

REACTION OF DIOLS AND TRIOLS WITH TRIALKYL ORTHOESTERS:
FACILE ONE-POT FORMATION OF OXACYCLIC COMPOUNDS FROM
TRIOLS†

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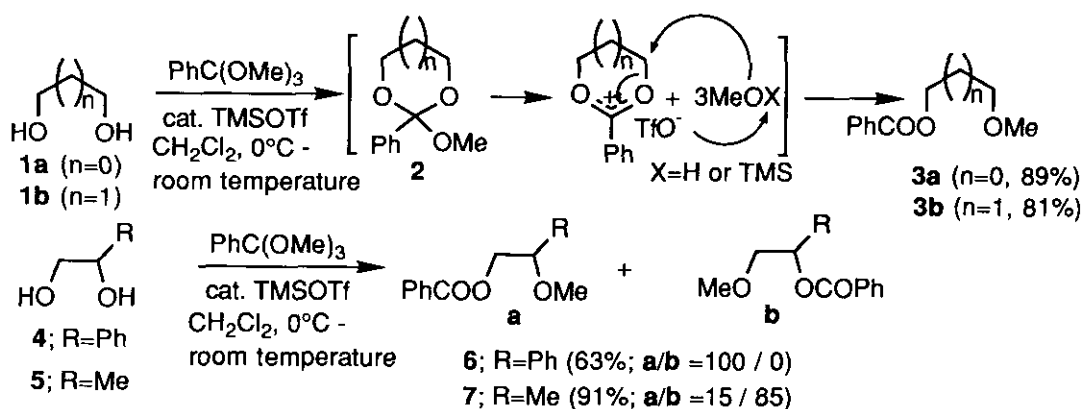
Abstract-Reaction of diols and triols with trialkyl orthoesters was studied and
facile one-pot formation of oxacyclic compounds from triols was developed.

Substituted oxacyclic molecules, such as tetrahydrofurans and tetrahydropyrans, are found widely in polyether antibiotics¹ and marine *Laurencia* metabolites.² Although many methods have been devised for constructing them so far,³ a new strategy is still strongly desirable. We present here a facile one-pot formation of substituted oxacyclic molecules by reaction of triols and trialkyl orthoesters.

Orthoesters are versatile agents and work as superior electrophiles by forming dioxenium cations.⁴ 1,3-Dioxolan-2-ylum ions formed by treatment of 2-alkoxy-1,3-dioxolane type orthoesters react with nucleophiles at the 2 or 4 position, depending on the nature of the nucleophiles, and also when the 2-substituted 2-alkoxy-1,3-dioxolanes were treated with a catalytic amount of BF₃ to give the corresponding 1-acyloxy-2-alkoxyethanes.⁵ These results suggest that direct conversion of diols to the corresponding alkoxyalkyl esters is possible in one-pot operation. In fact, the reactions of ethylene glycol (**1a**) and propanediol (**1b**) with trimethyl orthobenzoate [PhC(OMe)₃] in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) proceeded to give the

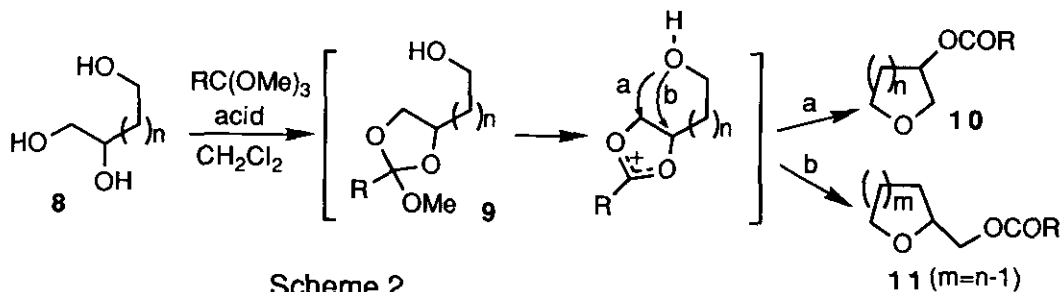
†This paper is dedicated to Professor Edward C. Taylor on the occasion of his 70th birthday.

corresponding methoxyalkyl benzoates (**3a**) and (**3b**), respectively, *via* cyclic orthoester (**2**) then dioxenium cation. A similar reaction was also observed in cases of compounds (**4**) and (**5**): the ratios of the products (*a* / *b*) were determined by ^1H -nmr spectroscopy (Scheme 1).



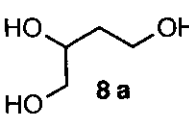
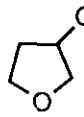
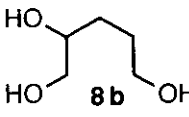
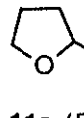
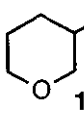
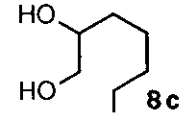
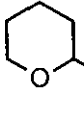
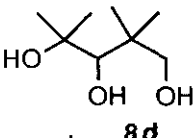
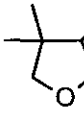
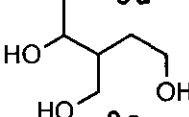
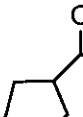
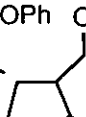
Scheme 1

From these results, one can easily imagine that the triols (**8**), with a suitably positioned hydroxy group, give the cyclic ethers *via* dioxenium cation intermediates from cyclic orthoesters (**9**) as depicted in Scheme 2. Reactions of triols (**8**) and 1.1 equivalent of trialkyl orthoesters in the presence of a catalytic amount of acid in CH_2Cl_2 were carried out to obtain the oxacyclic compounds (**10**) or (**11**). The results are summarized in the Table. Several aspects are noteworthy. First, TMSOTf is a superior choice as an acid (runs 1 and 5 vs runs 2 and 6). Secondly, PhC(OMe)_3 gave better results than trimethyl ortho acetate [MeC(OMe)_3] (runs 1 and 5 vs runs 3 and 7). Thirdly, ring closure proceeds selectively (5-membered ring formation in the cases of **8a** and **8b**, and 6-membered ring formation in the case of **8c**). Forthly, reaction proceeds smoothly in the case of formation of a crowded tetrahydrofuran ring (entry 8). Fifthly, 1,3-diol system also works without any trouble, though regioselectivity is not as high (entry 9).



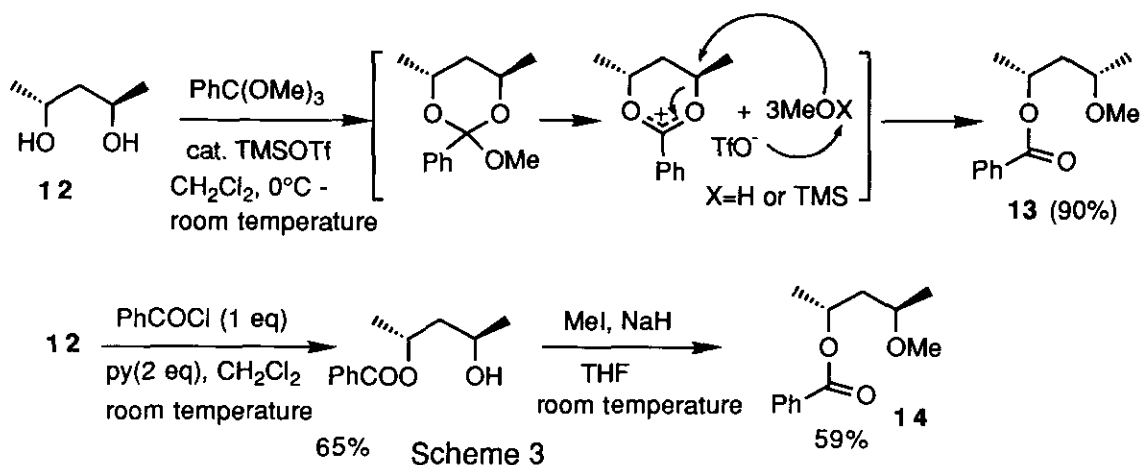
Scheme 2

Table. Reaction of Triols with Trimethyl orthoesters in the Presence of Acid

Run	Triols	Reaction Conditions	Products (Yields) ^{a)}
1	 8a	PhC(OMe) ₃ , cat. TMSOTf, 0°C, 2 h	 10a ; R=Ph (99%)
2		PhC(OMe) ₃ , cat. p-TsOH, 0°C, 2 h	10a (95%)
3		MeC(OMe) ₃ , cat. TMSOTf, 0°C, 2 h	10b ; R=Me (44%)
4	 8b	PhC(OMe) ₃ , cat. TMSOTf, 0°C, 2 h	 11a (55%)  10c (8%)
5	 8c	PhC(OMe) ₃ , cat. TMSOTf, 0°C, 2 h	 11b ; R=Ph (89%)
6		PhC(OMe) ₃ , cat. p-TsOH, 0°C, 3 h	11b (68%)
7		MeC(OMe) ₃ , cat. TMSOTf, 0°C, 2 h	OCOR 11c ; R=Me (57%)
8	 8d	PhC(OMe) ₃ , cat. TMSOTf, 0°C, 0.5 h	 10d (84%)
9	 8e	PhC(OMe) ₃ , cat. TMSOTf, 0°C, 2 h	 10e  10f 10e/10f = 1/2 ^{b)} (94%) ^{c)}

a) Yields are not optimized. b) The ratio was determined by ¹H-nmr spectroscopy.c) Total yield of **10e** and **10f**.

The reaction using chiral diol and orthoester was found to give an inversion product. Thus, reaction of (-)-(2*R*,4*R*)-2,4-pentanediol (**12**) with PhC(OMe)₃ in the presence of a catalytic amount of TMSOTf provided (-)-(2*R*,4*S*)-2-benzoyloxy-4-methoxypentane (**13**) in excellent yield. The stereochemistry of **13** and complete inversion by S_N2 attack of MeO⁻ at the 4-position of dioxenium cation intermediate were ascertained by comparison with (-)-(2*R*,4*R*)-2-benzoyloxy-4-methoxypentane (**14**), which was prepared by monobenzoylation and successive methylation of **12**⁶ (Scheme 3).



In conclusion, we found that direct formation of methoxyalkyl esters and oxacyclic compounds was caused by reaction of several diols and triols with trimethyl orthoesters. Although the synthetic methodology of substituted tetrahydrofurans *via* the cyclic dioxonium cations formed by oxidation of benzylidene acetals with a suitable positioned hydroxyl group has been reported,⁷ our methodology can give the cyclic ether compounds from the unprotected triols in one-pot operation and has a great advantage in a practical point of view.

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6. Spectroscopic data of **13**: $[\alpha]_D -35^\circ$ ($c=3.0$, CHCl_3). $^1\text{H-Nmr}$ (200M Hz, CDCl_3) δ : 1.19 (3H, d, $J=6.2$ Hz), 1.38 (3H, d, $J=6.4$ Hz), 1.6-1.7 (1H, m), 2.9-2.1 (1H, m), 3.30 (3H, s), 3.4-3.5 (1H, m), 5.2-5.4 (1H, m), 7.4-7.6 (3H, m), 8.0-8.1 (2H, m). Spectroscopic data of **14**: $[\alpha]_D -80^\circ$ ($c=0.8$, CHCl_3). $^1\text{H-Nmr}$ (200M Hz, CDCl_3) δ : 1.17 (3H, d, $J=6.0$ Hz), 1.36 (3H, d, $J=6.4$ Hz), 1.7-1.9 (2H, m), 3.28 (3H, s), 3.3-3.5 (1H, m), 5.3-5.5 (1H, m), 7.3-7.6 (3H, m), 7.9-8.1 (2H, m).
Compounds (**13**) and (**14**) are easily distinguishable to each other by $^1\text{H-nmr}$ spectra, since the signals of methylene groups of them appear in completely different regions.
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