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Alkenyl *O*- and *C*-glycopyranoside homodimerization by olefin metathesis reaction

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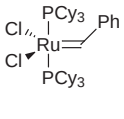
Using ruthenium-catalyzed olefin metathesis, several *O*- and *C*-allyl and *O*-pentenyl D-galactopyranoside and lactoside homodimers were prepared in high yields.

Multivalent neoglycoconjugates have been exhaustively utilized to probe and enhance carbohydrate–protein interactions at the molecular level.[1] Moreover, glycoclusters[2] and dendrimers[3] are also emerging as potential carbohydrate-based therapeutic agents.[4] Several examples exist in which ligand-induced receptor and protein dimerization occurred as a general mechanism for signal transduction.[5] It is conceivable that signal transduction and receptor shedding could also be triggered by carbohydrate oligomers.[6]

Transition metal catalyzed olefin metathesis has gained an important position in organic syntheses in recent years.[7–10]



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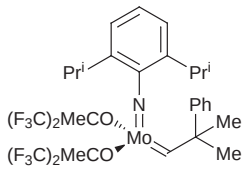

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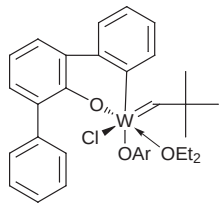

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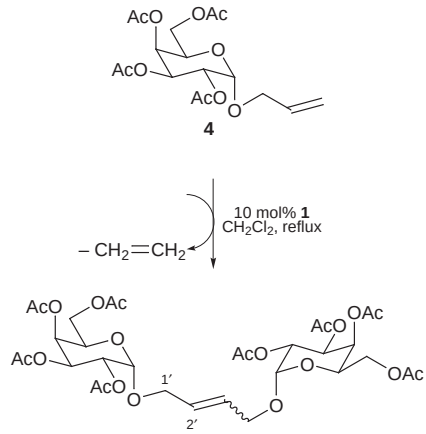
Ruthenium carbene complex **1** developed by Grubbs and coworkers[7] and Schrock's molybdenum catalyst **2**[8] are very useful in this respect. Because of its unique properties, high reactivity, stability to air, and remarkable functional group tolerance, benzylidenebis(tricyclohexylphosphine)dichlororuthenium **1** has been chosen as the catalyst of the year. Ruthenium and molybdenum carbenoids have been scarcely used in carbohydrate chemistry.[9] It seemed appealing to apply the olefin metathesis reaction toward the synthesis of carbohydrate homodimers. The only example of carbohydrate homodimerization was reported by Descotes *et al.*[10] in his sugar bolaform syntheses using a tungsten aryloxo complex such as **3**. However, the tungsten-catalyzed alkenyl glycoside homodimerizations were unsuccessful with *O*-allyl glycosides as well as benzyl-protected sugar derivatives. Herein, we report the efficient and high yielding synthesis of some biologically important carbohydrate homodimers starting from either peracetylated or perbenzylated *O*- and *C*-allyl as well as *O*-pentenyl galactopyranosides using ruthenium benzylidene complex **1** (Scheme 1).

Treatment of allyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside **4** with 10 mol% of Grubbs' catalyst **1** in refluxing CH_2Cl_2 under a nitrogen atmosphere resulted in the clean formation of homodimer **5** in 92% yield as a mixture of *E* and *Z* stereoisomers in 5:1 molar ratio (Scheme 1).† The only other by-products isolated from these sequential [2+2] cycloaddition and cycloreversion equilibria were the recovered starting material (3%) along with trace amount of cross-metathesis product obtained from the initially released styrene. In order to compare the catalytic activity of Grubbs' catalyst **1** to that of Schrock's catalyst **2**, we repeated the reaction between **4** and 10



Scheme 1

mol% of **2** in CH_2Cl_2. The reaction, performed under Schlenk conditions, provided the same dimer **5** in 80% yield. Since in both cases the yields were more or less the same, catalyst **1** was preferred because of its operational simplicity.

The ratio of the inseparable *E* and *Z* isomers was determined from analysis of the ^{1}H NMR spectrum of the crude mixture. It is generally accepted that the carbon α to a double bond is more shielded in the *Z* isomer than in the *E* isomer due to the γ effect.[11] So, the empirical relationship $\delta_{\alpha(Z)} < \delta_{\alpha(E)}$ allowed us to determine the relative configuration of the *E* and *Z* stereoisomers. For instance, the ^{13}C NMR spectrum of **5** showed the α carbon of the *Z* isomer at δ 63.5, whereas that of the *E* isomer appeared at δ 67.4 ($\Delta\delta$ 3.9 ppm).

Similarly, olefin metathesis of the corresponding peracetylated β-anomer **6** with 10 mol% of catalyst **1** under the same reaction conditions provided homodimer **7** in 95% yield as a mixture of *E* and *Z* isomers in a 4:1 ratio (Table 1).‡ To further explore the scope of this reaction, *O*-pentenyl β-D-galactopyranoside **8**, allyl β-lactoside **9**, α-*C*-allyl galactopyranoside **10**[12] and β-*C*-allyl galactopyranoside **11**[13] were prepared and reacted with Grubbs' catalyst under the same reaction conditions to give compounds **12–15** respectively. The reactions proceeded successfully with high yields and the results are summarized in Table 1. Then we turned our attention to the synthetically more useful benzyl protected sugars, using allyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside **16**. Treatment of **16** with **1** also proceeded smoothly to provide **17** in 76% yield.

In conclusion, Grubbs's ruthenium benzylidene catalyzed olefin metathesis reaction was applied toward the synthesis of polyfunctionalized carbohydrate homodimers for the preparation of potential cross-linkers of biological interest in signal transduction. The reaction is general, high yielding, and compatible with the usual carbohydrate protecting groups. Further work is now in progress to explore the scope of the reaction.

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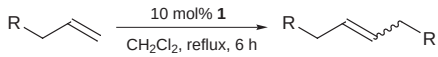
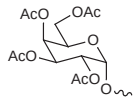
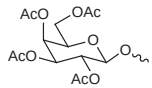
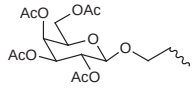
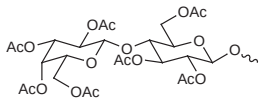
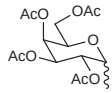
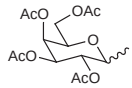
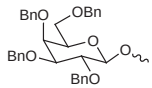
Table 1 Olefin self metathesis of alkenyl *O*- and *C*-glycopyranosides



4,6,8–11,16 **5,7,12–15,17**

Entry	Substrate	R	Product (*E*/*Z*)	Yield (%)
1	**4**		**5** (5/1)	92
2	**6**		**7** (4/1)	95
3	**8**		**12** (5/1)	85
4	**9**		**13** (4/1)	89
5	**10**		**14** (2/1)	82
6	**11**		**15** (1/1)	75
7	**16**		**17** (3/1)	76

Notes and references

† *Typical procedure*: 100 mg (0.148 mmol) of **9** was dissolved in 1 ml of dry CH_2Cl_2. After addition of 6 mg (10 mol%) of catalyst **1**, the resulting purple colored solution was allowed to reflux under N_2 atmosphere for 6 h, to give a black solution which was directly purified by silica gel column chromatography to afford 87.2 mg of **13** (89%) as a solid.

‡ All compounds showed satisfactory NMR (Bruker AMX 500 MHz) and mass spectral data. *Selected data* for **5**: HRMS FAB: calc. for $C_{32}H_{44}O_{20}$ 748.7. Found 749.2 (M + 1), $\delta_H(CDCl_3)$ 5.78 (t, 1 H, *J* 2.8, H-2′, *E* isomer), 5.71 (t, 1H, *J* 3.9, H-2′, *Z* isomer), 5.43 (dd, 1H, *J* 3.4, 1.3, H-4), 5.36–5.30 (m, 1H, H-3), 5.12–5.07 (m, 2H, H-2), 4.22–3.98 (m, 5H, H-1′a, H-1′b, H-5, H-6a, H-6b), 2.11–1.95 (4s, 12 H, 4 ∞ OAc); $\delta_C(CDCl_3)$ 170.3, 170.3, 170.1, 169.9 (C=O), 128.8 (C-2′, *Z* isomer), 128.5 (C-2′, *E* isomer), 95.6 (C-1, *Z* isomer), 95.5 (C-1, *E* isomer), 67.4 (C-1′, *E* isomer), 63.5 (C-1′, *Z* isomer). For **7**: $\delta_H(CDCl_3)$ 5.69 (t, 1H, *J* 2.5, H-2′, *E* isomer), 5.6 (t, 1H, *J* 4.1 Hz, H-2′, *Z* isomer); $\delta_C(CDCl_3)$ 128.6, 64.3 (C-2′ and C-1′ for *Z* isomer), 128.1, 68.7 (C-2′ and C-1′ for *E* isomer). For **12**: $\delta_H(CDCl_3)$ 5.33–5.31 (m, 2H, H-4, H-2′, *E* and *Z*); $\delta_C(CDCl_3)$ 129.9, 28.5 (C-2′ and C-1′ for *E* isomer), 129.4, 23.3 (C-2′ and C-1′ for *Z* isomer). For **14**: $\delta_H(CDCl_3)$ 5.48 (t, 1H, *J* 4.5, H-2′, *Z* isomer), 5.45 (t, 1H, *J* 3.7, H-2′, *E* isomer); $\delta_C(CDCl_3)$ 128.0, 29.9 (C-2′ and C-1′ for *E* isomer), 126.8, 24.8 (C-2′ and C-1′ for *Z* isomer). For **15**: $\delta_H(CDCl_3)$ 5.50–5.45 (m, 1H, H-2′, *E* and *Z* isomer); $\delta_C(CDCl_3)$ 128.5, 35.4 (C-2′ and C-1′ for *E* isomer), 127.3, 30.2 (C-2′ and C-1′ for *Z* isomer).

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