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A General Solution to the Synthesis of Triquinanes by a Palladium Catalyzed Process.

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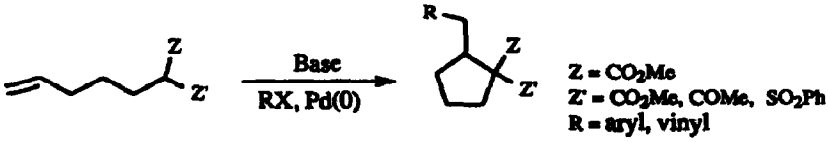
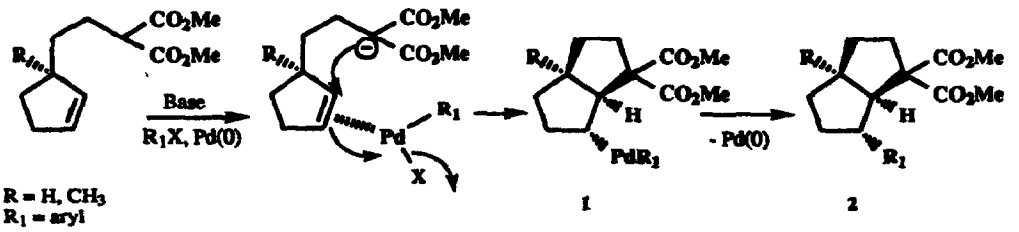
Abstract : A previously described palladium-catalyzed tandem cyclisation leading to linear triquinanes has been generalized by disfavoring the competing Heck reaction. Two structural factors (nature of the nucleophile and of the vinylic halogen) play an important role in this generalization.

The development of methods for the synthesis of five membered ring systems continues to receive extensive attention, due mainly to the search for efficient synthetic routes to prostaglandins and polyquinanes[1].

We have previously described[2] a new palladium mediated cyclopentanation of alkenes bearing a nucleophilic substituent.

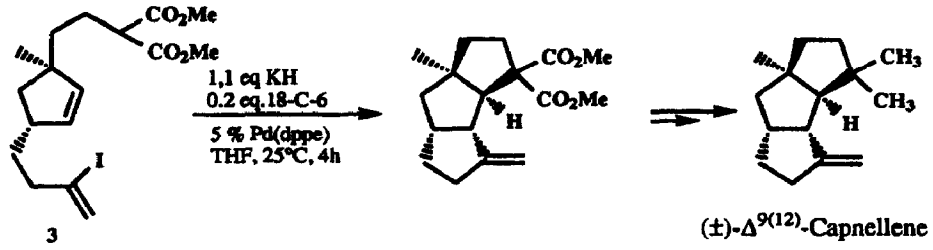


This cyclisation which is successful only for the formation of five-membered rings has been applied to the stereocontrolled formation of diquinanes.[3] The stereoselectivity of this process indicates that its mechanism involves a nucleophilic attack onto the unsaturation activated by the electrophilic palladium (II) complex formed by the oxidative addition of the metal by the arylic halide. Finally, a reductive elimination from **1** leads to the reaction product **2** *(scheme 1)*.



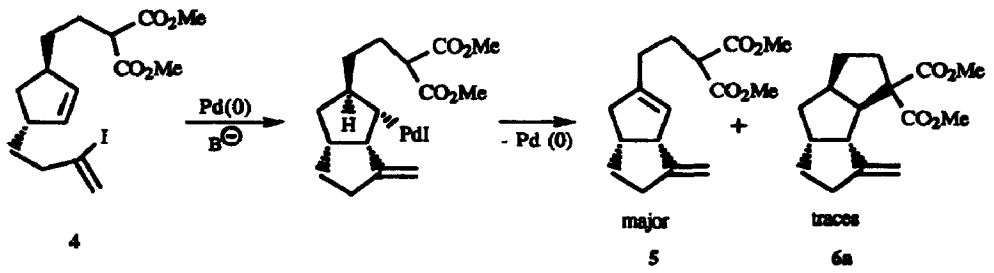
Scheme 1

By using the intramolecular version of this strategy, we have recently reported a method for the construction of tricyclopentanoids and described a new synthesis of (±) $\Delta^{9(12)}$ capnellene.[4] *(scheme 2)*



Scheme 2

This new route to the triquinanes offers two benefits : its brevity and the ready availability of starting materials. Unfortunately, it suffers from a lack of generality. In the case of compound **4**, where the angular methyl group is missing, a competing reaction occured : the classical intramolecular Heck reaction[5] was prevalent leading to bicyclic compound *5* accompanied by only traces of the desired triquinane **6a** *(scheme 3)*



Scheme 3

In order to have a versatile strategy for a unified approach to linear condensed cyclopentanoids, we decided to investigate some aspects of this tandem cyclisation by slightly changing the structure of the starting material **4**.

The difference of reactivity observed between the two substrates **3** and **4** during this reaction catalyzed by a palladium (0) complex is obviously due to the presence of the angular methyl group. Indeed, in view of the methyl steric hindrance, the palladium catalyzed alkene insertion of the vinylic halide (Heck reaction) must be slowed down in the case of **3** to permit the privileged attack of the enolate onto the electrophilically activated unsaturation.

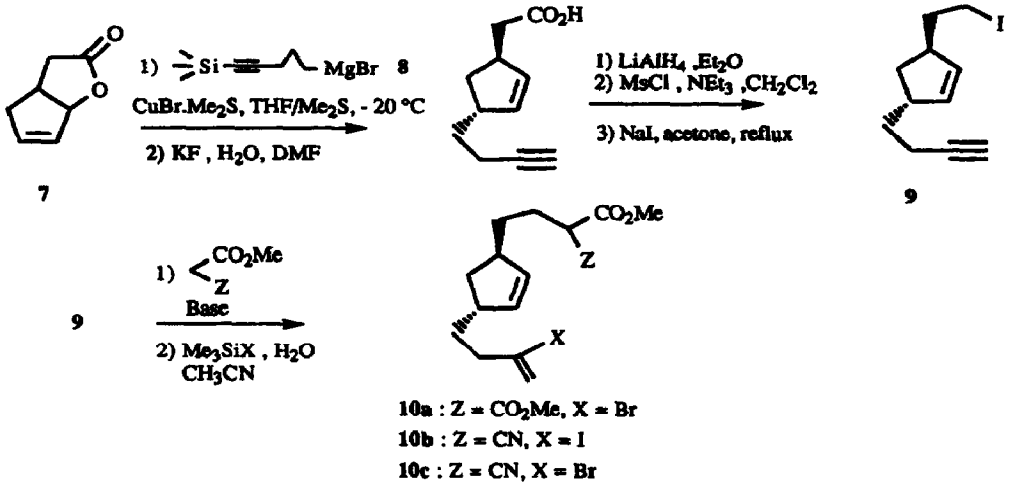
Consequently, in order to generalize this new palladium-catalyzed bis-cyclisation reaction, we had to find conditions which favour the nucleophilic attack against the alkene insertion of the organopalladium halide.

To do this, we can :

- either use a more " agressive" nucleophile than dimethymalonate i.e. the methylcyanoacetate. The choice of methylcyanoacetate is explained by recent work from our laboratory.[6]

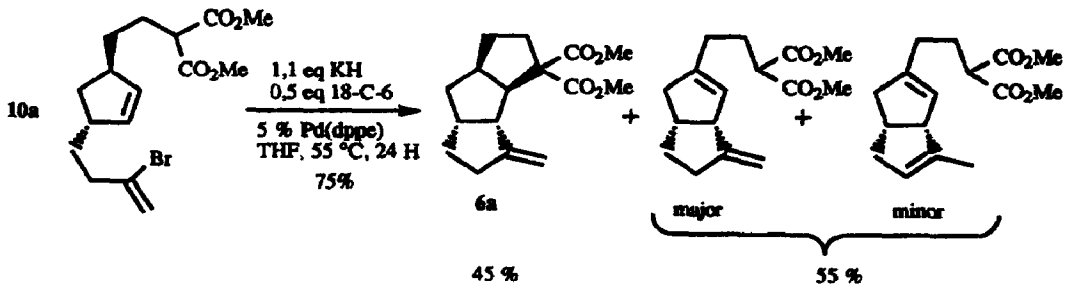
- or disfavour the insertion by using a vinylic bromide instead of a vinylic iodide since it is well known that the Heck cyclisation of the vinylic iodides is appreciably faster than that of vinylic bromides.[7]
- or apply these two conditions simultaneously.

So, the required cyclisation precursors **10a-c** were prepared by an efficient seven-steps route starting from the readily available vinyl lactone **7** [8] and the well known 1-trimethylsilyl-4 butynyl magnesium bromide **8** [9], using a sequence analogous to that described for the synthesis of compound **3** [4] *(scheme 4)*



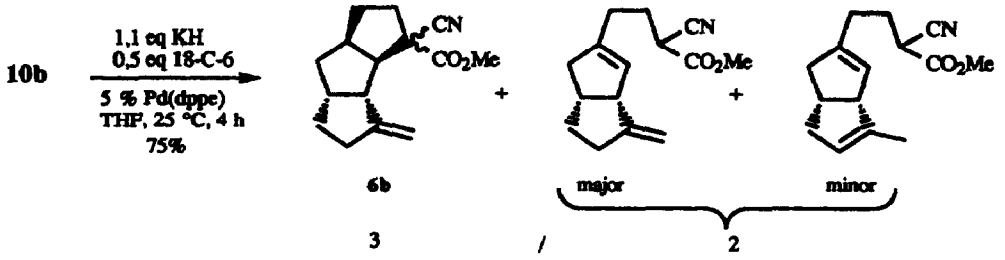
Scheme 4

When **10-a** was subjected to our bis-cyclisation reaction conditions (1.1 equivalent of KH, 0.2 equivalent of 18-crown-6, 5 mol % Pd(dppe), THF, room temperature) the starting material was not consumed. We found, however, that substrate **10a** cyclized at 55°C in the presence of 0.5 equivalent of 18-crown-6 to give a 45/55 mixture of the desired tricyclic compound **6a** and bicyclic products formed by the standard Heck reaction with a total yield of 75%.[10] **6a** could be readily separated from other isomers by careful medium pressure liquid chromatography.



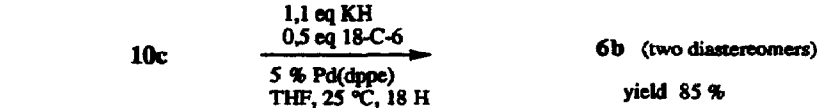
This first study demonstrates the importance of the nature of the vinylic halogen.

For comparative purposes, compound **10b** was then subjected to the same experimental parameters and fully transformed, at room temperature, in 4 h, to a mixture of the expected triquinane **6b** (two diastereoisomers) and, again, compounds resulting from the intramolecular Heck reaction in a 3:2 ratio (yield : 75%)



This result clearly indicates the **prominent part played by the nature of the nucleophile.**

Finally, treatment of **10c** with 5 mol % Pd(dppe), 1.1 equivalent of KH, 0.5 equivalent of 18-crown-6 at room temperature for 18 h resulted in the formation of only **6b** in two diastereomeric forms (3 : 2 ratio) with a total yield of 85%.



The desired bis-cyclisation reaction must have proceeded with high yields with no sign of side reactions, as judged by NMR and GC analyses.

This last result provides evidence for the generality of this new bis-cyclisation reaction and answers the question concerning the factors that may influence such reaction to the detriment of intramolecular Heck cyclisation.

Further exploitation of this is under active investigation and the results will be reported in due course.

References and notes

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10. Full spectroscopic data, consistent with the structures given, have been obtained for all compounds reported herein and the ratio of isomers was determined by capillary G.C. analysis.

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