

# From Galactose to Highly Functionalized Seven- and Eight-Membered Carbocyclic Rings by Ring-Closing Metathesis

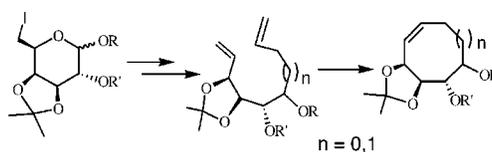
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## ABSTRACT



A short synthesis of highly functionalized seven- and eight-membered carbocyclic rings from galactose derivatives has been achieved. The key steps are a zinc-mediated reductive ring opening of 6-iodogalactopyranoses and a subsequent ring-closing olefin metathesis using Grubbs' ruthenium catalyst.

Carbohydrate to carbocycle transformations offer an attractive route for the synthesis of optically active natural products. Although a wide range of methods for producing functionalized cyclohexane and cyclopentane derivatives from sugars are available,<sup>1,2</sup> few reports have been published on the preparation of medium sized (seven- and eight-membered) carbocyclic rings.<sup>3,4</sup> The interest in the construction of such rings is largely due to their presence in an increasing number of biologically active compounds.

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(1) For reviews see: (a) Dalke, D. I.; Sinay, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 773. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.

(2) For recent examples, see: (a) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195. (b) Sollogoub, M.; Mallet, J.-M.; Sinay, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 362. (c) Kan, T.; Nara, S.; Ozawa, T.; Shirahama, H.; Matsuda, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 355. (d) Collam, C. S.; Lowry, T. L. *Org. Lett.* **2000**, *2*, 167. (e) Hyltöf, L.; Poulsen, C. S.; Madsen, R. *Chem. Commun.* **1999**, 2101. (f) Kornienko, A.; d'Alarcao, M. *Tetrahedron: Asymmetry* **1999**, *10*, 827. (g) Ovaa, H.; Codée, J. D. C.; Lastrager, B.; Overkleeft, H. S.; van der Marel, G.; van Boom, J. *Tetrahedron Lett.* **1999**, *40*, 5063.

(3) For the synthesis of cycloheptane derivatives from carbohydrates, see: (a) Marco-contelles, J.; de Opazo, E. *Tetrahedron Lett.* **1999**, *40*, 4445; *Tetrahedron Lett.* **2000**, *41*, 2439. (b) Boyer, F.-D.; Lallemand, J.-Y. *Tetrahedron* **1994**, *50*, 10443. (c) Duclos, O.; Duréault, A.; Depeyaz, J. C. *Tetrahedron Lett.* **1992**, *33*, 1059 and 8061.

(4) For the synthesis of cyclooctane derivatives from sugars, see ref 2b and Werschum, B.; Thiem, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2793.

In particular, cyclooctanoid natural products remain prominent synthetic challenges owing to the difficulties associated with cyclooctane chemistry.<sup>5</sup>

Ring-closing metathesis (RCM) has emerged as one of the most popular methods for the construction of unsaturated cyclic systems from acyclic dienes.<sup>6</sup>

Despite the unfavorable thermodynamic factors that impede the preparation of eight-membered rings, this method has been successfully applied to the synthesis of carbocyclic rings of this size.<sup>7</sup> Herein we describe the use of this reaction in a flexible approach to unsaturated medium-carbocyclic rings from readily available galactose derivatives, using

(5) For reviews, see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 81.

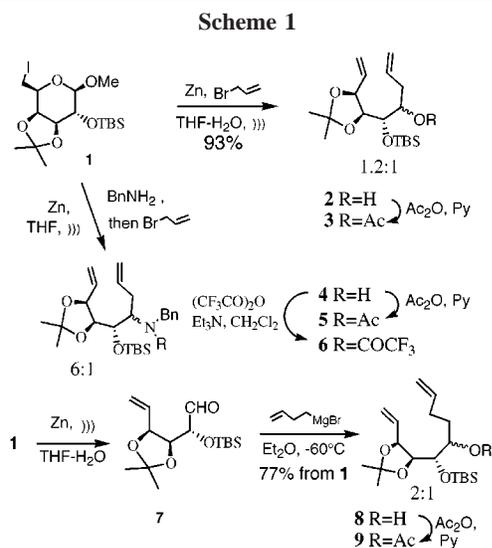
(6) For recent reviews concerning ring-closure metathesis reactions, see (a) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(7) For earlier examples of cyclooctene syntheses by RCM, see: ref 6. For more recent applications, see: (a) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Méndez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259. (b) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742 and references therein. (c) Bourgeois, D.; Pancrazi, A.; Ricard, L. P.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 726. For recent reports on the synthesis of cyclic ethers of eight-membered ring, see: Clark, J. S.; Mamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372. Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.

Grubbs' commercially available ruthenium catalyst [(PCy<sub>3</sub>)<sub>2</sub>-Cl<sub>2</sub>Ru=CHPh].

The RCM precursors were prepared from either methyl 6-deoxy-6-iodo-3,4-isopropylidene-2-*O*-(*tert*-butyldimethylsilyl)-D-galactopyranoside **1**<sup>8</sup> or from 6-deoxy-6-iodo-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside **10**.<sup>9</sup>

Zinc-mediated reductive ring opening of **1** under sonication in aqueous THF in the presence of allyl bromide cleanly afforded diene **2** in 93% yield as a mixture of *syn* and *anti* (1.2:1) isomers separable by flash chromatography.<sup>10</sup> On the other hand, a one-pot reductive ring opening, amination, and allylation of **1** was achieved with zinc dust in the presence of benzylamine followed by the addition of allyl bromide in anhydrous THF under sonication<sup>11</sup> and led to amino diene **4** as a 6:1 mixture of diastereomers in 65% yield. In this transformation, the intermediate aldehyde **7** was intercepted with the amine prior to the alkylation. In fact, in the absence of amine or the alkylating agent, reductive ring opening of **1** gave **7** in nearly quantitative yield. Treatment of this compound with butenylmagnesium bromide at 0 °C afforded alcohol **8** as a mixture of diastereomers (2:1 ratio, 77% overall yield). Alcohols **2** and **8** and amine **4** were acetylated respectively to **3**, **5**, and **9** under standard conditions (Scheme 1).



The seven- and eight-membered ring precursors **12**–**17** were constructed starting from **10** as illustrated in Scheme 2.

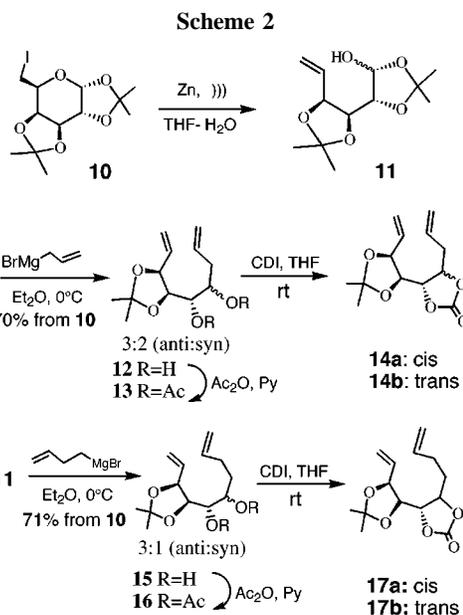
(8) Compound **1** was prepared from methyl 3,4-*O*-isopropylidene-D-galactopyranoside in two steps by iodation with PPh<sub>3</sub>-I<sub>2</sub> reagent followed by silylation with TBSOTf in 2,6-lutidine/CH<sub>2</sub>Cl<sub>2</sub>. Chiara, J. L.; Martinez, S.; Bernabé, M. *J. Org. Chem.* **1996**, *61*, 6488.

(9) Compound **10** is readily prepared by iodation of the commercially available 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose: Garegg, P. J.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 681.

(10) All new compounds were characterized by analytical and spectroscopic data. Yields are for isolated, chromatographically purified products.

(11) See ref 2e. We thank professor Robert Madsen for experimental details for the preparation of amino diene **4**.

(12) Table 2 in ref 6b points to the ease of closing seven-membered monocycles as compared with the formation of cyclooctenes.



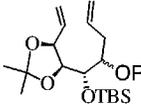
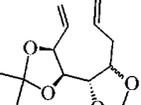
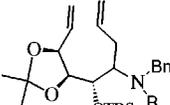
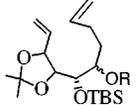
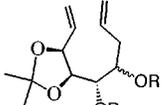
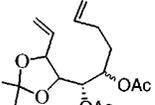
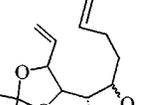
2. Reductive ring opening with zinc dust under sonication converted **10** to the hitherto unknown hemiketal **11** as a mixture of diastereomers, which was treated with allylmagnesium bromide to afford **12** as a 3:2 separable mixture of diastereomers in 70% overall yield. The *syn* configuration of the minor isomer was assigned later on the basis of the X-ray structure of the RCM reaction product **25a**. It is worthy of note that when this transformation was performed in a one-pot procedure under the Barbier conditions as above, a mixture of products was obtained from which the desired product **12** was isolated in low yield. This diol was converted into diacetate **13** (Ac<sub>2</sub>O, Py, rt) or cyclic carbonate **14** (1,1'-carbonyldiimidazole, THF, rt) in high yields.

Similarly, reaction of **11** with butenylmagnesium bromide at 0 °C in ether gave diene **15** as a 3:1 mixture of diastereomers in 71% yield from **10**. In this case, the stereochemistry of the vicinal diol in the major isomer has been found to be *anti* on the basis of the X-ray structure of cyclized products **28b** and **29b**. The diol moiety was then protected either as diacetate **15** or the cyclic carbonate **16** as shown in Scheme 2.

The dienes prepared above were submitted to RCM using 5–7% Grubbs' catalyst in CH<sub>2</sub>Cl<sub>2</sub>, and the results are summarized in Table 1. In this study, the metathesis reaction was carried out either separately on each diastereomer of dienes or on the mixture. In the latter case, the separation was undertaken at this stage. Except for carbonates **14**, both diastereomers led to the cyclized products roughly in the same yield. As expected,<sup>12</sup> carbocyclization of dienes **2**, **3**, **5**, **6**, and **13** was readily achieved at room temperature with 5% catalyst to furnish substituted cycloheptenes in excellent yield. Under these conditions, diol **12** and amino diene **4** failed to give any cyclization product (Table 1). Amino-

(13) See ref 3 and Pearson, A. J.; Katiyar, S. *Tetrahedron* **2000**, *56*, 2297. Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615.

**Table 1.** Substituted Cycloheptenes and Cyclooctenes by RCM with Grubbs' Catalyst in CH<sub>2</sub>Cl<sub>2</sub>

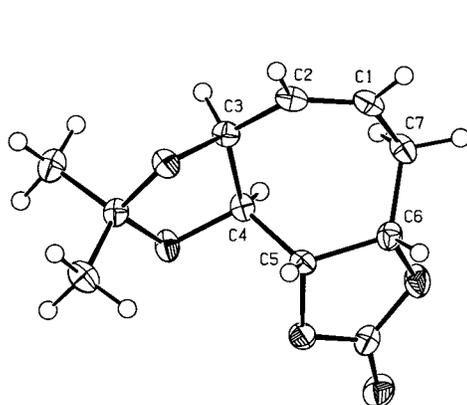
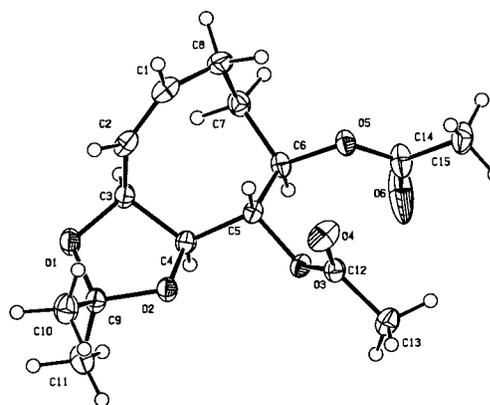
diene	% cat., temp	product	yield (%)	diene	% cat., temp	product	yield (%)
	<b>2</b> R=H <b>3</b> R=Ac	<b>18</b> R=H <b>19</b> R=Ac	92 97		5%, rt 10%, rt	<b>25a</b> cis <b>25b</b> trans	95 82
	<b>4</b> R=H <b>5</b> R=Ac <b>6</b> R=COCF <sub>3</sub>	<b>20</b> R=H <b>21</b> R=Ac <b>22</b> R=COCF <sub>3</sub>	— 98 93		5%, 40°C	<b>26</b> R=H <b>27</b> R=Ac	— 94
	<b>12</b> R=H <b>13</b> R=Ac	<b>23</b> R=H <b>24a</b> R=Ac cis <b>24b</b> R=Ac trans	— 94		7%, 40°C	<b>28a</b> cis <b>28b</b> trans	93
					5%, 40°C	<b>29a</b> cis <b>29b</b> trans	96

polyhydroxylated cycloheptanes such as **21** and **22** may be used as intermediates in the synthesis of calystegines and related tropane alkaloids.<sup>13</sup>

RCM reaction of cis and trans cyclic carbonates **14a** and **14b** gave the corresponding cycloheptenes **25a** and **25b**, respectively, in high yield. However, while the conversion of the syn isomer **14a** was achieved after 2 h in the presence of 5% catalyst, cyclization of the trans isomer needed 10% catalyst and more than 24 h to be complete. The cis

configuration of **25a** was deduced from detailed NMR studies and confirmed by X-ray crystallographic analysis (Figure 1).

We turned next to the more problematic formation of the eight-membered ring. Exposure of diene **8** containing a free hydroxyl group to RCM conditions gave a mixture with predominant formation of a dimer. In contrast, the corresponding acetate **9** was successfully converted into cyclooctene **27** (5 mol % of catalyst, 0.006 M in CH<sub>2</sub>Cl<sub>2</sub> at reflux) in 94% yield. Under these conditions, protected diols

**ORTEP drawing of cycloheptene 25a****ORTEP drawing of cyclooctene 28b****Figure 1.** X-ray structures of **25a** and **28b**.

**16** and **17** led to cyclooctenes **28** and **29**, respectively, in excellent yield (Table 1). The structures of these compounds were assigned on the basis of spectroscopic data, and the relative stereochemistry of each was determined by X-ray crystallographic analysis of diacetate **28b** and cyclic carbonate **29b** (Figure 1 and Supporting Information).

In conclusion, we have described a rapid route to highly functionalized cycloheptenes and cyclooctenes involving zinc-mediated reductive ring opening of readily available

carbohydrate derivatives, followed by a ring-closing metathesis reaction using the commercially available Grubbs' catalyst.

**Supporting Information Available:** Spectroscopic data for compounds and **19**, **21**, **22**, **24a**, **24b**, **25a**, **25b**, **28b**, and **29b**. X-ray crystal data for compounds **25a**, **28b**, and **29b**. This material is free of charge via the Internet at <http://pubs.acs.org>.

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