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Bromobenzoylation of Methyl α-D-Mannopyranoside: Synthesis and Spectral Characterization

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Abstract. The widening importance of carbohydrate derivatives as unrivaled potential antimicrobial and therapeutic drugs has attracted attentionto the synthesis of mannopyranoside derivatives. In the present study, regioselective 3-bromobenzoylation of methyl α-D-mannopyranoside (1) was carried out using the direct method and gave the corresponding 6-*O*-(3-bromobenzoyl) derivative (2) in excellent yield. A number of 2,3,4-tri-*O*-acyl derivatives (3–10) of this 6-substitution product using a wide variety of acylating agents were also prepared in order to obtain newer derivatives of synthetic and biological importance. The chemical structures of the newly synthesized compounds were ascertained by analyzing their physicochemical, elemental, and spectroscopic data. Additionally, the X-ray powder diffraction (XRD) of these acylated products was studiedfor quantitatively identifying crystalline compounds.Therefore, due to the importance of carbohydrates, it might be useful to develop a good method for the synthesis of carbohydrate-based drugs of the current global situation for health and disease.

Keywords: methyl α-D-mannopyranoside, benzoylation, derivatives, spectroscopy, XRD.

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Бромобензоилирование метил α-D-маннопиранозида: синтез и спектральная характеристика

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Аннотация. Растущее значение производных углеводов как ценных потенциальных антимикробных и терапевтических препаратов привлекло внимание к синтезу производных маннопиранозида. В настоящем исследовании было выполнено региоселективное 3-бромбензоилирование метил-α-D-маннопиранозид (1) прямым методом и получено соответствующее производное 6-*O*-(3-бромбензоила) (2) с высоким выходом. Ряд 2,3,4-три-*O*-ацильных производных (3–10) указанного 6-замещенного продукта с использованием широкого спектра ацилирующих агентов был также создан с целью получения новых производных, имеющих синтетическую и биологическую важность. Химические структуры новых синтезированных соединений установлены путем анализа их физико-химических, элементных и спектроскопических данных. Кроме того, для количественной идентификации кристаллических соединений исследована рентгеновская порошковая дифракция (XRD) указанных ацилированных продуктов. Таким образом, учитывая важность углеводов, было бы полезно разработать надежный метод синтеза препаратов на основе углеводов в современной глобальной ситуации относительно вопросов здоровья и заболеваний.

Ключевые слова: метил-α-D-маннопиранозид, бензоилирование, производные, спектроскопия, рентгеновская дифракция.

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Introduction

Carbohydrates are an important class of natural products that belongs to the class of organic compounds found in living organisms on earth. They are involved in several processes of life such as glycolysis or glucogenesis [1]. In addition to their role as an energy source, they also play an important role in several biological signaling and recognition processes, such as immune response, inflammatory reactions, cancer metathesis and viral infections [2, 3]. Carbohydrates are frequentbuilding blocks for the synthesis of drugs. Since carbohydrates are highly functionalized molecules with several

stereocenters, their *de novo* synthesis is a challenging issue although, an arsenal of methods have been developed to facilitate their production. Unfortunately, most of the approaches are lengthy and require sophisticated protecting-group strategies [4].

All these processes are potential targets for therapeutic intervention and carbohydrate-based drugs are rapidly being engaged by the modern biotechnology and pharmaceutical industry [5]. Chemists and biochemists have developed new methods to rapidly synthesize oligosaccharides, enabling them to generate complex polysaccharides and analogs of natural products. However, carbohydrate researchers consider selective acylation as one of the most important and versatile methods for the protection of the hydroxyl groups. Various methods for selective acylation have so far been developed and successfully employed in carbohydrate chemistry [6-8]. Of these, the direct method is considered as one of the most effective and versatile [9].

From the literature survey, it was revealed that a large number of biologically active compounds contain aromatic, heteroaromatic and acyl substituents [10, 11]. Nitrogen, sulphur, and halogen-containing substituents are also known to enhance the biological activity of the parent compound [11, 12]. It is also known that if an active nucleus is linked to another active nucleus, the resulting molecule may show greater potential for biological activity [12]. The benzene and substituted benzene nuclei play an important role as a common denominator of various biological activities [13]. From our previous works we also observed that in many cases the combination of two or more acyl substituents in a single molecular framework enhances the biological activity by manyfold than their parent nuclei [14-16].

Encouraged by our findings [17-20] and also above literature reports, we synthesized a series of methyl α-D-mannopyranoside (1) (Fig. 1) derivatives deliberately incorporating a wide variety of probable biologically active components to the D-glucose moiety. The synthetic part is reported herefor the first time.

Experimental

Materials and methods

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Evaporation was performed under reduced pressure on a Buchi rotary evaporator. Thin-layer chromatography was performed on Kieselgel GF_{254} and visualization was accomplished by spraying the plates with 1% H_2SO_4, followed by heating at 150–200 °C until colouration took place. Column chromatography was performed with silica gel G_{60}. ^{1}H-NMR (400 MHz) (unless otherwise specified)

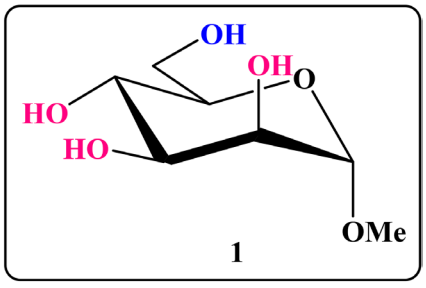

Fig. 1. Structure of themethyl α-D-mannopyranoside (1)

spectra were recorded for solutions in deuterochloroform (internal tetramethylsilane) with a Bruker nuclear magnetic resonance spectrophotometer. Infrared spectral analyses were recorded using a Fourier-transform infrared (FTIR) spectrophotometer (IR Prestige-21, Shimadzu, Japan) within 200–4000 cm^{-1}. Mass spectra of the synthesized compounds were obtained by liquid chromatography-electrospray ionization tandem mass spectrometry in positive ionization mode. All reagents used were commercially available Sigma-Aldrich (Germany) and were used as received unless otherwise specified.

Synthesis

Toward the goal of developing broadly useful strategies for organic synthesis, our research labof carbohydrate and nucleosidechemistry (LCNC) is intended to prepare a series of D-mannopyranoside derivatives for use as test compounds for biological evaluation. Additionally, over the past several years, LCNC has been actively engaged in the synthesis of carbohydrate derivatives containing various acyl groups to investigate their antibacterial, antifungal, anticancer properties with computational studies [21-23].

A solution of the methyl α-D-mannopyranoside (**1**) (100 mg, 0.51 mmol) in dry*N*, *N*-dimethylaniline (3 ml) was cooled to -5 °C when 3-bromobenzoyl chloride (0.07 ml, 1.1 molar eq.) was added. The solution was stirred at 0 °C for six hours and then kept standing overnight at room temperature. The reaction mixture was shaken with a few pieces of ice and then extracted with chloroform (3×3 ml). The organic layer was washed successively with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and distilled water. The organic layer was dried ($MgSO_4$), filtered and the filtrate evaporated off under reduced pressure to leave a syrup. Purification of the resulting syrupy residue was achieved by silica gel column chromatography with $CH_3OH/CHCl_3$ = 1/8 (v/v,R_f = *0.*51) as eluent to afford the 3-bromobenzoate derivative **2** (182.6 mg) which was used in the next stage.

Methyl 6-*O*-(3-bromobenzoyl)-α-D-mannopyranoside (2): Yield 80.30% as crystalline solid, M.P. 100–102 °C (EtOAC–C_6H_{14}), R_f = 0.51 ($CH_3OH/CHCl_3$ = 1/8, v/v). FTIR: ν_{max} 1685 (-CO), 3385–3420 cm^{-1} (br, -OH). ^{1}H -NMR (400 MHz, $CDCl_3$): δ_H8.01 (1H, s, Ar-H), 7.67 (1H, d, J = 7.7 Hz, Ar-H), 7.37 (1H, d, J = 7.6 Hz, Ar-H), 7.21 (1H, t, J = 7.6 Hz, Ar-H), 5.50 (1H, m, H-6a), 5.37 (1H, m, H-6b), 4.74 (1H, s, H-1), 4.18 (1H, d, J = 3.2 Hz, H-2), 4.09 (1H, t, J = 9.2 Hz, H-4), 4.00 (1H, dd, J = 3.1 and 9.3 Hz, H-3), 3.79 (1H, m, H-5), 3.41 (3H, s, 1-OC*H*$_3$). LC-MS $[M+1]^+$383.90.

Anal Calcd. for $C_{14}H_{23}O_7Br$: % C, 43.91, H, 6.04; found: % C, 43.93, H, 6.03.

General procedure for the direct 6-*O*-acylation of 2,3,4-tri-*O*-acyl derivatives (3-10)

A suspension of the 3-bromobenzoate derivative (**2**, 126 mg, 0.18 mmol) in dry *N*,*N*-dimethylaniline (3 ml) was cooled to 0 °C and treated with 3.3 molar equivalent ofbutyryl chloride (0.90 ml) with continuous stirring by maintaining 0 °C for 6-7 hours. Stirring was continued overnight at room temperature. TLC analyses showed the complete conversion of reactants into a single product. Work-up as described earlier and chromatographic purification with $CH_3OH/CHCl_3$ mixture as eluent, afforded the butyryl derivative **3** (120 mg) as a crystalline solid. Recrystallization from ethyl acetate-hexane gave the butyryl derivatives (**3**) as crystalline solid.

Similar reaction and purification method was employed to synthesize compounds **4** (120 mg), **5** (110 mg), **6** (150 mg), **7** (147 mg), **8** (110 mg), **9** (100 mg), and **10** (170 mg).

Methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-butyryl-α-D-mannopyranoside (3): Yield 84.0% as crystalline solid, M.P. 85–87 °C (EtOAC–C_6H_{14}), R_f = 0.53 ($CH_3OH/CHCl_3$ = 1/8, v/v). FTIR: ν_{max} 1687 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.83 (1H, s, Ar-H), 7.66 (1H, d, J = 7.5 Hz, Ar-H), 7.54 (1H, d, J = 7.5 Hz, Ar-H), 7.33 (1H, t, J = 7.5 Hz, Ar-H), 5.74 (1H, s, H-1), 5.68 (1H, d, J = 3.2 Hz, H-2), 5.19 (1H, dd, J = 3.1 and 9.1 Hz, H-3), 4.78 (1H, t, J = 9.2 Hz, H-4), 4.50 (1H, m, H-6a), 4.36 (1H, m, H-6b), 4.19 (1H, m, H-5), 3.42 (3H, s, 1-OCH_3), 2.36 {6H, m, 3×$CH_3CH_2CH_2$CO-}, 1.77 (6H, m, 3×$CH_3CH_2CH_2$CO-), 0.99 {9H, m, 3×C$H_3(CH_2)_2$CO-}. LC-MS $[M+1]^+$593.90.

Anal Calcd. for $C_{26}H_{41}O_{10}Br$: % C, 52.66, H, 6.96; found: % C, 52.68, H, 6.97.

Methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-pentanoyl-α-D-mannopyranoside (4): Yield 84.10% as crystalline solid, M.P. 138–140 °C (EtOAC–C_6H_{14}), R_f = 0.52 ($CH_3OH/CHCl_3$ = 1/8, v/v). FTIR: ν_{max} 1697 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.04 (1H, s, Ar-H), 7.86 (1H, d, J = 7.4 Hz, Ar-H), 7.74 (1H, d, J = 7.5 Hz, Ar-H), 7.36 (1H, t, J = 7.4 Hz, Ar-H), 5.24 (1H, s, H-1), 5.01 (1H, d, J = 3.3 Hz, H-2), 4.81 (1H, dd, J = 3.2 and 9.1 Hz, H-3), 4.66 (1H, t, J = 9.0 Hz, H-4), 4.52 (1H, m, H-6a), 4.16 (1H, m, H-6b), 4.02 (1H, m, H-5), 3.40 (3H, s, 1-OCH_3), 2.39 {6H, m, 3×$CH_3(CH_2)_2CH_2$CO-}, 1.48 (6H, m, 3×$CH_3CH_2CH_2CH_2$CO-), 1.31 {6H, m, 3×$CH_3CH_2(CH_2)_2$CO-}, 0.91 {9H, m, 3×C$H_3(CH_2)_3$CO-}. LC-MS $[M+1]^+$635.90.

Anal Calcd. for $C_{29}H_{47}O_{10}Br$: % C, 54.85, H, 7.45; found: % C, 54.87, H, 7.46.

Methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-hexanoyl-α-D-mannopyranoside (5): Yield 90.24% as crystalline solid, M.P. 88–90 °C (EtOAC–C_6H_{14}), R_f = 0.54 ($CH_3OH/CHCl_3$ = 1/8, v/v). FTIR: ν_{max} 1697 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.00 (1H, s, Ar-H), 7.76 (1H, d, J = 7.5 Hz, Ar-H), 7.72 (1H, d, J = 7.5 Hz, Ar-H), 7.28 (1H, t, J = 7.4 Hz, Ar-H), 5.20 (1H, s, H-1), 5.14 (1H, d, J = 3.3 Hz, H-2), 4.88 (1H, dd, J = 3.2 and 9.1 Hz, H-3), 4.60 (1H, t, J = 9.0 Hz, H-4), 4.41 (1H, m, H-6a), 4.36 (1H, m, H-6b), 4.11 (1H, m, H-5), 3.42 (3H, s, 1-OCH_3), 2.36 {6H, m, 3×$CH_3(CH_2)_3CH_2$CO-}, 1.61 {6H, m, 3×$CH_3(CH_2)_2CH_2CH_2$CO-}, 1.25 {12H, m, 3×$CH_3(CH_2)_2CH_2CH_2CH_2$CO-}, 0.89 {9H, m, 3×C$H_3(CH_2)_4$CO-}. LC-MS $[M+1]^+$677.90.

Anal Calcd. for $C_{32}H_{53}O_{10}Br$: % C, 56.77, H, 7.88; found: % C, 56.76, H, 7.89.

Methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-heptanoyl-α-D-mannopyranoside(6): Yield 71.31% as crystalline solid, M.P. 108–110 °C (EtOAC–C_6H_{14}), R_f = 0.51 ($CH_3OH/CHCl_3$ = 1/9, v/v). FTIR: ν_{max} 1685 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.05 (1H, s, Ar-H), 7.74 (1H, d, J = 7.6 Hz, Ar-H), 7.54 (1H, d, J = 7.6 Hz, Ar-H), 7.30 (1H, t, J = 7.6 Hz, Ar-H), 4.89 (1H, s, H-1), 4.74 (1H, d, J = 3.5 Hz, H-2), 4.71 (1H, dd, J = 3.3 and 9.0 Hz, H-3), 4.66 (1H, t, J = 9.1 Hz, H-4), 4.40 (1H, m, H-6a), 4.35 (1H, m, H-6b), 4.10 (1H, m, H-5), 3.44 (3H, s, 1-OCH_3), 2.36 {6H, m, 3×$CH_3(CH_2)_4CH_2$CO-}, 1.68 {6H, m, 3×$CH_3(CH_2)_3CH_2CH_2$CO-}, 1.38 {18H, m, 3×$CH_3(CH_2)_3CH_2CH_2$CO-}, 0.89 {9H, m, 3×C$H_3(CH_2)_5$CO-}. LC-MS $[M+1]^+$719.90.

Anal Calcd. for $C_{35}H_{59}O_{10}Br$: % C, 58.47, H, 8.26; found: % C, 58.46, H, 8.28%.

Methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-octanoyl-α-D-mannopyranoside (7): Yield 90.11% as crystalline solid, M.P. 121–123 °C (EtOAC–C_6H_{14}), R_f = 0.55 ($CH_3OH/CHCl_3$ = 1/8, v/v). FTIR: ν_{max} 1698 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.04 (1H, s, Ar-H), 7.67 (1H, d, J = 7.7 Hz, Ar-H), 7.53 (1H, d, J = 7.6 Hz, Ar-H), 7.33 (1H, t, J = 7.6 Hz, Ar -H), 5.09 (1H, s, H-1), 5.04 (1H, d, J = 3.5 Hz,

H-2), 4.88 (1H, dd, J = 3.3 and 9.0 Hz, H-3), 4.79 (1H, t, J = 9.1 Hz, H-4), 4.38 (1H, m, H-6a), 4.31 (1H, m, H-6b), 4.00 (1H, m, H-5), 3.42 (3H, s, 1-OCH_3), 2.36 {6H, m, 3×$CH_3(CH_2)_5CH_2$CO-}, 1.71 {6H, m, 3×$CH_3(CH_2)_4CH_2CH_2$CO-}, 1.29 {24H, m, 3×$CH_3(CH_2)_4(CH_2)_2$CO-}, 0.89 {9H, m, 3×$CH_3(CH_2)_6$CO-}. LC-MS $[M+1]^+$761.90.

Anal Calcd. for $C_{38}H_{65}O_{10}Br$: % C, 59.98, H, 8.60; found: % C, 59.99, H, 8.62.

Methyl 6-***O***-(3-bromobenzoyl)-2,3,4-tri-***O***-lauroyl-α-D-mannopyranoside (8): Yield 80.24% as crystalline solid, M.P. 109–111 °C (EtOAC–C_6H_{14}), R_f = 0.52 ($CH_3OH/CHCl_3$ = 1/8, v/v). FTIR: ν_{max} 1688 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.01 (1H, s, Ar-H), 7.78 (1H, d, J = 7.5 Hz, Ar-H), 7.59 (1H, d, J = 7.5 Hz, Ar-H), 7.41 (1H, t, J = 7.5 Hz, Ar-H), 5.11 (1H, s, H-1), 5.07 (1H, d, J = 3.6 Hz, H-2), 4.91 (1H, dd, J = 3.3 and 9.0 Hz, H-3), 4.71 (1H, t, J = 9.2 Hz, H-4), 4.35 (1H, m, H-6a), 4.30 (1H, m, H-6b), 4.07 (1H, m, H-5), 3.41 (3H, s, 1-OCH_3), 2.37 {6H, m, 3×$CH_3(CH_2)_9CH_2$CO-}, 1.66 {6H, m, 3×$CH_3(CH_2)_8CH_2CH_2$CO-}, 1.27 {48H, m, 3×$CH_3(CH_2)_8CH_2CH_2$CO-}, 0.91 {9H, m, 3×$CH_3(CH_2)_{10}$CO-}. LC-MS $[M+1]^+$929.90.

Anal Calcd. for $C_{50}H_{89}O_{10}Br$: % C, 64.65, H, 9.65; found: % C, 64.67, H, 9.66.

Methyl 6-***O***-(3-bromobenzoyl)-2,3,4-tri-***O***-palmitoyl-α-D-mannopyranoside (9): Yield 78.47% as crystalline solid, M.P. 100–102 °C (EtOAC–C_6H_{14}), R_f = 0.53 ($CH_3OH/CHCl_3$ = 1/9, v/v). FTIR: ν_{max} 1697 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.88 (1H, s, Ar-H), 7.71 (1H, d, J = 7.4 Hz, Ar-H), 7.66 (1H, d, J = 7.5 Hz, Ar-H), 7.40 (1H, t, J = 7.6 Hz, Ar -H), 5.06 (1H, s, H-1), 4.66 (1H, d, J = 3.5 Hz, H-2), 4.51 (1H, dd, J = 3.2 and 9.1 Hz, H-3), 4.41 (1H, t, J = 9.1 Hz, H-4), 3.85 (1H, m, H-6a), 3.70 (1H, m, H-6b), 3.67 (1H, m, H-5), 3.42 (3H, s, 1-OCH_3), 2.36 {6H, m, 3×$CH_3(CH_2)_{13}CH_2$CO-}, 1.69 {78H, m, 3×$CH_3(CH_2)_{13}CH_2$CO-}, 1.26 {9H, s, $(CH_3)_3$CCO-}, 0.90 {9H, m, 3×$CH_3(CH_2)_{14}$CO-}. LC-MS $[M+1]^+$1097.90.

Anal Calcd. for $C_{62}H_{113}O_{10}Br$: % C, 67.88, H, 10.37; found: % C, 67.87, H, 10.39.

Methyl 6-***O***-(3-bromobenzoyl)-2,3,4-tri-***O***-trityl-α-D-mannopyranoside (10): Yield 88.15% as crystalline solid, M.P. 111–113 °C (EtOAC–C_6H_{14}), R_f = 0.55 ($CH_3OH/CHCl_3$ = 1/9, v/v). FTIR: ν_{max} 1692 cm^{-1} (-CO). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 8.05 (1H, s, Ar-H), 7.85 (1H, d, J = 7.7 Hz, Ar-H), 7.66 (1H, d, J = 7.6 Hz, Ar-H), 7.36 (18H, m, 3×Ar-H), 7.33 (27H, m, 3×Ar-H), 7.31 (1H, t, J = 7.5 Hz, Ar -H), 5.23 (1H, s, H-1), 5.00 (1H, d, J = 3.7 Hz, H-2), 4.90 (1H, dd, J = 3.5 and 9.2 Hz, H-3), 4.61 (1H, t, J = 9.2 Hz, H-4), 4.25 (1H, m, H-6a), 4.22 (1H, m, H-6b), 4.16 (1H, m, H-5), 3.43 (3H, s, 1-OCH_3). LC-MS $[M+1]^+$1109.90.

Anal Calcd. for $C_{71}H_{65}O_7Br$: % C, 76.90, H, 5.90; found: % C, 76.92, H, 5.91.

X-ray powder diffraction

The single-crystal X-ray diffraction method is mainly used for structure determination while the X-ray powder diffraction method is mainly used for quantitative identification of crystalline compounds. The diffraction pattern of crystal structure also provides information on determining the dimension of the unit cell of the crystal lattice and the atomic arrangement within the cell. X-ray powder diffraction was performed using Rigaku Dmax2200PC diffractometer (Rigaku Corporation, Tokyo, Japan) and Cu Kα-radiation (ƛ=1.54060 A^o, intensity range 5° ≤ 2θ ≤ 90°) at 40 KeV and 40 mA and step length of 0.06^o with step time 1s in the scan range of 2θ from 0°–50° [24]. By using Bragg's law, the interlayer d-spacing was calculated. If h, k, and l represent the miller indices, the rules of the determination of crystal lattice type are as follows (Table 1).

Table 1. Rules of the determination of crystal lattice type

Lattice type	Rules for reflection to be observed
Primitive, P	None
Body centered, I	hkl; h+k+l= 2n
Face centered, F	hkl; h,k,l either all odd or all even
Side centered, C	hkl; h+k= 2n
Rhombohedral	hkl; -h+k+l= 3n or h-k+l= 3n

Results and discussion

Chemistry

The present work reported here was to study regioselective 3-bromobenzoylation ofmethyl α-D-mannopyranoside (**1**) using the direct method (Fig. 2). The resulting 3-bromobenzoylation products were converted to a number of derivatives using a series of acylating agents e.g., butyryl chloride, pentanoyl chloride, hexanoyl chloride, heptanoyl chloride, octanoyl chloride, lauroylchloride, palmitoyl chloride and trityl chloride (Table 2).

Characterization and selective 3-bromobenzoylation of mannopyranoside

Our initial effort was to treatment of methyl α-D-mannopyranoside (**1**) with 3-bromobenzoyl chloride as an acylating agent in dry DMF at –5 °C and after usual work-up, compound **2** was obtained in good yields. This compound was sufficiently pure for use in the next stages. However,

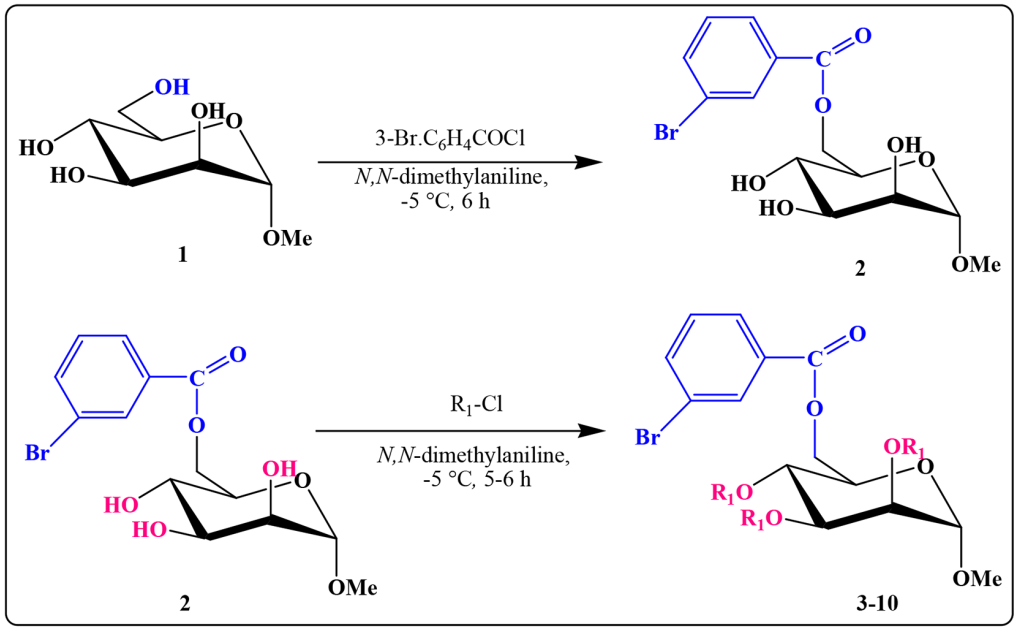

Fig. 2. Reagents and conditions: dry $HCON(CH_3)_2$, −5 °C, DMAP, stirrer for 5–6 h, R_1= several acyl halides (**3**–**10**)

Table 2. List of the synthesized compounds of methyl α-D-mannopyranoside derivatives (**2-10**)

Entry	Acyl group (**6-OH**)	Acyl group (R_1)
1	--	--
2	3-Br.C_6H_4CO-	--
3	3-Br.C_6H_4CO-	$CH_3(CH_2)_2CO$-
4	3-Br.C_6H_4CO-	$CH_3(CH_2)_3CO$-
5	3-Br.C_6H_4CO-	$CH_3(CH_2)_4CO$-
6	3-Br.C_6H_4CO-	$CH_3(CH_2)_5CO$-
7	3-Br.C_6H_4CO-	$CH_3(CH_2)_6CO$-
8	3-Br.C_6H_4CO-	$CH_3(CH_2)_{10}CO$-
9	3-Br.C_6H_4CO-	$CH_3(CH_2)_{14}CO$-
10	3-Br.C_6H_4CO-	Ph_3CO-

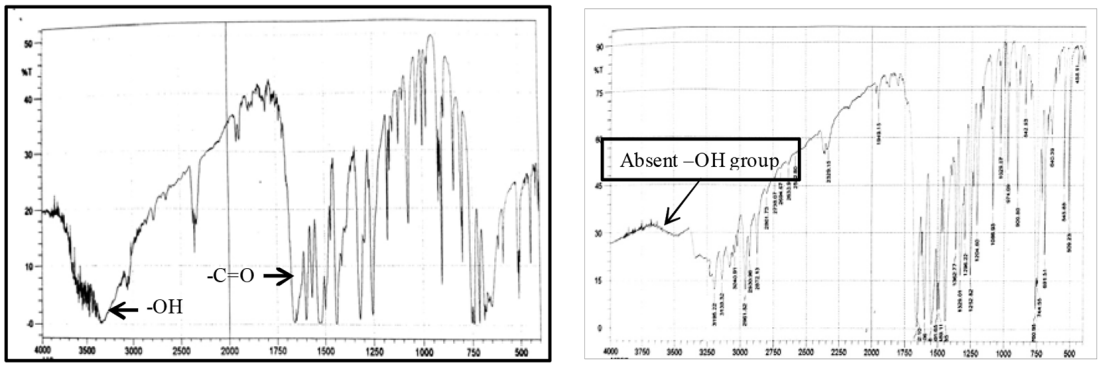

Fig. 3. IR spectrum of the compounds **2** (right) and **3** (left)

an analytical sample was prepared by recrystallization from ethyl acetate-hexane. The IR spectrum of compound **2** showed absorption bands at 1685 cm^{-1} (-CO stretching) and 3385-3420 cm^{-1} (br, -OH) (-OH stretching), thereby suggesting the presence of carbonyl and hydroxyl groups in the molecule (Fig. 3). In its ^{1}H-NMR spectrum the one-proton singlet at δ 8.01 (Ar-H), two one-proton doublets at δ 7.67 (J 7.7 Hz) and δ 7.37 (J 7.6 Hz), and one-proton triplet at δ 7.21 (J 7.6 Hz, Ar-H) corresponded to the aromatic protons inthe 3-bromobenzoyl group (Fig. 4). The large downfield shift of C-6 protons to δ 5.50 (as m, H-6a) and δ 5.37 (as m, H-6b) from their precursor (**1**) values and the resonances of other protons in their anticipated positions showed the attachment of 3-bromobenzoyl group less hindered and more reactive position at 6. Further support for the structure of compound **2** was achieved from its mass spectrum which displayed the molecular ion peak at *m/z*$[M+1]^+$ 383.90 that corresponded to the molecular formula of $C_{14}H_{23}O_7Br$. Complete analysis of the IR,^{1}H-NMR, and mass spectra of this compound was in agreement withmethyl 6-*O*-(3-bromobenzoyl)-α-D-mannopyranoside (**2**). This result is similar to that observed by Kawsar *et al.* [25].

The structure of compound **2** was supported by the preparation of its butyryl derivative **3**. IR spectrum showed only absorption band at 1687 cm^{-1} for -CO stretching but there is no –OH stretching band (Fig. 3). As expected the^1 H-NMR spectrumof this compound contained characteristics of two

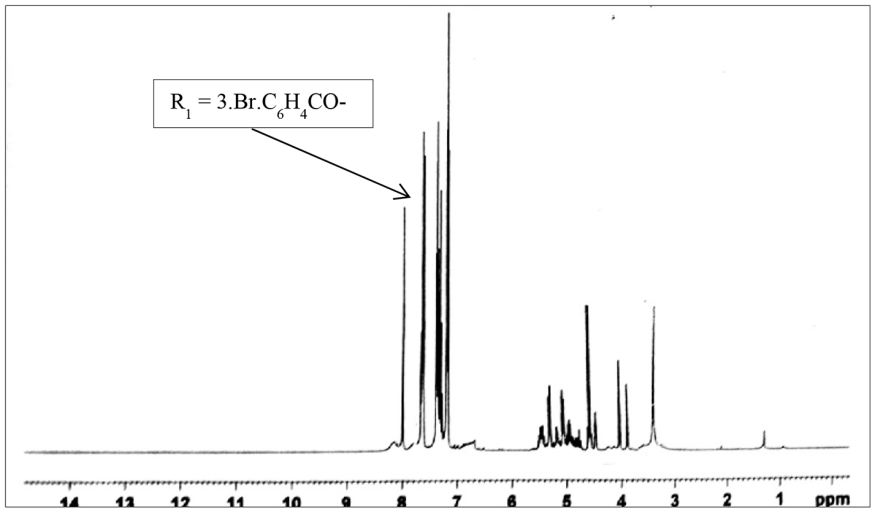

Fig. 4. ^{1}H-NMR spectra of the compound **2**

six-proton multiplets at δ 2.36 {3×$CH_3CH_2CH_2CO$-} and δ 1.77 {3×$CH_3CH_2CH_2CO$-} and nine-proton multiplet at δ 0.99 {3×$CH_3(CH_2)_2CO$-} corresponding to the one butyryl group. The downfield shifts of C-2 (δ 5.68, d, J 3.2 Hz, H-2), C-3 (δ 5.19, dd, J 3.1 and 9.1 Hz, H-3), and C-4 (δ 4.78, t, J 9.2 Hz, H-4), as compared to the precursor triol **2** (δ 3.72; δ 4.10; δ 4.18), indicated the attachment of the three butyryl groups at positions 2, 3 and 4. The mass spectrum of compound **3** contained a molecular ion peak at *m/z* $[M+1]^+$593.90 that corresponded to the same molecular formula, $C_{26}H_{41}O_{10}Br$. By complete analysis of the IR,^{1}H-NMR and massspectra, the structure of the tributyrate was ascertained as methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-butyryl-α-D-mannopyranoside (**3**). The structure of 3-bromobenzoyl derivative **2** was confirmed by preparing its pentanoyl derivative **4** with pentanoyl chloride.

Additional support for the structure accorded to compound (**2**) was obtained by its conversion to its hexanoyl derivative (**5**). Thus, the reaction of compound **2** with hexanoyl chloride at freezing temperature, furnished the compound (**5**) in excellent yields, 90.24%. The ^{1}H-NMR spectrum of the compound **5** displayed two six-proton multiplets at δ 2.36 {3×$CH_3(CH_2)_3CH_2CO$-}, and δ 1.61 {3×$(CH_3)_2CH_2CH_2CO$-}, twelve-proton multiplet at δ 1.25 {3×$CH_3(CH_2)_2CH_2CH_2CO$-} and nine-proton multiplet at δ 0.89 {3×$CH_3(CH_2)_4CO$-} showing the attachment of three hexanoyl groups in the molecule. The resonance for C-2, C-3 and C-4 appeared at δ 5.14, δ 4.88 and δ 4.60 which shifted downfield from their precursor values indicating the presence of the three hexanoyl groups. Complete analysis of all spectra enabled us to propose the structure of this compound as methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-hexanoyl-α-D-mannopyranoside (**5**). As same as the structure accorded to compound **2** was finally confirmed by transformation and identification of its heptanoy l**6**, octanoy **l7**, lauroy l**8**, and palmitoy l**9** derivatives and these structures were established by analysis of their spectroscopic data.

Finally, tritylation was carried out with an excess of trityl chlorideand isolated title derivative (**10**). In its ^{1}H-NMR spectrum two characteristic peaks; eighteen-proton multiplet at δ 7.36 (3×Ar-H) and a twenty-seven-proton multiplet at δ 7.33 (3×Ar-H) was due to the three trityl groups in the molecule. The rest of the protons resonated in their anticipated positions and this led us to propose a structure

of this compound as methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-trityl-α-D-mannopyranoside (**10**). The synthesis was found to be very promising since in all the cases, a single, mono-substitution product was isolated in reasonably high yields. These newly synthesized products may be used as important precursors for the modification of the mannopyranoside molecule at different positions.

XRD measurements

Crystallographic structures of the synthesized compounds (**7**, **8** and **10**) were evaluated by the X-ray powder diffraction at room temperature. All the compounds **7**, **8** and **10** showed many lines with high intensity in their X-ray diffraction pattern (Fig. 5 and 6) which indicates that all the compounds are well crystalline. The XRD pattern of the synthesis compounds ispresented in Table 3.

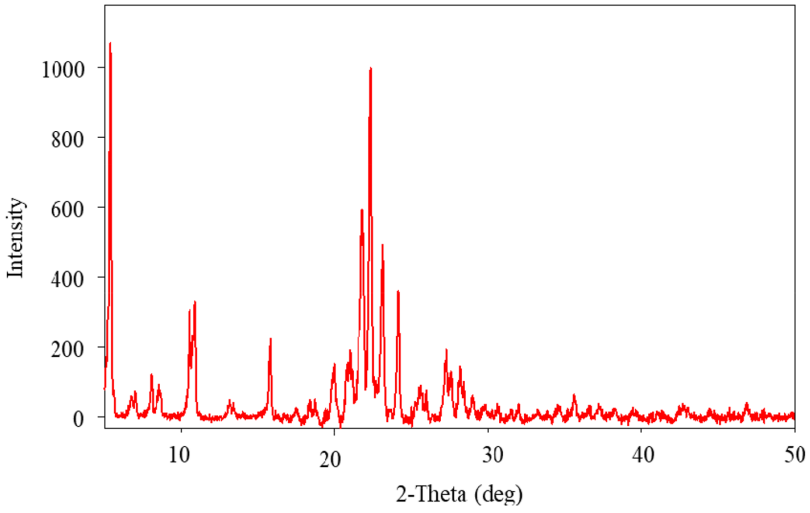

Fig. 5. XRD pattern of methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-octanoyl-α-D-mannopyranoside (**7**)

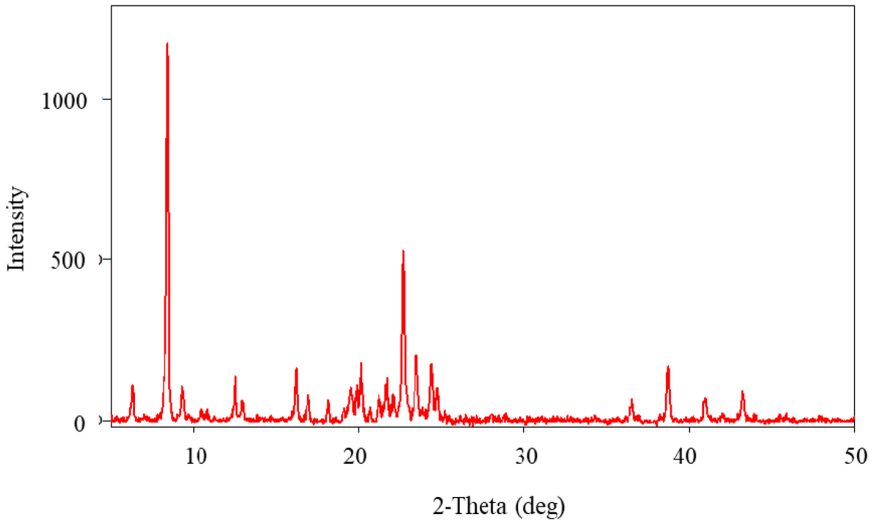

Fig. 6. XRD pattern of methyl 6-*O*-(3-bromobenzoyl)-2,3,4-tri-*O*-lauroyl-α-D-mannopyranoside (**8**)

The XRD patterns of the pure synthesized compounds under optimized conditions were displayed in the 2θ range of (0°–50°). The peaks at 2θ value corresponding to 5.391 & 21.846 (h,k,l: 110 & 400); 8.464 & 22.654 (h,k,l: 110 & 220) and 9.799 & 19.617 (h,k,l: 110 & 122) for compounds **7**, **8** and **10** respectively. These peaks indicated the formation of typical phases of compounds **7**, **8** and **10**. According to the phase analysis, compounds synthesized under this method have high purity and no impurities were detected in the XRD pattern. In addition by

Table 3. Peak lists of the compounds **7**, **8** and **10**

Compound No	Relative intensity	2θ (deg.)	θ (deg.)	$Sin^2\theta$	Ratio	$h^2+k^2+l^2$	(h k l)	d (ang)
7	V. Strong	5.391	2.6955	0.0022	1	100	100	16.38
	Weak	10.916	5.8805	0.0091	4	112	112	8.099
	Strong	21.846	10.923	0.0359	16	400	400	4.065
	Strong	22.351	11.1755	0.3375	17	223	223	3.974
	Medium	23.099	11.5495	0.040	18	330	330	3.847
8	V. Strong	8.464	4.232	0.0054	1	100	100	10.438
	Strong	22.654	11.327	0.0385	8	220	220	3.9218
	Weak	23.449	11.7245	0.0412	8	220	220	3.791
	Weak	24.383	12.1915	0.0445	8	220	220	3.647
	Weak	38.702	19.351	0.1097	20	224	224	2.324
10	Weak	9.799	4.8995	0.0073	1	100	100	9.019
	V. Strong	19.617	9.8085	0.0290	4	122	122	4.521
	Weak	20.267	10.1317	0.0309	4	122	122	4.3780
	Weak	20.794	10.397	0.0325	4	122	122	4.268

applying the rules (Table 1) for the determination of the lattice type, we have assigned the lattice structure of the synthesized compounds. It was found that compound **8** was satisfied the rule, h+k+l=2n and determined as a body-centered lattice and compound **7** also satisfied the rule, h+k=2n and ascertained as the side-centered lattice. Besides the compound **10** wasdiscerned as a primitive typein which no rule was followed.

Conclusion

In this paper, regioselective3-bromobenzoylation of methyl α-D-mannopyranoside (**1**) by applying the efficient direct method was unique in that the reaction provided a single mono-substitution product in reasonably good yields. The 3-bromobenzoylderivative **2** was further derivatized using a series of acyl chlorides. These acyl chlorides were deliberately chosen to introduce probably biologically prone atoms or groups to find biologically active D-mannopyranoside derivatives. Thus, structural modifications of the most active acylated derivatives determined in this study might provide favorable target compounds for further studies as potential antimicrobial agents.

Author contributions

S.M.A.K. designedthe whole study; F.Y and M.R.A. performed the synthetic experiment and A.H. accomplished XRD analysis. S.M.A.K. interpreted the spectral data and wrote the manuscript. All authors have read and approved the final version of this paper.

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Declaration of interest

The authors declare no conflict of interest.

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