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Sulfuric acid immobilized on silica: an excellent catalyst for Fischer type glycosylation☆

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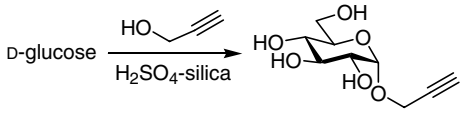
Abstract—Fischer glycosylation, a widely used technique for the preparation of simple alkyl or aryl glycosides, has a few drawbacks including the use of strong mineral acids, excess alcohols, high temperature and long reaction times. This manuscript highlights a modification using sulfuric acid immobilized on silica as catalyst for the preparation of glycosides from free sugars such as D-glucose, D-galactose, D-mannose, L-rhamnose, L-fucose, *N*-acetyl-D-glucosamine and D-maltose with a diverse range of alcohols to afford a series of useful sugar derivatives in good to excellent yields.

Simple alkyl and aryl glycosides of free sugars are extremely useful for both synthetic and biological studies. For example, benzyl,[1] allyl[2] or *p*-methoxybenzyl[3] glycosides are used for temporary anomeric protection during oligosaccharide synthesis as they can be removed when needed to make glycoconjugates, whereas long chain alkyl glycosides, for example, *n*-octyl[4] and *n*-dodecyl are often used as substrates for enzymatic transformations and other biological studies. Furthermore, propargyl glycosides are of great interest for 'Click Chemistry' approaches to mimic various biodynamic carbohydrate structures[5] and glycoconjugates. Fischer glycosylation is the best choice for preparing these simple alkyl or aryl glycosides from free sugars. However, this procedure suffers from some serious drawbacks such as the use of a large quantity of alcohol (critical for expensive alcohols) and strong mineral acids at reflux conditions for long reaction times.[6] Thus neutralization and purification of the final product becomes an issue for these transformations. Recently, microwave assisted Fischer type glycosylation has been reported,[7] but this is not suitable for large-scale preparation of these important starting materials. Moreover, alcohols are not ideal substrates for microwave assisted processes.

In our ongoing efforts to prepare oligosaccharide mimics to develop drug-like molecules, we often required glycosides as synthons. In the search for an alternative procedure for Fischer type glycosylation, we envisioned sulfuric acid immobilized on silica (H_2SO_4–silica)[8] as an efficient alternative for the required transformation using a lower quantity of alcohol and shorter reaction time. Moreover, purification would only require filtration. Herein, we report our findings on H_2SO_4–silica[9] catalyzed Fischer type glycosylations with various alcohols and free sugars.

In a simple reaction, D-glucose (180 mg, 1 mmol) was suspended in propargyl alcohol (290 μL, 5 mmol) and stirred at 65 °C. H_2SO_4–silica (5 mg) was added and stirring was continued until all the solids had dissolved (~2.5 h). At this point, TLC (CH_2Cl_2–MeOH; 5:1) showed complete conversion of the starting D-glucose to a faster running component. After cooling to room temperature, the reaction mixture was transferred to a short (4 cm × 1 cm) silica gel column and the excess propargyl alcohol was eluted with CH_2Cl_2 (20 mL) followed by elution of the product glycoside with CH_2Cl_2–MeOH (15:1) to afford the desired propargyl glycoside in 75% yield (Scheme 1). For detailed characterization, the product was per-O-acetylated using Ac_2O (4 equiv) and catalytic H_2SO_4–silica. ^1H and ^{13}C NMR



Scheme 1. Synthesis of propargyl glucoside.

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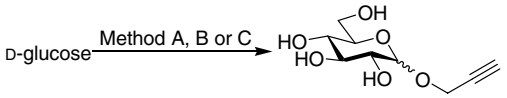
spectroscopy of the per-O-acetylated product revealed formation of the desired glycoside in a 6:1 (α/β) ratio. The anomeric mixture was separated by flash chromatography. Although formation of furanoside and acyclic acetals in small quantities is common with this type of reaction, no such by-product was evident here.

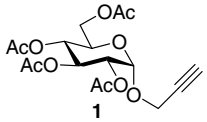
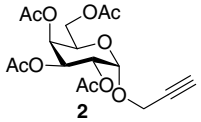
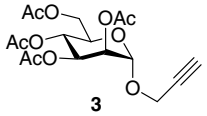
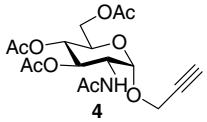
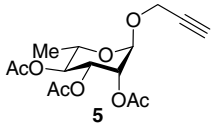
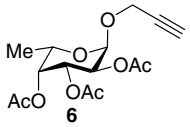
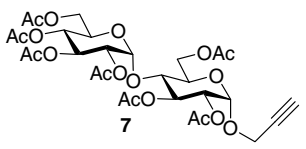
A similar reaction was performed except on this occasion the reaction mixture was allowed to stir at room temperature for 12 h after complete dissolution of the starting sugar. The product was processed in a similar way and then per-*O*-acetylated. After purification of the acetate, NMR showed a significant improvement in anomeric selectivity (10:1, α/β) due to the slow shifting of the equilibrium towards the thermodynamic product. The same result was obtained when the reaction was allowed to continue under heating for an additional 3 h. Comparisons between the anomeric selectivity of propargyl glycoside prepared under different conditions are illustrated in Table 1. As we were interested in preparing a library of propargyl glycosides, the reaction was performed with other sugars (mono and disaccharides) following Method C and the results are summarized in Table 2. For D-mannose, L-rhamnose and *N*-acetyl-D-glucosamine, heating for 2 h was sufficient for complete α-selectivity. It is worth noting that a 100 mmol scale reaction with D-glucose using the same stoichiometry and reaction conditions afforded the desired product in similar yield and anomeric selectivity.

Table 1. Comparison between anomeric selectivities obtained by different methods



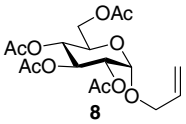
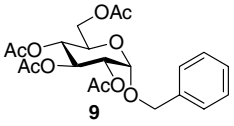
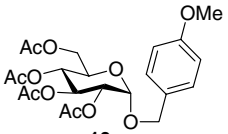
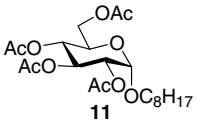
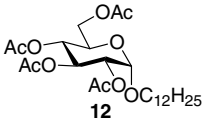
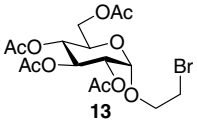
Method	α/β	Yield (%)
Method A. 2.5 h stirring at 65 °C (until complete dissolution of starting material)	6:1	75
Method B. After 2.5 h heating at 65 °C, the mixture was allowed to stir at room temperature for 12 h	10:1	81
Method C. Stirring continued at 65 °C for an additional 3 h after complete dissolution	10:1	80

Table 2. Preparation of propargyl glycosides from free sugars[a]

Starting material	Product	Time (h)	Yield (%)	α/β
D-Glucose	 **1**	5.5	80	10:1
D-Galactose	 **2**	6	79	10:1
D-Mannose	 **3**	2	83	1:0
N-Acetyl-D-glucosamine	 **4**	2	80	1:0
L-Rhamnose	 **5**	2	82	1:0
L-Fucose	 **6**	4	74	12:1
D-Maltose[b]	 **7**	8	69	11:1

[a] 1 mmol of sugar was reacted with 5 mmol of propargyl alcohol and 5 mg H_2SO_4–silica.
[b] For maltose, 10 mmol of propargyl alcohol was used for 1 mmol of sugar.

Table 3. Preparation of glycosides of D-glucose with various alcohols[a]

Alcohol	Product	Time (h)	Yield (%)	α/β
Allyl alcohol	 **8**	6	79	10:1
Benzyl alcohol	 **9**	7	78	10:1
p-Methoxybenzyl alcohol	 **10**	7	75	11:1
n-Octanol	 **11**	6	81	13:1
n-Dodecanol	 **12**	8	76	12:1
2-Bromo ethanol	 **13**	6	82	11:1

[a] 1 mmol of D-glucose was reacted with 5 mmol of alcohol and 5 mg of H_2SO_4–silica in each case.

Next, we focussed our attention on other alcohols in order to generalize the method and to access various glycosides for future use. Thus, D-glucose was used as a representative sugar and the glycosylation reactions were performed with benzyl, allyl, *p*-methoxybenzyl, 2-bromoethyl (which can be converted to the corresponding azido derivative and used in the 'Click' reaction), *n*-octyl and dodecyl alcohol. To our satisfaction, all the reactions proceeded smoothly to furnish the desired glycosides in good to excellent yields and anomeric selectivity. The results are described in Table 3. All compounds were characterized as their per-*O*-acetylated derivatives by ^1H and ^{13}C NMR spectroscopies and mass spectrometry. NMR data for selected compounds are given in the reference section.[10]

As a control, when the glycosylation reaction was performed without H_2SO_4–silica, no product formation was evident even after heating for 12 h at 60 °C. This confirms the utility of H_2SO_4–silica as a catalyst for the reaction.

In conclusion, we have shown that H_2SO_4–silica can be used successfully as a catalyst to prepare various alkyl and aryl glycosides from free sugars through Fischer type glycosylation using less equivalents of alcohol and in shorter times. The strategy is equally applicable for large-scale preparations. The propargyl glycosides prepared will be studied as glycomimetics and the results will be communicated in due course.

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9. *Preparation of H_2SO_4–silica*: To a slurry of silica gel (10 g, 200–400 mesh) in dry diethyl ether (50 mL) was added commercially available concd H_2SO_4 (3 mL) with shaking for 5 min. The solvent was evaporated under reduced pressure resulting in free flowing H_2SO_4–silica which was then dried at 110 °C for 3 h.
10. *Analytical data of selected compounds*: Compound **1**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.50 (t, 1H, *J* 9.8 Hz, H-3), 5.30 (d, 1H, *J* 3.6 Hz, H-1), 5.10 (t, 1H, *J* 9.8 Hz, H-4), 4.92 (dd, 1H, *J* 3.6 Hz, 9.8 Hz, H-2), 4.32–4.23 (m, 3H, CH_2—C≡CH, H-6^a), 4.10–4.03 (m, 2H, H-5, H-6^b), 2.47 (t, 1H, *J* 2.4 Hz, CH_2—C≡C*H*), 2.10, 2.08, 2.04, 2.02 (4s, 12H, 4 × COC*H*$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 170.5, 170.2, 169.5, 169.3 (4 × *C*OCH$_3$), 94.8 (*C*-1), 78.5 (CH_2—*C*≡CH), 75.9 (CH_2—C≡*C*H), 70.7, 70.2, 68.7, 68.1, 61.9 (*C*-6), 55.9 (*C*H$_2$—C≡CH), 20.9 (4 × CO*C*H$_3$). HRMS: Calcd for $C_{17}H_{26}O_{10}N$ (M+NH$_4$): 404.1557; found *m*/*z* 404.1561. Compound **2**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 5.47 (br d, 1H, *J* 2.2 Hz, H-4), 5.36 (dd, 1H, *J* 3.2 Hz, 9.8 Hz, H-3), 5.32 (d, 1H, *J* 3.2 Hz, H-1), 5.14 (dd, 1H, *J* 3.2 Hz, 9.8 Hz, H-2), 4.27 (m, 2H, C*H*$_2$—C≡CH), 4.14–4.07 (m, 3H, H-5, H-6^a, H-6^b), 2.47 (t, 1H, *J* 2.4 Hz, CH$_2$—C≡C*H*), 2.15, 2.10, 2.05, 1.99 (4s, 12H, 4 × COC*H*$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 170.2 (2), 169.8, 169.4 (4 × *C*OCH$_3$), 95.2 (*C*-1), 78.0 (CH$_2$—*C*≡CH), 75.6 (CH$_2$—C≡*C*H), 68.0, 67.7, 67.2, 67.1, 61.5 (*C*-6), 55.9 (*C*H$_2$—C≡CH), 21.0 (2), 20.9 (2) (4 × CO*C*H$_3$). HRMS: Calcd for $C_{17}H_{26}O_{10}N$ (M+NH$_4$): 404.1557; found *m*/*z* 404.1559. Compound **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.30 (dd, 1H, *J* 2.4 Hz, 9.3 Hz, H-3), 5.26 (m, 2H, H-2, H-4), 5.02 (s, 1H, H-1), 4.29 (br d, 2H, *J* 2.1 Hz, C*H*$_2$—C≡CH), 4.28 (dd, 1H, *J* 4.2 Hz, 12.3 Hz, H-6^a), 4.10 (dd, 1H, *J* 2.4 Hz, 12.3 Hz, H-6^b), 4.08 (m, 1H, H-5), 2.47 (t, 1H, *J* 2.1 Hz, CH$_2$—C≡C*H*), 2.20, 2.11, 2.05, 2.00 (4s, 12H, 4 × COC*H*$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 170.4, 169.7, 169.6 (2) (4 × *C*OCH$_3$), 96.5 (*C*-1), 78.3 (CH$_2$—*C*≡CH), 76.1 (CH$_2$—C≡*C*H), 69.6, 69.4, 69.2, 66.3, 62.5 (*C*-6), 55.6 (*C*H$_2$—C≡CH), 21.1 (2), 20.9 (2) (4 × CO*C*H$_3$). HRMS: Calcd for $C_{17}H_{26}O_{10}N$ (M+NH$_4$): 404.1557; found *m*/*z* 404.1560. Compound **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.76 (d, 1H, *J* 9.3 Hz, N*H*), 5.18 (t, 1H, *J* 9.6 Hz, H-3), 5.11 (t, 1H, *J* 9.6 Hz, H-4), 5.01 (d, 1H, *J* 3.9 Hz, H-1), 4.32 (dt, 1H, *J* 3.9 Hz, 9.3 Hz, 9.6 Hz, H-2), 4.27 (m, 2H, C*H*$_2$—C≡CH), 4.23 (dd, 1H, *J* 4.5 Hz, 12.3 Hz, H-6^a), 4.07 (dd, 1H, *J* 2.4 Hz, 12.3 Hz, H-6^b), 3.96 (m, 1H, H-5), 2.47 (t, 1H, *J* 2.4 Hz, CH$_2$—C≡C*H*), 2.09, 2.02, 2.01 (3s, 9H, 3 × COC*H*$_3$), 1.95 (s, 3H, NHCOC*H*$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 171.3, 170.7, 170.2 (3 × *C*OCH$_3$), 169.3 (NH*C*OCH$_3$), 96.6 (*C*-1), 78.6 (CH$_2$—*C*≡CH), 75.9 (CH$_2$—C≡*C*H), 71.3, 68.7, 68.4, 62.1 (*C*H$_2$—C≡CH), 55.6 (*C*-6), 53.7 (*C*-2), 23.3 (NHCO*C*H$_3$), 21.0, 20.9, 20.8 (3 × CO*C*H$_3$). HRMS: Calcd for $C_{17}H_{27}O_9N_2$ (M+NH$_4$): 403.1717; found *m*/*z* 403.1720. Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.23 (dd, 1H, *J* 2.4 Hz, 9.6 Hz, H-3), 5.21 (br s, 1H, H-2), 5.02 (t, 1H, *J* 9.6 Hz, H-4), 4.90 (s, 1H, H-1), 4.24 (d, 2H, *J* 2.4 Hz, C*H*$_2$—C≡CH), 3.87 (m, 1H, H-5), 2.45 (t, 1H, *J* 2.4 Hz, CH$_2$—C≡C*H*), 2.16, 2.03, 1.98 (3s, 9H, 3 × COC*H*$_3$), 1.24 (d, 3H, *J* 7.2 Hz, H-6). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.8, 169.7 (2) (3 × *C*OCH$_3$), 96.4 (*C*-1), 78.6 (CH$_2$—*C*≡CH), 75.7 (CH$_2$—C≡*C*H), 71.2, 69.9, 69.3, 67.2, 54.9 (*C*H$_2$—C≡CH), 21.1, 21.0, 20.9 (3 × CO*C*H$_3$), 17.6 (C-*C*H$_3$). HRMS: Calcd for $C_{15}H_{24}O_8N$ (M+NH$_4$): 346.1502; found *m*/*z* 346.1503. Compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.24 (dd, 1H, *J* 3.3 Hz, 8.7 Hz, H-3), 5.22 (br d, 1H, *J* 3.3 Hz, H-4), 5.18 (d, 1H, *J* 3.6 Hz, H-1), 5.05 (dd, 1H, *J* 3.6 Hz, 8.7 Hz, H-2), 4.20 (d, 2H, *J* 2.4 Hz, C*H*$_2$—C≡CH), 4.16 (q, 1H, *J* 6.6 Hz, H-5), 2.40 (t, 1H, *J* 2.4 Hz, CH$_2$—C≡C*H*), 2.13, 2.04, 1.94 (3s, 9H, 3 × COC*H*$_3$), 1.11 (d, 3H, *J* 6.6 Hz, H-6). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 170.0, 169.8, 169.5 (3 × *C*OCH$_3$), 94.9 (*C*-1), 78.6 (CH$_2$—*C*≡CH), 75.1 (CH$_2$—C≡*C*H), 71.2, 67.7 (2), 64.9, 55.4 (*C*H$_2$—C≡CH), 20.6, 20.5, 20.4 (3 × CO*C*H$_3$), 16.0 (C-*C*H$_3$). HRMS: Calcd for $C_{15}H_{24}O_8N$ (M+NH$_4$): 346.1502; found *m*/*z* 346.1505. Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.78 (m, 1H, CH$_2$—C*H*=CH$_2$), 5.43 (t, 1H, *J* 10.2 Hz, H-3), 5.35–5.21 (2d, 2H, CH$_2$—CH=C*H*$_2$), 5.08 (d, 1H, *J* 3.9 Hz, H-1), 5.04 (t, 1H, *J* 6.3 Hz, *J* 10.2 Hz, H-4), 4.86 (dd, 1H, *J* 3.9 Hz, 10.2 Hz, H-2), 4.18–4.11 (m, 2H, C*H*$_2$—CH=CH$_2$), 4.10–3.99 (m, 3H, H-5, H-6^a, H-6^b), 2.10, 2.07, 2.04, 2.01 (4s, 12H, 4 × COC*H*$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 170.1, 169.8, 169.2, 168.8 (4 × *C*OCH$_3$), 133.3 (CH$_2$—*C*H=CH$_2$), 117.9 (CH$_2$—CH=*C*H$_2$), 94.7 (*C*-1), 70.6 (*C*H$_2$—CH=CH$_2$), 70.0, 68.6, 68.3, 67.3, 61.7 (*C*-6), 20.4 (2), 20.3 (2) (4 × CO*C*H$_3$). HRMS: Calcd for $C_{17}H_{28}O_{10}N$ (M+NH$_4$): 406.1713; found *m*/*z* 406.1711. Compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.44 (t, 1H, *J* 9.6 Hz, H-3), 5.04 (d, 1H, *J* 3.9 Hz, H-1), 5.02 (t, 1H, *J* 9.6 Hz, H-4), 4.82 (dd, 1H, *J* 3.9 Hz, 9.6 Hz, H-2), 4.25 (dd, 1H, *J* 4.5 Hz, 12.0 Hz, H-6a), 4.06 (dd, 1H, *J* 2.4 Hz, 12.0 Hz, H-6^b), 3.98 (m, 1H, H-5), 3.66, 3.44 [2m, 2H, OC*H*$_2$–(CH$_2$)$_6$–CH$_3$], 2.09, 2.06, 2.02, 2.00 (4s, 12H, 4 × COC*H*$_3$), 1.58 [m, 2H, OCH$_2$–C*H*$_2$–(CH$_2$)$_5$–CH$_3$], 1.26 [m, 10H, OCH$_2$–CH$_2$–(C*H*$_2$)$_5$–CH$_3$], 0.92 [t, 3H, OCH$_2$–CH$_2$–(CH$_2$)$_5$–C*H*$_3$]. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.9, 169.7 (2), 168.7 (4 × *C*OCH$_3$), 95.5 (*C*-1), 72.8, 71.7, 68.6 (2), 67.1, 60.1 (*C*-6), 31.7, 29.2, 26.0 (2), 25.7, 22.5, 20.8, 20.5, 20.4 (2) (4 × CO*C*H$_3$), 14.0 [OCH$_2$–CH$_2$–(CH$_2$)$_5$–*C*H$_3$]. HRMS: Calcd for $C_{22}H_{40}O_{10}N$ (M+NH$_4$): 478.2652; found *m*/*z* 478.2653. Compound **12**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.45 (t, 1H, *J* 9.9 Hz, H-3), 5.07 (d, 1H, *J* 3.9 Hz, H-1), 5.04 (t, 1H, *J* 9.9 Hz, H-4), 4.86 (dd, 1H, *J* 3.9 Hz, 9.9 Hz, H-2), 4.29 (dd, 1H, *J* 4.2 Hz, 12.3 Hz, H-6^a), 4.11 (dd, 1H, *J* 2.1 Hz, 12.3 Hz, H-6^b), 3.92 (m, 1H, H-5), 3.63–3.47 [m, 2H, OC*H*$_2$–(CH$_2$)$_{10}$–CH$_3$], 2.11, 2.08, 2.04, 2.01 (4s, 12H, 4 × COC*H*$_3$), 1.62 [m, 2H, OCH$_2$–C*H*$_2$–(CH$_2$)$_9$–CH$_3$], 1.29 [m, 18H, OCH$_2$–CH$_2$–(C*H*$_2$)$_9$–CH$_3$], 0.95 [t, 3H, OCH$_2$–CH$_2$–(CH$_2$)$_9$–C*H*$_3$]. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.8, 169.7, 169.6, 168.9 (4 × *C*OCH$_3$), 95.7 (*C*-1), 72.6, 71.5, 68.6, 68.4, 67.0, 61.1 (*C*-6), 32.1, 29.7 (2), 28.5, 28.3, 27.9, 27.6, 26.5, 25.7, 22.5, 20.8 (2), 20.5, 20.4 (4 × CO*C*H$_3$), 14.0 [OCH$_2$–CH$_2$–(CH$_2$)$_9$–*C*H$_3$]. HRMS: Calcd for $C_{26}H_{48}O_{10}N$ (M+NH$_4$): 534.3278; found *m*/*z* 534.3280. Compound **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.45 (t, 1H, *J* 9.3 Hz, H-3), 5.13 (d,

1H, *J* 3.6 Hz, H-1), 5.03 (t, 1H, *J* 9.3 Hz, H-4), 4.83 (dd, 1H, *J* 3.6 Hz, 9.3 Hz, H-2), 4.25 (dd, 1H, *J* 4.8 Hz, 12.3 Hz, H-6[a]), 4.15–4.07 (m, 2H, H-5, H-6[b]), 4.00, 3.85 (2m, 2H, OCH_2–CH_2–Br), 3.52 (t, 2H, *J* 5.8 Hz, OCH_2–CH_2–Br), 2.09, 2.08, 2.03, 2.02 (4s, 12H, $4 \times COCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.0, 169.7, 169.5, 169.1 ($4 \times COCH_3$), 95.8 (*C*-1), 70.6, 69.8, 68.6 (OCH_2–CH_2–Br), 68.3, 67.6, 61.7 (*C*-6), 29.6 (OCH_2–CH_2–Br), 20.5 (2), 20.4 (2) ($4 \times COCH_3$). HRMS: Calcd for $C_{16}H_{27}O_{10}NBr$ ($M+NH_4$): 472.0818; found *m*/*z* 472.0819.