# Synthesis of Protected Glycopyranosylidene 1,1-Diazides

Jean-Pierre Praly,* Fabien Péquery, Carméla Di Stèfano, Gérard Descotes

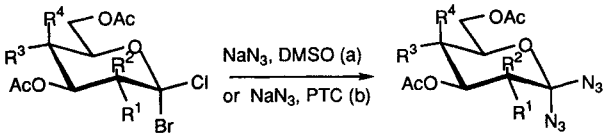
Laboratoire de Chimie Organique II associé au CNRS, Université Claude-Bernard Lyon I, CPE-ESCIL, 43 Boulevard du 11 Novembre 1918, F-69622 Villeurbanne, France

*Received 17 November 1995*

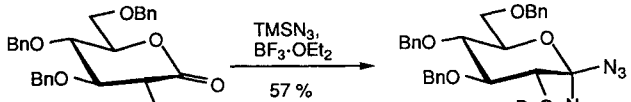
Treatment of peracetylated 1-bromo-β-D-glycopyranosyl chlorides with sodium azide in DMSO or, better, under PTC conditions, led to the corresponding glycopyranosylidene 1,1-diazides, in fair to excellent yield. Tetra-*O*-benzyl-D-glucono-1,5-lactone was converted into the corresponding diazide in 57% yield on treatment with trimethylsilyl azide in the presence of boron trifluoride–diethyl ether complex.

Treatment of peracetylated β-D-glycopyranosyl chlorides with excess *N*-bromosuccinimide under free-radical conditions constitutes the only practical access to the corresponding anomeric chlorobromosugars[1] **1**, **2** and **3**[2] (D-*gluco*, D-*manno*, D-*galacto* configuration). Such dihalides have opened several routes to previously unknown compounds. For example, halogen exchange took place readily in the presence of silver fluoride to give the corresponding anomeric difluorides[1] which, on deacetylation, afforded enzyme substrate analogs useful for inhibition studies.[2,3] Under glycosylation conditions with primary alcohols (MeOH, EtOH), **1** and **2** afforded the corresponding sugar ortholactones in high yield.[4] Whereas substitution of both halogen atoms in **1** by azide anions was shown initially to give the corresponding diazide **4**,[5] peracetylated D-glucono-1,5-ortholactones lend themselves to exchange of one alkoxy group only[6] when treated with trimethylsilyl azide in the presence of boron trifluoride–diethyl ether complex. This offered a high-yielding route to peracetylated alkyl 1-azido-D-glucopyranosides (1(*R*)/1(*S*) ratio 2 : 1) which, in our hands, could not be converted to diazides even under forcing conditions. However, the obtained mono and diazides were shown to undergo unprecedented and stereocontrolled ring expansions on photolysis[7,8] or thermolysis[9] whereas treatment of diazide **4** with triphenylphosphine led to a novel triazolo-fused sugar phosphinimine.[10] These synthetic developments required improved preparations of glycopyranosylidene 1,1-diazides which are reported herein.

Our first reported synthesis of **4** from **1** in 60% yield resorted to silver azide which is prone to explosive decomposition. Use of sodium azide dissolved in a polar aprotic solvent (DMF, HMPA, DMSO) offered a safer alternative. Azidation in DMF generally requires heating whereas HMPA was shown to promote dehydrobromination[1] in the case of **1**. These drawbacks guided our choice towards DMSO as the solvent. Treatment of dihalides **1**, **2** and **3** with excess $NaN_3$ dissolved in DMSO led to the desired diazides **4**, **5** or **6** in 61%, 8%, and 57% yield, respectively. The oily materials **4** and **6** contained no impurities visible by $^1H$ NMR, so that no additional purification was needed in most cases. Although this procedure appeared satisfactory as regards to safety and simplicity, yields ranged from low to moderate even though TLC plates showed only traces (for **5**) and often no side products (for **4** and **6**). Albeit substitution of other encumbered anomeric bromides was shown to occur in high yield under similar conditions,[11] the observed moderate selectivities could stem from the nucleophilic reactivity of DMSO being able to compete with the desired displacements. This assumption was supported by the fact that trials to prepare 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl chloride by stirring the α-bromide in the presence of anhydrous LiCl in DMSO failed, whereas using the literature procedure[12] resorting to HMPA was successful.




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | | % (a) | % (b) |
|---|---|---|---|---|---|---|---|
| **1** | OAc | H | OAc | H | **4** | 61 | 82 |
| **2** | H | OAc | OAc | H | **5** | 8 | 36 |
| **3** | OAc | H | H | OAc | **6** | 57 | 65 |




**7** **8**

Phase-transfer catalysis[13] represented another straightforward and mild method applicable to the synthesis of sugar 1,1-diazides. However, warnings appeared in the literature[14] to underline hazards due to possible reactions between azide salts and halogenated solvents leading to potentially unstable compounds. For this reason, dichloromethane was used for the transformation of **1**, but benzene instead appeared more appropriate in the case of **2** due to the prolonged reaction times required for its complete consumption. Since all the gathered data concerning these reactions point to an $S_N2$ mechanism, the low reactivity of **2** is most probably due to shielding of the β face by the axial acetoxy group at C-2 (D-*manno* configuration) hence, hindering bromine displacement. The corresponding peracetylated D-mannopyranosylidene 1,1-dichloride present up to ca. 10%[1] in **2** was even less reactive since it could be detected by $^{13}C$ NMR in **5** after prolonged treatment. However, the yields recorded under these conditions (82%, 36%, and 65% for **4**, **5** and **6** respectively) were significantly higher, confirming the value of the PTC procedure.

Diazide **8** was prepared by a different route from the corresponding benzyl-protected lactone.[15] Under acidic catalysis, such a lactone has been shown to react with diols[16] or silyl-protected diols,[17] to yield the corresponding spiro ortholactones. Use of trimethylsilyl azide instead appeared a convenient analogous way to the diazides. Indeed, compound **8** was obtained in 57% yield after purification by column chromatography.[18] All the prepared diazides were colorless and stable oils, which showed no decomposition on storage at 0°C. In the IR spectra, diazides **4**, **5** or **6** show a single absorption band near 2130 $cm^{-1}$ ($\nu$ $N_3$), whereas two separated bands are visible for **8**.

In conclusion, we propose three methods for preparing anomeric sugar 1,1-diazides from either acetylated sugar dihalides or tetrabenzyl D-glucono-1,5-lactone. In the first case, halogen substitution was more efficiently achieved by using PTC conditions as compared to treatment with $NaN_3$ in DMSO. Both methods led, in fair to excellent yields, to the D-*gluco* and D-*galacto* diazides of such a high grade that further purification could be avoided. Halogen displacement occurred less selectively in the case of the less reactive D-*manno* configurated dihalide **2**. Whatever the method, substrate reactivity decreased in the following order: D-*gluco* > D-*galacto* > D-*manno*. When applying the PTC method to unreactive substrates, for safety reasons, benzene is to be recommended as the organic solvent. Treatment of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone with trimethylsilyl azide in the presence of boron trifluoride–diethyl ether afforded the corresponding benzylated 1,1-diazide. Since the required substrates are readily available, the proposed methods constitute simple, efficient and safe preparations of protected glycopyranosylidene 1,1-diazides.

**Azidation Reactions in DMSO; General Procedure:**
A suspension of $NaN_3$ (0.78 g, 12 mmol) in dry DMSO (12 mL) was stirred at r.t. until the $NaN_3$ was completely dissolved (~ 1 h). After addition of the chlorobromosugar (1.337 g, 3 mmol), the mixture, protected from light with an aluminum foil, was stirred at r.t. until completion of the transformation. Although the starting material and the product have similar mobilities ($R_f$ ~ 0.65, EtOAc/hexane 4:6), disappearance of the substrate was indicated by the absence of a pink-colored[19] spot on the TLC plates after spraying with a bromine-specific reagent. Although compounds **1**, **2** and **3** were no longer present after 1.5, 24 and 2.5 h, respectively, stirring was generally maintained for a longer time (5–12, 48 and 12 h) to insure complete transformation of minor amounts of the more stable *gem*-dichloride present (~ 10%) in the starting material. Then, the reaction mixture was diluted with water (20 mL) and extracted with $Et_2O$ (3 × 30 mL). Washing of the ether phase followed by drying ($Na_2SO_4$) and concentration led to a residue of high purity as shown by $^{13}C$ NMR. Column chromatography on silica gel with EtOAc/hexane (4:6) as eluent gave analytical samples of diazides **4** and **6** as colorless syrups in 61% and 57% yields respectively, while **5** (8%) remained contaminated by ca. 5% of the C-1 dichloride.

**Azidation Reactions Under PTC Conditions; General Procedure:**
A mixture of $CH_2Cl_2$ (or benzene, for unreactive substrates) (13 mL) and sat. aq $NaHCO_3$ (13 mL) containing $Bu_4NHSO_4$ (1.018 g, 3 mmol), $NaN_3$ (1.95 g, 30 mmol) and the chlorobromosugar (1.337 g, 3 mmol) was vigorously stirred at r.t. until TLC monitoring showed complete consumption of the substrate (the reaction time might vary depending on stirring efficiency). After separation of the organic phase, the aqueous layer was extracted with $CH_2Cl_2$ (2 × 15 mL). After drying ($Na_2SO_4$) and concentration, the residue from the final extractions and the main $CH_2Cl_2$ phase[14] were directly applied to a silica gel column eluted with EtOAc/hexane (25:75) to give the pure diazide. When using benzene as the organic phase and $Et_2O$ for extractions, the diazide obtained after solvent removal was pure enough to avoid further purification steps, although **5** contained the corresponding C-1 dichloride (~ 10%). Applied to substrates **1**, **2** and **3** this procedure (solvent, reaction time, %) led to diazides **4** ($CH_2Cl_2$, 20 h, 82%), **5** ($C_6H_6$, 2–3 weeks, 36%) and **6** ($C_6H_6$, 72 h, 65%). Use of $NaHCO_3$ in smaller amounts (9 mmol) for preparing **5** did not improve the yield.

*2,3,4,6-Tetra-O-acetyl-D-glucopyranosylidene Diazide* **(4)**; colorless syrup; $[\alpha]_D$ + 141 ($c$ = 0.6, $CHCl_3$).

UV (EtOH): $\lambda_{max}$ ($\varepsilon$): 264 (22), 218 nm (180).

IR ($CCl_4$): $\nu$ = 2125 $cm^{-1}$ ($N_3$).

$^1H$ NMR ($CDCl_3$, 200.13 MHz): $\delta$ = 5.37 (t, 1H, $J_{2,3}$ = 9.9, $J_{3,4}$ = 9.6 Hz, H-3), 5.23 (d, 1H, H-2), 5.16 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.17 (dq, 1H, $J_{5,6}$ = 4.6, $J_{5,6'}$ = 2.1 Hz, H-5), 4.28 (dd, 1H, $J_{6,6'}$ = 12.7 Hz, H-6), 4.18 (dd, 1H, H-6'), 2.12, 2.11, 2.04, 2.00 (4 s, 12H, acetyl).

$^{13}C$ NMR ($CDCl_3$, 50.32 MHz): $\delta$ = 170.49, 169.81, 169.32, 169.04 (C=O), 99.90 (C1), 72.08, 70.77, 67.55, 72.17 (C2, C3, C4, C5), 61.11 (C6), 20.63, 20.50, 20.50, 20.29 (4$CH_3$).

*2,3,4,6-Tetra-O-acetyl-D-mannopyranosylidene Diazide* **(5)**; colorless oil; $[\alpha]_D$ + 82 ($c$ = 1.1, $CHCl_3$).

IR (neat): $\nu$ = 2130 $cm^{-1}$ ($N_3$).

$^1H$ NMR ($CDCl_3$, 300.13 MHz): $\delta$ = 5.24 to 5.34 (m, 3H, H-2, H-3, H-4), 4.14 (m, 1H, $J_{5,6}$ = 3.1, $J_{5,6'}$ = 4.7 Hz, H-5), 4.30 (dd, 1H, $J_{6,6'}$ = 12.3 Hz, H-6), 4.25 (dd, 1H, H-6'), 2.23, 2.12, 2.07, 1.98 (4 s, 12H, acetyl).

$^{13}C$ NMR ($CDCl_3$, 50.3 MHz): $\delta$ = 170.5, 169.6, 169.6, 169.1 (C=O), 99.5 (C-1), 72.6, 69.1, 64.8, 71.1 (C-2, C3, C4, C5), 61.8 (C6), 20.65, 20.65, 20.53, 20.49 (4$CH_3$).

MS (CI) $NH_3$: $m/z$ (%) = 432 $[M + 18]^+$, 372 $[M - N_3]^+$.

*2,3,4,6-Tetra-O-acetyl-D-galactopyranosylidene Diazide* **(6)**; colorless syrup; $[\alpha]_D$ + 155 ($c$ = 0.7, $CHCl_3$).

IR (neat): $\nu$ = 2130 $cm^{-1}$ ($N_3$).

$^1H$ NMR ($CDCl_3$, 200.13 MHz): $\delta$ = 5.465 (dd, 1H, $J_{3,4}$ = 2.8, $J_{4,5}$ = 1.1 Hz, H-4), 5.443 (d, 1H, $J_{2,3}$ = 10.3 Hz, H-2), 5.205 (dd, 1H, H-3), 4.37 (t, 1H, $J_{5,6}$ = ~ 6.5, $J_{5,6'}$ = ~ 6.5 Hz, H-5), 4.17 (d, 2H, H-6, H-6'), 2.070, 2.066, 1.986, 1.983 (4 s, 12H, acetyl).

$^{13}C$ NMR ($CDCl_3$, 50.32 MHz): $\delta$ = 170.29, 169.98, 169.75, 169.28 (C=O), 100.60 (C1), 71.49, 68.90, 67.02, 69.58 (C2, C3, C4, C5), 60.92 (C6), 20.61, 20.57, 20.48, 20.42 (4$CH_3$).

**2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosylidene Diazide (8):**
2,3,4,6-Tetra-*O*-benzyl-D-glucono-1,5-lactone (0.538 g, 1 mmol), $TMSN_3$ (1.152 g, 1.315 mL, 10 mmol) and $BF_3 \cdot OEt_2$ (0.568 g, 0.507 mL, 4 mmol) were dissolved in dry $CH_2Cl_2$ (10 mL) at 0°C. The reaction mixture was protected from light and stirred for 48 h under nitrogen while temperature was allowed to rise to r.t. Completion of the reaction was indicated by TLC with $CH_2Cl_2$/EtOAc/hexane (2:1:9) which showed the formation of a new, more mobile compound together with minor polar contaminants. Addition of sat. aq $NaHCO_3$ (20 mL) and workup led to a residue which was purified by column chromatography (same eluent) to give 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene diazide; yield: 0.347 g (57%) as a colorless syrup.

$[\alpha]_D$ + 147.5 ($c$ = 0.7, $CHCl_3$).

IR (neat): $\nu$ = 2130, 2110 $cm^{-1}$ ($N_3$).

$^1H$ NMR ($CDCl_3$, 300.13 MHz): $\delta$ = 3.87 (ddd, 1H, $J_{4,5}$ = 9.5, $J_{5,6}$ = ~ 3, $J_{5,6'}$ = ~ 1.5 Hz, H-5), 3.83 and 3.73 (2t, $J_{2,3}$ = 9.1, $J_{3,4}$ = ~ 9.5 Hz, H-3, H-4), 3.75 (dd, 1H, $J_{6,6'}$ = 11 Hz, H-6), 3.72 (dd, 1H, H-6'), 3.65 (d, 1H, H-2), 4.95, 4.87, 4.81, 4.79, 4.76, 4.61, 4.55, 4.52 (8 d, $J_{gem}$ = ~ 11 Hz, benzyl), 7.1 to 7.4 (m, 20H, phenyl).

$^{13}C$ NMR ($CDCl_3$, 50.32 MHz): $\delta$ = 138.32, 138.02, 138.00, 137.41 (arom, *ipso*), 128.48, 128.23, 128.03, 127.91, 127.89, 127.84, 127.76 (arom *CH*), 101.59 (C1), 82.77, 76.85, 75.28, 84.14 (C2, C3, C4, C5), 67.80 (C6), 75.96, 75.67, 75.17, 73.49 (C benzyl).

*Support from Université Claude-Bernard Lyon I and Centre National de la Recherche Scientifique is gratefully acknowledged. Elemental analyses were performed by the Service Central d'Analyses (CNRS, Solaize, France). Mr Peter Haug is thanked for the PTC synthesis of compound* **5**.

(1) Praly, J.-P.; Brard, L.; Descotes, G.; Toupet, L. *Tetrahedron* **1989**, *45*, 4141.
(2) Srinivasan, K.; Konstantinidis, A.; Sinnott, M.L.; Hall, B.G. *Biochem. J.* **1993**, *291*, 15.
(3) Konstantinidis, A.; Sinnott, M.L. *Biochem. J.* **1991**, *279*, 587.
(4) Praly, J.-P.; El Kharraf, Z.; Corringer, P.-J.; Descotes, G. *Tetrahedron* **1990**, *46*, 65.
(5) Praly, J.-P.; El Kharraf, Z.; Descotes, G. *J. Chem. Soc., Chem. Commun.* **1990**, 431.
(6) Praly, J.-P.; Di Stèfano, C., Bouchu, M.-N.; El Kharraf, Z., Faure, R.; Descotes, G. *Tetrahedron* **1993**, *49*, 9759.
(7) Praly, J.-P.; Di Stèfano, C.; Descotes, G.; Faure, R. *Tetrahedron Lett.* **1994**, *35*, 89.
(8) Di Stèfano, C.; Descotes, G.; Praly, J.-P. *Tetrahedron Lett.* **1994**, *35*, 93.
(9) Yokoyama, M.; Matsushita, M.; Hirano, S.; Togo, H. *Tetrahedron Lett.* **1993**, *34*, 5097.
(10) Pintér, I.; Kovács, J.; Kajtár-Peredy, M.; Argay, G.; Kálmán, A.; Somsák, L.; Györgydeák, Z.; Praly, J.-P.; Descotes, G. EUROCARB VIII, Sevilla, July 2–7, 1995, Abstr. A-134. Kovács, J.; Pintér, I.; Kajtár-Peredy, M.; Praly, J.-P.; Descotes, G. *Carbohydr. Res.* **1995**, *279*, C1.
(11) Praly, J.-P.; Di Stèfano, C.; Descotes, G.; Faure, R.; Somsák, L.; Eperjesi, I. *Tetrahedron Lett.* **1995**, *36*, 3329.
(12) Blanc-Muesser, M.; Defaye, J.; Driguez, H. *Carbohydr. Res.* **1978**, *67*, 305.
(13) Tropper, F.D.; Andersson, F.O.; Braun, S.; Roy, R. *Synthesis* **1992**, 618.
(14) Peat, N.P.; Weintraub, P.M. Chem. Eng. News April 19, **1993**, 4. Hruby, V.J.; Boteju, L.; Li, G. *ibid* October 11, **1993**, 2.
(15) Benhaddou, R.; Czernecki, S.; Farid, W.; Ville, G.; Xie, J.; Zegar, A. *Carbohydr. Res.* **1994**, *260*, 243.
(16) Horito, S.; Asano, K.; Umemura, K.; Hashimoto, H.; Yoshimura, J. *Carbohydr. Res.* **1983**, *121*, 175.
(17) Yoshimura, J.; Asano, K.; Umemura, K.; Horito, S.; Hashimoto, H. *Carbohydr. Res.* **1983**, *121*, 187.
(18) In our hands, attempts to extend this methodology to 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexono-1,5-lactone were not promising.
(19) Detection of bromine containing products on TLC plates requires spraying first a fluorescein solution in abs. EtOH (0.1% w/v) then a 1:1 (v/v) mixture of $H_2O_2$ (30% in water) and HOAc followed by charring. Bromine containing compounds produce pink-colored spots on the plates.