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LETTERS

Ring closing metathesis of sterically hindered 1,6 - dienes: A new approach to 5-membered branched cyclitols

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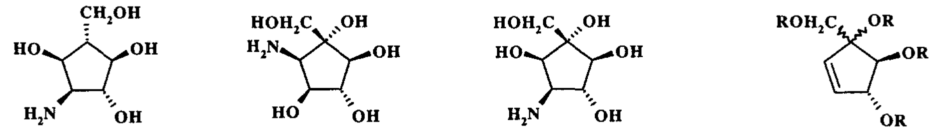
Abstract : A sterically hindered 1,6-dienic system underwent clean ring-closing metathesis using Schrock's catalyst. The product was converted into new 5-membered branched cyclitols and is a potential precursor of other biologically relevant aminocyclitols.

The compatibility of ring-closing metathesis (RCM) reaction conditions with most functional groups has recently led several research teams, including ours, to use this method as an approach to highly functionalized carbocycles as found in cyclitols and aminocyclitols.[1,2,3] The known sensitivity of RCM to steric effects, however, can be a serious limitation: in particular, ring closure efficiency drops dramatically as the degree of substitution of carbon atoms α to the olefinic system increases.[4,5] We have previously observed a marked difference between the Schrock's (A) and Grubb's (B) catalysts (see table),[6] in the case of a "difficult" RCM, the former reagent leading to milder reaction conditions and better yields.[2] This led us to examine the possible use of the Schrock's catalyst for the synthesis of sterically demanding carbocycles of type **1**, which are possible advanced common intermediates for the synthesis of 5-membered branched cyclitols and aminocyclitols (Scheme 1).



Component of allosamidine, a chitinase inhibitor

Component of trehazoline, a trehalase inhibitor

Found in certain bacteriohopanoides

1

Scheme 1

The synthesis starts from enone **2**, obtained in two steps from commercially available 2,3,5-tri-*O*-benzyl-*D*-arabinofuranose as described earlier.[2] Treatment with vinylmagnesium bromide gave exclusively the 3(*S*) dien-ol **3**. The excellent stereoselectivity of this reaction as compared with our earlier observations using allylmagnesium bromide has some precedent.[7,8] A variety of conditions were used for the metathesis reaction (Table). Very good results were obtained using diene **4** and Schrock's catalyst under strict exclusion of moisture and oxygen. It is to be noted that even the tertiary hydroxyl group in **3** is not tolerated when using Schrock's catalyst and had to be protected as the corresponding TMS ether.[9] Functionalization of the cyclized intermediate **5** [10] has been studied briefly: although **5** itself was resistant to OsO_4-catalyzed *cis*-dihydroxylation, the free alcool **6** could be readily converted in high yield to a 2 : 1 mixture of the protected new cyclitols **8** and **9**. On the other hand, palladium(II)-catalyzed rearrangement of allylic acetate **7** , afforded **10**, albeit in modest (19%)

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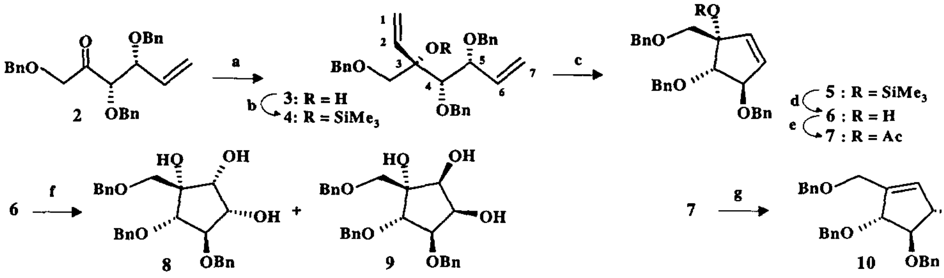
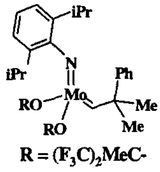
yield. The corresponding tetrabenzyl derivative (Ac →Bn) has been converted to trehazolamine.[11] To the best of our knowledge, **5** is the most densely substituted 5-membered ring yet obtained in good yield by RCM.[6] Further functionalization towards 5-membered pseudo-sugars is underway and will be the object of a full paper.

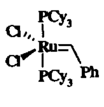


(a) CH_2=CH-MgBr (1M in THF), THF, -78°C - 20°C, 16 h, 98% ; (b) TMSOTf (1.6 eq.), 2,6-lutidine (2.5 eq.), r.t.,16 h, 94% ; (c) Schrock's catalyst, (10 mol %), benzene, r.t.,16h, 90%; (d) $Bu_4N^+F^-$ (3 eq), THF, 0°C - 20°C, 16 h, 97%; (e) Ac_2O, NEt_3, DMAP, THF, 50°C, 48 h, 70% ; (f) OsO_4 (cat.), NMO, THF/acetone/water 4/4/1, 20°C, 16 h, 61% (**8**) and 34 % (**9**) ; (g) $PdCl_2$ $(CH_3CN)_2$ (10 mol %), benzoquinone, THF, reflux, 16 h, 19 %.

Scheme 2



A



B

Catalyst (mol %)	Substrate, conc.	Solvent	Conditions	Yield
B (20 %)	3 (0.04 M)	CH_2Cl_2	10 days (reflux)	29 %
	4 (0.01 M)	CH_2Cl_2	7 days (reflux)	No Reaction
A (10 %)	4 (0.15 M)	C_6H_6	16 h (r.t.)	90 %

Table

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We thank Dr. P.Bisseret for fruitful discussions and Dr. D. le Nouen for NMR analyses. We thank the Fondation de l'Ecole Nationale Supérieure de Chimie de Mulhouse for financial support to Odile Sellier (fellowship Léon Denivelle).

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[6] Both catalysts are available from STREM.

[7] Similar results have been reported very recently. Kapferer, P.; Sarabia, F.; Vasella, A. *Helv.Chim.Acta* **1999**, *82*, 645-656. These authors describe the succesfull RCM of a sterically hindered 1,7-diene, using Grubb's catalyst, to afford valienamine.

[8] The different behaviour of allylmagnesium bromide as compared to other Grignards when reacting with ketones bearing α chelating groups has been already noted. Alberto Marco, J.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, J. *J.Org.Chem.* **1998**, *63*, 698-707.

[9] For good results, utmost care should be used when working with the Schrock's catalyst. We use the following precautions : all manipulations were carried out under Ar, using glove box techniques. Freshly purchased catalyst is divided in small (10 mg) portions and then stored in vials, under Ar athmosphere, at -20°C. See also: Calimente, D.; Postema, M.H.D. *J.Org.Chem.* **1999**, *64*, 1770-1771.

[10] NMR data is in agreement with the reported structures : **5** ^{1}H-NMR (C_6D_6, 250MHz) δ 0.27 (9H, s), 3.54 (2H, AB, J = 9.4 Hz), 4.16 (1H, d, J = 3.9 Hz), 4.39 (2H, ABq, J = 12.2 Hz), 4.53 (2H, ABq, J = 12.1 Hz), 4.76 (2H, ABq, J = 11.8 Hz), 4.85 (1H, dt, J = 3.9, 1.6 Hz), 5.88 (1H, dd, J = 6.2, 1.6 Hz), 5.95 (1H, dd, J = 6.2, 1.6 Hz), 7.12-7.50 (15H, m). ^{13}C-NMR ($CDCl_3$, 62.9MHz) δ 2.23, 71.59, 72.20, 73.37, 76.06, 83.97, 84.20, 88.29, 127.35-128.33, 133.59, 136.42, 138-140.

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