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Synthesis of 2-Vinylcyclopentanols by SmI_2/Pd(0)-Promoted Carbohydrate Ring-Contraction.

José M. Aurrecoechea* and Beatriz López

Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, Apartado 644, 48080 Bilbao, Spain

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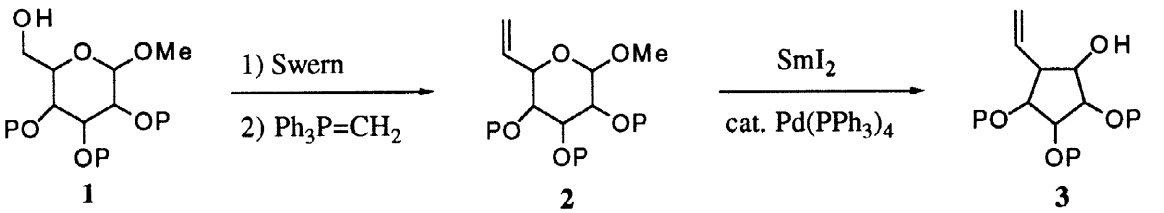
Abstract: The treatment of methyl 5-vinylpyranosides with SmI_2/cat. Pd(0) results in the formation of 2-vinylcyclopentanols. This process represents a new direct transformation of a carbohydrate structure into a functionalized carbocycle. The salient feature of this reaction is the preferred *trans*-relationship observed between the newly created stereocenters which is opposite to that found with alternative methodology. Moderate diastereoselectivities combined with high chemical yields provide preparatively useful yields of the major carbocyclic *trans*-diastereomer.

The search for new methods that allow the construction of chiral substances with control of the absolute and relative stereochemistry is under intense scrutiny in the synthetic field. The high chirality content of carbohydrate derivatives makes these substances attractive as chiral templates for the construction of functionalized chiral carbocyclic and heterocyclic building blocks.[1] While a number of strategies exist for the conversion of carbohydrates into carbocycles,[1-4] these involve too often methodology that leaves the resulting carbocycle devoid of some of the functionality present in the original carbohydrate-like structure. Furthermore, few of those strategies effect a *direct* carbohydrate to carbocycle conversion.[2-4] Among them, suitable vinyl carbohydrate acetals **2**, upon treatment with zirconocene and $BF_3{\cdot}Et_2O$, undergo ring-contraction to afford *cis*-2-vinylcyclopentanols[3a,4] **3** which are amenable of further elaboration into biologically active substances.[4] We now report that the treatment of the aforementioned **2** with SmI_2 and catalytic amounts of $Pd(PPh_3)_4$ (Scheme 1) also produces a ring-contraction leading directly to high yields of polyhydroxylated 2-vinylcyclopentanols **3** where the preferred stereochemical arrangement between the vinyl and new hydroxyl groups is *trans*.[5,6]



Scheme 1

The substrates **2** required for this study were prepared[3a] from readily available protected carbohydrate derivatives **1** by Swern oxidation[3b] followed by Wittig olefination (Scheme 1).

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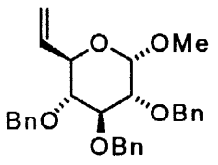
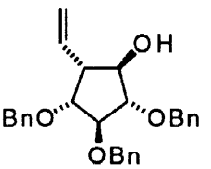
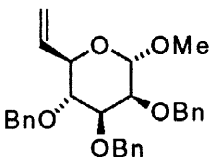
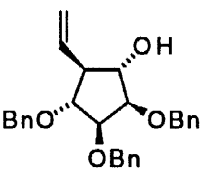
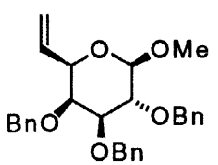
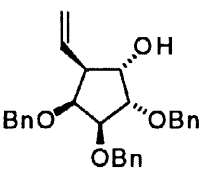
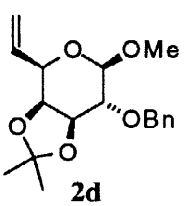
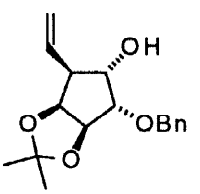
Treatment of **2a-d** with SmI_2 (3 equiv.) and $Pd(PPh_3)_4$ (5 mol%) at 75 °C led in all cases to high yields of vinylcyclopentanols **3** as diastereomeric mixtures (Table 1).[7] All the diastereomers were readily separated and the individual isomers were unambiguously assigned relative stereochemistries at C_1 and C_5 (cyclopentanol numbering) through NOE-difference experiments.

Table 1. Formation of Cyclopentanes from Methyl Pyranosides with SmI_2/cat. $Pd(PPh_3)_4$.

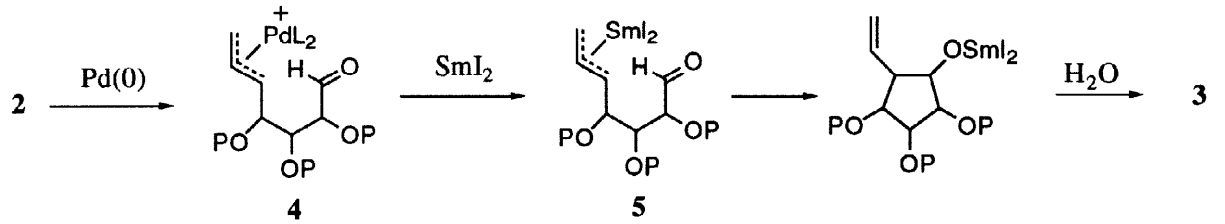
Precursor	Yield (%)[a]	Product[b]	Diast. ratio[c,d]	*Trans / cis*[e,f]
 **2a**	78	 **3a**	3:66:10:21	69:31
 **2b**	78	 **3b**	52:11:37:0	63:37
 **2c**	67	 **3c**	71:3:1:25	74:26
 **2d**	79	 **3d**	70:0:5:25	70:30

[a] Isolated yields. [b] All new products have been characterized by their spectroscopic (^1H- and ^{13}C-NMR, IR) data and combustion analysis or HRMS. Only major diastereomer shown. [c] Relative amounts of isolated products. [d] (1*S*,5*S*)/(1*R*,5*R*)/(1*S*,5*R*)/(1*R*,5*S*) ratio. [e] *Trans / cis* refers to the relative orientation of vinyl and hydroxyl groups. [f] (1*S*,5*S*) + (1*R*,5*R*) / (1*S*,5*R*) + (1*R*,5*S*) ratio.

In contrast to the related zirconocene-mediated carbohydrate ring-contraction,[3a] that leads predominantly to a *cis*-relationship between the newly created C_1 and C_5 stereocenters, this SmI_2/Pd(0)-promoted reaction affords preferentially a *trans*-relationship. After chromatographic separation the overall yield obtained for the major product is preparatively useful in most cases. Both the reactivity and the stereochemical trends observed during cyclization were substrate dependent. Thus, in addition to the preferred *trans*-relationship observed between the vinyl and hydroxyl groups, the glucose- and mannose-derived substrates also displayed a preference for a *trans*-relationship between the hydroxyl group and the adjacent benzyloxy substituent whereas for the more selective galacto derivatives the opposite was found. On the other hand, the reaction of the galacto

acetal **2c** could be readily performed in very high yield (93%) at room temperature whereas the corresponding gluco- and manno-substrates **2a,b** were inert at that temperature.[8] Surprisingly, in the latter case the reaction was much less stereoselective and nearly equal amounts of *cis* and *trans* products were obtained. While this drop of selectivity with decreasing temperature is not without precedent in SmI_2 chemistry[9] its origin remains unexplained.

The formation of cyclopentane products can be rationalized by a Pd(0)-promoted ring-opening of **2** leading to an intermediate **4** that contains both a π-allyl palladium complex and an aldehyde moiety (Scheme 2). Reduction of the palladium complex by SmI_2 and carbonyl addition of the resulting allylsamarium species **5** would then lead to the observed products. Remarkably, if intermediate **5** is indeed involved, its cyclization is faster than the alternative elimination of the adjacent benzyloxy substituent.[10]



Scheme 2

The predominant *trans*-selectivity observed in these cyclizations is surprising when compared to the related SmI_2/Pd(0)-promoted intramolecular cyclization of a ketone containing an appended vinyloxirane moiety.[5d] This latter case is also assumed to proceed trough allylsamarium intermediates but affords preferentially a *cis*-product presumably through a chelated cyclic transition structure.[11] If a similar mechanism is indeed operating, the different stereochemical outcome shown by the reactions reported here could then be due to a combination of factors derived from differences in reaction conditions and substrate structure.[12]

In conclusion, this new SmI_2/Pd(0)-promoted sequential carbohydrate ring-opening followed by carbocyclization affords high yields of polysubstituted enantiomerically pure compounds with moderate *trans*-selectivity. The method gives a direct access to important building blocks in the form of stereoisomers which are not directly available by related alternative transformations.

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7. Representative Procedure: A solution of **2** (0.63 mmol) and $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) in dry THF (4 mL) was added under Ar to SmI_2 (*ca* 0.1 M in THF, 19 mL, 1.88 mmol) and the mixture was refluxed for 2.5 h. After cooling and aqueous work-up, purification by flash chromatography and HPLC afforded the diastereomeric vinylcyclopentanols.
8. Examples of higher reactivity in galactopyranosides compared to the corresponding gluco-analogs have been previously observed: MiljKovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597-7604. However, in the present case, the enhanced reactivity in the galacto-derivative is more likely related to the β-orientation of the MeO group that probably facilitates orbital overlap in the formation of intermediate **4** (Scheme 2).
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12. Molander's reaction[5d] takes place at -30°C whereas ours are performed at 75°C. In comparison, substrate **1c** affords, as mentioned above, increasing amounts of *cis*-products (vinyl and hydroxyl bearing carbons) when the reaction is carried out at lower temperatures, in line with the results reported in ref. 5d.