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Catalytic synthesis of novel 4-*C*-glycosyl coumarins using a domino Heck reaction/lactonization process

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ABSTRACT

A catalytic synthesis of novel 4-linked *C*-glycosyl coumarins was achieved using a domino Heck reaction/lactonization process. Methyl 3-glycosyl cinnamates were prepared from methyl 4-glycosyl-but-2-enoates using a panel of aryl iodides under Heck conditions. A direct application of this new methodology was made toward preliminary hemagglutination inhibition assays against galectins-1 and -3. C-Galactoside **30** had an IC_{50} of 313 μM against galectin-1.

Coumarins exhibit a wide range of functions including varied biological activities.[1] When coupled to carbohydrate residues, coumarins have shown application as antibacterial,[2] anticoagulant,[3] anticancer agents[4] and as a fluorescent probe for ultrafast DNA dynamics.[5] Joining carbohydrates to coumarins via C–C bond, could provide more valuable and glycosidically stable analogs for various biological investigations. A large number of glycosyl coumarin derivatives, including some with *O*- or *C*-glycosidic linkages, occur naturally.[6] Figure 1 shows natural products such as Dauroside D,[7] C6 coumarinyl glycoside[8] and the family presented in this study. Coumarins can be classically synthesized by the Perkin,[1a,9] Pechmann,[1a,10] Knoevenagel,[8] Wittig,[11] and Kostanecki-Robinson,[12] Reformatsky,[13] and more recently cross-metathesis[14] and palladium coupling reactions.[15] Most methods lack generality and efficiency, therefore the use of a mild catalytic methodology to create the coumarin backbone in presence of sensitive functional groups is thus required. The first synthesis of *C*-glycosyl coumarin derivatives was made by Mahling et al.[16] and since then, most of the reports presented the synthesis of *C*-aryl coumarin glycosidic linkages having the aryl of the coumarins attached at the anomeric position of the carbohydrate residues.[17] However, to the best of our knowledge, no report on the anomerically 4-C-linked glycocoumarins is known. To this end, we used a domino Heck reaction/lactonization process.[15a] Transition metal-catalyzed cross-couplings have proven to be powerful tools for mild and highly efficient carbon–carbon bond formations. Among these processes, those involving palladium (Heck) catalysis are particularly powerful for the synthesis of complex molecules, owing to their excellent level of selectivity and high functional group tolerance.[18] Consequently and on the basis of previous expertise in our group,[19] the palladium(0)-catalyzed Heck reaction was used to synthesize C-linked glycomimetics bearing a panel of substituted methyl cinnamate or coumarin derivatives. When carbohydrates are connected with such varied decorations, a large number of diverse and novel biologically useful glycoconjugates can be generated.[20] In continuation of our interest in the applications of organometallic catalysis toward the synthesis of carbohydrate analogs,[19] we report herein a convenient synthesis of various *C*-glycosyl coumarins using the Heck reaction.

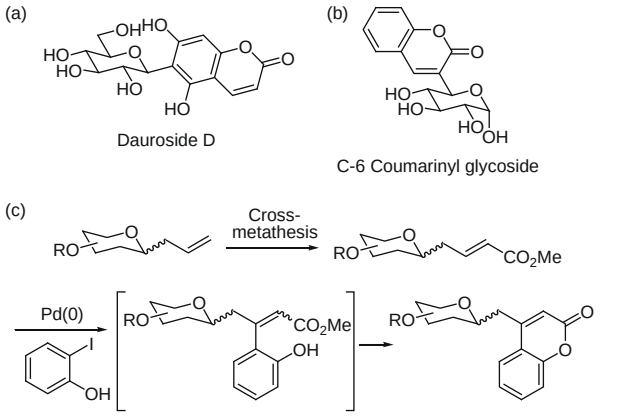

Figure 1. Various coumarin C-glycosides: (a) Dauroside D;[7] (b) C-5 coumarinyl glycoside,[8] and (c) this work.

The syntheses were initiated with the known *C*-allyl mannopyranosides **1**,[21] **2**,[22] and *C*-allyl galactopyranosides **3**,[21] **4**[23] which were subjected to a cross-metathesis reaction, using Grubbs' second generation catalyst and methyl acrylate to provide unsaturated esters **5**–**8**, respectively, in yields ranging from 68% to 94% (Table 1).[19]

The next step involved Heck couplings onto unsaturated esters **5**–**8**. The reaction was optimized with respect to the catalyst, base, phase transfer catalyst, ligand, solvent, temperature, and reaction

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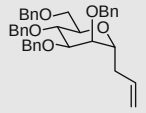
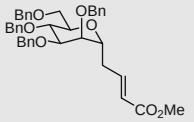
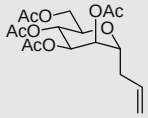
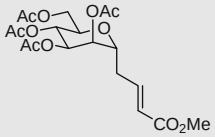
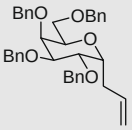
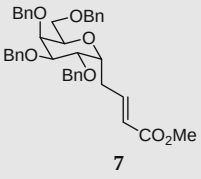
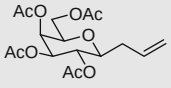
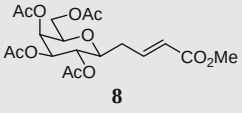
Table 1
Synthesis of unsaturated esters **5–8** from a cross-metathesis reaction catalyzed by Grubbs' second generation catalyst starting with *C*-allyl glycosides **1–4**

Entry	Substrates	Products	Yields[a] (%)
1	 **1**	 **5**	82
2	 **2**	 **6**	92
3	 **3**	 **7**	68
4	 **4**	 **8**	94

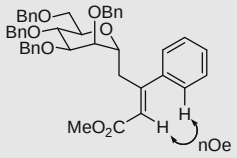
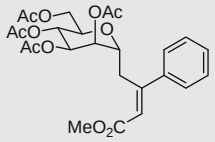
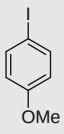
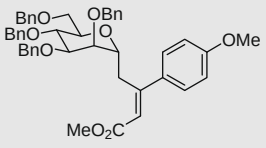
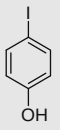
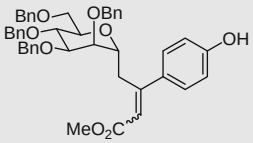
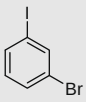
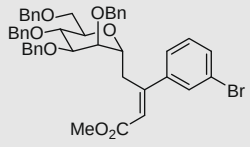
[a] Yields refer to isolated pure products using methyl acrylate, Grubbs' second generation catalyst in refluxing dichloromethane for 3 h.

time. The optimal conditions were found to be $Pd(OAc)_2$ (10 mol %), $NaHCO_3$ (3 equiv), Bu_4NBr (1 equiv) in DMF (0.16 M) at 85 °C for 12 h. Having glycosides **5–8** with a diversity of protecting groups and anomeric configurations in hand, we performed the Heck coupling[18] under optimized conditions with a panel of substituted aryl iodides. Table 2 shows the synthesis of various methyl 3-mannosylcinnamates **13–17** from unsaturated esters **5** and **6** using aryl iodides **9–12**. C-Mannosides **13–17** were isolated from good to excellent yields (42–81%). The *E*-isomers of the double bond were isolated for all cinnamates except when 4-iodophenol (entry 4) was used (*E*/*Z* ratio of 7:1 as determined by ^1H NMR). The stereochemistry of the double bond in mannoside **13** was confirmed by NOE experiments. The allylic proton and ortho protons from the phenyl group showed a strong interaction (10%), thus indicating that the double bond had the *E*-configuration (entry 1).

Table 3 shows the Heck reaction on C-galactosides **7** and **8** with aryl iodides **9**, **11**, and **18**. Methyl *C*-galactosyl cinnamates **19–23** were isolated in 56 to 84% yields. The *E*-isomers were usually obtained except, again when 4-iodophenol (entry 2) and 3-iodobenzyl alcohol (entry 3) were used as aryl partners. In both cases a 2:1 stereoisomeric ratio was obtained in favor of the *E*-isomers.

When 2-iodophenol **24** and 2-iodophenyl acetate **25** were used as aryl partners, 4-linked glycosyl coumarins were directly isolated obviously originating from a Heck reaction followed in situ by a lactonization process (Table 4). Under standard Heck conditions, unsaturated esters **5**, **7**, and **8** were transformed into *C*-glycosyl coumarins **26–28** in very good (75%) to good yields (43%). The *C*-glycosyl coumarins likely resulted from the standard Heck reaction with the usual syn β-elimination of the palladium to get the *E*-isomer, then isomerization of the double bond, under basic reaction conditions, followed by lactonization.[24]

Table 2
Heck reaction on mannosides **5** and **6** with various aryl iodides **9–12** to provide methyl cinnamate mannosyls **13–17**

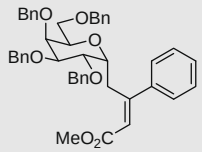
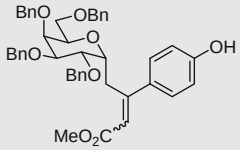
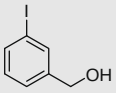
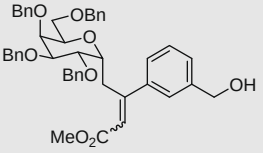
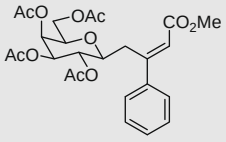
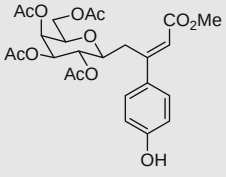
Entry	Substrates	Aryl halides	Products	Yield[a] (%)
1	**5**	 **9**	 **13**	70
2	**6**	**9**	 **14**	68
3	**5**	 **10**	 **15**	51
4	**5**	 **11**	 **16**	81[b]
5	**5**	 **12**	 **17**	42

[a] Yields refer to isolated pure products using $Pd(OAc)_2$, TBABr, $NaHCO_3$, ArI **9–12** in DMF at 85 °C for 12 h.
[b] *E*/*Z* ratio (7:1).

To illustrate the potential usefulness of these new compounds, some of the above-mentioned unprotected galactosides were evaluated as ligands against galectin-1 and -3 (Gal-1 and -3).[25] Galectins[26] are a family of cytosolic β-D-galactoside binding proteins. The roles of the galectins family are numerous, but a striking common feature of all galectins is the strong modulation of their expression during development, differentiation stages, and under different physiological or pathological conditions.[27] Studies have demonstrated that Gal-3 is involved in cancer and tumor progression,[28] and can regulate apoptotic process[29] together with Gal-1[30] which can additionally act as a soluble host factor that promotes HIV-1 infectivity through stabilization of virus attachment to host cells.[31] Unprotection of acylated galactosides **8**, **22**, **23**, and **28** with methanolic sodium methoxide afforded free alcohols **29–32**, respectively, in excellent yield.

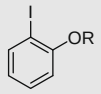
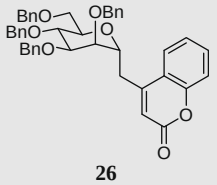
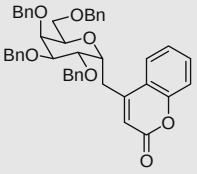
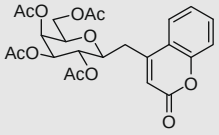
All compounds and control (D-galactose) were tested by inhibition of hemagglutination assay at a concentration of 1 μM of both galectins. Hemagglutination assays were performed using

Table 3
Heck reaction on C-galactosides **7**, **8** with aryl iodides **9**, **11**, and **18** to provide methyl 3-galactosyl cinnamates **19–23**

Entry	Substrates	Aryl halides	Products	Yield[a] (%)
1	**7**	**9**	 **19**	64
2	**7**	**11**	 **20**	84[b]
3	**7**	 **18**	 **21**	73[b]
4	**8**	**9**	 **22**	74
5	**8**	**11**	 **23**	56

[a] Yields refer to isolated pure products using $Pd(OAc)_2$, TBABr, $NaHCO_3$, ArI **9**, **11**, **18** in DMF at 85 °C for 12 h.
[b] *E/Z* ratio (2:1).

Table 4
Synthesis of 4-linked coumarin *C*-glycosyls **26–28** using a domino Heck reaction/lactonization process

Entry	Substrates	Aryl halides	Products	Yield[a] (%)
1	**5**	 **24** R = OH **25** R = OAc	 **26**	52
2				43
3	**7**	**24**	 **27**	75
4		**25**		48
5	**8**	**24**	 **28**	75
6		**25**		48

[a] Yields refer to isolated pure products using $Pd(OAc)_2$, TBABr, $NaHCO_3$, ArI **24** and **25** in DMF at 85 °C for 12 h.

red blood cells, type O, fixed with 3% glutaraldehyde–0.0025% NaN_3 in PBS[31] to confer both lectins equal relative affinities. Galactosides **29**, **30**, and **32** had IC_{50}s of 5000, 313, and 2500 μM, respectively, against Gal-1 and were almost all inactive against Gal-3. Methyl 3-*C*-galactosyl cinnamate **30** was not only the most promising candidate (160 times better than natural ligand galactose, IC_{50} 50 mM) against galectin-1, but was also highly selective compared to Gal-3.[32]

In conclusion, we described a convenient regioselective catalytic synthesis of *C*-glycosyl coumarin derivatives using a domino Heck reaction/lactonization process when 2-iodophenol was used. When other types of iodoaryl were employed, methyl *C*-glycosyl cinnamates were isolated with good stereochemistry control of the double bond. This method allowed an efficient synthesis of 4-substituted coumarins bearing carbohydrates in only two catalytic synthetic steps from readily available *C*-allyl glycosides. Direct application was made toward evaluation of various unprotected galactosides against Gal-1 and -3. Galactoside precursor **30** had IC_{50} of 313 μM against Gal-1.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.134.

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