DIRECT REGIOSELECTIVE FORMATION OF POLYSUBSTITUTED TETRAHYDROFURANS FROM UNPROTECTED POLYOLS†

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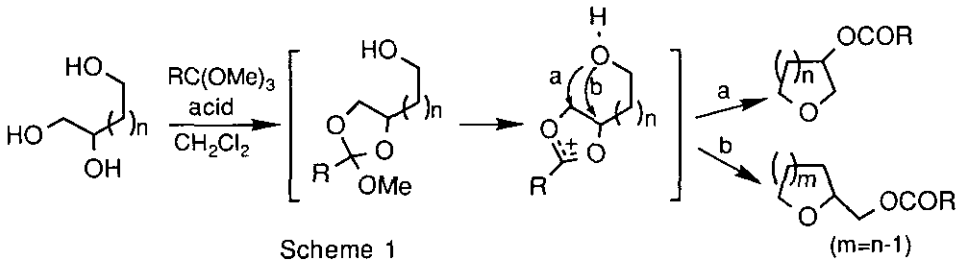
Abstract-The reaction of unprotected polyols (tetraols, pentitol and hexitol) with trimethyl orthobenzoate in CH_2Cl_2-MeOH afforded polysubstituted tetrahydrofurans in a one-pot synthesis.

Substituted oxacyclic molecules, such as tetrahydrofurans and tetrahydropyrans, are widely found in polyether antibiotics[1] and marine Laurencia metabolites.[2] Although many methods have been devised for their tsynthesis,[3] 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 CH_2Cl_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).[4]

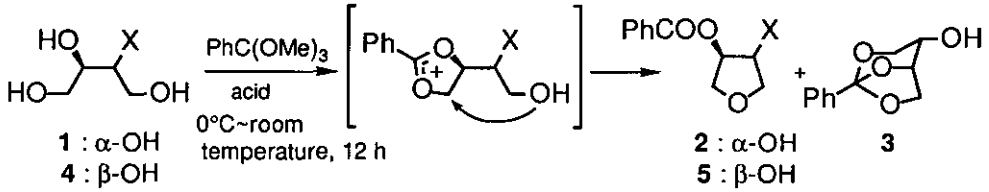
As an extension of the method, we now applied it to the unprotected high-order alcohols such as tetraols, pentitols, and hexitols. In these cases, of course, the solubility of the substrate in the reaction solvent came into



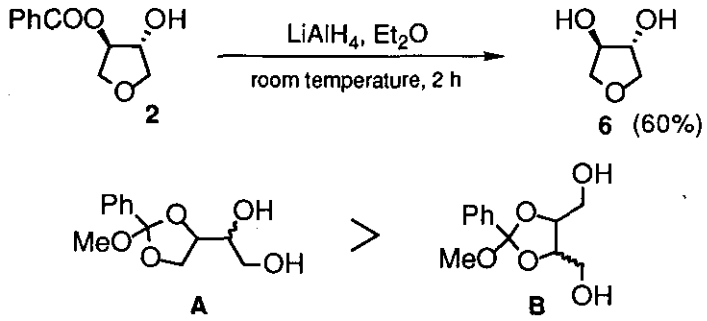
Scheme 1

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

question. The reaction solvent was first examined using (±)-threitol (**1**) and trimethyl orthobenzoate [$PhC(OMe)_3$] (1.5 equiv.) (Scheme 2). Although CH_2Cl_2 did not dissolve the alcohol and the cyclic orthoester (**3**)[5] was obtained in DMF (Entry 4), the use of CH_2Cl_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**).[6] The reaction of *meso*-erythritol (**4**) gave the *cis*-substituted monobenzoate (**5**)[5] 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**).



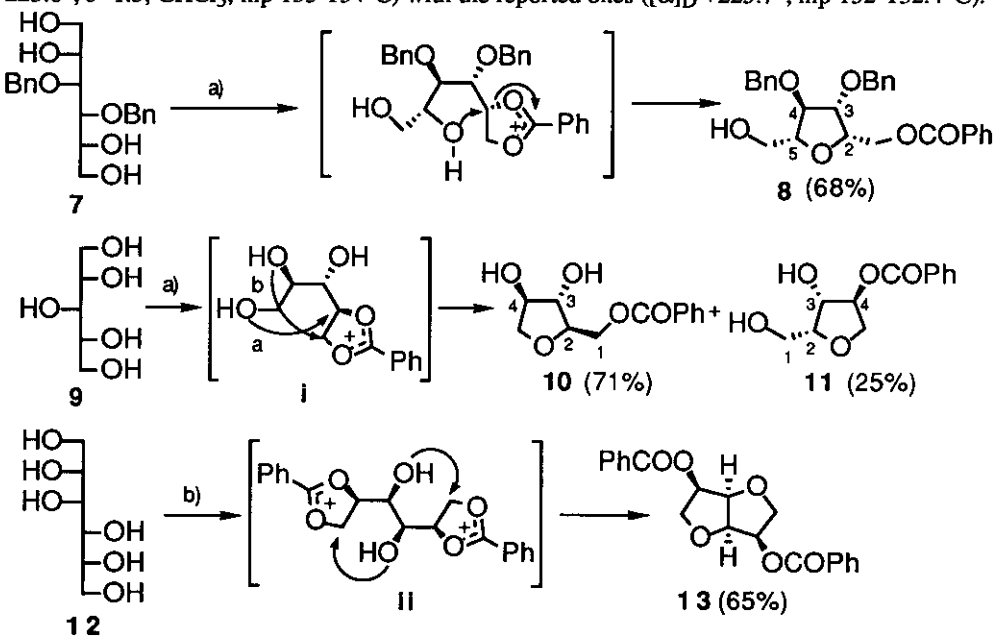
Entry	Substrate	Reaction Conditions	Product	Yield
1	**1**	cat. TMSOTf, CH_2Cl_2	insoluble	
2		cat. TMSOTf, CH_2Cl_2/MeOH=3/1	**2**	87%
3		cat. TMSOTf, MeOH	**2**	70%
4		cat. TMSOTf, DMF	**3**	68%
5		cat. TfOH, CH_2Cl_2/MeOH=3/1	**2**	87%
6	**4**	cat. TfOH, CH_2Cl_2/MeOH=3/1	**5**	88%



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**)[5] ($[\alpha]_D$ +48.5°, *c*=1.2, $CHCl_3$) 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.[7] Xylitol (**9**) afforded two tetrahydrofurans, *trans-trans* and *cis-trans* substituted tetrahydrofurans (**10** and **11**)[5] in a ratio of 3 : 1. A ^{1}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 $PhC(OMe)_3$ afforded the bicyclic tetrahydrofuran (**13**) directly *via* two dioxcenium intermediates as shown in **ii**, whereas the use of 1.1 equiv. of $PhC(OMe)_3$ gave **13** in low yield (31%). The structure of **13** was deduced from its ir spectra, ^{1}H-nmr spectroscopies, and ^{1}H-^{1}H COSY and was ascertained by comparison of its optical rotation and melting point ($[\alpha]_D$ +225.0°, *c*=1.5, $CHCl_3$; mp 133-134°C) with the reported ones ($[\alpha]_D$ +225.7°; mp 132-132.4°C).[8]



Reaction conditions; a) $PhC(OMe)_3$ (1.5 equiv.), cat. TfOH, CH_2Cl_2-MeOH (3/1), 0°C~room temperature, 12 h; b) $PhC(OMe)_3$ (3 equiv.), cat. TfOH, CH_2Cl_2-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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