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LETTERS

Cross-metathesis and ring-closing metathesis of olefinic monosaccharides

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Abstract—Cross-metathesis (CM) of a variety of carbohydrate-based C-6 and olefins with related C-1 and C-6 carbohydrate-based olefins proved to be unselective. CM was selective when an unhindered straight chain olefin was coupled with a carbohydrate-based C-6 olefin. When related short chain alkenols were tethered, via a Me_2Si linker, to a suitably protected carbohydrate-based C-6 olefin, good yields of ring-closed products were obtained with the second-generation Grubbs catalyst **3**. A few examples where two carbohydrate-based olefinic alcohols were tethered via a Me_2Si linker and subjected to ring-closing metathesis (RCM) have also been examined. © 2002 Elsevier Science Ltd. All rights reserved.

Olefin metathesis has attracted a great deal of attention from the synthetic community as evidenced by the large number of papers and reviews[1] that have appeared on the subject. This has been due in large part to the availability of a variety of catalysts[2–5] with varying degrees of stability and reactivity. Metathesis chemistry has become quite popular in the realm of carbohydrate chemistry as evidenced from two recent reviews on the subject.[6,7]

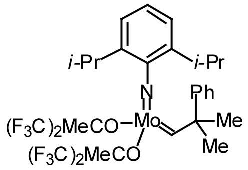
Our group has published several papers that involve an esterification–RCM approach directed towards the synthesis of *C*-disaccharides[8–10] and *C*-glycosides[11] and, in this letter, we present our initial results of a tethering–RCM metathesis approach towards stable *C*-saccharide-type derivatives.[12] These compounds have potential as enzyme inhibitors and as stable carbohydrate mimics.

Our present approach to carbohydrate mimics is partly inspired by the work of several groups[13,14] and some of which were even employed for the preparation of *C*-disaccharides.[15–18]

The cross-metathesis (CM)[19] of a simple carbohydrate-based olefin such as **5** with a variety of simple straight-chain olefinic alcohols was initially examined using 20 mol% of **3**.[4] It was found that the hydroxyl group on the straight-chain alcohol must be protected (entries 1–3 versus 5–8, Table 1) and used in a two-fold excess for efficient CM to occur and the reaction proceeded best in hot dichloromethane (entries 3 and 4 versus 5). The yields with different olefinic alcohols (entries 5–8) were found to be acceptable and, in all the cases, the *trans* isomer was the major isomer produced.[20]

It was then surmised that the use of RCM might be one way to improve the overall efficiency of the process. By tethering[21] the straight chain olefin alcohol to O-4 on the sugar, the metathesis reaction now becomes intramolecular. For this, access to alkene **11** was needed, and it was readily prepared from **7** as shown in Scheme 1.

A variety of tethered derivatives **12** were prepared as shown (Table 2) and subjected to RCM with 10–15 mol%



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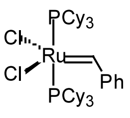

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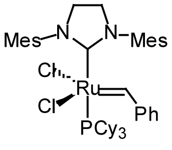

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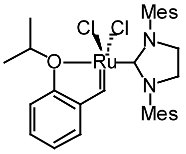

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Keywords: olefin; tethering; cross-metathesis; RCM; *C*-disaccharide.

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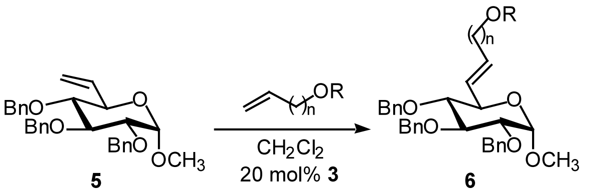
Table 1. CM of **5** with alkenyl acetates[a]



Entry	*n*	R	Temp. (°C)	Yield[c] (%)
1	1	H	23	13
2	1	H	40	15
3	3	H	83[b]	7
4	3	Ac	23	17
5	4	Ac	40	66
6	3	Ac	40	56
7	2	Ac	40	49
8	1	Ac	40	69

[a] The reactions were carried out with 2 equiv. of the straight chain olefin.

[b] Reaction carried out in 1,2-dichloroethane.

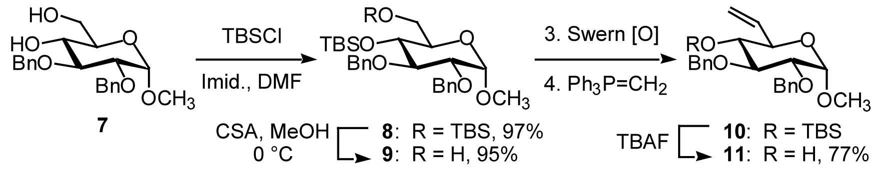
[c] Yields refer to chromatographically homogeneous materials.

of catalyst **3** at ambient temperature. In almost every one of the cases, good yields of RCM products were obtained with the *cis*-isomer predominating in all the cases.

When the tether increased in length (entries 6 and 7, Table 2), the head-to-tail dimerization product[22] (**14** and **15**) and the simple dimer **16** began to appear in the product distribution (Fig. 1).

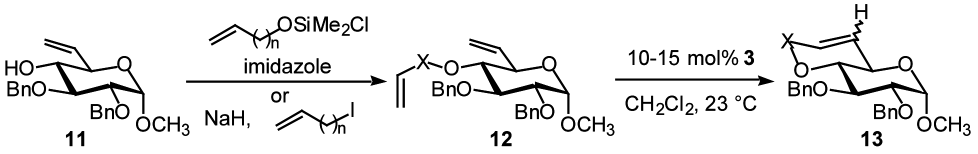
Next, the cross-metathesis of several sugar-based olefins was examined. Roy[23] and others[6] have carried out some work in the area of metathetical-based sugar olefin dimerization. We expected mixtures of compounds and our expectations proved to be correct. Mixtures of cross-coupled and dimerization products were formed in roughly equal amounts, and Scheme 2 shows the yields of the desired products. The CM was carried out with 20 mol% of catalyst **3** and an equimolar amount of each olefin. The *trans* isomer was the major isomer formed in almost all of the cases we examined. It was observed that compound **20** was formed in higher yield than most of the other examples, and this is likely due to the fact that one of the olefin coupling partners is considerably less sterically hindered.

One way of circumventing this problem was to tether the two olefins and carry out a RCM reaction in lieu of a non-selective CM reaction. We decided to follow the precedent for tethering established by Sinaÿ.[16] Compound **11** was deprotonated with a slight excess of *n*-butyllithium, and the formed lithium alkoxide was quenched with an excess of Me_2SiCl_2. The reaction was then concentrated under high vacuum and then exposed to alcohol **22a** in the presence of imidazole to give the coupled product **23a**[24] in 67% yield. RCM with the second-generation Grubbs catalyst **3**, in hot



Scheme 1.

Table 2. RCM of the tethered derivatives **12**[a]



Entry	X	Yield of **12** (%)	Yield of **13**[c] (%)	Ratio (*Z*:*E*)[d]
1	$-CH_2O\text{-}SiMe_2-$	64[b]	74	1:0
2	$-CH_2CH_2O\text{-}SiMe_2-$	64[b]	81	4.8:1
3	$-CH_2CH_2CH_2O\text{-}SiMe_2-$	61[b]	84	3.6:1
4	$-CH_2-$	95	90	1:0
5	$-CH_2CH_2-$	8	96	1:0
6	$-CH_2CH_2CH_2-$	91	79	1:trace[e]
7	$-CH_2CH_2CH_2CH_2-$	92	40	2.1:1[f]

[a] Yields refer to chromatographically homogeneous materials.

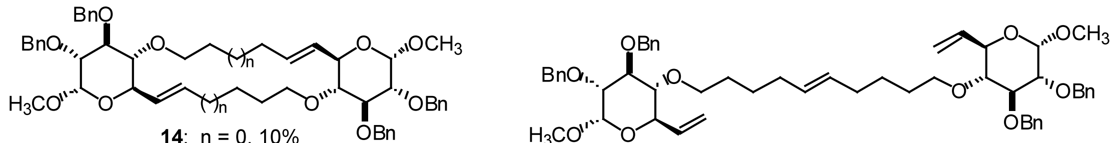
[b] 15–25% of **11** was recovered from these reactions.

[c] Reaction carried out at 0.02 M in substrate.

[d] Determined from coupling constants in the ^1H NMR spectra.

[e] The head to tail isomer **14** was isolated in 10% yield.

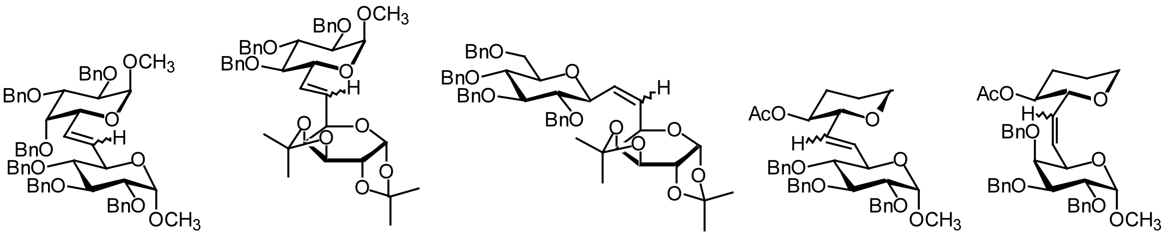
[f] The head to tail isomer **15** was isolated in 24% yield along with 14% of dimer **16**.



14: n = 0, 10%
15: n = 1, 24%

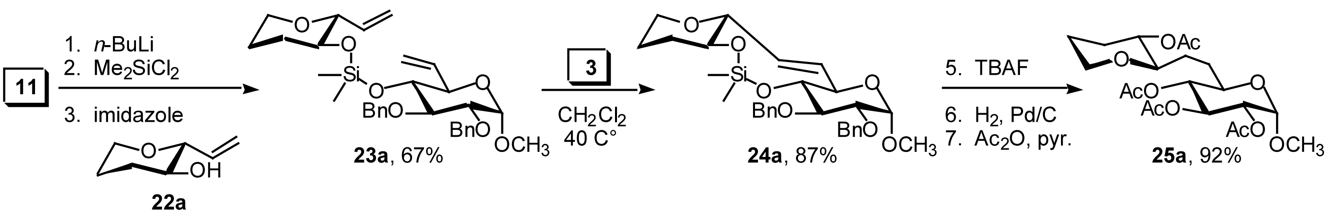
16: 14%

Figure 1.



17, 24% **18**, 18% **19**, 26% **20**, 44% **21**, 29%

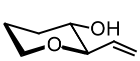
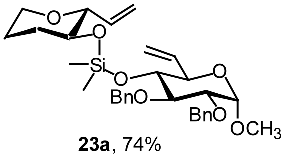
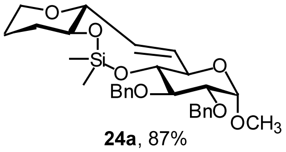
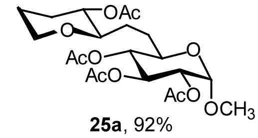
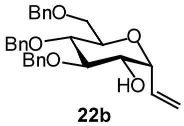
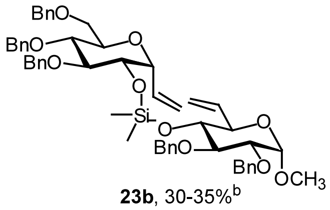
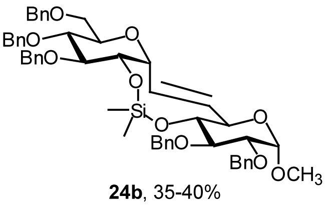
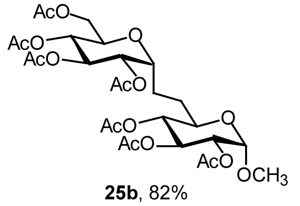
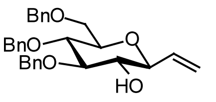
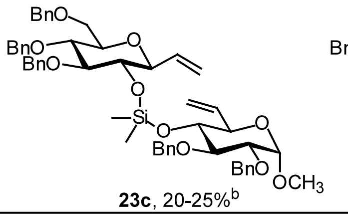
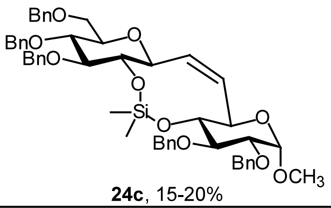
Scheme 2.



22a **23a**, 67% **24a**, 87% **25a**, 92%

Scheme 3.

Table 3. Tethering-RCM approach to (1→6)-*C*-disaccharides[a]

Entry	Olefin-Alcohol **22**	Tethered Derivative **23**	Alkene **24**[c, d]	*C*-Disaccharide **25**[e]
1	 **22a**	 **23a**, 74%	 **24a**, 87%	 **25a**, 92%
2	 **22b**	 **23b**, 30-35%[b]	 **24b**, 35-40%	 **25b**, 82%
3	 **22c**	 **23c**, 20-25%[b]	 **24c**, 15-20%	–

[a]Yields refer to chromatographically homogeneous materials. [b]Compounds exist as a mixture of rotamers as evidenced by ^{1}H NMR analysis. [c]See text for a description of the exact catalyst loading used. [d]Stereochemistry of the alkene was determined from coupling constants in the ^{1}H NMR spectra. [e]Yields are for three steps, i. TBAF ii. H_2, Pd/C iii. Ac_2O, pyridine, 4-DMAP.

dichloromethane, gave an 87% yield of **24a**[25] as a single *trans*-isomer. The protecting groups were removed (TBAF followed by H_2, Pd/C), and the resulting crude tetrol was peracetylated to give the *C*-disaccharide-like compound **25a** in good overall yield (Scheme 3).

Given our success with the example shown in Scheme 3, we decided to tether a more functionalized carbohydrate alcohol-olefin to **11** in order to prepare a (1→6)-linked-*C*-disaccharide.[26] Known alcohol **22b**[27] was tethered with **11**, but in this case, the tethering chemistry proceeded poorly giving **23b** in only 30–35% yield with the majority of the mass balance being recovered alcohols **11** and **22b** (entry 2, Table 3). Also, both the ^{1}H and ^{13}C NMR spectra of **22b** showed the appearance of extra signals indicating the presence of rotamers.[28] The crude material was nevertheless exposed to catalyst **3** in the hope that a favorable equilibrium would allow for the complete conversion of the product **24b** if the RCM was carried out at elevated temperatures. The RCM reaction of **23b** was very sluggish and proceeded to give **24b** in only 35–40% yield with reaction temperatures of 60°C and 30 mol% of **3** added in two to three portions over several hours. The efforts made to optimize[29] this sequence did not significantly improve the overall yield of **24b**, but did produce enough material to allow for its full characterization and conversion to **25b** (entry 2, Table 3).

Similar results were obtained with the corresponding β-vinyl derivative. Olefinic alcohol **22c**[30] was tethered to **11** to give **23c**, once again as a mixture of compounds. In this case, the RCM reaction (**23c**→**24c**) proved to be even less efficient proceeding in only 10–15% yield with 30–40 mol% of **3** added portionwise over several hours at 60°C (entry 3, Table 3).

It is clear that a tethering approach to such carbohydrate mimics is superior to simple CM. The dimethylsilyl linker works well for relatively unhindered pyran rings and simple olefin alcohols, but not with fully oxygenated monosaccharides. We are currently screening a variety of linkers to try and improve the overall efficiency of this tethering-RCM approach to both α- and β-(1→6)-linked-*C*-disaccharides.

Acknowledgements

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23. Roy, R.; Dominique, R.; Das, S. K. *J. Org. Chem.* **1999**, *64*, 5408–5412.
24. **23a**: *n*-BuLi (386 μl, 1.43 M in hexanes, 0.551 mmol) was added dropwise via syringe to a −78°C solution of olefin-alcohol **11** (157 mg, 0.424 mmol) in THF (3 ml). The resulting solution was stirred for 15 min at −78°C and then Me$_2$SiCl$_2$ (153 μl, 1.27 mmol) was added in one portion and the solution was allowed to warm to ambient temperature and was stirred for 3 h. The solution was carefully concentrated under high vacuum, diluted with THF (3 ml) and a solution of olefin **22a** (92 mg, 0.424 mmol) and imidazole (43 mg, 0.636 mmol) in THF (2 ml) was rapidly added via cannula and the resulting solution stirred at ambient temperature for 13 h. The reaction was diluted with water (5 ml) and extracted with dichloromethane (3×10 ml) and the combined organic extracts dried and concentrated. Flash chromatography of the residue over silica gel (4×23 cm) with 10→40% Et$_2$O/hexanes/1% Et$_3$N gave olefin **23a** (157 mg, 67%) as a pure oil (R_f=0.21, TLC silica, 40% Et$_2$O–hexanes; ^{1}H NMR, 500 MHz) oil: $[\alpha]_D$=+75.7 (*c* 1.00, CH$_2$Cl$_2$); FT-IR (neat) 2935, 1454, 1410, 1371, 1256, 1194, 1035, 1007, 921, 903, 872, 851, 796, 734, 697 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37–7.23 (m, 10H, Ar*H*), 5.92–5.83 (m, 2H, *H*-9, *H*-6), 5.35 (ddd, 1H, *J*=17, 1.5, 1.5 Hz, C=C*H*$_2$), 5.27 (ddd, 1H, *J*=17, 1.5, 1.5 Hz, C=C*H*$_2$), 5.22 (d, 1H, *J*=11 Hz, C=C*H*$_2$), 5.15 (ddd, 1H, *J*=11, 2.0, 2.0 Hz, C=C*H*$_2$), 4.97 (d, 1H, *J*=11 Hz, OC*H*$_2$Ph), 4.79 (d, 1H, *J*=11 Hz, OC*H*$_2$Ph), 4.71 (d, 1H, *J*=12.5 Hz, OC*H*$_2$Ph), 4.59 (d, 1H, *J*=12.5 Hz, OC*H*$_2$Ph), 4.58 (d, 1H, *J*=3.5 Hz, *H*-1), 3.98 (dd, 1H, *J*=9.5, 6.5 Hz, *H*-10), 3.92–3.87 (m, 1H, *H*-14), 3.78 (dd, 1H, *J*=9.0, 9.0 Hz, *H*-3), 3.51–3.42 (bm, 3H, *H*-11, *H*-5, *H*-2), 3.40–3.28 (bm, 2H, *H*-14, *H*-4), 3.37 (s, 3H, OC*H*$_3$), 2.10–2.03 (m, 1H, *H*-12), 1.64–1.56 (m, 2H, 2×*H*-13), 1.50–1.40 (m, 1H, *H*-12), 0.05 (s, 3H, SiC*H*$_3$); 0.04 (s, 3H, SiC*H*$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 139.0, 138.1, 136.7, 135.5, 128.4, 128.1, 128.1, 127.8, 127.4, 127.2, 118.1, 116.5, 97.9, 82.7, 81.4, 80.2, 75.2, 74.9, 73.2, 72.2, 71.2, 67.4, 55.2, 33.5, 25.4, −0.94, −1.49; HRMS (FAB): calcd for C$_{31}$H$_{42}$O$_7$Si (M+Na)+577.2592, found 577.2572.
25. **24a**: Catalyst **3** (5.1 mg, 6.0 mmol, 9.8 mol%) was added to a solution of diene **23a** (34 mg, 61.3 mmol) in dichloromethane (3 ml). The reaction was heated to 40°C for 4 h and then one more portion of **3** (5.2 mg, 6.1 mmol, 10 mol%) was added and the reaction heated for 4 h. At this point, the reaction was deemed complete by TLC and was concentrated in vacuo. Flash chromatography of the residue over silica gel (4×23 cm) with 10→40% Et$_2$O/hexanes/1% Et$_3$N gave the olefin **24a** (32.3 mg, 87%) as a pure (R_f=0.70, TLC silica, 50% EtOAc–hexanes; ^{1}H NMR, 500 MHz) beige solid: mp=71–72°C; $[\alpha]_D$=+93.7 (*c* 1.00, CH$_2$Cl$_2$); FT-IR (neat) 2961, 2932, 2821, 1730, 1467, 1257, 1216, 1106, 1083, 1053 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35–7.24 (m, 10H, Ar*H*), 5.54 (dd, 1H, *J*=16, 8.5 Hz, *H*-6), 5.45 (dd, 1H, *J*=16, 9.0 Hz, *H*-7), 4.83 (d, 1H, *J*=11 Hz, OC*H*$_2$Ph), 4.79 (d, 1H, *J*=12.5 Hz, OC*H*$_2$Ph), 4.74 (d, 1H, *J*=11 Hz, OC*H*$_2$Ph), 4.62 (d, 1H, *J*=11.5 Hz, OC*H*$_2$Ph), 4.53 (d, 1H, *J*=3.5 Hz, *H*-1), 4.00 (dd, 1H, *J*=9.0, 9.0 Hz, *H*-1′), 3.90 (ddd, 1H, *J*=11, 4.0, 1.5 Hz, *H*-5′), 3.78 (dd, 1H, *J*=9.0, 9.0 Hz, *H*-3), 3.53 (dd, 1H, *J*=8.5, 8.5 Hz, *H*-5), 3.45 (dd, 1H, *J*=9.5, 3.5 Hz, *H*-2), 3.37 (s, 3H, OC*H*$_3$), 3.34 (dd, 1H, *J*=12, 2.5 Hz, *H*-5′), 3.21–3.14 (m, 2H, *H*-4, *H*-2′), 2.02–1.94 (m, 1H, *H*-3′), 1.77–1.62 (m, 2H, 2×*H*-4′) 1.54–1.44 (m, 1H, *H*-3′), 0.10 (s, 3H, SiC*H*$_3$), 0.07 (s, 3H, SiC*H*$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 138.8, 138.3, 132.4, 129.4, 128.4, 128.4, 128.3, 128.1, 127.9, 127.9, 127.5, 98.4, 84.6, 81.5, 79.6, 75.8, 74.6, 73.7, 73.6, 70.4, 67.4, 55.2, 32.6, 25.7, −.3.4, −3.9; HRMS (FAB): calcd for C$_{29}$H$_{38}$O$_7$Si (M+Na)+ 549.2279, found 549.2279.
26. For a comprehensive review on the synthesis of *C*-saccharides, see: Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133–1167.
27. Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707–2709.
28. This premise is further supported by the presence of extra peaks in the ^{1}H NMR spectrum of the product that results when **11** is dimerized with 0.5 equiv. of Me$_2$SiCl$_2$.
29. The use of catalyst **4** did not result in any improvement in yield of **24** and we have not yet examined the RCM reaction with catalyst **1**.
30. (a) Hanessian, S.; Liak, T. J.; Dixit, D. M. *Carbohydr. Res.* **1981**, *88*, C14–C19; (b) Bellosta, V.; Czernecki, S. *Carbohydr. Res.* **1993**, *244*, 275–284.