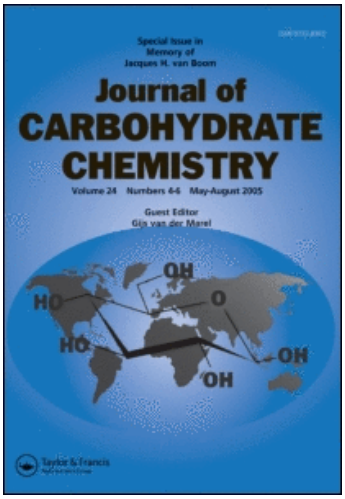


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Influence of the Benzyloxycarbonyl Protective Group on Glycosylation with Mannopyranosyl Donors

Alain Morère[a]; Fouzi Mouffouk[a]; Simon Leiris[a]; Alain Leydet[a]; Jean-Louis Montero[a]
[a] Laboratoire de Chimie Biomoléculaire, UMR CNRS 5032, Université Montpellier II - ENSCM., France

To cite this Article Morère, Alain , Mouffouk, Fouzi , Leiris, Simon , Leydet, Alain and Montero, Jean-Louis(2006) 'Influence of the Benzyloxycarbonyl Protective Group on Glycosylation with Mannopyranosyl Donors', Journal of Carbohydrate Chemistry, 25: 6, 451 — 459
To link to this Article: DOI: 10.1080/07328300600859759
URL: http://dx.doi.org/10.1080/07328300600859759

Journal of Carbohydrate Chemistry, 25:451–459, 2006

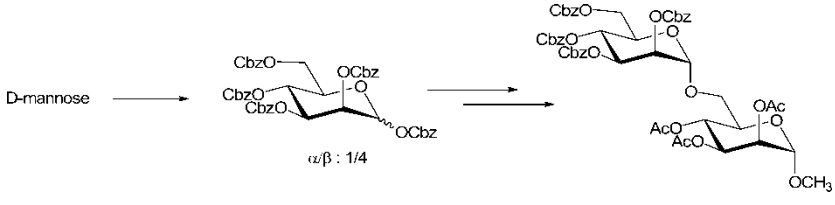
ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300600859759

Influence of the Benzyloxycarbonyl Protective Group on Glycosylation with Mannopyranosyl Donors

Alain Morère, Fouzi Mouffouk, Simon Leiris, Alain Leydet, and Jean-Louis Montero

Laboratoire de Chimie Biomoléculaire, UMR CNRS 5032, Université Montpellier II – ENSCM., France

The perbenzyloxycarbonylation of D-mannose, D-glucose, and D-galactose was achieved in high yield. In the mannose series, the selective removal of the anomeric benzyloxycarbonyl group followed by the activation of the anomeric position furnished, depending on the activation conditions, either a bromo glycosyl donor or a trichloroacetimidate donor. The trichloroacetimidate donor, protected by benzyloxycarbonyl groups, was used successfully for the synthesis of a disaccharide.



Keywords Benzyloxycarbonyl, Protective group, Glycosylation

INTRODUCTION

Sugars fully protected by esters (e.g., Ac, Bz) play a very important role in carbohydrate synthesis. They are commonly used for the preparation of

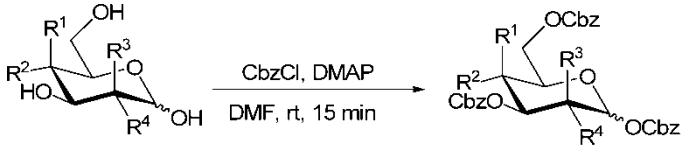
Received December 28, 2005; accepted May 30, 2006.
Address correspondence to Alain Morère, Laboratoire de Chimie Biomoléculaire, UMR CNRS 5032, Université Montpellier II – ENSCM., 8, rue de l'Ecole Normale, 34296, Montpellier cedex 05, France. E-mail: morere@univ-montp2.fr

glycosyl donors employed, for instance, in oligosaccharide synthesis. Peracylated saccharides are easily prepared and because of their importance most of these protected sugars are commercially available. However, neither acetates nor benzoates can be removed under hydrogenolysis conditions. Therefore, we attempted to protect all hydroxyl groups of several D-hexoses by hydrogenolabile benzyl carbonate in order to determine if such perbenzyloxycarbonylated saccharides could be used in saccharidic synthesis.

The benzyloxycarbonyl group (Cbz) has been reported to be useful in carbohydrate synthesis, not only for N-protection of amino sugars,[1] but also to protect alcohols. For instance, a selective monobenzyloxycarbonylation of a primary alcohol was made in the presence of a lipase.[2] On the other hand, the benzyloxycarbonylation at all of the secondary positions on 6-*O*-(4-methoxy)tritylated glycopyranosides was achieved in high yield by use of CbzCl and DMAP.[3,4] Recently, the Cbz group was shown to be an efficient tool for high-yielding regioselective monobenzyloxycarbonylation of secondary alcohols in glycopyranoside series.[5] Moreover, when compared to benzyl ethers, benzyl carbonates are not only removed more readily,[6] but also allow hydroxyl group protection under softer conditions than those employed for benzylation reactions.

RESULTS AND DISCUSSION

Before studying the influence of the Cbz group on glycosylation reaction, we had to prepare perbenzyloxycarbonylated monosaccharides. Unfortunately, methods generally used for peracylation of saccharides[7] were unsuccessfully applied to the perbenzyloxycarbonylation of D-glucose, D-mannose, and D-galactose. Blocking experiments with CbzCl in basic medium favored the formation of cyclic carbonates,[8] and procedure using pyridine as solvent and CbzCl as acylating reagent did not afford the expected perprotected sugars **4–6**, even in the presence of a catalytic amount of DMAP. Therefore, pyridine was replaced by DMF, which is a very good solvent for sugars, and DMAP was used as the base. Under such conditions, the reaction proceeds very smoothly and quickly. Indeed, it was complete within 15 min after addition of CbzCl to the mixture of sugar and DMAP dissolved in DMF. The perbenzyloxycarbonylated monosaccharides **4**, **5**, and **6** were obtained in 90%, 95%, and 90% starting from **1**, **2**, and **3,** respectively. It is worth pointing out that only β-anomers were obtained in the D-gluco (**5**) and D-galactopyranose (**6**) series. More surprisingly, the β-anomer was also mainly obtained in the D-mannopyranose (**4**) series (Sch. 1). The stereochemistry at the anomeric center of the manno perbenzyloxycarbonylated derivative **4** was confirmed by the magnitude of the coupling constant between the anomeric carbon and its directly attached hydrogen. Indeed, in **4α** the $^{1}J_{C1\text{-}H1}$ is 178 Hz while in **4β** the $^{1}J_{C1\text{-}H1}$ is smaller, 163 Hz.



1 : R^1= R^4= H ; R^2= R^3= OH
2 : R^1= R^3= H ; R^2= R^4= OH
3 : R^2= R^3= H ; R^1= R^4= OH

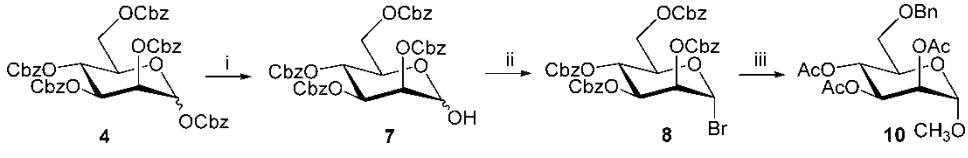
4 : R^2= R^3= OCbz (90%, α/β 1/4)
5 : R^2= R^4= OCbz (95%, β)
6 : R^1= R^4= OCbz (90%, β)

Scheme 1

This anomeric selectivity could be explained by an anomeric *O*-acylation reaction.[9] In this reaction, the anomeric alcoholate reacts on the acylating reactant and the stereochemistry is controlled by the increased nucleophilicity of the equatorial oxygen atom. Therefore, the kinetic control of the anomery favors the formation of β-anomers.

In order to determine the influence of the benzyloxycarbonyl protective group on the glycosylation reaction, we had to first selectively deprotect then activate the anomeric position of a perbenzyloxycarbonylated monosaccharide. For this study, we chose the mannose series because of the interest we have in the synthesis of analogs of the mannose 6-phosphate recognition marker and to their binding affinity for the mannose 6-phosphate/insulin-like growth factor II receptor (M6P/IGF2R).[10] We have to emphasize that the benzyl carbonate can be removed either by hydrogenolysis or under aminolysis conditions, as we demonstrated it recently.[6] Therefore, starting from the α,β-anomeric mixture of the perbenzyloxycarbonylated mannopyranose **4**, the anomeric benzyloxycarbonyl group was selectively removed by using hydrazinium acetate.[11] Generally, the solvent used in this reaction is DMF. In our case, the best results were obtained by using acetonitrile to give the tetrabenzyloxycarbonylated mannopyranose **7** in 90% yield (Sch. 2).

The next step consisted of an activation of the hemiacetal into a stable glycosyl donor. Among the numerous glycosylation procedures described in the literature, we focused on the Koenigs-Knorr reaction[12] and on the



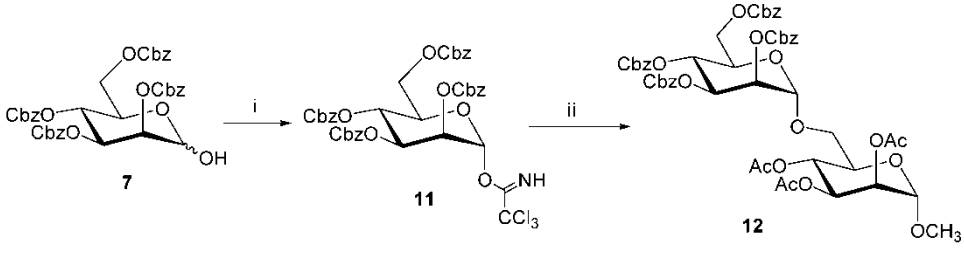
Reagents and conditions. i : NH_2-NH_2.AcOH, CH_3CN, reflux, 1 h, 90%. ii : $BiBr_3$, Me_3SiBr, CH_2Cl_2, 20° C, 1 h, 80%. iii : methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside **9**, AgOTf, collidine, CH_2Cl_2, -45 °C then rt, 3 h, 60%.

Scheme 2

trichloroacetimidate method.[13] The activation step during the Koenigs-Knorr method is the replacement of the anomeric hydroxyl group by a bromine atom. The bromine was introduced at the anomeric position of **7** according to the soft $BiBr_3/Me_3SiBr$ procedure.[14] The glycosyl donor **8**, obtained in 80% yield, was directly used after purification by flash chromatography. Following the same $BiBr_3/Me_3SiBr$ procedure, an attempt of direct incorporation of the bromine at the anomeric position of the perbenzyloxycarbonylated mannopyranose **4** failed to give compound **8**. The glycosylation reaction was promoted by addition of silver triflate[15] into a mixture of the glycosyl donor **8** and methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside **9** as the acceptor. However, the formation of the expected disaccharide was not observed even at low temperature. Under these conditions, the methyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-α-D-mannopyranoside **10** was the only isolated product (60%). This is a consequence of the participating feature of the Cbz group. Indeed, during the Koenigs-Knorr reaction the oxycarbenium intermediate is stabilized by the Cbz group at position 2 and the positive charge is partially delocalized on the carbonyl of this Cbz group. We suppose that this delocalization leads to the cleavage of the C-O bond of the benzyloxy group and that the benzylium intermediate thus generated is trapped by the glycosyl acceptor, leading in this way to the benzyl ether derivative **10**. Moreover, the formation of **10** was accompanied by the liberation, from the mannosyl donor **8**, of the 1,2-cyclic carbonate, which was only detected, among other byproducts, by FABMS analysis of the crude reaction mixture.

The trichloroacetimidate method, which is certainly one of the most applicable procedures for glycoside bond formation, was also studied. The glycosyl donor **11** was prepared in 95% yield by reaction of **7** with trichloroacetonitrile in the presence of NaH (Sch. 3). TMSOTf-promoted glycosylation of **11** and **9** gave disaccharide **12** in 65% yield.

In conclusion, we have shown that the benzyloxycarbonyl protective group can be used for the peracylation of D-hexoses. We have also demonstrated that an anomeric benzyl carbonate can be selectively removed by using



Reagents and conditions. i : NaH, CCl_3CN, CH_2Cl_2, 20 °C, 1 h, 95%. ii : methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside **9**, TMSOTf, CH_2Cl_2, -70 °C then rt, 1 h, 65%.

Scheme 3

hydrazinium acetate and that the resulting hemiacetal can be activated as a glycosyl bromide or as a trichloroacetimidate donor. The later activation allowed the formation of a disaccharide in 65% yield, showing that a glycosyl donor containing benzyl carbonates can be used successfully in disaccharide synthesis. Based on the trichloroacetimidate method, work is under progress to study (1) the outcome of the glycosylation when involving a secondary hydroxyl group of a protected acceptor and (2) the coupling stereoselectivity when gluco- or galacto-perbenzyloxycarbonylated derivatives are used as glycosyl donors.

EXPERIMENTAL

General Experimental

Analytical TLC was performed using aluminum-coated TLC plates 60-F_{254} (Merck). Plates were developed with (1) UV light (254 nm) and (2) immersion in a 10% H_2SO_4/EtOH solution followed by charring. Silica gel column chromatography was performed with silica gel 60A (Carlo Erba). Optical rotations were measured at the sodium D-line with a Perkin-Elmer-241 polarimeter. Fast atom bombardment (FAB) mass spectra were recorded on a Jeol JMS-DX300 spectrometer in positive (FAB+) mode and using either 3-nitrobenzylic alcohol (NBA) or glycerol/thioglycerol (1:1) mixture (G/T). ^{1}H NMR spectra were recorded on a Brüker DRX 400 (400 MHz) at 25°C. Chemical shifts (δ) are given in ppm and referenced using residual solvent signal (7.24 ppm for $CHCl_3$). The following abbreviations were used to explain the signal multiplicities or characteristics: s (singlet), d (doublet), dd (double doublet), ddd (double double doublet), t (triplet), dt (double triplet), and m (multiplet). ^{13}C NMR spectra were recorded on an Avance Brüker 400 (100.6 MHz). Chemical shifts (δ) are reported in ppm and referenced to $CDCl_3$ (77.0 ppm).

General procedure for the perbenzyloxycarbonylation. To a solution of D-hexose (1 g; 5.5 mmol) in DMF (30 mL), the DMAP (8.13 g; 66 mmol) was added. After 10 min under stirring, the CbzCl (9.5 mL, 66 mmol) was added dropwise at rt. After addition, the reaction mixture was stirred at rt for 15 min, then diluted by Et_2O, and salts were removed by filtration. The filtrate was washed twice with water, dried (Na_2SO_4), and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane-EtOAc, 7:3).

1,2,3,4,6-Penta-*O*-benzyloxycarbonyl-α-D-mannopyranose (**4**). Following the general procedure, the anomers of **4** (4.24 g, 90%; α/β 1:4) were obtained as white powders and were separated during the chromatography.

4α: $[\alpha]_D = +22^\circ$ (*c* 1, $CHCl_3$). Rf = 0.58 (CH_2Cl_2: hexane, 8:2). ^{1}H NMR ($CDCl_3$) δ 4.15 (ddd, 1H, $J_{5,4} = 7.2$ Hz, $J_{5,6a} = 5.2$ Hz, $J_{5,6b} = 3.0$ Hz, H-5), 4.28 (dd, 1H, $J_{6a,6b} = 11.9$ Hz, H-6a), 4.39 (dd, 1H, H-6b), 4.79–5.60 (m, 13H, H-2, H-3, H-4, 5PhCH_2), 6.13 (d, 1H, $J_{1,2} = 1.8$ Hz, H-1), 7.33–7.41 (m, 25H, 5 C_6H_5). ^{13}C NMR ($CDCl_3$) δ = 154.7, 154.1, 154.0, 153.9, 152.4, 135.0, 134.8, 134.7, 134.5, 134.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 93.5, 72.3, 71.4, 70.7, 70.6, 70.4, 70.3, 70.0, 69.6, 65.8. FABMS (m/z): 873 $(M + Na)^+$, 851 $(M + H)^+$.

4β: $[\alpha]_D = -11^\circ$ (*c* 1, $CHCl_3$). Rf = 0.43 (CH_2Cl_2: hexane, 8 : 2). ^{1}H NMR ($CDCl_3$) δ 3.94 (dt, 1H, $J_{5,4} = 9.5$ Hz, $J_{5,6a} = J_{5,6b} = 4.9$ Hz, H-5), 4.38–4.46 (m, 2H, H-6a, H-6b), 5.06–5.37 (m, 12H, H-3, H-4, 5 Ph-CH_2), 5.57 (dd, 1H, $J_{2,1} = 1.1$ Hz, $J_{2,3} = 3.1$ Hz, H-2), 5.83 (d, 1H, H-1), 7.27–7.40 (m, 25H, 5C_6H_5). ^{13}C NMR ($CDCl_3$) δ = 154.6, 153.9, 153.8, 152.9, 135.0, 134.7, 134.6, 134.4, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 93.0, 74.1, 72.6, 71.3, 70.7, 70.5, 70.4, 70.0, 69.7, 65.8. FABMS (m/z): 873 $(M + Na)^+$, 851 $(M + H)^+$.

Anal. Calcd. for $C_{46}H_{42}O_{16}$ (850.82): C, 64.94; H, 4.98. Found: C, 64.78; H, 4.92.

1,2,3,4,6-Penta-*O*-benzyloxycarbonyl-β-D-glucopyranose (**5**). Following the general procedure, **5** (4.43 g, 95%) was obtained as a white powder. $[\alpha]_D = -41^\circ$ (*c* 1, $CHCl_3$). Rf = 0.45 (CH_2Cl_2: hexane, 8:2). ^{1}H NMR ($CDCl_3$) δ = 3.96 (td, 1H, $J_{5,4} = 9.8$ Hz, $J_{5,6a} = J_{5,6b} = 3.9$ Hz, H-5), 4.35–4.43 (m, 2H, H-6a, H-6b), 5.03–5.23 (m, 13H, H-2, H-3, H-4, 5 Ph-CH_2), 5.69 (d, 1H, $J_{1,2} = 8$ Hz, H-1), 7.28–7.41 (m, 25H, 5 C_6H_5). FABMS (m/z): 873 $(M + Na)^+$, 851 $(M + H)^+$.

Anal. Calcd. for $C_{46}H_{42}O_{16}$ (850.82): C, 64.94; H, 4.98. Found: C, 64.83; H, 4.94.

1,2,3,4,6-Penta-*O*-benzyloxycarbonyl-β-D-galactopyranose (**6**). Following the general procedure, **6** (4.21 g, 90%) was obtained as a white powder. $[\alpha]_D = -32^\circ$ (*c* 1, $CHCl_3$). Rf = 0.49 (CH_2Cl_2: hexane, 8:2). ^{1}H NMR ($CDCl_3$) δ 4.07–4.13 (m, 1H, H-5), 4.29–4.32 (m, 2H, H-6a, H-6b), 4.96 (dd, 1H, $J_{3,4} = 3.3$ Hz, $J_{3,2} = 10.3$ Hz, H-3), 5.12–5.20 (m, 10H, 5 Ph-CH_2), 5.24 (dd, 1H, $J_{2,1} = 8.2$ Hz, H-2), 5.46 (dd, 1H, $J_{4,5} = 1$ Hz, H-4), 5.61 (d, 1H, H-1), 7.27–7.41 (m, 25H, 5 C_6H_5). FABMS (m/z): 873 $(M + Na)^+$.

Anal. Calcd. for $C_{46}H_{42}O_{16}$ (850.82): C, 64.94; H, 4.98. Found: C, 64.75; H, 5.03.

2,3,4,6-Tetra-*O*-benzyloxycarbonyl-D-mannopyranose (**7**). To a solution of the perbenzyloxycarbonyl derivative **4** (1 g, 1.2 mmol) in dry acetonitrile (10 mL) was added the hydrazinium acetate (0.25 g, 2.7 mmol). The reaction mixture was refluxed under stirring for 1 h and then diluted with CH_2Cl_2. The solution was washed with water, dried (Na_2SO_4), and concentrated.

The syrupy residue was purified by column chromatography on silica gel (hexane-EtOAc, 7:3) to give **7** (0.77 g, 90%) as a viscous oil. Rf = 0.43 (hexane-EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 3.29 (d, 1H, $J_{OH,1} = 3.1$ Hz, OH), 4.26–4.35 (m, 4H, H-1, H-5, H-6a, H-6b), 5.13–5.33 (m, 11H, H-2, H-3, H-4, 4 Ph-CH_2), 7.28–7.40 (m, 20H, 4 C_6H_5). FABMS (m/z): 739 $(M + Na)^+$.

Anal. Calcd. for $C_{38}H_{36}O_{14}$ (716.68): C, 63.68; H, 5.06. Found: C, 63.57; H, 5.02.

2,3,4,6-Tetra-*O*-benzyloxycarbonyl-α-D-mannopyranosyl bromide (**8**). To a solution **7** (0.3 g, 4.18 10^{-4} mol) in dry CH_2Cl_2 (15 mL) was added a catalytic quantity of $BiBr_3$ (0.02 g, 4.5 10^{-5} mol). Then Me_3SiBr (0.21 mL, 1.6 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise under stirring at 0°C. After the addition, the reaction mixture was allowed to warm to rt, stirred for 1 h, and then washed with water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (hexane-EtOAc, 7 : 3) to afford compound **8** (0.26 g, 80%) as a yellow syrup. $[\alpha]_D = -35^\circ$ (*c* 1, $CHCl_3$). Rf = 0.77 (hexane-EtOAc, 7 : 3). ^{1}H NMR ($CDCl_3$) δ 4.15–4.19 (m, 1H, H-5), 4.26 (dd, 1H, $J_{6a,6b} = 12$ Hz, $J_{6a,5} = 5.1$ Hz, H-6a), 4.41 (dd, 1H, $J_{6b,5} = 3$ Hz, H-6b), 5.07–5.38 (m, 11H, H-2, H-3, H-4, 4 Ph-CH_2), 6.15 (d, 1H, $J_{1,2} = 1.8$ Hz, H-1), 6.99–7.46 (m, 20H, 4 C_6H_5). FABMS (m/z): 802 $(M + Na)^+$.

Methyl 2,3,4-tri-*O*-acetyl-6-*O*-benzyl-α-D-mannopyranoside (**10**). To a solution of methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside **9** (0.04 g, 1.25 10^{-4} mol), AgOTf (0.06 g, 2.5 10^{-4} mol), and collidine (0.016 mL, 1.25 10^{-4} mol) in dry CH_2Cl_2 (4 mL) was added **8** (0.2 g, 2.5 10^{-4} mol) in dry CH_2Cl_2 (2 mL) under stirring at −45°C. After the addition, the reaction mixture was allowed to warm to rt, stirred for 3 h, and then washed with water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed (petroleum ether-EtOAc, 7:3) to provide **10** (0.03 g, 60%) as a viscous oil. $[\alpha]_D = +43^\circ$ (*c* 1, $CHCl_3$). Rf = 0.43 (hexane-EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H, CH_3CO_2), 2.00 (s, 3H, CH_3CO_2), 2.17 (s, 3H, CH_3CO_2), 3.44 (s, 3H, OCH_3), 3.50 (d, 2H, $J_{6,5} = 4.3$ Hz, H-6), 3.88–4.01 (m, 1H, H-5), 4.54 (d, 1H, $J_{a,b} = 11.9$ Hz, H-a Ph-CH_2), 4.64 (d, 1H, H-b Ph-CH_2), 4.75 (d, 1H, $J_{1,2} = 1.5$ Hz, H-1), 5.24 (t, 1H, $J_{2,3} = 1.5$ Hz, H-2), 5.29–5.36 (m, 2H, H-3, H-4), 7.20–7.83 (m, 5H, C_6H_5). FABMS (m/z): 433 $(M + Na)^+$, 411 $(M + H)^+$.

Anal. Calcd. for $C_{20}H_{26}O_9$ (410.42): C, 58.53; H, 6.39. Found: C, 58.47; H, 6.33.

2,3,4,6-Tetra-*O*-benzyloxycarbonyl-α-D-mannopyranosyl trichloroacetimidate (**11**). To a solution of **7** (0.38 g, 5.3 10^{-4} mol) in dry CH_2Cl_2 (10 mL) was added the NaH (0.016 g, 6.8 10^{-4} mol) at rt. After stirring for 10 min, the trichloroacetonitrile (0.22 mL, 3.8 mmol) was added. The reaction

mixture was stirred at rt for 1 h and then washed with water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel (hexane-EtOAc, 7:3) to provide **11** (0.44 g, 95%) as a white powder. $[\alpha]_D = -54^\circ$ (*c* 1, $CHCl_3$). Rf = 0.78 (hexane-EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 4.27–4.45 (m, 3H, H-5, H-6a, H-6b), 5.1–5.5 (m, 11H, 4 Ph-CH_2, H-2, H-3, H-4), 6.42 (d, 1H, $J_{1,2} = 1.9$ Hz, H-1), 7.28–7.43 (m, 20H, 5 C$_6H_5$), 8.90 (s, 1H, NH). FABMS (m/z): 882 $(M + Na)^+$.

Anal. Calcd. for $C_{40}H_{36}Cl_3NO_{14}$ (861.07): C, 55.79; H, 4.21. Found: C: 55.68; H, 4.16.

Methyl 2,3,4,6-tetra-*O*-benzyloxycarbonyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-mannopyranoside (**12**). To a solution of the methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside (0.07 g, 2.18 10^{-4} mol) and trichloroacetimidate **11** (0.37 g, 4.3 10^{-4} mol) in dry CH_2Cl_2 (5 mL) was added molecular sieves (4-Å, 0.1 g). The solution was cooled at -70°C and the TMSOTf (0.008 mL, 4.36 10^{-5} mol) was added dropwise. After the addition, the solution was allowed to warm to rt and stirred for 1 h. The reaction mixture was neutralized with $NaHCO_3$ (0.2 g) and washed with water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed (petroleum ether-EtOAc, 7:3) to afford **12** (0.14 g, 65%) as a colorless oil. $[\alpha]_D = +17^\circ$ (*c* 1, $CHCl_3$). Rf = 0.43 (petroleum ether-EtOAc, 7:3). ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, CH_3CO_2), 2.03 (s, 3H, CH_3CO_2), 2.14 (s, 3H, CH_3CO_2), 3.34 (s, 3H, OCH_3), 3.60 (dd, 1H, $J_{6a,6b} = 10.9$ Hz, $J_{6a,5} = 2.2$ Hz, H6a), 3.80 (dd, 1H, $J_{6b,5} = 6.3$ Hz, H-6b), 3.84–3.90 (m, 1H, H-5), 4.09–4.2 (m, 1H, H-5′), 4.25 (dd, 1H, $J_{6'a,6'b} = 11.8$ Hz, $J_{6'a,5} = 3.0$ Hz, H-6′a), 4.25 (dd, 1H, $J_{6'b,5} = 5.9$ Hz, H-6′b), 4.68 (d, 1H, $J_{1,2} = 1.8$ Hz, H-1), 4.98 (d, 1H, $J_{1',2'} = 1.4$ Hz, H-1′), 5.05–5.34 (m, 14H, H-2, H-3, H-4, H-2′, H-3′, H-4′, 4Ph-CH_2), 7.23–7.81 (m, 20H, 4 C$_6H_5$). FABMS (m/z): 1041 $(M + Na)^+$.

Anal. Calcd for $C_{51}H_{54}O_{22}$ (1018.96): C, 60.11; H, 5.34. Found: C, 59.85; H, 5.37.

REFERENCES

[1] Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991.

[2] Pulido, R.; Gotor, V. Enzymic regioselective alkoxycarbonylation of hexoses and pentoses with carbonate oxime esters. J. Chem. Soc., Perkin Trans I **1993**, 589–592.

[3] Morère, A.; Mouffouk, F.; Chavis, C.; Montero, J.-L. The benzyloxycarbonyl protective group: a good alternative to the benzyl protective group in the glycopyranoside and the glycofuranoside series. Tetrahedron Lett. **1997**, *38*, 7519–7522.

[4] Morère, A.; Menut, C.; Vidil, C.; Skaanderup, P.; Thorsen, J.; Roque, J.-P.; Montero, J.-L. Benzyloxycarbonyl group: an alternative protective group in the mannose series. Carbohydr. Res. **1997**, *300*, 175–178.

[5] Morère, A.; Mouffouk, F.; Jeanjean, A.; Leydet, A.; Montero, J.-L. High yield regioselective monobenzyloxycarbonylation of secondary alcohols in glycopyranoside series. Carbohydr. Res. **2003**, *338*, 2409–2412.

[6] Mouffouk, F.; Morère, A.; Vidal, S.; Leydet, A.; Montero, J.-L. Selective removal of benzyl carbonate used as a protecting group in carbohydrate chemistry. Synth. Commun. **2004**, *34*, 303–307.

[7] Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Vogel's Textbook of Practical Chemistry*, 5th ed.; Longman Scientific & Technical: London, 1989; 637–664.

[8] Barker, G.R.; Gillam, I.C.; Lord, P.A.; Douglas, T.; Spoors, J.W. Ribose and its derivatives. IX. The use of carbonyl esters in synthesis of α derivatives. J. Chem. Soc. **1960**, 3885–3889.

[9] Schmidt, R.R. New methods for the synthesis of glycosides and oligosaccharides—are there alternatives to the Koenigs-Knorr method? Angew. Chem. Int. Ed. Eng. **1986**, *25*, 212–235.

[10] Vidal, S.; Garcia, M.; Montero, J.-L.; Morère, A. Synthesis and biological evaluation of new mannose 6-phosphate analogues. Bioorg. Med. Chem. **2002**, *10*, 4051–4056.

[11] Boullanger, P.; Jouineau, M.; Bouammali, B.; Lafont, D.; Descotes, G. The use of N-alkoxycarbonyl derivatives of 2-amino-2-deoxy-D-glucose as donors in glycosylation reactions. Carbohydr. Res. **1990**, *202*, 151–164.

[12] Koenigs, W.; Knorr, E. Derivatives of grape sugar and galactose. Ber. **1901**, *34*, 957–981.

[13] Schmidt, R.R.; Jung, K.-H. Oligosaccharide synthesis with trichloroacetimidates. Hanessian, S., Ed. In *Preparative Carbohydrate Chemistry*; Marcel Dekker: New-York, 1997, 283–311.

[14] Montero, J.-L.; Winum, J.-Y.; Leydet, A.; Kamal, M.; Pavia, A.A.; Roque, J.-P. A convenient preparation of peracetylated glycosyl halides using bismuth(III) halides as catalysts. Carbohydr. Res. **1997**, *297*, 175–180.

[15] Hanessian, S.; Banoub, J. Chemistry of the glycosidic linkage. An efficient synthesis of 1,2-trans-disaccharides. Carbohydr. Res. **1977**, *53*, C13–C16.