

Access to the Protoilludane Core by Gold-Catalyzed Allene-vinylcyclopropane Cycloisomerization

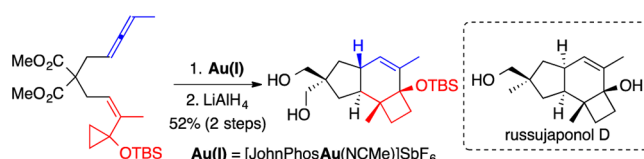
Anthony Pitaval, David Leboeuf, Julien Ceccon, and Antonio M. Echavarren^{*,†}

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16,
43007 Tarragona, Spain

aechavarren@iciq.es

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ABSTRACT



Gold(I)-catalyzed allene-vinylcyclopropane cycloisomerization leads to the tricyclic framework of the protoilludanes in a single step by a reaction that involves a cyclopropane ring expansion and a Prins cyclization.

Illudanes and protoilludanes have attracted much attention from the perspective of their biosynthesis,¹ biology,² and organic synthesis.³ Representative members of this numerous family of sesquiterpenes are Δ^6 -protoilludene (**1**),^{4,5} illudol,⁶ repraesentin A (**3**),⁷ and russujaponol D (**4**)⁸ (Figure 1).

Access to this class of compounds still poses important synthetic challenges due to their structural complexity.

[†] Additional address: Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, 43007 Tarragona, Spain.

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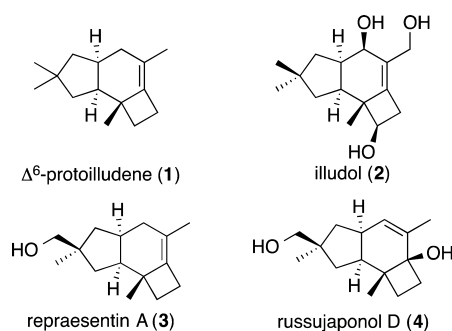


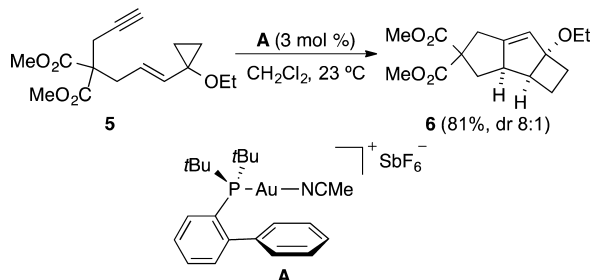
Figure 1. Representative protoilludane sesquiterpenes.

As part of a program on the development of new gold(I)-catalyzed cascade reactions for the synthesis of complex sesquiterpenes,⁹ we now report a new approach for the construction of the skeleton of this family of natural products in one single step through a gold-catalyzed cycloisomerization.

Cycloisomerization reactions catalyzed by gold(I) complexes have been intensively investigated and represent one of the most powerful methods for the construction of complex molecules in a single step.¹⁰ Among these various transformations, we demonstrated that complex tricyclic compounds such as **6** with an octahydrocyclobuta[*a*]pentalene skeleton

can be obtained by a sequence involving a ring expansion and a Prins cyclization from cyclopropylene **5** (Scheme 1).^{11,12}

Scheme 1. Gold(I)-Catalyzed Cycloisomerization of Cyclopropylene **5**¹¹

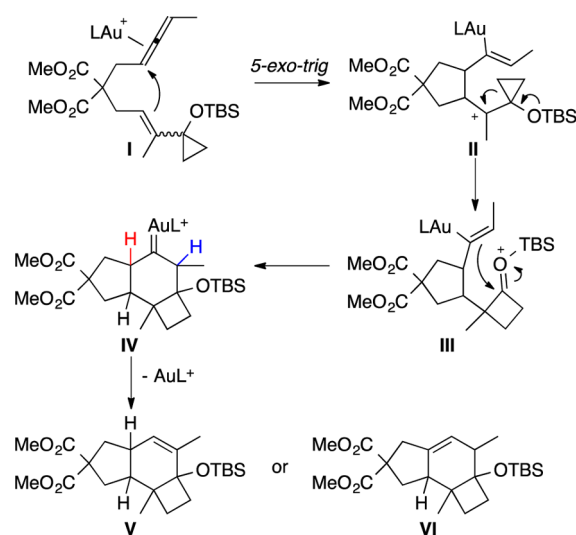


Based on this work, we decided to prepare the related cyclization of allenes with vinylcyclopropanes to access the carbon skeleton of the illudanes from a common intermediate. A plausible mechanism for this reaction is depicted in Scheme 2. Coordination of AuL^+ to the allene (**I**) could trigger a 5-*exo-trig* cyclization to furnish cationic intermediate **II**, which could undergo a ring expansion to generate **III**. A Prins cyclization of the vinyl gold with the oxonium cation could give gold(I) carbene intermediate **IV**. Finally, proton elimination followed by demetalation would provide **V** or **VI**. Regarding the relative configuration of **II**, precedents exist for the formation of related intermediates with both the *cis* or *trans* configuration in gold(I)-catalyzed cycloisomerizations of allenenes.¹³

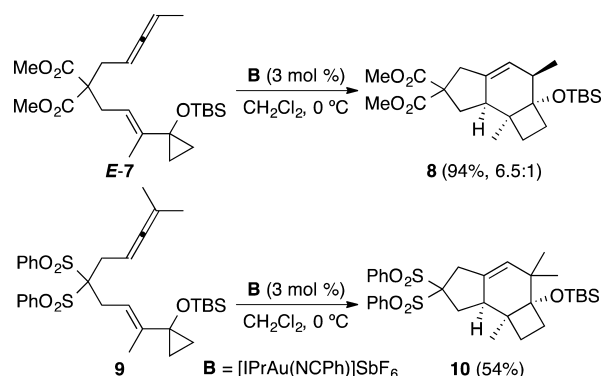
We first studied the reaction of substrate **E-7**. The cyclization was carried out satisfactorily using $[\text{IPrAu}(\text{NCPh})]\text{SbF}_6$ (**B**) (3 mol %) in CH_2Cl_2 at 0 °C to give **8** in 94% yield as a 6.5:1 mixture of two alkene regioisomers (Scheme 3).¹⁴ On the other hand, cyclization of substrate **9** with two methyl

groups at the allene terminus furnished tricyclic compound **10** in 54% yield as a single isomer.

Scheme 2. Gold-Catalyzed Allene-vinylcyclopropane Cycloisomerization



Scheme 3. Gold(I)-Catalyzed Cyclization of Allene-*E*-vinylcyclopropanes **E-7** and **9**



Although the allene-vinylcyclopropane cyclization provided the desired tricyclic system as originally planned, the relative configuration of **8** and **10** was the opposite to that of the natural protoilludenes. In keeping with the stereospecificity demonstrated in gold(I)-catalyzed cyclization of related enynes,¹⁰ we prepared substrate **Z-7** from known malonate **11**¹⁵ (Scheme 4). Thus, the anion of malonate **11** was alkylated with mesylate **12** to give allenyl malonate **13** in 86% yield. The acetal was then hydrolyzed to furnish aldehyde **14** (88%), which was alkenylated with phosphonate **15** to yield ketone **16** in almost quantitative yield with the desired *Z* configuration.^{12b,16} Finally, formation of silylenol ether with TBSOTf and Et_3N , followed by

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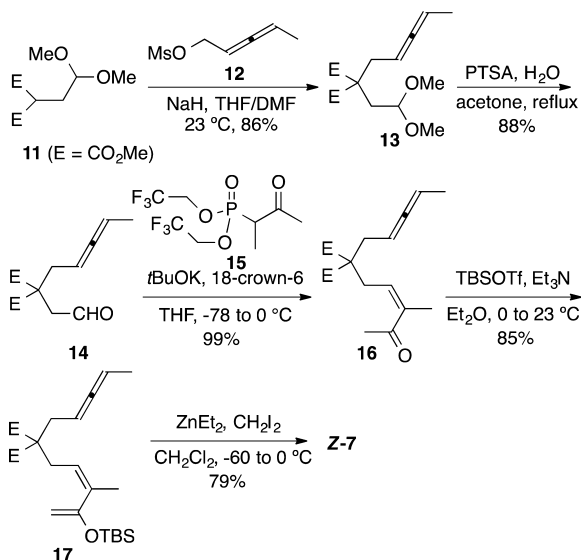
(14) The minor isomer **8b** could not be isolated, and its structure was tentatively assigned as a derivative of 3,7b-dimethyl-1,2,4a,5,6,7,7a,7b-octahydro-2aH-cyclobuta[e]inden-2a-ol (stereoisomer of **18a**, Scheme 5), with the *trans* configuration between the five- and six-membered rings.

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Simmons–Smith cyclopropanation, led to **Z-7** (67% over two steps).

Scheme 4. Synthesis of Substrate **Z-7**



Cyclization of **Z-7** was best carried out in 1,2-dichloroethane at 23 °C in the presence of catalyst **A** (3 mol %).¹⁷ The reaction led to the formation of two major products **18a** and **18b** in a 2:1 ratio (82%, NMR yield), which could not be separated by chromatography (Scheme 5). Their structures were assigned by transformation into crystalline derivatives. First, reduction of the malonate with LiAlH_4 led to the isolation of crystalline diol **19** in 52% yield (2 steps from **Z-7**), whose structure was determined by X-ray diffraction, which confirmed the *trans* configuration at the junction between the five- and six-membered rings (Figure 2).^{18a} On the other hand, desilylation with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), followed by esterification with *p*-nitrobenzoyl chloride and recrystallization, furnished ester **20** in 20% yield (2 steps from **Z-7**), whose structure was again assigned by X-ray diffraction (Figure 2).^{18b} Hydrogenation of **19** in an autoclave under 50 bar of H_2 using a Pearlman catalyst furnished **21** in 95% yield as a single diastereoisomer. Monotosylation of the diol followed by LiAlH_4 reduction gave alcohol **22** in 60% yield as a 1:1 mixture of diastereoisomers at the newly formed stereocenter, which is structurally related to russujaponol D (**4**).

We also explored the introduction of the oxygen functionality on the six-membered ring by hydroboration/oxidation (Scheme 6). The reaction led to a mixture of several diastereomeric alcohols, which could not be separated by chromatography. However, treatment of this mixture with Dess–Martin periodinane gave two ketones **23a** and **23b** in 59% and 19% yields respectively, whose

Scheme 5. Gold(I)-Catalyzed Cyclization of **Z-7**

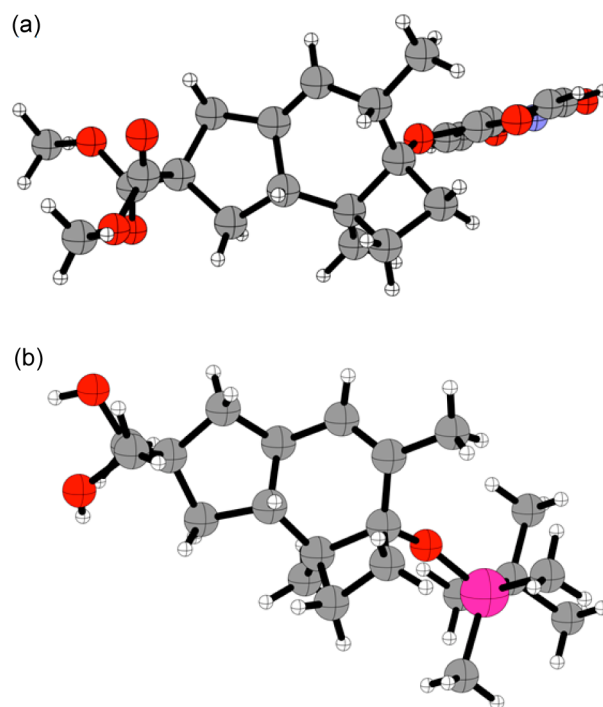
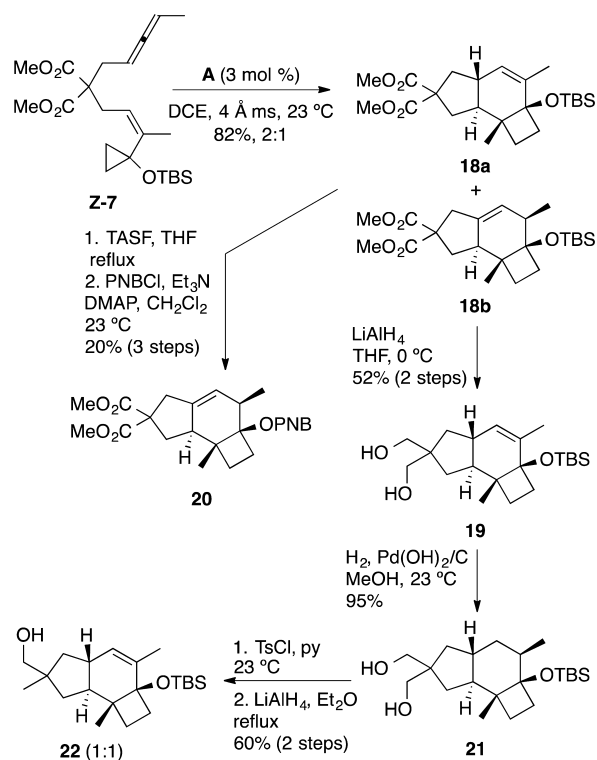


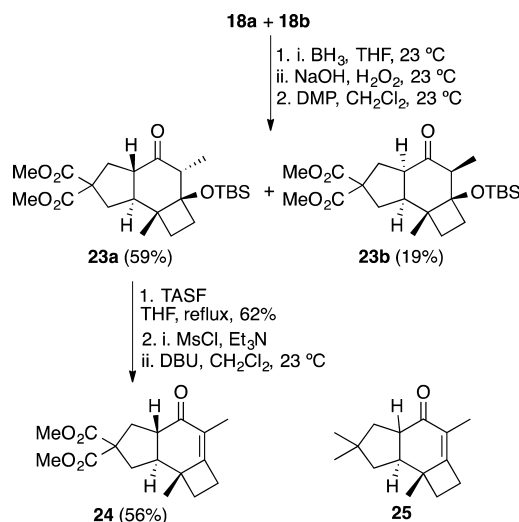
Figure 2. X-ray structures of **19** (a) and **20** (b).

relative configurations were determined by NOE analysis. The TBS group of the major compound **23a** was removed with TASF, and the resulting alcohol was converted into

(17) See Supporting Information for a screening of catalysts.
 (18) (a) X-Ray crystal structure of **19**: CCDC 953503. (b) X-Ray crystal structure of **20**: CCDC 953502.

an unstable mesylate intermediate, which was eliminated with DBU to furnish enone **24**. No epimerization was observed under these conditions to give the corresponding *cis*-stereoisomer of **24**.¹⁹

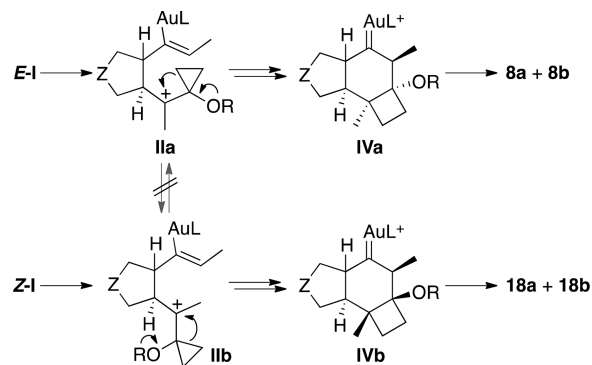
Scheme 6. Transformations of Compounds **18a** and **18b**



Our results demonstrate that intermediates **IIa** and **IIb** do not undergo equilibration and that the cyclopropylcarbenium to cyclobutane ring expansions occurs stereospecifically to form **IVa** or **IVb**, by intramolecular Prins reaction (Scheme 7). Regarding the configuration of cyclopentanes **IIa** and **IIb**, formation of **18a** as the major product in the cyclization of **Z-7** suggests that the gold(I)-catalyzed allene-vinylcyclopropane cycloisomerization leads to intermediates **II** with the *trans*-relative configuration. However, compounds **8a** and **18b** could arise from either *trans*- or *cis*-configured intermediates.

(19) DFT calculations (B3LYP, 6-31G*) on model *cis*- and *trans*-**25** show that the *trans* isomer is the most stable ($\Delta\Delta H^\circ = 2.5 \text{ kcal} \cdot \text{mol}^{-1}$).

Scheme 7. Stereospecific Cyclizations of *E*- and *Z*-I



In summary, we have shown that the gold-catalyzed allene-vinylcyclopropane cycloisomerization leads directly to complex tricyclic compounds with the skeleton of the protoilludanes. Ongoing work is focused on exploring new routes and catalysts to access the desired *cis*-fusion as well as on developing asymmetric syntheses of these natural compounds.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.