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Methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-*α*-D-ribofuranoside: isolation, crystal structure and conformation

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ABSTRACT

The X-ray crystal structure of methyl 2-deoxy-3,5-*di-O-p*-toluoyl-*α*-D-ribofuranoside (**5**) presented here, is a unique example of an alpha-configured, methyl 2-deoxyribofuranoside with the same protecting group at positions C3 and C5. Methyl 2-deoxy-3,5-*di-O-p*-toluoyl-*α/β*-D-ribofuranoside (**3**), exists as a mixture of alpha and beta anomers from which we isolated a single anomer on recrystallization from acetone. TLC analysis indicated the presence of a single compound with NMR analysis in support of the alpha anomer. SC-XRD analysis showed that methyl glycoside (**5**) crystallizes from acetone as the alpha anomer in the monoclinic space group *I*2. Methyl glycoside (**5**) possesses a glycosidic bond length of 1.408 Å with pseudorotational analysis showing the conformation of the five-membered ring to be ^{0}E (O4-*endo*) with $P = 89.9^\circ$ and $\varphi_m = 64.4^\circ$.

1. Introduction

The Hoffer chlorosugar (**4**) [1–3] is an important building block that is widely used for the preparation of nucleosides and analogues with therapeutic value and physicochemical significance [4–13]. It is prepared in three steps from 2-deoxy-D-ribose (**1**) via methyl glycosides (**2**) and (**3**) (Scheme 1) [14]. Methyl 2-deoxy-3,5-*di-O-p*-toluoyl-*α/β*--D-ribofuranoside (**3**) exists as a chromatographically separable mixture of alpha and beta anomers [15]. This mixture of anomers (**3**) has itself been well utilized for the preparation and study of various C-nucleosides where a carbon-carbon bond connects the heterocyclic base or analogue to the sugar ring [16–21]. We recrystallized the anomeric mixture (**3**) from acetone and isolated for the first time, X-ray diffraction-quality crystals, shown by TLC (Fig. S6) to be a single compound with NMR analysis (Fig. S1–S3) in support of the alpha anomer (**5**). SC-XRD analysis [22] (Table S1–S7) confirmed the structure (**5**) (Fig. 1), providing a unique example of an alpha-configured, methyl 2′-deoxyribofuranoside with the same protecting group at C3 and C5.

2. Results and discussion

Methyl 2-deoxy-3,5-*di-O-p*-toluoyl-*α/β*-D-ribofuranoside (**3**) was prepared according to the literature procedure [14] (Scheme 1). Firstly, 2-deoxy-D-ribose (**1**) was converted in near quantitative yield to the methyl glycoside (**2**) using methanolic HCl, generated *in situ* by the reaction of acetyl chloride with methanol. Following this, esterification of methyl glycoside (**2**) using *p*-toluoyl chloride in pyridine gave the C3 and C5-protected methyl glycoside (**3**) as a crimson syrup that, with careful drying, solidified to give product (**3**) in near quantitative yield.

Methyl 2-deoxy-3,5-*di-O-p*-toluoyl-*α/β*-D-ribofuranoside (**3**) was recrystallized from acetone to give the alpha-configured, methyl glycoside (**5**). Although recrystallization of mixture (**3**) from ethyl acetate was also possible, the methyl glycoside product (**5**) obtained from acetone was superior in the X-ray diffraction quality crystals produced and the absence of residual solvent peaks in the proton and carbon NMR spectra.

TLC analysis (hexane-ethyl acetate, 2:1) of alpha methyl glycoside (**5**) showed it to be marginally more mobile (R_f 0.45) than the beta anomer (R_f 0.39) (Fig. S6).

Proton NMR analysis (Fig. S1) of alpha methyl glycoside (**5**) showed the anomeric proton ($\delta = 5.19$ ppm) to be a doublet of doublets with $^{3}J_{H1,H2\beta} = 5.4$ Hz and $^{3}J_{H1,H2\alpha} = 1.0$ Hz. The weaker coupling between the anomeric H and the H_α of the neighbouring methylene group, is consistent with their near perpendicular relationship (Fig. 1). In the carbon NMR spectrum (Fig. S2), the corresponding anomeric C signal appears at $\delta = 105.07$ ppm where a residual trace (<5 %) of the beta

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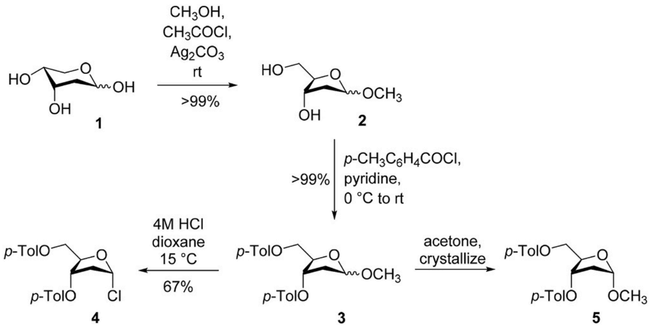

Scheme 1. The preparation [14] of the Hoffer chlorosugar (**4**) from 2-deoxy-D-ribose (**1**) via methyl glycosides (**2**) and (**3**) with isolation of the crystalline, alpha anomer (**5**).

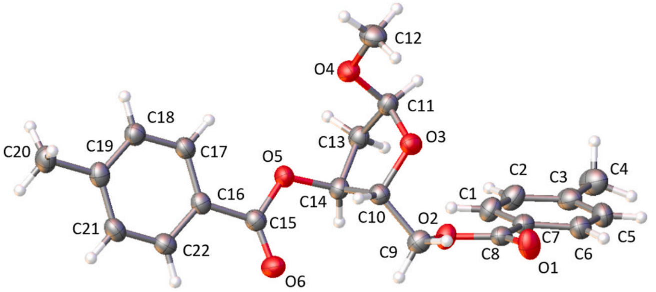

Fig. 1. The asymmetric unit of alpha-configured, methyl glycoside (**5**) at 100 K with adopted numbering and thermal ellipsoids drawn at 50 % probability.

anomer can also be seen (δ = 105.64 ppm). The proton correlations exhibited by the NOESY spectrum (Fig. S3) support the alpha configuration of methyl glycoside (**5**). The IR spectrum was consistent with the structure of methyl glycoside (**5**) [3035 (C–H sp^2), 2929 (C–H sp^3), 1709 (C═O), and 1611 cm^{-1} (C═C)] (Fig. S5). The vibrational properties of methyl glycoside (**5**) align with the literature values where strong, significant absorptions are apparent in the region 1150–1000 cm^{-1}, attributable to stretching vibrations of the glycosidic bond [23]. In the HRMS, there was agreement between the mass found (407.067) and the mass calculated (407.147) for the monosodium adduct ($C_{22}H_{24}NaO_6$) of methyl glycoside (**5**).

Methyl glycoside (**5**) crystallizes from acetone as light-yellow crystals in the monoclinic space group *I*2. The methyl glycoside (**5**) possesses the alpha configuration with a glycosidic bond length of 1.408 Å (Table S6). Pseudorotational analysis [24] of methyl glycoside (**5**) shows the conformation of the five membered ring to be ^{0}E (O4-*endo*) with P = 89.9° and φ_m = 64.4°. Coulombic interactions O3⋯H-C11 (2.00 Å) and O4⋯H-C13 (2.43 Å), facilitated by the C10–O3–C11–O4 torsion angle (90°) (Table S6), supports likely contribution of the anomeric effect to the selection of the alpha anomer (**5**) [25]. Evident from the molecular packing in the unit cell of the alpha anomer (**5**) (Fig. 2) are weak intermolecular interactions observed between O5⋯H–C12 (2.77 Å) and O1⋯H–C9 (2.87 Å) accompanied by weak intramolecular interactions O3⋯H–C12 (2.53 Å) and O6⋯H–C14 (2.67 Å). These values are consistent with reported methyl glycoside derivatives [26,27].

Representative analogues (6) to (**12**) of the known, crystalline methyl glycosides are shown in Fig. 3. The beta-configured methyl glycoside (6) [27] with *p*-nitrobenzoyl protecting groups at C3 and C5, is a close analogue of alpha methyl glycoside (**5**) but with a marginally

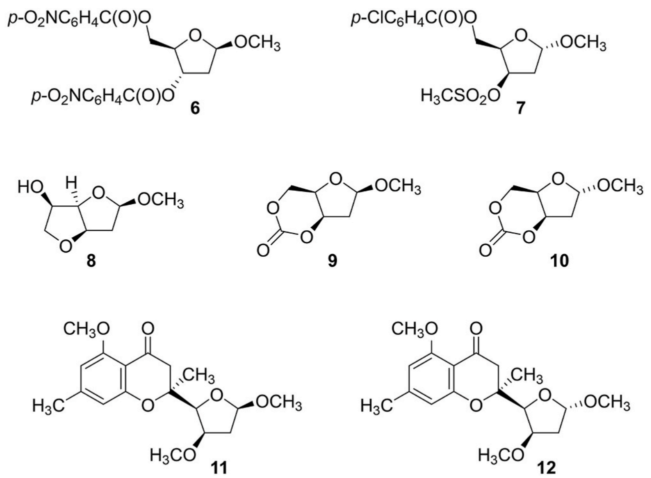

Fig. 3. The structural formulae of methyl glycosides (6) [27] and (7) [28] and bicyclic analogues (8) [29], (9) and (10) [30], (11) and (12) [31] with their CSD-CCDC, X-ray crystal structure accession codes (6) (1154687), (7) (774265), (8) (2233189), (9) (1532105), (10) (1532104), (11) (1531358), and (12) (1531360).

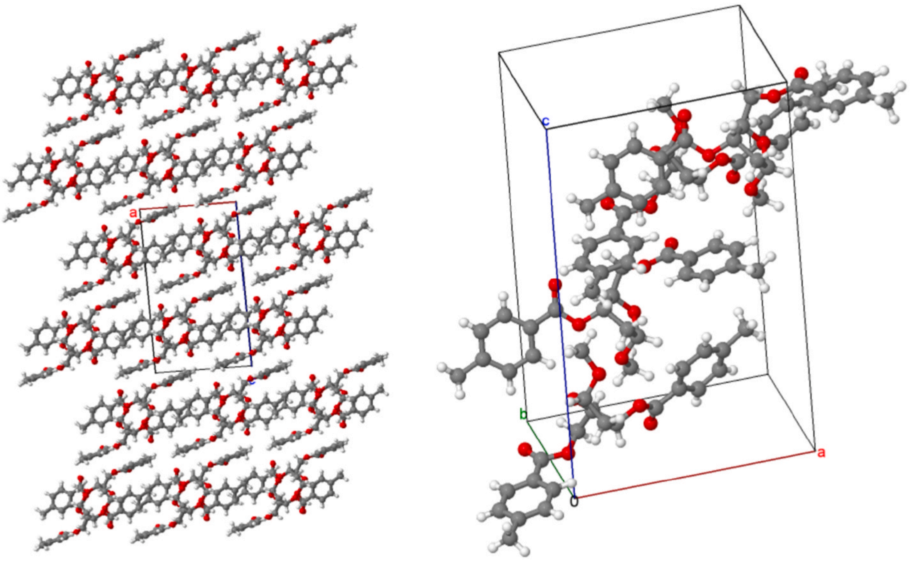

Fig. 2. Molecular packing (left) in the unit cell (right) exhibited by alpha-configured, methyl glycoside (**5**).

longer (1.413 Å) glycosidic bond and sugar ring conformation intermediate between ${}^{1}_{0}T$ and ${}^{1}E$ with $P = -68.3^\circ$ and $\varphi_m = 33.7^\circ$. Slight shortening of the glycosidic bond is apparent in C3-epimeric, alpha methyl glycoside (7) (1.400 Å) [28] and is near identical to the glycosidic bond length in the bicyclic, beta methyl glycoside (8) (1.401 Å) [29]. The glycosidic bond lengths in the beta- and alpha-configured pair of anomers (9) (1.408 Å) and (10) (1.406 Å) [30], are near identical as also observed for the beta- and alpha-configured pair of anomers (11) (1.391 Å) and (12) (1.398 Å) [31] (Fig. 3).

3. Conclusion

Methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-*α*/*β*-D-ribofuranoside (**3**) exists as a mixture of alpha and beta anomers from which a single anomer was isolated on recrystallization from acetone to give SC-XRD quality crystals. TLC analysis showed the crystals to be a single compound with NMR analysis in support of the alpha anomer (**5**). SC-XRD confirmed the structure of (**5**) to provide a unique example of an alpha-configured, methyl 2-deoxyribofuranoside with the same protecting group at C3 and C5. In the pentose series, anomer-selective crystallization processes have been studied, in-depth and in detail [32]. Given the sensitivities of selective crystallization to multiple parameters including solvent choice, it was unexpected but pleasing to achieve notable, alpha anomer-selective crystallization of methyl glycoside (**3**).

4. Materials and methods

4.1. General

NMR spectra were recorded on an Ascend 400 spectrometer (Bruker, Rheinstetten, Germany) with ^{1}H (400.1 MHz) and ^{13}C (100.6 MHz) spectra referenced to $CDCl_3$. Mass analysis was performed using a MALDI 8020 spectrometer (Shimadzu, Kyoto, Japan). Infrared analysis was performed using an iS5 FT-IR (ATR) spectrometer (Thermo Scientific Nicolet, Madison, WI, USA). Melting point determination was carried out using a Thermo Galen hot stage microscope (Reichert-Jung, Vienna, Austria). TLC analysis was carried out on pre-coated 60 F_{254} (Merck, Gillingham, UK) aluminium-backed plates and visualised under UV (254 nm).

4.2. Preparation of methyl 2-deoxy-3,5-di-O-p-toluoyl-α-D-ribofuranoside (5)

Methyl 2-deoxy-3,5-di-*O*-*p*-toluoyl-*α*/*β*-D-ribofuranoside (**3**) was prepared by the literature procedure [14] and recrystallized from acetone to give the title compound (**5**) as light-yellow crystals; m.p. 79–82 °C; TLC [hexane-ethyl acetate (2:1)]: R_f 0.45; IR (neat solid): ν_{max} 3035, 2929, 1709, 1611, 1451, 1271, 1177, 1067, 840, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.19 (ddd, 1H, *J* 14.6, 2.2, 1.0 Hz, 2-CH_2), 2.40 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.55 (ddd, 1H, *J* 14.6, 8.2, 5.4 Hz, 2-CH_2), 3.42 (s, 3H, OCH_3), 4.53 (m, 3H, 4-CH, 5-CH_2), 4.63 (dd, 1H, *J* 13.0, 4.8 Hz, 5-CH_2), 5.19 (dd, 1H, *J* 5.4, 1.0 Hz, 1-CH), 5.41 (ddd, 1H, *J* 8.2, 3.6, 2.2 Hz, 3-CH), 7.20–7.24 (m, 4H, Ar–H), 7.25 (d, 2H, *J* 7.2 Hz, Ar–H), 7.91 (d, 2H, *J* 8.4 Hz, Ar–H), 7.93 ppm; ^{13}C NMR ($CDCl_3$): δ 21.68, 21.70, 39.27, 55.11, 64.32, 74.62, 80.97, 105.07, 127.04, 127.11, 129.10, 129.12, 129.70, 129.82, 143.80, 143.95, 166.30, 166.51 ppm; HRMS (LDI) (calcd for [M+Na] $C_{22}H_{24}NaO_6$ 407.147, found 407.067).

4.3. X-ray diffraction analysis

A suitable crystal of methyl glycoside (**5**) with dimensions 0.12 × 0.04 × 0.02 mm^3 was selected and mounted on a MITIGEN holder in oil on a Rigaku 007HF diffractometer with HF Varimax confocal mirrors, an UG2 goniometer and HyPix Arc-100 detector diffractometer. The crystal was kept at a steady I = 100(2) K during data collection. The structure was solved with the ShelXT 2018/2 [33] solution program using dual methods and by using Olex2 1.5 [34] as the graphical interface. The model was refined with ShelXL 2019/3 [35] using full matrix least squares minimization on F2.

4.4. Crystal data

$C_{22}H_{24}O_6$, $Mr = 384.41$, monoclinic, *I*2 (No. 5), a = 12.2335(2) Å, b = 7.86180(10) Å, c = 20.9000(3) Å, $\beta = 91.1740(10)^\circ$, $\alpha = \gamma = 90^\circ$, $V = 2009.68(5)$ Å^3, $T = 100(2)$ K, $Z = 4$, $Z' = 1$, $\mu(\text{Cu K}_\alpha) = 0.760\ \text{mm}^{-1}$, 34321 reflections measured, 3587 unique ($R_{int} = 0.0412$) which were used in all calculations. The final wR_2 was 0.0829 (all data) and R_1 was 0.0318 ($I \geq 2\ \sigma(I)$).

CRediT authorship contribution statement

Eleanor Dodd: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Simon J. Coles:** Writing – review & editing, Resources. **William Fraser:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Data availability statement

Crystallographic data were deposited at CSD (CIF deposition number; 2503002).

Abbreviations

ATR	Attenuated Total Reflectance
CSD	Cambridge Structural Database
CCDC	Cambridge Crystallographic Data Centre
CIF	Crystallographic Information File
HRMS	High Resolution Mass Spectrometry
IR	Infrared
LDI	Laser Desorption Ionisation
MALDI	Matrix-Assisted Laser Desorption Ionisation
m.p.	Melting Point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
R_f	Retention Factor
rt	Room Temperature
SC	Single Crystal
TLC	Thin Layer Chromatography
UV	Ultraviolet
XRD	X-ray Diffraction

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2026.109831.

Data availability

Data will be made available on request.

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