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A CONVENIENT PROCEDURE FOR THE REGIOSELECTIVE MONOPROTECTION OF 1,n-DIOLS

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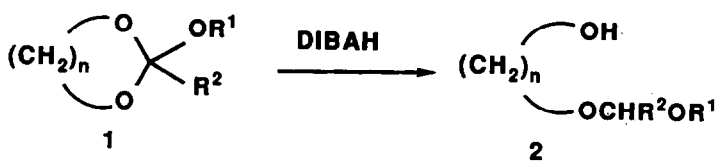
ABSTRACT: A method is described for regioselective monoprotection of 1,n-diols. The new process depends on regioselective cleavage of orthoester, which is prepared in situ from 1,n-diols and trialkylorthoesters. The produced mono-acetal is useful in subsequent steps as a normal acetal type protecting group.

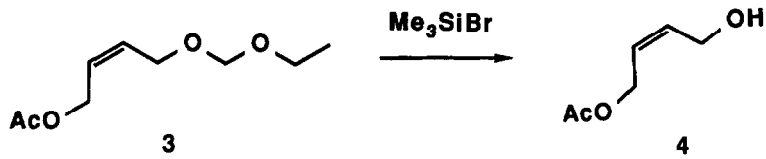
Selective monoprotection of one hydroxyl function in a polyhydroxylic system often presents an important problem in organic synthesis.[1] Regioselective protection is generally only possible if there are hydroxyl groups of different stereoelectronic or conformational factors. Partial esterification has most frequently been utilized for this purpose, and an acceptable yield of the monoprotected product was achieved under the carefully controlled reaction conditions.[1] On the other hand, selective protection of the polyhydroxyl compound using the acetal type protecting groups, e.g. THP or MEM, do not proceed in high yields, although they are widely used in organic synthesis.

In connection with research which recently led to the stereoselective cleavage of homochiral acetals in our laboratory,[2] we had occasion to study the similar reductions of orthoesters using organoaluminum reagents.[3] The orthoester of type **1** was treated with DIBAH in non-polar solvent systems to give smoothly the acetal of type **2** as the major product.[3]



1 2

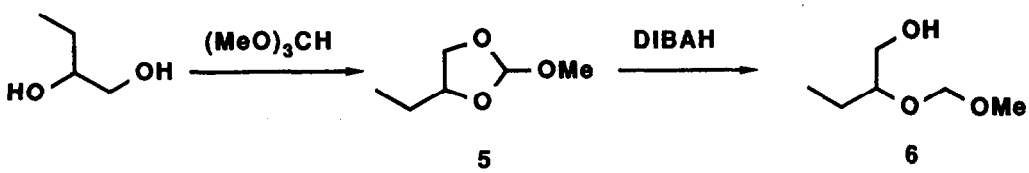
The above transformation should provide an ideal method for the differential functionalization of hydroxyl groups. Although the similar transformation of 1,n-diol to mono-benzyl ether via acetal has been reported by Takano,[4] the present method provides an effective method to give an acetal derivative directly. Consequently, the resulting acetal can be cleaved under mild acidic conditions: for example, the reaction conditions described by Hanessian and coworkers for removal of MOM protecting group proved adequate.[5] Accordingly, the acetal **3** was stirred in dichloromethane containing 4A molecular sieves was added excess trimethylsilyl bromide, and the mixture was stirred for 1 h at -30°C then 6.5 h at 0°C to give the desired monoacetate **4** smoothly.



3 4

Although the observed selectivity of the orthoester cleavage is potentially highly useful as a synthetic method for the differential functionalization of diols, the preparation of the starting labile orthoester is sometimes problematic. In fact, while the orthoester was cleanly generated by acid-catalyzed exchange reaction with trialkylorthoester and starting 1,n-diol, isolation of the produced labile orthoester was only accomplished either by direct distillation (the orthoesters of low b.p.) or addition of excess triethylamine, concentration in vacuo, and elution of a remaining oil through a short-path silanised silica gel (Merck 7719) column. Fortunately, however, the solution of the produced orthoester could be directly exposed with excess DIBAH without any isolation procedure, and the tedious isolation process could be circumvented. Thus, the one-pot procedure was successfully applied starting from a variety of 1,n-diols. Some of the results are shown in Table 1.

The apparently high efficiency of the method is synthetically intriguing. However, even more important is the observed high regioselectivity for the cleavage of unsymmetrical orthoester of type **5**, which produced the acetal **6** selectively.[3,6] In fact, many procedures have been reported for the selective protection of the primary hydroxyl function in the presence of secondary alcohols.[7] In contrast, there are no reliable methods available for the preferential protection of secondary over primary hydroxyls.[8]



5 6

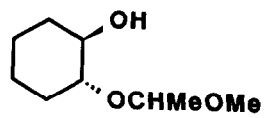
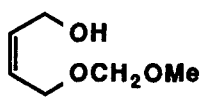
The use of orthoester-DIBAH as a method for selective protection of 1,n-diols[9] can be illustrated by the experimental procedure as follows:

General Procedure for the monoprotection of 1,n-diols.

A mixture of trimethylorthoformate (212 mg, 2.00 mmol), diol (1.00 mmol), and a catalytic amount of D-10-camphorsulfonic acid (2.3 mg, 1 mol%) in dry dichloromethane (1 ml) was stirred at room temperature for 24 h. The reaction was analyzed by tlc to be >90% completion of the exchange. The solution so obtained was cooled to -78°C. Diisobutylaluminum hydride (10 ml of a 1.00 M hexane solution, 10 mmol) was then added dropwise and the resulting mixture was stirred at -78°C for 30 min and at 0°C for 10 min. The reaction mixture was then poured into

an aqueous sodium hydroxide (2 N) and the product was extracted with ether repeatedly. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to leave an oil which was purified by column chromatography on silica gel.

Table 1. Monoprotection of 1,n-Diols

entry	Diol	Conditions[a]	Product (% yield)[b]	Isomer Ratio[c]
1	$HO(CH_2)_2OH$	A	$HO(CH_2)_2OCH_2OCH(^iPr)_2$ (93)	
2	HOCHMeCHMeOH	B	$HOCHMeCHMeOCH_2OEt$ (85)	
3	trans-1,2-Cyclo-hexanediol	D	 (73)	
4	$HO(CH_2)_3OH$	A	$HO(CH_2)_3OCH_2OCH(^iPr)_2$ (90)	
5	$HOCH_2CMe_2CH_2OH$	B	$HOCH_2CMe_2CH_2OCH_2OEt$ (99)	
6	$HOCH_2CMePrCH_2OH$	C	$HOCH_2CMePrCH_2OCH_2OMe$ (92)	
7	$HO(CH_2)_4OH$	C	$HO(CH_2)_4OCH_2OMe$ (46)	
8	Z-2-butene-1,4-diol	C	 (78)	
9	$HO(CH_2)_5OH$	C	$HO(CH_2)_5OCH_2OMe$ (<20)	
10	$HOCH_2CHMeOH$	B	$HOCH_2CHMeOCH_2OEt$ (98)	5:1
11	$HOCH_2CHPrOH$	B	$HOCH_2CHPrOCH_2OEt$ (93)	12:1
12		C	$HOCH_2CHPrOCH_2OMe$ (80)	13:1
13	$HOCH_2CH_2CHMeOH$	B	$HOCH_2CH_2CHMeOCH_2OEt$ (90)	31:1
14	$HOCHMeCH_2CMe_2OH$	B	(<5 if any)[d]	

[a]A: The diol was stirred with tri(2,4-dimethyl-3-pentyl)orthoformate at room temperature for 24 h; B: with triethylorthoformate for 24 h; C: with trimethylorthoformate for 24 h; D: with trimethylorthoacetate for 48 h. See the general procedure of text. [b]Isolated yield after column chromatography on silica gel. [c]Determined by GC analysis. [d]The major product was the corresponding 1,3-dioxane, see ref. 3.

It should be noted that not all diols could be successfully protected by our procedure. For example, 1,4-butanediol or 1,5-pentanediol gave poor results because of the unfavorable 7 or 8-membered heterocyclic ring systems. Despite this limitation, we feel this method does represent a general solution to the problem of selective protection of 1,n-diols.

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References and Notes

1. For a review, see: Wilkinson, S. G. In "Comprehensive Organic Chemistry"; Vol. 1; Pergamon Press; New York, 1979; p 681ff; Greene, T. W. "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc., New York, 1981; Fuhuhop, J.; Penzlin, G. "Organic Synthesis", pp 143ff, Verlag Chemie, Weinheim, 1983.

2. Ishihara, K.; Mori, A.; Yamamoto, H. **Tetrahedron Lett.**, 1987, **28**, 6613 and references cited therein.

3. Previously the orthoester was shown to be cleaved using aluminum ate complex or Grignard reagent, see: Eliel, E. L.; Nader, F. W., **J. Am. Chem. Soc.**, 1970, **92**, 584; **idem, ibid.**, 1970, **92**, 3045; Bailey, W. F.; Croteau, A. A., **Tetrahedron Lett.**, 1981, **22**, 545; Bailey, W. F., Rivera, A. D., **J. Org. Chem.**, 1984, **49**, 4958; **ibem, ibid.**, 1987, **52**, 1559; see also Stork, G.; Rychnovsky, S. D., **J. Am. Chem. Soc.**, 1987, **109**, 1565.

4. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. **Chem. Lett.**, 1983, 1593. See also, Mikami, T.; Asano, H.; Mitsunobu, O. **ibid.**, 1987, 2033.

5. Hanessian, S.; Delorme, D.; Dufresne Y. **Tetrahedron Lett.**, 1984, **25**, 2515.

6. The observed selectivity may also be attributed to the tight complexation between the orthoester and oxygenophilic aluminum reagent to give a species having the OR group effectively locked in an equatorial orientation as already discussed in reference 3. For a borane catalyzed reductive cleavage of cyclic acetals, see Fleming, B.; Bolker, H. I., **Can. J. Chem.**, 1974, **52**, 888.

7. Jung, M. E.; Speltz, L. M. **J. Am. Chem. Soc.**, 1976, **98**, 7882.

8. The selective acid-catalyzed reaction of cyclic acetals with acetic anhydride: Bailey, W. F.; Rivera, A. D., **J. Org. Chem.**, 1984, **49**, 4958.

9. For a recent selective protection of 1,n-diols, see McDougal, P. G.; Rico, J. G.; Oh, Y-I.; Dondon, B. D., **J. Org. Chem.**, 1986, **51**, 3388.

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