

DIRECT REGIOSELECTIVE FORMATION OF POLYSUBSTITUTED  
TETRAHYDROFURANS FROM UNPROTECTED POLYOLS†

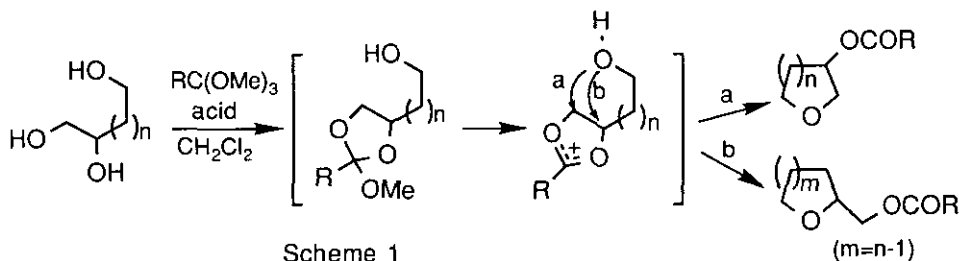
Hiromichi Fujitaka,\* Hidetoshi Kitagawa, Michinori Kondo, and Yasuyuki Kita\*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka,  
Suita, Osaka 565, Japan

**Abstract**-The reaction of unprotected polyols (tetraols, pentitol and hexitol) with trimethyl orthobenzoate in  $\text{CH}_2\text{Cl}_2$ -MeOH afforded polysubstituted tetrahydrofurans in a one-pot synthesis.

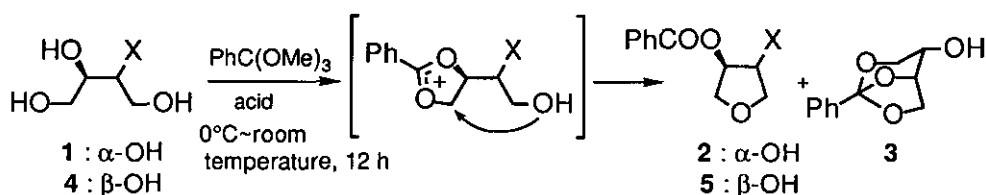
Substituted oxacyclic molecules, such as tetrahydrofurans and tetrahydropyrans, are widely found in polyether antibiotics<sup>1</sup> and marine *Laurencia* metabolites.<sup>2</sup> Although many methods have been devised for their synthesis,<sup>3</sup> a new strategy is still strongly desirable. Recently, we reported the direct formation of substituted oxacyclic molecules by the reaction of triols and trialkyl orthoesters in the presence of a catalytic amount of acid using  $\text{CH}_2\text{Cl}_2$  as the reaction solvent. The reaction is very useful because unprotected triols directly give oxacyclic molecules in high yields *via* the cyclic orthoester followed by the dioxenium cation (Scheme 1).<sup>4</sup>

As an extension of the method, we now applied it to the unprotected high-order alcohols such as tetraols, pentitols, and hexitols. In these cases, of course, the solubility of the substrate in the reaction solvent came into

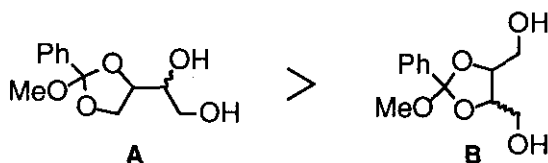
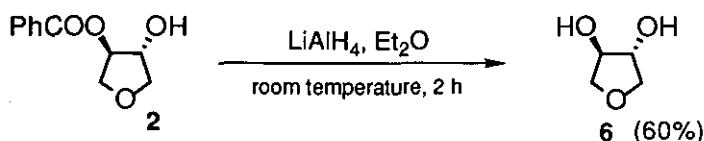


†This paper is dedicated to professor Alan R. Katritzky on the occasion of his 65th birthday.

question. The reaction solvent was first examined using ( $\pm$ )-threitol (**1**) and trimethyl orthobenzoate [ $\text{PhC}(\text{OMe})_3$ ] (1.5 equiv.) (Scheme 2). Although  $\text{CH}_2\text{Cl}_2$  did not dissolve the alcohol and the cyclic orthoester (**3**)<sup>5</sup> was obtained in DMF (Entry 4), the use of  $\text{CH}_2\text{Cl}_2$ -MeOH (3/1) or MeOH gave the 3,4-*trans*-substituted tetrahydrofuran (**2**) (Entries 2, 3). As an acid catalyst, TfOH was also effective (Entry 5). The structure and stereochemistry of **2** was unambiguously determined by converting it to the 3,4-dihydroxytetrahydrofuran (**6**).<sup>6</sup> The reaction of *meso*-erythritol (**4**) gave the *cis*-substituted monobenzoate (**5**)<sup>5</sup> in high yield. These results suggest that formation of the dioxenium cation intermediates occurred regioselectively. In other words, the first orthoester formation occurs at the sterically less hindered position (rate of the orthoester formation;  $A > B$ ).



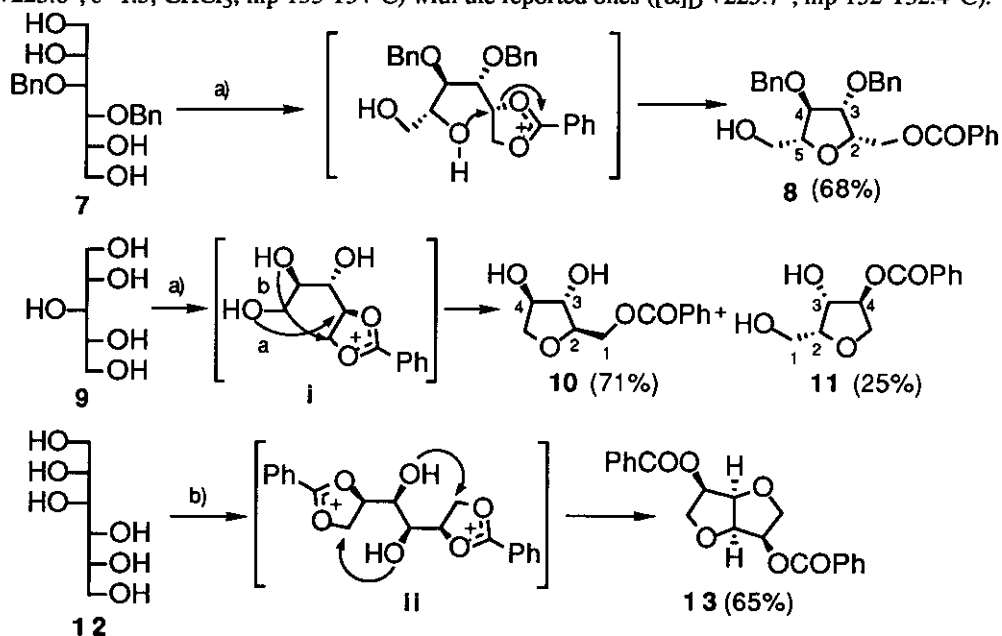
Entry	Substrate	Reaction Conditions	Product	Yield
1	<b>1</b>	cat. TMSOTf, $\text{CH}_2\text{Cl}_2$	insoluble	
2		cat. TMSOTf, $\text{CH}_2\text{Cl}_2/\text{MeOH}=3/1$	<b>2</b>	87%
3		cat. TMSOTf, MeOH	<b>2</b>	70%
4		cat. TMSOTf, DMF	<b>3</b>	68%
5		cat. TfOH, $\text{CH}_2\text{Cl}_2/\text{MeOH}=3/1$	<b>2</b>	87%
6	<b>4</b>	cat. TfOH, $\text{CH}_2\text{Cl}_2/\text{MeOH}=3/1$	<b>5</b>	88%



Scheme 2

Application to other polyols was next studied (Scheme 3). 3,4-Di-*O*-benzyl-D-mannitol (**7**) afforded the 2,3,4,5-tetrasubstituted tetrahydrofuran (**8**)<sup>5</sup> ( $[\alpha]_D +48.5^\circ$ ,  $c=1.2$ ,  $\text{CHCl}_3$ ) in good yield. The stereochemistry of compound (**8**) was determined by the proton-proton coupling constants of the monoacetylated derivative. Thus, the coupling constant of 3.6 Hz between H-2 and H-3, no coupling between H-3 and H-4 and small coupling constant of 1.0 Hz between H-4 and H-5 indicated the *cis* relationship of the C-2 and C-3 substituents and *trans*

relationship of the C-3 and C-4 as well as C-4 and C-5 substituents.<sup>7</sup> Xylitol (9) afforded two tetrahydrofurans, *trans-trans* and *cis-trans* substituted tetrahydrofurans (10 and 11)<sup>5</sup> in a ratio of 3 : 1. A <sup>1</sup>H NMR study for determining the stereochemistry of the products was carried out using their diacetylated derivatives (10a, 11a). *Trans* stereochemistry of C-3 and C-4 of compounds(10)and(11)were determined from small H-3-H-4 coupling constants of 1.0 Hz for 10a and 1.3 Hz for 11a, since small H-3-H-4 coupling constants of 1.0 Hz for compound (2) with a *trans* relationship and a fairly large one of 5.3 Hz for compound(5)with a *cis* relationship were observed. The stereochemistry of the C-2 and C-3 substituents of compounds(10)and(11)were deduced from the coupling constants between H-2 and H-3, 2.3 Hz for 10a and 4.0 Hz for 11a (see ref. 7). The observed NOE between H-1 and H-3 in 10a as well as H-2 and H-3 in 11a also supported the assigned structures. These products may be obtained from the same dioxenium ion intermediate **i** in two different courses (route a or b). The reaction of a hexitol, D-mannitol (12), with 3 equiv. of PhC(OMe)<sub>3</sub> afforded the bicyclic tetrahydrofuran (13) directly *via* two dioxcenium intermediates as shown in **ii**, whereas the use of 1.1 equiv. of PhC(OMe)<sub>3</sub> gave 13 in low yield (31%). The structure of 13 was deduced from its ir spectra, <sup>1</sup>H-nmr spectroscopies, and <sup>1</sup>H-<sup>1</sup>H COSY and was ascertained by comparison of its optical rotation and melting point ( $[\alpha]_D^{+225.0^\circ}$ ,  $c=1.5$ , CHCl<sub>3</sub>; mp 133-134°C) with the reported ones ( $[\alpha]_D^{+225.7^\circ}$ ; mp 132-132.4°C).<sup>8</sup>



Reaction conditions; a) PhC(OMe)<sub>3</sub> (1.5 equiv.), cat. TfOH, CH<sub>2</sub>Cl<sub>2</sub>-MeOH (3/1), 0°C-room temperature, 12 h; b) PhC(OMe)<sub>3</sub> (3 equiv.), cat. TfOH, CH<sub>2</sub>Cl<sub>2</sub>-MeOH (3/1), 0°C-room temperature, 12 h.

Scheme 3

As previously mentioned, regio- and stereoselective cyclic ether formation was attained by the reaction of polyols and trimethyl orthobenzoate in the presence of a catalytic amount of acid. The present method has the following advantages: i) a very simple procedure, ii) the use of polyols without protection of the hydroxy functions, and iii) the selective protection of the hydroxyl function as a benzoate during the cyclization reaction, which allows the ready transformation of the resulting polysubstituted tetrahydrofurans.

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