

Communications to the Editor

[Chem. Pharm. Bull.]
36(10)4244—4247(1988)

3-METHOXYBENZYL (3-MPM) AND 3,5-DIMETHOXYBENZYL (3,5-DMPM) PROTECTING GROUPS
FOR THE HYDROXY FUNCTION LESS READILY REMOVABLE THAN 4-METHOXYBENZYL (MPM)
AND 3,4-DIMETHOXYBENZYL (DMPM) PROTECTING GROUPS BY DDQ OXIDATION

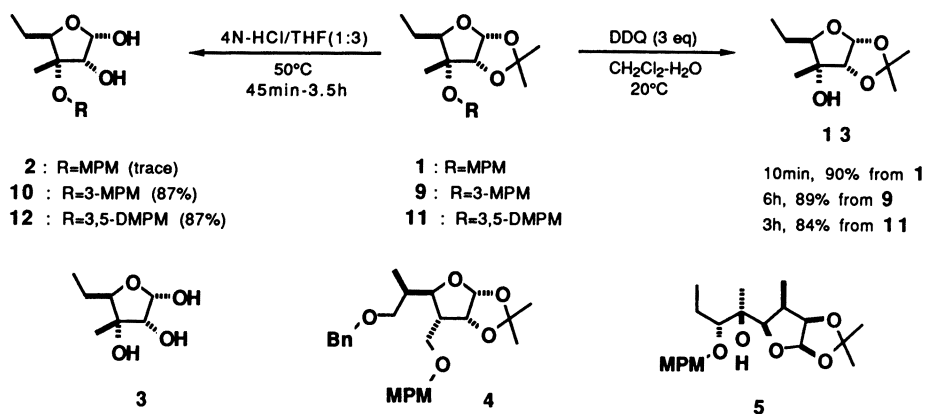
Noriyuki Nakajima, Reiko Abe, and Osamu Yonemitsu*

Faculty of Pharmaceutical Sciences, Hokkaido University,
Kita-12, Nishi-6, Kitaku, Sapporo 060, Japan

New protecting groups for the hydroxy function, 3-methoxybenzyl (3-MPM) and 3,5-dimethoxybenzyl (3,5-DMPM) groups are slowly removed by DDQ oxidation at room temperature and distinguished from readily removable 4-methoxybenzyl (MPM). They are stable to strong acids.

KEYWORDS — protecting group; hydroxy function; DDQ oxidation; selective deprotection; 3-methoxybenzyl; 3,5-dimethoxybenzyl

Although various protecting groups for the hydroxy function are now available,¹⁾ new protecting groups with different selectivities are sometimes required, especially in the synthesis of large and complex compounds. 4-Methoxybenzyl (MPM) and 3,4-dimethoxybenzyl (DMPM) groups, recently developed for the protection of the hydroxy function and selectively removed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation,²⁾ have been successfully applied in the synthesis of complex natural products such as macrolide and polyether antibiotics.³⁾ Because of their unique deprotection the MPM and DMPM protecting groups are undoubtedly useful in organic synthesis, especially in the synthesis of complex molecules. But special caution is sometimes required when compounds bearing tertiary hydroxy groups protected with MPM and/or DMPM groups are treated with a warm strong acid. For example, when **1** was treated with 4N-HCl in THF at 50°C under



the deprotection conditions of the 1,2-isopropylidene group, the MPM group was almost completely lost to give mainly a triol-hemiacetal (3) together with a trace of the expected product (2), whereas the MPM groups used as the protecting group of primary and secondary hydroxy groups (e.g., 4, 5) remained unaffected under similar acidic conditions, and the corresponding de-isopropylidene products were isolated in high yields.⁴⁾

Therefore, in order to find a new protecting group which can be distinguished from MPM, DMPM, and benzyl (Bn) groups under their deprotection conditions and is much more stable to acid, various mono- (MPM), di- (DMPM) and tri-methoxybenzyl (TMPM) protected compounds of phenethyl alcohol were synthesized and subjected to the oxidative deprotection with DDQ. The results are summarized in the Table I, and 3-methoxybenzyl (3-MPM) and 3,5-dimethoxybenzyl (3,5-DMPM) groups were chosen as promising protecting groups. Since their reactivity to DDQ is intermediate between those of MPM and Bn groups, they were expected to be stable under acidic conditions and to be differentiated from MPM and DMPM groups under careful DDQ oxidation conditions.

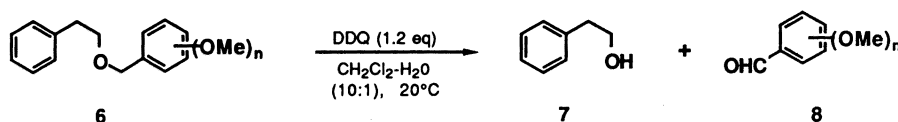
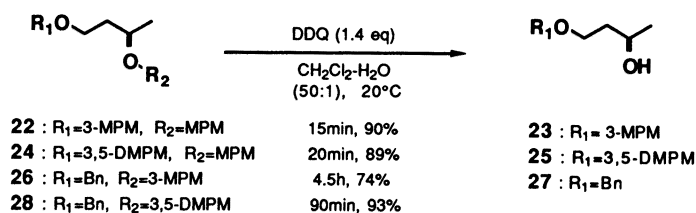
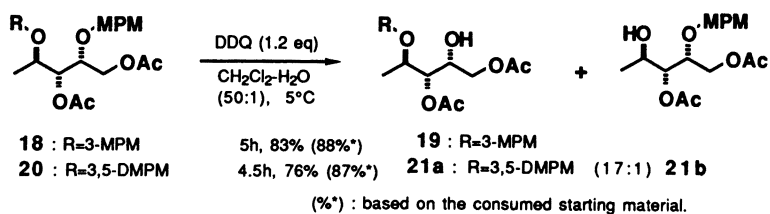
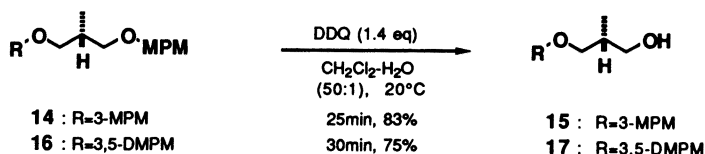


Table I. Removal of MPM, DMPM, and TMPM Protecting Groups with DDQ in CH₂Cl₂-H₂O at 20°C

Entry	Protecting group	Time (h)	Yield (%)		Entry	Protecting group	Time (h)	Yield (%)	
			7	8				7	8
1	DMPM	<0.33	86	84	6	2-MPM	3.5	93	70
2	MPM	0.33	89	86	7	3,5-DMPM	8	73	92
3	2,3,4-TMPM	0.5	60	75	8	2,3-DMPM	12.5	75	73
4	3,4,5-TMPM	1	89	89	9	3-MPM	24	80	94
5	2,5-DMPM	2.5	95	16	10	2,6-DMPM	27.5	80	95

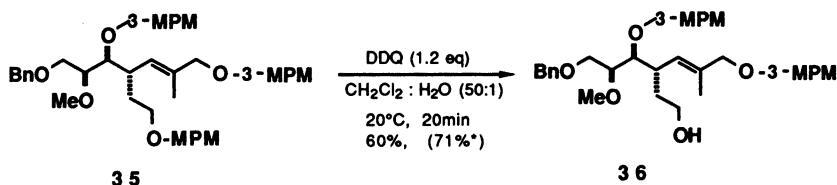
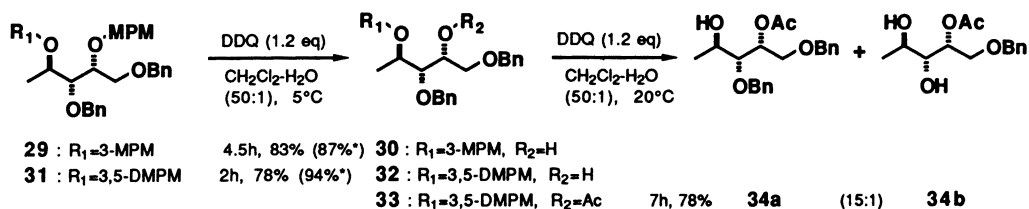
In fact, on treatment with 4N-HCl 9 and 11 gave the corresponding de-isopropylidene compounds 10 and 12, respectively, without any detectable loss of the 3-MPM and 3,5-DMPM groups. The MPM group of 1 was removed to give 13 by DDQ oxidation within only 10 min, whereas the 3-MPM (9) and 3,5-DMPM groups (11) required 6 and 3 h, respectively.

Selective deprotection of the MPM groups in the presence of the 3-MPM, 3,5-DMPM and Bn groups was examined next. When 14, in which primary alcohols are protected with MPM and 3-MPM groups, was treated with 1.4 equiv of DDQ at room temperature, only the MPM group was removed to give 15 in high yield. Compound 16, having a 3,5-DMPM group instead of the 3-MPM group, similarly gave 17. Compound 18 having secondary O-MPM and O-3-MPM groups afforded 19. Similarly 20 gave mainly 21a with more than 94% selectivity. Secondary O-MPM groups of 22 with a primary O-3-MPM group and 24 with a primary O-3,5-DMPM group were removed with complete selectivity to give 23 and 25, respectively. Selective removal of the 3-MPM and 3,5-DMPM groups



in the presence of Bn groups was examined next; both 26 and 28 gave the sole product (27) within several hours.

When 29 having the MPM, 3-MPM and Bn groups was oxidized at 5°C, only the MPM group was removed to give 30, and similarly 31 afforded 32, whose acetate (33) was then treated with DDQ at room temperature to remove the 3,5-DMPM group selectively and the expected product (34a) was obtained with more than 93% selectivity. Finally, a rather complex compound (35) gave the de-MPM product (36) under the typical conditions in acceptable yield.



Application of this simple method to the synthesis of more complex compounds such as macrolide and polyether antibiotics is now under study.

REFERENCES AND NOTES

- 1) T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, New York, 1981, pp. 10-86.
- 2) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., **23**, 885 (1982); Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, ibid., **25**, 5393 (1984); K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, and O. Yonemitsu, Tetrahedron, **42**, 3021 (1986); N. Nakajima, K. Horita, R. Abe, and O. Yonemitsu, Tetrahedron Lett., **29**, 4139 (1988).
- 3) Methynolide: Y. Oikawa, T. Tanaka, and O. Yonemitsu, Tetrahedron Lett., **27**, 3647 (1986); Y. Oikawa, T. Tanaka, T. Hamada, and O. Yonemitsu, Chem. Pharm. Bull., **35**, 2196 (1987); T. Tanaka, Y. Oikawa, N. Nakajima, T. Hamada, and O. Yonemitsu, ibid., **35**, 2203 (1987). Tylonolide: T. Tanaka, Y. Oikawa, T. Hamada, and O. Yonemitsu, Tetrahedron Lett., **27**, 3651 (1986); Chem. Pharm. Bull., **35**, 2209, 2219 (1987). Pikronolide: N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa, and O. Yonemitsu, J. Am. Chem. Soc., **108**, 4645 (1986); N. Nakajima, T. Tanaka, T. Hamada, Y. Oikawa, and O. Yonemitsu, Chem. Pharm. Bull., **35**, 2228 (1987). Erythronolide A: H. Tone, T. Nishi, Y. Oikawa, M. Hikota, and O. Yonemitsu, Tetrahedron Lett., **28**, 4569 (1987). Erythronolide B: A. F. Sviridov, M. S. Ermolenko, D. V. Yashunsky, V. S. Borodkin, and N. K. Koshetkov, Tetrahedron Lett., **28**, 3835, 3839 (1987). Aplysiatoxin: P. Park, C. A. Broka, B. F. Johnson, and Y. Kishi, J. Am. Chem. Soc., **109**, 6205 (1987). Salinomycin: K. Horita, S. Nagato, Y. Oikawa, and O. Yonemitsu, Tetrahedron Lett., **28**, 3253 (1987); K. Horita, S. Nagato, Y. Oikawa, and O. Yonemitsu, Tetrahedron Lett., in press. Lasalocid A and isolasalocid A: I. Noda, K. Horita, Y. Oikawa, and O. Yonemitsu, in preparation.
- 4) Y. Oikawa, T. Nishi, and O. Yonemitsu, J. Chem. Soc. Perkin Trans. 1, **7**, 19 (1985).

(Received September 5, 1988)