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Subtle Stereochemical and Electronic Effects in Iridium-Catalyzed Isomerization of *C*-Allyl Glycosides

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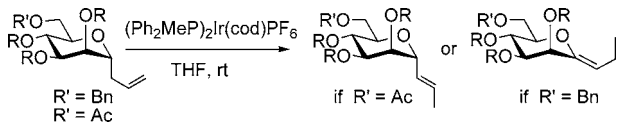
ABSTRACT



Stereoselective isomerization of *C*-allyl glycosides into (*E*)-*C*-vinyl glycosides or (*Z*)-*exo*-glycals was carried out in the presence of the cationic iridium(I) catalyst [$(Ph_2MeP)_2Ir(cod)PF_6$]. The products of the isomerization were affected by the relative 1,2-stereochemical relationships and by the nature of the protecting groups. These effects are discussed along with a plausible reaction mechanism.

Diverse processes for olefin isomerization continue to be topics of widespread interest.[1] Regio- and stereoselective double-bond migration in 1,3-dioxepines provides useful building blocks for polyether synthesis,[2] and isomerization of allyl to enol ethers have been used to remove allyl protecting groups[3] as well as to provide convenient routes to the enol ether components for Claisen rearrangements.[4] Olefin isomerizations to more stable alkenes were reported with many metal catalysts such as nickel,[5] rhodium,[6] ruthenium,[7] palladium,[8] and iridium.[9] Iridium(I)-based reagents are useful catalysts in chemo- and stereoselective isomerization of alkenes, particularly in allyl and allyl silyl ethers.[10] Owing to its unique catalytic properties, iridium [$(Ph_2MeP)_2Ir(cod)PF_6$][11] catalyzed isomerization reactions have also been successfully applied in the total synthesis of natural products[12] and in carbohydrate chemistry, to make α- and *β*-*C*-glycosides of *N*-acetylglucosamine and *C*-neoglycopeptides[13] and for the deprotection of allyl protecting group.[14] In all the above cases, the isomerizations were limited to affording *C*-vinyl glycosides only. Consequently, there are still needs to further develop simple, convenient, and practical methods to completely isomerize *C*-allyl glycosides to

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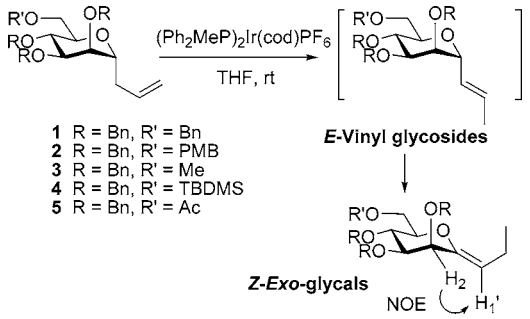
prepare the important family of *exo*-glycals. However, there is no report of such isomerization processes using iridium catalysts.

In continuation of our interests in the applications of organometallic catalysts in carbohydrate chemistry,[15] we report herein a mild and convenient method for the isomerization of *C*-allyl mannosides and rhamnosides to the corresponding *exo*-glycals using iridium catalyst [$(Ph_2MeP)_2Ir(cod)PF_6$] (Scheme 1).

Scheme 1. Isomerization of *C*-Allyl Mannosides **1**−**5**

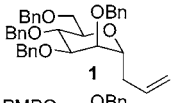
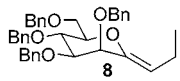
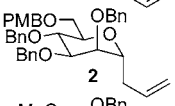
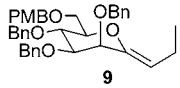
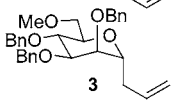
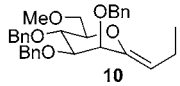
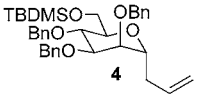
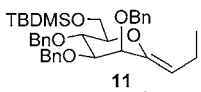
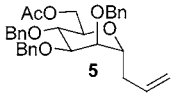
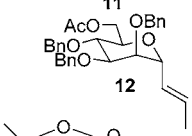
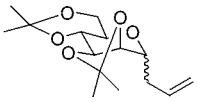
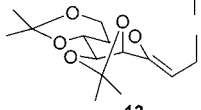
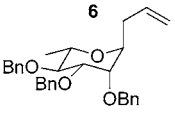
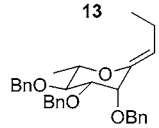


Starting *C*-allyl glycosides[16−22] **1**−**7**,[17a] **15**,[17a] **16**,[21a] and **17**[21] were prepared from methyl α-*D*-glycosides by benzylation[16] followed by Sakurai's *C*-allylation.[17] *C*-Allyl α-mannosides, modified at O-6 (**2**, **3**, **4**,[18] **5**[18c]), were prepared by deacetylation followed by protection using the appropriate protecting groups. *C*-Allyl β-mannoside **15** was synthesized from tetrabenzyl mannopyranose,[18] and *C*-allyl α/β-mannoside **20**[18a] was prepared using a published procedure.[19] The inseparable anomeric mixture of *C*-allyl α/β-mannoside **6**[18b] was obtained by deacetylation of **20** followed by acetalation. Peracetylated β-galactoside **21** was synthesized according to Taketo et al.,[20] and the perbenzylated derivative **18**[21] was obtained by deacetylation of **21** followed by benzylation (NaH, BnBr, DMF). The riboside **22**[20a] was prepared from peracetylated ribose[21] and the riboside **19**[20b] from **22** by deacetylation followed by benzylation.

α-Mannoside **1** was initially isomerized using 10% Ir(I) catalyst pretreated with hydrogen to afford the expected C-vinyl mannoside **23**[8a] in 84% yield after 24 h at room temperature.

However, when the reaction time was prolonged to 48 h, an unprecedented, more thermodynamically stable *exo*-glycal **8** was obtained with exclusive *Z*-configuration in 80% yield (Table 1). The protecting group of **1** was then systematically varied at O-6 to investigate its potential role in the outcome of the reaction. Hence, the corresponding PMB (**2**), methyl (**3**), TBDMS (**4**), and acetyl (**5**)-protected analogues, together with the bis-acetonide **6** and *C*-allyl α-rhamnoside **7**, possessing the same 1,2-*trans* geometry were similarly treated with the same general overall outcome (Table 1). Interestingly, compound **4** provided only 38% of the *exo*-glycal, accompanied by 53% of the partially migrated C-vinyl intermediate (**11a**, not shown). Moreover, O-6 acetate-protected mannoside **5** failed to afford the glycal and gave only the vinyl analogue **12** in 81% yield (entry 5). These findings suggest that a bulky TBDMS or carbonyl-protecting groups (acetyl) have detrimental effects in the anomeric proton abstraction by the catalyst.

Table 1. Isomerization of *C*-Allyl Glycosides **1**−**7** into (*Z*)-*exo*-Glycals

entry	substrate	time (h)	product	yield (%)
1	 **1**	48	 **8**	80
2	 **2**	24	 **9**	77
3	 **3**	18	 **10**	77
4[a]	 **4**	60	 **11**	38
5	 **5**	48	 **12**	81
6	 **6**	24	 **13**	88
7	 **7**	24	 **14**	92

[a] Compound **4** provided 38% of the (*Z*)-*exo*-glycal **11** and 53% of the corresponding vinyl mannoside **11a** (see text).

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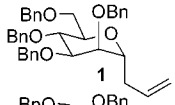
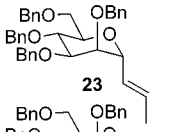
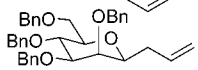
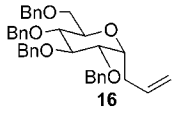
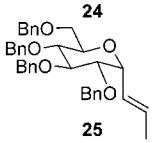
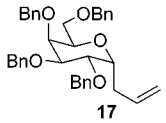
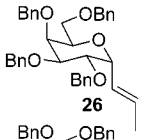
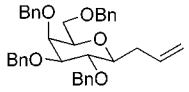
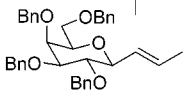
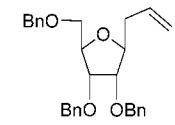
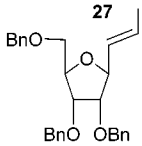
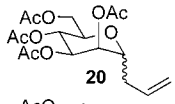
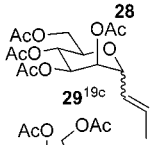
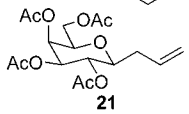
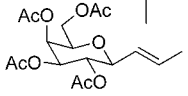
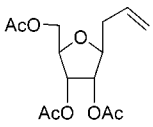
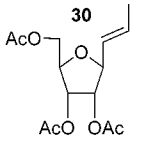
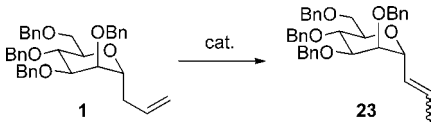
To exploit this observation as a general methodology, the fully benzylated *C*-allyl mannoside **15** (*β*-anomer), α-glucoside **16**, α- and *β*-galactosides (**17**, **18**), and riboside **19** were subjected to the same isomerization conditions. Surprisingly, none of these C-allyl glycosides were fully isomerized to give the *exo*-glycals. Rather, all reactions provided good yields of the *C*-vinyl derivatives **24**, **25**, **26**,[22] and **27**−**31** (Table 2). The above observations hold even after exposure to longer reaction time or higher temperature or in the presence of varied amount of catalyst. Furthermore, to evaluate the role of the general protecting groups in this process, the *C*-allyl tetra-*O*-acetylated α/*β*-D-mannoside **20**, tetra-*O*-acetylated galactoside **21**, and tri-*O*-acetylated riboside **22** were subjected to the isomerization process under similar reaction conditions, and the results are summarized in Table 2. Thus, ester protecting groups were not compatible with the formation of *exo*-glycals resulting from further isomerization of initially obtained C-vinyl analogues.

Table 2. Isomerization of *C*-Allyl Glycosides **1** and **8**−**15** into (*E*)-Vinyl Glycosides

entry	substrate	time (h)	product	yield (%)
1	 **1**	24	 **23**	84
2	 **15**	48	**24**	65
3	 **16**	48	 **25**	89
4	 **17**	48	 **26**	83
5	 **18**	48	 **27**	90
6	 **19**	48	 **28**	77
7	 **20**	48	 **29**[19c]	84
8	 **21**	48	 **30**	92
9	 **22**	48	 **31**	89

After the isomerization of the mannoside derivatives with the iridium catalyst was done, the same reaction conditions were attempted with two different palladium catalysts known to provide analogous isomerization. Both catalysts failed to fully isomerize mannoside **1** into the corresponding *exo*-glycal **8** but succeeded in isomerizing it to the intermediate *C*-vinyl mannoside **23**, albeit with poorer stereoselectivity. The results of the isomerization of mannoside **1** with iridium and palladium catalysts are summarized in Table 3.

Table 3. Isomerization of Mannoside **1** to **23** with Different Catalysts



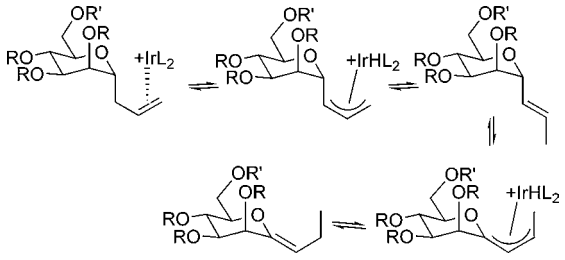
entry	catalyst	time (h)	solvent	temp	yield (*E*:*Z*)
1	$(Ph_2MeP)_2Ir(cod)PF_6$	24	THF	rt	80 (>95:0)
2	$PdCl_2$	18	benzene[8a]	reflux	84 (2.8:1)
3	$(PhCN)_2PdCl_2$	120	toluene[8b]	reflux	75 (4.3:1)

The configuration of the double bond in the *exo*-glycosides was determined by NOE experiments. For instance, irradiation of the H-2 proton in glycoside **8** at *δ* 4.01 ppm (d, $J = 3.3$ Hz) caused an enhancement (12.4%) of the signal at *δ* 4.82 ppm (t, $J = 7.2$ Hz, H-1′), which indicated that the double bond in mannoside **8** had the (*Z*)-configuration (Scheme 1).

The isomerization mechanism of alkenes by iridium catalysts[10a] usually involves the oxidative addition of an allylic C−H bond to the Ir(I) complex to give *π*-allyliridium species, followed by reductive elimination to afford the more stable doubly substituted alkene.

In the case of glycosides **5** and **15**−**22**, abstraction of the proton at C-1 does not happen because of steric hindrance or electronic factors, so only the *C*-vinylic glycosides were obtained. In the case of *C*-allyl mannosides **1**−**4** and **6** and rhamnoside **7**, the observed isomerization into *exo*-glycals may be due to chelation between O-2 and the iridium, thus dominating the steric/electronic factors (Scheme 2);[23] hence the fully isomerized *exo*-glycals were obtained. In the case

Scheme 2. Proposed Mechanism of Isomerization

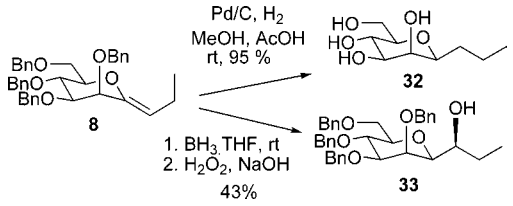


of *C*-allyl β-D-mannoside **15**, similar results were not observed, presumably because the catalyst could not reach the axial H-1.In the cases of acetylated mannosides **5** and **20**, galactoside **21**, and riboside **22**, the hypothesized chelation between the ester carbonyl oxygen and the iridium may dominate, thus pulling the iridium catalyst away from the H-1 protons. Consequently, only *C*-vinylic glycosides were obtained. In the case of mannoside **4**, the *exo*-mannoside **11** and *C*-vinyl mannoside **11a** were obtained in 38% and 53% yields, respectively. Here, the bulky substituent TBDMS lowered the yield of the corresponding *exo*-mannoside **11** (Table 1, entry 4). It is postulated herein that the O-2 configuration as well as the nature of the protecting groups at O-6 were involved in the complete isomerization process.

exo-Glycals are valuable synthetic intermediates in natural product synthesis. However, their syntheses are cumbersome.[24] 1-*exo*-Methylene sugars are accessible by a few procedures.[25,26] Substituted *exo*-glycals may also be obtained by Wittig olefination,[26] Ramberg−Backlund rearrangement,[27] and [2,3]-Wittig sigmatropic rearrangements.[28] However, all of these methods require multiple steps and in some cases harsh reaction conditions. Additionally, all of the starting glycosides had the same benzyl protecting groups, which make further modification of the sugar moieties of *exo*-glycals more problematic.

Here we have reported a novel approach to prepare *exo*-glycals with different protecting groups under mild conditions. To use the *exo*-mannosides as chiral intermediates, we reduced mannoside **8** with Pd/C, which afforded the C-propyl β-D-mannoside **32** (Scheme 3). Hydroboration[29] of **8** with BH_3·THF followed by oxidative workup with $NaOH/H_2O_2$ afforded β-mannoside **33** (43%). Hydroboration of **8** with 9-BBN followed by oxidative workup with $NaOH/H_2O_2$ afforded β-D-mannoside **33** in only 31% yield. The absolute stereochemistry of the hydroxyl group on C-2′ in β-D-mannoside **33** was determined by Mosher's method,[30] which was consistent with the previously reported hydroboration reaction.[30] Unfortunately, the ruthenium-catalyzed cross metathesis reactions of *exo*-mannoside **8** were not successful.

Scheme 3. *exo*-Glycals as Versatile Intermediates for the Synthesis of Various Functionalized β-Glycosides



In conclusion, isomerization of *C*-allyl glycosides mediated by iridium(I) catalyst has been shown to occur in good yields and with excellent *Z*-selectivity, depending on the nature of the sugars and the protecting groups.

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Supporting Information Available: Experimental procedures and spectral data for compounds **8**−**14** and **24**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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