Indium-Mediated Alkynylation in C-Glycoside Synthesis

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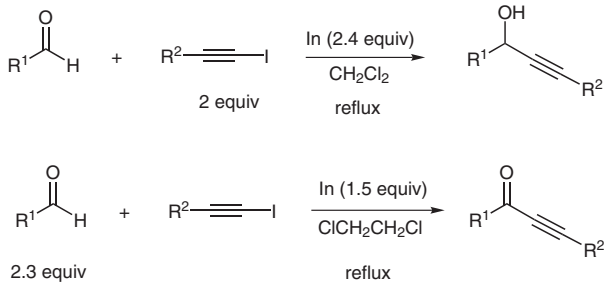
Abstract: The indium-mediated alkynylation of perbenzylated or peracetylated formylglucose is a pathway for the synthesis of various C-glycosides. Hydroxylated, ketonic, mono- or difluorinated, and methylated C-glycosides were thus obtained.

Key words: indium, alkynylation, C-glycoside, fluorination

The synthesis of non-natural glycosides, in which the glycosidic oxygen is replaced by a methylene group, has received great interest during the last decades. Numerous methods have been described for the preparation of C-glycosides.[1] Moreover, the replacement of the anomeric oxygen bond by a difluoromethylene group is promising for the synthesis of new glycoconjugates, as this unit is considered bioisosteric and isoplanar to oxygen.[2]

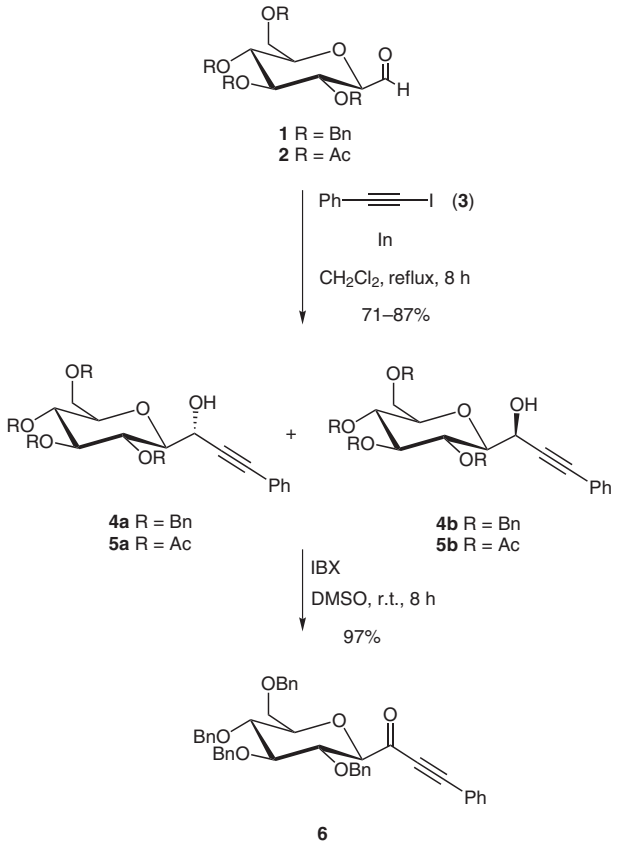
We recently described the indium-mediated alkynylation of carbonyl derivatives.[3] In the case of aldehyde alkynylation, this reaction allows the preparation of propargylic alcohols or ketones according to the experimental conditions depicted in Scheme 1. In refluxing dichloromethane in the presence of two equivalents of alkynyl iodide the propargylic alcohol was obtained, whereas in refluxing dichloroethane and with the aldehyde in excess (2.3 equiv) the reaction led to the propargylic ketone via an in situ Oppenauer-type oxidation.



Scheme 1 Indium-mediated aldehyde alkynylation

Continuing our work in C-glycoside synthesis,[4] we applied this reaction to 2,3,4,6-tetra-*O*-benzyl-1-formylglucopyranose (**1**) and 2,3,4,6-tetra-*O*-acetyl-1-formylglucopyranose (**2**) prepared according to literature procedures.[5,6] The alkynylation was accomplished by mixing the aldehyde **1** or **2** with two equivalents of phenylacetylene iodide **3** in dichloromethane in the presence of indium (2.4 equiv). It led to the corresponding propargylic alcohols **4** and **5** in 87% and 71% yields, respectively; both were obtained as mixtures of diastereomers in a ratio of 65:35 (Scheme 2). In the first case, the diastereomers were separated by chromatography on silica gel; the major product was less polar than the minor product. Even though the diastereoselectivity was low, it was in the same sense as in the case of Mg, Zn, or Ce reagents described by Genêt and co-workers.[7]

In order to obtain the corresponding propargylic ketone **6**, we first applied the conditions allowing the in situ oxidation of the alcohol (excess of aldehyde in dichloroethane). Unfortunately, the expected ketone was not obtained, which is not surprising as we showed that the indium-mediated oxidation did not always proceed in the case of enolisable aldehydes.[3b] On the other hand, ketone **6** was easily



Scheme 2 Indium-mediated alkynylation of 2,3,4,6-tetra-*O*-benzyl-1-formylglucopyranose (**1**) and 2,3,4,6-tetra-*O*-acetyl-1-formylglucopyranose (**2**)

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obtained in 97% yield from the mixture of propargylic alcohols **4a** and **4b** by an oxidation with 2-iodoxybenzoic acid (IBX) (Scheme 2).

These two compounds **4** and **6** can be fluorinated in order to lead to the corresponding mono- and *gem*-difluorinated derivatives. We put the fluorination of propargylic alcohol **4a** into practice by treatment with commercial diethylaminosulfur trifluoride (DAST) at room temperature in dichloromethane. The expected fluorinated derivative **7** was thus obtained in 96% yield as a mixture of diastereomers in a ratio of 62:38. Compound **4b** led to **7** in 90% yield and in a similar diastereomeric ratio (68:32). Both reactions afforded the same diastereomer as main product (Scheme 3).

In the case of propargylic ketone **6** the difluorination was performed in neat DAST at 55 °C leading to **8** in 42% yield (Scheme 4). This last compound is interesting because the difluoromethylene group is isosteric to oxygen.

In order to access a C-glycoside with a methylene group in β-anomeric position, we first tried the Barton–McCombie deoxygenation of alcohol **4**.

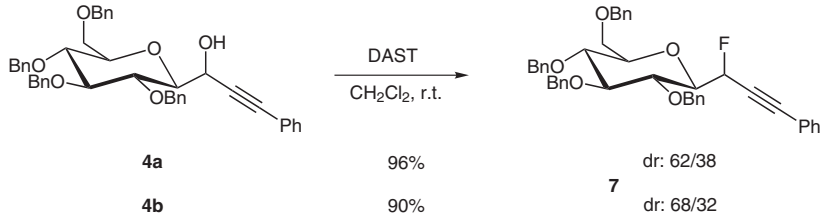
Unfortunately no reduction of the xanthate intermediate or the thiocarbonyldiimidazoyl derivative occurred by treatment with Bu_3SnH/AIBN. This was certainly due to the presence of the conjugated C–C triple bond. As the reduction of this triple bond by treatment with tosylhydrazide did not succeed, we decided to realize the synthetic pathway starting from propargylic alcohol **5** bearing acetate protecting groups on the sugar moiety. In this case, after palladium-catalyzed hydrogenation, the alcohol **9** was obtained and led to the desired dehydroxylated product by successive treatment with thiocarbonyldiimidazole and tributyltin hydride (Scheme 5).

We have shown herein the utility of the indium-mediated alkynylation reaction for the synthesis of a variety of C-glycosides starting from aldehydic sugar moieties. We are presently investigating the application of this pathway for the synthesis of C-glycosylated aminoacids using an acetylenic iodide of an aminoacid derivative.

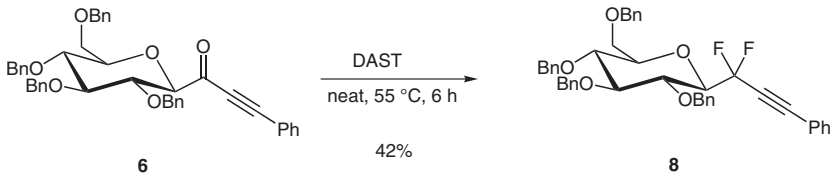
IR spectra were recorded on a Bruker Tensor 27 spectrophotometer. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 250 DPX (250 MHz) spectrometer. Indium was purchased from Aldrich and was activated by stirring in vacuo for 30 min. CH_2Cl_2 was dried over anhyd P_2O_5. 2-Iodoxybenzoic acid (IBX) was prepared according to a literature procedure.[8] Optical rotations were determined at 25 °C in $CHCl_3$, 589 nm, on a JASPO DIP 370 instrument.

Iodophenylacetylene (3)

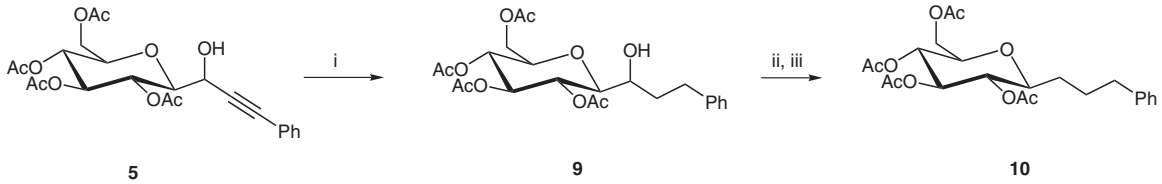
A mixture of I_2 (1.218 g, 4.8 mmol) and morpholine (1.14 mL, 13.1 mmol) in benzene (5 mL) was stirred for 30 min at r.t. until the formation of an orange solution. Phenylacetylene (980 mg, 4.35 mmol) diluted in benzene (8 mL) was then added and the medium was stirred at 45 °C for 24 h. After filtration and washing with Et_2O (20 mL), the organic phase was washed with aq NH_4Cl soln, $NaHCO_3$ soln, and H_2O. After drying with $MgSO_4$ and filtration, the solvent was removed under reduced pressure. The crude product was puri-



Scheme 3 Propargylic alcohol fluorination by DAST



Scheme 4 Propargylic ketone fluorination by DAST



Scheme 5 *Reagents and conditions:* (i) H_2, 10% Pd/C, dioxane–EtOH–H_2O (2:2:1), 3 h, 95%; (ii) $In_2C{=}S$ (10 equiv), DMAP (15 equiv), THF, 70 °C, 5 h; (iii) Bu_3SnH (10 equiv), AIBN (1 equiv), toluene, 85 °C, 3 h, 54%.

fied by flash chromatography on silica gel (PE–EtOAc, 9:1) to give **3** (2.01 g, 92%) as a yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25 (m, 3 H), 7.42 (m, 3 H).

^{13}C NMR (62 MHz, $CDCl_3$): δ = 6.6, 94.1, 123.2, 128.1, 128.7, 132.2.

1-(2,3,4,6-Tetra-*O*-benzyl-D-gluco-β-*C*-pyranosyl)-3-phenylprop-2-yn-1-ol (4)

To activated In (276 mg, 2.40 mmol) was added a solution of iodophenylacetylene (**3**) (456 mg, 2.00 mmol) in anhyd CH_2Cl_2 (2.5 mL). Aldehyde **1** (553 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was introduced to the medium, which was refluxed overnight. The mixture was treated with a sat. $NaHCO_3$ soln (10 mL) and extracted with CH_2Cl_2 (10 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE–EtOAc, 85:15) and the two diastereomers **4a** (374 mg, 57%) and **4b** (198 mg, 30%) were thus separated.

4a

IR (neat): 3357, 3030, 2864, 1490 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.00 (s, 1 H, OH), 3.49–3.86 (m, 7 H, H-1 to H-6, H-6′), 4.58–4.99 (m, 9 H, PhCH_2, C*H*OH), 7.18–7.44 (m, 25 H, Ar).

^{13}C NMR (62 MHz, $CDCl_3$): δ = : 62.1 (CHOH), 68.6 (C-6), 73.3, 75, 75.3, 75.5 (Ph*C*H$_2$), 78.1, 78.3, 78.9, 80.5 (C-2 to C-5), 84.9 (*C*≡C), 86.8 (C-1), 88.4 (C≡*C*), 122.7 (Ar-C), 126.9–128.4 (Ar-CH), 131.7 (Ar-CH), 137.8–138.4 (Ar-C).

4b

IR: 3431, 2862, 1490 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.00 (s, 1 H, OH), 3.51–3.82 (m, 7 H, H-1 to H-6, H-6′), 4.60–4.94 (m, 9 H, PhCH_2, C*H*OH), 7.22–7.41 (m, 25 H, Ar).

^{13}C NMR (62 MHz, $CDCl_3$): δ = 63.2 (CHOH), 68.6 (C-6), 73.3, 75.1, 75.4, 75.7 (Ph*C*H$_2$), 78.3, 79.2, 79.8, 80.7 (C-2 to C-5), 86.4 (*C*≡C), 86.5 (C≡*C*), 86.8 (C-1), 122.4 (Ar-C), 127.6–128.4 (Ar-CH), 131.7 (Ar-CH), 138.0–138.3 (Ar-C).

1-(2,3,4,6-Tetra-*O*-acetyl-D-gluco-β-*C*-pyranosyl)-3-phenylprop-2-yn-1-ol (5)

According to the same procedure as for **4**, **2** (389 mg, 1.08 mmol) was transformed into **5** (355 mg, 71%) and obtained as a mixture of diastereomers.

^{1}H NMR (250 MHz, $CDCl_3$; **5a** + **5b**): δ = 1.99–2.09 (m, 12 H, OAc), 2.77 (s, 1 H, OH), 3.61–3.83 (m, 2 H, H-1, H-5), 4.10–4.37 (m, 2 H, H-6, H-6′), 4.58 (s, 1 H, C*H*OH), 5.10–5.30 (m, 3 H, H-2 to H-4), 7.23–7.47 (m, 5 H, Ar).

^{13}C NMR (62 MHz, $CDCl_3$; **5a**): δ = 20.6 (*C*H$_3$COO), 61.7 (*C*HOH), 62.8 (C-6), 68.4, 68.9, 74.0 (C-2 to C-4), 75.9 (C-5) 79.3 (C-1), 85.0 (*C*≡C), 85.8 (C≡*C*), 122.1, 128.3, 128.8 (Ar-CH), 131.6 (Ar-C), 169.4, 169.8, 170.3, 170.7 (CO).

^{13}C NMR (62 MHz, $CDCl_3$; **5b**): δ = 20.6 (*C*H$_3$COO), 61.7 (*C*HOH), 62.1 (C-6), 68.3, 68.7, 74.1 (C-2 to C-4), 75.9 (C-5) 79.4 (C-1), 85.0 (*C*≡C), 86 (C≡*C*), 122.1, 128.3, 128.8 (Ar-CH), 131.8 (Ar-C), 169.4, 169.8, 170.3, 170.7 (CO).

1-(2,3,4,6-Tetra-*O*-benzyl-D-gluco-β-*C*-pyranosyl)-3-phenylprop-2-yn-1-one (6)

To the mixture of **4a** and **4b** (240 mg, 0.366 mmol) in anhyd DMSO (6.5 mL) was added in one portion IBX (154 mg, 0.550 mmol). After stirring overnight, H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (PE–EtOAc, 85:15) to give **6** (232 mg, 97%); $[\alpha]_D^{25}$ –5.8 (*c* 6.9 $CHCl_3$).

IR (neat): 3030, 2917, 2203, 1673, 1496 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.55–3.80 (m, 6 H, H-2 to H-6, H-6′), 4.03 (d, *J* = 9.3 Hz, 1 H, H-1), 4.56–4.92 (m, 8 H, PhCH_2), 7.20–7.49 (m, 25 H, Ar)

^{13}C NMR (62 MHz, $CDCl_3$): δ = 68.7 (C-6), 73.5,75.1, 74.8, (Ph*C*H$_2$), 78.1, 79.4, 79.5, 83.7 (C-2 to C-5), 86.4 (C-1), 87.0 (*C*≡C), 94.5 (C≡*C*), 119.7 (Ar-C), 127.6–128.5 (Ar-CH), 133.4 (Ar-CH), 137.5–138.3 (Ar-C), 183.33 (CO).

HRMS (CI): *m*/*z* [M + NH_4]$^+$ calcd for $C_{43}H_{44}NO_6$: 670.3169; found: 670.3170.

3-(2,3,4,6-Tetra-*O*-benzyl-D-gluco-β-*C*-pyranosyl)-3-fluoro-1-phenylpropyne (7)

To a DAST soln (54 mg, 0.33 mmol) in anhyd CH_2Cl_2 at –78 °C was added dropwise the alcohol **4a** or **4b** (154 mg, 0.235 mmol) in 2 mL of CH_2Cl_2. After stirring for 1 h, the temperature was allowed to reach 20 °C and stirring was continued for one additional hour. The mixture was treated with MeOH (2 mL) and a spatula of $NaHCO_3$ was added. The crude product was concentrated in vacuo and then purified by flash chromatography on silica gel (PE–EtOAc, 9:1) to give **7** as a mixture of diastereomers (149 mg, 96% starting from **4a**; 139 mg, 90% starting from **4b**).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.43–3.76 (m, 7 H, H-1 to H-6, H-6′), 4.53–4.85 (m, 8 H, PhCH_2), 5.55 (d, *J* = 48 Hz, 1 H, CHF), 7.11–7.35 (m, 25 H, Ar).

^{13}C NMR (62 MHz, $CDCl_3$; major diastereomer): δ = 68.4 (C-6), 73.4, 75.1, 75.2, 75.8 (Ph*C*H$_2$), 78.1, 78.4, 79.5, 79.9 (C-2 to C-5), 82.3 (*C*≡C), 83.20 (d, *J* = 123 Hz, CHF), 86.84 (C-1), 90 (C≡*C*), 121.5 (Ar-C), 127.4–129.0 (Ar-CH), 132.0 (Ar-CH), 137.7–138.4 (Ar-C).

^{13}C NMR (62 MHz, $CDCl_3$; minor diastereomer): δ = 68.9 (C-6), 73.4, 75.1, 75.2, 75.6 (Ph*C*H$_2$), 77.8, 78.5, 79.5, 80.1 (C-2 to C-5), 80.4 (d, *J* = 123 Hz, CHF), 82.5 (*C*≡C), 86.84 (C-1), 89.8 (C≡*C*), 121.5 (Ar-C), 127.4–129.0 (Ar-CH), 132.0 (Ar-CH), 137.7–138.4 (Ar-C).

^{19}F NMR (235 MHz, $CDCl_3$; major diastereomer): δ = –185.5 (dd, *J* = 47, 11.8 Hz).

^{19}F NMR (235 MHz, $CDCl_3$; minor diastereomer): δ = –189.5 (dd, *J* = 47, 23.6 Hz).

HRMS (CI): *m*/*z* [M + NH_4]$^+$ calcd for $C_{43}H_{45}NO_5F$: 674.3282; found: 674.3270.

3-(2,3,4,6-Tetra-*O*-benzyl-D-gluco-β-*C*-pyranosyl)-3,3-difluoro-1-phenylpropyne (8)

Compound **6** (183 mg, 0.280 mmol) and DAST (361 mg, 2.24 mmol) were heated at 55 °C for 6 h. The mixture was treated with MeOH (2 mL) and a spatula of $NaHCO_3$ was added. The crude product was concentrated under reduced pressure and then purified by flash chromatography on silica gel (PE–EtOAc, 9:1) to give **8** as a yellow oil (80 mg, 42%); $[\alpha]_D^{25}$ –0.15 (*c* 5.4 $CHCl_3$).

IR (neat): 3030, 2918, 2242, 1493 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.48–3.77 (m, 7 H, H-1 to H-6, H-6′), 4.47–4.83 (m, 8 H, PhCH_2), 7.10–7.38 (m, 25 H, Ar).

^{13}C NMR (62 MHz, $CDCl_3$): δ = 68.39 (C-6), 77.7, 78.8, 79.2, 79.5 (C-2 to C-5), 80.1 (*C*≡C), 86.5 (C-1), 88.6 (C≡*C*), 113.3 (dd, *J* = 239 Hz, CF_2), 119.9 (Ar-C), 127.4–128.4 (Ar-CH), 132.2 (Ar-CH), 137.7–138.3 (Ar-C).

^{19}F NMR (235 MHz, $CDCl_3$): δ = –88.66 (dd, *J* = 285, 7 Hz, 1 F), –91.44 (dd, *J* = 284, 7 Hz, 1 F).

HRMS (CI): *m*/*z* [M + NH_4]$^+$ calcd for $C_{43}H_{44}NO_6F_2$: 692.3188; found: 692.3190.

1-(2,3,4,6-Tetra-*O*-acetyl-D-gluco-β-*C*-pyranosyl)-3-phenylpropan-1-ol (9)

To a solution of propargylic alcohol **5** (355 mg, 0.770 mmol) in dioxane–EtOH–H_2O, (2:2:1) (6 mL) was added 10% palladium on carbon (81 mg). The medium was shaken for 3 h under 1 atm of H_2, then filtered through celite and the solvents were removed under reduced pressure. Compound **9** (340 mg, 95%) was obtained as mixture of diastereomers and used without purification.

^{1}H NMR (250 MHz, $CDCl_3$; **9a**+**9b**): δ = 1.91–2.00 (m, 14 H, OAc, C*H*$_2$CHOH), 2.45 (s, 1 H, OH), 2.58 (m, 1 H, PhC*H*H), 2.75 (m, 1 H, PhCH*H*), 3.21 (d, *J* = 8.4 Hz, 1 H, H-1), 3.39 (s, 1 H, C*H*OH), 3.50–3.59 (m, 1 H, H-5), 3.97–4.22 (m, 2 H, H-6, H-6′), 4.92–5.16 (m, 3 H, H-2 to H-4), 7.10–7.23 (m, 5 H, Ar).

^{13}C NMR (62 MHz, $CDCl_3$; **9a**): δ = 21.0 (*C*H_3COO), 32.5 (*C*H_2CHOH), 35.1 (Ph*C*H_2), 62.7 (C-6), 68.0 (CHOH), 69.0, 69.5, 74.5 (C-2 to C-4), 76.2 (C-5) 79.6 (C-1), 125.5, 128.0, 128.2 (Ar-CH), 141.4 (Ar-C), 169.1, 169.9, 170.2, 170.7 (CO).

^{13}C NMR (62 MHz, $CDCl_3$; **9b**): δ = 21.1 (*C*H_3COO), 32.1 (*C*H_2CHOH), 33.0 (Ph*C*H_2), 62.5 (C-6), 70.31 (CHOH), 68.6, 68.8, 74.9 (C-2 to C-4), 76.2 (C-5) 80.7 (C-1), 125.5, 128.0, 128.2 (Ar-CH), 141.4 (Ar-C), 169.1, 169.9, 170.2, 170.7 (CO).

1-(2,3,4,6-Tetra-*O*-acetyl-D-gluco-β-*C*-pyranosyl)-3-phenylpropane (10)

To a solution of **9** (99 mg, 0.214 mmol) in 2 mL of THF under Ar were added thiocarbonyldiimidazole (382 mg, 2.14 mmol) and DMAP (392 mg, 3.21 mmol) and the mixture was heated at 70 °C for 5 h. The medium was then concentrated under reduced pressure and filtered through celite in order to remove the excess thiocarbonyldiimidazole and DMAP. The residue was then diluted with anhyd toluene and Bu_3SnH (577 mL, 2.14 mmol) and AIBN (35 mg, 0.21 mmol) were successively added under Ar. This mixture was heated at 85 °C for 3 h. After concentration in vacuo, the crude product was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 1:1) to give **10** (52 mg, 54%) as a colorless oil; $[\alpha]_D^{25}$ –9.9 (*c* 3.5 $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.46 (m, 4 H, CHC*H*$_2$C*H*$_2$), 1.91 (m, 12 H, OAc), 2.53 (t, *J* = 7.6 Hz, 2 H, PhC*H*$_2$), 3.33 (m, 1 H, H-1), 3.52 (m, 1 H, H-1), 4.00 (dd, *J* = 12.0, 2.0 Hz, 1 H, H-6), 4.17 (dd, *J* = 12.3, 5.0 Hz, 1 H, H-6′), 4.80 (t, *J* = 9.6 Hz, 1 H, H-2), 4.96 (t, *J* = 9.7 Hz, 1 H, H-3), 5.08 (t, *J* = 9.2 Hz, 1 H, H-4), 7.07–7.23 (m, 5 H, Ar-CH).

^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.7 (*C*H_3COO), 26.6 (CHCH$_2$*C*H$_2$), 30.5 (CH*C*H$_2$), 35.3 (Ph*C*H$_2$), 62.3 (C-6), 68.6 (C-3), 71.8 (C-2), 74.3 (C-4), 75.6 (C-5), 77.5 (C-1), 125.7, 128.2, 128.3 (Ar-CH), 141.9 (Ar-C), 169.4, 169.6, 170.3, 170.6 (CO).

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{31}O_9$: 451.1968; found: 451.1971.

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