Carbohydrate Research, 121 (1983) 125–134
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

CYCLIZATION OF 2,3,4,5-TETRA-*O*-ACETYLGALACTARIC BIS-(AROYLHYDRAZIDES) TO SACCHARIDE BIS(1,3,4-OXADIAZOLYL) DERIVATIVES*

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(Received March 10th, 1983; accepted for publication, April 5th, 1983)

ABSTRACT

Condensation of 2,3,4,5-tetra-*O*-acetylgalactaroyl dichloride with two equivalents of various aroylhydrazines gave the corresponding 2,3,4,5-tetra-*O*-acetylgalactaric bis(aroylhydrazides). Condensative and dehydrative cyclization of these bis(hydrazides) with triethyl orthoformate and phosphoryl chloride, respectively, gave the corresponding 3,3′-(2,3,4,5-tetra-*O*-acetylgalactar-1,6-dioyl)-bis(5-aryl-2-ethoxy-2,3-dihydro-1,3,4-oxadiazole) and 1,2,3,4-tetra-*O*-acetyl-1,4-bis(5-aryl-1,3,4-oxadiazol-2-yl)-*galacto*-tetritols. The elucidation of the structure of the compounds prepared is discussed and mechanistic pathways for their formation are proposed.

INTRODUCTION

1,3,4-Oxadiazole and oxadiazoline derivatives are among the most widely utilized materials, both biologically and industrially. Biologically, they are used as carcinostatic[2], anticonvulsive[3], hypotensive[4], hypoglycemic[5], muscle-relaxant[6], amebicidal[7], bactericidal[8], fungicidal[9], and leprostatic[10] agents. In industry, they find application as scintillators[11], photoinitiators in electrophotography[12], and fluorescent whiteners[13]. Bis(1,3,4-oxadiazoles) have good thermal stability, and are used in heat-transfer fluids[14]. In agriculture, they are used as insecticides[15], in combating unwanted vegetation[16], and in preventing nitrification of the soil[17]. These activities and applications inspired continuation of the work we started[18,20–26] on the synthesis of saccharide 1,3,4-oxadiazoles. The saccharide moieties of these compounds would enhance their penetration into biological systems and, therefore, contribute to their activities.

One approach for the synthesis of the first known saccharide 1,3,4-oxadiazole derivative was the oxidative cyclization of the acetates of *aldehydo* sugar aroylhydrazones[18]. Tronchet and Moskalyk used this approach for the synthesis of "inverted" C-nucleoside analogs containing 1,3,4-oxadiazole rings[19]. A second ap-

*Sugar Oxadiazoles, Part VI. For Part V, see ref. 1.

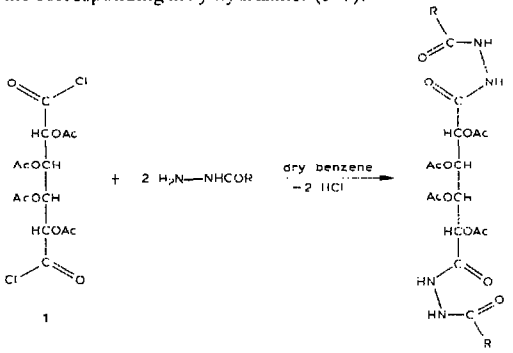
0008-6215/83/$ 03.00

proach was the dehydrative cyclization of aldaric bis(aroylhydrazide) acetates by heating with phosphoryl chloride[20] or thionyl chloride[21]. Continuing our work[18,20–26] on the synthesis, from saccharide aroylhydrazones and aroylhydrazides, of nitrogen heterocycles having saccharide chains, we now report the synthesis of some new 2,3,4,5-tetra-*O*-acetyl-galactaric bis(aroylhydrazides) (**8–13**), as well as their condensative and dehydrative cyclization to saccharide bis(1,3,4-oxadiazolyl) derivatives (**19–24** and **28–31**).

RESULTS AND DISCUSSION

Condensation of 2,3,4,5-tetra-*O*-acetylgalactaroyl dichloride[27] (**1**) with two equivalents of *m*-toluoylhydrazine (**2**) in dry benzene gave a crystalline product in good yield. Elemental analysis of this product gave values corresponding to those calculated for the molecular formula $C_{30}H_{34}N_4O_{12} \cdot H_2O$, and its infrared spectrum showed two Amide-I absorption bands, at 1710 and 1680 cm^{-1}, in addition to the NH and *O*-acetyl bands at 3360 and 1760 cm^{-1}, respectively. The ^1H-n.m.r. spectrum of this product showed signals at δ 2.08 and 2.12 (6 H, 2 C_6H_4Me), 2.25 and 2.60 (12 H, 4 OAc), 7.15–8.1 (8 H, 2 C_6H_4), and 10.10 and 10.75 (deuteratable, 4 H, 2 CONHNHCO). From these data, the condensation product was formulated as 2,3,4,5-tetra-*O*-acetylgalactaric bis(*m*-toluoylhydrazide) (**8**). A methanolic solution of the bis(hydrazide) **8** gave a reddish-brown coloration with 3% methanolic ferric chloride solution, indicating that its hydrazido groups exhibit hydrazide–hydrazidic acid tautomerism, and could, therefore, exist in either, or both, of the tautomeric structures **14** and **17**.

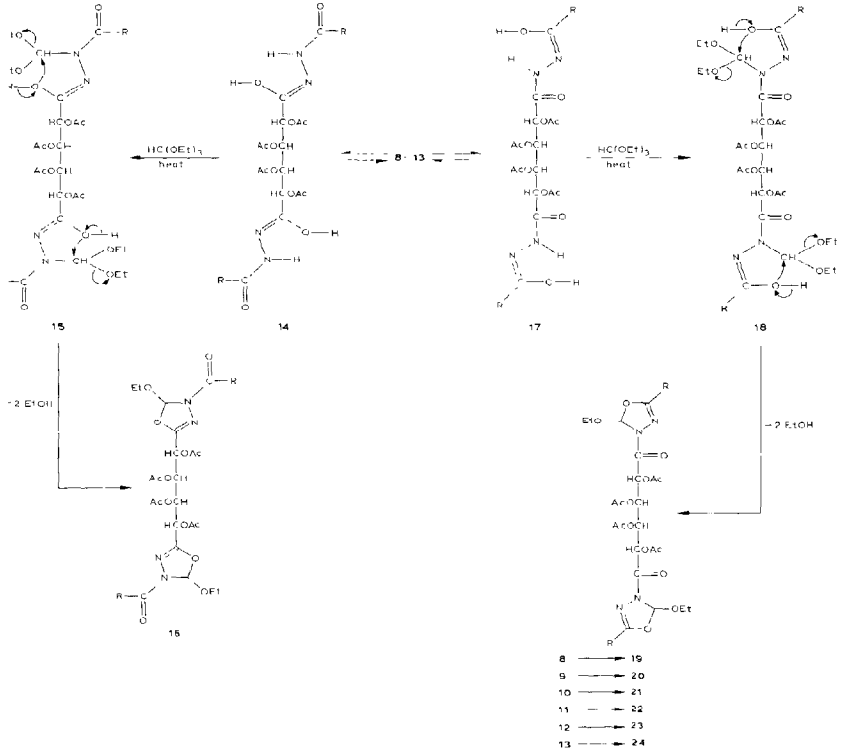
The bis (hydrazides) **9–13** were similarly prepared by condensation of **1** with the corresponding aroylhydrazines (**3–7**).



1

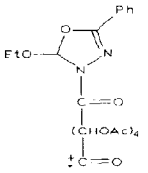
2	R = C_6H_4Me-*m*	8
3	R = C_6H_4Cl-*o*	9
4	R = C_6H_4Cl-*m*	10
5	R = C_6H_4Br-*p*	11
6	R = C_6H_4Br-*m*	12
7	R = $C_6H_4NO_2$-*p*	13

When **8** was heated with an excess of triethyl orthoformate in 1,4-dioxane, there was obtained a crystalline product having the molecular formula $C_{36}H_{42}N_4O_2$ which contains six carbon atoms (or two three-carbon fragments) more than the starting bis(hydrazide). The product gave no coloration with ferric chloride, indicating the loss of the four hydrazido protons of the parent bis(hydrazide) during its reaction with triethyl orthoformate; this was confirmed by the molecular absorption spectrum of the product, which showed bands at 1770 (OAc), 1710 (OCN), and 1600 cm^{-1} (C=N), and lacked the amide-I and NH absorptions of the starting bis(hydrazide). These data showed that condensative cyclization of the bis(hydrazide) **8** had taken place, to give either or both of the bis(1,3,4-oxadiazolinyl) derivatives (**16** and **19**) arising from the reaction of triethyl orthoformate with either or both of the two possible tautomeric forms **14** and **17**.



Just as in the reaction with noncarbohydrate hydrazides[28], each hydrazido proton of the enolic form of **14** and **17** condenses with one molecule of triethyl orthoformate, to give the respective, intermediate condensation-product (**15** or **18**). Subsequent elimination of one molecule of ethanol from each hydrazido group of the condensation intermediate results in heterocyclization, to afford each of the 1,3,4-oxadiazoline rings of **16** or **19**. The net result is the formation of the bis(1,3,4-oxadiazolin-3-yl) derivatives **16** or **19** from **14** or **17**, respectively, through the introduction of two three-carbon fragments.

Thin-layer chromatography of the cyclization product in various systems showed that it contained only one component. This was, therefore, taken to signify that only one of the two cyclization products, **16** or **19**, theoretically possible was selectively formed. The ^{1}H-n.m.r. spectrum of the product obtained showed signals at δ 1.13 (t, 6 H, 2 CH_2Me), 1.66–2.50 (18 H, 4 OAc + 2 C_6H_4Me), 3.65 (q, 4 H, 2 CH_2Me), 6.80 (s, 2 H, two oxadiazoline-ring protons), and 7.30–7.80 (m, 8 H, 2 C_6H_4Me). The spectrum was devoid of the deuteratable, four-proton signals of the hydrazido groups, characteristic of the parent bis(hydrazide). These data could be reconciled with both of the two cyclization products, **11** and **18**, theoretically possible, and cannot distinguish between them. In a previous report[25] from this laboratory, 2,3,4,5-tetra-*O*-acetylgalactaric 1,6-bis(benzoylhydrazide) was similarly cyclized with triethyl orthoformate, and the product was unequivocally assigned the structure of 3,3′-(2,3,4,5-tetra-*O*-acetylgalactar-1,6-dioyl)-bis(2-ethoxy-2,3-dihydro-5-phenyl-1,3,4-oxadiazole), and not the alternative structure theoretically possible, namely, 1,2,3,4-tetra-*O*-acetyl-1,4-bis(3-benzoyl-2-ethoxy-2,3-dihydro-1,3,4-oxadiazol-5-yl)-*galacto*-tetritol. This assignment was based on the mass-spectral fragmentation-pattern of the cyclization product, which showed, in



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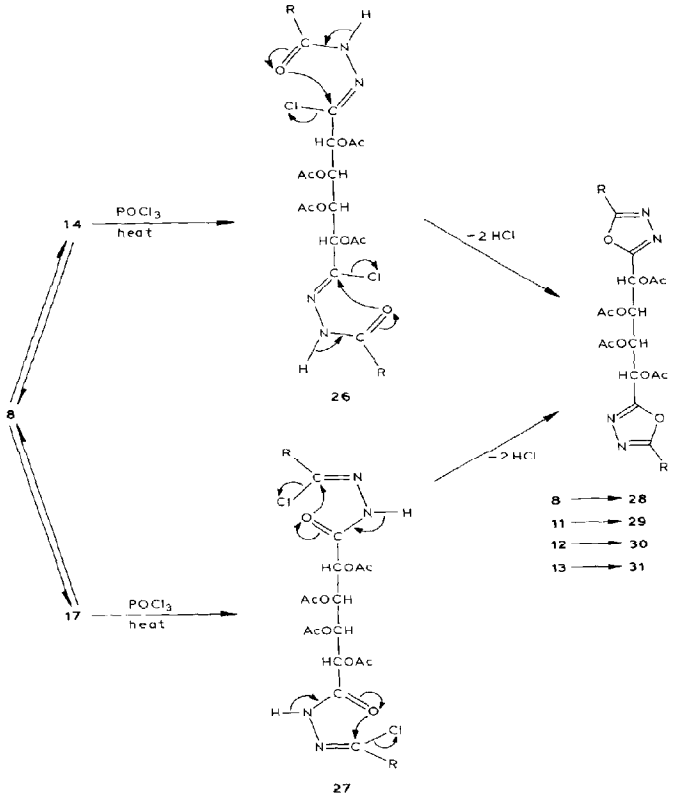
addition to the molecular ion at *m/z* 726, fragment **25** at *m/z* 535. This fragment would be expected only from the assigned structure, and not from the alternative. By analogy, therefore, the cyclization product of the bis(*m*-toluoylhydrazide) **8** is assigned the structure of 3,3′-(2,3,4,5-tetra-*O*-acetylgalactar-1,6-dioyl)-bis(2-ethoxy-2,3-dihydro-5-*m*-tolyl-1,3,4-oxadiazole) (**19**).

The bis(hydrazides) **9**–**13** were also cyclized with triethyl orthoformate, to give the corresponding 3,3′-(2,3,4,5-tetra-*O*-acetylgalactar-1,6-dioyl)-bis(5-aryl-2-ethoxy-2,3-dihydro-1,3,4-oxadiazoles) (**20**–**24**).

On heating with phosphoryl chloride, the bis(hydrazide) **8** gave a product whose elemental analysis agreed with the molecular formula $C_{30}H_{30}N_4O_{10}$. This formula contains two fewer molecules of water than the parent bis(hydrazide) **8**. The product gave no coloration with ferric chloride, suggesting the loss of the hydrazido protons which enable the parent bis(hydrazide) to form a characteristic coloration with this reagent through the enolic form. This was corroborated by the infrared spectrum of the product, which lacked CONH or NH absorption bands and showed only OAc and C=N absorptions, at 1760 and 1630 cm^{-1}, respectively. These data constituted evidence for the dehydrative cyclization of the bis(hydrazide) **8** with phosphoryl chloride, to give 1,2,3,4-tetra-*O*-acetyl-1,4-bis(*m*-tolyl-1,3,4-oxadiazol-2-yl)-*galacto*-tetritol (**28**).



In this case, each 1,3,4-oxadizole ring is formed through the reaction of the hydrazidic acid residue (enolized hydrazido residue) of either **14** or **17**, or both, with phosphoryl chloride, to give either hydrazidoyl chloride intermediate **26** or **27**, or both. Nucleophilic attack of the oxygen atom of the hydrazido carbonyl on the carbon atom of the hydrazidoyl chloride of either **26** or **27**, or both, with concomitant elimination of a molecule of hydrogen chloride results in heterocyclization, to give the bis(1,3,4-oxadiazol-2-yl) derivative (**28**).

Similar dehydrative cyclization of the bis(hydrazides) **8** and **11–13** by heating with phosphoryl chloride gave the corresponding 1,2,3,4-tetra-*O*-acetyl-1,4-bis(5-aryl-1,3,4-oxadiazol-2-yl)-*galacto*-tetritols (**28–31**).

The saccharide 1,3,4-oxadiazoline (**19–24**) and 1,3,4-oxadiazole (**28–31**) derivatives prepared are interesting from the point of view of being capable of various ring transformations into new types of saccharide heterocyclic compounds.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus and are uncorrected. Homogeneity of the compounds prepared was checked by t.l.c. on plates precoated with Merck silica gel G (layer thickness 0.25 mm), used without pretreatment. The distance of solvent travel was 5 cm, and the spots were detected with iodine vapor or by spraying with 20% sulfuric acid followed by heating the chromatograms on a hot plate for a few minutes. I.r. spectra were recorded, for potassium bromide discs, with a Unicam SP-1025 spectrophotometer, and ^{1}H-n.m.r. spectra were recorded, for solutions in deuteriopyridine containing tetramethylsilane as the internal standard, with a Varian EM-390 spectrometer; chemical shifts are given on the δ scale. Microanalysis was performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

*2,3,4,5-Tetra-O-acetylgalactaric bis(*m*-toluoylhydrazide)* (**8**). — To a solution of 2,3,4,5-tetra-*O*-acetylgalactaroyl dichloride[27] (**1**; 1 g) in dry benzene (150 mL) was added a solution of *m*-toluoylhydrazine (**2**; 0.7 g) in the same solvent (50 mL), and the mixture was heated for 20 min at 100°, and cooled to room temperature; and the product that separated was filtered off, washed with ethanol, and recrystallized from 1,4-dioxane, to give 1 g (67%) of **8**; m.p. 258–263°; ν_{max}^{KBr} 3360 (NH), 1760 (OAc), 1710, 1680 (Amide-I), and 745 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 2.25–2.60 (12 H, 4 OAc), 2.08 and 2.12 (6 H, 2 C_6H_4Me), 7.15–7.75 (m, 8 H, 2 C_6H_4Me), and 10.10 and 10.20 (4 H, 2 CONH–NHCO). A solution of **8** in pyridine gave a reddish-brown coloration with 3% methanolic ferric chloride solution.

Anal. Calc. for $C_{30}H_{34}N_4O_{13} \cdot H_2O$: C, 54.5; H, 5.5; N, 8.5. Found: C, 54.5; H, 5.1; N, 8.7.

2,3,4,5-Tetra-O-acetylgalactaric bis(o-chlorobenzoylhydrazide) (**9**). — Compound **9** was prepared from **1** and (*o*-chlorobenzoyl)hydrazine (**3**) as described for the preparation of **8** (yield 75%); m.p. 245–248°; ν_{max}^{KBr} 3380 (NH), 1770 (OAc), 1710, 1685 (Amide-I), and 750 cm^{-1} (Ar).

Anal. Calc. for $C_{28}H_{28}Cl_2N_4O_{12}$: C, 49.2; H, 4.1; N, 8.2. Found: C, 49.5; H, 4.5; N, 8.5.

2,3,4,5-Tetra-O-acetylgalactaric bis(m-chlorobenzoylhydrazide) (**10**). — Compound **10** was prepared from **1** and (*m*-chlorobenzoyl)hydrazine (**4**) as described for the preparation of **8** (yield 81%); m.p. 250–254°; ν_{max}^{KBr} 3380 (NH), 1765 (OAc), 1710, 1680 (Amide-I), and 740 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 2.1–2.6 (12 H, 4 OAc), 7.33–8.00 (m, 8 H, 2 C_6H_4), and 10.33–10.55 (4 H, 4 NH).

Anal. Calc. for $C_{28}H_{28}Cl_2N_4O_{12}$: C, 49.2; H, 4.1. Found: C, 49.6; H, 4.5.

2,3,4,5-Tetra-O-acetylgalactaric bis(p-bromobenzoylhydrazide) (**11**). — Compound **11** was prepared in 78% yield by the reaction of **1** with (*p*-bromobenzoyl)hydrazine (**5**) as for the preparation of **8**; m.p. 292°; ν_{max}^{KBr} 3385 (NH), 1760 (OAc), 1700, 1680 (Amide-I), and 760 cm^{-1} (Ar).

Anal. Calc. for $C_{28}H_{28}Br_2N_4O_{12} \cdot H_2O$: C, 42.6; H, 3.8; N, 7.1. Found: C, 42.3; H, 3.9; N, 7.3.

2,3,4,5-Tetra-O-acetylgalactaric bis(m-bromobenzoylhydrazide) (**12**). — Compound **12** was prepared in 72% yield by the condensation of **1** with (*m*-bromobenzoyl)hydrazine (**6**) as described for the preparation of **8**; m.p. 265–268°; ν_{max}^{KBr} 3385 (NH), 1760 (OAc), 1705, 1675 (Amide-I), and 740 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 1.9–2.3 (12 H, 4 OAc), 7.3–8.2 (m, 8 H, 2 C_6H_4), and 10.3–10.52 (4 H, 4 NH).

Anal. Calc. for $C_{28}H_{28}Br_2N_4O_{12}$: C, 43.5; H, 3.6; N, 7.3. Found: C, 43.0; H, 3.8; N, 7.3.

2,3,4,5-Tetra-O-acetylgalactaric bis(p-nitrobenzoylhydrazide) (**13**). — Compound **13** was prepared in 86% yield by condensation of **1** with (*p*-nitrobenzoyl)hydrazine (**7**) as described for the preparation of **8**; m.p. 270–273°; ν_{max}^{KBr} 3285 (NH), 1760 (OAc), 1700, 1660 (Amide-I), and 710 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 1.9–2.65 (12 H, 4 OAc), 7.9–8.45 (m, 8 H, 2 C_6H_4), and 10.42–10.75 (4 H, 4 NH).

Anal. Calc. for $C_{28}H_{28}N_6O_{16} \cdot H_2O$: C, 46.5; H, 4.2; N, 11.6. Found: C, 46.6; H, 4.7; N, 11.9.

3,3'-(2,3,4,5-Tetra-O-acetylgalactar-1,6-dioyl)-bis(2-ethoxy-2,3-dihydro-5-m-tolyl-1,3,4-ozadiazole) (**19**). — To compound **8** (1 g) in 1,4-dioxane (10 mL) was added triethyl orthoformate (5 mL), and the mixture was boiled under reflux until complete dissolution had occurred (~25 h). The mixture was cooled, and evaporated to dryness; the product crystallized from ethanol, to give 0.9 g (77%) of **19**; m.p. 210–215°; ν_{max}^{KBr} 1770 (OAc), 1710 (CON), 1600 (C=N), 1070 (C–O–C), 950 (C–O), and 750 cm^{-1} (Ar); δ 1.13 (t, 6 H, 2 CH_2*Me*), 1.85–2.0 (s, 3 H, C_6H_4*Me*), 2.0–2.65 (12 H, 4 OAc), 3.65 (q, 4 H, 2 CH_2Me), and 7.3–7.8 (m, 8 H, 2 C_6H_4). A solution of **19** in ethanol gave no coloration with 3% methanolic ferric chloride solution.

Anal. Calc. for $C_{36}H_{42}N_4O_{14} \cdot H_2O$: C, 56.0; H, 5.7; N, 7.3. Found: C, 56.1; H, 5.7; N, 7.8.

3,3'-(2,3,4,5-Tetra-O-acetylgalactar-1,6-dioyl)-bis[5-(o-chlorophenyl)-2-ethoxy-2,3-dihydro-1,3,4-oxadiazole] (**20**). — Compound **20** was prepared from **9** as described for the preparation of **19** (yield 59%); m.p. 200–203°; ν_{max}^{KBr} 1755

(OAc), 1710 (CON), 1625 (C=N), 1090 (C–O–C), 1015 (C–O), and 700 cm^{-1} (Ar).

Anal. Calc. for $C_{34}H_{36}Cl_2N_4O_{14}$: C, 51.3; H, 4.5. Found: C, 51.0; H, 4.5.

3,3'-(2,3,4,5-Tetra-O-acetylgalactar-1,6-dioyl)-bis[5-(m-chlorophenyl)-2-ethoxy-2,3-dihydro-1,3,4-oxadiazole] (**21**) — Compound **21** was prepared in 68% yield from **10** as described for the preparation of **19**; m.p. 239–242°; ν_{max}^{KBr} 1765 (OAc), 1710 (CON), 1600 (C=N), 1090 (C–O–C), 950 (C–O), and 750 cm^{-1} (Ar).

Anal. Calc. for $C_{34}H_{36}Cl_2N_4O_{14} \cdot H_2O$: C, 50.2; H, 4.7; N, 6.9. Found: C, 50.2; H, 5.1; N, 6.9.

3,3'-(2,3,4,5-Tetra-O-acetylgalactar-1,6-dioyl)-bis[5-(p-bromophenyl)-2-ethoxy-2,3-dihydro-1,3,4-oxadiazole] (**22**). — Compound **22** was prepared in 79% yield from **11** as described for the preparation of compound **19**; m.p. 270°; ν_{max}^{KBr} 1760 (OAc), 1700 (CON), 1595 (C=N), 1090 (C–O–C), 1045 (C–O), and 760 cm^{-1} (Ar).

Anal. Calc. for $C_{34}H_{36}Br_2N_4O_{14}$: C, 46.2; H, 4.1; N, 6.3. Found: C, 46.1; H, 4.1; N, 6.7.

3,3'-(2,3,4,5-Tetra-O-acetylgalactar-1,6-dioyl)-bis[5-(m-bromophenyl)-2-ethoxy-2,3-dihydro-1,3,4-oxadiazole] (**23**). — Compound **23** was prepared in 71% yield from **12** as described for the preparation of compound **19**; m.p. 190–195°; ν_{max}^{KBr} 1760 (OAc), 1705 (CON), 1630 (C=N), 1090 (C–O–C), 1045 (C–O), and 760 cm^{-1} (Ar); ^{1}H-n.m.r.: δ 1.2 (t, 6 H, 2 CH_2Me), 1.7–2.65 (12 H, 4 OAc), 3.73 (q, 4 H, CH_2Me), and 7.3–8.2 (m, 8 H, 2 C_6H_4).

Anal. Calc. for $C_{34}H_{36}Br_2N_4O_{14} \cdot H_2O$: C, 44.4; H, 4.4; N, 6.1. Found: C, 43.8; H, 3.8; N, 6.6.

3,3'-(2,3,4,5-Tetra-O-acetylgalactar-1,6-dioyl)-bis[2-ethoxy-2,3-dihydro-5-(p-nitrophenyl)-1,3,4-oxadiazole] (**24**). — Compound **24** was prepared in 78% yield from **13** as described for the preparation of compound **19**; m.p. 195–198°; ν_{max}^{KBr} 1750 (OAc), 1665 (CON), 1600 (C=N), 1070 (C–O–C), 1015 (C–O), and 750 cm^{-1} (Ar).

Anal. Calc. for $C_{34}H_{36}Br_2N_6O_{18}$: C, 50.0; H, 4.4; N, 10.3. Found: C, 49.8; H, 4.8; N, 10.2.

1,2,3,4-Tetra-O-acetyl-1,4-bis(5-m-tolyl-1,3,4-oxadiazol-2-yl)-galacto-tetritol (**28**). — A mixture of **8** (0.5 g) and phosphoryl chloride (5 mL) was boiled under reflux until complete dissolution occurred (15 min), cooled to room temperature, poured into cold, saturated sodium hydrogencarbonate solution (100 mL), and extracted with chloroform (4 × 50 mL). The extracts were combined, washed with water (5 × 50 mL), dried (Na_2SO_4), and evaporated. The product crystallized from methanol, to give **28** (0.3 g, 75%): m.p. 205–208°; ν_{max}^{KBr} 1760 (OAc) and 955, 930 cm^{-1} (oxadiazole ring).

Anal. Calc. for $C_{30}H_{30}N_4O_{10}$: C, 59.4; H, 5.0; N, 9.2. Found: C, 59.2; H, 5.0; N, 9.0.

1,2,3,4-Tetra-O-acetyl-1,4-bis[5-(p-bromophenyl)-1,3,4-oxadiazol-2-yl]-galacto-tetritol (**29**). — Compound **29** was prepared in 80% yield from **11** as for the

preparation of compound **28**; m.p. 230–235°; ν_{max}^{KBr} 1770 (OAc) and 1010–950 cm^{-1} (oxadizaole rings).

Anal. Calc. for $C_{28}H_{24}Br_2N_4O_{10}$: C, 45.7; H, 3.3; N, 7.6. Found: C, 45.6; H, 3.8; N, 7.6.

1,2,3,4-Tetra-O-acetyl-1,4-bis[5-(m-bromophenyl)-1,3,4-oxadiazol-2-yl]-galacto-*tetritol* (**30**). — Compound **30** was prepared in 70% yield from **12** as for the synthesis of **28**; m.p. 280–283°; ν_{max}^{KBr} 1720 (OAc) and 1080–1010 cm^{-1} (oxadiazole rings).

Anal. Calc. for $C_{28}H_{24}Br_2N_4O_{10}$: C, 45.7; H, 3.3. Found: C, 46.2; H, 3.7.

1,2,3,4-Tetra-O-acetyl-1,4-bis[5-(p-nitrophenyl)-1,3,4-oxadiazol-2-yl]-galacto-*tetritol* (**31**). — Compound **31** was prepared in 80% yield from **13** as for the synthesis of **28**; m.p. 232–235°; ν_{max}^{KBr} 1760 (OAc) and 1020–1000 cm^{-1} (oxadiazole rings).

Anal. Calc. for $C_{28}H_{24}N_6O_{14}$: C, 50.3; H, 3.6. Found: C, 50.8; H, 3.8.

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