Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 338 (2003) 2409–2412
CARBOHYDRATE RESEARCH
www.elsevier.com/locate/carres

Note

High yield regioselective monobenzyloxycarbonylation of secondary alcohols in glycopyranoside series

Alain Morère,* Fouzi Mouffouk, Audrey Jeanjean, Alain Leydet, Jean-Louis Montero

Laboratoire de Chimie Biomoléculaire (UMR 5032), Université Montpellier II-ENSCM, 8 Rue de l'Ecole Normale, F-34296 Montpellier, France

Received 18 October 2002; received in revised form 28 July 2003; accepted 18 August 2003

Abstract

The regioselective monobenzyloxycarbonylation of secondary alcohols in methyl 6-*O*-(4-methoxytrityl)-α-D-manno-, gluco- and galactopyranoside has been achieved in high yields (74–85%) by using benzyl chloroformate in the presence of 4-dimethylaminopyridine and/or 1,4-diazabicyclo[2.2.2]octane.

Keywords: Regioselectivity; Protecting group; Glycopyranoside series; Benzyloxycarbonyl group

In saccharide synthesis, a selective protection of primary alcohol is commonly achieved using bulky protecting groups such as trityl or silyl derivatives. On the other hand, regioselectivity for the secondary hydroxyl groups is more demanding. Chemical differences observed in glycopyranoside series between 2-OH, 3-OH and 4-OH are usually small: few effective methods have been developed to enhance these differences in reactivity and the methods generally used afford mixtures of products.[1,2] Among the chemical protocols described in the literature, we can cite the method using dibutyltin oxide and the phase transfer reactions applied for the mono-alkylation or mono-esterification of compounds containing more than one secondary hydroxyl groups.[3–6] Concerning the partial acetylation of carbohydrates, new methods, using BOP–Cl or $ZnCl_2$, have been reported.[7,8]

From these studies, we can deduce that in the α-D-glucopyranoside series the 2-OH is slightly more reactive than the 3-OH or 4-OH groups. Moreover, equatorial hydroxyl groups are more accessible than axial hydroxyl groups and therefore more reactive. However, it is worth mentioning that in aqueous basic medium the 2-OH axial group in mannopyranoside series[6] is more nucleophilic while it is the 3-OH equatorial group in organic medium.

The chemical differentiation of the three secondary alcohols in the glycopyranoside series still remains an important challenge and the combinatorial chemistry using carbohydrates as polyfunctional scaffolds needs such approaches for its development. Indeed, to achieve molecular diversity starting from glycopyranoside all primary and secondary hydroxyl groups have to be orthogonally protected. In order to afford new tools in this field, we developed a method for the preparation of monosaccharides regioselectively protected by a benzyloxycarbonyl group (Z). This group, which can be easily removed under hydrogenolysis conditions, is widely used in peptide synthesis[9] and has been hardly reported in carbohydrate chemistry, except for the N-protection of aminosugars or for the selective benzyloxycarbonylation of the primary hydroxyl groups.[10–12] We have shown that the benzyloxycarbonylation at all of the secondary positions on 6-*O*-(4-methoxytrityl)glycopyranosides was easily achieved to yield tri-carbonates using benzyloxycarbonyl chloride (ZCl) in the presence of 4-dimethylaminopyridine (DMAP).[13,14] This benzyloxycarbonylation was obtained in high yields (85–90%) using 2.3 equivalents of ZCl and DMAP for each secondary hydroxyl groups.[13] With other organic bases (pyridine or ethyldiisopropylamine in excess), we obtained mixtures of mono-, di- or triprotected com-

* Corresponding author. Tel.: +33-4-67144345; fax: +33-4-67144344.
E-mail address: morere@univ-montp2.fr (A. Morère).

0008-6215/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2003.08.007

pounds with the highest yield of monobenzyloxycarbonylated derivatives. An aqueous basic medium has to be avoided since these conditions are known to favour the obtention of cyclic carbonates.[15,16] Therefore, the choice of the organic bases, which depends on strength and steric hindrance factors, is essential to obtain a selective benzyloxycarbonylation.

A mixture of 1,4-diazabicyclo[2.2.2]octane (DABCO) and DMAP as the basic species gave the best results (Scheme 1) and monobenzyloxycarbonylation proceeds rapidly. After addition of ZCl to a mixture of DABCO, DMAP and methyl 6-*O*-(4-methoxytrityl)-α-D-mannopyranoside (**1**),[14] monobenzyloxycarbonylation was complete in 15 min as shown by thin layer chromatography (TLC) and the reaction mixture was immediately diluted with dichloromethane in order to avoid the formation of poly-benzyloxycarbonylated derivatives. In this way, after extraction then purification by column chromatography on silica gel, the 3-carbonate **2** was obtained in 85% yield and its structure was confirmed by ^{1}H NMR spectroscopy and FABMS.

Compared to starting material **1**, the H-3 undergoes a displacement to downfield shift. The doublet of doublets appears at δ 4.98 ppm and J values, of 9.6 and 3.2 Hz, are consistent with, respectively, a trans-diaxial relationship between H-3 and H-4, and an equatorial-axial relationship between H-3 and H-2.

As expected, the equatorial 3-OH group of the α-D-mannopyranoside series is the most reactive of the secondary hydroxy group in triol **1**. We wish to emphasise that the shorter the reaction time, the higher are both yield and regioselectivity.

This method has been successfully extended to α-D-glucopyranoside series in which the equatorial 2-OH group was the more reactive among the secondary hydroxy groups. Thus, methyl 6-*O*-(4-methoxytrityl)-α-D-glucopyranoside[17] (**3**) gave compound **4** in 80% yield (Scheme 1), no other product being observed by TLC. This selectivity is in agreement with a study effected on the methyl 4,6-*O*-benzylidene-α-D-glucopyranoside.[18]

In α-D-galactopyranoside series, the 2-carbonate **6** was obtained from **5**[19] in 74% yield with only the DABCO (3 equivalents) as the base (Scheme 1). The structural characterization of compounds **4** and **6** has been fully determined by ^{1}H NMR spectroscopy and FABMS.

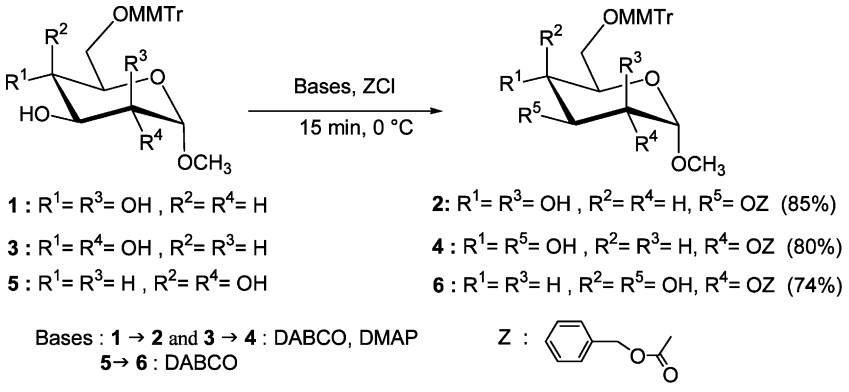
The next step was to determine what could be the regioselectivity when the starting material is the methyl 6-*O*-(4-methoxytrityl)-β-D-glucopyranoside[19] (**7**) (Scheme 2). Under the same conditions as those previously described, we observed the formation of the 3-carbonate **8** in 31% yield and the 2-carbonate **9** in 43% yield. This suggests that in the absence of an anomeric axial group, the 3-OH is as reactive as the 2-OH toward the benzyloxycarbonylation.

In conclusion, the regioselective monobenzyloxycarbonylation of secondary alcohols in α-D-manno-, α-D-gluco- and α-D-galactopyranoside series has been achieved in high yields. Presumably, the higher selectivity of the benzyloxycarbonyl chloride compared to the usual acid chlorides in such reactions is related to the lower reactivity of the former reagent. Our results underlined that in the α-D-mannopyranoside series the 3-OH is the more reactive secondary alcohol. On the other hand, in the α-D-gluco- or α-D-galactopyranoside series, the 2-OH is the more reactive group. In each case, a mixture of mono- and/or poly-derivatized products was not observed. Therefore, the use of benzyloxycarbonyl as selective protecting group for secondary alcohols is of great interest to obtain monosaccharides with all primary and secondary hydroxyl groups orthogonally protected.

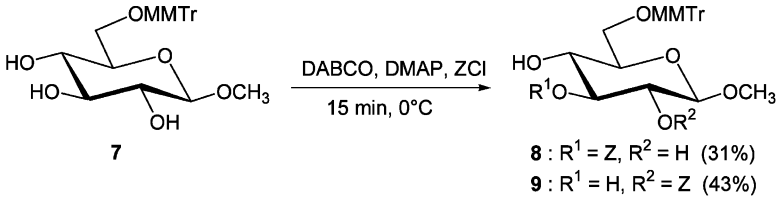
1. Experimental

1.1. General methods

Optical rotations were determined using a Perkin–Elmer 241 polarimeter. Melting points were determined using a Büchi 530 apparatus. ^{1}H NMR spectra were



Scheme 1.



Scheme 2.

determined with a DRX 400 Bruker spectrometer. Mass spectra were measured with a DX 300 JEOL spectrometer in the FAB^+ ion mode, with nitrobenzyl alcool (NBA) as matrix. E. Merck Silica Gel 60 F254 (0.25 mm) plates were employed for analytical TLC. Compounds were revealed by UV light (254 nm) and 20% aq H_2SO_4 sprayings. Column chromatography was performed on Silica Gel 60 (E. Merck, Darmstadt, Germany).

1.2. Methyl 3-*O*-benzyloxycarbonyl-6-*O*-(4-methoxytrityl)-α-D-mannopyranoside (2)

Methyl 6-*O*-(4-methoxytrityl)-α-D-mannopyranoside[14] (**1**) (1.0 g, 2.15 mmol), DABCO (0.6 g, 5.35 mmol) and DMAP (0.2 g, 1.6 mmol) were dissolved in 100 mL of CH_2Cl_2. To the mixture, cooled at 0 °C and stirred for 15 min, was added dropwise benzyloxycarbonyl chloride (1.2 mL, 8.5 mmol) in 20 mL of CH_2Cl_2. After 15 min, the reaction was complete as revealed by TLC (4:1 hexane–Et_2O). The soln was immediately diluted with 100 mL of CH_2Cl_2, washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (4:1 hexane–Et_2O) to afford **2** as a white amorphous powder by concentration (1.10 g, 85%). $[\alpha]_D$ +34° (*c* 0.5, CH_2Cl_2). Mp 65–70 °C. ^1H NMR ($CDCl_3$): δ 2.15 (d, 1 H, $J_{OH,4}$ 5.1 Hz, OH-4), 2.70 (d, 1 H, $J_{OH,2}$ 3.4 Hz, OH-2), 3.34 (s, 3 H, C*H*$_3$–O C-1), 3.4 (d, 2 H, $J_{6,5}$ 4.8 Hz, H-6), 3.68 (d, 1 H, $J_{5,4}$ 9.7 Hz, H-5), 3.73 (s, 3 H, C*H*$_3$OTr), 3.95 (td, 1 H, $J_{4,3}$ 9.7 Hz, H-4), 4.02 (dd, 1 H, $J_{2,1}$ 1.5, $J_{2,3}$ 1.8 Hz, H-2), 4.67 (d, 1 H, H-1), 4.90 (dd, 1 H, H-3), 5.12 (s, 2 H, Ph–C*H*$_2$), 6.78–7.43 (m, 19 H, 3 C_6H_5, C_6H_4). FABMS (NBA): *m*/*z*, 600 ($[M]^+$). Anal. Calcd for $C_{35}H_{36}O_9$: C, 69.99; H 6.04. Found: C, 69.62; H 6.09.

1.3. Methyl 2-*O*-benzyloxycarbonyl-6-*O*-(4-methoxytrityl)-α-D-glucopyranoside (4)

Starting from **3**[17] (1.0 g, 2.15 mmol), DABCO (0.6 g, 5.35 mmol), DMAP (0.2 g, 1.6 mmol), ZCl (1.2 mL, 8.5 mmol) and using the same procedure as for **2**, compound **4** was obtained as a white amorphous powder (1.03 g, 80%). $[\alpha]_D$ +56° (*c* 0.5, CH_2Cl_2). Mp 78–82 °C. ^1H NMR ($CDCl_3$): δ 2.87 (d, 1 H, $J_{OH,4}$ 2.4 Hz, OH-4), 3.10 (d, 1 H, $J_{OH,3}$ 3.0 Hz, OH-3), 3.24 (dd, 1 H, $J_{6a,6b}$ 10.3, $J_{6a,5}$ 5.6 Hz, H-6a), 3.25 (s, 3 H, C*H*$_3$–O C-1), 3.30 (dd, 1 H, $J_{6b,5}$ 5.6 Hz, H-6b), 3.42 (td, 1 H, $J_{4.5} = J_{4.3} =$ 9.5 Hz, H-4), 3.61 (dt, 1 H, H-5), 3.64 (s, 3 H, C*H*$_3$OTr), 3.83 (td, 1 H, $J_{3,2}$ 9.5 Hz, H-3), 4.46 (dd, 1 H, $J_{2,1}$ 3.6 Hz, H-2), 4.86 (d, 1 H, H-1), 5.04 (s, 2 H, Ph–C*H*2), 6.74–7.38 (m, 19 H, 3 C_6H_5, C_6H_4). FABMS (NBA): *m*/*z*, 623 ($[M+Na]^+$). Anal. Calcd for $C_{35}H_{36}O_9$: C, 69.99; H, 6.04. Found: C, 69.48; H, 6.10.

1.4. Methyl 2-*O*-benzyloxycarbonyl-6-*O*-(4-methoxytrityl)-α-D-galactopyranoside (6)

Starting from **5**[19] (1.0 g, 2.15 mmol), DABCO (0.7 g, 6.24 mmol), ZCl (1.2 mL, 8.5 mmol) and using the same procedure as for **2**, compound **6** was obtained as a white amorphous powder (0.95 g, 74%). $[\alpha]_D$ +60° (*c* 0.5, CH_2Cl_2). Mp 70–73 °C. ^1H NMR ($CDCl_3$): δ 2.79 (d, 1 H, $J_{OH,3}$ 2.4 Hz, OH-3), 2.83 (d, 1 H, $J_{OH,4}$ 3.8 Hz, OH-4), 3.29 (dd, 1 H, $J_{6b,6a}$ 9.9, $J_{6a,5}$ 5.6 Hz, H-6a), 3.30 (s, 3 H, C*H*$_3$–O C-1), 3.35 (dd, 1 H, $J_{6b,5}$ 5.6 Hz, H-6b), 3.69 (s, 3 H, C*H*$_3$OTr), 3.77 (t, 1 H, H-5), 3.89 (m, 1 H, H-3), 3.94 (s, 1 H, H-4), 4.81 (dd, 1 H, $J_{2,1}$ 3.7, $J_{2,3}$ 9.8 Hz, H-2), 4.89 (d, 1 H, H-1), 5.08 (s 2 H, Ph–C*H*$_2$), 6.74–7.39 (m, 19 H, 3 C_6H_5, C_6H_4). FABMS (NBA): *m*/*z*, 623 ($[M+Na]^+$). Anal. Calcd for $C_{35}H_{36}O_9$: C, 69.99; H, 6.04. Found: C, 69.54; H, 6.08.

1.5. Methyl 2-*O*-benzyloxycarbonyl-6-*O*-(4-methoxytrityl)-β-D-glucopyranoside (8) and methyl 3-*O*-benzyloxycarbonyl-6-*O*-(4-methoxytrityl)-β-D-glucopyranoside (9)

Starting from **7**,[19] and using the same procedure as for **2** and **4**, the 3-carbonate **8** (0.4 g, 31%) and the 2-carbonate **9** (0.55 g, 43%) were obtained as viscous oils.

Methyl 3-*O*-benzyloxycarbonyl-6-*O*-(4-methoxytrityl)-β-D-glucopyranoside (**8**): $[\alpha]_D$ −20° (*c* 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.45 (d, 1 H, $J_{OH,2}$ 2.5 Hz, OH-2), 2.84 (d, 1 H, $J_{OH,4}$ 3.3 Hz, OH-4), 3.31–3.46 (m, 4 H, H-2, H-5, H-6, H-6′), 3.49 (s, 3 H, C*H*$_3$–O C-1), 3.67 (td, 1 H, $J_{4.5} = J_{4.3} = 9.3$ Hz, H-4), 3.71 (s, 3 H, C*H*$_3$OTr), 4.19 (d, 1 H, $J_{1.2}$ 7.8 Hz, H-1), 4.73 (t, 1 H, $J_{3,2}$ 9.3 Hz, H-3), 5.13 (s, 2 H, C*H*$_2$–Ph), 6.75–7.38 (m, 19 H, 3 C_6H_5, C_6H_4). FABMS (NBA): *m*/*z*, 623 ($[M+Na]^+$). Anal. Calcd for $C_{35}H_{36}O_9$: C, 69.99; H, 6.04. Found: C, 69.57; H, 6.08.

Methyl 2-*O*-benzyloxycarbonyl-6-*O*-(4-methoxytrityl)-β-D-glucopyranoside (**9**): $[\alpha]_D$ −21° (*c* 0.4,

$CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.56 (s, 1 H, OH), 2.85 (s, 1 H, OH), 3.32–3.60 (m, 5 H, H-3, H-4, H-5, H-6, H-6′), 3.43 (s, 3 H, CH_3–O C-1), 3.73 (s, 3 H, CH_3–OTr), 4.28 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.58 (t, 1 H, $J_{2,1} = J_{2,3} = 8.0$ Hz, H-2), 5.13 (s, 2 H, CH_2–Ph), 6.76–7.39 (m, 19 H, 3 C_6H_5, C_6H_4). FABMS (NBA): m/z, 623 ($[M+Na]^+$). Anal. Calcd for $C_{35}H_{36}O_9$: C, 69.99; H, 6.04. Found: C, 69.68; H, 6.05.

Acknowledgements

We are grateful to the 'Conseil Scientifique de l'Université Montpellier II' for financial support.

References

1. Garegg, P. J. *Pure Appl. Chem.* **1984**, *56*, 845–858.
2. Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11–109.
3. Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363–2369.
4. David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643–663.
5. Garegg, P. J.; Iversen, T.; Oscarson, S. *Carbohydr. Res.* **1976**, *50*, C12–C14.
6. Garegg, P. J.; Iversen, T.; Oscarson, S. *Carbohydr. Res.* **1977**, *53*, C5–C7.
7. Liguori, A.; Procopio, A.; Romeo, G.; Sindona, G.; Uccella, N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1783–1786.
8. Hanessian, S.; Kagotani, M. *Carbohydr. Res.* **1990**, *202*, 67–79.
9. Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer: Berlin, 1984.
10. Shiozaki, M.; Deguchi, N.; Macindoe, W. M.; Arai, M.; Miyazaki, H.; Mochizuki, T.; Tatsuta, T.; Ogawa, J.; Maeda, H.; Kurakata, S. *Carbohydr. Res.* **1996**, *283*, 27–51.
11. Pulido, R.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1993**, 589–592.
12. Chauvin, C.; Plusquellec, D. *Tetrahedron Lett.* **1991**, *32*, 3495–3498.
13. Morère, A.; Mouffouk, F.; Chavis, C.; Montero, J.-L. *Tetrahedron Lett.* **1997**, *38*, 7519–7522.
14. Morère, A.; Menut, C.; Vidil, C.; Skaanderup, P.; Thorsen, J.; Roque, J.-P.; Montero, J.-L. *Carbohydr. Res.* **1997**, *300*, 175–178.
15. Barker, G. R.; Gillam, I. C.; Lord, P. A.; Douglas, T.; Spoors, J. W. *J. Chem. Soc.* **1960**, 3885–3889.
16. Hall, L. D.; Hough, L. *J. Chem. Soc.* **1963**, 5301–5307.
17. Ramirez, F.; Mandal, S. B.; Marecek, J. F. *J. Org. Chem.* **1983**, *48*, 2008–2013.
18. Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **2000**, *41*, 9305–9309.
19. Rej, R. N.; Glushka, J. N.; Chew, W.; Perlin, A. S. *Carbohydr. Res.* **1989**, *189*, 139–148.