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Ring-closing olefin metathesis of prearranged *C*-allyl saccharides for the synthesis of *C*-butenyl linked homo- and hetero-disaccharides

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Abstract

Synthesis of *C*-butenyl-linked homo- and hetero-disaccharides was achieved via ring-closing olefin metathesis employing the Grubb's catalyst.

Oligosaccharides have been found to play a vital role in intercellular communication and cell-mediated processes.[1] This finding has directed many chemists to design and synthesize glyco-conjugates for the study of glycobiology as well as therapeutic and pharmaceutical development.[2] However, like proteins and nucleic acids, carbohydrates are susceptible to biodegradation, thus limiting their therapeutic potential and use in biological studies. *C*-Glycosides,[3] one of the glycomimetics which constitute potential non-hydrolysable epitopes, have therefore attracted considerable interest.

After the development of ruthenium benzylidene catalyst **1**,[4] the ring-closing metathesis (RCM) reaction has become a powerful tool for organic synthesis[5] due to its compatibility with a variety of functional groups and commercial availability.[6] Most applications of catalyst **1** in carbohydrate chemistry are ring-closing metathesis for the synthesis of fused or spiro monosaccharide derivatives.[7] Although the use of catalyst **1** in the synthesis of α,α'-*O*- and *C*-alkenyl-linked disaccharides has been reported,[5a] most of the examples are the synthesis of homodimeric pyranosides using cross-metathesis (CM).[8] Surprisingly, to our knowledge, there are only two examples of the synthesis of *C*/*O*-alkenyl-linked hetero-disaccharides using CM.[8b] This limitation is due to the synthesis of heterodimers by CM of two different terminal olefins often encountering the problem of obtaining undesired homodimers, as shown in Fig. 1. To avoid this formidable self-metathesis problem, we designed and used RCM in conjunction with prearranged *C*-allyl saccharides. By switching the reaction from intermolecule (CM) to intramolecule (RCM), many *C*-butenyl-linked hetero-disaccharides were easily obtained.

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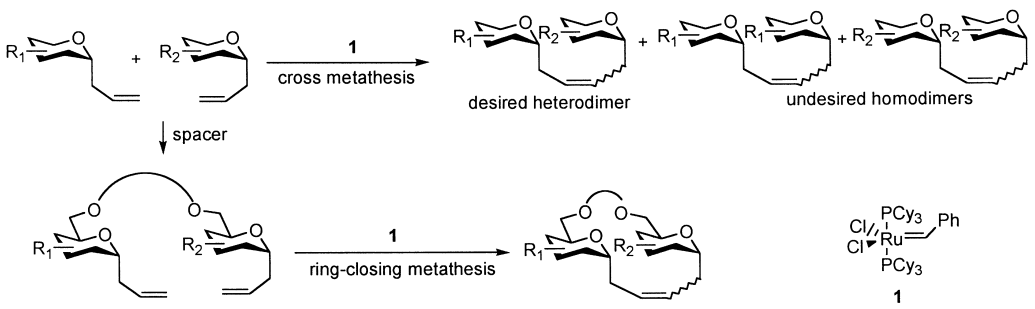
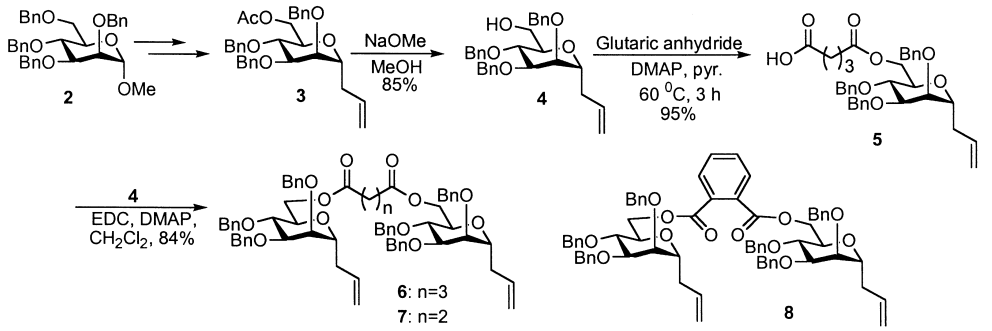


Figure 1.

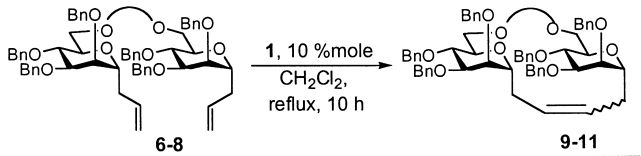
To study the effects of spacers on the *Z*:*E* ratios of RCM products, three different spacers, glutaryl, succinyl, and phthaloyl, were used for the synthesis of spacer-linked *C*-allyl mannosides, **6**, **7**, and **8**, respectively, as shown in Scheme 1. Compound **3** was chosen as starting material due to its having an orthogonal protecting group at the primary hydroxyl that spacer can be inserted through. It was obtained by a one-pot synthesis method[9] from readily available α-methyl mannopyranoside **2**, followed by hydrolysis of the acetyl group to give **4**. The glutaryl spacer was introduced into the primary hydroxyl group by acylation of **4** with glutaric anhydride.[10] The resulting carboxyl acid **5** was then coupled with **4** in the presence of EDC and DMAP to give **6**. Compounds **7** and **8** were obtained by using similar methods as mentioned above. RCM reactions of these *C*-allyl mannosides were proceeded in CH_2Cl_2 (0.06 M) with 10 mol% of catalyst **1** at refluxing temperature for 10 h. The *Z*- and *E*-isomers were determined ^{1}H NMR and ^{13}C NMR. For these homo-disaccharides, the coupling constant of the vinyl proton with the allyl protons of the *Z*-isomer was ca. 4.2 Hz, and that of the *E*-isomer was ca. 3.5 Hz. The allyl carbon of the *Z*-isomer appeared at ca. 26 ppm and that of the *E*-isomer at ca. 31 ppm. As shown in Table 1, while the use of different spacers did not influence reaction yields, it changed the *Z*:*E* ratios. When a more rigid spacer, phthaloyl group, was used, the ratio of *Z*-isomer increased.



Scheme 1.

In order to extend this method for the synthesis of *C*-butenyl-linked disaccharides, more glutaric linked *C*-allyl saccharides were synthesized and tested, as shown in Table 2.[11] These results showed excellent yields (80–94%) with the *Z*-isomers as the favoured product. It should be noted that in the cases of homodimers, the orientation of hydroxyl groups of glycosides influenced the *Z*:*E* ratios (Entry 1 of Table 1, and Entries 1 and 2 of Table 2). The *Z*- and *E*-isomers of butenyl

Table 1

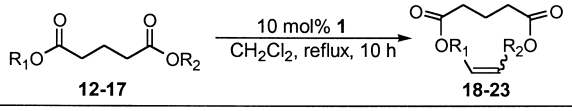


6-8 **9-11**

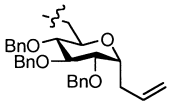
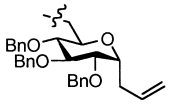
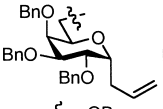
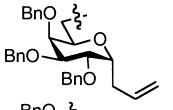
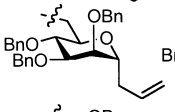
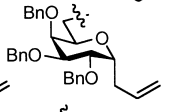
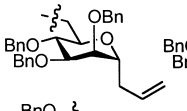
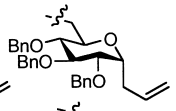
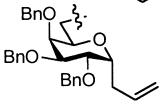
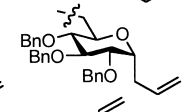
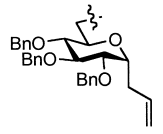
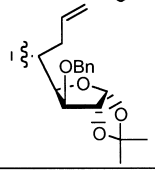
Entry		Product (*Z*/*E*)	Yield (%)
1	**6**	**9** (1.2/1)	88
2	**7**	**10** (1.5/1)	77[a]
3	**8**	**11** (2.3/1)	88

[a]: 12% of starting material was recovered

Table 2



12-17 **18-23**

Entry	R_1	R_2		Product (*Z*/*E*)	Yield(%)
1			**12**	**18** (1.7/1)	85
2			**13**	**19** (2.9/1)	94
3			**14**	**20** (1.4/1)	86
4			**15**	**21** (1.9/1)	86
5			**16**	**22** (2.2/1)	91
6			**17**	**23** (3.8/1)	80

linked hetero-disaccharides showed different vinyl proton splitting patterns in ^{1}H NMR spectrum, which were used for their identification. The splitting patterns of the vinyl protons in the *E*-isomer were the AB type ($\Delta\nu/J$ ~3.1) and the coupling constant was ca. 14 Hz; those of the *Z*-isomers were very closed ($\Delta\nu/J$ ~2.3) and could not be distinguished.[12] It should be noted that 'head to tail' type 1,6′ butenyl linked diglucoside, **23**, was also obtained.

In conclusion, we have demonstrated in this work a straightforward method for the synthesis of *C*-butenyl-linked hetero-disaccharides. The strategy is based on the Grubbs' catalyst for RCM, used in conjunction with prearranged *C*-allyl saccharides. By changing the spacer, the diastereoisomers *Z*:*E* ratio could be modulated.

Acknowledgements

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11. Selected data for compound **19***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97 (ddd, $J=7.5$ Hz, 2H), 1.97–2.06 (m, 2H), 2.29 (ddd, $J=15.2$, 7.6, 7.6 Hz, 2H), 2.33–2.38 (m, 2H), 2.44 (ddd, $J=15.2$, 7.6, 7.6 Hz, 2H), 3.49–3.56 (br, 2H), 3.77 (dd, $J=5.1$, 3.0 Hz, 2H), 2.93–4.03 (m, 6H), 4.10–4.18 (m, 2H), 4.44 (d, $J=12.0$ Hz, 2H), 4.48 (d, $J=12.0$ Hz, 2H), 4.52 (d, $J=12.0$ Hz, 2H), 4.57 (d, $J=12.0$ Hz, 2H), 4.61 (d, $J=12.4$ Hz, 2H), 4.66 (d, $J=12.4$ Hz, 2H), 5.09 (t, $J=11.4$ Hz, 2H), 5.43 (t, $J=4.7$ Hz, 2H), 7.15–7.50 (m, 30H). HRMS (FAB) calcd for $C_{63}H_{69}O_{12}$ ($M+H^+$): 1017.4789. Found: 1017.5023. Compound **20***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91–2.06 (m, 1H), 1.96 (q, $J=7.2$ Hz, 2H), 2.15–2.35 (m, 4H), 2.35–2.55 (m, 3H), 3.52–3.63 (m, 3H), 3.78 (dd, $J=6.4$, 3.2 Hz, 2H), 3.86–4.16 (m, 7H), 4.43–4.73 (m, 13H), 5.05 (t, $J=11.6$ Hz, 1H), 5.40–5.52 (m, 2H), 7.15–7.45 (m, 30H). Calcd for $C_{63}H_{69}O_{12}$ ($M+H^+$): 1017.4789. Found: 1017.4882. Compound **21***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85–2.05 (m, 2H), 2.22–2.55 (m, 8H), 3.28 (dd, $J=9.6$, 8.7 Hz, 1H), 3.44 (dd, $J=4.7$, 3.1 Hz, 1H), 3.57 (dd, $J=7.9$, 2.8 Hz, 1H), 3.68 (dd, $J=12.1$, 2.6 Hz, 1H), 3.71 (dd, $J=9.2$, 5.7 Hz, 1H), 3.75–3.88 (m, 2H), 3.77 (dd, $J=4.4$, 2.7 Hz, 1H), 3.96 (dt,

$J = 10.6$, 2.4 Hz, 1H), 4.06 (td, $J = 8.4$, 3.2 Hz, 1H), 4.12–4.23 (m, 2H), 4.26 (dd, $J = 11.3$, 2.5 Hz, 1H), 4.41 (s, 2H), 4.48 (s, 2H), 4.49 (d, $J = 11.5$ Hz, 1H), 4.41–4.50 (m, 5H), 4.56 (d, $J = 11.0$ Hz, 1H), 4.57 (d, $J = 11.0$ Hz, 1H), 4.63 (d, $J = 11.5$ Hz, 1H), 4.66 (d, $J = 11.0$ Hz, 1H), 4.77 (d, $J = 10.9$ Hz, 1H), 4.87 (d, $J = 11.0$ Hz, 1H), 4.95 (d, $J = 10.9$ Hz, 1H), 5.05 (t, $J = 11.4$ Hz, 1H), 5.47–5.62 (m, 2H), 7.05–7.14 (m, 2H), 7.23–7.45 (m, 28H). Calcd for $C_{63}H_{69}O_{12}$ ($M+H^+$): 1017.4789. Found: 1017.4637. Compound **23***Z*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 3H), 1.46 (s, 3H), 1.75–2.08 (m, 3H), 2.17–2.55 (m, 6H), 2.55–2.66 (m, 1H), 3.22 (dd, $J = 9.6$, 8.4 Hz, 1H), 3.63–3.74 (m, 1H), 3.74–3.86 (m, 2H), 3.88 (dd, $J = 7.6$, 3.2 Hz, 1H), 3.98–4.10 (m, 2H), 4.21 (dd, $J = 9.6$, 3.0 Hz, 1H), 4.34–4.44 (m, 2H), 4.50–4.70 (m, 5H), 4.72–4.79 (m, 1H), 4.80–4.95 (m, 2H), 5.19 (dt, $J = 9.6$, 3.6 Hz, 1H), 5.43–5.69 (m, 2H), 5.92 (d, $J = 3.6$ Hz, 1H), 7.20–7.40 (m, 20H). Calcd for $C_{51}H_{59}O_{12}$ ($M+H^+$): 863.4028. Found: 863.4028.

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