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Regioselective domino metathesis of 7-oxanorbornene derivatives as a new stereoselective entry into 2,6-dioxabicyclo[4.3.0]nonenes

Odón Arjona*, Aurelio G. Csákÿ, M. Carmen Murcia and Joaquín Plumet*

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

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Abstract

Domino metathesis of allyl- and propargyl-(2-*endo*-7-oxanorborn-5-enyl) ethers with allyl acetate in the presence of Grubbs' ruthenium catalyst affords stereoselectively substituted *cis*-fused bicyclic ethers (2,6-dioxabicyclo[4.3.0]non-8-enes).

Olefin metathesis has emerged recently as a powerful tool in synthesis and for applications to natural product synthesis.[1] In particular, the ring opening metathesis of bicyclic alkenes deserves special consideration from a stereochemical point of view, as the chiral information contained in the starting material is conserved throughout the process. In this context, the combination of ring-opening (ROM), ring closing (RCM) and cross (CRM) metathesis (domino metathesis) has allowed for the construction of [n.3.0] bicyclic alkenes from norbornenes in a stereocontrolled way.[2]

On the other hand, the *cis*-fused 2,6-dioxa[4.3.0]nonane skeleton **1** is ubiquitous among natural products and annulated nucleotide antibiotics.[3] In this way, we expected that the domino metathesis of allyl- **2** and propargyl-[4] **3** oxanorbornenic ethers[5] (Scheme 1) could constitute a straightforward entry to the systems[6] **4** and **5**, respectively.

Compounds **2** and **3** were prepared by *O*-alkylation of the related 2-*endo*-7-oxanorborn-5-ene alcohols[7] (KH/DMF, allyl bromide or propargyl bromide). Treatment of compounds **3** with allyl acetate in the presence of Grubbs' ruthenium catalyst[8] ($Cl_2(PCy_3)_2Ru{=}CHPh$, 8% mol) afforded the *cis*-fused 8-(2-propene)-2,6-dioxabicyclo[3.4.0]nonenes **5** as the only reaction products[9] (Scheme 2). Catalytic hydrogenation of **5** gave compounds[10] **7**.

On the other hand, the reaction of compounds **2** under the same conditions gave the related *cis*-fused 2,6-dioxabicyclic compounds **4** as major products, together with minor amounts of the

* Corresponding authors. Fax: 34 91 3944100; e-mail: plumety@eucmax.sim.ucm.es

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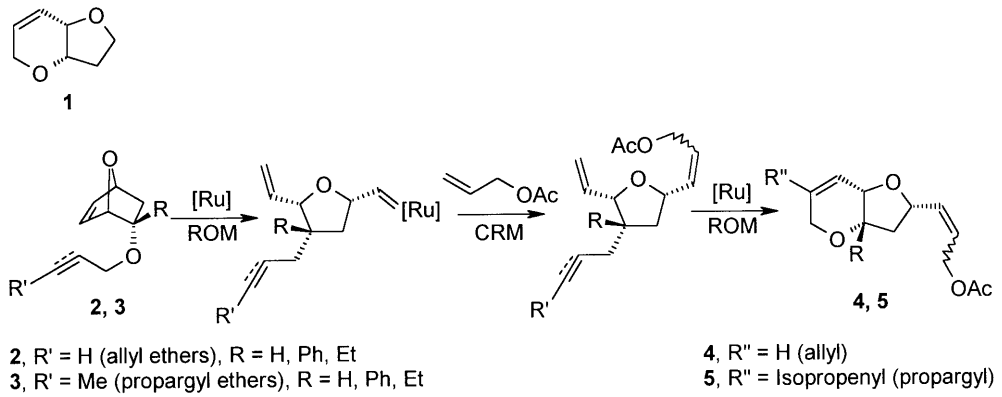
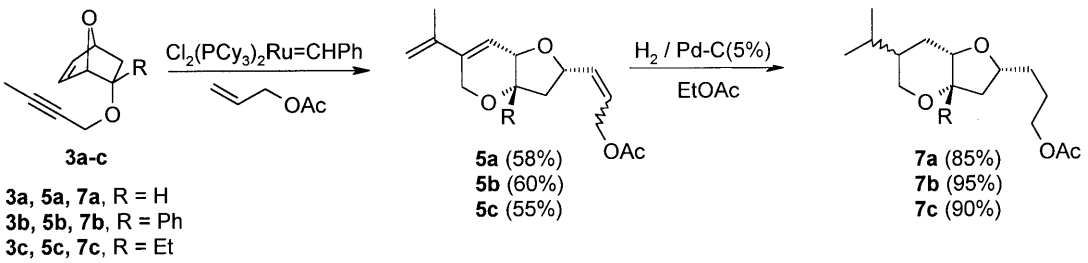
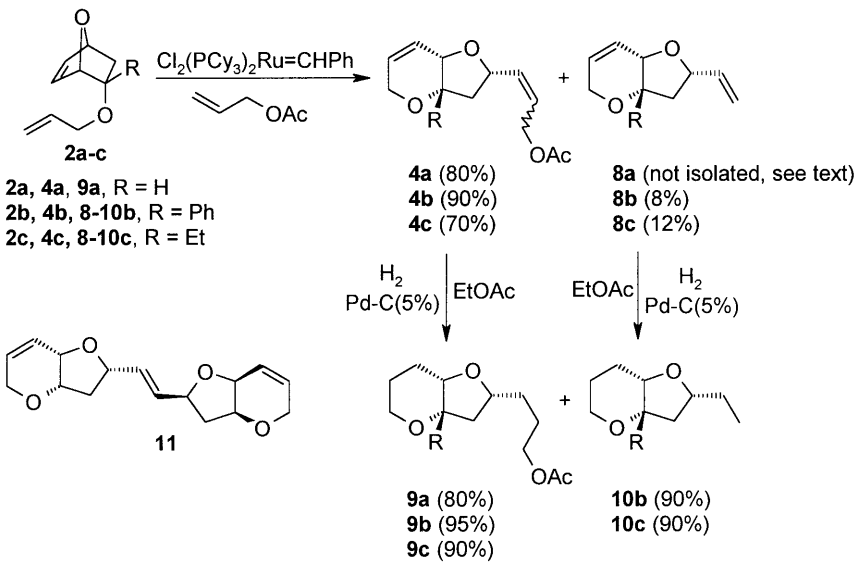


Scheme 1.



Scheme 2.

regioisomeric bicycles **8** as a mixture of *E* and *Z* diastereomers (Scheme 3). Catalytic hydrogenation of **4** and **8** gave compounds[10] **9** and **10**, respectively. It should be pointed out that compound **8a** was not isolated, but dimerized under the reaction conditions to give **11** (10% isolated yield).



Scheme 3.

In conclusion, *cis*-fused 2,6-dioxabicyclo[4.3.0]non-8-enes either with an alkenyl chain at C-3 or at C-3 and C-8 can be stereoselectively prepared from 7-oxanorbornene derivatives by a domino metathesis, starting from the corresponding allyl or propargyl ether, respectively. Furthermore, the procedure is suitable for the introduction of a quaternary stereogenic center at C-5 of the resulting bicycle. Extension of this methodology to the stereoselective synthesis of other bicycles interesting in natural products chemistry is also in progress and will be published in due course.

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9. Compounds **5** were obtained as 1:1 mixture of the *E* and *Z* isomers.
10. All compounds described herein were fully characterized on the basis of their analytical and spectroscopical data. Experimental procedure for the domino metathesis: To a solution of the oxabicyclic compound **2** or **3** (0.46 mmol) and vinyl acetate (0.46 mmol) in anhydrous CH_2Cl_2 (4 mL), was added $(Cy_3P)_2Cl_2Ru{=}CHPh$ (0.037 mmol) dissolved in CH_2Cl_2 (1 mL). The reaction mixture was stirred at rt for 3 h. After conversion was complete (TLC monitoring), the solvent was removed under reduced pressure. The reaction mixture was purified by chromatography (silica gel, hexane:ethyl acetate = 3:2).