New C-aryl alditols from Diels-Alder adducts of sugar nitroalkenes

Noelia Araújo, Manuel Baños, María V. Gil, Luis E. Cáceres, Emilio Román,* and José A. Serrano

Departamento de Química Orgánica e Inorgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain
E-mail: roman@unex.es

Abstract
2-Nitro-, 2-amino- and 2-acetamido-1-(penta-O-acetylpentitol-1´-yl)benzenes were prepared using previously reported Diels-Alder cycloadducts obtained from sugar-derived nitroalkenes with d-galacto and d-manno configurations as starting materials. Deacetylation and oxidative cleavage of the sugar side-chain of nitrobenzene pentitol peracetates yielded nitrobenzaldehydes. From 2-nitro-1-(D-galacto-pentitol-1´-yl)benzene also 1´,4´- and 2´,5´-anhydro derivatives were synthesized.

Keywords: Nitro compounds, C-aryl alditols, anhydro derivatives, C-nucleosides, aromatization

Introduction

Compounds with an open-chain monosaccharide unit linked through a C–C single bond to a hetero- or carboaromatic ring have received attention due to their diverse biological properties.1–8 Thus, the nitrobenzene derivative chloramphenicol1,2 inhibits protein synthesis, the methoxy–benzene derivative karacilin3 possesses antiviral activity in vitro against herpes viruses. This type of substances, namely C-aryl alditols, can be considered as acyclo-C-nucleoside analogues that by intramolecular dehydration could provide C-nucleosides; some of the latter, either natural or synthetic, have been reported to have a broad range of useful antitumor, antifungal and antibiotic properties, thus encouraging the development of methodologies toward this class of products.8–11 Besides, the C-aryl alditol substructure is also present in some natural products, like the 5-(4-aminophenyl)-1,2,3,4-tetrahydroxypentane moiety of methanopterin, a cofactor involved in the biological reduction of CO2 to CH4.12

Based on our previous experience with Diels-Alder reactions of sugar derivatives,13–15 we report herein the synthesis of several C-aryl alditols. Cycloadducts obtained from d-galacto- and d-manno-3,4,5,6,7-penta-O-acetyl-1,2-dideoxy-1-nitrohept-1,2-enitols 1a,16 1b17 (Figure 1) with furan, 1-acetoxy-, or 1-trimethylsilyloxybuta-1,3-dienes were used as starting materials. As an
example of an acid-catalyzed dehydration of the polyhydroxyalkyl chain in 1-(D-galacto-pentitol-1′-yl)-2-nitrobenzene 6c, we describe the preparation of 2′,5′- and 1′,4′-anhydro derivatives 10 and 11.

Results and Discussion

Upon treatment with DBU in dichloromethane at room temperature both the D-galacto cycloadduct 2a and a 50:50 mixture of 2a and its stereoisomer 3a underwent aromatization by anti- and syn-E2 elimination of acetic acid, thus furnishing 1-(1′,2′,3′,4′,5′-penta-O-acetyl-D-galacto-pentitol-1′-yl)-2-nitrobenzene 6a in good yields (Figure 1). Similarly, a 65:35 mixture of D-manno adduct 4b and its stereoisomer 5b afforded 1-(1′,2′,3′,4′,5′-penta-O-acetyl-D-manno-pentitol-1′-yl)-2-nitrobenzene 6b (85%). By comparison with closely related reactions, the milder conditions now used for these processes are noticeable: Treatment of 2a or 4b with sodium acetate in boiling THF only induced anti-elimination of acetic acid, yielding nitrocyclohexadienes, under these conditions, stereoisomers of 2a and 4b did not undergo the desired syn-elimination, probably because of the unfavorable conformation that has to be adopted by the cyclohexene ring.

Compound 6b was also obtained by potassium carbonate-induced elimination of acetic acid from the crude mixture of 7-oxanorbornene stereoisomers 7b, followed by treatment of the resulting product with acetic anhydride in pyridine at room temperature. As previously reported, this reaction could involve a base-induced β-elimination of the heteroatom bridge, followed by aromatization as the result of the elimination of acetic acid. The procedure is very simple and easy, and could be an alternative to other methods that have been used in related reactions, in which 7-oxabicyclo[2.2.1]hept-2-ene systems yielded substituted benzenes by treatment with TiCl4-LiAlH4.

Determination of structures of nitrobenzene pentitol peracetates 6a and 6b is based on their analytical and spectroscopic data. The 1H and 13C NMR spectra of both compounds show four protons and six carbon atoms in the aromatic region; the values of the vicinal proton coupling constants in the sugar side-chain are similar to those of their starting materials, thus supporting the same extended conformation in the acyclic carbohydrate moiety.

Treatment of 6a and 6b with potassium carbonate in 90% methanol yielded the deacetylated derivatives 6c and 6d, respectively. Oxidative cleavage of the pentahydroxypentyl side-chains in 6c and 6d with sodium metaperiodate in MeOH/H2O (1:1) led to 2-nitrobenzaldehyde 6f, thus supporting the proposed structures of their respective starting materials and demonstrating that they differ merely in the configuration of their sugar chains.

Following the method described by Cowan, reduction of the nitro group in nitrobenzene alditols 6a and 6b with NaBH4/Cu(OAc)2 in methanol yielded the corresponding aniline derivatives: 6b afforded 2-(1′,2′,3′,4′,5′-penta-O-acetyl-D-manno-pentitol-1′-yl)aniline 8b as the only product, whereas 6a led to a 2:1 mixture of 2-(1′,2′,3′,4′,5′-penta-O-acetyl-D-galacto-
pentitol-1′-yl)aniline 8a and 2-(2′,3′,4′,5′-tetra-O-acetyl-d-galacto-pentitol-1′-yl)acetanilide 9e. The formation of the latter product is explained by an intramolecular migration of the acetyl group at C-1′ to the amino group. The difference in behavior of 6a and 6b suggests that the migration could be due to spatial proximity of C-1′ acetate and the amino group in the D-galacto configuration of the sugar side-chain, which is not the case with the D-manno configuration. Supporting evidence of the structure of acetanilide 9e is provided by the chemical shift of H-1′ at δ 5.69 in 9e, which is shifted downfield to δ 6.06 in the peracetylated derivative 9a.23

In order to explore the dehydrating cyclization of C-aryl alditols, nitrobenzene pentitol 6c was refluxed in 1% sulfuric acid in isopropyl alcohol. Compounds 10 (62%) and 11 (20%) with 2′,5′-anhydro and 1′,4′-anhydro rings, respectively, were isolated. These results agree with those previously reported.24 When the sugar chain is linked to a π-deficient heterocycle, C-1′ is usually not involved in the cyclization process, and 2′,5′-anhydro derivatives are formed. Accordingly, the 1H NMR spectrum of 11 in DMSO-d6 displays a triplet signal corresponding to the hydroxyl group at C-5′; such a signal is absent in the spectrum of 10. The 13C NMR chemical shifts are similar to those reported for closely related compounds;25 the signal for C-5′ appears at δ 73.1 for 10, and at δ 60.0 for 11 in agreement with the type of cyclization proposed.

![Figure 1](image-url)
Concerning the dehydration mechanism, we believe that the formation of 10 probably involves an attack of the C-2 hydroxyl group at C-5 displacing its protonated hydroxyl group. The magnitude of the coupling constant ($J_{2,3} = 3.5$ Hz) in 10 supports the $\alpha$-anomeric configuration; this is within the range of related 3,6-anhydro-D-galactose derivatives. A small coupling constant ($\tilde{J} = 0.5–4.0$ Hz) has been observed between the proton at the ring carbon bearing the C-substituent and the proton at the vicinal ring carbon.

Probably, the cyclization leading to 11 involves a benzylic carbocation intermediate generated in acid medium, and accordingly, proof of its structure cannot be based on mechanistic grounds. The $\alpha$-anomeric configuration is in agreement with the absence of a NOESY effect between the H-1 and H-4, and is consistent with the steric hindrance that would be present in the transition state leading to the $\beta$-anomer with all substituents in the furanoid ring cis oriented; also, the coupling constant ($J_{1,2} = 7.8$ Hz) is similar to that previously reported ($\tilde{J} = 8.0$ Hz) for 1-benzyl-4,5,6,7-tetrahydro-2-$\alpha$-D-lyxo-furanosyl-6,6-dimethylindol-4-one.

On the other hand, 3-glyco-2-nitrophenols 16a and 16b were prepared from crude hydrolysis mixtures of the corresponding cycloadducts 12–15 by treatment with dimethylsulfoxide and acetic anhydride. As described previously, these reagents oxidize primary or secondary alcohols to carbonyl compounds, whereas in our case the oxidation led to nitrophenols 16a and 16b, probably through the enol form of the initially formed cyclohexenone. The assignment of structures 16a and 16b is based on spectroscopic data as well as on those obtained from the respective hexaacetylated derivatives 17a and 17b, or the deacetylated derivatives 16c and 16d. Oxidative cleavage of the penta hydroxypentyl chains of the latter two compounds with sodium metaperiodate in MeOH/H2O (1:1) afforded, in both cases, the known 3-hydroxy-2-nitrobenzaldehyde 16f, thus providing additional support for structures 16a and 16b.

In conclusion, Diels-Alder cycloadducts obtained from sugar-derived nitroalkenes with furan, 1-acetoxy-, or 1-trimethylsilyloxybuta-1,3-diene are suitable precursors of C-aryl alditols. Intramolecular cyclization of the sugar chains leads to C-nucleoside analogues. The potential of the nitro group, easily convertible to other functionalities, opens an access to a variety of this class of compounds.

**Experimental Section**

**General.** Solutions were concentrated at reduced pressure below 40 °C. Silica Gel 60 (Merck, 230–400 mesh ASTM) was used for column chromatography, which was carried out using a dry-column mode. Thin layer chromatography (TLC) was performed on precoated Merck Kieselgel 60 GF254 aluminium-backed plates; visualization with UV light or iodine vapor. Preparative thin layer chromatography (PTLC) was performed using silica gel (Merck 60 GF254). Reagents were used as supplied by Aldrich Chemical Co. NMR spectra were recorded on a Bruker AC/PC spectrometer (400.13 MHz for $^1$H, 100.62 MHz for $^{13}$C) with TMS or residual CHCl3 or DMSO as internal standards. Evaluation of NMR signals is based on spin decoupling, heteronuclear
chemical shift correlation spectroscopy and DEPT experiments. IR spectra were recorded on Perkin-Elmer 399 and FT-IR MIDAC Corporation spectrophotometers. Solid samples were examined as KBr disks, and liquids as thin films on NaCl plates. Melting points were determined in open capillary tubes on an Electrothermal 8100 capillary melting point apparatus. Optical rotations were determined at 20±2 °C with a Perkin-Elmer 241 polarimeter.

1-(1´,2´,3´,4´,5´-Penta-O-acetyl-d-galacto-pentitol-1´-yl)-2-nitrobenzene (6a). To a stirred solution of (1S,2R,3S)-1-O-acetyl-3-(1´,2´,3´,4´,5´-penta-O-acetyl-d-galacto-pentitol-1´-yl)-2-nitrocyclohex-5-en-1-ol15 (2a; 0.70 g, 1.28 mmol) in CH2Cl2 (6 mL) was added DBU (0.15 mL, 1.00 mmol). After 16 h at room temperature, the mixture was poured onto ice-cold water (50 mL), extracted with CH2Cl2 (3×25 mL); the combined extracts were washed successively with HCl (1 M, 2×25 mL), saturated aqueous NaHCO3 (2×25 mL), and water (2×25 mL). The organic layer was decolorized with activated charcoal, dried (MgSO4), filtered and evaporated to yield 6a as a pale yellow oil that crystallized from Et2O/petroleum ether (0.51 g, 82%); mp 91–93 °C; Rf 0.29 (Et2O/petroleum ether, 2:1); [α]D +5.6 (c 0.50, CHCl3); IR (KBr) νmax (cm–1): 3020 (H–Car), 1735 (C=O), 1540, 1375 (NO2), 1230, 1060 (C–O–C); 1H NMR (CDCl3): δ 8.12 (1H, dd, J3,5 = 1.3 Hz, J3,4 = 8.1 Hz, H-3), 7.7–7.4 (3H, m, H-4, H-5, H-6), 6.55 (1H, d, J1´,2´ = 1.2 Hz, H-1´), 5.69 (1H, dd, J2´,3´ = 10.1 Hz, J1´,2´ = 1.2 Hz, H-2´), 5.59 (1H, dd, J3´,4´ = 1.8 Hz, J2´,3´ = 10.1 Hz, H-3´), 5.38 (1H, m, H-4´), 4.34 (1H, dd, J4´,5´ = 4.8 Hz, J5´,5´ = 11.5 Hz, H-5´), 3.90 (1H, dd, J4´,5´ = 7.6 Hz, J5´,5´ = 11.5 Hz, H-5´), 2.20, 2.17, 2.04, 2.01, 1.83 (each 3H, 5 s, 5 CH3); 13C NMR (CDCl3): δ 170.4, 170.3, 170.0, 169.6, 168.8 (OOC), 147.0 (C-2), 132.9 (C-1), 133.3, 129.2, 127.9, 125.4 (C-3, C-4, C-5, C-6), 68.9, 68.1, 68.0, 67.6 (C-1´, C-2´, C-3´, C-4´), 62.1 (C-5´), 20.7, 20.6, 20.5, 20.1 (CH3). Anal. Calcd. for C21H25NO12: C, 52.17; H, 5.21; N, 2.90. Found: C, 52.06; H, 5.27; N, 2.76.

Following this procedure, diastereoisomer 3a yielded 6a (75%).

1-(1´,2´,3´,4´,5´-Penta-O-acetyl-d-manno-pentitol-1´-yl)-2-nitrobenzene (6b).

Method A: Following the procedure as described above for the preparation of 6a, a 65:35 mixture of (1R,2S,3R) and (1S,2S,3R)-1-O-acetyl-3-(1´,2´,3´,4´,5´-penta-O-acetyl-d-manno-pentitol-1´-yl)-2-nitrocyclohex-5-en-1-ol15 (4b and 5b) afforded 6b (85%) as an oil; Rf 0.23 (EtO/petroleum ether, 2:1); [α]D +2.5 (c 0.40, CHCl3); IR (film) νmax (cm –1): 3040 (H–C ar), 1750 (C=O), 1545, 1380 (NO2), 1230, 1070 (C–O–C); 1H NMR (CDCl3): δ 7.86 (1H, d, J3,4 = 7.8 Hz, H-3), 7.61 (1H, d, J5,6 = 4.8 Hz, H-6), 7.47 (1H, dd, J4,5 = 3.4 Hz, J3,4 = 7.8 Hz, H-4), 7.44 (1H, dd, J4,5 = 3.4 Hz, J5,6 = 4.7 Hz, H-5), 6.50 (1H, d, J1´,2´ = 9.9 Hz, H-1´), 5.61 (dd, J1, J2,3 = 9.4 Hz, J2,3 = 1.7 Hz, H-3´), 5.52 (1H, dd, J2,3 = 1.8 Hz, J1,2 = 10.0 Hz, H-2´), 5.08 (1H, dd, J3,4 = 9.5 Hz, J4,5 = 2.7 Hz, J4,5 = 4.8 Hz, H-4´), 4.24 (1H, dd, J4,5 = 2.7 Hz, J5,5 = 10.0 Hz, H-5´), 4.13 (1H, dd, J4,5 = 4.7 Hz, J5,5 = 10.0 Hz, H-5´), 2.21, 2.11, 2.06, 2.04, 1.80 (each 3H, 5 s, 5 CH3); 13C NMR (CDCl3): δ 170.3, 169.7, 169.6, 169.4, 169.3 (OOC), 148.9 (C-2), 132.9, 129.3, 128.3, 124.2 (C-3, C-4, C-5, C-6), 131.1 (C-1), 70.6 (C-1´), 67.6, 67.2, 66.1 (C-2´, C-3´, C-4´), 61.7 (C-5´), 20.5, 20.4, 20.2 (CH3).
Method B: To a solution of the crude mixture of oxanorbornenes $7^{13}$ (0.30 g, 0.60 mmol) in MeOH (90%, 8 mL) was added K$_2$CO$_3$ (0.35 g, 2.53 mmol). After stirring for 1 h at room temperature the resulting solution was neutralized with Amberlite IR-120 (H$^+$) resin, then filtered and the filtrate concentrated to a residual oil that was treated with pyridine (1.5 mL) and Ac$_2$O (1.5 mL). After 14 h at room temperature, the crude product was poured onto ice cold water (50 mL), extracted with CH$_2$Cl$_2$ (3 x 25 mL). The extracts were combined, washed successively with HCl (1 M, 2 x 25 mL), saturated aqueous NaHCO$_3$ (2 x 25 mL), and water (2 x 25 mL). Upon drying (MgSO$_4$) and concentration a pure (by TLC) oil was obtained (0.27 g, 94%).

2-Nitro-1-(d-galacto-pentitol-1'-yl)benzene (6c). To a solution of 1-(1',2',3',4',5'-penta-O-acetyl-d-galacto-pentitol-1'-yl)-2-nitrobenzene (6a, 1.50 g, 3.10 mmol) in MeOH (90%, 38 mL) was added K$_2$CO$_3$ (1.70 g, 12.30 mmol). After stirring for 24 h at room temperature the reaction mixture was neutralized with Amberlite IR-120 (H$^+$) and evaporated to yield a colorless oil (0.74 g, 88%); $\text{Rf} = 0.32$ (benzene/MeOH, 3:1); $\left[\alpha\right]_D$ –120.0 ($c$ 0.50, pyridine); IR (film) $\tilde{\nu}_{\text{max}}$ (cm$^{-1}$) 3600–3100 (O-H), 3020 (H–Car), 1550, 1360 (NO$_2$), 1215, 1080 (C–O–C); $^1$H NMR (DMSO-d$_6$): $\delta$ 7.90 (1H, d, $J_{3,4} = 6.9$ Hz, H-3), 7.85 (1H, dd, $J_{5,6} = 8.0$ Hz, $J_{4,6} = 1.0$ Hz, H-6), 7.68 (1H, t, $J_{3,4} = J_{4,5} = 7.2$ Hz, H-4), 7.46 (1H, t, $J_{4,5} = J_{5,6} = 7.6$ Hz, H-5), 5.48 (1H, s, H-1'), 4.5–3.9 (5H, m, 5 OH, D$_2$O exchangeable), 3.8–3.4 (5H, m, H-2', H-3', H-4', H-5', H-5''); $^{13}$C NMR (DMSO-d$_6$): δ 147.8 (C-2), 139.0 (C-1), 132.2, 130.7, 127.6, 123.3 (C-3, C-4, C-5, C-6), 72.5 (C-1'), 70.1, 69.8, 66.6 (C-2', C-3', C-4'); 63.2 (C-5').

2-Nitrobenzaldehyde (6f). To a stirred solution of 2-nitro-1-(D-galacto-pentitol-1'-yl)benzene (6c; 0.15 g, 0.55 mmol) in MeOH (50%, 12 mL) was added NaIO$_4$ (0.53 g, 2.48 mmol). After 15 min at room temperature, the mixture was extracted with CH$_2$Cl$_2$ (3 x 20 mL), the extracts were combined, washed with water (2 x 20 mL), dried (MgSO$_4$), and evaporated to yield an oil (0.068 g, 82%); IR and $^1$H NMR data match those reported for 2-nitrobenzaldehyde.$^{21}$ This procedure converted also 1-(D-manno-pentitol-1'-yl)-2-nitrobenzene (6d, 0.80 g, 1.65 mmol) into 6f (77%).

2-Nitrobenzaldehyde (6f). To a stirred solution of 2-nitro-1-(D-galacto-pentitol-1'-yl)benzene (6c; 0.15 g, 0.55 mmol) in MeOH (50%, 12 mL) was added NaIO$_4$ (0.53 g, 2.48 mmol). After 15 min at room temperature, the mixture was extracted with CH$_2$Cl$_2$ (3 x 20 mL), the extracts were combined, washed with water (2 x 20 mL), dried (MgSO$_4$), and evaporated to yield an oil (0.068 g, 82%); IR and $^1$H NMR data match those reported for 2-nitrobenzaldehyde.$^{21}$ This procedure converted also 1-(D-manno-pentitol-1'-yl)-2-nitrobenzene (6d) into 6f (77%).

2-(1',2',3',4',5'-Penta-O-acetyl-d-galacto-pentitol-1'-yl)aniline (8a) and 2-(2',3',4',5'-tetra-O-acetyl-d-galacto-pentitol-1'-yl)acetanilide (9e). To a stirred solution of 1-(1',2',3',4',5'-penta-O-acetyl-d-galacto-pentitol-1'-yl)-2-nitrobenzene (6a, 2.00 g, 4.00 mmol) in MeOH (60 mL) was added a saturated solution of Cu(AcO)$_2$ (16 mL). The mixture was treated with NaBH$_4$ (2.10 g, stepwise; 3 x 0.70 g, each five min). After 30 min, the reaction mixture was filtered, and the filtrate was diluted with Et$_2$O (120 mL) and washed with saturated aqueous NaHCO$_3$ (3 x 50
mL). The aqueous layer was extracted with Et₂O (100 mL), the combined organic extracts were dried (MgSO₄) and evaporated to yield an oil (1.70 g, 91%), which was shown to be a 2:1 mixture of 8a and 9e; Rₛ 0.32 and 0.41, respectively (Et₂O/petroleum ether, 3:1). Although attempts to separate these two products were unsuccessful, their respective NMR data could be obtained from enriched samples (PTLC).

8a: ¹H NMR (CDCl₃): δ 7.66 (1H, d, J₅,₆ = 3.4 Hz, H-6), 7.3–7.0 (1H, m, H-3), 7.13 (1H, br d, J₄,₅ = 7.2 Hz, H-5), 6.69 (1H, m, H-4), 6.28 (1H, d, J₁:₂ = 5.2 Hz, H-1´), 5.65 (1H, dd, J₁:₂ = 5.2 Hz, J₂:₃ = 8.3 Hz, H-2´), 5.39 (1H, dd, J₃:₄ = 2.3 Hz, J₂:₃ = 8.2 Hz, H-3´), 5.30 (1H, m, H-4´), 4.4–3.8 (2H, m, 2 NH, D₂O exchangeable), 4.20 (dd, 1 H, J₄:₅ = 5.1 Hz, J₅:₅´ = 11.7 Hz, H-5´), 3.85 (1H, dd, J₄:₅´ = 7.1 Hz, J₅:₅´ = 11.9 Hz, H-5´´), 2.07, 2.03, 2.01, 1.99, 1.94 (each 3H, 5 s, 5 CH₃); ¹³C NMR (CDCl₃): δ 170.3, 170.1, 169.9, 169.1 (OCOCH₃), 144.4 (C-1), 139.3 (C-4), 128.5 (C-5), 119.8 (C-2), 118.5 (C-3), 117.0 (C-6), 70.6 (C-1´), 68.8, 68.6, 67.9 (C-2´, C-3´, C-4´), 61.8 (C-5´), 20.6, 20.5, 20.3 (CH₃).

9e: ¹H NMR (CDCl₃): δ 7.96 (1H, d, J₅,₆ = 1.8 Hz, H-6), 7.3–7.0 (1H, m, H-3), 7.28 (1H, s, NH, D₂O exchangeable), 7.06 (1H, br d, J₄,₅ = 7.5 Hz, H-5), 6.69 (1H, m, H-4), 5.69 (2H, m, H-1´, H-2´), 5.30 (2H, m, H-3´, H-4´), 4.33 (1H, dd, J₄:₅ = 4.8 Hz, J₅:₅´ = 11.5 Hz, H-5´), 3.85 (1H, dd, J₄:₅´ = 7.1 Hz, J₅:₅´ = 11.5 Hz, H-5´´), 3.43 (1H, s, OH, D₂O exchangeable), 2.27, 2.13, 1.90, 1.79 (each 3H, 4 s, 4 CH₃); ¹³C NMR (CDCl₃): δ 170.2, 169.9, 169.8, 169.7, 168.7 (OCOCH₃), 160.8 (NHCOCH₃), 139.3 (C-1), 135.7 (C-4), 127.4 (C-3), 127.5 (C-5), 119.8 (C-2), 118.5 (C-6), 71.1 (C-1´), 68.2, 67.8, 67.5 (C-2´, C-3´, C-4´), 62.0 (C-5´), 20.8, 20.5, 20.0 (OCOCH₃, NHCOCH₃).

2-(1´,2´,3´,4´,5´-Penta-O-acetyl-d-galacto-pentitol-1´-yl)acetanilide (9a). To a solution of a c.a. 2:1 mixture of 2-(1´,2´,3´,4´,5´-penta-O-acetyl-d-galacto-pentitol-1´-yl)aniline (8a) and 2-(2´,3´,4´,5´-tetra-O-acetyl-d-galacto-pentitol-1´-yl)acetanilide (9e) (0.40 g, 0.88 mmol) in pyridine (4 mL) was added Ac₂O (2 mL). After 18 h at 0 ºC the reaction mixture was poured onto water (100 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were washed with HCl (1 M, 50 mL) and saturated aqueous NaHCO₃ (50 mL), dried (MgSO₄), and concentrated to yield 9a as an oil, which crystallized from Et₂O/petroleum ether (0.37 g, 86%); mp 93–95 ºC; Rₛ 0.32 and 0.41, respectively (Et₂O/petroleum ether, 3:1); [a]D +14.4 (c 0.50, CHCl₃); IR (KBr) νmax (cm⁻¹) 3420 (NH), 1745  (C=O), 1365, 1225 (C–N), 1225, 1080 (C–O–C); ¹H NMR (CDCl₃): δ 8.44 (1H, s, D₂O exchangeable NH), 7.74 (1H, d, J₅,₆ = 7.6 Hz, H-6), 7.33 (2H, m, H-3, H-4), 7.18 (1H, t, J₄,₅ = 7.6 Hz, H-5), 6.06 (1H, d, J₁:₂ = 5.9 Hz, H-1´), 5.73 (1H, t, J₂:₃ = J₁:₂ = 5.9 Hz, H-2´), 5.25 (2H, m, H-3´, H-4´), 4.10 (1H, dd, J₄:₅ = 5.3 Hz, J₅:₅´ = 11.3 Hz, H-5´), 3.82 (1H, dd, J₄:₅´ = 7.0 Hz, J₅:₅´ = 11.3 Hz, H-5´´), 2.24, 2.06, 1.99, 1.96, 1.95, 1.94 (each 3H, 6 s, NHCOCH₃, 5 OCOCH₃); ¹³C NMR (CDCl₃): δ 170.1, 170.0, 169.8, 169.5, 168.9, 168.5 (5 OCOCH₃, NHCOCH₃), 135.4 (C-1), 129.3, 127.9, 125.2 (C-3, C-4, C-5, C-6), 127.0 (C-2), 70.2, 69.3, 68.2, 67.2 (C-1´, C-2´, C-3´, C-4´), 61.4 (C-5´), 23.7, 20.4, 20.2, 20.1, 19.9 (NHCOCH₃, 5 OCOCH₃). Anal. Calcd for C₂₃H₂₉NO₁₁: C, 55.75; H, 5.90; N, 2.83. Found: C, 55.97; H, 6.06; N, 2.78.
2-(1',2',3',4',5'-Penta-O-acetyl-D-manno-pentitol-1'-yl)aniline (8b). By the same procedure as described for the preparation of 8a and 9e, 1-(1',2',3',4',5'-penta-O-acetyl-D-manno-pentitol-1'-yl)-2-nitrobenzene (6b, 0.40 g, 0.83 mmol) yielded 8b as an oil, which crystallized from Et2O/petroleum ether (0.25 g, 67%); mp 150–152 °C; $\alpha$D $+67.3 (c 0.60, CHCl3); IR (KBr) $\tilde{\nu}$max (cm$^{-1}$) 3490, 3440 (NH$_2$), 3020 (H–C ar), 1750 (C=O), 1375, 1240 (C–N), 1240, 1040 (C–O–C); 1H NMR (CDCl3): $\delta 7.16$ (1H, d, $J_{3,4} = 7.5$ Hz, H-3), 7.08 (1H, t, $J_{4,5} = J_{5,6} = 7.5$ Hz, H-5), 6.71 (1H, t, $J_{3,4} = J_{4,5} = 7.5$ Hz, H-4), 6.62 (1H, d, $J_{5,6} = 7.5$ Hz, H-6), 5.81 (2H, m, H-1', H-2'), 5.62 (1H, dd, $J_{2,3'} = 1.1$ Hz, $J_{3,4'} = 9.1$ Hz, H-3'), 5.10 (1H, m, H-4'), 4.22 (1H, dd, $J_{4',5'} = 2.5$ Hz, $J_{5',5''} = 12.4$ Hz, H-5'), 4.16 (2H, m, 2 NH, D 2O exchangeable), 4.09 (1H, dd, $J_{4',5''} = 5.0$ Hz, $J_{5',5''} = 12.5$ Hz, H-5'''), 2.15, 2.07, 2.05, 2.04, 1.79 (each 3H, 5 s, 5 CH$_3$); 13C NMR (CDCl3): $\delta 170.4, 169.7, 169.5, 169.0$ (O$_2$C OCH$_3$), 145.2 (C-1), 129.5, 128.8 (C-3, C-5), 119.5 (C-2), 118.1, 116.6 (C-4, C-6), 69.1, 68.8, 67.9, 67.3 (C-1', C-2', C-3', C-4'), 61.7 (C-5'), 20.6, 20.4, 19.9 (CH$_3$). Anal. Calcd for C$_{21}$H$_{27}$NO$_{10}$: C, 55.62; H, 6.00; N, 3.09. Found: C, 55.87; H, 5.93; N, 3.06.

(2R,3R,4S)-2-((S)-hydroxy[2-nitrophenyl]methyl)tetrahydrofuran-3,4-diol (10) and (2R,3S,4R,5R)-2-((hydroxymethyl)-5-(2-nitrophenyl)tetrahydrofuran-3,4-diol (11). To a solution of 2-nitro-1-(D-galacto-pentitol-1'-yl)benzene (6c; 0.10 g, 0.37 mmol) in i-PrOH (10 mL) was added H$_2$SO$_4$ (1%, 100 mL), and the mixture was refluxed for 4 days. The reaction mixture was neutralized with saturated aqueous NaHCO$_3$, the solvent was evaporated, and the crude residue was subjected to column chromatography (EtOAc/EtOH, 6:1). Concentration of fractions with $\tilde{\alpha}$D 0.71 and 0.64 afforded oils, which were characterized as 10 (0.058 g, 62%) and 11 (0.019 g, 20%), respectively. 10: $\alpha$D $+29.1 (c 0.51, DMSO); IR (film) $\tilde{\nu}$max (cm$^{-1}$) 3500–3100 (O–H), 3030 (H–C ar), 1540, 1370 (NO$_2$), 1215, 1095 (C–O); 1H NMR (DMSO-d$_6$): $\delta 7.85$ (1H, d, $J_{3,4} = 8.0$ Hz, H-3), 7.81 (1H, d, $J_{2,3} = 7.8$ Hz, H-6), 7.69 (1H, t, $J_{4,5} = J_{5,6} = 7.5$ Hz, H-5), 7.50 (1H, t, $J_{4,5} = J_{3,4} = 7.8$ Hz, H-4), 5.83 (1H, d, $J = 5.1$ Hz, OH, D$_2$O exchangeable), 5.23 (2H, br s, 2 OH, D$_2$O exchangeable), 5.19 (1H, d, $J_{1,2} = 3.4$ Hz, H-1'), 3.91 (2H, br s, H-3', H-4'), 3.81 (1H, t, $J_{2,3} = 3.5$ Hz, H-2'), 3.77 (1H, dd, $J_{3,5'} = 9.1$ Hz, $J_{4,5'} = 4.2$ Hz, H-5''), 3.60 (1H, dd, $J_{4,5'} = 2.7$ Hz, H-5'''); 13C NMR (DMSO-d$_6$): $\delta 148.2$ (C-2), 136.9 (C-1), 132.5, 130.2, 128.2, 123.6 (C-3, C-4, C-5, C-6), 87.2 (C-2'), 77.9, 76.6 (C-3', C-4'), 73.1 (C-5'), 67.4 (C-1'). Anal. Calcd. for C$_{11}$H$_{13}$NO$_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.69; H, 5.08; N, 5.45.

11: $\alpha$D $-34.5 (c 0.55, DMSO); IR (film) $\tilde{\nu}$max (cm$^{-1}$): 3500–3100 (O–H), 3030 (H–C ar), 1545, 1375 (NO$_2$), 1220, 1150, 1080 (C–O); 1H NMR (DMSO-d$_6$): $\delta 7.78$ (1H, d, $J_{3,4} = 8.0$ Hz, H-3), 7.66 (2H, m, H-5, H-6), 7.51 (1H, t, $J_{4,5} = J_{3,4} = 7.6$ Hz, H-4), 5.17 (1H, d, $J = 7.1$ Hz, 2'-OH, D$_2$O exchangeable), 5.06 (1H, d, $J_{1,2} = 7.8$ Hz, H-1'), 4.99 (1H, d, $J = 3.4$ Hz, 3'-OH, D$_2$O exchangeable), 4.62 (1H, t, $J = 4.9$ Hz, 5'-OH, D$_2$O exchangeable), 4.11 (1H, m, H-4'), 4.05 (1H, t, $J_{2,3'} = J_{3,4'} = 4.0$ Hz, H-3'), 4.00 (1H, dd, $J_{1,2'} = 7.8$ Hz, $J_{2,3'} = 4.0$ Hz, H-2'), 3.65 (1H, dd, $J_{3,5'} = 10.7$ Hz, $J_{4,5'} = 5.1$ Hz, H-5''), 3.50 (1H, dd, $J_{4,5'} = 5.6$ Hz, $J_{5,5'} = 10.8$ Hz, H-5''); 13C NMR (DMSO-d$_6$): $\delta 149.0$ (C-2), 139.2 (C-1), 132.4, 128.5, 128.3, 123.6 (C-3, C-4, C-5, C-
H-4), 6.54 (1H, d, J = 7.6 Hz, H-5), 7.25 (1H, dd, J1,2 = 9.8 Hz, H-3′), 5.36 (1H, m, H-4′), 4.38 (1H, dd, J3′,4′ = 9.8 Hz, H-2′), 5.62 (1H, dd, J3′,4′ = 1.6 Hz, J2′,3′ = 9.9 Hz, H-3′), 5.34 (1H, m, H-4′), 4.33 (1H, dd, J1′,2′ = 5.0 Hz, J5′,5′′ = 11.5 Hz, H-5′), 3.88 (dd, 1H, J4′,5′ = 4.0 Hz, J5′,5′′ = 11.5 Hz, H-5′′), 2.20, 2.18, 2.02, 1.99, 1.79 (each 3H, 5 s, 5 CH₃); 13C NMR (CDCl₃): δ 170.4–168.7 (OCHO), 152.6 (C-1), 149.6 (C-2), 128.6 (C-3), 125.1 (C-5), 121.4 (C-4), 110.8 (C-6), 69.5, 68.5, 68.1, 67.7 (C-1′, C-2′, C-3′, C-4′), 62.0 (C-5′), 20.7, 20.5, 20.2, 20.1 (CH₃).

1-Acetoxy-3-(1′,2′,3′,4′,5′-penta-O-acetyl-d-galacto-pentitol-1′-yl)-2-nitrobenzene (17a). Acetylation of 16a (0.10 g, 0.20 mmol) with pyridine (1.0 mL) and acetic anhydride (0.5 mL) quantitatively gave hexaacetate 17a as an oil; Rf 0.54 (Et₂O/petroleum ether, 2:1); [α]D +20.0 (c 0.45, CHCl₃); IR (film) ν max (cm⁻¹): 3370 (OH), 3030 (H–Car), 1750 (C=O), 1225, 1065 (C–O–C); 1H NMR (CDCl₃): δ 7.47 (1H, t, J₅,₆ = 7.7 Hz, H-6), 7.47 (1H, t, J₅,₆ = J₄,₅ = 7.7 Hz, H-5), 7.49 (1H, dd, J₄,₅ = 1.2 Hz, J₅,₆ = 7.6 Hz, H-4), 6.62 (1H, d, J1′,2′ = 1.9 Hz, H-1′), 5.71 (1H, dd, J2′,3′ = 9.8 Hz, J1′,2′ = 2.0 Hz, H-2′), 5.63 (1H, dd, J3′,4′ = 1.8 Hz, J2′,3′ = 9.8 Hz, H-3′), 5.36 (1H, m, H-4′), 4.38 (1H, dd, J4′,5′ = 4.8 Hz, J5′,5′′ = 12.0 Hz, H-5′), 3.91 (1H, dd, J4′,5′ = 4.2 Hz, J5′,5′′ = 11.8 Hz, H-5′′), 2.27, 2.20, 2.18, 2.02, 1.99, 1.79 (each 3H, 6 s, 6 CH₃); 13C NMR (CDCl₃): δ 170.2–168.0 (OCHO), 154.6 (C-1), 149.6 (C-2), 128.7 (C-3), 125.1 (C-5), 116.5 (C-6), 69.1, 68.4, 68.1, 67.6 (C-1′, C-2′, C-3′, C-4′), 62.0 (C-5′), 20.6, 20.5, 20.2, 19.9 (CH₃).

3-(1′,2′,3′,4′,5′-Penta-O-acetyl-d-manno-pentitol-1′-yl)-2-nitrophenol (16b). Following the procedure described above for the preparation of 16a, a mixture of (1S,2R,3S)-, (1R,2R,3S)-, (1R,2S,3R)-, and (1S,2S,3R)-3-(1′,2′,3′,4′,5′-penta-O-acetyl-d-manno-pentitol-1′-yl)-2-nitrocyclohex-5-en-1-ol15 (12b–15b) afforded 16b as an oil, which was purified by column chromatography (Et₂O/petroleum ether, 1:1) (66%); Rf 0.26 (Et₂O/petroleum ether, 2:1); [α]D −18.0 (c 0.50, CHCl₃); IR (film) ν max (cm⁻¹): 3370 (OH), 3030 (H–Car), 1750 (C=O), 1215, 1065 (C–O–C); 1H NMR (CDCl₃): δ 9.93 (1H, br s, phenolic OH, D₂O exchangeable), 7.47 (1H, t, J₅,₆ = J₄,₅ = 7.9 Hz, H-5), 7.19 (1H, dd, J₄,₆ = 1.0 Hz, H-6), 7.01 (1H, dd, J₄,₆ = 1.0 Hz, J₄,₅ = 8.0 Hz, H-4), 6.54 (1H, d, J₃,₄ = 9.6 Hz, H-1′), 5.64 (1H, dd, J₃,₄ = 9.0 Hz, J₂,₃ = 1.7 Hz, H-3′), 5.51 (1H, dd, J₂,₃ = 1.7 Hz, J₁,₂ = 9.6 Hz, H-2′), 5.06 (1H, m, H-4′), 4.22 (1H, dd, J₄,₅ = 2.8 Hz, J₅,₅′ = 10.5 Hz, H-5′), 4.10 (1H, dd, J₄,₅ = 4.7 Hz, J₅,₅′ = 10.5 Hz, H-5′′), 2.19, 2.10, 2.06, 2.02, 1.82, (each 3H, 5 s, 5 CH₃); 13C NMR (CDCl₃): δ 170.5, 169.8, 169.6, 169.4, 169.3
1-Acetoxy-3-(1',2',3',4',5'-penta-O-acetyl-d-manno-pentitol-1'-yl)-2-nitrobenzene (17b).

Acetylation of 16b (0.10 g, 0.20 mmol) with pyridine (1.0 mL) and acetic anhydride (0.5 mL) quantitatively gave hexaacetate 17b as an oil; \( R_f 0.57 \) (Et\(_2\)O/petroleum ether, 2:1); \([\alpha]_D^{26} -26.0 \) (c 0.50, CHCl\(_3\)); IR (film) \( \tilde{\nu} \) max (cm\(^{-1}\)): 3030 (H–Car), 1750 (C=O), 1225, 1045 (C–O–C); \(^1\)HNMR (CDCl\(_3\)): \( \delta \) 7.52 (1H, dd, \( J_{4,6} = 1.2 \) Hz, \( J_{5,6} = 7.7 \) Hz, H-6), 7.58 (1H, t, \( J_{5,6} = J_{4,5} = 7.6 \) Hz, H-5), 7.26 (1H, dd, \( J_{4,6} = 1.2 \) Hz, \( J_{4,5} = 7.6 \) Hz, H-4), 6.55 (1H, d, \( J_{4',5'} = 9.2 \) Hz, H-1’), 5.73 (1H, dd, \( J_{2',3'} = 1.6 \) Hz, \( J_{1',2'} = 9.2 \) Hz, H-2’), 5.63 (1H, dd, \( J_{3',4'} = 8.8 \) Hz, \( J_{2',3'} = 1.6 \) Hz, H-3’), 5.06 (1H, m, H-4’), 4.24 (1H, dd, \( J_{4',5'} = 2.8 \) Hz, \( J_{5',5''} = 12.1 \) Hz, H-5’), 4.11 (1H, dd, \( J_{4',5''} = 4.7 \) Hz, \( J_{5',5''} = 12.2 \) Hz, H-5’’), 2.26, 2.20, 2.19, 2.01, 1.99, 1.80 (each 3H, 6 s, 6 CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 170.3–168.1 (COCH\(_3\)), 152.3 (C-2), 136.1 (C-1), 128.7 (C-4), 128.3 (C-5), 127.7 (C-3), 118.4 (C-6), 70.0 (C-1’), 68.3, 67.4, 66.7 (C-2’, C-3’, C-4’), 62.0 (C-5’), 20.8, 20.4, 20.4, 20.0 (CH\(_3\)).

3-Hydroxy-2-nitrobenzaldehyde (16f).

To a solution of 3-(1’,2’,3’,4’,5’-penta-O-acetyl-D-galacto-pentitol-1’-yl)-2-nitrophenol (16a, 0.50 g, 1.00 mmol) in MeOH (90%, 15 mL) was added K\(_2\)CO\(_3\) (0.50 g, 3.62 mmol). After stirring at room temperature for 24 h, TLC (Et\(_2\)O-petroleum ether, 2:1) showed complete consumption of 16a with one product at \( R_f 0.20 \) present. Neutralization with Amberlite IR-120 (H\(^+\)) and evaporation of the solvent gave a colorless oil, which was dissolved in MeOH (50%, 20 mL). The solution was stirred with NaIO\(_4\) (1.00 g, 4.67 mmol) at room temperature for 15 min. Then, the mixture was extracted with CH\(_2\)Cl\(_2\) (3 \times 20 mL), the combined extracts were washed with water (3 \times 20mL), dried and evaporated to yield an oil, which was purified by column chromatography (Et\(_2\)O-petroleum ether, 1.5:1). Crystallization from petroleum ether afforded a solid identified as 3-hydroxy-2-nitrobenzaldehyde (0.090 g, 54%); mp 150–152 °C (lit.\(^{30}\) mp 150–151 °C); \( R_f 0.29 \) (Et\(_2\)O/petroleum ether, 2:1); IR (KBr) \( \tilde{\nu} \) max (cm\(^{-1}\)): 3600 (OH), 3030 (H–Car), 3030 (C–H aldehyde) 1715 (C=O), 1530, 1330 (NO\(_2\)); \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 10.19 (1H, s, CHO), 9.75 (1H, s, D\(_2\)O exchangeable OH), 7.71 (1H, t, \( J_{5,6} = 7.5 \) Hz, H-5), 7.62 (1H, d, \( J_{5,6} = 7.5 \) Hz, H-6), 7.25 (1H, d, \( J_{4,5} = 7.5 \) Hz, H-4); \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 193.4 (CHO), 155.3 (C-3), 140.0 (C-2), 136.2 (C-5), 132.3 (C-1), 124.3, 122.5 (C-4, C-6).

By this procedure, 3-hydroxy-2-nitrobenzaldehyde (16f; 61%) was also obtained from 16b.

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