Reductive Cyclization of Carbohydrate 2-Nitrophenylhydrazones to Chiral Functionalized 1,2,4-Benzotriazines and Benzimidazoles

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Received September 30, 1998

Dedicated to Professor Horst Wilde on the occasion of his 60th birthday

The 2-nitrophenylhydrazones **2** of D-*arabino*-2-hexulopyranosonic acid, D-arabinose, D-galactose and D-galacturonic acid are used as precursors to form chiral functionalized 1,2,4-benzotriazines and benzimidazoles by reductive cyclization methods. Catalytic hydrogenation provided the amine derivatives which are cyclized and air oxidized in alkaline solution to yield the novel 1,2,4-benzotriazines **3** as the main products, while on acid catalysis the benzimidazoles **4** are formed.

J. Heterocyclic Chem., **36**, 589 (1999).

The combination with carbohydrate units offers a possibility to equip achiral heterocycles with a hydrophilic and chiral moiety. Such functionalized heterocycles, *e.g.* saccharidic 1,2,4-triazine-diones, are of interest due to their biological activity [1-4]. One approach to obtain a carbohydrate-heterocycle combination is the glycosidation of a heterocycle, as recently reported for a nucleoside analogue [5]. However, on principle the cyclization of an appropiately functionalized saccharide precursor should also give rise to a heterocycle with a chiral and hydrophilic substituent. A suitable method for ring closure is the reductive cyclization of nitro compounds, *e.g.* of ketone and aldehyde 2-nitrophenylhydrazones. Thus, we have reported on reductive cyclizations to form pyrazolo[1,5-*a*]benzimidazoles [6,7], 1,2,4-benzotriazines [8], benzo[1,2-*b*][5,4-*b*']bis(1*H*-imidazo[1,2-*b*]pyrazoles) [9] and pyridazino[1,6-*a*]benzimidazoles [10]. Furthermore, certain aldehyde 2-aminophenylhydrazones have been shown to react either to 1,2,4-benzotriazines by air oxidation or to benzimidazoles in acidic solution [11]. Surprisingly, carbohydrate 2-nitrophenylhydrazones, though known for a long time for the characterization of carbohydrates [12], have not been used as yet for precursors for cyclization reactions.

We wish to report here on the reductive cyclization reaction of 2-nitrophenylhydrazones of D-*arabino*-2-hexulosonic acid, D-arabinose, D-galactose and D-galacturonic acid as an approach to 1,2,4-benzotriazines and benzimidazoles with a chiral and hydrophilic substituent.

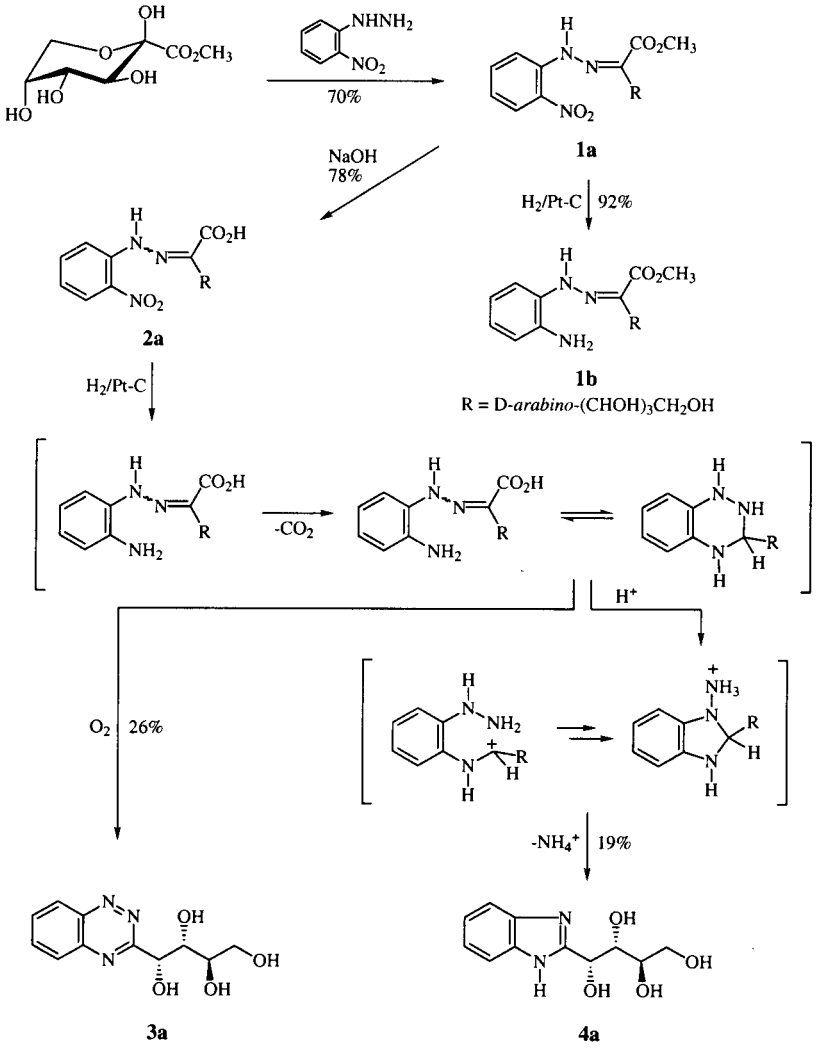
Results and Discussion.

We reported the synthesis of D-*arabino*-2-hexulosonic acid (2-oxo-D-gluconic acid) by the fermentative oxidation of D-glucose with *Serratia marcescens* as well as the optimized oxidation of 2,3-4,5-di-*O*-isopropyliden D-fructose with potassium permanganate [13]. Reaction of the crystalline methyl D-*arabino*-2-hexulosonate with 2-nitrophenylhydrazine afforded methyl (Z)-2-(2-nitrophenylhydrazono)-D-*arabino*-hexulosonate **1a**. Saponification of **1a** with sodium hydroxide or reaction of the crude fermentation solution of D-*arabino*-2-hexulosonic acid with 2-nitrophenylhydrazine led to the 2-(2-nitrophenylhydrazono)-D-*arabino*-hexulosonic acid **2a**. The catalytic hydrogenation of nitro compound **1a** in methanol over platinum on carbon at normal pressure afforded methyl (*Z*)-2-(2-aminophenylhydrazono)-D-*arabino*-hexulosonate **1b** (Scheme 1).

In contrast to related systems, ester **1b** on heating and treating with acids did neither cyclize to a 3,3-disubstituted 1,2,4-benzotriazine [14] nor was condensation of the amino group with the methoxycarbonyl unit to form a 1,2,5-benzotriazepine system [15] observed. However, saponification of **1b** or catalytic hydrogenation of **2a** in tetrahydrofuran led to a complex mixture of aromatic amines which were easily oxidized by air. From the oxidized reaction mixture 3-(D-*arabino*-tetritol-1-yl)-1,2,4-benzotriazine **3a** was isolated. In the same manner hydrogen peroxide or iron(III) salts were used as oxidants, but without increasing the yield of **3a**.

However, when the reaction mixture of **2a** was acidified and heated immediately after hydrogenation 2-(D-*arabino*-tetritol-1-yl)-1*H*-benzimidazole **4a** was obtained. Formation of **4a** is accompanied by loss of ammonia. Air oxidation was remarkably suppressed by the acidic conditions. Therefore, the competitive **3a** was not observed. The low yields of **3a** and **4a** resulted from the complex reaction. Many side products, especially the decomposition of the phenylhydrazone with the loss of the carbohydrate moiety, were observed by tlc. Furthermore, the steric hindrance, the influence of the (*E*/*Z*)-isomers as well as the decarboxylation may complicate the reaction. We suppose that the decarboxylation occurs before cyclization. In this case the steric hindrance would be smaller, and the hydrazono carbon be more electrophilic. As another indication, methyl ester **1b** did not react to provide any 1,2,4-benzotriazine derivative. The equilibrium between the D-arabinose 2-aminophenylhydrazone and the corresponding 1,2,3,4-tetrahydro-1,2,4-benzotriazine interme-

Scheme 1

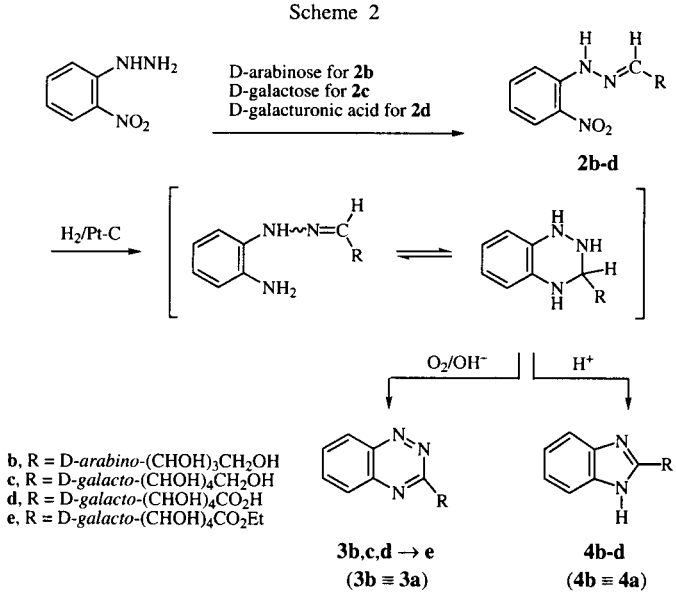


diates is suggested in analogy to similar equilibria reported from aldehyde 2-aminophenylhydrazones [11].

We expected, that an alternative approach to the novel 3-(polyol-1-yl)-1,2,4-triazines should be accessible by the hydrogenation of aldose 2-nitrophenylhydrazones. To prove this principally, the readily available 2-nitrophenylhydrazones of D-arabinose (**2b**), D-galactose (**2c**), and D-galacturonic acid (**2d**) have been synthesized as models whereas we abstained from the synthesis of the 2-nitrophenylhydrazones of D-glucose or D-mannose due to the reported difficulties [12] (Scheme 2).

Indeed, the catalytic hydrogenation of **2b-d** followed by air oxidation in alkaline solution gave rise to the 1,2,4-benzotriazines. Reaction of D-arabinose 2-nitrophenylhydrazone **2b** resulted in the expected 3-(D-*arabino*-tetritol-1-yl)-1,2,4-benzotriazine **3b**, which is structurally identical with **3a** obtained from **2a**. Nevertheless, again the occurrence of many side products is a feature of the cyclizations of **2b-d** to

Scheme 2

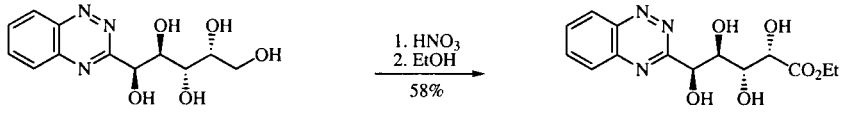


b, R = D-*arabino*-$(CHOH)_3CH_2OH$
c, R = D-*galacto*-$(CHOH)_4CH_2OH$
d, R = D-*galacto*-$(CHOH)_4CO_2H$
e, R = D-*galacto*-$(CHOH)_4CO_2Et$

the 1,2,4-benzotriazines **3**. The reaction of D-galacturonic acid 2-nitrophenylhydrazone **2d** proved to be especially difficult. Due to the influence of the acidic carboxyl group already during hydrogenation of **2d** 5-(benzimidazol-2-yl)-2,3,4,5-tetrahydroxy-L-*galacto*-valerianic acid **4d** was observed as an unwanted byproduct, which was difficult to separate. To circumvent this problem, the hydrogenation was performed with the hydrazinium salt of **2d**. Air oxidation in alkaline solution gave rise to 5-(1,2,4-benzotriazin-3-yl)-2,3,4,5-tetrahydroxy-L-*galacto*-valerianic acid **3d** which without prior isolation was immediately esterified with ethanol to form ethyl 5-(1,2,4-benzotriazin-3-yl)-2,3,4,5-tetrahydroxy-L-*galacto*-valerianate **3e**. Ester **3e** was superior to carboxylic acid **3d** in the separation from byproducts by column chromatography over silica gel.

Alternatively, 3e was obtained by the selective terminal oxidation of the D-galactose derivative **3c** by a method using nitric acid [16] followed by esterification (Scheme 3).

Scheme 3



3c **3e**

2-(D-*arabino*-Tetritol-1-yl)-1*H*-benzimidazole **4b**, 2-(D-*galacto*-pentitol-1-yl)-1*H*-benzimidazole **4c**, and 5-(benzimidazol-2-yl)-2,3,4,5-tetrahydroxy-L-*galacto*-valerianic acid **4d** were obtained after treating the hydrogenation solutions of 2-nitrophenylhydrazones **2b-d** with hydrochloric acid. Naturally, compound **4b** was identical with **4a**. However, it has to be mentioned that the synthetic approach to the benzimidazoles **4b** and **4d** reported here, though novel on principle is lower in yield in comparison with the condensation of 1,2-phenylendiamine with aldoses [17] aldonic acids [18].

In summary, we have reported on the synthesis of a novel type of chiral 3-functionalized 1,2,4-benzotriazines **3** by the first reductive cyclization of carbohydrate 2-nitrophenylhydrazones, as of D-*arabino*-2-hexulosonic acid, D-arabinose, D-galactose and D-galacturonic acid. Modification of the reaction conditions led to chiral 2-functionalized benzimidazoles **4**.

EXPERIMENTAL

Melting points were measured on a Boetius micro hot-stage and are corrected. The ir spectra were obtained on a Carl Zeiss Jena spectrometer M80 in potassium bromide. UV spectra were measured with a Beckman DU-650 spectrometer. The nmr spectra were recorded with a Varian Gemini 200 (^{1}H, 199.975 MHz; ^{13}C, 50.289 MHz) or Varian Unity 400 (^{1}H, 399.97552 MHz) with hexamethyldisiloxane as the internal standard. Mass spectra were recorded on a VG Masslab Manchester VG 12-250 spectrometer (70 eV EI ionisation). Optical rotations were determined with a semiautomatic polarimeter Polartronic-D (Schmidt & Haensch) using the Na-D line. Tlc was performed on precoated Silica gel 60 F_{254} aluminum sheets (Merck), spots were visualized by gentle heating. Silica gel 60 (0.063-0.200 mm) (Merck) was used for column chromatography. Elemental analyses were performed on a Heraeus CHN-O-Rapid analyzer. A fermentation solution containing D-*arabino*-2-hexulopyranosonic acid and sodium D-*arabino*-2-hexulopyranosonate and crystalline methyl β-D-*arabino*-2-hexulopyranosonate have been used, both prepared according to our published method [13].

General Procedure for the Preparation of the Hydrazones **1a**, and **2b-d**.

To a stirred solution of 10 mmoles of the corresponding carbohydrate (2.08 g methyl D-*arabino*-2-hexulosonate for **1a**, 1.50 g of D-arabinose for **2b**, 1.80 g of D-galactose for **2c**, 2.12 g of D-galacturonic acid for **2d**) in water (5 ml) a warm solution of 2-nitrophenylhydrazine (1.53 g, 10 mmoles) in methanol (70 ml), and concentrated hydrochloric acid [(1 ml) for the reaction to **1a**, **2b**, **2c**, only], and ethanol [(60 ml) for **2d**, only] was added. The reaction mixture was heated for 1 hour. After cooling the precipitated hydrazones were filtered and recrystallized from aqueous methanol, except **2d** which was recrystallized from aqueous ethanol.

Methyl (*Z*)-2-(2-Nitrophenylhydrazono)-D-*arabino*-hexulosonate (**1a**).

Compound **1a** was obtained as yellow crystals (2.40 g, 70%), mp 174-176°; ir: ν NH and OH 3400, CO 1710, 1610 cm^{-1}; uv (water): λ (log ε) (water) 219 (3.70), 286 (3.60), 322 (3.66), 413 (3.51); ^{1}H nmr (200 MHz, dimethyl-d_6 sulfoxide): δ 3.45-3.78 (m, 4H, $H_{4'}$, $H_{5'}$, $H_{6'a}$, $H_{6'b}$), 3.84 (s, 3H, CH_3), 4.20-4.80 (m, 4H, 4 x OH), 4.78 (d, 1H, $H_{3'}$, $J_{3',4'}$ = 3.3 Hz), 7.08 (dd, 1H, H_4, $J_{4,5}$ = 7.1 Hz), 7.73 (dd, 1H, H_5), 8.17-8.23 (m, 2H, H_3, H_6), 13.75 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 52.5 (OCH_3), 63.7 (C-6'), 70.7 (C-5'), 71.7 (C-4'), 72.7 (C-3'), 116.7 (C-6), 120.8 (C-4), 125.9 (C-3), 132.5 (C-2), 136.7, 136.8, 140.4 (C-1, -5, -2'), 162.2 (C-1'), ms: m/z 343 (M^+, 2), 325 (2), 312 (10), 293 (11), 252 (60), 220 (80), 207 (100), 190 (40).

Anal. Calcd. for $C_{13}H_{17}N_3O_8$: C, 45.48; H, 4.99; N, 12.24. Found: C, 45.61; H, 5.30; N, 12.51.

D-Arabinose (*E*)-2-Nitrophenylhydrazone (**2b**).

Compound **2b** was obtained as orange crystals (2.17 g, 76%), mp 177-178° (lit [12] mp 180°).

D-Galactose (*E*)-2-Nitrophenylhydrazone (**2c**).

Compound **2c** was obtained as yellow crystals (1.90 g, 86%), mp 171-172° (lit [12] mp 172°).

D-Galacturonic Acid 2-Nitrophenylhydrazone (**2d**).

Compound **2d** was obtained as yellow crystals (3.22 g, 98%), as a 4:1-mixture of (*E*/*Z*)-isomers of **2d**, mp 171-172°; ir: ν NH and

OH 3410, NO_2 1510, NO_2 1340 cm^{-1}; uv (water): λ (log ε) 227 (4.29), 272 (4.08), 431 (3.83); ^1H nmr (200 MHz, dimethyl-d_6 sulfoxide): (*E*)-isomer: δ 3.00-5.50 (m, 9H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, 1'-OH, 2'-OH, 3'-OH, 4'-OH, 5'-OH), 6.86 (m, 1H, H_4), 7.60 (m, 1H, H_5), 7.82 (m, 2H, H_6, $H_{6'}$), 8.06 (m, 1H, H_3), 10.85 (s, 1H, NH); ^{13}C nmr (dimethyl-d_6 sulfoxide): (*E*)-isomer: δ 69.9, 70.2, 61.7, 72.1 (C-2', C-3', C-4', C-5'),116.1 (C-6), 118.0 (C-4), 125.8 (C-3), 130.5 (C-2), 136.5 (C-5), 142.0 (C-1), 151.4 (C-6'), 175.7 (C-1'); ms: m/z 311 (M^+ -H_2O, 3), 231 (43), 194 (5), 138 (100).

Anal. Calcd. for $C_{12}H_{15}N_3O_8$: C, 43.77; H, 4.59; N, 12.76. Found: C, 43.65, H, 4.98; N, 13.07.

Methyl (*Z*)-2-(2-Aminophenylhydrazono)-D-*arabino*-hexulosonate (**1b**).

A suspension of **1a** (343 mg, 1 mmole) in methanol (50 ml) was hydrogenated over platinum on carbon (10%, 50 mg) at normal pressure and room temperature until the consumption of hydrogen ceased. The catalyst was filtered, washed with methanol (5 ml) and the filtrate evaporated *in vacuo*. The remaining product was recrystallized from methanol to give 288 mg (92%) of orange crystals of **1b**, mp 124-126°, ir: ν NH, OH 3400, CO 1680 cm^{-1}; uv (ethanol): λ (log ε) 244 (3.93), 362 (4.06), 366 (4.06); ^1H nmr (200 MHz, dimethyl-d_6 sulfoxide): δ 3.18-3.70 (m, 5H), 3.79 (s, 3H, CH_3), 4.24-4.62 (m, 4H), 4.70-4.90 (m, 2H), 6.62-6.83 (m, $3H_{arom}$), 7.29 (d, 1H, H_6, $J_{5,6}$ = 7.1 Hz), 11.85 (s, 1H, NH), ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 51.8 (OCH_3), 63.8 (C-6'), 69.4 (C-5'), 71.9 (C-4'), 73.0 (C-3'), 114.9 (C-6), 117.8 (C-3), 118.6 (C-4), 122.8 (C-5), 128.5 (C-2), 131.2 (C-1), 135.9 (C-2'), 163.2 (C-1'); ms: m/z 313 (M^+, 8), 295 (30), 278 (5), 263 (3), 131 (87), 107 (100).

Anal. Calcd. for $C_{13}H_{19}N_3O_6$: C, 49.84; H, 6.11. Found: C, 49.85; H, 6.07.

2-(2-Nitrophenylhydrazono)-D-*arabino*-hexulosonic Acid (**2a**).

Method 1: Saponification of **1a**.

To a suspension of **1a** (1.70 g, 5 mmoles) in water (50 ml) a solution of sodium hydroxide (10 ml, 0.5 *N*) was added within 30 minutes. The red solution was stirred for another 10 minutes. Hydrochloric acid (10 ml, 2 *N*) was then added. The precipitate was filtered and washed with water (5 ml). Recrystallization of the residue gave 1.35 g (78%) of orange crystals of **2a**, mp 133-134°, ir: ν OH 3450, CO 1620, NO_2 1340 cm^{-1}, uv (H_2O): λ (log ε) 284 (3.96), 315 (4.10), 422 (3.82); ^1H nmr (200 MHz, dimethyl-d_6 sulfoxide), (*E/Z*)-mixture (3:2): δ 3.43-3.67 (m, 2 x 4H), 4.00-5.40 (m, 2 x 7H), 6.21 (s, 2 x 1H), 7.02 (m, 2 x 1H, H_4), 7.70 (m, 2 x 1H, H_5), 8.16 (m, 2 x 2H, H_3, H_6), 13.18 (s, 1H, (*E*)-NH), 13.97 (s, 1H, (*Z*)-NH), ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 63.8, 63.9 (2 x C-6'), 70.8, 70.9 (2 x C-5'), 71.5, 71.6 (2 x C-4'), 72.7, 73.1 (2 x C-3'), 116.9 (2 x C-6'), 119.7, 120.2 (2 x C-4), 125.8 (2 x C-3), 132.1, 132.2 (2 x C-2), 136.4, 136.5 (2 x C-5), 139.4, 140.5, 140.7, 141.0 (2 x C-1, 2 x C-2'), 163.9, 165.6 (2 x C-1').

Anal. Calcd. for $C_{12}H_{15}N_3O_8$ x H_2O (347.29): C, 41.50; H, 4.93. Found: C, 41.54; H, 5.36.

Method 2: Reaction of a Fermentation Solution with 2-Nitrophenylhydrazine.

A solution of 2-nitrophenylhydrazine (1.53 g, 10 mmoles) dissolved in warm methanol (30 ml) and acetic acid (0.5 ml) was added to a fermentation solution of D-*arabino*-2-hexulosonic acid (15 ml, 0.76 mole/l) at 50°. The reaction mixture was stirred for an hour and then allowed to cool to room temperature. The precipitate was filtered and washed with water (5 ml). Recrystallization from water gave 3.12 g (90%) of orange crystals of **2a**.

General Procedure for the Hydrogenation to Form the 1,2,4-Benzotriazines **3b** and **3c**.

A suspension of the corresponding hydrazone (2.08 g, 6.0 mmoles) of **2a** for **3a** in tetrahydrofuran (60 ml); 2.00 g (7.0 mmoles) of **2b** for **3b** in ethanol (200 ml); 0.41 g (1.3 mmoles) of **2c** for **3c** in ethanol (30 ml) and methanol (80 ml) was hydrogenated over 10% platinum on carbon (0.09 g for **2a** to **3a**; 0.26 g for **2b** to **3b**; 0.08 g for **2c** to **3c**) at normal pressure and room temperature until the consumption of hydrogen was complete.

3-(D-*arabino*-Tetritol-1-yl)-1,2,4-benzotriazine (**3a**).

This compound was obtained after stirring the hydrogenation mixture of **2a** for 3 days in an open flask. The catalyst was filtered and the residue extracted with boiling methanol (2 x 50 ml). After filtration, the extracts were evaporated *in vacuo*. The remaining dark syrup was extracted by refluxing with ethyl acetate (3 x 30 ml) for 15 minutes. On cooling the crude product precipitated slowly. Recrystallization from chloroform/methanol (4:1, v/v) gave 0.42 g (26%) of **3a** as yellow crystals, mp 173-175°; $[\alpha]_D^{26}$ -51° (methanol/water (2:1, v/v), c 0.67); ir: ν OH 3350, CH 770 cm^{-1}; uv (water): λ (log ε) 235 (4.40), 308 (3.60), 339 (3.29); ^1H nmr (200 MHz, dimethyl-d_6 sulfoxide): δ 3.68 (m, 2H, $H_{4'a}$, $H_{4'b}$), 3.65 (m, 1H, $H_{3'}$), 3.98 (m, 1H, $H_{2'}$), 4.37 (m, 1H, 4'-OH), 4.50 (d, 1H, 2'-OH, $J_{2',2'\text{-OH}}$ = 7.4 Hz), 4.75 (d, 1H, 3'-OH, $J_{3',3'\text{-OH}}$ = 5.6 Hz), 5.13 (d, 1H, 1'-OH, $J_{1',1'\text{-OH}}$ = 7.8 Hz), 5.47 (dd, 1H, $H_{1'}$, $J_{1',1'\text{-OH}}$ = 7.8, $J_{1',2'}$ = 2.2 Hz), 8.03 (m, 1H, H_7), 8.17 (m, 2H, H_5, H_6), 8.60 (d, 1H, H_8, $J_{7,8}$ = 7.2 Hz); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 63.8 (C-4'), 71.6 (C-3'), 73.2 (C-2'), 74.7 (C-1'), 128.6 (C-5), 129.3 (C-4a), 131.2 (C-7), 136.5 (C-6), 140.1 (C-8a), 146.5 (C-8), 166.4 (C-3); ms: m/z 251 (M^+, 8), 223 (M^+ -N_2, 52), 190 (32), 174 (16), 161 (20), 103 (100), 76 (37).

Anal. Calcd. for $C_{11}H_{13}N_3O_4$ x H_2O: C, 49.07; H, 5.61; N, 15.61. Found: C, 49.40; H, 5.79; N, 15.62.

Furthermore, this compound was obtained from the hydrogenation mixture of **2b**. After addition of sodium hydroxide (0.30 g, 7.5 mmoles) in water (10 ml) the mixture was refluxed for a minute, the catalyst filtered and the solution stirred at room temperature for 2 days. After cooling to 0° the crude product precipitated was filtered and stirred with an ion exchange resin (Amberlite IR 120 (H^+)) in chloroform/methanol (100 ml, 4:1, v/v) until a weak acid reaction was observed. The mixture was heated for a minute and the resin was filtered. The product precipitated on cooling. Recrystallization from chloroform/methanol (4:1, v/v) gave 0.66 g (35%) of yellow crystals of **3b**, mp 173-175°.

3-(D-*galacto*-Pentitol-1-yl)-1,2,4-benzotriazine (**3c**).

This compound was obtained from the hydrogenation mixture of **2c**. After addition of a solution of ethanolic sodium ethanolate (13 ml, 0.1 *N*) and water (10 ml) the mixture was refluxed for 10 minutes. The catalyst was filtered and the solution was stirred at room temperature for 2 days in an open flask. After the solution was cooled, the crude product precipitated and the precipitate was filtered. Recrystallization from chloroform/methanol (1:1, v/v) gave 0.17 g (46%) of yellow needles of **3c**, mp 220-222°; $[\alpha]_D^{26}$ + 37.5 (methanol/water (2:1, v/v), c 0.67); ir: ν OH 3410, CH 770 cm^{-1}; uv (water): λ (log ε) 231 (4.40), 303 (3.56), 328

(3.36); ^{1}H nmr (200 MHz, dimethyl-d_6 sulfoxide): δ 3.41 (m, 2H, $H_{5'a}$, $H_{5'b}$), 3.68 (m, 2H, $H_{3'}$, $H_{4'}$), 4.16 (m, 2H, 5'-OH, $H_{2'}$), 4.39 (m, 3H, 2'-OH, 3'-OH, 4'-OH), 5.05 (d, 1H, 1'-OH, $J_{1'1'\text{-OH}}$ = 8.2 Hz), 5.49 (dd, 1H, $H_{1'}$, $J_{1',1'\text{-OH}}$ = 8.2 Hz, $J_{1',2'}$ = 2.0 Hz), 7.97 (m, 1H, H_7), 8.13 (m, 2H, H_5, H_6), 8.57 (d, 1H, H_8, $J_{7,8}$ = 8.2 Hz); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 64.0 (C-5'), 70.3 (C-4'), 70.7 (C-3'), 73.8 (C-2'), 74.4 (C-1'), 129.3 (C-5), 130.0 (C-4a), 131.8 (C-7), 137.2 (C-6), 140.8 (C-8a), 147.2 (C-8), 167.4 (C-3); ms: m/z 281 (M^+, 4), 253 (M^+ - N_2, 17), 190 (8), 174 (16), 161 (52), 103 (100), 76 (43).

Anal. Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.37; N, 14.94. Found: C, 51.30; H, 4.97; N, 14.98.

Ethyl 5-(1,2,4-Benzotriazin-3-yl)-2,3,4,5-tetrahydroxy-L-*galacto*-valerianate (**3e**).

Method 1: Catalytic Hydrogenation of **2d**.

To a suspension of **2d** (0.30 g, 0.9 mmoles) in methanol (5 ml) was added hydrazine monohydrate (1.0 ml, 20 mmoles). The mixture was stirred for 3 hours. The yellow salt was filtered, washed with methanol (2 ml), and hydrogenated in methanol (20 ml) over 5% platinum on carbon (0.09 g) at normal pressure and room temperature until the consumption of hydrogen ceased. After addition of sodium hydroxide (0.15 g, 3.7 mmoles) in water (3 ml) the mixture was refluxed for a minute and the catalyst filtered. The filtrate was stirred at room temperature for 2 days in an open flask. Ethanol (10 ml) was added to the solution and the brown precipitate formed was filtered. The filtrate was neutralized with an ion exchange resin (Amberlite IR 120 (H^+)). The resin was filtered and the yellow filtrate evaporated *in vacuo*. The residue was dissolved in absolute ethanol (10 ml) and concentrated sulfuric acid (1 drop) was added. The mixture was refluxed for 2 hours, evaporated to a volume of 2 ml and purified immediately by column chromatography with chloroform/ethanol (20:3, v/v) to yield 63 mg (22%) of yellow needles of **3e**, mp 193-196°, ir: ν 3410 OH, 1730 CO, 1640, 770 CH cm^{-1}; uv (water): λ (log ε) 229 (4.33), 303 (3.66), 326 (3.47); ^{1}H nmr (400 MHz, dimethyl-d_6 sulfoxide): δ 1.76 (t, 3H, CH_3, J = 7.1 Hz), 3.98 (m, 1 H, $H_{2'}$), 4.08 (m, 3H, OCH_2CH_3, $H_{4'}$), 4.28 (d, 1H, $H_{3'}$, $J_{3',3'\text{-OH}}$ = 7.6 Hz), 4.57 (d, 1H, 4'-OH, $J_{4',4'\text{-OH}}$ = 7.5 Hz), 4.82 (d, 1H, 3'-OH, $J_{3',3'\text{-OH}}$ = 8.2 Hz), 4.92 (d, 1H, 2'-OH, $J_{2',2'\text{-OH}}$ = 8.4 Hz), 5.10 (d, 1H, 5'-OH, $J_{5',5'\text{-OH}}$ = 8.4 Hz), 5.43 (dd, 1H, $H_{5'}$, $J_{4',5'}$ = 1.5, $J_{5',5'\text{-OH}}$ = 8.4 Hz), 7.96 (m, 1H, H_7), 8.09 (m, 2H, H_5, H_6), 8.53 (d, 1H, H_8, $J_{7,8}$ = 8.4 Hz); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 14.2 (CH_3), 60.1 (OCH_2CH_3), 70.5 (C-3'), 71.9 (C-2'), 72.4 (C-5'), 73.0 (C-4'), 128.3 (C-5), 129.1 (C-4a), 130.9 (C-7), 136.3 (C-6), 139.9 (C-8a), 146.2 (C-8), 166.1 (C-3), 173.7 (C-1'); ms: m/z 323 (M^+, 11), 295 (36), 277 (11), 250 (12), 232 (9), 220 (23), 190 (17), 175 (19), 161 (63), 147 (29), 133 (27), 117 (12), 103 (100), 76 (50), 61 (20), 44 (19).

Anal. Calcd. for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30; N, 13.00. Found: C, 51.70; H, 5.46; N, 13.21.

Method 2: Terminal Oxidation of **3c** with Nitric Acid.

A solution of **2c** (75 mg, 0.27 mmole) in nitric acid (3 ml, 68%) was stirred for 3 days. After cooling to 0° the brown solution was adjusted with potassium carbonate to *p*H = 4. The mixture was evaporated *in vacuo*. To the residue ethanol (10 ml) and concentrated sulfuric acid (1 drop) were added. The mixture was refluxed for 2 hours, evaporated to a volume of 2 ml and immediately purified by column chromatography with chloroform/ethanol (20:3, v/v) to yield 51 mg (22%) of yellow needles of **3e**, mp 193-196°.

General Procedure for the Hydrogenation to Form the Benzimidazoles **4b-d**.

A suspension of 3.0 mmoles of the corresponding hydrazone (1.21 g of **2a** for **4a**; 1.00 g of **2b** for **4b**; 1.10 g of **2c** for **4c**; 1.15 g of **2d** for **4d**) in methanol (50 ml, and 20 ml for **4d**) was hydrogenated over 5% platinum on carbon (0.15 g) at normal pressure and room temperature until the consumption of hydrogen ceased. Then, under a nitrogen atmosphere concentrated hydrochloric acid was added until the solution turned red. The mixture was heated and the catalyst filtered. After the filtrate was refluxed for 30 minutes ethyl acetate (25 ml) was added and the solution refluxed for another 2 hours. After cooling the crude products precipitated.

2-(D-*arabino*-Tetritol-1-yl)-1*H*-benzimidazole (**4a**).

Recrystallization from aqueous ethanol gave 0.18 g (19%) on starting from **2a**, and 0.34 g (41%) on starting from **2b** respectively, of colorless crystals of **4a**, mp 233-234° (lit [18] mp 234-235°); ^{1}H nmr (200 MHz, dimethyl-d_6 sulfoxide, deuterium oxide): δ 3.40-3.73 (m, 4H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{4'b}$), 5.06 (d, 1H, $H_{1'}$, $J_{1',2'}$ = 2.0 Hz), 7.13 (m, 2H, H_4, H_7), 7.48 (m, 2H, H_5, H_6); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 63.8 (C-4'), 67.8 (C-3'), 71.3 (C-2'), 74.1 (C-1'), 115.0 (C-4, -7), 121.4 (C-5, -6), 138.7 (C-3a, C-7a), 157.6 (C-2), ms: m/z 238 (M^+, 9), 207 (17), 177 (34), 161 (20), 148 (100), 131 (8), 119 (26).

2-(D-*galacto*-Pentitol-1-yl)-1*H*-benzimidazole (**4c**).

Recrystallization from aqueous ethanol gave 0.13 g (14%) of colorless crystals of **4c**, mp 196-197°, ir: ν OH 3410, CN 1740 cm^{-1}; uv (water): λ (log ε) 240 (3.60), 268 (3.80), 275 (3.77); ^{1}H nmr (200 MHz, dimethyl-d_6 sulfoxide): δ 3.36-4.00 (m, 8H, 3 x OH, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'a}$, $H_{5'b}$), 5.10 (s, 1H, OH), 5.43 (s, 1H, $H_{1'}$), 6.56 (s, 1H, 1'-OH), 7.50 (m, 2H, H_4, H_7), 7.73 (m, 2H, H_5, H_6), 14.67 (s, 1H, NH), ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 63.8 (C-5'), 67.9 (C-4'), 69.7 (C-3'), 70.5 (C-2'), 73.5 (C-1'), 114.8 (C-4, -7), 126.4 (C-5, -6), 132.0 (C-3a, -7a), 158.0 (C-2); ms: m/z 268 (M^+, 5), 250 (3), 237 (3), 213 (3), 207 (10), 197 (5), 177 (20), 161 (13), 148 (100), 132 (7), 118 (26), 103 (4).

Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.70; H, 6.43; N, 10.39.

5-(Benzimidazol-2-yl)-2,3,4,5-tetrahydroxy-L-*galacto*-valerianic Acid (**4d**).

Recrystallization from water gave 0.35 g (36%) of colorless crystals of **4d**, mp 184-185° (lit [19] mp 186°); ^{1}H nmr (200 MHz, dimethyl-d_6 sulfoxide + deuterum oxide): δ 3.91 (m, 3H, $H_{2'}$, $H_{3'}$, $H_{4'}$), 5.16 (s, 1H, $H_{5'}$), 7.20 (m, 2H, H_4, H_7), 7.55 (m, 2H, H_5, H_6); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 67.1, 70.3, 71.4, 72.9 (C-2', -3', -4', -5'), 114.8 (C-4, -7), 122.4 (C-5, -6), 137.3 (C-3a, C-7a), 157.3 (C-2), 175.9 (C-1').

Acknowledgement.

The financial support for this work by the Umweltforschungszentrum Leipzig-Halle and the Fonds der Chemischen Industrie is gratefully acknowledged.

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