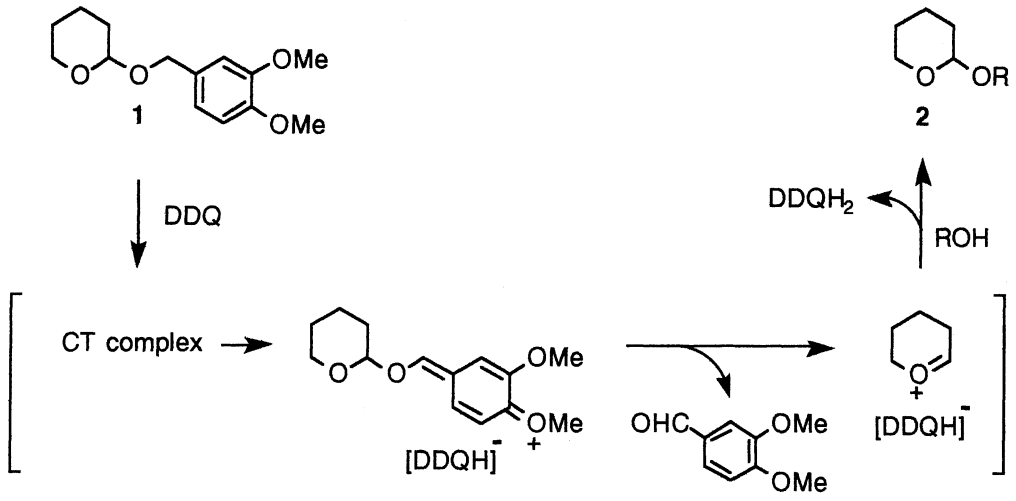
CHEMISTRY LETTERS, pp. 85-88, 1993.

Utility of 3,4-Dimethoxybenzyl (DMPM) Glycosides. A New Glycosylation Triggered by 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) Oxidation

Junji INANAGA,* Yasuo YOKOYAMA, and Takeshi HANAMOTO
Institute for Molecular Science, Myodaiji, Okazaki 444

A new glycosylation which proceeds through the formation of charge transfer (CT) complex of DMPM glycosides with DDQ followed by the oxidation-triggered fragmentation of the intermediates has been developed. Primary, secondary, and tertiary alcohols are used as glycosyl acceptors for the formation of 2-deoxyglycoside derivatives.

Invention of new glycosyl donors for the glycosylation has been and still is of intense interest in carbohydrate chemistry.[1] We propose here a new glycosyl donor, DMPM glycoside, which can be activated by the DDQ oxidation.[2] In this process, the DMPM group; it was originally devised as a useful protective group for hydroxyl functions;[3] works as an activating group through the formation of its CT complex with DDQ as shown in Scheme 1.



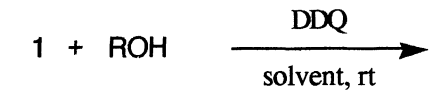
Scheme 1.

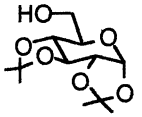
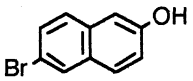
In the first place, 3,4-dimethoxybenzyl tetrahydropyranyl ether (**1**)[4] was employed as a model compound, and its transetherification with 1-octanol to give **2** (R=octyl) was examined in various solvents.

As shown in Table 1 (Runs 1-4), the use of more polar solvent gave a better yield (C_6H_6 < CH_2Cl_2 < THF < CH_3CN).[5] The order may reflect the relative stability of the ionic intermediates in each solvent. The reaction with

other alcohols, including a sugar alcohol and a phenol, also proceeded smoothly to give the corresponding THP ethers in good yields.[6]

Table 1. Transetherification of **1** in Various Solvents and with Various Alcohols [a]



Run	Solvent	ROH	Time/h	Yield[b]/%
1	C_6H_6	1-Octanol	0.5	34
2	CH_2Cl_2	1-Octanol	0.5	41
3	THF	1-Octanol	0.5	56
4	CH_3CN	1-Octanol	0.5	99
5	CH_3CN		0.5	63
6	CH_3CN	2-Octanol	2	69
7	CH_3CN/CH_2Cl_2 (1 : 1)[c]	Cholesterol	0.5	84
8	CH_3CN		3	54

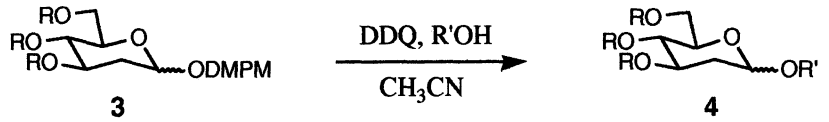
a) A mixture of **1** (0.2 mmol), ROH (0.2 mmol), and DDQ (0.24 mmol) was stirred for 0.5 h. b) Isolated yield. c) The mixed-solvent was used due to the low solubility of cholesterol.

Then, the method was applied to the glycosylation of DMPM 3,4,6-tri-*O*-acetyl-2-deoxyglucopyranoside (**3**, R=Ac)[7] and its tri-*O*-benzyl derivative (**3**, R=Bn). The results are summarized in Table 2. A representative procedure follows. (Run 1) A mixture of **3** (R=Ac, 44 mg, 0.1 mmol), 1-octanol (13 mg, 0.1 mmol), and DDQ (30 mg, 0.12 mmol) in CH_3CN (3 mL) was stirred at room temperature for 3 h under argon. The initial deep blue solution of the CT complex has gradually changed to dark orange-red. Evaporation of the solvent followed by chromatographic purification of the residue on silica gel afforded the corresponding **4** (R=octyl, 34.2 mg, 85%) as an oil.

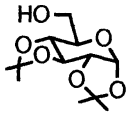
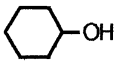
Primary and secondary alcohols, and even *tert*-butyl alcohol reacted to give the corresponding glycosides (**4**) in good yields. The stereoselectivities observed in these reactions are, however, generally low (α/β=1.2/1~2/1). In the reaction with 2-octanol a considerable amount of 3,4,6-tri-*O*-acetyl-2-deoxyglucose (**4**, R'=H) was produced as a by-product (ca. 30%) (Run 3). This may arise via the attack of 2-octanol on the benzylic carbon of the DMPM glycopyranoside (route b) followed by hydrolysis as shown in Scheme 2.[8] Therefore, the reaction temperature was raised to 80 °C in the hope that the framgmentation step (liberation of 3,4-dimethoxybenzaldehyde, route a)

would be accelerated competing with the side reaction. As expected, better yields were obtained as shown in runs 4-7. Unfortunately, however, the use of DMPM 2,3,4,6-tetra-*O*-benzylglucopyranoside[9] as a glycosyl donor did not afford the desired glycosides even at 80 °C, but simply caused the C-O bond cleavage of the DMPM ether to give the corresponding pyranose.

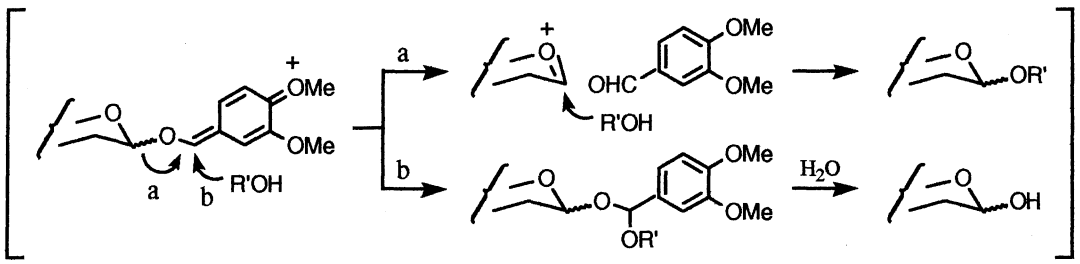
Table 2. Glycosylation of DMPM 2-Deoxyglucopyranosides (**3**) with Various Alcohols[a]



3 **4**

Run	R	R'OH	Temp/°C	Time/h	Yield[b]/%
1	Ac	1-Octanol	23	3	85
2	Ac		23	4	72
3	Ac	2-Octanol	23	3	65
4	Ac	2-Octanol	80	0.5	85
5	Ac		80	1	96
6	Ac	Cholesterol	80	1	85
7	Ac	*t*-BuOH	80	1	74
8	Bn	*t*-BuOH	23	3	63

a) For the reaction conditions, see the text. b) Isolated yield.



Scheme 2.

The present method, which is characterized by the unique oxidative activation process,[10] would be useful for the synthesis of a variety of 2-deoxyglycosides as an alternative to the previous methods.[11]

References

1) For recent reviews, see: A. F. Bochkov and G. E. Zaikov, "Chemistry of O-Glycosidic Bond", Pergamon Press (1979): H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, **21**, 155 (1982); *Chem. Soc. Rev.*, **13**, 15 (1984); R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **25**, 212 (1986); *Pure Appl. Chem.*, **61**, 1257 (1989); H. Kunz, *Angew. Chem., Int. Ed. Engl.*, **26**, 294 (1987); K. Suzuki and T. Nagasawa, *Yuki Gosei Kagaku Kyokai Shi*, **50**, 378 (1992).

2) This work was presented at the 60th Semiannual Meeting of the Chemical Society of Japan, Hiroshima, October (1990), Symposium paper, II, 1F309, p. 728. A similar approach utilizing a *p*-methoxybenzyl glycoside as a glycosyl donor has been presented by M. Yamaura et al. at the 64th Semiannual Meeting of the Chemical Society of Japan, Niigata, October (1992), Symposium paper, II, 1C218 and 1C219, p. 782-783.

3) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982); Y. Oikawa, K. Horita, and O. Yonemitsu, *ibid.*, **26**, 1541 (1985).

4) Prepared by mixing 2,3-dimethoxybenzyl alcohol with 3,4-dihydro-2*H*-pyran (DHP) in the presence of PPTS.

5) However, in basic polar solvents such as DMF, DMSO, or HMPA, the reaction was seriously retarded.

6) Recently, DDQ-catalyzed tetrahydropyranylation of alcohols with DHP has been reported. K. Tanemura, T. Horaguchi, and T. Suzuki, *Bull. Chem. Soc. Jpn.*, **65**, 304 (1992).

7) Prepared as a mixture of 1-α- and 1-β-isomer (22:78) from 3,4,6-tri-*O*-acetyl-D-glucal and 3,4-dimethoxybenzyl alcohol according to the standard methods [J. Thiem, H. Karl, and J. Schwentner, *Synthesis*, **1978**, 696; K. Tatsuta, A. Tanaka, K. Fujimoto, and M. Kinoshita, *J. Am. Chem. Soc.*, **99**, 5826 (1977)]. α-Isomer (more polar): ^{1}H NMR δ=6.87 (3H, m), 4.93 (2H, m), 4.82 (1H, d, J=11.6 Hz), 4.60 (1H, dd, J=2.0, 9.6 Hz), 4.53 (1H, d, J=11.6 Hz), 4.32 (1H, dd, J=3.0, 12.2 Hz), 4.15 (1H, dd, J=2.3, 12.2 Hz), 3.88 (6H, s), 3.60 (1H, m), 2.31 (1H, m), 2.11 (3H, s), 2.03 (3H, s), 2.02 (3H, s), and 1.81 (1H, m). β-Isomer (less polar): ^{1}H NMR δ=6.87 (3H, m), 5.35 (1H, ddd, J=5.0, 5.3, 11.9 Hz), 5.01 (2H, m), 4.61 (1H, d, J=11.9 Hz), 4.44 (1H, d, J=11.9 Hz), 4.32 (1H, dd, J=4.6, 12.5 Hz), 4.05 (1H, dd, J=2.3, 12.5 Hz), 4.02 (1H, m), 3.90 (3H, s), 3.88 (3H, s), 2.25 (1H, ddd, J=1.0, 5.3, 12.9 Hz), 2.11 (3H, s), 2.03 (3H, s), 2.00 (3H, s), and 1.84 (1H, ddd, J=3.6, 11.9, 12.9 Hz).

8) In order to suppress this side reaction, methyl group was introduced at the benzylic position of the substrate. However, the reaction of the corresponding 1-(3',4'-dimethoxy)phenylethyl glucopyranoside also afforded the corresponding glucopyranose exclusively.

9) Prepared as a mixture of 1-α- and 1-β-isomer (82:18) from 2,3,4,6-tetra-*O*-benzylglucopyranose and 3,4-dimethoxybenzyl bromide according to the standard method. C. Czernecki, C. Georgoulis, and C. Provelenghiou, *Tetrahedron Lett.*, **1976**, 3535.

10) For the halonium ion-promoted glycosylation, see D. R. Mootoo, V. Date, and B. Fraser-Reid, *J. Am. Chem. Soc.*, **110**, 2662 (1988); J. C. Lopez and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, **1991**, 159; H. Kunz, P. Werning, and M. Schultz, *Synlett.*, **1990**, 631.

11) For the synthesis of 2-deoxyglycosides, see for example: T. Yamanoi and T. Inazu, *Chem. Lett.*, **1990**, 849; S. Kobayashi, K. Koide, and M. Ohno, *Tetrahedron Lett.*, **31**, 2435 (1990); B. Fraser-Reid, P. Konradsson, D. R. Mootoo, and U. Udodong, *J. Chem. Soc., Chem. Commun.*, **1988**, 823; J. Szymoniak and P. Sinay, *Tetrahedron Lett.*, **1979**, 545; K. C. Nicolaou, S. P. Seitz, and D. P. Papahatjis, *J. Am. Chem. Soc.*, **105**, 2430 (1983); K. Toshima, Y. Nozaki, and K. Tatsuta, *Tetrahedron Lett.*, **32**, 6887 (1991).

(Received October 7, 1992)