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CD and NMR assignment of the anomeric configuration of 4-(5-deoxy-α,β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole C-nucleoside analogs ☆

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ABSTRACT

Acid-catalyzed dehydrative cyclization of 5-deoxy-L-*manno*-pentitol-1-yl)-2-heptulose bisphenylhydrazone and subsequent reflux with copper sulfate gave an anomeric mixture of 4-(5-deoxy-α,β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole C-nucleoside analogs. The mixture was separated by chromatography, and the anomeric compositions configurations of the components were determined by CD, NMR, mass spectroscopy, and acylation.

1. Introduction

We have been interested recently in the synthesis of C-nucleoside analogs by the acid-catalyzed dehydrative cyclization of polyhydroxyalkyl heterocycles.[1–7] This reaction gives an anomeric mixture of C-nucleosides. The dehydrative cyclization of a tetrahydroxytetryl heterocycle side chain is stereospecific, affording glycofuranosyl C-nucleoside anomers having in the cyclized product a trans arrangement of the base moiety and the 2′-OH group. On the other hand, the cyclization of a pentahydroxypentyl side chain[2,7] in acid medium is not so stereospecific, with the formation of anomeric pairs of glycofuranosyl and glycopyranosyl C-nucleoside analogs with and without inversion at C-1′. In this work, the anomeric configurations of the formed C-nucleosides were determined by CD measurements in light of the CD-triazole rule[8] and were confirmed by NMR spectroscopic measurements.

2. Results and discussion

Treatment of 4-(5-deoxy-L-*manno*-pentitol-1-yl)-2-heptulose bisphenylhydrazone (**1a**) with methanolic sulfuric acid and subsequent reflux with copper sulfate afforded an anomeric mixture of the C-nucleoside analogs, namely, 4-(5-deoxy-α- and β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazoles (**2**) and (**3**), respectively (Scheme 1). The two anomers were separated by column chromatography on an anion-exchange resin with gradient elution using aqueous methanol. The anomeric configuration of the products was misassigned, on the basis of NMR spectroscopy from the chemical shift of the methyl and H-4′ signals, analogous to the procedure used for 6-deoxy pyranosides.[10]

Recently, we used circular dichroism for assigning the anomeric configuration of *C*-glycosyl-2-phenyl-2*H*-1,2,3-triazoles. The CD spectra of a series of 4-(tetrahydroxytetryl-1-yl)-2-phenyl-2*H*-1,2,3-triazoles[11,12] and 4-(pentahydroxypentyl-1-yl)-2-phenyl-2*H*-1,2,3-triazoles[8,13] were studied. A correlation between the sign of the Cotton effect at the maximum UV absorption and the absolute configuration of the hydroxyl group α to the triazole base moiety was obtained. Compounds having hydroxyl groups α to the triazole base moiety and to the right in a Fischer projection formula (D-glycero or *S* chirality) show a positive Cotton effect at the maximum UV absorption. Those having the hydroxyl group to the left in a Fischer projection (L-glycero or *R* chirality) show negative Cotton effect. This correlation has been stated as the CD-triazole rule[8] for anomeric configuration assignment of C-nucleoside triazole analogs. This correlation was applied for glycofuranosyl,[11,12] glycopyranosyl[8,13], and 5′-hydroxymethylfuranosyl C-nucleoside triazole analogs[8,13] without exception. In this work, it is extended to 5′-deoxyfuranosyl analogs. The CD spectrum of **1** (Fig. 1) showed a positive Cotton effect at the maximum UV absorption, manifested by the right-hand configuration of the

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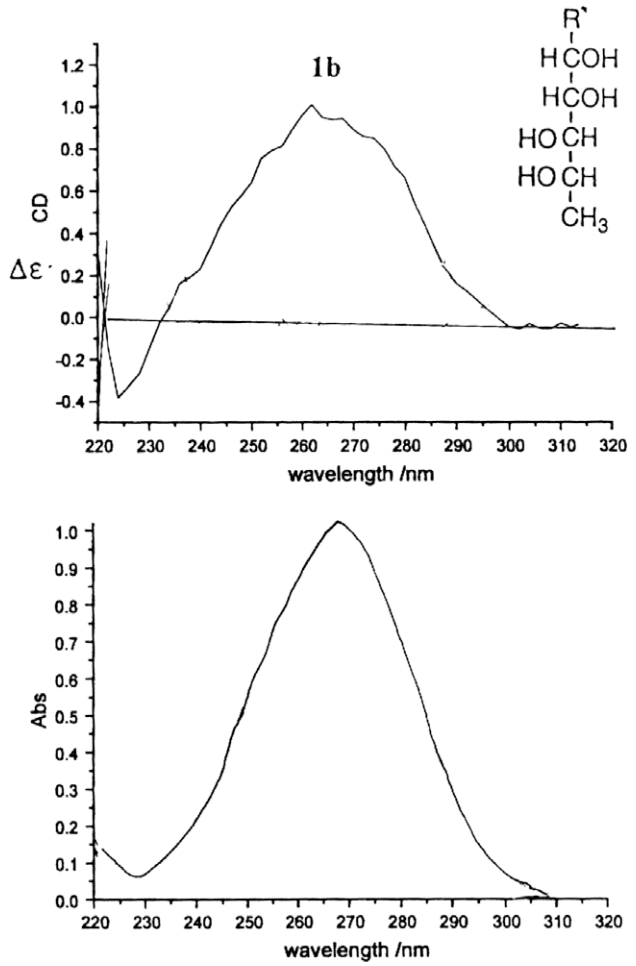


Figure 1. CD spectrum of 4-(5-deoxy-L-*manno*-pentitol-1-yl)-2-pheny1-2*H*-1,2,3-triazole **1b** in methanol.

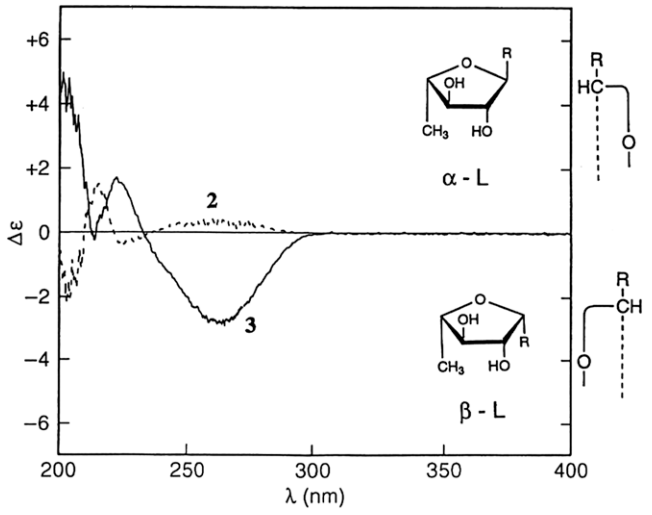


Figure 2. CD Spectra of 4-(5-deoxy-α-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3- triazole (**2**) (——) and 4-(5-deoxy-β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3- triazole (**3**) (—).

1′-OH group. The CD spectra of compounds **2** and **3** (Fig. 2) showed opposite Cotton effects in the same region. Compound **2** showed a positive Cotton effect identical to **1**, indicating that the right-hand configuration of the ring oxygen of its Fischer projection formula, that is, the α-L-configuration of the furanosyl group formed. The CD spectrum of compound **3** showed a negative Cotton effect in the same region in accord with the left-hand configuration of the ring oxygen, that is, the β-L-configuration of the furanosyl group formed. Compound **3** showed a higher spectrum amplitude than did compound **2**, which can be attributed to a different population of conformations. This CD assignment of the anomeric configuration of compounds **2** and **3** is opposite to the assignment obtained[9] from NMR measurements. Similar correction for the NMR assignment of the anomeric configuration by CD measurements was obtained.[8]

The CD anomeric assignment of **2** and **3** was ascertained by applying different NMR criteria. Compound **2** showed the anomeric proton H-1′ as a doublet at δ 4.83 ($J_{1',2'}$ 6.1 Hz) (Table 1). Compound **3** showed the anomeric proton H-1′ as a doublet at δ 5.09 ($J_{1',2'}$ 5.6 Hz). The anomeric configuration cannot be obtained from the coupling constant $J_{1',2'}$ values, since these values are not consistently diagnostic. However, comparing the chemical shift values of H-1′, compound **3** has the anomeric proton at lower field (δ 5.09) than compound **2** (δ 4.83). This is in accord[7] with the cis arrangement of H-1′ and H-2′ for compound **3**, that is, the 5′-deoxy-β-L-arabinofuranosyl configuration. Its anomer **2** having the anomeric proton upfield (δ 4.82) was assigned the trans arrangement of H-1′ and H-2′, that is, the 5-deoxy-α-L-arabinofuranosyl configuration. Analogously, the anomeric proton (H-1′) for the acetyl derivative **4** was shown upfield (δ 5.28) to that of the anomeric analogue **5** (δ 5.39) in accord with the *trans* arrangement of H-1′ and H-2′ for **4** and cis arrangement of H-1′ and H-2′ for **5**. Compound **2** was obtained from **1** without inversion in the configuration at C-1′, and **3** was obtained from **1** with inversion in the configuration at C-1′.

The anomeric configurations of some rhamnopyranosyl anomers[14] were obtained from the chemical shifts of the methyl peaks. The C-5′–CH_3 peak for the α-anomer is located at higher field than the β-anomer. For 5-deoxy-L-arabinofuranosyl anomers **2** and **3**, compound **2** showed the C-4′–CH_3 peak at higher field (δ 1.21) than that for compound **3** (δ 1.33), in accord with the α-L-configuration for **2** and β-L-configuration for **3**. The opposite correlation was obtained for the H-4′ signal for **2** and **3**. The α-L-anomer **2** showed deshielding of the H-4′ peak (δ 3.91) relative to that for the β-L-anomer **3** (δ 3.75). Analogously, the acetyl derivatives **4** and **5** showed the same correlation (Table 1). The C-4′–CH_3 for compound **4** was shown upfield (δ 1.45) to that for compound **5** (δ 1.51), and the H-4′ signal for compound **4** was deshielded (δ 4.28) relative to that for compound **5** (δ 4.07), in accord with the α-L-configuration for **4** and the β-L-configuration for **5**.

The anomeric configuration of **2** and **3** can also be confirmed from the ^{13}C NMR data (Table 2). The anomeric carbon atom C-1′ for compound **2** was shown with a downfield chemical shift (δ 77.2) relative to that for **3** (δ 76.6), in accord[7] with the *trans* arrangement of H-1′ and H-2′ for **2** and *cis* arrangement of H-1′ and H-2′ for **3**. Similar observations were evident for compounds **4** and **5**. Compound **4** showed a downfield shift of C-1′ (δ 77.1) relative to that for **5** (δ 76.9). This is in accord with the α-L configuration for **4** and the β-L-configuration for **5**. The anomeric configuration can be confirmed from the ^{13}C chemical shift of the CH_3 peak for compounds **2** and **3**. The α-L-anomer **2** showed the methyl peak at higher field (δ 20.6) than that for the β-L-anomer **3** (δ 20.7). Similarly, the methyl peak of the α-L acetyl anomer **4** was shown at higher field (δ 20.0) than that for the β-L acetyl anomer **5** (δ 20.8). The ^{13}C chemical shift of C-4′ showed the opposite correlation. The C-4′ of the α-L-anomers **2** (δ 82.4) and **4** (δ 79.5) were more deshielded than the corresponding resonances for the β-L-anomers **3** (δ 81.8) and **5** (δ 77.4), respectively.

Table 1
Chemical shift (δ) and first-order coupling constants (J, Hz)[a] for compounds **1–5** at 500 MHz

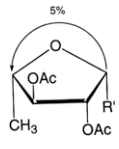
Compd	Glycosyl moiety							2-Phenyl-2*H*-1,2,3-triazole moiety			
	H–1′	H–2′	H–3′	H–4′	OH	OAc	CH_3	H-5	H-*o*	H-*m*	H-*p*
1b[b]	4.72d $J_{1',2'}$ 9.2	3.93d $J_{2',3'}$ 0.0	3.43d $J_{3',4'}$ 7.7	3.58m	5.49d *J* 5.4 4.46 *J* 5.4 4.27 *J* 8.4 4.22 *J* 7.7		1.11d *J* 6.2	7.94s	7.96d	7.52t	7.36t
2[b]	4.83d $J_{1',2'}$ 6.1	4.16q	3.62d	3.91m	5.01d *J* 5.4 5.31 d *J* 3.8		1.21d *J* 11.1	8.06s	7.96d	7.53t	7.38
3[b]	5.09d $J_{1',2'}$ 5.6	3.99m	2.47d	3.75m	5.33 *J* 3.9 5.12 *J* 5.4		1.33d *J* 6.3	7.90s	4.46d *J* 8.6	7.52t	7.37t
4[c]	5.28d $J_{1',2'}$ 3.5	5.60t *J* 2.9, *J* 2.3	5.02t *J* 2.4	4.28m		2.14s 2.03s	1.45d *J* 6.3	7.82s	8.05d	7.47t	7.34t
5[c]	5.39d $J_{1',2'}$ 3.9	6.96d *J* 3.1	4.94t *J* 1.6 *J* 2.3	4.07m		2.14s 1.96 s	1.51d *J* 6.1	7.83s	8.02d	7.46t	7.34t

[a] J values after the addition of CD_3CO_2D.
[b] In Me_2SO-d_6.
[c] In $CDCl_3$.

Table 2
^{13}C NMR data and chemical shifts (δ) for compounds **1–5** at 125.8 MHz

Compd	Glycosyl moiety							2-Phenyl-2*H*-1,2,3-triazole moiety					
	C–1′	C–2′	C–3′	C–4′	CO	OCH_3	CH_3	C-4	C-5	C-*a*	C-*o*	C-*m*	C-*p*
1[a]	66.3	71.8	73.8	66.7			21.4	153.8	139.9	135.4	118.5	130.2	127.8
2[a]	77.2	79.4	82.8	82.4			20.6	135.2	139.7	151.1	118.8	130.2	128.1
3[a]	76.6	78.8	83.0	81.4			20.7	139.7	136.8	148.3	130.1	118.6	127.9
4[b]	77.1	82.0	82.5	79.5	170.3 170.1	21.0 18.5	20.00	139.8	134.0	147.7	119.0	129.3	127.7
5[b]	76.9	77.1	82.5	77.4	170.0 169.3	21.0 19.1	20.8	139.7	135.2	144.9	118.9	129.4	127.7

[a] In Me_2SO-d_6 + CD_3CO_2D.
[b] In $CDCl_3$.



5

Figure 3. NOE difference for 4-(2,3-di-*O*-acety1-5-deoxy-β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole **5**.

The NOE experiment is an even more reliable[12] tool for anomeric assignment. The NOE difference for **5** (Fig. 3) showed 5% enhancement at H-4′ upon irradiation at H-1′. This indicates the presence of H-1′ and H-4′ on the same face of the β-L-furanosyl ring.

The specific rotation at the D-line for compound **3** was more negative ($[\alpha]_D$ −138.4) than that for **2** ($[\alpha]_D$ −28.7), indicating *cis* relationship of the base moiety and the tail CH_3 group at the 5-deoxy-L-arabinofuranosyl ring, that is, the β-L-configuration of **3** and the α-L-configuration of **2**. Similar correlation[12] was observed for compounds having the L-threofuranosyl ring. The β-L-threofuranosyl anomer was more negative in its optical rotation than the α-L-threofuranosyl anomer.

3. Conclusions

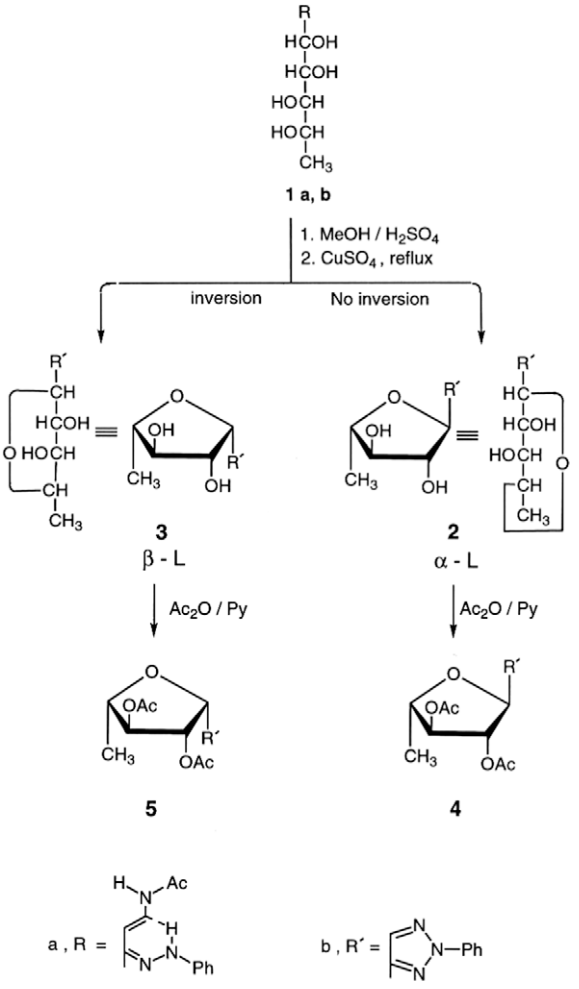
The anomeric configuration of 4-(5-deoxy-α- and β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole analogs was reinvestigated in light of the CD-triazole rule for anomeric assignment. The anomer having the ring oxygen at C-1′ on the Fischer projection formula to the right (D-glycero or *S* chirality) showed a positive Cotton effect at the maximum UV absorption in accord with the α-L-configuration. The anomer having the ring oxygen to the left (L-glycero or *R* chirality) showed a negative Cotton effect in accord with the β-L-configuration. This indicates that the CD-triazole rule[8] is applicable for 5-deoxyl-L-arabinofuranosyl anomers, in addition to the glycofuranosyl, glycopyranosyl, and 5′-hydroxymethyl furanosyl analogs. This allows the correction of the anomeric configurations obtained solely from NMR measurements and confirmed by different NMR criteria. Compound **2** was obtained from

1 without inversion in the configuration at the carbon atom α to the triazole base moiety, and compound **3** was obtained with inversion. The acid-catalyzed dehydrative cyclization of 5-deoxy-L-*manno*-pentitol-1-yl side chain is a nonstereospecific process. It is therefore necessary to use more than one spectroscopic method for anomeric assignment of C-nucleosides.

4. Experimental

4.1. General methods

Melting points were determined with a Fisher–Johns instrument and are uncorrected. Evaporations were performed under diminished pressure below 70 °C. Thin-layer chromatography (TLC) was conducted on silica gel (Kieselgel G, E. Merck, Darmstadt, Germany) with solvent **A**, 3:1 toluene–MeOH; **B**,1:3 EtOAc–*n*-hexane. Compounds were detected under shortwave UV light at 254 nm. Optical rotations were recorded with Perkin–Elmer 141 and Jasco P1030 instruments (10 cm, 1 mL microcell). CD measurements were recorded for solutions in MeOH on a Jasco 720 WI spectropolarimeter at concentrations 0.25–0.3 mg/mL MeOH (0.2 mL microcell). ^{1}H NMR spectra were recorded with a Jeol Ex 400 MHz spectrometer using tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded with a Jeol/JNM ECA 500 at 125 MHz. Assignment of peaks was verified by ^{1}H–^{13}C COSY experiments. Mass spectra were recorded with electrospray-ionizaton Microtof instrument. The sample was dissolved in methanol, and a 500 μg/mL solution of sodium formate in 0.1% formic acid solution was used as the standard calibration solution. Combustion analyses were carried out at the Chemistry Department, Faculty of Science, Cairo University.



Scheme 1. Synthesis and anomeric assignment of 4-(5-deoxy-α and β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole C-nucleoside analogs.

4.2. 4-(5-Deoxy-L-*manno*-pentitol-1-yl)-2-phenyl-2*H*-1,2,3-triazole (1b)

Compound **1b** was prepared from 7-deoxy-L-*manno*-pentitol-1-yl-heptulosebisphenylhydrazone **1a** by refluxing with copper sulfate as in the standard procedure. Compound **1a** was prepared from the precursor 7-deoxy heptoses[15,16] by the action of phenylhydrazine. Compound **1b** was obtained as colorless needles: mp 152–54 °C; R_f 0.44 (**A**); $[\alpha]_D$ +22.2 (*c* 1.01, MeOH); λ_{max} (MeOH) 266.9 (log ε, 4.3). For ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2; circular dichroism data in MeOH at 22 °C: observed CD; λ (Δε), 266.9 (+0.99). Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.04. Found: C, 56.13; H, 6.39; N, 14.94.

4.3. 4-(5-Deoxy-β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-trazole (3)

Compound **3** was separated from the anomeric mixture on a column of Dowex-1×8 (OH^-) anion-exchange resin by elution with 60% MeOH by a standard procedure.[9] Recrystallization of the solid obtained from water gave colorless needles: mp 120–122 °C. (lit.[9] mp 118–120 °C); $[\alpha]_D$ −138.4 (*c* 1.5, MeOH); λ_{max} (MeOH) 265.8 (log ε 4.3). For ^{1}H NMR and ^{13}C NMR data, see Tables 1 and 2; circular dichroism data in MeOH at 22 °C; observed CD; λ (Δε), 265.4 (−2.9).

4.4. 4-(5-Deoxy-α-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole (2)

Compound **2** was eluted from the column of Dowex-1×8 (OH^-) ion-exchange resin with 90% MeOH. The solid residue was recrystallized from benzene–*n*-hexane as colorless needles: mp 88 °C (lit.[9] mp 88 °C); $[\alpha]_D$ −28.7 (*c* 3.0, MeOH); λ_{max} 266.6 (log ε 4.3). For ^{1}H NMR and ^{13}C NMR data see Tables 1 and 2; circular dichroism data in MeOH at 22 °C; observed CD; λ (Δε), 260.2 (+0.4).

4.5. 4-(2,3-Di-*O*-acetyl-5-deoxy-α-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole (4)

Compound **2** (10 mg, 0.02 mmol) in pyridine (2 mL) was treated with Ac_2O (2 mL) and kept at room temperature for 12 h. The mixture was evaporated until dry, and traces of pyridine were removed by spin coevaporation with toluene. The dry residue was chromatographed on a short column (1 × 10 cm) of Silica Gel 60, eluting with solvent **B**, giving a colorless syrup (yield 17 mg). For ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRMS of the molecular ion peak calcd for $C_{17}H_{19}N_3O_5Na$: *m*/*z* 368.1222; found, *m*/*z* 368.1226.

4.6. 4-(2,3-Di-*O*-acetyl-5-deoxyl-β-L-arabinofuranosyl)-2-phenyl-2*H*-1,2,3-triazole (5)

Compound **3** (13 mg, 0.037 mmol) in pyridine (2 mL) was treated with Ac_2O (2 mL) and kept at room temperature for 24 h. The mixture was poured into crushed ice, extracted with CH_2Cl_2, and the organic layer was separated, washed with satd aq $CuSO_4$, and water, then dried over anhyd Na_2SO_4 and filtered. The filtrate was evaporated to a syrup that was chromatographed on a short column (1 × 10 cm) of Silica Gel 60, eluting with solvent **B**. It gave a colorless syrup (20 mg); R_f 0.67 (**B**). For ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRMS of the molecular ion peak calcd for $C_{17}H_{19}N_3O_5Na$: *m*/*z* 368.1222; found, *m*/*z* 368.1217.

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