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Synthesis of Polyoxygenated Bicyclic Systems Containing Medium-Sized Rings from Carbohydrates via Tandem Metathesis of Dienynes

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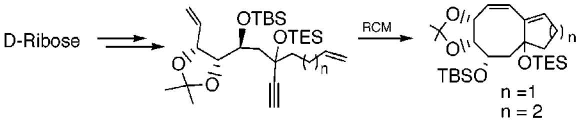
ABSTRACT



Highly functionalized (5-7), (5-8), and (6-8) ring systems have been prepared from carbohydrates via tandem ring-closing metathesis of dienynes.

Bridged and fused bicyclic systems containing medium-sized rings are widely found in biologically active natural products, and development of new synthetic approaches to these skeletons continues to be an important goal.[1,2]

Since the pioneering work by the groups of Grubbs and Schrock, the ring-closing metathesis (RCM) reaction of dienes[3] and to a lesser extent of enynes[4] has become a powerful tool for the synthesis of a variety of cyclic structures, especially for medium-sized and macrocyclic ring systems, which would be difficult to achieve, if at all, using traditional methods.[5] In comparison, the tandem dienyne metathesis reaction leading to bicyclic compounds is less well documented. The few examples reported are confined to the assembly of compounds containing unsubstituted or alkyl-substituted dienynes.[6] An account describing the formation of a bicyclic system incorporating an eight-membered ring by RCM of dienynes has only recently been reported.[7] Our previous work on the preparation of polyoxygenated medium-sized carbocycles from carbohydrates[8] led us to focus on the construction of polyfunctionalized carbobicyclic products that contain seven- and eight-membered rings by tandem RCM of dienynes using Grubbs' ruthenium catalysts **1**[9] and **2**[10] as indicated in Figure 1.

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(1) For reviews on eight-membered ring carbocycle construction see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.

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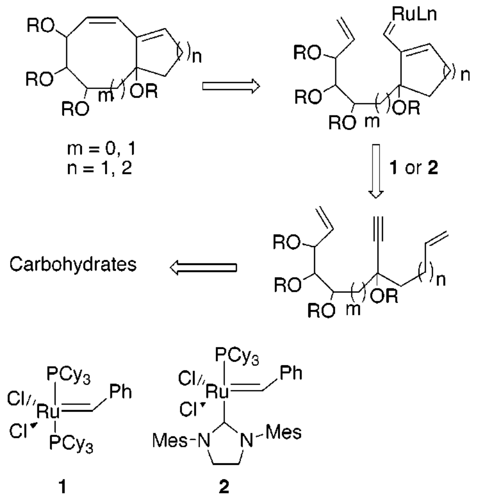
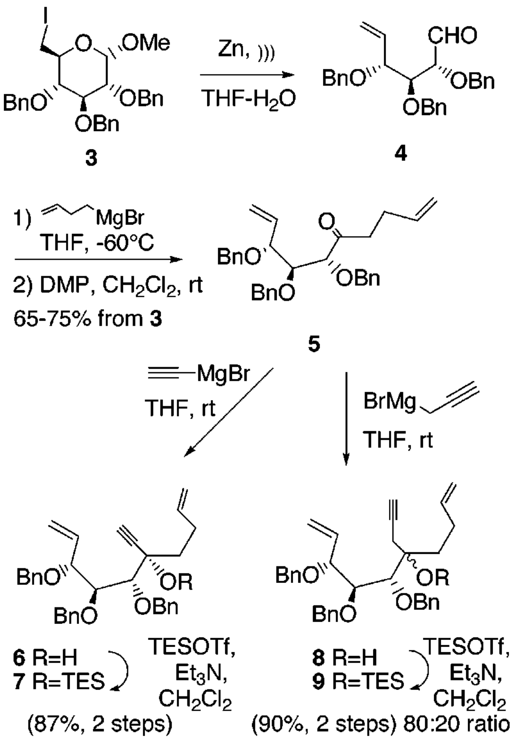


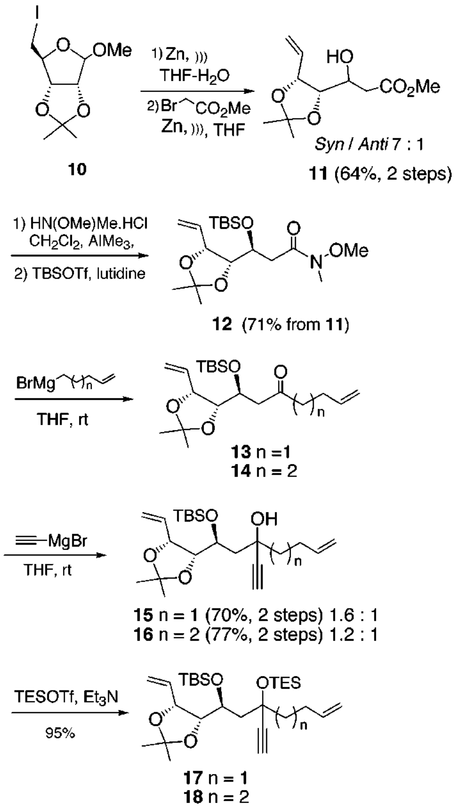
Figure 1.

The polyoxygenated dienynes used in this study were readily prepared from (+)-glucose and (+)-ribose as illustrated in Schemes 1 and 2. Reductive ring-opening with zinc dust under sonication converted **3** to aldehyde **4** in nearly quantitative yield. Treatment of **4** with butenylmagnesium bromide at −60 °C followed by Dess−Martin oxidation of the resulting crude alcohols furnished **5** in 65−75% overall yield from **4**[8c] (Scheme 1). Ketone **5** reacted with excess ethynylmagnesium bromide in THF at room temperature, presumably via a chelation-controlled transition model, to give **6** as the only isolated diastereomer. The configuration of the hydroxyl group at the newly created chiral center in **6** was tentatively assigned to be *syn* in agreement with the stereochemical outcome of the addition of Grignard reagents to α-alkoxy carbonyl compounds.[11] Addition of propargylmagnesium bromide to **5** was less stereoselective, affording **8** as a mixture of diastereomers in a 80:20 ratio. Hydroxyl groups of **6** and **8** were then protected as the triethylsilyl ethers **7** and **9** in 87% and 90% overall yields, respectively.

Scheme 1



Scheme 2



Dienyne precursors to the (5-8) and (6-8) ring systems were prepared as depicted in Scheme 2. Zinc-mediated reductive ring opening of **10**[12] in aqueous THF followed by treatment of the resulting aldehyde with methyl bromoacetate under the Reformatsky reaction conditions led to **11** as a diastereomeric mixture (7:1) in 64% yield. These isomers could be separated by flash column chromatography, and the *syn* configuration of the major isomer was assigned as above and confirmed later on the basis of the RCM reaction product (vide infra). The major diastereomer was used for the rest of the synthetic sequence. This *β*-hydroxy ester was uneventfully converted to the Weinreb amide[13] **12** in the

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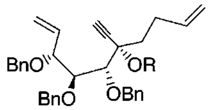
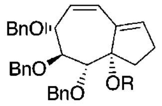
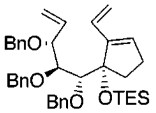
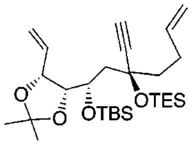
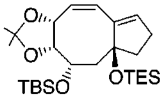
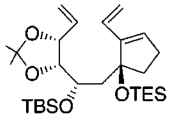
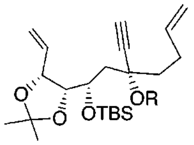
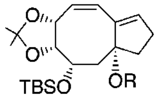
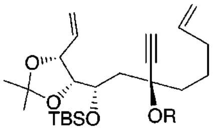
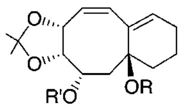
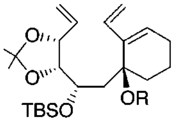
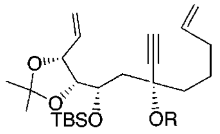
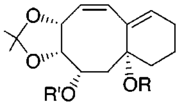
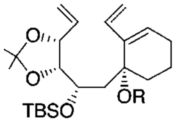
Table 1. Ring-Closing Metathesis of Dienynes

entry	dienyne	catalyst (%), time	product (Yield %^{a})	
				
1	**6** R=H	**1** (10%), 17h^b	**19** R=H (64)	—
2	**6**	**2** (10%), 6h^b	**19** (95)	—
3	**7** R=TES	**1** (10%), 17h^b	**20** R=TES (77)	**21** (11)
4	**7**	**2** (10%), 6h^b	**20** (96)	—
				
5	**17a**	**1** (20%), 28h^{b,c}	—	**23** (85)
6	**17a**	**2** (10%), 24h^b	**22** (94)	—
				
7	**15b** R=H	**2** (10%), 23h^b	**24** R=H (79)	
8	**17b** R=TES	**2** (10%), 17h^b	**25** R=TES (96)	
				
9	**16a** R=H	**2** (10%), 3d^b	—	**27** R=H (61) + SM (21)
10	**18a** R=TES	**2** (10%), 3d^{b,c}	**26** R=TES TBAF THF, rt → **29** R=H (41)	+ **28** R=TES + **27** R=H (46)
				
11	**16b** R=H	**2** (10%) 2.5d^b	**30** R=H , R'=TBS (53)	**31** R=H (36)
12	**18b** R=TES	**2** (10%) 5h^b	**32** R=TES, R'=TBS (96) TBAF THF, rt → **33** R=R'=H	—

^{a}isolated yield. ^{b}in refluxing dichloromethane. ^{c}in refluxing benzene.

usual manner in 71% yield. Treatment of **12** with butenylmagnesium bromide or pentenylmagnesium bromide at 0 °C in THF afforded ketones **13** and **14**, respectively. Addition of ethynylmagnesium bromide to these ketones gave alcohols **15** and **16** as easily separable mixtures of diastereomers in 1.6:1 and 1.2:1 ratios, respectively, in good overall yields. These alcohols were then protected as their triethylsilyl ethers **17** and **18**.

The dienynes prepared above were subjected to RCM reactions using commercially available catalysts **1** or **2**[14] as 3.5 × 10^{-3} M solutions in refluxing dichloromethane or benzene; the results are summarized in Table 1.

As shown in the Table, the fused (5-7) ring system could be obtained either from alcohol **6** or from its triethylsilyl ether **7** using catalysts **1** or **2** (entries 1−4). As expected, the tandem RCM reaction using catalyst **2** proceeded much faster than with its parent complex **1** and converted **6** and **7** to the corresponding bicyclic[5.3.0] compounds **19** and **20** in significantly improved yields.[15]

A more dramatic illustration of the difference in RCM activity of complexes **1** and **2** was observed during the construction of fused (5-8) and (6-8) bicyclic cores. Initial attempts on dienyne **17a** (the major isomer) using catalyst **1** (20%) in either refluxing CH_2Cl_2 or benzene for 17 h failed to give the corresponding polyoxygenated fused bicyclic compound. Instead the monocyclic compound **23** was obtained as the only isolated product in 85% yield (entry

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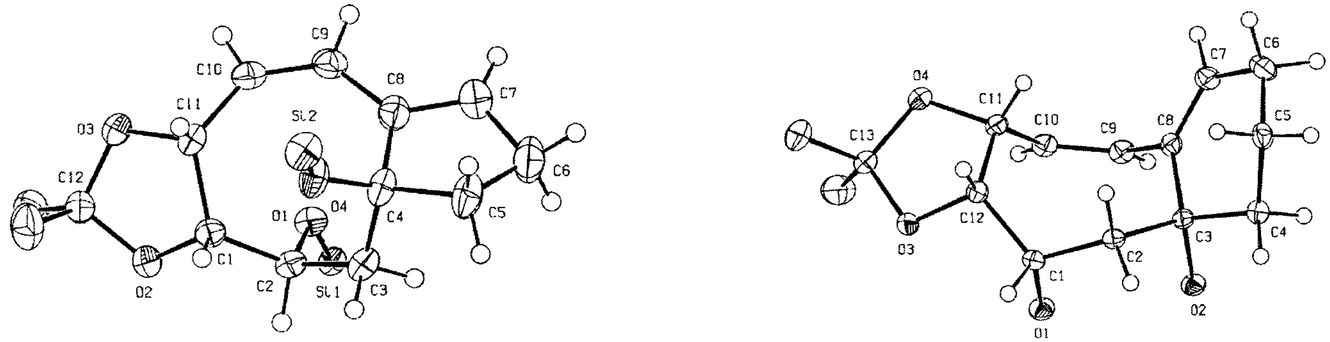
(14) Catalysts **1** and **2** were purchased from Strem Chemicals, Inc.

(15) Whereas triethylsiyl ether **20** is stable enough to be stored in the refrigerator for weeks, the free alcohol **19** was found to be rather labile and easily decomposed.



ORTEP drawing of **22**
(For purpose of clarity alkyl groups on silicon atoms are omitted)

ORTEP drawing of **33**

Figure 2. X-ray structures of **22** and **33**.

5). In contrast, the use of catalyst **2** (10% in refluxing CH_2Cl_2 for 24 h) converted **17a** into the desired bicyclic[6.3.0] derivative **22** in 94% yield. This bicyclic structure was assigned on the basis of spectroscopic data, and the configurations of OTBS (α) and OTES (β) groups were obtained by X-ray crystallographic analysis (Figure 2). Under the same conditions the minor isomer **17b** underwent the tandem cyclization affording **25** (α-OTES) in 96% yield. Interestingly, the corresponding free alcohol **15b** was also successfully converted to the bicyclic compound **24**, albeit in lower yield (entry 7).

Construction of the fused (6-8) ring systems was next investigated. Treatment of dienyne **18a** (the major isomer) with catalyst **2** (10 mol %) in refluxing dichloromethane or benzene for 3 days gave an inseparable mixture of **26** and **28**. For separation purpose the TES ether was selectively cleaved (TBAF, THF, rt) leading to the easily separated bicyclic alcohol **29** and the cyclohexene derivative **27** (1:1 ratio) in 87% overall combined yield (entry 10). Under the same conditions, the corresponding free alcohol **16a** gave **27** (66%) together with the starting material (21%). In sharp contrast, the minor isomer **18b**, on treatment with catalyst **2** (10%) in refluxing CH_2Cl_2 for only 5 h smoothly underwent the tandem RCM reaction leading to the fused (6-8) bicyclic product **32** in an almost quantitative yield. This substrate was readily desilylated (TBAF, THF, rt) to furnish diol **33** as a crystalline compound that was confirmed by X-ray analysis (Figure 2).

Attempts at tandem RCM reaction on the free alcohol **16b** with catalyst **2** in refluxing CH_2Cl_2 for a prolonged time led to the bicyclic compound **30** together with the cyclohexene derivative **31** in 53% and 36% yields, respectively (entry 11).

The notable difference in reactivity of dienyne **18a** in comparison to its epimer **18b** toward the tandem RCM reaction is unclear at present. However, it is likely that the formation of the (6-8) bicyclic product **26** from **18a** is thermodynamically unfavorable. Molecular model of this compound showed severe transannular interactions due to the bulky OTES group in the β position. Such an effect does not exist in the corresponding α-OTES compound **32** (Figure 2).

In summary, we have shown that highly functionalized carbobicyclic systems containing seven- and eight-membered rings can be prepared in very good yields from carbohyrates via tandem ring-closing metathesis of dienynes. Further studies on the application of these results to target orientated synthesis are currently under investigation.

Supporting Information Available: Characterization data for compounds **6**, **7**, **9**, **15**−**25**, **27**, **29**, **31**−**33** and X-ray crystal data for compounds **22** and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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