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Stereoselective Synthesis of Linear and Angular Triquinanes Skeletons via the Zinca-Ene-Allene Reactions

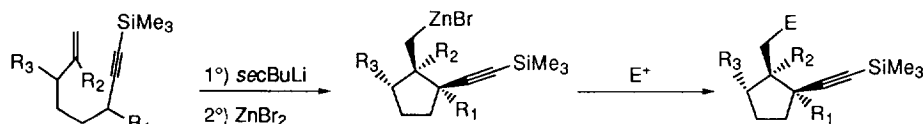
Christophe Meyer, Ilane Marek*, Jean-F. Normant*

Laboratoire de Chimie des Organoéléments, associé au C.N.R.S., Tour 44-45
 Université P. et M. Curie, 4 Place Jussieu, 75252 Paris Cedex 05. Fax (+33) 44 27 71 50

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Abstract: The zinca-ene-allene reaction allows a new diastereoselective and straightforward alternative to the angular and linear triquinane framework synthesis.

Linear and angular tricyclopentanoïd skeletons constitute an important class of natural product structure¹. Although numerous pathways for the synthesis of triquinane frameworks were described in the literature², the need for diastereoselective and convergent synthesis is still a challenge. Recently, we have described a new carbocycle synthesis via an intramolecular zinca-ene-allene reaction³ as described in Scheme 1.

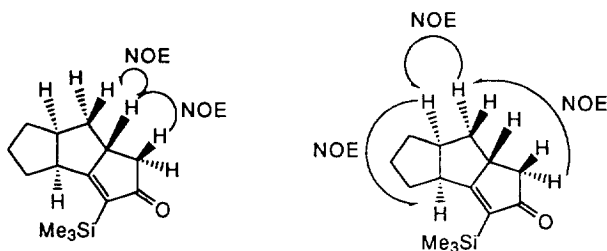


Scheme 1

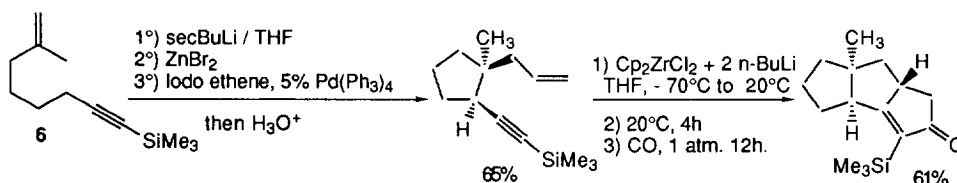
This cyclisation is stereoselective and a single diastereoisomer is formed, even when a tertiary and a quaternary center are linked in the process. Moreover, the zinca-ene-allene carbocyclisation has been successfully applied to the diastereoselective synthesis of polysubstituted tetrahydrofurans⁴ and substituted exomethylene-cyclopentanes⁵. In order to extend the scope of this reaction, we report in this letter that this methodology can also be applied to the diastereoselective synthesis of either linear or angular tricyclopentanoïds starting from the same precursor.

8-(Trimethylsilyl)-1-octen-7-yne **1** was cleanly metalated with *s*BuLi in THF at -45°C ⁶ followed by the addition of 1 equiv of zinc salt⁷ to lead to the corresponding allenyl zinc bromide intermediate⁸. After warming the solution to room temperature, this organometallic cyclizes *in less than 5 min.* to give the cyclic organozinc bromide **2**. This latter can be fonctionnalized by a coupling reaction⁹ with 1-iodo ethene in the presence of a catalytic amount of Pd(PPh₃)₄ or by the reaction with allyl bromide after transmetalation of **2** into an organocopper reagent¹⁰. In both cases, the cyclic products **3** and **4** were isolated as single isomers.

Enyne **3** was treated with a "ZrCp₂" reagent generated in situ by the reaction of Cp₂ZrCl₂ with 2 equiv of nBuLi¹¹ and, without isolation, the zirconatricyclic product was subjected to the carbonylation reaction. The tricyclic ketone **5**, isolated as a pure material in 50% yield, is obtained as single diastereoisomer (Scheme 2). Surprisingly, when the same reaction was performed at lower concentration (0.1 instead of 0.5 mol.l⁻¹) the diastereoselectivity decreases to 83/17. The stereochemical assignment of **5** is based on Nuclear Overhauser effects, which point to a *cis-anti-cis* tricyclopentanoid framework characteristic of several natural linear triquinanes, which is thus obtained in 2 steps from the enyne **1**.

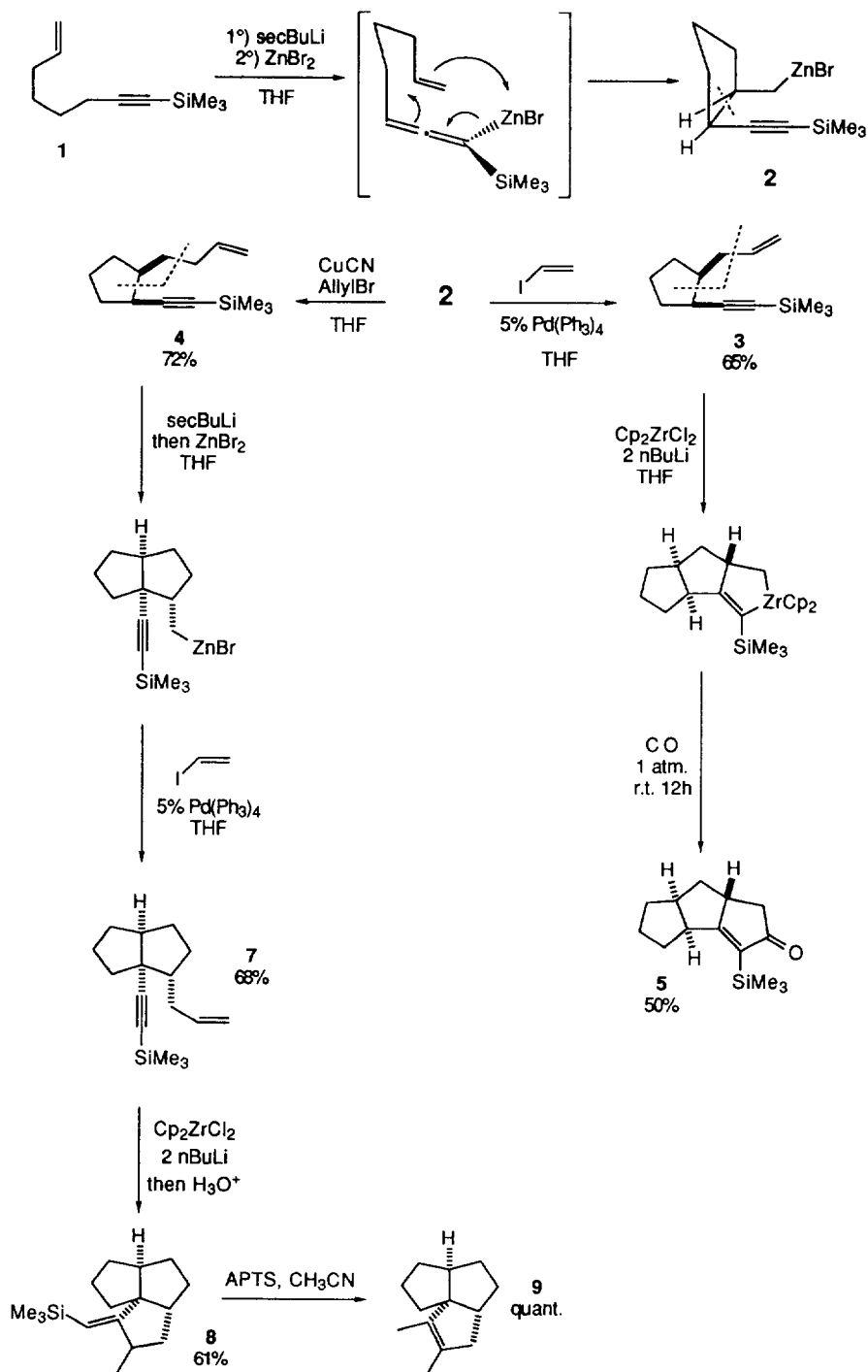


The same methodology can also be applied from a α,α -disubstituted enyne to give, in a two steps procedure from the acyclic enyne **6**, the methyl substituted linear tricyclic enone as a single diastereoisomer.



Starting from the enyne **4** (Scheme 2), synthesized from the enyne **1** in 72% yield, and submitting it to the zinca-ene-allene experimental condition³ (metalation - transmetalation - cyclization) the corresponding bicycloorganozinc bromide was, at first, obtained. The latter was treated with vinyl iodide in the presence of a catalytic amount of Pd(Ph₃)₄⁹ to give the bicyclo enyne **7** in 68% yield as a single diastereoisomer. Treatment of **7** by the Negishi's reagent¹¹ followed by an acidic hydrolysis leads to **8** which can be directly submitted to the desilylation procedure¹². Under these conditions, the exomethylene double bond migrates to form the thermodynamically stable olefin **9** a pattern also found in natural triquinanes. So, starting from a linear enyne **1**, the angular skeleton of triquinane can be easily elaborated, leading to a single diastereoisomer in 4 steps via two zinca-ene-allene reactions, followed by the zirconium cyclization reaction and an acidic desilylation treatment.

In conclusion, the zinca-ene-allene reaction allows a new diastereoselective and straightforward alternative to the angular and linear triquinane framework synthesis. Specific examples of natural triquinanes syntheses will be described in a forthcoming full paper.



Scheme 2

References and notes :

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6. The enyne can also be metalated in Et₂O at +10°C. Hydrolysis of the reaction mixture produced the starting enyne and its allenic counterpart in a 60/40 ratio.
7. The addition of zinc salt modified the propargyl / allenyl ratio of the hydrocarbons arising from protonation of the corresponding organometallic, and allows the intramolecular carbometalation reaction.
8. Zincation of the propargylic anion takes place with extremely high regioselectivity to produce the allenic zinc bromide derivative, determined by the IR spectrum see Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565
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