Ring-Closing Metathesis in Carbohydrate Annulation**

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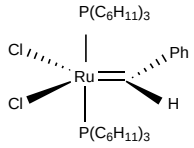
The Chiron Approach to the synthesis of chiral target molecules from carbohydrates is now a well established component in the armoury of organic chemistry.[1] A key element of this strategy is the range of methods available for the synthesis of cyclic compounds that include some or all of the carbon atoms of the original carbohydrate.[2] We have made several contributions to this area of carbohydrate annulation by using Robinson annulation,[3] aldol condensation,[4] radical cyclization,[5] and through the application of these ideas to the synthesis of a C-ring synthon of taxol.[6] In recent times there has been considerable interest in new applications of the ring-closing metathesis (RCM) reaction[7] by using the Grubbs catalyst **1**.[8] Carbohydrate substrates have been subjected to RCM to produce oxygen and nitrogen heterocyclic sugar derivatives.[9] The formation of macrocyclic lactones on sugar substrates in a RCM reaction was first reported by Descotes[10] using a tungsten catalyst. More recently lactonization using the Grubbs catalyst **1** has been reported,[11] along with applications in the synthesis of tricolorin A[12] and (+)-cyclitophellitol from xylose.[13]



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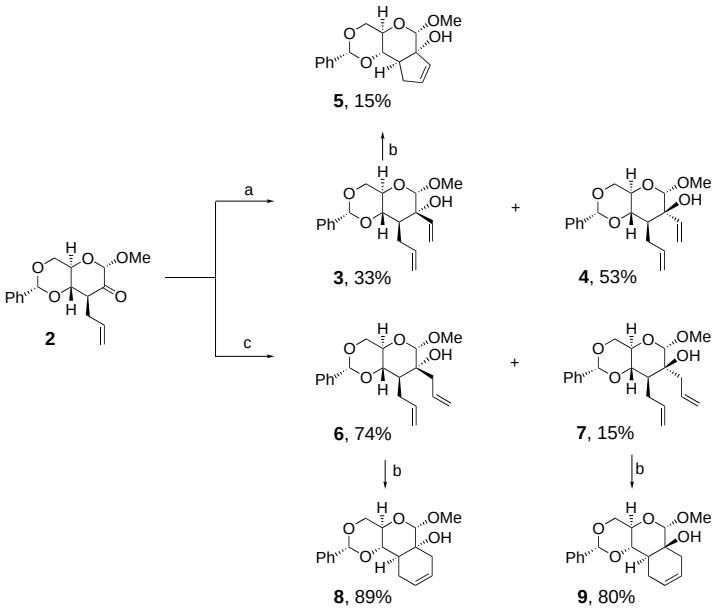
As part of our continuing program on new methods for carbohydrate annulation we became interested in the application of RCM in the preparation of carbocyclic- and spiroannulated sugars to produce methods that could be applied in our synthetic route to taxoids[14] and other natural products. We report here our studies on the synthesis of five-, six-, and eight-membered annulated sugars along with spiro systems.

The starting material was the ketone **2** (Scheme 1), a derivative of methyl-α-D-glucopyranoside.[15] Reaction with vinylmagnesium chloride gave a mixture of allylic alcohols **3** (33%) and **4** (53%). RCM with the Grubbs ruthenium catalyst[8] was not successful on the diene **4**, probably because of the steric strain that would be produced in the *trans*-fused 5-6 ring system in the product. However, a 15% yield of **5** was obtained in the RCM reaction of **3**, along with 75% of recovered starting material. In addition to the usual spectroscopic characterization an X-ray crystal structure of **5** was obtained.[12]



Scheme 1. Reagents and conditions: a) $H_2C{=}CHMgCl$, THF, reflux, 2 h; b) $[RuCl_2(CHPh)\{P(C_6H_{11})_3\}_2]$ (**1**), benzene, 60 °C, 48 h for **5** and 17 h for **8** and **9**; c) $H_2C{=}CHCH_2MgCl$, THF, 2 h.

Addition of allylmagnesium chloride to ketone **2** furnished the *cis* diene **6** (74%) and the *trans* diene **7** (15%). Both **6** and **7** underwent ring-closing metathesis to produce the annulated sugar derivatives **8** and **9** in yields of 89 and 80%, respectively. An X-ray crystal structure of **8** was obtained.[16] Clearly there is no steric impediment to the formation of the *cis* and *trans* 6-6 ring systems in **8** and **9**, respectively.

While the addition of an allyl Grignard reagent to ketone **2** gives the β-alcohol **6** as the major product, the addition of the vinyl Grignard reagent gives the α-alcohol **4** as the major product. This strange reversal in the stereoselectivity deserves some comment. The major difference between vinyl and allyl Grignard reagents is that allylic rearrangement is possible during the addition of an allyl Grignard compound to a ketone. We believe that allylic rearrangement is best accommodated by an axial attack of allylmagnesium chloride on ketone **2** to afford the β-alcohol **6** as the major product. With vinylmagnesium chloride, however, there is a small preference in favor of α-attack to give the alcohol **4**.

A recent publication[17] has highlighted the difficulty of synthesizing eight-membered rings with the normal ring closure methods, and reported the use of the Claisen rearrangement in the conversion of D-glucose into an enantiomerically pure cyclooctenone. The synthesis of eight-membered carbocyclic and heterocyclic rings by RCM has been reported by Grubbs.[18a] Further examples have also appeared,[18b] and include the total synthesis of dactylol[18c] and the preparation of eight-membered ether rings in a sequence starting from glyceraldehydacetonide using a molybdenum catalyst for the RCM reaction.[18d] Scheme 2 illustrates the

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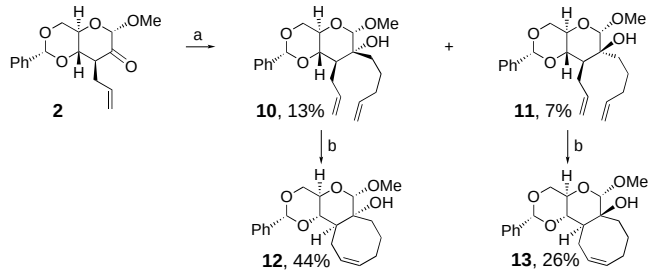
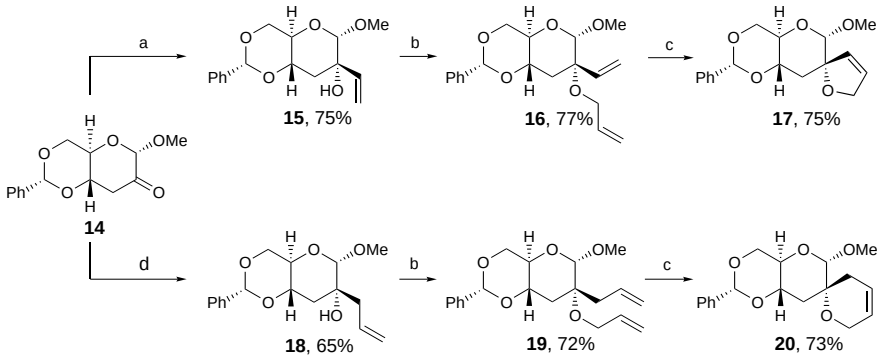


Scheme 2. Reagents and conditions: a) $H_2C{=}CH(CH_2)_3MgCl$, THF, reflux, 4 h; b) $[RuCl_2(CHPh)\{P(C_6H_{11})_3\}_2]$ (**1**), benzene, 31 h at 60 °C for **10**, and 17 h at 60 °C for **11**.

cyclooctaannulation of ketone **2** by RCM. The addition of the pentenyl Grignard reagent to the ketone **2** led to alcohols **10** and **11** in yields of 13 and 7%, respectively, along with a recovery of 37% starting material and 37% of a single alcohol that arises from reduction of the ketone **2**.[19] Dienes **10** and **11** were then treated with 9 mol% of catalyst **1** in benzene for 31 and 41 hours, respectively. This led to the cyclooctene derivatives **12** (44% yield with 32% recovered starting material) and **13** (26% yield with 48% recovered starting material). The assignment of structure **12** was confirmed by X-ray crystal structure analysis. The crystals were all weak diffractors, but the assignment of structure **12** was unambiguous.[16]

Methods for the synthesis of spiro-fused tetrahydrofuran or pyran ring systems are based on the addition of an appropriate reagent to a ketone, followed by spiroether formation,[20a] intramolecular radical addition,[20b] and intramolecular reaction of an oxonium ion on an allyl silane.[20c] The preparation of enantiomerically pure spiro products is achieved by starting from an enantiomerically pure ketone.[20d] We have applied RCM to the problem of spiroannulation (Scheme 3).[21] The starting point was the ketone **14**, a derivative of methyl-α-D-glucopyranoside.[22] Addition of vinylmagnesium chloride gave the allyl alcohol **15** in 75% yield. Deprotonation with sodium hydride, followed by allylation with allyl bromide furnished the ether **16** in 77% yield. Ring-closing metathesis of diene **16** gave the spiro-fused tricyclic compound **17** in 75% yield. The structure of **17** was confirmed by X-ray crystal structure analysis.[16] The equivalent reaction sequence with allylmagnesium chloride was also successful. Ketone **14** was converted into alcohol **18** in 65% yield, and subsequent conversion into the allyl ether **19** furnished the RCM substrate in 72% yield. This compound underwent RCM to give the spiro-fused dihydropyran system **20** in 73% yield. The structure of **20** was confirmed by X-ray crystal structure analysis.[16]



Scheme 3. Reagents and conditions: a) $H_2C{=}CHMgCl$, THF, reflux, 2 h; b) NaH, $CH_2{=}CHCH_2Br$, THF; c) $[RuCl_2(CHPh)\{P(C_6H_{11})_3\}_2]$ (**1**), benzene, 60 °C, 36 h; d) $CH_2{=}CHCH_2MgCl$, THF, 2 h.

In conclusion we have shown that ring-closing metathesis is an effective method for the annulation of glucose derivatives. Further studies are underway on the utilization of the enantiomerically pure annulated products in organic synthesis.

Experimental Section

All rections were performed under nitrogen. Solvents were dried by using standard methods. The yields reported refer to products purified by column chromatography.

Typical synthetic procedure for the ruthenium catalyzed RCM reaction: Nitrogen gas was bubbled for 2–3 minutes through a solution of the diolefin **7** (86 mg, 0.25 mmol) in benzene (10 mL). The catalyst **1** (4 mol%) was then added and the mixture heated at 60 °C for 17 h. The solvent was then removed under reduced pressure, and the crude reaction mixture purified by column chromatography (silica gel, petroleum ether (40–60 °C)/diethyl ether (3/1 → 2/1) to yield the cyclohexaannulated sugar derivative **9** as a colorless oil (63 mg, 80%).

Physical and spectroscopic data for **9**: $[\alpha]_D^{18} = +8.8$ ($c = 6.0$ in $CHCl_3$); $R_f =$ 0.13, petroleum ether (40–60 °C)/diethyl ether (1/1); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.51-7.33$ (m, 5H, Ph), 5.76 (m, 1H, 9-H), 5.60 (m, 1H, 8-H), 5.53 (s, 1H, 11-H), 4.39 (s, 1H, 1-H), 4.25 (dd, $J = 3.6$, 9.0 Hz, 1H, 6 eq-H), 3.93–3.77 (t, $J = 9.0$ Hz, 1H, 6 ax-H; m, 1H, overlapping, 5-H), 3.65 (t, $J =$ 10.6 Hz, 1H, 4-H), 3.41 (s, 3H, OMe), 2.60 (m, 1H, C*H*H, 7-H), 2.47 (m, 1H, C*H*H, 10-H), 2.16 (dt, $J = 5.2$, 10.6 Hz, 1H, 3-H), 2.04 (s, 1H, O*H*), 2.02 (m, 1H, overlapping, CH*H*, 10-H), 1.86 (dd, $J = 4.4$, 18.2 Hz, 1H, CH*H*, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 138.2$ (C, Ph), 129.3 (CH, Ph), 128.6 (CH, Ph), 126.5 (CH, Ph), 126.1 (CH, C9), 123.5 (CH, C8), 103.3 (CH, C1), 102.3 (CH, C11), 80.2 (CH, C4), 71.9 (C, C2), 69.7 (CH_2, C6), 64.5 (CH, C5), 55.5 (CH_3, OMe), 37.6 (CH, C3), 34.3 (CH_2, C7), 24.4 (CH_2, C10); HR-MS (FAB): *m/z* (%): 319 (34) [*M*H$^+$]; calcd for $C_{18}H_{23}O_5$ [*M*H$^+$]: 319.1546; found: 319.1544.

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Catalytic Mechanism of the Metal-Free Hydrogenase from Methanogenic Archaea: Reversed Stereospecificity of the Catalytic and Noncatalytic Reaction**

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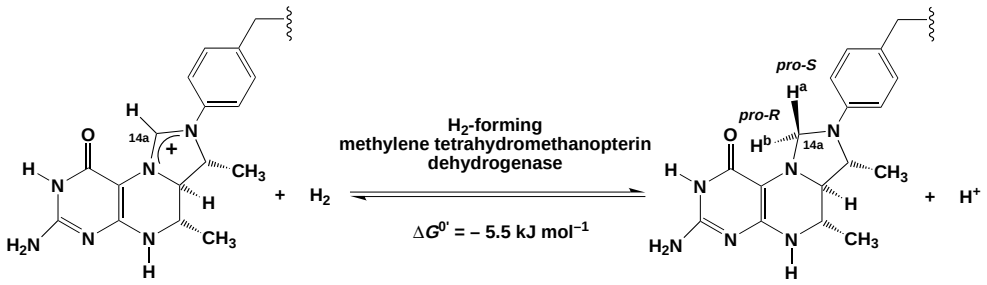
Hydrogenases are enzymes that catalyze reactions with molecular hydrogen (H_2) either as substrate or as product.[1] They usually contain a redox-active nickel/iron or iron center that binds and activates H_2. Typically hydrogenases also contain several iron–sulfur clusters that transfer electrons to an electron acceptor.[2–4] In addition, most methanogenic archaea express a metal-free hydrogenase which, therefore, can neither activate H_2 nor catalyze electron transport.[5] All available evidence indicates that this enzyme activates the hydrogen acceptor, which then directly reacts with H_2.[6]

The metal-free hydrogenase catalyzes the reversible reduction of N^5,N^{10}-methenyl tetrahydromethanopterin (methenyl-H_4MPT, **1**) with H_2 to N^5,N^{10}-methylene tetrahydromethanopterin (methylene-H_4MPT, **2**; $\Delta G^{\circ\prime} = -5.5$ kJ mol^{-1}; Scheme 1).[7] This reaction is involved in the reduction of CO_2 with H_2 to form CH_4 in methanogenic archaea.[8, 9] The enzyme catalyzes a direct hydride transfer from H_2 into the *pro-R* position of **2**.[10] In addition, the enzyme catalyzes an exchange of the hydrogen atom in the *pro-R* position of **2** with the protons of water,[11] a methenyl-H_4MPT-dependent exchange of H_2 with the solvent,[12, 13] and a methenyl-H_4MPT-dependent *ortho/para* H_2 conversion.[14] These properties of metal-free hydrogenase are accounted for in the catalytic mechanism proposed in Scheme 2.[6] The mechanism is based



1 **2**

Scheme 1. The reaction catalyzed by the metal-free hydrogenase. For complete structures of **1** and **2** including sidechains, see references [5, 10].

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