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Note

Preparation of 6,6,1′,1′,6′,6′-hexadeutero sucrose

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Abstract—The preparation of 6,6,1′,1′,6′,6′-hexadeutero sucrose is reported. The synthesis is based on a triple oxidation of a protected sucrose 6,1′,6′-triol to the corresponding 6,1′,6′-tricarboxylic acid or ester, followed by reduction with lithium aluminium deuteride. This triple oxidation could be achieved either using cat. TEMPO–NaOCl (to the acid) or PDC–Ac_2O–*t*-BuOH (to the *t*-butyl carboxylic ester).

Keywords: Sucrose; Deuteration; Isotope; Oxidation; Uronic acids; Labelled compounds; TEMPO

Sucrose is a major food ingredient and is therefore the starting point of many biochemical processes related to nutrition. Our group being involved in the chemistry of sucrose, and in physicochemical studies of sucrose and some of its derivatives,[1–4] we became interested in the synthesis of a simple polydeuterated analogue of sucrose, which would be very easy to track by classical analytical methods.[5]

Indeed, labelled sugars are efficient probes used to elucidate biological mechanisms. For example, commercially available radioactive [^{3}H]- and [^{14}C]-sucroses have been recently used as tracers for translocation experiments in plants,[6] as a probe for membrane integrity by permeability measurements,[7] or in studies directly related with carbohydrate chemistry such as in the enzymatic synthesis of labelled fructooligosaccharides.[8] Also, [^{3}H]-1-fluorosucrose, used for evidencing the presence of a sucrose carrier in sugar beet roots, was prepared by sucrose synthase coupling.[9,10] Deuterium or carbon 13 labelled sucroses are also interesting as they can be used for analytical purposes without the specific requirement associated with handling of radioactive materials. ^{13}C-Sucrose is known and prepared by biosynthesis under $^{13}CO_2$ atmosphere.[11,12]

Only few deuterated sucroses are described. Two defined C-monodeutero sucrose analogues, namely, 2- and 3-monodeuterosucroses, have been obtained by deuteride reduction of 2- and 3-oxo-sucrose.[13,14] Also, the synthesis of a poly-C-deuterated sucrose analogue has been reported by Raney nickel catalysed deuteration of sucrose in refluxing deuterium oxide.[15–17] This very direct dehydrogenation–deuteration sequence[18–21] provides deuteration at all carbon atoms bearing a hydroxyl group. However, significant variations in the rates of H–D exchange[15] at different positions and in the final deuteration level have been observed (d_{11} or d_5)[15–17] and, in the case of a series of monosaccharides, competitive undesired epimerisations have been shown to be difficult to prevent.[22] Using the same method, a d_5 sucrose analogue was obtained (instead of the d_{11} one as in Refs. 15 and 16) when microwave activation is used.[17] Other isotope incorporations in carbohydrate

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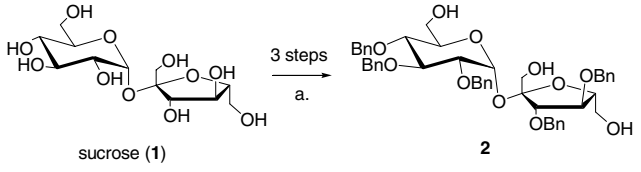
chemistry such as ^{12}C- or ^{13}C-cyanide addition followed by deuterium reduction,[23] molybdate catalysed C-1–C-2 rearrangement[24] or radical reduction of halides by Bu_3SnD[25] are unlikely to fit with the sucrose target.

Among possible deuteration levels and positions, 6,6,1′,1′,6′,6′-hexadeutero sucrose was chosen for several reasons. First, the difference in mass units for hexadeutero sucrose ($M = 348$) compared to sucrose ($M = 342$) provides a clear signature in mass spectroscopy. Second, as soon as sucrose is cleaved into a mixture of glucose and fructose, a mass difference persists for each of these two monosaccharides allowing further tracking of their chemical outcome, moreover being different (+2 for glucose and +4 for fructose). Third, transformation of CH_2OH groups into CD_2OH groups by the oxidation–reduction sequence described in this paper does not provide any epimer or regioisomer mixture. Finally, the selection of all three primary hydroxyl groups of sucrose as a starting point of the synthesis is an easy sequence.

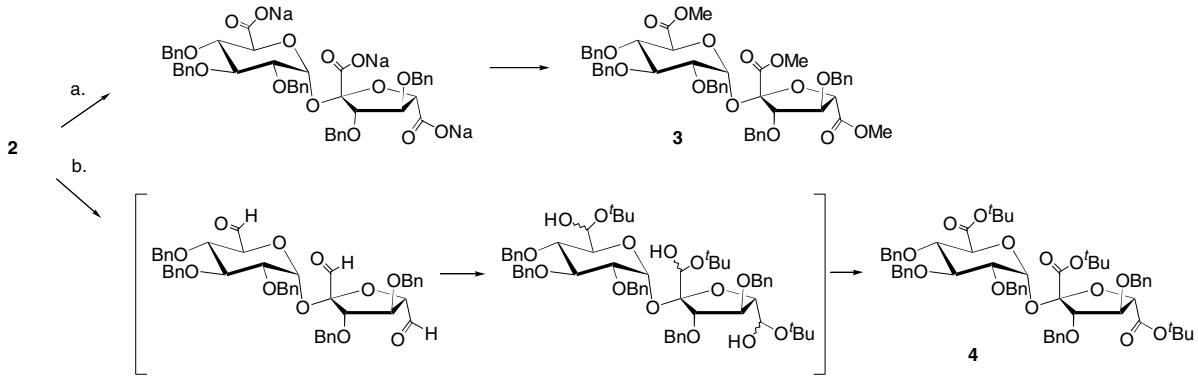
The starting triol **2** (2,3,4,3′,4′-pentabenzyl sucrose) was prepared from sucrose in a three-step sequence (Scheme 1) based on the selective protection (TBDMS)[26] of the three primary hydroxyl groups followed by the benzylation (BnBr, NaH, DMF) of all secondary hydroxyl groups and TBAF desilylation in THF. The silylation–benzylation–TBAF desilylation sequence used here is an alternative to the tritylation–benzylation–detritylation, which is also convenient, provided that strictly controlled acid conditions are used for the deprotection step in order to prevent concomitant cleavage of the very labile glycosidic bond.[27,28]



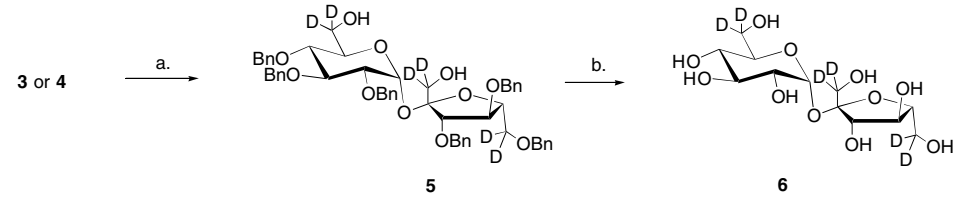
Scheme 1. Preparation of sucrose triol **2**. Reagents and conditions: (a) Refs. 27 and 28 (1) TBDMSCl, pyridine, cat. DMAP, 70 °C, 64%; (2) NaH, BnBr, DMF, 0 °C then rt, 53%; (3) TBAF, THF, 60 °C, 77%.

Two methods were compared for the oxidation of triol **2** (Scheme 2). The oxidation by the NaOCl–KBr–cat. TEMPO system[29,30] under the conditions of Davis and Flitsch[31] in basic heterogeneous medium (using here THF as the organic phase) led to a tricarboxylic acid salt (sodium or potassium form), which was not isolated. The crude tricarboxylate was treated with CH_3I in DMF leading to the methyl triester **3**. Alternatively, the PDC–*t*-BuOH–Ac_2O method for the oxidation of primary alcohols to their corresponding *t*-butyl carboxylic esters was evaluated. This method first described by Corey et al.[32] involves the oxidation of intermediate *tert*-butylic hemiketals and was shown to be efficient in the case of a glucidic substrate for the preparation of uronates. Some variations in the order of addition of the reagents and the work-up procedure have been reported,[33–35] notably a slow addition of the alcohol in the oxidising system, which proved to be more efficient in our case. Triester **4** was thus obtained. The best yields were obtained when a solution of triol **2** in CH_2Cl_2 was added dropwise to the mixture of reagents, using 2 equiv of PDC per CH_2OH group. Careful precipitation of the chromium salts in ether on a silica gel column allowed an easy cleaning and purification of tri *t*-butyl tricarboxylic ester **4**, which was obtained in 51% yield. The use of PDC in DMF, which normally provides the corresponding carboxylic acid, failed to produce the triacid from **2** but provided a complex mixture of degradation products among which monosaccharidic derivatives were identified.

Trimethyl ester **3** was then submitted to the reduction by $LiAlD_4$ in THF leading to triol **5** in 63% yield, following a procedure described for the synthesis of labelled ribonucleosides.[36] A similar approach and using the bulkier *t*-butyl ester **4** proved to be less reactive, providing **5** in 46% yield (Scheme 3). The best yields were



Scheme 2. Oxidation of sucrose triol **2**. Reagents and conditions: (a) (1) cat. TEMPO–NaOCl–KBr, $NaHCO_3$, THF–H_2O, 0 °C; (2) CH_3I, DMF, rt, 37%. (b) PDC, CH_2Cl_2, Ac_2O, *t*-BuOH, 51%.



Scheme 3. Deuteration and deprotection. Reagents and conditions: (a) $LiAlD_4$, THF, −78 °C to rt, 63% from **3** and 46% from **4**; (b) H_2, 10% Pd/C, EtOH–H_2O, rt, quant.

Table 1. Selected ^{13}C NMR chemical shift values for non-deuterated and deuterated sucrose and 2,3,4,3′,4′-pentabenzyl sucrose[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-2′	C-3′	C-4′	C-5′
Sucrose (**1**)	92.54	71.43	72.91	69.56	72.76	104.04	76.71	74.32	81.73
Sucrose-d_6 (**6**)	92.58	71.46	72.96	69.59	72.67	104.03	76.76	74.36	81.66
Pentabenzyl sucrose (**2**)	91.57	79.41	82.43	78.22	74.20	106.56	86.75	82.90	82.90
Pentabenzyl sucrose-d_6 (**5**)	91.65	79.32	82.52	78.25	74.29	106.56	86.80	82.76	82.76

[a] At 75 MHz in D_2O for **1** and **6** and in $CDCl_3$ for **2** and **5**.

obtained using 2.5 equiv of $LiAlD_4$ and work-up procedures using classical acidic treatment or precipitation of aluminium salts under basic conditions gave similar results. Good yields were also obtained using the alternative 'basic' work-up: for *n* g of $LiAlH_4$ (or $LiAlD_4$), addition of *n* mL of water, then *n* mL of 15% NaOH, then 3*n* mL of water in order to produce a granular precipitate, which can be easily filtered.[37,38] The final deprotection was achieved by palladium catalysed hydrogenolysis in EtOH providing 6,6,1′,1′,6′,6′-hexadeutero sucrose (**6**) in quantitative yield. Dilution with water during the reaction, maintaining pH > 5, prevented the acid catalysed glycosidic bond cleavage. When the acidity of the medium was not controlled, hydrolysis of the disaccharidic backbone was observed leading to mixtures of hexadeuterosucrose, dideuteroglucose and tetradeuterofructose, these two latter being mixtures of anomers.

Spectroscopic data of sucrose (**1**) and hexadeuterosucrose (**6**) were compared. In the ^1H NMR spectra of **6**, H-6, H-1′ and H-6′ are absent, and the very small deuterium-hydrogen coupling constants[39] only widen the peaks for H-5 and H-5′. H-5 exhibits a doublet ($J_{4,5} = 10.1$ Hz) proving the trans diaxial relationship between H-4 and H-5, and the coupling constant of 8.4 Hz between H-4′ and H-5′ is also very close of the natural value (8.2 Hz) for sucrose, therefore confirming that no epimerisation took place during the oxidation–reduction sequence. Chemical shifts are also conserved. In the ^{13}C NMR spectrum, longer relaxation time for C-6, C-1′ and C-6′ gave as expected signals, which did not reach more than the noise level.[13,14,40] Extremely close chemical shifts values for all other carbon atoms suggest that the conformation is not affected by the deuteration (Table 1). This conservation is observed for sucrose (**1** and **6**) and the pentabenzylated sucroses (**2** and **5**). Finally, the conservation of the conformation of hexadeuterosucrose (**6**) in aqueous solution is confirmed by the rotatory power (+64), very close to that of sucrose (+66). The lower value for **6** is consistent with the molecular mass variation (+1.7%).

In conclusion, the preparation of 6,6,1′,1′,6′,6′-hexadeutero sucrose, a defined polydeuterated sucrose analogue, has been achieved in 6 steps (or 7 depending on the oxidation method) from sucrose. Starting from the known pentabenzyl sucrose having all three primary hydroxyl groups available, the oxidation–reduction sequence was performed using either the Corey procedure for the uronate synthesis by direct oxidation of primary alcohols to their corresponding *t*-butyl ester, or the TEMPO–NaOCl method. Deuteride reduction and deprotection provided the hexadeutero analogue, which proved to behave in a very similar manner compared to sucrose. Further studies of the physicochemical and biological behaviour of this analogue are programmed.

1. Experimental

1.1. General methods

Sucrose was obtained from Béghin-Say. Chromatography solvents were purchased from SDS and Carlo Erba. HPLC solvents were purchased from SDS. Reactions were monitored by TLC using glass silica gel plates (Merck 60 F_{254}). The plates were developed using UV light and vapourisation with a solution of 10% H_2SO_4 in EtOH (v/v). Flash chromatography separations were performed using Merck Gerudan Silica Gel Si 60 (40–63 μm). NMR spectra were recorded on Bruker AC spectrometers at 75.47 MHz for ^{13}C NMR and

300.13 MHz (or 500.13 MHz) for ^{1}H NMR. Assignment of carbon resonances is based on C–H correlations. Mass spectra were recorded by the Centre de Spectrométrie de Masse of the Université Claude Bernard (Villeurbanne). Microanalyses were performed by the Service Central d'Analyse of the CNRS (Vernaison). Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Known triol **2** was obtained from sucrose in 3 steps: a solution of sucrose in pyridine (7 mL per mmol) was treated with TMDPSCl (3.8 equiv) and DMAP (cat. 10 mg per mmol) for 10 h at 70 °C. The mixture is concentrated, diluted with AcOEt and water (10 mL per mmol each). After extraction of the aqueous layer with AcOEt, the combined organic layers are washed with 1 M HCl (5 mL/mmol), dried and purified by flash chromatography, giving 2,3,4,3′,4′-penta-*O*-benzyl-tri-*O*-(*tert*-butyldiphenylsilyl)-sucrose (Ref. 26). To a solution of this latter in DMF (25 mL/mmol) cooled at 0 °C was added NaH (2.1 equiv per OH). After 15 min, benzyl bromide (2.1 equiv Per OH) was added and the mixture was stirred at rt during 15 h, then poured in iced water (same volume) and neutralised by addition of 1 M HCl. The products were extracted with ether and the organic phase was dried over $MgSO_4$, concentrated and purified by flash chromatography (CH_2Cl_2/hexanes, 1:1 v/v). Treatment of the fully protected derivative with TBAF (1.1 equiv per OH) in THF (5 mL per mmol) at 60 °C overnight led to triol **2** after extraction with CH_2Cl_2 (3 times), drying over $MgSO_4$, concentration and flash chromatography of the residue (CH_2Cl_2/MeOH, 4:1 v/v) in 26% overall yield from sucrose.

1.2. Trimethyl 2,3,4,3′,4′-penta-*O*-benzyl sucrose tricarboxylate (3)

To a solution of triol **2** (2.8 g, 3.5 mmol) in THF (100 mL) were added saturated aqueous $NaHCO_3$ (60 mL), TEMPO (120 mg, 0.768 mmol), KBr (660 mg, 5.546 mmol) and NBu_4Cl (660 mg, 2.375 mmol). To this mixture cooled to 0 °C was added dropwise over 3 h a mixture of aqueous NaOCl (13% w/w, 260 mL) and saturated aqueous $NaHCO_3$ (100 mL). The reaction mixture was then warmed to rt and isopropanol (35 mL) was added. After 30 min of stirring at rt, the mixture was evaporated to dryness and the crude residue was suspended in anhydrous DMF (135 mL). CH_3I (5.7 mL) was added and the mixture was stirred vigorously during 15 h. After dilution with diethyl ether (20 mL), the salts were filtrated and washed with ether (3×20 mL) and the etheral solutions were combined and concentrated. Flash chromatography of the residue (hexane/AcOEt: 3:1 v/v) led to pure **3** (1.1 g, 37%) as a colourless oil. Compound **3**: $[\alpha]_D^{20}$ +31 (*c* 0.9, CH_2Cl_2). Anal. Calcd for $C_{50}H_{52}O_{14}$: C, 68.5; H, 6.0. Found: C, 68.6; H, 6.0. HRMS-FAB+: $[M+Li]^+$ 883.3517; found, 883.3530. IR *v* (cm^{-1}): 736, 697, 1027, 1091, 1147, 1743. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.61 (dd, 1H, $J_{2-3} = 9.5$ Hz, H-2); 3.64 (s, 3H, CO_2Me); 3.68 (s, 3H, CO_2Me); 3.72 (t, 1H, H-4); 3.74 (s, 3H, CO_2Me); 3.97 (t, 1H, $J_{3-4} = 9.5$ Hz, H-3); 4.46 (d, 1H, $J_{3'-4'} = 5.7$ Hz, H-3′); 4.52 (t, 1H, H-4′); 4.54–4.59 (m, 3H, CH_2Ph); 4.59 (d, 1H, $J_{4'-5'} = 5.0$ Hz, H-5′); 4.61–4.65 (m, 3H, CH_2Ph); 4.72–4.82 (m, 3H, CH_2Ph); 4.76 (d, 1H, $J_{4-5} = 10.4$ Hz, H-5); 4.95 (d, 1H, $J = 11.7$ Hz, CH_2Ph); 5.77 (d, 1H, $J_{1-2} = 3.5$ Hz, H-1); 7.22–7.35 (m, 25H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.89, 53.11, 53.52 (3CO_2*Me*); 71.69 (C-5); 72.97, 73.40, 73.83, 75.53, 76.26 (5*C*H_2Ph); 79.64 (C-2); 80.27 (C-4); 80.64 (C-5′); 81.45 (C-3); 84.06 (C-4′); 85.70 (C-3′); 93.30 (C-1); 104.29 (C-2′); 128.19–139.24 (5Ph); 168.51, 170.46, 170.95 (3*C*O_2Me).

1.3. Tri-*tert*-butyl 2,3,4,3′,4′-penta-*O*-benzyl sucrose tricarboxylate (4)

tert-Butanol (3.5 mL, 37.40 mmol) and Ac_2O (1.8 mL, 18.90 mmol) were added to a solution of PDC (1.37 g, 3.65 mmol) in CH_2Cl_2 (15 mL) under N_2 atmosphere and the mixture was stirred at rt. Then a solution of triol **2** in CH_2Cl_2 (21.8 mL) was added (500 mg, 0.63 mmol) and stirring was continued for 4 h. The reaction mixture was then poured into a column of ether containing a short pad of silica gel. After 15 min, time for all chromium salts to precipitate, the column was eluted with ether. After concentration and flash chromatography of the residue (hexane/AcOEt: 9:1 v/v), pure ester **4** was obtained as a colourless oil (322 mg, 51%). Compound **4**: $[\alpha]_D^{20}$ +27 (*c* 0.9, CH_2Cl_2). HRMS-FAB$^+$: $[M+Na]^+$ 1025.4674; found, 1025.4663. IR *v* (cm^{-1}): 736, 697, 1095, 1156, 1737, 2931, 2978. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42, 1.45, 1.47 (3s, 27H, CMe_3); 3.64 (dd, 1H, $J_{2-3} = 9.5$ Hz, H-2); 3.75 (t, 1H, $J_{3-4} = 9.6$ Hz, H-4); 4.08 (t, 1H, H-3); 3.35–4.43 (m, 3H, H-3′, H-4′, H-5′); 4.53–4.70 (m, 6H, CH_2Ph); 4.71 (d, 1H, $J_{4-5} = 10.2$ Hz, H-5); 4.80–5.00 (m, 4H, CH_2Ph); 6.04 (d, 1H, $J_{1-2} = 3.4$ Hz, H-1); 7.22–7.39 (m, 25H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.48, 28.56, 28.67 (3CMe_3); 72.57 (CH_2Ph); 72.63 (C-5); 73.65, 75.10, 76.17 (4CH_2Ph); 80.01 (C-5′); 80.08 (C-2); 80.59 (C-4); 81.40 (C-3); 82.14, 82.85, 83.54 (3CMe_3); 84.59 (C-4′); 85.79 (C-3′); 92.36 (C-1); 103.55 (C-2′); 127.96–139.50 (5Ph); 167.67, 169.14, 170.02 (3CO_2CMe_3).

1.4. 6,6,1′,1′,6,6′-Hexadeutero-2,3,4,3′,4′-penta-*O*-benzyl sucrose (5)

To a 1 M solution of $LiAlD_4$ in THF (0.5 mL, 0.50 mmol) cooled at −78 °C under nitrogen atmosphere was added a solution of triester **3** (176 mg, 0.201 mmol) in THF (0.5 mL). After 10 min of stirring

at −78 °C, the mixture was warmed to rt and stirred further for 15 min. Saturated aqueous ammonium chloride (5 mL) was then added and the products were extracted by CH_2Cl_2 (3 × 10 mL). The combined organic layers were filtered, dried and concentrated under reduced pressure, and flash chromatography (CH_2Cl_2/Me_2CO, 9:1 v/v) of the residue provided the triol **5** (100 mg, 63%) as a colourless oil. The same procedure applied to *tert*-butyl triester **4** gave triol **5** in 46% yield. Compound **5**: $[\alpha]_D^{20}$ +10 (*c* 1.2, CH_2Cl_2). HRMS-FAB$^+$: $[M+Li]^+$ 805.4046; found, 805.4051. Anal. Calcd for $C_{47}H_{46}D_6O_{11}$: C, 70.7; H + D, 7.3. Found: C, 70.5; H + D, 7.0. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90, 2.79, 3.36 (3s, 3H, 3OH); 3.57 (t, 1H, $J_{3-4} = 9.5$ Hz, $J_{4-5} = 9.8$ Hz, H-4); 3.64 (dd, 1H, $J_{2-3} = 9.8$ Hz, H-2); 3.98 (s, 1H, H-5′); 4.05 (d, 1H, $J_{3'-4'} = 5.1$ Hz, H-4′); 4.09 (t, 1H, $J_{2-3} = 9.5$ Hz, H-3); 4.12–4.19 (m, 2H, H-5, H-3′); 4.52–5.01 (m, 10H, CH_2Ph); 5.31 (d, 1H, $J_{1-2} = 3.5$ Hz, H-1); 7.28–7.49 (m, 25H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 73.02, 73.42 ($2CH_2Ph$); 74.29 (C-5); 75.65, 76.23 ($3CH_2Ph$); 78.25 (C-4); 79.32 (C-2); 82.52 (C-3); 82.76 (C-4′, C-5′); 86.80 (C-3′); 91.65 (C-1); 106.56 (C-2′); 128.27–138.90 (Ph).

1.5. 6,6,1′,1′,6,6′-Hexadeuterosucrose (6)

To a solution of triol **5** (124 mg, 0.155 mmol) in EtOH (2.2 mL) was added 10% Pd/C (80 mg) and the mixture was stirred under H_2 (1 atm) at rt for 2 h while water was added regularly (total 2.2 mL) in order to maintain the pH > 5. After centrifugation and filtration, the solution was evaporated to dryness and the pure deuterosucrose **6** white solid was freeze dried (54 mg, quant.). $[\alpha]_D^{20}$ +64 (*c* 0.9, H_2O). HRMS-FAB+: $[M+Na]^+$ ($C_{12}H_{16}D_6O_{11}Na$) 371.1436; found, 371.1442. Anal. Calcd for $C_{47}H_{46}D_6O_{11}$: C, 70.7; H + D, 7.3. Found: C, 70.5; H + D, 7.0. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.45 (t, 1H, H-4); 3.55 (dd, 1H, $J_{2-3} = 9.9$ Hz, H-2); 3.75 (t, 1H, $J_{3-4} = 9.3$ Hz, H-3); 3.82 (d, 1H, $J_{4-5} = 10.1$ Hz, H-5); 3.87 (d, 1H, $J_{4'-5'} = 8.4$ Hz, H-5′); 4.04 (t, 1H, H-4′); 4.20 (d, 1H, $J_{3'-4'} = 8.8$ Hz, H-3′); 5.40 (d, 1H, $J_{1-2} = 3.8$ Hz, H-1). ^{13}C NMR (D_2O, 75 MHz) δ 69.59 (C-4); 71.46 (C-2); 72.67 (C-5); 72.96 (C-3); 74.36 (C-4′); 76.76 (C-3′); 81.66 (C-5′); 92.58 (C-1); 104.03 (C-2′).

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