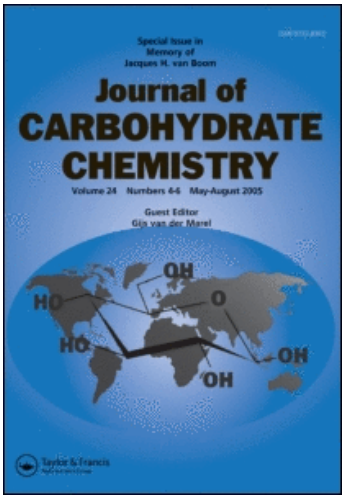

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Synthesis of Some Unusual (1,2,4-Oxadiazole)-Linked Hexenopyranosides and Mannopyranosides

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Synthesis of Some Unusual (1,2,4-Oxadiazole)-Linked Hexenopyranosides and Mannopyranosides

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A copper-catalyzed reaction of propargyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside with 3-(4-azidophenyl)-1,2,4-oxadiazoles gave the corresponding hexenopyranosides bearing an 1,2,4-oxadiazole subunit in the aglyconic part of the molecule. The same reaction between ethyl 4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside and acetylenic 1,2,4-oxadiazoles afforded the corresponding hexenopyranosides carrying a triazole and a 1,2,4-oxadiazole ring at C-4 of the carbohydrate. Combination of the two sequences gave hexenopyranosides displaying two 1,2,4-oxadiazole subunits, each one being embedded in the C-1 and C-4 frameworks, of the carbohydrate moiety. A simple dihydroxylation reaction of these unsaturated carbohydrates yielded a series of mannopyranosides bearing one or two 1,2,4-oxadiazole subunits at C-1 or C-4. These new compounds were evaluated for their cytotoxic activities against two cell strains: NCI-H_{292} (lung carcinoma) and Hep-2 (larynx carcinoma), some of them presenting impressive cell growth inhibitions.

Keywords Cu-catalyst, [3 + 2] Cycloaddition, Hexenopyranoside, Mannopyranoside, 1,2,4-Oxadiazole-based carbohydrate

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INTRODUCTION

The 1,2,4-oxadiazole ring system is present in a large variety of compounds possessing interesting biological activities, as well as in natural products.[1] Substituted 1,2,4-oxadiazoles have been receiving considerable attention as bioisosteres of amides and esters, and have been implicated in peptide chemistry and in the development of peptidomimetics.[2] Compounds containing this heterocyclic subunit have been used as anti-inflammatory agents;[3] as agonists of benzodiazepine,[4] muscarinic,[5] and sphingosine-1-phosphate-1 ($S1P_1$) receptors;[6] as antagonists of integrin[7] and interleukin-8;[8] as anticancer agents;[9] and as antikinetoplastid parasites.[10]

Due to the above-mentioned important biological properties, it appeared interesting to incorporate the oxadiazole units in the carbohydrate framework. Effectively, tying of sugars to other simpler molecules is often employed to deal with targeting mechanism of action and/or pharmacology.[11] Surprisingly, only a few attempts have been made in order to synthesize oxadiazole-linked carbohydrates. Oxadiazoles linked to a glycofuranose,[12] a glycopyranose,[2e,13] and also an unsaturated glycopyranose[14] skeleton have been described. In a program concerning the incorporation of heterocyclic moieties in carbohydrates, we recently reported the incorporation of an 1,2,4-oxadiazole unit at position 1 of various carbohydrates[15] using the copper-catalyzed procedure for the [3 + 2] cycloaddition (or "click chemistry")[16] between a glycoside containing an anomeric azide functionality and an oxadiazole bearing a terminal acetylenic group, and at position 4 of ethyl α-D-mannopyranoside via the palladium-catalyzed reaction of 5-(4-hydroxyphenyl)-1,2,4-oxadiazoles with ethyl α-*O*-Δ^2-glucopyranoside followed by a bishydroxylation of the later compounds.[17]

Here, we describe easy access to a new series of 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside and α-D-mannopyranoside derivatives carrying one oxadiazole moiety connected to other groups attached to C-1 or/and to C-4 positions using this [3 + 2] cycloaddition reaction. Further, some preliminary results concerning the biological activity of these compounds are reported.

RESULTS AND DISCUSSION

We chose to carry out the [3 + 2] cycloaddition reaction between two sets of 1,2,4-oxadiazoles, one containing a terminal acetylenic group like **1** and **2**, and the other bearing an azido function like **3** (Fig. 1). The preparation of 1,2,4-oxadiazoles **1**–**2** has already been described by our group.[15] Azido 1,2,4-oxadiazoles **3** were prepared from nitro-oxadiazoles **4**[18] by reduction with tin chloride to afford the amino oxadiazoles **5**; in situ transformation to the diazo derivatives followed by substitution with sodium azide gave the expected azido oxadiazoles **3a** and **3b** in an overall yield of 91% and 76%, respectively (Sch. 1).

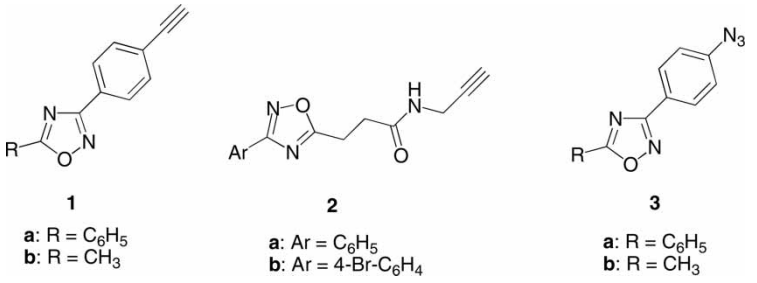
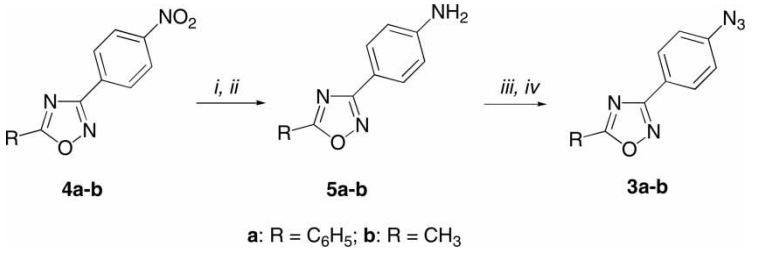


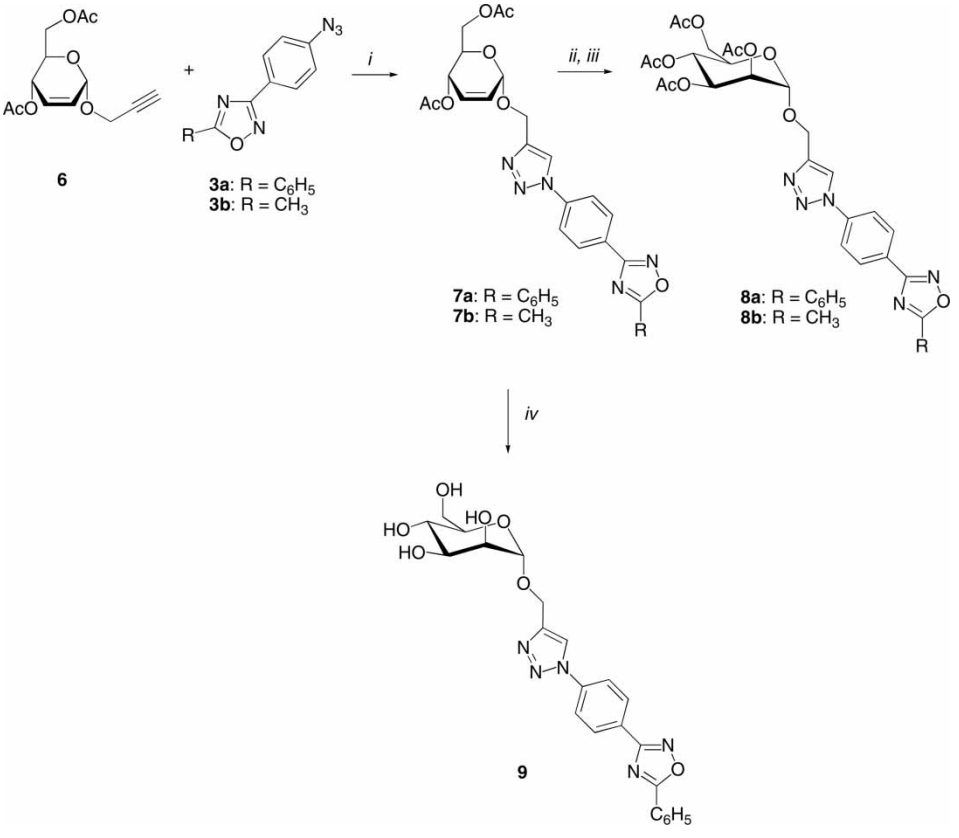
Figure 1: Structure of 1,2,4-oxadiazoles.

First we introduced the 1,2,4-oxadiazole subunit on the aglycon moiety. For this purpose, the copper(I)-catalyzed 1,3-dipolar cycloaddition of azido oxadiazoles **3a**–**b** was performed with propargyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **6** using a 1:1 (v/v) mixture of dichloromethane and water as the solvent in the presence of $Cu(OAc)_2$ and sodium ascorbate (Sch. 2).[19] The corresponding cycloadducts **7a** and **7b** were obtained in 91% and 87% yield, respectively. The unsaturated carbohydrates **7a**–**b** were subjected to the dihydroxylation reaction under Upjohn conditions (catalytic OsO_4/NMO), followed by acetylation of the mixture, to afford the corresponding {1-[4-(1,2,4-oxadiazol-3-yl)phenyl]-1*H*-1,2,3-triazol-4-yl}methyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosides **8a** and **8b** in 67% and 72% yield, respectively (Sch. 2). It should to be noticed that deacetylated mannopyranoside **9** could be directly obtained from unsaturated carbohydrate **7a** in 84% chemical yield using the dihydroxylation reaction followed by deacetylation in the presence of potassium carbonate (Sch. 2).

In order to introduce the 1,2,4-oxadiazole subunit at C-4 of the carbohydrate scaffold, we used the sequence previously published by our group for the preparation of unsaturated [1,2,3]-triazole-linked glycoconjugates.[20] The copper(I)-catalyzed 1,3-dipolar cycloaddition of ethyl 4-azido-6-*O*-*tert*-butyldimethylsilyl-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside **10**[21] with acetylenic oxadiazoles **1** and **2a**–**b** was performed in a 1:1 (v/v) mixture of dichloromethane



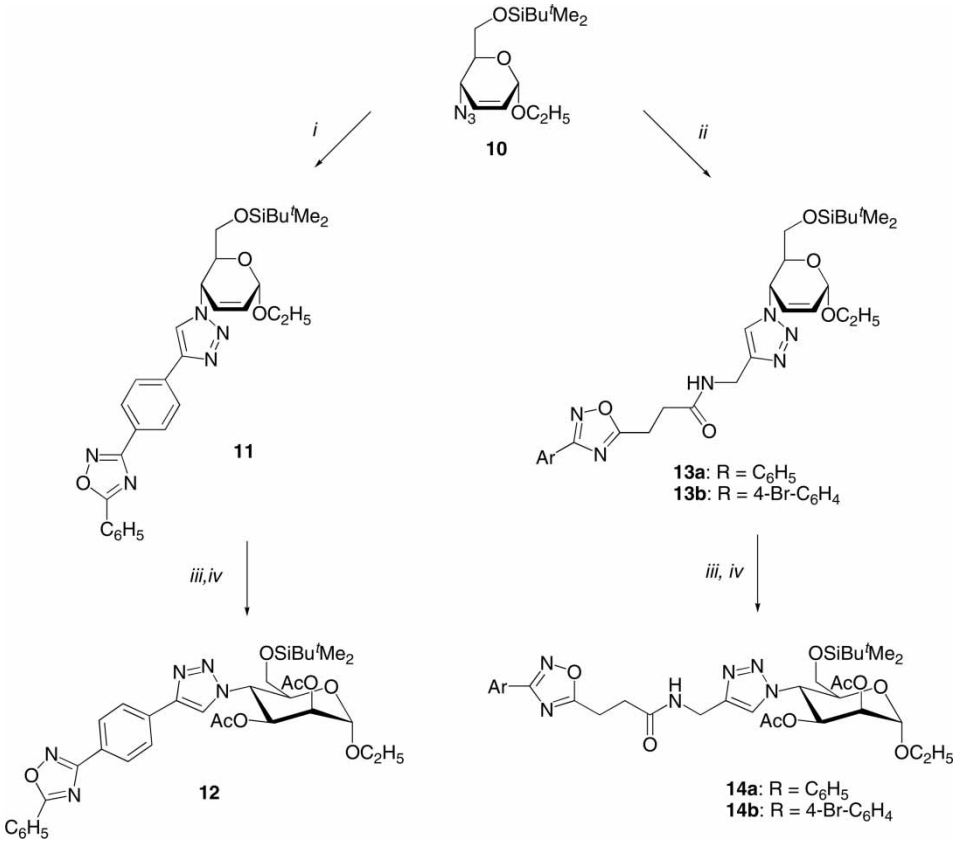
Scheme 1: Synthesis of 1,2,4-oxadiazoles **5**. *Reagents and conditions*: *i*) $SnCl_2$, C_2H_5OH, reflux; *ii*) aq. $NaHCO_3$, rt; *iii*) CH_2Cl_2, aq. HCl, then $NaNO_2$, 0°C; *iv*) NaN_3, 0°C, then rt.



Scheme 2: Synthesis of compounds **7**, **8**, and **9**. *Reagents and conditions: i*) $Cu(OAc)_2$ (20 mol%), sodium ascorbate (40 mol%), H_2O/CH_2Cl_2 (1:1), rt; *ii*) OsO_4 (1 mol%), NMO, CH_3COCH_3/H_2O (4:1), rt for compound **8a** or K_2OsO_4. 2 H_2O (1 mol%), NMO, citric acid, *tert*-BuOH/H_2O (1:1), rt for compound **8b**; (*iii*) Ac_2O, C_5H_5N, rt; *iv*) $K_2OsO_4 \cdot 2\ H_2O$ (1 mol%), NMO, citric acid, *tert*-BuOH/H_2O (1:1), then K_2CO_3, H_2O, CH_3OH, rt.

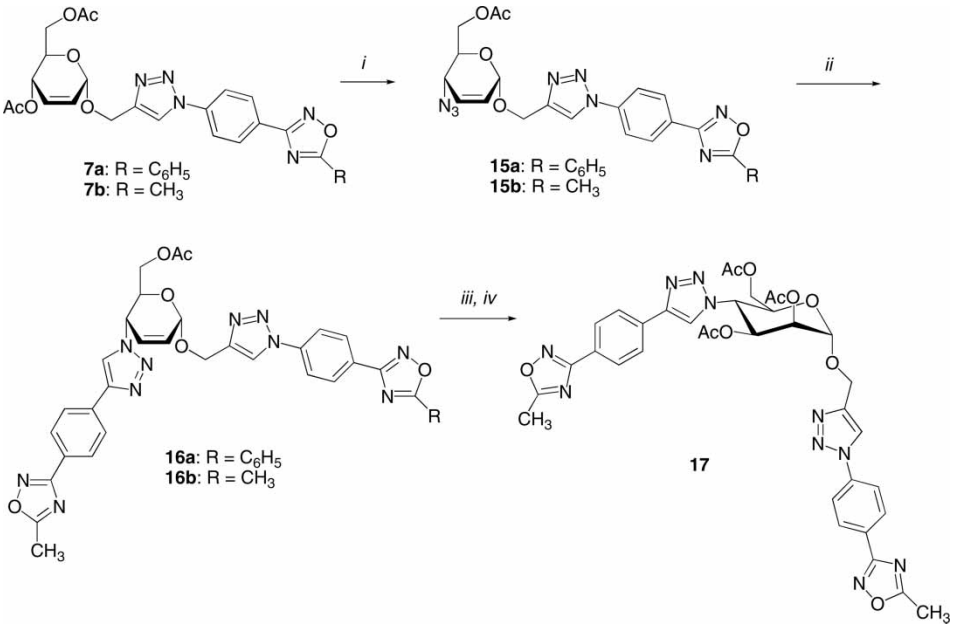
and water as the solvent in the presence of $Cu(OAc)_2$ and sodium ascorbate (Sch. 3)[19] to afford the corresponding cycloadducts **11** and **13a**–**b** in 80%, 79%, and 77% yield, respectively. Dihydroxylation of these unsaturated carbohydrates **11** and **13a**–**b** under Upjohn conditions (catalytic OsO_4/NMO), followed by acetylation of the mixture, afforded the corresponding ethyl 4-deoxy-2,3,6-tri-*O*-acetyl-α-D-mannopyranosides **12**, **14a**, and **14b**, bearing the oxadiazole subunit at position 4, in 65%, 65%, and 84% yield, respectively (Sch. 3).

Finally, the introduction of two 1,2,4-oxadiazole subunits at the anomeric position and at position 4 of the mannopyranose backbone was envisioned using the two above-mentioned methodologies. Reaction of unsaturated carbohydrates **7a**–**b**, prepared as described before, with sodium azide in the presence of a catalytic amount of $Pd_2(dba)_3$ + dppb [or 1,4-bis(diphenylphosphino)-butane] in tetrahydrofuran at 50°C[21] afforded regio- and stereospecifically the



Scheme 3: Synthesis of compounds **11**, **12**, **13**, and **14**. *Reagents and conditions: i*) 1,2,4-oxadiazole **1a**, $Cu(OAc)_2$ (20 mol%), sodium ascorbate (40 mol%), H_2O/CH_2Cl_2 (1:1), rt; *ii*) 1,2,4-oxadiazole **2**, $Cu(OAc)_2$ (20 mol%), sodium ascorbate (40 mol%), H_2O/CH_2Cl_2 (1:1), rt; *iii*) OsO_4 (1 mol%), NMO, CH_3COCH_3/H_2O (4:1), rt; *iv*) Ac_2O, C_5H_5N, rt.

corresponding allylic azides **15a** and **15b** in 69% and 39% yield, respectively (Sch. 4). As previously shown, the structures of compounds **15a**–**b** were assigned on the basis of the ^{1}H NMR spectral analysis.[21] The vicinal coupling constants $J_{4,5} = 10.0$ Hz and 9.8 Hz for compounds **15a** and **15b**, respectively, indicated a *trans* diaxial relationship between H-4 and H-5, proving the *erythro* configuration. The copper(I)-catalyzed 1,3-dipolar cycloaddition of unsaturated azido carbohydrates **15a**–**b** with 3-(4-ethynylphenyl)-1,2,4-oxadiazoles **1a**–**b** afforded the unsaturated carbohydrates **16a** and **16b**, bearing two oxadiazoles subunits at position 1 and 4, in 80% and 71% yield, respectively. Finally dihydroxylation of unsaturated carbohydrate **16b** under Upjohn conditions (catalytic OsO_4/NMO), followed by acetylation of the obtained mixture, afforded the corresponding 2,3,6-tri-*O*-acetyl-4-deoxy-α-D-mannopyranoside **17**, bearing two oxadiazole subunits at the anomeric position and at position 4, in 42% yield.



Scheme 4: Synthesis of compounds **16** and **17**. *Reagents and conditions*: *i*) NaN_3, $Pd_2(dba)_3$, dppb, THF/H_2O (1.5:1), 50°C; *ii*) **1b**, $Cu(OAc)_2$ (20 mol%), sodium ascorbate (40 mol%), H_2O/CH_2Cl_2 (1:1), rt; *iii*) K_2OsO_4. $2H_2O$ (1 mol%), NMO, citric acid, *tert*-BuOH/H_2O (1:1), rt; *iv*) Ac_2O, C_5H_5N, rt.

All the synthesized compounds have been evaluated for their cytotoxic activities against two cell strains: NCI-H_{292} (lung carcinoma) and Hep-2 (larynx carcinoma) based on the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[22–24] The preliminary results showed that these activities varied from 5% to 70% for NCI-H_{292} and from 3% to 61% for Hep-2 of cell growth inhibition. The most potent compounds are **8a**, **16a**, and **16b** with 55%, 57%, and 61% of cell growth inhibition (NCI), respectively, while compounds **16a**, **16b**, and **8a** inhibited the cell growth by 44%, 50%, and 58% in the Hep-2 cell strain, respectively. Further tests are actually under development and the results will be published in the future.

CONCLUSION

In conclusion, 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides bearing an 1,2,4-oxadiazole subunit at the anomeric position were easily obtained via a copper-catalyzed reaction of propargyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside with 3-(4-azidophenyl)-1,2,4-oxadiazoles. Ethyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosides bearing an 1,2,4-oxadiazole unit at C-4 were obtained from ethyl 4-azido-

2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside and acetylenic 1,2,4-oxadiazoles in the presence of $Cu(OAc)_2$ as the catalyst. The combination of these two sequences gave the corresponding hexenopyranosides bearing two 1,2,4-oxadiazole subunits at C-1 and at C-4 of the carbohydrate moiety. A series of mannopyranosides bearing one or two 1,2,4-oxadiazole subunits at C-1 or C-4 of the carbohydrate moiety via a simple dihydroxylation reaction of these unsaturated carbohydrates were also synthesized. Some preliminary results showed that there were some interesting cytotoxic activities against NCI-H_{292} and Hep-2 cell strains, compounds **8a**, **16a**, and **16b** presenting impressive cell growth inhibitions.

EXPERIMENTAL

General Procedure

All commercially available reagents were used as received. All reactions were monitored by TLC analysis (TLC plates GF_{254} Merck). Air- and moisture-sensitive reactions were performed under inert atmosphere. Melting points were determined on a Büchi apparatus and are uncorrected. Column chromatography was performed on silica gel 60 (230–240 mesh, Merck). Optical rotations were recorded using a Perkin-Elmer 241 polarimeter. NMR spectra were recorded with a Bruker AMX 300 spectrometer and referenced as following: ^1H (300 MHz), internal $SiMe_4$ at δ 0.00 ppm, ^{13}C (75 MHz), internal standard at δ 77.23 ppm. Exact mass measurements of the molecular ions were obtained on a Finnigan Mat 95 XL spectrometer. 3-(4-Ethynylphenyl)-5-phenyl-1,2,4-oxadiazole (**1a**),[25] 3-(4-ethynylphenyl)-5-methyl-1,2,4-oxadiazole (**1b**),[25] 3-(3-phenyl-1,2,4-oxadiazol-5-yl)-*N*-(prop-2-yn-1-yl)propanamide (**2a**),[25] 3-[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]-*N*-(prop-2-yn-1-yl)propanamide (**2b**),[25] ethyl 4-azido-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranoside (**10**),[21] and 2-propynyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**6**)[26] were prepared according to the literature.

General Procedure for the Preparation of Oxadiazoles 3

A solution of nitro oxadiazole **4** (4.1 mmol) in ethanol (50 mL) was heated at reflux in the presence of $SnCl_2$ (3.1 g, 16.4 mmol). After total consumption of the starting material, observed by TLC, the mixture was treated with an aqueous $NaHCO_3$ solution until pH 8.0. The resulting suspension was extracted with ethyl acetate (3 × 100 mL). Evaporation of the solvent in vacuo afforded the crude amino derivative **5**, which was used in the next step without further purification. This amino derivative **5** was dissolved in CH_2Cl_2 (30 mL), and a 6 N aqueous solution of HCl (30 mL) was added at 0°C. To this biphasic system was added dropwise a saturated aqueous

solution of $NaNO_2$ (10 mL). After stirring for 30 min at 0°C, NaN_3 (530 mg, 8.2 mmol) was added at 0°C. Stirring was pursued for 30 min, and the mixture was allowed to warm to rt. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with an aqueous solution of $NaHCO_3$, then brine, and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave a residue that was purified by column chromatography on silica gel to afford pure oxadiazole **3**.

*3-(4-Azidophenyl)-5-phenyl-1,2,4-oxadiazole (**3a**)*

Yield 91%; yellow solid; mp 114°C; R_f 0.76 (petroleum ether/EtOAc 3:2); ^1H NMR ($CDCl_3$): 7.04 (br d, $J = 8.7$ Hz, 2H, H_{arom}), 7.38–7.50 (m, 4H, H_{arom}), 7.99–8.09 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): 119.8, 124.0, 124.6, 127.9, 128.5, 129.5, 133.1, 143.2, 168.5, 176.1.

Anal. Calcd. for $C_{14}H_9N_5O$ (263.25): C, 63.87; H, 3.45. Found: C, 63.88; H, 3.56.

*3-(4-Azidophenyl)-5-methyl-1,2,4-oxadiazole (**3b**)*

Yield 76%; brown solid; mp 70°C; R_f 0.71 (petroleum ether/EtOAc 3:2); ^1H NMR ($CDCl_3$): 2.64 (s, 3H, CH_3), 7.10 (br d, $J = 8.8$ Hz, 2H, H_{arom}), 8.04 (br d, $J = 8.8$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 12.7, 119.8, 123.8, 129.3, 143.2, 168.0, 177.0.

EI-HRMS Calcd. for $C_9H_7N_5O$ [M^+]: 201.0651. Found: 201.0660.

General Procedure for the Preparation of Carbohydrate–triazole-Linked Oxadiazoles

The acetylenic compound (1.1 mmol) and the azido compound (1 mmol) were suspended in 1:1 mixture of CH_2Cl_2 and water (4 mL). To this solution was added a mixture of $Cu(OAc)_2$ (36 mg, 0.2 mmol) and sodium ascorbate (79 mg, 0.4 mmol). The resulting mixture was stirred under nitrogen at rt until TLC analysis indicated complete consumption of the starting reagents. The reaction contents were diluted with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was separated, and the water phase was extracted again with CH_2Cl_2 (5 mL). The combined organic layers were dried over Na_2SO_4 and filtered. Removal of the solvent in vacuo gave a residue that was purified by column chromatography on silica gel using the indicated eluent to give the corresponding carbohydrate–triazole-linked 1,2,4-oxadiazole.

*{1-[4-(5-Phenyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**7a**)*

This compound was obtained by reacting acetylenic carbohydrate **6** (295 mg) and oxadiazole **3a** (263.2 mg) for 24 h; yield 91%; colorless solid; mp

180°C; R_f 0.69 (EtOAc/petroleum ether 7:3); $[\alpha]_D^{20}$ +25 ($c = 1.0$, CH_2Cl_2); ^1H NMR ($CDCl_3$): 2.09 (s, 3H, OAc), 2.12 (s, 3H, OAc), 4.15–4.32 (m, 3H, H-5, H-6), 4.84 (d, $J = 12.4$ Hz, 1H, CH_2), 5.04 (d, $J = 12.4$ Hz, 1H, CH_2), 5.25 (br s, 1H, H-1), 5.37 (br d, $J = 9.4$ Hz, 1H, H-4), 5.88 (ddd, $J = 10.2$, 2.1, 1.8 Hz, 1H, H-2), 5.95 (br d, $J = 10.2$ Hz, 1H, H-3), 7.55–7.67 (m, 3H, H_{arom}), 7.93 (br d, $J = 8.7$ Hz, 2H, H_{arom}), 8.11 (s, 1H, =CH-N), 8.24 (br d, $J = 8.1$ Hz, 2H, H_{arom}), 8.37 (br d, $J = 8.9$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 21.2, 21.3, 61.8, 63.3, 65.6, 67.5, 94.3, 120.9, 121.1, 124.4, 127.7, 128.5, 129.4, 129.5, 130.0, 133.3, 139.1, 145.9, 168.2, 170.6, 171.2, 176.4.

Anal. Calcd. for $C_{27}H_{25}N_5O_7$ (531.52): C, 61.01; H, 4.74. Found: C, 61.11; H, 4.80.

*{1-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-ERYTHRO-hex-2-enopyranoside (**7b**)*

This compound was obtained by reacting acetylenic carbohydrate **6** (295 mg) and oxadiazole **3b** (201.2 mg) for 23 h; yield 87%; colorless solid; mp 176°C; R_f 0.32 (petroleum ether/EtOAc 3:2); $[\alpha]_D^{20}$ +29 ($c = 1.0$, CH_2Cl_2); ^1H NMR ($CDCl_3$): 2.09 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.69 (s, 3H, CH_3), 4.17 (ddd, $J = 9.3$, 4.9, 2.5 Hz, 1H, H-5), 4.21 (dd, $J = 12.2$, 2.3 Hz, 1H, H-6), 4.29 (dd, $J = 12.2$, 5.3 Hz, 1H, H-6), 4.83 (d, $J = 12.5$ Hz, 1H, CH_2), 5.02 (d, $J = 12.5$ Hz, 1H, CH_2), 5.25 (s, 1H, H-1), 5.36 (br d, $J = 9.3$ Hz, 1H, H-4), 5.87 (ddd, $J = 10.2$, 2.5, 1.7 Hz, 1H, H-2), 5.94 (br d, $J = 10.2$ Hz, 1H, H-3), 7.89 (br d, $J = 8.7$ Hz, 2H, H_{arom}), 8.09 (s, 1H, =CH-N), 8.24 (br d, $J = 8.7$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 12.8, 21.2, 21.3, 61.8, 63.2, 65.7, 67.5, 94.3, 120.9, 121.1, 127.6, 127.7, 129.3, 130.0, 139.1, 145.9, 167.7, 170.6, 171.2, 177.3.

Anal. Calcd. for $C_{22}H_{23}N_5O_7$ (469.45): C, 56.29; H, 4.94. Found: C, 56.52; H, 4.98.

*Ethyl 6-O-(tert-butyldimethylsilyl)-2,3,4-trideoxy-4-{4-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-1-yl}-α-D-erythro-hex-2-enopyranoside (**11**)*

This compound was obtained by reacting azido carbohydrate **10** (182 mg) and oxadiazole **1a** (271 mg) for 20 h; yield 80%; colorless solid; mp 58–59°C; R_f 0.24 (petroleum ether/EtOAc 9:1); $[\alpha]_D^{20}$ +121.1 ($c = 1.0$, CH_2Cl_2); ^1H NMR ($CDCl_3$): 0.00 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.85 (s, 9H, CMe_3), 1.26 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.60 (dq, $J = 9.5$, 7.2 Hz, 1H, OCH_2CH_3), 3.62 (dd, $J = 11.7$, 4.7 Hz, 1H, H-6), 3.71 (dd, $J = 11.7$, 2.3 Hz, 1H, H-6), 3.89 (dq, $J = 9.5$, 7.2 Hz, 1H, OCH_2CH_3), 4.13 (ddd, $J = 9.6$, 4.7, 2.1 Hz, 1H, H-5), 5.15 (br s, 1H, H-1), 5.42 (br d, $J = 9.6$ Hz, 1H, H-4), 6.00 (br d, $J = 11.0$ Hz, 1H, H-2), 6.08 (ddd, $J = 10.0$, 2.5, 2.5 Hz, 1H, H-3), 7.50–7.62 (m, 3H, H_{arom}), 7.90 (s, 1H, =CH-N), 7.96 (d, $J = 8.5$ Hz, 2H, H_{arom}), 8.10–8.25 (m, 4H,

H_{arom}); ^{13}C NMR ($CDCl_3$): −5.0, 15.7, 18.7, 26.3, 55.4, 62.8, 64.7, 71.6, 94.2, 119.4, 126.4, 128.1, 128.5, 128.5, 129.5, 129.9, 133.2, 133.5, 147.7, 169.0, 176.1.

Anal. Calcd. for $C_{30}H_{37}N_5O_4Si$ (559.73): C, 64.37; H, 6.66. Found: C, 63.88; H, 6.68.

*N-({1-[Ethyl 6-O-(tert-butyldimethylsilyl)-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranosid-4-yl]-1H-1,2,3-triazol-4-yl}methyl)-3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanamide (**13a**)*

This compound was obtained by reacting azido carbohydrate **10** (182 mg) and oxadiazole **2a** (281 mg) for 19 h; yield 79%; colorless oil; R_f 0.2 (CH_2Cl_2/EtOAc 4:1); $[\alpha]_D^{20}$ +61.2 ($c = 1.0$, CH_2Cl_2); ^1H NMR ($CDCl_3$): 0.00 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.87 (s, 9H, CMe_3), 1.24 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.81 (t, $J = 7.2$ Hz, 2H, CH_2), 3.30 (t, $J = 7.0$ Hz, 2H, CH_2), 3.53 (dd, $J = 11.7$, 4.9 Hz, 1H, H-6), 3.57 (dq, $J = 9.6$, 7.1 Hz, 1H, OCH_2CH_3), 3.64 (dd, $J = 11.7$, 2.2 Hz, 1H, H-6), 3.86 (dq, $J = 9.6$, 7.1 Hz, 1H, OCH_2CH_3), 4.06 (ddd, $J = 9.8$, 4.9, 2.2 Hz, 1H, H-5), 4.51 (dd, $J = 15.2$, 5.6 Hz, 1H, CH_2N), 4.57 (dd, $J = 15.2$, 5.6 Hz, 1H, CH_2N), 5.11 (br s, 1H, H-1), 5.30 (br d, $J = 9.8$ Hz, 1H, H-4), 5.85 (br d, $J = 10.0$ Hz, 1H, H-2), 6.00 (ddd, $J = 10.0$, 2.8, 2.6 Hz, 1H, H-3), 6.64 (br t, $J = 5.6$ Hz, 1H, NH), 7.43–7.52 (m, 3H, H_{arom}), 7.57 (s, 1H, =CH-N), 8.02 (dd, $J = 7.7$, 2.2 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): −5.1 −5.0, 15.6, 18.7, 22.7, 26.2, 32.3, 35.2, 55.2, 62.7, 64.6, 71.2, 94.2, 121.9, 127.1, 127.7, 127.9, 129.2, 129.5, 131.5, 145.2, 168.5, 170.8, 179.2.

Anal. Calcd. for $C_{28}H_{40}N_6O_5Si$ (568.74): C, 59.13; H, 7.09. Found: C, 59.51; H, 7.20.

*N-({1-[Ethyl 6-O-(tert-butyldimethylsilyl)-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranosid-4-yl]-1H-1,2,3-triazol-4-yl}methyl)-3-[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]propanamide (**13b**)*

This compound was obtained by reacting azido carbohydrate **10** (182 mg) and oxadiazole **2b** (368 mg) for 17 h; yield 77%; colorless solid; mp 39°C; R_f 0.1 (CH_2Cl_2/EtOAc 4:1); $[\alpha]_D^{20}$ +56.5 ($c = 1.0$, CH_2Cl_2); ^1H NMR ($CDCl_3$): 0.00 (s, 6H, $SiCH_3$), 0.87 (s, 9H, CMe_3), 1.25 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.81 (t, $J = 7.0$ Hz, 2H, CH_2), 3.30 (t, $J = 7.0$ Hz, 2H, CH_2), 3.52 (dd, $J = 11.5$, 4.7 Hz, 1H, H-6), 3.57 (dq, $J = 9.6$, 7.1 Hz, 1H, OCH_2CH_3), 3.64 (dd, $J = 11.5$, 2.2 Hz, 1H, H-6), 3.87 (dq, $J = 9.6$, 7.1 Hz, 1H, OCH_2CH_3), 4.06 (ddd, $J = 9.8$, 4.7, 2.2 Hz, 1H, H-5), 4.51 (dd, $J = 15.2$, 5.6 Hz, 1H, CH_2N), 4.57 (dd, $J = 15.2$, 5.6 Hz, 1H, CH_2N), 5.11 (br s, 1H, H-1), 5.30 (br d, $J = 9.8$ Hz, 1H, H-4), 5.87 (br d, $J = 10.0$ Hz, 1H, H-2), 6.02 (ddd, $J = 10.0$, 2.8, 2.5 Hz, 1H, H-3), 6.34 (br t, $J = 5.6$ Hz, 1H, NH), 7.55 (s, 1H, =CH-N), 7.61 (dd, $J = 8.7$, 1.9 Hz, 2H, H_{arom}), 7.91(dd, $J = 8.7$, 1.9 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): −5.0, −5.1, 15.6, 18.7, 22.7, 26.2, 32.3, 35.2, 55.3, 62.7, 64.6, 71.2, 94.2, 121.9, 126.0, 126.1, 127.9, 129.3, 129.6, 132.5, 145.1, 167.8, 170.7, 179.5.

Anal. Calcd. for $C_{28}H_{39}BrN_6O_5Si$ (647.64): C, 51.93; H, 6.07. Found: C, 52.02; H, 6.22.

*{1-[4-(5-Phenyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 6-O-acetyl-2,3,4-trideoxy-4-{4-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-1-yl}-α-D-erythro-hex-2-enopyranoside (**16a**)*

This compound was obtained by reacting **15a** (566 mg) and acetylenic oxadiazole **1b** (184 mg) for 24 h; yield 80%; colorless solid; mp 207°C; R_f 0.74 (EtOAc); $[\alpha]_D^{20}$ +56 ($c = 1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 2.09 (s, 3H, OAc), 2.66 (s, 3H, CH_3), 4.13 (dd, $J = 12.2$, 4.7 Hz, 1H, H-6), 4.29 (dd, $J = 12.2$, 2.8 Hz, 1H, H-6), 4.44 (ddd, $J = 9.8$, 4.7, 2.8 Hz, 1H, H-5), 4.90 (d, $J = 12.2$ Hz, 1H, CH_2), 5.05 (d, $J = 12.2$ Hz, 1H, CH_2), 5.41 (br s, 1H, H-1), 5.50 (br d, $J = 9.8$ Hz, 1H, H-4), 6.08 (br d, $J = 10.2$ Hz, 1H, H-2), 6.18 (ddd, $J = 10.2$, 2.6, 2.5 Hz, 1H, H-3), 7.55–7.67 (m, 3H, H_{arom}), 7.90 (s, 1H, =CH-N), 7.93 (d, $J = 8.7$ Hz, 2H, H_{arom}), 7.95 (d, $J = 8.6$ Hz, 2H, H_{arom}), 8.12 (d, $J = 8.5$ Hz, 2H, H_{arom}), 8.16 (s, 1H, =CH-N), 8.24 (br d, $J = 8.2$ Hz, 2H, H_{arom}), 8.37 (br d, $J = 8.9$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 12.8, 21.1, 55.9, 61.9, 63.1, 69.0, 94.0, 119.3, 120.9, 121.4, 124.4, 126.4, 127.0, 127.9, 128.3, 128.6, 129.5, 129.6, 133.1, 133.4, 139.0, 145.5, 147.9, 168.2, 168.4, 170.9, 176.4, 177.0.

ESI-HRMS Calcd. for $C_{36}H_{30}N_{10}O_6Na$ $[M + Na]^+$: 721.2247. Found: 721.2244.

*{1-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 6-O-acetyl-2,3,4-trideoxy-4-{4-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-1-yl}-α-D-erythro-hex-2-enopyranoside (**16b**)*

This compound was obtained by reacting **15b** (497 mg) and acetylenic oxadiazole **1b** (184 mg) for 18 h; yield 71%; colorless solid; mp 203°C; R_f 0.52 (EtOAc); $[\alpha]_D^{20}$ +44 ($c = 0.5$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 2.09 (s, 3H, OAc), 2.67 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.12 (dd, $J = 12.2$, 4.9 Hz, 1H, H-6), 4.28 (dd, $J = 12.2$, 2.8 Hz, 1H, H-6), 4.43 (ddd, $J = 9.6$, 4.9, 2.8 Hz, 1H, H-5), 4.89 (d, $J = 12.3$ Hz, 1H, CH_2), 5.04 (d, $J = 12.3$ Hz, 1H, CH_2), 5.40 (br s, 1H, H-1), 5.50 (br d, $J = 9.6$ Hz, 1H, H-4), 6.08 (br d, $J = 10.0$ Hz, 1H, H-2), 6.17 (ddd, $J = 10.0$, 2.5, 2.3 Hz, 1H, H-3), 7.91 (br d, $J = 8.5$ Hz, 2H, H_{arom}), 7.92 (br d, 2H, $J = 8.7$ Hz, H_{arom}), 7.96 (s, 1H, =CH-N$_l$), 8.12 (br d, $J = 7.7$ Hz, 2H, H_{arom}), 8.14 (s, 1H, =CH-N), 8.25 (br d, $J = 8.5$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 12.8, 21.2, 55.8, 62.0, 63.0, 69.0, 94.0, 119.2, 121.0, 121.4, 126.5, 128.3, 129.4, 129.5, 133.1, 145.5, 162.7, 170.9, 177.0.

HRMS-ESI Calcd. for $C_{31}H_{28}N_{10}O_6Na$ $[M + Na]^+$: 659.2091. Found: 659.2074.

General Procedure for the Preparation of Azidocarbohydrates 15

The catalytic system was prepared by stirring for 1 h in a Schlenk tube under argon $Pd_2(dba)_3$ (35 mg, 0.038 mmol) and 1,4-bis(diphenylphosphino)butane or dppb (64 mg, 0.15 mmol) in tetrahydrofuran (1.5 mL). This solution was added under argon to a Schlenk tube containing the unsaturated carbohydrate **7** (0.38 mmol) and sodium azide (65 mg, 0.42 mmol) in a mixture of THF/water (1.5 mL/2 mL). The mixture was stirred at 50°C for 2 h. The solution was concentrated in vacuo, water (3 mL) was added, and the organic compound was extracted with ether (3 × 10 mL). The combined extracts were washed successively with an aqueous 1 M solution of HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4. Removal of the solvent in vacuo gave a residue that was submitted to column chromatography on silica gel using petroleum ether/EtOAc as the eluent to afford the corresponding pure unsaturated azido carbohydrate **15**.

*{1-[4-(5-Phenyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 6-O-acetyl-4-azido-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranoside (**15a**)*

Yield 69%; colorless solid; mp 146°C; R_f 0.72 (EtOAc/petroleum ether 7:3); $[\alpha]_D^{20}$ +65 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 2.14 (s, 3H, OAc), 3.95 (br d, J = 10.0 Hz, 1H, H-4), 4.01 (ddd, J = 10.0, 4.7, 2.3 Hz, 1H, H-5), 4.31 (dd, J = 12.1, 4.7 Hz, 1H, H-6), 4.41 (dd, J = 12.1, 2.3 Hz, 1H, H-6), 4.83 (d, J = 12.4 Hz, 1H, CH_2), 5.02 (d, J = 12.4 Hz, 1H, CH_2), 5.24 (br s, 1H, H-1), 5.98 (ddd, J = 10.0, 2.4, 2.0 Hz, 1H, H-2), 6.05 (br d, J = 10.0 Hz, 1H, H-3), 7.55–7.67 (m, 3H, H_{arom}), 7.93 (d, J = 8.6 Hz, 2H, H_{arom}), 8.12 (s, 1H, =CH-N), 8.23 (br d, J = 8.3 Hz, 2H, H_{arom}), 8.35 (br d, J = 8.9 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 21.3, 54.8, 61.8, 63.7, 68.4, 94.0, 120.9, 121.2, 124.4, 127.7, 128.6, 128.7, 129.5, 129.6, 133.4, 139.1, 145.9, 168.2, 171.1, 176.4.

Anal. Calcd. for $C_{25}H_{22}N_8O_5$ (514.49): C, 58.36; H, 4.31. Found: C, 58.49; H, 4.34.

*{1-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 6-O-acetyl-4-azido-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranoside (**15b**)*

Yield 39%; colorless solid; mp 124°C; R_f 0.33 (EtOAc/CH_2Cl_2 3:7); $[\alpha]_D^{20}$ +56 (c = 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 2.13 (s, 3H, OAc), 2.69 (s, 3H, CH_3), 3.94 (br d, J = 9.8 Hz, 1H, H-4), 4.00 (ddd, J = 9.8, 4.7, 2.3 Hz, 1H, H-5), 4.31 (dd, J = 12.1, 4.7 Hz, 1H, H-6), 4.40 (dd, J = 12.1, 2.3 Hz, 1H, H-6), 4.82 (d, J = 12.4 Hz, 1H, CH_2), 5.00 (d, J = 12.4 Hz, 1H, CH_2), 5.23 (br s, 1H, H-1), 5.97 (ddd, J = 10.2, 2.3, 2.1 Hz, 1H, H-3), 6.04 (br d, J = 10.2 Hz, 1H, H-2), 7.90 (br d, J = 8.9 Hz, 2H, H_{arom}), 8.09 (s, 1H, =CH-N), 8.25 (br d, J = 8.6 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 12.8, 21.2, 54.8. 61.8, 63.7, 68.4, 94.0, 121.0, 121.1, 127.7, 128.7, 129.3, 139.1, 145.9, 167.7, 171.1, 177.4.

HRMS-ESI Calcd. for $C_{20}H_{20}N_8O_5Na$ $[M + Na]^+$: 475.1454. Found: 475.1456.

General Procedure for the Bishydroxylation of Unsaturated Carbohydrates

Method A

To a solution of unsaturated carbohydrate derivative (0.5 mmol) in a 4:1 mixture of acetone/water (10 mL) was added OsO_4 (0.585 mg, 5 μmol) and *N*-methylmorpholine-*N*-oxide (229 mg, 2 mmol) at 0°C. The reaction mixture was stirred overnight at rt, $NaHSO_3$ (250 mg) was then added, and the contents were stirred for 30 min at rt. The reaction mixture was diluted with water (2.5 mL) and extracted with EtOAc (2 × 5 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was evaporated in vacuo to give the corresponding diol. The crude residue was directly acetylated using Ac_2O (153 mg, 1.5 mmol) in pyridine (3 mL) for 1 day. After removing the solvent in vacuo, the residue was purified by column chromatography on silica gel using the indicated eluent to afford the corresponding oxadiazole-linked ethyl mannopyranoside.

Method B

To the unsaturated carbohydrate (0.5 mmol) and citric acid (96 mg, 0.5 mmol) dissolved in a 1:1 mixture of *tert*-butyl alcohol/water (6 mL) was added potassium osmate dihydrate (1.84 mg, 5 μmol), followed by *N*-methylmorpholine *N*-oxide (117 mg, 1 mmol). The reaction mixture was stirred at rt until disappearance of the starting material. The reaction mixture was diluted with water (2.5 mL) and extracted with EtOAc (2 × 5 mL). The organic layer was separated and dried over Na_2SO_4, and the solvent was evaporated in vacuo to give the corresponding diol. The crude residue was directly acetylated using Ac_2O (153 mg, 1.5 mmol) in pyridine (3 mL) for 1 day. After removing the solvent in vacuo, the residue was purified by column chromatography on silica gel using the indicated eluent to afford the corresponding oxadiazole-linked ethyl mannopyranoside.

*{1-[4-(5-Phenyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**8a**)*

This compound was obtained starting from **7a** (266 mg) according to method A in 67% yield; colorless solid; mp 71°C; R_f 0.41 (petroleum ether/EtOAc 3:2); $[\alpha]_D^{20}$ +37 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 2.00 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.17 (s, 3H, OAc), 4.07–4.16 (m, 1H, H-5), 4.5 (dd, J = 12.2, 2.2 Hz, 1H, H-6), 4.33 (dd, J = 12.2, 5.2 Hz, 1H, H-6), 4.81 (d, J = 12.6 Hz, 1H, CH_2), 4.97 (d, J = 12.6 Hz, 1H, CH_2), 5.03 (br s, 1H,

H-1), 5.30 (br d, $J = 3.1$ Hz, 1H, H-2), 5.32 (dd, $J = 9.6$, 9.6 Hz, 1H, H-4), 5.38 (dd, $J = 9.6$, 3.1 Hz, 1H, H-3), 7.55–7.67 (m, 3 H, H_{arom}), 7.95 (br d, $J = 8.9$ Hz, 2H, H_{arom}), 8.14 (s, 1H, =CH-N), 8.24 (br d, $J = 8.3$ Hz, 2H, H_{arom}), 8.38 (br d, $J = 8.7$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 21.0, 21.1, 21.2, 61.4, 62.8, 66.5, 69.2, 69.4, 69.8, 97.4, 121.0, 121.4, 124.4, 127.8, 128.5, 129.4, 129.5, 133.3, 139.0, 145.0, 168.2, 170.1, 170.3, 170.4, 171.0, 176.4.

HRMS-ESI Calcd. for $C_{31}H_{31}N_5O_{11}Na$ $[M + Na]^+$: 672.1918. Found: 672.1927.

*{1-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**8b**)*

This compound was obtained starting from **7b** (235 mg) according to method B in 72% yield; colorless solid; mp 61°C; R_f 0.63 (EtOAc); $[\alpha]_D^{20}$ +42 ($c = 1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.17 (s, 3H, OAc), 2.69 (s. 3H, CH_3), 4.11–4.17 (m, 2H, H-5, H-6), 4.32 (dd, $J = 12.3$, 5.4 Hz, 1H, H-6), 4.80 (d, $J = 12.5$ Hz, 1H, CH_2), 4.96 (d, $J = 12.5$ Hz, 1H, CH_2), 5.02 (br s, 1H, H-1), 5.29 (dd, $J = 4.7$, 1.9 Hz, 1H, H-2), 5.35 (dd, $J = 9.4$, 9.0 Hz, 1H, H-4), 5.38 (dd, $J = 9.4$, 3.4 Hz, 1H, H-3), 7.92 (dd, $J = 8.7$, 1.7 Hz, 2H, H_{arom}), 8.12 (s, 1H, =CH-N), 8.26 (dd, $J = 8.7$, 1.9 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 12.8, 21.0, 21.1, 21.2, 61.3, 62.8, 66.4, 69.2, 69.4, 69.8, 97.3, 121.0, 121.4, 127.7, 129.3, 139.0, 144.9, 167.7, 170.0, 170.3, 170.4, 171.0, 177.3.

Anal. Calcd. for $C_{26}H_{29}N_5O_{11}$ (587.54): C, 53.15; H, 4.98. Found: C, 53.10; H, 5.13.

*Ethyl 2,3-di-O-acetyl-6-O-(tert-butyldimethylsilyl)-4-deoxy-4-{4-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-1-yl}-α-D-mannopyranoside (**12**)*

This compound was obtained starting from **11** (214 mg) according to method A in 65% yield; colorless solid; mp 74°C; R_f 0.77 (CH_2Cl_2/EtOAc 9:1); $[\alpha]_D^{20}$ +59.5 ($c = 1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$):–0.05 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), 0.86 (s, 9H, CMe_3), 1.23 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.79 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.34 (dd, $J = 11.9$, 3.1 Hz, 1H, H-6), 3.53 (dq, $J = 9.8$, 7.1 Hz, 1H, OCH_2CH_3), 3.61 (dd, $J = 11.9$, 1.5 Hz, 1H, H-6), 3.75 (dq, $J = 9.8$, 7.1 Hz, 1H, OCH_2CH_3), 4.32 (br d, $J = 10.7$ Hz, 1H, H-5), 4.87 (d, $J = 1.7$ Hz, 1H, H-1), 5.04 (dd, $J = 11.3$, 10.7 Hz, 1H, H-4), 5.31 (dd, $J = 3.4$, 1.7 Hz, 1H, H-2), 5.91 (dd, $J = 11.3$, 3.4 Hz, 1H, H-3), 7.47–7.59 (m, 3H, H_{arom}), 7.85 (s, 1H, =CH-N), 7.92 (d, $J = 8.3$ Hz, 2H, H_{arom}), 8.16 (dd, $J = 6.6$, 1.7 Hz, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): –5.1, –4.9, 15.4, 18.7, 20.9, 21.2, 26.2, 56.8, 62.1, 64.4, 69.1, 69.5, 71.8, 97.8, 121.5, 124.6, 126.4, 127.1, 128.5, 128.6, 129.5, 133.2, 133.4, 146.9, 169.0, 169.6, 170.3, 176.2.

HRMS-ESI Calcd. for $C_{34}H_{44}N_5O_8Si$ $[M + H]^+$: 678.2959. Found: 678.2979.

*N-({1-[Ethyl 2,3-di-O-acetyl-6-O-(tert-butyldimethylsilyl)-4-deoxy-α-D-mannopyranosid-4-yl]-1H-1,2,3-triazol-4-yl}methyl)-3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanamide (**14a**)*

This compound was obtained starting from **13a** (219 mg) according to method A in 65% yield; colorless oil; R_f 0.2 (CH_2Cl_2/EtOAc 4:1); $[\alpha]_D^{20}$ +44.4 ($c = 0.6$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 0.00 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.93 (s, 9H, CMe_3), 1.30 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.85 (s, 3H, OAc), 2.18 (s, 3H, OAc), 2.84 (t, $J = 7.2$ Hz, 2H, CH_2), 3.28–3.35 (m, 3H, H-6, CH_2), 3.52–3.66 (m, 2H, OCH_2CH_3, H-6), 3.81 (dq, $J = 9.8$, 7.2 Hz, 1H, OCH_2CH_3), 4.36 (br d, $J = 10.0$ Hz, 1H, H-5), 4.51 (d, $J = 5.5$ Hz, 2H, CH_2N), 4.93 (br s, 1H, H-1), 5.01 (dd, $J = 10.9$, 10.6 Hz, 1H, H-4), 5.34 (dd, $J = 3.2$, 1.8 Hz, 1H, H-2), 5.87 (dd, $J = 11.3$, 3.2 Hz, 1H, H-3), 6.56 (br t, $J = 5.5$ Hz, 1H, NH), 7.47–7.52 (m, 3H, H_{arom}), 7.60 (s, 1H, =CH-N), 8.07 (dd, $J = 5.0$, 1.8 Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$):–5.2, –4.9, 15.3, 18.6, 20.8, 21.2, 22.7, 26.2, 32.4, 35.4, 56.6, 61.9, 64.3, 69.2, 69.4, 71.4, 97.7, 127.1, 127.8, 129.2, 131.5, 168.6, 169.5, 170.3, 170.7, 179.1.

HRMS-ESI Calcd. for $C_{32}H_{46}N_6O_9SiNa$ $[M + Na]^+$: 709.2993. Found: 709.2992.

*N-({1-[Ethyl 2,3-di-O-acetyl-6-O-(tert-butyldimethylsilyl)-4-deoxy-α-D-mannopyranosid-4-yl]-1H-1,2,3-triazol-4-yl}methyl)-3-[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]propanamide (**14b**)*

This compound was obtained starting from **13b** (258 mg) according to method A in 84% yield; colorless solid; mp 48°C; R_f 0.2 (CH_2Cl_2/EtOAc 3:2); $[\alpha]_D^{20}$ +37.0 ($c = 1.0$. CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 0.00 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.93 (s, 9H, CMe_3), 1.29 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 1.85 (s, 3H, OAc), 2.18 (s, 3H, OAc), 2.84 (t, $J = 7.3$ Hz, 2H, CH_2), 3.31 (m, 3H, CH_2, H-6), 3.59 (dq, $J = 9.8$, 7.1 Hz, 1H, OCH_2CH_3), 3.64 (br d, $J = 13.0$ Hz, 1H, H-6), 3.81 (dq, $J = 9.8$, 7.1 Hz, 1H, OCH_2CH_3), 4.37 (br d, $J = 10.2$ Hz, 1H, H-5), 4.51 (dd, $J = 11.7$, 5.8 Hz, 1H, CH_2N), 4.58 (dd, $J = 11.7$, 5.5 Hz, 1H, CH_2N), 4.93 (br s, 1H, H-1), 5.01 (dd, $J = 11.2$, 10.2 Hz, 1H, H-4), 5.33 (br d, $J = 3.2$ Hz, 1H, H-2), 5.87 (dd, $J = 11.1$, 3.2 Hz, 1H, H-3), 6.82 (br t, $J = 5.5$ Hz, 1H, NH), 7.61 (s, 1H, =CH-N), 7.64 (d, $J = 8.5$ Hz, 2H, H_{arom}), 7.95 (d, $J = 8.5$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): –5.2, –4.9, 15.3, 18.6, 20.8, 21.2, 22.6, 26.2, 32.3, 35.3, 56.6, 61.9, 64.3, 69.2, 69.4, 71.4, 97.7, 126.1, 129.3, 132.5, 167.9, 169.4, 170.3, 170.6, 179.4.

HRMS-ESI Calcd. for $C_{32}H_{45}BrN_6O_9SiNa$ $[M + Na]^+$: 787.2098. Found: 787.2093.

*{1-[4-(5-Methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl 2,3,6-tri-O-acetyl-4-deoxy-4-{4-[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-1-yl}-α-D-mannopyranoside (**17**)*

This compound was obtained starting from **16b** (318 mg) according to method B in 42% yield; colorless solid; mp 205°C; R_f 0.58 (EtOAc); $[\alpha]_D^{20}$ +18

($c = 0.5$, CH_2Cl_2); ^1H NMR ($CDCl_3$): 1.86 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.22 (s, 3H, OAc), 2.67 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.99 (dd, $J = 12.2$, 4.5 Hz, 1H, H-6), 4.19 (br d, $J = 12.2$ Hz, 1H, H-6), 4.73 (br d, $J = 10.4$ Hz, 1H, H-5), 4.89 (d, $J = 12.5$ Hz, 1H, CH_2), 5.02 (dd, $J = 10.4$, 10.2 Hz, 1H, H-4), 5.04 (d, $J = 12.5$ Hz, 1H, CH_2), 5.17 (br s, 1H, H-1), 5.42 (br s, 1H, H-2), 6.17 (dd, $J = 9.2$, 2.1 Hz, 1H, H-3), 7.93–7.96 (m, 5H, H_{arom}, =CH-N), 8.13 (br d, J = 7.9 Hz, 2H, H_{arom}), 8.20 (s, 1H, =CH-N), 8.28 (br d, $J = 8.5$ Hz, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): 12.8, 20.8, 21.1, 21.3, 57.8, 61.6, 62.9, 68.7, 68.9, 69.4, 97.4, 120.4, 121.1, 121.6, 126.5, 127.1, 127.8, 128.3, 129.4, 132.9, 144.8, 147.6, 162.7, 169.6, 170.2, 170.7, 177.0, 177.4.

HRMS-ESI Calcd. for $C_{35}H_{34}N_{10}O_{10}Na$ $[M + Na]^+$: 777.2357. Found: 777.2352.

*{1-[4-(5-Phenyl-1,2,4-oxadiazol-3-yl)phenyl]-1H-1,2,3-triazol-4-yl}methyl-α-D-mannopyranoside (**9**)*

To the unsaturated carbohydrate **7a** (700 mg, 1.3 mmol) and citric acid (250 mg, 1.3 mmol) dissolved in a 1:1 mixture of *tert*-butyl alcohol/water (60 mL) was added potassium osmate (5 mg, 13 μmol), followed by *N*-methylmorpholine *N*-oxide (305 mg, 2.6 mmol). The reaction mixture was stirred at rt until disappearance of the starting material. Then the reaction mixture was diluted with water (20 mL) and methanol (50 mL), and potassium carbonate (540 mg, 3.9 mmol) was added. After 20 h, the precipitated solid was filtered, and the solid was washed with EtOAc (5 mL) and water (5 mL). Drying of the solid afforded compound **9** (400 mg, 60%). Colorless solid; mp 190°C; R_f 0.2 (EtOAc); $[\alpha]_D^{20}$ −72 ($c = 0.25$, DMSO); ^1H NMR (DMSO-d_6): 3.40 (br d, $J = 10.0$ Hz, 1H, H-4), 3.42–3.58 (m, 3H, H-5, H-6), 3.65–3.70 (m, 2H, H-2, H-3), 4,67 (d, $J = 12.2$ Hz, 1H, CH_2), 4.80 (d, $J = 12.2$ Hz, 1H, CH_2), 4.82 (br s, 1H, H-1), 7.67–7.80 (m, 3H, H_{arom}), 8.15 (br d, $J = 8.7$ Hz, 2H, H_{arom}), 8.22 (br d, $J = 7.7$ Hz, 2H, H_{arom}), 8.32 (br d, $J = 8.7$ Hz, 2H, H_{arom}), 8.91 (s, 1H, =CH-N); ^{13}C NMR (DMSO-d_6): 59.4, 61.6, 67.4, 70.5, 71.2, 74.6, 99.6, 120.8, 122.7, 123.5, 126.3, 128.2, 129.0, 129.9, 133.8, 138.9, 145.4, 167.7, 175.9.

HRMS-ESI Calcd. for $C_{23}H_{23}N_5O_7Na$ $[M + Na]^+$: 504.1495. Found: 504.1487.

Cytotoxic Activity

The cytotoxic activity assays were based on the MTT method or the 3-(4,5-dimethylazol-2-yl)-3,5-diphenyltetrazolium bromide method.[22–24] For the cytotoxicity evaluation, the cell strains Hep-2 (larynx carcinoma) and NCI-H_{292} (lung carcinoma) with proved viability were used. The cells were grown in MEM (Minimal Essential Medium)[23] with 10% bovine fetal serum containing 1% antibiotics solution (penicillin 1000 UI/mL + streptomycin 250 mg/mL)

and 1% glutamine (200 μM). A cellular suspension containing 5.10^4 cells/mL was used and distributed in plates of 96 wells. The test samples containing the drug in different concentrations (1.25, 2.5, 5.0, and 10.0 μg/mL) dissolved in DMSO (0.1 mL) were added into each well. The plates were incubated for 72 h at 37°C in an atmosphere containing 5% of CO_2. After incubation, 15 μL of MTT in phosphate-buffered saline solution (5 mg/mL) was added into each well. After 2 h the culture medium was removed and 100 μL of DMSO was added in each well in order to solubilize the formazan crystals.[27] The measurements were performed in a Multskan ELX 800 cell reader at 595 nm.

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