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A Simple and Efficient $PdCl_2$ Mediated Conversion of γ,δ-Olefinic Alcohols into C-Glycosides

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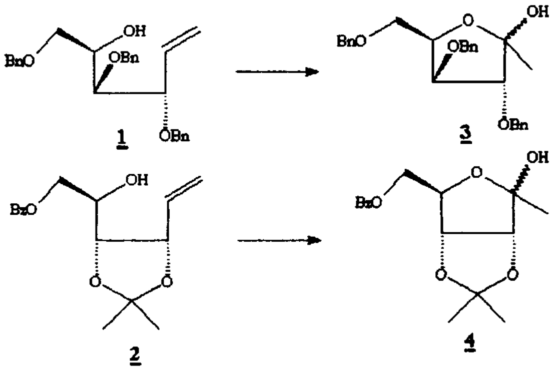
Abstract: An efficient and mild intramolecular oxidative nucleophilic cyclisation protocol has been developed for the conversion of γ, δ-olefinic alcohols into the hemiketals, which in turn on deoxygenation led to the very important C-glycoside class of compounds. © 1997 Elsevier Science Ltd.

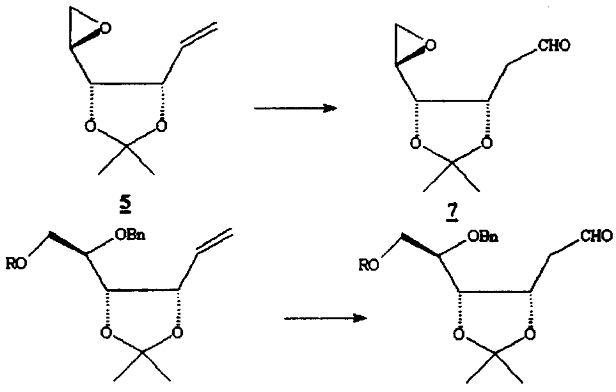
C-Glycosides[1] or C-saccharides have attracted the attention of synthetic organic chemists in the recent times, due to their use as mimics for natural counterparts in enzymatic and metabolic studies. Added to this, several bio-active natural products[2] and complex nucleosides[3] have C-glycosides as part structures. A recent report[4] by Kool et al on the synthesis of artificial DNA base , a thymine like imposter molecule, having a difluorophenyl C-glycoside indicates the ever lasting importance of C-glycosides in the life processes. Owing to the importance of such systems several methods have been developed[5] for the synthesis of C-glycosides. Herein, we describe the results of our protocol, using Pd(II) catalyst, for the oxidative conversion of γ,δ-olefinic alcohols into the C-glycosides through the corresponding hemiketals.

Wacker reaction, conversion of terminal olefins into methyl ketones by Pd(II) catalysed oxidation is a well established synthetic reaction[6]. According to a literature survey[7], the regiochemical outcome of such a reaction is dependant on the substituents that are present in the olefinic moieties, thereby leading either to ketones or aldehydes exclusively or a mixture of products.



With this background, olefinic alcohols[8] 1 and 2, having alkoxy and 1,3-dioxolane substituents, were subjected to oxidative cyclisation with $PdCl_2$-CuCl-O_2 in aq. CH_3CN (1:7) at room temperature under standard reaction conditions. The hemiketals 3 and 4, that are formed by Markownikoff addition, were found to be the exclusive products[10] with no trace of aldehydes found in the reaction mixtures. From the above two reactions, in contrast to earlier reports, it is very clearly evident that, in the presence of internal nucleophile, a facile intramolecular nucleophilic oxidative cyclisation by a preferred 5-exo mode of cyclisation[9] leading to 5-membered ring[6c-e] rather than the substituents (cyclic or acyclic) present would determine the regiochemical outcome of the products.

To consolidate the above observation, substrates 5 and 6 were subjected to PdCl$_2$ mediated oxidation. The reaction was found to be very sluggish and gave the aldehydes 7 and 8 (anti Markownikoff addition products) as exclusive products along with the recovery of major amount of starting materials. This reaction further supports our results in this study, that a) the internal nucleophile rather than the substituents determines the regiochemical outcome of the reaction and b) the internal nucleophile facilitates the faster rate of reaction to obtain the hemiketals.



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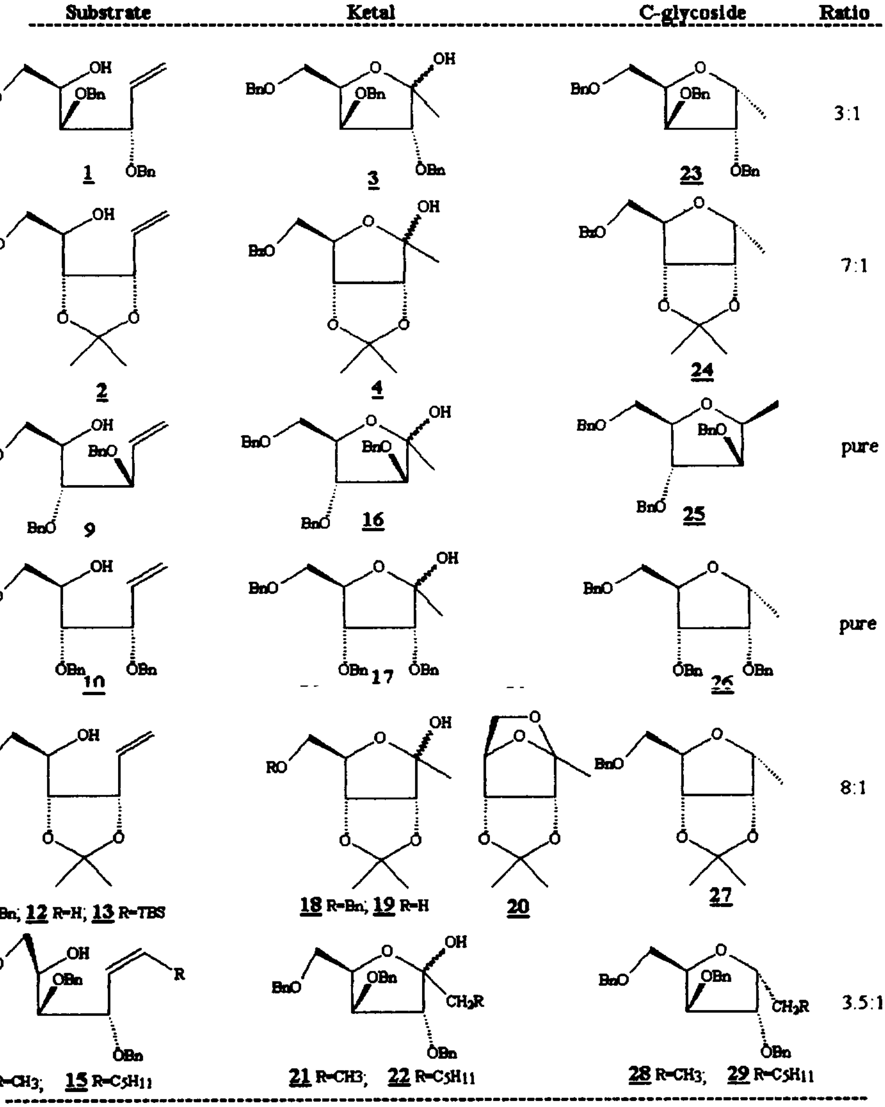
6 R=Bn ; 6a R=H

8 R=Bn ; 8a R=H

After establishing the importance of internal nucleophile, it was aimed at the formation of 6-membered rings. However, δ,ε-olefinic alcohol **6a** when treated with PdCl$_2$ under standard reaction conditions gave aldehyde **8a** rather than the 6-membered hemiketal, thus indicating the facile formation only of 5-membered rings.

To substantiate the generality of this protocol several olefinic alcohols 9-13 with a variety of stereocentres and protecting groups were subjected to oxidative cyclisation reactions to afford the products 16-19 in 75-87% yields. In the case of the oxidation of olefins 12(R=H) and 13(R=TBS) hydroxy hemiketal 19 was the first product that is formed at room temperature. However, prolongation of the reaction either at room temperature (48 Hrs) or at 40° C (24 Hrs) afforded the very useful 1,5-anhydro sugar 20, in the presence of additional hydroxy group[11]. Extension of this protocol for the internal olefins 14 and 15, having an alkyl side chain also gave the expected products 21 and 22 respectively. Thus from the above study it is very clearly evident , both for the terminal/internal olefins in the presence of internal nucleophile, irrespective of the substituents, the regiochemical outcome is same.

The thus obtained hemiketals and 1,5-anhydro sugars find a wide use in organic synthetic chemistry for ex. deoxygenation of the hemiketal hydroxy group would lead into C-glycoside class of compounds. Accordingly the



20: m.p. 83-84°C; **25**:$[\alpha]_D$ +17.2° (c 1.34, $CHCl_3$); **26**: $[\alpha]_D$ -6.78° (c 1.3, $CHCl_3$)

reductive deoxygenation of the hemiketals **3, 4, 17, 18, 21** and **22** with Et_3SiH-BF_3Et_2O[12], led to the formation of C-α- D-glycosides **23, 24, 26-29** respectively as major compounds while **16** gave C-β-D-glycoside **25** exclusively. The *cis* - stereochemical outcome of the deoxygenation is dependant on the stereo chemistry of the adjacent center of hemiketals.

Thus, in the present protocol, a mild and efficient method for the formation of hemiketals and 1,5-anhydro sugars as exclusive products by Pd(II)- mediated oxidation of olefins by internal nucleophile is achieved. Due to the presence of internal nucleophile, irrespective of the nature of the substituents, the reaction gave the Markownikoff addition products exclusively. These products were efficiently converted into the C-glycosides. The utility of the present methodology for the synthesis of pseudo sugars, C-saccharides and inositol C-saccharides is in progress. Thus, this method, utilizing Pd(II)- mediated oxidation of olefines, in presence of internal alcohols would find a wide use in organic synthetic chemistry.

General Procedure: A mixture of olefin (1mmol), $PdCl_2$ (0.1mmol) and CuCl (1mmol) in aq.CH_3CN (2 ml; 1:7) was stirred at room temperature while bubbling O_2 gas for 30 min. to 2 Hrs. The reaction mixture was filtered and washed with ether. Evaporation of solvent and purification of residue by column chromatography (Si-gel, 4:1 pet.ether-ethyl acetate) furnished the products.

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