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Note

The benzyloxycarbonyl group: An alternative protective group in the mannose series

Alain Morère, Chantal Menut, Carole Vidil, Philip Skaanderup, Jesper Thorsen, Jean-Pierre Roque, Jean-Louis Montero *

Laboratoire de Chimie Biomoléculaire Associé au CNRS, Université de Montpellier II, CC073 Place E. Bataillon, F-34095 Montpellier, France

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Abstract

A procedure for the *O*-benzyloxycarbonylation at positions 2–4 in the mannose series is described. Starting from methyl 6-*O*-(4-methoxy)trityl-α-D-mannopyranoside, methyl 2,3,4-tri-*O*-benzyloxycarbonyl-6-*O*-(4-methoxy)trityl-α-D-mannopyranoside was obtained. © 1997 Elsevier Science Ltd.

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Protective groups traditionally used in oligosaccharide synthesis for primary or secondary alcohols are acetates, benzoates or benzyl ethers; a selective protection of primary alcohols is commonly achieved by a trityl group [1]. Among these protective groups, benzyl ethers are the only ones which may be removed under hydrogenolysis conditions, with sometimes low yields.

Protection by a benzyloxycarbonyl group (Z), widely used in peptide synthesis [2], has been little reported in carbohydrate chemistry, except for *N*-protection of amino sugars. Nevertheless, considering that this group is hydrogenolysis and therefore susceptible to removal under mild conditions, it seemed interesting to extend its utilization to secondary alcohols of carbohydrates.

Previous experiments were performed by use of benzyloxycarbonyl chloride, in basic medium; this procedure favoured the obtention of cyclic carbonates [3,4]. The benzyloxycarbonyl group has also been used by Shiozaki for primary hydroxyl group protection in the synthesis of a 1-*O*-carboxyalkyl GLA-60 analogue [5]. Furthermore, Pulido showed that the reaction of D-mannopyranose, D-glucopyranose and D-galactopyranose with acetone *O*-(benzyloxycarbonyl)oxime in dioxane at 60 °C in the presence of a lipase from *Candida antarctica* (Novo SP 435) afforded selective benzyloxycarbonylation of the primary hydroxyl group [6].

The possibility of using this protective group was investigated in the mannose series in order to generate a free hydroxyl group at C-6 for subsequent functionalisation.

The first step of our synthesis consisted in a (4-methoxy)tritylation of the primary hydroxyl group of methyl α-D-mannopyranoside **1** [7–9] (Scheme 1). Benzyloxycarbonylation at positions 2, 3 and 4 of the resulting (4-methoxy)trityl derivative **2** was achieved with benzyloxycarbonyl chloride in the presence of *N*-ethyldiisopropylamine (EDIA) and dimeth-

* Corresponding author.

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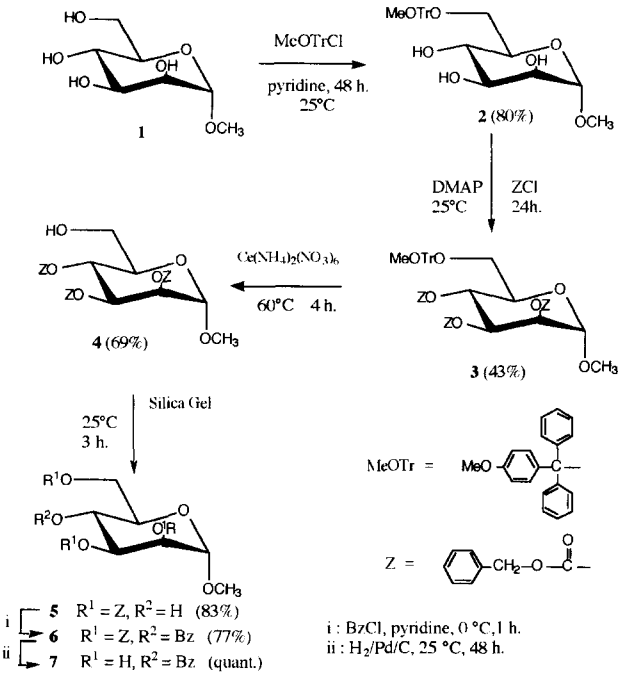

Scheme 1.

ylaminopyridine (DMAP) at room temperature, affording the fully protected derivative **3** in 43% yield after purification by silica gel flash column chromatography.

Detritylation of **3** proved cumbersome since a trifluoracetic acid (30%) treatment [10] in CH_2Cl_2 led to degradation of the product as visualized by TLC, and the use of HCl (1 M in 4:1 acetone:water) at 80 °C [11] gave only partial deprotection of **3**. However, alcohol **4** was finally obtained by an oxidoreduction with ceric ammonium nitrate [12] in 69% yield after purification by preparative thin layer chromatography.

An attempted purification by column chromatography (neutral Al_2O_3 or SiO_2) of **4** resulted in the formation of a less polar product **5**. The NMR analysis of **5** revealed the presence of a free hydroxyl group at C-4 resulting from C-4 → C-6 migration of the benzyloxycarbonyl group. The transformation of **4** into **5** also occurred, with 83% yield, on treatment of the former with a suspension of silica gel in CH_2Cl_2 for 3 h at room temperature. Transesterification reactions have often been described for dialkylcarbonates. They involve generally the displacement of the carbonyl group by a more nucleophilic agent, here the primary hydroxyl group [13].

We have checked that the OH-4 group in **5** is readily available for further functionalisation by preparing the 4-benzoate **6** in 77% yield. Methyl 4-*O*-benzoyl-α-D-mannopyranoside **7** could then easily be obtained quantitatively by hydrogenolysis with $H_2/Pd/C$ at 25 °C.

This study shows that the benzyloxycarbonyl group can be used for selective protection of hydroxyl groups in saccharides. The present application represents an interesting perspective in the synthesis of oligosaccharides.

1. Experimental

General methods.—Optical rotations were determined using a Perkin–Elmer 241 polarimeter. ^1H NMR spectra were recorded with a BRUKER DRX 400 spectrometer using Me_4Si as the internal standard for solutions in $CDCl_3$. Chemical shifts are expressed in δ values (ppm). Mass spectra were measured with a DX 300 JEOL spectrometer in the FAB^+ ion mode. Reactions and purifications were monitored by TLC on pre-coated plates of silica gel 60 F_{254} (layer thickness 0.20 mm, E. Merck, Darmstadt, Germany) eluting with 8:2 Et_2O–hexane. The compounds were visualized by spraying with 5% H_2SO_4 in ethanol and heating at 120 °C. Flash column chromatography was performed on silica gel 60 (E. Merck, Darmstadt, Germany) using a flow of approximately 3.5 mL/min. Solvents were removed under vacuum using a rotary evaporator (bath temperature 40 °C).

Methyl 2,3,4-tri-O-benzyloxycarbonyl-6-O-(4-methoxyphenyldiphenylmethyl)-α-D-mannopyranoside (**3**).—Methyl 6-*O*-(4-methoxyphenyldiphenylmethyl)-α-D-mannopyranoside **2** (2 g, 4.29 mmol) and the catalyst, 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (0.42 g, 3.44 mmol, 0.8 eq.), were placed in a Schlenck tube. The reaction was carried out in distilled CH_2Cl_2 (8 mL) and under nitrogen atmosphere. Distilled *N*-ethyldiisopropylamine (EDIA) (12 mL, 70.10 mmol) was added, followed by distilled benzyloxycarbonyl chloride (10 mL, 70.52 mmol). The reaction was slightly exothermic. The solution was magnetically stirred for approximately 24 h at room temperature. The solution was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography on a column (65 g of silica gel) eluted successively with 95:5 and 85:15 hexane–Et_2O to give **3**, (1.58 g, 43%) as a white amorphous powder, $[\alpha]_D^{20}$ −20° (*c* 6.38, $CHCl_3$). ^1H NMR: δ 7.37–6.70 (m, 29 H, 5

C_6H_5 and C_6H_4), 5.15 (dd, 1 H, $J_{1,2}$ 1.6, $J_{2,3}$ 4.3 Hz, H-2), 5.12–5.05 (m, 4 H, H-3,4 and Ph-CH_2), 5.04 (d, 1 H, $J_{a,b}$ 12.1 Hz, H-a Ph-CH_2), 5.00 (d, 1 H, H-b Ph-CH_2), 4.89 (d, 1 H, $J_{a',b'}$ 12.1 Hz, H-a' Ph-CH_2), 4.78 (d, 1 H, H-b' Ph-CH_2), 4.78 (d, 1 H, H-1), 3.85 (m, 1 H, H-5), 3.66 (s, 3 H, OCH_3), 3.39 (s, 3 H, C-1 OCH_3), 3.18–3.17 (m, 2 H, 2 H-6). FABMS (nitrobenzyl alcohol): *m/z* 892 (3, $[M + Na]^+$), 869 (7.5, $[M + H]^+$), 792 (4, $[M - Ph + H]^+$), 273 (79, $[CH_3OTr]^+$), 91 (100, $[C_7H_7]^+$).

Methyl 2, 3, 4 - tri - O - benzyloxycarbonyl - α - D - mannopyranoside (**4**).—Compound **3** (1.1 g, 1.27 mmol) and $Ce(NH_4)_2(NO_3)_6$ (0.075 g, 0.14 mmol, 0.1 eq.) were dissolved in acetonitrile (8 mL, 75.4 mmol) and 3 drops of water, and kept under magnetic stirring at 60 °C. After 4 h the reaction was complete and the mixture was extracted with CH_2Cl_2. After washing with water, the extract was dried (Na_2SO_4), filtered and concentrated. The product **4** was purified by preparative TLC (Silica Gel 60 F_{254}, 20 × 20 cm, layer thickness 0.25 mm) using 4:1 Et_2O–hexane as the eluent, giving a yield of 69% (0.520 g) as a syrup. $[\alpha]_D^{20}$ −9° (*c* 1.15, $CHCl_3$). ^1H NMR: δ 7.45–7.07 (m, 15 H, 3 Ph), 5.22–5.02 (m, 9 H, 3 Ph-CH_2 and H-2,3,4), 4.75 (s, 1 H, H-1), 3.70 (ddd, 1 H, $J_{4,5}$ 9.9, $J_{5,6a}$ 6.0, $J_{5,6b}$ 2.5 Hz, H-5), 3.63 (ddd, 1 H, $J_{6a,OH}$ 4.3 Hz, $J_{6a,6b}$ 12.6 Hz, H-6a), 3.58 (ddd, 1 H, $J_{6b,OH}$ 4.3 Hz, H-6b), 3.38 (s, 3 H, OCH_3), 2.28 (t, 1 H, OH). FABMS (glycerol–thioglycerol): *m/z* 873 (1, $[M + H + 3$ gly$]^+$), 781 (1, $[M + H + 2$ gly$]^+$), 689 (8, $[M + H +$ gly$]^+$), 597 (14, $[M + H]^+$), 91 (100, $[C_7H_7]^+$).

Methyl 2, 3, 6 - tri - O - benzyloxycarbonyl - α - D - mannopyranoside (**5**).—Compound **4** (0.320 g, 0.54 mmol) was dissolved in CH_2Cl_2 (20 mL) and stirred with silica gel (10 g) for 3 h. The crude product was purified by column chromatography (1:1 Et_2O–hexane). Product **5** was obtained as a syrup (0.266 g, 83%). $[\alpha]_D^{20}$ −17° (*c* 2.8, $CHCl_3$). ^1H NMR: δ 7.32–7.24 (m, 15 H, 3 C_6H_5), 5.14–5.07 (m, 5 H, 2 Ph-CH_2 and H-2), 5.06 (d, 1 H, $J_{a,b}$ 12.1 Hz, H-a Ph-CH_2), 5.04 (d, 1 H, $J_{a,b}$ 12,1 Hz, H-b Ph-CH_2), 4.95 (dd, 1 H, $J_{2,3}$ 3.4, $J_{3,4}$ 9.6 Hz, H-3), 4.71 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1), 4.40 (dd, 1 H, $J_{5,6a}$ 4.9, $J_{6a,6b}$ 11.9 Hz, H-6a), 4.37 (dd, 1 H, $J_{5,6b}$ 2.5 Hz, H-6b, $J_{5,6b}$ 11,9 Hz), 3.84 (dt, 1 H, $J_{4,5}$ 9.6 $^3J_{4,OH}$ 4.9 Hz, H-4), 3.77 (ddd, 1 H, H-5), 3.29 (s, 3 H, OCH_3), 2.58 (d, 1 H, H–OH). FABMS (glycerol–thioglycerol): *m/z* 873 (1, $[M + H + 3$ gly$]^+$), 781 (1, $[M + H + 2$ gly$]^+$), 689 (8, $[M + H +$ gly$]^+$), 597 (14, $[M + H]^+$), 91 (100, $[C_7H_7]^+$).

Methyl 4-O-benzoyl-2,3,6-tri-O-benzyloxycarbonyl-α-D-mannopyranoside (**6**).—A solution of **5** (0.046 g, 0.078 mmol) in pyridine (1 mL) was treated with distilled benzoyl chloride (0.14 mL, 1.21 mmol, 15 eq.) at room temperature for 1 h. The pyridine was evaporated and coevaporated with toluene several times. Traces of pyridine still left were removed by eluting them with hexane on a silica gel column. It was difficult also to remove the excess of benzoyl chloride but an extraction with 1 M NaOH and CH_2Cl_2 followed by drying (Na_2SO_4), filtration and concentration was successful. The purified product was obtained as a syrup (0.042 g, 77%), $[\alpha]_D^{20}$ −82° (*c* 0.27, $CHCl_3$). ^1H NMR: δ 7.90 (dd, 2 H, $^4J_{o,p}$ 1.1, $^3J_{o,m}$ 7.8 Hz, OOCPh-O), 7.50 (tt, 1 H, $^3J_{p,m}$ 7.8 Hz, OOCPh-P), 7.35 (t, 2 H, OOCPh-M), 7.32–7.08 (m, 15 H, 3 Ph), 5.44 (t, 1 H, $J_{3,4}$, $J_{4,5}$ 9.9 Hz, H-4), 5.35 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-3), 5.14 (dd, 1 H, $J_{1,2}$ 1.7 Hz, H-2), 5.09 (d, 1 H, $J_{a,b}$ 12.0 Hz, Ph-CH_2-a), 5.06 (d, 1 H, Ph-CH_2-b), 5.04 (d, 1 H, $J_{a',b'}$ 12.2 Hz, Ph-CH_2-a'), 5.02 (d, 1 H, Ph-CH_2-b'), 4.97 (d, 1 H, $J_{a'',b''}$ 12.3 Hz, Ph-CH_2-a''), 4.95 (d, 1 H, Ph-CH_2-b''), 4.77 (d, 1 H, H-1), 4.26 (dd, 1 H, $J_{5,6a}$ 7.0, $J_{6a,6b}$ 11.9 Hz, H-6a), 4.20 (dd, 1 H, $J_{5,6b}$ 2.8 Hz, H-6b), 4.06 (ddd, 1 H, H-5), 3.32 (s, 3 H, OCH_3). FABMS (nitrobenzyl alcohol): *m/z* 739 (0.75, $[M + K]^+$), 723 (7.5, $[M + Na]^+$), 702 (0.5, $[M + H]^+$), 105 (49, $[C_7H_5O]^+$), 91 (100, $[C_7H_7]^+$).

Methyl 4-O-benzoyl-α-D-mannopyranoside (**7**).—A soln of **6** (0.043g, 0.06 mmol) in EtOH (20 mL) and a few drops of CH_2Cl_2, shaken under $H_{2(g)}$ for 48 h in the presence of 10% Pd–C as catalyst, gave **7** in quantitative yield as a syrup after filtration and concentration. ^1H NMR: δ 8.06 (d, 2 H, $J_{o,m}$ 7.5 Hz, OOCPh-O), 7.61 (t, 1 H, $J_{p,m}$ 7.5 Hz, OOCPh-P), 7.46 (2 H, OOCPh-M), 5.40 (t, 1 H, $J_{3,4}$, $J_{4,5}$ 9.7 Hz, H-4), 4.79 (s, 1 H, H-1), 4.05 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-3), 3.95 (d, 1 H, H-2), 3.80–3.60 (m, 3 H, H-5 and 2 H-6), 3.39 (s, 3 H, OCH_3), 1.43–1.37 (m, 3 H, 3 OH). FABMS (nitrobenzyl alcohol): *m/z* 321 (17, $[M + Na]^+$), 105 (26, $[C_7H_5O]^+$), 91 (44, $[C_7H_7]^+$), 23 (100, $[Na]^+$).

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