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PROTECTION OF ALCOHOLS AS THEIR (*p*-METHOXYBENZYLOXY)METHYL ETHERS.

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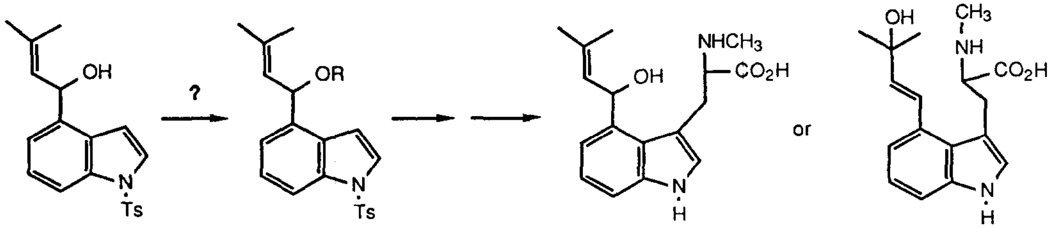
Abstract: Protection of even tertiary alcohols can be accomplished by treatment with *p*-methoxybenzyl chloromethyl ether. Deprotection can be effected under mild conditions using the DDQ reaction conditions described by Oikawa.

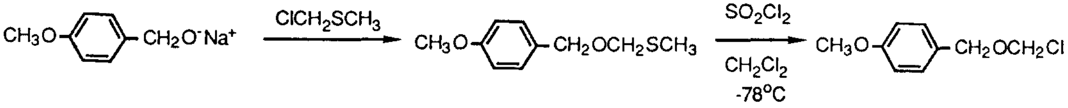
During our efforts to probe the biosynthesis of the ergot alkaloids through the total synthesis of possible intermediates along the biosynthetic pathway, the need for a protecting group of the secondary alcohol function of the 4-substituted indole I emerged.[1,2] While this alcohol could be protected as its SEM ether,[3] we found that the SEM group could not be cleaved at the end of the synthesis after the amino acid appendage at C-3 had been installed. Of the many known protecting groups for alcohols,[4] only use of the *p*-methoxybenzyl group[5] appeared suitable for the problem at hand. Unfortunately, all attempts to install this protecting group using the procedures described by Oikawa and modifications thereof proved unrewarding.



I   II   III   IV

Consequently, we sought to develop a hybrid of the SEM ether and MPM ether protecting groups through use of the (*p*-methoxybenzyloxy)methyl ether group for alcohol protection. We anticipated that this protecting group would be removable under oxidative conditions, and that alcohol protection might be accomplished for even somewhat hindered alcohols as a consequence of the presence of the chain elongating $-CH_2O-$ group.

The *p*-methoxybenzyl chloromethyl ether required to initiate this study was prepared according to the method of Undheim[6] by reaction of the sodium salt of *p*-methoxybenzyl alcohol with chloromethyl methyl sulfide. The sulfur compound resulting from this reaction was treated with sulfuryl chloride in methylene chloride at -78° C to afford the required chloride. While this chloromethyl ether has been reported to undergo decomposition on storage, we have found that it remains suitable for alcohol group protection for at least three days if stored in a refrigerator.



PMBM-Cl

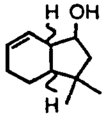
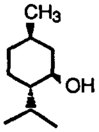
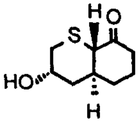
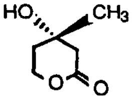
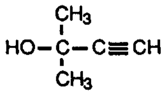
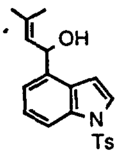
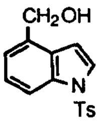
The nine alcohols listed in Table I were protected as their (*p*-methoxybenzyloxy)methyl ethers (PMBM ethers) by simply admixing them with an excess of PMBM-Cl in methylene chloride as solvent and stirring under nitrogen in the presence of diisopropylethylamine for 3-30 hr. Even the tertiary alcohol group of mevalonic lactone could be protected in high yield with this reagent.

For deprotection the reaction conditions described by Oikawa for removal of the MPM protecting group proved adequate. Accordingly, the PMBM ethers were stirred in CH_2Cl_2-H_2O (18:1) with 1.2-1.5 equivalents of DDQ at room temperature. Deprotection was accomplished in reasonable yield in the majority of the cases examined. It is worth noting that the secondary allylic alcohol of entry 7 underwent rearrangement to the tertiary alcohol on deprotection. In the case of the PMBM ether of geraniol (entry 8) some oxidation to geranial was found to accompany this oxidative cleavage step. Lastly, deprotection can also be accomplished by acid treatment (3:1 THF/6 *M* HCl, 50° C, 6 h) as found for the PMBM ether of cholesterol.

General procedures for the protection-deprotection steps follow:

Protection: To a solution of the alcohol in dry methylene chloride (~60 mg/1 mL) under a nitrogen atmosphere was added sequentially diisopropylethylamine (5 equiv.) and *p*-methoxybenzyl

Table 1. Protection of Some Representative Alcohols as Their (*p*-Methoxybenzyloxy)methyl Ether Derivatives

Entry	Alcohol	Protection step % yield; time (h)	Deprotection step % yield; time (h)
1		96; 4	96; 4
2		96; 4	81; 2
3		78; 4	88; 4
4	cholesterol	78; 4	88; 1 (90; 6)[a]
5		84; 30	89; 10
6	 $HO-C(CH_3)_2-C\equiv CH$	89; 5	——[b]
7		100; 10	65; 1[c]
8	geraniol	95; 5	63; 3 (+21% geranial)
9		96; 5	63; 2

a. Deprotection was accomplished with 3:1 THF/6M HCl, 50°C.

b. Deprotection was complicated by product volatility.

c. Only the rearranged tertiary alcohol was isolated in this case.

chloromethyl ether (3 equiv.). After the mixture was stirred at rt for 2 to 5 h, an additional equivalent of the chloromethyl ether was added. The reaction mixture was stirred at rt until the reaction was deemed complete by tlc analysis. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel. The PMBM ether derivatives all exhibit signals in their ^1H NMR spectra at the following approximate chemical shifts: δ 3.8 (-OMe), 4.6 (Ar-CH_2-O), 4.8 (O-CH_2-O), and 7.3 and 6.9 (AA'XX' system of the aromatic ring protons appearing as two doublets with *J* ~8.5 Hz).

Deprotection: The protected alcohol (~30 mg) from above was dissolved in ~1 mL of an 18:1 mixture of CH_2Cl_2-H_2O. DDQ (1.2-1.5 equiv) was added portionwise to the solution, and the reaction mixture was stirred at room temperature for 1 to 10 h (Table I). The resulting precipitate was removed by filtration, and the filtrate was concentrated and purified by flash chromatography on silica gel.

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