From Carbohydrates to Polyoxygenated Cyclooctenes via Ring-Closing Metathesis

François-Didier Boyer,[†] Issam Hanna,*[,‡] and Steven P. Nolan[§]

Unité de Phytopharmacie et Médiateurs Chimiques, I.N.R.A., Route de Saint-Cyr, F-78026 Versailles, France, Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau, France, and Department of Chemistry, University of New Orleans, Louisiana 70148

hanna@poly.polytechnique.fr

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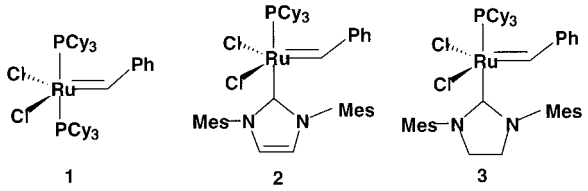
The construction of eight-membered rings, present in many biologically active natural products, remains a prominent synthetic challenge owing to the difficulties associated with cyclooctane chemistry.[1] Of all ring sizes, the formation of these compounds by intramolecular ring closure reactions is the most difficult. Despite the unfavorable thermodynamic factors that impede the preparation of eight-membered rings, the olefin ring-closing metathesis reaction (RCM)[2] has been successfully applied to the synthesis of carbocyclic rings of this size.[3] The presence in the substrates of conformational constraints, such as preexisting rings, greatly facilitated the assembly of cyclooctyl derivatives. In some cases the commercially available Grubbs ruthenium catalyst **1** has been shown to be of great efficiency.[4] In contrast, previous attempts to cyclize conformationaly flexible acyclic dienes to eight-membered carbocycles using **1** have proven unsuccessful. It has been shown that the replacement of one of the phosphine ligands in **1** with a sterically demanding nucleophilic carbene (e.g., *N*,*N*′-bis(mesityl)imidazol-2-ylidene, IMes) to yield **2**[5] leads to increased ring-closing activity. This catalyst and its saturated imidazol-2-ylidene analogue **3**[6] have been applied to several handicapped cases where they displayed activity beyond that of the parent complex **1**.[7]



Carbohydrate to carbocycle transformations offer an attractive route for the synthesis of optically active natural products.[8] Although a wide range of methods for producing functionalized five-, six-, and seven-membered rings from sugars are available,[9,10] only two reports have been published on the preparation of cyclooctenes using Claisen rearrangement of 2-methylene-C-vinyl glycosides.[11] In an extension of our previous work on the synthesis of medium-sized rings from carbohydrates,[12] we report here studies dealing with substitution pattern effects on the construction of polyoxygenated cyclooctenes by RCM reaction and a comparative investigation of the reactivity of catalysts **1** and **2**.

The RCM precursors were prepared from methyl 6-deoxy-6-iodoglycosides **8a**−**c**[13] as illustrated in Scheme 1. Reductive ring-opening with zinc dust under sonication converted **8** to aldehyde **9** in nearly quantitative yield. Treatment of **9** with butenylmagnesium bromide at −60 °C in THF and subsequent protection of the resulting alcohol **10** afforded acetate **11** in 63−77% overall yield from **8**. While addition of the Grignard reagent to **9b** (R = TBDMS) in ether gave a single alcohol, this reaction has been found less stereoselective in THF and led, after protection, to **11b** as a mixture of diastereomers in 1.3:1 ratio. In the same manner **11a** (R = Bn) and **11c** [R = triethylsilyl (TES)] were obtained as a mixture of dia-

[†] Unité de Phytopharmacie et Médiateurs Chimiques, I.N.R.A.
[‡] Ecole Polytechnique.
[§] University of New Orleans.

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Scheme 1

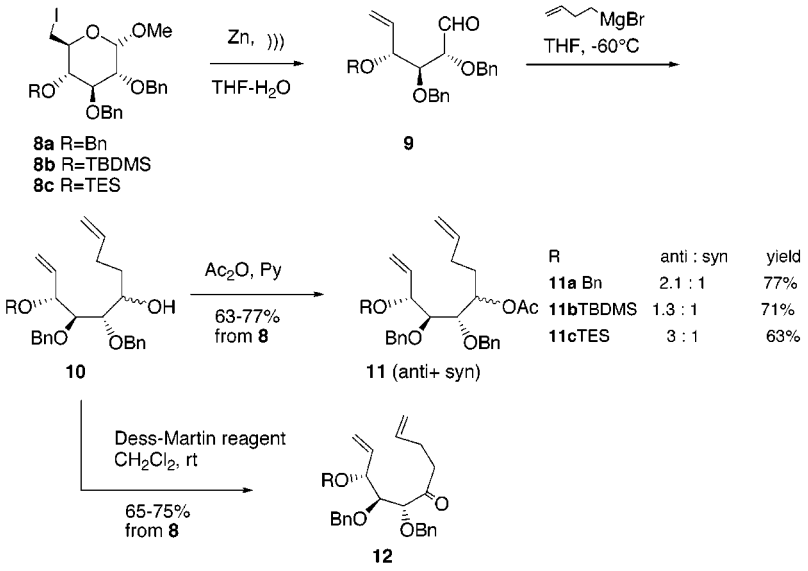
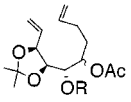
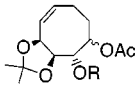
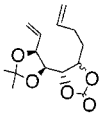
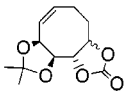
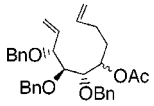
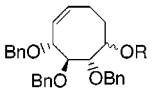
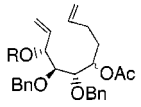
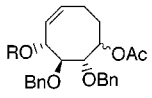
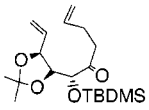
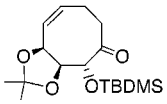
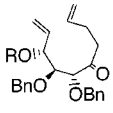
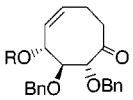


Table 1. RCM for Cyclooctene Derivatives Using Catalysts 1 or 2

Entry	Diene	Catalyst (%), time	Cyclooctene	Yield[a]
				
1	**13** R=Ac	**1** (7%), 2h[b]	**23** R=Ac	93[d]
2	**14** R=TBDMS	**1** (5%), 2h[b]	**24** R=TBDMS	94[d]
				
3	**15**	**1** (5%), 2h[b]	**25**	96[d]
				
4	**16a** (isomer syn)	**1** (10%), 3h[b]	**26a** R=Ac (cis)	96
5	**16b** (isomer anti)	**1** (10%), 18h[b]	**26b** R=Ac (trans)	49
6		**1** (10%), 18h[c]	**26b**	40
7	**16b**	**2** (10%), 5.5h[c]	MeONa, MeOH → **27b** R=H	95
				
8	**17** R=TBDMS	**2** (6%), 2.5h[c]	**28** R=TBDMS	95
9	**18** R=TES		**29** R=TES	94
				
10	**19**	**1** (13%), 21h[b]	**30**	68
11	**19**	**2** (10%), 1.5h[b]	**30**	86
				
12	**20** R=Bn	**2** (10%), 22h[b]	**31** R=Bn	66
13	**21** R=TBDMS		**32** R=TBDMS	67
14	**22** R=TES		**33** R=TES	68

[a] Isolated yield. [b] In refluxing dichloromethane. [c] In refluxing benzene. [d] Reference 12.

stereomers in 2.1:1 and 3:1 ratios, respectively. The anti configuration of the new asymmetric center in the major isomer was assigned on the basis of the RCM reaction product (vide infra). On the other hand, oxidation of the crude alcohols **10** with the Dess−Martin periodinane reagent[16] furnished ketones **12** in 65−75% overall yield from **8**.

The dienes prepared above were submitted to RCM in $(3-6) \times 10^{-3}$ M solution in dichloromethane or benzene. For dienes **13**−**18** (Table 1), the reaction was carried out either separately on each diastereomer or on the mixture. In the latter case, the separation was undertaken at this stage. It is worthy of note that, except for diene **16**, both diastereomers led to the cyclized products roughly in the same yield.

As can be seen from the results compiled in Table 1, dienes **13**−**15** bearing one or two acetonide groups gave the corresponding cyclooctenes **23**−**25** in excellent yield using Grubbs catalyst **1** in refluxing dichloromethane.[12] The same catalyst has been found efficient for the cyclization of the syn acetate **16a**, affording **26a** in 96% yield. However, when the isomer anti **16b** was treated with catalyst **1** (10 mol %) either in refluxing dichloromethane or benzene for 18 h, the cyclized product **26b** was obtained in modest yield (49 and 40%, respectively). In contrast, catalyst **2** in refluxing benzene converted **16b** into **26b** in 95% yield (Table 1, entries 4−7). Hydrolysis of this isomer (MeONa, MeOH, rt) led to the cyclooctenol derivative **27b** which is identical to the product described by Sinaÿ et al.[11a] Thus the anti configuration of the acetate group in this compound is established.

Treatment of diene **17**, in which the allylic benzyloxy group (OBn) was replaced by *tert*-butyldimethylsilyloxy (OTBDMS), with catalyst **1** (10%) in refluxing CH_2Cl_2 for 24 h gave the corresponding dimer (mixture of *Z* and *E* isomers) as the only isolated product in 64% yield. At higher temperature (refluxing benzene), **17** led to a mixture of the desired cyclooctene **28** and the dimerization product together with unreacted starting material. The same results were obtained with diene **18**. A resolution of this problem was provided by the use of catalyst **2**. In fact, treatment of **17** and **18** with 6% of **2** in refluxing benzene for 2.5 h delivered **28** and **29**, respectively, in 95% and 94% yields (entries 8 and 9).

The RCM reactions of dienones **19**−**22** were next investigated. Treatment of **19** with **1** in refluxing dichloromethane (13 mol %) for 21 h afforded cyclooctenone **30** in 68% yield (entry 10). Use of catalyst **2** (10 mol % in refluxing CH_2Cl_2 for 1.5 h) increased the yield to 86%. In the cases of dienones **20**−**22** only the use of catalyst **2** allowed the preparation of corresponding cyclooctenones in synthetically useful yields (66−68%) (entries 12−14). Obviously, the easier reaction with **19** is the result of the presence of the acetonide group which acts as a conformational constraint. The lower reactivity of ketodienes **20**−**22** compared to the corresponding acetates **16**−**18** suggested that carbonyl group might coordinate to the ruthenium metal center, as does free hydoxyl group,[17] changing catalyst properties.

In summary, we have developed a concise route to polyoxygenated cyclooctenes from carbohydrates using the ring-closing metathesis. In this reaction, 1,3-bis-(mesityl)imidazol-2-ylidene ruthenium complex **2** shows enhanced RCM activity compared to its parent **1**. Even in the absence of the acetonide group which acts as a conformational contraint, catalyst **2** has been found efficient for the eight-membered ring annulation.

Supporting Information Available: Experimental procedure and characterization data for compounds **23**−**26b** and **28**−**33**. This material is available free of charge via Internet at http://pubs.acs.org.

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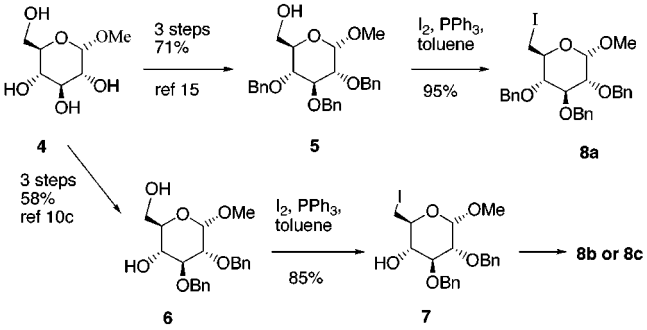
(13) Compounds **8a**−**c** were prepared by the known procedures starting from methyl-α-D-glucopyranoside **4** as indicated in the following scheme. Compounds **7** and **8a** were obtained by iodination with PPh_3-I_2 reagent,[14] **8b** and **8c** from **7** by silylation with TBDMSOTf or TESOTf in 2,6-lutidine−CH_2Cl_2.



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