Chemistry of Natural Compounds and Bioorganic Chemistry

Linear dependence of the glycosylation stereoselectivity of *O*-trityl ethers by carbohydrate 1,2-*O*-cyanoalkylidene derivatives on anion concentrations. Effect of substituents in the glycosyl acceptor and a new mechanism of 1,2-*cis*-glycosides formation

P. I. Kitov, Yu. E. Tsvetkov, L. V. Backinowsky, and N. K. Kochetkov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

The dependence of the stereochemical outcome of trityl-cyanoalkylidene condensation (α/β-ratio of disaccharides) on the concentration of a catalyst ($TrClO_4$) was studied. The dependence was shown to be linear over a wide range of concentrations of the catalyst. The mechanism of the reaction and the effect of the nature of protective groups in the glycosyl acceptor on the stereochemistry of glycosylation are discussed. A new mechanism of 1,2-*cis*-glycosides formation is proposed.

Key words: trityl-cyanoalkylidene condensation, mechanism of glycosylation.

The present work is a continuation of studies on the mechanism of the trityl-cyanoethylidene condensation,[1] *i.e.*, the glycosylation of *O*-trityl ethers with 1,2-*O*-cyanoalkylidene derivatives of saccharides in the presence of triphenylmethylium salts (Scheme 1).

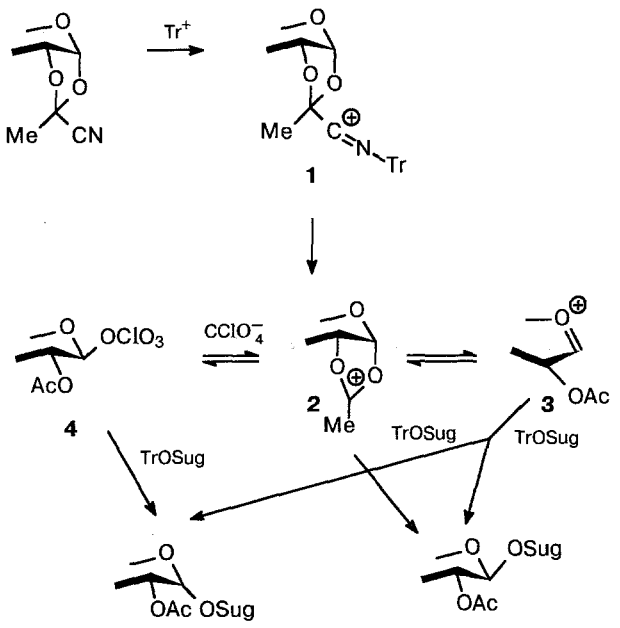
As has been shown previously on the basis of the kinetics of the process,[2,3] the reaction of cyanoalkylidene derivative with the triphenylmethylium cation is the rate-determining stage affording nitrilium complex **1** (Scheme 1), which apparently is not glycosylated directly, but is dissociated to form 1,3-dioxolenium ion **2**. Glycosylation of the trityl ether with bicyclic ion **2** gives the target 1,2-*trans*-glycoside; hence in most cases the reaction proceeds with a high stereoselectivity. However, in some cases the stereospecificity of the reaction is violated, since both 1,2-*trans*- and 1,2-*cis*-glycosides are formed. This phenomenon indicates that ion **2** is not the only intermediate in the reaction.

As a rule, the formation of the 1,2-*cis*-isomers in such glycosylation reactions, where the glycosyl-donors with the participating group at C(2) are used, is explained by the presence of glycosyl-cation **3** in the

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1158—1163, June, 1995.

1066-5285/95/4406-1119 $12.50

Scheme 1



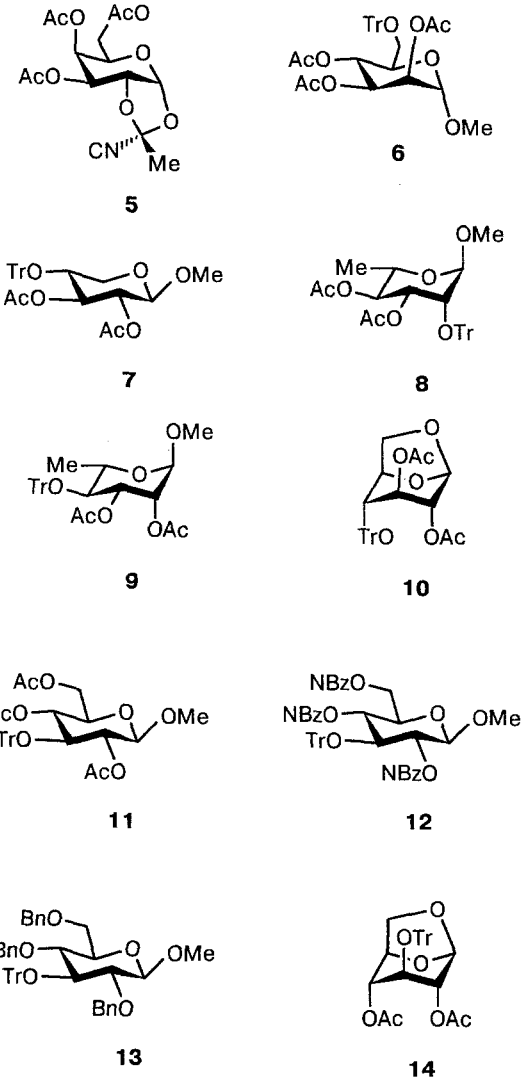
reaction mixture; **3** is in an equilibrium with 1,3-dioxolenium ion **2**, while the attack the oxygen atom of the glycosyl acceptor on the planar glycosyl cation should proceed non-stereoselectively.

On the other hand, the effect of the concentration of ClO_4^- (see Ref. 4) and also the nature of the anion of the trityl salt[4,5] on the stereochemistry of the trityl-cyanoethylidene condensation were found. On the basis of these observations, the hypothesis on the intermediate formation of glycosyl perchlorate **4** as the precursor of 1,2-*cis*-glycosides was proposed.

In the present work, quantitative aspects of the concentration effects of ClO_4^- on the stereochemistry of trityl-cyanoethylidene condensation are investigated using the example of the cyanoethylidene derivative (CED) of D-galactopyranose **5** (see Ref. 6), because the violation of stereospecificity of the reaction in this case is most prominent.[5]

Some secondary trityl ethers, **7**, **8**, **9**, **10**, **11** (see Ref. 4, 7—9, respectively), **12**, **13**, and **14** and one primary ether **6** (see Ref. 10), (for the latter we also revealed the violation of glycosylation stereospecificity)[3] were used as glycosyl-acceptors.

The glycosylation reactions were carried out under standard conditions CH_2Cl_2, the initial ratio [CED]/[TrOSug]=1:1.05, the concentration of the catalyst ($TrClO_4$) was varied in the 1—10 mg mL^{-1} range, (6—60 mol.% *vs.* CED **5**. The solubility of $TrClO_4$ in the reaction mixture is *ca.* 12 mg mL^{-1}). Since the triphenylmethylium cation is not involved in the glycosylation stage,[2] and its concentration cannot influence on the stereochemical composition of the final products, the concentration of $TrClO_4$ affects the stereochemistry of the reaction only due to the ClO_4^- ion. The concentration of ClO_4^- may be also varied by the addition of the corresponding tetraalkylammonium salt (as it was made in the work previously published[4]). However, it was shown recently that the "neutral" cation NR_4^+ was capable of changing the energy of the glycosyl-donor due to coordination with the leaving group,[11,12] hence in this work the required concentration of ClO_4^- was achieved using $TrClO_4$ to exclude an unpredictable effect of the quaternary ammonium cation.



The mixtures of α- and β-disaccharides obtained as a result of glycosylation were analyzed by GLC (in the case of trityl ethers **12** and **13** the GLC analysis was carried out after removal of protective groups and acetylation). The disaccharides synthesized were identified reliably by comparison with authentic samples. New disaccharides **15—18** were isolated and characterized; their structures were confirmed by ^1H NMR spectra. The data on the series of experiments are given in Figs. 1 and 2.

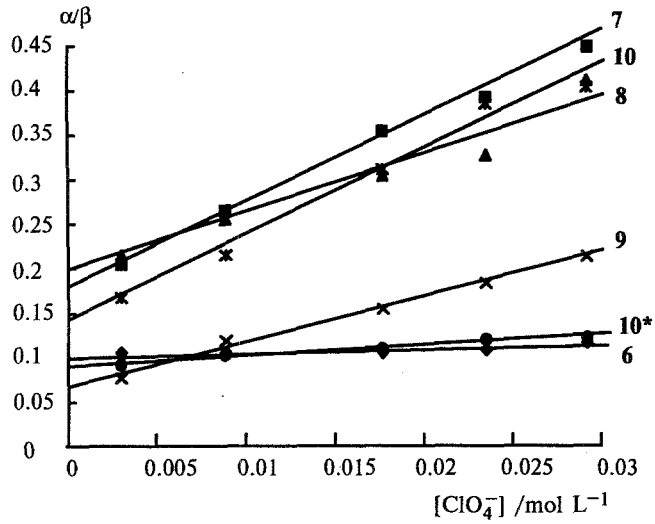


Fig. 1. Concentration dependence of the stereochemical data on the glycosylation of trityl ethers **6**, **7**—**10** (series **10*** is related to the reaction of **10** in the presence of TfO^- as the counterion).

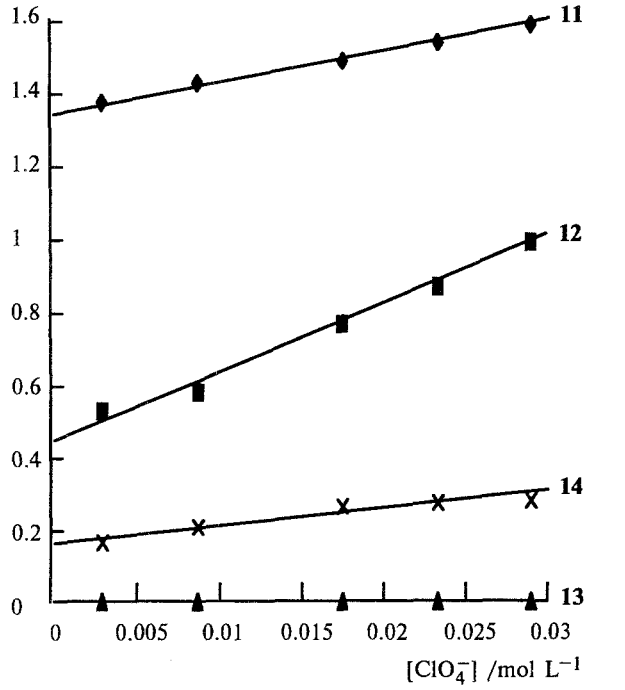
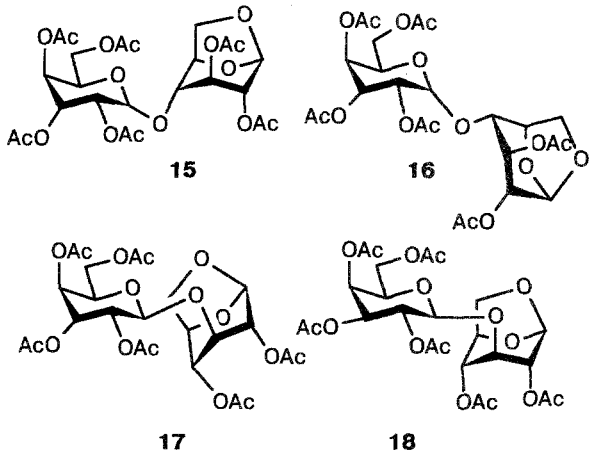


Fig. 2. Concentration dependence of the stereochemical data on the glycosylation of trityl ethers **11**—**14**.

In all cases studied, the dependence of stereoselectivity of the reaction on the concentration of ClO_4^- is linear and it is described by the equation:

$$\alpha/\beta = a[ClO_4^-] + b,$$



The dependence is in accordance with the reaction mechanism presented in Scheme 1; the mechanism implies the participation of glycosyl-perchlorates **4** in the formation of 1,2-*cis*-glycosides. The values of coefficients (*a*) and (*b*) are given in Table 1. The parameter (*a*) means the sensitivity of the α/β ratio to the change of the concentration of the ClO_4^- anion. It is evidently that the value of (*a*) for the given pair CED—trityl ether should change by variation of the nucleophilicity of the anion, because the equilibrium between dioxolenium ion **2** and product of **4** type resulting from anion **2** through nucleophilic opening must be shifted. For example, when replacing ClO_4^- by the significantly less nucleophilic trifluoromethanesulfonate anion (TfO^-),[13] the equilibrium between cation **2** and glycosyl-triflate shifts to the first one in comparison with the equilibrium cation **2** ⇌ glycosyl-perchlorate **4** that it should decrease in the (*a*) parameter.

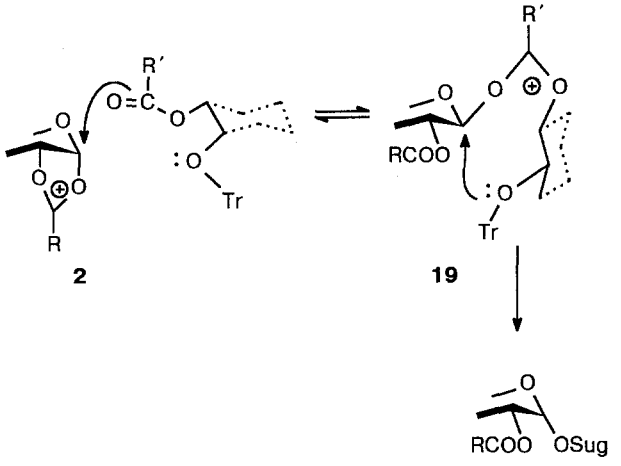
In this context, we studied the dependence of the stereoselectivity of glycosylation on the concentration of TfO^- for trityl ether **10**. AgOTf was used as the initiator of the reaction, assuming that the Ag^+ cation initiates the reaction; after some time, as a result of glycosylation, the triphenylmethylium cation was formed; the latter carried the reaction forward,[14] and, simultaneously, the triflate anion was a counterion for all positively charged species. In fact, replacing ClO_4^- by the less nucleophilic TfO^- decreases the (*a*) parameter more than 7 times.

The important peculiarity of the obtained dependences is that the α/β ratio does not tend to be zero, *i.e.*, the reaction does not become stereospecific by extrapolation to the zero concentration of the anion (trityl ether **13**, for which the reaction is stereospecific in whole range of concentrations, is the only exception). This means that glycosyl perchlorate **4** is not the only intermediate affording 1,2-*cis*-glycosides. The (*b*) coefficient characterizes quantitatively the part of 1,2-*cis*-glycosides, which are formed without participation of glycosyl perchlorates **4**.

The glycosyl cation is customarily assumed to be a precursor of 1,2-*cis*-glycosides (for example, see Refs. 1,

5, 15). We propose the alternative pathway to the formation of 1,2-*cis*-glycosides involving intermolecular dioxacarbenium ion **19**. The latter may be formed by the interaction of cation **2** with the carbonyl oxygen of the acyl group located in the vicinal position to the trityl group of the glycosyl acceptor (Scheme 2). The subsequent intramolecular glycosylation of **19** must afford 1,2-*cis*-glycoside due to the fixed 1,2-*trans*-configuration of the latter. The formation of glycosyl acetates in specific cases as side products of trityl-cyanoethylidene condensation[16] attests to the possibility of intermolecular nucleophilic interaction of acyl groups as demonstrated in Scheme 2.

Scheme 2

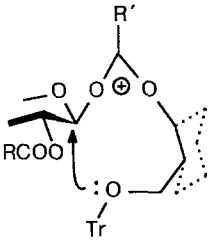


The data on trityl ethers **11**—**14**, which differ only in the nature of protecting groups around the trityloxy group or the conformation of the pyranose ring confirm the proposed mechanism assuming the participation of the acyl substituents. Thus, the replacement of the acetyl protecting group by the significantly less participating *p*-nitrobenzoyl groups is likely to decrease the probability of the formation of the intermolecular ion of **19** type thus decreasing the portion of 1,2-*cis*-glycoside formed by the proposed mechanism. In fact, for *p*-nitrobenzoylated trityl ether **12**, the (*b*) coefficient is three times smaller than that for its acetylated analog **11**. On going to totally benzylated derivative **13**, the absence of participating neighboring groups leads to decrease in the (*b*) coefficient to zero (see Table 1). The effect of the neighboring benzyl group on the stereoselectivity of the glycosylation of trityl ethers was found previously.[17] The result of the preparative glycosylation of **13** is illustrative for the synthetic possibilities of benzylated trityl ethers; it gives stereospecifically the corresponding disaccharide, *i.e.*, methyl-2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside in 82 % yield.

The examination of molecular models shows that the formation of the nonstrained seven-membered cyclic transition state giving intramolecular glycosylation of dioxacarbenium ion **19** is possible only when the dihedral angle between the acyloxy and trityloxy groups is *ca.* 60°, *i.e.*, when these groups are in *trans*-diequatorial or *cis*-configuration. In the case of *trans*-diaxial configuration, as in trityl ether **14**, the formation of the nonstrained transition state is impossible; thus the probability of the realization of this mechanism decreases strikingly. It is manifested by a *ca.* 10-fold decrease in the (*b*) coefficient in comparison with the conformationally flexible diequatorial "analog" **11** (see Table 1).

It should be noted that the similar increase in 1,2-*trans*-stereoselectivity of the Koenigs—Knorr reaction observed by change in the conformation of glycosyl acceptors has been previously described[18,19] as an effect of the double stereodifferentiation. However, in some described cases[18,19] the glycosyl-acceptor contain the neighboring functional groups capable of participation, therefore the proposed mechanism of the intramolecular glycosylation of intermolecular dioxacarbenium ion can also serve as the additional factor affecting the formation of 1,2-*cis*-glycosides.

The relatively unfavorable (due to the entropy factor) formation of eight-membered transition state of **20** type, which is necessary for the intramolecular glycosylation, in comparison with seven-membered transition state in the case of the secondary glycosyl-acceptors, may be one of the reasons of high 1,2-*trans*-stereoselectivity of the glycosylation of primary glycosyl-acceptors[1] (both alcohols and trityl ethers).



20

Table 1. Coefficients (L mol^{-1}) for the linear dependence of the stereochemical outcome of the glycosylation of trityl ethers **6**—**14** with galactose cyanoethylidene derivative **5** on the concentration of $TrClO_4$ and those for trityl ether **10** on the concentration of AgOTf

Trityl ether	*a*	*b*
6	0.34	0.103
7	9.2	0.18
8	5.7	0.2
9	4.8	0.068
10	9.6	0.14
10 (AgOTf)	1.3	0.087
11	15.6	1.32
12	16.2	0.42
13	0	0
14	14.7	0.13

Experimental

Triphenylmethylium perchlorate was prepared using the known procedure[20] and purified additionally as it was previously reported.[21] Silver trifluoromethanesulfonate was prepared using the described method.[22] The preparation of solvents and reagents for the reaction was carried out using high-vacuum procedures.[21] The reaction was carried out at 25 °C. The GLC analysis was performed with a Hewlett-Packard 5890 chromatograph equipped with a flame-ionization detector and an Ultra-1 column. The NMR spectra were recorded with a Bruker WM-250 instrument in $CDCl_3$. The specific rotations were measured with a Jasco DIP-360 polarimeter for solutions in chloroform. The column chromatography (CC) was carried out on Silpearl silica gel (Czechoslovakia).

1,6-Anhydro-2,3-di-*O*-acetyl-4-*O*-trityl-β-D-glucopyranose (10). 2,4,6-Collidine (1 mL) was added to a solution of 1,6-anhydro-2,3-di-*O*-acetyl-β-D-glucopyranose[23] (610 mg, 2.48 mmol) in CH_2Cl_2 (4 mL), and then $TrClO_4$ was added portionwise to produce a stable yellow coloration. After 0.5 h, MeOH (1 mL) was added, and the mixture was diluted with chloroform (30 mL), washed with aqueous $NaHCO_3$, concentrated, and dried *in vacuo*. After CC (benzene—ether), the yield was 1.03 g (85 %); m.p. 240—241 °C, $[\alpha]_D$ −5.2° (c 1.4). ^1H NMR, δ: 5.40 (br.t, 1 H, H(1)); 4.68 (m, 7 lines, 1 H, H(3)); 4.50 (br.t, 1 H, H(2)); 3.84 (d.q, 1 H, H(5)); 3.66 (d.d, 1 H, H(6a), $J_{5,6}$ = 6 Hz, $J_{6a,6b}$ = 8 Hz); 3.56 (br.t, 1 H, H(4)); 3.42 (d.d, 1 H, H(6b), $J_{5,6b}$ = 6 Hz); 2.24, 1.96 (2s, 6 H, $OCOCH_3$).

Methyl 2,4,6-tri-*O*-(4-nitrobenzoyl)-3-*O*-trityl-β-D-glucopyranoside (12). A solution of MeONa (1 mL) was added to trityl ether **11** (1.27 g, 2.26 mmol) in MeOH (10 mL). After 3 days pyridine was added, then KU-2(H^+) cation exchanger was added, the solvent was removed, the residue was dissolved in pyridine (3 mL), and 4-nitrobenzoyl chloride (2 mL) was added. After 16 h, the excess reagent was decomposed with MeOH, the solution was evaporated, and the residue was evaporated several times with heptane. After CC (benzene—ether), the yield was 1.24 g, (81 %), foam, $[\alpha]_D$ +20.3° (c 0.4). ^1H NMR, δ: 5.73 (t, 1 H, H(4), $J_{3,4} = J_{4,5}$ = 9 Hz); 5.52 (d.d, 1 H, H(2), $J_{1,2}$ = 7 Hz, $J_{2,3}$ = 9 Hz); 4.56 (d.d, 1 H, H(6a), $J_{5,6a}$ = 3, $J_{6a,6b}$ = 12.5 Hz); 4.37 (d.d, 1 H, H(6b), $J_{5,6b}$ = 5 Hz); 4.34 (d, 1 H, H(1)); 3.95 (t, 1 H, H(3)); 3.75 (d.d.d, 1 H, H(5)); 3.45 (s, 3 H, OMe).

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-trityl-β-D-glucopyranoside (13). A mixture of methyl 3-*O*-trityl-β-D-glucopyranoside (150 mg, 0.34 mmol), prepared analogously to **12**, and 80 % NaH (50 mg) in DMF (4 mL) was stirred for 0.5 h; then BnBr (0.2 mL) was added. After 3 h, MeOH was added, the mixture was diluted with ethyl acetate (50 mL) and washed with water. After CC (hexane—ethyl acetate), the yield was 141 mg (76 %), $[\alpha]_D$ −9.9° (c 0.6). ^1H NMR, δ: 4.59 (s, 2 H, OCH_2Ph); 4.56 (d, 1 H, OCH_2Ph, J_{hem} = 12.5 Hz); 4.45 (d, 1 H, OCH_2Ph, J_{hem} = 11 Hz); 4.25 (d, 1 H, H(1), $J_{1,2}$ = 6.5 Hz); 4.22 (d, 1 H, OCH_2Ph, J_{hem} = 12.5 Hz); 3.99 (d, 1 H, OCH_2Ph, J_{hem} = 11 Hz); 3.78—3.59 (m, 4 H, H(2), H(3), H(4), H(5)); 3.55—3.45 (m, 2 H, H(6a), H(6b)); 3.31 (s, 3H, OMe).

1,6-Anhydro-2,4-di-*O*-acetyl-3-*O*-trityl-β-D-glucopyranose (14). 2,4,6-Collidine (0.5 mL) was added to a solution of 1,6-anhydro-2,4-di-*O*-benzoyl-β-D-glucopyranose[24] (390 mg, 1.05 mmol) in CH_2Cl_2 (4 mL), and then $TrClO_4$. (0.7 g) was added portionwise. After 1 h, MeOH (1 mL) was added, the mixture was diluted with chloroform (30 mL), washed with aqueous $NaHCO_3$, and the solution was concentrated and dried *in vacuo*. The residue was dissolved in MeOH (4 mL), and a solution of MeONa (1 mL) was added. After 4 h, AcOH (0.5 mL) was added and a solution was concentrated. The residue was dried, and pyridine (5 mL) and Ac_2O (5 mL) were added. After 1 h, the mixture was treated with MeOH at 50 °C, the solution was evaporated, and the residue was evaporated several times with heptane. After CC (benzene—ether), the yield was 410 mg, (80 %), m.p. 201—202 °C, $[\alpha]_D$ −20.5° (c 0.7). ^1H NMR, δ: 5.43 (br.t, 1 H, H(1)); 4.63 (br.d, 1 H, H(2)); 4.52 (br.d, 1 H, H(5)); 4.36 (d.d, 1 H, H(6a), $J_{5,6a}$ = 1 Hz, $J_{6a,6b}$ = 7.5 Hz); 4.00 (br.s, 1 H, H(4)); 3.81(d.d, 1 H, H(6b)), $J_{5,6b}$ = 6 Hz), 3.77 (m, 5 lines, 1 H, H(3)); 2.02, 2.00 (2s, 6 H, $OCOCH_3$).

The measurement of the dependence of the stereochemical outcome of glycosylation on the concentration of a counterion. $TrClO_4$ was dissolved in CH_2Cl_2 and aliquots containing 1, 3, 6, 8 and 10 mg (0.003, 0.009, 0.018, 0.023 and 0.029 mmol, respectively) of $TrClO_4$ were taken. The solvent was removed *in vacuo*, reaction vessels were evacuated and filled with dry argon. A mixture of cyanoethylidene derivative of galactose **5** (0.05 mmol) and the trityl ether studied (0.051 mmol) was dissolved in CH_2Cl_2 (5 mL) and the solution of reagents (1 mL) were placed into each catalyst-containing reaction vessel by a syringe under dry argon. The vessels were sealed and kept at 20 °C for 3 to 16 h depending on the concentration of the catalyst. Then chloroform containing 1 % of pyridine (30 mL) was added to the mixtures to decompose the catalyst, the solutions were washed with water, evaporated, dissolved in chloroform (0.5 mL) and analyzed by GLC. In the case of reactions with trityl ethers **12** and **13**, the products were analyzed after preliminary removal of protecting groups (deacylation of **12** and hydrogenolysis of **13**) and subsequent acetylation.

The properties of the newly synthesized disaccharide derivatives are given below.

1,6-Anhydro-2,3-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranose (15), m.p. 207—208 °C (ethyl acetate—hexane), $[\alpha]_D$ −74.1° (c 2.57). ^1H NMR, δ: 5.41 (br.t, 1 H, H(2)); 5.34 (br.d, 1 H, H(4′), $J_{3',4'}$ = 3.5 Hz); 5.23 (d.d, 1 H, H(2′), $J_{1',2'}$ = 8, $J_{2',3'}$ = 10.5 Hz); 5.11 (br.m, 5 lines, 1 H, H(3)); 5.00 (d.d, 1 H, H(3′)); 4.77 (d, 1 H, H(1′)); 4.56 (m, 1 H, H(5)); 4.50 (br.d, 1 H, H(1)); 4.12 (d.d, 1 H, H(6′a), $J_{5',6'a}$ = 5.5 Hz, $J_{6'a,6'b}$ = 10 Hz); 4.06 (m, 1 H, H(5′)); 4.00 (d.d, 1 H, H(6′b), $J_{5',6'b}$ = 6 Hz), 3.95 (d.d, 1 H, H(6a)); 3.77 (d.d, 1 H, H (6b), $J_{5,6b}$ = 6, $J_{6a,6b}$ = 8 Hz); 3.53 (m, 1 H, H(4)); 2.11×2, 2.09, 2.03, 2.00, 1.95 (5s, 18 H, $OCOCH_3$).

1,6-Anhydro-2,3-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-β-D-glucopyranose (16), $[\alpha]_D$ +35.5° (c 1.03). ^1H NMR, δ: 5.50 (d.d, 1 H, H(4′), $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 1.5 Hz); 5.46 (m, 1 H, H(2)); 5.42 (d.d, 1 H, H(3′), $J_{2',3'}$ = 10.5 Hz, $J_{3',4'}$ = 3.5 Hz); 5.34 (d, 1 H, H(1)′, $J_{1',2'}$ = 3.5 Hz); 5.10 (d.d, 1 H, H(2′)); 4.79 (m, 5 lines, 1 H, H(1)); 4.76 (m, 1 H, H(5)); 4.58 (m, 1 H, H(3)); 4.57 (d.d.d, 1 H, H(5′)); 4.17 (d.d, 1 H, H(6′a); $J_{5',6'a}$ = 5.5 Hz, $J_{6'a,6'b}$ = 11 Hz); 4.05 (d.d, 1 H, H(6′b), $J_{5',6'b}$ = 7 Hz); 3.98 (d.d, 1 H, H(6a), $J_{5,6a}$ = 1, $J_{6a,6b}$ = 7.5 Hz); 3.78 (d.d, 1 H, H(6b), $J_{5,6b}$ = 5.5 Hz); 3.46 (br.m, 1 H, H(4)); 2.19, 2.16, 2.12×2, 2.06, 2.02 (5s, 18 H, $OCOCH_3$).

1,6-Anhydro-2,4-di-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranose (17), $[\alpha]_D$ −46.7° (c 0.6). ^1H NMR, δ: 5.43 (br.t, 1 H, H(1)); 5.39 (d.d, 1 H, H(4′), $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 1.5 Hz); 5.19 (d.d, 1 H, H(2′), $J_{1',2'}$ = 7.5 Hz, $J_{2',3'}$ = 10.5 Hz); 5.04 (d.d, 1 H, H(3′)); 4.82 (br.d, 1 H, H(4)); 4.79 (d, 1 H, H(1′)); 4.60 (m, 1 H, H(5));

4.44 (br.d, 1 H, H(2)); 4.18 (d.d, 1 H, H(6'a), $J_{5',6'a}$ = 6.5 Hz, $J_{6'a,6'b}$ = 11 Hz); 4.10 (d.d, 1 H, H(6'b), $J_{5',6'b}$ = 7 Hz); 4.06 (d.d, 1 H, H(6a), $J_{5,6a}$ = 1.5 Hz, $J_{6a,6b}$ = 7.5 Hz); 3.92 (d.d.d, 1 H, H(5')); 3.71 (br.t, 1 H, H(3)); 3.70 (d.d, 1 H, H(6b), $J_{5,6b}$ = 5.5 Hz); 2.16, 2.15×2, 2.09, 2.03, 1.99 (5s, 18 H, $OCOCH_3$).

1,6-Anhydro-2,4-di-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-β-D-glucopyranose (18), $[\alpha]_D$ +116.5° (c 0.46), ^{1}H NMR, δ: 5.49 (d.d, 1 H, H(4'), $J_{3',4'}$ = 3 Hz, $J_{4',5'}$ = 2 Hz), 5.48 (br.t, 1 H, H(1)); 5.38 (d, 1 H, H(1'), $J_{1',2'}$ = 4 Hz), 5.30 (d.d, 1 H, H(3'), $J_{2',3'}$ = 11 Hz); 5.15 (d.d, 1 H, H(2')); 4.78 (br.m, 1 H, H(2)); 4.62–4.56 (m, 2 H, H(4), H(5)); 4.44 (t.d, 1 H, H(5'), $J_{5',6'a}$ = $J_{5',6'b}$ = 7 Hz); 4.19 (d.d, 1 H, H(6'a), $J_{5',6'a}$ = 6.5 Hz, $J_{6'a,6'b}$ =11 Hz); 4.16 (d.d, 1 H, H(6a), $J_{5,6a}$ = 1 Hz); 4.06 (d.d, 1 H, H(6'b)); 3.82 (m, 1 H, H(6b)); 3.69 (m, 5 lines, 1 H, H(3)); 2.16, 2.14, 2.13, 2.09, 2.05, 2.00(6s, 16 H, $OCOCH_3$).

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside, yield from CED **5** and trityl ether **13** in a preparative synthesis was 82 %, $[\alpha]_D$ −5.6° (c 1.38). ^{1}H NMR, δ: 5.36 (d.d, 1 H, H(4'), $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 1 Hz); 5.27 (d.d, 1 H, H(2'); $J_{1',2'}$ = 8 Hz, $J_{2',3'}$ = 10.5 Hz); 5.16 (d, 1 H, H(1')); 5.01 (d, 1 H, OCH_2Ph, J_{hem} = 10 Hz); 4.98 (d.d, 1 H, H(3')); 4.95 (d, 1 H, OCH_2Ph, J_{hem} = 10 Hz); 4.66 (d, 1 H, OCH_2Ph, J_{hem} = 12 Hz); 4.58 (d, 1 H, OCH_2Ph, J_{hem} = 10 Hz); 4.56 (d, 1 H, OCH_2Ph, J_{hem} = 12 Hz); 4.43 (d, 1 H, OCH_2Ph, J_{hem} = 10 Hz); 4.27 (d, 1 H, H(1), $J_{1,2}$ = 8 Hz); 4.16 (d.d, 1 H, H(6a); $J_{5,6a}$ = 8, $J_{6a,6b}$ = 11 Hz), 4.03 (t, 1 H, H(3*), $J_{2,3}$ = $J_{3,4}$ = 9 Hz); 3.98 (d.d, 1 H, H(6b), $J_{5,6b}$= 6 Hz); 3.76 (m 1 H, H(5')); 3.75 (t, 1 H, H(4)*, $J_{3,4}$= $J_{4,5}$ = 9 Hz); 3.70 (d.d, 1 H, H(6'a), $J_{5',6'a}$ = 4.5 Hz, $J_{6'a,6'b}$ = 10 Hz); 3.55 (d.d, 1 H, H(6'b), $J_{5',6'b}$ = 8.5 Hz); 3.60 (s, 3H, OMe); 3.43 (d.d.d, 1 H, H(5)); 3.39 (d.d, 1 H, H(2)); 2.14, 2.13, 2.04, 2.01 (4s, 12 H, $OCOCH_3$).

The present work was partially supported by the Russian Foundation for Basic Research (Project No. 93-03-18196) and the International Science Foundation (Grant MBV 000).

References

1. N. K. Kochetkov, *Tetrahedron*, 1987, **43**, 2389.
2. P. I. Kitov, Yu. E. Tsvetkov, L. V. Backinowsky, and N. K. Kochetkov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1485 [*Russ. Chem. Bull.*, 1993, **42**, 1423 (Engl. Transl.)].
3. P. I. Kitov, Yu. E. Tsvetkov, L. V. Backinowsky, and N. K. Kochetkov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1992 ([*Russ. Chem. Bull.*, 1993, **42**, 1909 (Engl. Transl.)].
4. L. V. Backinowsky, N. E. Nifant'ev, and N. K. Kochetkov, *Bioorg. Khim.*, 1984, **10**, 226 [*Sov. J. Bioorg. Chem.*, 1984, **10** (Engl. Transl.)].
5. N. K. Kochetkov, V. I. Betaneli, and I. A. Kryazhevskikh, *Carbohydr. Res.*, 1993, **244**, 85.
6. V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowsky, and N. K. Kochetkov, *Carbohydr. Res.*, 1979, **68**, C11.
7. L. V. Backinowsky, Yu. E. Tsvetkov, N. F. Balan, N. E. Bayramova, and N. K. Kochetkov, *Carbohydr. Res.*, 1980, **85**, 209.
8. T. Otake, T. Sonobe, and T. Suame, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3109.
9. E. M. Klimov, N. N. Malysheva, A. V. Demchenko, and N. K. Kochetkov, *Dokl. Akad. Nauk*, 1992, **325**, 297 [*Dokl. Chem.*, 1992, **325** (Engl. Transl.)].
10. A.-J. Watters, R. C. Hockett, and C. S. Hudson, *J. Am. Chem. Soc.*, 1939, **61**, 1528.
11. P. J. Garegg, P. Konradsson, and J.-L. Maloisel, *VIIth European Carbohydrate Symposium, Cracow*, 1993, A-080.
12. P. J. Garegg, P. Konradsson, and J.-L. Maloisel, *VIIth European Carbohydrate Symposium, Cracow*, 1993, A-079.
13. N. S. Zefirov, A. S. Koz'min, V. D. Sorokin, and V. V. Zhdankin, *Zh. Org. Khim.*, 1982, **18**, 1768 [*J. Org. Chem. USSR.*, 1982, **18** (Engl. Transl.)].
14. S. A. Nepogod'ev, L. V. Backinowsky, and N. K. Kochetkov, *Bioorg. Khim.*, 1986, **12**, 940 [*Sov. J. Bioorg. Chem.*, 1986, **12** (Engl. Transl.)].
15. H. Paulsen, Angew. *Chem. Int. Ed. Engl.*, 1982, **21**, 155.
16. N. K. Kochetkov, N. N. Malysheva, M. I. Struchkova, and E. M. Klimov, *Bioorg. Khim.*, 1985, **11**, 391 [*Sov. J. Bioorg. Chem.*, 1985, **11** (Engl. Transl.)].
17. N. E. Nifant'ev, L. V. Backinowsky, and N. K. Kochetkov, *Carbohydr. Res.*, 1989, **191**, 13.
18. N. M. Spijker and C. A. A. van Boeckel, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 180.
19. N. M. Spijker, J. E. M. Basten, and C. A. A. van Boeckel, *XVIIth International Carbohydrate Symposium*, Paris, 1992, A201, 236.
20. H. J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, 1960, **25**, 1442.
21. N. K. Kochetkov, V. I. Betaneli, M. V. Ovchinnikov, and L. V. Backinowsky, *Tetrahedron*, 1981, **37**, Suppl. 9, 145.
22. D. G. Russel and J. B. Senior, *Can. J. Chem.*, 1980, **58**, 22.
23. D. Shapiro, Y. Rabinsohn, A. J. Acher, and A. Diver-Haber, *J. Org. Chem.*, 1970, **35**, 1464.
24. M. Cerny, V. Gut, and J. Pacak, *Collect. Czech. Chem. Comm.*, 1961, **26**, 2542.

* The assignments of the signals may be interchanged.

Recieved January 12, 1995