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ARTICLE *in* ORGANIC LETTERS · OCTOBER 2002

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ORGANIC LETTERS

2002
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Synthesis of 2,6-Dideoxysugars via Ring-Closing Olefinic Metathesis

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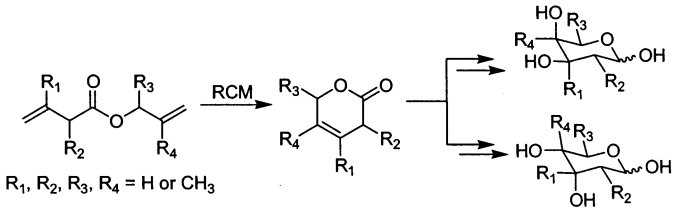
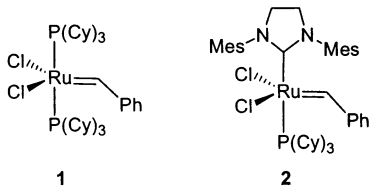
Received August 9, 2002

ABSTRACT



Grubbs' $RuCl_2(=CHPh)(PCy_3)_2$ (catalyst 1) and $RuCl_2(=CHPh)(PCy_3)(IMess)$ (catalyst 2) complexes have been successfully utilized in the construction of β,γ-unsaturated δ-lactones containing various substitution patterns of methyl groups. Asymmetric dihydroxylation followed by reduction leads to 3,4-*cis*-dihydroxy-2,6-dideoxypyranoses, which have proven to play very important biological roles as key components of natural products.

The ring-closing metathesis (RCM) reaction continues to play a powerful role in the construction of complex organic molecules.[1] The development of ruthenium carbene complexes (**1** and **2** Figure 1) by Grubbs and co-workers is particularly notable because of the remarkable functional group tolerance, operational simplicity, high stability, and availability.[2] Although used extensively to form large-membered macrocycles and nitrogen-containing heterocylces, only a few examples are found in the literature for the formation of α,β-unsaturated γ- and δ-lactones.[3] To the best of our knowledge, there is no precedence for the RCM production of β,γ-unsaturated δ-lactones.



1 **2**

Figure 1. Grubbs first (**1**) and second (**2**) generation catalysts.

Deoxysugars and deoxysugar oligosaccharides are important integrated components in biological systems.[4] Because of the high density of stereogenic centers in these compounds, their synthesis from nonchiral compounds represents a challenge for synthetic chemists. All diastereomers of the 2,6-dideoxypyranoses have been previously synthesized and are all found in nature in medicinally interesting glycosides.[5] Our strategy for the synthesis of 2,6-dideoxypyranosides was to utilize the RCM reaction for the forma-

(1) For recent reviews see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077. (c) Furstner, A. Angew. *Chem., Int. Ed*. **2000**, *39*, 3013−3043. (d) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565−588. (e) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (h) Blechert, S.; Schuster, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056.

(2) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Fu, G. C.; Nguyen, S. B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857. (c) Nyguyen S. B. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858−9859.

(3) For α,β-unsaturated γ-lactones see: (a) Furstner, A.; Dierkes, T. *Org. Lett.* **2000**, *2*, 2463−2465. For α,β-unsaturated γ- and δ-lactones see: (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187−4188. (c) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, *17*, 1743−1744. (d) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1874−1876. (e) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651−4654.

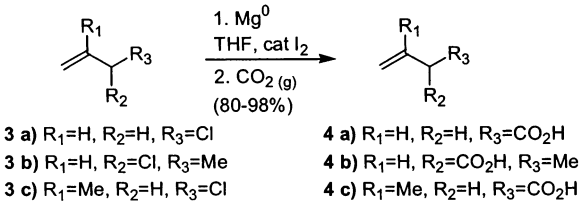
(4) Kirschning, A.; Bechtholdt, A. F. W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1−84.

10.1021/ol026710m CCC: $22.00
Published on Web 10/01/2002

tion of β,γ-unsaturated δ-lactones. Asymmetric dihydroxylation (AD) of these highly functionalized compounds followed by borohydride reduction would result in the desired compounds. The dihydroxylation of these β,γ-unsaturated cyclic systems introduces *cis*-hydroxyl groups in the C(4)- and C(5)-positions of the δ-lactone. Our route, which starts from simple precursors, is amenable to variations at several positions and proves valuable in the diastereoselective synthesis of an array of highly functionalized δ-lactones, which can be easily converted to 2,6-dideoxypyranosides.

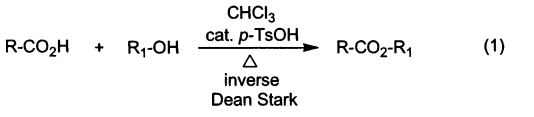
Our reaction sequence takes advantage of the formation of simple homoallylic esters. First, acids **4a**−**c** were prepared via a Grignard reaction (Scheme 1).[6] By introducing readily

Scheme 1. Grignard Syntheses of Homoallylic Acids



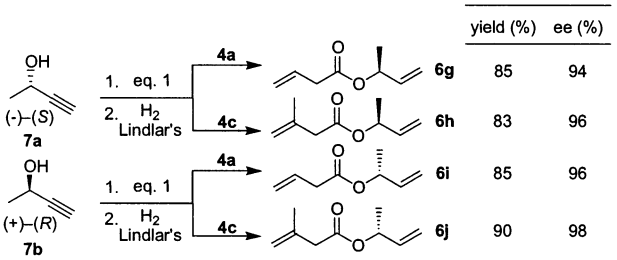
available homoallylic alcohols **5a** and **5b**, compounds **6a**−**f** were prepared via a Fisher esterification by employing an inverse Dean−Stark trap utilizing chloroform as the azeotroping solvent (Table 1).[7] It is important to note that esterification did not work efficiently under Fisher conditions with azeotroping solvents toluene or benzene.[8] Ester precursors for D- and L-pyranosides were prepared from readily available chiral propargylic alcohols (−)-(*S*)-**7a** and (+)-(*R*)-**7b** (Scheme 2).

Table 1. Utilizing an Inverse Dean−Stark Trap for the Formation of Terminal Substituted Olefinic Esters



entry	acid	alcohol	ester	time (h)	yield (%)
1	**4a**	**5a**	**6a**	8	98
2	**4b**	**5a**	**6b**	16	75
3	**4c**	**5a**	**6c**	16	95
4	**4a**	**5b**	**6d**	16	95
5	**4b**	**5b**	**6e**	16	72
6	**4c**	**5b**	**6f**	24	85

Scheme 2. Preparation of Stereodefined Olefinic Esters



	yield (%)	ee (%)
6g	85	94
6h	83	96
6i	85	96
6j	90	98

Esterification followed by reduction with Lindlar's catalyst proved to be the method of choice for producing both the (*R*)- [corresponding to (D)] and (*S*)- [corresponding to (L)] enantiomers for the construction of pyranosides.

The ring-closing metathesis of compounds **6a**−**j** proceeded in high yields. Grubbs' $RuCl_2(=CHPh)(PCy_3)_2$ catalyst **1** proved to be efficient for compounds **6a**,**c**,**d**,**g**−**j**, producing yields similar to those obtained with the use of $RuCl_2(=CHPh)(PCy_3)(IMes)$ catalyst **2**, as illustrated in Table 2. Reaction conditions were optimized to run in either dichloromethane or chloroform under refluxing conditions in the 0.01 M range. It was observed that under increased concentration conditions (i.e., >0.01 M), a cross-metathesis product would arise with the use of both **1** and **2**.[9]

The major difference between the two catalysts is their relative reactivity. Catalyst **1** worked best at 5 mol %, whereas catalyst **2** worked on a 1 mol % scale. Also entry 6 in Table 2 illustrates the formation of a tetrasubstituted olefin in which catalyst **1** gave no evidence of the δ-lactone. This reactivity difference can be reasoned that due to the lack of carbene stabilization provided by the absence of π-interactions, the imidazole ligand is more basic than the tricyclohexylphosphine analogue. The higher basicity translates into an increased activity of $RuCl_2(=CHPh)(PCy_3)(IMes)$ (catalyst **2**).[2a] In an attempt to optimize the reaction conditions, various amounts of $Ti(OiPr)_4$ were added.[3a−c,e,10] The rationale for its addition has to do with alleviating the formation of a seven-membered stable metal complex in which the Ru chelates to the carbonyl oxygen of the ester, which can potentially slow the conversion rate. GC monitor-

(5) (a) Ulven, T.; Carlsen, P. H. J. *Eur. J. Org. Chem.* **2001**, 3367−3374 (and references therein). (b) Shafer, C. M.; Molinski, T. F. *Carbohydr. Res.* **1998**, *310*, 223−228. (c) Roush, W. R.; Straub, J. A. *Tetrahedron Lett.* **1986**, *27*, 3349−3352. (d) Bock, K.; Lundt, I.; Pedersen, C.; Refn, S. *Acta Chem. Scand.* **1986**, *B40*, 740−744. (e) Roush, W. R.; Brown, J. R. *J. Org. Chem.* **1983**, *48*, 5093−5101. (f) Chmielewski, M. *Tetrahedron* **1979**, *35*, 2067−2070.

(6) Oppolzer, W.; Kuendig, E. P.; Bishop, P. M.; Perret, C. *Tetrahedron Lett.* **1982**, *23*, 3901−3904.

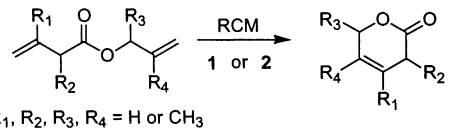
(7) Harcken, C.; Bruckner, R.; Rank, E. *Chem. Eur. J.* **1998**, *4*, 2342−2352.

(8) DCC coupling provided the desired ester in high yield but the unwanted dicyclohexylurea byproduct proved difficult to remove.

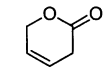
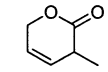
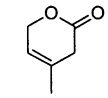
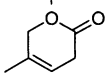
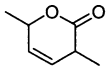
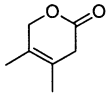
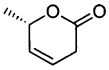
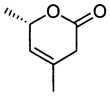
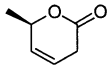
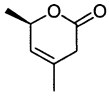
(9) (a) Toste, D. F.; Chatterjee, A. K.; Grubbs, R. H. *Pure Appl. Chem.* **2002**, *74*, 7−10. (b) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807−810 (and references therein). (c) Sukkari, H. E.; Gesson, J.-P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043−4046.

(10) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.

Table 2. Synthesis of Methyl-Substituted δ-Lactones via Ring-Closing Metathesis



R_1, R_2, R_3, R_4 = H or CH_3

entry	compound	product[a]		yield (%)[b] 1	2
1	**6a**		**8a**	82	97
2	**6b**		**8b**	N/A	83
3	**6c**		**8c**	81	97
4	**6d**		**8d**	83	96
5	**6e**		**8e**	N/A	75
6	**6f**		**8f**	NR	52
7	**6g**		**8g**	87	93
8	**6h**		**8h**	95	97
9	**6i**		**8i**	87	93
10	**6j**		**8j**	95	97

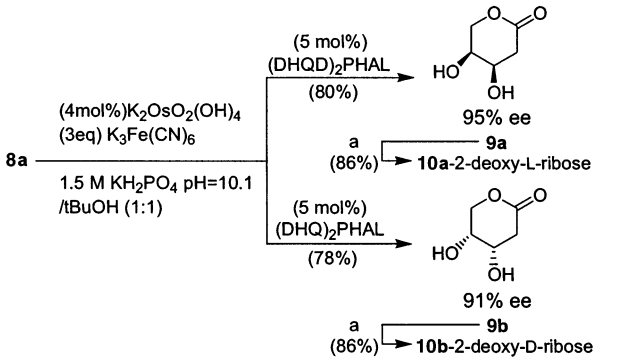
[a] Reaction concentration was 0.01 M. [b] Isolated yield from column chromatography. N/A = no attempt; NR = no reaction.

ing provided direct evidence for complete conversion. Column chromatography ensued after each β,γ-unsaturated δ-lactone formed for the purposes of removing the cross-metathesis product (<1% w/w) and Ru catalyst.[11] Compounds **8b** and **8e** (entries 2 and 5, Table 2) proved to be relatively unstable at room temperature and quickly decomposed into the more highly stable conjugated compounds.

The asymmetric dihydroxylation was attempted utilizing a number of procedural protocols.[12] The readily available AD-mix (both α and β) gave both poor yields and low d.r. The use of methanesulfonamide in the reaction led to product degredation. Commercially available AD-mixes consist of 0.4 mol % $K_2[OsO_2(OH)_4]$, 1 mol % $(DHQD)_2PHAL$ (AD-mix β) or $(DHQ)_2PHAL$ (AD-mix α), 3 equiv of $K_3[Fe(CN)_6]$, and 3 equiv of K_2CO_3.[13] In the case of internal olefins, the addition of at least a stoichiometric amount of a hydrolysis aid such as Et_4NOAc or $MeSO_2NH_2$ is required to obtain reasonable reaction rates due to hydrolysis problems or sterically hindered intermediate osmate esters. It was found that the optimal reaction conditions were met when the substrates were subjected to mild basic conditions such as 1.5 M KH_2PO_4 at pH 10.1, 4 mol % $K_2OsO_2(OH)_4$, 3 equiv of $K_3Fe(CN)_6$, and 5 mol % ligand. It is known that internal olefins react best at pH values between 11.2 and 12 due to an enhanced hydrolysis of the intermediate osmate esters under strong basic conditions.[14] It was observed that the diastereoselectivity of the reaction was lower when the reaction was run with high pH values (ca. pH 12.0).

With achiral substrates, the chiral ligand induces the expected configuration according to the Sharpless mnemonic (Scheme 3). However, when the methodology was applied to those compounds of preset chirality (entries 1−8, Table 3), the desired dihydroxylated compound had a tendency to arise as a mixture of diastereomers in the "mismatched" cases. These diastereomers were purified by column chromatography. The diastereomeric ratios were calculated from data obtained by NMR and confirmed by utilizing a Chiraldex B-PH 30 m × 0.32 mm capillary GC column (β-cyclodextrin permethylated hydroxypropyl) by first converting the free hydroxyls to the trifluoroacetates. Attempts to invoke the dihydroxylation in the absence of the chiral ligand gave an 80:20 mix with compounds **9c**, **9e**, **9g**, and **9j**.

Scheme 3. Asymmetric Dihydroxylation for the Synthesis of 2-Deoxyribolactone



[a] Key: (a) $Na(CN)BH_3$, 1.0 M AcOH/AcONa pH 5.2.

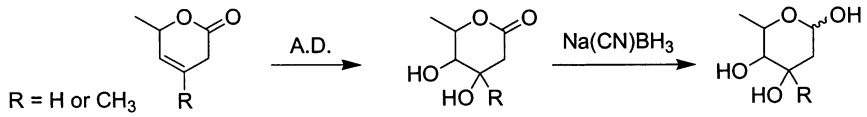
(11) For the removal of ruthenium byproducts see: (a) Ahn, Y. M.; Yang, K. L.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413. (b) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259−1261. (c) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137−4140.

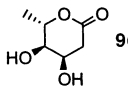
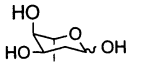
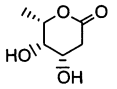
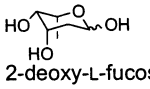
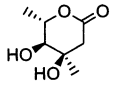
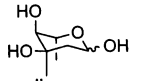
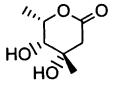
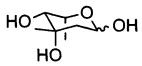
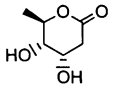
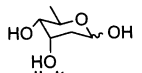
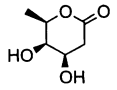
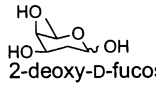
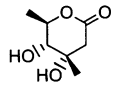
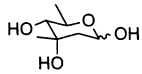
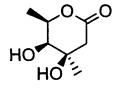
(12) Reviews: (a) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Johnson, R. A.; Sharpless, K. B. *Asymmetric Catalysis in Organic Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 227−272. (c) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317−1349.

(13) Preparation of AD mixes: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768−2771.

(14) Mehltretter, G. M.; Dobler, C.; Sundermeier, U.; Beller, M. *Tetrahedron Lett.* **2000**, *41*, 8083−8087.

Table 3. Conversion of β,γ-Unsaturated δ-Lactones to 2,6-Dideoxysugars



entry	compound	ligand	dihydroxylated lactone	de. (%)	2,6-dideoxysugar		yield (%)[a]	$[\alpha]_D^{23}$ [b]
1	**8g**	$(DHQD)_2PHAL$	 **9c**	97	 L-digitoxose	**10c**	88	-43°
2	**8g**	$(DHQ)_2PHAL$	 **9d**	33	 2-deoxy-L-fucose	**10d**	25	-45°
3	**8h**	$(DHQD)_2PHAL$	 **9e**	97	 L-olivomycose	**10e**	83	-17°
4	**8h**	$(DHQ)_2PHAL$	 **9f**	40	 L-mycarose	**10f**	35	-27°
5	**8i**	$(DHQ)_2PHAL$	 **9g**	98	 D-digitoxose	**10g**	88	43°
6	**8i**	$(DHQD)_2PHAL$	 **9h**	33	 2-deoxy-D-fucose	**10h**	20	48°
7	**8j**	$(DHQ)_2PHAL$	 **9i**	98	 D-mycarose	**10i**	92	28°
8	**8j**	$(DHQD)_2PHAL$	 **9j**	40	 2,6-dideoxy-3-methyl-lyxose	**10j**	32	14°

[a] Overall yield after chromatography based on the starting β,γ-unsaturated δ-lactones. [b] $c = 1.0$, D_2O.

Reduction of the lactone to the lactol was accomplished with aqueous $Na(CN)BH_3$ to give the final 2,6-dideoxysugar.

In conclusion, we have demonstrated a feasible route into 2,6-dideoxysugars employing a RCM and an AD strategy. This chemistry provides an avenue into a number of β,γ-unsaturated δ-lactones that can be easily converted into an array of deoxygenated sugar derivatives. We have found that the use of $Ti(OiPr)_4$ as a chelating agent was not required in the RCM reaction, but did serve to expedite the overall reaction (16 h to 6 h). Asymmetric dihydroxylation of chirally biased molecules provided access into the *cis*-hydroxyl diastereomers.

Acknowledgment. We thank the Herman Frasch Foundation, grant no. 449-HF97, administered by the American Chemical Society, as well as the Dryfus Foundation for a Jean Dreyfus Boissevain Undergraduate Scholarship for J.S.M. P.R.A. gratefully recognizes important discussions with Dr. M. S. Van Nieuwenhze.

Supporting Information Available: Detailed descriptions of experimental procedures, as well as a listing of all spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026710M