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Reagent-Dependent Regioselective Control in Multiple Carbohydrate Esterifications

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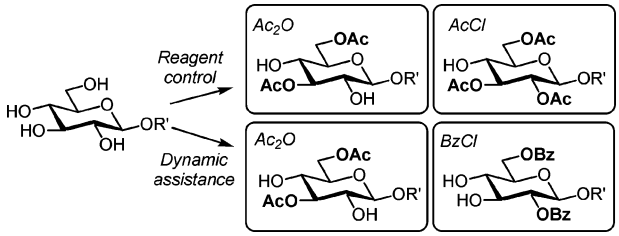

Regioselective control in organotin-mediated multiple acylation of carbohydrates is presented. The acylation reagent could be efficiently used to direct the product formation. Reagent-dependent thermodynamic and kinetic control and dynamic assistance mechanisms are suggested, resulting in the efficient preparation of building blocks that normally require many steps with traditional synthesis.

Regioselectivity is a prominent challenge in carbohydrate chemistry since carbohydrates contain several hydroxyl groups of similar reactivity. Selective protecting groups and efficient protecting group strategies are therefore of crucial importance to efficiently obtain desired carbohydrate structures. Carbohydrate hydroxyl groups differ somewhat in reactivity depending on whether they are anomeric, primary, or secondary and also depending on their configurations. These differences in reactivity can sometimes be utilized so that a desired protection pattern can be achieved in one step without the use of more complex reaction sequences.[1,2] For obtaining monosubstituted compounds in one or a few steps, the use of organotin reagents such as tributyltin oxide or dibutyltin oxide[3] provides a useful means to efficient regioselective acylations,[4] alkylations,[5] silyations,[6] sulfonylations,[7] and glycosylations.[8] Stannylene acetals are easily prepared and generally lead to intermediate structures with predictable reactivities. In these reactions, stoichiometric amounts of organotin reagent are normally used.

However, of particular importance in this respect is the possibility of acquiring multiple protections in single-step processes, and so far, no efficient, general methods have been developed. Interestingly, a protocol was recently described where products with one or two free hydroxyl groups were produced by use of excess organotin reagent.[9] This potentially general approach is very convenient and efficient for multiple protection schemes. Combining this organotin method with the Lattrell-Dax (nitrite-mediated) carbohydrate epimerization method addressed recently,[10] very convenient and highly efficient methods to modify carbohydrate structures that traditionally require many steps can be developed.[11−16] Such structures are increasingly important for many biological processes or as drug candidates.[17,18]

In order to advance the organotin-mediated multiple carbohydrate protection method, a study of regioselective single-step acylations of unprotected pyranosides was initiated. During this study, it was, however, found that the multiple esterification processes were highly dependent on the acyl reagent used. These interesting results prompted us to further explore the mechanisms how the multiple carbohydrate esterification process was regioselectively controlled and to predict the outcome of structures that normally require many steps with traditional synthesis.

The general multiprotection process is outlined in Scheme 1. The unprotected glycoside was first treated with an excess amount (2−3 equiv) of dibutyltin oxide, producing a stannylene intermediate that was not isolated. This intermediate was subsequently treated with the acylation reagent to yield the protected products in a one-pot process.

When acetyl chloride was used in the acylation process, the main product using galactoside **1** as reactant was found to be the 4,6-di-*O*-acetyl product **2** (35%), together with lower amounts of triacetylated products (Scheme 2, see also the Supporting Information). To our surprise, a different pattern was, however, formed when acetic anhydride was instead used as the acylating reagent. In this case, the 3,6-di-*O*-acetyl product **3** (46%) proved to be the major product of the process, whereas no 4,6-di-*O*-acetyl product **2** could be isolated. Similar differences were found when 3 equiv of organotin reagent was used in the process, yielding the 3,4,6-tri-*O*-acetyl product **4** (57%) when acetyl chloride was used and the 2,3,6-tri-*O*-acetyl product

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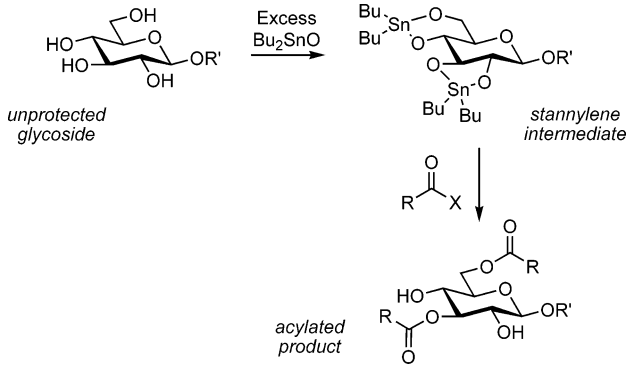
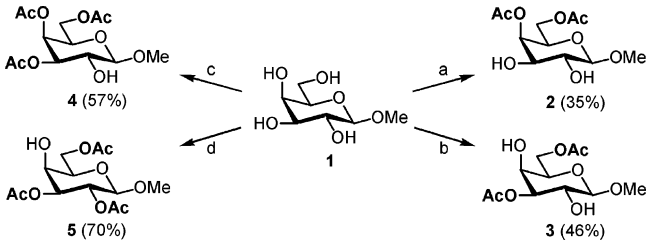
SCHEME 1. Example of Organotin-Mediated Multiple Carbohydrate Esterification



SCHEME 2. Reagent-Dependent Multiprotection of Methyl β-D-Galactopyranoside 1[a]

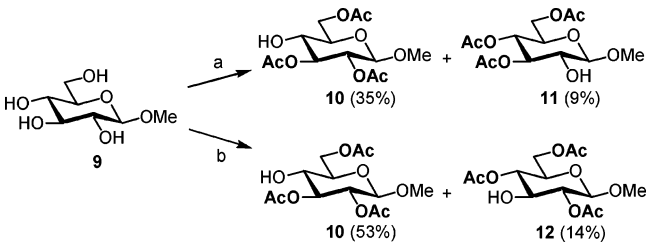


[a] Reagents and conditions: (a) (i) Bu_2SnO (2.2 equiv), MeOH, 70 °C, 2 h, (ii) AcCl, toluene, 0−22 °C, 6 h; (b) (i) Bu_2SnO (2.2 equiv), MeOH, 70 °C, 2 h, (ii) Ac_2O, toluene, 0−22 °C, 6 h; (c) (i) Bu_2SnO (3.3 equiv), MeOH, 70 °C, 2 h, (ii) AcCl, toluene, 0−22 °C, 6 h; (d) (i) Bu_2SnO (3.3 equiv), MeOH, 70 °C, 2 h, (ii) Ac_2O, toluene, 0−22 °C, 6 h.

5 (70%) when acetic anhydride was employed, respectively. This difference in product formation was subsequently further explored. Recently, an organotin-mediated benzoyl group migration pattern was suggested for different diols and also carbohydrates.[19,20] This effect could also be used in the present case, starting from galactoside **1** and employing benzoyl group migration at higher temperature. The 4,6-di-*O*-benzoyl product **6** (80%) was thus obtained (see the Supporting Information). At lower temperature, the 3,6-di-*O*-benzoyl product **7** (90%) was instead formed suggesting that no migration can take place under these conditions. Benzoyl migration to the 3,4,6-tri-*O*-benzoyl product **8** (90%) was also formed at higher temperature when 3 equiv of organotin reagent was used. By comparison with the results for the acetylating reagents, this seems to suggest that an organotin-mediated acetate group migration can in this case take place already at room temperature, but only when acetyl chloride is used. The relatively high yields of the 4,6-di-*O*-acetyl product **2** and the 3,4,6-tri-*O*-acetyl product **4** are in this case thermodynamically controlled by acetyl migration at lower temperature.

According to the tentative organotin benzoyl group migration mechanism suggested,[19,20] the resulting alkoxystannane intermediate is able to attack the neighboring acyl carbonyl group with acyl transfer as a consequence. If this mechanism is valid, it is reasonable to assume that acyl groups in general are able to migrate under these conditions, however showing different migration rates. It is well-known that acetyl groups are more reactive than benzoyl groups in migration reactions, thus explaining the effect of benzoyl migration at elevated temperature whereas acetyl groups migrate already at room temperature.

SCHEME 3. Reagent-Dependent Multiprotection of Methyl β-D-Glucopyranoside 9[a]



[a] Reagents and conditions: (a) (i) Bu_2SnO (2.2 equiv), MeOH, 70 °C, 2 h, (ii) Ac_2O, toluene, 0−22 °C, 6 h; (b) (i) Bu_2SnO (2.2 equiv), MeOH, 70 °C, 2 h, (ii) AcCl, toluene, 0−22 °C, 6 h.

However, this tentative mechanism does not take into account the apparent effects of acetic anhydride. In contrast to benzoyl chloride and acetyl chloride, it was found that migration with acetic anhydride does not seem to take place at room temperature. The high yield of, for example, the 2,3,6-tri-*O*-acetyl product **5** using acetic anhydride is rather an effect of kinetic control. Thus, the experimental data indicate that migration could only be observed with acetyl chloride at room temperature (thermodynamic control), whereas acetic anhydride proved inefficient in this reaction (kinetic control). More subtle differences were recorded for glucoside **9** due to similar reactivities of the stannylene acetals (Scheme 3). However, this interpretation also accounts for why, in addition to the 2,3,6-tri-*O*-acetyl product **10** mainly formed, the 3,4,6-tri-*O*-acetyl product **11** was formed when glucoside **9** was treated with acetic anhydride, whereas the 2,4,6-tri-*O*-acetyl product **12** was formed when acetyl chloride was used under the same conditions. No 2,4,6-tri-*O*-acetyl product **12** could be formed using acetic anhydride on account of its thermodynamically controlled formation.

A tentative explanation as to why migration takes place with acetyl chloride, whereas it is inefficient with acetic anhydride, is outlined in Figure 1. With acetyl chloride, the migration follows the route presented in Figure 1a, based on previous studies,[20] where the resulting chloride anion coordinates to the tin center. However, with acetic anhydride, bidentate coordination of the resulting acetate to the organotin intermediate takes place instead,[21−23] dramatically reducing the Lewis acidic effect of the organotin-intermediate so that transesterification will not take place (Figure 1b), and the kinetic product is formed.

According to this explanation, it was hypothesized that this kinetically controlled reaction should become thermodynamically controlled at higher temperature from temperature-dependent reversibility of the acetoxystannane complex. With acetic anhydride, the yield of the kinetic product 2,3,6-tri-*O*-acetylgalactoside **5** also decreased from 70% at room temperature to 18% at 90 °C due to the acetyl group migration from the 3-position to the 4-position. In this case, however, low selectivity between the 2- and 3-positions yielded a mixture of 2,4,6-tri-*O*-acetylgalactoside **13** and 3,4,6-tri-*O*-acetylgalactoside **4**. Similar results were in this case obtained for benzoyl group

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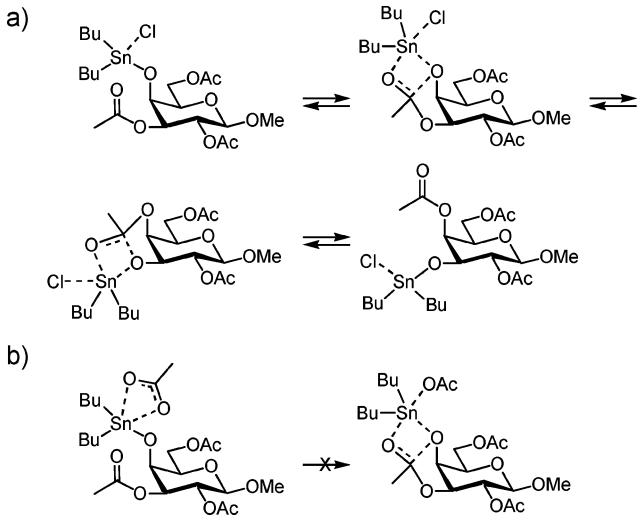
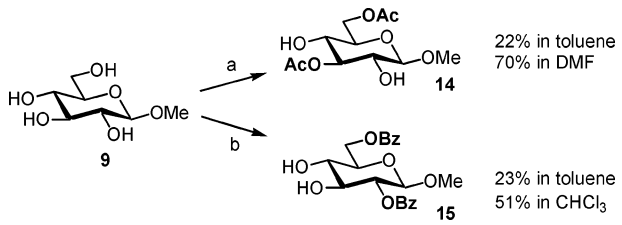


FIGURE 1. Difference in organotin-mediated acetyl migration: (a) acetyl chloride used as reagent, generating a monodentate chlorostannane complex; (b) acetic anhydride used as reagent producing a less reactive bidentate acetoxystannane.

SCHEME 4. Reagent-Dependent Multiprotection of Methyl *β*-D-Glucopyranoside 9[a]



[a] Reagents and conditions: (a) (i) Bu_2SnO (2.2 equiv), MeOH, 70 °C, 2 h, (ii) Ac_2O, toluene or DMF, 0−22 °C, 6 h; (b) (i) Bu_2SnO (2.2 equiv), MeOH, 70 °C, 2 h, (ii) BzCl, toluene or $CHCl_3$, 0−22 °C, 6 h.

migration at high temperature when benzoyl chloride was used (see the Supporting Information).

Upon analysis of the resulting product compositions when using acetic anhydride as acylation reagent, a reactivity order of the hydroxyl groups can be estimated. For *β*-D-galactoside, the reactivity order can be arranged as 3 > 6 > 2 > 4. Furthermore, the stability order can instead be arranged as 6 > 4 > 3 > 2 from the migration results using acetyl chloride as acylation reagent. Similarly, the reactivity order for the different hydroxyl groups of the *β*-D-glucoside in organotin-mediated esterification can be arranged as 6 > 3 = 2 > 4 and the stability order as 6 > 2 > 3 > 4.

However, the results obtained also reveal an additional reagent-controlled migration mechanism (Scheme 4). For example, the 3,6-di-*O*-acetyl-glucoside **14** was obtained with acetic anhydride, whereas the 2,6-di-*O*-benzoyl glucoside **15** was instead obtained with benzoyl chloride at room temperature. Since no organotin-mediated migration occurred with neither acetic anhydride nor benzoyl chloride at room temperature, it is clear that these results are not brought about by the migration mechanism mentioned above. The studies also indicated that only the 3,6-di-*O*-acetyl glucoside **14** was obtained when the stannylene intermediate was treated with acetic anhydride and no other di-*O*-acetyl products. When the intermediate was allowed to react with benzoyl chloride on the other hand, the 2,6-di-*O*-benzoyl glucoside **15** was always obtained in higher yield than the 3,6-di-*O*-benzoyl glucoside **16** (see the Supporting Information). This was especially pronounced in chloroform, where the 2,6-di-*O*-benzoyl glucoside **15** was obtained in 51% yield.

As reported, poor selectivity was obtained for acylation of the hydroxyl groups in the 2- and 3-positions of *β*-D-glucosides when the hydroxyl groups in the 4- and 6-positions were protected with benzylidene groups.[7,24] However, in the examples with the different acylation reagents mentioned above, good selectivity was instead obtained between the 2- and 3-positions of the free glucoside **9**. Based on these findings, a tentative *dynamic assistance* mechanism is suggested (Figure 2). Thus, for the acylation reagent benzoyl chloride, by virtue of the large organotin group in the 4-position obstructing the approaching benzoyl group, the accessibility of the 3-position is disfavored. As a result, high selectivity was obtained for the 2-position (Figure 2a**)**. For the acylation reagent acetic anhydride on the other hand, the generated acetate group can bridge the two tin centers, inducing stannylene migration from the 2,3-position to the 3,4-position. As a result of this tentative dynamic assistance mechanism, the 3-position was acylated with high selectivity (Figure 2b).

In the course of the studies, it was also found that the solvent played an important role for the outcome of the multiprotection reactions (cf. Scheme 4). To further explore how the solvent polarity influences the selectivity, a range of solvents of different polarity were evaluated. To avoid acyl group migration, acetic anhydride was chosen as acylation reagent. The results are displayed in Table 1, clearly indicating the solvent importance in the reactions. For galactoside **1**, although the 3,6-di-*O*-acetyl product **3** was obtained in moderate yield in toluene (46%), this product was obtained in 90% yield in DMF and 75% yield in acetonitrile (Table 1).

For the glucoside **9**, a similar pattern was seen. Whereas the 3,6-di-*O*-acetyl product **14** was obtained in very low yield in toluene (22%), it could be obtained in 70% yield in DMF. The experimental data clearly indicate that the solvent can indeed control the selectivity of the organotin-mediated esterification reactions. Good selectivity was always obtained when the esterification reactions were done in the more polar solvent. The reason for this effect is likely due to decreased reactivity of the esterification reagent from solvent-induced destabilization of the stannylene intermediates.[25]

Finally, the results obtained for the *β*-D-galactosides and the *β*-D-glucosides were applied to two other carbohydrate structures, methyl α-D-mannoside **17** and methyl α-D-glucoside **18**. In agreement with previous reports,[24] it was reasoned that the 1,2-*cis*-glucoside would possess a reactivity order in the organotin-mediated multiprotection reactions of 6 > 2 > 3 > 4, due to increased electron density of the 2-hydroxyl group, and possibly also to diminished dynamic assistance effects. The 1,2-*trans*-mannoside would on the other hand follow the order 6 > 3 > 2 > 4, mainly due to the axial configuration of the 2-position. These predictions proved valid in these reactions, and both the di-*O*-acetyl and the tri-*O*-acetyl products for both structures could be produced in good yields. In conclusion, it has been shown that organotin-mediated multiple carbohydrate esterifications can be controlled by the acylating reagent and the solvent polarity. When acetyl chloride is used, the reactions

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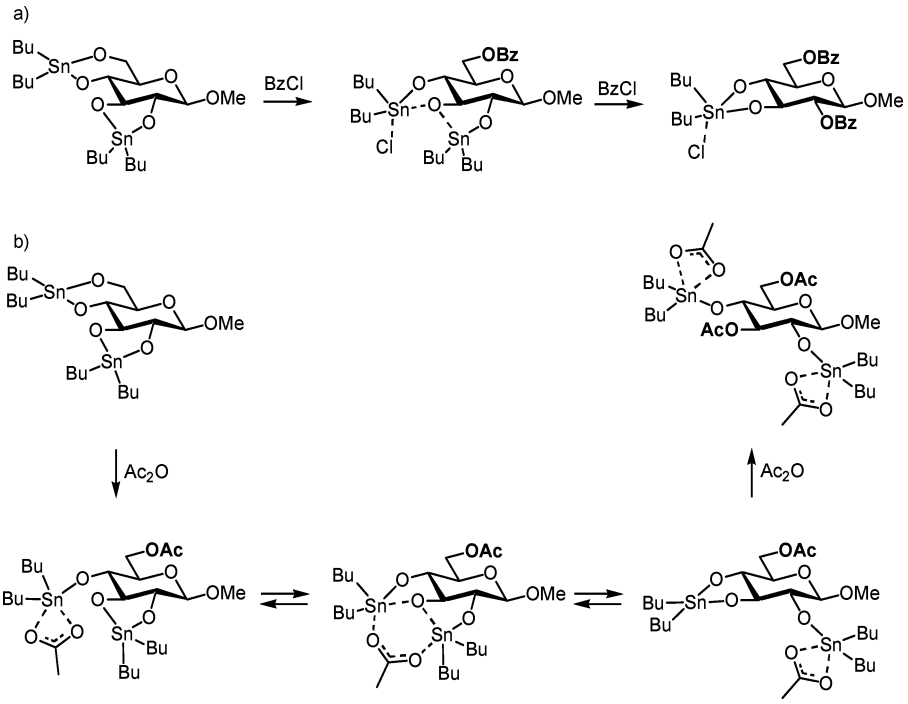
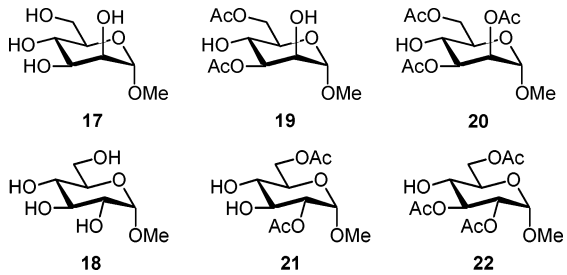


FIGURE 2. Dynamic assistance controlled acylation: (a) acylation with benzoyl chloride preferentially occurring in the 2-position; (b) acetate-assisted migration of the stannylene resulting in acetylation in the 3-position.

TABLE 1. One-Pot Organotin-Mediated Multiple Carbohydrate Esterification Using Acetic Anhydride in Polar Solvents



17 **19** **20**

18 **21** **22**

reactant	solvent	reagent (equiv)	product	yield[a] (%)
1	DMF	Ac_2O (2.2)	3,6-di-OAc-β-D-Gal **3**	90
1	CH_3CN	Ac_2O (2.2)	3,6-di-OAc-β-D-Gal **3**	75
1	CH_3CN	Ac_2O (3.3)	2,3,6-tri-OAc-β-D-Gal **5**	85
9	DMF	Ac_2O (2.2)	3,6-tri-OAc-β-D-Glc **14**	70
9	CH_3CN	Ac_2O (3.3)	2,3,6-tri-OAc-β-D-Glc **10**	85
17	CH_3CN	Ac_2O (2.2)	3,6-di-OAc-α-D-Man **19**	80
17	CH_3CN	Ac_2O (3.3)	2,3,6-tri-OAc-α-D-Man **20**	90
18	CH_3CN	Ac_2O (2.2)	2,6-di-OAc-α-D-Glc **21**	80
18	CH_3CN	Ac_2O (3.3)	2,3,6-tri-OAc-α-D-Glc **22**	90

[a] Isolated yield.

are under thermodynamic control, whereas when acetic anhydride is employed, kinetic control takes place. A dynamic assistance control has also been suggested for stannylene migration induced by acetate. Very good selectivity can furthermore be obtained in more polar solvents. These results have been used in the efficient preparation of a range of prototype carbohydrate structures.

Experimental Section

General Acylation Procedure. Methyl β-D-glycoside (194 mg, 1 mmol) and dibutyltin oxide (550 mg, 2.2 mmol) were dissolved in 30 mL of methanol and refluxed for 2 h. After evaporation of the solvent, the residue was dried under vacuum and then dissolved in 10 mL of solvent (toluene, DMF, or chloroform). After the solution was cooled to 0−5 °C, a solution of acylation reagent (2.2 mmol or 3.3 mmol) in anhydrous solvent (1 mL) was added dropwise and then allowed to react at room temperature for 2−12 h. The resulting mixture was directly purified by flash column chromatography (2:1 to 1:1 hexane−ethyl acetate), yielding the acylated products.

Methyl 4,6-di-*O*-benzoyl-β-D-galactopyranoside (6): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−8.14 (m, 10 H), 5.66 (d, 1 H, $J_{3,4}$ 3.2 Hz), 4.55 (dd, 1 H, $J_{6a,6b}$ 11.3 Hz, $J_{6a,5}$ 6.7 Hz), 4.34 (dd, 1 H, $J_{6a,6b}$ 11.3 Hz, $J_{6b,5}$ 6.7 Hz), 4.27 (d, 1 H, $J_{1,2}$ 7.8 Hz), 4.04 (t, 1H, $J_{6,5}$ 6.7 Hz), 3.89 (dd, 1 H, $J_{2,3}$ 9.62 Hz, $J_{3,4}$ 3.2 Hz), 3.77 (dd, 1 H, $J_{1,2}$ 7.8 Hz, $J_{2,3}$ 9.62 Hz), 3.58 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6, 166.3, 133.7, 133.4, 130.2, 129.9, 129.7, 129.4, 104.1, 72.5, 72.1, 71.5, 70.2, 62.6, 57.5; $[\alpha]^{20}_D = -57$ ($c = 1.8$, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}O_8 \cdot {}^1/_2H_2O$: C, 61.31; H, 5.64. Found: C, 61.26; H, 5.30.

Methyl 3,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (8): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.2−8.1 (m, 15 H), 5.91 (d, 1 H, $J_{3,4}$ 3.45 Hz), 5.39 (dd, 1 H, $J_{3,2}$ 10.1 Hz, $J_{4,3}$ 3.45 Hz), 4.65 (dd, 1 H, $J_{6a,6b}$ 11.3 Hz, $J_{6a,5}$ 6.5 Hz), 4.47 (d, 1 H, $J_{1,2}$ 7.6 Hz), 4.37 (dd, 1 H, $J_{6a,6b}$ 11.3 Hz, $J_{6b,5}$ 6.5 Hz), 4.24 (d, 1 H, $J_{5,6}$ 6.5 Hz), 4.10 (dd, 1 H, $J_{2,3}$ 10.1 Hz, $J_{2,1}$ 7.6 Hz), 3.64 (s, 3 H); ^{13}C NMR ($CDCl_3$ 125 MHz) δ 166.2 166.1 165.6, 133.7, 133.4, 133.3, 130.1 130.0, 129.9, 129.6, 129.4, 129.3, 128.7, 128.6, 128.4, 104.5, 73.5, 71.4, 70.1, 68.3, 62.2, 57.7; $[\alpha]^{20}_D = -3$ ($c = 2.6$, $CHCl_3$). Anal. Calcd for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found: C, 66.17; H, 5.08.

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Supporting Information Available: General methods and product distributions for acylation reactions in toluene. This material is available free of charge via the Internet at http://pubs.acs.org.

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