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COMMUNICATIONS

# Continuous synthesis of bromoalkyl glycosides by Fischer glycosylation in a microreactor

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## Abstract

In this study, bromoalkyl glycosides were successfully synthesized in microreactor scale by Fischer glycosylation. Yields between 24 and 40% after purification were achieved using various acidic catalysts and conditions. In some experiments, yields 180% higher than with previously known methods could be achieved. This study showed also that reversed-phase flash chromatography is more successful than normal-phase flash chromatography for the purification of bromoalkyl glycosides. Furthermore, longer bromoalcohols were shown to be more compatible than shorter bromoalcohols under these reaction conditions.

**Keywords** Microreactor · Carbohydrates · Fischer glycosylation · Glycosides · Bromides · Linker

## Introduction

Carbohydrates play a major role in a multitude of biological processes and procedures, for example in signaling, cell–cell communication, and molecular and cellular targeting [1, 2]. Thus, there is great interest in the synthesis of glycomimetics for biochemical and medical purposes [3, 4]. It is important to equip these glycomimetic molecules with a functionalized spacer to allow binding to transport molecules or to solid surfaces. Bromoalkyl glycosides are important components in a variety of syntheses of glycomimetics, such as the synthesis of glycosylated nordihydroguaiaretic acids as anti-cancer compounds [5]. Bromoalkyl glycosides are very promising for use as functionalized spacers [6]. In order to apply bromoalkyl glycosides on an industrial scale, production on a technical scale is necessary. For synthesis of more complex or functionalized glycosides various modern glycosylation methods, either chemical or biochemical, are available such as the trichloroacetimidate method[7–9] or usage of enzymes[10]. Nonetheless modern glycosylation methods are related to more or less complex protecting strategies resulting in multistep reactions. Therefore, until date, the Fischer glycosylation is still an interesting method for the synthesis of glycosides [11]. Indeed, various variants have been implemented in the past decades including the use of microwave irradiation[12], various catalysts[13–15] and ionic liquids[16, 17]. For these, however, challenges such as the thermodynamic handling of the chemical synthesis

**Article highlights**
- In the experiments in which 10-bromo-1-decanol was used as the bromoalcohol, yields were achieved exceeding more than 180% compared to other methods.
- Various acidic catalysts and reaction conditions have been monitored.
- For the purification of the glycosides, reversed phase chromatography was used instead of normal phase chromatography, as in normal phase chromatography additional side reactions occured.

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of glycosides by Fischer glycosylation must be overcome. A promising approach for this is the production of bromoalkyl glycosides in a continuously operated microreactor [18]. Microreactors are already used today for various organic syntheses [19]. Microreaction technology is characterised by an excellent mass and heat transfer and thus enables higher yields and selectivity in syntheses compared to conventional batch processes. It thus offers the possibility to design these syntheses efficiently and to optimise their reaction conditions [20]. Furthermore, microreaction technology enables processes with greatly improved sustainability and efficiency in terms of energy and material consumption. The high selectivity, associated with the synthesis of biomolecules in the microreactor, enables the rapid development of important products for biomedical applications and their production processes. As a result, the development and production of medical products from laboratory to production scale becomes more cost- and time-efficient [19].

Fischer glycosylation is an acid-catalysed name reaction in which reducing saccharides react with an alcohol to form a glycoside as shown in Fig. 1. The reaction mechanism of Fischer glycosylation results in a mixture of stereoisomers. This mixture consists of pyranosides and furanosides, which are in chemical equilibrium via open-chain intermediates. The α- and β-pyranosides are thermodynamically more stable than the furanosides, with the α-pyranoside being the thermodynamically more stable anomer [21].

Microreaction technology is a technology for a scaled-down design of process plants, for example reactors [22]. Fischer glycosylations have already been successfully carried out in microreactors. It has been shown that similar yields are achievable as for example using microwave radiation, which is the current state of the art [23]. However, microwave-mediated processes suffer from their poor scalability and, in some cases with Fischer glycosylations, also from an explosion risk due to the existing headspace caused by the used and potentially flammable alcohols. Appropriate thermodynamic handling of microreactors provides a safe and time-saving method for this form of energy-intensive chemistry. There is also no risk of explosion when using a microreactor, as the microreactor has a negligible headspace. Further, the development of a continuous process of Fischer glycosylation in the microreactor provides a promising basis for numbering-up the process. [23]

## Results and discussion

Table 1 shows the experiences of the study. The yields mentioned in the tables refer to yields achieved after purification.

In experiments with 2-bromo-ethanol, qualitative detection of the product was possible in test number 3. In experiment number 6, methoxyethanol could be detected after purification. This is an indication that the 2-bromoethanol in the NP column reacts with the methanol-containing solvent. It was possible to detect the product in test number 3 because a preparative TLC (thin layer chromatography) was used instead of the column for purification which reduced the contact time of the product with the solvent and the column. In experiment number 2, reversed phase (RP – C18) silica gel was used instead of normal phased (NP) silica gel, but no product was detected either. This may be due to the fact that under these experimental conditions no product or only little amounts could be obtained and therefore, the quantity was below the detection limit. In experiment number 3, in which product could be qualitatively detected, the temperature in the reactor was significantly higher, at 120 °C instead of 90 °C. This is an indication that higher temperatures are more likely to afford the desired product.

No product was detectable in the experiments with 3-bromo-1-propanol. It is assumed that 2-bromoethanol and 3-bromo-1-propanol as bromoalcohols are probably too reactive due to the higher electrophilicity of the carbon bearing the bromine. Therefore, compared to the longer bromoalcohols, for example 6-bromo-hexan-1-ol, very little product is produced under these reaction conditions, or the product already reacts with other substances in the reactor or in the NP chromatography. Though no side products have been isolated or identified the TLC analysis of the reaction mixture supports our assumption.

In the experiments with n-octanol, no product was detectable after purification by NP-silica gel, or a liquid–liquid extraction. Only when purified by RP-silica gel, product could be isolated. The protonic acids $H_2SO_4$, trifluoroacetic acid and the Lewis acid Trimethylsilyl trifluoromethanesulphonate (TMSOTf) were tested as catalysts in the experiments with n-octanol. RP silica gel was only used in the purification of the experiments with Lewis acid. In the thin layer chromatographies of the reactor outflow of the experiments with $H_2SO_4$ and trifluoroacetic acid, spots with the same RF value were detected as when using TMSOTf.

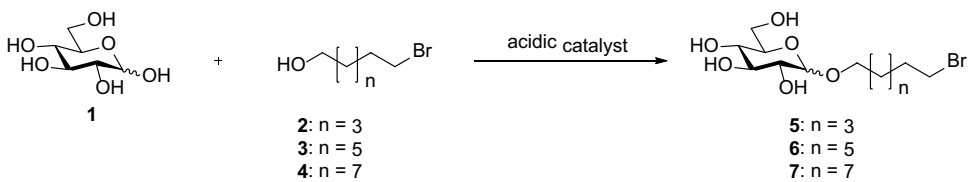


**Fig. 1** Visualisation of the Fischer glycosylation with D-glucose (**1**) and longer bromoalcohols

**Table 1** Results of the feasibility study of a continuous synthesis of bromoalkyl glycosides in the microreactor by Fischer glycosylation

| Nr | Materials | Process conditions in the microreactor | Purification method | Yield / % |
|---|---|---|---|---|
| 1 | 2-Bromoethanol (50 mmol)<br>**1** (8.33 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 10 min<br>Temperature: 75 °C | NP-Flash-Chromatography, 60 g Silica gel,<br>Eluent: DCM 83.33% (v/v) and Methanol 16.67% (v/v) | - |
| 2 | 2-Bromoethanol (36.67 mmol)<br>**1** (6.10 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 10 min<br>Temperature: 90 °C | RP-Flash-Chromatography, 60 g C18-Silica gel,<br>Eluent: $H_2O$ 5% (v/v) and Ethanol 95% (v/v) | - |
| 3 | 2-Bromoethanol (50 mmol)<br>**1** (8.33 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 10 min<br>Temperature: 120 °C | Preperative DC instead of flash-chromatography<br>Eluent: DCM 83.33% (v/v) and Methanol 16.67% (v/v) | Qualitative evidence |
| 4 | 2-Bromoethanol (36.67 mmol)<br>**1** (6.10 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 10 min<br>Temperature: 120 °C | NP-Flash-Chromatography, 60 g Silica gel,<br>Eluent: DCM 90% (v/v) and Methanol 10% (v/v) | - |
| 5 | 2-Bromoethanol (50 mmol)<br>**1** (8.33 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 15 min<br>Temperature: 120 °C | NP-Flash-Chromatography, 60 g Silica gel,<br>Eluent: DCM 90% (v/v) and Methanol 10% (v/v) | - |
| 6 | 2-Bromoethanol (16.67 mmol)<br>**1** (2.78 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 5 min<br>Temperature: 120 °C | NP-Flash-Chromatography, 60 g Silica gel,<br>Eluent: DCM 90% (v/v) and Methanol 10% (v/v) | Methoxy-ethanol as product identified |
| 7 | 3-Bromo-1-propanol (45 mmol)<br>**1** (7.5 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 10 min<br>Temperature: 75 °C | NP-Flash-Chromatography, 60 g Silica gel, Eluent: DCM 90% (v/v) and Methanol 10% (v/v) | - |
| 8 | 3-Bromo-1-propanol (15 mmol)<br>**1** (2.5 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 10 min<br>Temperature: 90 °C | NP-Flash-Chromatography, 60 g Silica gel, Eluent: DCM 95% (v/v) and Methanol 5% (v/v) | - |
| 9 | n-Octanol (7.5 mmol)<br>**1** (1.25 mmol)<br>$H_2SO_4$ (100 µL) | Retention time: 5 min<br>Temperature: 120 °C | NP-Flash-Chromatography, 60 g Silica gel, Eluent: DCM 91% (v/v) and Methanol 9% (v/v) | - |
| 10 | n-Octanol (7.5 mmol)<br>**1** (1.25 mmol)<br>Trifluoroacetic acid (100 µL) | Retention time: 5 min<br>Temperature: 120 °C | NP-Flash-Chromatography, 60 g Silica gel, Eluent: Ethyl acetate 90% (v/v) and Methanol 10% (v/v) | - |
| 11 | n-Octanol (7.5 mmol)<br>**1** (1.25 mmol)<br>Trifluoroacetic acid (300 µL) | Retention time: 5 min<br>Temperature: 120 °C | Liquid–liquid extraction with sodium chloride solution and THF instead of flash chromatography | - |
| 12 | n-Octanol (7.5 mmol)<br>**1** (1.25 mmol)<br>TMSOTf (225 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 60% (v/v) and Ethanol 40% (v/v) | 12 |
| 13 | n-Octanol (22.5 mmol)<br>**1** (3.75 mmol)<br>TMSOTf (675 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 60% (v/v) and Ethanol 40% (v/v) | 39 |
| 14 | **3** (BrOct) (15 mmol)<br>**1** (2.5 mmol)<br>TMSOTf (225 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 60% (v/v) and Ethanol 40% (v/v) | 24 |
| 15 | **3** (BrOct)(7.5 mmol)<br>**1** (1.25 mmol)<br>TMSOTf (225 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 70% (v/v) and Ethanol 30% (v/v) | 40 |
| 16 | **2** (BrHex) (7.5 mmol)<br>**1** (1.25 mmol)<br>TMSOTf (225 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 70% (v/v) and Ethanol 30% (v/v) | 34 |

**Table 1** (continued)

| Nr | Materials | Process conditions in the microreactor | Purification method | Yield / % |
|---|---|---|---|---|
| 17 | **2** (BrHex) (7.5 mmol)<br>**1** (1.25 mmol)<br>TMSOTf (225 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 60% (v/v) and Ethanol 40% (v/v) | 26 |
| 18 | **4** (BrDec) (7.5 mmol)<br>**1** (1.25 mmol)<br>TMSOTf (225 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 60% (v/v) and Ethanol 40% (v/v) | 33 |
| 19 | **4** (BrDec) (7.5 mmol)<br>**1** (1.25 mmol)<br>TMSOTf (225 µL) | Retention time: 5 min<br>Temperature: 120 °C | RP-Flash-Chromatography, 60 g Silica gel, Eluent: $H_2O$ 60% (v/v) and Ethanol 40% (v/v), after the elution of the dibromide $H_2O$ 50% (v/v) and Ethanol 50% (v/v) | 33 |

However, the spots were slightly less intense than in the experiments with TMSOTf as catalyst (using comparable amounts of reaction solution). Therefore, it is assumed that the use of $H_2SO_4$ and trifluoroacetic acid also produced product, but with lower yields compared to TMSOTf.

Furthermore, in the experiments with the longer bromoalcohols 6-bromo-1-hexanol, 8-bromo-1-octanol and 10-bromo-1-decanol, the corresponding dibromides could be isolated. It is assumed, that these represent impurities in the bromoalcohols. In support of that, a corresponding spot in TLC indicatied a second compound in the commercially available bromoalcohols.

The yield calculations in this project did not take into account the losses of reaction solution that occurred when the syringes were reconnected to the syringe pump. Product is also lost during the overall process for obtaining the bromoalkyl glycosides, for example when the fractions are combined during quenching. Here, a certain amount of solution remains in each flask in which the effluent from the microreactor has been fractionated. These losses are quite small, however, still have an significant impact at such small volumes. In the experiments in which bromoalkylglycosides were synthesised, the volume of the reaction solution was 3 mL to 4.5 mL. In this case, losses of a few 100 µL have an impact on the yield of the overall process. Therefore, it can be expected that even higher yields in the overall process can be achieved when using more reaction solution, as the losses in the overall process do not change. This would also be a possible explanation for the fact that the yields in the experiments with 6-bromo-1-hexanol were lower than in Williams et al. [18]. Also, one important difference between experiments 12 and 13 was that experiment number 13 used three times the reactants and catalyst than experiment number 12. In experiment number 13, the yield more than tripled compared to experiment number 12.

Furthermore, it is not certain what influence the solvent dependent dilution of the reaction solution has on the yield. Williams et al. [18] did not use a solvent in their experiments. Omitting the solvent could possibly further increase the yield of product.

## Conclusions

Here we demonstrate the successful synthesis of different bromoalkyl glycosides using a microreactor.

Yields of between 24 and 40% could be achieved in this project. Williams et al. [18] reported a yield of 39% in experiments with 6-bromo-1-hexanol, a yield of 27% in experiments with 8-bromo-1-octanol, as well as a yield of 18% in experiments using 10-bromo-1-decanol. Thus, in this project, the yields could be increased by approximately 150% in the experiments with 8-bromo-1-octanol and by more than 180% in experiments with 10-bromo-1-decanol. An interesting approach towards an industrial scale could be the numbering up which means parallel usage of higher amounts of such easy to use and cost-saving microreactors, nonetheless the challenge of isolation and work-up still needs to be addressed intensively.

## Experimental

Figure 2 schematically shows the overall process of producing the bromoalkyl glycosides. The microreactor was conditioned with DMSO, which was also used for the production of the reaction solution and rinsed after the reaction. The reactor was then dried with air. Stopping the reaction was done by neutralising the acid, which was used as a catalyst, with 150 µL triethylamine. The solution was then purified by column chromatography. The fractions from the column chromatography that contained product were then combined. Organic solvents were removed by using a rotary evaporator. The resulting solution in water finally was lyophylised resulting in purest possible product. The process control as well as the column chromatographic work up was monitored analytically with RP-TLC(RP-Silica Gel 60 F254, M&N, layer thickness 0.2 mm) with detection by Cerium(IV) ammonium nitrate.

The amount of DMSO as solvent in the reaction solutions was variable and depended on the solubility of the

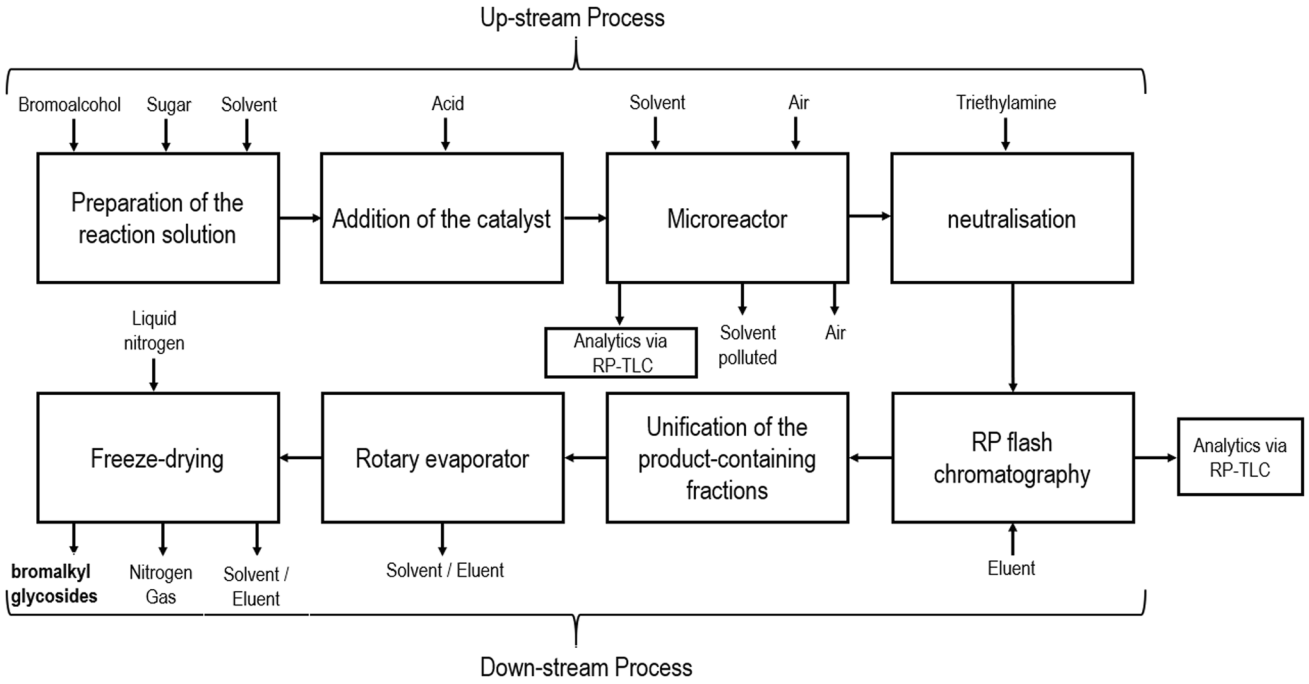


**Fig. 2** Schematic of the overall process for obtaining the bromoalkyl glycosides from bromoalcohols and reducing sugars

glucose in the solution. In the experiments with 6-bromo-1-hexanol, 6 mL DMSO was used and in the experiments with 8-bromo-1-octanol and 10-bromo-1-decanol 7 mL.

Figure 3 shows the set-up of the microreactor. The reaction solution enters the reactor system through a syringe pump. Air enters the system when the syringe is changed. A three-way valve is used to remove air that arises during syringe changes before they enter the reactor system. From the three-way valve, the reaction solution enters the microreactor, which is located in an oil bath were the temperature can be adjusted. The effluent from the reactor is fractionated into 1.5 mL Falcons, which are located in a corresponding stand. The microreactor model LTF V from the manufacturer Little Things Factory GmbH was used. The microreactor is made of borosilicate and has a volume of 1.7 mL. The channel size is 1 mm. The total system has a volume of 3.1 mL. The tubing and connections are made of Teflon, so that temperatures of up to 300 °C are possible without damaging components.

Column chromatography was performed with 60 g RP silica gel. A mixture of ethanol and water served as eluent. In the experiments with 6-bromo-1-hexanol, a mixture of 30%

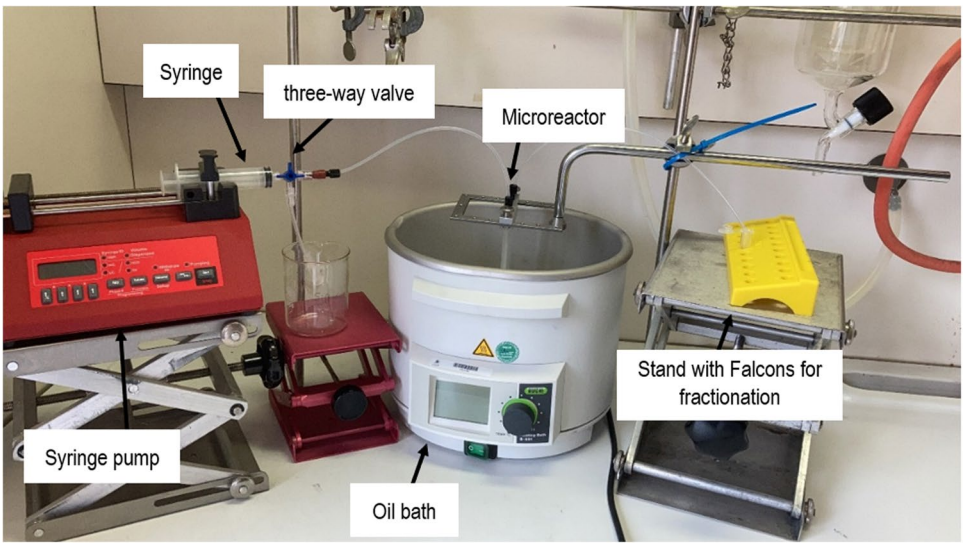


**Fig. 3** Set-up of the overall microreactor system

ethanol and 70% water was used, in the experiments with 8-bromo-1-octanola mixture of 30% ethanol and 70% water until DMSO was eluted. Subsequently, further purification was carried out with an eluent of 40% ethanol and 60% water. In the experiments with 10-bromo-1-decanol, a mixture of 40% ethanol and 60% water was used until the elution of the dibromide. Subsequently, further purification was carried out with an eluent of 50% ethanol and 50% water.

1H NMR and 13C NMR spectra were recorded on a Bruker Avance 200. Chemical shifts are reported in ppm relative to solvent signals (CDCl3: δH = 7.26 ppm, δC = 77.0 ppm; DMSO-d6: δH = 2.49 ppm, δC = 39.7 ppm; CD3OD: δH = 4.78 ppm, δC = 49.3 ppm). Signals were assigned by first-order analysis and assignments were supported, where feasible, by two-dimensional 1H, 1H and 1H, 13C correlation spectroscopy. Coupling constants are reported in Hz.

Electrospray ionization mass spectra (ESI) were performed on Sciex API QTRAP Mass Spectrometer (AB Sciex LLC, Framingham, MA, United States). The mass spectrometer was operated in the positive ion mode with an electrospray voltage of 5000 V at 200 °C, curtain gas at 25 psi, collision gas at 6 psi, nebulizing gas at 25 psi and auxiliary gas at 25 psi. All quadrupoles were working at unit resolution.

**6-Bromohexyl-α/β-D-glucopyranoside 5 (α/β ratio ~ 1.5:1)**

**$^{1}$H-NMR** (200.1 MHz, $CD_3OD$) **α-compound**: $\delta = 4.81$ (d, $J = 4.0$, 1H, H-1), 4.00–3.33 (m, 8H, H-2, H-3, H-4, H-5, H-6a, H-6b, $OCH_2$), 3.49 (t, $J = 6.6$, 2H, $BrCH_2$), 1.88 (quint, $J = 6.7$, 2H, $C\underline{H}_2CH_2Br$), 1.68 (m, 2H, $OCH_2C\underline{H}_2$), 1.49 (m, 4H, $2 \times CH_2$);

**β-compound**: $\delta = 4.29$ (d, $J = 7.8$, 1H, H-1), 4.00–3.33 (m, 7H, H-3, H-4, H-5, H-6a, H-6b, $OCH_2$), 3.49 (t, $J = 6.6$, 2H, $BrCH_2$), 3.21 (dd, $J = 8.7$, 7.8, 1H, H-2), 1.88 (quint, $J = 6.7$, 2H, $C\underline{H}_2CH_2Br$), 1.68 (m, 2H, $OCH_2C\underline{H}_2$), 1.49 (m, 4H, $2 \times CH_2$);

**$^{13}$C-NMR** (50.3 MHz, $CD_3OD$) **α-compound**: $\delta = 100.0$ (C-1), 77.8 (C-3), 75.1 (C-5), 73.6 (C-2), 71.8 (C-4), 68.9 ($O\underline{C}H_2$), 62.7 (C-6), 33.9 ($\underline{C}H_2Br$), 30.4 ($\underline{C}H_2CH_2Br$), 29.0 ($OCH_2\underline{C}H_2$), 26.4, 26.2 ($2 \times CH_2$);

**β-compound**: $\delta = 104.3$ (C-1), 78.1 (C-3), 75.1 (C-5), 73.5 (C-2), 71.6 (C-4), 70.7 ($O\underline{C}H_2$), 62.8 (C-6), 34.4 ($\underline{C}H_2Br$), 30.5 ($\underline{C}H_2CH_2Br$), 28.9 ($OCH_2\underline{C}H_2$), 26.4, 26.2 ($2 \times CH_2$);

**(ESI–MS): *m/z*** $[M + Na]^+$: 365.3;

TLC (RP): $R_f = 0.51$ (mobile phase: ethanol/water = 1:1.5, colouring agent Cerium(IV) ammonium nitrate).

**8-Bromooctyl-α/β-D- glucopyranoside 6 (α/β ratio ~ 1.25:1)**

**$^{1}$H-NMR** (200.1 MHz, $CD_3OD$) **α-compound**: $\delta = 4.79$ (d, $J = 3.7$, 1H, H-1), 3.99–3.29 (m, 8H, H-2, H-3, H-4, H-5, H-6a, H-6b, $OCH_2$), 3.46 (t, $J = 6.7$, 2H, $BrCH_2$), 1.87 (quint, $J = 7.0$, 2H, $C\underline{H}_2CH_2Br$), 1.66 (m, 2H, $OCH_2C\underline{H}_2$), 1.55–1.31 (m, 4H, $4 \times CH_2$);

**β-compound**: $\delta = 4.27$ (d, $J = 7.7$, 1H, H-13.99–3.29 (m, 7H, H-3, H-4, H-5, H-6a, H-6b, $OCH_2$), 3.46 (t, $J = 6.7$, 2H, $BrCH_2$), 3.19 (dd, $J = 8.9$, 7.7, 1H, H-2), 1.87 (quint, $J = 7.0$, 2H, $C\underline{H}_2CH_2Br$), 1.66 (m, 2H, $OCH_2C\underline{H}_2$), 1.55–1.31 (m, 4H, $4 \times CH_2$);

**$^{13}$C-NMR** (50.3 MHz, $CD_3OD$) **α-compound**: $\delta = 100.1$ (C-1), 77.9 (C-3), 75.1 (C-5), 73.6 (C-2), 71.9 (C-4), 69.1 ($O\underline{C}H_2$), 62.7 (C-6), 34.0 ($\underline{C}H_2Br$), 30.5 ($\underline{C}H_2CH_2Br$), 30.3 ($OCH_2\underline{C}H_2$), 29.8, 29.1 27.2, 27.0 ($4 \times CH_2$);

**β-compound**: $\delta = 104.3$ (C-1), 78.1 (C-3), 75.1 (C-5), 73.6 (C-2), 71.7 (C-4), 70.8 ($O\underline{C}H_2$), 62.8 (C-6), 34.4 ($\underline{C}H_2Br$), 30.7 ($\underline{C}H_2CH_2Br$), 30.5 ($OCH_2\underline{C}H_2$), 29.8, 29.1 27.2, 27.0 ($4 \times CH_2$);

**(ESI–MS): *m/z*** $[M + Na]^+$: 393.3;

TLC (RP): $R_f = 0.38$(mobile phase: ethanol/water = 1:1, colouring agent Cerium(IV) ammonium nitrate).

**10-Bromodecyl-α/β-D-glucopyranoside 7 (α/β ratio ~ 2:1)**

spectroscopic data are consistent with published ones [18].

**(ESI–MS): *m/z*** $[M + Na]^+$: 421.6;

TLC (RP): $R_f = 0.33$ (mobile phase: ethanol/water = 1:1, colouring agent Cerium(IV) ammonium nitrate).

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## Declarations

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** Informed consent not applicable.

**Conflicts of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. All Author declare that they have no conflict of interest.

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