Carbohydrate Synthesis

A Double Ring-Closing Metathesis Approach for the Synthesis of β-*C*-Trisaccharides**

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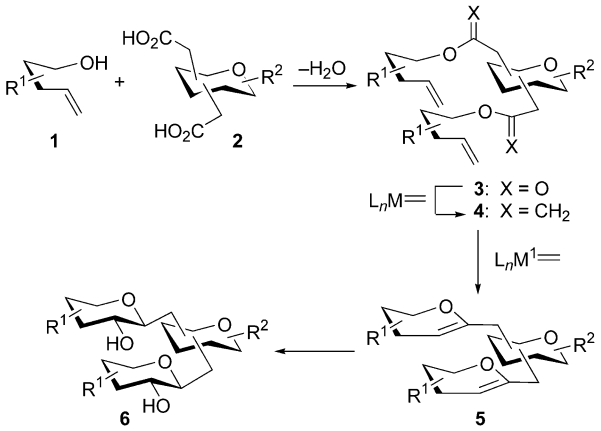
The synthesis of *C*-glycosides, compounds in which the interglycosidic oxygen atom has been replaced by a carbon atom, has received considerable attention from both the synthetic[1] and biological[2] point of view. They comprise an important class of stable carbohydrate mimics and the debate regarding their validity as conformational mimics of the parent *O*-glycosides is ongoing.[3]

Although there have been many interesting and unique approaches to the synthesis of *C*-glycosides,[4] the preparation of *C*-saccharides,[5] whether they are *C*-disaccharides or higher homologues, has been considerably more challenging. The first *C*-trisaccharide synthesis by Kishi and co-workers[6] clearly showed that these compounds could be prepared and, since that time, several other research groups[7] have targeted these carbohydrate-based compounds for synthesis. There are two main challenges associated with the synthesis of *C*-saccharides. The first challenge is the difficulty associated in functionalizing one carbohydrate ring (or open chain) followed by its subsequent attachment to the anomeric center of a second (or more) monosaccharide unit(s). To address this, several approaches to the synthesis of a variety of differentially linked *C*-saccharides[5] have been developed and we have recently published a unified and versatile strategy for a convergent and efficient synthesis of (1→6)-β-*C*-disaccharides[8] and a variety of differentially linked β-*C*-disaccharides.[9] Our ring-closing-metathesis (RCM)[10] approach is flexible enough to deliver a wide variety of *C*-glycoside-type structures.[11] We now report that our metathesis-based approach can be used to efficiently synthesize a variety of β-*C*-trisaccharides through a highly efficient double enol ether–olefin RCM cyclization[12] that provides the products in excellent overall yield after functionalization of the newly formed double bonds.

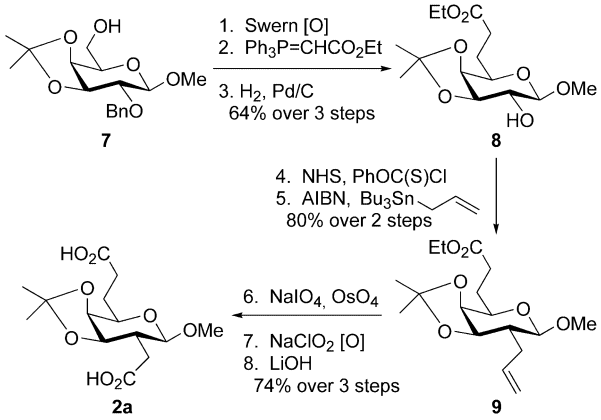
The general approach begins with dehydrative coupling of olefin alcohol **1** with a suitable carbohydrate-based diacid such as **2** to give diester **3** (Scheme 1). Methylenation of **3** is



Scheme 1. Double RCM approach to *C*-trisaccharides. L = ligand, M = metal.

followed by a double RCM reaction to give bis-*C*-glycal **5**. Functionalization of the bis-glycal double bonds then delivers the β-*C*-trisaccharide **6**.

In our previous *C*-disaccharide work[8,9] the installation of only one acetyl group onto the pyranose ring was needed, whereas in this case the preparation of a diacetyl derivative was required. We permitted the nature of the diacid to dictate the type of chemistry that would be used for its preparation. Scheme 2 shows the use of both Wittig- and Keck-type



Scheme 2. Preparation of diacid **2a**. Bn = benzyl, NHS = *N*-hydroxysuccinimide, AIBN = azobisisobutyronitrile.

allylation chemistry for the synthesis of diacid **2a**. The primary alcohol on **7**[13] was oxidized, olefinated, and hydrogenated, which served to reduce the double bond and cleave the benzyl group, to furnish **8**. The Robins-based[14] radical precursor was then installed by using the *N*-hydroxysuccinimide method[15] and Keck allylation[16] then delivered compound **9** as the sole isomer. Two-step oxidative cleavage of the olefin in **9** to an intermediate monoacid was followed by saponification to give diacid **2a**.

We relied upon a slightly different set of reactions to prepare acid **2b** (Scheme 3). Diol **10** was selectively esterified to provide the stable keto-monophosphonate **11**, after Swern

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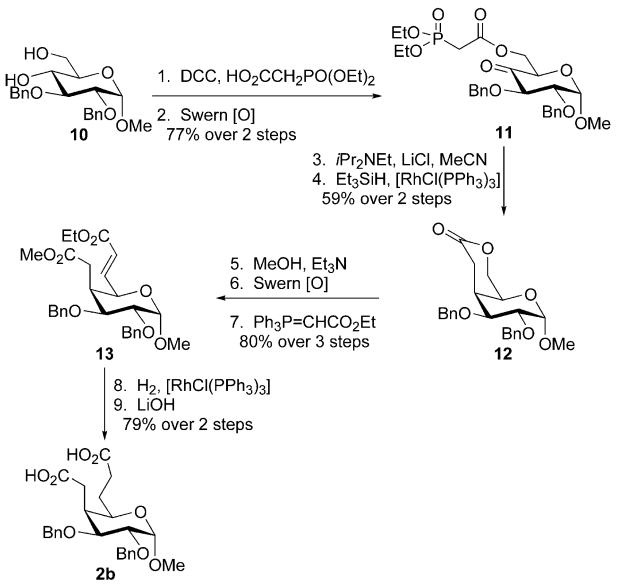
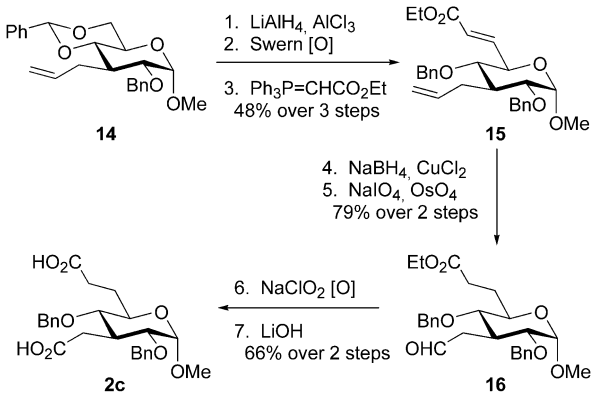


Scheme 3. Preparation of diacid **2b**. DCC = *N*,*N*′-dicyclohexylcarbodiimide.

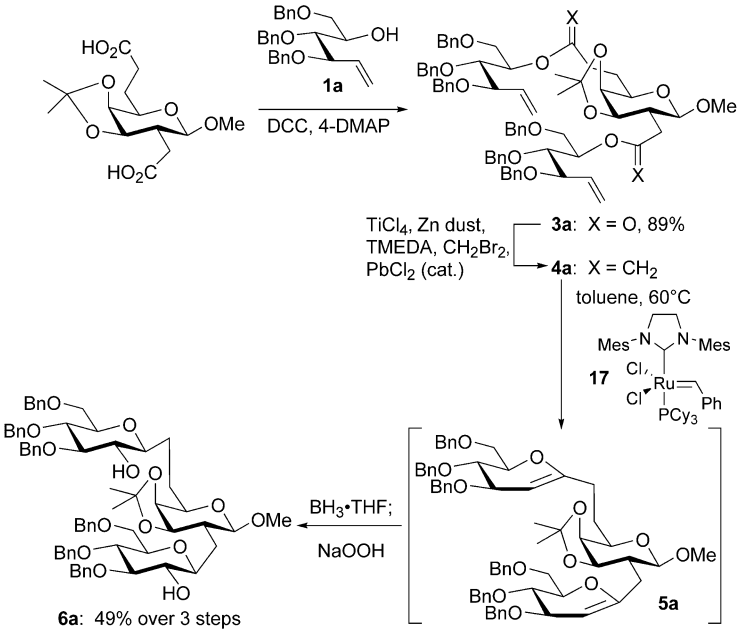
oxidation of the remaining secondary alcohol. Masamune–Roush olefination[17] gave an intermediate unsaturated lactone that, under a variety of different reduction conditions, gave exclusively lactone **12** possessing the *galacto* configuration at the C4 position. Methanolysis of **12**, according to the conditions of Corey et al.,[18] was followed by oxidation and Wittig reaction to form **13**. Reduction of the olefin was followed by bis-saponification to deliver the 4,6-diacid **2b** in good overall yield (Scheme 3).

Diacid **2c** was prepared by a slightly different strategy, as shown in Scheme 4. Known olefin **14**[9] was converted into α,β-unsaturated ester **15** in three steps, and conjugate reduction[19] was followed by oxidative cleavage of the remaining double bond to afford **16**. Oxidation and saponification of **16** then delivered the target diacid **2c** in good overall yield (Scheme 4).



Scheme 4. Preparation of diacid **2c**.

The stereochemistry of all the diacids, esters, and/or allylated derivatives was rigorously established by NOE, proton-decoupling and two-dimensional NMR spectroscopy experiments. In theory, the esters could be differentiated and distinctive olefin alcohols installed sequentially[20] but, in the present work, we chose to install the same olefin alcohol on each acid function. DCC-mediated coupling of diacid **2a** with two equivalents of alcohol **1a** gave diester **3a** in good yield (Scheme 5). Methylenation[21] of **3a** with an excess of the Takai reagent and subsequent RCM with the second-generation Grubbs catalyst **17**[22] (35 mol%) gave the intermediate



Scheme 5. Double RCM synthesis of β-*C*-trisaccharides. 4-DMAP = 4-dimethylaminopyridine, TMEDA = N,N,N′,N′-tetramethylethylenediamine, Mes = β-morpholinoethanesulfonic acid, Cy = cyclohexyl, THF = tetrahydrofuran.

bis-*C*-glycal **5a**. The bis-*C*-glycal was not isolated but instead was directly subjected to hydroboration by BH_3·THF.[23] Subsequent oxidative workup then afforded the *C*-trisaccharide **6a** in 49% yield over three steps.[24]

Table 1 shows the examples that have been prepared thus far. Ester formation (**1**+**2**→**3**), mediated by DCC and 4-DMAP, proved to be routine, except for the case shown in entry 5 (Table 1). A large excess of the methylenating reagent was required for the methylenation (**3**→**4**) reactions to be driven to completion. In all the cases, 35–40 mol% of the RCM catalyst **17** was needed to achieve a complete reaction. It is noteworthy that the three-step protocol works quite well even when both groups to be cyclized are on the same side of the pyranose ring, as in **3b** (entry 2, Table 1). No evidence of other cyclized products was noted by thin-layer chromatography (TLC) or crude NMR spectroscopy of the crude reaction mixtures. In one case (entry 8), we isolated the bis-glycal **5h**, since hydroboration gave a mixture of two inseparable products.

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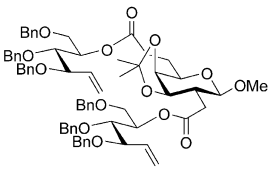
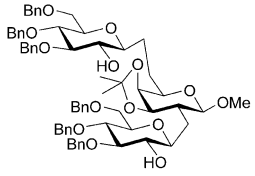
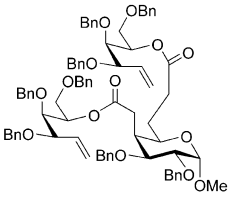
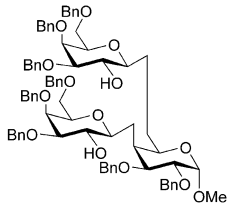
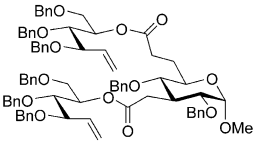
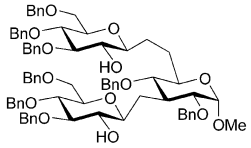
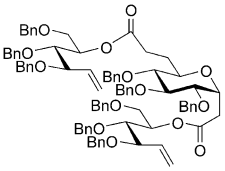
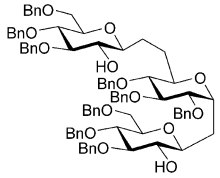
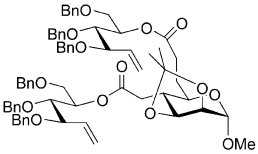
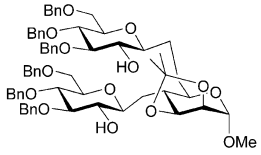
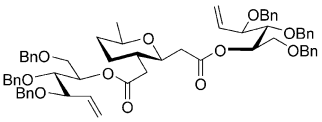
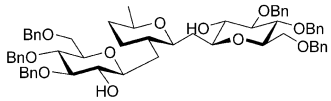
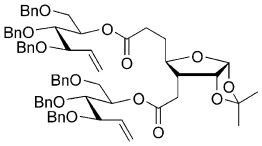
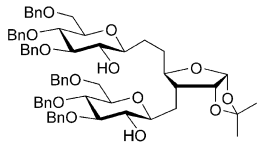
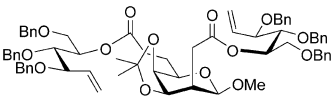
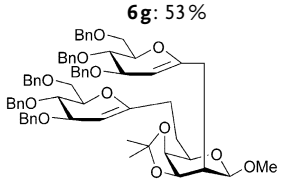
Table 1: Synthesis of β-*C*-trisaccharides by double RCM.[a]

Entry	Diester **3**	*C*-Trisaccharide **6**[b]
1	 **3a**: 89%	 **6a**: 49%
2	 **3b**: 84%	 **6b**: 55%
3	 **3c**: 74%	 **6c**: 57%
4	 **3d**: 88%	 **6d**: 59%
5	 **3e**: 48%[c]	 **6e**: 33%[d]
6	 **3f**: 88%	 **6f**: 50%
7	 **3g**: 87%	 **6g**: 53%
8	 **3h**: 76%	 **6h**: 57%[e]

[a] Yields refer to chromatographically homogeneous material. Yields are for three steps: methylenation, RCM (35–40 mol% of **17**), and hydroboration/oxidative workup. [b] Stereochemistry at the C1 and C2 positions was determined by acetylation and analysis of the H2 coupling constant in the ^{1}H NMR spectra. [c] A fair amount of recovered mono-1,6-ester was isolated from the reaction mixture. [d] In this case, the RCM reaction was stopped early and the bis-*C*-glycal was isolated, purified (48%, unoptimized), and then subjected to hydroboration (66%, unoptimized). [e] In this case, the yield is for two steps (methylenation and RCM) since hydroboration gave an inseparable mixture of two isomers.

The above results show that our double RCM approach for *C*-trisaccharide synthesis is viable and efficient. Application of this methodology to other congeners is currently underway and will be reported in due course.

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[24] All new compounds were fully characterized by ^{1}H, ^{13}C, DEPT, GCOSY, and GHMQC NMR spectroscopy, IR spectroscopy, exact mass spectrometry, and optical rotation measurements. See the Supporting Information for further details.

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