Communications to the Editor

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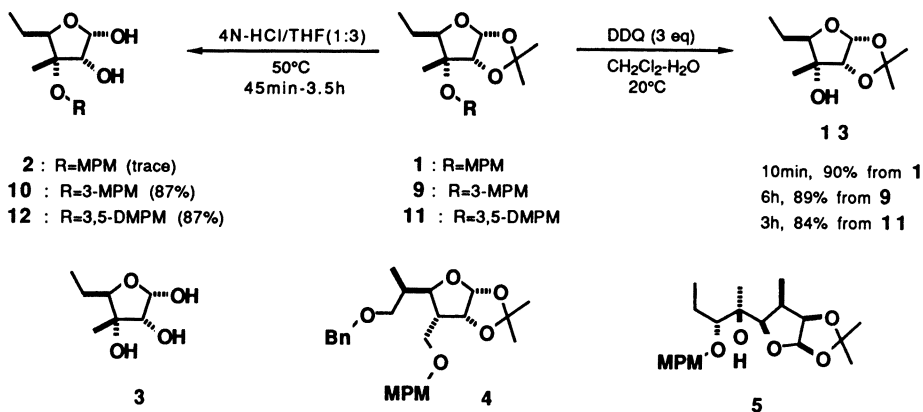AND 3,4-DIMETHOXYBENZYL (DMPM) PROTECTING GROUPS BY DDQ OXIDATION

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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-Methoxy-
benzyl (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 anti-
biotics.[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

2 : R=MPM (trace)
10 : R=3-MPM (87%)
12 : R=3,5-DMPM (87%)

1 : R=MPM
9 : R=3-MPM
11 : R=3,5-DMPM

13

10min, 90% from 1
6h, 89% from 9
3h, 84% from 11

4N-HCl/THF(1:3)
50°C
45min-3.5h

DDQ (3 eq)
CH₂Cl₂-H₂O
20°C

3

Bn

MPM   4

MPM

5

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.
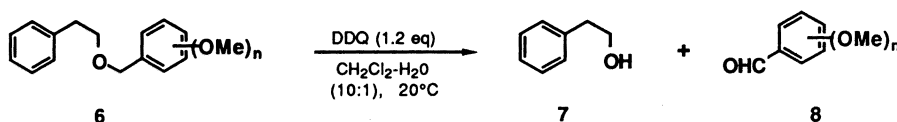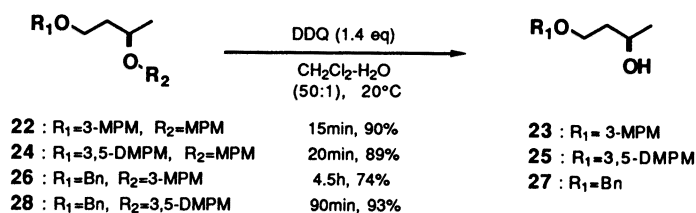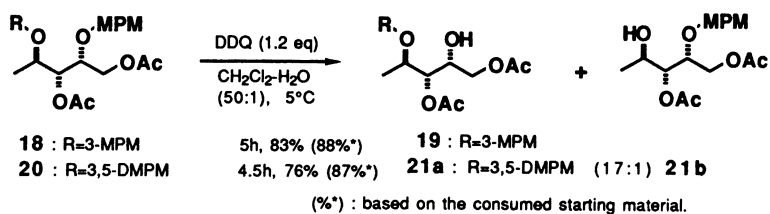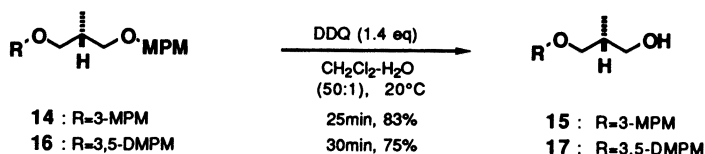

Table I. Removal of MPM, DMPM, and TMPM Protecting Groups with DDQ
          in CH_2Cl_2-H_2O at 20°C

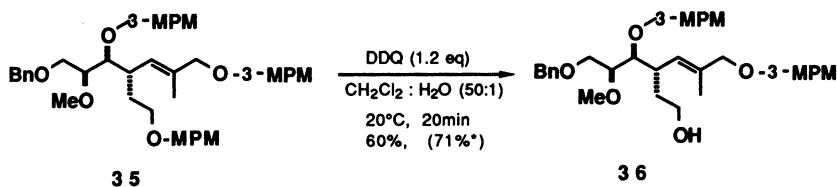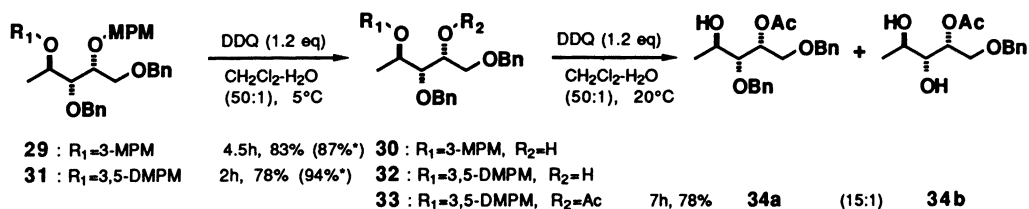| Entry	Protecting group	Time (h)	Yield (%) 7	8	Entry	Protecting group	Time (h)	Yield (%) 7	8
1	DMPM	<0.33	86	84	6	2-MPM	3.5	93	70
2	MPM	0.33	89	86	7	3,5-DMPM	8	73	92
3	2,3,4-TMPM	0.5	60	75	8	2,3-DMPM	12.5	75	73
4	3,4,5-TMPM	1	89	89	9	3-MPM	24	80	94
5	2,5-DMPM	2.5	95	16	10	2,6-DMPM	27.5	80	95

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 prsence 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

14 : R=3-MPM
16 : R=3,5-DMPM

DDQ (1.4 eq)
CH₂Cl₂-H₂O
(50:1), 20°C

25min, 83%
30min, 75%

15 : R=3-MPM
17 : R=3,5-DMPM

18 : R=3-MPM
20 : R=3,5-DMPM

DDQ (1.2 eq)
CH₂Cl₂-H₂O
(50:1), 5°C

5h, 83% (88%*)
4.5h, 76% (87%*)

19 : R=3-MPM
21a : R=3,5-DMPM   (17:1) **21b**

(%*) : based on the consumed starting material.

22 : R₁=3-MPM, R₂=MPM
24 : R₁=3,5-DMPM, R₂=MPM
26 : R₁=Bn, R₂=3-MPM
28 : R₁=Bn, R₂=3,5-DMPM

DDQ (1.4 eq)
CH₂Cl₂-H₂O
(50:1), 20°C

15min, 90%
20min, 89%
4.5h, 74%
90min, 93%

23 : R₁= 3-MPM
25 : R₁=3,5-DMPM
27 : R₁=Bn

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.

29 : R₁=3-MPM
31 : R₁=3,5-DMPM

4.5h, 83% (87%*)
2h, 78% (94%*)

DDQ (1.2 eq)
CH₂Cl₂-H₂O
(50:1), 5°C

30 : R₁=3-MPM, R₂=H
32 : R₁=3,5-DMPM, R₂=H
33 : R₁=3,5-DMPM, R₂=Ac

DDQ (1.2 eq)
CH₂Cl₂-H₂O
(50:1), 20°C

7h, 78% **34a**   (15:1) **34b**

35

DDQ (1.2 eq)
CH₂Cl₂ : H₂O (50:1)
20°C, 20min
60%, (71%*)

36

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

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