dissolved in dry CD_3Cl, CD_3CN, or DMSO-d_6 (0.5 mL), and the dried mixture was directly used to perform ^1H NMR tests.

Syntheses. *Methyl 2-O-Acetyl-4,6-O-benzylidene-α-D-glucopyranoside (**2a**).*[15] Methyl 4,6-O-benzylidene-α-D-glucopyranoside (100 mg) was allowed to react with acetic anhydride (37 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 12 h in the presence of tetrabutylammonium acetate (64 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 101 mg of compound **2** (88%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49−7.26 (m, 5H, Ph), 5.56 (s, 1H, CH), 4.97 (d, 1H, J = 4 Hz, H_1), 4.83−4.79 (dd, 1H, J_1 = 3.6 Hz, J_2 = 9.6 Hz, H_2), 4.32−4.29 (dd, 1H, J_1 = 3.6 Hz, J_2 = 10 Hz, H_{6a}), 4.19 (t, 1H, J_1 = 9.6 Hz, J_2 = 9.2 Hz, H_3), 3.89−3.79 (m, 1H, H_5), 3.77 (t, 1H, J_1 = 10 Hz, J_2 = 10.4 Hz, H_{6b}), 3.57 (t, 1H, J_1 = 9.6 Hz, J_2 = 9.2 Hz, H_4), 3.41 (s, 1H, OMe), 2.16 (s, 1H, OAc).

*Methyl 3-O-Acetyl-2,6-di-O-benzyl-β-D-galactopyranoside (**15**).*[15] Methyl 2,6-di-O-benzyl-β-D-galactopyranoside (100 mg) was allowed to react with acetic anhydride (28 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8 h in the presence of tetrabutylammonium acetate (48 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 100 mg of compound **15** (90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31−7.26 (m, 10H, Ph × 2), 4.89 (dd, 1H, J_1 = 3.2 Hz, J_2 = 10 Hz, H_3), 4.85 (d, 1H, J = 12 Hz, $PhCH_2$), 4.64−4.55 (m, 3H, $PhCH_2$), 4.36 (d, 1H, J = 8 Hz, H_1), 4.13 (d, 1H, J = 3.2 Hz, H_4), 3.81−3.64 (m, 4H, H_2, H_5, H_{6a}, H_{6b}), 3.59 (s, 1H, OMe), 2.05 (s, 1H, OAc).

*Methyl 3-O-Acetyl-4,6-O-benzylidene-α-D-galactopyranoside (**17**).*[24] Methyl 4,6-O-benzylidene-α-D-galactopyranoside (100 mg) was allowed to react with acetic anhydride (37 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 12 h in the presence of tetrabutylammonium acetate (64 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 104 mg of compound **17** (90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.54−7.28 (m, 5H, Ph), 5.54 (s, 1H, CH), 5.15 (dd, 1H, J_1 = 3.2 Hz, J_2 = 10.4 Hz, H_3), 4.98 (d, 1H, J = 3.6 Hz, H_1), 4.40 (s, 1H, H_4), 4.32 (dd, 1H, J_1 = 2 Hz, J_2 = 12.4 Hz, H_{6a}), 4.29−4.17 (m, 1H, H_5), 4.09 (dd, 1H, J_1 = 1.6 Hz, J_2 = 12.4 Hz, H_{6b}), 3.75 (s, 1H, H_2), 3.50 (s, 1H, OMe), 2.19 (s, 1H, OAc), 2.01 (d, 1H, J = 10.8 Hz, OH).

*Methyl 2-O-Acetyl-4,6-O-benzylidene-β-D-glucopyranoside (**18**).*[24] Methyl 4,6-O-benzylidene-β-D-glucopyranoside (100 mg) was allowed to react with acetic anhydride (37 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 12 h in the presence of tetrabutylammonium acetate (64 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 98 mg of compound **18** (85%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51−7.26 (m, 5H, Ph), 5.55 (s, 1H, CH), 4.92 (t, 1H, J_1 = 8 Hz, J_2 = 9.2 Hz, H_2), 4.43 (d, 1H, J = 8 Hz, H_1), 4.37 (dd, 1H, J_1 = 5.2 Hz, J_2 = 10.8 Hz, H_{6a}), 3.91−3.85 (m, 1H, H_3), 3.80 (t, J_1 = 10.4 Hz, J_2 = 10.4 Hz, H_{6b}), 3.59 (t, 1H, J_1 = 9.2 Hz, J_2 = 9.6 Hz, H_4), 3.51 (s, 1H, OMe), 3.48−3.42 (m, 1H, H_5), 2.67 (s, 1H, OH), 2.15 (s, 1H, OAc).

*Methyl 4-O-Acetyl-2,6-di-O-benzyl-β-D-glucopyranoside (**19a**) and Methyl 3-O-Acetyl-2,6-di-O-benzyl-β-D-glucopyranoside (**19b**).*[34] Methyl 2,6-di-O-benzyl-β-D-glucopyranoside (100 mg) was allowed to react with acetic anhydride (28 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8 h in the presence of tetrabutylammonium acetate (48 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 53 mg of compound **19a** (48%) and 47 mg of compound **19b** (42%).

Data for **19a**: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32−7.26 (m, 10H, Ph × 2), 4.95−4.87 (m, 2H, $PhCH_2$, H_4), 4.67 (d, 1H, J = 11.2 Hz, $PhCH_2$), 4.59−4.51 (m, 2H, $PhCH_2$), 4.33 (d, 1H, J = 8 Hz, H_1), 3.67 (t, J_1 = 8.1 Hz, J_2 = 8.2 Hz, H_3), 3.59 (m, 6H, H_5, H_{6a}, H_{6b}, OMe), 3.30 (t, 1H, J_1 = 7.6 Hz, J_2 = 7.6 Hz, H_2), 3.59 (s, 1H, OMe), 1.99 (s, 1H, OAc).

Data for **19b**: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.26 (m, 10H, Ph × 2), 5.00 (t, 1H, J_1 = 7.6 Hz, J_2 = 9.6 Hz, H_3), 4.85 (d, 1H, J = 12 Hz, $PhCH_2$), 4.63−4.56 (m, 3H, $PhCH_2$), 4.37 (d, 1H, J = 7.6 Hz, H_1), 3.78−3.77 (m, 2H, H_5, H_{6a}), 3.65−3.58 (m, 4H, OMe, H_4), 3.52−3.47 (m, 1H, H_{6b}), 3.34 (t, 1H, J_1 = 9.2 Hz, J_2 = 7.6 Hz, H_2), 2.02 (s, 1H, OAc).

*Methyl 2,3-Di-O-benzyl-6-O-acetyl-α-D-glucopyranoside (**20**).*[15] Methyl 2,3-di-O-benzyl-α-D-glucopyranoside (100 mg) was allowed to react with acetic anhydride (28 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8 h in the presence of tetrabutylammonium acetate (48 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 101 mg of compound **20** (91%). ^1H NMR (DMSO-d_6, 400 MHz): δ 7.40−7.28 (m, 10H, Ph × 2), 5.04−4.67 (m, 4H, $PhCH_2$ × 2), 4.65 (d, 1H, J = 3.6 Hz, H_1), 4.46−4.41 (dd, 1H, J_1 = 4.8 Hz, J_2 = 12 Hz, H_{6a}), 4.25−4.22 (dd, 1H, J_1 = 2.4 Hz, J_2 = 12 Hz, H_{6b}), 3.84−3.74 (m, 2H, H_3, H_5), 3.53 (dd, 1H, J_1 = 3.6 Hz, J_2 = 9.6 Hz, H_2), 3.47−3.41 (m, 4H, H_4, OMe), 2.51 (s, 1H, OH), 2.10 (s, 1H, OAc).

*Methyl 2,3-Di-O-benzyl-6-O-acetyl-α-D-galactopyranoside (**21**).*[15] Methyl 2,3-di-O-benzyl-α-D-galactopyranoside (100 mg) was allowed to react with acetic anhydride (28 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8 h in the presence of tetrabutylammonium acetate (48 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 103 mg of compound **21** (93%). ^1H NMR (DMSO-d_6, 400 MHz): δ 7.41−7.27 (m, 10H, Ph × 2), 4.96 (d, 1H, J = 4.8 Hz, OH), 4.79 (d, 1H, J = 3.6 Hz, H_1), 4.72−4.56 (m, 4H, $PhCH_2$ × 2), 4.15−4.11 (m, 2H, H_{6a}, H_{6b}), 4.08−4.03 (m, 1H, H_4), 3.80−3.74 (m, 2H, H_2, H_5), 3.69−3.65 (dd, 1H, J_1 = 10.4 Hz, J_2 = 3.0 Hz, H_3), 3.26 (s, 3H, OCH_3), 2.02 (s, 3H, OAc).

*Methyl 2,3-Di-O-benzyl-6-O-acetyl-α-D-mannopyranoside (**22**).*[15] Methyl 2,3-di-O-benzyl-α-D-mannopyranoside (100 mg) was allowed to react with acetic anhydride (28 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8 h in the presence of tetrabutylammonium acetate (48 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 101 mg of compound **22** (91%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39−7.28 (m, 10H, Ph × 2), 5.32 (d, 1H, J = 6.0 Hz, OH), 4.77 (d, 1H, J = 0.8 Hz, H_1), 4.65−4.62 (m, 4H, $PhCH_2$ × 2), 4.35−4.31 (dd, 1H, J_1 = 12.0 Hz, J_2 = 1.8 Hz, H_{6a}), 4.10−4.03 (m, 1H, H_{6b}), 3.81−3.80 (m, 1H, H_2), 3.69−3.61 (m, 1H, H_4), 3.66−3.51 (m, 2H, H_3, H_5), 3.26 (s, 3H, OCH_3), 2.02 (s, 3H, OAc).

*2-Phenyl-2-hydroxyethyl Acetate (**24**).*[15] 1-Phenyl-1,2-ethanediol (50 mg) was allowed to react with acetic anhydride (38 μL, 1.1 equiv) in dry acetonitrile (1 mL) at 40 °C for 8 h in the presence of tetrabutylammonium acetate (66 mg, 0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexane/EtOAc = 2:1), affording 59 mg of compound **24** (90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42−7.28 (m, 5H, Ph), 4.98−4.95 (dd, 1H, J_1 = 8.4, J_2 = 3.2 Hz, CH), 4.32−4.15 (m, 2H, CH_2), 2.12 (s, 3H, OAc).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods; Table S1; ^1H NMR spectra of compounds **2a**, **15**, **17**, **18**, **19a**, **19b**, **20**, **21**, **22**, and **24**; H-bond tests of compounds **1**, **4**, **6**, and **7** by ^1H NMR; computational methods; and Cartesian coordinates and total energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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