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Application of the Grubbs Ring-Closure Olefin Metathesis in the Synthesis of *Trans*-Fused Oxacycles

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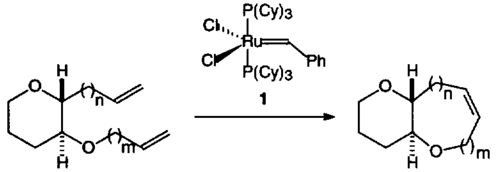
Abstract: A highly efficient and flexible route to trans-fused oxacycles is outlined, which is based on the formation of seven-, eight-, and nine-membered oxacycles by ring-closing metathesis (RCM) as the key step. © 1997 Elsevier Science Ltd.

The development of synthetic routes to *trans*-fused polyethers[1] has attracted considerable attention, due partly to the interesting biological activity of these compounds and also to the persistent challenges associated with constructing *ortho*-condensed oxacycles with defined relative and absolute stereochemistry.

The transition metal alkylidene-catalyzed olefin metathesis reaction[2] is rapidly emerging as a powerful tool in organic synthesis. Of particular interest are ring-closing metathesis reactions (RCM) catalyzed by transition metal complexes several elegant examples of which have recently appeared.[3] In this communication we report our preliminary results, based on the olefin metathesis reaction, for the generation of cyclic *trans*-fused ethers using ruthenium alkylidene **1**[4] as the catalyst (eq 1).



(1)

A notable limitation for RCM is the synthesis of heterocycles of more than seven atoms.[2] In particular, eight-membered rings have proven to be a special case. The generality and scope of the RCM process to give *trans*-fused ethers was investigated by employing a variety of alkylidene substrates. As illustrated in Table 1, the reaction can deliver in an essentially quantitative formation a series of seven- and eight-membered rings (entries 1 -4). RCM of **10** gave the nine-membered oxacycle **11** albeit in modest yields (entry 5). Interestingly the larger 13-membered ring **13** is formed, as a mixture of (E) and (Z) isomers [(E) : (Z) ~ 1:2], in 58% yield (entry 6). These results,[5] clearly reveal that the intramolecular transition state arrangement is affected not only by the ring size but also by the conformation of the bicyclic skeleton.

Despite the successes of this general approach to ring construction, much remain to be improved in terms of scope, convenience and generality. The striking functional-group tolerance of ruthenium complex **1**[6] significantly expands the scope of the ring-closing metathesis process for the synthesis of *trans*-fused polyethers.

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References and notes

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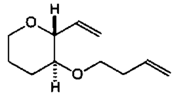
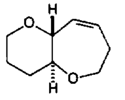
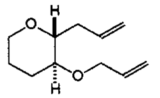
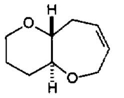
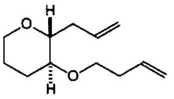
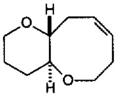
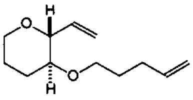
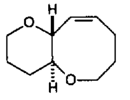
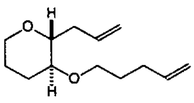
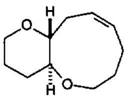
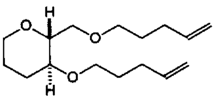
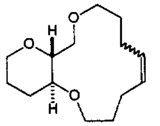
5. The unsaturated oxabicycles reported here were identified with those prepared from their respective oxathiacyclic precursor followed by Ramberg-Bäcklund olefination process: Alvarez, E.; Delgado, M.; Díaz, M.T.; Pérez, R.; Martín, J.D. *Tetrahedron Lett.* **1996**, *37*, 2865-2868.
6. The catalyst (**1**) used in these studies was purchased from Strem Chemicals (France).

Table 1

Entry	Substrate	Product	Yield % and Conditions
1	 **2**	 **3**	> 95%, 0.2 mmol scale, 10 mol% **1**, 6×10^{-3} M (CH_2Cl_2), 25 °C, 4 h
2	 **4**	 **5**	> 95%, 0.2 mmol scale, 10 mol% **1**, 6×10^{-3} M (CH_2Cl_2), 25 °C, 4 h
3	 **6**	 **7**	> 95%, 0.1 mmol scale, 20 mol% **1**, 6×10^{-3} M (CH_2Cl_2), 25 °C, 4 h
4	 **8**	 **9**	> 95%, 0.3 mmol scale, 10 mol% **1**, 6×10^{-3} M (CH_2Cl_2), 25 °C, 4 h
5	 **10**	 **11**	40%, 0.1 mmol scale, 20-30 mol% **1**, 5×10^{-3} M (CH_2Cl_2), 25 °C - 50 °C, 3 days. 45%, 0.2 mmol scale, 30 mol% **1**, 5×10^{-3} M (C_6H_6), 25 °C - 60 °C, 2 days.
6	 **12**	 **13** [(E) : (Z) ~ 1:2]	58%, 0.1 mmol scale, 30 mol% **1**, 5×10^{-3} M (C_6H_6), 25 °C, 12 h.

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