SYNTHESIS, CHARACTERIZATION, *IN SILICO* OPTIMIZATION, AND CONFORMATIONAL STUDIES OF METHYL 4-*O*-PIVALOYL-α-L-RHAMNOPYRANOSIDES

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ABSTRACT Considering promising biological activities of natural and synthetic rhamnopyranoside esters, we have synthesized several methyl 4-*O*-pivaloyl-α-L-rhamnopyranosides *via* selective 2,3-*O*-acetonide protection of methyl α-L-rhamnopyranoside (**4**) followed by C-4 pivaloylation, and deprotection. The synthesized 4-*O*-pivaloate **7** and its 2,3-di-*O*-esters **8a-e** are characterized by spectroscopy and are optimized by using density functional theory (DFT). The free energy and bond angles thus calculated are used to establish the probable conformation(s). The 2,3-*O*-acetonide protected rhamnopyranosides **5-6** are found to be slightly distorted from the regular $^1C_4$ conformation, and exist between the chair and twist-boat (skew) conformation while other pivaloyl esters **7-8a-e** exist in regular $^1C_4$ chair conformation.

Keywords: Conformational study, DFT optimization, Methyl α-L-rhamnopyranoside, Pivaloyl esters, Protection-deprotection method.

1. INTRODUCTION

Carbohydrates are the most ubiquitous of all biological molecules, which play a pivotal role in many biological processes, and yet some of the least are understood (Gregurick et al., 1999). Unfortunately, several natural carbohydrate compounds possess poor binding affinities and pharmacokinetic properties (Hevey, 2019). Hence, their structural modification improves their applicability in various fields including drug candidates (Dhavale & Matin, 2005; Matin, 2006). Carbohydrate esters, especially monosaccharide-based sugar esters (SEs), exhibited diverse biological functions in all kinds of organisms (Matin et al., 2005). The presence of one or more lipophilic moieties (ester parts) and hydrophilic carbohydrate moiety improves their biodegradability, non-toxicity, and wide range of industrial and medicinal applications (Awual, 2017; Matin et al., 2019a; Kazmi et al., 2012; Matin et al., 2020a). For instance, the solubility and anti-carcinogenic properties of glucose aspirin ester (**1**, Figure 1) were improved eight to seven-fold and nine-fold, respectively, in comparison with original aspirin (Jacob & Tazawa, 2012).

Among the bioactive SEs, natural and synthetic rhamnopyranoside derived esters were found to be at the exigent level of importance due to chromogenic (Zhang et al., 2008), promising antimicrobial (Matin & Ibrahim, 2010; Kabir et al., 2002), antiviral (Matin et al., 2020b) and pharmacological properties (Matin, 2014; Matin et al., 2008). For example, naturally occurring novel rhamnopyranose esters (e.g. **2a-d**) exhibited excellent scaffolds for triple-negative breast cancer suppressive agents with very low IC_{50} values (4.95 μM) (Elmaidomy et al., 2020). L-Rhamnose derived dendron could display multivalent interactions with antibodies in anticancer immunotherapy (Alsarraf et al., 2020). The pyranonaphthoquinone antibiotics such as nanaomycin D, granaticin, kalafungin, and medermycin (**3**, Figure 1) contain methyl α-L-rhamnopyranoside (**4**; methyl 6-deoxy-α-L-mannopyranoside) as an important constituent which also renders improved antimicrobial, and antitumor activities with enhanced solubility (Shalaby et al., 1994a). Rhamnopyranoside esters can also be used for synthetic intermediates, and related bioactive products (Yadav et al., 2013).

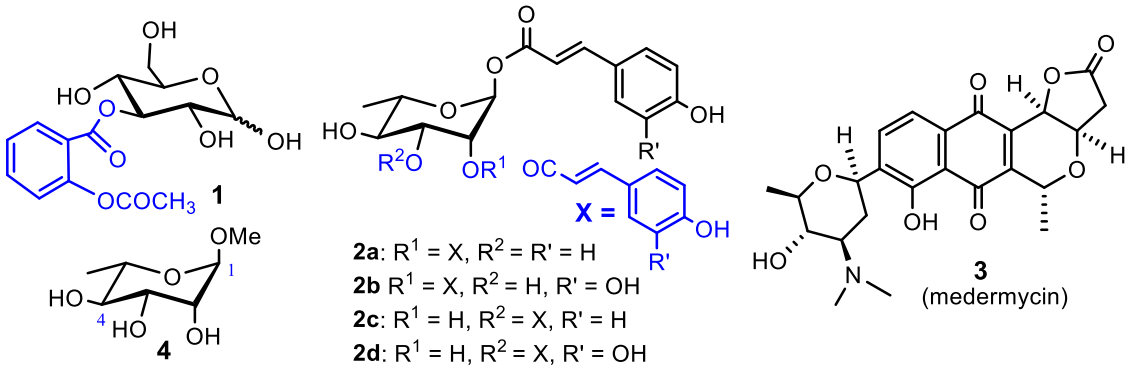


Figure 1. Pharmacologically active SEs **1**, **2a-d** and **3**.

However, esterification of rhamnopyranoside **4** at a certain position is always not possible as it contains three secondary hydroxyl groups of similar reactivity. It generally produces a mixture of mono-, di- and tri-*O*-acyl esters (Lawandi et al., 2016). Several methods such as direct (Kabir & Matin, 1996; Matin et al., 2020c), dibutyltin oxide (DBTO) (Kabir & Matin, 1994; Kabir & Matin, 1997), enzymatic (Luo et al., 2013), and catalytic methods (Liu et al., 2017; Matin et al., 2019b) were employed in the past decades. They have both advantages and shortcomings. In addition, their structural characterization is tedious and needs different analytical methods simultaneously (Bukowicki et al., 2015). It was observed (Kabir et al., 2003) that selective unimolar acylation of **4** employing both the direct and DBTO methods furnished regioselectivity at C-3 position only. Nevertheless, many bioactive rhamnopyranosides possess ester/substituents at the C-4 position. Keeping this in mind, we adopted the protection-deprotection technique (Matin et al., 2016) for esterification at the C-4 position, and reported herein. Many researchers reported that rhamnopyranoside **4** and its tri-*O*-acyl esters have $^1C_4$ conformation (Shalaby et al., 1994b). However, the incorporation of an isopropylidene ring between 2-OH and 3-OH positions along with bulky ester moieties might have changed their conformations. Hence, for conformational investigation, all the synthesized rhamnopyranosides **5-7** and **8a-e** are optimized by using DFT (density functional theory). The resulting conformations and molecular orbital properties are reported here.

2. EXPERIMENTAL

2.1. General methods and techniques

The chemicals and solvents used for the synthesis were commercially available (Aldrich), and were used as received. Some solvents were distilled before use. TLC (thin layer chromatography) was conducted on prepared silica gel plates (Kieselgel GF_{254}) and visualized by spraying 1% sulphuric acid with methanol followed by heating ~200 °C until the appearance of a blackish colour. Column chromatography (CC) was performed with silica gel G_{60} in different solvent systems and is duly mentioned. Infrared spectra of the compounds were taken on an FT-IR (IRPrestige-21 spectrophotometer, Shimadzu Scientific Instruments) in chloroform solution. Both the ^{1}H NMR and ^{13}C NMR spectra (Bruker DPX-400 spectrometer, Switzerland) were scanned in $CDCl_3$ solution. Delta (δ) scale (ppm, reference tetramethylsilane) was used for the chemical shifts. Coupling constant (*J*) values are presented in Hz. Elemental analyses (EA) were performed with a C,H-analyser (EuroVector, EA3100).

2.2. Synthesis of the compounds

Methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**5**): This mono-acetonide **5** was synthesized from methyl α-L-rhamnopyranoside (**4**) by treating with DMP (2,2-dimethoxypropane, as solvent and reagent) with catalytic *p*-toluenesulphonic acid in 96**% a**s a clear thick liquid according to reported procedure (Yadav et al., 2013; Lawandi et al., 2016).

Methyl 4-*O*-pivaloyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**6**): Pivaloyl chloride (1.824 g, 15.127 mmol) was added to a cooled solution of mono-acetonide **5** (3.0 g, 13.745 mmol) in dry pyridine (12 mL) followed by addition of catalytic amount of DMAP. After 12 h the reaction mixture was quenched with ice-water and extracted with organic solvent (DCM) in a separating funnel. Concentration of the combined extracts followed by CC purification gave pivaloyl ester **6** (4.076 g, 98%) as syrup. R_f = 0.48 (Petroleum ether (PE)-ethyl acetate = 10:1); FT-IR ($CHCl_3$): 1738 cm^{-1} (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.85 (s, 1H), 4.79 (dd, *J* = 10.1 and 7.3 Hz, 1H), 4.05-4.11 (m, 2H), 3.63-3.70 (m, 1H), 3.43 (s, 3H), 1.51 (s, 3H), 1.28 (s, 3H), 1.17 (s, 9H), 1.11 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.4, 109.7, 98.0, 75.9(2), 74.1, 63.9, 54.9, 38.7, 27.6, 26.4, 27.1(3), 17.0; Anal. Calcd. for $C_{15}H_{26}O_6$ (302.37): C, 59.58; H, 8.67. Found: C, 59.66; H, 8.73.

Methyl 4-*O*-pivaloyl-α-L-rhamnopyranoside (**7**): Reaction of the mono-ester **6** (3.0 g, 9.922 mmol) with AcOH (96%) (20 mL) below 40 ºC was conducted for 9-10 h. Usual concentration, co-evaporation with toluene followed by chromatographic purification gave pivaloate **7** (2.160 g, 83%) as a thick liquid. R_f = 0.49 (PE-ethyl acetate = 1:1); FT-IR ($CHCl_3$): 3440-3190 (OH), 1739 cm^{-1} (CO); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.75 (t, *J* = 9.8 Hz, 1H), 4.70 (s, 1H), 3.90 (d, *J* = 3.4 Hz, 1H), 3.82 (dd, *J* = 9.8 and 3.4 Hz, 1H), 3.73-3.79 (m, 1H), 3.36 (s, 3H), 2.65-2.81 (s, 2O*H*), 1.20 (br s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 179.7, 100.5, 75.3, 74.8, 70.4, 65.4, 55.1, 39.0, 27.1(3), 17.4; Anal. Calcd. for $C_{12}H_{22}O_6$ (262.30): C, 54.95; H, 8.45. Found: C, 55.01; H, 8.44.

2.2.1. General method for 2,3-di-O-esterification of pivaloate 7

For the preparation of 2,3-di-*O*-esterification of **7**, the direct method was used. In this method, the diol **7** (0.2 g, 0.762 mmol) in basic pyridine solution was added to different acylating agents (2.2 eq.) at 0 ºC. A small quantity of 4-dimethylamino pyridine (DMAP) was also added to this solution. Stirring was

continued for several hours at 25 ºC until the completion of the reaction. After completion, the reaction was stopped with ice-water and extracted with organic solvent (DCM). Work-up, concentration, and purification through silica gel CC (gradient elution with petroleum ether (PE) to PE-ethyl acetate) gave the desired rhamnopyranoside related novel esters **8a-e** reasonably in good yields.

Methyl 2,3-di-*O*-acetyl-4-*O*-pivaloyl-α-L-rhamnopyranoside (**8a**): Syrup (97%); R_f = 0.51 (PE-ethyl acetate = 10:1); FT-IR ($CHCl_3$): 1736, 1729(2) cm^{-1} (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.28 (dd, *J* = 10.2 and 3.4 Hz, 1H), 5.18 (d, *J* = 3.4 Hz, 1H), 5.03 (t, *J* = 10.0 Hz, 1H), 4.58 (s, 1H), 3.78-3.85 (m, 1H), 3.35 (s, 3H), 2.10 (s, 3H), 1.91 (s, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.4, 170.1, 169.7, 98.5, 70.5, 69.9, 69.0, 66.4, 55.1, 38.8, 26.9(3), 20.8, 20.6, 17.3; Anal. Calcd. for $C_{16}H_{26}O_8$ (346.38): C, 55.48; H, 7.57. Found: C, 55.56; H, 7.60.

Methyl 2,3-di-*O*-methanesulphonyl-4-*O*-pivaloyl-α-L-rhamnopyranoside (**8b**): Thick oil (91%); R_f = 0.53 (PE-ethyl acetate = 10:1); FT-IR ($CHCl_3$): 1734 (CO), 1362, 1359 cm^{-1} (SO_2); ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.00-5.07 (m, 3H), 4.85 (s, 1H), 3.80-3.86 (m, 1H), 3.40 (s, 3H), 3.15 (s, 3H), 3.05 (s, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.2, 98.5, 75.8, 74.2, 69.4, 66.6, 55.4, 39.0, 38.6, 38.9, 27.1(3), 17.3; Anal. Calcd. for $C_{14}H_{26}O_{10}S_2$ (418.48): C, 40.18; H, 6.26. Found: C, 40.22; H, 6.34.

Methyl 2,3-di-*O*-octanoyl-4-*O*-pivaloyl-α-L-rhamnopyranoside (**8c**): Yellow liquid (87%); R_f = 0.57 (PE-ethyl acetate = 10:1); FT-IR ($CHCl_3$): 1744(2), 1737 cm^{-1} (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 5.24 (dd, *J* = 9.9 and 3.2 Hz, 1H), 5.20 (d, *J* = 3.2 Hz, 1H), 5.00 (t, *J* = 9.8 Hz, 1H), 4.59 (s, 1H), 3.66-3.74 (m, 1H), 3.37 (s, 3H), 2.33 (t, *J* = 7.7 Hz, 4H), 1.55-1.64 (m, 4H), 1.21-1.36 (br s, 16H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.11 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.0, 172.6, 172.2, 98.9, 72.2, 69.6, 69.2, 66.0, 55.1, 38.8, 34.1, 31.6, 29.5(4), 29.3, 29.0, 28.8, 25.0, 24.3, 22.6, 27.3(3), 17.3, 14.0, 13.9; Anal. Calcd. for $C_{28}H_{50}O_8$ (514.69): C, 65.34; H, 9.79. Found: C, 65.40; H, 9.82.

Methyl 2,3-di-*O*-(2-chlorobenzoyl)-4-*O*-pivaloyl-α-L-rhamnopyranoside (**8d**): Syrup (82%); R_f = 0.55 (PE-ethyl acetate = 10:1); FT-IR ($CHCl_3$): 1735, 1695, 1688 cm^{-1} (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.26-7.48 (m, 5H), 7.16-7.22 (m, 1H), 5.73 (dd, *J* = 10.1 and 3.0 Hz, 1H), 5.60 (d, *J* = 3.0 Hz, 1H), 5.39 (t, *J* = 9.9 Hz, 1H), 4.83 (s, 1H), 3.95-4.01 (m, 1H), 3.41 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.3, 164.5, 164.0, 134.1, 134.0, 133.0, 132.9, 131.8(2), 131.1, 130.8, 129.0, 128.6, 126.6, 126.5, 98.3, 71.1, 70.7, 69.9, 66.5, 55.2, 38.7, 26.9(3), 17.4; Anal. Calcd. for $C_{26}H_{28}Cl_2O_8$ (539.40): C, 57.89; H, 5.23. Found: C, 57.95; H, 5.28.

Methyl 2,3-di-*O*-(4-chlorobenzoyl)-4-*O*-pivaloyl-α-L-rhamnopyranoside (**8e**): Syrup (85%); R_f = 0.56 (PE-ethyl acetate = 10:1); FT-IR ($CHCl_3$): 1742, 1696, 1680 cm^{-1} (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.97 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.63 (dd, *J* = 10.1 and 3.1 Hz, 1H), 5.55 (d, *J* = 3.1 Hz, 1H), 5.36 (t, *J* = 10.0 Hz, 1H), 4.83 (s, 1H), 4.00-4.07 (m, 1H), 3.46 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.1, 164.7, 164.4, 140.1, 139.0, 131.2(2), 130.8, 129.4, 129.0, 128.5, 127.0(2), 98.6, 70.9, 70.7, 70.0, 66.3, 55.5, 38.6, 26.9(3), 17.5; Anal. Calcd. for $C_{26}H_{28}Cl_2O_8$ (539.40): C, 57.89; H, 5.23. Found: C, 57.98; H, 5.29.

2.3. Computational details

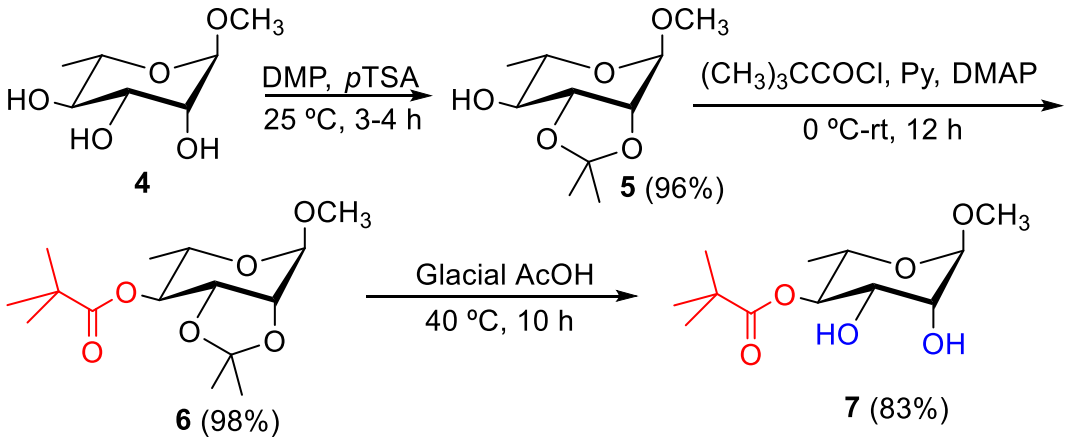
Nowadays various computational techniques and molecular mechanics are getting popular to the researchers to solve the essential structural and conformational outcome of sugar molecules (Mainal et al., 2001). In this context, to fulfil our objectives the computations of the geometries and energies of the rhamnopyranoside **4**, and its esters **5-8a-e** are conducted by using the density functional theory (DFT). The initial geometry of methyl α-L-rhamnopyranoside (**4**) was downloaded from the online database structure namely ChemSpider. The other ester **5-7** and **8a-e** structures were built with the GaussView (5.0) program (Frisch et al., 2013). The structures **4-7** and **8a-e** were then optimized with the Gaussian 09 program. We have opt density functional theory (B3LYP)/6-311G (*d*,*p*) and (B3LYP)/6-311G, ++, (*d*,*p*) level basis sets (Matin & Chakraborty, 2020; Matin et al., 2020d). For conformational study we have optimized compound **4**, **5C**, **5TB**, **5B**, **6C**, **6TB**, **6B** and **7** with (B3LYP)/6-311G, ++, (*d*,*p*) basis set which took 2-4 days for optimization per compound.

3. RESULTS AND DISCUSSION

3.1. Preparation of regio-selective 4-O-pivaloylrhamnopyranoside

Deoxy-monosaccharides especially rhamnopyranoside like **4** type compounds have a particular interest in their applications as intermediates during the research of branched-chain deoxy sugars and C-4 substituted rhamnose which mimics many natural products of biological importance (Shalaby et al., 1994a). Thus, we carried out regio-selective pivaloylation of the rhamnopyranoside **4** using the protection-deprotection technique. The study was extended with further di-*O*-derivatization, the establishment of conformation, and thermodynamic property calculations.

Methyl α-L-rhamnopyranoside (**4**) on reaction with DMP and *p*TSA (cat.), using literature procedure (Matin et al., 2016), gave the 2,3-*O*-monoacetonide **5** in 96% yield. Here the isopropylidene selectively formed at *cis*-vicinal glycol system between C-2 and C-3 hydroxyl groups. Having protected rhamnopyranoside **5** in hand, we conducted its unimolar pivaloylation with pivaloyl chloride in pyridine and obtained a faster-moving syrup in excellent yield (Scheme 1).



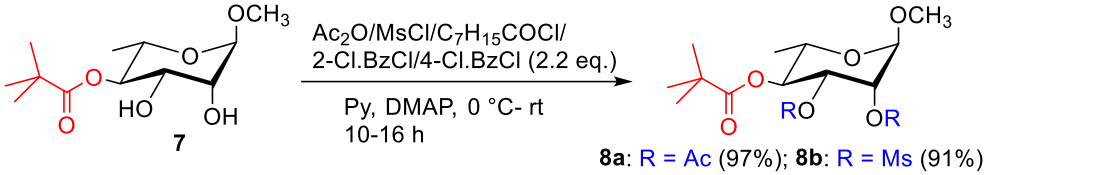
Scheme 1. Synthesis of regio-selective ester **7**.

The infrared spectrum showed a characteristic carbonyl peak at 1738 cm^{-1}, whereas the OH stretching band was totally absent there and thus indicated attachment of the pivaloyl group in the molecule. Again, its proton NMR showed a characteristic nine-proton singlet at δ 1.17 for the pivaloyl (trimethyl acetyl) group in this molecule. Related other protons appeared in the anticipated positions (Kabir et al., 2002). This fact was also confirmed by analysing its carbon NMR spectrum where pivaloyl-related extra carbon signals (at δ 177.4, 38.7, and 27.1(3)) were observed. More importantly, the proton at C-4 position appears very downfield (at δ 4.79) when compared with its precursor acetonide **5** (at δ 3.28-3.33) (Kabir et al., 2002). This vital observation ultimately confirmed the addition of only one pivaloyl group at position C-4 of this syrupy compound. All these data along with elemental analysis (EA) established the structure of this synthesized syrup as **6**.

In the next step, as shown in Scheme 1, removal of the acetonide functionality was conducted by treating mono-acetonide **6** with AcOH at ~40 ºC for several hours, followed by CC which provided a liquid in good yield. The new appearance of the OH stretching band at 3440-3190 cm^{-1} in its infrared spectrum demonstrated the removal of the acetonide group. More evidence in favour of this observation was found from its proton and carbon NMR spectral analyses where methyl signals related to the acetonide group were completely absent. However, a broad singlet exchangeable with D_2O and integrated for two protons at δ 2.65-2.81 was found, and thus, confirmed the deprotection of the acetonide group from the molecule. The rest of the proton and carbon NMR spectra along with DEPT-135 and EA established the structure as **7**.

3.2. Conversion of 7 into novel 2,3-di-O-acyl esters 8a-e

Due to our continuous interest to search newer derivatives of rhamnopyranoside, we have synthesized five new 2,3-di-*O*-ester derivatives of pivaloate **7** (as it has free C-2 OH and C-3 OH). The newer five acylating agents used were Ac_2O, MsCl, $C_7H_{15}COCl$, 2-chlorobenzoyl chloride, and 4-chlorobenzoyl chloride. The reaction of the pivaloate **7** and dimolar Ac_2O in the solvent pyridine (catalytic DMAP) followed by CC furnished a faster-moving thick syrup (97%; Scheme 2).



Scheme 2. Preparation of **8a-e**.

The FT-IR spectrum showed carbonyl bands at 1736 and 1729(2) cm^{-1}, and the absence of the OH band indicated the addition of acetyl group(s) in this product. This was initially supported by analysing its proton NMR spectrum wherein two singlets at δ 2.10 and 1.91, each integrated for three protons, were assigned for two acetyl groups. Also, protons of C-2 and C-3 positions were found to shift downfield at δ 5.18 and 5.29, respectively than the precursor diol **7** (δ 3.90 and 3.82, respectively). This rendered that acetyl groups are incorporated with 2-OH and 3-OH. Further evidence in this favour comes from its ^{13}C NMR spectrum where related carbon signals resonated at δ 170.1, 169.7 (CH_3CO), 20.8, and 20.6 (CH_3CO). DEPT-135 showed the absence of methylene carbons (CH_2) in it.

Corroboration of all the spectral and analytical results confirmed its structure as **8a** (Scheme 2).

Having successful preparation of **8a**, similar reaction, work-up, and purification were employed for diol **7** with mesyl chloride and obtained an oil (91%; Scheme 2). In addition to the CO stretching band (1734 cm^{-1}) it showed characteristic SO_2 stretching bands at 1362, and 1359 cm^{-1} in its infrared spectrum. Its ^1H NMR showed mesyl characteristic protons at δ 3.15 (s, 3H, SO_2CH_3) and 3.05 (s, 3H, SO_2CH_3). Mesyl groups related to carbon signals were observed at δ 39.0 and 38.6 in its carbon NMR spectrum. Its DEPT spectrum showed an absence of CH_2 carbons. On the basis of all spectroscopic and analytical data, the structure was given as **8b**.

The reaction of the same pivaloate **7** with dimolar octanoyl chloride furnished a liquid in 87% yield (Scheme 2). Its infrared spectrum exhibited characteristic bands at 1744(2) and 1737 cm^{-1} (CO). Additional thirty protons in its proton NMR spectrum, compared to its precursor diol **7**, in the aliphatic region [2.33 (t, 4H) 1.55-1.64 (m, 4H) 1.21-1.36 (s, 16H), 0.86 (t, 6H)] were assigned for two octanoyloxy groups. Considering the downfield shift of the protons of C-2 and C-3 positions, ^{13}C NMR, and DEPT-135 analyses this liquid compound was named as **8c**.

Again, treatment of **7** with 2-chlorobenzoyl chloride gave a faster-moving compound (82%; Scheme 2). Its FT-IR showed characteristic bands at 1735, 1695, 1688 cm^{-1} (CO), and no bands in the OH region. In the proton NMR spectrum, it showed a total of eight aromatic protons corresponding to the two chlorobenzoyl groups which were absent in its starting molecule. Compiling all spectral and EA data the compound was confirmed as **8d** (Scheme 2).

Lastly, the reaction of **7** and 4-chlorobenzoyl chloride furnished syrup in 85% (Scheme 2). Its FT-IR spectrum exhibited bands at 1742, 1696, and 1680 cm^{-1}. Extra eight aromatic protons appeared in its proton NMR spectrum indicating the presence of two 4-chlorobenzoyl groups in the molecule. ^{13}C NMR spectrum also confirmed related signals at δ 164.7, 164.4 (2×CO), 140.1, 139.0, 131.2(2), 130.8, 129.4, 129.0, 128.5 and 127.0(2) (Ar-*C*). It has thus given the structure as **8e**.

3.3. Conformational analysis

The conformational behaviours of bioactive compounds are the basic factor for interactions with receptor proteins (Sawada et al., 2006). In addition to spectroscopic methods quantum mechanical techniques have been used for the structure and conformation elucidation (Noorbatcha et al., 2002). Considering biological utility various workers reported that methyl α-L-rhamnopyranoside (**3**) (Matin et al., 2021; Shalaby et al., 1994a), methyl 4-*O*-benzyl-α-L-rhamnopyranoside (**9**) (Pendrill et al., 2014), and methyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (**10**) (Shalaby et al., 1994b) exist in $^1C_4$ conformation from their X-ray crystal structures (Figure 2).

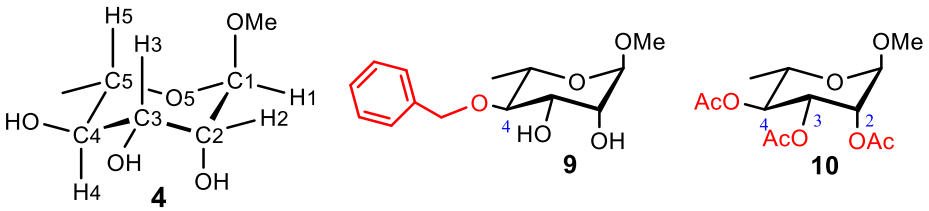


Figure 2. Rhamnopyranoside **4**, **9** and **10**.

In compounds **5** and **6**, the presence of a fused isopropylidene group with the pyranose ring, and in **7**-**8a-e** the presence of bulky acyl group might have created an extra distortion towards the ring. Hence, we optimized all the compounds **4**-**8a-e** with the DFT at the RB3LYP level of theory using a 6-311G (*d*,*p*) basis set. A similar type of RB3LYP level of theory was used by Sawada et al. (2006) for the conformational study of a biomolecule named neuraminic acid. The optimized structures at 298.15 K (1.0 atm) are shown in Figure 3. All the compounds **4**-**8a-e** were found to have C1 symmetry.

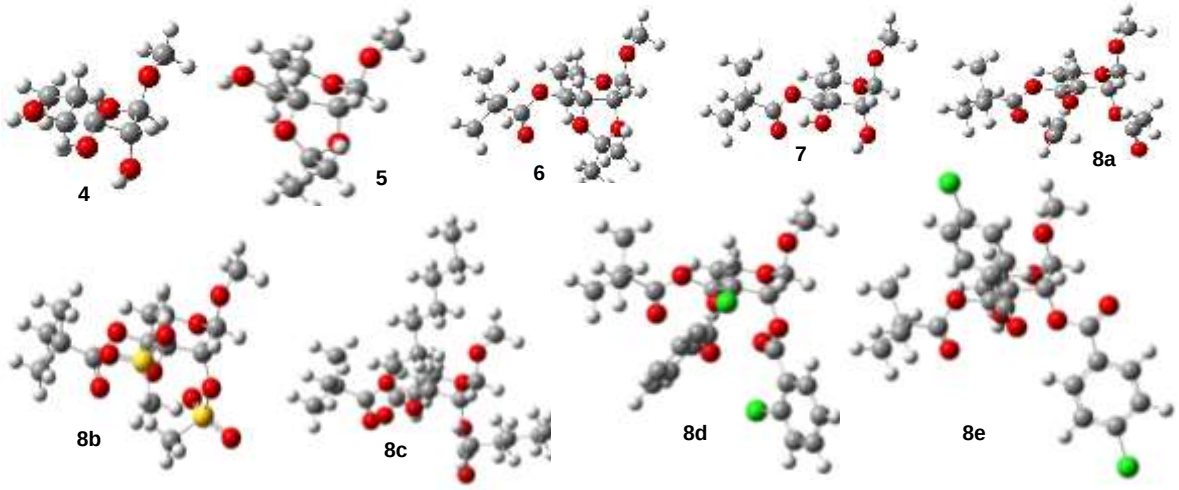


Figure 3. DFT optimized structures of rhamnopyranoside **4**-**8a-e**.

The study indicated that the optimized structure of acetonide-protected **5** (chair, **5C**) and **6** (chair, **6C**) didn't match properly with $^1C_4$ conformation. While rhamnopyranoside **4** and its non-acetonide esters **7**-**8a-e** exist almost in normal $^1C_4$ conformation. Their selected ring bond angles and dihedral angles, as shown in Table 1, indicated that in acetonide compound **5** and **6** bond angles at ∠O5-C1-C2, ∠C1-C2-C3 and ∠C2-C3-C4 increased, while at ∠C4-C5-O5 and at ∠C5-O5-C1 decreased than the parent rhamnopyranoside **4**. Again, the dihedral angle at ∠H1-C1-C2-H2 increased (~9º), whereas, decreased considerably at ∠H2-C2-C3-H3 (~17-19º) and ∠H3-C3-C4-H4 (~14-16º) compared to **4**. This huge change in dihedral angle caused the deviation of **5** and **6** from regular $^1C_4$ conformation. With the opening of the acetonide group, as in **7**, both the bond angles and dihedral angles appeared almost similar to the rhamnopyranoside **4** indicating the appearance of regular $^1C_4$ conformation.

Table 1. Bond angle and dihedral angle of rhamnopyranoside **4**-**7**.

Compound	Bond angle in degree					
	O5-C1-C2	C1-C2-C3	C2-C3-C4	C3-C4-C5	C4-C5-O5	C5-O5-C1
4	112.5	110.5	110.6	109.7	109.1	116.9
5	113.9	115.5	113.6	110.3	107.3	115.3
6	113.8	115.9	112.7	110.9	107.2	115.2
7	112.8	110.6	110.5	110.1	108.6	115.8
	Dihedral angle in degree					
	H1-C1-C2-H2	H2-C2-C3-H3	H3-C3-C4-H4	H4-C4-C5-H5		
4	74.93	50.69	-176.70	-178.27		
5	85.10	31.58	-162.93	-176.37		
6	84.29	32.71	-160.08	-179.65		
7	75.47	50.27	-174.39	176.45		

*All these values were calculated from 6-311G (++) (*d*,*p*) sets.

For clarification and validation of the above deviation properly, we have also optimized twist-boat (**5TB**, **6TB**) and boat (**5B**, **6B**) of both the acetonide-protected rhamnopyranosides. However, as shown in Table 2 and Figure 4, the chair form possessed the minimum energy among the chair, twist-boat, and boat of each of **5** and **6**.

Table 2. Optimized minimum free energy of protected rhamnopyranoside **5** and **6**.

Conformer	Minimum energy (Hartree)	Conformer	Minimum energy (Hartree)
5C	-768.22683451	**6C**	-1038.90227022
5TB	-768.22510886	**6TB**	-1038.89662104
5B	-768.22510881	**6B**	-1038.87585582

*All these values were calculated from 6-311G (++) (*d*,*p*) basis set. C = chair; TB = twist-boat; B = boat. (1 Hartree = 627.509 kcal/mol)

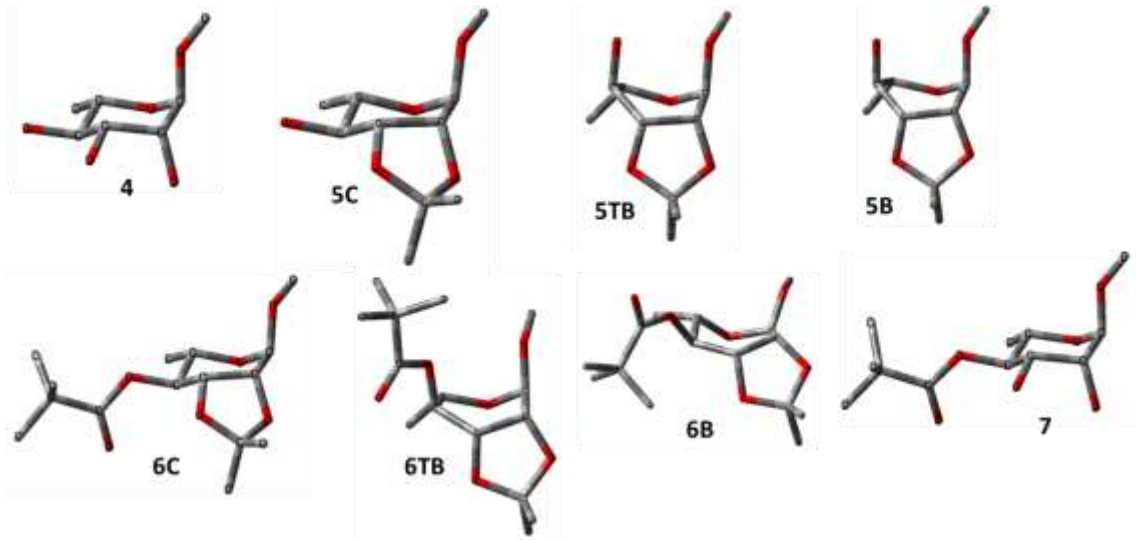


Figure 4. DFT optimized conformers of protected rhamnopyranoside **4**-**7**.

The lowest free energy was found for chair conformation for both the compounds (**5C** and **6C**). **5C** bears 1.083 kcal/mol lower energy than **5TB** and **5B** indicating more stability of chair conformation. However, **5C** didn't completely match with $^{1}C_{4}$ conformation (Figure 4) having slight distortion at C1, C2, C3, and O5 positions. This is further supported by the observed conformational

relationship between two adjacent carbons such as C1(OMe)-C2(O) has slightly deviated anti, C2(O)-C3(O) deviated to eclipsed (in compound **4** gauche), and C3(O)-C4(O) remains gauche. Actually, it is in between the chair and twist-boat conformation.

Similarly, the lowest free energy was found for the **6C** conformation, which was stabilized by 3.55 kcal/mol from **6TB**, and 16.58 kcal/mol from **6B** (Table 2). The bulky pivaloyl group at the C4 axial position caused more repulsive steric interactions with the C1 axial OCH_3 group in the conformers **6TB** and **6B**. Thus, conformer **6C** with 2,3-*O*-isopropylidene group deviates from proper $^1C_4$ conformation (Figure 4) at C1, C2, C3, and O5 positions, and adopts slightly distorted $^1C_4$ conformation.

3.4. Molecular orbital analysis

Finally, molecular orbitals of **4**-**8a-e** in the forms of HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energy levels, their gaps (Δε) hardness, softness, and dipole moments (DM) are calculated from their optimized structures (Muhammad et al., 2021). These results as presented in Table 3 indicated that acetonide-protected compound **5** (C, TB, and B forms) possess slightly lower Δε than the non-acetonide compounds **4**, **7**, and **8a-e**. Incorporation of pivaloyl groups at C-4 positions of **5**, as in **6**, slightly increased Δε value. Removal of acetonide group (**7**) and further addition of acyl groups (**8a-e**) increased their HOMO-LUMO gaps. The higher gaps (Δε) are indicators of lower chemical softness (as observed in Table 3) and higher kinetic stability of the molecules. Interestingly, chair conformations (as in **5C** and **6C**, Figure 5) possess the smallest gaps among the chair (C), twist boat (TB), and boat (B) forms (Table 3) indicating their more reactive nature with higher softness. Dipole moments of **5C** and **6C** were found lower than that of the **5B** and **6B**.

Table 3. Orbitals and related properties of **4**-**8a-e**.

Mol.	εHOMO (eV)	εLUMO (eV)	Gap (Δε, eV)	Hardness (η)	Softness (S)	DM (Debye)
4	-7.2184	0.5165	6.7019	3.351	0.298	2.241
5C	-6.8333	0.8095	6.0238	3.012	0.332	1.141
5TB	-6.8333	0.8095	6.0238	3.012	0.332	1.308
5B	-6.8322	0.8093	6.0229	3.011	0.332	1.309
6C	-7.1990	-0.3257	7.5247	3.762	0.266	2.457
6TB	-7.1552	-0.3820	7.5372	3.769	0.265	2.101
6B	-7.2673	-0.3763	7.6436	3.822	0.262	3.601
7	-7.5697	-0.5257	8.0954	4.048	0.247	3.921
8a	-7.4042	-0.0946	7.5027	3.751	0.267	6.869
8b	-7.7049	-0.0985	7.8034	3.902	0.256	2.382
8c	-7.3068	-0.2054	7.5122	3.756	0.266	8.476
8d	-6.9060	-1.7257	8.6317	4.316	0.232	4.267
8e	-7.1743	-1.8983	9.0726	4.536	0.220	4.917

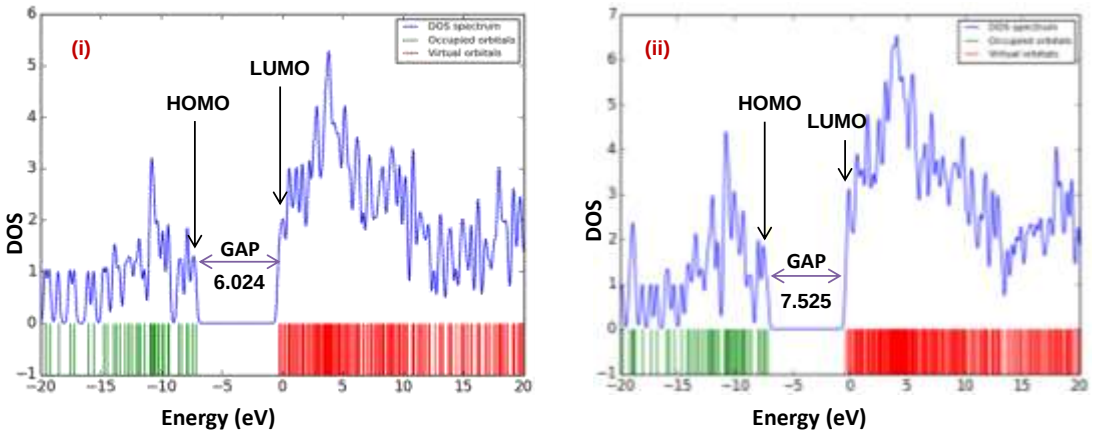


Figure 5. DOS plot indicating orbital gaps in (i) **5C** and (ii) **6C**.

4. CONCLUSION

In the present study, selective pivaloylation of rhamnopyranoside **4** was successfully achieved using the acetonide protection-deprotection technique in good yield. The 4-*O*-pivaloate **7** was then used for the preparation of several novel 2,3-di-*O*-esters. The density functional theory (RB3LYP, 6-311G, *d,p*) based study indicated that the acetonide protected **5** and **6** slightly deviated from regular $^1C_4$ conformation while rhamnopyranoside **4** and its free esters **7**-**8a-e** exist in almost regular $^1C_4$ conformation. The synthetic strategy, conformational behaviour, and molecular orbital properties would be able to shed light on understanding their interactions with receptor proteins in the biological system.

5. ACKNOWLEDGEMENT

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6. CONFLICT OF INTEREST

The authors have no competing interests.

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