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KINETIC ACETALIZATION FOR 1,2- AND 1,3-DIOL PROTECTION BY THE REACTION OF p-METHOXYPHENYLMETHYL METHYL ETHER WITH DDQ

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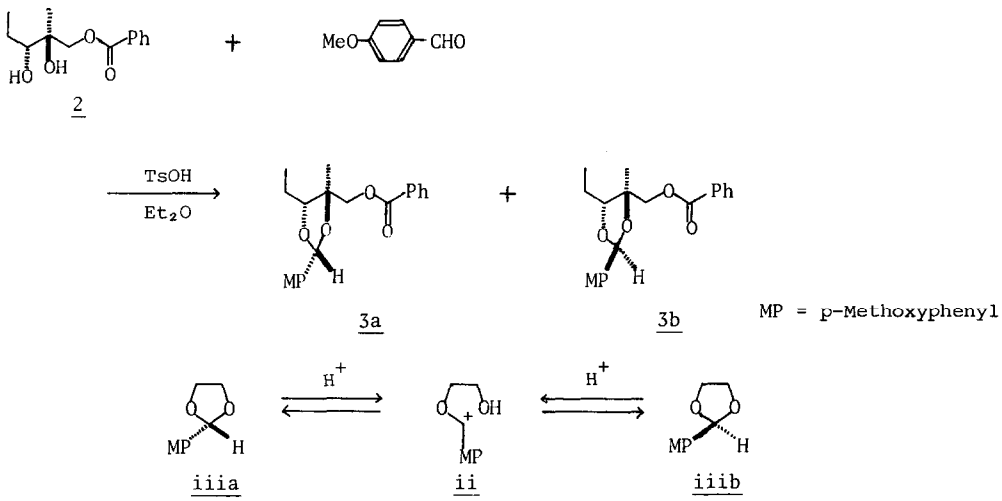
Abstract When 1,2- and 1,3-diols were treated with p-methoxyphenylmethyl methyl ether (MPMME) in the presence of DDQ, the kinetically controlled oxidative acetalization occurred smoothly even in case of acid-labile compounds to give p-methoxybenzylidene acetals rather stereoselectively.

New hydroxy protecting groups with specific properties are still being required in the synthesis of complex natural products, particularly in the area of polyketide derived macrolide and polyether antibiotics. Polyhydroxy functionality present in this class of natural products[1] involves a variety of 1,2- and 1,3-diol systems, which are usually protected as cyclic acetals and ketals, primarily because of their ease of both formation and removal, stability under the basic conditions required for alkylation, acylation, etc., and regid conformation. The most commonly used protecting groups are isopropylidene ketals and benzylidene acetals,[2] and sometimes the latter is much more favorable especially in highly crowded molecules because of the less steric hinderance.

However, there are two major problems: One is that benzylidene acetals formed under conventional acid-catalyzed conditions are usually diastereoisomeric mixtures with respect to the benzylic carbon. The other, which is more serious, associated with formation and cleavage conditions arises when an acid-labile functionality is present. Although very few methods of cyclic acetalization for 1,2- and 1,3-diols under non-acidic conditions are known,[3] they are limited only to simple substrates and the yields are generally unsatisfactory.

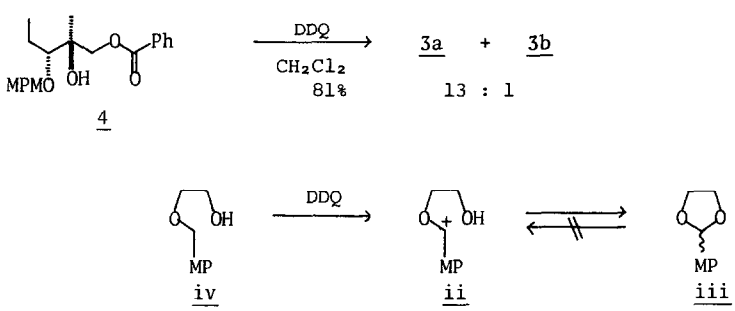
In connection with our synthetic studies of macrolide and polyether antibiotics, we required a new method for the acetalization which could solve the above problems. We report here the oxidative acetalization of 1,2- and 1,3-diols with p-methoxyphenylmethyl methyl ether (MPMME; 1) in the presence of DDQ as an oxidant under almost neutral conditions to provide a general solution for the problems, especially for the second one, and this new method will be useful in a wide range of synthetic organic chemistry.

When 2 was treated with p-methoxybenzaldehyde in the presence of p-toluenesulfonic acid at room temperature for 20 min, 3a[4a,b] and 3b[4b,c] were obtained as a 3.4 : 1 mixture.[5] Under acidic conditions two stereoisomers with respect to the benzylic carbon such as 3a and 3b must be in equilibrium (Scheme 1), and hence a thermodynamically controlled mixture is usually obtained.[6a-d] If this acetalization can be changed to a kinetically controlled reaction, alternatively, if we can synthesize these acetals without an acid catalyst, the ratio in the mixture is expected to change.[7]



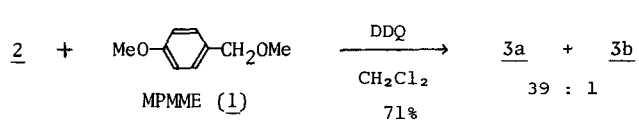
Scheme 1

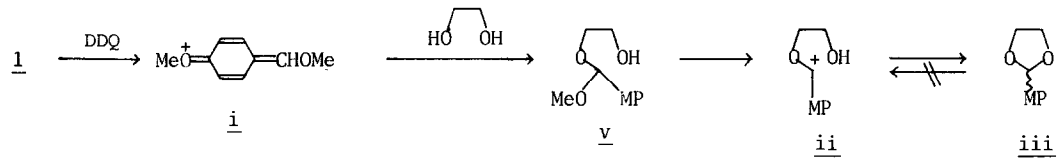
When 4 was treated with DDQ in dichloromethane[8] at room temperature for 1.5 h, a mixture of 3a and 3b was again obtained, but the ratio was considerably improved to 13 : 1.[5] Since weakly acidic DDHQ (dichlorodicyanohydroquinone) produced from DDQ is almost insoluble in the solvent,[9] the reaction mixture is maintained almost neutral throughout the reaction. Therefore, the acid-catalyzed back reaction (iii → ii) must be supressed,[10] and we may say this acetalization to be "kinetically controlled." When the above 13 : 1 mixture was allowed to stand in the presence of p-toluenesulfonic acid for several hours, the ratio dropped to 3 : 1.[5]



Scheme 2

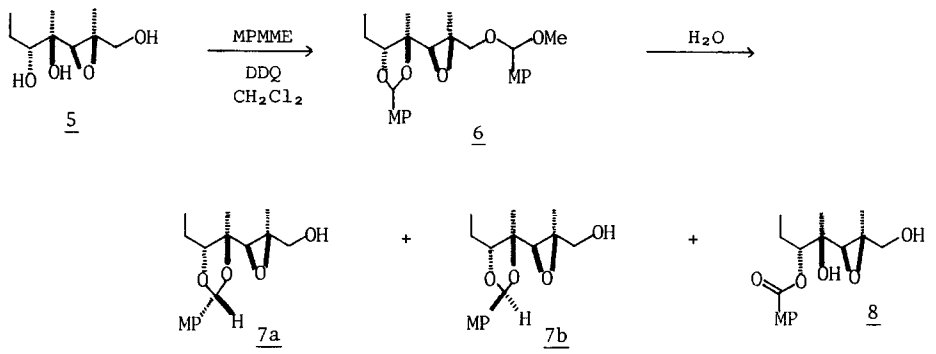
MPMME (1) is much more useful and practical for this kinetic acetalization. When a dichloromethane solution (20 ml) of 2 (1.45 mmol) and 1 (4.0 equiv) was treated with DDQ (2.2 equiv) at room temperature for 30 min, followed by filtration and washing with 5% sodium bicarbonate solution, the mixture of 3a and 3b was obtained in the ratio of 39 : 1.[5,10] The mechanism can be written as follows.





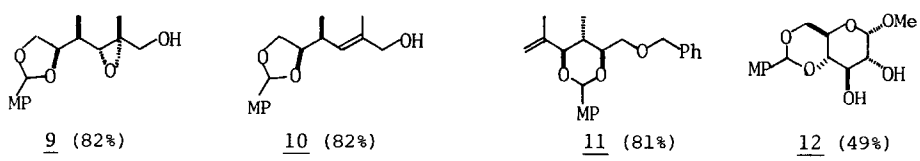
Scheme 3

When the conventional acid-catalyzed acetalization was employed, the acid-labile epoxy triol (5) afforded not the expected acetal, but the tetrahydrofuran derivative by intramolecular attack of the secondary hydroxy group to the epoxide. However, the reaction of 5 (14.6 mmol) and 1 (4.5 equiv) with DDQ (3.0 equiv) in dichloromethane (150 ml) at 16°C for 25 min gave the acetal (6), which was easily hydrolyzed to 7a[11a] and 7b[11b] as a 12 : 1 diastereoisomeric mixture[5] (70%) by the addition of water. The sole byproduct in this reaction was 8[11c] (11.2%) arising from further oxidation of 7 as previously reported.[12] Compound 8 was readily hydrolyzed with 3% methanolic potassium hydroxide to regenerate the starting material (5). It should be noted that the epoxy group was intact under the acetalization conditions.



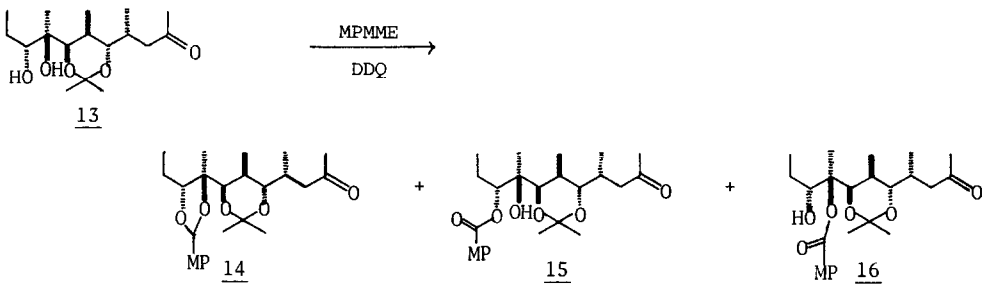
Scheme 4

Some additional examples from the corresponding diols are shown in Scheme 5. Although there was almost no stereoselection for the formation of 9 and 10 which were both obtained as 1.2 : 1 mixtures,[5] six-membered acetals, 11 and 12, were isolated as single stereoisomers.[5,13]



Scheme 5

The highly sterically hindered diol group on the axially oriented side chain of the 1,3-dioxane ring of 13 resisted the acetalization and required a large excess of 1 and DDQ, and hence further oxidation proceeded to yield mainly a mixture of the esters, 15 (40%) and 16 (20%), together with the expected acetal (14, 21%).



Scheme 6

The acetals synthesized here were successfully deprotected by the non-acidic method which was recently reported.[12] Finally, the kinetic acetalization presented in this communication may provide a widely useful new method for the protection of 1,2- and 1,3-diols,[14] even though there are some limitations especially for highly hindered compounds.

References and Notes

1) Reviews on macrolide antibiotics: S. Masamune, G. S. Bates, J. W. Corcoran, Angew. Chem. Int. Ed. Engl., 16, 585 (1977); K. C. Nicolaou, Tetrahedron, 33, 683 (1977). Reviews on polyether antibiotics: J. Westley, Adv. Appl. Microbiol., 22, 177 (1977); B. C. Pressman, Ann. Rev. Biochem., 45, 501 (1976).
2) Cf. T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc., 1981.
3) P. J. Garegg, L. Maraon, and C. G. Swahn, Acta Chem. Scand., 26, 518 (1972); P. J. Garegg and C. G. Swahn, ibid., 26, 3895 (1972); R. M. Munavu and H. H. Szmant, Tetrahedron Lett., 4543 (1975).
4) a) δ ($CDCl_3$); 1.12 (t, 3H, J 7.5 Hz), 1.47 (s, 3H), 1.6-1.7 (m, 2H), 3.80 (s, 3H), 3.82 (t, 1H, J 6.0 Hz), 4.29, 4.43 (ABq, 2H, J 12 Hz), 5.85 (s, 1H), 5.88 (d, 2H, J 9 Hz), 7.3-7.7 (m, 5H), 7.9-8.1 (m, 1H). b) Chemical shift of the H-2 proton in the 1,3-dioxolane ring: δ 6.13. c) Configuration was determined on the basis of the chemical shift of the H-2 proton in the 1,3-dioxolane ring. See ref. 6a-c.
5) The diastereomeric ratio was determined by NMR.
6) a) N. Baggett, A. B. Foster, and J. M. Webber, Chem. Ind., 136 (1965); b) N. Baggett, J. M. Duxbury, A. B. Foster, and J. M. Webber, J. Chem. Soc. (C), 268 (1966); c) E. L. Eliel and W. E. Willy, Tetrahedron Lett., 1775 (1975); d) W. E. Willy, G. Binsch, and E. L. Eliel, J. Am. Chem. Soc., 92, 5394 (1970).
7) It was observed that the acid-catalyzed reaction of benzaldehyde with 1,4-anhydroerythritol under homogeneous conditions produced initially the cyclic acetal with an endo-phenyl group selectively, followed by equilibration to give a nearly equimolar exo and endo mixture. See ref. 6a.
8) Distilled over phosphorus pentoxide and stocked over molecular sieves (4A).
9) Solubility in dichloromethane at 25°C: 0.4g/l; D. Walker and J. D. Hiebert, Chem. Rev., 67, 153 (1967).
10) It seems that the back reaction (iii → ii) takes place slowly in practice, since the 39 : 1 ratio in the reaction of 2 and MPMME dropped to 15 : 1 when the reaction was quenched after 1.5 h.
11) a) δ ($CDCl_3$); 1.12 (t, 3H, J 7.5 Hz), 1.38 (s, 3H), 1.43 (s, 3H), 1.6-2.0 (m, 2H), 3.05 (s, 1H), 3.6-3.8 (m, 3H), 3.80 (s, 3H), 5.76 (s, 1H), 6.88 (d, 2H, J 9 Hz), 7.57 (d, 2H, J 9 Hz). b) Chemical shift of the H-2 proton of the 1,3-dioxolane ring: δ 6.06. c) δ ($CDCl_3$); 0.97 (t, 3H, J 6.5 Hz), 1.29 (s, 3H), 1.51 (s, 3H), 1.7-1.9 (m, 2H), 2.47 (s, 1H), 3.17 (s, 1H), 3.58 (d, 1H, J 3.0 Hz), 3.65 (s, 1H), 3.86 (s, 3H), 5.08 (dd, 1H, J 4.0, 9.5 Hz), 6.93 (d, 2H, J 9.0 Hz), 8.06 (d, 2H, J 9.0 Hz).
12) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., 23, 889 (1982).
13) The yield of 12 was very poor because the starting material, methyl α-D-glucoside, was almost insoluble in dichloromethane.
14) We used this acetalization method effectively in the total synthesis of methynolide recently completed, which will be reported in due course.

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