

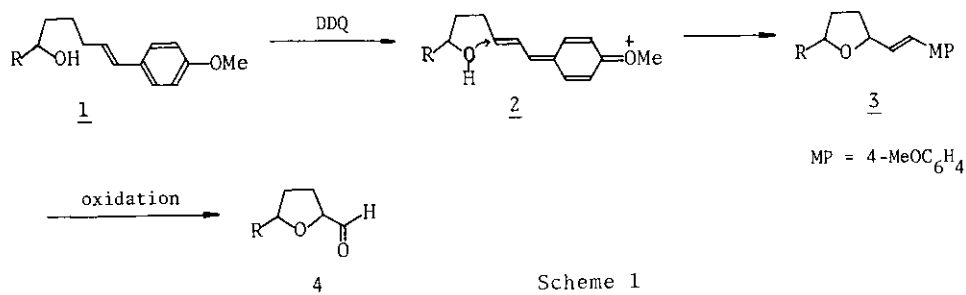
SYNTHESIS OF SUBSTITUTED TETRAHYDROFURANS AND TETRAHYDROPYRANS 1.
 OXIDATIVE CYCLIZATION OF p-METHOXYSTYRENE DERIVATIVES WITH DDQ

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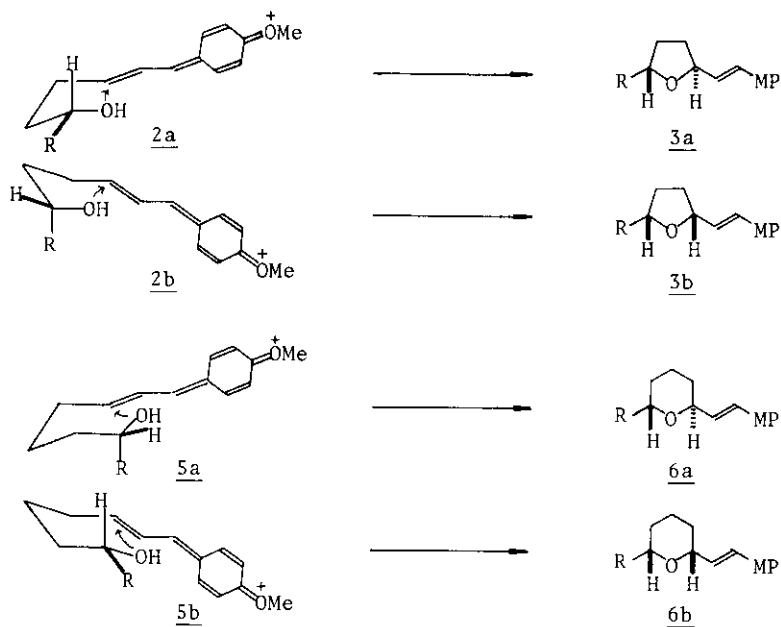
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Abstract — In the course of synthetic studies of polyether antibiotics, we tried to develop a new synthetic method of substituted tetrahydrofuran and tetrahydropyran rings. When p-methoxystyrene derivatives having a hydroxy group at a suitable position was treated with DDQ, an oxidative cyclization of E-olefins, not Z-olefins, occurred yielding substituted tetrahydrofurans and tetrahydropyrans, though in low yields.

In multistep synthesis of highly complex ionophore polyether antibiotics such as monensin,¹ lasalocid A,² lysocellin,³ and salinomycin,⁴ it is very important how to construct substituted tetrahydrofuran and tetrahydropyran rings bearing appropriately functionalized substituent groups with correct stereochemistry, because these rings are essential building blocks of the antibiotics. Recently, many new synthetic methods of tetrahydrofurans⁵ and tetrahydropyrans⁶ were developed and elegant total syntheses of complex polyether antibiotics⁷ have been reported. A few years ago, we also planned to synthesize two polyether antibiotics, salinomycin and isolasalocid A,⁸ as well as some macrolide antibiotics from D-glucose by a common methodology, and our initial interest has been focused on the synthesis of substituted tetrahydrofuran and tetrahydropyran ring systems from appropriate acyclic precursors. We report here a preliminary work on a new class of oxidative cyclization of p-methoxystyrene derivatives with DDQ. Benzylic oxidation (dehydrogenation) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been well studied,⁹ and recently new protecting groups for hydroxy function, MPM (p-methoxybenzyl) and DMPM (3,4-dimethoxybenzyl) groups, which are removable by DDQ oxidation under neutral conditions, were developed in this laboratory.¹⁰ Allylic oxidation in electron rich systems, e.g., p-methoxystyrene derivatives, are also well known.¹¹ Therefore, a p-methoxystyrene derivative (1) bearing a hydroxy group at the suitable position was expected to give a tetrahydrofuran derivative (3),¹² which are convertible into the corresponding aldehyde (4), via an oxidative cyclization of the dehydrated intermediate (2) as shown in Scheme 1. Similarly, a tetrahydro-



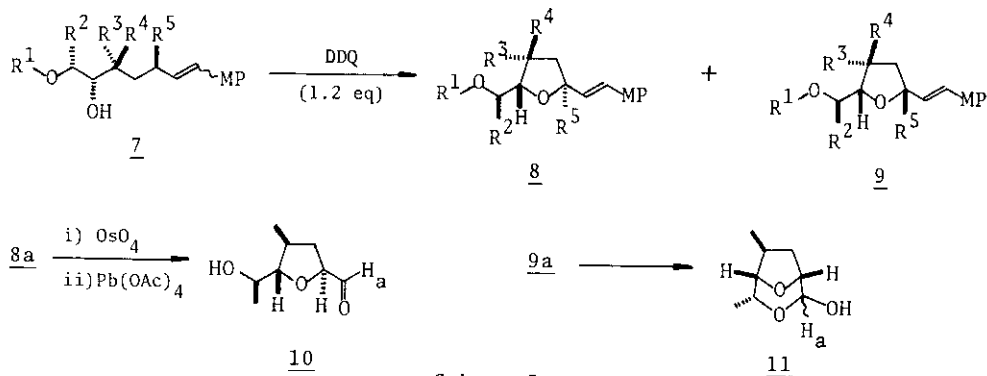
Scheme 1



Scheme 2

pyran derivative may be obtained from a homologous compound. If conformations in the transition states can be written as 2a, 2b, 5a, and 5b, 2a and 5b with an equatorial R group should be favorable giving 2,5-trans-tetrahydrofuran (3a) and 2,6-cis-tetrahydropyran (6b), respectively (Scheme 2).

When 7a (1.8 : 1 mixture of E- and Z-olefins) was treated with a small excess of DDQ in dichloromethane, only the E-isomer gave a 1.3 : 1 mixture of tetrahydrofurans,¹³ 8a and 9a, though in poor yield (25%) based on the consumed starting material. No detectable formation of tetrahydropyran derivatives was observed. In acetonitrile, the reaction was accelerated and completed within only 1 min, and the yield was slightly improved. The benzyl derivative (7b) gave a little better result giving 8b and 9b, which were also derived from 8a and 9a, respectively, by benzylation. Configurations of the tetrahydrofurans (8, 9) were readily determined by their NMR spectra and unequivocally confirmed by converting 8a and 9a into the aldehyde (10) [δ 9.67 (d, $J = 2.0$ Hz; H_a)] and a hemiacetal (11) [δ 4.59 (d, $J = 10.0$ Hz; equatorial H_a), 4.97 (dd, $J = 6.0, 2.0$ Hz; axial H_a)], respectively. Similarly, 7c gave 8c and 9c.



Scheme 3

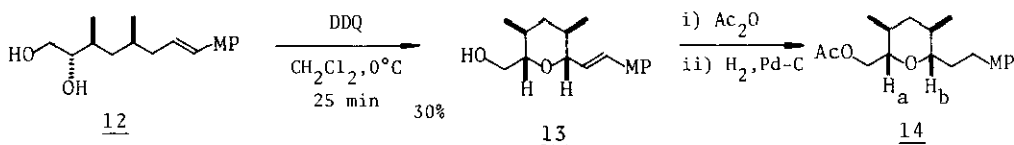
In acetonitrile, 7d and 7e also gave similar results, but under weakly acidic conditions the yield of 8e and 9e from 7e was slightly improved. In analogy with 8a and 9a, configurations of 8d and 9d were confirmed by their respective conversion into an aldehyde and a hemiacetal. A better stereoselectivity was observed in the oxidative cyclization of styrene derivatives bearing a methyl group at the allylic position, 7f and 7g, and the ratios were 5.0 : 1 and 3.9 : 1, respectively.

Table. Synthesis of Substituted Tetrahydrofurans from p-Methoxystyrene Derivatives by DDQ Oxidation

	R ¹	R ²	R ³	R ⁴	R ⁵	E/Z	solvent	temp (°C)	time (min)	yield (%)	8/9
<u>7a</u>	H	Me	H	Me	H	1.8	CH ₂ Cl ₂	0	25	25	1.2
							MeCN	0	1	35	1.3
<u>7b</u>	Bn	Me	H	Me	H	1.7	MeCN	0	0.7	57	1.5
<u>7c</u>	Bz	Me	H	Me	H	1.0	CH ₂ Cl ₂	rt ^a	8	34	2.0
<u>7d</u>	H	H	Me	OBn	H	1.6	MeCN	0	0.8	39	1.9
<u>7e</u>	Bn	H	Me	OBn	H	3.2	MeCN	0	0.8	38	1.4
							MeCN-AcOH ^b	0	2	47	1.5
<u>7f</u>	H	Me	H	Me	Me	1.0	CH ₂ Cl ₂	rt ^a	8	50	5.0
<u>7g</u>	Bn	Me	H	Me	Me	1.0	CH ₂ Cl ₂	rt ^a	8	38	3.9

^a room temperature. ^b (30 : 1).

A homologous styrene derivative (12; pure E-isomer) was also readily oxidized to give only the 2,6-cis-tetrahydropyran (13; 30%), whose structure was confirmed after conversion to 14 [δ 3.1] (ddd, J = 10, 7, 3 Hz; H_a), 2.64 (dt, J = 14, 8 Hz; H_b)].



Scheme 4

In conclusion, the oxidative cyclization with DDQ presented here may provide a new and simple method for the synthesis of substituted and functionalized tetrahydrofuran and tetrahydropyran ring systems found in many complex ionophore polyether antibiotics, though both the yield and the stereoselectivity are still unsatisfactory.

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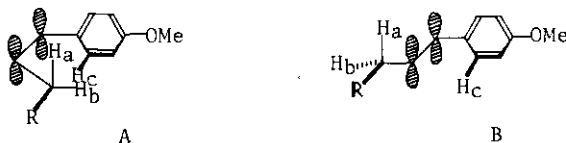
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12. Cf. K. Schofield, R. S. Ward, A. M. Choudhung, *J. Chem. Soc. (C)*, 2834 (1971).

13. The Z-isomer was unreactive in this oxidative cyclization with DDQ and invariably recovered unchanged. In fact, the pure Z-isomer of 7a was again recovered on treatment with DDQ in acetonitrile. All of other p-methoxystyrene derivatives (7, 12) gave similar results, which will be interpreted in terms of the following steric requirement. For the abstraction of the allylic hydrogen H_a with DDQ,¹⁴ it is necessary that in both conformation A (Z-isomer) and B (E-isomer) the p-orbitals and H_a lie in a common plane. The conformation A must be unfavorable because of a considerable steric repulsion between H_b and H_c , whereas there is no such a repulsion in the conformation B.



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