

Ring Closing Metathesis and Cross Metathesis of Carbohydrate Derivatives.

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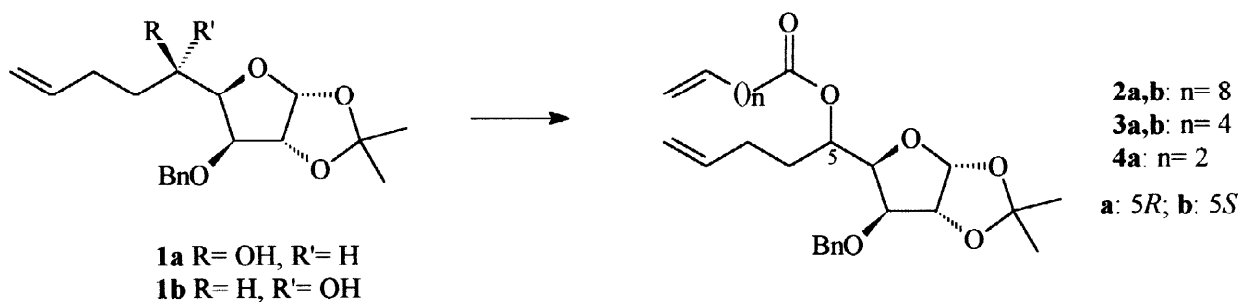
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Abstract: In connection with the synthesis of annonaceous acetogenins and analogs, RCM of unsaturated esters has been studied with the Grubbs benzylidene carbene catalyst to give 9 to 15 membered lactones in moderate to good yield. Cross metathesis between 2 carbohydrate derivatives and methyl undec-10-enoate is also reported. © 1998 Elsevier Science Ltd. All rights reserved.

Olefin metathesis has recently emerged as a widely applicable synthetic method for catalytic C-C bond formation.¹ The development by Schrock (Mo),² Basset (W)³ and Grubbs (Ru)⁴ of new catalysts which can tolerate a broad range of functional groups has been essential. For example, several applications of RCM (Ring Closing Metathesis) for the preparation of macrolides have been reported¹ since the pioneering work of Villemin.⁵ In this respect, it has been recently shown by Fürstner⁶ that the presence of remote functions plays a key role in favoring, in dilute solution, ring closure over the polymerisation process in the presence of the Grubbs carbene catalyst. Indeed, few examples of metathesis of carbohydrate derivatives have been reported by Descotes (RCM)⁷ and, more recently, by van Boom (RCM)⁸ and Blechert (cross metathesis).⁹

In connection with the synthesis of annonaceous acetogenins¹⁰ and analogs,¹¹ we have studied the formation of macrocyclic lactones from carbohydrate derivatives as a new process to link the THF and lactone moieties which are present in these natural products. Preliminary results of RCM are now reported along with cross metathesis.

Diastereoisomers **1a** and **1b**, prepared from diacetone-D-glucose, were used as model compounds and



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converted to **2a,b**, **3a,b** and **4b** by condensation with the corresponding unsaturated carboxylic acid (1 eq.) in presence of DCC (2 eq.) and DMAP (3 eq.) in diethyl ether (80-97 %). Metathesis reaction were carried out under N₂ at 20°C in dilute solution (6.10⁻³ M) using 10-20 % of *bis*(tricyclohexyl-phosphine)benzylidene ruthenium¹² (Table).

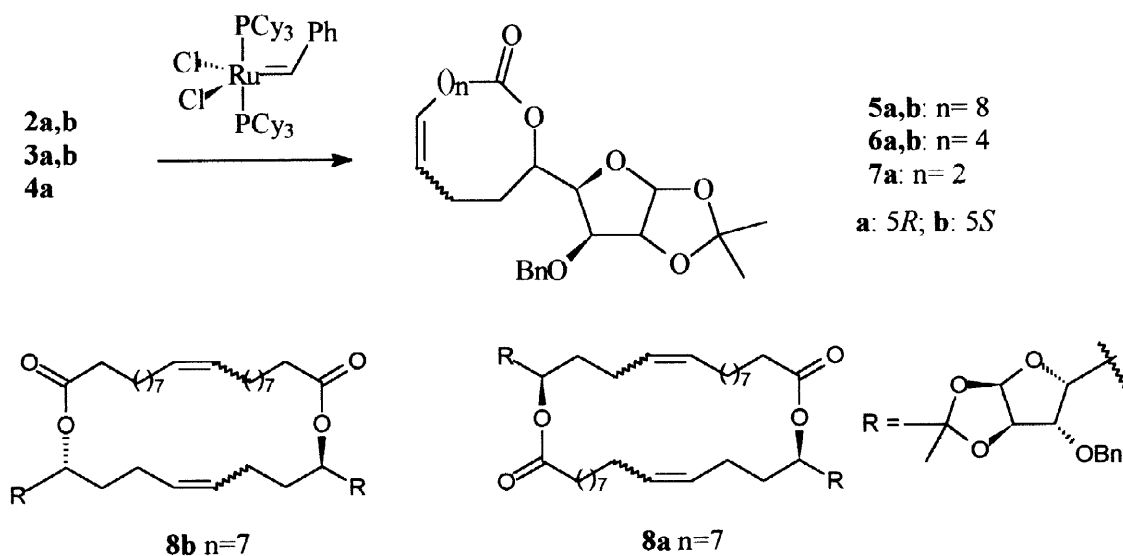
Table. RCM of esters **2**, **3** and **4**.

Entry	Ester	Solvent	Time (h)	Conversion (%)	Lactone (%) ^b
1	2a	CH ₂ Cl ₂	72	85	5a (38)
2	2a	id. ^a	30	91	5a (46)
3	2b	id.	96	68	5b (66)
4	3a	id.	72	92	6a (33)
5	3b	id.	96	89	6b (72)
6	3b	id.	96	38	7a (84)
7	3b	toluene	72	58	7a (84)

^a: slow addition of ester and catalyst via syringe pump.

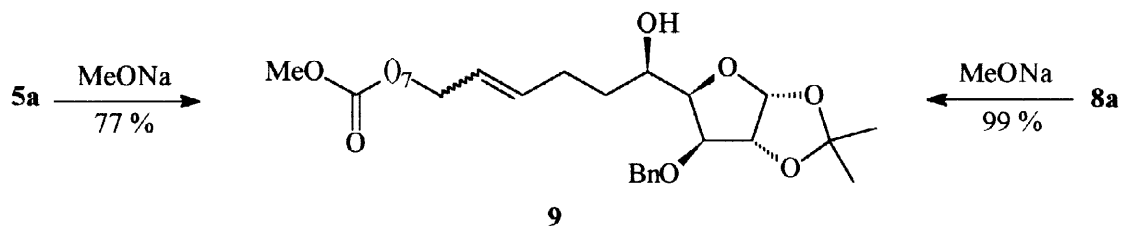
^b: isolated yield after flash chromatography based on starting material consumption.

RCM proceeds slowly (reactions were too slow with <10 % of the catalyst) giving lactones **5a,b**, **6a,b** and **7a** together with c.a. 10% of a corresponding dimer.¹³ The amount of recovered ester is high in the case of **4a** and this is not surprising since the 9 membered lactone **7a** (*Z*) is formed. However the material balance is very high in this case, in contrary to **2a,b** and **3a,b** indicating that no polymerisation takes place.



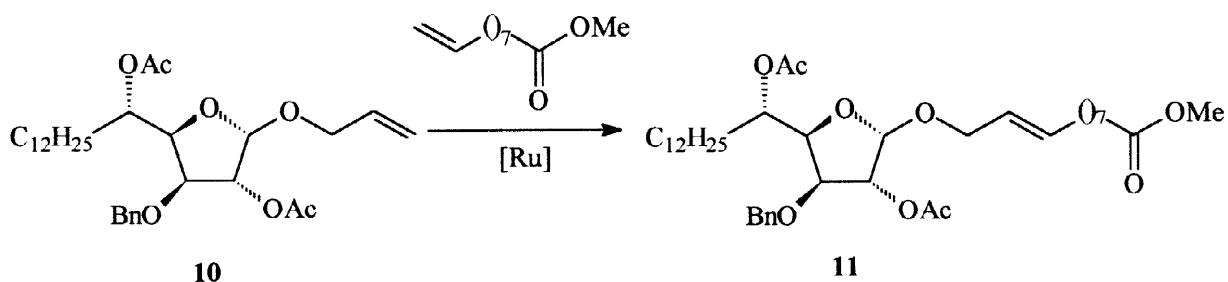
Due to polymerisation, the isolated yield of the 11 and 15 membered lactones **5a,b** and **6a,b** (*Z/E* c.a. 3/1 for both series) is moderate, the material balance being higher for the 5*S* esters **2b** and **3b**. The conversion

is slightly lower for the latter pointing a conformational bias in the catalytic cycle between the 5*R* and 5*S* series. Slow syringe pump addition of reactant and catalyst was also carried out for **2a**: the overall yield is better but the formation of dimer **8a** is not prevented. Indeed, two structures may be postulated for this minor dimer (13% isolated yield, >9/1 *E*): either head-to-tail (i.e. **8a**) or head-to-head (i.e. **8b**). The former structure was confirmed by methanolysis of both **5a** and **8a** which gives ester **9** in good yield in good cases. Similarly, methanolysis of the crude reaction mixture affords **9** in 40% isolated yield (no trace of compounds arising from hydrolysis of the head-to-head dimer was detected).



The formation of this dimer suggests that cross metathesis between alkenes such as **1b** and an unsaturated ester such as methyl undec-10-enoate may provide a simpler access to **9**. The reaction (too slow at $6 \cdot 10^{-3}$ M concentration) was carried out with 2 eq. of methyl undec-10-enoate and a 0.15 M solution of **1b** (72 h, 20°C, 25 % catalyst) to give a 44 % isolated yield of **9**.

This selective cross metathesis opens opportunities for the preparation of annonaceous acetogenins and analogs by coupling appropriate THF synthons with unsaturated esters or lactones. As an example, glycoside **10**, easily prepared from diacetone-D-glucose,¹⁴ affords **11** in 60% yield under the same reaction conditions as described above. A single *E* diastereomer is isolated as indicated by signals in ¹H NMR at δ 5.54 and 5.70 ppm with ³*J* = 14 Hz.



In conclusion, olefin metathesis of highly functionalised carbohydrate derivatives occurs in moderate to good yield with the Grubbs catalyst tested here. Although the amount of catalyst is too high for large scale synthesis, the use of other conditions such as solvent (see entries 6 and 7), temperature and added Lewis acid⁶ may improve the above RCM and cross metathesis. The latter should be studied in details to determine the essential parameters, e.g. protecting groups, chain length and substitution, for coupling of carbohydrate (or related) derivatives. This work is underway.

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References and Notes.

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