Partially Benzylated Derivatives of 6-Deoxy-D-glucose

Shinkiti KOTO,* Naohiko MORISHIMA,[1] Yoko MORI,[1] Hitoshi TANAKA, Seiichi HAYASHI, Yumi IWAI, and Shonosuke ZEN
School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108
(Received January 24, 1987)

Synopsis. Several partially benzylated derivatives of 6-deoxy-D-glucose (D-quinovose) were synthesized from appropriate di-*O*-benzyl-D-glucosides whose primary hydroxyl group is unprotected, via unimolar tosylation and subsequent reduction with $LiAlH_4$.

6-Deoxy-D-glucose (D-quinovose, **1**) consititutes various sugar-clusters occurring in saponins, antibiotics, etc.[2] An attempt to synthesize such clusters by a direct coupling reaction[3] between a protected saccharide with a hemiacetal OH and that with the OH to be glycosylated requires various benzyl derivatives of **1**. This report describes the synthetic routes for several D-quinovosyl donors and glycosyl acceptors of **1** from the known di-*O*-benzyl derivatives of appropriate D-glucosides with unprotected 6-OH.

The acceptor **13** had been synthesized from **11**[4] via unimolar tosylation and reduction by $LiAlH_4$ (LAH).[5] This routine was carried out for **2**[6] and **5**[7] to give **4** and **7**, respectively. Compound **7** was also obtained by a controlled benzylation[8] of **10**.

As for donors, **17** was first synthesized from **14**[9] via benzylation with $PhCH_2Br$ and NaH in DMF,[10] reduction and hydrolysis. It was found that an analogous benzylation of **14** in DMSO[11] mainly gave the 2,4-dibenzyl ether **23**.

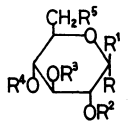
The replacement of one benzyl of **17** with participating Ac or non-participating allyl (AL) as a temporary protecting group[12] was then carried out. The 2-*O*-AL derivative **21** was synthesized from **18**[6] via tosylation and reduction, followed by allylation and hydrolysis. This process was also applied for the conversion of **22**[7] and **26**[13] into **25** and **29**, respectively.

The 2-*O*-Ac derivative **32** was synthesized from **31** by a through-process including orthoester formation.[14] The starting **31** was prepared from **14**[9] via LAH-reduction,[15] acetylation and acetolysis. On the other hand, the 3- and the 4-*O*-acetates **38** and **43** were syn-

Table 1. Physical and Analytical Data of Compounds

Cpd.	Mp (θ_m/°C) °C	$[\alpha]_D^{20}$ (*c*, $CHCl_3$) deg	Mol. Form.	Anal/% Calcd C	Calcd H	Found C	Found H
3	—	+73 (0.7)	$C_{34}H_{36}O_8S$	67.53	6.00	67.15	6.01
4	63—67	+117 (0.2)	$C_{27}H_{30}O_5$	74.63	6.96	74.81	6.88
6	65—69	+88 (0.7)	$C_{34}H_{36}O_8S$	67.53	6.00	67.56	6.06
7	41—43	+110 (1.4)	$C_{27}H_{30}O_5$	74.63	6.96	74.14	7.23
9	44—46	+72 (1.7)	$C_{20}H_{24}O_8S$	56.59	5.70	56.26	5.76
10	—	+130 (0.1)	$C_{13}H_{18}O_5$	61.40	7.28	60.59	7.08
12	—	+47 (1.4)	$C_{34}H_{36}O_8S$	67.53	6.00	67.50	6.01
13[a]	39—40	+72 (0.6)	$C_{27}H_{30}O_5$	74.63	6.96	74.34	6.96
15	—	+24 (4.5)	$C_{35}H_{38}O_8S$	67.74	6.19	67.85	6.15
16	—	+20 (2.2)	$C_{28}H_{32}O_5$	74.97	7.19	74.91	7.06
17	103—104	+13 (0.5)	$C_{27}H_{30}O_5$	74.63	6.95	74.37	6.90
19	59—61	+81 (2.0)	$C_{28}H_{32}O_8S$	63.62	6.10	63.23	6.09
20	106—109	+102 (1.0)	$C_{21}H_{26}O_5$	70.37	7.31	70.90	7.31
21	50—52	+19 (0.8)	$C_{23}H_{28}O_5$	71.85	7.34	71.02	7.28
23	—	+63 (1.1)	$C_{28}H_{32}O_8S$	63.62	6.10	64.34	6.49
24	—	+78 (1.2)	$C_{21}H_{26}O_5$	70.37	7.31	70.65	7.34
25	42—43	+35 (0.5)	$C_{23}H_{28}O_5$	71.85	7.34	71.27	7.34
27	—	+18 (2.0)	$C_{28}H_{32}O_8S$	63.62	6.10	63.76	6.14
28	—	+45 (0.5)	$C_{21}H_{26}O_5$	70.37	7.31	69.99	7.41
29	58—59	+38 (0.4)	$C_{23}H_{28}O_5$	71.85	7.34	71.60	7.26
32[b]	93—94	+63 (0.3)	$C_{22}H_{26}O_6$	68.38	6.78	68.16	6.85
34	55—57	−19 (1.5)	$C_{16}H_{24}O_9S$	48.97	6.16	48.17	6.34
35	41—42	−12 (0.8)	$C_{15}H_{24}O_9$	51.72	6.94	51.63	6.91
36	—	+18 (0.9)	$C_{23}H_{30}O_6$	68.64	7.51	68.90	7.65
38	100—101	+45 (0.3)	$C_{22}H_{26}O_6$	68.38	6.78	68.00	6.86
39	117—118[c]	−47 (0.5)	$C_{16}H_{21}O_7 \cdot 0.5H_2O$	57.48	6.63	57.68	6.87
40	65—66	−19 (0.3)	$C_{23}H_{30}O_7$	66.01	7.23	65.87	7.24
41	—	−10 (2.2)	$C_{30}H_{36}O_9S$	62.92	6.34	62.62	6.25
42	88	−36 (0.2)	$C_{23}H_{30}O_6$	68.64	7.51	68.45	7.37
43	100—103	+7 (0.3)	$C_{22}H_{26}O_6$	68.38	6.78	68.15	6.72

a) *Bull. Chem. Soc. Jpn.*, **54**, 2169 (1981); $[\alpha]_D$ +51.5° (*c* 0.84, $CHCl_3$). b) *Agr. Biol. Chem.* **47**, 2929 (1983); for L-form: mp 100—103 °C, $[\alpha]_D^{20}$ −54°—−48° (*c* 1.5, EtOH). c) Sintered at 98 °C.



Cpd.	R	R^1	R^2	R^3	R^4	R^5	Cpd.	R	R^1	R^2	R^3	R^4	R^5
1	OH,	H	H	H	H	H	**23**	OMe	H	Bn	H	Bn	OTs
2	OBn	H	H	Bn	Bn	OH	**24**	OMe	H	Bn	H	Bn	H
3	OBn	H	H	Bn	Bn	OTs	**25**	OH,	H	Bn	AL	Bn	H
4	OBn	H	H	Bn	Bn	H	**26**	OMe	H	Bn	Bn	H	OH
5	OBn	H	Bn	H	Bn	OH	**27**	OMe	H	Bn	Bn	H	OTs
6	OBn	H	Bn	H	Bn	OTs	**28**	OMe	H	Bn	Bn	H	H
7	OBn	H	Bn	H	Bn	H	**29**	OH,	H	Bn	Bn	AL	H
8	OBn	H	H	H	H	OH	**30**	OMe	H	Ac	Ac	Ac	H
9	OBn	H	H	H	H	OTs	**31**	OAc	H	Ac	Ac	Ac	H
10	OBn	H	H	H	H	H	**32**	OH,	H	Ac	Bn	Bn	H
11	OBn	H	Bn	Bn	H	OH	**33**	H	OME	H	H	H	OH
12	OBn	H	Bn	Bn	H	OTs	**34**	H	OME	H	H	H	OTs
13	OBn	H	Bn	Bn	H	H	**35**	H	OME	Ac	Ac	Ac	H
14	OMe	H	H	H	H	OTs	**36**	H	OME	Bn	H	Bn	H
15	OMe	H	Bn	Bn	Bn	OTs	**37**	H	OME	Bn	Ac	Bn	H
16	OMe	H	Bn	Bn	Bn	H	**38**	OH,	H	Bn	Ac	Bn	H
17	OH,	H	Bn	Bn	Bn	H	**39**	H	OME	H	H		
18	OMe	H	H	Bn	Bn	OH	**40**	H	OME	Bn	Bn	H	OH
19	OMe	H	H	Bn	Bn	OTs	**41**	H	OME	Bn	Bn	H	OTs
20	OMe	H	H	Bn	Bn	H	**42**	H	OME	Bn	Bn	H	H
21	OH,	H	AL	Bn	Bn	H	**43**	OH,	H	Bn	Bn	Ac	H
22	OMe	H	Bn	H	Bn	OH							

AL=$-CH_2CH{=}CH_2$, Bn=$-CH_2Ph$, ME=$-CH_2CH_2OMe$, Ts=$-SO_2C_6H_4Me$(p).

thesized from the 2-methoxyethyl (ME) glucoside **33**.[16] The acetate **35** derived from **33** was directly converted into the 2,4-dibenzyl ether **36** by a controlled benzylation[8,17] with $PhCH_2Cl$ and KOH in a 37% yield. The structure of the acetate **37** was confirmed by the measurement of ^1H NMR at 400 MHz; the most deshielded (δ=5.19) was H-3 among five ring protons.[8] Regeneration of 1-OH[17] gave **38**. The dibenzyl ether **40** was transformed into **43** via tosylation and reduction, followed by acetylation and regeneration of 1-OH.

Experimental[3,6-8]

The solvent systems for gradient elusion for column chromatography on silica gel were toluene-2-butanone (TB), hexane-EtOAc (HE), and $CHCl_3$-MeOH (CM).

Benzyl 3,4-Di-*O*-benzyl-6-*O*-tosyl-α-D-glucopyranoside (3). To a flask containing **2**[6] (443 mg) and tosyl chloride (225 mg), pyridine (4.5 ml) was added under stirring at −10 °C. The mixture was stirred for 1 h and then left for 3 h at room temp. Work-up[9] and chromatography (TB) gave **3** (378 mg, 64%).

A similar procedure was applied for **5**,[7] **8**,[18] **11**,[4] **18**,[6] **22**,[7] **26**,[13] **33**,[16] and **40** to give **6** (71%), **9** (60%, CM instead of TB), **12** (82%), **19** (75%), **23** (91%), **27** (75%), **34** (75%, CM instead of TB), and **41** (65%), respectively.

Benzyl 3,4-Di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (4). Compound **3** (269 mg) was refluxed in Et_2O (6 ml) containing LAH (70 mg) for 1 h. After quenching with EtOAc, filtration, and evaporation, chromatography (TB) gave **4** (179 mg, 92%).

A similar reduction was carried out for **6**, **12**, **15**, **19**, **23**, **27**, and **41** to afford **7** (74%), **13** (100%), **16** (98%), **20** (97%), **24** (84%), **28** (84%), and **42** (84%), respectively.

Methyl 2,3,4-Tri- and 2,4-Di-*O*-benzyl-6-*O*-tosyl-α-D-glucopyranosides (15 and 23). To a mixture of **14** (305 mg), $PhCH_2Br$ (1.2 ml) and DMF (3 ml), NaH in oil suspension (300 mg; 60% of NaH by wt) was added at 0 °C. The mixture was stirred for 50 min and then for 40 min at room temp. Work-up[10] and chromatography (HE) gave **15** (413 mg, 76%).

An analogous benzylation of **14** (154 mg) using $PhCH_2Br$ (0.45 ml), NaH in oil suspension (74 mg; 60% of NaH by wt), and DMSO (1.7 ml) for 45 min at 15 °C gave **15** (≈70 mg, ≈25%) and **23** (116 mg, 50%).

Benzyl 2,4-Di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (7). Compound **10** (33.3 mg) was stirred in $PhCH_2Cl$ (0.7 ml) containing crushed KOH (22 mg) for 1 h at 120 °C, followed by work-up and chromatography (TB),[8] to give **7** (30.4 mg, 53%).

2,3,4-Tri-*O*-benzyl-6-deoxy-D-glucopyranose (17). A mixture of **16** (295 mg), AcOH (4 ml), and aq H_2SO_4 (3M (M=mol dm^{-3}), 0.05 ml) was stirred for 2 h at 90 °C. Work-up and chromatography (TB)[19] gave **17** (118 mg, 42%).

2-*O*-Allyl-3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose (21). A mixture of **20** (80.4 mg), NaH in oil suspension (40.4 mg; 60% of NaH by wt), and ALBr (0.58 ml) was refluxed for 40 min. Filtration and evaporation gave a residue, which was stirred in a mixture of AcOH (1.6 ml) and aq H_2SO_4 (3M, 26

μl) for 1 h at 100 °C. Work-up and chromatography (TB)[19] gave **21** (39.3 mg, 46%).

A similar procedure was applied for **24** and **28** to furnish **25** (56%) and **29** (62%), respectively.

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside (30). A mixture of **14**[9] (500 mg), LAH (145 mg), and Et_2O (15 ml) was refluxed for 4 h. After quenching with EtOAc, filtration, and evaporation,[15] the solid obtained was acetylated with Ac_2O (10 ml) in pyridine (10 ml) for 2h at 80 °C. Evaporation and chromatography (TB) gave **30** (333 mg, 77% (Found: C, 51.50; H, 6.72%)), mp 73—75 °C, $[\alpha]_D^{20}$ +156° (*c* 0.8, $CHCl_3$) (lit,[20] mp 76—77 °C, $[\alpha]_D^{20}$ +153° (*c* 1.6, $CHCl_3$)).

A similar procedure was applied for **34** to give **35** (50%). The tosylate **9** was similarly reduced, followed by chromatography (CM) without acetylation, to give **10** (63%).

1,2,3,4-Tetra-*O*-acetyl-6-deoxy-α-D-glucopyranose (31). To a soln of **30** (107 mg) in Ac_2O (2.2 ml), a soln of H_2SO_4 in Ac_2O (10%, 1.2 ml) was added at 0 °C. The mixture was stirred for 1 h at room temp and then poured onto ice. Work-up and chromatography (TB) gave **31** (75.2 mg, 64% (Found: C, 50.68; H, 6.13%)), mp 116—118 °C, $[\alpha]_D^{20}$ +113° (*c* 0.3, $CHCl_3$) (lit,[21] mp 117 °C, $[\alpha]_D^{20}$ +122° (*c* 1.3, $CHCl_3$)).

2-*O*-Acetyl-3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose (32). To a soln of **31** (72.4 mg) in $CHCl_3$ (1 ml) containing AcBr (86 μl), H_2O (15 μl) was added at 0 °C. The mixture was stirred for 1 h at room temp and then evaporated. The residue was treated with 2,6-dimethylpyridine (0.14 ml) and ethanol (0.17 ml) in $MeNO_2$ (0.26 ml) overnight at room temp. The soln was diluted with $CHCl_3$ and poured into aq $NaHCO_3$ (5%, 5 ml). The organic layer was evaporated and then stirred in $PhCH_2Cl$ (1.5 ml) containing KOH (0.63 g) for 2 h at 120 °C. The mixture was diluted with toluene and washed with H_2O. The organic layer was evaporated and then stirred in aq AcOH (80%, 2 ml) for 1 h at 50 °C. Work-up and chromatography (TB)[14] gave **36** (33.0 mg, 39%).

2-Methoxyethyl 2,4-Di-*O*-benzyl-6-deoxy-β-D-glucopyranoside (36). A mixture of **35** (63.6 mg), crushed KOH (71.6 mg) and $PhCH_2Cl$ (1.5 ml) was stirred for 3.5 h at 100 °C. Work-up and chromatography (TB)[8] gave **36** (27.6 mg, 38%).

3-*O*-Acetyl-2,4-di-*O*-benzyl-6-deoxy-D-glucopyranose (38). Acetylation of **36** (27.5 mg) with Ac_2O (1 ml) and pyridine (1 ml), followed by chromatography (TB), gave **37** (28.4 mg); ^1H NMR recorded with a Varian XL-400 spectrometer in H-H COSY mode (CCl_4) δ=1.31 (3H, d, $J_{5,6}$=6.0 Hz, $C\underline{H}_3$-5), 1.98 (3H, s, $C\underline{H}_3CO$), 3.17 (1H, t, $J_{3,4}$=$J_{4,5}$=9.5 Hz, H-4), 3.33 (1H, dd, $J_{1,2}$=8.0 Hz, $J_{2,3}$=9.5 Hz, H-2), 3.38 (3H, s, $C\underline{H}_3O$), 3.46 (1H, m, H-5), 4.48 (1H, d, H-1), 5.19 (1H, t, H-3). This was then treated with $TiCl_4$ (4.3 μl) in CH_2Cl_2 (0.6 ml) for 15 min at room temp, processed, and adsorbed on silica-gel column.[17] The column was left overnight and then eluted with TB to give **38** (18.9 mg, 72% form **36**).

A similar two-step routine for **42** gave **43** (74%).

2-Methoxyethyl 4,6-*O*-Benzylidene-β-D-glucopyranoside (39). Compound **33**[16] (6.28 g) was treated with PhCHO (45 ml) containing $ZnCl_2$ (7 g) for 5.5 h at room temp. Work-up and crystallization with diisopropyl ether furnished **39** (5.72 g, 66%).

2-Methoxyethyl 2,3-Di-*O*-benzyl-β-D-glucopyranoside (40). The acetal **39** (300 mg) was stirred in $PhCH_2Cl$ (6 ml) containing KOH (0.8 g) for 5 h at 100 °C. After filtration and evaporation, the residue was stirred in aq AcOH (80%, 6 ml) for 0.3 h at 100 °C. Work-up and chromatography (TB) gave **40** (314 mg, 82%).

List of characteristic signals (δ) of ^1H NMR recorded at 90 MHz with a Varian EM-390 spectrometer (T=CCl_4, C=$CDCl_3$, W=D_2O (ext. TMS)); MC=$C\underline{H}_3$-5 (3H, d, *J*=6.0 Hz), MA=$C\underline{H}_3CO$ (3H, s), MT=$C\underline{H}_3C_6H_4$ (3H, s), MO=$C\underline{H}_3O$ (3H, s), B=>C$\underline{H}$Ph (1H, s), L=-C$\underline{H}$=CH_2 (1H, m): **3** (T; 2.36 (MT)), **4** (T; 1.17 (MC)), **6** (T; 2.37 (MT)), **7** (T; 1.13 (MC)), **9** (C; 2.40 (MT)), **10** (W; 1.63 (MC)), **12** (T; 2.34 (MT)), **13** (T; 1.16 (MC)), **15** (T; 2.34 (MT), **3.24** (MO)), **16** (T; 1.13 (MC), 3.27 (MO)), **17** (T; 1.16 (MC-α), 1.24 (MC-β)), **19** (T; 2.37 (MT), 3.30 (MO)), **20** (T; 1.17 (MC), 3.34 (MO)), **21** (T; 1.17 (MC-α), 1.21 (MC-β), ≈5.9 (L)), **23** (T; 2.37 (MT), 3.20 (MO)), **24** (T; 1.14 (MC), 3.26 (MO)), **25** (T; 1.15 (MC-α), 1.23 (MC-β), ≈5.8 (L)), **27** (T; 2.36 (MT), 3.21 (MO)), **28** (T; 1.13 (MC), 3.28 (MO)), **29** (T; 1.17 (MC-α), 1.25 (MC-β), ≈5.8 (L)), **32** (T; 1.18 (MC-α), 1.20 (MC-β), 1.91 (MA-α), 2.06 (MA-β)), **34** (C; 2.40 (MT), 3.33 (MO)), **35** (T; 1.19 (MC), 1.94 (MA), 1.96 (2MA), 3.27 (MO)), **36** (T; 1.19 (MC), 3.28 (MO)), **38** (T; 1.20 (MC-α), 1.21 (MC-β), 1.87 (MA-α), 1.95 (MA-β)), **39** (C; 3.37 (MO), 5.51 (B)), **40** (T; 3.26 (MO)), **41** (T; 2.41 (MT), 3.32 (MO)), **42** (T; 1.22 (MC), 3.27 (MO)); **43** (T; 1.07 (MC-α), 1.13 (MC-β), 1.86 (MA-α and MA-β)).

References

1) Present address: School of Nursing, Kitasato University, Kitasato, Sagamihara 228.

2) I. Kitagawa, *Kagaku Sosetsu*, **25**, 201 (1979); K. Okano, T. Nakamura, Y. Kamiya, and S. Ikegami, *Agric. Biol. Chem.*, **45**, 805 (1981), G. R. Pettit, G. M. Cragg, D. Gust, and P. Brown, *Can. J. Chem.*, **60**, 544 (1982); K. Harada, S. Ito, and M. Suzuki, *Tetrahedron Lett.*, **23**, 2479 (1982); H. Seto, N. Otake, M. Koyama, H. Ogino, Y. Kodama, N. Nishizawa, T. Tsuruoka, and S. Inouye, *ibid.*, **24**, 497 (1983); M. Honda and H. Komori, *ibid.*, **27**, 3369 (1986).

3) S. Koto, N. Morishima, K. Takenaka, C. Uchida, and S. Zen, *Bull. Chem. Soc. Jpn.*, **58**, 1464 (1985), S. Koto, K. Yago, S. Zen, F. Tomonaga, and S. Shimada, *ibid.*, **59**, 411 (1986).

4) A. Lubineau, A. Thieffry, and A. Veyrières, *Carbohydr. Res.*, **46**, 143 (1976).

5) M. Matsuzawa, K. Kubo, H. Kodama, M. Funabashi, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **54**, 2169 (1981).

6) S. Koto, N. Morishima, T. Yoshida, M. Uchino, and S. Zen., *Bull. Chem. Soc. Jpn.*, **56**, 1171 (1983).

7) S. Koto, S. Inada, T. Yoshida, M. Toyama, and S. Zen, *Can. J. Chem.*, **59**, 255 (1981).

8) S. Koto, K. Takenaka, N. Morishima, A. Sugimoto, and S.Zen, *Bull. Chem. Soc. Jpn.*, **57**, 3603 (1984) and the preceding reports.

9) F. Cramer, H. Otterbach, and H. Springmann, *Chem. Ber.*, **92**, 384 (1959).

10) J. S. Brimacombe, B. D. Jones, M. Stacey, and J. J. Willard, *Carbohydr. Res.*, **2**, 167 (1966).

11) T. Iwashige and H. Saeki, *Chem. Pharm. Bull.*, **15**, 1803 (1967).

12) C. A. A. van Boeckel and T. Beetz, *Recl. Trav. Chim. Pays-Bas*, **104**, 171 (1985).

13) K. Freudenberg and E. Plankenhorn, *Chem. Ber.*, **73**, 621 (1940).

14) S. Koto, N. Morishima, H. Sato, Y. Sato, and S. Zen, *Bull. Chem. Soc. Jpn.*, **58**, 120 (1985).

15) M. E. Evans, L. Long, Jr., and F. W. Parrish, *J. Org. Chem.*, **33**, 1074 (1968).

16) B. Helferich and H. H. Hiltmann, *Justus Liebigs Ann. Chem.*, **531**, 160 (1937).

17) N. Morishima, S. Koto, K. Kanemitsu, and S. Zen, *Chem. Lett.*, **1983**, 1189.

18) S. Koto, N. Morishima, C. Kusuhara, S. Sekido, T. Yoshida, and S. Zen., *Bull. Chem. Soc. Jpn.*, **55**, 2995 (1982).

19) S. Koto, N. Morishima, Y. Miyata, and S. Zen, *Bull. Chem. Soc. Jpn.*, **49**, 2639 (1976).

20) E. V. E. Roberts, J. C. P. Schwarz, and C. A. McNab, *Carbohydr. Res.*, **7**, 311 (1968).

21) S. Hardegger and R. M. Montavon, *Helv. Chim. Acta*, **29**, 1199 (1946).