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# STRUCTURE AND ANOMERIC CONFIGURATION OF THE 3,6-ANHYDRO-OSAZONE DERIVATIVES OBTAINED FROM D-*altro*-2-HEPTULOSE PHENYLOSAZONE*

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ABSTRACT

Dehydration of D-*altro*-2-heptulose phenylosazone with methanolic sulfuric acid afforded two 3,6-anhydro-osazone derivatives (**2** and **3**). Compound **3** was obtained as the preponderant isomer, with inversion at C-1 (C-3 of the starting osazone), and **2** was obtained without inversion. Refluxing of **3** with copper sulfate afforded the *C*-nucleoside analog, namely, 2-phenyl-4-β-D-ribofuranosyl-1,2,3-osotriazole (**4**). Acetylation of **4** afforded the tri-*O*-acetyl derivative **5**. The anomeric configuration was determined by c.d. and n.m.r. spectroscopy. The mass spectra of compounds **2**–**5** are discussed.

## INTRODUCTION

Monosaccharide 3,6-anhydro-osazones[2–4] are useful precursors for the synthesis of *C*-nucleoside analogs[5] required for biological investigations. They are considered a rich source for the supplementing of a wide variety of sugar moieties, especially those having rare configurations (which cannot readily be obtained by simple, synthetic methods). Saccharide 3,6-anhydroosazones are readily prepared by dehydrative cyclization of the hydroxyalkyl chain of monosaccharide osazones with methanolic sulfuric acid solution, but lack of knowledge as to the anomeric configuration of the products restricted the use of these compounds in the past for the synthesis of *C*-nucleoside analogs.

The dehydrative cyclization of monosaccharide osazones is usually accompanied by inversion in the configuration of C-3 of the starting osazone, producing two isomers, which makes their anomeric configuration of significant importance. An empirical rule, based on circular-dichroism measurements, was suggested[6] for assignment of the anomeric configuration of each of the products, but recently, high-resolution, n.m.r. studies of monosaccharide 3,6-anhydro-osazones[7,9] have revealed that n.m.r. spectroscopy can be a more reliable tool for the assignment of the anomeric configuration of each of the products. Moreover, it supported the

*Studies on Anhydro-Osazones. Part III. For Part II, see ref. 1.

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empirical rule[6], based on circular-dichroism measurements, for the assignment of the anomeric configuration of the 3,6-anhydro-osazones from hexoses.

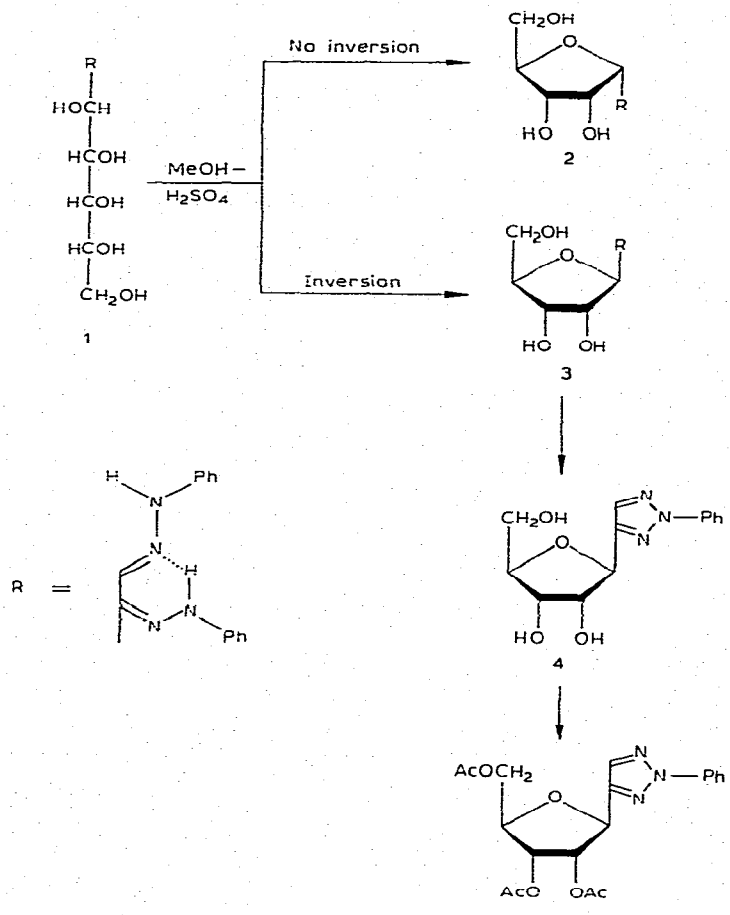
However, n.m.r.-spectral studies on higher monosaccharide phenylosazones[8,9] did not show a general correlation, analogous to that for the hexose phenylosazones[6], between the anomeric configuration and the configuration of the 4-hydroxyl group. The proportion of the minor isomer from heptulose phenylosazones is usually higher than that from hexulose phenylosazones. The minor isomer obtained from the latter compounds has a *cis* relationship between the bis(hydrazone) group and the 4-hydroxyl group (OH-2 of the glycosyl group formed). For higher monosaccharide analogs, contradictory results were obtained; D-*galacto*-2-heptulose phenylosazone[9] and D-*gluco*-2-heptulose phenylosazone[8] produce a higher proportion of the isomer having the *cis* relationship between the bis(hydrazone) group and the 4-hydroxyl group than that having the *trans* relationship. However, D-*manno*-2-heptulose phenylosazone[8] showed the opposite correlation; the isomer having a *trans* relationship between the bis(hydrazone) group and the 4-hydroxyl group was relatively higher in proportion than that having a *cis* relationship.

We now describe the synthesis, and separation, of two 3,6-anhydro-osazone derivatives obtained by dehydrative cyclization of D-*altro*-2-heptulose phenylosazone with methanolic sulfuric acid. The preponderant anomer was the one having the bis(hydrazone) group *trans* to the 4-hydroxyl group (OH-2 on the furanoid ring).

## DISCUSSION

Dehydration of D-*altro*-2-heptulose phenylosazone (**1**) by refluxing with methanolic sulfuric acid (with monitoring of the reaction by t.l.c.) afforded 3,6-anhydro-D-*allo*-2-heptulose phenylosazone (**3**) and 3,6-anhydro-D-*altro*-2-heptulose phenylosazone (**2**) in the ratio of 5 : 1. They were separated by fractional recrystallization, and purified by preparative t.l.c. Analogous to the dehydration of hexulose phenylosazones having a *trans* arrangement of the 3- and 4-hydroxyl groups in the Fischer projection formula, dehydration of **1** afforded more of the anomer **3**, having the bis(hydrazone) group *trans* to the 4-hydroxyl group (OH-2 on the furanoid ring) (see Scheme 1). However, the proportion of isomer **2** [having a *cis* relationship between the bis(hydrazone) group and the 4-hydroxyl group] is higher from **1** than from the hexulose phenylosazones.

Circular dichroism (c.d.) spectra of compounds **1**, **2**, and **3** (see Fig. 1) showed multiple Cotton-effects. The configuration of C-3 of these compounds (C-1 of the aldosyl group formed) is manifested by the sign of the Cotton effect at the long-wavelength absorption[6,10]. As previously observed[6], a positive Cotton-effect indicates the L-*glycero* configuration of C-3, and *vice versa*. However, compound **3** showed a negative Cotton-effect at 336–370 nm, opposite in sign to that of the precursor osazone **1**, suggesting the D-*allo* configuration for **3**, which is obtained with inversion in the configuration of C-3 of the precursor osazone (C-1 of the aldosyl group formed). On the other hand, compound **2** showed a negative Cotton-effect




Scheme 1

of the same sign as that of the precursor osazone **1** in the same region, suggesting the D-*altro* configuration for **3**, which is obtained from **1** without inversion of C-3. In the short-wavelength region, the spectrum of **3** was also the reverse of that of **1** and **2**; it showed two positive Cotton-effects, at 280–330 and 230–260 nm, which were opposite in sign to the Cotton effects of **1** and **3** in the same region.

Additional evidence supporting the chiroptical assignment was obtained by n.m.r.-spectral studies. The high-resolution (360 MHz), n.m.r. spectrum of compound **3** (see Fig. 2) showed the anomeric proton as a doublet centered at $\delta$ 4.24 having $J_{1',2'}$ 9.32 Hz. This coupling-constant value is in agreement[11,12] with either a *cis* or a *trans* arrangement for H-1′ and H-2′ of the ribofuranosyl group. The *trans* assignment of the anomeric proton of $\beta$-D-ribosyl derivatives on the basis of the observed coupling-constant, excluding conformational changes, can be certain[11,13] only if the coupling constant ($J_{1',2'}$) for the anomeric proton is $<3.5$ Hz.

On being refluxed with copper(II) sulfate, compound **3** afforded a *C*-nucleoside derivative, namely, 2-phenyl-4-$\beta$-D-ribofuranosyl-1,2,3-osotriazole (**4**). Its n.m.r.

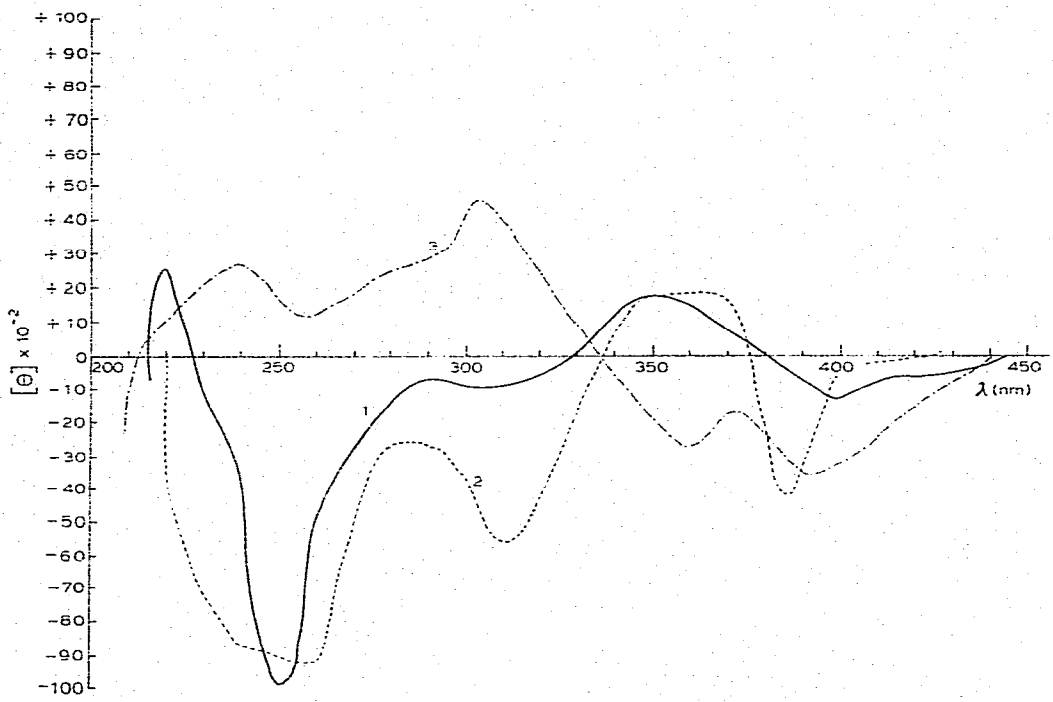



Fig. 1. C.d. spectra of (1) D-*altro*-2-heptulose phenylosazone (——), (2) 3,6-anhydro-D-*altro*-2-heptulose phenylosazone (....), and (3) 3,6-anhydro-D-*allo*-2-heptulose phenylosazone (–.–.–)

spectrum (see Fig. 3) showed the anomeric proton as a doublet centered at $\delta$ 4.60 ($J_{1',2'}$ 9.8 Hz). Although this coupling constant is large, and close to other values assigned[9] for the *cis* arrangement of H-1′ and H-2′ of the furanosyl group, the *trans* arrangement cannot be excluded, and the latter is only possible[11,13] if the coupling constant is $<3.5$ Hz. Likewise, a coupling constant of 9.1 Hz for the anomeric proton at $\delta$ 5.02 was obtained for the tri-*O*-acetyl derivative **5**, and subsequent acetylation caused little effect on the coupling constant of the anomeric proton of **4**. However, the anomeric assignment was made certain from the chemical shift of H-5 of the osotriazole moiety of **4**. It was found[5] that $\beta$-anomeric osotriazole *C*-nucleosides show H-5 at lower field than the corresponding $\alpha$ anomers. Compound **4** showed H-5 at $\delta$ 8.04, consistent with the values assigned[5] for the $\beta$-D configuration.

The isolation of the two 3,6-anhydro-osazones, **2** and **3**, from the dehydration of **1** indicates that racemization took place at C-3 of the precursor osazone **1** at some stage of the reaction; this may be explained by the formation of a 2-(phenylazo)-2-ene intermediate[14,15], or a carbonium-ion intermediate. The preponderance of the isomer **3** can be explained by its high thermodynamic-stability, due to the *trans* arrangement of the bis(hydrazone) group and the 2-hydroxyl group of the furanosyl ring, besides the favorable, *trans* arrangement of the exocyclic hydroxymethyl group and the 3-hydroxyl group (present in both compounds **2** and **3**).

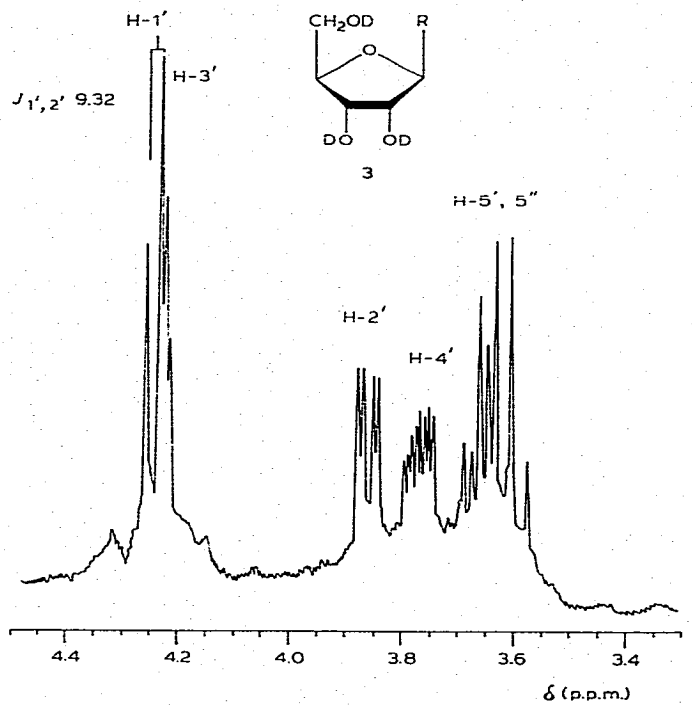



Fig. 2. N.m.r. spectrum, at 360 MHz, of 3,6-anhydro-D-*allo*-2-heptulose phenylosazone (3) + $CD_3CO_2D$ (high resolution, of the sugar moiety); R = bis(hydrazone) residue.

The mass spectra of the 3,6-anhydro-osazone derivatives **2** and **3** were identical: that is, they showed the same type of fragmentation. However, a difference in the intensity of some peaks, particularly the molecular-ion peaks 371 and 370 (see Experimental part), was found, and this can be attributed to the difference in the vapor pressure of isomers **2** and **3** (there is a wide difference in their melting points). The peaks at *m/z* 263 (M — PhNHNH), 262 (M — $PhNHNH_2$), 200, and 105 (PhCNH) also showed appreciable differences in intensity. However, compounds **2** and **3** showed the same base-peak at *m/z* 93, which correspond to $PhNH_2$.

The mass spectra of the β-D-*ribo* *C*-nucleoside derivative **4** showed a fragmentation pattern identical to that of the *lyxo* *C*-nucleoside analogs[9]. The carbon–carbon bond between the carbohydrate and the heterocycle is confirmed[16] by the lessened intensity of the peaks at *m/z* 145 (B + H) and 146 (B + 2 H), and the abundance of the peak at *m/z* 174 (B + 30). The latter was proposed[17] as a major fragment for the ribofuranosyl *C*-nucleosides, and recently[9] for the lyxofuranosylosotriazole *C*-nucleoside analogs, and can be used for the characterization of *C*-nucleosides in general[9]. Another characteristic peak for *C*-nucleosides[18] appeared at *m/z* 188 (B + 44) as an abundant peak, also abundant for the lyxofuranosyl analogs[9]; it is formed by the fragmentation of the O–C-1′ and C-2′–C-3′ bonds, as shown in Scheme 2. The weak peaks at *m/z* 247 (M — 30) and 246 (M — 31) demonstrate the

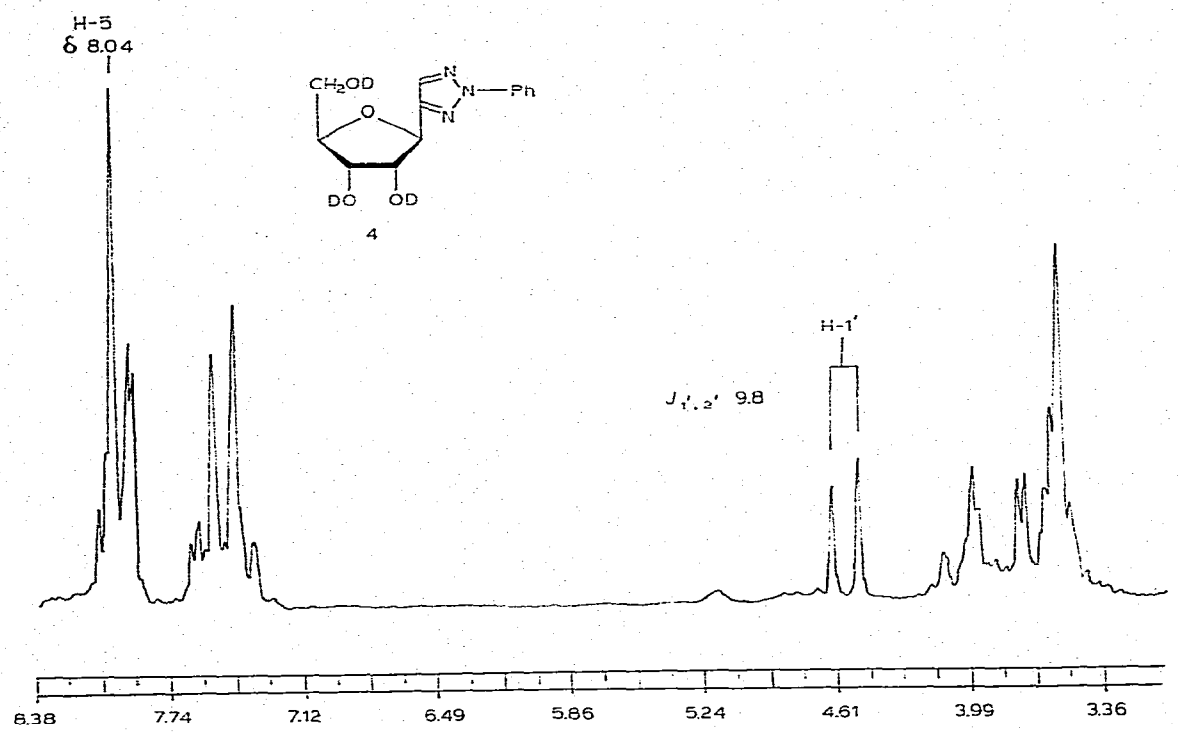
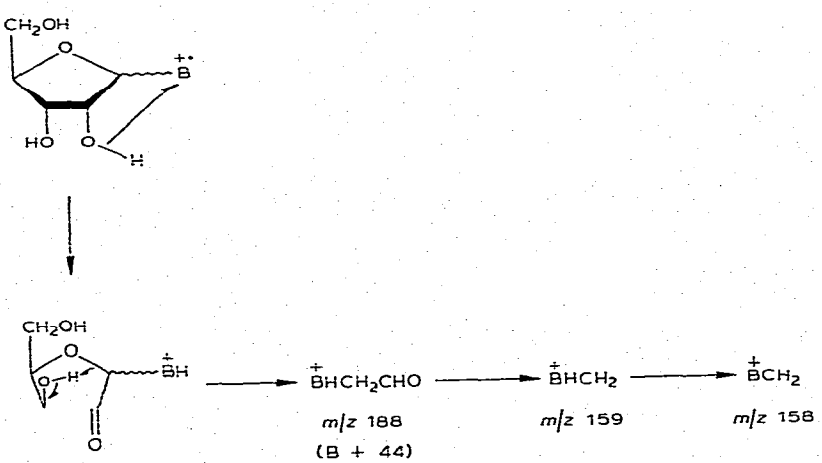



Fig. 3. N.m.r. spectrum, at 80 MHz, of 2-phenyl-4-β-D-ribofuranosyl-1,2,3-osotriazole (**4**) after addition of $CD_3CO_2D$.




B = 2-Phenyl-1,2,3-osotriazol-4-yl group

Scheme 2

presence of the exocyclic, hydroxymethyl group and the furanose structure of the sugar moiety.

The mass spectrum of the *ribo* *C*-nucleoside triacetate **5** showed a fragmentation pattern identical to that of the *lyxo* analogs[9]. The molecular-ion peaks M, M + 1, and M + 2 appeared at 403, 404, and 405. The base peak at *m/z* 43 corresponds to $CH_3CO$. The peaks characteristic for *C*-nucleosides, namely, B + 30 and B + 44, appeared at *m/z* 174 and 188, but with less intensity than for the precursor, *C*-nucleoside analog **4**.

## EXPERIMENTAL

*General.* — Melting points are uncorrected; evaporations were performed under diminished pressure below 60°. Thin-layer chromatography (t.l.c.) was conducted on silica gel (Kiesel gel G, Merck) with solvent *A*, 3:1 benzene–ethanol; or solvent *B*, 2:1:1 benzene–chloroform–ethanol. I.r. absorption spectra were recorded with a Beckman IR-33 instrument. U.v. absorption spectra were recorded with a Cary 17 instrument. Circular dichroism measurements were recorded with a Cary 60 spectropolarimeter, at a dynode voltage not >0.75 kV. N.m.r. spectra were recorded with Varian FT (80 MHz), Perkin–Elmer R-32 (90 MHz), and NTC (360 MHz) instruments. Mass spectra were obtained with a Dupont MS 21-492B spectrometer. Combustion analyses were performed in the Department of Chemistry, Purdue University.

D-altro-*2-Heptulose phenylosazone* (**1**). — A solution of D-*altro*-heptulose (prepared[19] from sedoheptulosan, 3 g) in hot water (100 mL) was heated with phenylhydrazine (7 mL) and acetic acid on a boiling-water bath for 3 h. The osazone that separated was collected, washed, and dried; yield 2.8 g. It was recrystallized from dilute methanol, to give yellow needles, m.p. 197–199° (lit.[20] m.p. 197°); $\nu_{max}^{KBr}$ 3400 (OH) and 1605 $cm^{-1}$ (C=N); $\lambda_{max}^{MeOH}$ 239, 300 (sh), and 357 nm (log ε 4.3, 4.1, and 4.3); $\lambda_{min}^{MeOH}$ 276 nm (log ε 4.0); circular dichroism data in methanol (*c* 0.04 mg/mL) at 22°; 445 ([*θ*] 0), 400 (−1,288), 380 (0), 350 (+1,932), 330 (0), 300 (−966), 290 (−644), 250 (−10,304), 228 (0), and 216 (0).

*3,6-Anhydro*-D-altro-*2-heptulose phenylosazone* (**2**). — D-*altro*-2-Heptulose phenylosazone (2 g) was boiled under reflux with 0.05% methanolic sulfuric acid (250 mL) for 5 h, the reaction being monitored by t.l.c.; after 5 h of refluxing, t.l.c. (solvent *A*) revealed the absence of the starting osazone, and formation of two more-mobile spots, in the ratio of 1:5, having $R_F$ 0.67 and 0.64, respectively (solvent *A*). The solution was poured into hot water, and the methanol was evaporated under diminished pressure. The precipitate obtained was filtered off, washed with water, and dried; yield 1.7 g. The mixture (0.7 g) was purified by chromatography on a column of silica gel, using 2-butanone saturated with water as the eluant. The yellow fractions were collected, and, on concentration, gave yellow needles which were rapidly filtered off, and dried; m.p. 245°; $R_F$ (of the faster-moving spot) 0.67 (solvent *A*) and 0.76 (solvent *B*); $\lambda_{max}^{MeOH}$ 237 (sh), 256, 305, and 377 nm (log ε 4.1, 4.1, 4.0,

and 4.2); $\lambda_{min}^{MeOH}$ 280 and 325 nm (log ε 3.9 and 4.0); mass-spectral data (selected ions): *m/z* 372 (5, M + 2), 371 (M + 1), 370 (85, M), 292 (5), 278 (9), 263 (12), 262 (7), 242 (13), 200 (7), 188 (28), 187 (7), 175 (7), 174 (16), 173 (7), 172 (6), 159 (7), 158 (13), 146 (7), 145 (9), 119 (17), 118 (9), 108 (10), 107 (9), 106 (10), 105 (17), 104 (13, PhCNH), 103 (4, PhCN), 94 (23), 93 (100, $PhNH_2$), 92 (77, PhNH), 91 (31, PhN), 78 (12, PhH), 77 (66, Ph), 73 (13), 70 (5), 66 (16), 65 (56, cyclopentadiene ion), 61 (7), 57 (16), 55 (7), 51 (16), 45 (18), and 43 (17); accurate measurement of the molecular-ion peak: Found 370.1640 (Calc. for $C_{19}H_{22}N_4O_4$, 370.1635); circular dichroism data in methanol (*c* 53 μg/mL) at 22°: 425 ([θ] 0), 400 (−420), 385 (−420), 376 (0), 365 (+1,890), 338 (0), 330 (−1,680), 310 (−5,670), 280 (−2,730), 255 (−9,240), and 230 (−7,140).

*3,6-Anhydro*-D-allo-*heptulose phenylosazone* (**3**). — This compound was isolated as a major product by fractional recrystallization of the residue from the mother liquor of **2**, and was purified by preparative t.l.c.; $R_F$ (of the slower-moving spot) 0.64 (solvent *A*) and 0.74 (solvent *B*). It was recrystallized from dilute methanol, to give yellow needles, m.p. 158–160°; $\nu_{max}^{KBr}$ 3345 (OH), 1595 (C=N), and 1485 and 740 $cm^{-1}$ (Ph); $\lambda_{max}^{MeOH}$ 260, 300 (sh), 340, and 386 (log ε 4.1, 3.9, 4.0, and 4.0); $\lambda_{min}^{MeOH}$ 280 and 356 (log ε 3.8 and 3.9); n.m.r. data (360 MHz; acetone-$d_6$): δ 3.65–4.29 (m, 9 H, 6 sugar protons and 3 OH), 6.8–7.46 (m, 10 H, aromatic protons), 7.75 (s, 1 H, aldimino proton), 9.77 (s, 1 H, nonchelated NH of C-1 hydrazone residue), and 12.39 (s, 1 H, chelated NH of C-2 hydrazone residue). After addition of $CD_3CO_2D$, the two NH protons and the three OH protons disappeared: δ 3.335–3.688 (m, 2 H, H-5′,5″), 3.743–3.779 (m, 1 H, H-4′), 3.840–3.874 (dd, 1 H, H-2′, $J_{2',3'}$ 2.77 Hz), 4.212–4.228 (m, 1 H, H-3′), and 4.228–4.253 (d, 1 H, H-1′, $J_{1',2'}$ 9.32); mass-spectral data (selected ions): *m/z* 372 (2, M + 2), 371 (12, M + 1), 370 (49, M), 352 (0.5, M − $H_2O$), 292 (1), 278 (7, M − PhNH), 263 (6), 262 (2), 242 (8), 200 (3), 188 (25), 175 (5), 174 (25), 173 (5), 172 (4), 159 (6), 158 (12), 146 (5), 145 (7), 119 (1), 118 (5), 108 (10), 107 (7), 106 (6), 105 (9), 104 (8, PhCNH), 103 (4, PhCN), 94 (16), 93 (100, $PhNH_2$), 92 (95, PhNH), 91 (22, PhNH), 85 (5), 78 (9, PhH), 77 (69, Ph), 73 (1), 70 (4), 66 (11), 65 (54, cyclopentadione ion), 61 (9), 57 (15), 53 (33), 51 (10), 45 (15), and 43 (15); accurate measurement of the molecular-ion peak: Found 370.1641 (Calc. for $C_{19}H_{22}N_4O_4$, 370.1635); circular dichroism data in methanol (*c* 40.4 μg/mL): 440 ([θ] 0), 390 (−3,562), 370 (−2,603), 360 (−2,877), 335 (0), 302 (+4,384), 295 (+3,014), 260 (+1,096), 240 (+2,745), 212 (0), and 210 (−2,192).

*Anal.* Calc. for $C_{19}H_{22}N_4O_5 \cdot 0.5\ H_2O$: C, 60.12; H, 5.85; N, 14.77. Found: C, 59.98; H, 6.31; N, 14.70.

*4-β-*D-*Arabinofuranosyl-2-phenyl-1,2,3-osotriazole* (**4**). — A suspension of **3** (1 g) in methanol (30 mL) was boiled under reflux with stirring, a solution of copper (II) sulfate (1 g) in water (30 mL) was added dropwise, and then 2 mL of 1-propanol was added. The mixture was boiled under reflux for 3 h, cooled, filtered, and the filtrate stirred with Amberlite IR-MB3 cation–anion-exchange resin. The resin was filtered off, and washed thoroughly with methanol, and the filtrate and washings were combined and evaporated to a syrup, which was distilled *in vacuo* at 220–230°/2

mm Hg, to give a colorless syrup; n.m.r. data (80 MHz, $Me_2SO$-$d_6$ + $CD_3CO_2D$): $\delta$ 3.53–4.00 (m, 5 H, H-2′,3′,4′,5′,5″), 4.60 (d, 1 H, H-1′, $J_{1',2'}$ 9.8), 7.38–7.68 (m, 3 H, meta and para protons of the phenyl group), 7.95–8.11 (m, 3 H, ortho protons of the phenyl group), and 8.04 (s, 1 H, H-5); mass-spectral data: *m/z* 279 (1, M + 2), 278 (12, M + 1), 277 (4, M), 247 (0.5, M − 30), 246 (0.3, M − 31), 200 (3, M − Ph), 188 (10, $BHCH_2CHO$, where B = 2-phenyl-1,2,3-osotriazol-4-yl moiety), 187 (7, $BCH_2CHO$), 175 (20, B + 31), 174 (100, B + 30), 173 (7, BCHO), 159 (7, $BHCH_2$), 158 (17, $BCH_2$), 146 (2, $BH_2$), 145 (0.6, BH), 144 (0.4, B), 118 (2, B − CN), 117 (2, B − HCN), 93 (4, $PhNH_2$), 92 (11, PhNH), 91 (19, PhN), 85 (6), 77 (21, Ph), 73 (7), 65 (8, cyclopentadiene ion), 60 (22), 57 (6), 51 (6), 45 (5), and 43 (8).

*2-Phenyl-4-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-1,2,3-osotriazole* (**5**). — A solution of **4** (60 mg) in pyridine (2 mL) was treated with acetic anhydride (2 mL), and kept for 24 h at room temperature. The mixture was evaporated to a syrup, and traces of pyridine were removed by repeatedly evaporating with toluene. The dry residue was distilled *in vacuo* at 200–215°/2 mm Hg, to give a colorless syrup; n.m.r. data (90 MHz, $CDCl_3$): $\delta$ 1.89, 2.02, 2.18 (t, 9 H, $CH_3CO$), 3.70–4.10 (m, 2 H, H-5′,5″), 4.20–4.50 (m, 1 H, H-4′), 4.98 (d, 1 H, H-1′, $J_{1',2'}$ 9.1 Hz), 5.23–5.41 (m, 1 H, H-3′), 5.71–5.82 (t, 1 H, H-2′), 7.23–7.57 (m, 3 H, meta and para protons of the phenyl group), 7.76 (s, 1 H, H-5), and 7.82–8.11 (m, 2 H, ortho protons of the phenyl group); mass-spectral data: *m/z* 405 (0.2, M + 2), 404 (1, M + 1), 403 (6, M), 343 (4, M − AcOH), 284 (5, M − H − 2 Ac), 283 (26, M − 2 H − 2 Ac), 277 (8), 242 (6, M − 2 Ac − H − $CH_2$=C=O), 241 (30), 240 (4), 188 (5, B + 44, where B = 2-phenyl-1,2,3-osotriazol-4-yl moiety), 187 (6, $BCH_2CHO$), 175 (B + 31), 174 (20, B + 30), 158 (5), 146 (0.7, $BH_2$), 145 (1, BH), 144 (0.3, B), 93 (1, $PhNH_2$), 92 (4, PhNH), 85 (10), 77 (9, Ph), and 43 (100, $CH_3CO$).

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