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COMMUNICATION

Stereoselective synthesis of C-2-methylene and C-2-methyl-C-glycosides by Claisen rearrangement of 2-vinyloxymethyl glycals†

Perali Ramu Sridhar* and Chalapala Sudharani

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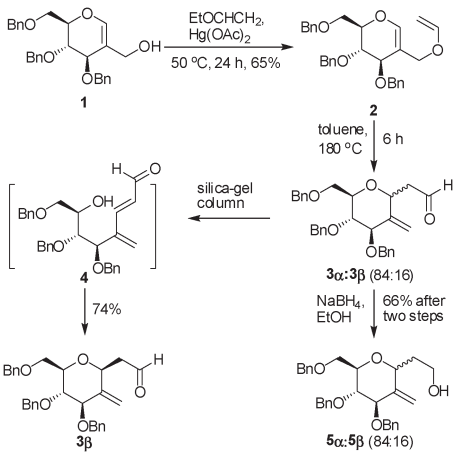
An efficient protocol for the stereoselective synthesis of C-2-methylene-α- and -β-C-glycosides by a Claisen rearrangement of 2-vinyloxymethyl glycal derivatives is reported. A plausible mechanism for the formation of α-selective-C-glycoside was proposed. The methodology was further extended to the high diastereoselective synthesis of C-2-methyl-C-glycosides.

Carbon branched sugars, in which the hydroxyl groups on pyranose/furanose ring is replaced with carbon are widely present in a number of natural products. Notably, C-2-methyl analogues of nucleosides have shown potential inhibitory activity against hepatitis C viral RNA replication.[1] On the other hand, C-2-methylene- and C-2-methyl-C-glycoside derivatives exist ubiquitously in nature as subunits of several highly bioactive natural products such as spliceostatins, spongistatins, phorboxazoles, brevenal, brevetoxin, gambieric acids and halichondrins *etc.*.[2] One of the widely used approaches for stereoselective construction of C-glycosides is a Claisen or Ireland-Claisen rearrangement[3] of glucal derived allylvinyl ethers that has been discussed extensively in the literature.[4,5] Due to the intriguing features of the Claisen-[3,3]-sigmatropic rearrangement reaction, it has been utilized to provide key intermediates for the total synthesis of a number of natural products possessing C-2,[6] C-3,[7] C-4[8] and C-5[9] carbon branched carbohydrate frameworks.

Surprisingly, all the reported Claisen rearrangement (CR) reactions involving carbohydrate moieties with *endo*-cyclic allyl alcohols include at least one chiral center in the rearrangement sequence, which directs the stereochemical course of the newly generated stereocenters. In our interest towards the stereoselective synthesis of C-branched sugars,[10] we envisaged that CR of glycal derived allylvinyl moieties might provide a straightforward access to the formation of C-2-methylene-C-glycosides and intern offer access to the preparation of 2-C-branched-C-glycosides. Even though, no chiral center is involved in the rearrangement sequence, we anticipated the reaction to proceed in a stereoselective fashion due to the concerted nature, highly organized transition state in CR reactions and the influence of additional stereocenters in the molecule. Chemoselective hydrogenation of the C-2-methylene group further provides an efficient route for the diastereoselective preparation of C-2-methyl-C-glycosides.

Thus, mercuric acetate-catalyzed *trans* vinylation of alcohol **1** with ethylvinyl ether provided the required 2-vinyloxymethyl-3,4,6-tri-*O*-benzyl-D-glucal **2** in 65% yield. When compound **2** was heated in a sealed tube at 180 °C for 6 h in toluene the reaction produced the expected C-2-methylene-C-glycosides **3*α*** and **3*β*** in 84 : 16 ratio, respectively.[11,12] Interestingly, the α-anomer **3*α*** was found to be very unstable and converted to the β-anomer **3*β***[13] in the purification process using silicagel column chromatography, probably *via* ring opening to form α,β-unsaturated aldehyde **4** followed by intramolecular *oxa*-Michael addition reaction. Whereas, direct reduction of the crude aldehyde mixture (**3*α*** and **3*β***) with $NaBH_4$/EtOH at −10 °C produced the corresponding alcohols **5*α*** and **5*β*** in a 84 : 16 ratio respectively (Scheme 1).

The formation of the major α-C-glycoside can be explained by considering the following facts. (a) Due to the vinylogous anomeric effect,[14] an oxocarbenium ion formation can be visualized during the course of the rearrangement. (b) The electrostatic stabilization of oxocarbenium ion by C-3 and C-4 alkoxy groups assume pseudo axial positions in their half chair conformation.[15] (c) The nucleophilic attack on the six membered ring oxocarbenium ion occur through a chair like transition state preferably along the axial trajectory.[16] Thus, for both the possible conformations, $^5H_4$ **2a** and $^4H_5$ **2b**, the CR will have an early transition state with bond breaking well in



Scheme 1 Claisen-rearrangement of 2-vinyloxymethyl glucal derivative.

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India. E-mail: prssc@uohyd.ernet.in; Fax: +91 4023012460; Tel: +91 4066794823

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advance with respect to bond making that may lead to the formation of ionic resonance structures **6a** and **6b**. For transition state **6a** the approach of nucleophilic carbon on to the oxocarbenium ion along the stereochemically preferred axial trajectory ensures *syn*-pentane interaction[17] that builds up between the nucleophile and substituent on C-5 as well as smaller *syn*-butanol[18] interaction with the substituent on C-3. Due to these interactions, the transition state **6a** *via* $^{5}H_{4}$ is destabilized compared to the transition state **6b** *via* $^{4}H_{5}$ in the reaction coordinate. As a result, the formation of C-2-methylene-α-C-glycoside **3*α*** is major through the lowest-energy transition sate, namely *via* $^{4}H_{5}$.

However, compound **3*α*** suffers with 1,3-diaxial interactions, that drives the formation of α,β-unsaturated aldehyde derivative **4** which might further undergo intramolecular *oxa*-Michael addition reaction to give stable C-2-methylene-β-C-glycoside **3*β*** during the purification process (Fig. 1). On the other hand, the direct reduction of the crude aldehyde mixture provides the corresponding C-2-methylene-C-glycosides **5*α*** and **5*β*** in 84 : 16 ratio respectively, reflecting the ratio in the crude aldehyde mixture.

Interestingly, galactose derived vinyl ether **7** upon CR provided a mixture of aldehyde **8*α*** as a single diastereomer along with unexpected aldehyde **9** in a ratio of 76 : 24 respectively. However, column chromatography of this mixture over silicagel provided only the ring opened α,β-unsaturated aldehyde derivative **10**.[19] A one-pot CR followed by reduction of the crude aldehyde provided alcohols **11** and **12**. Due to the difficulty in separation of this alcoholic mixture the crude product was acetylated to provide galactose derived C-2-methylene-C-glycoside **13** as a single diastereomer and C-2 alkylated galactal derivative **14** (Scheme 2).

The observation of unexpected aldehyde **9** supports the formation of fully separated ionic resonance structures in the proposed mechanism. As can be expected, the transition state **7a** with $^{5}H_{4}$ conformation will lead to the ionic resonance structure **15a**. The nucleophilic attack at the anomeric position (path a) *via* **15a** suffers with higher steric strain that prohibits the formation of C-2-methylene-β-C-glycoside **8*β***. On the other hand, nucleophilic attack at the less hindered site through a (1,3)-sigmatropic rearrangement (path b) leads to the formation of aldehyde **9** (Fig. 2).

Encouraged with the above results we further applied this methodology to various 2-vinyloxymethyl-glycal derivatives. Thus, rhamnal derived allylvinyl ether **16** upon CR provided the corresponding C-2-methylene-C-glycosides **17*α*** and **17*β*** in 87 : 13 ratio, respectively in good yield (Table 1, entry 1). Again, a similar kind of anomerization mentioned in the case of **3*α*** above was observed while carrying out the purification over silicagel leading to the formation of **17*β*** as a single diastereomer.

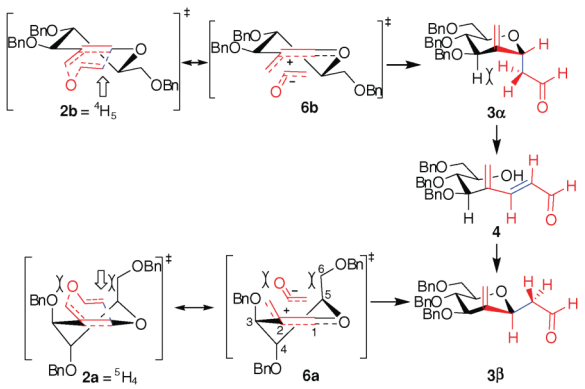
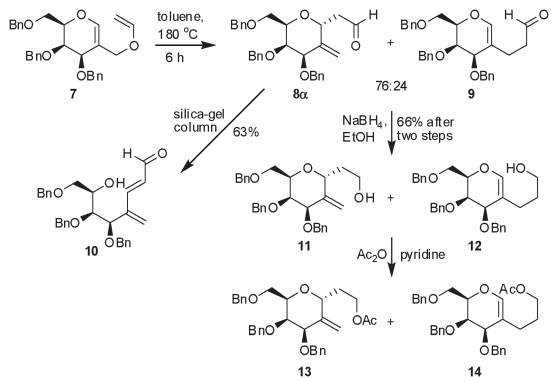


Fig. 1 Proposed mechanism for the Claisen rearrangement of 2-vinyloxymethyl glucal derivative.



Scheme 2 Claisen-rearrangement of 2-vinyloxymethyl galactal derivative.

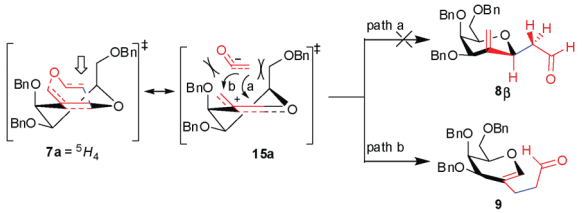
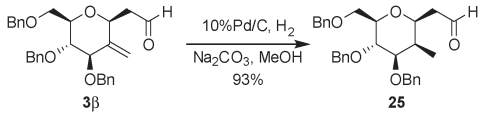


Fig. 2 Proposed mechanism for the unexpected formation of C-2-alkyl galactal derivative **9** under Claisen rearrangement reaction conditions.

Table 1 Synthesis of C-2-methylene-C-glycosides

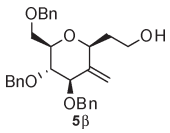
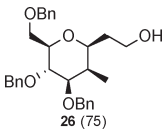
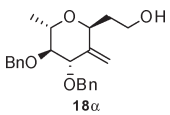
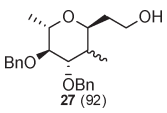
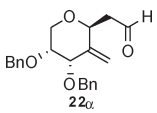
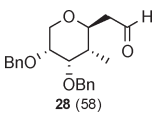
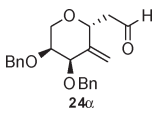
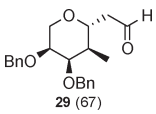
Entry	Vinyl ether	C-2 Methylene C-glycoside (%)[a]	α : β Ratio
1	**16**	**17**α:**17**β (88)[b]	87 : 13
2	**16**	**18**α:**18**β (85)[c]	87 : 13
3	**19**	**20**α:**20**β (73)	50 : 50
4	**21**	**22**α:**22**β (73)	50 : 50
5	**23**	**24**α:**24**β (72)	50 : 50

[a] Yield represents pure and isolated products. [b] The mixture upon column chromatography provided only **17*β*** as a single diastereomer. [c] The vinyl ether was subjected to CR and the obtained crude product was directly reduced with $NaBH_4$/EtOH.



Scheme 3 Synthesis of glucose derived C-2-methyl-β-C-glycoside.

Table 2 Synthesis of C-2-methyl-C-glycosides

Entry	C-2 Methylene C-glycoside	C-2 Methyl C-glycoside (%)[a]	1,2-*cis* : 1,2-*trans*
1	 5β	 **26** (75)	100 : 0
2	 18α	 **27** (92)	15 : 85
3	 22α	 **28** (58)	0 : 100
4	 24α	 **29** (67)	0 : 100

[a] Yield represents pure and isolated products.

Nevertheless, direct reduction of the crude aldehyde mixture, **17*α*** and **17*β***, provided C-2-methylene-C-glycosides **18*α*** and **18*β*** in 87 : 13 ratio respectively in 85% yield (Table 1, entry 2). However, pentose derived allylvinyl ethers **19**, **21** and **23** upon thermal CR provided a 50 : 50 mixture of **20*α* : 20*β***, **22*α* : 22*β*** and **24*α* : 24*β*** respectively in good yield (Table 1, entries 3, 4 and 5). These observations clearly indicate the significance of the C-5-substituent in directing the stereochemical outcome of the rearrangement reaction.

The importance of the methodology was further enhanced by applying it to synthesize a series of C-2-methyl-C-glycosides. Thus, C-2-methylene-β-C-glycoside **5*β*** was hydrogenated with 10% Pd/C, H_2 in MeOH in the presence of Na_2CO_3[20] to provide C-2-methyl-β-C-glycoside **25** as a single diastereomer in excellent yield, 93% (Scheme 3).

Further, application of the selective hydrogenation protocol to other C-2-methylene-C-glycosides **5*β***, **18*α***, **22*α*** and **24*α*** also provided C-2-methyl-C-glycosides **26–29** in excellent yields with very high diastereoselectivity (Table 2).

In conclusion, an efficient methodology for the stereoselective synthesis of C-2-methylene-C-glycosides as well as C-2-methyl-C-glycosides was developed. Importantly, the method is applicable to synthesize α- as well as β-C-glycosides in a stereoselective fashion. This novel method may provide an easy access to the synthesis of natural products possessing carbon branched sugar subunits.

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Note added after first publication

This article replaces the version published on 16th August 2012, which contained errors in Table 1.

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13 The configuration at the anomeric center was assigned by NOE experiments.

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