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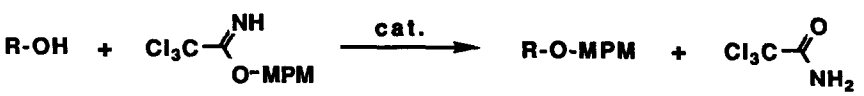
MPM (4-METHOXYBENZYL) PROTECTION OF HYDROXY FUNCTIONS UNDER MILD ACIDIC CONDITIONS

Noriyuki Nakajima, Kiyoshi Horita, Reiko Abe, and Osamu Yonemitsu*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Summary In order to establish a mild protection method for hydroxy functions with a MPM (4-methoxybenzyl) group, various types of hydroxy compounds were treated with MPM trichloroacetimidate in the presence of an acid catalyst. A catalytic amount (0.3 mol %) of trifluoromethanesulfonic acid was most effective and the reaction was completed within 40 min at room temperature even for highly sterically hindered hydroxy groups.

There have been many reports showing that introduction of a new protecting group[1] with distinct selectivity was crucial in multi-step syntheses of complex compounds such as polyketide-derived natural products as well as in peptide and nucleotide syntheses. The MPM (4-methoxybenzyl) protection of hydroxy functions, selectively deprotected by DDQ oxidation[2] and successfully applied to highly selective syntheses of a series of representative macrolide and polyether antibiotics,[3] provides another good example. Selective use of benzyl-type protecting groups such as MPM, DMPM (3,4-dimethoxybenzyl) and Bn (benzyl) is very effective,[4] but protection of hydroxy functions in complex molecules especially bearing alkali-sensitive groups under typical alkaline conditions, e. g., with Bn halides and sodium hydride in THF, was often accompanied by serious side reactions. We report here a practically useful MPM protection under very mild acidic conditions, in which alkali- and even usual acid-sensitive groups remained completely unaffected.

Bn trichloroacetimidate (1) was reported by Bundle and his colleagues[5] to be a versatile reagent for acid-catalyzed benzylation of hydroxy groups and several applications were published.[6] This reagent has now been extended to MPM trichloroacetimidate (2), which is easily prepared from MPM alcohol and trichloroacetonitrile in the presence of sodium hydride (10 mol%) and purified by distillation (b.p. 135-137°C/0.7 mmHg). Since 2 was much more reactive than **1** and very sensitive to strong acids, the MPM protection of **3** and **4** derived from D-glucose with **2** did not occur under typical Bundle conditions in the presence of 10 mol% of trifluoromethanesulfonic acid (TfOH) (Bn protection: entry 4, 5) owing to almost instant decomposition of 2 (entry 1, 2, 3). Therefore, milder reaction conditions were examined.



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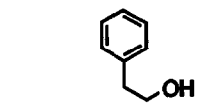
When **4** was treated with **2** in the presence of CSA (10-camphorsulfonic acid) in CH_2Cl_2, a clean reaction slowly occurred and after 2 days the expected MPM protected product was isolated in good yield (entry 6, 7), although no reaction occurred with less reactive **1** under the same conditions (entry 8, 9). The MPM protection of simple alcohols such as **7** was completed within 1 day (entry 10). PPTS (pyridinium p-toluenesulfonate) gave similar results (entry 11, 12). However, highly hindered hydroxy groups in **16** and **17** were unreactive with **2** in the presence of CSA or PPTS.

Treatment with trityl perchlorate (3 mol%) in CH_2Cl_2 caused only decomposition of **2** (entry 13); however, when ether was used in the place of CH_2Cl_2, the expected reaction occurred

Table I. Acid-catalyzed Benzyl (Bn) and 4-Methoxybenzyl (MPM) Protection of Alcohols with Bn (**1**) and MPM Trichloroacetimidate (**2**) at Room Temperature

Entry	Alcohol	Imidate (equiv)	Acid (mol%)[a]	Solvent	Time (h)	Yield (%)
1	**3**	**2** (2.0)	TfOH (10)	CH_2Cl_2		–[c]
2	**3**	**2** (2.0)	TfOH (10)	toluene		–[c]
3	**4**	**2** (2.0)	TfOH (10)	C_6H_{12}[b]–CH_2Cl_2		–[c]
4	**4**	**1** (1.5)	TfOH (10)	C_6H_{12}[b]–CH_2Cl_2	0.67	66
5	**4**	**1** (1.5)	TfOH (10)	Et_2O	2.5	84
6	**4**	**2** (2.0)	CSA (10)	CH_2Cl_2	48	79
7	**5**	**2** (2.0)	CSA (10)	CH_2Cl_2	48	79
8	**4**	**1** (1.5)	CSA (10)	CH_2Cl_2		–[d]
9	**6**	**1** (2.0)	CSA (10)	CH_2Cl_2		–[d]
10	**7**	**2** (2.0)	CSA (10)	CH_2Cl_2	25	86
11	**3**	**2** (2.0)	PPTS (10)	CH_2Cl_2	5	77
12	**8**	**2** (1.2)	PPTS (5)	CH_2Cl_2	19	88
13	**4**	**2** (2.0)	$TrClO_4$ (3)	CH_2Cl_2		–[c]
14	**4**	**2** (2.0)	$TrClO_4$ (3)	Et_2O	0.4	74
15	**6**	**2** (2.4)	$TrClO_4$ (3)	Et_2O	1	84
16	**9**	**2** (3.0)	$TrClO_4$ (3)	Et_2O	1	82
17	**10**	**2** (2.0)	$TrClO_4$ (3)	Et_2O	0.75	85
18	**11**	**2** (2.0)	$TrClO_4$ (3)	Et_2O	0.4	91
19	**12**	**2** (4.0)	$TrClO_4$ (3)	Et_2O	1	59
20	**13**	**2** (1.5)	$TrClO_4$ (3)	Et_2O	0.5	73
21	**14**	**2** (1.6)	$TrClO_4$ (3)	Et_2O	1	59
22	**4**	**2** (1.2)	TfOH (0.3)	Et_2O	0.17	77
23	**4**	**1** (1.5)	TfOH (0.5)	Et_2O		trace
24	**7**	**2** (2.0)	TfOH (0.3)	Et_2O	0.34	52
25	**8**	**2** (2.0)	TfOH (0.3)	Et_2O	0.17	82
26	**15**	**2** (2.0)	TfOH (0.3)	Et_2O	0.4	82
27	**16**	**2** (2.5)	TfOH (0.3)	Et_2O	0.58	71
28	**17**	**2** (4.0)	TfOH (0.3)	Et_2O	0.17	63
29	**17**	**1** (3.5)	TfOH (10)	Et_2O		–[d]

[a] Based on alcohols.
[b] Cyclohexane.
[c] Very rapid decomposition of **2**.
[d] No reaction.



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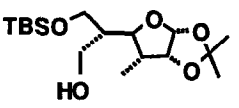

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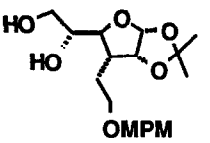

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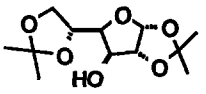

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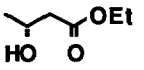

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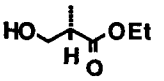

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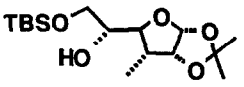

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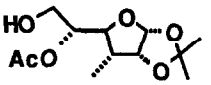

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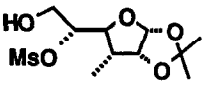

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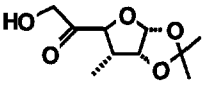

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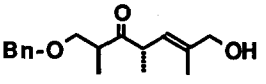

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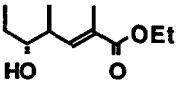

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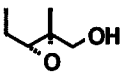

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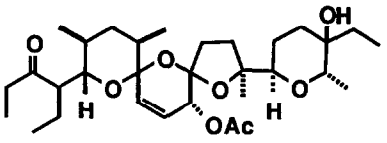

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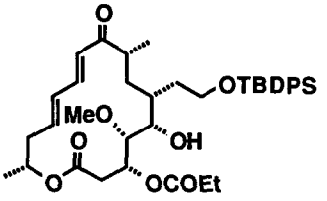

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smoothly and was completed within only 25 min (entry 14). Several substrates with various functional and protecting groups including sugar derivatives gave similar good results within 1 h (entry 15-21).

A very small amount of TfOH was more effective, e.g., the MPM protection of **4** in the presence of only 0.3 mol% of TfOH rapidly proceeded to completion within 10 min (entry 22),[7] although almost no reaction occurred with **1** (entry 23). This reaction was applied to simple substrates **7**, **8**, and **15** (entry 24-26) and complex synthetic intermediates **16** and **17** (entry 27, 28) of polyether and macrolide antibiotics.

The following merits of this simple MPM protection method should be emphasized. Because a

very small amount of the catalyst (TfOH) was used, both acid-sensitive groups (epoxide, bisspiroketal, acetonide, silyl) and alkaline-sensitive groups (ester, mesyl, silyl) were completely unaffected even in 1,2- and 1,3-diol systems.[9] Neither epimerization at the α-position of carbonyl groups (entry 12, 19, 21, 25, 27, 28) nor elimination of β-hydroxy comounds (entry 10, 12, 20, 21, 24, 25, 27, 28) was observed.

In conclusion, the method presented in this report is believed to be quite useful, especially for the MPM protection of various hydroxy groups in complex molecules.

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