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Extended RCM–ROM sequences: a novel approach to polyunsaturated trisaccharides

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ABSTRACT

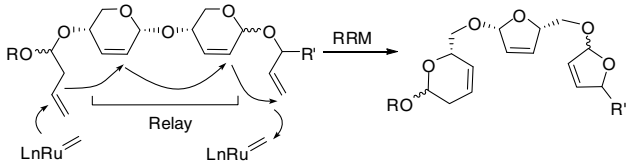
The first examples of RCM–ROM–RCM–ROM–RCM sequences involving non-strained heterocyclic relays are described. The method can be used for the preparation of polyunsaturated trisaccharides.

Ring-rearrangement metathesis (RRM)[1] refers to a particular type of metathetical cascade, in which a sequence of ring-closing metatheses (RCMs) and ring-opening metatheses (ROMs) converts cycloalkenes bearing one or two appending olefinic double bonds into new monocyclic or bicyclic systems, respectively. This process initially studied by Grubbs and co-workers[2] has been successfully used for the synthesis of bicyclic ethers[3] and piperidine- and pyrrolidine-containing alkaloids.[4] We recently extended the method to the preparation of polydeoxy disaccharides via an RCM–ROM–RCM sequence.[5]

An important question is whether this approach can still work with more complex systems (i.e., is it possible to perform extended metathetical cascades in a controlled manner so that the process can be synthetically useful?). In this work, our aim was to study the feasibility of complex RCM–ROM–RCM–ROM–RCM sequences. For this purpose, polyunsaturated trisaccharides, a class of molecules of current interest,[6] appeared to be good synthetic targets for testing the method. The general concept is shown in Scheme 1.

Recently described syntheses of polyunsaturated trisaccharides rely on the repeated coupling of modified monosaccharide units (Scheme 2).[6c,e] In contrast, the present approach involves assembling an advanced intermediate, which is then ring-rearranged to directly afford the desired product.

The feasibility of the concept was questionable. It is well known that the success or failure of a given RCM (or ROM) critically depends on a number of stereochemical and steric factors in a way that is still difficult to define. Thus, besides the desired RCM (ROM) product, the formation of side products (dimers, polymers, isomerized substrates etc.) is commonly observed. The problem increases in domino metatheses, where several unwanted pathways may compete with the desired reaction at each step of the cascade.



Scheme 1. General principle of the RRM approach to unsaturated trisaccharides.

Precedents from the literature were not encouraging: in fact, to the best of our knowledge, the conversion shown in Scheme 3 is the only reported example remotely related to our work. However, despite the presence of favorable, strained, relay moieties, only a low (10%) yield was obtained, using 1 mol/equiv of Grubbs 2nd generation (G-2) catalyst.[7] In our case, the use of non-strained relays further complicates the situation.

To assess the validity of our approach, we decided to prepare the new polyunsaturated 1-deoxytrisaccharide **1** and trisaccharide **2** (Scheme 4).

The synthetic strategy requires the preparation of an advanced intermediate (**3**), which should be available through coupling of

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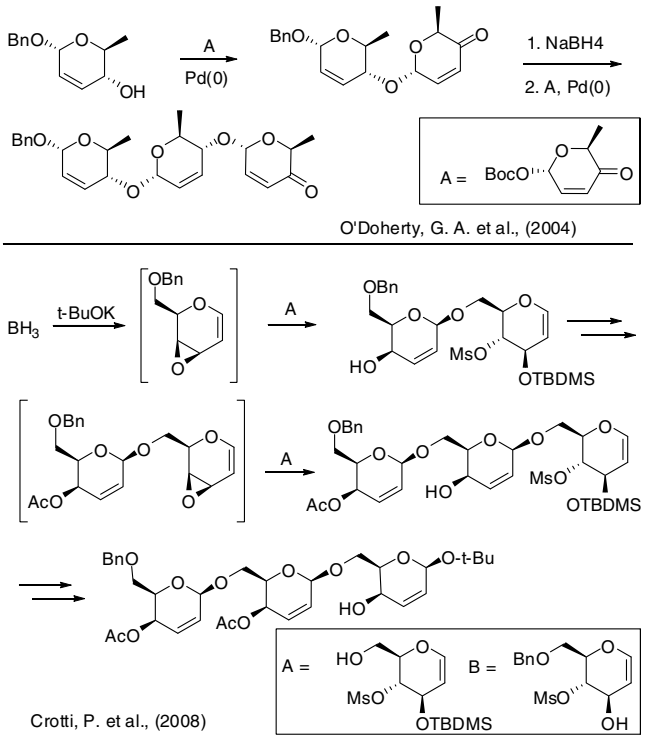
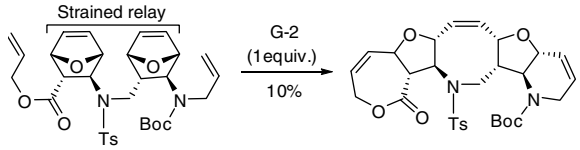
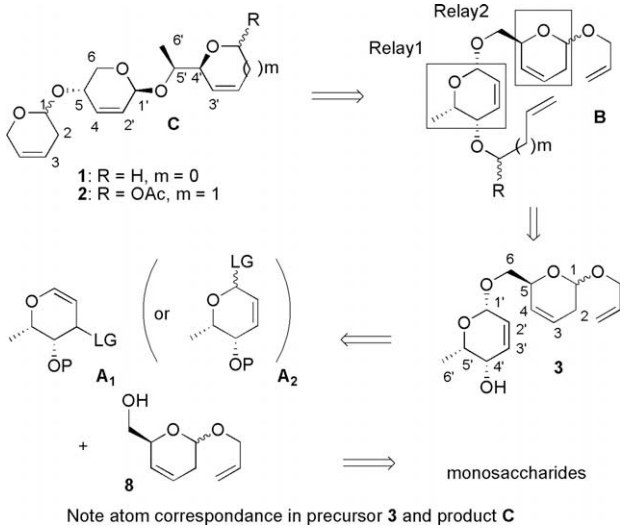


Scheme 2. Some recent polyunsaturated trisaccharide syntheses.



Scheme 3. A complex RRM leading to a pentacyclic product.



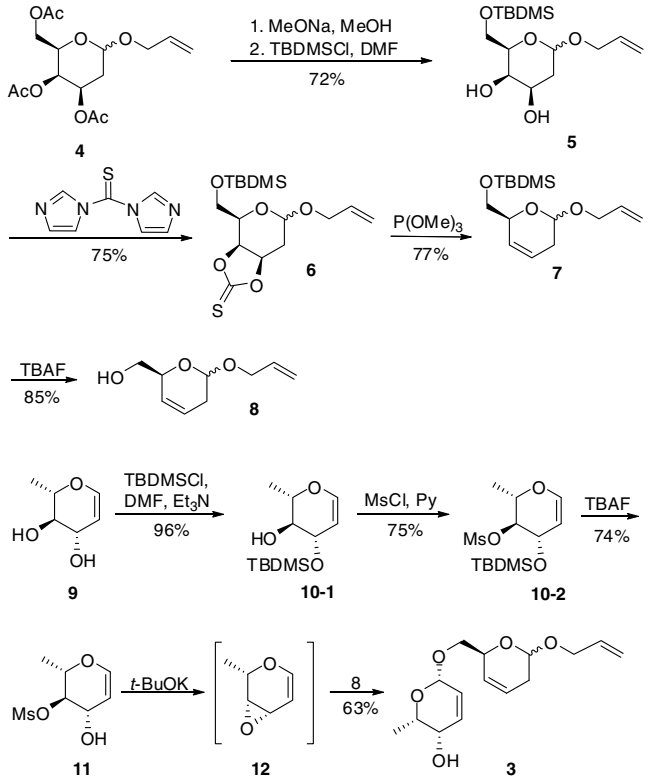
Scheme 4. Synthetic targets and synthetic strategy.

two precursors (A1 or A2 and **8** in Scheme 4) themselves derived from common monosaccharides. All but one of the four required olefinic double bonds are introduced prior to the coupling step, thus avoiding protective group manipulation on disaccharide intermediates, and the last olefin is installed immediately prior to the key metathesis step thus providing for the diversity potential of the method.

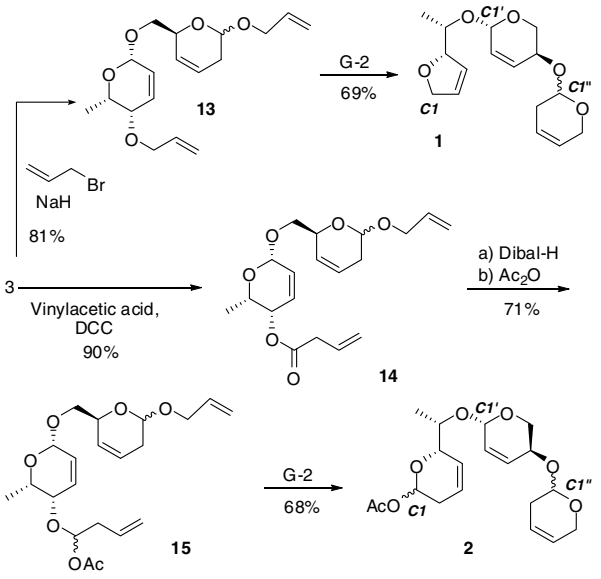
The synthesis of the pivotal intermediate **3** is depicted in Scheme 5. Deacylation of the known acetylated glycoside **4**[8] afforded the allyl 2-deoxygalactoside **5** as a 4:1 (α/β) mixture of anomers. After protection of the primary hydroxyl group as a *tert*-butyl-dimethylsilyl ether, the resulting diol was converted to the 3,4-dehydroglycoside **8** using Corey-Winter olefin formation conditions. The overall yield of the sequence is 35%. Several methods were examined for the coupling of fragments A and **8**. Activation of the anomeric position of A2 was unsuccessful and Ferrier-type reactions[9] using A1 as electrophile did not work, probably due to the high sensitivity of **8** to (Brönsted or Lewis) acidic conditions. The successful method shown in Scheme 5 uses Crotti's et al. methodology.[6e,10] Thus, 4-*O*-mesyl-L-rhamnal **11** was prepared from L-rhamnal **9** (selective silylation of the allylic hydroxyl in **9**, mesylation then desilylation).[11] Treatment of **11** with *t*-BuOK produced the transient vinyl-epoxide **12**, which was converted to **3** upon addition of the dehydrosugar **8**. During this conversion, the relative configuration OH-4′/Me-5′ is inverted (from trans to cis). The overall yield for this sequence is 31%.

Completion of the synthesis is shown in Scheme 6. Treatment of **3** with allyl bromide gave the allyl 4′-*O*-allyl glycoside **13**, while 4′-*O*-acylation with vinylacetic acid and mixed acetal formation according to Kopecky and Rychnovsky[12] afforded our second metathesis substrate **15** as a 1:1 mixture of isomers at the newly created acetalic carbon.

We then examined the key RRM sequence. Both **13** and **15** were submitted to classical RCM conditions[13] (G-2, 0.1 mol/equiv, substrate concentration = 0.002 M, toluene, 70 °C). To our pleasure, as shown in Scheme 6, the conversion was very effective in both cases, considering the complexity of the metathetical cascade, respectively, affording in good yield the desired tricyclic com-



Scheme 5. Synthesis of a pivotal intermediate.



Scheme 6. Preparation of the metathesis substrates and RRM.

pounds **1** (a 4:1 (α/β) mixture of anomers at anomeric carbon *C″1*) and **2**[14] as a 4:1 (α/β) mixture of anomers at anomeric carbon *C″1* and a 1:1 mixture of anomers at anomeric carbon *C*1 (see Scheme 6). This indicates that the various isomers/anomers present in **13** and **15** reacted to the same extent.

The remarkable efficacy of the metathetical rearrangements **13**→**1** and **15**→**2** deserves some comments. Conceivably, either the 1- or 4′-linked olefin (see Scheme 4, for numbering) may serve as a site of initiation of the sequence. However, control experiments showed that **8** was unchanged when submitted to the present metathesis conditions[15] suggesting that, for the desired cascade to proceed, initiation must take place on the 4′-linked olefin in **13** and **15**. Furthermore, following initiation, the system seems to be ideally preorganized, so that no unwanted side reaction is observed (no dimer or macrocyclic product is formed in the reaction).

In summary, we describe the (to the best of our knowledge) first preparatively useful, complex metathetical cascades using non-strained bicyclic heterocyclic systems as relay moieties.

With respect to polyunsaturated trisaccharide synthesis the approach differs conceptually from previously reported methods,[6c,e] and may allow a rapid access to non-classical saccharides otherwise difficult to synthesize. In the present exploratory study, we used mixtures of isomers/anomers but adaptation of the method for preparative purposes should be straightforward.

Acknowledgment

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Supplementary data

Full experimental procedures for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.048.

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13. *General procedure for RRM*: Under argon, at 70 °C, to a 0.002 M solution of the substrate in degassed toluene, was added Grubbs catalyst 2nd generation (10 mol %). The resulting mixture was stirred at 70 °C for 3 h, concentrated in vacuo, and purified by flash column chromatography on silica gel (10% EtOAc in cyclohexane) to provide the ring-rearranged product (a 4/1 mixture of anomers for **1** and a mixture of 4 diastereomers for **2**).
14. Compound **2** and, to a lesser extent, its precursor **15** and **1** were found to be rather unstable. In particular, **2** may be stored at −30 °C in frozen benzene only for a few days. This suggests that these intermediates would probably be quite difficult to obtain using more classical methods.
15. At higher concentrations (0.1 M), dimerization of **8** (but no RCM) is observed.