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The Benzyloxycarbonyl Protective Group : a Good Alternative to the Benzyl Protective Group in the Glycopyranoside and Glycofuranoside Series.

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Abstract : A procedure for the O-benzyloxycarbonylation of secondary alcohols in the glucose, galactose, mannose, ribose and deoxyribose series is described. Starting from the (4-methoxy)tritylated derivatives on the primary hydroxyl group, the fully protected compounds were obtained for the first time in high yields. © 1997 Published by Elsevier Science Ltd.

Among the protective groups traditionally used for secondary alcohols in polysaccharidec synthesis, benzylic ethers are the only ones which may be removed under hydrogenolysis conditions, but with sometimes low yields.

In the same way, the benzyloxycarbonyl group (Z) is also hydrogenolabile and therefore susceptible to be easily removed under mild conditions. Previous blocking experiments in the saccharidic series with benzyloxycarbonyl chloride in a basic medium, and this procedure favoured the formation of cyclic carbonates.[1,2] The benzyloxycarbonyl group has also been chosen for primary hydroxyl group protection under mild conditions.[3] Furthermore selective benzyloxycarbonylation of the primary hydroxyl group has been performed in the presence of a lipase from *Candida antarctica* (Novo SP 435).[4] Thus it looked promising to extend its use to secondary alcohols in the saccharidic series.

In a recent paper,[5] we have described the preparation of the benzyloxycarbonate at positions 2, 3, 4 on the (4-methoxy)tritylated derivative **1a** in the mannose series by use of benzyloxycarbonyl chloride in the presence of the N-ethyldiisopropylamine (EDIA) and a catalytic amount of 4-dimethylaminopyridine (DMAP). At that time, one of the limitations was the moderate yield (43%) of the fully blocked derivative **2a**. A noticeable improvement was obtained in the benzyloxycarbonylation step by use of stoechiometric DMAP instead of EDIA ; in this way, the mannosyl derivative **2a** was obtained in 90% yield after purification by column chromatography on silica gel (Fig. 1). This result has been successfully extended to pyranosides **2b** and **2c** (glucose, galactose series) and to furanosides **2'a** and **2'b** (ribose, deoxyribose series).[6]

The best results obtained in the detritylation step of **2a-c** or **2'a-b**, avoiding overdeprotection of the Z groups,[5] made use of an oxido-reduction procedure with ceric ammonium nitrate (CAN).[7] Thus, the primary alcohols **3a-c** and **3'a-b** were finally isolated in 60 to 90% yields after purification by column chromatography on silica gel.[8]

As we have pointed out in our previous report, the mannosyl derivative **3a** undergoes an extensive 4 → 6 rearrangement of the benzyloxycarbonyl protecting group and gave **4a** in 85% yield. This phenomenon happens when **3a** is allowed to stand for 3 hours in contact with silicagel.[9]

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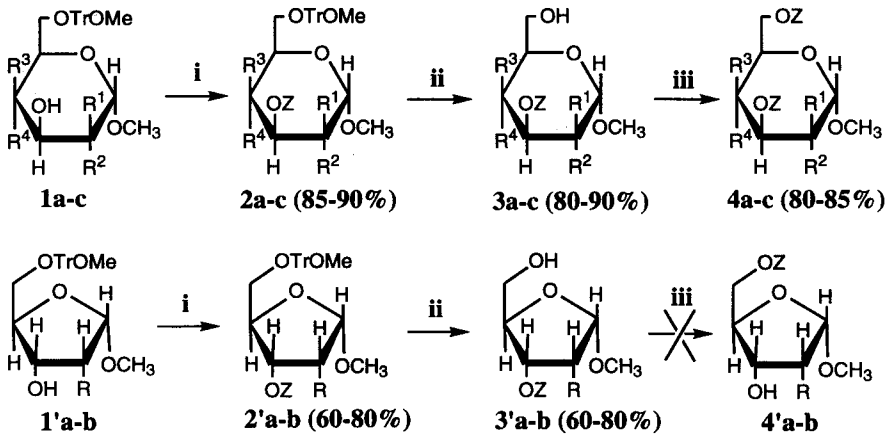

General conditions : **i** : CH_2Cl_2, ZCl*, DMAP, 25°C, 3h ; **ii** : CH_3CN:H_2O (97.5/2.5), $Ce(NH_4)_2(NO_3)_6$, 60° 3h ; **iii** : CH_2Cl_2, silica gel, 3h. *ZCl : $C_6H_5CH_2OCOCl$

Mannose series : R^2,R^3:H; **1a**: R^1,R^4:OH; **2a**: R^1,R^4:OZ; **3a**: R^1,R^4:OZ; **4a**: R^1:OZ; R^4:OH;
Glucose series : R^1,R^3:H; **1b**: R^2,R^4:OH; **2b**: R^2,R^4:OZ; **3b**: R^2,R^4:OZ; **4b**: R^2:OZ; R^4:OH;
Galactose series: R^1,R^4:H; **1c**: R^2,R^3:OH; **2c**: R^2,R^3:OZ; **3c**: R^2,R^3:OZ; **4c**: R^2:OZ; R^3:OH;
Ribose series : 1'a: R:OH. **2'a, 3'a, 4'a**: R:OZ. **Deoxyribose series : 1'b, 2'b, 3'b, 4'b**: R:H

Figure 1

It is worth mentioning that furanosides **3'a,b** are fairly stable under the same conditions, but the migration also occurred to the same extent (80-85%) with the gluco and galactopyranosides **3b,c** (Fig. 2). Such transesterification reactions have been described for dialkyl carbonates and involve generally the displacement of the carbonyl group by a more nucleophilic primary hydroxyl function.[10] Favorable stereochemical considerations account for such a migration in the appropriate hexopyranosyl series and render the pentofuranosyl sugars not concerned with this phenomenon.

The easy access to monohydroxy hexopyranosides of the type **3a-c** or **4a-c** makes them versatile and useful synthons for oligosaccharide synthesis.

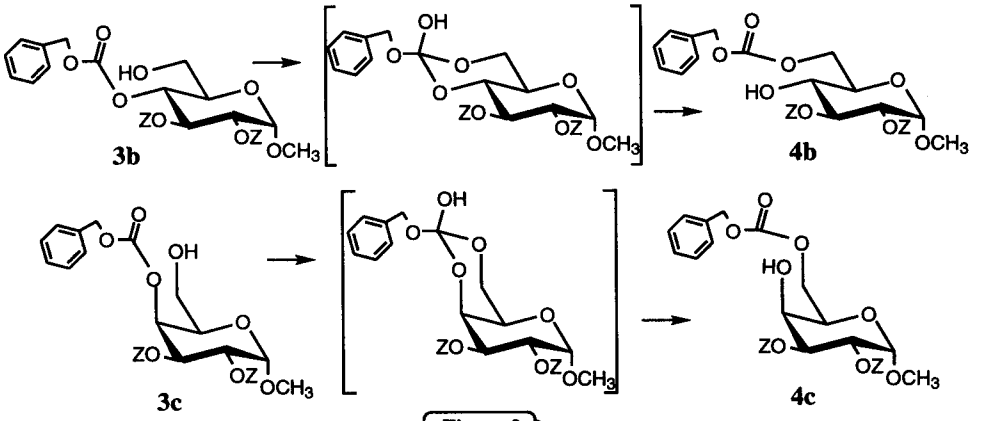

Figure 2

Product	^{1}H NMR ($CDCl_3$), Mass (FABMS m/z (Matrix. : Nitrobenzyl alcohol))	Yield %	$[\alpha]_D^{25}$ c = 1,$CHCl_3$
2b R^3, R^1= H R^2,R^4= OZ	7.37-6.7 (m, 29H, $5C_6H_5$, C_6H_4), 5.30 (t, 1H, $J_{3,2} = J_{3,4} = 9.5$ Hz, H-3), 5.08 (s, 2H, j-CH_2), 5.04 (d, 1H, $J_{1,2} = 3.6$ Hz , H-1), 5.01 (d, 1H, $J_{a,b} = 12.4$ Hz, H_a, j-CH_2), 4.96 (t, 1H, $J_{4,5} = 9.5$ Hz, H-4), 4.93 (ddd, 1H, $J_{5,6'} = 5.1$ Hz, $J_{5,6} = 2$ Hz, H-5), 4.91 (d, 1H, H_b, j-CH_2), 4.85 (d, 1H, H_a, j-CH_2), 4.79 (d, 1H, H_b, j-CH_2), 4.77 (dd, 1H, H-2), 3.88 (s, 3H, OCH_3), 3.54 (s, 3H, C-1 OCH_3), 3.21 (dd, 1H, $J_{6,6'} = 10.5$ Hz, H-6), 3.12 (dd, 1H, H-6') . 891 ($[M+Na]^+$, 1.9%), 868 ($[M]^+$, 1.9%), 91 ($[C_7H_7]^+$, 100%) .	86	+5
2c R^1, R^4= H R^2,R^3= OZ	7.2-6.7 (m, 29H, $5C_6H_5$, C_6H_4), 5.44 (t, 1H, $J_{3,4} = J_{4,5} = 3.3$ Hz, H-4), 5.13-4.9 (m, 9H, H-1, H-2, H-3, 3 j-CH_2), 3.87 (t, 1H, $J_{5,6} = J_{5,6'} = 6.5$ Hz, H-5), 3.69 (s, 1H, OCH_3), 3.28 (s, 3H, C-1 OCH_3), 3.27 (dd, 1H, $J_{6,6'} = 10.5$ Hz, H-6'), 3.06 (dd, 1H, H-6). 868($[M]^+$, 0.8%), 273 ($[CH_3OTr]^+$, 100%) .	90	+7
2'a R = OZ	7.20-6.70 (m, 24H, $4C_6H_5$, C_6H_4), 5.35 (dd, 1H, $J_{2,3} = 6.6$ Hz, $J_{3,4} = 4.6$ Hz, H-3), 5.18 (d.d, 1H, $J_{1,2} = 1.3$ Hz, $J_{2,3} = 4.6$ Hz, H-2), 5.08-4.98 (m, 4H, 2 j-CH_2), 4.95 (d, 1H, H-1), 4.26 (td, 1H, $J_{4,5} = J_{4,5'} = 4.3$ Hz, H-4), 3.74 (s, 3H, OCH_3), 3.32 (s, 3H, C-1 OCH_3), 3.28 (dd, 1H, $J_{5,5'} = 10.1$ Hz, H-5'), 3.16 (dd, 1H, H-5). 704 ($[M]^+$, 3.5%), 627 ($[M-C_6H_5]^+$, 3.9%), 273($[CH_3OTr]^+$,100%	80	+3
2'b R = H	7.20-6.70 (m, 19H, $3C_6H_5$, C_6H_4), 5.29 (ddd, 1H, $J_{2,3} = 6.6$ Hz, $J_{2',3} = 4.5$ Hz, $J_{3,4} = 3$ Hz, H-3), 5.22 (dd, 1H, $J_{1,2'} = 4.5$ Hz, $J_{1,2} = 3.3$ Hz, H-1), 5.20 (s, 2H, j-CH_2), 4.33 (td, 1H, $J_{4,5} = J_{4,5'} = 5.6$ Hz, H-4), 3.84 (s, 3H, OCH_3), 3.38 (s, 3H, C-1 OCH_3), 3.35 (dd, 1H, $J_{5,5'}$ 9.8 Hz, H-5'), 3.30 (dd, 1H, H-5), 2.41 (ddd, 1H, $J_{2',2}$ 14.2 Hz, H-2), 2.27 (ddd, 1H, H-2) . 577 ($[M+Na]^+$, 7.0%), 554 ($[M]^+$, 10.4%), 273 ($[CH_3OTr]^+$, 100%) .	60	-9
3b R^3, R^1= H R^2,R^4= OZ	7.71-7.04 (m, 15H , 3 C_6H_5), 5.35 (t, 1H, $J_{2,3} = J_{3,4} = 9.8$ Hz , H-3), 5.19-5.09 (m, 7H, H-1, 3 j-CH_2), 4.85 (t, 1H, $J_{4,5}$ 9.8 Hz, H-4), 4.67 (dd, 1H, $J_{2,1}$ 3.4 Hz, H-2), 3.84 (ddd, 1H, $J_{5,6'} = 3.8$ Hz, $J_{5,6} = 2$ Hz, H-5), 3.77 (ddd, 1H, $J_{6,6'} = 12.8$ Hz, $J_{6,OH} = 8$ Hz, H-6), 3.66 (ddd, 1H, H-6'), 3.42 (s, 3H, C-1 OCH_3), 2.44 (dd, 1H, OH) . 597 ($[M+H]^+$, 4.6%), 505 ($[M-C_6H_5-CH_2]^+$, 0.8%), 91 ($[C_7H_7]^+$, 100%) .	80	+5
3c R^1, R^4= H R^2,R^3= OZ	7.30-7.22 (m, 15H, 3 C_6H_5), 5.39 (d, 1H, $J_{3,4} = 3.2$ Hz , H-4), 5.19 (dd, 1H, $J_{2,3} = 9.8$ Hz, H-3), 5.11-4.99 (m, 8H, H-1, H-2, 3 j-CH_2), 4.02 (t, 1H, $J_{5,6} = J_{5,6'} = 6.5$ Hz, H-5), 3.50 (dd, 1H, $J_{6,6'} = 18.3$ Hz, H-6), 3.46 (dd, 1H, H-6'), 3.35 (s, 3H, C-1 OCH_3) . 619 ($[M+Na]^+$, 14.7%), 597 ($[M+H]^+$, 3.1%), 91 ($[C_7H_7]^+$, 100%) .	90	+7
3'a R =OZ	7.35-7.20 (m, 10H, 2 C_6H_5), 5.44 (dd, 1H, $J_{3,4} = 9.6$ Hz, $J_{3,2}$ 5 Hz, H-3), 5.27 (dd, 1H, $J_{2,1}$ 1.3 Hz, H-2), 5.17-5.15 (m, 4H, 2 j-CH_2), 5.03 (d, 1H, H-1), 4.32 (dt, 1H, $J_{4,5} = J_{4,5'} = 6.3$ Hz, H-4), 3.93-3.68 (m, 2H, H5, H5'), 3.44 (s, 3H, C-1 OCH_3), 2.55 (s, 1H, H_{OH}) . 445 ($[M+Na]^+$, 2.7%), 432 ($[M]^+$, 0.9%), 91 ($[C_7H_7]^+$, 100%) .	70	+2
3'b R = H	7.40-7.29 (m, 5H, C_6H_5), 5.17-5.15 (m, 2H, j-CH_2), 5.10 (dd, 1H, $J_{1,2'} = 5.1$ Hz, $J_{1,2} = 0.8$ Hz, H-1) 5.05 (ddd, 1H, $J_{3,2'} = 8$ Hz, $J_{3,4} = 3.6$ Hz, $J_{3,2} = 2$ Hz, H-3), 4.20 (q, 1H, $J_{4,5} = J_{4,5'} = 3.6$ Hz, H-4), 3.80-3.40 (m, 2H, H5, H5'), 3.37 (s, 3H , C-1 OCH_3), 2.70 (s, 1H, OH), 2.35 (ddd, 1H, $J_{2,2'} = 14.5$ Hz, H-2'), 2.12 (ddd, 1H, H-2). 305 ($[M+Na]^+$, 66.4%), 283 ($[M+H]^+$, 11.6%), 91 ($[C_7H_7]^+$, 100%) .	65	-69
4b R^3, R^1= H R^2 = OZ R^4 = OH	7.40-7.10 (m, 15H, $3C_6H_5$), 5.20 (s, 2H, j-CH_2), 5.19 (t, 1H, $J_{3,2} = J_{3,4} = 10.1$ Hz , H-3), 5.18 5.17 (m, 2H, j-CH_2), 5.15 (m, 2H, j-CH_2), 5.01 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1), 4.72 (dd, 1H, H-2), 4.52 (dd, 1H, $J_{6,6'} = 12$ Hz, $J_{6,5}$ 4.2 Hz, H-6), 4.42 (dd, 1H, $J_{6,5} = 2.7$ Hz, H-6'), 3.87 (dt, 1H, $J_{4,5} = 10.1$ Hz, H-4), 3.73 (t, 1H, Hz, H-5), 3.38 (s, 3H, C-1 OCH_3). 619 ($[M+Na]^+$, 6.2%), 597 ($[M+H]^+$, 2.7%), 91 ($[C_7H_7]^+$, 100%) .	85	+90
4c R^1, R^4= H R^2,= OZ R^3 = OH	7.31-7.18 (m, 15H, 3 C_6H_5), 5.2 (s, 2H, j-CH_2), 5.60-5.10 (m, 8H, H-2, H-3, 3 j-CH_2), 5.05 (s, 1H, $J_{1,2} = 3.2$ Hz, H-1), 4.32-4.25 (m, 2H, H-6, H-6'), 4.15-4.13 (m, 1H, H-4), 4.00 (t, 1H, $J_{5,6} = J_{5,6'} = 6.2$ Hz, H-5), 3.36 (s, 3H, C-1 OCH_3). 619 ($[M+Na]^+$, 6.2%), 597 ($[M+H]^+$, 36.4%), 91 ($[C_7H_7]^+$, 100%) .	80	+82

Table I

References and Notes.

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6 **General procedure for benzyloxycarbonylation of 1a, 1b, 1c, 1'a, 1'b :**
To a solution of monosaccharide (**1a**, **1b**, **1c**, **1'a** or **1'b**) (2 mmoles) and DMAP (2 eq./OH) in dichloromethane (10mL) was slowly added, at 0 °C, ZCl (2.3 eq./OH). After stirring at r.t. for 2 h, analytical TLC (CH_2Cl_2-hexane, 80:20, v/v) indicated uncomplete reaction. To the solution, ZCl (2.3 eq./OH) was then added in one drop and the mixture was stirred at r.t. for 1 h until analytical TLC (CH_2Cl_2-hexane, 80:20, v/v) indicated complete reaction. The solution was washed with water and extracted with CH_2Cl_2; the organic layer was dried over Na_2SO_4, and purified by column chromatography on silica gel using CH_2Cl_2-hexane (80:20, v/v). All the data are shown in Table I.

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8 **General procedure for detritylation of 2a, 2b, 2c, 2'a or 2'b :**
Fully blocked derivatives (5.7 mmoles) and 0.1 eq. of $Ce(NH_4)_2(NO_3)_6$ were dissolved in 8 mL of acetonitrile/H_2O (97.5:2.5, v/v). The solution was kept under magnetic stirring at 60 °C. After 3 h the reaction mixture was diluted with dichloromethane, washed with water and the organic layer was extracted with dichloromethane, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel eluted with Et_2O -hexane (80:20, v/v). All the data are shown in the Table I.

9 **Methyl 2,3,6-tri-O-benzyloxycarbonyl-a-D-glycopyranoside (5a, 5b, 5c) :**
Methyl 2,3,4-tri-O-benzyloxycarbonyl-a-D-glycopyranoside **4** (0.3 g, 0.5 mmol) was dissolved in 20 mL of dichloromethane and stirred with 10 g of silica gel for 3 h. The crude product was purified by column chromatography on silica gel, eluted with Et_2O-hexane (80:20, v/v). All the data are shown in the Table I.

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