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

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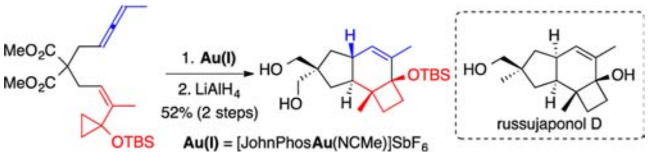
ABSTRACT



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.

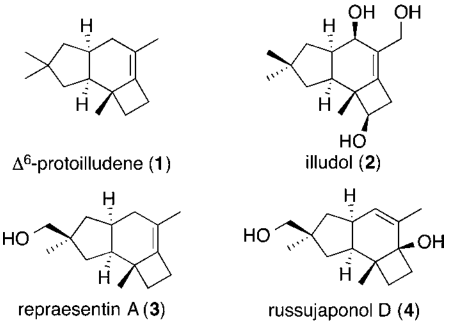


Figure 1. Representative protoilludane sesquiterpenes.

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

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(1) Zu, L.; Xu, M.; Lodewyk, M. W.; Cane, D. E.; Peters, R. J.; Tantillo, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 11369–11371.

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(5) For total synthesis, see: (a) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 440–443. (b) Oppolzer, W.; Nakao, A. *Tetrahedron Lett.* **1986**, *27*, 5471–5474.

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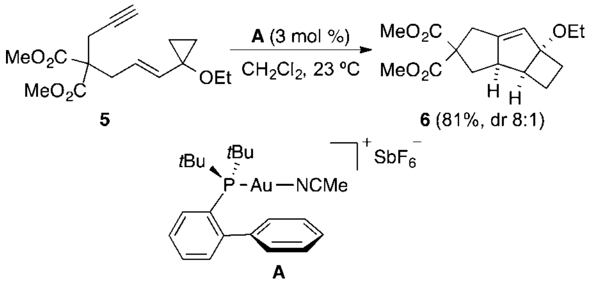
can be obtained by a sequence involving a ring expansion and a Prins cyclization from cyclopropylenyne **5** (Scheme 1).[11,12]

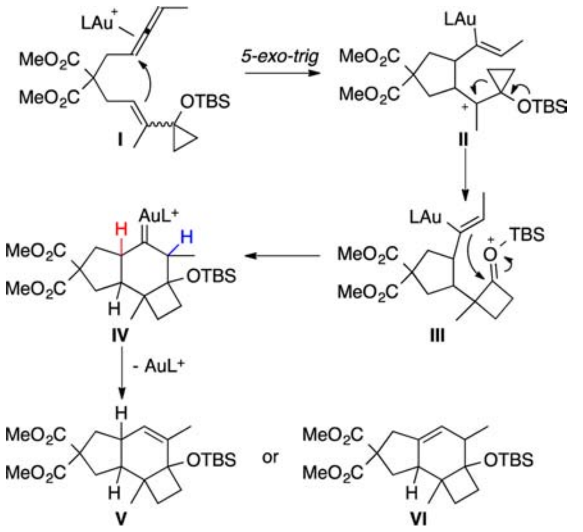
Scheme 1. Gold(I)-Catalyzed Cycloisomerization of Cyclopropylenyne **5**[11]



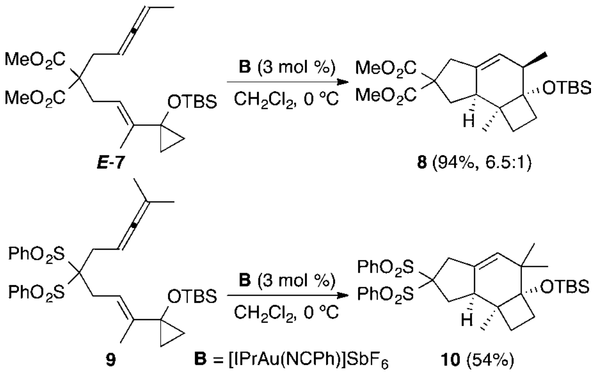
Based on this work, we decided to prepare the related cyclization of allenes with vinylcyclopropanes to access the carbon skeleton of the illudanes from a common intermediate. A plausible mechanism for this reaction is depicted in Scheme 2. Coordination of AuL$^+$ to the allene (**I**) could trigger 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 [IPrAu(NCPh)]SbF$_6$ (**B**) (3 mol %) in CH$_2$Cl$_2$ 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$_3$N, followed by

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(10) (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (e) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (g) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (h) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315. (i) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954–1993. (j) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994–2009.

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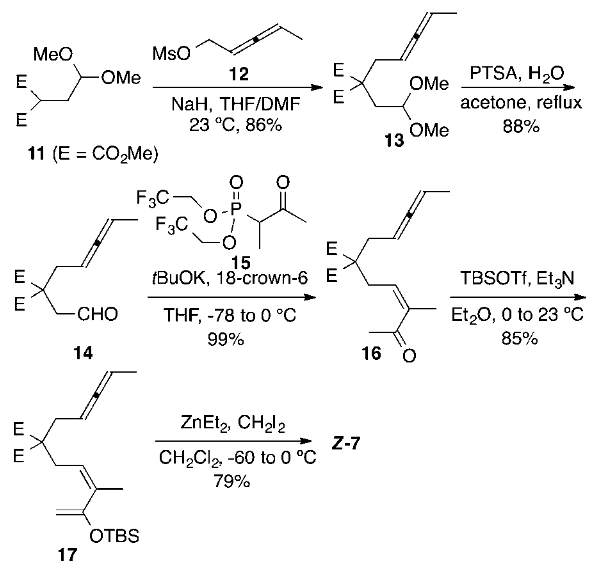
(14) The minor isomer **8b** could not be isolated, and its structure was tentatively assigned as a derivative of 3,7b-dimethyl-1,2,4a,5,6,7,7a,7b-octahydro-2a*H*-cyclobuta[*e*]inden-2a-ol (stereoisomer of **18a**, Scheme 5), with the trans configuration between the five- and six-membered rings.

(15) Shitani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54–55.

(16) Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* **1999**, *40*, 6725–6728.

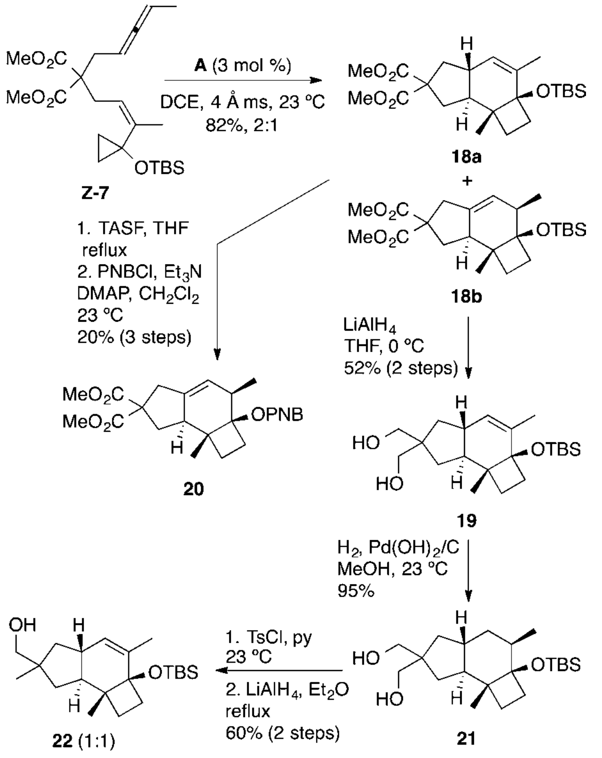
Simmons–Smith cyclopropanation, led to ***Z*-7** (67% over two steps).

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**).

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



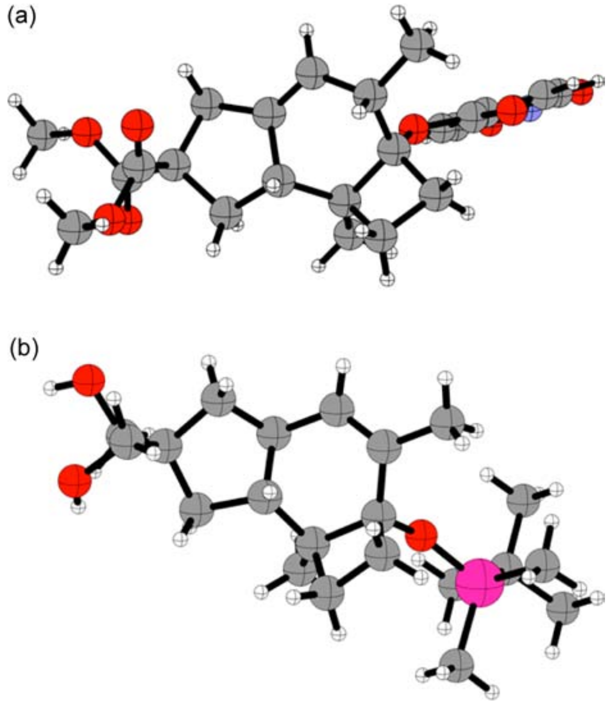


Figure 2. X-ray structures of **19** (a) and **20** (b).

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 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

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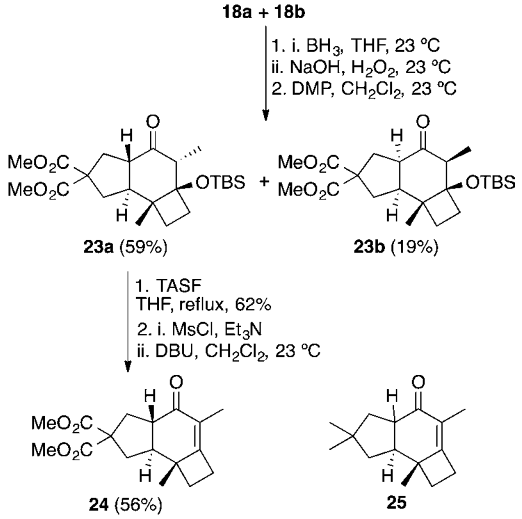
[17] See Supporting Information for a screening of catalysts.

[18] (a) X-Ray crystal structure of **19**: CCDC 953503. (b) X-Ray crystal structure of **20**: CCDC 953502.

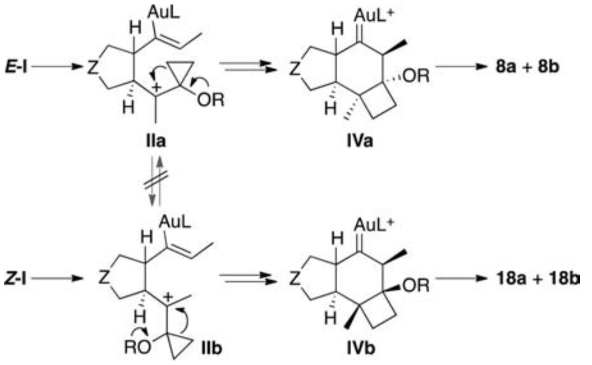
an unstable mesylate intermediate, which was eliminated with DBU to furnish enone **24**. No epimerization was observed under these conditions to give the corresponding *cis*-stereoisomer of **24**.[19]

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.

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.

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

The authors declare no competing financial interest.