

Tandem RCM-Pauson–Khand reaction for access to tricycles in one step†

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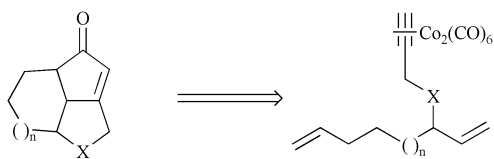
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Starting from conveniently designed dienes complexed to cobalt, a tandem RCM-intramolecular Pauson–Khand reaction yields tricyclic compounds. The methodology allows the synthesis of 6,5,5 and 7,5,5 systems.

An important strategy for the synthesis of natural products consists of applying transition metal catalyzed or mediated reactions to simple starting materials to obtain polycyclic scaffolds that can be further functionalized. Two powerful reactions that help in this aim are the RCM¹ and the Pauson–Khand² reaction. By means of the RCM reaction cycles going from 5 to 8 members, macrocycles are readily obtained. These cycloalkenes can be part of Pauson–Khand reactions. If an alkynyl moiety is suitably situated the RCM process followed by the intramolecular Pauson–Khand reaction would give a tricyclic structure, bearing a cyclopentenone. One problem would be the competition between RCM and enyne metathesis, but this could be avoided if the triple bond is complexed to cobalt prior to the RCM process. Green³ and Young⁴ have recently shown the feasibility of carrying out an RCM in structures containing cobalt hexacarbonyl-alkyne complexes.

This communication shows our first results in the tandem RCM-intramolecular Pauson–Khand reaction on acyclic dienes bearing a complexed triple bond. Cobalthexacarbonyl acts first as a protecting group and second as the mediator for the PKR. The methodology allows, the formation of tricyclic 6,5,5 and 7,5,5 structures including, in some examples, oxygen or nitrogen (Scheme 1). Related tricyclic structures *via* Pauson–Khand reactions for the total synthesis of natural products such as dendrobine,⁵ asteriscanolide⁶ and epoxydictymene⁷ have been obtained by other groups.

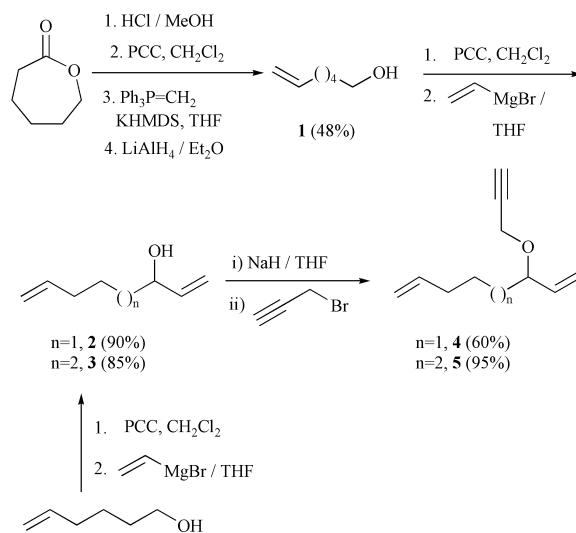


Scheme 1

Our first aim was the synthesis of substrates containing a propargyl ether moiety, which normally gives good results in Pauson–Khand reactions. Thus, starting from 5-hexen-1-ol and from ϵ -caprolactone we carried out the synthesis of compounds **4** and **5**, respectively, following the reactions depicted in Scheme 2. Thus, compound **4** was obtained in 54% overall yield after three steps, whereas compound **5** required seven steps and was obtained in 38% overall yield.

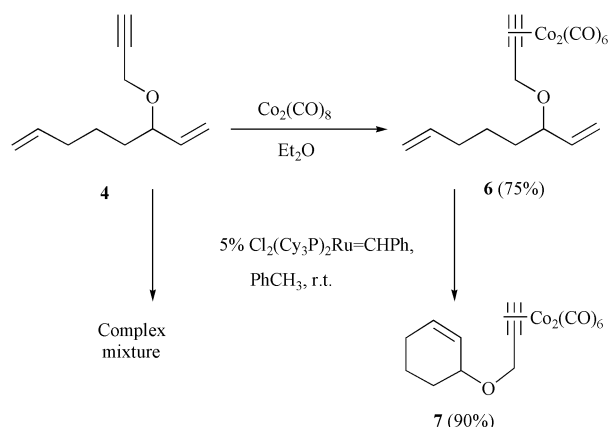
† Electronic supplementary information (ESI) available: spectral data and ¹H-NMR and ¹³C-NMR spectra for compounds **8**, **10**, **11**, **14a** and **14b**. See <http://www.rsc.org/suppdata/ob/b3/b302277c>

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Scheme 2

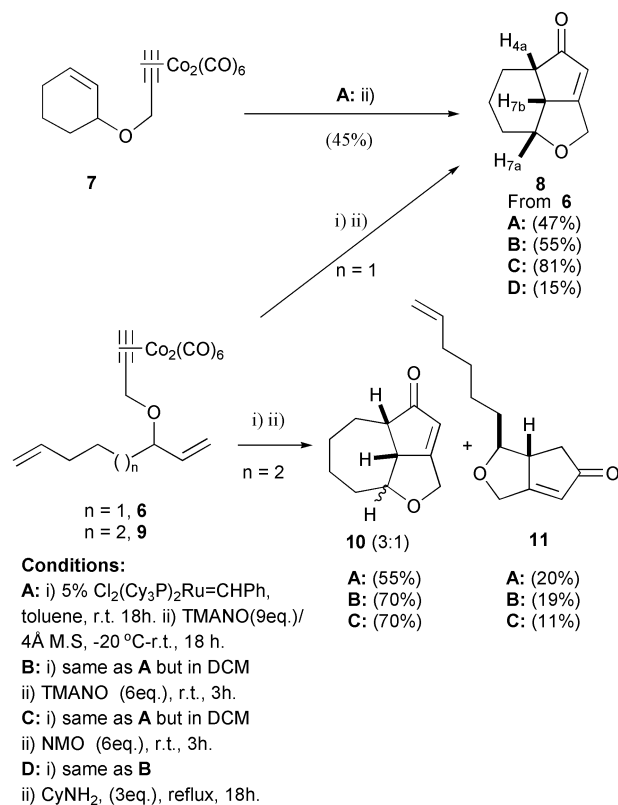
Compound **4** was submitted to reaction with 5% Grubbs' catalyst ($(\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru}=\text{CHPh}$), to explore the competition among the different possible metathesis processes. We obtained a complex crude mixture which could not be separated and that contained at least three metathesis products. Thus, we complexed compound **4** with cobalt and submitted the cobalthexacarbonyl-alkyne complex **6** to the same conditions. The reaction did not take place unless the cobalt complex was previously purified by means of a silica column chromatography. In that case a clean conversion to **7** was observed, obtaining this product in 90% yield after purification (Scheme 3).



Scheme 3

The next step was to effect the Pauson–Khand reaction on compound **7**. We obtained the desired compound **8**⁸ as only one diastereomer in 45% yield using our reported procedure.⁹ On

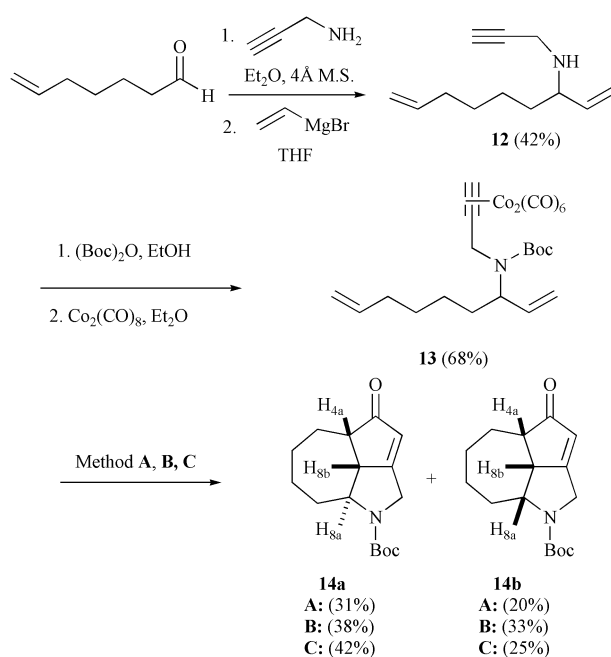
the other hand, we carried out the reaction of complex **6** with Grubbs' catalyst and when TLC showed the disappearance of starting material we added the promoters for the Pauson–Khand reaction. We compared three reaction conditions: molecular sieves and trimethylamine *N*-oxide (TMANO) as co-promoters in toluene at rt (method A),⁹ TMANO or NMO in DCM at rt (methods B and C), and Sugihara's procedure using cyclohexylamine in refluxing DCM (method D).¹⁰ We obtained the same diastereomer of **8** in 47%, 55%, 81% and 15% yield, respectively. Compound **5** was reacted with $\text{Co}_2(\text{CO})_8$ and the pure resulting complex **9** (79%) was treated under conditions A, B and C. In this case the RCM was not complete after 18 hours. NMR analysis of an aliquot of the reaction showed a 75% conversion. Addition of more ruthenium catalyst did not improve the conversion.¹¹ Thus we proceeded with the Pauson–Khand reaction and we obtained a 55% (method A) and 70% (methods B,C) yield of **10** as a mixture of diastereomers that could not be separated, along with 20% 19% and 11% of compound **11**, which was obtained as a single diastereomer, respectively.¹² The formation of a seven membered ring does not allow complete diastereoselection in the Pauson–Khand process (Scheme 4).



Scheme 4

The next step consisted of the synthesis of a nitrogen containing substrate. Thus, from 6-heptenal we carried out the synthesis of propargylamine **12** by reaction of the corresponding propargyl imine with a vinyl Grignard. Compound **12**, obtained in moderate yield, was protected as the Boc derivative and complexed with cobalt to give complex **13**. The tandem reaction of this substrate using methods A, B and C formed the desired tricyclic product **14** as a (3 : 2), (4 : 3) and (2 : 1) mixture of diastereomers, respectively,¹³ which were separated and assigned with NOE experiments (Scheme 5).¹⁴ The major isomer was in this case the *cis,trans* compound **14a**. Again, the formation of the seven membered ring has led to a mixture of diastereomers.

In summary a new access to tricyclic structures by means of a RCM-Pauson–Khand process is described. The methodology is



Scheme 5

currently being extended to new precursors of systems with different ring sizes.

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- We also tried the reaction with a second generation catalyst $(\text{Cy}_3\text{P})(\text{NHC})\text{Cl}_2\text{Ru}=\text{CHPh}$: M. Scholl, S. Ting, W. C. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956 This complex did not give any conversion even after 20 hours even when heating the reaction at 40 °C. Starting material was recovered.
- Compound **11** arises from the Pauson–Khand reaction of **9**.
- Calculated by integration of the signals corresponding to the olefinic proton in the ^1H -NMR spectrum of the crude mixture.
- Compound **14a**: no NOE increments in H_{8a} are observed when irradiating H_{8b} or H_{4a} . Compound **14b**: when irradiating H_{8b} a NOE increment of 8% was observed in the signal of H_{8a} and a 12% increment was observed in the signal of H_{4a} . The assignment of the signals was done with a COSY experiment.