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Ring-rearrangement metathesis of 3,6-dialkoxy-3,6-dihydro-2*H*-pyrans

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Abstract

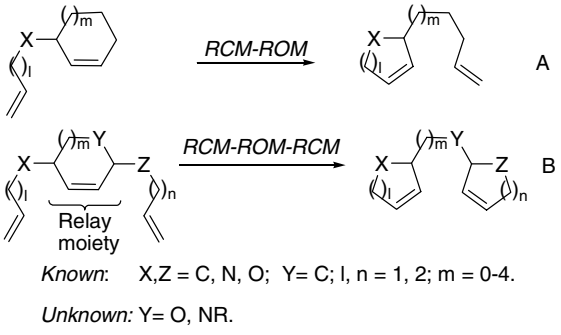
The first RCM–ROM–RCM sequence using a non-strained heterocycle as relay moiety is described. The course of the reaction strongly depends on the nature and relative configuration of the substituents in the starting trienic system. In addition, for a productive reaction to be observed, the site of initiation of the metathesis cascade is crucial. The compounds thus obtained may be useful for the synthesis of unusual polydeoxydisaccharides.

Keywords: Ring-rearrangement metathesis; Cascade metathesis; RCM; ROM

In the last decade, the olefin/alkyne metathesis reaction has become a major synthetic tool for the preparation of complex organic molecules. The intramolecular ring-closing metathesis (RCM), and the intermolecular cross-metathesis (CM) are now routinely used in organic synthesis. The intermolecular ring-opening metathesis (ROM) of strained cyclic olefins has been mainly used in polymer synthesis in the so-called ring-opening metathesis polymerization (ROMP).

In addition, a wide variety of 'domino' metatheses have been developed (RCM–ROM, CM–ROM, RCM–ROM–RCM, etc.) which increases the synthetic potential of this reaction. For these combinations the collective term 'ring-rearrangement metathesis' (RRM) has been proposed (Scheme 1).[1]

Among the various possible RRMs, the RCM–ROM–RCM cascade (B, Scheme 1) which allows the stereocontrolled formation of bicyclic systems from relatively simple monocyclic precursors is particularly useful. The method can be used, for example, for the preparation of bicyclic ethers[2] and piperidine- and pyrrolidine-containing alkaloids.[3] To the best of our knowledge, however, there is no example of type B RRM in which X, Y and Z are all heteroatoms.[4]



Scheme 1. Some synthetically useful metathetic cascades.

We were intrigued by the possibility of achieving RRM B using substrates in which X = Y = Z = O and $m = 1$. Despite a superficial similarity, there are significant differences between such systems and their carbocyclic counterpart (Y = C). In particular, an anomeric effect in the former type of substrates may operate to stabilize certain conformations.[5] This, in turn is likely to influence (positively or negatively) the metathetic process. Apart from

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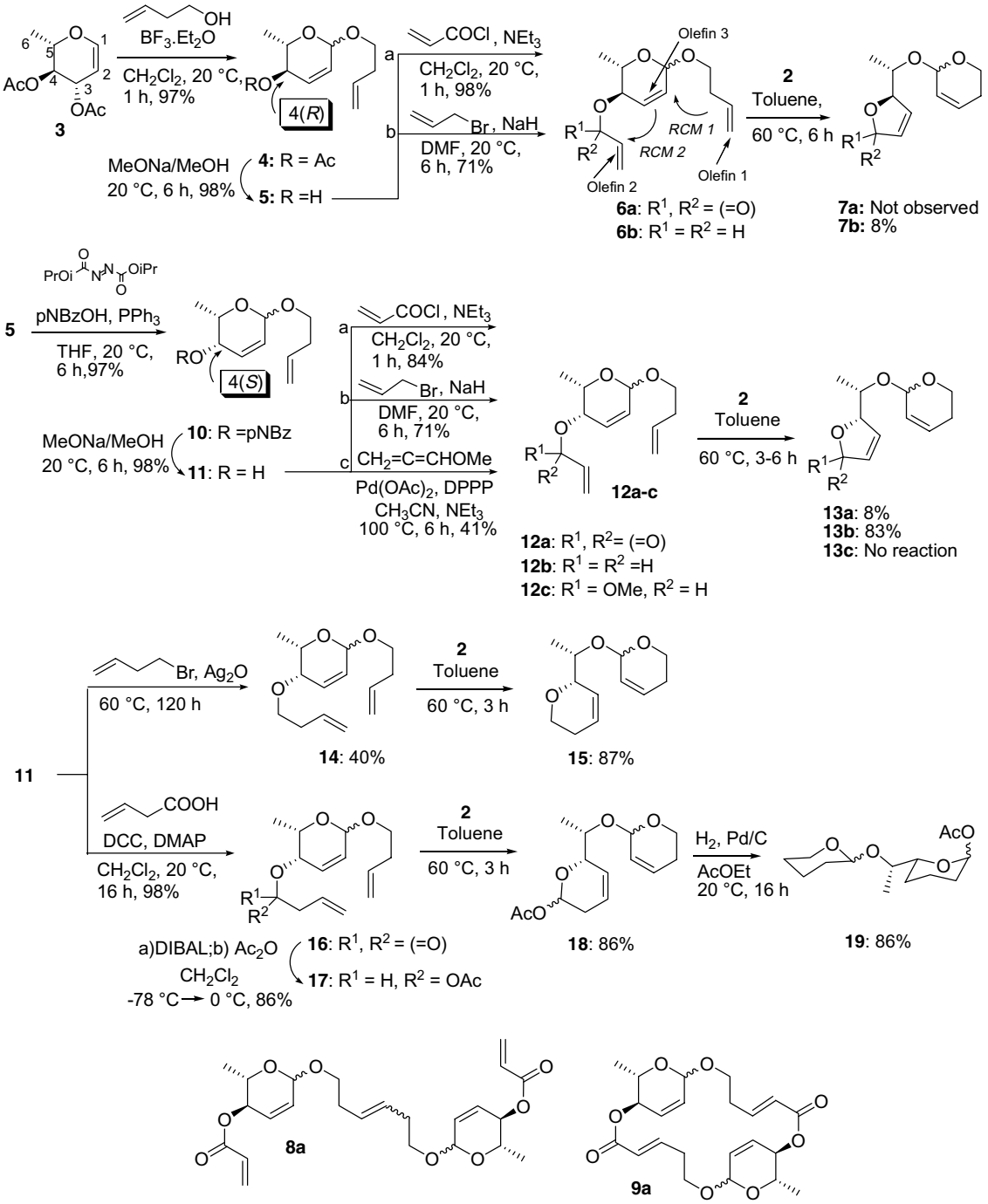
these mechanistic aspects, the product of the rearrangement is potentially useful as a versatile synthetic intermediate in the preparation of unusual disaccharides.[6] The required metathesis substrates were readily prepared as shown in Scheme 2: 3,4-bis(*O*-acetyl) rhamnal **3** was treated by but-3-en-1-ol in the presence of catalytic $BF_3{\cdot}Et_2O$ to afford 4(*R*) glycoside **4**,[7] as a 6:1 mixture of α and β anomers[8] in agreement with the literature data.[7] This was converted in two steps into the 4-*O*-acryloyl **6a**. The α and β anomers could not be separated and our studies were pursued using this mixture. Therefore, all subsequent products will be obtained as mixtures of a major and a minor anomer in a 6:1 ratio.

The first RCM–ROM–RCM sequence was then attempted using acrylate **6a** as the starting material. As can be seen in Scheme 2, formation of the expected disaccharide analogue **7a** was not observed. Instead, using the Grubbs 'first generation' catalyst **1**[9] in the presence of $Ti(OiPr)_4$[10] the cross metathesis dimer **8a** (ca. 30%) was obtained along with starting material (ca. 50%). Using



Scheme 2. RCM–ROM–RCM of 3,6-dialkoxy-3,6-dihydro-2*H*-pyrans.

the Grubbs 'second generation catalyst' **2**, we observed the formation of macrocycle **9a** (38%) along with dimer **8a** (7%) and starting material (50%).

In substrate **6a**, initiation of the metathetic process should occur at the more electron-rich olefin 1. If this is the case, the first step of the cascade, RCM 1, (see Scheme 2), does not proceed. This was confirmed by the behaviour of acetate **4** that was unchanged when submitted to the same methathesis conditions (**2**, toluene, 60 °C).

We then attempted to invert the sense of the sequence (RCM 2→ROM→RCM 1) by allowing the initiation to take place at the level of olefin 2. To this effect, the acrylate ester was replaced by an allyl ether to afford **6b** which was submitted to standard metathesis conditions (catalyst **2**, toluene, 60 °C). Only limited (<8%) conversion to the desired bicyclic ether **7b** (obtained as a 6:1, mixture of α and β anomers as determined by ^{1}H NMR) was observed and most of the starting material was recovered.

These results are markedly different from those reported in earlier studies using carbocyclic relay moieties.[2,3] A plausible explanation is as follows: according to Chauvin's mechanism,[11] a crucial step in the RCM catalytic cycle is the formation of a strained bicyclic metallacyclobutane. This is only possible when strict geometrical requirements are met, including an adequate conformational organization of the starting diene placing the two olefins in close proximity while minimizing steric effects.[12] In our case, the central dihydropyran ring in **6** exists in a stable half chair conformation (with an equatorial methyl group) and this is probably detrimental to the formation of a bicyclic transition state regardless of the initiation site (olefin 1, α or β anomer, or olefin 2).

Faced with these disappointing results, we decided to examine the effect on metathesis of inverting the C-4 stereochemistry (Scheme 2).

Inversion of the 4-hydroxyl group in compound **5** was achieved using the Mitsunobu procedure to afford 4 (*S*) glycoside **11**, which was converted into the corresponding acrylate ester **12a** and allyl ether **12b**. Compound **12a** was only poorly reactive but we could observe the formation (in low yield) of the ring-rearranged product **13a**. In contrast, the allyl ether **12b** reacted smoothly to afford bicyclic ether **13b**[13] (again as a 6:1 mixture of anomers) in excellent yield, indicating that initiation took place mainly at olefin 2.

We also prepared the ethylene ketal **12c** (Ref. 14b and references cited therein) which, surprisingly, proved to be non-reactive in the metathesis reaction. Inspection of the literature indicates that allylic *O*,*O*-acetals do participate in RCM[14] but the results may be explained by these species being involved in the propagation steps and we are not aware of examples in which involvement of allylic *O*,*O*-acetals at the initiation step has been shown. In our case, initiation must occur at the acrolein ketal moiety and our results suggest that allylic *O*,*O*-acetals do not readily participate in the initiation step of metathetic processes.[15]

The 4-*O*-allyl group was next replaced by a longer homoallyl moiety. The resulting triene **14** readily underwent clean metathetic conversion into bis-dihydropyrane **15**.

Finally, the mixed ketal **17** was obtained from **11** in two steps: formation of the 4-*O*-3-butenoyl ester and reduction of the latter with DIBAL then quenching with acetic anhydride according to Rychnovsky[16] (the success of this reaction depends on the careful control of the experimental conditions).[13] We were very pleased to observe the clean conversion of **17** to the bis-dihydropyrane **18** upon exposure to catalyst **2**. Reduction of the two olefinic double bonds in **18** provided **19**, the first disaccharide to be synthesized by cascade metathesis.

Thus, we have described the first RCM–ROM–RCM cascade using a non-strained, monocyclic heterocycle as a relay moiety. We show that the success of the reaction crucially depends on electronic and stereochemical factors. In particular, our results suggest that, although α,β-unsaturated ketals can participate in metathesis they cannot serve as initiation site for the reaction. The structural pattern of the newly formed compounds suggests that they could be useful as valuable intermediates for the synthesis of unusual disaccharides. This is illustrated by conversion of bisacetal **18** into a simple polydeoxy-1,6-disaccharide.

The study of RRM using different heterocyclic relay moieties is underway.

Acknowledgments

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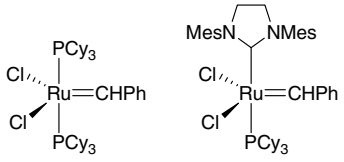
7. For the sake of simplicity, rhamnal was chosen (instead of e.g., glucal) as it contains only the hydroxyl groups necessary for the model studies. Preparation of 3,4-di-(*O*-acetyl)-L-rhamnal and Ferrier rearrangement: Zhang, G.; Shi, L.; Liu, Q.; Wang, J.; Li, L.; Liu, X. *Tetrahedron* **2007**, *63*, 9705–9711; and references cited therein.

8. Established by hydrogenation to the corresponding 1-butoxy-tetrahydropyrane derivative and inspection of the ^{1}H NMR spectra: the major anomer shows two small coupling constants for the anomeric proton.
9. Structure of the Grubbs catalysts used in this work:



1 **2**

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13. All new compounds have satisfactory analytical data (^{1}H and ^{13}NMR, MS and HRMS for key compounds). Experimental details and analytical data for compound **17**. Under argon, at −78 °C, to a solution of ester **16** (228 mg, 0.87 mmol, 1 equiv) in dichloromethane (7 mL), DIBAH (1.5 M in toluene, 1.16 mL, 1.74 mmol, 2 equiv) was added slowly over a period of 15 min (*caution*! the internal temperature must be kept below −72 °C). The solution was stirred for an additional 45 min at −78 °C and pyridine (211μL, 2.61 mmol, 3 equiv) was added dropwise, while maintaining the temperature below −76 °C. Then a solution of DMAP (214 mg, 1.74 mmol, 2 equiv) in dichloromethane (1.5 mL) was immediately added at a rate such as to maintain the temperature below −72 °C. Finally, acetic anhydride (492 μL, 5.22 mmol, 6 equiv) was added (again, the internal temperature must be kept below −72 °C). The resulting light yellow solution was stirred at −78 °C for 12 h, the mixture was warmed to 0 °C and stirred for an additional 30 min. The reaction was quenched by the sequential addition of $NH_4Cl_{(aq)}$ (5 mL) and saturated aqueous sodium potassium tartrate (5 mL). The resulting emulsion was stirred vigorously at 20 °C for one night. The resulting biphasic mixture was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (triethylamine-deactivated silica gel, 10% EtOAc in cyclohexane with 3% Et_3N) provided 220 mg (0.52 mmol, 86%) of the title compound as a clear, colorless oil.
^{1}H NMR ($CDCl_3$, 300 MHz) major isomer: δ 5.99 (m, 5H), 5.05 (m, 5H), 4.12 (m, 1H), 3.67 (m, 3H), 2.52 (m, 2H), 2.36 (m, 2H), 2.09 (m, 3H), 1.27 (m, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz) major isomer: δ 170.5, 134.9, 131.5, 129.1, 127.4, 118.6, 116.2, 98.4, 94.0, 71.6, 67.3, 65.5, 39.2, 34.0, 21.2, 16.1.
HRMS: calcd for $C_{16}H_{24}NaO_5$ 319.1521; found, 319.1525. Analytical data for ring-rearranged compounds **13b**, **15**, **18**: Compound **13b**: ^{1}H NMR ($CDCl_3$, 300 MHz) major isomer: δ 6.02 (m, 2H), 5.86 (dq, $J = 2.3$, 8.6 Hz, 1H), 5.72 (dtd, $J = 1.3$, 2.8, 10.1 Hz, 1H), 5.03 (t, $J = 1$ Hz, 1H), 4.96 (m, 1H), 4.67 (m, 2H), 3.98 (m, 2H), 3.71 (ddt, $J = 1$, 6.2, 11.1 Hz, 1H), 2.31 (m, 1H), 1.90 (dddt, $J = 1$, 4.1, 5.1, 17.8 Hz, 1H), 1.11 (d, $J = 6.4$ Hz,3H).
^{13}C NMR ($CDCl_3$, 75 MHz) major isomer: δ 129.1, 128.1, 126.7, 126.1, 92.0, 88.5, 75.6, 74.1, 57.2, 24.7, 14.7. HRMS: calcd for $C_{11}H_{16}NaO_3$ 219.0992; found, 219.0976.
Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02 (dd, $J = 6.0$, 9.6 Hz, 1H), 5.94 (m, 1H), 5.73 (m, 2H), 5.01 (br s, 1H), 4.24 (m, 1H), 3.97 (m, 3H), 3.68 (m, 2H), 2.29 (m, 2H), 1.90 (m, 2H), 1.21 β, 1.14 α (d, $J = 6.4$, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz) major isomer: δ 129.0, 127.1, 126.1 (2C), 92.23, 76.3, 73.9, 63.6, 57.2, 25.3, 24.7, 15.0. HRMS: calcd for $C_{12}H_{18}NaO_3$ 233.1154; found, 233.1149.
Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz) major isomer: δ 6.31 (d, $J = 4.4$ Hz, 1H), 6.03 (m, 1H), 5.84 (m, 2H), 5.70 (m, 1H), 5.01 (s, 1H), 4.46 (m, 1H), 3.95 (m, 2H), 3.70 (dd, $J = 6.1$, 11.1 Hz, 1H), 2.50 (m, 1H), 2.30 (m, 2H), 2.08 (s, 3H), 1.91 (m, 1H), 1.14 (d, $J = 6.4$ Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz) major isomer: δ 169.1, 128.1, 125.0, 124.6, 120.7, 91.6, 89.6, 72.9, 70.2, 56.4, 28.7, 27.7, 23.7, 13.7. HRMS: calcd for $C_{14}H_{20}NaO_5$ 291.1208; found, 291.1207.
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