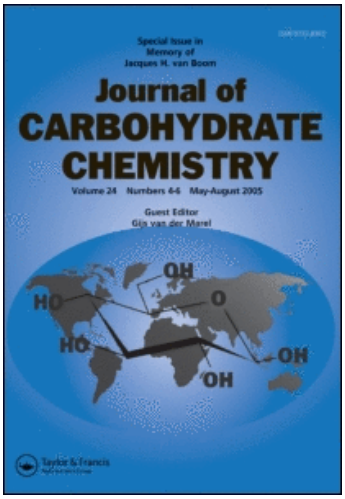

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THIOGLYCOSIDES AS POTENTIAL GLYCOSYL DONORS IN ELECTROCHEMICAL GLYCOSYLATION REACTIONS. PART 2: THEIR REACTIVITY TOWARD SUGAR ALCOHOLS.

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ABSTRACT

Constant potential electrolysis of the glycosyl donors *p*-methylphenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) and *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**4**) in dry acetonitrile in the presence of various primary and secondary sugar alcohols, performed in an undivided cell, gave β-linked disaccharide derivatives selectively in good yields. Oxidative coupling of *p*-methoxyphenyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**21**) with *p*-methoxybenzyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**16**) gave selectively the α-linked disaccharide **22** in good yield.

INTRODUCTION

In part one of this publication[1] we showed that peracetylated 1-thioglycosides are poor glycosyl donors in electrochemical glycosides synthesis using simple non sugar alcohols. The yields in these glycosylation reactions are low owing to degradation reactions, formation of orthoesters and α,β mixtures. Perbenzoylated 1-thioglycosides

lead to the formation of β-glycosides exclusively in moderate to good yields but the appearance of orthoesters cannot be totally avoided especially if primary unhindered alcohols are used. On the other hand, perbenzylated thioglycosides proved to be excellent glycoside donors with a marked β-selectivity. In the case of glucosamine derivatives, 2-deoxy-2-acetamido-1-thioglycosides lead exclusively to the formation of the 1,2-oxazoline derivative whereas the corresponding 2-phthalimido-2-deoxy-1-thioglycosides appeared to be excellent glycosides donors with a total β-selectivity. In certain instances small amounts of α-D-glycosyl fluorides were produced when lithium tetrafluoroborate was the supporting electrolyte. They presumably result from a nucleophilic attack on Gly^+ by BF_4^- and this reaction may offer an economic entry to glycosyl fluorides, which are usually prepared from elaborate reagents.[2] We now report on oligosaccharides syntheses using electrochemical glycosylations with various sugar alcohols.

RESULTS AND DISCUSSION.

The glycosylation reactions were conducted on the one mmole scale at room temperature under nitrogen in an undivided cell equiped with a woven or vitrous carbon anode and a platinum or nickel foam cathode as already described.[1] The supporting electrolyte was a 0.2M solution of lithium tetrafluoroborate in acetonitrile (32 mL) containing activated 3 Å powdered molecular sieves to keep the medium anhydrous and neutralize the acidity.

Entries 1, 2 and 3 (Table 1) with the primary alcohols **2**[3]and **6**[4]as the acceptors and the thioglycosides **1**[1] and **4**[1] as the donors clearly demonstrate the feasibility of electro-oxidative glycosylations, the yields being good to excellent. Thus, coupling of the thioglycoside **1** with the acceptor **2** gave the disaccharide **3** in 92% yield as a mixture of the two anomers (α:β = 24:76). The phthalimido derivative **4** reacted with compound **2** and **6** to give respectively the disaccharides **5** and **7**[5] in 70% and 64% yields. As already pointed out[1] perbenzylated 1-thioglycosides such as **1** reacted with a marked β-selectivity while *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**4**) lead exclusively, as usual, to the corresponding β disaccharide as a result of the presence of the bulky participating phthalimido group. The disaccharide **7**[5] was obtained in only 64% yield probably owing to the steric hindrance or remaining traces of acidity.

Electrochemical glycosylation of secondary alcohols was then investigated. Thus the thioglycoside **4** reacted with benzyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (**8**)[6] to

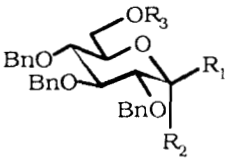
TABLE 1: Constant potential electrosyntheses of some di- and trisaccharides.

Entry	Donor (eq)	E_{ox} a (V)	Electrodes Anode/Cathode	Acceptor (eq)	time (h)	product(s)[b]	Yields	α:β
1	**1**[1] (1.0)	1.45	Vitrous C/Pt	**2**[3] (2.0)[c]	4.5	**3**[13]	92	24:76
2	**4**[1] (1.0)	1.52	Vitrous C/Pt	**2**[3] (1.0)	2.5	**5**	70	0:1
3	**4** (1.0)	1.52	Woven C/Ni foam	**6**[4] (1.0)	3.5	**7**[5]	64	0:1
4	**4** (1.0)	1.52	Vitrous C/Pt	**8**[6] (1.1)	4.5	**12**	71	0:1
5	**4** (1.0)	1.52	Woven C/Pt	**9**[7] (1.0)	2	**9**[7] **13** **14** **15**	26 33[d] 23[d] 9[d]	- 0:1 0:1 0:1
6	**21**[1] (1.0)	1.33	Woven C/Ni foam	**16**[8] (1.2)	3	**22**	76[d]	75:25

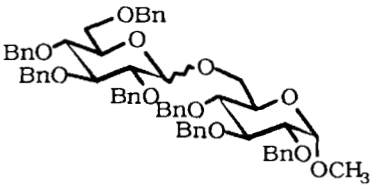
a. See Ref. 1. b. Isolated after flash chromatography. c. No molecular sieves were added.
d. Yields based on recovered starting diol **9**.

give the β-disaccharide **12** in 71% yield (Table 1, entry 4). Relying on the moderate reactivity of axial hydroxyl groups compared to equatorial ones we tested the electrochemical behavior of benzyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**9**)[7] toward the thioglycoside **4** which ensures a complete β-selectivity and so, should lead to a less complex final reaction mixture. However, reaction of **4** with one molar equivalent of **9** gave a complex reaction mixture which, after chromatography, afforded the unreacted starting diol **9** (26%), the β(1→3) linked disaccharide **13** (33%) and an inseparable mixture. Acetylation of the mixture and subsequent chromatography gave the trisaccharide **14** and the 3-acetylated β(1→4) linked disaccharide **15** in 23% and 9% yields respectively (Table 1, entry 5). The structures of **13** and **14** were assured using two dimensional ^1H-^1H NMR correlation spectroscopy (COSY). Therefore, it can be concluded that electrochemical glycosylation does not regioselectively discriminate between the C-4 axial and C-3 equatorial hydroxyl groups of **9**.

Next, we tried the electrosynthesis of lactosamine using *p*-methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (**10**)[1] as the donor and *p*-methoxybenzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**19**) as the acceptor. The starting material used for the synthesis of **19** was the readily available



1 R_1=*p*-*MePhS*, R_2=*H*, R_3=*Bn*
2 R_1=H, R_2=OMe , R_3=H



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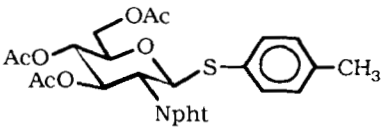

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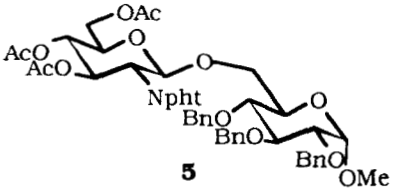

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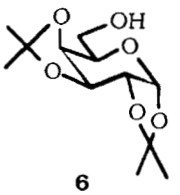

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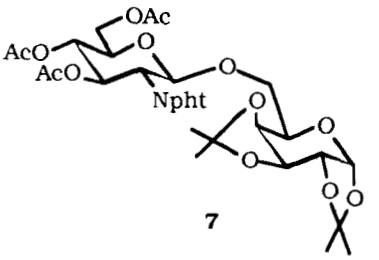
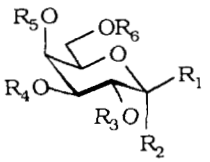
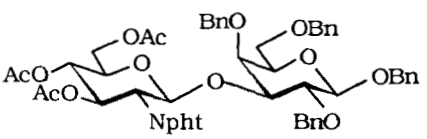


7

glucosamine derivative **16**[8] which after benzylation of the free hydroxyl group and hydrolysis of the benzylidene acetal gave *p*-methoxybenzyl 2-acetamido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**18**) in 80% yield. Classical treatment of **18** with dibutyltin oxide followed by benzyl bromide afforded **19** in 71% yield. However, when we tried the electrochemical oxidation of **10** in the presence of one molar equivalent of the acceptor **19**, to our surprise this led to total decomposition of **10** and no glycosylation product could be detected. Compound **19** was totally unaffected during the reaction.





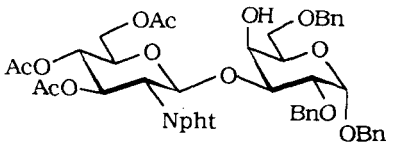
12

8 R_1=OBn, R_3=R_5=R_6=Bn, R_2=R_4=H

9 R_1=H, R_2=OBn, R_3=R_6=Bn, R_4=R_5=H

10 R_1=SPh(p-OMe), R_2=H, R_3=R_4=R_5=R_6=Bn

11 R_1=SPh(p-OMe), R_2=H, R_3=R_4=R_5=R_6=Bz



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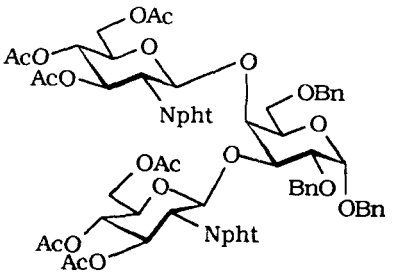

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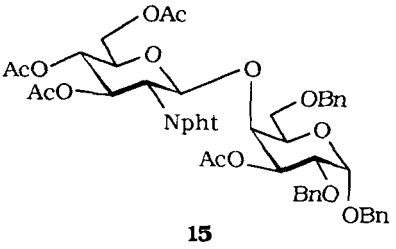

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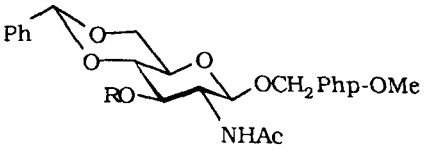
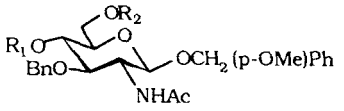


16 R=H

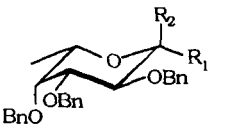
17 R=Bn

As the final part of this study we wondered if electrooxidation of thioglycosides could be used for preparation of the biologically important Lewis^x trisaccharide Gal-β(1→4) [Fuc α(1→3)] GlcNAc. We tried first the fucosylation reaction by coupling 2,3,4-tri-*O*-benzyl 1-thio-β-L-fucopyranoside (**21**)[1] with the *p*-methoxybenzyl glucosamine derivative **16**. In fact, electrochemical oxidation of **21** in the presence of 1.2 equivalent of the alcohol **16** (Table 1, entry 6) afforded the disaccharide **22** in 76% yield (based on the recovered starting material) with a marked α-selectivity (α:β, 75:25) which is, however, rather disappointing owing to the fact that using a traditional coupling procedure the perbenzylated fucopyranosyl bromide **20** gave in 84% yield, stereoselectively the α glycoside in the presence of tetrabutylammonium bromide (experimental part). The use of acetonitrile as the solvent, known to promote β-selectivity,[9] could explain the formation of a substantial amount of the β-anomer.



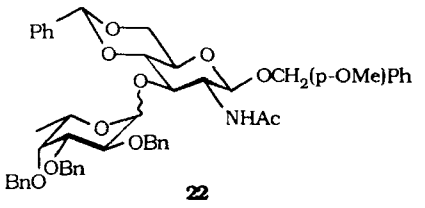
18 R_1=R_2=H

19 R_1=H, R_2=Bn



20 R_1=H, R_2=Br

21 R_1=S(p-OMe)Ph, R_2=H



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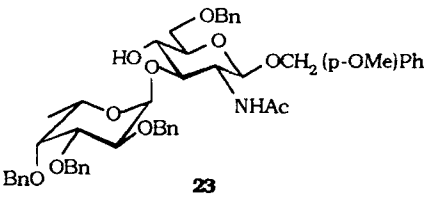

23

Galβ(1-4)
↓
Fuc(1-3)GlcNAc

24

The secondary alcohol **23** was prepared in 75% yield from the α-anomer of **22** through regioselective ring cleavage with $NaBH_3CN$ and hydrogen chloride in ether.[10] However, the electrochemical glycosylation of **23** with *p*-methoxyphenyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (**11**)[1] failed and no condensation occurred. In fact, after 5.5 h TLC indicated the complete disappearance of the thioglycoside **11**. Flash chromatography allowed us to recover 90% of **23** and 22% of perbenzylated α-D-galactopyranosyl fluoride[11] which is a usual side product when using lithium tetrafluoroborate as supporting electrolyte. This results are consistent with the observation that the hydroxyl group in similar derivatives of **23** is not very reactive.[12]

CONCLUSION

We have shown in this paper, that electrosyntheses of oligosaccharides are possible when reactive sugar alcohols such as in **2**, **6** or **8** are used . The results described in this and precedent paper indicate that electrooxidation of thioglycosides as an alternative method for glycoside synthesis, while having some clear limits, may find application in large scale preparation of simple glycosides. No expensive or dangerous promotors are used, making this methodology potentially attractive for certain industrial purposes.

EXPERIMENTAL

General methods. These were as described in the preceding paper[1] and all electrolyses were carried out on 1 mmole scales at room temperature in an undivided cell

using square electrodes (4cm^2) in anhydrous acetonitrile (32 mL) with lithium tetrafluoroborate (0.2M) as supporting electrolyte.

General procedures for the isolation of oligosaccharides 5, 12, 13, 14, 15 and 22. The electrolysed solution was filtered, concentrated and the residue dissolved in dichloromethane (40 mL) and water (40 mL). The organic phases were separated and the aqueous phase extracted with dichloromethane (2×40 mL). The combined organic phases were dried (magnesium sulfate), concentrated and the residue chromatographed on silica gel.

Methyl 6-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5). Flash chromatography (toluene-ether, 8:2), 619 mg (70%); mp 152-153 °C (EtOH), $[\alpha]_D^{20}$ +34° *(c* 1, $CHCl_3$); IR (KBr) ν 3034, 2886, 1746, 1714, 1497, 1456, 1384, 1242, 1166, 1082, 1045, 898, 746 and 718 cm^{-1}; ^{1}H NMR δ 7.77-7.45 (m, 4H, Phthalimido), 7.37-6.95 (m, 15H, aromatics), 5.79 (dd, 1H, $J_{3',2'}$=10.5, $J_{3',4'}$=9.0, H-3'), 5.44 (d, 1H, $J_{1',2'}$=8.5, H-1'), 5.18 (dd, 1H, $J_{4',5'}$=10, H-4'), 4.86-4.72 and 4.64-4.56 (m, 4H, J=11.0 and J=12.0, 2×OC$\underline{H}_2$Ph), 4.40 (m, 2H, H-2', OC$\underline{H}_2$Ph), 4.37 (d, 1H, $J_{1,2}$=3.5, H-1), 4.33 (dd, 1H, $J_{6'a,6'b}$=12,.0 $J_{6'a,5'}$=4.5, H-6'a), 4.17 (dd, 1H, $J_{6'b,5'}$=2.5, H-6'b), 4.13-4.04 (m, 2H, H-6a, OC$\underline{H}_2$Ph), 3.88 (m, 1H, H-5'), 3.84 (t, 1H, $J_{3,2}$=$J_{3,4}$=9.5, H-3), 3.71-3.61 (m, 2H, H-5, H-6b), 3.39 (dd, 1H, H-2), 3.24 (t, 1H, $J_{4,5}$=9.5, H-4), 3.17 (s, 3H, OCH_3), 2.08, 2.03 and 1.85 (3×s, 9H, 3×$COCH_3$); ^{13}C NMR δ 170.76, 170.65, 169.45 and 168.69 (C=O), 138.62-123.49 (aromatics), 98.31 and 97.90 (C-1 and C-1'), 81.84, 79.66, 71.91, 70.7, 69.15, 68.95, 66.06 and 54.95 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 75.67, 74.72, 73.37, 68.69 and 62.07 (O$\underline{C}H_2$Ph, C-6 and C-6'), 54.46 (OCH_3), 20.77, 20.64 and 20.45 (CO$\underline{C}H_3$).

Anal. Calcd for $C_{48}H_{51}NO_{15}$ (881.93): C, 65.37; H, 5.83; O, 27.21; N, 1.59. Found: C, 65.12; H, 5.72; O, 27.23; N, 1.58.

Benzyl 3-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside (12). Flash chromatography (toluene-ether, 9:1), 682 mg (71%); mp 138-139 °C (EtOH), $[\alpha]_D^{20}$ -11° *(c* 1, $CHCl_3$); IR (KBr) ν 3063, 3032, 2940, 2851, 2813, 1738, 1607, 1587, 1498, 1454, 1427, 1386, 1232, 1076, 953, 914, 893, 774 and 742 cm^{-1}; ^{1}H NMR δ 7.74-7.40 (m, 4H, phthalimido), 7.40-6.95 (m, 20H, aromatics), 5.84 (dd, 1H, $J_{3',2'}$=10.5, $J_{3',4'}$=9.0, H-3'), 5.69 (d, 1H, $J_{1',2'}$=8.5, H-1'), 5.15 (t, 1H, $J_{4',5'}$=9.0, H-4'), 4.88 and 4.80 (2×d, 2H, J=11.0 and J=12.0, OC$\underline{H}_2$Ph), 4.60-4.45 (m, 5H, OC$\underline{H}_2$Ph), 4.39 (dd, 1H, H-2'), 4.34 (d, 1H, $J_{1,2}$=7.5, H-1), 4.28 (dd, 1H, $J_{6'a,6'b}$=12.0, $J_{6'a,5'}$=4.5, H-6'a), 4.15 (dd, 1H, $J_{6'b,5'}$=2.5, H-6'b), 4.12 (d, 1H, J=12.0, OC$\underline{H}_2$Ph), 3.95 (d, 1H, $J_{4,3}$=3.0, $J_{4,5}$=0.0, H-4), 3.83-3.70 (m, 2H, $J_{3,2}$=9.5, H-3 and H-5'), 3.63 (dd, 1H, H-2), 3.58-3.45 (m, 3H, H-5, H-6a and H-6b), 2.20, 2.00 and 1.85 (3×s, 9H, 3×COCH3); ^{13}C NMR δ 170.55, 169.99, 169.52 and 167.72 (C=O), 138.67-123.38

(aromatics), 102.48 and 99.01 (C-1 and C-1'), 81.51, 78.25, 75.76, 73.39, 71.58, 70.45, 68.97 and 55.00 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 74.61, 73.71, 73.50, 70.63, 68.83 and 61.91 ($O\underline{C}H_2Ph$, C-6 and C-6'), 20.60 and 20.40 ($CO\underline{C}H_3$).

Anal. Calcd for $C_{54}H_{55}NO_{15}$ (958.03): C, 67.70; H, 5.79; O, 25.05; N, 1.46. Found: C, 67.37; H, 5.86; O, 25.34; N, 1.45.

Benzyl 3-*O*-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,6-di-*O*-benzyl-α-D-galactopyranoside (13), Benzyl 4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-3-*O*-acetyl-2,6-di-*O*-benzyl-α-D-galactopyranoside (15) and trisaccharide (14). From 1.626 g of **4**[1] (3 mmol) and 1.344g (3 mmol) of **9**[7] in acetonitrile (96 mL). Flash chromatography (toluene-ether, 8:2) afforded **9** (0.356 g, 26%) and the disaccharide **13** (0.625 g, 33% considering the recovered alcohol **9**); amorphous solid, $[\alpha]_D^{20}$ +64° (*c* 1, $CHCl_3$); IR (KBr) ν 3551, 3553, 3062, 3029, 3006, 2925, 2869, 1749, 1718, 1496, 1453, 1430, 1387, 1367, 1229, 1149, 1103, 1043, 973, 902, 740 and 722 cm^{-1}; ^1H NMR δ 7.75-7.55 (m, 4H, phthalimido), 7.40-6.88 (m, 15H, aromatics), 5.88 (dd, 1H, $J_{3',2'}$=10.5, $J_{3',4'}$=9.0, H-3'), 5.59 (d, 1H, $J_{1',2'}$=8.5, H-1'), 5.15 (t, 1H, $J_{4',5'}$=9.0, H-4'), 4.65-4.50 (m, 4H, $J_{1,2}$=4.0, $OC\underline{H}_2Ph$, H-1), 4.44 (dd, 1H, H-2'), 4.40 (d, 1H, J=12.0, $OC\underline{H}_2Ph$), 4.25 (dd, 1H, $J_{6'a,6'b}$=12.0, $J_{6'a,5'}$=5.5, H-6'a), 4.20-4.08 (m, 3H, $OC\underline{H}_2Ph$, H-6'b, H-6a), 4.03-3.94 (m, 3H, J=12.0, $J_{3,2}$=9.0, $J_{3,4}$=3.0, $OC\underline{H}_2Ph$, H-6b, H-3), 3.89 (m, 1H, H-5'), 3.75-3.53 (m, 3H, H-2, H-4, H-5), 2.74 (1H, OH), 2.03, 1.98 and 1.83 (3×s, 9H, 3×COCH3); ^{13}C NMR δ 170.39, 169.81, 169.28 and 167.42 (C=O), 137.99-123.35 (aromatics), 98.57 and 95.70 (C-1 and C-1'), 79.97, 74.05, 71.59, 70.13, 68.73, 68.13, 54.44 and 53.31 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 73.20, 72.61, 69.23, 68.84 and 61.77 ($O\underline{C}H_2Ph$, C-6 and C-6'), 20.38 and 20.18 ($CO\underline{C}H_3$).

Anal. Calcd for $C_{47}H_{49}NO_{15}$ (869.9): C, 65.04; H, 5.69; N, 1.61. Found: C, 65.03; H, 6.01; N, 1.60.

Further elution of the column afforded a mixture of products (0.902 g) which after acetylation in pyridine and acetic anhydride and subsequent flash chromatography (dichloromethane-ether, 95:5) gave pure **15** (0.179 g, 9%) and **14** (0.655 g, 23%), considering the recovered alcohol **9**). **15**, amorphous solid, $[\alpha]_D^{20}$ +56° (*c* 1, $CHCl_3$); IR (KBr) ν 3063, 3030, 2924, 2854, 2359, 2112, 1955, 1719, 1609, 1496, 1455, 1388, 1229, 1042, 883, 835, 791 and 723 cm^{-1}; ^1H NMR δ 7.90-7.60 (m, 4H, phthalimido), 7.38-6.78 (m, 15H, aromatics), 5.96 (dd, 1H, $J_{3',2'}$=10.5, $J_{3',4'}$=9.0, H-3'), 5.26 (d, 1H, $J_{1',2'}$=8.0, H-1'), 5.21 (dd, 1H, $J_{3,2}$=10.5, $J_{3,4}$=2.5, H-3), 5.15 (t, 1H, $J_{4',5'}$=9.0, H-4'), 4.70 (d, 1H, $J_{1,2}$=3.5, H-1), 4.65 (d, 1H, J=12.5, $OC\underline{H}_2Ph$), 4.61-4.43 (m, 3H, $OC\underline{H}_2Ph$), 4.37 (dd, 1H, H-2'), 4.25 (dd, 1H, $J_{6'a,6'b}$=12.0, $J_{6'a,5'}$=5.0, H-6'a), 4.19 (d, 1H, H-4), 4.07 (m, 1H, H-5), 4.03 (dd, 1H, $J_{6'b,5'}$=2.0, H-6'b), 3.80 (m, 1H, H-5'), 3.74-3.62 (m, 3H, $J_{6a,6b}$=10.5,

$J_{6a,5}$=5.0, J=11.5, H-6a, OC<u>H</u>$_2$Ph), 3.57 (dd, 1H, $J_{6b,5}$=7.0, H-6b), 3.32 (dd, 1H, H-2), 2.08, 2.05, 2.03 and 1.88 (4×s, 12H, 4×COCH3); ^{13}C NMR δ 170.69, 170.42, 170.03, 169.46 and 167.32 (C=O), 138.28-123.53 (aromatics), 97.98 and 95.32 (C-1 and C-1'), 75.12, 74.97, 71.84, 71.38, 69.94, 69.06, 68.70 and 54.63 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 73.13, 72.98, 69.40, 68.70 and 61.63 (O<u>C</u>H$_2$Ph, C-6 and C-6'), 20.68, 20.54 and 20.40 (CO<u>C</u>H$_3$).

Anal. Calcd for $C_{49}H_{51}NO_{16}$ (909.94): C, 64.68; H, 5.65; N, 1.54. Found: C, 64.56; H, 5.75; N, 1.37.

14, amorphous solid, $[\alpha]_D^{20}$ +85° (*c* 1, $CHCl_3$); IR (KBr) ν 3032, 2935, 2423, 2354, 2253, 2113, 1958, 1749, 1722, 1610, 1457, 1379, 1231, 1161, 1038, 906, 837, 795 and 726 cm^{-1}; ^{1}H NMR (the suffixes prime or double prime refer respectively to the different glucose units linked to galactose) δ 7.83-7.45 (m, 8H, phthalimido), 7.37-6.88 (m, 13H, aromatics), 6.45 (d, 2H, aromatics), 5.98 (dd, 1H, $J_{3',2'}$=10.5, $J_{3',4'}$=9.0, H-3'), 5.90 (d, 1H, $J_{1',2'}$=8.0, H-1'), 5.71 (dd, 1H, $J_{3'',2''}$=10.0, $J_{3'',4''}$=9.0, H-3''), 5.57 (d, 1H, $J_{1'',2''}$=8.5, H-1''), 5.32 (dd, 1H, $J_{4'',5''}$=10.0, H-4''), 5.18 (dd, 1H, $J_{4',5'}$=10.0, H-4'), 4.56 (dd, 1H, $J_{6'a,6'b}$ or $J_{6''a,6''b}$=12.0, $J_{6'a,5'}$ or $J_{6''a,5''}$=5.5, H-6'a or H-6''a), 4.56-4.42 (m, 3H, J=11.5, J=12.0, OC<u>H</u>$_2$Ph), 4.31 (dd, 1H, H-2'), 4.26 (dd, 1H, H-2''), 4.30-4.20 (m, 4H, OC<u>H</u>$_2$Ph, H-4, H-1, H-6'a or H-6''a), 4.14-4.04 (m, 2H, H-6'b, H-6''b), 3.96-3.81 (m, 4H, H-5', H-5'', H-3, H-5), 3.62 (dd, 1H, $J_{6a,6b}$=10.5, $J_{6a,5}$=5.0, H-6a), 3.49 (d, 1H, J=12.5, $J_{6b,5}$=7.0, OC<u>H</u>$_2$Ph, H-6b), 3.16-3.07 (m, 2H, J=12.5, $J_{2,1}$=4.0, $J_{2,3}$=10.0, H-2), 2.08, 2.06, 2.04, 1.90 and 1.87 (5×s, 18H, 6×COCH3); ^{13}C NMR (the suffixes prime or double prime refer respectively to the different glucose units linked to galactose) δ 170.48, 170.02, 169.53, 167.42 and 165.58 (C=O), 137.99-123.35 (aromatics), 100.65, 97.26 and 95.93 (C-1, C-1' and C-1''), 81.28, 74.05, 71.59, 70.13, 68.73, 68.13, 54.44 and 53.31 (C-2, C-3, C-4, C-5, C-2', C-3', C-4', C-5', C-2'', C-3'', C-4'' and C-5''), 73.20, 72.61, 69.23, 68.84 and 61.77 (O<u>C</u>H$_2$Ph, C-6, C-6' and C-6''), 20.38 and 20.18 (CO<u>C</u>H$_3$).

Anal. Calcd for $C_{67}H_{68}NO_{24}$ (1285.57): C, 62.61; H, 5.33; N, 2.18; O, 29.88. Found: C, 62.59; H, 5.56; N, 2.15; O, 29.84.

***p*-Methoxyphenylmethyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzyl-α-andβ-L-fucopyranosyl)-2-deoxy-β-D-glucopyranoside (22).** Flash chromatography (toluene-acetone, 9:1) afforded the starting sugar alcohol **16**[8] (200 mg), the α-anomer of **22** (352 mg, 57%, considering the recovered alcohol **16**) and the β-anomer of **22** (118 mg, 19%).

α-Anomer: mp 161 °C (EtOH), $[\alpha]_D^{20}$ -177° (*c* 1, CH_2Cl_2); IR (KBr) ν 3349, 3032, 2929, 2867, 1688, 1611, 1514, 1497, 1455, 1370, 1306, 1250, 1211, 1172, 1136, 1098, 1037, 989, 819, 762 and 745 cm^{-1}; ^{1}H NMR δ 7.50-7.22 (m, 20H, aromatics), 7.19 (d, 2H, J=8.5, *p*-methoxyphenyl), 6.86 (d, 2H, *p*-methoxyphenyl), 5.51 (s, 1H,

benzylidene), 5.49 (d, 1H, $J_{NH,2}$=7.5, NHAc), 5.07 (d, 1H, $J_{1',2'}$=3.5, H-1'), 4.96-4.80 (m, 4H, J=11.0, $J_{1,2}$=8.0, OC$\underline{H}_2$Ph or OC$\underline{H}_2$PhOMe, H-1), 4.78-4.70 (m, 2H, OC$\underline{H}_2$Ph or OC$\underline{H}_2$PhOMe), 4.65-4.55 (m, 2H, OC$\underline{H}_2$Ph or OC$\underline{H}_2$PhOMe), 4.48 (d, 1H, J=11.5, OC$\underline{H}_2$Ph or OC$\underline{H}_2$PhOMe), 4.36 (dd, 1H, $J_{6a,5}$=5.0, $J_{6a,6b}$=10.5, H-6a), 4.24 (t, 1H, $J_{3,2}$=9.5, $J_{3,4}$=9.5, H-3), 4.10-4.00 (m, 2H, H-5', H-2'), 3.92 (dd, 1H, $J_{3',2'}$=10.0, $J_{3',4'}$=2.5, H-3'), 3.84-3.73 (m, 4H, OCH_3, H-6b), 3.65-3.55 (m, 2H, H-4, H-4'), 3.55-3.42 (m, 2H, H-2, H-5), 1.57 (s, 3H, NHCOC$\underline{H}_3$), 0.83 (d, 3H, $J_{CH3,5'}$=6.5, CH_3); ^{13}C NMR δ 170.30 (C=O), 159.03, 138.56-126.15 and 113.77 (aromatics), 101.51 (C$\underline{H}$Ph), 99.84 and 98.19 (C-1 and C-1'), 80.79, 79.77, 77.55, 76.88, 74.89, 66.22 and 57.93 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 74.05, 72.57, 70.86, 68.82 and 66.84 (O$\underline{C}H_2$Ph, C-6, O$\underline{C}H_2$PhOMe), 55.25 (OCH_3), 23.17 (CO$\underline{C}H_3$), 16.29 (CH_3).

Anal. Calcd for $C_{50}H_{55}NO_{11}$ (845.99): C, 70.99; H, 6.55; N, 1.66; O, 20.80. Found: C, 70.34; H, 6.39; N, 1.53; O, 20.24.

β-Anomer: mp 187 °C (EtOH), $[\alpha]_D^{20}$ -106° (*c* 0.6, CH_2Cl_2); IR (KBr) ν 3306, 3063, 3031, 2875, 1658, 1613, 1562, 1514, 1496, 1453, 1371, 1303, 1248, 1178, 1071, 818, 732 and 698 cm^{-1}; ^{1}H NMR δ 7.44-7.10 (m, 22H, aromatics), 6.85 (d, 2H, J=8.5, *p*-methoxyphenyl), 5.82 (d, 1H, $J_{NH,2}$=7.0, NHAc), 5.34 (s, 1H, benzylidene), 5.00-4.50 (m, 8H, J=11.0 and J=11.5, OC$\underline{H}_2$Ph and OC$\underline{H}_2$PhOMe), 4.94 (d, 1H, $J_{1,2}$=8.0, H-1), 4.55 (d, 1H, $J_{1',2'}$=7.5, H-1'), 4.35 (dd, 1H, $J_{6a,5}$=5.0, $J_{6a,6b}$=10.5, H-6a), 4.25 (dd, 1H, $J_{3,2}$=9.5, $J_{3,4}$=9.0, H-3), 3.79 (s, 3H, OCH_3), 3.78-3.66 (m, 2H, H-6b, H-2'), 3.59 (t, 1H, $J_{4,5}$=9.5, H-4), 3.53-3.35 (m, 5H, H-2, H-5, H-3', H-5' and H-4'), 1.88 (s, 3H, NHCOC$\underline{H}_3$), 1.14 (d, 3H, $J_{CH3,5'}$=6.5, CH_3); ^{13}C NMR δ 171.36 (C=O), 150.89, 139.23-126.00 and 113.74 (aromatics), 103.69 (C$\underline{H}$Ph), 100.86 and 100.39 (C-1 and C-1'), 82.05, 81.69, 79.60, 76.60, 75.51, 70.14, 66.18 and 56.78 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 76.41, 74.75, 73.16, 70.73 and 68.74 (O$\underline{C}H_2$Ph, C-6, O$\underline{C}H_2$PhOMe), 55.26 (OCH_3), 23.63 (CO$\underline{C}H_3$), 16.94 (CH_3).

Anal. Calcd for $C_{50}H_{55}NO_{11}$(845.99): C, 70.99; H, 6.55; N, 1.66. Found: C, 70.79; H, 6.61; N, 1.50.

***p*-Methoxyphenylmethyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-β-D-glucopyranoside (22).** A solution of ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[11] in dichloromethane (36 mL) was cooled to 0 °C and bromine (320 μL, 1.1 equiv) was then added. After 40 min the reaction mixture was concentrated and reconcentrated after addition of toluene (2×40 mL) to afford crude **20**.[11] The crude fucosyl bromide was then dissolved in dichloromethane (5.5 mL) and then added at room temperature to a stirred solution of **16**[8] (1.314 g) and tetrabutylammonium bromide (1.944 g) in DMF (7.2 mL) containing 4Å molecular sieves (5.3g). After 18 h ethanol (2.5 mL) was added, the resulting mixture filtered,

diluted with toluene and poured in a magnetically stirred aqueous solution saturated with potassium hydrogencarbonate. The organic layer was separated, washed with water (2×40 mL), dried (magnesium sulfate) and concentrated. The residue was chromatographed (toluene-ethylacetate, 9:1) to afford the pure α-anomer of **22** (2.18g, 84%).

***p*-Methoxyphenylmethyl 2-Acetamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy- β-D-glucopyranoside (17).** To a solution of **16**[8] (1.288 g) in DMF (20 mL) was added benzyl bromide (3.2 mL) and then portionwise sodium hydride (0.12 g). After 4 h at room temperature the reaction mixture was cooled to 0 °C, filtered and the solid washed successively with ice cold tetrahydrofuran (3×30 mL) and ether (50 mL). Pure **17** was obtained as a colorless amorphous solid (1.387g, 89%); $[\alpha]_D^{20}$ -14° (*c* 0.5, CH_2Cl_2); IR (KBr) ν 3268, 3106, 2884, 1655, 1567, 1514, 1452, 1374, 1316, 1249, 1172, 1093, 1035, 964, 918, 821, 746 and 694 cm^{-1}; ^1H NMR δ 7.55-7.25 (m, 10H, aromatics), 7.20 (d, 2H, J=8.5, *p*-methoxyphenyl), 6.85 (d, 2H, *p*-methoxyphenyl), 5.59 (s, 1H, C<u>H</u>Ph), 5.36 (d, 1H, $J_{NH,2}$=7.5, NHAc), 4.99 (d, 1H, $J_{1,2}$=8.0, H-1), 4.89-4.82 and 4.63-4.50 (2×m, 4H, J=11.5, J=12.0, OC<u>H</u>$_2$Ph and OC<u>H</u>$_2$PhOMe), 4.38 (dd, 1H, $J_{6,6'}$=10.5, $J_{6,5}$=5.0, H-6), 4.23 (dd, 1H, $J_{3,2}$=10.0, $J_{3,4}$=9.5, H-3), 3.90-3.75 (m, 4H, H-6', OCH_3), 3.70 (t, 1H, $J_{4,5}$=9.5, H-4), 3.54 (m, 1H, H-5), 3.35 (ddd, 1H, H-2), 1.82 (s, 3H, NHCOC<u>H</u>$_3$); ^{13}C NMR δ 170.22 (C=O), 159.25, 138.37-126.03, 129.73, 129.21 and 113.84 (aromatics), 101.24 (<u>C</u>HPh), 99.38 (C-1), 82.78, 77.22, 65.96 and 57.74 (C-2, C-3, C-4 and C-5), 74.47, 71.02 and 68.84 (O<u>C</u>H$_2$Ph, C-6, O<u>C</u>H$_2$PhOMe), 55.28 (OCH_3), 23.56 (CO<u>C</u>H$_3$).

Anal. Calcd for $C_{30}H_{33}NO_7$ (519.59) : C, 69.35; H, 6.40; O, 21.55; N, 2.70. Found: C, 69.17; H, 6.23; O, 21.68; N, 2.83.

***p*-Methoxyphenylmethyl 2-Acetamido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside (18).** A stirred suspension of the benzylidene derivative **17** (2.342 g) in acetic acid-water (6:4, v/v. 100 mL) was heated at 60 °C for 8 h. The resulting clear solution was concentrated and reconcentrated after addition of toluene to afford a white solid (2.01 g, 95%); mp 196-198 °C (AcOEt), $[\alpha]_D^{20}$ -12° (*c* 1, MeOH); IR (KBr) ν 3294, 3070, 2857, 1650, 1549, 1515, 1456, 1409, 1373, 1308, 1251, 1161, 1082, 1031, 893, 813 and 741 cm^{-1}; ^1H NMR δ 7.50-7.25 (m, 5H, aromatics), 7.23 (d, 2H, J=8.5, *p*-methoxyphenyl), 6.86 (d, 2H, J=8.5, *p*-methoxyphenyl), 5.47 (d, 1H, $J_{NH,2}$=8.0, NHAc), 4.92 (d, 1H, $J_{1,2}$=8.5, H-1), 4.81-4.45 (4×d, 4H, J=11.5, OC<u>H</u>$_2$Ph and OC<u>H</u>$_2$PhOMe), 4.02 (dd, 1H, $J_{3,2}$=10.0, $J_{3,4}$=9.0, H-3), 3.88 (ddd, 1H, $J_{6,6'}$=12.0, $J_{6,5}$=3.5, $J_{6,OH}$=6.5, H-6), 3.80 (s, 3H, OCH_3), 3.78 (ddd, 1H, $J_{6',5}$=5.0, $J_{6',OH}$=7.0, H-6'), 3.60 (ddd, 1H, $J_{4,5}$=9.0, $J_{4,OH}$=3.0, H-4), 3.41 (m, 1H, H-5), 3.33 (ddd, 1H, H-2), 2.33 (d, 1H, $J_{4,OH}$=3.0, OH), 2.04 (t, 1H, OH), 1.88 (s, 3H, NHCOC<u>H</u>$_3$); ^{13}C NMR (CD_4O) δ 173.13 (C=O), 160.62

(PhOCH$_3$), 139.99 (OCH$_2$Ph), 130.76 and 140.47 (PhOCH$_3$), 129.90, 128.68 and 128.37 (OCH$_2$Ph), 114.57 (PhOCH$_3$), 100.97 (C-1), 83.86, 77.77, 71.86 and 56.14 (C-2, C-3, C-4 and C-5), 75.51, 71.07 and 62.63 (OCH$_2$Ph, C-6, OCH$_2$PhOMe), 55.62 (OCH$_3$), 23.01 (COCH$_3$).

Anal. Calcd for $C_{23}H_{29}NO_7$ (431.48): C, 64.02; H, 6.77; O, 25.96; N, 3.25. Found: C, 63.98; H, 6.61; O, 25.82; N, 3.09.

***p*-Methoxyphenylmethyl 2-Acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (19).** A solution of **18** (0.453 g) in toluene (60 mL) containing dibutyltin oxide (0.289 g) was refluxed for 18 h with concomitant azeotropic elimination of water and cooled to room temperature. Tetrabutylammonium bromide (0.171g) and benzyl bromide were then added and the reaction mixture heated at 60 °C for 7 h before concentration. Flash chromatography of the residue (hexane-ethyl acetate, 35:65, v/v) afforded pure **19** (0.386 g, 71%); mp 150-152 °C (EtOH), $[\alpha]_D^{20}$ -33° *(c* 1, $CHCl_3$); IR (KBr) ν 3065, 2977, 2874, 1723, 1601, 1594, 1491, 1451, 1368, 1267, 1176, 1107, 1027, 979, 939, 881, 854, 831, 803 and 708 cm^{-1}; ^{1}H NMR δ 7.40-7.28 (m, 10H, aromatics), 7.22 (d, 2H, J=8.5, *p*-methoxyphenyl), 6.85 (d, 2H, J=8.5, *p*-methoxyphenyl), 5.40 (d, 1H, $J_{NH,2}$=7.5, NHAc), 4.87 (d, 1H, $J_{1,2}$=8.0, H-1), 4.84-4.44 (m, 6H, J=11.5, 2×OCH$_2$Ph, OCH$_2$PhOMe), 3.97 (dd, 1H, $J_{3,2}$=10.0, $J_{3,4}$=8.5, H-3), 3.82-3.74 (m, 5H, $J_{6,5}$=$J_{6',5}$=5.0, OCH$_3$, H-6', H-6), 3.67 (ddd, 1H, $J_{4,5}$=9.0, $J_{4,OH}$=2.5, H-4), 3.52 (m, 1H, H-5), 3.35 (ddd, 1H, H-2), 2.72 (d, 1H, OH), 1.86 (s, 3H, NHCOCH$_3$); ^{13}C NMR δ 170.36 (C=O), 159.34 (PhOCH$_3$), 138.54-127.75 (aromatics), 129.71 (PhOCH$_3$), 129.44 and 113.78 (PhOCH$_3$), 98.85 (C-1), 80.38, 73.68, 73.28 and 56.91 (C-2, C-3, C-4 and C-5), 74.18, 73.59, 70.59 and 70.48 (OCH$_2$Ph, C-6, OCH$_2$PhOMe), 55.24 (OCH$_3$), 23.59 (COCH$_3$).

Anal. Calcd for $C_{30}H_{35}NO_7$ (521.62): C, 69.08; H, 6.76; O, 21.47; N, 2.69. Found: C, 69.01; H, 6.95; O, 21.41; N, 2.81.

***p*-Methoxyphenylmethyl 2-Acetamido-6-*O*-benzyl-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-β-D-glucopyranoside (23).** Sodium cyanoborohydride (0.662 g) and 4Å molecular sieves (3.0 g) were added to a solution of **22** (0.992 g) in anhydrous THF (12 mL) and the resulting reaction mixture cooled to 0 °C. A saturated ethereal solution of hydrochloric acid was then slowly added in order to maintain the pH at 1. After 3.5 h the reaction mixture was diluted with dichloromethane, filtered and poured in a stirred aqueous solution of potassium hydrogencarbonate. The organic layer was separated and the aqueous phase extracted with dichloromethane (2×40 mL). The combined organic phases were washed with water (2×100 mL), dried (magnesium sulfate) and concentrated. The residual solid was chromatographed (toluene-ethyl acetate, 85:15, v/v) to afford pure **23** (0.743 g, 75%); mp 179 °C (EtOH), $[\alpha]_D^{20}$ -77° *(c*

1, CH_2Cl_2); IR (KBr) ν 3374, 3303, 2870, 1652, 1613, 1548, 1514, 1497, 1453, 1367, 1306, 1248, 1208, 1071, 1024, 937, 821 and 734 cm^{-1}; ^1H NMR δ 7.43-7.26 (m, 20H, aromatics), 7.23 and 6.85 (2×d, 2×2H, J=8.5, *p*-methoxyphenyl), 5.40 (d, 1H, $J_{NH,2}$=7.5, NHAc), 5.00-4.92 (m, 2H, J=11.0, OC$\underline{H}_2$Ph, H-1'), 4.88-4.70 (m, 5H, OC$\underline{H}_2$Ph, H-1, OC$\underline{H}_2$PhOMe), 4.70-4.58 (m, 4H, OC$\underline{H}_2$Ph), 4.53 (d, 1H, J=11.5, OC$\underline{H}_2$PhOMe), 4.17 (1H, OH), 4.07 (m, 2H, $J_{2',1'}$=3.5, $J_{2',3'}$=10.0, H-2', H-5'), 3.93 (dd, 1H, $J_{3',4'}$=2.5, H-3'), 3.89-3.72 (m, 3H, H-3, H-6a, H-6b), 3.79 (s, 3H, OCH_3), 3.68 (m, 1H, H-4'), 3.53-3.35 (m, 3H, H-2, H-4, H-5), 1.55 (s, 3H, NHCOC$\underline{H}_3$), 1.13 (d, 3H, $J_{CH3,5'}$=6.5, CH_3); ^{13}C NMR δ 170.65 (C=O), 159.22 (P$\underline{h}$OMe), 138.39-127.43 (aromatics), 113.69 (P$\underline{h}$OMe), 99.14 and 98.99 (C-1 and C-1'), 84.06, 79.00, 77.14, 75.96, 74.93, 70.40, 68.01 and 55.83 (C-2, C-3, C-4, C-5, C-2', C-3', C-4' and C-5'), 75.12, 73.98, 73.44, 72.83, 69.52 and 66.21 (O$\underline{C}H_2$Ph, C-6, O$\underline{C}H_2$PhOMe), 55.23 (OCH_3), 23.11 (CO$\underline{C}H_3$), 16.64 (CH_3).

Anal. Calcd for $C_{50}H_{57}NO_{11}$ (848.01): C, 70.82; H, 6.78; N, 1.65; O, 20.75. Found: C, 69.87; H, 6.69; N, 1.67; O, 21.33.

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