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Facile synthesis of de-O-sulfated salacinols: Revision of the structure of neosalacinol, a potent α-glucosidase inhibitor

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ABSTRACT

Facile synthesis of de-O-sulfated salacinols (**3**) was developed by employing the coupling reaction of an epoxide, 1,2-anhydro-3,4-di-*O*-benzyl-D-erythritol (**9**) with 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-epithio-D-arabinitol (**10**) as the key reaction. The reported structure of a potent α-glucosidase inhibitor named neosalacinol (**8**), isolated recently from Ayurvedic medicine *Salacia oblonga*, was proved incorrect, and revised to be de-O-sulfated salacinol formate (**3c**) by comparison of the spectroscopic properties with those of the authentic specimen synthesized. Discrepancies and confusion in the literature concerning the NMR spectroscopic properties of salacinol (**1**) have also been clarified.

From the roots and stems of *Salacia* species plants, which have traditionally been used for the treatment of diabetes in Sri Lanka, India, and Thailand, the authors had isolated highly potent α-glucosidase inhibitors, salacinol (**1**) and kotalanol (**2**).[1] Their structure are quite unique, bearing thiosugar sulfonium sulfate inner salt comprised of 1-deoxy-4-thio-D-arabinofranosyl cation and 1-deoxyaldosyl-3-sulfate anion as shown in Figure 1. Their α-glucosidase inhibitory activities are potent, and have been revealed to be as high as those of voglibose and acarbose, which are widely used clinically these days.[1] De-O-sulfated analogs (**3** and **4**), which were readily derived from **1** and **2**, respectively, were also found to be as potent as the original sulfates (**1** and **2**).[2] Because of the intriguing structure and high α-glucosidase inhibitory activities, much attention has been focused on them, and intensive studies on the structure–activity relationships (SAR) have been reported.[3] Thereafter, the authors also isolated related thiosugar analogs, ponkolanol (**5**) and salaprinol (**6**) from the same species of plant,[2b] and absolute stereochemistry of **6** was successfully determined on the basis of the single crystal X-ray crystallographic analysis.[4] Meanwhile, Ozaki and co-workers reported the isolation of 13-memberd sulfoxide (**7**) as a more potent constituent from *Salacia reticulata*, mentioning that the compound was responsible for the α-glucosidase activity of the plants.[5] Later, the structure was revised, and the compound was proved to be kotalanol de-*O*-sulfate (**4**)[6] (Fig. 1).

Very recently, Asano group also reported the isolation of highly potent α-glucosidase inhibitor named neosalacinol from *Salacia oblonga*, and presented a thiosugar sulfonium-alkoxide inner salt structure (**8**) for the inhibitor, claiming that our proposed structure **3** was ambiguous, and the further investigation would be needed (Fig. 2).[7]

In this Letter, to clarify the structure of this potent inhibitor, three sulfonium salts (**3a**, **3b**, **3c**) have been synthesized via two routes. Of the three, spectral properties of **3c** were in accord with those reported by Asano and co-workers. The discrepancies and confusion appeared in the literature[7] concerning the NMR spectroscopic properties of salacinol (**1**) have also been clarified.

Synthesis of sulfonium salt (**3c**) *by the coupling reaction of epoxide* (**9**) *and thiosugar* (**10**): According to the protocol for the preparation of β-hydroxylated sulfonium compound,[8] a mixture of epoxide[9] **9** and thiosugar[3b,10] **10** was treated with tetrafluoroboric acid dimethyl ether complex ($HBF_4{\cdot}Me_2O$) at −60 °C. Preferred α-facial attack of the thiosugar to the epoxide **9** was observed, giving predominantly the corresponding α-isomer of the sulfonium tetrafluoloborate[11] (α-**11d**) along with a small amount of its β-isomer (β-**11d**) in 90% yield (α/β = ca. 9:1). These two diastereomers were successfully separated over silica gel column chromatography, and the relative stereochemistry of the side chain of the major compound was confirmed to be in anti relationship to the benzyloxymethyl moiety at C-4 on the basis of nuclear Overhauser effect spectroscopy (NOESY) experiments as shown in Scheme 1. Its FAB-MS spectrum run in the positive and negative modes showed

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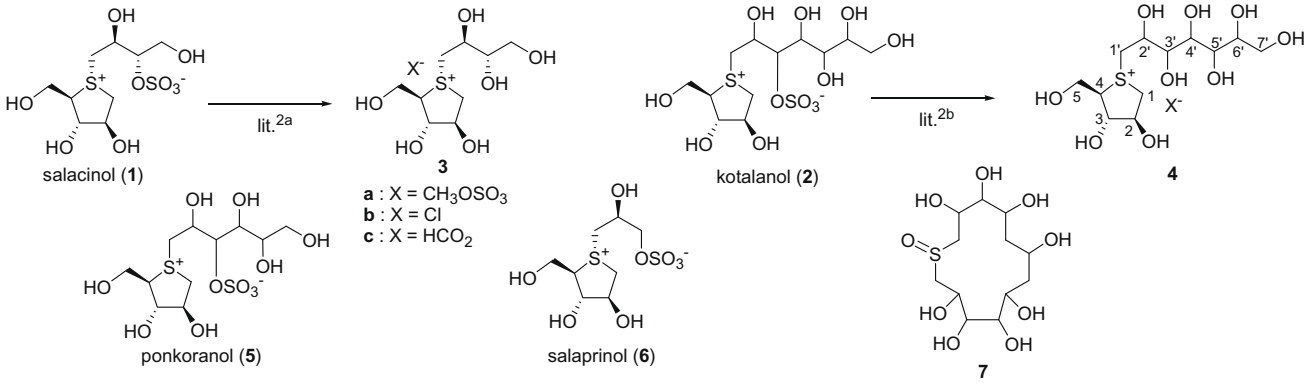


Figure 1. Thiosugar sulfonium sulfate inner salts **1**, **2**, **5** and **6** and related de-O-sulfated analogs **3** and **4**.

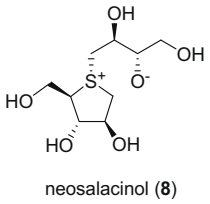
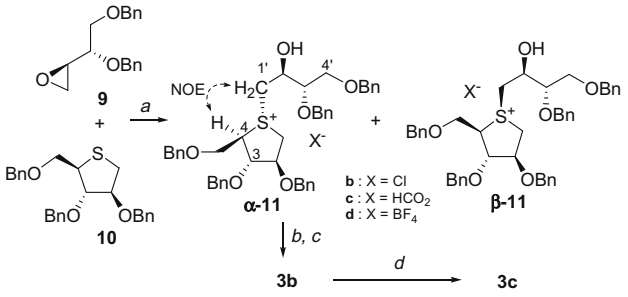


Figure 2. Proposed structure of neosalacinol (**8**).



Scheme 1. Reagents and conditions: (a) $HBF_4{\cdot}(CH_3)_2O$, CH_2Cl_2, −60 °C; (b) IRA-400 J (Cl^- form), MeOH–H_2O, rt; (c) H_2, Pd–C, 80% AcOH, 50–60 °C; (d) Dowex 1-X2 (HCO_2^- form), H_2O.

peaks at *m/z* 705 and *m/z* 87 corresponding to $[M-BF_4]^+$ and $[BF_4]^-$ ions, respectively. The major isomer α-**11d** was then treated with ion exchange resin IRA-400J (Cl^- form) to give the corresponding chloride (α-**11b**) in 95% yield.

The chloride α-**11b** was subjected to hydrogenolysis with palladium on carbon in 80% aq acetic acid to give the corresponding chloride **3b** in 90% yield. Its FAB-MS spectrum run in the positive mode showed a peak at *m/z* 255, and the compound was positive to the Beilstein test. The ^{13}C NMR spectrum of **3b** showed nine peaks reasonably related to the nine carbons of this sulfonium cation part.

The chloride **3b** was then treated with an ion exchange resin Dowex 1-X2 (HCO_2^- form) to give the corresponding formate (**3c**) in good yield. Its FAB-MS spectrum run in the positive mode showed, as well as **3b**, the peak at *m/z* 255. In its ^{13}C NMR spectrum measured in D_2O, a signal corresponding to HCO_2^- moiety was observed at δ_C 173.7 in addition to the nine peaks of the cation moiety. In its ^1H NMR spectrum, one-proton singlet due to HCO_2^- was clearly detected at δ_H 8.46 as shown in Figure 3 and the IR spectrum showed strong absorption at 1597 cm^{-1} typical for the carboxylate moiety. On the basis of these evidences, the presence of the formate anion in the molecule has been approved (Scheme 1).

Preparation of **3c** *via methanolysis of salacinol* (**1**): We had already reported that the acid catalyzed methanolysis of salacinol

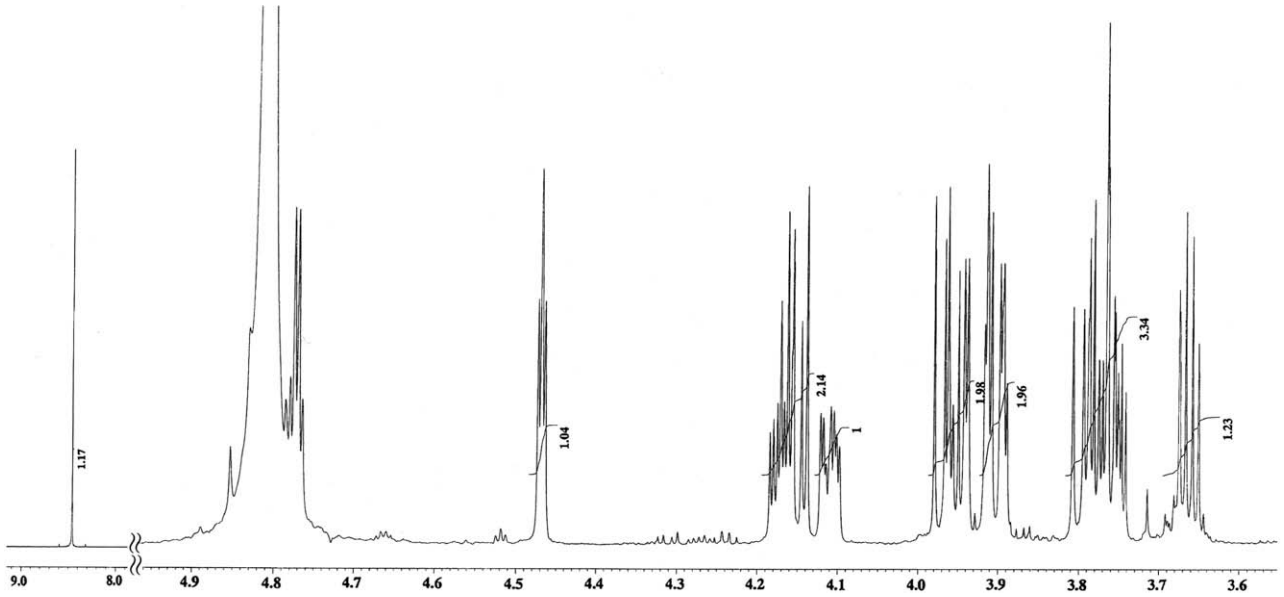
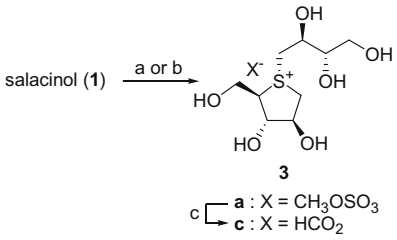


Figure 3. ^1H NMR spectrum of **3c** in D_2O (TSP as an internal standard).



Scheme 2. Reagents and conditions: (a) 5% HCl in MeOH, reflux[lit.7]; (b) 5% HCl in MeOH, 45 °C[lit.2a]; (c) Dowex 1-X2 (HCO_2^- form), H_2O.

(**1**) readily took place at 45 °C,[2a] giving the thiosugar-sulfonium methyl sulfate (**3a**) in 86% yield. In this study, the procedure by Asano and co-workers[7] has been reexamined. Thus, **1** was first heated under reflux in methanol containing 5% hydrogen chloride to give the corresponding methyl sulfate (**3a**) in 88% yield. The FAB-MS spectrum of **3a** run in the positive and negative modes showed peaks at *m/z* 255 and *m/z* 111, corresponding to $[M-CH_3OSO_3]^+$ ion and $[CH_3OSO_3]^-$ ion, respectively. In the ^1H and ^{13}C NMR spectra, peaks due to the $CH_3OSO_3^-$ anion were observed clearly at δ_H 3.68 and δc 55.2, respectively. The methyl sulfate **3a** was then treated with an ion exchange resin Dowex 1-X2 (HCO_2^- form) to give the corresponding formate (**3c**) in good yield. The NMR and MS spectroscopic properties of **3c** thus obtained were completely in accord with those of the specimen synthesized above (Scheme 2).

Asano and co-workers reported ^1H NMR spectroscopic properties of **8** measured in D_2O.[7] Comparison of their data with those of **3c** in D_2O obtained in the present study[12] did not correlate with each other. On the other hand, they mentioned in the experimental section the use of C_5D_5N and C_5D_5N–D_2O (5:1) as the solvents for NMR measurements. Surprisingly enough, the NMR spectral properties of **3c** in C_5D_5N–D_2O (5:1) showed perfect correlations with those reported with respect to all the signals with deviations of 0.10–0.12 and 0.4 ppm for ^1H and ^{13}C signals, respectively, as shown in Table 1. In this solvent, signal due to HCO_2^- appeared at δ_H 9.36 as a broad signal as shown in Table 1, and ^{13}C NMR peak due to HCO_2^- was hardly observed. As for the MS properties, Asano and co-workers assigned the peak at *m/z* 225 to the quasimolecular ion peak $[M+H]^+$. It is more reasonable to identify this peak as the sulfonium ion itself $[M]^+$ of **3c**. Thus, the structure of the compound they isolated has been unambiguously identified as formate of salacinol de-*O*-sulfate (**3c**). The anion HCO_2^- would be originated from the ion exchange resin during the isolation process.

In addition to this, we should comment here that ^1H and ^{13}C NMR spectral data of salacinol (**1**) in D_2O reported in the same literature[7] must be revised as those measured in pridine-d_5.[1c] The data of **1** in D_2O were collected in the present study, and are presented in Table 2.

In summary, we developed the facile synthesis of highly potent α-glucosidase inhibitors **3** by employing the coupling reaction of epoxide **9** with thiosugar **10** as the key reaction. Reexamination and careful comparison of the ^1H and ^{13}C NMR spectroscopic properties of the isolated inhibitor **8** with those of de-O-sulfated

Table 1
^1H and ^{13}C NMR data of neosalacinol (**8**) reported and de-O-sulfated salacinol formate (**3c**) synthesized in the present study (δ in ppm and *J* in Hz)

	Compound **8** in D_2O[lit.7] TSP as an internal standard (500 MHz and 125 MHz)		Compound **3c** in pyridine-d_5/D_2O (5:1) TMS as an external standard (500 MHz and 125 MHz)		Deviations of the chemical shifts	
	δ_H	δ_C	δ_H	δ_C	$\Delta\delta_H$	$\Delta\delta_C$
H-1a,1b	4.21 (br d)	50.9	4.33 (d-like, *J* = 2.9)	51.3	0.12	0.4
H-2	5.06 (br ddd)	78.1	5.18 (ddd-like, *J* = 2.9, 2.9, 2.6)	78.5	0.12	0.4
H-3	4.87 (dd, *J* = 2.5, 1.6)	78.3	4.98 (dd-like, *J* = 2.6, 1.7)	78.7	0.11	0.4
H-4	4.60 (br ddd)	72.5	4.70 (br dd-like, *J* = 9.7, 5.4)	72.9	0.10	0.4
H-5a	4.30 (dd, *J* = 11.9, 9.6)	59.9	4.42 (dd, *J* = 12.0, 9.7)	60.3	0.12	0.4
H-5b	4.38 (dd, *J* = 11.9, 5.5)		4.50 (dd, *J* = 12.0, 5.4)		0.12	
H-1′a	4.27 (dd, *J* = 13.0, 8.7)	51.1	4.38 (dd, *J* = 13.2, 8.9)	51.5	0.11	0.4
H-1′b	4.42 (dd, *J* = 13.0, 3.4)		4.52 (dd, *J* = 13.2, 3.4)		0.10	
H-2′	4.68 (ddd, *J* = 8.7, 6.2, 3.4)	68.4	4.80 (ddd, *J* = 8.9, 6.6, 3.4)	68.8	0.12	0.4
H-3′	4.19 (ddd, *J* = 6.2, 5.0, 4.4)	74.5	4.31 (m)	74.9	0.12	0.4
H-4′a	4.10 (dd, *J* = 11.2, 5.0)	63.0	4.22 (dd, *J* = 11.5, 5.0)	63.4	0.12	0.4
H-4′b	4.16 (dd, *J* = 11.2, 4.4)		4.28 (dd, *J* = 11.5, 4.0)		0.12	
HCO_2^-			9.36 (br s,)	173.7[a]		

[a] Datum in D_2O. The signal was hardly detected in pyridine–D_2O (5:1).

Table 2
^1H and ^{13}C NMR data of salacinol (**1**) in pyridine-d_5 and in D_2O (δ in ppm and *J* in Hz)

	Reported[lit.1c] (500 MHz and 125 MHz) in pyridine-d_5; an internal standard: TMS		Reported[lit.7] (500 MHz and 125 MHz) in D_2O; an internal standard: TSP		Observed (500 MHz and 125 MHz) in D_2O; an external standard: DSS	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
H-1a,1b	4.33 (br s)	50.7	4.32 (br d)	50.5	3.90 (d-like, *J* = 4.0)	50.5
H-2	5.10 (br s)	78.5	5.12 (s)	78.4	4.75 (ddd, *J* = 4.0, 4.0, 3.5)	79.5
H-3	5.12 (dd-like)	79.0	5.12 (s)	79.2	4.45 (dd., *J* = 3.5, 2.9)	80.3
H-4	4.69 (t-like)	72.6	4.70 (br t)	72.4	4.10 (ddd, *J* = 7.8, 4.9, 2.9)	72.7
H-5a	4.51 (dd, *J* = 11.6, 8.0)	60.2	4.53 (dd, *J* = 11.9, 7.3)	60.2	3.96 (dd, *J* = 10.9, 7.8)	61.7
H-5b	4.54 (dd, *J* = 11.6, 6.8)		4.55 (dd, *J* = 11.9, 6.4)		4.13 (dd, *J* = 10.9, 4.9)	
H-1′a	4.62 (dd, *J* = 13.1, 4.2)	52.6	4.63 (dd, *J* = 12.8, 4.1)	52.8	3.84 (dd, *J* = 13.6, 8.3)	52.4
H-1′b	4.76 (dd, *J* = 13.1, 4.9)		4.80 (dd, *J* = 12.8, 4.6)		4.00(dd, *J* = 13.6, 3.2)	
H-2′	4.99 (ddd, *J* = 7.6, 4.9, 4.2)	67.6	5.01 (br dt)	67.6	4.41 (ddd, *J* = - 8.3, 7.5, 3.2)	68.3
H-3′	5.25 (ddd, *J* = 7.6, 3.9, 3.7)	79.4	5.27 (dt, *J* = 7.7, 3.7)	79.3	4.36 (ddd, *J* = 7.5, 3.2, 3.2)	82.6
H-4′a	4.37 (dd, *J* = 11.6, 3.9)	62.2	4.38 (dd, *J* = 11.9, 3.7)	62.3	3.87 (dd, *J* = 12.6, 3.2)	62.2
H-4′b	4.60 (dd, *J* = 11.6, 3.7)		4.62 (dd, *J* = 11.9, 3.7)		3.97 (dd, *J* = 12.6, 3.2)	

salacinol (**3c**) concluded that the compound isolated by Asano group was formate of de-O-sulfated salacinol (**3c**). The authors recently detected de-O-sulfated salacinol (**3**) and de-O-sulfated kotalanol (**4**) in the cold water extract by means of LC–MS analysis. Further studies on the evaluation of extracts involving the contribution of these de-*O*-sulfates (**3** and **4**) are in progress.

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11. *Compound* **α-11d**: Colorless oil. $[\alpha]_D^{23}$ +4.25 (*c* 2.43, $CHCl_3$). IR (neat) 3503, 1496, 1452, 1400, 1362, 1211, 1087 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.62 (1H, dd, *J* = 10.6, 3.5 Hz, H-4′a), 3.67 (2H, d-like, *J* = 3.2 Hz, H-1a, H-1b), 3.68–3.73 (3H, m, H-4′b, H-5a and H-5b), 3.74–3.77 (1H, m, H-3′), 3.78 (1H, dd, *J* = 13.2, 6.9 Hz, H-1a′), 3.85 (1H, dd, *J* = 13.2, 3.8 Hz, H-1b′), 4.05 (1H, br-t like, *J* = *ca.* 7.6 Hz, H-4), 4.14 (1H, br s, OH), 4.19 (1H, br t-like, *J* = *ca.* 1.5 Hz, H-3), 4.29/4.36 (each 1H, d, *J* = 11.8 Hz, PhCH_2), 4.31–4.36 (2H, m, H-2, H-2′), 4.43–4.53 (6H, m, PhCH_2), 4.58/4.64 (each 1H, d, *J* = 11.2 Hz, PhCH_2), 7.08–7.35 (25H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.1 (C-1), 50.8 (C-1′), 66.0 (C-4), 66.7 (C-5), 68.5 (C-2′), 68.7 (C-4′), 71.7/72.0/72.9/73.4/73.5 (PhCH_2), 79.5 (C-3′), 82.3 (C-3) 82.5 (C-2), 127.8/127.88/127.90/128.0/128.1/128.2/128.3/128.36/128.40/128.43/128.47/128.51/128.6/128.7 (d, arom.), 135.9/136.1/136.8/137.5/137.6 (s, arom.). FAB-MS *m/z* 705 $[M-BF_4]^+$ (pos.), 87 $[BF_4]^-$ (neg.). HR-FAB-MS *m/z* 705.3220 ($C_{44}H_{49}O_6S$ requires 705.3250), 87.0027 (BF_4 requires 87.0030).
12. A mixture of salacinol (**1**, 50 mg, 0.15 mmol) and 5% methanolic hydrogen chloride (5 ml) was heated under reflux for 1 h. After removal of the solvent, the residue (60 mg) was purified on column chromatography (AcOEt/MeOH/H_2O, 20:4:1) to give the methyl sulfate **3a** (48 mg, 88%). Dowex 1-X2 (HCO_2^- form, 1 g) was well washed with H_2O. An aqueous solution of **3a** (10 ml) was treated with the half volume (ca. 500 mg) of the resin to give **3c** (32 mg, 82%) as an oil. Another half of the resin was washed with H_2O (10 ml), and the washings was concentrated in vacuo. The residue showed no signals due to HCO_2^- moiety in its ^1H NMR spectrum in D_2O. Compound **3c**: IR (neat) 3360, 1597, 1388, 1350, 1249, 1219, 1069, 1022 cm^{-1}. ^1H NMR (700 MHz, D_2O, internal standard: TSP) δ 3.66 (dd-like, *J* = 11.4, 5.6 Hz, H-4′a), 3.75 (ddd, *J* = 6.8, 5.6, 3.6 Hz, H-3′), 3.78 (dd, *J* = 11.4, 3.6 Hz, H-4′b), 3.79 (dd, *J* = 13.2, 9.4 Hz, H-1′a), 3.90 (dd, *J* = 13.2, 3.8 Hz, H-1a), 3.91 (dd, *J* = 13.2, 3.0 Hz, H-1′b), 3.95 (dd, *J* = 13.2, 3.2 Hz, H-1b), 3.96 (dd, *J* = 12.0, 9.2 Hz, H-5a), 4.11 (ddd, *J* = 9.2, 4.8, 2.6 Hz, H-4), 4.15 (dd, *J* = 12.0, 4.8 Hz, H-5b), 4.17 (ddd, *J* = 9.4, 6.8, 3.0 Hz, H-2′), 4.47 (dd-like, *J* = 3.2, 2.6 Hz, H-3), 4.77 (ddd-like, *J* = 3.8, 3.2, 3.2 Hz, H-2), 8.46 (1H, s, HCO_2). ^{13}C NMR (175 MHz, D_2O, internal standard: TSP) δ 51.0 (C-1), 52.3 (C-1′), 61.9 (C-5), 64.7 (C-4′), 70.3 (C-2′), 72.7 (C-4), 76.2 (C-3′), 79.7 (C-2), 80.3 (C-3), 173.7 (HCO_2^-). The spectral properties of **3c** in pyridine-d_5/D_2O (5:1) are presented in Table 1.