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DMPM (3,4-DIMETHOXYBENZYL) PROTECTING GROUP FOR HYDROXY FUNCTION MORE READILY REMOVABLE THAN MPM (P-METHOXYBENZYL) PROTECTING GROUP BY DDQ OXIDATION

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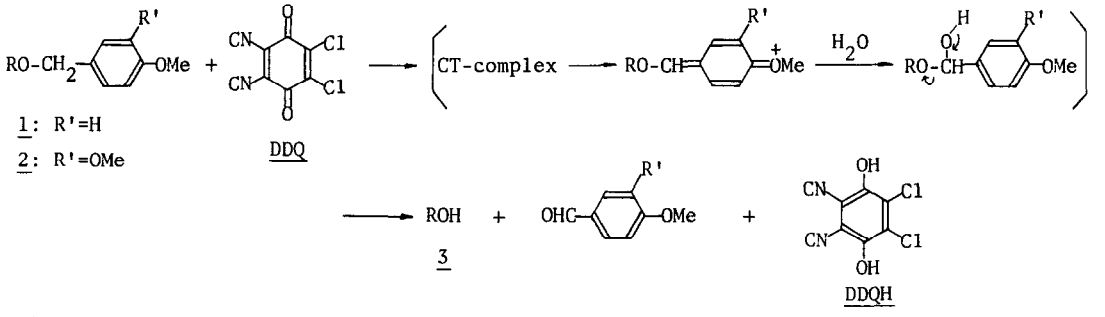
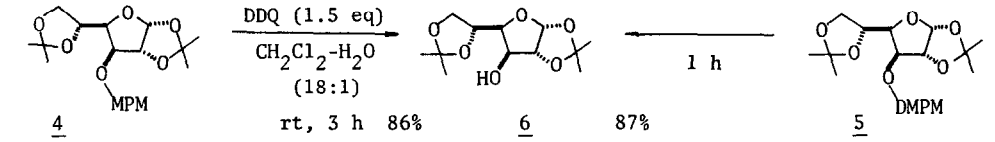
Summary. The DMPM (3,4-dimethoxybenzyl) protection for hydroxy function was deprotected more readily than the MPM (p-methoxybenzyl) protection by DDQ oxidation under neutral conditions, and applied to the synthesis of some synthons to macrolide and polyether antibiotics.

Although there are a number of protecting groups for hydroxy function, most of them are inherently more or less unstable under acidic conditions and the benzyl group is a typical exception.[2] In the course of our synthetic study of some macrolide and polyether antibiotics from D-glucose, the need for an acid-resistant protecting group other than the benzyl group became evident, and hence the MPM (p-methoxybenzyl) protection, which is removable by DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) oxidation under neutral conditions,[3] and its some extensions[4] have been recently developed. As an additional extension, we report here a DMPM (3,4-dimethoxybenzyl) protection, which is deprotected more readily than the MPM and exemplified by the synthesis of some synthons to macrolide and polyether antibiotics. The benzylic oxidation with DDQ has been well documented in benzene[5] and indole series,[6] and applied to the oxidative removal of the MPM protection of 1, which proceeded by the initial formation of the charge-transfer complex between the electron-donative methoxybenzene ring and electron-attractive DDQ, followed by dehydration and hydrolysis as shown in the following scheme.



Compound 2 was expected to be more reactive to the DDQ oxidation because 1,2-dimethoxybenzene with lower oxidation potential ($E_{1/2}$ 1.45 V) is more electron-donative than anisole ($E_{1/2}$ 1.78 V).[7,8] In fact, the MPM derivative of diacetoneglucose (4) was selectively deprotected by the treatment with excess DDQ (1.5 eq) in dichloromethane-water (18 : 1) at room temperature for 3 hr affording diacetoneglucose (6) in a high yield, but the deprotec-

tion of the corresponding DMPM derivative (5)[9] proceeded more rapidly under the same conditions and was completed within 1 hr. Some DMPM protected derivatives of a primary alcohol (7) and secondary alcohols (9, 11, 13) also gave quite readily the corresponding original alcohols (8, 10, 12, 14) though 12 was isolated in the hemi-acetal form, in high yields. Chemoselectivity of this DDQ oxidation was very high and benzyl, ester, olefin, and even aldehyde groups completely unaffected.



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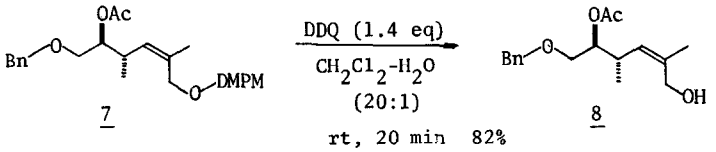

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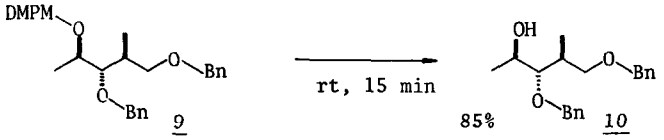

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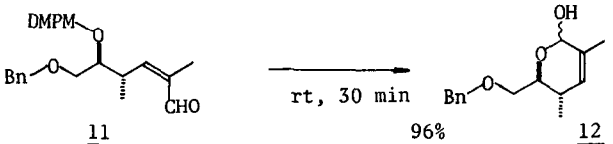

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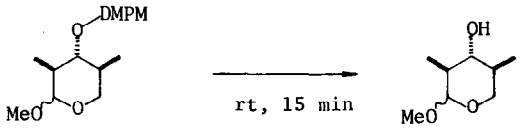


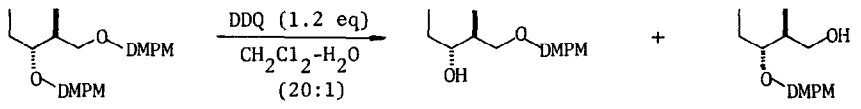
13 14

Bn: $C_6H_5CH_2$

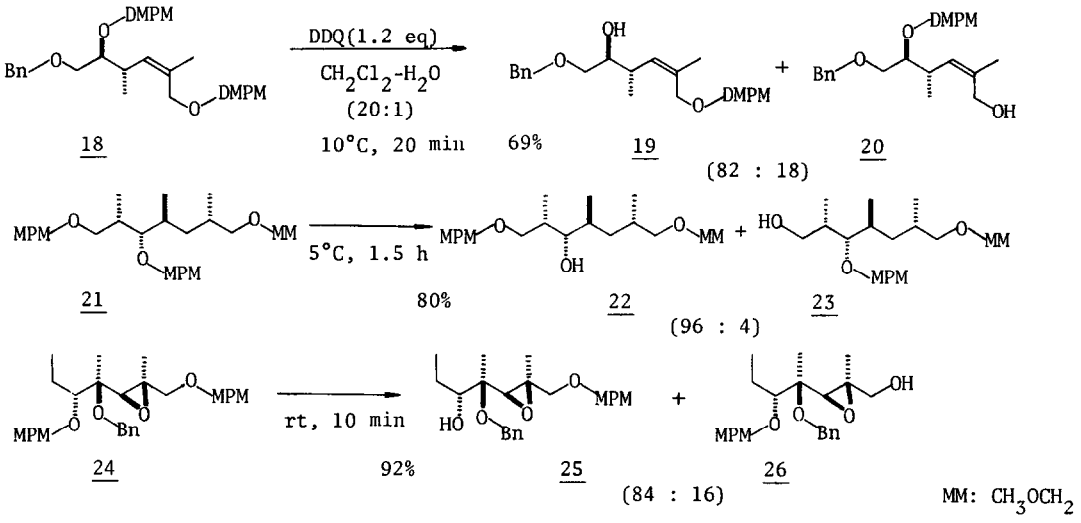
MPM: 4-CH_3O-$C_6H_4CH_2$

DMPM: 3,4-$(CH_3O)_2$-$C_6H_3CH_2$

Other selectivities of the DMPM group were next examined. The DMPM groups protecting secondary alcohols were usually more reactive than those protecting primary alcohols as shown in the following two examples (15, 18). This selectivity is permissible for practical use, though somewhat inferior to that in the case of the MPM derivatives (21, 24).

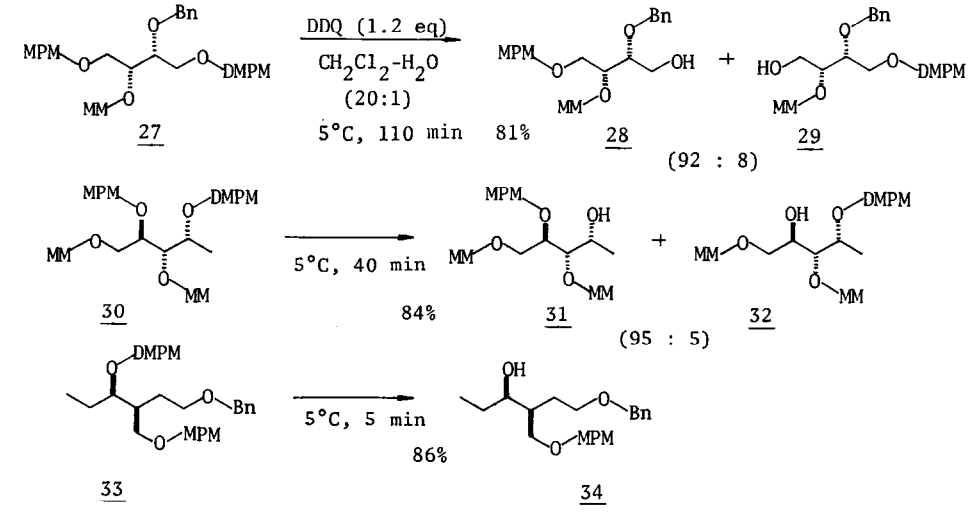


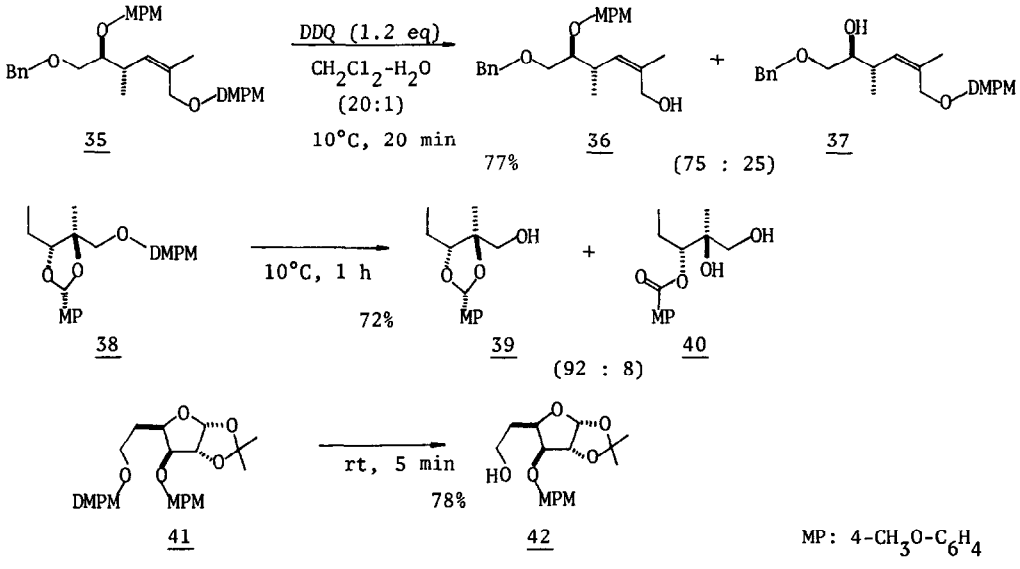
15 16 17



A more obvious selectivity was observed in the reactivity difference between MPM and DMPM groups. In both 27 with protected primary alcohols and 30 with protected secondary alcohols, the DMPM groups were almost selectively removed with 92 and 95% selectivities, respectively. The completely selective deprotection of the DMPM group was observed in the DDQ oxidation of 33 with the DMPM group protecting a secondary alcohol and the MPM group protecting a primary alcohol, and 34 was isolated as the sole product in a high yield. Even in the reverse cases (35, 38, 41) with the DMPM groups protecting primary alcohols and the MPM groups protecting secondary alcohols, the DMPM groups were likewise more readily deprotected. Actually, the selectivity in 35 was 75% and still unsatisfactory, but 38 gave a better result (92% selectivity). In the case of 41, 42 was the only isolable product.

Further applications especially in the synthesis of complex natural products such as macrolide and polyether antibiotics will be reported soon.





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7) A. Zweig, W. G. Hodgson, and W. H. Jura, J. Am. Chem. Soc., 86, 4124 (1964).

8) 1,4-Dimethoxybenzene, 1,2,3-trimethoxybenzene, and indole derivatives are more electron-donative, but 1,2-dimethoxybenzene derivatives are practically useful in terms of the ease of preparation and the stability to acid.

9) DMPM ethers were usually synthesized as follows: To a stirred suspension of NaH in DMSO or DMF was added dropwise a THF solution of alcohols at room temperature. After evolution of H_2 ceased, a THF solution or a powder of 3,4-dimethoxybenzyl (DMPM) chloride was added and the mixture was stirred for several hours. Usual workup gave the DMPM ethers in almost quantitative yields.

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