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Galactosylation by Use of β-Galactosidase: Chemo-Enzymatic Syntheses of Di- and Trisaccharides

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Abstract: The synthesis of various galactose containing disaccharides has been achieved by utilizing the transgalactosylation potential of ß-galactosidase from *Aspergillus oryzae*. Thus, using *p*-nitrophenyl-ß-D-galactoside **1** as galactosyl donor, thio-glucosides **2a-c**, thio-galactosides **5a**, **5b** and pent-4-enyl-glucoside **2d** have proved to be useful acceptors for the enzyme catalyzed disaccharide formation. We further demonstrated the synthetic potential of the disaccharides obtained by enzymatic synthesis in preparing trisaccharide **10** starting with **4a** and **4d** and applying chemical glycosylation procedures developed for thio- and pent-4-enyl glycosides.

INTRODUCTION

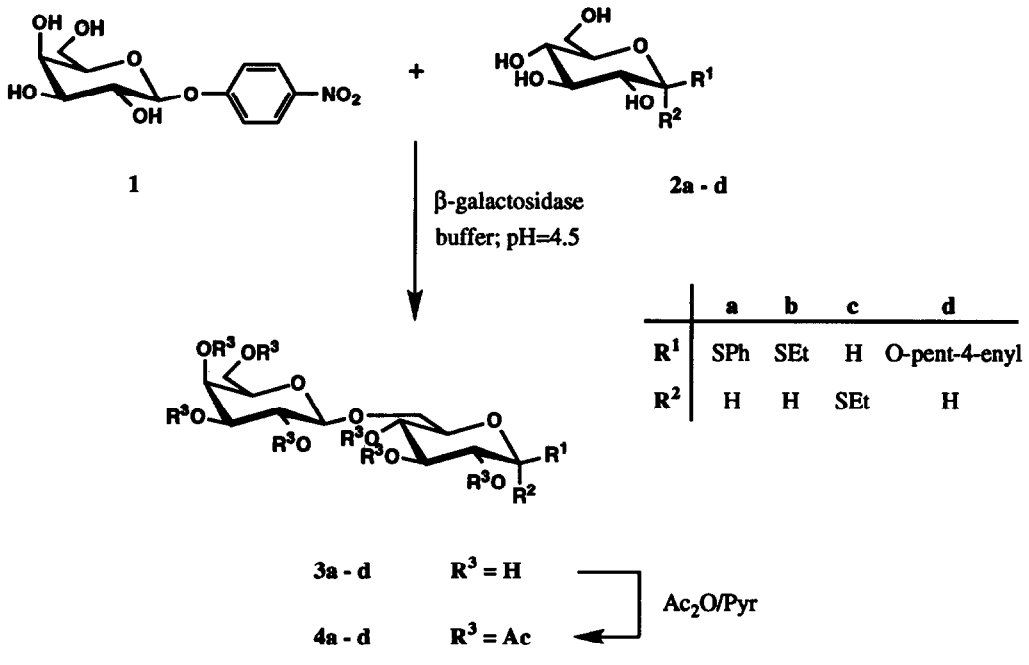
The various biological functions influenced by oligosaccharides[1] explain the synthetic effort in synthesis of these sugar chains composed of different monosaccharides. The development of methods for stereoselective formation of glycosidic linkages remains a sensible task.[2] Chemical syntheses of oligosaccharides usually require multistep reaction sequences and sophisticated protecting group strategies. Alternatively, enzymatic methods have been applied successfully for this purpose circumventing extensive protective group chemistry. In particular the use of glycosyltransferases[3] has demonstrated the advantage of the enzymatic approach. However, the high costs and the limited availability of many glycosyltransferases are major drawbacks for broad applications of these biocatalysts.

Another enzymatic approach is based on the transglycosylation activity of glycosidases. These hydrolytic enzymes are able to transfer in a kinetically controlled reaction a glycosyl donor to a glycosyl acceptor thus stereoselectively forming a glycosidic linkage. In addition, the regiochemistry of the transfer can be controlled by suitable substitution on the anomeric carbon of the glycosyl acceptor.[4-6] Among the class of glycosidases ß-galactosidase is one of the best investigated.[4-9] In ß-galactosidase catalyzed transglycosylation lactose as well as *o*- or *p*-nitrophenyl galactosides may be used as galactosyl donor. The enzyme accepts a broad variety of glycosyl acceptors including besides other monosaccharides[4-9] oximes,[10] diols,[11] allyl and propargyl alcohol,[12] steroids,[13] alkaloids[14] and amino acids.[6a,15]

RESULTS AND DISCUSSIONS

In our syntheses of disaccharides we utilized ß-galactosidase from *Aspergillus oryzae* (EC 3.2.1.23). This enzyme has been successfully applied in transgalactosylations by Nilsson,[4] Fernandez-Mayorales et al.,[5] Thiem et al.[6] and others.[7-9] We were interested in an easy access to various galacto-ß(1-6) linked disaccharides. This type of glycosides are from biological interest, for example 6-O-(ß-D-galactopyranosyl)-ß-D-galactopyranoside appears as subunit in the binding determinant of D-galactans to a family of immunoglobulins.[16,17] In the syntheses of our disaccharides we took advantage of the fact that ß-galactosidase preponderantly forms the ß(1-6) linkage due to the involvement of a more reactive primary hydroxyl function.[4] Concerning of acceptor glycosides investigated until now[4-9] it was reported that the regioselectivity obtained in ß-galactosidase catalyzed reactions is highly dependant on the atom linked to the anomeric carbon and the aglycon of the acceptor saccharide itself. Furthermore, an aglycon containing a phenyl group increases dramatically the yield of this reaction. However, since the donor glycoside itself may act as acceptor in competition with the desired monosaccharide a relatively complex product mixture has to be expected.

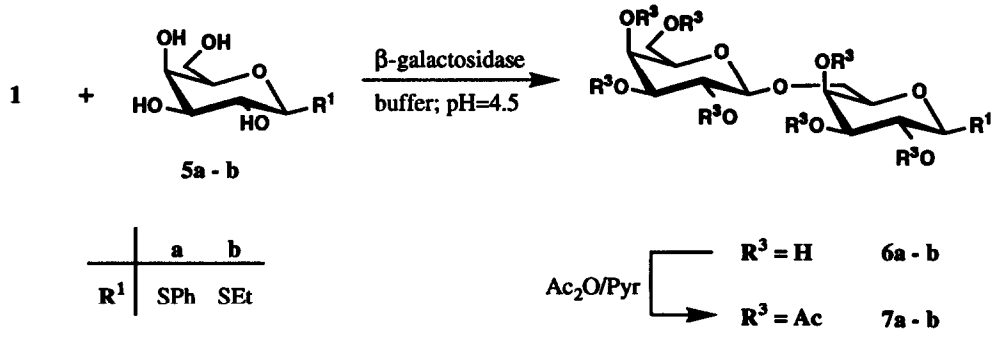
As donor substrates we utilized the well known *p*-nitrophenyl-ß-D-galactopyranoside **1** (Scheme 1). We performed the reactions in an aqueous buffer solution at a pH of 4.5. Our initial experiments with thiophenyl-ß-D-glucoside **2a** as acceptor substrate indicated that a transfer of the galactosyl residue to **2a** as well as to the



	a	b	c	d
R^1	SPh	SEt	H	O-pent-4-enyl
R^2	H	H	SEt	H

Scheme 1

donor galactoside **1** appeared yielding a mixture of the corresponding disaccharides in a ratio of 1 : 1 which could be partially separated by Biogel® P2 column chromatography. This result is in agreement with data reported from Thiem et al.[6a] and Nilsson.[4] However, when adding the donor galactoside **1** in small portions over a period of one hour to a solution of the glucoside **2a** in the presence of ß-galactosidase the yield of the product disaccharide **3a** was dramatically increased and no product arising from galactosyltransfer to the donor itself could be detected as judged by following the reaction with TLC (see experimental part). The disaccharide formed was isolated after denaturation of the enzyme by heating to 90° C and removal of water followed by acetylation and column chromatography of the peracetylated derivative **4a**. The corresponding unprotected disaccharide **3a** was obtained after saponification of the acetates. Having optimized this transgalactosylation and workup procedure, we tested a variety of thio- and pent-4-enyl gluco- and galactopyranosides (Scheme 1 and Scheme 2).



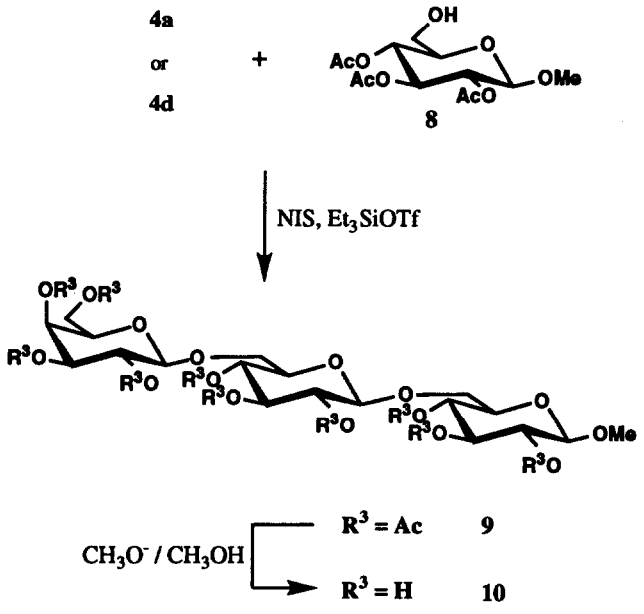
Scheme 2

The products formed are summarized in Table 1. The yields of the disaccharides **4a - 4d** and **7a - 7b** respectively obtained after acetylation are between 3 - 15%. Using organic cosolvents or lactose as galactosyl donor in the transgalactosylation reaction lead in all cases to a decrease in yields.[18] Thiophenyl- and pent-4-enyl glycosides were much better substrates than thioethyl glycosides. These results are in agreement with data obtained by others[4-6] thus again demonstrating that big, non polar aglycons in the acceptor monosaccharides are better than small ones. Another interesting observation is that galacto-configurated pyranosides are better acceptor substrates than the corresponding gluco derivatives which may reflect a special interaction of the enzyme with hydroxyl functions of the acceptor saccharide.

Table 1. Disaccharides synthesized by the use of ß-galactosidase

entry	acceptor monosaccharide	product disaccharide	reaction time (min)	yield (%)
1	**2a**	Gal ß(1-6) Gluc ß SPh **3a**	60	11
2	**2b**	Gal ß(1-6) Gluc ß SEt **3b**	90	3
3	**2c**	Gal ß(1-6) Gluc α SEt **3c**	90	3
4	**2d**	Gal ß(1-6) Gluc ß O-pent-4-enyl **3d**	60	13
5	**5a**	Gal ß(1-6) Gal ß SPh **6a**	60	15
6	**5b**	Gal ß(1-6) Gal ß SEt **6b**	90	9

To identify the regiochemistry of the glycosidic linkage present in the disaccharides synthesized we did extensive NMR studies. The complete assignment of the ^{1}H and ^{13}C signals was achieved by using several 2D NMR techniques.[19] In particular, phase sensitive DQF-COSY and HMQC experiments - performed with a preliminary BIRD puls and GARP-1 ^{13}C decoupling - allowed exact assignment of all protons and carbons. Furthermore, the glycosidic linkage could be evaluated unambiguously by measuring the long range ^{1}H, ^{13}C-connectivities (using coupling constants of 4 to 5 Hz) either from the anomeric carbon to the corresponding proton of the second saccharide unit or from the anomeric proton to the connected carbon respectively by utilizing HMBC spectra. Only in the case of thioethyl glycosides **2b**, **2c** and **5b** we observed in addition to the predominantly formed ß(1-6) a significant amount of a glycosidic ß(1-3) linkage (ß(1-6) : ß(1-3) = 6 : 1).



Scheme 3

To further demonstrate the synthetic potential of the disaccharides obtained by transgalactosylation we transformed **4a** and **4d** to the protected trisaccharide **9** and subsequently after saponification to **10** (Scheme 3) by using chemical glycosylation procedures developed for thio-[20] and pent-4-enyl[21] glycosides. Again, the proton and carbon signals of the corresponding ^{1}H and ^{13}C spectra were completely assigned by applying the NMR techniques described earlier.

The advantage of the syntheses presented is that starting with readily available glycosides a variety of disaccharides can be obtained by a simple enzymatic galactosylation procedure. Although the yields of product formation is generally moderate to low, ß-galactosidase catalyzed transgalactosylation circumvents multistep protection and deprotection sequences and, of course, is economically to perform since this enzyme is reasonable cheap. Furthermore, we demonstrated that thio- and pent-4-enyl glycosides are useful substrates in

this enzyme-catalyzed reaction. The synthetically useful disaccharides obtained can be further transformed to trisaccharides by applying well developed chemical glycosylation procedures.

EXPERIMENTAL

General: Chemicals were purchased from Aldrich and were reagent grade. ß-Galactosidase from *Aspergillus oryzae* (EC 3.2.1.23; Grade XI) was purchased from Sigma. Analytical thin layer chromatography was performed on Merck plates (silica gel F_{254}, 0.25 mm thick). Compounds were visualized by spraying with a solution of 3% $Ce(SO_4)_2$ in 2N H_2SO_4 followed by heating to 200 °C. Flash chromatography was performed using Merck silica gel 60 (0.04-0.063 mm thick).

NMR spectra were recorded on a BRUKER AM 400 spectrometer. In the spectroscopical data given we used superscripts to denote atoms or groups in di- and trisaccharides and to refer to the individual sugar residues and aglycons respectively. They are serially indicated beginning with the non-reducing residue. For example, in **3d** (Gal ß(1-6) Gluc ß-O-pent-4-enyl) the Gal-residue has no superscript, the Gluc-residue is indicated with (') and the pent-4-enyl aglycon with (").

Mass spectra were recorded on a BioIon 20 ^{252}Cf-plasma desorption time-of-flight mass spectrometer using *trans*-3-(3-pyridyl)-acrylic acid (PAA) as matrix for the peracetylated products. Optical rotations were measured on a Perkin Elmer polarimeter 141. Abbreviations used are as follows: hexane (PE), ethyl acetate (EA), dichloromethane (MC), methanol (MeOH).

General method for the enzymatic galactosylation (method A)

To a solution of 1 mmol of the acceptor substrate and 0.3 mmol *p*-nitrophenyl-ß-D-galactopyranoside **1** in 15 mL of phosphate buffer (pH = 4.5; 10 mM $MgSO_4$) 8 mg (40 U) of ß-galactosidase from *Aspergillus oryzae* were added. A solution of 1 mmol of **1** in 15 mL of phosphate buffer was continuously added to the reaction mixture over a period of 30 minutes to 90 min (exact time given in each entry). The progress of the reaction was followed by TLC (30% NH_3 : isopropanol : water = 3 : 7 : 2). After all of the galactopyranoside **1** has been consumed, the reaction was quenched by heating to 90 °C for 5 min. The denaturated enzyme was filtered off and the solvent was removed by coevaporation with toluene. The remaining crude material was acetylated by adding 10 mL of pyridine and 4 mL of acetic anhydride. After stirring for 10 h at room temperature, pyridine and acetic anhydride were removed in vacuum and the crude material was purified by flash chromatography (specific eluent given in each entry).

General method for deacetylation (method B)

The acetylated material was dissolved in 10 mL of methanol and 0.2 mL of a solution of sodium methoxyde in dry methanol (0.1M) was added. After completion of the reaction (judged by TLC), the pH was adjusted to 8 by the addition of solid CO_2. The solvent was removed in vacuum and the crude product was purified by flash chromatography (MeOH : MC = 2 : 1).

Thiophenyl-S-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(1-6)-O-2,3,4-tri-O-acetyl-ß-D-glucopyranoside (4a)

A solution of 272 mg (1mmol) of thiophenyl-S-ß-D-glucopyranoside[22] **2a** in 15 mL of buffer was treated with **1** and ß-galactosidase for 1 h according to method A (R_f = 0.4 (PE : EE = 1 : 1)). After flash chromatography (PE : EE = 2 : 1) 80 mg (11%) of **4a** were obtained. ^{1}H-NMR ($CDCl_3$) δ 1.95(2x), 1.96, 2.00, 2.03, 2.04, 2.13 (6 s, 21 H, acetyl-CH_3); 3.60 (dd, 1H, J = 7.1, 11.1 Hz, H-6a'); 3.72 (ddd, 1H, J = 2.0, 7.0, 10.2 Hz, H-5'); 3.84 (m, 1H, J = 6.7, 1.1 Hz, H-5); 3.86 (dd, 1H, J = 2.1, 11.2 Hz, H-6b'); 4.09 (dd, 1H, J = 6.7, 11.3 Hz, H6a); 4.14 (dd, 1H, J = 6.7, 11.3 Hz, H-6b); 4.50 (d, 1H, J = 8.0 Hz, H-1); 4.70 (d, 1H, J = 10.1 Hz, H-1'); 4.84 (dd, 1H, J = 9.4, 10.2 Hz, H-4'); 4.91 (dd, 1H, J = 10.1, 9.3 Hz, H-2'); 4.97 (dd, 1H, J = 10.5, 3.5 Hz, H-3); 5.18 (dd, 1H, J = 8.0, 10.5 Hz, H-2); 5.18 (t, 1H, J = 9.3 Hz, H-3'); 5.36 (dd, 1H, J = 3.5, 1.1 Hz, H-4); 7.3-7.44 (m, 5H, aromatic-H). ^{13}C-NMR ($CDCl_3$) δ 170.32; 170.15; 170.05(2x); 169.51(2x); 169.21; 132.35; 132.00; 129.15; 128.20; 101.18(C-1); 85.67(C-1'); 77.40(C-5'); 73.84(C-3'); 70.84(C-3); 70.82(C-5); 69.88(C-2'); 68.73(C-4'); 68.56(C-2); 68.38(C-6'); 67.03(C-4); 61.19(C-6); 20.70; 20.68; 20.63(2x); 20.56; 20.54(2x). MS (70 eV): m/e 878.83((M+PAA+H)$^+$; 100%; Calcd. 878.82).Anal. for $C_{32}H_{40}O_{17}S$ (728.72): Calcd. C, 52.74; H, 5.53; S, 4.40; Found C, 52.60; H, 5.41; S, 4.24.

Thiophenyl-S-(ß-D-galactopyranosyl)-(1-6)-O-ß-D-glucopyranoside (3a)

80 mg of **4a** were treated according to method B yielding 45 mg (94%) of **3a**.
^{1}H-NMR (D_2O) δ 3.52 (dd, 1H, J = 8.6, 9.9 Hz, H-2'); 3.63 (m, 1H, H-4'); 3.67 (m, 1H, H-2); 3.70 (m, 1H, H-3'); 3.71 (m, 1H, H-3); 3.73 (m, 1H, H-5); 3.83 (m, 1H, H-5'), 3.9 (m, 2H, H-6); 4.00 (dd, 1H, J = 11.7, 5.6 Hz, H-6a'); 4.05 (m, 1H, H-4); 4.33 (dd, 1H, J = 11.7, 0.8 Hz, H-6b'), 4.53 (d, 1H, J = 7.3 Hz, H-1); 5.02 (d, 1H, J = 9.9 Hz, H-1'), 7.59-7.75 (m, 5H, aromatic H). ^{13}C-NMR (D_2O) δ 134.14; 133.70; 131.59; 130.26; 105.07(C-1); 89.47(C-1'); 81.30(C-5'); 79.29(C-2); 77.28(C-5); 74.79(C-3); 73.88(C-2'); 72.93(C-3'), 71.33(C-4'); 70.80(C-4); 70.39(C-6'); 63.13(C-6).

Thioethyl-S-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(1-6)-O-2,3,4-tri-O-acetyl-ß-D-glucopyranoside (4b)

A solution of 224 mg (1mmol) thioethyl-S-ß-D-glucopyranoside[23] **2b** in 15 mL of buffer was treated with **1** and ß-galactosidase for 90 min according to method A (R_f = 0.35 (PE : EE = 1 : 1)). After flash chromatography (PE : EE = 3 : 2) 20.2 mg (3%) of **4b** were obtained. $[\alpha]_D^{20}$ = -7.3° ($CHCl_3$; c = 1.0). ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.4 Hz, H-2"); 1.98, 2.00, 2.03, 2.06(2x), 2.08, 2.15 (6 s, 21 H, acetyl-CH_3); 2.71 (m, 2H, H-1"); 3.59 (dd, 1H, J = 7.2, 11.0 Hz, H-6a'); 3.70 (m, 1H, J = 2.0, 7.1, 9.7 Hz, H-5'); 3.88 (dd, 1H, J = 2.0, 11.0 Hz, H-6b'); 3.89 (m, 1H, H-5); 4.14 (m, 2H, H-6); 4.47 (d, 1H, J = 10.0 Hz, H-1'), 4.53 (d, 1H, J = 8.0 Hz, H-1); 4.89 (t, 1H, J = 9.7 Hz, H-4'); 4.98 (t, 1H, J = 9.4 Hz, H-2'); 5.00 (dd, 1H, J = 3.7, 10.5 Hz, H-3); 5.12 (dd, 1H, J = 8.0, 10.5 Hz, H-2); 5.21 (t, 1H, J = 9.4 Hz, H-3'); 5.38 (dd, 1H, J = 3.6, 0.8 Hz, H-4); ^{13}C-NMR ($CDCl_3$) δ 170.31; 170.14; 170.08; 170.06; 169.59; 169.41; 169.39; 101.20(C-1); 83.13(C-1'); 77.27(C-5'); 73.80(C-3'); 70.82(C-5); 70.79(C-3); 69.92(C-2'); 69.05(C-4'), 68.60(C-2), 68.48(C-6'); 66.99(C-4); 61.18(C-6); 23.97(C-1"); 20.76; 20.68; 20.62; 20.61; 20.58(2x); 20.52; 14.81(C-2"). MS (70 eV): m/e 830.88 ((M+PAA+H)$^+$; 100%; Calcd. 830.78). Anal. for $C_{28}H_{40}O_{17}S$ (680.68): Calcd. C, 49.41; H, 5.92; S, 4.71 Found C, 49.09; H, 5.78; S, 4.56.

Thioethyl-S-ß-D-galactopyranosyl-(1-6)-O-ß-D-glucopyranoside (3b)

22 mg of **4b** were treated according to method B yielding 11 mg (94%) of **3b**.

^{1}H-NMR (D_2O) δ 1.41 (t, 3H, J = 7.5 Hz, H-2"); 2.90 (m, 2H, H-1"); 3.66 (dd, 1H, J = 7.8, 9.9 Hz, H-2); 3.70 (t, 1H, J = 9.6 Hz, H-2'); 3.78 (dd, 1H, J = 9.9, 3.4 Hz, H-3); 3.79 (dd, 1H, J = 9.6, 3.5 HZ, H-3'); 3.83 (m, 1H, J = 0.6, 4.3, 7.7 Hz, H-5); 3.90 (m, 2H, H-6); 4.00 (m, 2H, H-6'); 4.03 (m, 1H, H-5'); 4.05 (dd, 1H, J = 3.4, 0.6 Hz, H-4); 4.16 (dd, 1H, J = 3.4, 1.0 Hz, H-4'); 4.85 (d, 1H, J = 7.8 Hz, H-1); 4.62 (d, 1H, J = 9.7 Hz, H-1'). ^{13}C-NMR (D_2O) δ 105.30(C-1); 87.75(C-1'), 79.60(C-5'); 77.32(C-5); 75.91(C-3'); 74.86(C-3); 72.91(C-2); 71.56(C-2'), 71.30(C-6'); 71.09(C-4'), 70.77(C-4); 63.13(C-6); 26.32(C-1"); 16.65(C-2").

Thioethyl-S-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(1-6)-O-2,3,4-tri-O-acetyl-α-D-glucopyranoside (4c)

A solution of 224 mg (1mmol) of thioethyl-S-α-D-glucopyranoside[23] **2c** in 15 mL of buffer was treated with **1** and ß-galactosidase for 90 min according to method A (R_f = 0.35 (PE : EE = 1 : 1)). After flash chromatography 20.6 mg (3%) of **4c** (together with 15% the (1-3) linked isomer) were obtained. Total assignment of NMR-signals was possible in this inseparable mixture.

4c : ^{1}H-NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7.34 Hz, H-2"); 1.94, 1.97, 2.00, 2.01, 2.02, 2.04, 2.10 (7 s, 21 H, acetyl-CH_3); 2.50 (m, 2H, H-1"); 3.50 (dd, 1H, J = 5.9, 10.9 Hz, H-6a'); 3.86 (m, 1H, J = 1.1, 6.5, 6.9 Hz, H-5); 3.92 (dd, 1H, J = 2.1, 10.9 Hz, H-6b'); 4.08 (dd, 1H, J = 11.2, 6.9 Hz, H-6a); 4.15 (dd, 1H, J = 11.2, 6.5 Hz, H-6b); 4.37 (m, 1H, J = 2.1, 5.9, 10.2 Hz, H-5'); 4.44 (d, 1H, J = 8.0 Hz, H-1); 4.89 (dd, 1H, J = 10.2, 9.0 Hz, H-4'); 4.95 (dd, 1H, J = 5.7, 10.3 Hz, H-2'); 4.97 (dd, 1H, J = 3.4, 10.5 Hz, H-3); 5.19 (dd, 1H, J = 8.0, 10.5 Hz, H-2); 5.33 (dd, 1H, J = 10.3, 9.1 Hz, H-3'); 5.35 (dd, 1H, J = 1.1, 3.4 Hz, H-4); 5.63 (d, 1H, J = 5.7 Hz, H-1'). ^{13}C-NMR ($CDCl_3$) δ 170.32; 170.15; 170.06; 169.88; 169.84; 169.64; 169.34; 101.28(C-1); 80.92(C-1'); 70.86(C-3); 70.74(C-5); 70.71(C-2'); 70.57(C-3'); 69.07(C-4'); 68.50(C-2); 68.28(C-5'); 57.94(C-6'); 66.92(C-4); 61.11(C-6); 23.65(C1"); 20.51; 20.60(2x); 20.62(2x); 20.65; 20.70; 14.38(C-2"). MS (70 eV): m/e 830.72(M+PAA+H)$^+$; 100%; Calcd. 830.78).

(1-3-linked isomer, 15%) : ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, 3H, J = 7.3 Hz, H-2"); 1.93, 1.94, 2.02, 2.04, 2.05, 2.11(2x) (6 s, 21 H, acetyl-CH_3); 2.52 (m, 2H, H-1"); 3.88 (m, 1H, H-5); 3.97 (dd, 1H, J = 9.1, 10.2 Hz, H-3'); 4.07 (m, 1H, H-6a'); 4.09 (m, 2H, H-6); 4.19 (dd, 1H, J = 5.0, 12.3 Hz, H-6b'); 4.33 (m, 1H, J = 2.2, 4.9, 10.2 Hz, H-5'); 4.58 (d, 1H, J = 7.8 Hz, H-1); 4.91 (dd, 1H, J = 10.5, 3.5 Hz, H-3); 4.95 (dd, 1H, J = 9.1, 10.2 Hz, H-4'); 4.97 (dd, 1H, J = 5.8, 10.2 Hz, H-2'); 5.04 (dd, 1H, J = 7.8, 10.5 Hz, H-2); 5.32 (dd, 1H, J = 3.5, 1.2 Hz, H-4); 5.55 (d, 1H, J = 5.8 Hz, H-1'). ^{13}C-NMR ($CDCl_3$) δ 101.09(C-1); 81.42(C-1'); 76.56(C-3'); 72.70(C-2'); 71.00(C-3); 70.46(C-5); 68.96(C-2); 68.26(C-4'); 67.70(C-5'); 66.82(C-4); 62.14(C-6'); 60.96(C-6); 24.19(C-1"); 14.65(C-2").

Thioethyl-S-(ß-D-galactopyranosyl)-(1-6)-α-D-glucopyranoside (3c)

22 mg of the mixture **4c** were treated according to method B yielding 12 mg (99%) of an inseparable mixture containing **3c** and 15% of the (1-3)-linked product.

3c: (1-6-linked isomer): ^{1}H-NMR (D_2O) δ 1.41 (t, 3H, J = 7.3 Hz, H-2"), 2.79 (m, 2H, H-1"); 3.67 (m, 1H, H-4'); 3.68 (dd, 1H, J = 9.7, 7.9 Hz, H-2); 3.72 (m, 1H, H-3'); 3.79 (dd, 1H, J = 9.6, 3.4 Hz, H-3); 3.84

(m, 1H, H-5); 3.90 (m, 2H, H-6); 3.97 (dd, 1H, J = 5.6, 9.4 Hz, H-2'); 4.05 (dd, 1H, J = 4.7, 11.4 Hz, H-6a'); 4.06 (dd, 1H, J = 3.4, 0.7 Hz, H-4); 4.31 (dd, 1H, J = 2.2, 11.4 Hz, H-6b'); 4.33 (m, 1H, H-5'), 4.56 (d, 1H, J = 7.9 Hz, H-1); 5.57 (d, 1H, J = 5.6 Hz, H-1'). ^{13}C-NMR (D_2O) δ 105.49(C-1); 87.28(C-1'); 77.29(C-5); 75.74(C-3'); 74.88(C-3); 73.33(C-5'); 73.02(C-2'); 72.91(C-2); 71.48(C-4'); 70.82(C-4); 70.45(C-6'); 63.17(C-6); 26.38(C-1"); 16.20(C-2").

Pent-4-enyl-O-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(1-6)-O-2,3,4-tri-O-acetyl-ß-D-glucopyranoside (4d)

A solution of 248 mg (1mmol) of pent-4-enyl-O-ß-D-glucopyranoside **2d** in 15 mL of buffer was treated with **1** and ß-galactosidase according to method A (reaction time : 1 h, R_f = 0.45 (PE : EE = 1 : 1)). After flash chromatography (PE : EE = 2 : 1) 91.6 mg (13%) of **4d** were obtained. $[\alpha]_D^{20}$ = -14.9° ($CHCl_3$; c = 1.4). ^{1}H-NMR ($CDCl_3$) δ 1.64 (m, 2H, H-2"); 1.94, 1.95, 1.99, 1.20, 2.01, 2.015, 2.11 (7 s, 7x3H, acetate-CH_3); 2.06 (m, 2H, H-3"); 3.45 (m, 1H, J = 6.2, 7.2, 9.6 Hz, H-1"); 3.57 (dd, 1-H, J = 7.4, 10.9 Hz, H-6a'); 3.65 (m, 1H, J = 2.0, 7.3, 9.9 Hz, H-5'); 3.84 (dd, 1H, J = 2.0, 10.9 Hz, H-6b'); 3.85 (m, 1H, H-1"); 3.85 (m, 1H, J = 6.7, 1.1, 6.7 Hz, H-5); 4.08 (dd, 1H, J = 11.3, 6.7 Hz, H-6a); 4.13 (dd, 1H, J = 6.7, 11.3 Hz, H-6b); 4.42 (d, 1H, J = 7.8 Hz, H-1'); 4.51 (d, 1H, J = 7.8 Hz, H-1); 4.84 (dd, 1H, J = 9.4, 9.9 Hz, H-4'); 4.90 (dd, 1H, J = 7.9, 9.7 Hz, H-2'); 4.94 (m, 1H, J = 10.3, 1.2, 1.9 Hz, H-5a"); 4.95 (dd, 1H, J = 10.5, 3.4 Hz, H-3); 4.97 (m, 1H, J =1 7.0, 1.6, 1.9 Hz, H-5b"); 5.15 (dd, 1H, J = 9.4, 9.7 Hz, H-3'); 5.16 (dd, 1H, J = 8.0, 10.5 Hz, H-2); 5.34 (dd, 1H, J = 3.4, 1.1 Hz, H-4); 5.75 (tdd, 1H, J = 6.7, 10.3, 17.0 Hz, H-4"). ^{13}C-NMR ($CDCl_3$) δ 170.31; 170.18; 170.13; 170.02; 169.56; 169.25(2x); 137.72(C-4"); 115.10(C-5"); 101.16(C-1); 100.52(C-1'); 73.29(C-5'); 72.78(C-3'); 71.35(C-2'); 70.81(C-3); 70.80(C-5); 69.14(C-4'); 69.08(C-1"); 68.65(C-2); 68.22(C-6'); 66.98(C-4); 61.19(C-6); 29.77(C-3"); 28.51(C-2"); 20.71; 20.61; 20.59(2x); 20.57; 20.55; 20.51. MS (70 eV): m/e 854.76 $(M+PAA+H)^+$; 100%; Calcd. 854.78). Anal. for $C_{31}H_{44}O_{18}$ (704.68): Calcd. C, 52.84; H, 6.29 Found C, 52.38; H, 6.15.

Pent-4-enyl-O-(ß-D-galactopyranosyl)-(1-6)-O-ß-D-glucopyranoside (3d)

88.8 mg of **4d** were treated according to method B yielding 49 mg (95 %) of **3d**.
^{1}H-NMR (D_2O) δ 1.86 (m, 2H, H-2"); 2.27 (m, 2H, H-3"); 3.40 (dd, 1H, J = 8.0, 9.3 Hz, H-2'); 3.61 (m, 2H, H-4', H-3'); 3.68 (dd, 1H, J = 7.8, 10.0 Hz, H-2); 3.75 (m, 1H, H-5'); 3.78 (dd, 1H, J = 10.0, 3.4 Hz, H-3); 3.81 (m, 1H, H-1a"); 3.82 (m, 1H, H-5); 3.90 (m, 2H, H-6); 3.99 (dd, 1H, J = 5.6, 11.7 Hz, H-6a'); 4.05 (dd, 1H, J = 3.4, 1.0 Hz, H-4); 4.06 (dd, 1H, J = 6.7, 16.6 Hz, H-1b"); 4.34 (dd, 1H, J = 2.1, 11.7 Hz, H-6b'), 4.58 (d, 1H, J = 7.8 Hz, H-1); 4.59 (d, 1H, J = 8.1 Hz, H-1'), 5.15 (m, 1H, J = 10.4, 2.1, 1.1 Hz, H-5z"); 5.22 (m, 1H, J = 17.1, 2.1, 1.6 Hz, H-5e"); 6.04 (tdd, 1H, J = 6.7, 10.4, 17.1 Hz, H-4"). ^{13}C-NMR(D_2O) δ 140.97(C-4"); 116.95(C-5"); 105.49(C-1); 104.43(C-1'); 77.85(C-4'*); 77.30(C-5); 77.12(C-5'), 75.23(C-2'); 74.84(C-3); 72.88(C-2); 72.22(C-1"); 71.57(C-3'*); 70.78(C-4); 70.55(C-6'); 63.12(C-6); 31.50(C-3"); 30.20(C-2"). Carbon signals indicated with (*) may be interchanged.

Thiophenyl-S-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(1-6)-2,3,4-tri-O-acetyl-ß-D-galactopyranoside (7a)

A solution of 272 mg (1mmol) of thiophenyl-S-ß-D-galactopyranoside **5a** in 15 mL of buffer was treated with **1** and ß-galactosidase for 1 h according to method A (R_f = 0.4 (PE : EE = 1 : 1)). After flash

chromatography (PE : EE = 2 : 1) 108 mg (15%) of **7a** were obtained. $[\alpha]_D^{20}$ = -11.4° ($CHCl_3$; c = 1.1). ^{1}H-NMR ($CDCl_3$) δ 1.94(2x), 1.95, 2.03, 2.06, 2.10, 2.13 (6 s, 21 H, acetyl-CH_3); 3.74 (dd, 1H, J = 7.0, 10.9 Hz, H-6a'); 3.78 (dd, 1H, J = 4.7, 11.0 Hz, H-6b'); 3.84 (m, 1H, J = 1.2, 6.7 Hz, H-5); 3.91 (m, 1H, J = 0.9, 4.7, 7.0 Hz, H-5'); 4.08 (dd, 1H, J = 6.6, 11.1 Hz, H-6a); 4.13 (dd, 1H, J = 6.5, 11.1 Hz, H-6b); 4.48 (d, 1H, J = 8.0 Hz, H-1); 4.72 (d, 1H, J = 10.0 Hz, H-1'); 4.95 (dd, 1H, J = 10.5, 3.4 Hz, H-3); 5.01 (dd, 1H, J = 10.0, 3.3 Hz, H-3'); 5.51 (dd, 1H, J = 8.0, 10.6 Hz, H-2); 5.21 (t, 1H, J = 10.0 Hz, H-2'); 5.34 (dd, 1H, J = 3.4, 1.2 Hz, H-4); 5.38 (dd, 1H, J = 3.3, 1.0 Hz, H-4'); 7.28-7.46 (m, 5H, aromatic-H). ^{13}C-NMR ($CDCl_3$) δ 170 34; 170.19; 170.08; 170.05; 169.95; 169.43; 169.42; 133.00; 131.78; 129.09; 127.91; 100.73(C-1); 86.83(C-1'); 76.06(C-5'); 72.03(C-3'); 70.86(C-3); 70.77(C-5); 68.46(C-2); 67.76(C-4'); 67.25(C-2'); 67.23(C-6'); 66.94(C-4); 61.15(C-6); 20.82; 20.64(2x); 20.63(2x); 20.55; 20.53. MS (70 eV): m/e 878.73 $(M+PAA+H)^+$; 100%; Calcd. 878.82). Anal. for $C_{32}H_{40}O_{17}S$ (728.72): Calcd. C, 52.74; H, 5.53; S 4.40; Found C, 52.42; H, 5.39; S, 4.32.

Thiophenyl-S-(ß-D-galactopyranosyl)-(1-6)-O-ß-D-galactopyranoside (6a)

107 mg of **7a** were treated according to method B yielding 62 mg (96%) of **6a**.
^{1}H-NMR (D_2O) δ 3.62 (dd, 1H, J = 7.5, 9.9 Hz, H-2); 3.67 (dd, 1H, J = 3.3, 9.8 Hz, H-3); 3.67 (m, 1H, H-5); 3.75 (t, 1H, J = 9.6 Hz, H-2'); 3.83 (dd, 1H, J = 9.5, 3.3 Hz, H-3'); 3.86 (m, 2H, H-6); 4.00 (dd, 1H, J = 3.3, 1.0 Hz, H-4); 4.01 (m, 1H, H-6a'); 4.07 (m, 1H, H-5'); 4.13 (dd, 1H, J = 3.4, 10.5 Hz, H-6b'); 4.16 (dd, 1H, J = 3.3, 0.6 Hz, H-4'); 4.50 (d, 1H, J = 7.5 Hz, H-1); 4.95 (d, 1H, J = 9.6 Hz, H-1'); 7.52-7.71 (m, 5H, aromatic H). ^{13}C-NMR (D_2O) δ 134.64; 133.31; 131.57; 130.03; 104.88(C-1); 89.95(C-1'); 79.98(C-5'); 77.26(C-5); 75.90(C-3'); 74.79(C-3); 72.91(C-2); 71.24(C-2'); 71.12(C-4'); 70.91(C-6'); 70.75(C-4); 63.10(C-6). FAB-MS: 452.3 $(M+NH_4^+$; 100%).

Thioethyl-S-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(1-6)-O-2,3,4-tri-O-acetyl-ß-D-galactopyranoside (7b)

A solution of 224 mg (1mmol) of thioethyl-S-ß-D-galactopyranoside **5b** in 15 mL of buffer was treated with **1** and ß-galactosidase for 90 min according to method A. After flash chromatography (PE : EE = 3 : 2) 61 mg (9%) of **7b** were obtained. $[\alpha]_D^{20}$ = -10.0° ($CHCl_3$; c = 2.85). ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.3 Hz, H-2"); 1.92(2x); 1.98, 2.02(2x); 2.09(2x) (4 s, 21 H, acetyl-CH_3); 2.68 (m, 2H, H-1"); 3.68 (dd, 1H, J = 7.0, 10.6 Hz, H-6a'); 3.74 (dd, 1H, J = 5.1, 10.6 Hz, H-6b'); 3.84 (m, 1H, J = 1.0, 5.1, 7.0 Hz, H-5'); 3.85 (m, 1H, J = 1.0, 6.7 Hz, H-5); 4.06 (dd, 1H, J = 6.7, 11.3 Hz, H-6a); 4.11 (dd, 1H, J = 6.7, 11.3 Hz, H-6b); 4.43 (d. 1H, J = 10.0 Hz, H-1'); 4.46 (d, 1H, J = 7.9 Hz, H-1); 4.93 (dd, 1H, J = 3.5, 10.5 Hz, H-3); 4.97 (dd, 1H, J = 3.3, 10.0 Hz, H-3'); 5.11 (dd, 1H, J = 7.9, 10.5 Hz, H-2); 5.16 (t, 1H, J = 10.0 Hz, H-2'); 5.31 (dd, 1H, J = 3.5, 1.0 Hz, H-4); 5.35 (dd, 1H, J = 3.3, 1.0 Hz, H-4'). ^{13}C-NMR ($CDCl_3$) δ 170.26; 170.09; 170.00(2x); 169.89; 169.50; 169.24; 100.57(C-1); 83.83(C-1'); 75.81(C-5'); 71.92(C-3'); 70.62(C-3); 70.67(C-5); 68.38(C-2); 67.70(C-4'); 67.23(C-2'); 66.86(C-4); 66.81(C-6'); 61.60(C-6); 24.19(C-1"); 20.72; 20.62; 20.59; 20.56; 20.53; 20.48; 20.45; 14.74(C-2"). MS (70 eV): m/e 830.84 $(M+PAA+H)^+$; 100%; Calcd. 830.78). Anal. for $C_{28}H_{40}O_{17}S$ (680.68): Calcd. C, 49.41; H, 5.92; S, 4.71 Found C, 49.13; H, 5.78; S, 4.62.

Thioethyl-S-(ß-D-galactopyranosyl)-(1-6)-O-ß-D-galactopyranoside (6b)

61 mg of **7b** were treated according to method B yielding 34 mg (97%) of **6b**.

^{1}H-NMR (D_2O) δ 1.41 (t, 3H, J = 7.5 Hz, H-2"); 2.90 (m, 2H, H-1"); 3.66 (dd, 1H, J = 7.9, 10.0 Hz, H-2); 3.70 (dd, 1H, J = 9.7, 9.6 Hz, H-2'); 3.78 (dd, 1H, J = 3.5, 10.0 Hz, H-3); 3.79 (dd, 1H, J = 9.6, 3.4 Hz, H-3'); 3.83 (m, 1H, H-5); 3.9 (m, 2H, H-6); 4.00 (m, 1H, H-6a'); 4.03 (m, 1H, H-5'), 4.05 (dd, 1H, J = 3.5, 0.8 Hz, H-4); 4.15 (dd, 1H, J = 3.4, 0.6 Hz, H-4'); 4.16 (m, 1H, H-6b'); 4.58 (d, 1H, J = 7.9 Hz, H-1); 4.62 (d, 1H, J = 9.7 Hz, H-1'). ^{13}C-NMR (D_2O) δ 105.29(C-1); 87.75(C-1'); 79.59(C-5'); 77.31(C-5); 75.90(C-3'); 74.85(C-3); 72.91(C-2); 71.54(C-2'); 71.28(C-6'); 71.07(C-4'); 70.76(C-4); 63.12(C-6); 26.32(C-1"); 16.63(C-2").

Methyl-O-(2,3,4,6-tetra-O-acetyl-ß-D-galactopyranosyl)-(1-6)-O-(2,3,4-tri-O-acetyl-ß-D-glucopyranosyl)-(1-6)-O-2,3,4-tri-O-acetyl-ß-D-glucopyranoside (9)

Method C (from thiophenyl glycoside **4a**): A mixture of 66.7 mg (0.09 mmol) glycosyl donor **4a** and 58.2 mg (0.18 mmol) of acceptor methyl-O-2,3,4-tri-O-acetyl-ß-D-glucopyranoside **8** was coevaporated twice with toluene to remove traces of water. After drying in vacuum for 2 h the mixture was dissolved in 10 mL of dry dichloromethane. Then 300 mg of activated molecular sieves (4Å) and 51 mg (0.22 mmol.) of *N*-iodosuccinimide (NIS) were added. After stirring for 10 min, 0.1 equiv. triethylsilyltriflate (as a solution in dichloromethane) were added at room temperature over a period of 15 minutes until all the donor substrate has been consumed (as judged by TLC). The reaction was quenched by the addition of 10 mL of a saturated $Na_2S_2O_3$ solution and 10 mL of a 10% $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted 3 times with 40 mL portions of dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and and the solvent removed in vacuum. The crude product was purified by flash chromatography (PE : EE = 1 : 1, R_f = 0.2) to yield 39 mg (46%) of **9**.

Method D (from pent-4-enyl glycoside **4d**) : A mixture of 51 mg (0.07 mmol) glycosyl donor **4d** and 28 mg (0.09 mmol) of acceptor methyl-O-2,3,4-tri-O-acetyl-β-D-glucopyranoside **8** was coevaporated twice with toluene to remove traces of water. After drying in vacuum for 2 h the mixture was dissolved in 15 mL of dry dichloromethane. Then 300 mg of activated molecular sieves (4Å) and 41 mg (0.18 mmol) of NIS were added. After stirring for 15 min 1.1 equiv. of triethylsilyltriflate (as a solution in dichloromethane) were added over a period of 35 min until all of the donor has been consumed (as judged by TLC). The reaction was quenched by the addition of 10 mL of a saturated $Na_2S_2O_3$ solution and 10 mL of a 10% $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted 3 times with 40 mL portions of dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and and the solvent removed in vacuum. The crude product was purified by flash chromatography (PE : EE = 1 : 1) to yield 20 mg (29%) of **9**.

^{1}H-NMR ($CDCl_3$) δ 1.91, 1.92, 1.93, 1.96, 1.97(2x), 1.98, 1.99, 2.02, 2.08 (9s, 30 H, acetyl-CH_3); 3.44 (s, 3H, OCH_3); 3.54 (dd, 1H, J = 6.1, 10.8 Hz, H-6a"); 3.55 (dd, 1H, J = 6.6, 10.8 Hz, H-6a'); 3.60 (m, 1H, H-5'); 3.61 (m, 1H, H-5"); 3.84 (dd, 1H, J = 2.0, 10.8 Hz, H-6b"); 3.85 (m, 1H, H-5); 3.88 (dd, 1H, J = 2.0, 10.8 Hz, H-6b'); 4.07 (m, 2H, H-6); 4.33 (d, 1H, J = 8.0 Hz, H-1"); 4.48 (d, 1H, J = 7.9 Hz, H-1); 4.50 (d, 1H, J = 8.0 Hz, H-1'); 4.85 (m, 1H, H-4'); 4.87 (m, 1H, H-4"); 4.87 (dd, 1H, J = 9.6, 8.0 Hz, H-2"), 4.88 (dd, 1H, J = 8.0, 9.7 Hz, H-2'); 4.96 (dd, 1H, J = 3.4, 10.5 Hz, H-3); 5.11 (2H, m, H-3', H-3"); 5.13 (dd, 1H, J = 7.9, 10.5 Hz, H-2); 5.32 (dd, 1H, J = 3.3, 0.9 Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ 170.36; 170.22; 170.18(2x); 170.03; 169.57; 169.50; 169.40(2x); 169.27; 101.49(C-1"); 101.20(C-1); 100.71(C-1');

73.27(C-5"*); 73.26(C-5'*); 72.83(C-3'**); 72.81(C-3"**); 71.22(C-2"); 71.13(C-2'); 70.82(2x, C-5, C-3); 69.17(C-4"); 68.96(C-4'); 68.61(C-2); 68.19(C-6'); 67.87(C-6"); 67.05(C-4); 61.23(C-6); 56.94(OCH_3). Carbon signals indicated with (*) or (**) may be interchanged. MS (70 eV): m/e 1088.71 $(M+PAA+H)^+$; 100%; Calcd. 1088.94).

Methyl-O-(ß-D-galactopyranosyl)-(1-6)-O-(ß-D-glucopyranosyl)-(1-6)-O-ß-D-glucopyranoside (10)

39 mg of **9** were treated according to method B to obtain 20 mg (95%) of **10**.

^{1}H-NMR (D_2O) δ 3.40 (dd, 1H, J = 8.0, 9.3 Hz, H-2"); 3.46 (dd, 1H, J = 7.9, 9.5 Hz, H-2'); 3.61 (2H, m, H-4', H-4"); 3.63 (m, 1H, H-3"); 3.64 (m, 1H, H-3'); 3.68 (dd, 1H, J = 7.8, 10.0 Hz, H-2); 3.70 (s, 3H, OCH_3); 3.75 (m, 2H, H-5', H-5"); 3.79 (dd, 1H, J = 10.0, 3.5 Hz, H-3); 3.83 (m, 1H, J = 0.8, 4.4, 7.8 Hz, H-5); 3.90 (m, 2H, H-6); 3.99 (dd, 1H, J = 5.8, 11.7 Hz, H-6a"); 4.00 (dd, 1H, J = 5.6, 11.8 Hz, H-6a'); 4.06 (dd, 1H, J = 3.5, 0.8 Hz, H-4); 4.35 (dd, 1H, J = 1.8, 11.7 Hz, H-6b"); 4.36 (dd, 1H, J=1.9, 11.8 Hz, H-6b'); 4.52 (d, 1H, J = 8.0 Hz, H-1"); 4.58 (d, 1H, J = 7.8 Hz, H-1); 4.66 (d, 1H, J = 8.0 Hz, H-1'). ^{13}C-NMR (D_2O) δ 105.60(C-1); 105.46(C-1"); 105.08(C-1'); 77.81(C-3"); 77.72(C-3'); 77.30(C-5); 77.08(C-5'*); 77.04(C-5"*); 75.20(2x, C-2', C-2"); 74.84(C-3); 72.89(C-2); 71.58(C-4"); 71.51(C-4'); 70.92(C-6"); 70.80(C-4); 70.60(C-6'); 63.13(C-6); 59.56(OCH_3). FAB-MS: 536.4 $(M+NH_4^+$; 100%).

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