ORGANIC LETTERS

2000
Vol. 2, No. 17
2651−2654

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

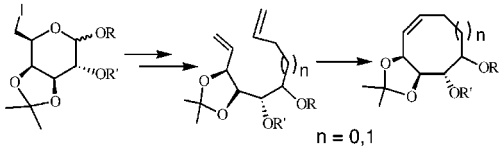
Issam Hanna*,† and Louis Ricard‡

Laboratoire de Synthèse Organique associé au CNRS and Laboratoire "Hétéroéléments et Coordination" associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau Cedex, France

hanna@poly.polytechnique.fr

Received June 9, 2000

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,[1,2] few reports have been published on the preparation of medium sized (seven- and eight-membered) carbocyclic rings.[3,4] The interest in the construction of such rings is largely due to their presence in an increasing number of biologically active compounds.

In particular, cyclooctanoid natural products remain prominent synthetic challenges owing to the difficulties associated with cyclooctane chemistry.[5]

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

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.[7] Herein we describe the use of this reaction in a flexible approach to unsaturated medium-carbocyclic rings from readily available galactose derivatives, using

† Laboratoire de Synthèse Organique associé au CNRS.
‡ Laboratoire "Hétéroéléments et Coordination" associé au CNRS.

(1) For reviews see: (a) Dalko, D. I.; Sinaÿ, 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.; Sinaÿ, 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) Hyldtof, 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.; Depezay, J. C. *Tetrahedron Lett.* **1992**, *33*, 1059 and 8061.

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

(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 concernig 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 syntesis 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.

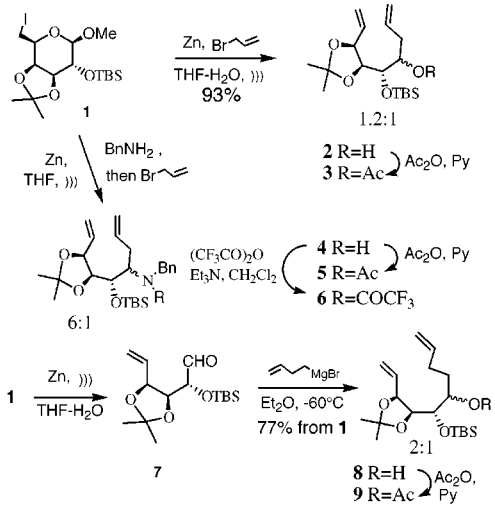
10.1021/ol006182j CCC: $19.00
Published on Web 07/27/2000

Grubbs' commercially available ruthenium catalyst [$(PCy_3)_2Cl_2Ru{=}CHPh$].

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

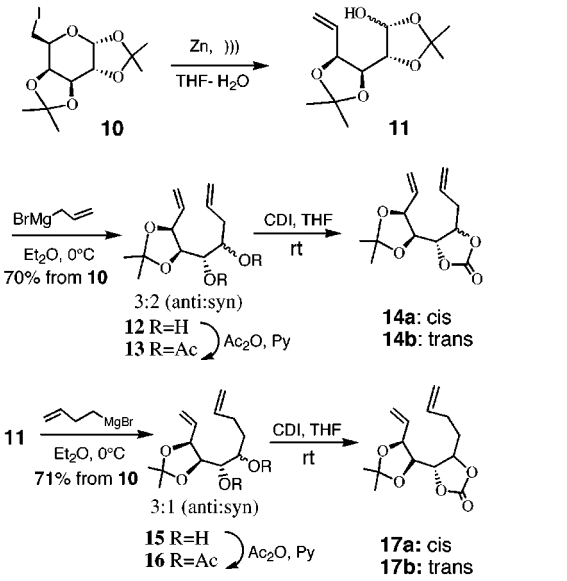
Zinc-mediated reductive ring opening of **1** under sonication in aqueous THF in the presence of allyl bromide cleanly afforded diene **2** in 93% yield as a mixture of syn and anti (1.2:1) isomers separable by flash chromatography.[10] On the other hand, a one-pot reductive ring opening, amination, 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[11] and led to amino diene **4** as a 6:1 mixture of diatereomers 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).

Scheme 1



The seven- and eight-membered ring precursors **12**−**17** were constructed starting from **10** as illustrated in Scheme 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 diatereomers 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 perfomed 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_2O, Py, rt) or cyclic carbonate **14** (1,1′-carbonyldiimidazole, THF, rt) in high yields.

Scheme 2



Similary, 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_2Cl_2, 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 sepration was undertaken at this stage. Except for carbonates **14**, both diastereomers led to the cyclized products roughly in the same yield. As expected,[12] 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-

(8) Compound **1** was prepared from methyl 3,4-*O*-isopropylidene-D-galactopyranoside in two steps by iodation with PPh_3-I_2 reagent followed by silylation with TBSOTf in 2,6-lutidine/CH_2Cl_2. 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.

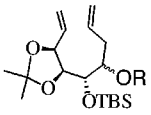
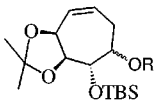
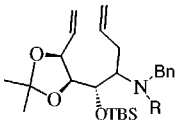
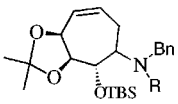
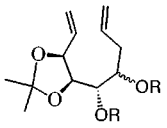
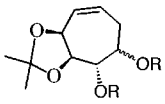
(10) All new compounds were characterized by analytical and spectroscopic data. Yields are for isolated, chromatographically purified products.

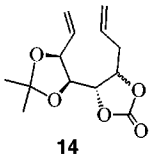
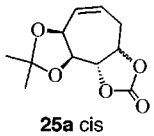
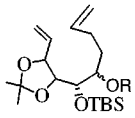
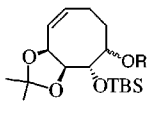
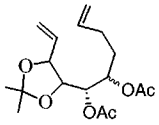
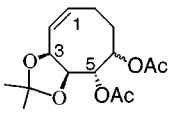
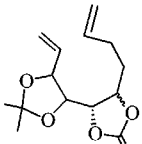
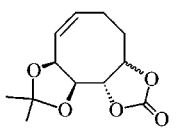
(11) See ref 2e. We thank professor Robert Madsen for experimental details for the preparation of amino diene **4**.

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

(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_2Cl_2

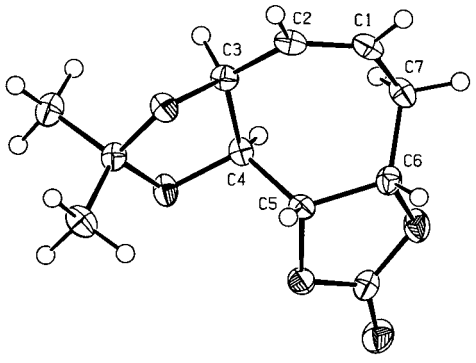
diene	% cat., temp	product	yield (%)
			
2 R=H **3** R=Ac	5%, rt 5%, rt	**18** R=H **19** R=Ac	92 97
			
4 R=H **5** R=Ac **6** R=$COCF_3$	5%, rt 5%, rt	**20** R=H **21** R=Ac **22** R=$COCF_3$	— 98 93
			
12 R=H **13** R=Ac	5%, rt	**23** R=H **24a** R=Ac cis **24b** R=Ac trans	— 94

diene	% cat., temp	product	yield (%)
			
14	5%, rt 10%, rt	**25a** cis **25b** trans	95 82
			
8 R=H **9** R=Ac	5%, 40°C	**26** R=H **27** R=Ac	— 94
			
16	7%, 40°C	**28a** cis **28b** trans	93
			
17	5%, 40°C	**29a** cis **29b** trans	96

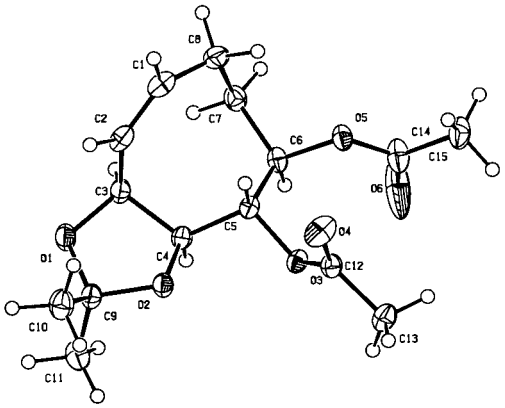
polyhydroxylated cycloheptanes such as **21** and **22** may be used as intemediates in the synthesis of calystegines and related tropane alkaloids.[13]

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 successfuly converted into cyclooctene **27** (5 mol % of catalyst, 0.006 M in CH_2Cl_2 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 carbohyrate 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.

OL006182J