GOLD(I)-CATALYZED CYCLOADDITIONS AND THEIR APPLICATION IN THE SYNTHESIS OF NATURAL PRODUCTS

Helena Armengol i Relats

UNIVERSITAT ROVIRA i VIRGILI

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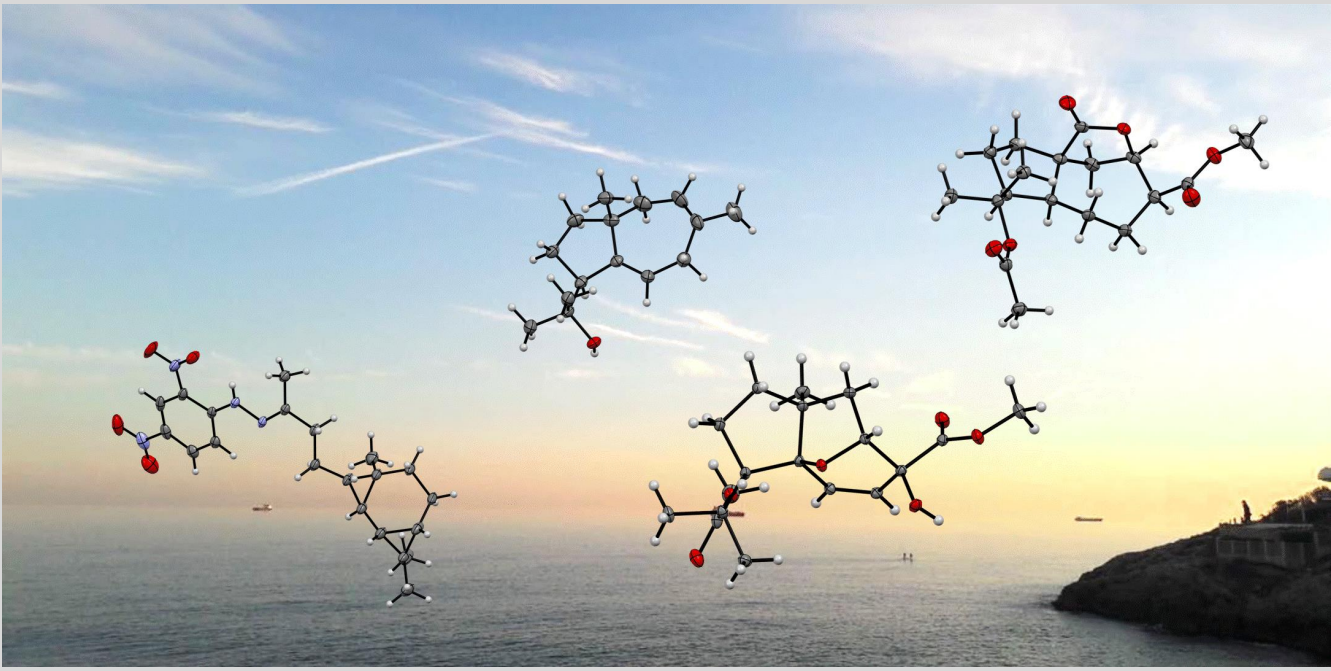

DOCTORAL THESIS
2021

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DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

Institute of Chemical Research of Catalonia (ICIQ)

UNIVERSITAT ROVIRA i VIRGILI

ICIQ Institut Català d'Investigació Química

Tarragona 2021

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ICIQ Institut Català d'Investigació Química

I STATE that the present study, entitled "*Gold(I)-Catalyzed Cycloadditions and their Application in the Synthesis of Natural Products*", presented by Helena Armengol i Relats for the award of the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, August 31st, 2021

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren

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At the moment of writing this Doctoral Thesis the results described herein were reported in following publications:

H. Armengol-Relats,[+] M. Mato,[+] A. M. Echavarren, "Assembly of Complex 1,4-Cycloheptadienes by (4 + 3) Cycloaddition of Rhodium(II) and Gold(I) Non-Acceptor Carbenes" *Angew. Chem. Int. Ed.* **2021**, *60*, 1916-1922; ([+]:equal contribution).

D. Scharnagel, I. Escofet, **H. Armengol-Relats**, M. E. de Orbe, J. N. Korber, A. M. Echavarren, "Acetylene as a Dicarbene Equivalent via Gold(I) Catalysis: Total Synthesis of Waitziacuminone in One Step" *Angew. Chem. Int. Ed*. **2020**, *59*, 4888-4891.

Publications not discussed in this manuscript:

H. Armengol-Relats, M. Mato, I. Escofet, A. M. Echavarren, "Assembling Complex Structures through Cascade and Cycloaddition Processes via Non-Acceptor Gold or Rhodium Carbenes" *Synthesis* **2021**, DOI: 10.1055/a-1535-3215.

I. Escofet, **H. Armengol-Relats**, H. Bruss, M. Besora, A. M. Echavarren, "On the Structure of Intermediates in Enyne Gold(I)-Catalyzed Cyclizations: Formation of *trans*-Fused Bicyclo[5.1.0]octanes as a Case Study" *Chem. Eur. J.* **2020**, *26*, 15738-15745.

J. G. Mayans, **H. Armengol-Relats**, P. Calleja, A. M. Echavarren "Gold(I)-Catalysis for the Synthesis of Terpenoids: From Intramolecular Cascades to Intermolecular Cycloadditions" *Isr. J. Chem.* **2018**, *58*, 639-658.

M. E. Muratore, A. I. Knovalov, **H. Armengol-Relats**, A. M. Echavarren, "Diastereospecific Gold(I)-Catalyzed Cyclization Cascade for the Controlled Preparation of N- and N,O-heterocycles" *Chem. Eur. J.* **2018**, *24*, 15613-15621.

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Prologue

This manuscript is divided in five parts including a general introduction, three research chapters and a general conclusion. Each chapter has five sections, these being a specific introduction in the topic, objectives, results and discussion, conclusions and a detailed experimental section.

The **General Introduction** gives an overview on homogeneous gold catalysis and its application in the total synthesis of natural products.

Chapter 1. presents the reaction discovery and optimization of three intermolecular gold(I)-catalyzed transformations based on acetylene activation. It also includes the reaction scope and mechanistic studies based on DFT calculations. The project was developed in collaboration with Dr. Dagmar Scharnagel, Dr. Imma Escofet, Dr. M. Elena de Orbe and J. Nepomuk Korber. The results have been published in *Angew. Chem. Int. Ed*. **2020**, *59*, 4888 – 4891.

Chapter 2. describes the development of a new gold(I)-catalyzed cyclosiomerization/cycloaddition cascade that allows for the construction of complex hydroazulene products. An insight into the reaction mechanism is included, mostly based on computational studies. The presented results have been published in *Angew. Chem. Int. Ed.* **2021**, *60*, 1916-1922 and reviewed in *Synthesis* **2021**, DOI: 10.1055/a-1535-3215.

Chapter 3. summarizes out efforts towards the total synthesis of three members of the daucane family of natural products. The synthetic strategy is based on the previously developed gold(I)-catalyzed cycloisomerization/cycloaddition reaction described in Chapter 2. These results have not been published to the date of this Thesis elaboration.

The **General Conclusion** includes final remarks on the research results disclosed in the different chapters and it is found at the end of this Doctoral Thesis.

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Abbreviations and Acronyms

The abbreviations and acronyms used in this Doctoral Thesis follow the recommendations from *"Guidelines for authors"* published in *Journal of Organic Chemistry*.
Additional abbreviations and acronyms are listed below:

APCI	Atmospheric Pressure Chemical Ionization
BAr^F_4	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
CyJohnPhos	(2-Biphenyl)dicyclohexylphosphine
ESI	Electrospray Ionization
HRMS	High Resolution Mass Spectrometry
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L-Selectride	Lithium tri-*sec*-butylborohydride
Men	Menthyl
Ms	Mesylate
Ns	2-nitrobenzene-1-sulfonyl
NTf_2	Bis(trifluoromethyl)imidate
OTf	Trifluoromethanesulfonate
*t*BuXPhos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
Ts	*p*-toluenesulfonyl

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Abstract

The potential of gold(I) catalysis on the synthesis of natural products has been widely explored in the last decades. This Doctoral Thesis presents our efforts to expand the applications of gold(I)-catalyzed cycloadditions on total synthesis. First, we have developed a new methodology for acetylene activation by means of gold(I) catalysis, in which the ligand on the gold(I) catalyst can tune the reaction outcome, either for the formation of (*Z*,*Z*)-1,3-dienes or towards bis-cyclopropanes. This method was applied to the one-step total synthesis of waitziacuminone. In second place, we have stablished a novel cycloisomerization/cycloaddition cascade which allows for the rapid and efficient construction of hydroazulenes, from enynes and dienes. The mechanism of this reaction was studied experimentally and computationally, finding a strong dependence on the nature of the diene partner and on the gold(I) catalyst employed. Finally, this strategy was applied to a common synthetic route towards aspterric acid, penigrisacid A and schisanwilsonene A. The carbon-skeletons of the three natural products were synthetized and characterized by x-ray diffraction.

General Objectives

The main objectives of this Doctoral Thesis are the development of new gold(I)-catalyzed cycloaddition reactions and the study of their application in the synthesis of different naturally occurring compounds. In particular, our investigations focused on:

- The exploration of acetylene as a reaction partner in gold(I)-catalyzed intermolecular reactions with different olefinic substrates and their application on the total synthesis of waitziacuminone.

- The design of a novel cycloisomerization/(4+3)-cycloaddition tandem reaction for the synthesis of complex hydroazulene products and a detailed mechanistic study by means of DFT calculations.

- The divergent synthetic approach to three carotene-like natural products based on our previously developed gold(I)-catalyzed cascade reaction, namely aspterric acid, penigrisacid A and schisanwilsonene A.

A more detailed description of the objectives can be found in the corresponding chapters.

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General Introduction

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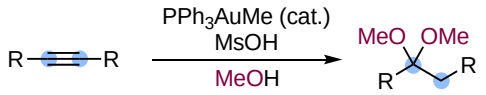
Homogeneous Gold Catalysis

The beginning of homogeneous gold catalysis

For a long time, during the outburst of transition metal-catalyzed transformations, gold was believed to be catalytically inactive.[1] Its first application was in the field of heterogeneous catalysis, in an early report by Bond, as a catalyst in olefin hydrogenation.[2] The first example in homogeneous gold catalysis was reported in 1986 by Ito and Hayashi, in the asymmetric aldol reaction of aldehydes with *iso*-cyanides.[3] However, the field remained poorly explored until 1998, when Teles developed the gold(I)-catalyzed synthesis of acetals by alcohol addition to alkynes (scheme 1). Few years later, Tanaka applied similar reaction conditions to access ketones and aldehydes from the same unsaturated substrates.[4]



Scheme 1. Gold(I)-catalyzed acetal formation from alkynes.

Since then, during these last decades, homogeneous gold catalysis been widely exploited, becoming a versatile tool for the construction of molecular complexity under mild conditions and in an orthogonal manner to other transition metals.[5]

Relativistic effects and their consequences

The singular proprieties of this element appear as a result of the relativistic effects.[6] Relativistic effects arise from the high speed of electrons orbiting close to a heavy nucleus. This involves an increase in the mass of the internal electrons, which causes a contraction of the Bohr radius of their orbits (*s* and *p*). Consequently, the electrons in the *d* and *f* orbitals are more shielded and experience weaker nuclear attraction. This effect is most significant for atoms with filled *4d* and *5f* orbitals and it reaches a maximum for gold.

This phenomenon explains the high electronegativity of gold, its tendency to form strong Au-Au interactions and its high Lewis acidity. Particularly, the low electron-electron

1. A. S. K. Hashmi, Gold Bull. 2004, 37, 51-65.
2. G. C. Bond, P. A. Sermon, G. Webb, D. A. Buchanan, P. B. Wells, J. Chem. Soc., Chem. Commun., 1973, 444b-445
3. Y. Ito, M. Sawamura, T. Hayashi, J. Am. Chem. Soc. 1986, 108, 6405–6406.
4. a) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, Angew. Chem. Int. Ed. 2002, 41, 4563-4565. b) E. Mizushima, T. Hayashi, M. Tanaka, Org. Lett. 2003, 5, 3349-3352.
5. a) A. Fürstner, Chem. Soc. Rev. 2009, 38, 3208–3221. b) C. Obradors, A. M. Echavarren, Acc. Chem. Res. 2014, 47, 902–912.c) L. Fensterbank, M. Malacria, Acc. Chem. Res. 2014, 47, 953–965. e) R. Dorel, A. M. Echavarren, Chem. Rev. 2015, 115, 9028–9072.
6. Gorin, D. J.; Toste, F. D. Nature 2007, 446, 395–403, and references cited therein.

repulsion in the diffused *5f* orbital makes gold a remarkably soft Lewis acid, which therefore preferentially activates soft electrophiles.

An additional consequence of this effect is the bond-strength increase of the Au-L interaction (L = ligand). This translates into a high dependance of the catalyst performance on the steric and electronic proprieties of the ligand (figure 1).[7]

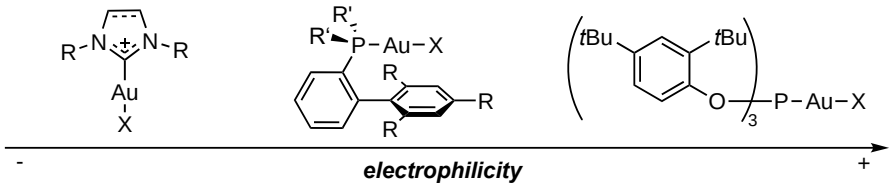


Figure 1. Ligand effect on the electrophilicity of gold(I) complexes.

Complexes bearing phosphite ligands are highly electrophilic which usually translates into highly reactive. On the other end, the use of σ-donating *N*-heterocyclic carbene ligands generates less electrophilic complexes and thus less reactive, but more selective. Finally, phosphine-gold(I) complexes have an intermediate behavior. Within this class, we find gold(I) complexes bearing Buchwald-type ligands, which allow for highly selective and versatile catalysis.[8]

Gold(I) chloride complexes [LAuCl] are poorly reactive and thus they are commonly used as precatalysts, which get activated upon chloride abstraction. Silver salts are typically used as chloride scavengers, forming AgCl as byproduct. However, this *in situ* activation of the gold precatalysts can lead to the undesired formation of dinuclear gold(I) complexes and to parallel silver-mediated processes.[9] In order to avoid these "silver effects", alternative approaches include the use of neutral complexes [LAuX], where X^- is a weakly coordinating anionic ligand (such as OTf^-), or the preparation of cationic complexes [LAuL']X, where L' is a neutral ligand and X^- a counterion.[10] The effect of this *a priori* innocent counterion has also been under study.[11] Finally, these complexes enter the catalytic cycle by ligand exchange with a molecule of substrate, following an associative mechanism.[12]

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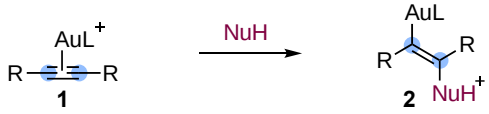
8 G. Zuccarello, M. Zanini, A. M. Echavarren, Isr. J. Chem. 2020, 60, 360–372.
9 a) A. Homs, I. Escofet, A. M. Echavarren, Org. Lett. 2013, 15, 5782–5785. b) A. Zhdanko, M. E. Maier, ACS Catal. 2015, 5, 5994–6004.c) Z. Lu, J. Han, G. B. Hammond, B. Xu, Org. Lett. 2015, 17, 4534–4537.
10 B. Ranieri, I. Escofet, A. M. Echavarren, Org. Biomol. Chem. 2015, 13, 7103–7118.
11 (a) Jia, M.; Bandini, M. ACS Catal. 2015, 5, 1638–1652. Veenboer, R. M. P.; Collado, A.; Dupuy, S.; Lebl, T.; Falivene, L.; Cavallo, L.; Cordes, D. B.; Slawin, A. M. Z.; Cazin, C. S. J.; Nolan, S. P. Organometallics 2017, 36, 2861−2869.
12. a) Komiya, S.; Albright, T. A.; Hoffmann, R.; Kochi, J. K. J. Am. Chem. Soc. 1976, 98, 7255–7265; b) Dickson, P. N.; Wehrli, A.; Geier, G. Inor. Chem. 1988, 27, 2921–2925; c) Schmidbaur, H.; Schier, A. Organometallics 2010, 29, 2–23.

Activation of π-bonds

As explained by the relativistic effects, gold(I) is a soft Lewis acid, which preferentially binds to soft electrophiles, such as unsaturated C-C bonds. Indeed, gold(I) π-complexes with alkenes, allenes and alkynes have been isolated and crystallized.[13] In the presence of other functional groups, including alkenes, the apparent alkynophilic character of gold is due to the higher reactivity of the resulting gold-alkyne π-complexes.[14] Comparison studies have actually concluded that gold(I) π-complexes with electron-rich alkenes are thermodynamically favored over those with alkynes.[15]

The binding mode of the gold(I)-unsaturation bond can be described with the Dewar-Chatt-Duncanson model for donor-acceptor interactions.[16] This is formed by a donating substrate-to-metal σ-interaction, in which the unsaturation donates electron density to an empty *d*-orbital of the metal, and a metal-to-substrate π-interaction, in which the metal donates from a filled *d*-orbital into the empty π* antibonding orbital of the substrate.



Scheme 2. Nucleophilic attack on complex **1**.

Upon coordination to gold(I), alkyne-complex **1** can undergo an outer-sphere nucleophilic attack,[17] in which the nucleophile adds trans to the gold center, leading to *trans*-alkenyl species **2** (scheme 2). These can later react in different manners, leading to a wide variety of products.

Nature of gold(I) carbenes

Among the evolution possibilities of alkenyl species **2**, gold(I) carbenes have been evoked as crucial intermediates for several transformations (figure 2).[18] The definition of these species as Fischer carbenes or gold(I)-stabilized carbocations, which can be drawn as resonance forms, generated some debate.[19] The bonding mode of these species was

13. For a selected example see: a) Brown, T. J.; Widenhoefer, R. A. J. Organomet. Chem. 2011, 696, 1216–1220.
14. García-Mota, M.; Cabello, N.; Maseras, F.; Echavarren, A. M.; Pérez-Ramírez, J.; López, N. ChemPhysChem 2008, 9, 1624–1629.
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16. a) M. J. S. Dewar, Bull. Soc. Chim. Fr. 1951, 18, C71-C79; b) J. Chatt, L. A. Duncanson, J. Chem. Soc. 1953, 2939-2947.
17. a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. J. Am. Chem. Soc. 2004, 126, 4526–4527; b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, N. W. Org. Lett. 2004, 6, 4391–4394.
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19. a) Y. Wang, M. E. Muratore, A. M. Echavarren, Chem. Eur. J. 2015, 21, 7332–7339; b) R. J. Harris, R. A. Widenhoefer, Chem. Soc. Rev. 2016, 45, 4533–4551.

postulated by Toste involving a three-center four-electron σ-hyperbond, where the ligand and the carbene donate electrons to the gold; and two π-bonds, which consist in the the π-back donation of gold, from its filled *5d* orbitals, to the ligand and to the carbene (figure 2).[20]

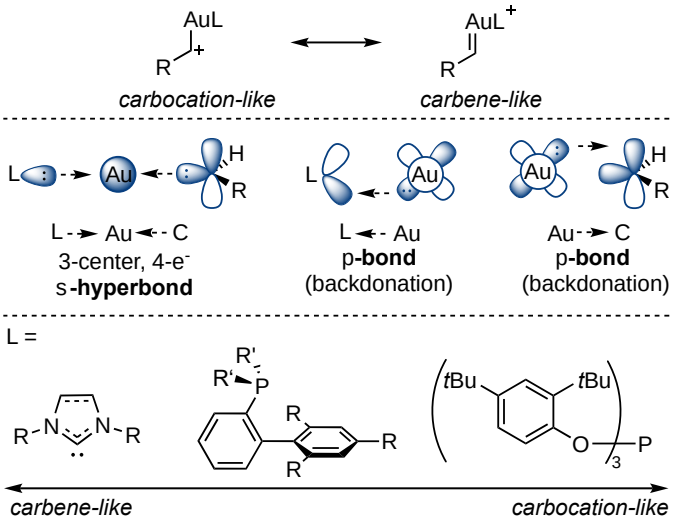


Figure 2. Binding model for gold(I) carbene intermediates.

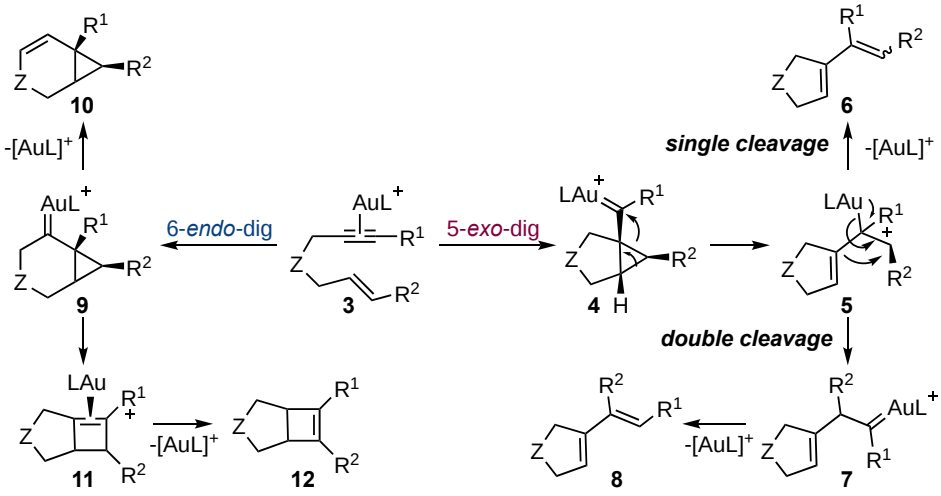
The reactivity of these intermediates as α-gold carbocations or gold carbenes is highly dependent on the ligand (L) and the carbon substituents on the substrate (R). Strongly σ-donating N-heterocyclic carbene ligands increase the electron density around gold, enhancing the π-back donation to the carbene and thus favoring a carbene-like reactivity. Phosphite ligands present the opposite characteristics, leading their corresponding gold intermediates to react as a carbocation.

Cyclization of enynes

Among the different reactions promoted by gold(I), gold(I)-catalyzed cycloisomerizations of 1,*n*-enynes had a significant impact on the field. The increase in molecular complexity that can be achieved in a single chemical transformation, made these reactions particularly interesting.[5] Additionally, depending on the substitution pattern at the alkene and the alkyne, as well as on catalyst employed, the 1,6-enynes cycloisomerizations

20. Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard III, W. A.; Toste, F. D. Nat. Chem. 2009, 1, 482–486.

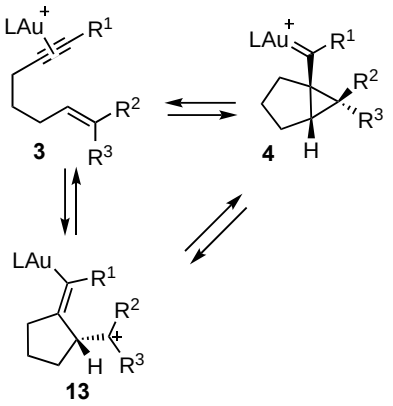
can follow different reaction pathways, leading to different products (Scheme 3).[21] Upon gold(I) coordination, complexes **3** undergo 5-*exo*-dig cycloisomerization leading to cyclopropyl gold(I) carbenes **4**. These can evolve towards dienes **6** and **8**, via single/double cleavage rearrangements. Alternatively, 6-endo-dig cycloisomerization of **3** provides cyclopropyl gold(I) carbene **9**. This can either lead to **10**, by α-proton elimination,[22] or it can undergo a ring expansion, followed by double bond isomerization, providing cyclobutene **10**.



Scheme 3. Reaction pathways for the cycloisomerization of 1,6-enynes.

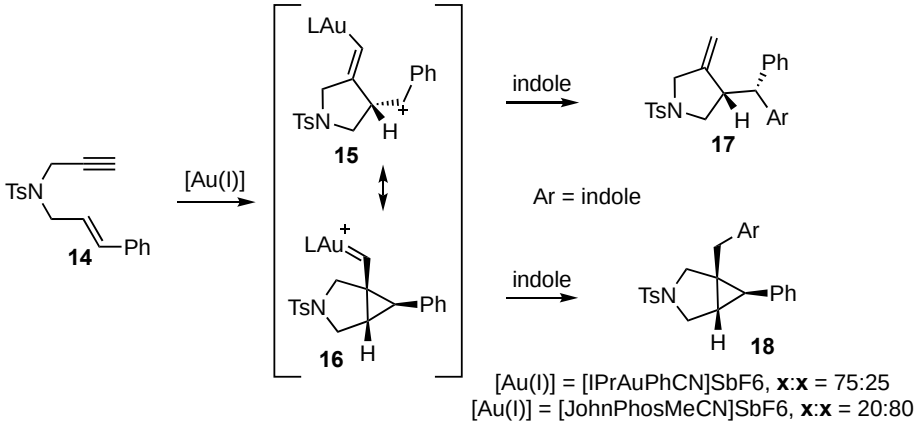
Cyclopropyl gold(I) carbenes **4** and **9** are highly distorted species that can be seen as gold-stabilized homoallylic carbocations (scheme 4).[23] These structures (**4** and **13**) are usually drawn as resonance forms. Very recently, an in-depth computational study on the nature of these intermediates was reported by our group.[24] In this report, an energy barrier for the interconversion of **4** into **13** was located by means of DFT, suggesting that these species are in equilibrium. As found experimentally, the preferential formation of open form **13** versus cyclopropyl gold(I) carbene **4** was found to be highly dependent on the substitution pattern of the alkene and the alkyne.

21. a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148; b) Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105–6111.
22. Young, T. L.; Youn, K. K.; Young, K. C. *J. Org. Chem.* **2009**, *74*, 7922–7934.
23. Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7892–7895.
24. I. Escofet, H. Armengol-Relats, H. Bruss, M. Besora, A. M. Echavarren, Chem. Eur. J. 2020, 26, 15738 – 15745



Scheme 4. Nature of cyclopropyl gold(I) carbene intermediates.

Regarding the effect of the ligand on the gold(I) catalyst for the structure of cyclopropyl gold(I) carbene **16** or its open analogue **15** (scheme 5), a similar scenario to that of simple gold(I) carbenes was found (depicted in the previous section).[25]

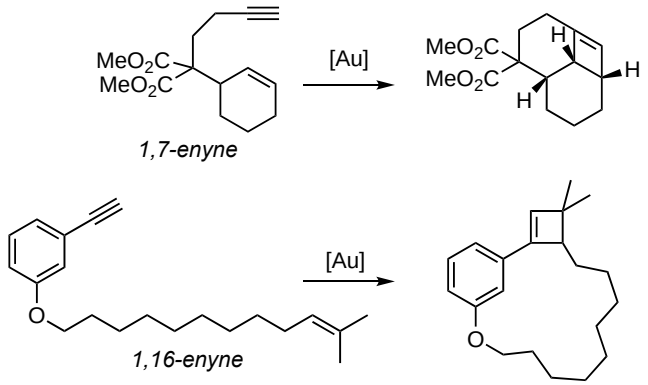


Scheme 5. Ligand effect on the nucleophilic trapping of cyclopropyl gold(I) carbenes

In the reaction of 1,6-enyne **14**, cyclopropyl gold(I) carbene **15/16** is formed by 5-*exo*-dig cyclization, and it is later trapped by a molecule of indole to give products **17** and **18**. Depending on the carbene-like character of intermediate **15/16**, the attack on the carbene carbon is favored, as with the NHC-ligand IPr, leading to **18** as the major product. Using less a σ-donating phosphine ligand (JohnPhos), intermediate **15/16** has a more carbocation-like structure, giving preferentially product **17**.

25. C. H. M. Amijs, C. Ferrer, A. M. Echavarren, Chem. Commun. 2007, 698-700.

Finally, 1,*n*-enynes with n>6 can undergo formal [2+2] cycloadditions[21] under gold(I) catalysis, which provides a useful methodology for the construction of macrocycles, alternative to the reported methods (Scheme 6).[26]



Scheme 6. Cyclization of 1,7 and 1,16-enynes.

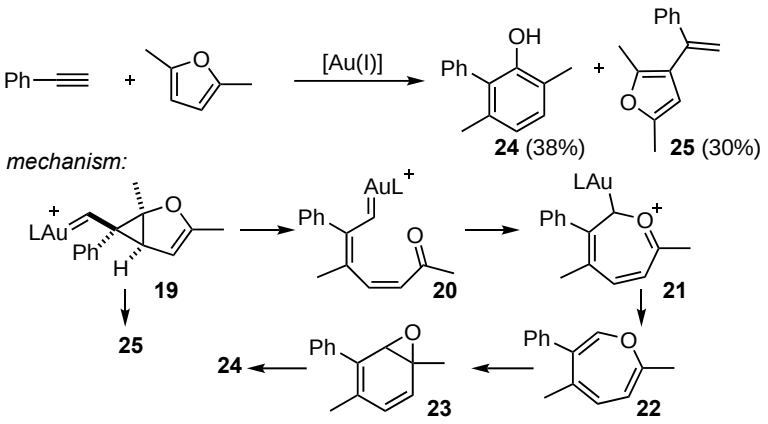
Intermolecular reactions of alkynes with alkenes

While the advances in intramolecular gold(I)-catalyzed reactions of alkynes with alkenes have been very significant over the last two decades (enyne cycloisomerization), the corresponding intermolecular processes have suffered slower development. The reasons why these reactions have resulted more challenging include that the conceivable products of these transformations are also alkenes, which can compete with the initial unsaturated substrates as potential ligands for gold. This can involve product inhibition due to catalyst deactivation by coordination to the product. Additionally, the olefinic products can act as nucleophiles and attack the gold intermediates, leading to oligomers or polymers.[27]

The first example was reported by Hashmi in 2006, in the reaction of phenyl acetylene with 2,5-dimethylfuran (scheme 7).[28] The intramolecular version had been previously developed by the same group using gold(III) salts.[29] The scope of this transformation was later expanded to the use of several alkynes and furans.[30] The mechanism of this reaction was studied experimentally and theoretically, suggesting that cyclopropyl gold carbene **19** is formed upon the attack of the furan to the activated alkyne. This intermediate rearranges

26. a) Obradors, C.; Leboeuf, D.; Aydin, J.; Echavarren, A. M. Org. Lett. 2013, 15, 1576–1579; b) Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. Org. Lett. 2016, 18, 1614–1617.
27 . a) Brown, T. J.; Dickens, M. G.; Widenhoefer, R. A. Chem. Commun. 2009, 6451–6453; b) Urbano, J.; Hormigo, A. J.; de Frémont, P.; Nolan, S. P; Díaz-Requejo, M. M.; Pérez, P. J. Chem. Commun. 2008, 759–761.
28. Hashmi, A. S. K.; Blanco, M. C.; Kurpejović, E.; Frey, W.; Bat, J. W. Adv. Synth. Catal. 2006, 348, 709–713.
29. A. S. K. Hashmi, T. M. Frost, J. W. Bats, J. Am. Chem. Soc. 2000, 122, 11553–11554.
30. Huguet, N.; Leboeuf, D.; Echavarren, A. M. Chem. Eur. J. 2013, 19, 6581–6585.

to generate the oxepine **22** which is in equilibrium with epoxide **23**, that finally leads to furan **24**. Alternatively intermediate **19** can lead to side product **25**.



Scheme 7. Phenol synthesis by reaction of phenyl acetylene with 2,5-dimethylfuran.

The field of intermolecular gold(I) catalysis has been widely developed in the last years, mostly including the reaction of heteroalkynes.[31] Additional examples are discussed in the introduction of Chapter 1.

31. Review intermolecular gold(I) catalysis

Gold Catalysis in Total Synthesis

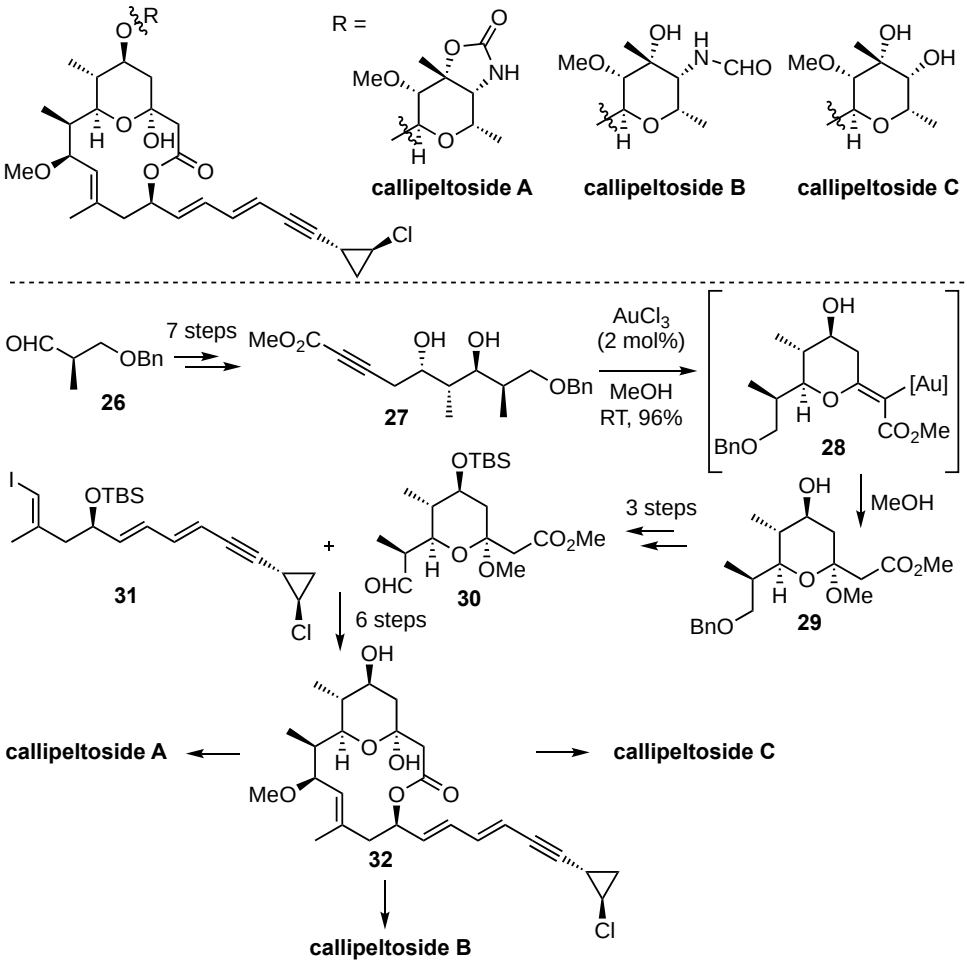
The ability of gold catalysis to build up molecular complexity from simple starting materials has prompted many groups to develop total synthesis of natural products based on a gold-catalyzed key step.[32] Upon electrophilic π-activation several ketalizations, hydroalcoxylations, hydroaminations and cascade cyclizations of 1,n-enynes can be initiated to give polycyclic structures otherwise difficult to access. These strategies have allowed the synthesis of a considerable number of natural products and unnatural analogues, in a concise and efficient manner. In the following section, selected examples will be presented to highlight the versatility of gold catalysis in organic synthesis.

Ketalyzation

The Ley group[33] reported the convergent synthesis of callipeltosides A, B, and C which were isolated from the shallow water lithistida marine sponge *Callipelta sp*.[34] These natural products display important cytotoxic activity against NSCLC-N6 human bronchopulmonary non-small-cell-lung carcinoma (IC_{50} 11.26 – 30.0 $\mu g \cdot mL^{-1}$) and only differ structurally in their sugar moiety.

While other laboratories[35] have completed the syntheses of callipeltosides A and C, this report summarizes the first synthesis of callipeltoside B (scheme 8). In the presence of catalytic amounts of $AuCl_3$, homopropargyl diol **27** (7 steps from aldehyde **26**) undergoes alkoxycyclization to give vinylgold intermendiate **28** which reacts *in situ* with a molecule of methanol do give desired pyrane **29**. Upon functional group interconversion, fragments **30** and **31** are merged over a 6-step sequence to yield common intermediate **32**.

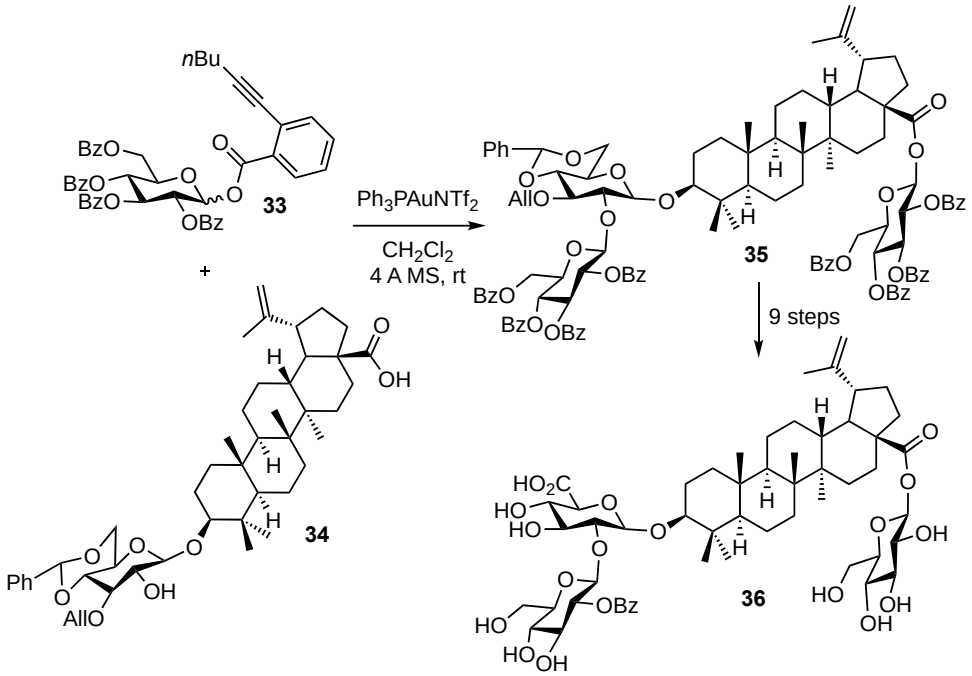
32. a) M. Rudolph, A. S. K. Hashmi, Chem. Soc. Rev. 2012, 41, 2448–2462; b) D. Pflästerer, A. S. K. Hashmi, Chem. Soc. Rev. 2016, 45, 1331–1367; c) J. G. Mayans, H. Armengol-Relats, P. Calleja, A. M. Echavarren, Isr. J. Chem. 2018, 58, 639–658; d) P. Y. Toullec, V. Michelet, Isr. J. Chem. 2018, 58, 578–585.
33. J. R. Frost, C. M. Pearson, T. N. Snaddon, R. A. Booth, S. V. Ley, Angew. Chemie - Int. Ed. 2012, 51, 9366–9371.
34 a) A. Zampella, M. V. D'Auria, L. Minale, C. Debitus, Tetrahedron 1997, 53, 3243–3248; b) A. Zampella, M. V. D'Auria, L. Minale, C. Debitus, C. Roussakis, J. Am. Chem. Soc. 1996, 118, 11085–11088.
35. a) B. M. Trost, J. L. Gunzner, O. Dirat, Y. H. Rhee, J. Am. Chem. Soc. 2002, 124, 10396–10415; b) I. Paterson, R. D. M. Davies, R. Marquez, Angew. Chemie - Int. Ed. 2001, 40, 603–607; c) I. Paterson, R. D. M. Davies, A. C. Heimann, R. Marquez, A. Meyer, 2003, 1–4; d) H. Huang, J. S. Panek, Org. Lett. 2004, 6, 4383–4385; e) B. M. Trost, J. L. Gunzner, J. Am. Chem. Soc. 2001, 123, 9449–9450.



Scheme 8. Total synthesis of callipeltosides A-C.

Glycosylation

The mild reaction conditions under which gold(I)-catalyzed transformations operate allow for a broad functional group tolerance. Thus, gylcosylations methods[36] based on the gold(I)-promoted activation of triple bonds have been developed and applied in a number of total synthesis of sacharides. In comparison, more oxophilic Lewis acids can lead to unwanted rearrangements and uncontrolled product distrubutions.[37]

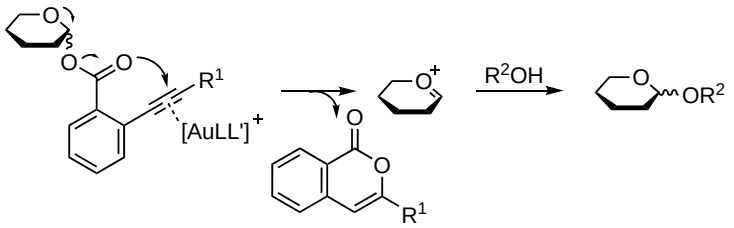


Scheme 9. Total synthesis of **36** by gold(I)-catalyzed glycosylation.

As an example, the group of Yu has emploeyd glycosyl *ortho*-alkynylbenzoates as donors such as **33** in the total synthesis of Betulenic acid trisaccharide **36** (scheme 9).[38] Activation of the alkyne by $Ph_3PAuNTf_2$ triggers the nucleophilic attack of the proximal carbonyl oxygen (scheme 10) and in turn, the cleavage of the glycosidic bond to give a molecule of isocumarin and the corresponding oxonium cation. The nucleophilic alcohol

36. a) Y. Li, Y. Yang, B. Yu, Tetrahedron Lett. 2008, 49, 3604–3608; b). W. Liu, Q. Chen, J. Liang, Z. Du, K. Zhang, X. Zheng, G. A. O'Doherty, Synlett 2015, 26, 1683–1686; c) A. K. Kayastha, S. Hotha, Beilstein J. Org. Chem. 2013, 9, 2147–2155; d) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang, B. Yu, Chem. Eur. J. 2010, 16, 1871–1882; e) B. Yu, Acc. Chem. Res. 2018, 51, 507–516; f) W. Li, B. Yu, Chem. Soc. Rev. 2018, 47, 7954–7984; g) G. Sureshkumar, S. Hotha, Tetrahedron Lett. 2007, 48, 6564–6568. H. S. Hotha, S. Kashyap, J. Am. Chem. Soc. 2006, 128, 9620–9621.
37. a) C. Gauthier, J. Legault, S. Lavoie, S. Rondeau, S. Tremblay, A. Pichette, J. Nat. Prod. 2009, 72, 72–81; b) D. Thibeault, C. Gauthier, J. Legault, J. Bouchard, P. Dufour, A. Pichette, Bioorganic Med. Chem. 2007, 15, 6144–6157.
38. Y. Li, J. Sun, B. Yu, Org. Lett. 2011, 13, 5508–5511.

and carboxylic acid functional groups attack the oxonium intermediate affording the glycosylation product.



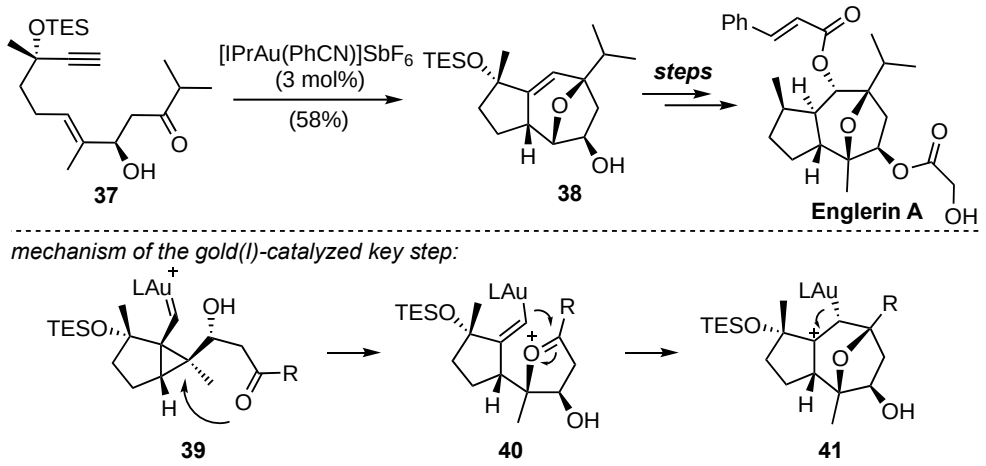
Scheme 10. Gold(I)-catalyzed glycosylation: mechanism.

Enyne cycloisomerization

Enyne cycloisomerization is probably the most common strategy for the synthesis of complex molecules by means of gold (I) catalysis. Among these methodologies, the gold(I)-catalyzed cascade isomerization of ketoenynes allows for the rapid construction of oxygen-bridged tricyclic compounds, in a [2+2+2] cycloaddition reaction.[39] This method was applied to the total synthesis of orientariol F[40] and englerins A and B[41] (scheme 11). The later compounds were isolated from *Phyllanthus engleri* and englerin A was found to be highly active (at nM scale; IC_{50} = 45 nM) against the growth of renal cancer cells.[42] Due the unique properties of this product for the selective inhibition of renal cancer cell line growth, several synthetic approaches have been reported.[32c]

In the gold(I)-catalyzed synthetic strategy, upon 5-*exo*-dig cyclization of ketoenyne **37** (scheme 11), cyclopropyl gold(I) carbene **39** undergoes the intramolecular attack of the carbonyl moiety leading to oxonium intermediate **40**. Prins-type cyclization of **40** leads to cation **41**, which after demetallation delivers product **38**. This intermediate was further derivatized to the natural product.

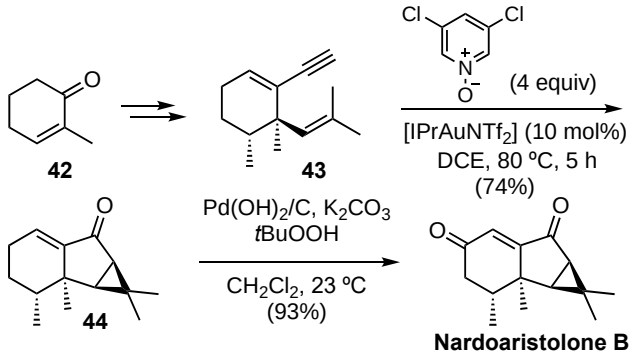
39. E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, Angew. Chem. Int. Ed. 2006, 45, 5452-5455
40. a) E. Jiménez-Núñez, K. Molawi. A. M. Echavarren, Chem. Commun. 2009, 7327–7329, b) C.-L. Wang, B.-F. Sun, S.-G. Chen, R. Ding, G. Q. Lin, J.-Y. Xu, Y.-J. Shang, Synlett 2012, 263–266
41. a) Q. Zhou, X. Chen, D. Ma, Angew. Chem. Int. Ed. 2010, 49, 3513–3516; Angew. Chem. 2010, 122, 3591–3594; b) K. Molawi, N. Delpont, A. M. Echavarren, Angew. Chem. Int. Ed. 2010, 49, 3517–3519
42. a) C. Sourbier, B. I. Scroggins, R. Ratnayake, I. L. Prince, S. Lee, M.-J. Lee, P. L. Nagy, Y. H. Lee, J. B. Trepel, J. A. Beutler, W. M. Linehan, L. Neckers, Cancer Cell 2013, 23, 228–237; b) Y. Akbulut, H. J. Gaunt, K. Muraki, M. J. Ludlow, M. S. Amer, A. Bruns, N. S. Vasudev, L. Radtke, M. Willot, S. Hahn, T. Seitz, S. Ziegler, M. Christmann, D. J. Beech, H. Waldmann, Angew. Chem. Int. Ed. 2015, 54, 3787–3791; c) M. Willot, M. Christmann, Nat. Chem. 2010, 2, 519–520; d) W. J. Chain Synlett 2011, 2605–2608; c) Z. Wu, S. Zhao, D. M. Fash, Z. Li, Z.; W. J. Chain, J. A. Beutler, J. Nat. Prod. 2017, 80, 771–781.



Scheme 11. Total synthesis of englerin A.

This method allowed for a scale-up synthesis of this natural product and several unnatural analogues, which were used to study their biological proprieties.[43]

An example on oxidative gold(I)-catalyzed enyne cyclizations applied to total synthesis was reported by our group in 2015, in an approach to nardoaristolone B (scheme 12).[44] The strategy relied on the gold(I)-catalyzed oxidative cyclization of 1,5-enyne **43**,[45] which was based on a methodology previously described by Liu.[46]

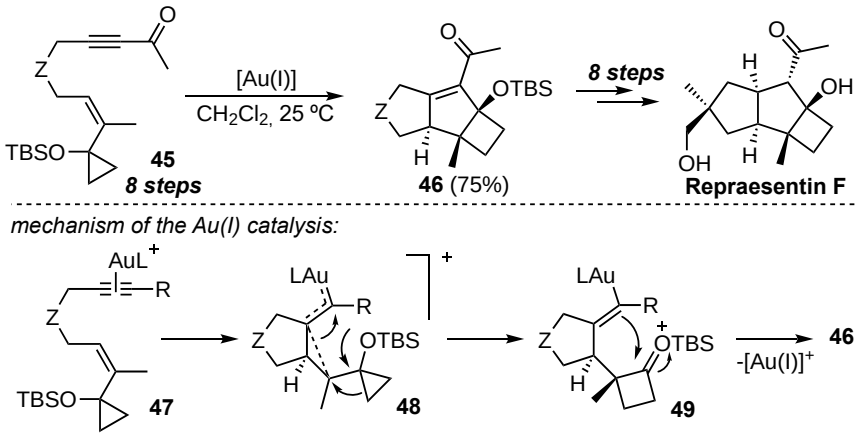


Scheme 12. Total synthesis of nardoaristolone B.

43. a) L. López-Suárez, L. Riesgo, F. Bravo, T. T. Ransom, J. A. Beutler, A. M. Echavarren, ChemMedChem 2016, 11, 1003-1007; b) Wu, Z.; Suppo, J. S.; Tumova, S.; Strope, J.; Bravo, F.; Moy, M.; Weinstein, E. S.; Peer, C. J.; Figg, W. D.; Chain, W. J.; Echavarren, A. M.; Beech, D. J.; Beutler, J. A.; ACS Med. Chem. Lett. 2020, 11, 1711-1716.
44. M. A. Liu, Y.-H. Duan, Y.-L. Hou, C. Li, H. Gao, Y. Dai, X.-S. Yao, Org. Lett. 2013, 15, 1000–1003.
45. A. Homs, M. E. Muratore, A. E.; Echavarren, Org. Lett. 2015, 17, 461–463.
46. D. Vasu, H.-H. Hung, S. Bhunia, S. A. Gawade, A. Das, R.-S. Liu, Angew. Chem. Int. Ed. 2011, 50, 6911–6914.

Substrate **43** was prepared in an enantioselective manner from 2-methyl-2-cyclohexenone (**42**). Palladium catalyzed allylic oxidation of **44** delivered the natural product in excellent yield.

Finally, another recent example on gold(I)-catalyzed enyne cycloisomerizations in the synthesis of natural products, was recently reported by our group (scheme 13).[47] Repraesentin F was isolated from the fruiting bodies of Lactarius repraesentaneus, a fungus species found in Japan, and it was found to be a plant-growth promoter. [48] In our synthetic strategy, the unusual decahydrocyclobuta[a]pentalene skeleton, was constructed by gold(I)-catalyzed cycloisomerization cascade of cyclopropyl enyne **45**. A similar methodology was previously developed for related allene-vinylcyclopropane substrates.[49]



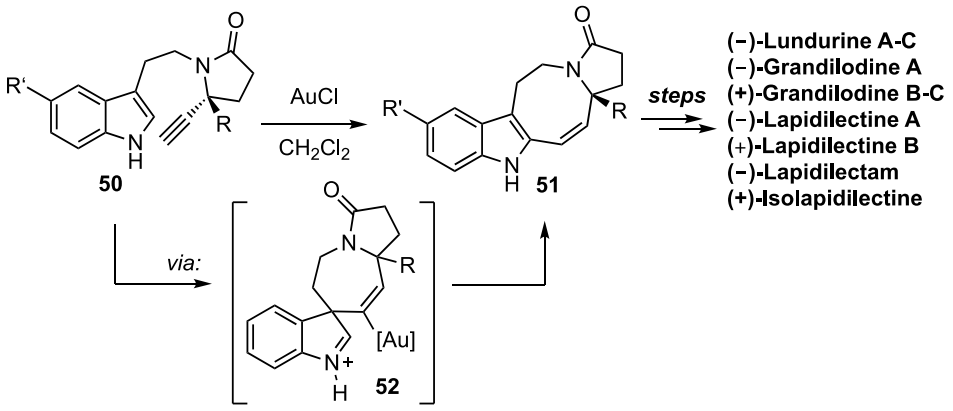
Scheme 13. Total synthesis of repraesentin F. Z = C(CO_2Me); [Au(I)] = *t*BuXPhosAuMeCN]BAr_4^F.

The gold(I)-catalyzed key step starts with the activation of enyne **45**, which upon coordination to gold in complex **47** undergoes a 5-*exo*-dig cycloisomerization leading to intermediate **48**. This suffers ring expansion to deliver **49**. A Prins-type cyclization affords tricyclic product **46**, which was converted into the natural product in 8 steps.

47. S. Ferrer, A, M. Echavarren, Org. Lett. 2018, 20, 5784−5788
48. Hirota, M.; Shimizu, Y.; Kamo, T.; Makabe, H.; Shibata, H.; Biosci., Biotechnol., Biochem. 2003, 67,1597−1600.
49. A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, Org. Lett. 2013, 15, 4580-4583.

Hydroarylation

Our group has recently exploited the potential of the gold-catalyzed intramolecular hydroarylation of indoles[50] to construct the pyrroloazocine indole core in **51** (scheme 14). This common intermediate was used in the total syntheses of lundurines A-C[51] and seven members of the lapidilectine/grandilodine[52] family of natural products. The gold(I) catalyst employed in this case was AuCl (no ligand) and the formation of a *spiro*-intermediate **52** was experimentally proven. Substrate **50** undergoes a 7-*endo*-dig cycloisomerization and a final 1,2-alkyl shift leads to product **52**.



Scheme 14. Total synthesis of lundurinn, grandilodines and lapidilectines.

Miscellaneous examples

In the last years a number of research groups have chosen homogeneous gold catalysis for their key steps in several total syntheses of natural products. Some of the latest examples were reported by the group of Carreira and Reisman.

50. a) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, Chem. - A Eur. J. 2007, 13, 1358–1373; b) W. Damm, J. Dickhaut, F. Wetterich, B. Giese, Tetrahedron Lett. 1993, 34, 431–434; c) L. Zhang, Y. Wang, Z. J. Yao, S. Wang, Z. X. Yu, J. Am. Chem. Soc. 2015, 137, 13290–13300.; d) C. Ferrer, A. Escribano-Cuesta, A. M. Echavarren, Tetrahedron 2009, 65, 9015–9020.
51. M. S. Kirillova, M. E. Muratore, R. Dorel, A. M. Echavarren, J. Am. Chem. Soc. 2016, 138, 3671–3674.
52. F. M. Miloserdov, M. S. Kirillova, M. E. Muratore, A. M. Echavarren, J. Am. Chem. Soc. 2018, 140, 5393–5400.

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Chapter 1.
Acetylene Activation by Gold(I) Catalysis

UNIVERSITAT ROVIRA I VIRGILI
GOLD(I)-CATALYZED CYCLOADDITIONS AND THEIR APPLICATION IN THE SYNTHESIS OF NATURAL PRODUCTS
Helena Armengol i Relats

Introduction

Acetylene

Acetylene generation

Acetylene is the simplest possible alkyne, with its molecular formula being C_2H_2. It is a naturally occurring gas which has been detected in interstellar space.[53] It is an indispensable raw material for modern society, due to its high combustion energy, which is useful to obtain high temperature flames for welding, in construction, for example.[54] However, its use in base chemical synthesis is scarcer due to its high production costs.[55] Although acetylene-based routes are often shorter and more selective, olefin-based alternatives result overall cheaper due to the high energy needed for the production of acetylene.

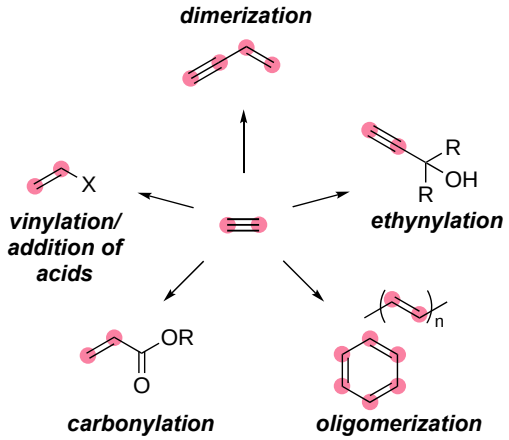
Formation of acetylene is highly endothermic, with a standard free enthalpy of formation (ΔH^o_f) of 226 kJ/mol and this explains that its synthesis is expensive, because it requires very high temperatures: higher than 1000 K for its formation from methane. Additionally, as shown by its ΔH^o_f, acetylene is thermodynamically unstable, and at 2000K it decomposes into elemental carbon and molecular hydrogen.

The most common synthetic approaches to acetylene are from coal and quicklime (calcium oxide) and from cracking processes. In the first, initially calcium carbide is formed by reaction of quicklime and coal at 2000 ºC. This step also produces a stoichiometric amount of carbon monoxide, which can be derived to synthesis gas. Secondly, CaC_2 and water produce acetylene and calcium hydroxide. Regarding the cracking processes, they can be divided in three classes: partial combustion, electrothermic cracking and thermal cracking.

Chemical applications of acetylene

Chemical activation of acetylene has been applied to different fields of chemistry: starting with polymer science but also homogeneous and heterogeneous catalysis for small molecule synthesis. Among the chemical uses of acetylene, we can distinguish five main categories (scheme 15):[55] dimerization, ethynylation, oligomerization, carbonylation and vinylation. Probably the most important application is its use for the synthesis of vinylchloride, as this monomer is widely used to prepare PVC (polyvinylchloride).

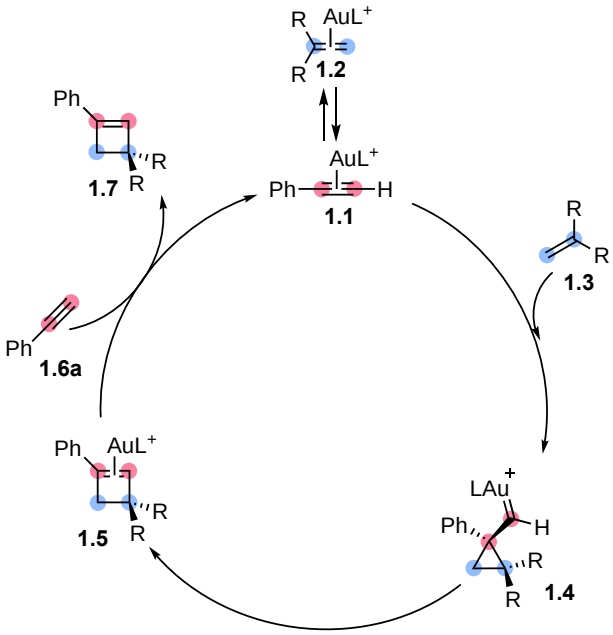
53. J. H. Lacy, N. J. Evans II, J. M. Achtermann, D. E. Bruce, J. F. Arens, J. S. Carr, *Astrophys. J. Lett.* **1989**, *342*, L43–L46.
54. A. Williams, D. B. Smith, *Chem. Rev.* **1970**, *70*, 267–293.
55. I. T. Trotuş, T. Zimmermann, F. Schüth, *Chem. Rev.* **2014**, *114*, 1761–1782.



Scheme 15. Chemical transformations of acetylene.

Intermolecular Gold(I)-Catalyzed Reactions of Alkynes with Alkenes

As mentioned in the General Introduction, the field of intermolecular gold(I) catalysis has suffered slower development compared to the analogous intramolecular transformations. As previously described, the first example of an intermolecular gold(I)-catalyzed reaction between an alkyne and an alkene was reported by the group of Hashmi in 2006, using furans as the olefin partner.[28] Few years later, our group described the gold(I)-catalyzed (2+2)-cycloaddition of terminal arylalkynes with simple alkenes.[56] In this transformation, as previously postulated for the intramolecular version, after electrophilic activation of the phenylacetylene in complex **1.1**, olefin **1.3** attacks giving rise to cyclopropylgold(I) carbene **1.4**. This intermediate undergoes ring expansion to afford complex **1.5**, which after ligand exchange, delivers cyclobutene **1.7** and restarts the catalytic cycle.

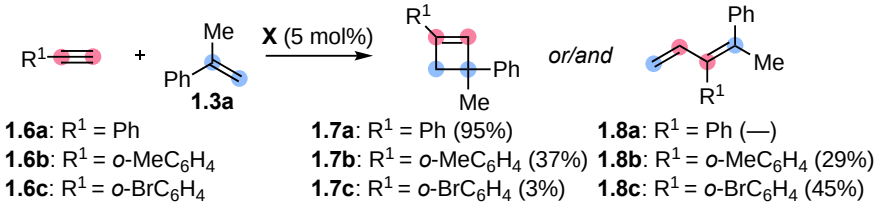


Scheme 16. Mechanism of the gold(I)-catalyzed (2+2)-cycloaddition of alkynes with alkenes.

The enantioselective version of this transformation was achieved using digold-Josiphos complexes.[57]

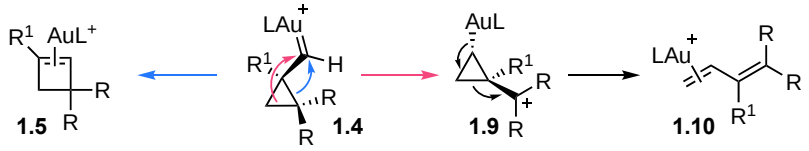
56. V. López-Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294.
57. C. García-Morales, B. Ranieri, I. Escofet, L. López-Suarez, C. Obradors, A. I. Konovalov, A. M. Echavarren, *J. Am. Chem. Soc.* **2017**, *139*, 13628–13631.

When aryl acetylene **1.6** presents *ortho*-substituents, dienes **1.8** were formed, along with the corresponding cyclobutenes **1.7** (scheme 17).[58] While phenylacetylene (**1.6a**) gave **1.7a** as a single product and isomer, *ortho*-tolylacetylene (**1.6b**) gave a 1.3:1 mixture of cyclobutene **1.7b** and diene **1.8b**. (*Ortho*-bromophenyl)acetylene (**1.6c**) delivered diene **1.8c** as the main product, and only traces of cyclobutene **1.7c** were obtained.



Scheme 17. Cyclobutene **1.7** *versus* diene **1.8** formation.

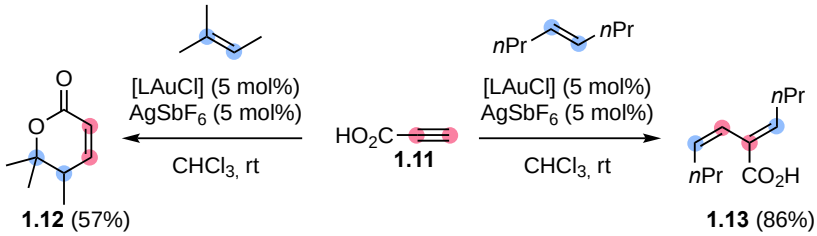
Dienes **1.8** arise from the same cyclopropylgold(I) carbene intermediate **1.4** (scheme 18), which instead of ring expansion towards **1.5** (blue pathway), suffers a 1,3-migration giving carbocation **1.9** (pink pathway). Upon gold elimination, complex **1.10** gets formed, which would ultimately lead to product **1.8**, after decomplexation. DFT calculations on this mechanism and experimental studies conclude that the selectivity between both pathways depends essentially on the bulkiness of aryl R^1 and not on electronic factors.



Scheme 18. Proposed mechanism for the evolution of **1.4** towards **1.5** and **1.10**.

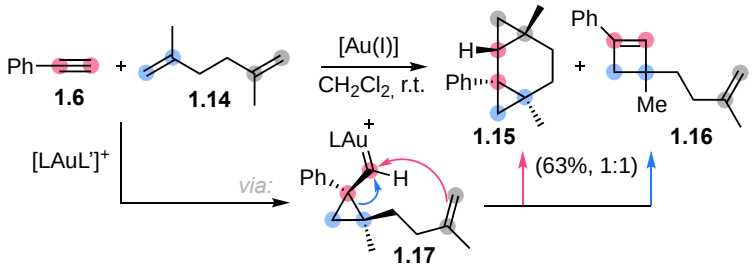
This formal insertion of the alkyne between the two olefinic carbons had been reported before in the reaction of propiolic acid (**1.11**) with cyclic olefins, by the groups of Yu and Shin (scheme 19).[59] In this case, depending on the olefin partner, lactones **1.12** were formed, in a formal (4+2)-cycloaddition reaction, or the enyne metathesis could take place affording diene products **1.13**.

58. M. E. De Orbe, L. Amenós, M. S. Kirillova, Y. Wang, V. López-Carrillo, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2017**, *139*, 10302–10311.
59. H. S. Yeom, J. Koo, H. S. Park, Y. Wang, Y. Liang, Z. X. Yu, S. Shin, *J. Am. Chem. Soc.* **2012**, *134*, 208–211.



Scheme 19. Gold(I)-catalyzed reactions of propiolic acid with olefins.

In the first report for the reaction arylalkynes with olefins, 1,5-dienes such as **1.14** were also used as reaction partners.[56] As an example, the reaction between phenylacetylene (**1.6**) and 2,5-dimethyl-1,5-hexadiene (**1.14**) afforded a 1:1 mixture of cyclobutene **1.16** and tricyclo[5.1.0.0^{2,4}]octane **1.15** (scheme 20). This tricyclic compound (**1.15**) arises from an intramolecular trapping of cyclopropyl gold(I)carbene **1.17** with the second olefin moiety, in a cyclopropanation manner. This pathway competes with the previously described ring expansion, leading to cyclobutenes **1.16** (or analogues **1.7** in scheme 16).



Scheme 20. Reaction of phenylacetylene with 2,5-dimethyl-1,5-hexadiene.

This tricyclic skeleton is found in few natural products such as myliol and waitziacuminone (figure 3). The latter will be presented in the following section. On the other hand, myliol[60] presents an additional fused 5-membered ring and the opposite relative configuration between the two cyclopropane rings.

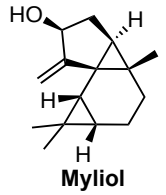
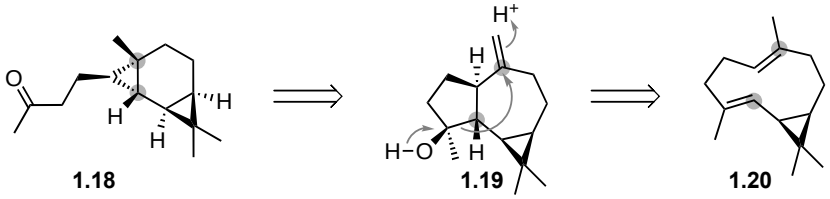


Figure 3. Absolute configuration of myliol.

60. H. Nozaki, *J. Chem. Soc. Perkin Trans. 2* **1979**, 514–518.

Waitziacuminone

Waitziacuminone (**1.18**) is a naturally occurring sesquiterpenoid which was first isolated in 1989 from the aerial parts of *Waitzia acuminata*, an Australian plant species from the tribe *Inuleae*.[61] This natural product has been isolated as an enantiopure compound in two additional occasions from two other plant species, namely *Jamesoniella colorata*[62] and *Baccharis dracunculifolia.*[63]



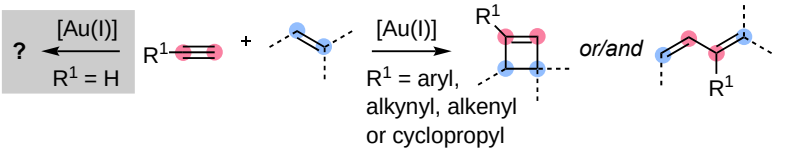
Scheme 21. Waitziacuminone (**1.18**), spathulenol (**1.19**) and bicyclogermacrene (**1.20**).

In its first isolation paper, Jakupovic et al. propose that waitziacuminone is a decomposition product from spathulenol (**1.19**) (scheme 21). This is a very common sesquiterpene alcohol, counting with over 8000 references in SciFinder. It is formed upon oxidation of bicyclogermacrene (**1.20**), even by simple exposition of this diene to air, at room temperature.[64] While **1.19** and **1.20** have been synthetically prepared in different occasions,[65] no total synthesis of **1.18** had been reported to date. Additionally, no biological testing of **1.18** has been done to evaluate its proprieties.

61. J. Jakupovic, A. Schuster, F. Bohlmann, R. M. King, L. Haegi, *Phytochemistry* **1989**, *28*, 1943–1948.
62. U. M. Hertewich, J. Zapp, H. Becker, *Phytochemistry* **2003**, *63*, 227–233.
63. P. Weyerstahl, C. Christiansen, H. Marschall, *Liebigs Ann.* **1995**, 1039–1043.
64. M. Toyota, H. Koyama, M. Mizutani, Y. Asakawa, *Phytochemistry* **1996**, *41*, 1347–1350.
65 . H. Surburg, A. Mondon, *Chem. Ber.* **1981**, *114*, 118–131; F.P. van Lier, T. G. H. Hesp, L. M. van der Linde, A. J. A. van der Weerdt, *Tetrahedron Lett.* **1985**, *26*, 2209–2210; D. N. Tran, N. Cramer, *Chem. Eur. J.* **2014**, *20*, 10654–10660.

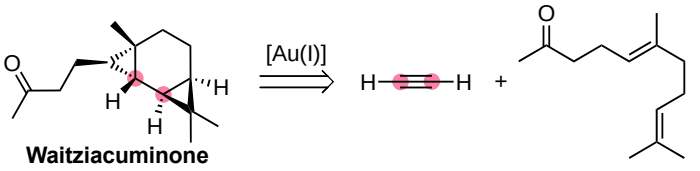
Objectives

The main goal of this chapter is to explore the reactivity of acetylene as reaction partner in intermolecular gold(I)-catalyzed reactions with alkenes (scheme 22). We will study the mechanism of these new transformations by means of DFT calculations.



Scheme 22. Exploring the reactivity of acetylene with alkenes under gold(I) catalysis.

Next we will examine the reaction between acetylene and 1,5-dienes to afford tricyclo[5.1.0.0^{2,4}]octanes (as shown for arylalkynes in scheme 20). Finally, we aim to prove the synthetic utility of this methodology in a one-step total synthesis of waitziacuminone from geranyl acetone (scheme 23).



Scheme 23. Retrosynthetic proposal for the total synthesis of waitziacuminone.

Results and Discussion

Reaction Discovery and Optimization

Although acetylene gas is commercially available in pressurized bottles, special equipment such as high-pressure reactors and the corresponding pressure regulator and connector is required in order to use them. Alternatively, as mentioned in the Introduction, acetylene can be prepared by reaction of calcium carbide with water. Inspired by the two-vessel Y-shaped flask designed by the group of Ananikov,[66] we decided to employ this convenient set up for the *in-situ* generation of acetylene in our gold(I) catalysis (Figure 4). A solution of catalyst and substrate were placed in one of the vessels and calcium carbide in the other, covered with a layer of organic solvent.[67] Upon water addition and stirring, the CaC_2 gets in contact with the water producing acetylene, which diffuses within the Y-shaped flask and dissolves in the solution in the second vessel, containing the catalyst and substrate.

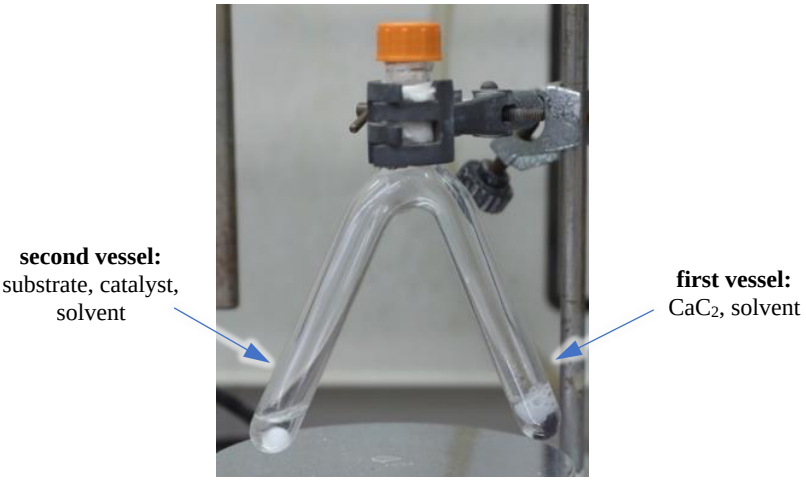
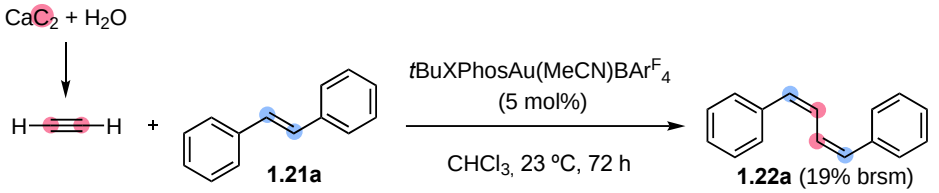


Figure 4. Y-shaped two-vessel flask.

Initially, we evaluated the reaction of acetylene with *E*- and *Z*-stilbene in the presence of [*t*BuXPhosAuMeCN]BAr^F_4 as the catalyst (Scheme 24),[68] which was previously found to be the best catalyst for intermolecular [2+2] cycloaddition reactions between alkynes and alkenes. We were very pleased to find that *E*-stilbene (**1.21a**) afforded (*Z*,*Z*)-1,3-diene **1.22a**

66. V. V. Voronin, M. S. Ledovskaya, E. G. Gordeev, K. S. Rodygin, V. P. Ananikov, *J. Org. Chem.* **2018**, *83*, 3819–3828.
67. This solvent needs to have higher density than water, so that when water is added, it stays above the protective solvent layer and the interaction with CaC_2 does not occur until stirring is started.
68. These experiments were performed by Dr. M. Elena de Orbe during her PhD studies.

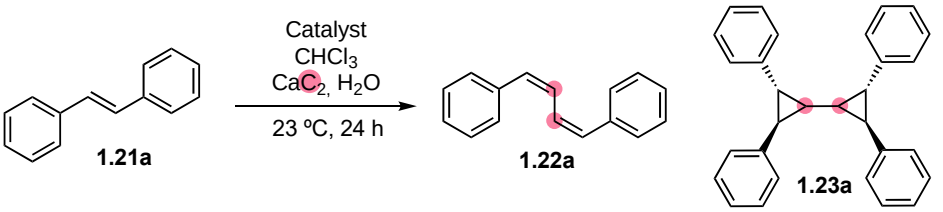
in 19% yield as a single isomer, in which the two carbon units derived from acetylene are formally inserted between the two olefinic carbons of stilbene.



Scheme 24. Initial attempt for *the* activation of acetylene by a gold(I) catalyst.

On the other hand, *Z*-stilbene was unreactive under the same reaction conditions. Thus, we decided to perform the reaction optimization using *E*-stilbene as model substrate. Brief catalyst screening revealed the formation of *bis*cyclopropane **1.23a** as the main product, depending on the ligand of choice (table 1).[69] This prompted us to optimize the two reactions parallelly.

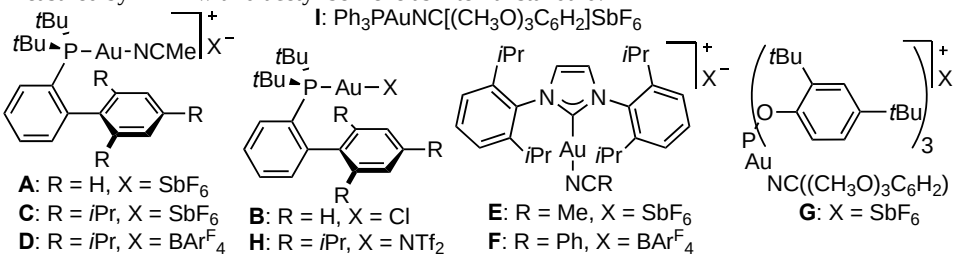
Table 1. Initial catalyst screening for the reaction with **1.21a**.



Entry	Catalyst	Conversion [%][a]	1.22a [%][a]	1.23a [%][a]
1	none / $AgSbF_6$ / $NaBAr^F_4$	0	0	0
3	**C**	11	7	-
4	**H**	6	5	-
5	**D**	35	25	<1
6	**E**	7	<1	6
7	**F**	(64)	1	56
8	**G**	18	4	4
9	**I**	5	1	1
10	**A**	41	24	11
11	**B** + $NaBAr^F_4$	(58)	15	41
12	$InCl_3$	0	0	0
13	$PtCl_2$	0	0	0
14	CuCl	0	0	0
15	$Rh(OAc)_2$	0	0	0

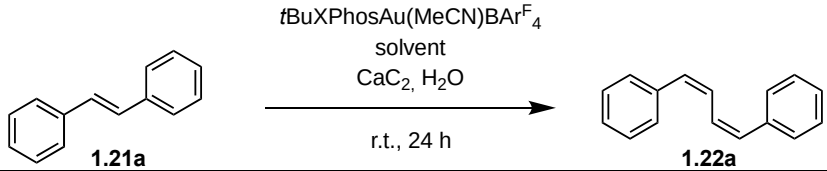
69. These experiments were performed by Dr. Dagmar Scharnagel.

[a] Measured by NMR with diacetyl benzene as internal standard.



We started the optimization towards the formation of diene **1.22a** with a solvent screening (table 2). We found that dichloromethane provided the highest conversion, although similar to chloroform. Aromatic solvents provided similar conversions and yields, although the reactants were not completely soluble.

Table 2. Solvent screening.

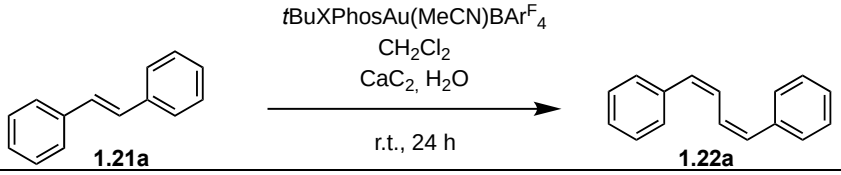


Entry	Solvent	Conversion [%][a]	1.22a [%][a]	1.23a [%][a]
1	$CHCl_3$	35	25	-
2	CH_2Cl_2	45	33	-
3	$ClCH_2CH_2Cl$	30	21	-
4	THF[b]	0	-	-
5	PhMe[b,c]	9	9	-
6	PhCl	41	28	-
7	$PhCF_3$[c]	38	25	2

[a] Measured by NMR with diacetyl benzene as internal standard. [b] $CHCl_3$ in the chamber with carbide. [c] Reactants not soluble enough.

Next, we evaluated the effect of the temperature and concentration (table 3). We found 0.2 M as optimal, since higher concentration provided a dirtier reaction crude and lower concentration gave lower conversion and yields (entries 1-3). Lowering the temperature also translated into lower conversion and increasing it did not improve the results obtained at room temperature (entries 4-7). In order to get reliable results, we used chloroform instead of dichloromethane for the reactions at 40 and 60 ºC.

Table 3. Concentration and temperature screening.



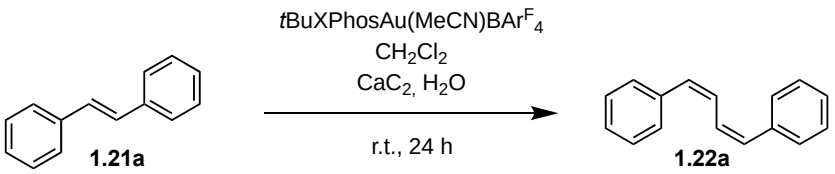
1.21a **1.22a**

Entry	Concentration	Temperature	Conversion [%][a]	1.22a [%][a]	1.23a [%][a]
1	0.5 M	23 ºC	46	30	diverse
2	0.2 M	23 ºC	45	33	-
3	0.05 M	23 ºC	27	19	-
4	0.2 M	7 ºC	24	18	-
5	0.2 M	40 ºC	27	18	-
6[b]	0.2 M	40 ºC	24	23	-
7[b]	0.2 M	60 ºC	19	11	-

[a] Measured by NMR with diacetyl benzene as internal standard. [b] In $CHCl_3$ instead of CH_2Cl_2.

We found that reducing the catalyst loading below 5 mol% had a detrimental effect on the conversion and the yield of the reaction (table 4, entries 2-4). However, increasing it to 10 mol% delivered higher conversion of the starting material but provided the same amount of product **1.22a** as with half that catalyst loading. This indicates product decomposition or the presence of side reactions with larger concentration of the catalyst. We also slightly increased the acetylene pressure by increasing the amount of CaC_2 (maintaining the volume of the flask) (entry 5), albeit no significant effect was observed.

Table 4. Catalyst loading and pressure evaluation.



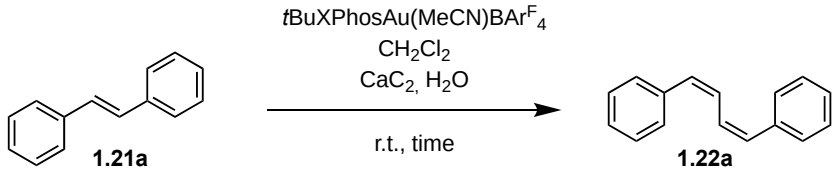
1.21a **1.22a**

Entry	Equiv. CaC_2	mol% cat.	Conversion [%][a]	1.22a [%][a]	1.23 a [%][a]
1	5.9	10	60	34	-
2	5.9	5	45	33	-
3	5.9	4	32	20	-
4	5.9	2	17	12	-
5	8.8	5	42	27	-

[a] Measured by NMR with diacetyl benzene as internal standard.

Finally, we stopped the reaction at different times to monitor its progress (table 5). We found that shorter time translated into lower conversion and yield (entry 3) while longer time afforded higher conversion but also lower yield (entry 1). This again was in agreement with the proposed product decomposition or side reactions with extended reaction times.

Table 5. Time monitoring.

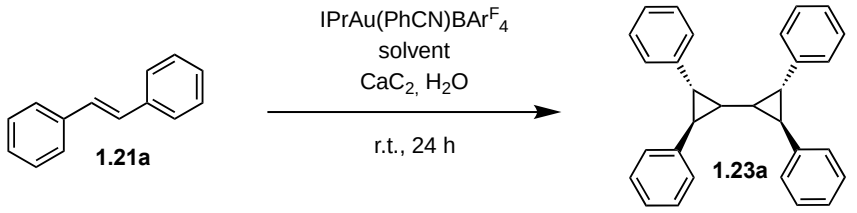


Entry	Reaction time (h)	Conversion [%][a]	1.22a [%][a]	1.23a [%][a]
1	48	49	32	messy
2	24	45	33	-
3	14	39	28	-

[a] Measured by NMR with diacetyl benzene as internal standard.

Next, we optimized the reaction towards the formation of biscyclopropane **1.23a**. Noteworthy, in this reaction acetylene acts as a double carbene, reacting with two units of stilbene **1.21a** in a stereoselective manner. First, we evaluated the solvent effect and monitored the reaction timing (tables 6 and 7, respectively). Again, dichloromethane was found to be the optimal solvent for this transformation.

Table 6. Solvent screening for the reaction towards **1.23**

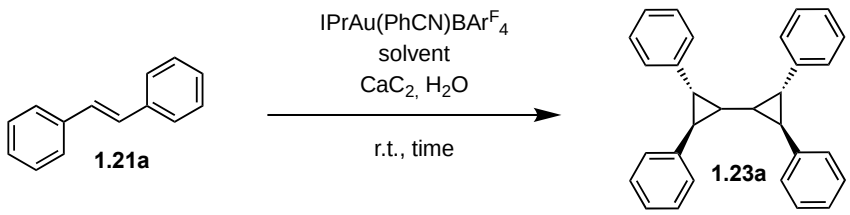


Entry	Solvent	Conversion [%][a]	1.22a [%][a]	1.23a [%][a]
1	$CHCl_3$	(64)	1	56
2	CH_2Cl_2	(87)	3	84
3	PhCl	(58)	1	57

[a] Measured by NMR with diacetyl benzene as internal standard.

After 3 hours reaction time, over 50% conversion was achieved but only after 24 h almost 90 % conversion was observed (table 7).

Table 7. Time monitoring.

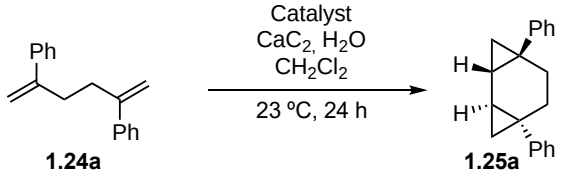


Entry	Reaction time (h)	Conversion [%][a]	1.22a [%][a]	1.23a [%][a]
1	24	(87)	3	84
2	14	(75)	2	68
3	6	(67)	2	59
4	3	(57)	1	45

[a] Measured by NMR with diacetyl benzene as internal standard.

This class of *bis*cyclopropanes had not been observed before in intermolecular reactions of alkynes with simple alkenes. However, double cyclopropanation of 1,5-dienes was obtained in a *ca* 1:1 ratio with the corresponding cyclobutene, when aryl-alkynes were used as substrates.[56] When 1,5-diene **1.24a** was used in the reaction with acetylene, tricyclo[5.1.0.02,4]octane **1.25a** was obtained as the only product and as a single isomer. The different steric and electronic properties of the gold(I) catalysts of choice did not influence the reaction outcome significantly, since both IPr, JohnPhos and *t*BuXPhos delivered the desired product in comparable yields and selectivities (table 8).

Table 8. Catalyst and concentration screening for the reaction with **1.24a**.



Entry	Catalyst	Concentration	Yield 6a [%]
1[a]	JohnPhosAu(MeCN)BAr$^F_4$	0.2M	64
2	*t*BuXPhosAu(MeCN)BAr$^F_4$	0.2M	67
3	*t*BuXPhosAu(MeCN)BAr$^F_4$	0.05M	67
4	IPrAu(PhCN)BAr$^F_4$	0.2M	51
5	IPrAu(PhCN)BAr$^F_4$	0.05M	63
6	(2,4-*t*BuC$_6$H$_3$O)$_3$PAu[(CH$_3$O)$_3$C$_6$H$_2$CN]SbF$_6$	0.2M	19[b]
7	Ph$_3$PAu[(CH$_3$O)$_3$C$_6$H$_2$CN]SbF$_6$	0.2M	25[b]
8	AuCl	0.2M	-

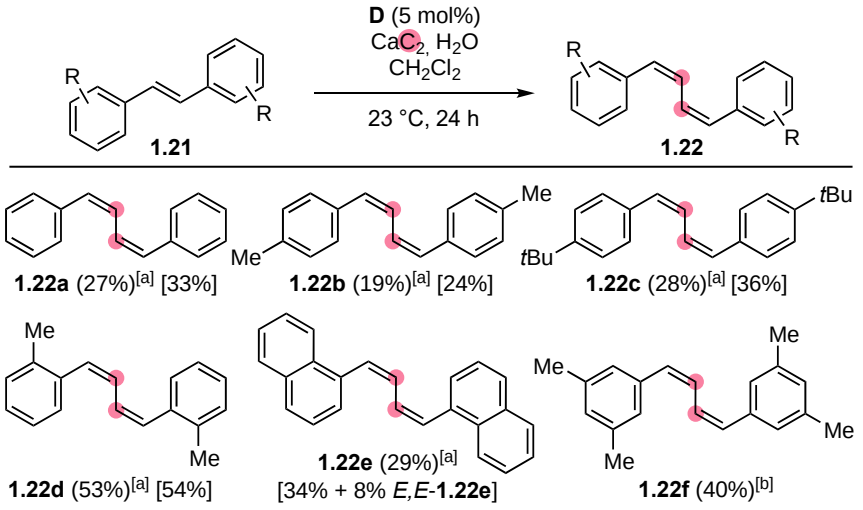
9	AuCl/LiCl	0.2M	-

[a] Complex prepared *in situ* from equimolar amounts of JohnPhosAuCl and $NaBAr^F{}_4$.
[b] Isolated as a mixture with starting material and minor side product.

Scope and Limitations

We investigated the scope under the optimized reaction conditions. Limited by the low molecular weight of acetylene, we could not use light olefin substrates, thus we selected stilbenes **1.21** as the optimal reaction partners. With the optimized reaction conditions, we found that *ortho*-, *meta*- and *para*-methyl substituents on the aromatic rings were well tolerated, giving (*Z*,*Z*)-1,3-diene products **1.22** in low to moderate yields (table 9). 1-naphtyl stilbene also delivered the desired product **1.22e**, although *E*/*Z* double bond isomers were obtained in this case. Strong electron-donating or electron-withdrawing groups provided complex mixtures (due to over-reactivity) and no reaction, respectively.

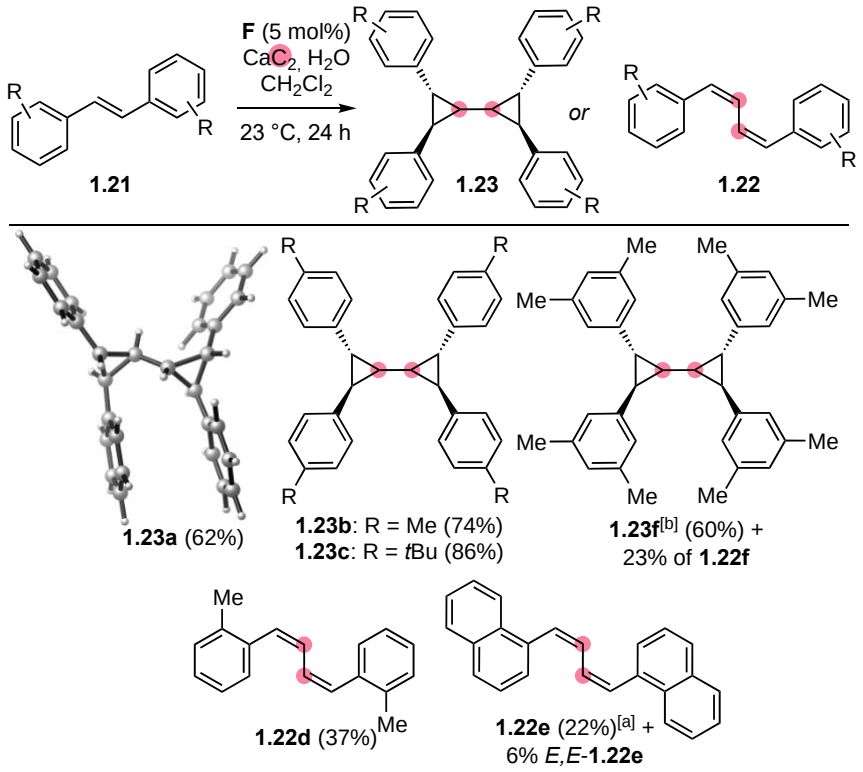
Table 9. Scope for the formation of dienes**1.22**.



For the double cyclopropanation reaction, *meta*- and *para*-substituents were well tolerated, delivering products **1.23** in moderate to good yields (table 10). However, *ortho*-substitution impeded the second cyclopropanation to take place, and rearrangement into 1,3-dienes **1.22** was faster, delivering only product **1.22e**. *Meta*-substitution afforded a mixture of products for stilbenes **1.23f** and **1.22f**. Interestingly, a single isomer of biscyclopropanes **1.23** was obtained, this being the *meso* product. This was confirmed by x-ray diffraction of crystalline **1.23a**. Considering that a possible mixture of diasteroisomers could be difficult to determine by NMR, a sample of **1.23a** was analyzed by chiral GC,

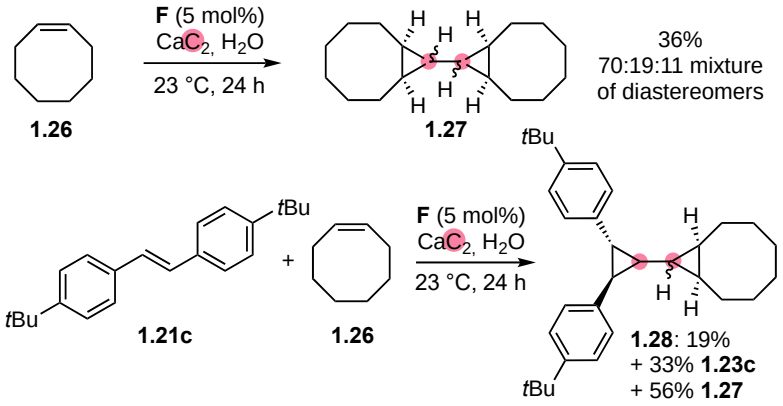
HPLC and SFC techniques,[70] and in none of the analysis more than one pick was observed. This indicates that only one isomer is present in the product and that it is a *meso* compound.

Table 10. Scope biscyclopropanes **1.23**.



Cyclooctene (**1.26**) was also submitted to the optimized reaction conditions, alone and together with functionalized stilbene **1.21c** (scheme 25). In the first case, we found that three different isomers of biscyclopropane product **1.27** were formed. From the cross-substrate experiment, we obtained the three possible products: **1.28**, **1.23c** and **1.27**.

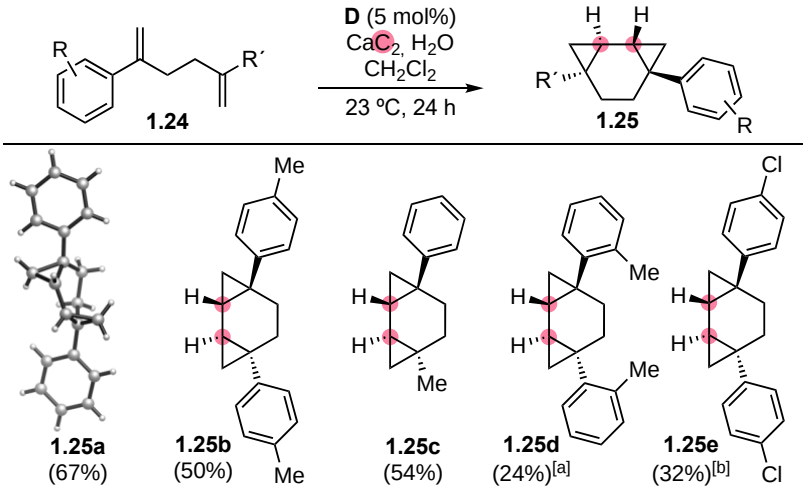
70. Add ChromTAE results.



Scheme 25. Reactions with cyclooctene (**x**).

Similarly, for the reaction with 1,5-dienes **1.24**, *ortho*-methyl diene **1.24d** delivered tricyclic **1.25d** in low yields, while *para*-substitution was well tolerated giving good yields of products **1.25b** (table 11). Even *para*-chloro substrate **1.24e** delivered the desired product **1.25e**, although longer reaction times were needed, due to its inherent lower reactivity. Unsymmetric diene **1.24c** afforded the corresponding tricyclic compound **1.25c** in good yield. The relative configuration of the 4 newly formed stereocenters could be determined by x-ray diffraction of crystalline **1.25a**.

Table 11. Scope tricyclic compounds **1.25**.



In an attempt to expand the scope of this transformations, 1,6-dienes **1.29a-d** were submitted to the optimized reaction conditions (figure 5). Unfortunately, the reaction was found not to be selective, providing inseparable mixtures of different products.

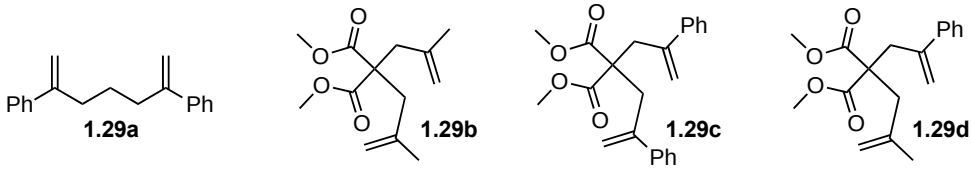
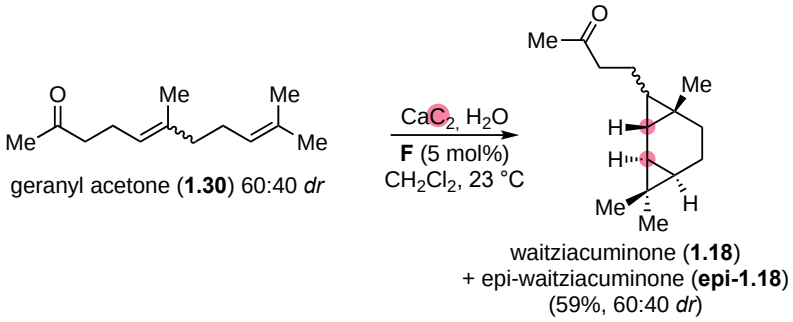


Figure 5. Tested substrates which did not provide good results.

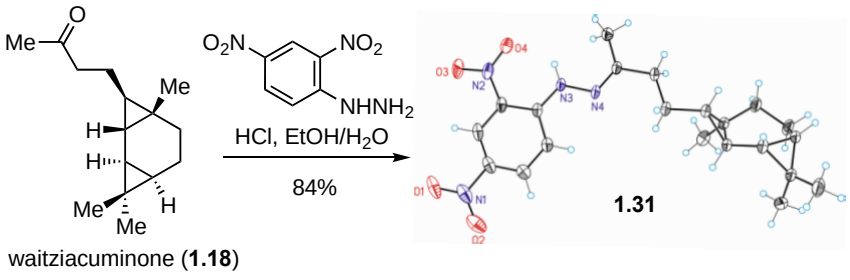
Total Synthesis of Waitziacuminone

To probe the synthetic usefulness of this methodology, we applied it to the one-step total synthesis of waitziacuminone (**1.18**), by preforming a double cyclopropanation of geranyl acetone (**1.30**), as the diene substrate (scheme 26). Using the commercially available 60:40 mixture of geranyl/neryl acetone provided a 60:40 mixture of epimers **1.18** and **epi-1.18**.



Scheme 26. Total synthesis of waitziacuminone.

The natural product was obtained as a single isomer when using diastereomerically pure geranyl acetone (**1.30**), proving that the reaction is stereospecific. Its relative configuration was confirmed by x-ray diffraction of its hydrazine derivative **1.31** (scheme 27). This is the first total synthesis of this sesquiterpene to date. We used a small quantity of the synthetic natural product to evaluate its biological activity.[71]



Scheme 27. Formation of crystalline hydrazine **1.31**.

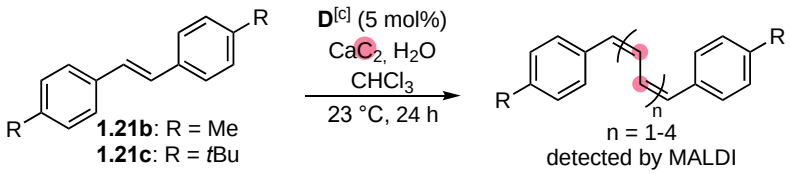
71. Collaboration with Australia.

Mechanistic investigations

Acetylene oligomerization

Interested by the low yielding of the reaction for the formation of dienes **1.22**, we analyzed the crude material by mass spectrometry and we found products with up to 4 units of acetylene (scheme 28). This indicates that products **1.22** are suitable substrates to engage in the gold(I)-catalyzed reaction with acetylene and thus continue to react providing acetylene-oligomers. Attempts to optimize the polymerization reaction in order to get larger oligomers were not successful when using the Y-shaped reactor. We envisioned that higher pressures of acetylene would provide larger oligomers. Unfortunately, even using commercially available acetylene gas, 1-1.2 bar is the highest pressure we have been able to use this far, obtaining similar results to those in the Y-shaped reactor.

We also made a small temperature screening, which showed that indeed more polymerization is obtained at higher temperatures (observing broader signals by ^{1}H-NMR).[72] However, quantification methods to determine the amount of each polymer are still under study in our laboratories.



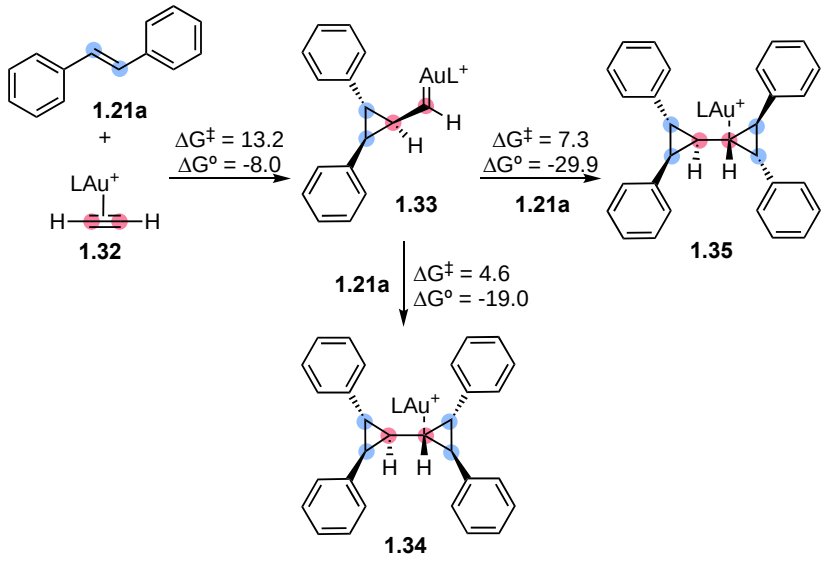
Scheme 28. Acetylene oligomerization.

Computational studies

In order to shed light on the mechanism and selectivity of these reactions, we performed DFT calculations. First, we studied the double cyclopropanation reaction, since we were interested in providing an explanation for the selective formation of *meso*-biscyclopropane **1.23a** versus its chiral isomer **1.23a'**.[73] After coordination to gold(I), intermediate **1.32** reacts with a molecule of stilbene leading to cyclopropyl gold(I) carbene **1.33** (scheme 29). This intermediate could then be trapped in a syn or anti fashion with a second molecule of stilbene. This second cyclopropanation determines the stereochemistry of the product (meso or chiral). The calculated energy barriers for this step indicate that the *syn*-cyclopropanation is favored by over 3 kcal/mol, providing *meso* product **1.34** exclusively (at room

72. Tania Medina (Echavarren group) is currently working on the development and optimization of this polymerization reaction.
73. These DFT calculations were performed by Dr. Imma Escofet.

temperature). These results are in agreement with the experimental observations, where chiral compound **1.23a'** was never detected. [74]

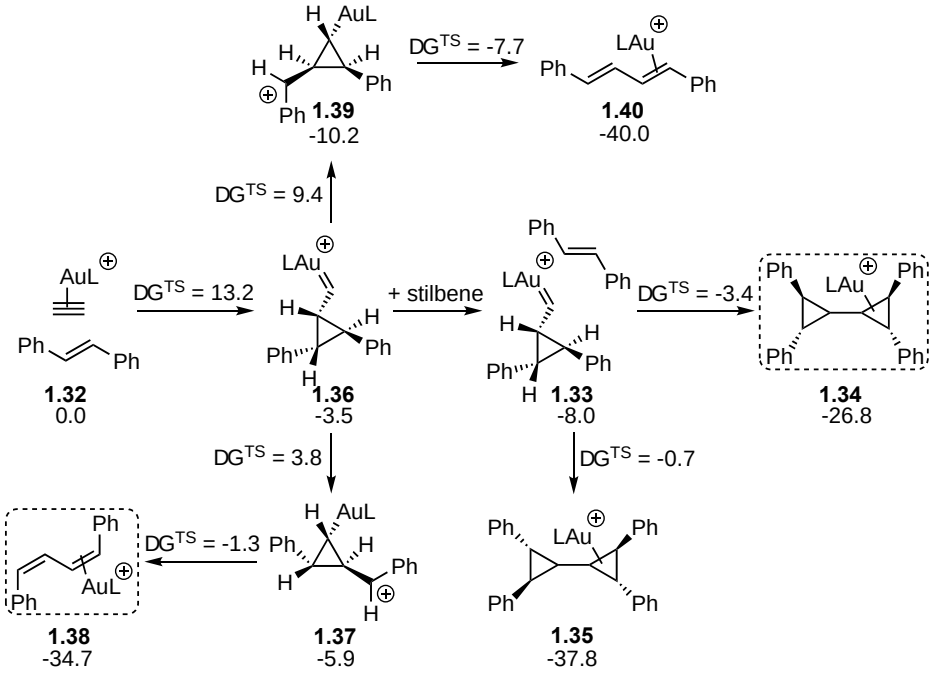


Scheme 29. DFT calculations for the double cyclopropanation reaction. L = PMe_3.

Continuing with these DFT calculations, we wanted to explain the different reactivity observed with different catalysts. Thus, we first calculated the full mechanistic picture with the simplified system, L = PMe_3 (scheme 30).

Surprisingly, we found that a large stabilization was occurring when a second molecule of stilbene was included in the calculated structure (4.5 kcal/mol difference was found between **1.36** and **1.33**, which only differ by the presence of a neighboring stilbene). Instead of reacting with a second molecule of stilbene, intermediate **1.36** could rearrange into carbocations **1.37** and **1.39** by carbon migration. These could then deliver diene-complexes **1.38** and **1.49**, which after ligand exchange would afford corresponding (*E*,*E*)- and (*Z*,*Z*)-diene products **1.22a**.

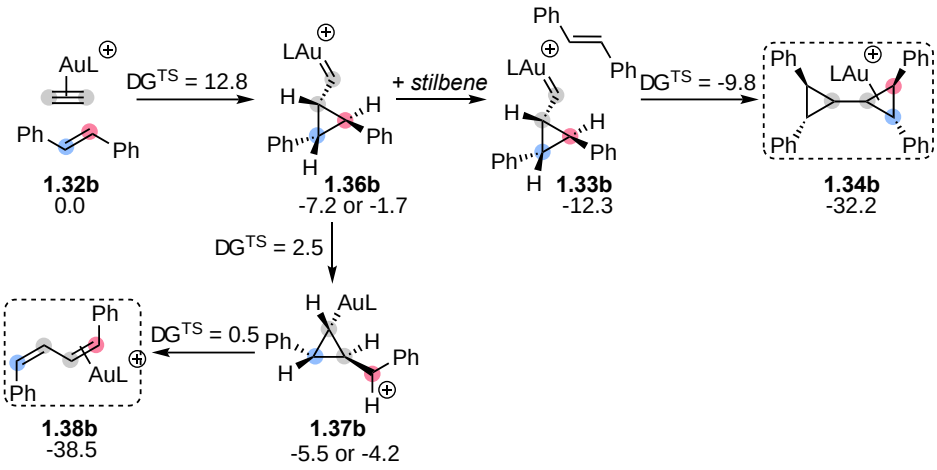
74. We also calculated the energy profile for the reaction of acetylene with geranyl acetone. These results are not included in this thesis, since they were already discussed in the PhD thesis of Dr. Imma Escofet.



Scheme 30. Full mechanistic picture by DFT calculations. L = PMe_3.

In agreement with the experimental results, the mechanistic pathway towards (*Z*,*Z*)-**1.22a**, via **1.37**, is kinetically favored versus the one leading to (*E*,*E*)-**1.22a**, via **1.39**, by 5.6 kcal/mol. This translates into complete selectivity towards (*Z*,*Z*)-**1.22a**, under the reaction conditions (at room temperature). However, the energy barriers for the stepwise diene formation (towards products **1.22a**) are higher than those leading to biscyclopropanes **1.23a**. These results suggest that for this simplified system, using trimethylphosphine as the ligand in the gold(I) catalyst, the double cyclopropanation reaction is favored versus the intramolecular rearrangement towards complex **1.38** and thus **1.22a** should be the only obtained product.

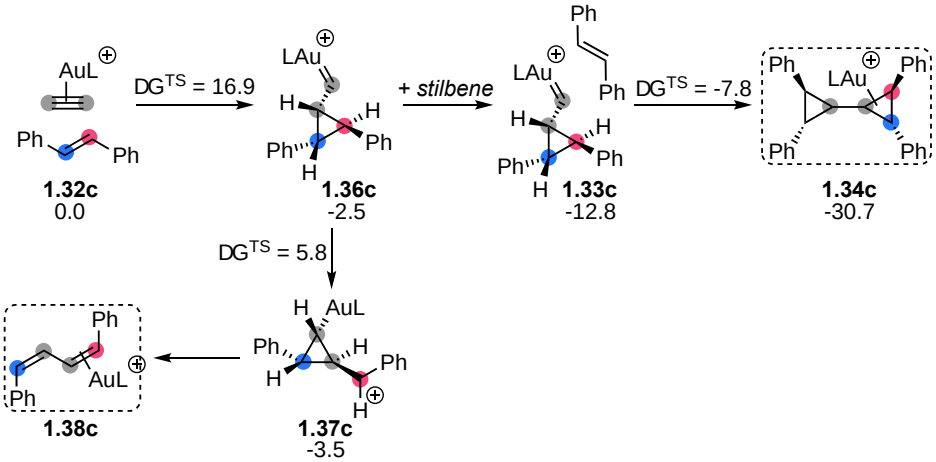
In order to explore this hypothesis, we decided to computationally study the full mechanism with the two optimized conditions: using catalysts **D** and **F**, which display different reactivity, the first leading selectively to diene **1.22a** and the second to biscyclopropane **1.23a**. We started with L = *t*BuXPhos, since this system is the one providing the opposite selectivity to that predicted for L = PMe_3 (scheme 31).



Scheme 31. DFT calculations with L = *t*BuXPhos.

We found that an outer-sphere interaction with a second molecule of stilbene provided again 5 kcal/mol of stabilization, from intermediate **1.36b** to **1.33b**. Regardless of this stabilization, the relative activation energy of **1.33b** towards **1.34b** is of only 2.5 kcal/mol, while rearrangement of **1.36b** to **1.37b** has a barrier of 9.7 kcal/mol. This strongly disagrees with the experimental results, as with this catalytic system, only product **1.23a** was obtained (from complex **1.38b**).

Similarly, when using L = IPr (scheme 32), the most favored pathway was towards the formation of **1.34c**, which would ultimately deliver product **1.23a**. In this case, this is consistent with the experimental results. Interestingly, the stabilization of intermediate **1.36c** by outer-sphere interaction with a molecule of stilbene in **1.33c** is of 10.3 kcal/mol (while in the systems with phosphine ligands, it was of *c.a.* 5 kcal/mol, see schemes 30 and 31).



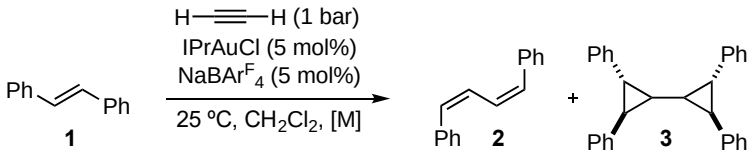
Scheme 32. DFT calculations with L = IPr.

Intrigued by the unmatching computational results, we realized that the only step we were not able to study by DFT calculations was the probability for intermediate **1.36** to meet a second molecule of stilbene to form outer-sphere complex **1.33**. This could be calculated with an approximation to the diffusion rate.

Experimental mechanistic studies

Finally, in an attempt to rationalize the different reactivity observed using complexes **D** and **F**, we evaluated the dilution effect on the system with the IPr-Au catalyst. As shown before, in the optimized reaction conditions, this catalytic system only provides bis-cyclopropane **1.23a**. However, diluting the reaction mixture from 0.2 to 0.05 M, we were able to invert the selectivity towards diene **1.22a** (table 12, entry 1-5). This suggests that the activation barrier for the formation of the products is similar to the diffusion rate.

Table 12. Effect on the concentration [a]

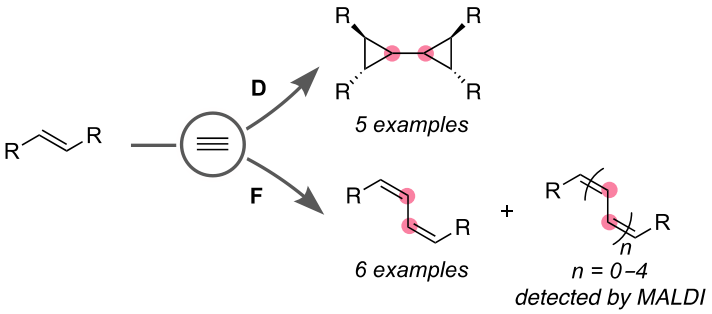


Entry	Concentration [M]	Time (h)	Ratio 1:2:3
1	0.2	24	0:1:13
2	0.05	24	X:1:3.8
3	0.014	72	X:1:1.2
4	0.010	72	X:1:0.9
5	0.005	72	X:1:0.5

a. The 5 reactions were performed in a HEL reactor with 5 separate reaction tubes, to ensure that they were all set at the exact same pressure.

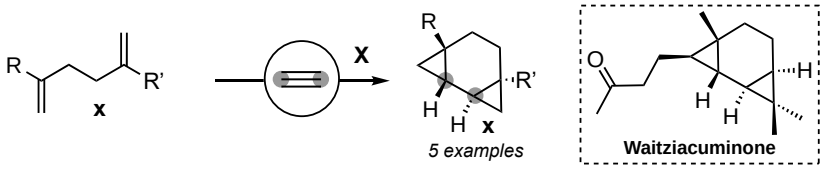
Conclusions

We have been able to use acetylene for the first time as a reaction partner in intermolecular gold(I) catalysis. *Meso*-biscyclopropanes and 1,3-dienes were obtained by reaction with stilbenes, by using different gold(I) catalysts (scheme 33). The first were formed upon a double cyclopropanation reaction, where acetylene acts as a double carbene equivalent, and the latter were result of a formal acetylene insertion between the two olefinic carbons of stilbenes. We found that the diene products could engage the acetylene insertion reaction, as confirmed by the detection of oligomers, with up to 4 incorporated units of acetylene.



Scheme 33. Reactions of acetylene with stilbenes.

Reaction with 1,5-dienes afforded tricyclo[5.1.0.$0^{2,4}$]octanes and we used this methodology for the first and one-step total synthesis of waitziacuminone. Finally, we have studied the mechanism of these new transformations by DFT calculations, in an attempt to provide a rational for the different reactivity and selectivity observed experimentally.



Scheme 34. Double cyclopropanation of 1,5-dienes.

Experimental Section

General Information

Unless otherwise stated, all the reactions were performed under air in HPLC grade solvents. In case inert conditions were used, dry solvents were obtained from a PureSolv^{TM} solvent purification system (where they passed through an activated alumina column). All solvents and other chemicals were used as received. Reactions were followed using a GC-MS apparatus, by TLC (thin layer chromatography) or by NMR analysis. Analytical thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck 60 F_{254}) using UV light as the visualizing agent and an acidic solution of vanillin in ethanol or basic solution of $KMnO_4$ in water as stain. Chromatographic purifications were carried out using flash grade silica gel (PanReac Silica Gel 60, 40-63 μm) or automated flash column chromatographer CombiFlash Companion. Preparative thin layer chromatography was performed on TLC plates (Analtec Silica Gel GF UV254, 20×20 cm, 1000 μm). Melting points were determined using a Mettler Toledo MP70 melting point apparatus. NMR spectra were recorded at 298 K on BrukerAvance Ultrashield NMR spectrometers (300 MHz, 400 MHz, 500 MHz and 500 MHz with CryoProbe). Chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual solvent (For ^{1}H NMR: $CDCl_3$ at 7.26 ppm, CD_2Cl_2 at 5.31 ppm, C_6D_6 at 7.16 ppm, for $^{13}C\{^{1}H\}$ NMR: $CDCl_3$ at 77.16 ppm, CD_2Cl_2 at 54.00 ppm, C_6D_6 at 128.06 ppm). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br s = broad singlet. Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on MicroTOF Focus or Maxis Impact spectrometers (both from Bruker Daltonics). For the MALDI-TOF experiments, an AutoFlex spectrometer from Bruker Daltonics was employed. X-ray diffraction data were collected at 100 K on a Rigaku MicroMax-007HF, Mo *Kα* rotating anode, equipped with a Pilatus 200 K detector or on a Bruker APEX DUO, Mo *Kα* Microfocus source E025 IuS anode, equipped with an APEX DUO detector using omega scans.

Synthetic Procedures and Characterization of Compounds

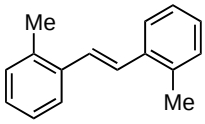
General procedure: Au(I)-catalyzed acetylene activation in a Y-shaped flask

The reaction was performed in a two-chamber reactor (volume approx. 30 mL) with a screw cap (see fig. 1). A stirring bar was placed in each vessel and the first vessel was loaded with calcium carbide (technical, ≥ 75%; 100 mg, 1.17 mmol, 5.9 equiv. unless otherwise stated). A solution of the alkene **1.21** or the diene **1.24** (200 μmol) and the gold complex (5 mol% unless otherwise stated) in the indicated solvent (1 mL unless otherwise stated; HPLC

grade) was loaded into the second vessel. The same solvent (1 mL) was added to the first vessel (caution: If the solvent in the second vessel has a lower density than water, $CHCl_3$ was used in the first vessel), followed by careful addition of water (100 µL, 5.55 mmol, 27.8 equiv.). The reactor was immediately sealed, and the mixture was stirred at 23 ºC for 24 h (the stirring speed was slowly increasing to 600 rpm over the first 10 min). The reaction mixture of the second vessel was taken out with a syringe and, for reactions with stilbene (**1**) as substrate, 1,4-diacetylbenzene (16.2 mg, 100 µmol) was added as internal standard. The solvent was removed at 23 ºC and the crude was analyzed by NMR.

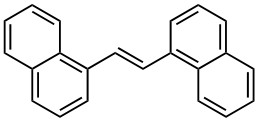
Synthesis of starting materials

(*E*)-2,2'-Dimethylstilbene (1d)



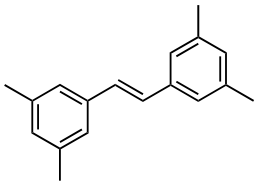
To a solution of Grubbs 2nd generation catalyst (50.9 mg, 60.0 µmol, 2 mol%) in CH_2Cl_2 (3 ml) under Ar was added 1-methyl-2-vinylbenzene (388 µl, 3.00 mmol). The resulting mixture was stirred at 40 °C for 18 h and evaporated. Flash column chromatography (cyclohexane/EtOAc 100:0 to 95:5) and recrystallization from MeOH delivered (*E*)-2,2'-dimethylstilbene (**1d**; 202 mg, 970 µmol, 65%) as colourless crystals. The spectroscopic data for **1d** are in accordance with those reported in literature.[2]

(*E*)-1,2-Di(naphthalen-1-yl)ethene (1e)



To a solution of 1-bromonaphthalene (350 µL, 2.50 mmol, 2.00 equiv.) and (*E*)-1,2-bis(tributylstannyl)ethene (669 µl, 1.25 mmol) in DMF (10 mL) inside the glovebox was added $Pd(PPh_3)_4$ (86.7 mg, 75.0 µmol, 6 mol%). The reaction was heated at 100 ºC for 24 h under Ar in the dark, left to cool to r.t. and diluted with water (30 mL). The mixture was extracted with chloroform (3 x 50 mL). The combined extracts were washed with brine (2 x 30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude was purified by flash column chromatography (cyclohexane) and the solids were suspended in MeOH (10 mL), heated to reflux for 30 min and filtrated to deliver (*E*)-1,2-di(naphthalen-1-yl)ethene (**1e**; 273 mg, 974 µmol, 78%) as a colourless solid. The spectroscopic data for **1e** are in accordance with those reported in literature.[3]

(*E*)-1,2-Bis(3,5-dimethylphenyl)ethene (1f)



To a stirred suspension of zinc powder (487 mg, 7.45 mmol, 2.50 equiv.) in tetrahydrofuran (5 mL) in a flame dried two-neck flask under argon atmosphere was added titanium(IV) chloride (427 µL, 3.88 mmol, 1.30 equiv.) dropwise at 0 °C. After stirring for 10 min, the corresponding aldehyde (400 mg, 2.98 mmol, 1.00 equiv.) was added and the reaction mixture refluxed for 17 h. Upon completion, the reaction mixture was cooled to 23 °C, filtered with tetrahydrofuran (2 × 20 mL) and

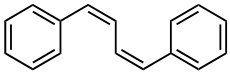
concentrated. The residue was dissolved in dichloromethane (10 mL), filtered through a silica plug with dichloromethane (3 × 10 mL) and the solvent removed *in vacuo*. Crystallization from hexane delivered **1f** (154 mg, 0.65 mmol, 44%) as colourless crystals. The spectroscopic data for **1f** are in accordance with those reported in literature.[4]

Synthesis of dienes 4

General procedure B: preparation of diene compounds 4

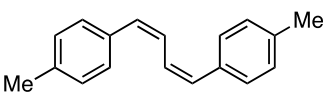
The reaction was performed in a two-chamber reactor with a screw cap. A stirring bar was placed in each vessel and the first vessel was loaded with calcium carbide (technical, ≥ 75%; 100 mg, 1.17 mmol, 5.9 equiv.). A solution of the alkene 1 (200 µmol) and tBuXPhosAu(MeCN)BAr^F_4 (15.3 mg, 10.0 µmol, 5 mol%) in CH_2Cl_2 (1 mL) was loaded into the second vessel. CH_2Cl_2 (1 mL) was added to the first vessel, followed by careful addition of water (100 µL, 5.55 mmol, 27.8 equiv.). The reactor was immediately sealed, and the mixture was stirred at 23 ºC for 24 h (stirring speed was slowly increasing to 600 rpm over the first 10 min). The reaction mixture of the second vessel was taken out with a syringe and 1,4-diacetylbenzene (16.2 mg, 100 µmol) was added as internal standard. The solvent was removed at 23 ºC and the crude was analysed by NMR.

(1*Z*,3*Z*)-1,4-Diphenylbuta-1,3-diene (4a)



The product was prepared from (*E*)-stilbene (36.1 mg, 200 µmol) according to general procedure B. Purification by flash column chromatography (cyclohexane) delivered *Z,Z*-diene **4a** as an inseparable mixture with starting material (30.1 mg; 37% diene, 54.0 µmol, 27%; 63% stilbene, 105 µmol, 53%). The spectroscopic data for diene **4a**[5] and stilbene **1a**[6] are in accordance with those reported in literature.

(1*Z*,3*Z*)-1,4-Di-p-tolylbuta-1,3-diene (4b)



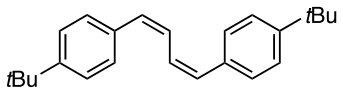
The product was prepared from (*E*)-4,4'-dimethylstilbene[7] (41.7 mg, 200 µmol) according to general procedure B. Purification by flash column chromatography (cyclohexane) delivered *Z,Z*-diene **4b** as an inseparable mixture with starting material (13.2 mg; 66% diene, 37.2 µmol, 19%; 34% stilbene, 21.5 µmol, 11%).

Diene **4b**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.1 Hz, 4H), 7.24 – 7.17 (m, 4H), 6.75 – 6.67 (m, 2H), 6.61 – 6.53 (m, 2H), 2.41 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.2, 134.7, 131.7, 129.2, 129.1, 126.5, 21.4. **HRMS** (APCI) calculated for $[C_{18}H_{19}]^+$ 235.1481, found [M + H]+ 235.1487.

(*E*)-4,4'-dimethylstilbene (**1b**): **^{1}H NMR** (400 MHz $CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 4H), 7.24 – 7.17 (m, 4H), 7.08 (s, 2H), 2.39 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.4, 134.9, 129.5, 127.8, 126.2, 21.4.

The diene **4b** has been mentioned in literature,[8] but no spectroscopic data are published. The spectroscopic data of (*E*)-4,4'-dimethylstilbene (**1b**) are in accordance with those reported in literature.[7]

(1*Z*,3*Z*)-1,4-Bis(4-(tert-butyl)phenyl)buta-1,3-diene (4c)



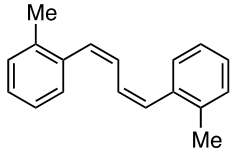
The product was prepared from (*E*)-4,4'-di-tert-butylstilbene[9] (58.5 mg, 200 µmol) according to general procedure B. Purification by flash column chromatography (cyclohexane) delivered *Z,Z*-diene **4c** as an inseparable mixture with starting material and minor side products (24.7 mg; 72% diene, 55.8 µmol, 28%; 24% stilbene, 20.3 µmol, 10%).

Diene **4c**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 8H), 6.78 – 6.70 (m, 2H), 6.60 – 6.52 (m, 2H), 1.37 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.4, 134.8, 131.6, 129.1, 126.4, 125.3, 34.8, 31.5. **HRMS** (APCI) calculated for $[C_{24}H_{31}]^+$ 319.2420, found $[M + H]^+$ 319.2421.

(*E*)-4,4'-di-tert-butylstilbene (**4c**): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 4H), 7.43 – 7.37 (m, 4H), 7.09 (s, 2H), 1.36 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.7, 134.9, 127.9, 126.3, 125.7, 34.8, 31.5.

The spectroscopic data of (*E*)-4,4'-di-tert-butylstilbene (**1c**) are in accordance with those reported in literature.[9]

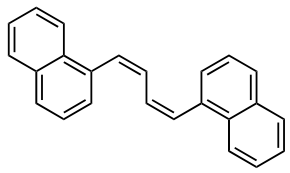
(1*Z*,3*Z*)-1,4-Di-o-tolylbuta-1,3-diene (4d)



The product was prepared from (*E*)-2,2'-dimethylstilbene (**1d**; 41.7 mg, 200 µmol) according to general procedure B. Purification by flash column chromatography (cyclohexane) delivered *Z,Z*-diene **4d** as an inseparable mixture with starting material (33.8 mg; 74% diene, 107 µmol, 53%; 26% stilbene, 42.2 µmol, 21%).

The spectroscopic data for diene **4d**[10] and stilbene **1d**[2] are in accordance with those reported in literature.

(1*Z*,3*Z*)-1,4-Di(naphthalen-1-yl)buta-1,3-diene (4e)

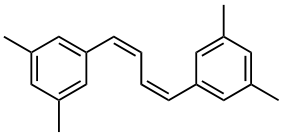


The product was prepared from (*E*)-1,2-di(naphthalen-1-yl)ethene (56.1 mg, 200 µmol) according to general procedure B (8% *E,E*-**4e'** could be observed in the crude). Purification by flash column chromatography (cyclohexane) delivered *Z,Z*-diene **4e** as an inseparable mixture with starting material (34.4 mg; 52% diene, 58.4 µmol, 29%; 48% stilbene, 58.8 µmol, 29%).

Diene **4e**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 – 7.99 (m, 2H), 7.92 – 7.82 (m, 4H), 7.60 (d, J = 7.0, Hz, 2H), 7.58 – 7.50 (m, 6H), 7.08 – 7.00 (m, 2H), 6.84 – 6.76 (m, 2H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 134.5, 133.8, 131.6, 130.2, 128.8, 128.6, 128.0, 127.7, 126.2, 126.1, 125.4, 125.1. **HRMS** (APCI) calculated for $[C_{24}H_{19}]^+$ 307.1481, found $[M + H]^+$ 307.1481.
(*E*)-1,2-Di(naphthalen-1-yl)ethene (**1e**): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.30 – 8.24 (m, 2H), 7.93 (s, 2H), 7.92 – 7.82 (m, 6H), 7.58 – 7.50 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.5, 133.9, 132.0, 129.2, 128.6, 128.4, 126.3, 126.1, 125.9, 124.1, 124.0.

(1*Z*,3*Z*)-1,4-Bis(3,5-dimethylphenyl)buta-1,3-diene (4f)



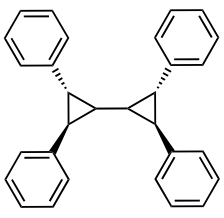
The product was prepared from stilbene (47.3 mg, 200 µmol) according to slightly modified general procedure B. Instead of CH_2Cl_2, $CHCl_3$ was used as solvent and the reaction was run at 40 ºC. Purification by flash column chromatography (cyclohexane) delivered *Z,Z*-diene **4f** (21 mg, 80.0 µmol, 40%) as a white solid.
M.p. = 108 °C (cyclohexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.04 (s, 4H), 6.93 (s, 1H), 6.74 – 6.66 (m, 2H), 6.56 – 6.47 (m, 2H), 2.35 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.8, 132.1, 129.1, 127.1, 126.7, 21.5. **HRMS** (ESI) calculated for $[C_{20}H_{23}]^+$ 263.1794, found $[M + H]^+$ 263.1795.

Synthesis of bicyclopropyl compounds 5

General procedure C: preparation of bicyclopropyl compounds 5

The reaction was performed in a two-chamber reactor with a screw cap. A stirring bar was placed in each vessel and the first vessel was loaded with calcium carbide (technical, ≥ 75%; 100 mg, 1.17 mmol, 5.9 equiv.). A solution of the alkene **1** (200 µmol) and IPrAu(PhCN)BAr^F_4 (15.5 mg, 10.0 µmol, 5 mol%) in CH_2Cl_2 (1 mL) was loaded into the second vessel. CH_2Cl_2 (1 mL) was added to the first vessel, followed by careful addition of water (100 µL, 5.55 mmol, 27.8 equiv.). The reactor was immediately sealed, and the mixture was stirred at 23 ºC for 24 h (stirring speed was slowly increasing to 600 rpm over the first 10 min). The reaction mixture of the second vessel was taken out with a syringe and the solvent was removed at 23 ºC.

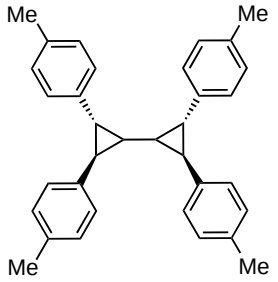
(2R,2'S,3R,3'S)-2,2',3,3'-Tetraphenyl-1,1'-bi(cyclopropane) (5a)



The product was prepared from stilbene (36.1 mg, 200 µmol) according to general procedure C. Purification by flash column chromatography (cyclohexane/EtOAc 100:1 to 95:5) and trituration with cyclohexane (1 mL) delivered the bicyclopropyl compound 5a (24.0 mg, 62.1 µmol, 62%) as a colourless solid. Crystallization by vapor diffusion from cyclohexane/CH_2Cl_2 yielded crystals suitable for X-ray analysis.
M.p. = 158 – 161 °C (cyclohexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 4H), 7.24 – 7.08 (m, 12H), 6.88 – 6.82 (m, 4H), 2.46 (dd, J = 8.7, 5.8 Hz, 2H), 2.35 (t, J = 5.1

Hz, 2H), 1.19 – 1.11 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.1, 138.9, 129.3, 128.3, 128.2, 126.7, 126.2, 125.8, 32.2, 29.8, 28.6. **HRMS** (APCI) calculated for $[C_{30}H_{27}]^+$ 387.2107, found $[M + H]^+$ 387.2108.

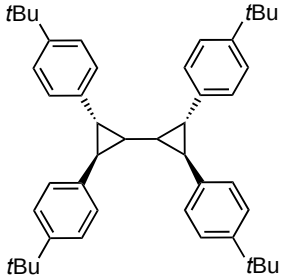
(2R,2'S,3R,3'S)-2,2',3,3'-Tetra-p-tolyl-1,1'-bi(cyclopropane) (5b)



The product was prepared from (*E*)-4,4'-dimethylstilbene[7] (41.7 mg, 200 µmol) according to general procedure C. Purification by flash column chromatography (cyclohexane/EtOAc 100:1 to 95:5) and trituration with cyclohexane (1mL) delivered the bicyclopropyl compound **5b** (32.9 mg, 74.3 µmol, 74%) as an off-white solid.

M.p. = 206 – 208 °C (cyclohexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, J = 7.8 Hz, 4H), 7.03 (d, J = 7.7 Hz, 4H), 6.97 (d, J = 7.8 Hz, 4H), 6.73 (d, J = 8.0 Hz, 4H), 2.35 (dd, J = 8.5, 5.5 Hz, 2H), 2.31 (s, 6H), 2.29 (s, 6H), 2.26 (t, J = 5.1 Hz, 2H), 1.12 – 1.04 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.2, 136.0, 135.5, 135.1, 129.1, 129.0, 128.8, 126.8, 31.7, 29.4, 28.1, 21.1. **HRMS** (APCI) calculated for $[C_{34}H_{35}]^+$ 443.2733, found $[M + H]^+$ 433.2735.

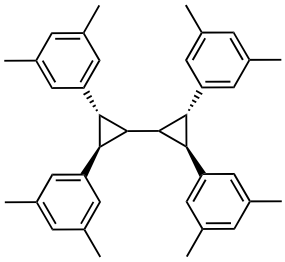
(2R,2'S,3R,3'S)-2,2',3,3'-Tetrakis(4-(tert-butyl)phenyl)-1,1'-bi(cyclopropane) (5c)



The product was prepared from (*E*)-4,4'-di-tert-butylstilbene[9] (58.5 mg, 200 µmol) according to general procedure C. Purification by flash column chromatography (cyclohexane/EtOAc 100:1 to 95:5) and trituration with MeOH (2 mL) delivered the bicyclopropyl compound **5c** (52.3 mg, 85.6 µmol, 86%) as an off-white solid.

M.p. = 282 – 283 °C (cyclohexane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 8H), 7.17 – 7.13 (m, 4H), 6.77 – 6.73 (m, 4H), 2.37 (dd, J = 8.7, 5.7 Hz, 2H), 2.29 (t, J = 5.0 Hz, 2H), 1.31 (s, 18H), 1.27 (s, 18H), 1.11 – 1.05 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.9, 148.5, 139.3, 136.2, 128.9, 126.8, 125.1, 125.0, 34.5, 34.4, 31.6, 31.5, 31.4, 29.1, 28.0. **HRMS** (APCI) calculated for $[C_{46}H_{59}]^+$ 611.4611, found [M + H]+ 611.4633.

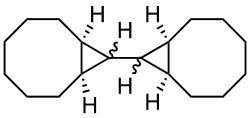
(2R,2'S,3R,3'S)-2,2',3,3'-tetrakis(3,5-dimethylphenyl)-1,1'-bi(cyclopropane) (5f)



The product was prepared from stilbene (47.3 mg, 200 µmol) according to slightly modified general procedure B. Instead of CH_2Cl_2, $CHCl_3$ was used as solvent and the reaction was run at 40 ºC. Purification by flash column chromatography (100% pentane to 2% diethyl ether in pentane) bicyclopropane **5f** (30 mg, 60.1 µmol, 60%) as a yellowish solid as well as a mixture of 1,3-diene **4f** and starting material **1f** (in total 23% yield calculated from crude NMR).

M. p. = 107 °C (pentane). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 6.95 (s, 4H), 6.82 (s, 2H), 6.78 (s, 2H), 6.54 (s, 4H), 2.40 – 2.28 (m, 6H), 2.24 (s, 12H), 2.18 (s, 12H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ = 142.3, 139.2, 137.7, 137.6, 127.8, 127.5, 127.4, 124.8, 31.6, 29.9, 28.3, 21.3, 21.2. **HRMS** (ESI) calculated for $[C_{38}H_{43}]^+$ 499.3359, found $[M + H]^+$ 499.359.

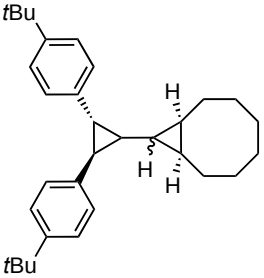
(1S,1'S,8R,8'R)-9,9'-Bi(bicyclo[6.1.0]nonane) (5g)



The product was prepared from (Z)-cyclooctene (26.1 µL, 200 µmol) according to general procedure C. Purification by flash column chromatography (cyclohexane) delivered a 70:19:11 mixture of three diastereomers of bicyclopropyl compound **5g** (8.9 mg, 36.1 µmol, 36%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 – 1.98 (m, 1.4H), 1.97 – 1.91 (m, 0.44H), 1.86 – 1.76 (m, 2.16H), 1.75 – 1.60 (m, 6H), 1.59 – 1.49 (m, 2H), 1.47 – 1.30 (m, 8H), 1.26 – 1.11 (m, 2.16H), 0.98 – 0.85 (m, 1.84H), 0.69 – 0.56 (m, 2.16H), 0.56 – 0.46 (m, 1.84H), 0.37 – 0.30 (m, 1.08H), 0.30 – 0.26 (m, 0.22H), -0.10 (dt, J = 8.2, 4.7 Hz, 0.7H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 30.0, 30.0, 30.0, 27.1, 27.1, 26.8, 26.8, 26.8, 24.9, 24.1, 22.7, 22.6, 22.0, 21.5, 18.8, 18.44, 18.41, 12.6. **HRMS** (APCI) calculated for $[C_{18}H_{31}]^+$ 247.2420, found $[M + H]^+$ 247.2419.

(1SR,8RS)-9-((2SR,3SR)-2,3-Bis(4-(tert-butyl)phenyl)cyclopropyl)bicyclo[6.1.0]nonane (5h)



The product was prepared from (E)-4,4'-di-tert-butylstilbene[9] (29.2 mg, 100 µmol) and (Z)-cyclooctane (13.0 µL, 100 µmol) according to general procedure C. Purification by flash column chromatography (cyclohexane/EtOAc 100:1 to 95:5) delivered a 45:55 mixture of two diastereomers of the desired product **5h** (8.0 mg, 18.7 µmol, 19%) as a colourless gum as well as the symmetric products **5c** (10.2 mg, 16.7 µmol, 33%) and **5g** (6.9 mg, 28.0 µmol, 56%).

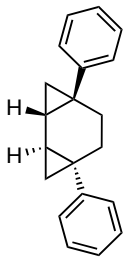
^{1}H NMR (500 MHz, $CDCl_3$) 7.33 (d, J = 8.2 Hz, 4H), 7.28 – 7.23 (m, 2H), 7.15 (d, J = 8.3 Hz, 1.1H), 7.12 (d, J = 8.3 Hz, 0.9H), 2.45 – 2.39 (m, 1H), 2.23 (t, J = 5.5 Hz, 0.55H), 2.15 (t, J = 5.3 Hz, 0.45H), 1.94 – 1.88 (m, 0.55H), 1.86 – 1.79 (m, 1H), 1.72 – 1.58 (m, 3.45H), 1.52 – 1.18 (m, 25H), 0.95 – 0.73 (m, 1H), 0.73 – 0.46 (m, 2H), 0.42 (q, J = 8.7 Hz, 0.55H), -0.04 (q, J = 5.0 Hz, 0.45H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.4, 148.4, 148.3, 148.3, 140.3, 140.2, 136.5, 136.4, 128.8, 128.7, 126.0, 125.7, 125.2, 125.2, 124.8, 124.7, 34.4 (2 signals), 34.4 (2 signals), 32.5, 32.4, 31.4, 31.4 (2 signals), 31.4, 29.7, 29.7 (2 signals), 29.7, 28.5, 26.61, 26.58, 26.57 (2 signals), 26.5, 26.4, 24.9, 23.4, 23.3, 22.8, 22.5, 22.3, 18.9, 18.5, 17.3. **HRMS** (APCI) calculated for $[C_{32}H_{45}]^+$ 429.3516, found $[M + H]^+$ 429.3523.

Synthesis of tricyclo[5.1.0.02,4]octanes 6

General procedure D: preparation of tricyclo[5.1.0.02,4]octanes 6

The reaction was performed in a two-chamber reactor with a screw cap. A stirring bar was placed in each vessel and the first vessel was loaded with calcium carbide (technical, ≥ 75%; 100 mg, 1.17 mmol, 5.9 equiv.). A solution of the diene **7** (200 µmol) and *t*BuXPhosAu(MeCN)BAr^F_4 (15.3 mg, 10.0 µmol, 5 mol%) in CH_2Cl_2 (1 mL) was loaded into the second vessel. CH_2Cl_2 (1 mL) was added to the first vessel, followed by careful addition of water (100 µL, 5.55 mmol, 27.8 equiv.). The reactor was immediately sealed, and the mixture was stirred at 23 ºC for 24 h (stirring speed was slowly increasing to 600 rpm over the first 10 min). The reaction mixture of the second vessel was taken out with a syringe and the solvent was removed at 23º C.

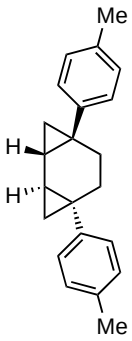
(1SR,2SR,4RS,7RS)-4,7-Diphenyltricyclo[5.1.0.0^{2,4}]octane (6a)



The product was prepared from hexa-1,5-diene-2,5-diyldibenzene[11] (46.9 mg, 200 µmol) according to general procedure D. Purification by flash column chromatography (cyclohexane) delivered the tricyclic compound **6a** (34.9 mg, 134 µmol, 67%) as a colourless solid. Crystallization by vapor diffusion from cyclohexane/CH_2Cl_2 yielded crystals suitable for X-ray analysis.

M.p. = 119 – 121 °C (cyclohexane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 8H), 7.24 – 7.19 (m, 2H), 2.14 – 2.04 (m, 2H), 2.01 – 1.91 (m, 2H), 1.68 – 1.62 (m, 2H), 1.11 (t, J = 4.6 Hz, 1H), 0.96 (dd, J = 8.1, 4.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1, 128.4, 127.9, 125.9, 27.2, 25.4, 20.4, 15.0. **HRMS** (APCI) calculated for $[C_{20}H_{21}]^+$ 261.1638, found $[M + H]^+$ 261.1643.

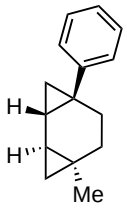
(1SR,2SR,4RS,7RS)-4,7-Di-p-tolyltricyclo[5.1.0.0^{2,4}]octane (6b)



The product was prepared from 4,4'-(hexa-1,5-diene-2,5-diyl)bis(methylbenzene)[11] (52.5 mg, 200 µmol) according to general procedure D. Purification by flash column chromatography (pentane) delivered the tricyclic compound **6b** (28.8 mg, 100 µmol, 50%) as a colourless solid.

M.p. = 97 – 99 °C (pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 (dt, J = 8.1, 2.0 Hz, 4H), 7.11 (d, J = 8.0 Hz, 4H), 2.33 (s, 6H), 2.08 – 1.97 (m, 2H), 1.95 – 1.83 (m, 2H), 1.59 – 1.56 (m, 2H), 1.03 (t, J = 4.5 Hz, 2H), 0.88 (dd, J = 8.0, 4.7 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.2, 135.4, 129.1, 127.8, 27.4, 24.4, 21.1, 20.8, 15.7. **HRMS** (APCI) calculated for $[C_{22}H_{25}]^+$ 289.1951, found $[M + H]^+$ 289.1951.

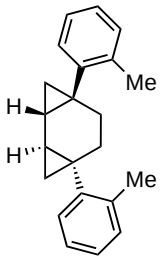
(1SR,2SR,4SR,7RS)-4-Methyl-7-phenyltricyclo[5.1.0.0^{2,4}]octane (6c)



The product was prepared from (5-methylhexa-1,5-dien-2-yl)benzene[12] (34.5 mg, 200 µmol) according to general procedure D. Purification by flash column chromatography (pentane) delivered the tricyclic compound **6c** (21.2 mg, 107 µmol, 54%) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.25 – 7.21 (m, 2H), 7.18 – 7.13 (m, 1H), 1.97 – 1.90 (m, 1H), 1.80 – 1.72 (m, 2H), 1.64 – 1.55 (m, 1H), 1.46 (ddd, J = 8.0, 5.0, 2.7 Hz, 1H), 1.04 (s, 3H), 1.04 – 1.00 (m, 1H), 0.84 (t, J = 4.7 Hz, 1H), 0.80 (dd, J = 8.2, 4.4 Hz, 1H), 0.59 (t, J = 4.4 Hz, 1H), 0.34 (dd, J = 7.9, 4.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.0, 128.3, 127.9, 125.8, 27.1, 26.9, 26.5, 24.9, 21.4, 20.5, 15.9, 15.6, 15.5. **HRMS** (APCI) calculated for $[C_{15}H_{19}]^+$ 199.1481, found $[M + H]^+$ 199.1477.

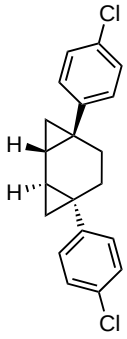
(1SR,2SR,4RS,7RS)-4,7-Di-o-tolyltricyclo[5.1.0.02,4]octane (6d)



The product was prepared from 2,2'-(hexa-1,5-diene-2,5-diyl)bis(methylbenzene)[11] (52.5 mg, 200 µmol) according to general procedure D. Purification by flash column chromatography (cyclohexane) and preparative thin layer chromatography (cyclohexane) delivered the an inseparable mixture of tricyclic compound **6d** (24.8 mg, approx. 55%; approx. 13 mg, 47 µmol, 24%) and various diene side products as a colourless resin.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.22 – 7.12 (m, 6H), 2.45 (s, 6H), 2.01 – 1.89 (m, 2H), 1.84 – 1.73 (m, 2H), 1.70 – 1.64 (m, 2H), 1.27 (t, J = 4.5 Hz, 1H), 0.86 (dd, J = 8.1, 4.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.7, 137.5, 130.5, 130.3, 126.4, 126.1, 26.6, 24.9, 20.0, 19.3, 15.9. **HRMS** (APCI) calculated for $[C_{22}H_{25}]^+$ 289.1951, found $[M + H]^+$ 289.1950.

(1SR,2SR,4RS,7RS)-4,7-bis(4-chlorophenyl)tricyclo[5.1.0.0^{2,4}]octane (6e)

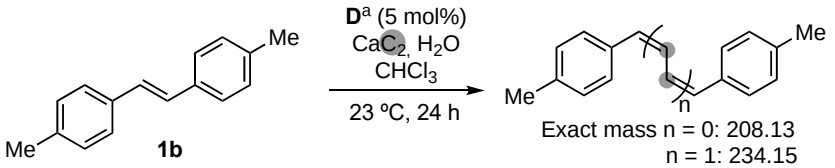


The product was prepared from 4,4'-(hexa-1,5-diene-2,5-diyl)bis(chlorobenzene)[11] (7e; 52.5 mg, 200 µmol) according to general procedure D. The crude was resubmitted to the reaction conditions 3 times to increase the conversion. Finally, the crude was treated with KMnO4 (32 mg, 0.20 mmol, 1.0 equiv.) in acetone (2 mL) to oxidize the remaining starting material. After 1 h, water (50 mL) was added and the aqueous phase extracted with dichloromethane (3 × 20 mL). The organic layer was dried over sodium sulphate, filtered and concentrated. Purification by flash column chromatography (pentane) delivered the tricyclic compound **6e** (21.0 mg, 64 µmol, 32%) as a colourless solid.

M.p. = 174 °C (pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (dt, J = 8.9, 2.3 Hz, 4H), 7.18 (dt, J = 8.7, 2.5 Hz, 4H), 2.018 – 1.96 (m, 2H), 1.92 – 1.80 (m, 2H), 1.59 – 1.54 (m, 2H), 1.04 (t, J = 4.7 Hz, 2H), 0.88 (dd, J = 8.4, 4.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.4, 131.7, 129.3, 128.6, 27.1, 24.3, 20.8, 15.9. **HRMS** (ESI) calculated for $[C_{20}H_{19}Cl_2]^+$ 329.0858, found $[M + H]^+$ 329.0864.

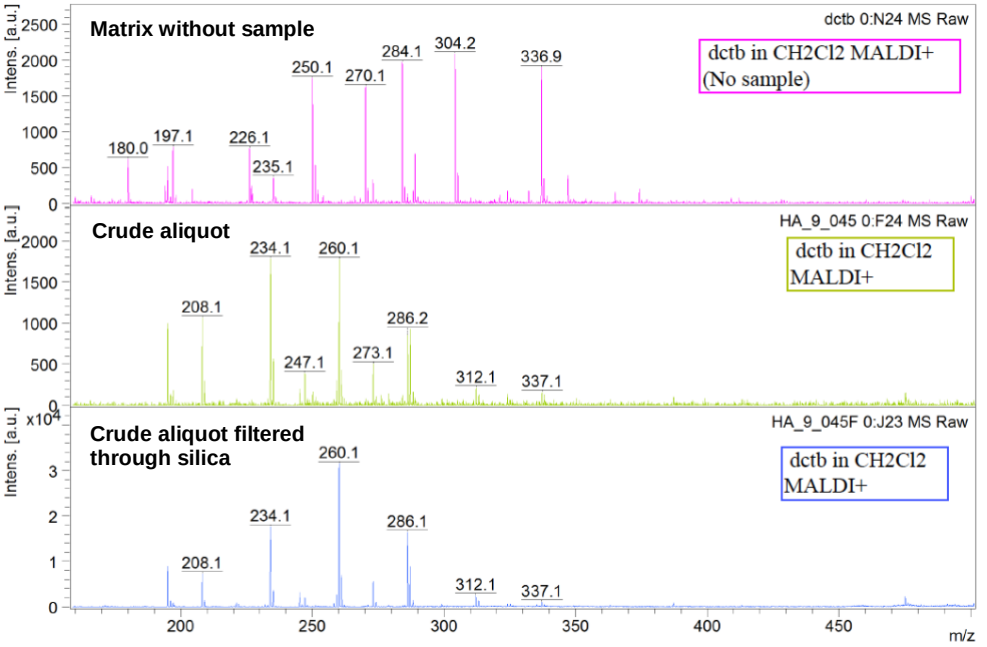
Oligomerization experiments

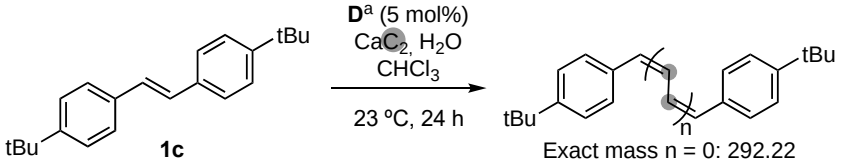
Substrates **1b** and **1c** were submitted under the optimized reaction conditions in chloroform (5 mol% of catalyst, 0.2 M, 23 ºC). After 24 h, the reaction was stopped and a small aliquot of crude was submitted to MALDI-TOF MS analysis. Another aliquot of the crude was filtered through a short silica path and also submitted to MALDI-TOF MS analysis. The corresponding results are shown below.



Exact mass n = 0: 208.13
n = 1: 234.15
n = 2: 260.17
n = 3: 286.19
n = 4: 312.21
n = 5: 338.23

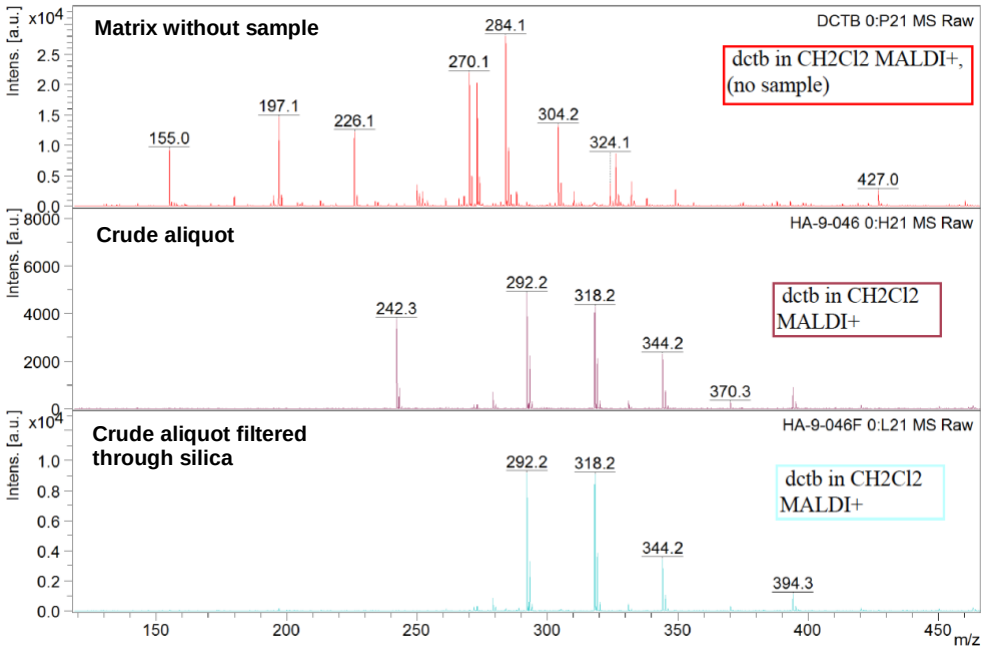
[a] Complex prepared *in situ* from equimolar amounts of *t*BuXPhosAuCl and $NaBAr^{F}_{4}$.





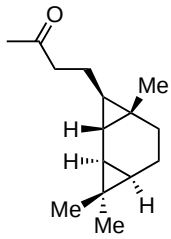
Exact mass n = 0: 292.22
n = 1: 318.24
n = 2: 344.26
n = 3: 370.28

[a] Complex prepared *in situ* from equimolar amounts of *t*BuXPhosAuCl and $NaBAr^{F}_{4}$.



Total synthesis of waitziacuminone

Waitziacuminone (9)

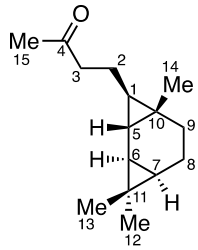


The natural product was prepared from isomerically pure geranyl acetone[13] (38.9 mg, 200 µmol) according to general procedure C with IPrAu(PhCN)BAr^F_4 as catalyst. Purification by flash column chromatography (pentane/Et_2O 97:3 to 96:4) delivered the natural product **9** (25.8 mg, 117 µmol, 59 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (t, J = 7.5 Hz, 2H), 2.16 (s, 3H), 1.72 – 1.60 (m, 2H), 1.59 – 1.47 (m, 2H), 1.00 (s, 3H), 0.93 (s, 3H), 0.93 – 0.89 (m, 1H) 0.89 (s, 3H), 0.78 (ddd, J = 13.3, 11.6, 4.3 Hz, 1H), 0.53 (ddd, J = 8.7, 7.4, 5.3 Hz, 1H), 0.49 (d, J = 9.0 Hz, 1H), 0.26 (ddd, J = 7.9, 6.7, 4.9 Hz, 1H), 0.02 (d, J = 4.9 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 209.5, 44.3, 33.0, 31.8, 30.2, 28.3, 24.4, 22.4, 21.8, 20.6, 19.8, 19.4, 18.6, 16.4, 16.1. **^{13}C NMR** (101 MHz, C_6D_6) δ 206.3, 43.8, 33.3, 32.2, 29.5, 28.4, 24.4, 22.7, 22.0, 21.0, 19.9, 19.3, 18.6, 16.7, 16.3.

The spectroscopic data of waitziacuminone (**9**) are in accordance with those reported in literature.[14]

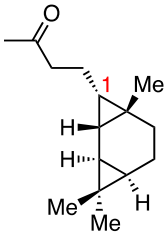
Table 13. Comparison of NMR shifts of natural and synthetic waitziacuminone (**x**)



position	^{1}H NMR natural ($CDCl_3$)	^{1}H NMR synthetic ($CDCl_3$, 400 MHz)	^{13}C NMR natural (C_6D_6)a	^{13}C NMR synthetic (C_6D_6, 101 MHz)
1	0.26 (ddd, J = 8, 6.5, 5 Hz)	0.26 (ddd, J = 7.9, 6.7, 4.9 Hz)	32.2	32.2
2	1.67 (m) 1.52 (m)	1.72 – 1.60 (m) 1.59 – 1.47 (m)	24.3	24.4
3	2.53 (t, J = 7.5 Hz)	2.53 (t, J = 7.5 Hz)	43.7	44.8
4	-	-	206.3	206.3
5	0.01 (br d, J = 5 Hz)	0.02 (d, J = 4.9 Hz)	21.8	22.0
6	0.49 (br d, J = 8.5 Hz)	0.49 (d, J = 9.0 Hz)	20.9	21.0
7	0.53 (ddd, J = 8.5, 8.5, 5.5 Hz)	0.53 (ddd, J = 8.7, 7.4, 5.3 Hz)	22.7	22.7
8	1.60 (m) 0.90 (m)	1.72 – 1.60 (m) 0.93 – 0.89 (m)	16.7	16.7
9	1.55 (m) 0.77 (m)	1.59 – 1.47 (m) 0.78 (ddd, J = 13.3, 11.6, 4.3 Hz)	33.2	33.3
10	-	-	18.6	18.6
11	-	-	19.8	19.9

12	0.88 (s)b	0.89 (s)	28.3	28.4
13	1.00 (s)	1.00 (s)	16.2	16.3
14	0.92 (s)b	0.93 (s)	19.3	19.3
15	2.16 (s)	2.16 (s)	29.4	29.5

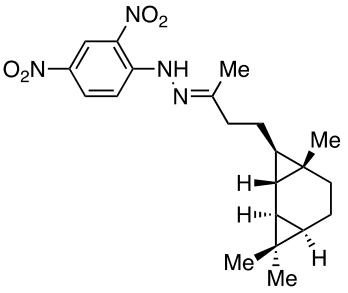
1-epi-Waitziacuminone (epi-9)



The epimer *epi*-**9** of the natural product was prepared from commercially available geranyl acetone containing 40% of neryl acetone (38.9 mg, 200 µmol) according to general procedure C with IPrAu(PhCN)BAr^F_4 as catalyst. Purification by flash column chromatography (pentane/Et_2O 98:2 to 95:5) delivered waitziacuminone (**9**) and its epimer *epi*-**9** (60:40 mixture of diastereomers; 25.9 mg, 118 µmol, 59%) as a colourless oil. Separation by preparative HPLC (Chiralpak IA 250x4.6mm, 5µm, pentane/MTBE 95:5, 1ml/min, 210 nm) delivered pure 1-*epi*-waitziacuminone (*epi*-**9**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54 – 2.40 (m, 2H), 2.16 (s, 3H), 1.73 – 1.65 (m, 1H), 1.61 – 1.45 (m, 2H), 1.39 – 1.33 (m, 1H), 1.04 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.86 – 0.71 (m, 2H), 0.57 – 0.48 (m, 2H), 0.24 (d, J = 8.5 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.6, 44.0, 30.2, 28.1, 27.0, 26.4, 24.3, 22.5, 20.1, 18.4, 17.4, 17.2, 17.0, 16.5, 16.2. **HRMS** (ESI) calculated for $[C_{15}H_{24}NaO]^+$ 243.1719, found $[M + Na]^+$ 243.1713.

2,4-Dinitrophenylhydrazone of waitziacuminone 10

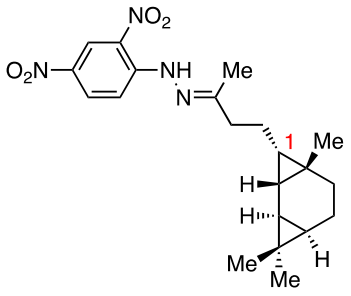


Waitziacuminone (9; 23.9 mg, 108 µmol) was diluted in EtOH (0.3 mL) and treated with a solution of (2,4-dinitrophenyl)hydrazine (813 µL; 0.2 M in conc. HCl/EtOH/H_2O 7.5:10:35) and the reaction was stirred for 2 h. Water (5 mL) was added, the mixture was extracted with DCM (3x 5 mL) and the combined organic layers were dried over Na_2SO_4. Flash column chromatography (cyclohexane/ Et_2O 98:2) delivered a 85:15 mixture of isomers of hydrazone **10** (36.7 mg, 91.6 µmol, 84%) as a yellow resin, which solidified upon addition of EtOH and evaporation. Crystallization by vapor diffusion from 1,2-difluorobenzene/MeOH yielded crystals suitable for X-ray analysis.

M.p. = 99 – 102 °C (cyclohexane/CH2Cl2). Mayor isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.13 (d, J = 2.6 Hz, 1H), 8.29 (ddd, J = 9.6, 2.6, 0.8 Hz, 1H), 7.98 (d, J = 9.6 Hz, 1H), 2.59 – 2.48 (m, 2H), 2.08 (s, 3H), 1.79 – 1.70 (m, 1H), 1.69 – 1.59 (m, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.94 – 0.90 (m, 1H), 0.90 (s, 3H), 0.79 (ddd, J = 13.2, 11.6, 4.3 Hz, 1H), 0.57 – 0.50 (m, 1H), 0.49 (d, J = 8.6 Hz, 1H), 0.35 – 0.29 (m, 1H), 0.06 (d, J = 4.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.5, 145.4, 137.8, 130.1, 129.1, 123.7, 116.6, 39.6, 33.1, 32.1, 28.3, 26.8, 22.5, 22.0, 20.6, 19.9, 19.4, 18.6, 16.5, 16.2, 16.1. Minor isomer (significant signals**):** **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.28 (s, 1H), 2.16 (s, 3H), 0.96 (s,

3H), 0.95 (s, 3H), 0.88 (s, 3H), 0.76 – 0.70 (m, 1H), 0.42 (d, J = 8.7 Hz, 1H), 0.11 (d, J = 4.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.4, 145.4, 137.7, 128.9, 123.8, 116.4, 31.9, 28.2, 25.7, 21.8, 20.5, 19.3, 16.4, 16.1. **HRMS** (ESI) calculated for $[C_{21}H_{28}N_4NaO_4]^+$ 423.2003, found $[M + Na]^+$ 423.2006.

2,4-Dinitrophenylhydrazone of 1-epi-waitziacuminone epi-10



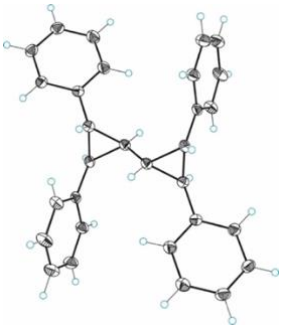
The isolated 1-*epi*-waitziacuminone (*epi*-**9**) was transformed into its hydrazone according to the procedure used for waitziacuminone. Flash column chromatography (cyclohexane/ Et_2O 98:2) delivered the hydrazone *epi*-**10** as a yellow crystalline solid. Crystallization by vapor diffusion from 1,2-difluorobenzene/MeOH yielded crystals suitable for X-ray analysis.

M.p. = 131 – 134 °C (cyclohexane/CH_2Cl_2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.04 (s, 1H), 9.13 (d, J = 2.6 Hz, 1H), 8.31 (dd, J = 9.6, 2.6 Hz, 1H), 7.97 (d, J = 9.6 Hz, 1H), 2.54 – 2.41 (m, 2H), 2.08 (s, 3H), 1.76 – 1.69 (m, 1H), 1.69 – 1.60 (m, 1H), 1.60 – 1.50 (m, 1H), 1.44 – 1.38 (m, 1H), 1.06 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.89 – 0.74 (m, 2H), 0.62 (q, J = 7.5 Hz, 1H), 0.54 (td, J = 8.5, 6.3 Hz, 1H), 0.28 (dd, J = 12.8, 8.5 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.4, 145.3, 137.6, 130.0, 129.0, 123.6, 116.5, 39.1, 28.1, 27.1, 26.3, 24.4, 22.5, 22.4, 18.3, 17.4, 17.2, 16.9, 16.4, 16.2, 16.0. **HRMS** (ESI) calculated for $[C_{21}H_{28}N_4NaO_4]^+$ 423.2003, found $[M + Na]^+$ 423.1196.

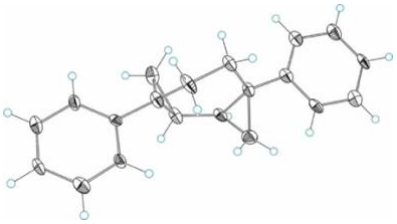
Crystal structures

The supplementary crystallographic data for this Chapter has been published and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

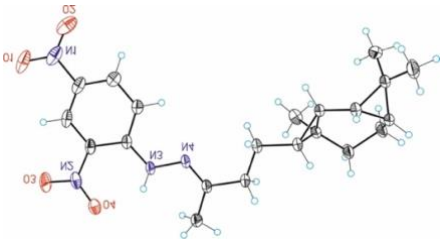
Bicyclopropyl compound 5a
CCDC 1971217



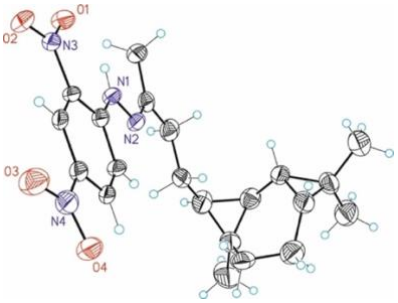
Tricyclo[5.1.0.02,4]octane 6a
CCDC 1971218



2,4-Dinitrophenylhydrazone of waitziacuminone (10)
CCDC 1971429



2,4-Dinitrophenylhydrazone of 1-epi-waitziacuminone (epi-10)
CCDC 1971216

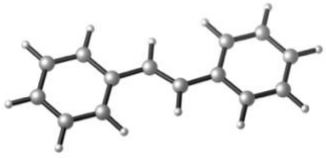


DFT calculations

Computational methods

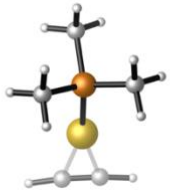
Calculations were performed by means of the Gaussian 09 suite of programs.[75] DFT was applied using M06-D3[76]. The SDD basis set and ECP was used to describe Au.[77] The 6-31G(d) basis set[78] was employed for all remaining atoms (C, H, P and O). Full geometry optimizations were carried out in dichloromethane, through an implicit solvent SMD.[79] The stationary points were characterized by vibrational analysis. Transition states were identified by the presence of one imaginary frequency while minima by a full set of real frequencies. The connectivity of the transition states was confirmed by the relaxation of each transition state towards both the reactant and the product. Reported energies are potential energies (E) and free energies (G) in solution, computed at 298 K and 1 atm.

Optimized structures



1a

E = - 540.276142 Hartrees
G = - 540.098925 Hartrees



Int1a

E = - 673.904179606 Hartrees
G = - 673.799679 Hartrees

75 Gaussian 09, Revision B.1, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., Petersson, G. A., Nakatsuji, H., Caricato, M., Li, X., Hratchian, H. P., Izmaylov, A. F., Bloino, J., Zheng, G., Sonnenberg, J. L., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Montgomery, J. A., Peralta, Jr. J. E., Ogliaro, F., Bearpark, M., Heyd, J. J., Brothers, E., Kudin, K. N., Staroverov, V. N., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Rega, N., Millam, J. M., Klene, M., Knox, J. E., Cross, J. B., Bakken, V., Adamo, C., Jaramillo, J., Gomperts, R., Stratmann, R. E., Yazyev, O., Austin, A. J., Cammi, R., Pomelli, C., Ochterski, J. W., Martin, R.L., Morokuma, K., Zakrzewski, V. G., Voth, G. A., Salvador, P., Dannenberg, J. J., Dapprich, S., Daniels, A. D., Farkas, Ö., Foresman, J. B., Ortiz, J. V., Cioslowski, J., Fox, D. J. Gaussian, Inc., Wallingford CT **2009**.

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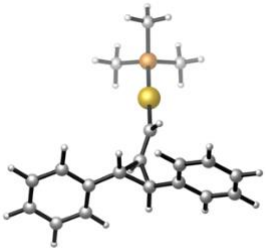
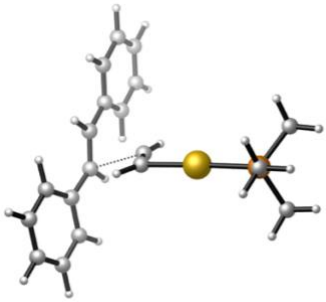


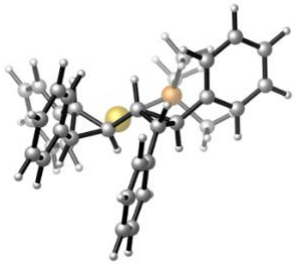
Int2a

E = - 1754.52088294 Hartrees
G = - 1754.010248 Hartrees



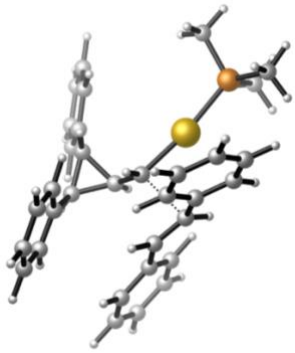
TS1a_Int2a

E = - 1214.17912493 Hartrees
G = - 1213.877563 Hartrees



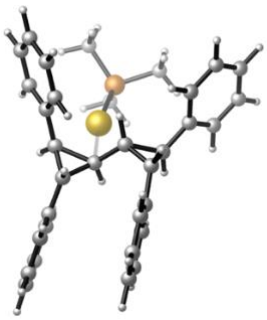
Int3a

E = - 1754.57308100 Hartrees
G = - 1754.057943 Hartrees



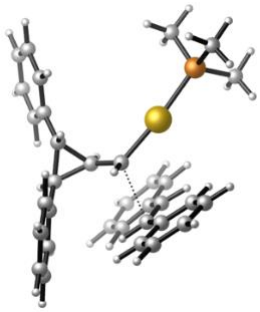
TSInt2a_Int3a

E = - 1754.51094917 Hartrees
G = - 1753.998576 Hartrees



Int4a

E = - 1754.55848972 Hartrees
G = - 1754.040464 Hartrees



TSInt2a_Int4a

E = - 1754.51479281 Hartrees
G = - 1754.002938 Hartrees

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Chapter 2.

Assembly of hydroazulenes by a Au(I)-catalyzed cycloisomerization/(4+3)-cycloaddition reaction

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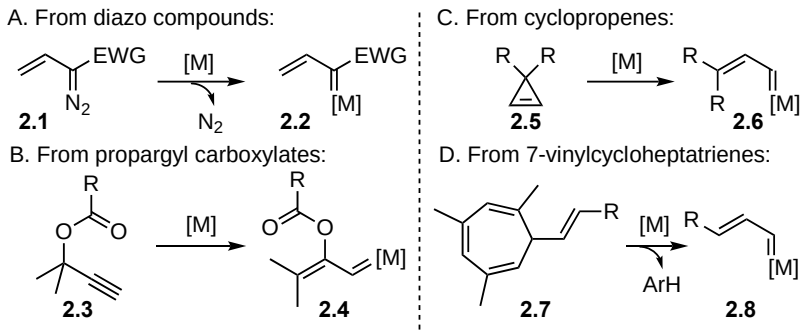
Introduction

Generation of Gold(I)-vinylcarbenes

Metal vinylcarbenes **2.2** are versatile intermediates which have been mostly accessed by metal decomposition of vinyl diazo compounds **2.1** (scheme 35, A).[80] This strategy has been widely employed but it presents the inherent problems associated to diazo compounds,[81] which limit these methodologies to the use of acceptor metal carbenes.[82] Diazo compounds have served as metal carbene precursors for rhodium, ruthenium, platinum and palladium, among other metal complexes.[83] However, it was not until 2005, when Nolan, Díaz-Requejo and Pérez reported its first trapping with gold.[84] This methodology has been widely used to access simple gold(I) carbenes[85] and other metal vinylcarbenes.[86]



Scheme 35. Methods for the generation of metal vinylcarbenes.

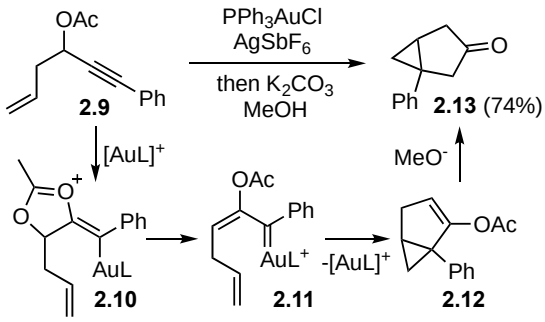
80. a) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou , *Chem. Rev.* **2010**, *110*, 704 – 724; b) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857 – 1869; c) Q.-Q. Cheng , Y. Deng, M. Lankelma, M. P. Doyle , *Chem. Soc. Rev.* **2017**, *46* , 5425 – 5443.
81. J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **2005**,1479 –1492.
82. a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861 –2904; b) D. Zhu, L. Chen, H. Fan, Q. Yao, S. Zhu, *Chem. Soc. Rev.* **2020**, *49*, 908 –950.
83. M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**.
84. M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo, P. J. Pérez , *Angew. Chem. Int. Ed.*, **2005**, *44*, 5284 – 5288
85 a) For a review: F. Wie, C. Song, Y. Ma, L. Zhou, C.-H. Tung, Z. Xu, *Sci. Bull.* **2015**, *60*, 1479 – 1492; b) Selected examples: A. Prieto, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, P. Pérez-Galán, N. Delpont, A. M. Echavarren, Tetrahedron **2009**, *65*, 1790 – 1793; J. F. Briones, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134* , 11916 – 11919; Z.-Y. Cao , X. Wang , C. Tan , X.-L. Zhao , J. Zhou and K. Ding , *J. Am. Chem. Soc.* **2013**, *135*, 8197 – 8200.
86 a) X. Xu, M. P. Doyle, *Acc. Chem. Res.* **2014**, *47*, 139 – 1405; b) B. T. Parr, H. M. L. Davies, *Nat. Commun.* **2014**, *5*, 4455; c) D. J. Lee et al., *J. Am. Chem. Soc.* **2014**, *136*, 11606–11609.

Alternatively, metal vinylcarbenes **2.4**, and specifically gold(I) vinylcarbenes, can be prepared from propargylic carboxylates **2.3**, by 1,2-acyl migration (scheme 35, B)[87] or from cyclopropenes **2.5**, by a metal-mediated ring opening to provide structure **2.6** (scheme 35, C).[88] Additionally, our group has recently applied the retro-Buchner reaction of 7-vinyl-1,3,5-cycloheptatrienes **2.7** to generate gold(I) vinyl carbenes **2.8** (scheme 35, D).[89]

Selected examples and applications in (4+3) cycloadditions

Cycloaddition reactions stick out for their potential to rapidly build up molecular complexity. The use of gold(I) vinylcarbenes as the "3" fragment in cycloaddition reactions has been widely explored, leading the formation of 5, 6 and 7-membered rings.[86] For the latter, these intermediates present as an ideal reaction partner to undergo (4+3) cycloadditions together with readily available 1,3-dienes. In this section we will discuss selected examples on the different methods for the generation of gold(I) vinylcarbenes and their specific application in (4+3) cycloaddition reactions.

The generation of intermediates similar to **2.4** upon 1,2-acyl migration, has been widely used since it was discovered in the gold(I)-catalyzed Rautenstrauch rearrangement, by Fürstner (scheme 36).[90]



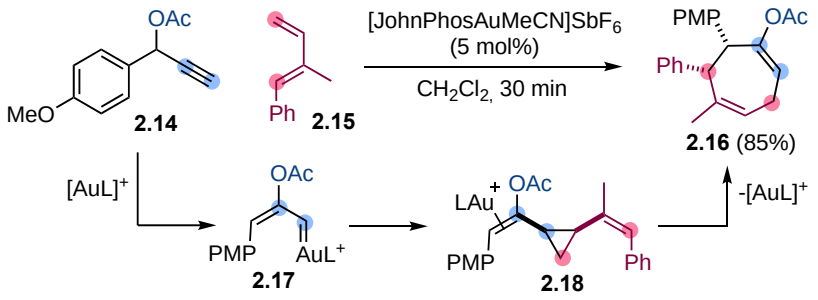
Scheme 36. Fürstner's discovery of a gold(I) catalyzed Rautenstrauch rearrangement

In this reaction, 1,5-enyne **2.9** undergoes a 1,2-acyl migration leading to vinyl carbene **2.11**. Cyclopropanation affords intermediate **2.12**, which under basic conditions delivers the product **2.13**. Although there was some initial experimentation to determine the order

87. a) N. Marion, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2750 – 2752; b) X.-Z. Shu, D. Shu , C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41* , 7698 – 7711; c) R. K. Shiroodi and V. Gevorgyan , *Chem. Soc. Rev.* **2013**, *42* , 4991 – 5001.
88. R. Vicente, Synthesis 2016, 48, 2343 – 2360.
89. a) B. Herlé, P. M. Holstein, A. M.. Echavarren, *ACS Catal.* **2017**, *7*, 3668 − 3675; b) M. Mato, A. M. Echavarren, *Org. Lett.* **2018**, *20*, 14, 4341 – 4345.
90. V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654 – 8655.

of migration/cyclopropanation in this reaction,[91] it was undoubtedly confirmed to be as drawn when the intermolecular version was developed by Toste.[92]

An example of its application in (4+3) cycloaddition reactions was reported by Nevado in 2011 (scheme 37).[93] Reaction of **2.14** with 1,3-diene **2.15** in the presence of a gold(I) catalyst afforded cycloheptadiene product **2.16** in good yields. Their mechanistic proposal relies on a two-step process, which involves an initial cyclopropanation to afford intermediate **2.18**, followed by a Cope-rearrangement (thermal or gold-catalyzed) into the corresponding 7-membered ring. A similar transformation was later developed by the group of Zhang,[94] using vinylindoles as the diene substrate, and by Shi, using furans intramolecularly.[95]



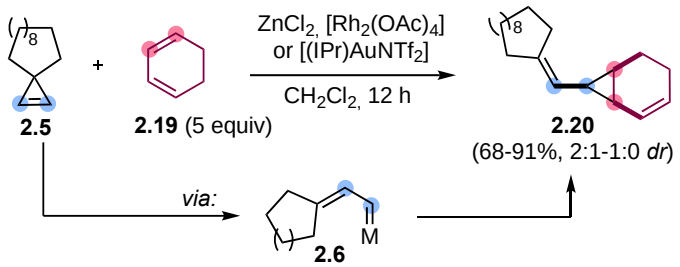
Scheme 37. Nevado's synthesis of cycloheptadienes **2.16** by cyclopropanation/Cope rearrangement

Alternatively, propargylic carboxylates similar to **2.14** can rearrange into allenyl esters by 1,3-acyl migration, opening a parallel spectrum of possibilities for different reactivity.[96]

Regarding the application of gold(I) vinylcarbenes **2.6** generated upon cyclopropenes ring opening, few methodologies have been developed, involving both intra-[97] and intermolecular processes.[98] An intramolecular example where cyclopropenes were used as

91. C. Fehr, J. Galindo, *Angew. Chem. Int. Ed.* **2006**, *45*, 2901 – 2904
92. M. J. Johansson, D. J. Gorin, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 18002 – 18003.
93. D. Garayalde, K. Krüger, C. Nevado, *Angew. Chem. Int. Ed.* **2011**, *50*, 911 – 915.
94. Y. Li, C.-Z. Zhu, J. Zhang, *Eur. J. Org. Chem.* **2017**, 6609 – 6613.
95. J.-M. Yang, X.-Y. Tang, M. Shi, *Chem. Eur. J.* **2015**, *21*, 4534 – 4540
96. a) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614 – 12615; b) N. Marion, P. de Frémont, G. Lemière , E. D. Stevens, L. Fensterbank , M. Malacria, S. P. Nolan, *Chem. Commun.* **2006**, 2048 – 2050; c) N. Marion, G. Lemière, A. Correa, C. Costabile, R. S. Ramon, X. Moreau, P. de Frémont, R. Dahmane, A. Hours, D. Lesage, J.-C. Tabet, J.-P. Goddard, V. Gandon, L. Cavallo, L. Fensterbank, M. Malacria, S. P. Nolan,*Chem. Eur. J.*, **2009**, *15*, 3243 – 3260; d) G. Lemière, V. Gandon, K. Cariou, T. Fukuyama, A. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2007**, *9*, 2207 – 2211; e) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A.-L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993 – 3006; f) L. Fensterbank, M. Malacria, *Acc. Chem. Res.* **2014**, *47*, 953 – 965.
97. For a recent review: A. Archambeau, F. Miege, C. Meyer, J. Cossy, *Acc. Chem. Res.* **2015**, *48*, 1021 – 1031.
98. For selected examples; a) J. T. Bauer, M. S. Hadfield, A.-L. Lee, *Chem. Commun.* **2008**, 6405 – 6407; b) R. J. Mudd, P. C. Young, J. A. Jordan-Hore, G. M. Rosair, A.-L. Lee, *J. Org. Chem.* **2012**, *77*, 7633 – 7639.

gold(I) vinylcarbene precursors and subsequently involved in a formal (4+3) cycloaddition reaction was recently reported by Hyland and Hashmi.[99] Also in 2019, López and Vicente reported the synthesis of 1,2-divinylcylopropanes **2.20** which do not undergo Cope-rearrangement under the reaction conditions, resembling a frustrated (4+3) cycloaddition (scheme 38).[100] These are prepared by vinyl cyclopropanation of 1,3-dienes by rhodium, zinc or gold carbenes **2.6**.



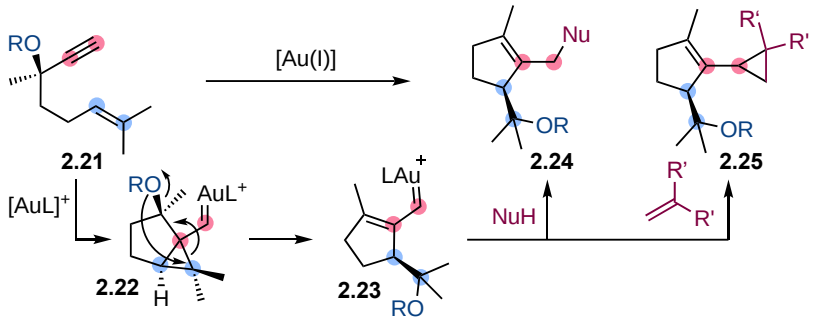
Scheme 38. Access to 1,2-divinylcyclopropanes **2.20** from cyclopropenes **2.5**.

Finally, on the retro-Buchner approach, species **2.8** have been employed for the synthesis of cyclopentadienes by (3+2)-cycloaddition reaction with allenes[101] or in common metal carbene transformations (not involving the reaction of the vinyl moiety), such as olefin cyclopropanations.[102] Previously to this Thesis, this methodology had not been applied to the synthesis of cycloheptadienes by (4+3)-cycloaddition reaction.

Reactivity of 1,6-enynes bearing a propargylic ether

An alternative strategy to access gold(I) vinyl carbenes was developed by our group, involving the cycloisomerization cascade of 1,6-enynes **2.21**, which bear a propargylic ether or carboxylate (scheme 39).[103] These can undergo a tandem process, starting by the selective activation of the triple bond by the gold(I) catalyst, which undergoes a 5-*exo*-dig cycloisomerization leading to cyclopropyl gold(I) carbene **2.22**. The ether or carboxylate group present in the propargylic position can then migrate to the most electrophilic carbon of the cyclopropane ring to deliver vinylcarbene **2.23**.

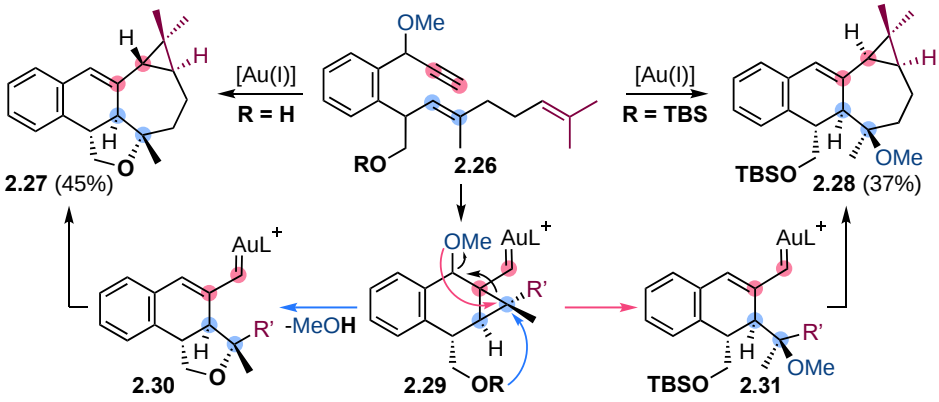
99. M. A. Drew, S. Arndt, C. Richardson, M. Rudolph, A. S. K. Hashmi, C. J. T. Hyland, *Chem. Commun.* **2019**, *55*, 13971 – 13974.
100. J. González, A. de la Fuente, M. J. González, L. Díez de Tejada, L. A. López, R. Vicente, *Beilstein J. Org. Chem.* **2019**, *15*, 285 – 290.
101. X. Yin, M. Mato, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2017**, *56*,14591 – 14595.
102. M. Mato, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2019**, *58*, 2088 – 2092.
103. For a recent account: H. Armengol-Relats, M. Mato, I. Escofet, A. M. Echavarren, *Synthesis* **2021**, DOI: 10.1055/a-1535-3215



Scheme 39. Generation of gold(I) vinylcarbenes **2.23** from enynes **2.21**. R=Ac, Me, etc.

These intermediates have been trapped intra- and intermolecularly by different carbon nucleophiles such as olefins (leading to cyclopropanation products **2.25**), indoles or 1,3-dicarbonyl compounds (delivering products **2.24**). However, in none of these examples, has the vinyl moiety been involved in the final nucleophilic addition, limiting the applications of species **2.23** to a 1-C carbene synthon.

This methodology for the generation of vinyl carbenes **2.23** has been applied to the total synthesis of some natural products[103] and it has been extended to benzene-linked 1,7-enynes **2.26** (scheme 40).[24] Interestingly, in this last example, the final cyclopropanation can afford selectively *trans*- or *cis*-fused cyclopropanes **2.27** and **2.28** depending on the rigidity of carbene intermediates **2.30**-**2.31**. The presence of a free hydroxy group in the side chain in **2.29** (when R = H) affords less flexible carbene **2.30** after methanol elimination, which leads to *trans*-fused cyclopropane **2.27** as a single isomer.



Scheme 40. Evolution of dienynes **2.26** under gold(I) catalysis.

Alternatively, TBS-protected substrate **2.26** (when R = TBS) affords *cis*-fused cyclopropane **2.28**, *via* methoxy-migration to generate vinylcarbene **2.31**. The stereochemistry of both structures was unambiguously assigned by single crystal x-ray diffraction.

As found for 1,5-enynes **2.9** (scheme 36), other 1,n-enynes bearing a propargylic carboxylate,[104] including 1,6 enynes such as **2.21**,[105] can also undergo a 1,2-acyl migration prior to the cyclopropanation step. This difference in the reactivity order is usually under substrate control but it can also be directed by the catalyst.

State of the art in the synthesis of hydroazulenes

Azulene (**2.32**) is a naphthalene isomer with a 5/7 bicyclic skeleton (figure 6). It was named after its dark blue appearance, physically due to its strong dipole character.[106] Its structure was successfully characterized in 1936 by Pfau and Plattner.[107] Based on this, the term "hydroazulene" is used to describe a partially or fully saturated analogue of azulene. The interest on this family of compounds arises from its presence in biologically-active natural products such as guaianolides (**2.34**).[108]

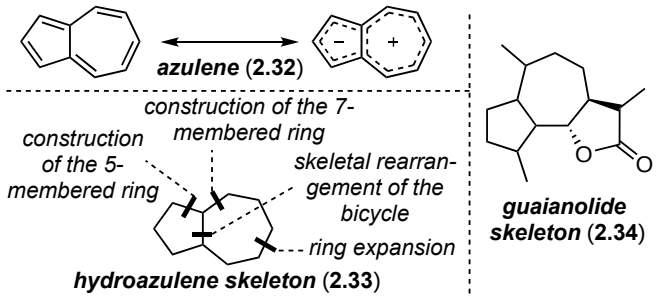


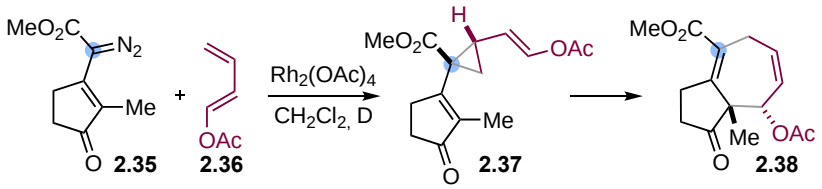
Figure 6. Azulene (**2.32**), hydroazulene (**2.33**) and its classical synthetical approaches.

Different synthetic procedures have been developed for the synthesis of this bicyclic skeleton over the years (figure 6).[109] Among them, we can distinguish four classical approaches, which include the construction of the second carbocycle on the previously prepared one, both starting from cyclopentanes or cycloheptanes, skeletal rearrangements of linear substrates, macrocycles or other bicycles, and ring expansion methods usually starting from tricyclic compounds.

104. a) X. Moreau, J.-P. Goddard, M. Bernard, G. Lemière, J. M. López-Romero, E. Mainetti, N. Marion, V. Mouriès, S. Thorimbert, L. Fensterbank, M. Malacria, *Adv. Synth. Catal.* **2008**, *350*, 43 – 48; b) F.-D. Boyer, X. Le Goff, I. Hanna, *J. Org. Chem*. **2008**, *73*, 5163 – 5166; c) I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem. Soc*. **2009**, *131*, 2056 – 2057;
105. A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006 – 3019
106. J. Michl, E. W. Thulstrup, *Tetrahedron*, **1976**, *32*, 205 – 209.
107. T. Nozoe, S. Ito, Recent Advances in the Chemistry of Azulenes and Natural Hydroazulenes, in Fortschritte der Chemie Organischer Naturstoffe, L. Zechmeister (ed.), Springer-Verlag, 1961.
108. For a recent review: A. Bosco, R. M. Golsteyn, *Molecules* **2017**, 22, 459.
109. Reviews: a) J. Marshall, *Synthesis* **1972**, 517 – 525; b) M. Vanderwalle, P. de Clercq, *Tetrahedron* **1985**, *41*, 1767 – 1831.

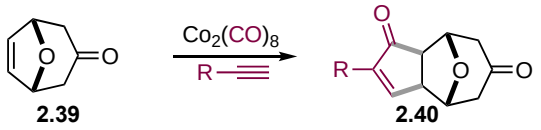
Selected examples for the synthesis of hydroazulenes

In this section we have summarized few examples, for each of the classical approaches that we have mentioned in figure 6. For the construction of the seven-membered ring on a five-membered carbocycle, Davies applied a rhodium-catalyzed cyclopropanation/Cope rearrangement, starting from diazo cyclopentenone **2.35** (scheme 41).[110] Rhodium catalysis allows the formation of divinylcyclopropane **2.37**, which undergoes a (3,3)-sigmatropic rearrangement to deliver the 5/7-fused bicyclic structure in **2.38**.[111] Other common methods for the construction of the of the second ring starting from cyclopentanes or cyclopentenes are intramolecular cyclizations involving ring closing metathesis,[112] organometallic additions[113] or transition metal-catalyzed couplings.[114]



Scheme 41. Davies' synthesis of hydroaxulenes by cyclopropanation/Cope rearrangement.

As an alternative, an example of the synthesis of hydroazulenes from partially unsaturated cycloheptanes was developed by Schore (scheme 42).[115] The construction of the five-membered ring in **2.40** was accomplished via an intermolecular Pauson-Khand reaction of **2.39** with a terminal alkyne.

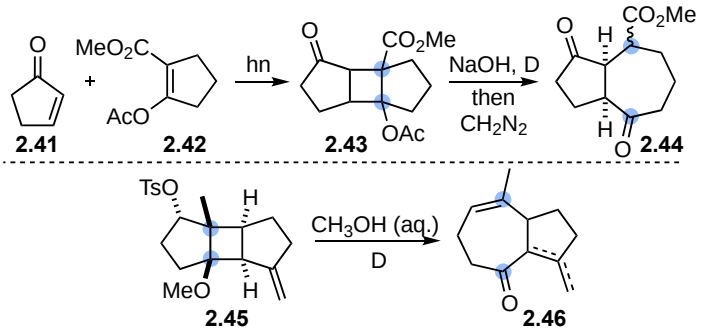


Scheme 42. Schore's synthesis of **2.40** by Pauson-Khand reaction.

Regarding the ring fragmentation of a tricyclic compound, hydroazulene **2.44** was prepared by Liu,[116] by a photochemical [2+2] cycloaddition of **2.41** and **2.42**, followed by ring expansion under basic conditions (scheme 43). This procedure led to **2.44** as a mixture of diastereomers. A similar approach was also reported by Schore,[117] starting from product

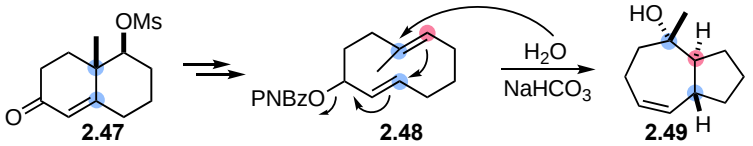
110. W. R. Cantrell Jr., H. M. L. Davies, J. Org. Chem. 1991, 56, 723 – 727.
111. For other examples: H. Davies, Tetrahedron 1993, 49, 5203 – 5223.
112. N. B. Bennett, B. M. Stoltz, Chem. Eur. J. 2013, 19, 17745 – 17750
113. G. B. Dudley, S. J. Danishefsky, Org. Lett. 2001, 3, 2399–2402
114. P. Gao, S. P. Cook, Org. Lett. 2012, 14, 3340–3343
115. B. E. La Belle, M. J. Knudsen, M. M. Olmstead, H. Hope, M. D. Yanuck, N. E. Schore, J. Org. Chem. 1985, 50, 25, 5215–5222
116. H. J. Liu, Synthetic Commun. 1974, 4, 237 – 241.
117. V. Sampath, E. C. Lund, M. J. Knudsen, M. M. Olmstead, N. E. Schore, J. Org. Chem. 1987, 52, 3595 – 3603.

2.45 (scheme 43). In this case, elimination of the tosylate group triggered the ring-opening of the internal cyclobutene leading to **2.46** as a mixture of double bond isomers.



Scheme 43. Cyclobutane ring opening for the formation of hydroazulenes **2.44** and **2.46**.

Additionally to these methodologies, many procedures based on the cyclization of linear substrates or on transannular rearrangements of macrocycles have been developed over the years.[109] As an early example, hydroazulene **2.49** was obtained by treatment of macrocyclic product **2.48** with a basic aqueous solution (scheme 44).[118] The construction of **2.48** was accomplished in several steps from ketomesylate **2.47**.

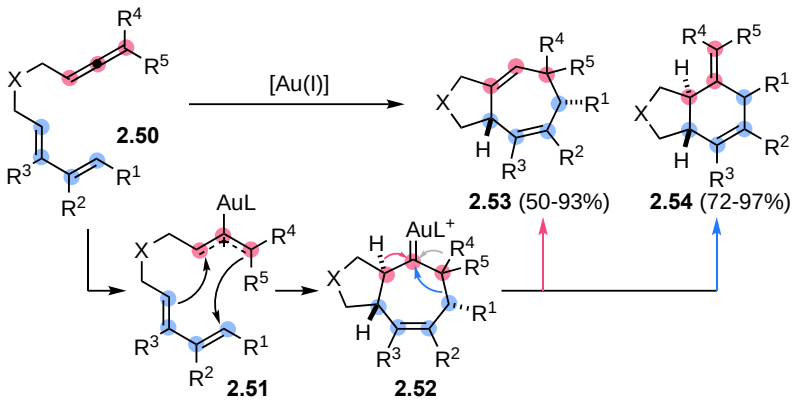


Scheme 44. Synthesis of hydoazulene **2.49** by a transannular cyclization of **2.48**.

Synthesis of hydroazulenes by gold(I) catalysis

Among the cyclization approaches where the two rings are formed in one step from a linear substrate, gold(I) catalysis has served as a powerful tool for the assembly of the hydroazulene skeleton. Within this class of transformations, we find the intramolecular (4+3) cycloaddition reaction of allenedienes **2.50** developed parallelly by the groups of Mascareñas and López (scheme 45), [119] and the group of Toste.[120]

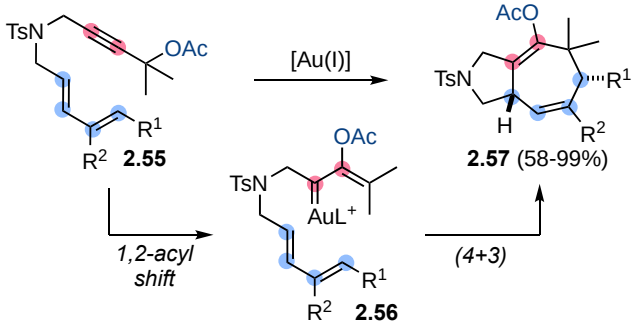
118. J. A. Marshall, W. F. Huffman, J. Am. Chem. Soc. 1970, 92, 6358 – 6359
119. Recent account: J. L. Mascareñas, I. Varela, F. Lopez, Acc. Chem. Res. 2019, 52, 465 – 479.
120. P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, J. Am. Chem. Soc. 2009, 131, 6348 – 6349.



Scheme 45. Mascareñas and López' (4+3) cycloaddition reaction of allenedienes **2.50**.

Upon coordination of allene **2.50** to the gold(I) catalyst, gold(I) allyl cation **2.51** gets formed. This can then undergo a (4+3) cycloaddition leading to gold(I) carbene **2.52**. Finally, 1,2-hydride shift (or in some cases 1,2-R^4 shift), which was calculated to be the rate-limiting step, delivers product **2.53**.[121] This transformation forges the 5/7 bicyclic system from an acyclic substrate in good yield and diastereoselectivity. The enantioselective version has also been achieved by using chiral phosphoramidite-gold(I) catalysts.[122] Alternatively, depending on the gold(I) catalyst employed, a ring contraction could take place (blue pathway) delivering products **2.54**.[123]

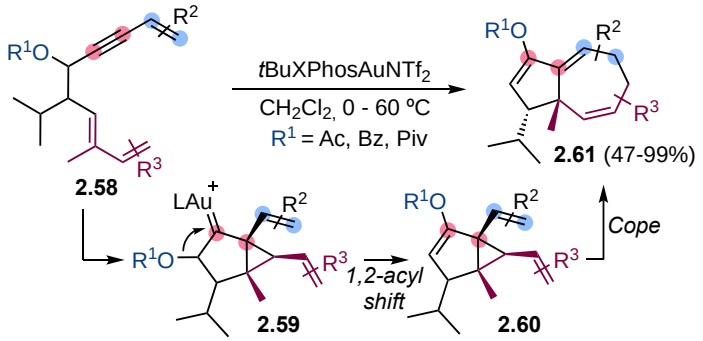
Similar products **2.57** were obtained by Chan in 2014,[124] from dienynes **2.55** (scheme 46), as an intramolecular example of Nevado's reaction depicted in scheme 37. The advantage of the intramolecular version is that it allows for the construction of a bicyclic skeleton from a linear substrate.



Scheme 46. Chan's synthesis of aza-hydroazulenes **2.57** from dienynes **2.55**.

121. B. Trillo, F. Lopez, S. Montserrat, G. Ujaque, L. Castedo, A. Lledoś, J. L. Mascareñas, *Chem. Eur. J.* **2009**, *15*, 3336 – 3339.
122. I. Alonso, H. Faustino, F. López, J. L. Mascareñas, *Angew. Chem. Int. Ed.* **2011**, *50*, 11496 – 11500.
123. I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas, *J. Am. Chem. Soc.* **2009**, *131*, 13020 – 13030.
124. W. Rao, Sally, S. N. Berry, P. W. H. Chan, *Chem. Eur. J.* **2014**, *20*, 13174 – 13180.

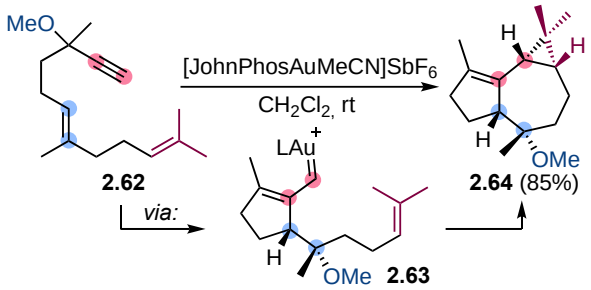
Another interesting example was reported by Gasosz[125] and later studied computationally by Wang,[126] starting from polyenyne **2.58** (scheme 47). Oppositely to what was found for substrates **2.9**, for instance in Fürstner's example (scheme 36), in this case the 5-*endo*-dig cyclization takes place first, forming carbene **2.59**, and in second place, the 1,2-acyl shift occurs. Finally, a gold(I)-catalyzed or thermal Cope rearrangement of divinylcyclopropane **2.60** delivers hydroazulene **2.61**.



Scheme 47. Gold(I)-catalyzed cycloisomerization/Cope-rearrangement of **2.58**.

Other cyclization approaches by means of gold(I) catalysis have been developed for the synthesis of 5/7 bicyclic compounds, not involving formal (4+3) cycloaddition reactions.[5] Some of these approaches were reported by our group, for example based on the cycloisomerization of ketoenynes,[127] described in the General Introduction, or on the reactivity of 1,6-enynes bearing a propargylic ether, summarized in the previous section (scheme 39-40).[128] In the latter, under gold(I) catalysis, dienynes such as **2.62** could undergo a cycloisomerization/OR-migration/cyclopropanation cascade sequence to afford tricyclic compounds **2.64**, bearing a cyclopropanated hydroazulene core (scheme 48). This methodology was applied to the total synthesis of some members of the aromadendrane family of natural products.[129]

125. C. Ziping, F. Gagosz, *Angew. Chem. Int. Ed.* **2013**, *52*, 9014 – 9018
126. M.-R. Li, G.-C. Wang, *RSC Adv.* **2016**, *6*, 73454 – 73468
127. Intramolecular: E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327 – 7329; intermolecular: C. Obradors, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 3547 – 3551.
128. E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2009**, *48*, 6152 – 6155.
129. J. Carreras, M. Livendahl, P. R. McGonigal, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2014**, *53*, 4896 – 4899.

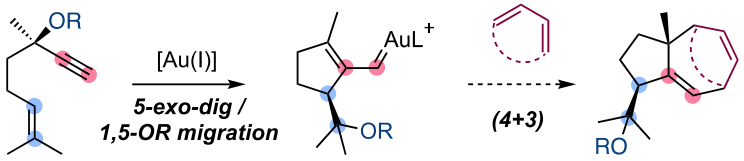


Scheme 48. Cycloisomerization cascade of diene **2.62** under gold(I) catalysis.

To summarize this section, although considerable progress has been done in the field of hydroazulene synthesis by gold(I) catalysis, the reported procedures involve intramolecular cyclizations/rearrangements, where the two rings are formed in one step from a linear substrate. Despite the advantage of having high stereoselectivities, this limits their applications and scope. Thus, an intermolecular approach which would allow the formation of the two rings in one step, from two independent starting materials, would broaden the combination possibilities, expanding the scope of readily available hydroazulenes, by means of gold catalysis.

Objectives

In this chapter, we aim to develop a new method for the construction of hydroazulenes by merging two well-stablished methodologies: the first involving the gold(I)-catalyzed isomerization of 1,6-enynes bearing a propargylic ether into α,β-unsaturated gold(I)-carbenes; and the second being the (4+3)-cycloaddition reaction of metalvinylcarbenes with 1,3-dienes (scheme 49). In order to do this, we will focus first on the reaction optimization and then evaluate the scope of this transformation. Finally, we will study the mechanism of this transformation by means of DFT calculations and time-lapse and control experiments.

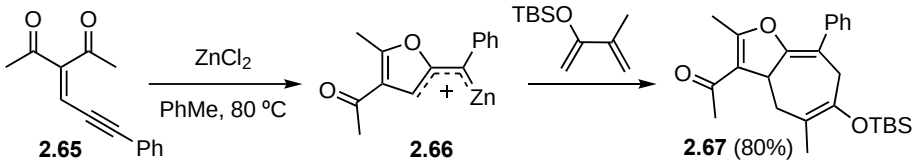


Scheme 49. Gold(I)-catalyzed tandem cycloisomerization/(4+3)-cycloaddition reaction

Results and Discussion

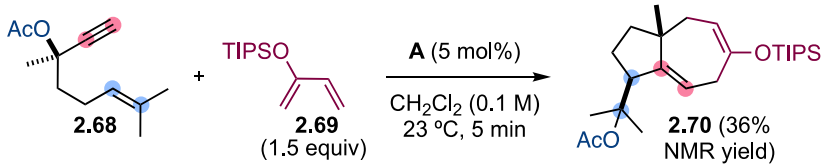
Reaction Discovery and Optimization

Our initial strategy was based on a similar reaction reported by the group of Liang using zinc (II) catalysts (scheme 50).[130] In this example, the (4+3)-cycloaddition took place using an electronically biased diene, which presumably favors a stepwise cycloaddition with allylic zinc cation **2.66**, formed upon cyclization of **2.65**.



Scheme 50. Liang's reaction with zinc chloride.

Thus, we selected similar diene **2.69**, with less labile TIPS group, for our initial experiments (scheme 51). We were pleased to find that compound **2.70** was obtained in 36% NMR yield as the main product in our first attempt, by reaction of enyne **2.68** with commercially available [JohnPhosAuMeCN]SbF_6 (**A**) after only 5 minutes.

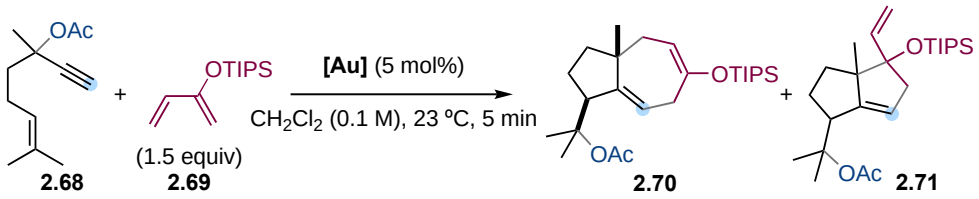


Scheme 51. First attempt on the cycloisomerization/(4+3)-cycloaddition reaction.

Subsequently, we addressed the reaction optimization, starting with a brief catalyst screening (table 14). We found that **2.70** was the main product detected in the reaction with all the catalysts we used. Slightly better results were obtained with catalysis **A** and **D** (entries 1 and 4). Interestingly, using bulkier complex **B** we obtained a 1:1 ratio of (4+3)-adduct **2.70** and byproduct **2.71** (entry 2). Compound **2.71** is product of a formal (3+2)-cycloaddition.

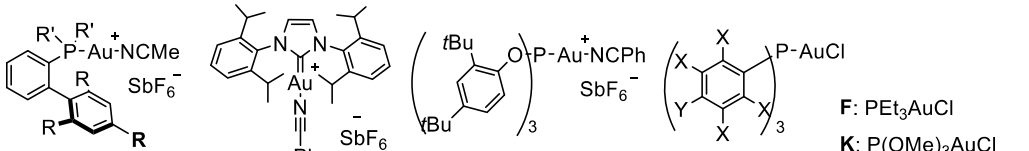
Table 14. Catalyst screening for the reaction of **2.68** and **2.69**.

130. B. Song, L.-H. Li, X.-R. Song, Y.-F. Qiu, M.-J. Zhong, P.-X. Zhou, Y.-M. Liang, *Chem. Eur. J.* **2014**, *20*, 5910 – 5913.



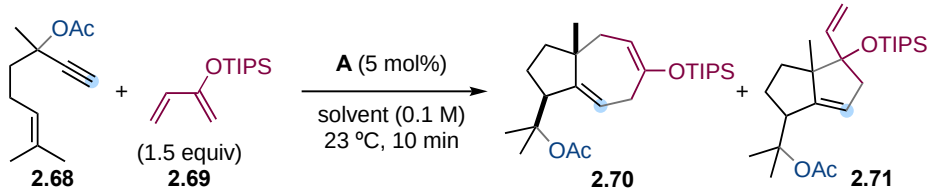
2.68 **2.69** **2.70** **2.71**

Entry	Catalyst	Yield 2.70 (%)	Yield 2.71 (%)
1	**A**	36%	2% + 4%
2	**B**	17%	14%
3	**C**	18%	-
4	**D**	33%	-
5	**G**	22%	2%
6	**H**	25%	-



For convenience, we continued the reaction optimization with catalyst **A**, although, as we have mentioned, catalyst **D** provided similar yield. First, we evaluated the solvent effect (table 15). We found that dichloromethane was performing the best compared to other solvents, also commonly used in gold(I) catalysis such as toluene. Interestingly, heptane provided similar yield (entry 7), although the catalyst was not fully soluble in it.

Table 15. Initial solvent screening.



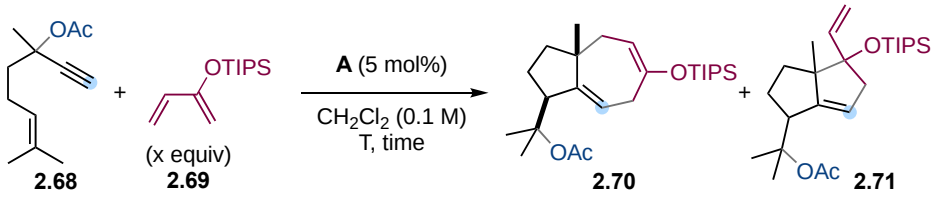
2.68 **2.69** **2.70** **2.71**

Entry	Solvent	Yield 2.70 (%)	Yield 2.71 (%)
1	CH_2Cl_2	36%	2% + 4%
2	EtOAc	22%	-
3	PhMe	23%	traces
4	1,4-dioxane	22%	-
5	acetone	-	-
6	$(CHCl_2)_2$	23%	-

7	heptane	39%	3% + 2%

Next, we analyzed the effect of the number of diene equivalents added, together with the temperature (table 16). We found that increasing the equivalents of diene from 1.5 to 3 translated in a 10% increase in yield (entries 1 and 2), while 5 equivalents of **2.69** afforded comparable results to 3 equivalents (entry 3). A decrease in temperature to 0 ºC, provided similar results and slightly longer reaction times (entries 4 and 5).

Table 16. Diene equivalents and temperature evaluation.

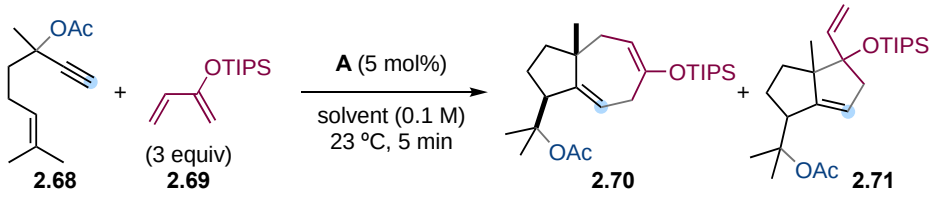


2.68 **2.69** **2.70** **2.71**

Entry	2j (equiv.)	Temperature (°C)	time (min)	Yield 2.70 (%)	Yield 2.71 (%)
1	1.5	23	5	36%	2% + 4%
2	3.0	23	5	47%	2% + 5%
3	5.0	23	5	49%	2% + 5%
4	1.5	0	15	34%	6% + 10%
5	3.0	0	15	45%	3% + 7%

Based on the results summarized in tables 15 and 16, we extended the solvent screening to other chlorinated solvents using 3 equivalents of diene **2.69** (table 17). We found very similar results using dichloromethane, chloroform or a 1:1 mixture of heptane/dichloromethane (entries 1, 2 and 4). 1,2-Dichloroethane provided slightly lower yield of **2.70** and an increase of side product **2.71** (entry 3).

Table 17. Second solvent screening.



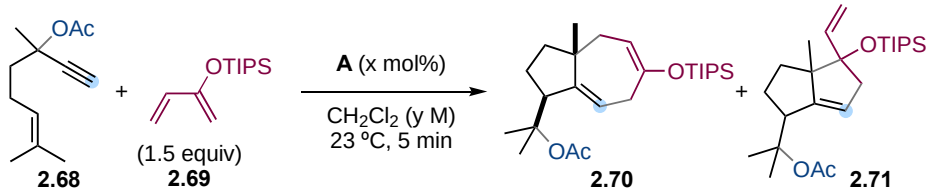
2.68 **2.69** **2.70** **2.71**

Entry	Solvent	Yield 2.70 (%)	Yield 2.71 (%)
1	CH_2Cl_2	47%	2% + 5%
2	CH_2Cl_2/heptane (1:1)	44%	-

3	$(CH_2Cl)_2$	41%	6% + 10%
4	$CHCl_3$	49%	-

Parallelly, we screened different catalyst loadings and concentrations (table 18). We found no significant effect of this variables. Thus, we decided to use 1 mol% of catalyst and different concentration depending on the scale of the reaction, for the scope evaluation and its application on the total synthesis of aspterric acid (Chapter 3).

Table 18. Catalyst loading and concentration evaluation.

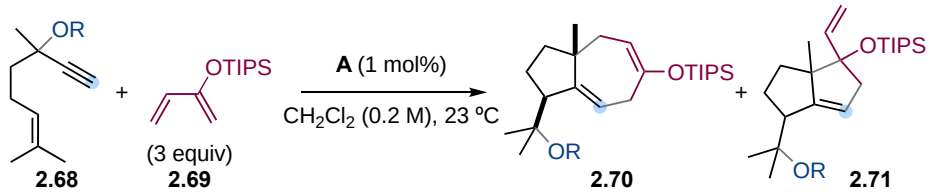


2.68 **2.69** **2.70** **2.71**

Entry	Catalyst mol%	Concentration (M)	Yield 2.70 (%)	Yield 2.71 (%)
1	5	0.1	36%	2% + 4%
2	5	0.2	41%	6% + 10%
3	5	0.5	38%	2% + 4%
4	5	1.0	35%	2% + 4%
5	2	0.1	40%	4% + 7%
6	1	0.5	38%	3% + 6%

Finally, we decided to evaluate different migrating groups on enynes **2.68** (table 19). As described in previous reports, *para*-nitrophenol ether was found to give the best results and thus we adopted enyne **2.68b** as the optimal substrate, although 2 hours were required to achieve full conversion (entry 2). Methyl and benzyl ethers **2.68c** and **2.68d** provided complex mixtures of products, where we were not able to isolate/detect adducts **2.70** or **2.71** (entries 3 and 4).

Table 19. Migrating group evaluation.



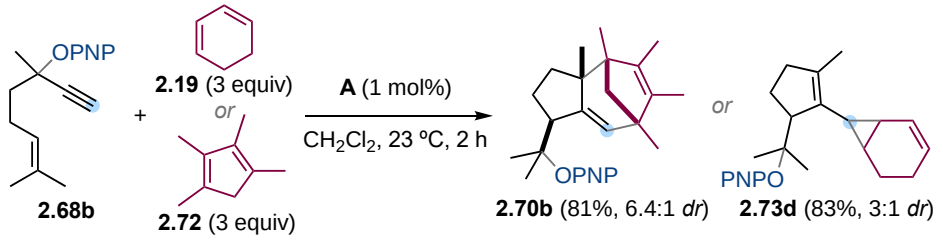
2.68 **2.69** **2.70** **2.71**

Entry	R	Yield 2.70 (%)	Yield 2.71 (%)
1	Ac	47%	traces

2[a]	PNP	68%	7%
3[b]	Me	-	-
4[b]	Bn	-	-

a. 2h reaction time. b. Complex mixture.

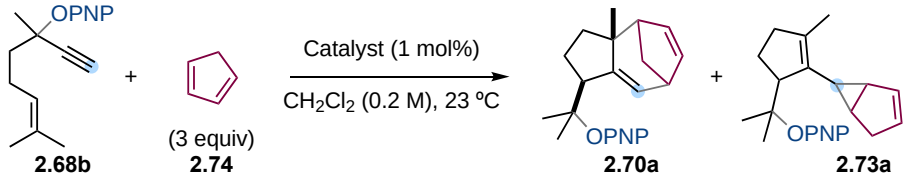
With the optimized conditions in hand, we decided to analyze the reactivity of different dienes with enyne **2.68** and catalyst **A**. Initially we took cyclohexadiene (**2.19**) and 1,2,3,4-tetramethylcyclopentadiene (**2.72**) as reaction partners (scheme 52). We found that cyclohexadiene provided only cyclopropane **2.73d**, in good yield and a 3:1 diastereomeric ratio, while **2.72** afforded only cycloheptadiene **2.70b**, with good yield and 6.4:1 *dr*.



Scheme 52. Reaction of **2.68** with dienes **2.19** and **2.72**.

This difference in reactivity prompted us to reevaluate the catalyst used for this transformation when using less electronically biased dienes. In this regard, we chose cyclopentadiene (**2.74**) as model substrate (table 20).

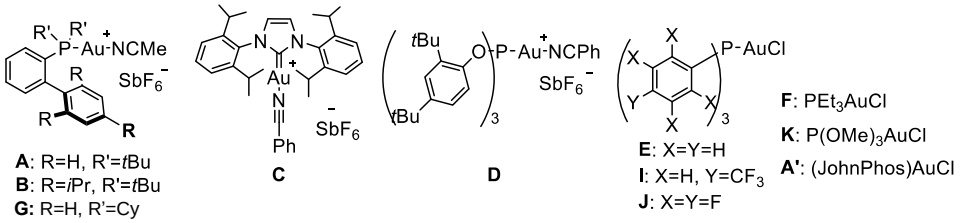
Table 20. Catalyst screening with cyclopentadiene as the reaction partner.



Entry	Catalyst	Conversion	Yield 2.70a	Yield 2.73a
1[a]	**A**	100%	26% (7:1)	51% (12:1)
2[a]	**B**	93%	40% (5.7:1)	36%
3[a]	**C**	100%	36% (17:1)	12%
4[a]	**D**	100%	60% (5:1)	4%
5[a,b]	**E**	100%	40% (4.7:1)	19%
6[a,b]	**F**	91%	27% (4.4:1)	31%
7[a,b]	**I**	86%	48% (5:1)	8%
8[c,b]	**J**	100%	18%	traces
9[a,b]	**K**	91%	44% (4.5:1)	13%

10[c,d]	$[Rh(TFA)_2]_2$	-	-	-
11[c]	$PtCl_2$	90%	traces	-
12[c]	$InBr_3$	83%	-	-
13[c]	$AuCl_3$	35%	9%	traces
14[c]	$AgSbF_6$	30%	-	-
15[c]	AuCl	33%	6%	traces
16[a,b]	**A'**	90%	25% (7.3:1)	42%
17[c]	**A**	100%	18% (8:1)	30%

a. 2 h reaction time. b. Addition of 1 mol% of $NaBAr^F_4$. c. 24 h reaction time. d. 40 °C.



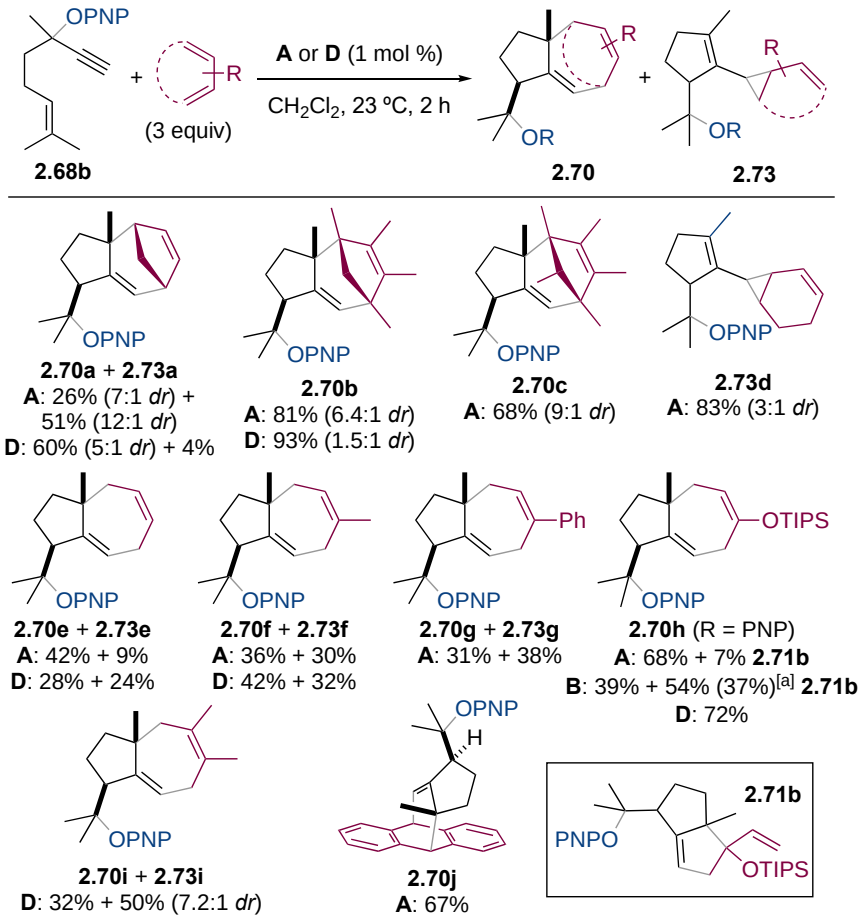
We found that the ratio between products **2.70a** and **2.73a** was very sensitive to the catalyst of choice. For instance, catalyst **A**, which provided **2.70** as the main product in the reaction with 2-oxydiene **2.69**, afforded cyclopropane **2.73a** as the major product in the reaction with cyclopentadiene (**2.74**) (entry 1). Complex **B**, as found for the reaction with **2.69** yielded (4+3)-adduct **2.70a** and byproduct **2.73a** in a *c.a.* 1:1 ratio (entry 2). Electronics were found to be key for selectivity, as exemplified using complexes **E** and **I** in combination with $NaBAr^F_4$: triphenylphosphine complex **E** afforded **2.70a** and **2.73a** in a 2:1 ratio while more electrophilic *tris*(*para*-(CF_3)phenyl)phosphine complex **I** increased the selectivity towards **2.70a** to 6:1 (entries 5 and 7). Similar effect was found when comparing triethylphosphine complex **F** to trimethylphosphite complex **K** (entries 6 and 9): while **K** provided **2.70a** as the main product in a 4:1 selectivity ratio, **F** gave **2.73a** as the main product, although with almost no selectivity (1.1:1 ratio of products). Other Lewis acids were evaluated as catalysts, giving different levels of conversion of enyne **2.68b**, but with only traces of products **2.70a** or **2.73a** (entries 11-15). Rhodium (II) trifluoroacetate dimer, used for similar cycloaddition reactions,[131] did not provide any conversion (entry 10). Finally, longer reaction times translated into a decrease in yield, probably due to product decomposition, but maintaining the ratio between **2.70a** and **2.73a** (entry 1 and 17).

131. Parallelly to this work, Mauro Mato (Echavarren group) developed a similar $[Rh(TFA)_2]_2$-catalyzed (4+3)-cycloaddition reaction from 7-vinyl-1,3,5-trimethylcycloheptatrienes and 1,3-dienes. The results are included in the publication we share but will not be discussed in this thesis.

Diene Scope Evaluation

With these results in hand, we decided to analyze the performance of catalysts **A** and **D** with different dienes (table 21). These two catalysts were selected because they gave the opposite selectivity between products **2.70** and **2.73**, as found in table 20 (entries 1 and 4). As we mentioned in this table, the selectivity between products **2.70a** and **2.73a** was inverted when using one catalytic system or the other. Contrarily, tetramethylcyclopentadiene afforded only (4+3)-adduct **2.70b** with both catalysts, although the diastereoselectivity was higher when using **A**. Similar reactivity was observed for pentamethylcyclopentadiene, which afforded **2.70c** as the only product, in a 9:1 *dr*.

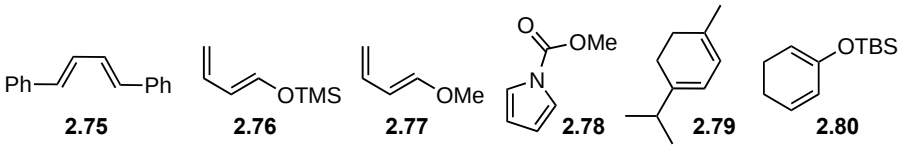
Table 21. Diene scope evaluation with catalysts **A** and **D**.



Yields of both **2.70** and **2.73** are indicated for each substrate, unless only one of the two products (depicted) was obtained. [a] In parenthesis, isolated yield of **2.71b** after treatment with catalytic HCl in ethanol for 24 h and purification.

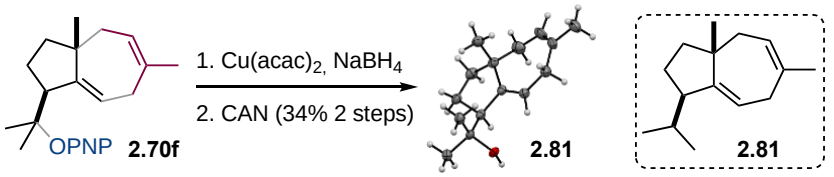
Acyclic 1,3-dienes afforded little selectivity between the two products with both catalytic systems (**2.70e-g** and **2.73e-g**). Interestingly, with 1,3-butadiene we observed the opposite effect in selectivity when changing catalyst **A** for **D**, as **2.70e** and **2.73e** were obtained in a 4:1 ratio with **A** and 1.2:1 ratio with **D**. Regarding the influence of the electronics of the substrate on the ratio of products, comparing 2-methylbutadiene and 2-phenylbutadiene we found a moderate switch in selectivity, as the more nucleophilic afforded (4+3)-adduct **2.70f** as the major product, while 2-phenylbutadiene gave cyclopropane **2.73g** more favorably. 2,3-dimethyl-1,3-butadiene also afforded cyclopropane **2.73i** as the main product of the reaction, in a 1.6:1 selectivity ratio with **2.70i**. Finally, anthracene was found to be a good reaction partner leading to (4+3)-adduct **2.70j** selectively in 67% yield. As found for acetate enyne 2.68a, PNP-enyne 2.68 delivered 2.70h as the main product in all the catalytic systems. Additionally formal (3+2)-cycloaddition adduct **2.71b** could be isolated and characterized by treatment of the reaction crude HCl in ethanol.

Other diene substrates such as cyclic 2-oxy-1,3-diene **2.80** or more nucleophilic cyclohexadiene **2.79** were also employed in the gold(I) catalysis with enyne **2.68b**, leading to complex mixtures of products (scheme 53).



Scheme 53. Substrates that provided a complex mixture of products.

Deprotection of the PNP group in product **2.70f** was achieved in a two-step sequence affording crystalline alcohol **2.81** (scheme 54). This allowed the confirmation of the relative configuration of the (4+3)-product by X-ray diffraction. Compound **2.81** is a hydroxylated analogue of carota-1,4-diene (**2.82**), which is a natural product isolated from the leaves of *Rosa rugosa*.



Scheme 54. Derivatization of **2.70** into **2.81**.

Mechanistic Investigations

Kinetic profile by ^{1}H-NMR monitoring

We monitored the reaction between PNP-enyne **2.68b** and TIPSO-diene **2.69** (3 equiv.) with catalyst **D** (2 mol %) in deuterated chloroform (0.1 M) at 0 °C by ^{1}H-NMR. No intermediate species could be detected under these conditions. The kinetic profile is represented in figure 7.

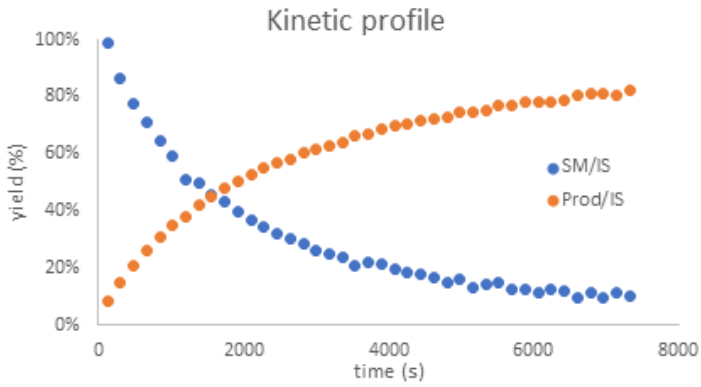


Figure 7. Representation of concentration (% with respect to an internal standard) *versus* time.

Same result was observed when monitoring the reaction at -20 ºC (although with longer reaction time).

Exposition of 2.70f and 2.73f to higher temperatures

We studied the thermal decomposition of products **7f** and **8f** under different conditions.

First, a solution of **2.70f** and **2.73f** in $(CDCl_2)_2$ was gradually warmed up in an NMR tube in the presence of trichloroethene as internal standard (figure 8). The mixture of products was stable up to 120 ºC in $(CDCl_2)_2$, when both compounds fully decomposed after 12 h. No interconversion of **2.73f** into **2.70f** was observed.

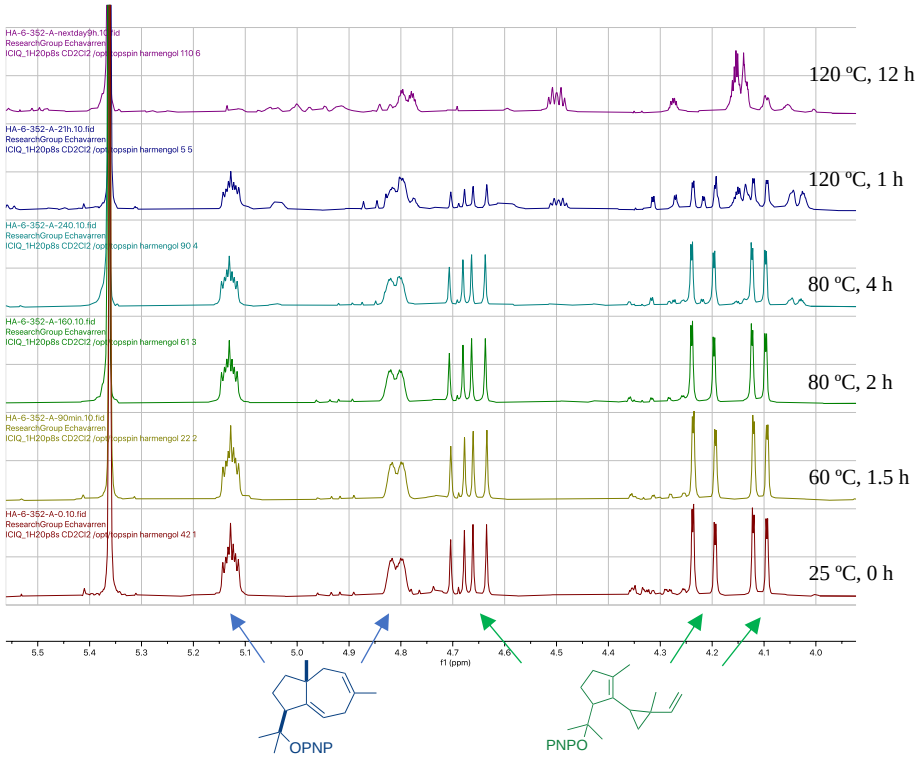


Figure 8. ^{1}H-NMR spectra evolution of a solution of **8f** and **7f** over time and temperature increase.

In a parallel experiment, to a solution of **2.70f** and **2.73f** in $(CDCl_2)_2$ was added catalyst **A** (5 mol%) and the mixture was gradually warmed up in an NMR tube in the presence of trichloroethene as internal standard (figure 9). Some decomposition could be observed at 60 ºC after 20 h. Although in this case **7f** had a slower decomposition than **2.73f**, no interconversion of **2.73f** into **2.70f** was observed.

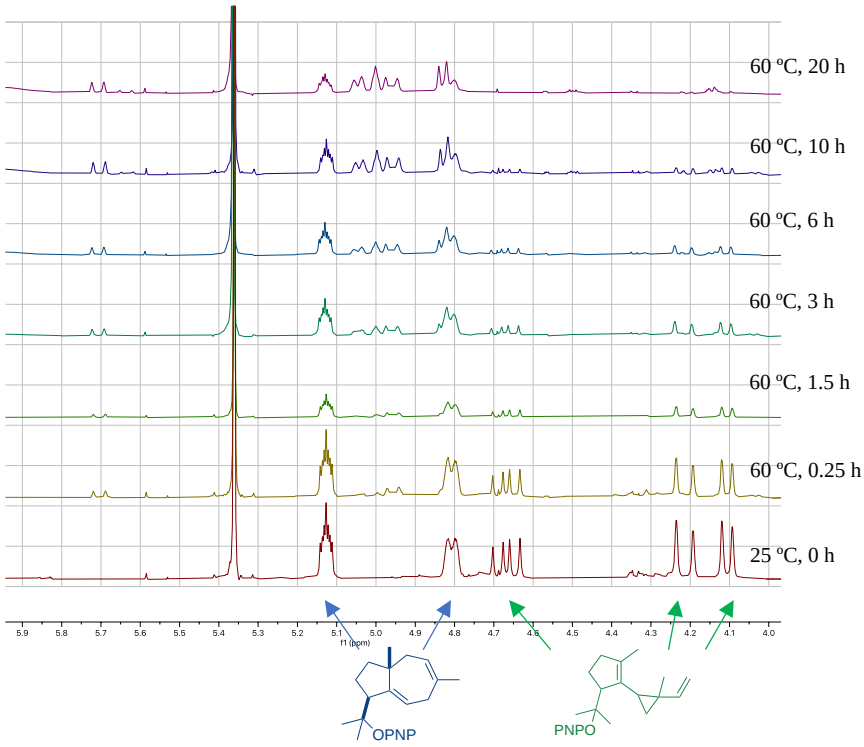
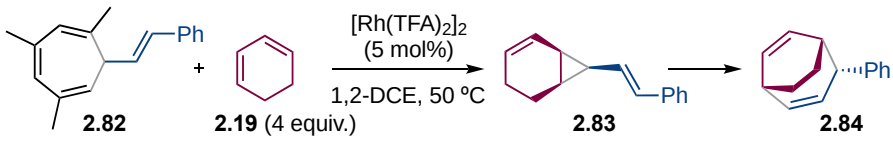


Figure 9. ^{1}H-NMR spectra evolution of a solution of **2.70f** and **2.73f** over time and temperature increase in the presence of catalytic Au(I).

These results indicate that **2.73f** is not an intermediate of the reaction, since it does not rearrange into **2.70f** neither in the presence or absence of a gold(I) catalyst. This is in contrast with the rhodium (II) catalysis for a similar system, where divinylcyclopropane **2.83**, structurally related to **2.73** rearranges in the presence and absence of catalyst into the corresponding cycloheptadiene **2.84** (scheme 55).[132] Intermediate **2.83** could be detected and quantified by monitoring of the reaction by ^{1}H-NMR (figure 10). Presumably the different reactivity of these two substrates depends on steric factors: more substituted olefins render a more energetically demanding Cope-rearrangement which results in a more favorable decomposition of **2.73** at high temperatures.



Scheme 55. Rhodium(II)-catalyzed retro-Buchner/(4+3)-cycloaddition reaction.

132. These experiments were performed by Mauro Mato (Echavarren group).

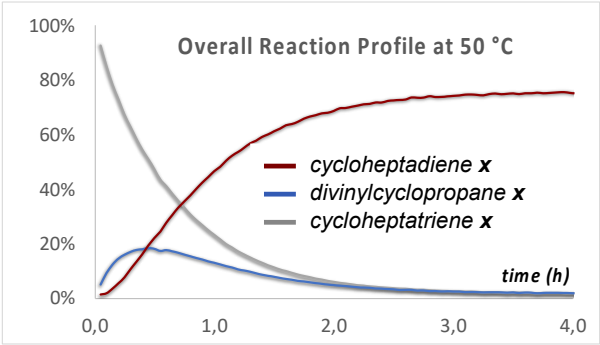
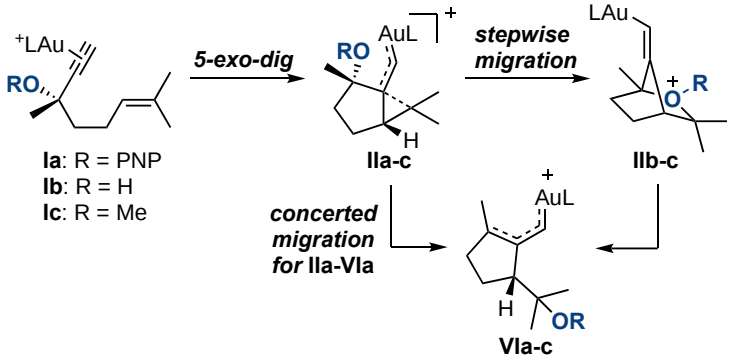


Figure 10. Representation of concentration (% with respect to an internal standard) versus time

DFT Calculations

Preliminary computational study of the reaction with 2-methoxy-1,2-butadiene

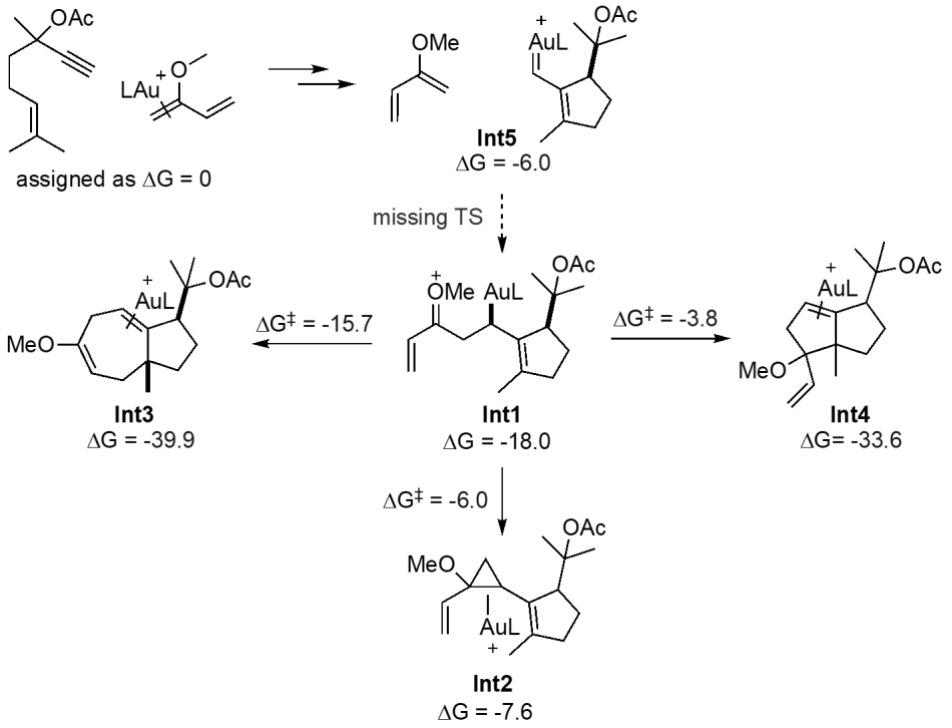
To get a preliminary idea of the mechanism of this transformation and as an exercise to get initiated in the field of DFT calculations, we studied the reaction between enyne **2.68a** and 2-methoxy-1,3-butadiene using trimethylphosphine as a simplified ligand for the gold(I) catalyst. The first steps of this transformation consist in the cycloisomerization/1,5-OR-migration of enyne **2.68a** to give gold(I) carbene **VIa**. This sequence of steps was previously studied by our group using OH, OMe, and OPNP-enynes **Ia-c** (scheme 56),[133] so we did not repeat the computational study for analogous OAc-enyne **2.68a**.



Scheme 56. Theoretical studies on the 1,5-OR migration from **I** to **VI**. L = PMe_3.

Thus, we started the calculations with carbene **Int5** and its nucleophilic trapping to form **Int1** (scheme 57). Oxonium cation **Int1** was found to quickly cyclize giving **Int3**, with a low energy barrier of 2.3 kcal/mol. Formation of cyclopropane **Int2** was found to have considerably high activation energy (12 kcal/mol), and an almost barrierless reverse reaction barrier to give back **Int1**. Additionally, **Int1** could be converted into **Int4**, with a 14.2 kcal/mol barrier.

133. P. Calleja, Ó. Pablo, B. Ranieri, M. Gaydou, A. Pitaval, M. Moreno, M. Raducan, A. M. Echavarren, Chem. Eur. J. **2016**, *22*, 13613 – 13618.

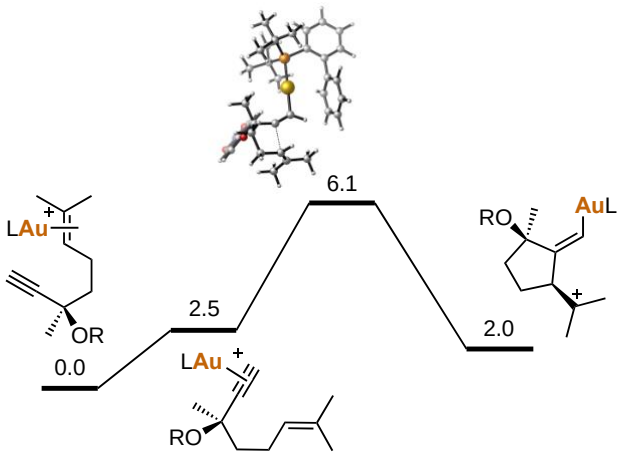


Scheme 57. Calculated energy profile for the reaction of carbene **Int5** with a diene.

These results explain a clear preference for the formation of (4+3)-adduct Int3, more favorable than the other computed pathways by at least 9.7 kcal/mol, which explains the good selectivity for similar OTIPS-diene **2.69**. However, it does not explain the formation of analogous **2.71**, neither in small amount, since the calculated energy barrier is too high to compete with the pathway towards **Int4**.

Computational study of the reaction with cyclopentadiene

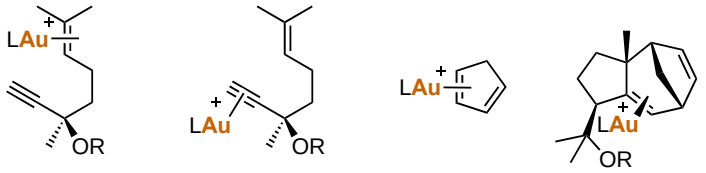
Considering these preliminary results, we decided to extend the calculations to the full system: computing PNP-enyne **2.68b** and the whole structure of catalyst **A**. We chose to study the reaction with cyclopentadiene as this substrate was showing different selectivity than 2-oxy-1,3-diene **2.69**. As we mentioned in the previous section, the first sequence of steps of the gold(I) catalyzed cascade reaction was previously studied by our group. However, according to our previous report, the rate determining step towards carbene intermediate **IX** is the 5-*exo*-dig cycloisomerization of enyne **2.68b**. Thus, we extrapolated the reported calculations to the full system (using JohnPhos as the ligand for gold) to find the energy of the rate determining step of the cycle (scheme 58).



Scheme 58. Calculated energy profile of the cycloisomerization of enyne **2.68**.

Establishing the zero-energy

From the gold(I) complexes with the starting materials, the lowest energy found was for the complex of 6a through the alkene moiety, and thus this was established as the relative zero energy of the system (scheme 59). However, XIIb, corresponding to product 7a bound to gold, has lower energy than free 7a (-1.8 kcal/mol), indicating mild product inhibition. This means that for the second catalytic cycle to start, additional 1.8 kcal/mol will have to be overcome. Thus, in the second catalytic cycle, the highest energy barrier of the system, which is the 5-exo-dig cycloisomerization with 6.1 kcal/mol, will increase to 7.9 kcal/mol.



VIII (6a-Au alkene complex)	**6a-Au alkyne complex**	**Cp-Au**	**XIIb**
0.0	2.5	1.1	-1.8

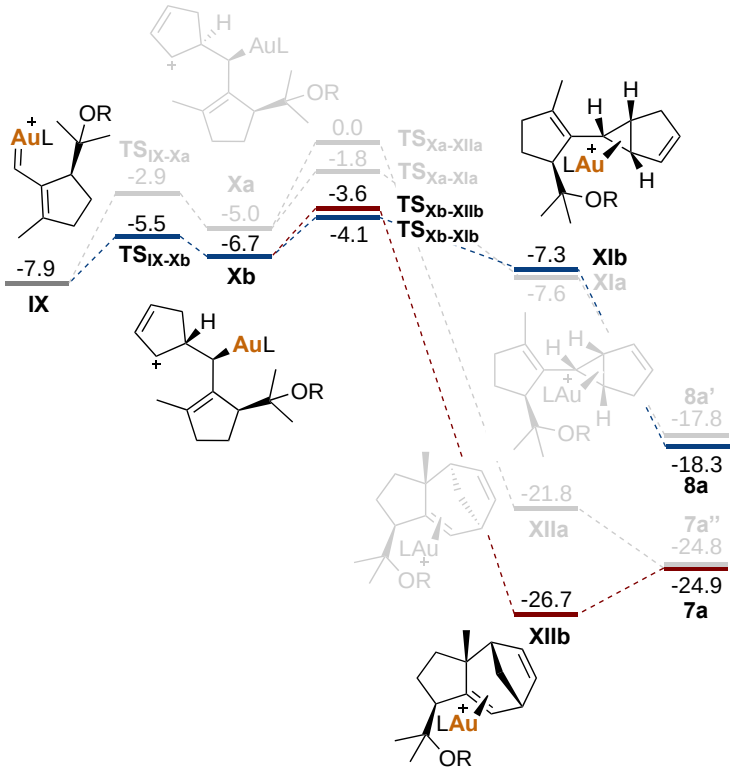
Scheme 59. Calculated relative energies of gold(I)-complexes.

In this system, the product inhibition does not translate into a detectable slowing down of the reaction, because 7.9 kcal/mol is still a relatively low energy barrier to overcome at 25 ºC. This explains why experimentally the reaction is completed in less than 2 h and the NMR-monitoring does not exhibit the typical product inhibition kinetic profile.

Intermolecular trapping of carbene I

Upon enyne cycloisomerization and OR-migration, cyclopentadiene can approach carbene IX from two different faces, leading to intermediates Xa and Xb (scheme 60). We

found that the pathway towards Xb is more favorable by 2.6 kcal/mol. From favored allyic cation Xb, the 3-membered ring in XIb and 7-membered ring in XIIb can be closed, via TSXb-XIb and TS Xb-XIIb, respectively. The formation of XIb versus XIIb is favored by 0.5 kcal/mol, which translates into a calculated 2:1 ratio of products 2.73a/2.70a. Analogously, Xa can evolve towards intermediates XIa and XIIa via TSXa-XIa and TS Xa-XIIa respectively, with a difference of 1.8 kcal/mol. This pathway would lead to the decomplexation delivers products 7a, 7a'', 8a and 8a'.



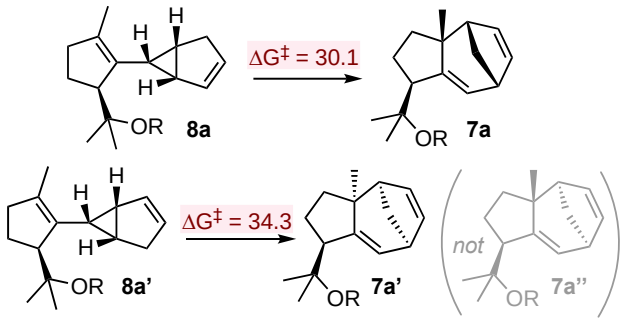
Scheme 60. Energy profile for the trapping of **IX** with cyclopentadiene.

We also attempted to calculate a concerted pathway for the formation of intermediates XI and XII. However, we could not find any transition state connecting carbene XI with the cyclized products in a concerted manner.

Au-free Cope rearrangement

We computed the hypothetical thermal Cope-rearrangement and we found that cyclopropane 8a can rearrange into 7a via a TS of 30.1 kcal/mol. Analogously, 8a' can lead to 7a' through an energy barrier of 34.3 kcal/mol. Interestingly, in this last case, 8a' has to adopt a less stable conformation in order for the rearrangement to take place, explaining the higher energy barrier. Additionally, 7a'' cannot be obtained by rearrangement of neither 8a

and 8a', since the thermal Cope rearrangement follows a stereospecific mechanism. Thus 7a'' can only be formed by stepwise 4+3 cycloaddition of intermediate IX.



Scheme 61. Calculated energy barriers for the thermal Cope-rearrangement.

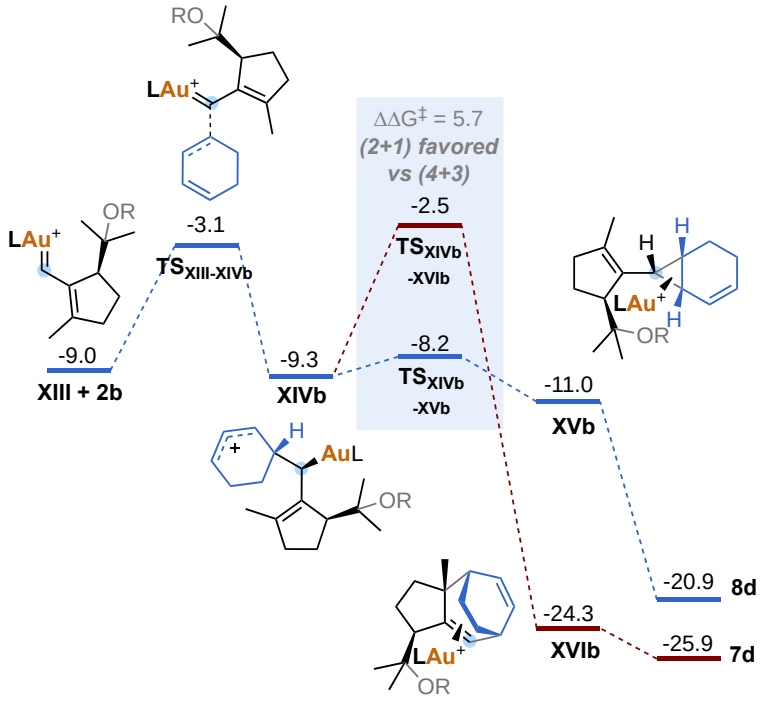
Experimentally we found that decomposition of 8a and 8a' is faster than the Cope rearrangement for these substrates.

Computational study of the reaction with cyclohexadiene

Since experimentally we found that cyclohexadiene provided different reactivity than cyclopentadiene, we decided to study the reaction mechanism by means of DFT calculations.

Intermolecular trapping of the gold(I) carbene

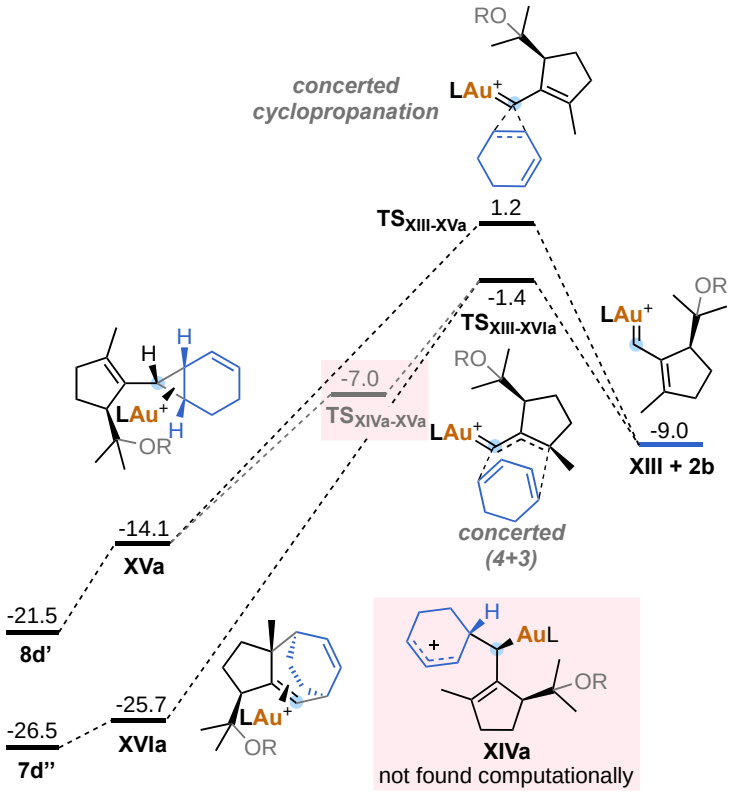
Since the first sequence of steps is again the isomerization of 6a, we focused on the intermolecular trapping of the vinylcarbene with cyclohexadiene, in intermediate XIII + 2b. As found for cyclopentadiene, the diene can approach from two different orientations. The most favored one (scheme 62) affords allylcarbocation XIVb via TSXIII-XIVb. This intermediate can then evolve to form the 3-membered or the 7-membered carbocyclic products XVb and XVIb via TSXIVb-XVb and TSXIVb-XVIb respectively. The difference in energy of these two transition states is of 5.7 kcal/mol, which under kinetic control would account for an exclusive formation of XVb, which after decomplexation would afford cyclopropane 8d after decomplexation (as observed experimentally).



Scheme 62. Energy profile for the intermolecular trapping of carbene **XIII** with cyclohexadiene.

For the less favored attack of the diene to the carbene (scheme 63), a more complex scenario was found. It is worth mentioning that this would in any case only lead to the minor isomeric products of the reaction. Analogous intermediate XIVa was not found, and we were only able to allocate the (2+1) and (4+3) concerted cycloadditions. Interestingly, in

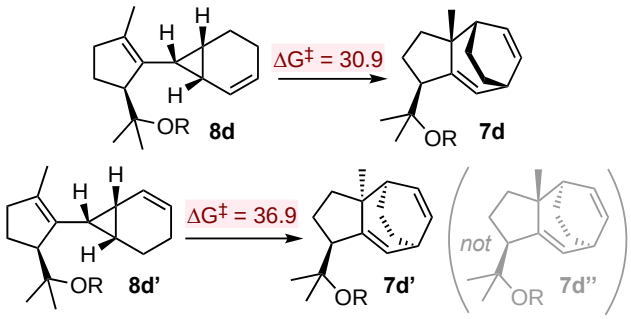
this case the concerted (4+3) pathway via TSXIII-XVIa is lower in energy than the concerted cyclopropanation via TSXIII-XVa by 2.6 kcal/mol. We attempted to calculate the stepwise process but we could only find a guess for a potential TSXIVa-XVa with an energy of -7.0 kcal/mol, by freezing the coordinates involved in the ring-closing transformation. We also tried to locate a concerted pathway for the (2+1) and (4+3) cycloaddition reactions in the other orientation (scheme 62) towards XVb and XVIb but we were not successful. Thus, we concluded that depending on the orientation of cyclohexadiene, a concerted or stepwise mechanism was taking place.



Scheme 63. Energy profile of the less favored trapping of carbene **XIII** with cyclohexadiene.

Au-free Cope rearrangement

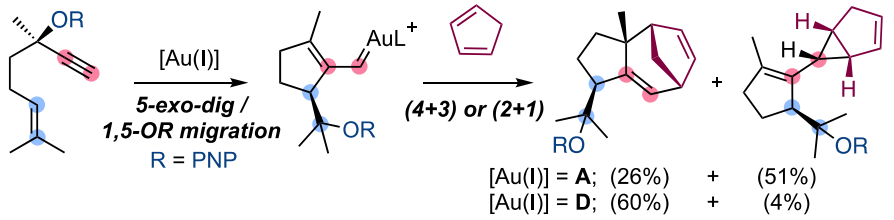
As for the reaction with cyclopentadiene, we calculated the energy barriers of the thermal (3,3)-sigmatropic rearrangement for divinylcyclopropanes 8d and 8d'. Similar energy values were found compared to 8a and 8a', being of 30.9 kcal/mol for 8d rearranging into 7d and 36.9 kcal/mol for 8d' rearranging into 7d' (and not 7d''). These barriers are again high enough not to occur at room temperature.



Scheme 64. Calculated energy barriers for the thermal Cope-rearrangement.

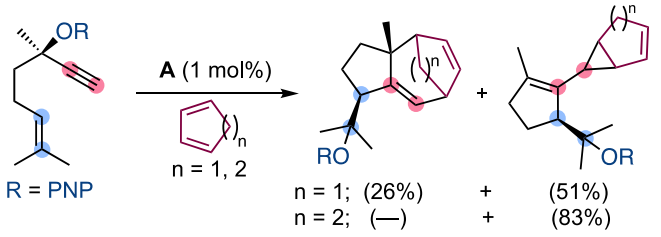
Conclusions

We have developed a new methodology based on gold(I) catalysis for the synthesis of hydroazulenes from 1,3-dienes and 1,6-enynes bearing a propargyl ether. The reaction proceeds via a vinyl gold(I) carbene intermediate, which is formed upon gold(I)-promoted 5-*exo*-dig cyclization and 1,5-OR migration of the enyne (scheme 65). Intermolecular trapping of these species with a diene leads to the (4+3) and/or (2+1) cycloaddition products. Depending on the catalyst employed, the construction of (4+3)-adducts competes with the formation of cyclopropanation products, leading to a switch in selectivity in some cases, as when using cyclopentadiene as substrate.



Scheme 65. Different selectivity of catalysts **A** and **D**.

DFT calculations on the mechanism suggest that the divinylcyclopropanes are not intermediates of the reaction towards the (4+3)-adduct. Additionally, exploration of scope revealed a strong dependance on the diene nature for the selectivity ratio between the two cycloadditon products (scheme 66). This was supported by the theoretical study performed for the reaction with cyclopentadiene and with cyclohexadiene.



Scheme 66. Different selectivity of products with cyclopentadiene and cyclohexadiene.

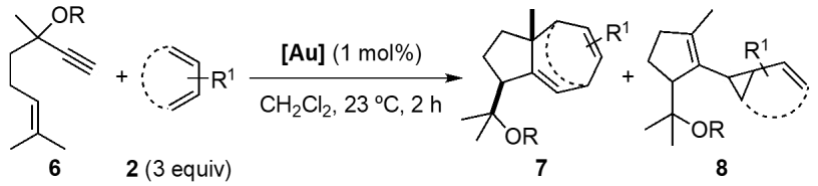
Experimental Section

General Information

Please refer to the experimental section of Chapter 1 for general information about the experimental procedures.

Synthetic Procedures and Characterization of Compounds

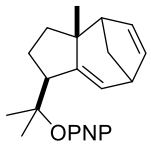
General Procedure C: Gold(I) Catalysis



A solution of enyne **6a** or **6'** (1 equiv) and diene **2** (3 equiv) in CH_2Cl_2 (0.2 M) was placed in a 2 or 5 mL screw-cap vial. Au(I) catalyst (1 mol %) was added in one portion and the mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC or GC-MS and after total consumption of the starting material, it was quenched by adding one drop of triethylamine. The solvent was evaporated at low pressure and the crude material was purified by silica gel column chromatography to give **7**, **8** or a mixture of both.

Characterization Data for the New Compounds

(±)-(1*S*,3*R*)-3-Methyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,7-hexahydro-4,7-methanoazulene (7a)



Prepared following general procedure C, by reaction of **6** (27.3 mg, 0.10 mmol, 1 equiv.) with **2a** (19.8 mg, 0.30 mmol, 3 equiv.) using catalyst **D**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound together with traces compound **8a** as a pale-yellow oil (21.7 mg, 4.8:1 dr, 64% yield).

Some ^{1}H and ^{13}C NMR signals of the minor isomer could be assigned.

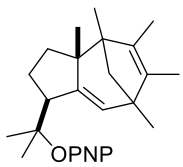
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.07 (m, 2H, *overlapping with minor*), 7.09 – 7.00 (m, 2H, *overlapping with minor*), 6.33 (ddd, J = 5.6, 2.7, 0.8 Hz, 1H), 6.19 (dd, J = 5.7, 3.1 Hz, *1H minor isomer*), 5.97 (dd, J = 5.7, 2.7 Hz, *1H minor isomer*), 5.89 (dt, J = 5.4, 1.6 Hz, 1H), 5.66 (dd, J = 5.6, 3.1 Hz, 1H), 2.82 – 2.76 (m, *1H minor isomer*), 2.74 (dd, J = 5.1, 3.1 Hz, 1H), 2.73 – 2.65 (m, 2H), 2.52 (t, J = 3.5 Hz, *1H minor isomer*), 2.03 (d, J = 9.9 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.82 – 1.76 (m, 1H), 1.72 (dddd, J = 12.8, 8.7, 6.9, 1.0 Hz, 1H),

1.39 (s, 3H), 1.38 (s, 3H), 1.37 (s, *3H minor isomer*), 1.36 (s, *1H minor isomer*), 1.33 (d, J = 0.7 Hz, 3H), 1.29 – 1.24 (m, 1H), 1.21 (dd, J = 12.3, 7.0 Hz, 1H), 1.08 (s, *3H minor isomer*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.5, 142.8, 142.5 (*minor*), 141.8, 138.3, 135.2 (*minor*), 130.4 (*minor*), 130.3, 129.9, 125.3, 125.3 (*minor*), 122.1 (*minor*), 122.1, 8m4.6, 84.2 (*minor*), 54.9 (*minor*), 54.1, 50.3, 46.5 (*minor*), 45.4, 42.9 (*minor*), 41.1 (*minor*), 40.2, 39.4, 37.5 (*minor*), 32.4, 27.6, 25.7, 25.7, 25.6 (*minor*), 25.5, 24.2 (*minor*), 22.5 (*minor*). **HRMS** (ESI+): m/z calc. for $[C_{21}H_{25}NNaO_3]^+$: 362.1727, found: 362.1730.

Analogous reaction with catalyst **A** delivered product **7a** as a 1:2 mixture with **8a**, 26% (7:1) and 51% (12:1) calculated yields and *dr* respectively. Some ^{1}H NMR signals of both isomers of **8a** could be assigned.

^{1}H NMR (500 MHz, $CDCl_3$ δ 8.19 – 8.07 (m, 2H, *all isomers overlapping*), 7.09 – 7.00 (m, 2H, *all isomers overlapping*), 6.33 (ddd, J = 5.6, 2.7, 0.8 Hz, 1H **7a** *major*), 6.19 (dd, J = 5.7, 3.1 Hz, *1H **7a** minor*), 5.97 (dd, J = 5.7, 2.7 Hz, *1H **7a** minor*), 5.89 (dt, J = 5.4, 1.6 Hz, 1H **7a** *major*), 5.66 (dd, J = 5.6, 3.1 Hz, 1H **7a** *major*), 5.64 – 5.60 (m, *1H **8a** minor*), 5.57 (ddd, J = 5.6, 2.3, 1.1 Hz, 1H **8a** *major*), 5.37 (d, J = 5.3 Hz, *1H **8a** minor*), 5.34 (ddd, J = 5.3, 2.9, 1.8 Hz, 1H **8a** *major*), 2.86 (dq, J = 9.3, 1.4 Hz, , 1H **8a** *major*), 2.81 – 2.75 (m, *1H **7a** minor*), 2.74 (dd, J = 5.1, 3.1 Hz, 1H **7a** *major*), 2.72 – 2.63 (m, 2H **7a** *major*), 2.53 – 2.50 (m, *1H **7a** minor*), 2.48 – 2.38 (m, 1H **8a** *major*), 2.38 – 2.23 (m, 1H **8a** *major and* minor), 2.13 (dd, *J* = 16.6, 9.7 Hz, 1H **8a** *major*), 2.05 – 1.97 (m, 2H **8a** *major*), 1.93 – 1.89 (m, 2H, **8a** *major* and overlapping), 1.89 – 1.84 (m, *all isomers overlapping*), 1.82 – 1.77 (m, *all isomers overlapping*), 1.75 (t, J = 1.4 Hz, 3H, **8a** *major*), 1.47 (s, 3H **8a** *major*), 1.39 (s, 3H **7a** *major*), 1.38 (s, 3H **7a** *major*), 1.37 (s, 3H **8a** *major*), 1.32 (d, J = 0.7 Hz, 3H **7a** *major*), 1.29 – 1.24 (m, 2H, *overlapping signals*), 1.21 (dd, J = 12.4, 6.9 Hz, 3H **7a** *major*), 1.08 (s, *3H **7a** minor*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.7, 162.5, 143.4, 142.8, 142.5, 141.9, 141.8, 138.3, 135.2, 130.3, 130.2, 130.1, 129.9, 129.8, 129.4, 129.4, 129.2, 126.0, 125.4, 125.3, 125.3, 125.2, 124.7, 122.1, 122.1, 121.7, 121.7, 121.0, 120.8, 120.4, 117.6, 87.3, 84.5, 58.3, 56.4, 54.9, 54.1, 50.3, 46.5, 45.4, 44.1, 42.9, 41.0, 40.1, 39.4, 37.7, 37.5, 37.2, 32.8, 32.3, 31.3, 29.3, 27.6, 27.1, 25.9, 25.7, 25.6, 25.6, 25.5, 25.4, 25.3, 24.9, 24.4, 24.2, 24.2, 22.8, 22.5, 21.9, 21.7, 20.1, 15.3, 15.2.

(±)-(1*S*,3*S*)-3,4,5,6,7-Pentamethyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,7-hexahydro-4,7-methanoazulene (7b)

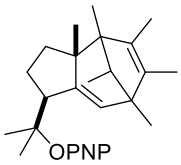


Prepared following general procedure C, by reaction of **6** (55.7 mg, 0.20 mmol, 1 equiv.) with **2d** (73.3 mg, 0.60 mmol, 3 equiv.) using catalyst **A**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound as a pale-yellow oil (65.4 mg, 81% yield, 6.4:1 dr).

Some ^{1}H NMR signals of the minor isomer could be assigned.

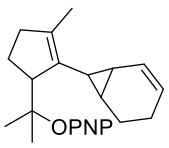
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.11 (m, 2H), 7.10 – 7.03 (m, 2H), 5.79 (t, J = 1.7 Hz, 1H), 5.62 (d, J = 1.7 Hz, *1H minor isomer*), 2.80 (t, J = 9.4 Hz, *1H minor isomer*), 2.63 (t, J = 9.5 Hz, 1H), 1.93 (d, J = 9.6 Hz, 1H), 1.81 – 1.72 (m, 2H), 1.73 – 1.66 (m, 2H), 1.60 (d, J = 1.2 Hz, *3H minor isomer*), 1.57 (q, J = 1.2 Hz, 3H), 1.54 (d, J = 1.2 Hz, *3H minor isomer*), 1.53 (q, J = 1.3 Hz, 3H), 1.41 (s, 3H), 1.37 (d, J = 2.6 Hz, 3H), 1.25 (dd, J = 9.6, 1.6 Hz, 1H), 1.21 (d, J = 0.7 Hz, 3H), 1.13 (s, 3H), 1.06 (s, 3H), 1.04 (s, *3H minor isomer*), 0.94 (s, *3H minor isomer*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.5, 147.0, 142.9, 136.5, 132.5, 125.3, 125.2, 122.3, 84.6, 53.7, 52.4, 51.5, 48.2, 46.9, 32.9, 25.9, 25.6, 24.9, 21.6, 21.0, 19.9, 12.7, 10.7.
HRMS (ESI+): m/z calc. for $[C_{25}H_{33}NNaO_3]^+$: 418.2353, found: 418.2341. Analogous reaction with catalyst **D** delivered product **7b** in 93% yield and 1.5:1 dr.

(±)-(1*S*,3*S*)-3,4,5,6,7,9-Hexamethyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,7-hexahydro-4,7-methanoazulene (7c)



Prepared following general procedure C, by reaction of **6** (54.7 mg, 0.20 mmol, 1 equiv.) with **2e** (82.0 mg, 0.60 mmol, 3 equiv.) using catalyst **A**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound as a pale-yellow oil (55.8 mg, 68% yield, 9:1 dr). Some ^{1}H NMR signals of the minor isomer could be assigned.
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.11 (m, 2H), 7.08 – 7.02 (m, 2H), 5.79 (d, J = 1.8 Hz, 1H), 5.65 (d, J = 1.7 Hz, *1H minor isomer*), 2.80 (t, J = 9.4 Hz, *1H minor isomer*), 2.64 (t, J = 9.3 Hz, 1H), 2.16 (q, J = 6.7 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.72 – 1.64 (m, 2H), 1.55 (q, J = 1.2 Hz, 3H), 1.50 (t, J = 1.2 Hz, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.19 (d, J = 0.8 Hz, 3H), 1.00 (s, 3H), 0.94 (d, J = 1.9 Hz, 3H), 0.88 (s, *3H minor isomer*), 0.67 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.6, 143.6, 142.6, 142.1, 138.8, 128.7, 125.3, 122.3, 84.6, 54.8, 53.9, 50.5, 49.7, 49.7, 33.1, 25.9, 25.7, 24.7, 21.5, 18.2, 15.9, 12.9, 11.2, 11.0.
HRMS (ESI+): m/z calc. for $[C_{26}H_{35}NNaO_3]^+$: 432.2509, found: 432.2505.

7-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)bicyclo[4.1.0]hept-2-ene (8d)

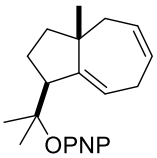


Prepared following general procedure C, by reaction of **6** (54.7 mg, 0.20 mmol, 1 equiv.) with **2b** (48.1 mg, 0.60 mmol, 3 equiv.) using catalyst **A**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound as a colorless oil (58.7 mg, 83% yield, 3:1 dr, *endo*/*exo* cyclopropane isomers unassigned). Some ^{1}H NMR signals of the minor isomer could be assigned.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.00 (m, 2H, both isomers), 7.12 – 6.92 (m, 2H, both isomers), 5.97 – 5.92 (m, *1H minor isomer*), 5.92 – 5.85 (m, 1H), 5.56 (ddd, J = 10.0, 6.0, 2.3 Hz, 1H), 5.47 (ddd, J = 9.1, 6.3, 2.1 Hz, *1H minor isomer*), 3.38 (d, J = 9.4 Hz, 1H), 3.28 (d, J = 9.3 Hz, *1H minor isomer*), 2.30 (q, J = 9.0, 8.1 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.97 – 1.86 (m, 3H), 1.82 (t, J = 1.3 Hz, 3H), 1.79 – 1.73 (m, 1H), 1.72 – 1.65 (m, 1H), 1.64 – 1.57 (m, 2H), 1.46 (s, 3H), 1.41 (s, *3H minor isomer*), 1.34 (s, 3H), 1.25 (s, 3*H minor isomer*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6, 141.3, 133.8, 126.5, 126.0, 125.4, 125.3, 121.0, 87.3, 56.5, 37.3, 25.8, 25.7, 24.9, 24.3, 22.9, 19.5, 18.4, 15.5, 14.0. **HRMS** (ESI+): m/z calc. for $[C_{22}H_{27}NNaO_3]^+$: 376.1883, found: 376.1877.

Analogous reaction with catalyst **D** gave a complex mixture of products, including **8d** and many not characterized side-products.

(±)-(1*S*,3*R*)-3-Methyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,7-hexahydroazulene (7e)



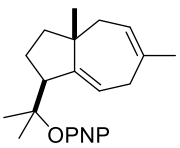
Prepared following general procedure C, by reaction of **6** (54.7 mg, 0.20 mmol, 1 equiv.) with **2c** (162 mg, 20% in hexane, 0.60 mmol, 3 equiv.) using catalyst **A**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound together with compound **8e** as a colorless oil (34.1 mg, 4.7:1 ratio, 51% overall yield: 42% + 9% calculated yields).

Some ^{1}H and ^{13}C NMR signals of **8e** could be assigned.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.08 (m, 2H *overlapping with **8e***), 7.08 – 7.01 (m, 2H *overlapping with **8e***), 5.85 (dtd, J = 5.9, 2.3, 1.1 Hz, 1H), 5.68 – 5.59 (m, 1H), 5.55 (dtdd, J = 11.6, 4.3, 2.9, 1.1 Hz, 1H), 5.32 (ddd, J = 17.1, 10.3, 8.3 Hz, *1H **8e***), 5.00 (dd, J = 17.1, 1.7 Hz, *1H **8e***), 4.80 (dd, J = 10.3, 1.7 Hz, *1H **8e***), 3.19 – 3.11 (m, 1H), 3.08 – 2.97 (m, 1H), 2.94 – 2.83 (m, 1H), 2.34 (dt, J = 15.7, 2.9 Hz, 1H), 2.08 (dddd, J = 15.7, 7.9, 1.9, 0.8 Hz, 1H), 1.81 – 1.75 (m, 1H), 1.75 – 1.74 (m, *3H **8e***), 1.60 – 1.55 (m, 1H), 1.56 – 1.53 (m, 1H), 1.50 – 1.44 (m, 1H), 1.43 (s, *3H **8e***), 1.41 (s, 3H), 1.37 (s, 3H), 1.34 (s, *3H **8e***), 1.13 (s, 3H), 1.00 – 0.91 (m, *2H **8e***), 0.85 (ddt, J = 10.7, 4.3, 2.2 Hz, *2H **8e***). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.4 (***8e***), 161.8, 149.9, 142.6, 141.8 (***8e***), 140.7 (***8e***), 134.5 (***8e***), 127.3, 127.3 (***8e***), 125.4, 125.3 (***8e***), 122.2, 121.5, 121.2, 112.0 (***8e***), 86.9 (***8e***), 86.0, 58.6 (***8e***), 54.6, 46.9, 41.6, 41.5, 37.8 (***8e***), 30.7, 27.3, 26.4, 25.9 (***8e***), 25.5 (***8e***), 24.2 (***8e***), 24.1, 23.1, 22.4 (***8e***), 20.6 (***8e***), 17.3 (***8e***), 15.1 (***8e***). **HRMS** (ESI+): m/z calc. for $[C_{20}H_{25}NNaO_3]^+$: 350.1727, found: 350.1721.

Analogous reaction with catalyst **D** delivered a mixture of **7e** and **8e** in 28% and 24% calculated yields.

(±)-(1*S*,3*R*)-3,6-Dimethyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,7-hexahydroazulene (7f)



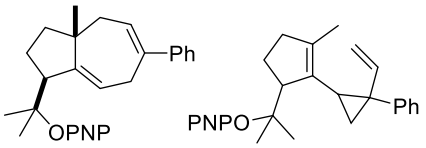
Prepared following general procedure C, by reaction of **6** (137 mg, 0.50 mmol, 1 equiv.) with **2f** (102 mg, 1.50 mmol, 3 equiv.) using catalyst **A**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound together with compound **8f** as a colorless oil (131.5 mg, 1.2:1 ratio, 77% overall yield: 42% + 35% calculated yields).

^{1}H NMR signals of both compounds could be partially assigned by analogy.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.02 (m, 4H, **7f** + **8f**), 7.11 – 7.05 (m, 2H), 7.03 – 6.97 (m, 2H), 5.77 (ddd, J = 5.4, 4.4, 2.2 Hz, 1H, **7f**), 5.46 – 5.41 (m, 1H, **7f**), 5.31 (dd, J = 17.2, 10.6 Hz, 1H, **8f**), 4.85 (dd, J = 17.2, 1.3 Hz, 1H, **8f**), 4.75 (dd, J = 10.5, 1.3 Hz, 1H, **8f**), 3.23 – 3.04 (m, 2H), 2.90 – 2.82 (m, 2H), 2.38 – 2.10 (m, 4H), 2.01 (dd, J = 15.3, 8.3 Hz, 1H), 1.96 – 1.78 (m, 3H), 1.76 (t, J = 1.4 Hz, 3H), 1.70 (t, J = 1.8 Hz, 3H), 1.59 – 1.50 (m, 3H), 1.40 (s, 6H), 1.37 (s, 3H), 1.36 (s, 3H), 1.10 (s, 3H), 1.09 (s, 3H), 1.05 (dd, J = 8.6, 4.4 Hz, 1H, **8f**), 0.71 (dd, J = 6.6, 4.4 Hz, 1H, **8f**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4, 161.9, 149.8, 147.0, 142.6, 141.9, 141.2, 134.1, 133.1, 125.3, 122.2, 122.1, 122.1, 120.9, 120.5, 109.6, 86.7, 86.0, 58.8, 54.6, 46.3, 41.4, 41.1, 37.7, 35.5, 26.9, 26.5, 26.4, 26.3, 25.4, 25.3, 24.5, 24.0, 23.2, 22.9, 22.5, 16.6, 15.4. **HRMS** (ESI+): m/z calc. for $[C_{21}H_{27}NNaO_3]^+$: 364.1883, found: 364.1877.

Analogous reaction with catalyst **D** delivered a mixture of **7f** and **8f** in 42% and 32% calculated yields.

(±)-(1*S*,3*R*)-3-Methyl-1-(2-(4-nitrophenoxy)propan-2-yl)-6-phenyl-1,2,3,3,4,7-hexahydroazulene (7g) and (8g)



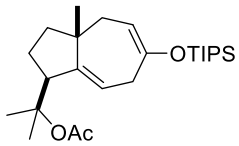
Prepared following general procedure C, by reaction of **6** (27.3 mg, 0.10 mmol, 1 equiv.) with **2h** (39.1 mg, 0.30 mmol, 3 equiv.) using catalyst **A**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered a mixture of **7g** and **8g** as a colorless oil (28.0 mg, 1:1.2 ratio, 69% overall yield: 31% + 38% calculated yields).

^{1}H NMR signals of both compounds could be partially assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 3H), 8.14 – 8.08 (m, 2H), 7.36 – 7.28 (m, 6H), 7.25 – 7.17 (m, 6H), 7.13 – 7.05 (m, 2H), 6.93 – 6.86 (m, 2H), 6.10 (dd, J = 17.2, 10.5 Hz, 1H, **8g**), 6.00 (ddt, J = 8.5, 4.3, 1.3 Hz, 1H, **7g**), 5.87 (td, J = 5.0, 2.2 Hz, 1H, **7g**), 4.93 (d, J = 1.2 Hz, 1H, **8g**), 4.90 (dd, J = 17.2, 1.2 Hz, 1H, **8g**), 3.43 – 3.30 (m, 2H, **7g**), 3.19 (tt, J = 7.9, 2.6 Hz, 1H), 3.14 (s, 0.5H), 2.49 (ddd, J = 14.8, 1.8 Hz, 1H), 2.38 (d, J = 9.4 Hz, 1H), 2.28 (dd, J = 15.0, 8.5 Hz, 1H), 2.23 – 2.14 (m, 0H), 2.11 – 2.01 (m, 1H), 1.98 – 1.92 (m, 1H), 1.91 (t, J = 1.5 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.78 (t, J = 1.4 Hz, 3H, **8g**), 1.76 (dd, J = 6.8, 5.0 Hz, 1H), 1.70 – 1.67 (m, 1H), 1.61 – 1.58 (m, 1H), 1.57 – 1.49 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.28 (s, 3H), 1.27 – 1.25 (m, 3H), 1.18 (s, 3H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 162.2, 161.9, 149.8, 145.3, 144.1, 142.6, 141.7, 140.0, 139.4, 132.1, 128.4, 128.3, 128.3, 128.3, 127.8, 127.6, 127.6, 127.1, 126.7, 126.7, 126.3, 126.1, 126.0, 125.6, 125.4, 125.3, 122.2, 122.2, 121.3, 120.8, 120.1, 112.2, 87.0, 85.9, 56.9, 54.9, 46.1, 41.3, 37.7, 37.5, 33.8, 32.3, 29.8, 29.0, 26.4, 26.2, 25.5, 25.1, 25.1, 25.1, 24.8, 24.5, 23.5, 21.6, 21.6, 21.2, 15.5, 15.5, 15.3. **HRMS** (ESI+): m/z calc. for $[C_{26}H_{29}NNaO_3]^+$: 426.2040, found: 426.2032.

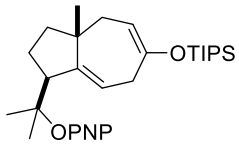
(±)-2-((1*S*,3*R*)-3-Methyl-6-((triisopropylsilyl)oxy)-1,2,3,3,4,7-hexahydroazulen-1-yl)propan-2-yl acetate (7h')



Prepared following general procedure C, by reaction of **6'** (9.7 mg, 0.050 mmol, 1 equiv.) with **2j** (34.0 mg, 0.15 mmol, 3 equiv.) using catalyst **D**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound as a colorless oil (9.5 mg, 45% yield).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.48 (ddd, J = 6.1, 4.1, 2.3 Hz, 1H), 4.95 (ddd, J = 8.9, 3.5, 1.5 Hz, 1H), 3.25 (t, J = 8.4 Hz, 1H), 3.10 – 2.91 (m, 2H), 2.24 – 2.16 (m, 1H), 1.94 (s, 3H), 1.89 (dd, J = 15.1, 8.9 Hz, 1H), 1.72 – 1.64 (m, 2H), 1.51 – 1.48 (m, 2H), 1.47 (s, 3H), 1.40 (s, 3H), 1.20 – 1.12 (m, 3H), 1.10 – 1.07 (m, 18H), 0.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.6, 150.1, 149.9, 117.6, 104.3, 85.6, 53.5, 46.3, 41.3, 38.2, 35.9, 26.0, 25.4, 23.9, 22.9, 22.7, 18.2, 12.8. **HRMS** (ESI+): m/z calc. for $[C_{25}H_{44}NaO_3Si]^+$: 443.2952, found: 443.2956.

(±)-Triisopropyl(((1*S*,3*R*)-3-methyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,7-hexahydroazulen-6-yl)oxy)silane (7h)

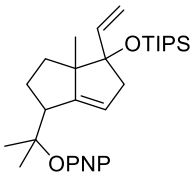


Prepared following general procedure C, by reaction of **6** (13.7 mg, 0.050 mmol, 1 equiv.) with **2j** (34.0 mg, 0.15 mmol, 3 equiv.) using catalyst **D**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound as a pale-yellow oil (18.0 mg, 72% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.20 – 8.09 (m, 2H), 7.14 – 7.05 (m, 2H), 5.75 (ddd, J = 5.5, 4.4, 2.3 Hz, 1H), 4.97 (dd, J = 8.9, 3.5 Hz, 1H), 3.19 – 3.09 (m, 1H), 3.10 – 2.92 (m, 2H), 2.23 (dq, J = 15.0, 3.0 Hz, 1H), 1.93 (ddt, J = 15.2, 9.0, 1.0 Hz, 1H), 1.82 – 1.71 (m, 1H), 1.59 – 1.40 (m, 3H (overlap with water peak)), 1.39 (s, 3H), 1.37 (s, 3H), 1.22 – 1.13 (m, 3H), 1.12 (s, 3H), 1.11 – 1.05 (m, 18H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 162.2, 150.3, 150.2, 125.5, 122.5, 118.7, 104.6, 86.3, 55.0, 46.5, 41.6, 38.5, 36.1, 26.8, 26.4, 24.1, 23.1, 18.3, 18.3, 13.1. **HRMS** (ESI+): m/z calc. for $[C_{29}H_{45}NNaO_4Si]^+$: 522.3010, found: 522.3012.

Analogous reaction with catalyst **A** delivered a mixture of **7h** and **9** in 68% and 7% calculated yields.

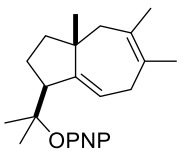
Triisopropyl((6-methyl-4-(2-(4-nitrophenoxy)propan-2-yl)-1-vinyl-1,2,4,5,6,6-hexahydropentalen-1-yl)oxy)silane (9)



Prepared following general procedure C, by reaction of **6** (54.7 mg, 0.20 mmol, 1 equiv.) with **2j** (136 mg, 0.60 mmol, 3 equiv.) using catalyst **B**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered a mixture of the title compound together with compound **7h** as a colorless oil (54% and 39% NMR yields, respectively). The mixture was dissolved in EtOH (2 mL) and 2 drops of concentrated HCl were added. The solution was stirred for 24 h at 23 °C. Then it was diluted with water and extracted with DCM. The organic layer was washed with a saturated solution of $NaHCO_3$ and brine. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered compound **9** as a colorless oil (36.8 mg, 37% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 – 8.12 (m, 2H), 7.07 – 7.00 (m, 2H), 5.87 (ddd, J = 17.6, 10.9, 0.9 Hz, 1H), 5.38 (dt, J = 3.8, 1.9 Hz, 1H), 5.05 (dd, J = 10.9, 1.3 Hz, 1H), 4.97 (dd, J = 17.6, 1.3 Hz, 1H), 2.98 (dd, J = 15.0, 4.2 Hz, 1H), 2.75 – 2.69 (m, 2H), 2.10 – 1.96 (m, 2H), 1.70 – 1.56 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.25 (s, 3H), 1.11 (d, J = 7.4 Hz, 3H), 1.05 (br s, 19H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.3, 155.7, 142.9, 126.0, 125.4, 121.9, 120.1, 119.2, 112.8, 86.8, 84.2, 62.9, 49.9, 46.6, 31.0, 30.8, 25.3, 24.8, 19.8, 18.5, 18.5, 17.9, 13.5, 12.8. **HRMS** (ESI+): m/z calc. for $[C_{29}H_{45}NNaO_4Si]^+$: 522.3010, found: 522.3004.

(1S,3aR)-3,5,6-Trimethyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,7-hexahydroazulene (7i)



Prepared following general procedure C, by reaction of **6** (57.2 mg, 0.21 mmol, 1 equiv.) with **2g** (49.3 mg, 0.60 mmol, 2.9 equiv.) using catalyst **D**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound together with compound **8i** as a colorless oil (61.2 mg, 1:1.6 ratio, 82% overall yield: 32% + 50% calculated yields).

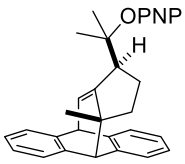
Note: **7i** and **8i** are susceptible to oxidation, thus they are not stable to prolonged exposure to air at room temperature, neither dry or in solution. NMR signals appear in the aldehyde region when **7i** and **8i** decompose.

^{1}H NMR signals of both compounds could be partially assigned by analogy.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.07 (m, 4H, **7i** + **8i**), 7.12 – 6.97 (m, 4H, **7i** + **8i**), 5.63 (ddd, J = 5.3, 4.3, 2.0 Hz, 1H, **7i**), 4.71 (dd, J = 1.9, 0.8 Hz, 1H, **8i**), 4.66 (p, J = 1.4

Hz, 1H, **8i**), 3.13 – 2.95 (m, 3H, **7i** + **8i**), 2.68 (d, J = 23.9 Hz, 1H, **7i**), 2.48 (d, J = 14.0 Hz, 1H, **7i**), 2.39 – 2.26 (m, 2H, **7i** + **8i**), 2.23 – 2.12 (m, 2H, **7i** + **8i**), 1.96 – 1.88 (m, 2H), 1.83 (dt, J = 8.3, 2.8 Hz, 1H), 1.77 (t, J = 1.4 Hz, 3H, **8i**), 1.75 – 1.71 (m, 3H, **7i**), 1.68 – 1.65 (m, 3H, **7i**), 1.64 – 1.58 (m, 2H), 1.55 (d, J = 1.5 Hz, 3H, **8i**), 1.47 – 1.42 (m, 2H), 1.38 (s, 3H, **8i**), 1.38 (s, 3H, **7i**), 1.37 (s, 3H, **7i**), 1.35 (s, 3H, **8i**), 1.34 – 1.30 (m, 1H), 1.24 – 1.19 (m, 2H), 1.13 (s, 3H, **8i**), 1.06 (s, 3H, **7i**), 0.59 (dd, J = 6.6, 4.5 Hz, 1H, **8i**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.1, 162.0, 149.4, 148.5, 142.3, 142.1, 140.6, 133.8, 128.1, 127.0, 125.2, 125.1, 125.0, 123.4, 122.7, 122.0, 121.9, 121.6, 121.4, 108.7, 86.9, 85.7, 59.3, 54.6, 48.0, 45.5, 41.0, 37.7, 36.7, 25.8, 25.7, 25.5, 25.2, 24.7, 24.5, 23.9, 23.8, 23.7, 23.4, 23.3, 21.6, 20.6, 19.7, 18.8, 15.3. **HRMS** (ESI+): m/z calc. for $[C_{22}H_{29}NNaO_3]^+$: 378.2040, found: 378.2053.

(±)-(1*S*,3*R*)-3-Methyl-1-(2-(4-nitrophenoxy)propan-2-yl)-1,2,3,3,4,9-hexahydro-4,9-[1,2]benzenobenzo[*f*]azulene (7j)

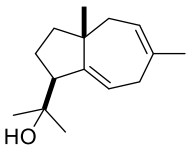


Prepared following general procedure C, by reaction of **6** (54.7 mg, 0.20 mmol, 1 equiv.) with anthracene (**2q**) (107 mg, 0.60 mmol, 3 equiv.) using catalyst **A**. Column chromatography (silica gel, 100% cyclohexane to 100:1 cyclohexane/EtOAc) delivered the title compound as a white foam (60.7 mg, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.05 (m, 2H), 7.30 – 7.23 (m, 3H (overlap with $CHCl_3$ residual peak), 7.17 – 7.05 (m, 5H), 6.97 – 6.90 (m, 2H), 6.19 (dd, J = 8.2, 1.9 Hz, 1H), 4.24 (d, J = 8.2 Hz, 1H), 3.87 (s, 1H), 2.69 – 2.61 (m, 1H), 1.77 – 1.66 (m, 1H), 1.65 – 1.57 (m, 1H), 1.52 – 1.43 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 0.98 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.1, 147.8, 144.1, 143.6, 142.6, 142.1, 138.9, 129.3, 128.8, 128.0, 126.0, 125.8, 125.7, 125.7, 125.4, 125.2, 123.5, 122.3, 84.7, 56.4, 55.4, 47.4, 45.6, 35.7, 26.1, 25.8, 25.1, 23.8. **HRMS** (ESI+): m/z calc. for $[C_{30}H_{29}NNaO_3]^+$: 474.2040, found: 474.2039. **MP** (EtOAc): 81-84 °C.

Deprotection of the Hydroxylated Skeleton of (7fb)

(±)-2-((1*S*,3*R*)-3,6-Dimethyl-1,2,3,3,4,7-hexahydroazulen-1-yl)propan-2-ol (7fa)



To a suspension of copper(II) acetylacetonate (12.5 mg, 0.048 mmol, 0.20 equiv.) and a mixture of **7f** and **8f** (81.3 mg, 0.238 mmol, 1.3:1 ratio, 1 equiv.) in ethanol (2.4 mL) was added sodium borohydride (27.0 mg, 0.71 mmol, 3 equiv.) at 0 °C and the mixture was stirred for 2 h at room temperature. Water was then added and the mixture was filtered through a short pad of Celite. The reaction mixture was extracted twice with EtOAc, and dried over $MgSO_4$ before removing the solvent under reduced pressure. The crude mixture was dissolved in acetonitrile (10 mL) and cooled to 0 °C. A solution of $(NH_4)_2Ce(NO_3)_6$ (CAN, 365 mg, 0.67

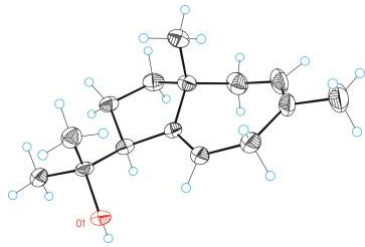
mmol, 2.8 equiv.) in distillated water (3.3 mL) was added dropwise to the reaction mixture. After stirring for 10 minutes at 0 °C, water was added, the mixture was extracted with EtOAc and washed with 10 % $NaHSO_3$, 10 % $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatography (silica gel, 10:1 cyclohexane/EtOAc) delivered the title compound as a red crystalline solid (8.3 mg, 30% yield based on **7f**, over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (td, J = 5.0, 2.1 Hz, 1H), 5.49 – 5.41 (m, 1H), 2.84 (br s, 2H), 2.72 – 2.61 (m, 1H), 2.27 (d, J = 15.4 Hz, 1H), 1.96 (dd, J = 15.1, 8.2 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.70 (t, J = 1.7 Hz, 3H), 1.53 – 1.46 (m, 2H), 1.45 – 1.35 (m, 1H), 1.24 (s, 3H), 1.17 (s, 3H), 1.08 (s, 3H), (the O*H* signal is missing). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0, 134.4, 122.7, 120.5, 73.4, 57.0, 46.0, 41.8, 40.9, 35.1, 30.2, 26.4, 26.4, 25.8, 23.9. **HRMS** (ESI+): m/z calc. for $[C_{15}H_{24}NaO]^+$: 243.1719, found: 243.1720. **MP** (EtOAc): 69–72 °C.

Crystal structure

The supplementary crystallographic data for this Chapter has been published and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

Hydroxy-derivative of carota-1,4-diene 1.81 (CCDC2027381**).**



DFT Calculations

Computational Methods

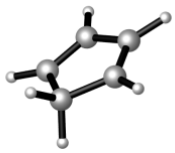
All DFT calculations were carried out with the Gaussian 09 package. Frequency calculations were analyzed to characterize the nature of the stationary points as minima (no imaginary frequency) or transition states (one imaginary frequency). Additionally, relaxation of transition states towards previous and next intermediates was used to verify the connectivity of the transition states. For the preliminary study we used PMe_3 as the ligand for gold, the B3LYP functional was used for optimizations and frequency calculations together with the basis set SDD for gold and 6-31G(d,p) for C, H, O, P atoms.

For the full system calculations with cyclohexadiene and cyclopentadiene as substrates, the B3LYP functional was also used for optimizations and frequency calculations, but in this case combined with the LANL2DZ (and the associated pseudopotential) basis set for gold, and the 6-31G(d,p) basis set for all the other atoms (C, H, P, N, O). Finally, potential energies were refined using the LANL2TZ basis set for gold, and the 6-311++G(d,p) for all the other atoms.

Solvation Model Based (SMD) was used to simulate dichloromethane solvent throughout all calculations. Unless otherwise stated, all the energies presented are potential (E) and free energies (G) in solution at 298.15 K and 1 atm in kcal/mol. Optimized geometries were visualized using CYLView.

Optimized structures

Cp calculations



Cp

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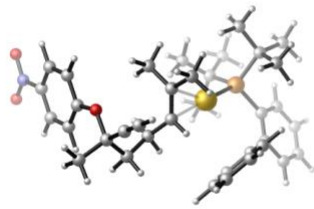

VIII (6a-Au alkene complex)

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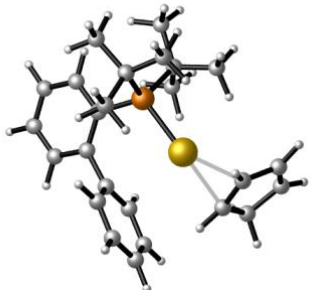
E (SP) = -2157.16341302 Hartrees



Cp-Au complex

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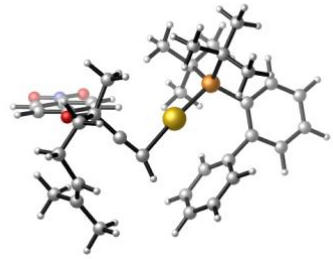

6a-Au alkyne complex

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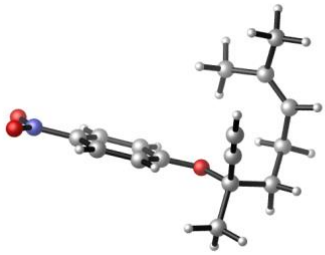

Enyne (6a)

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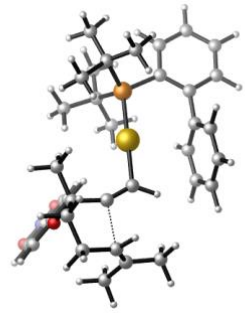

TS **(5-exo-dig)**

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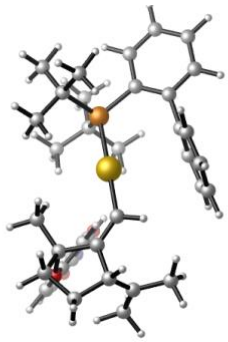

Int (5-exo-dig)

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G (opt) = -2156.052651 Hartrees
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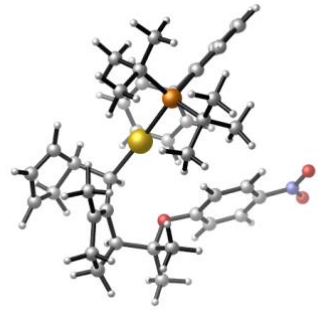

Xa

E (opt) = -2350.88666210 Hartrees
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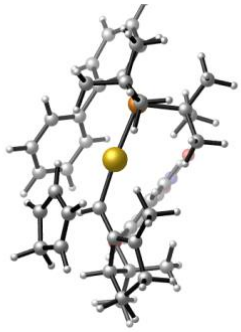
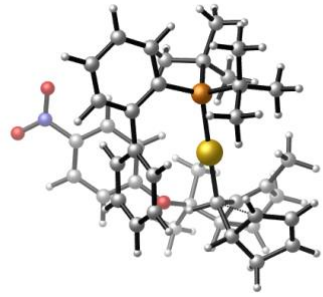
E (SP) = -2351.37050837 Hartrees



IXa

E (opt) = -2350.88232379 Hartrees
G (opt) = -2350.125518 Hartrees
E (SP) = -2351.37058260 Hartrees



TS_{Xa-XIa}

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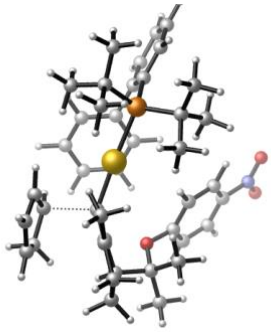

TS_{IXa-Xa}

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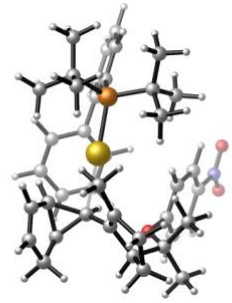

XIa

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G (opt) = -2350.132989 Hartrees
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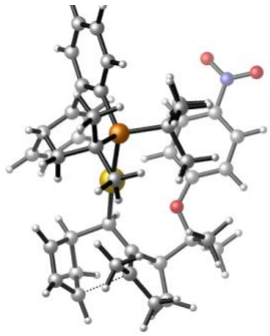

$TS_{Xa-XIIa}$

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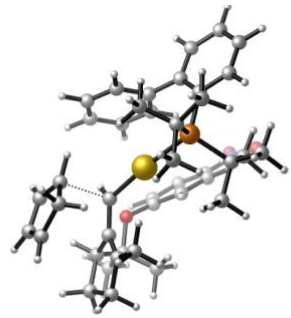

TS_{IXb-Xb}

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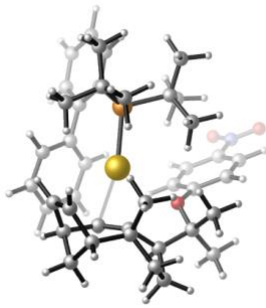

XIIa

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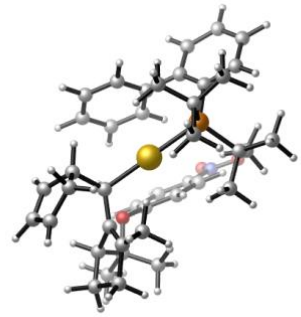

Xb

E (opt) = -2350.89185843 Hartrees
G (opt) = -2350.129395 Hartrees
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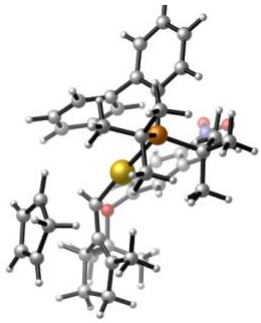

IXb

E (opt) = -2350.88343487 Hartrees
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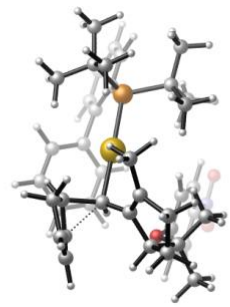

TS_{Xb-XIa}

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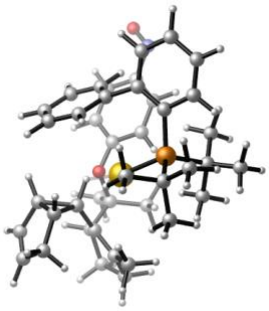

XIb

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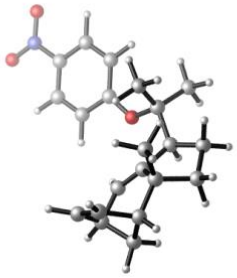

7a''

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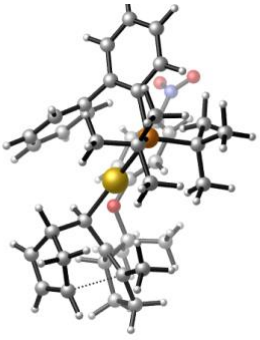

$TS_{Xb\text{-}XIIb}$

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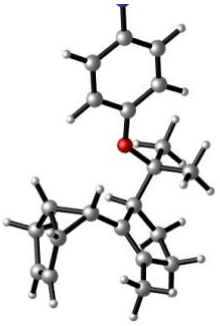

8a'

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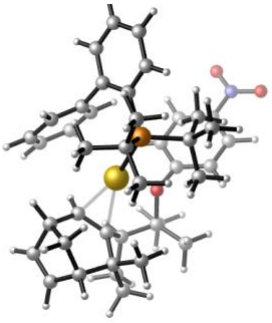

XIIb

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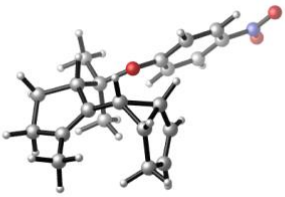
E (SP) = -2351.41420741 Hartrees



8a' (turned)

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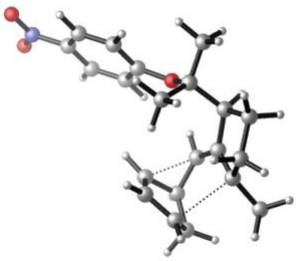

$TS_{8a'-7a'}$

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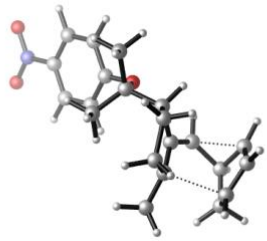

TS_{8a-7a}

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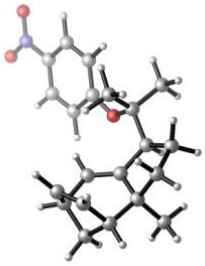

7a'

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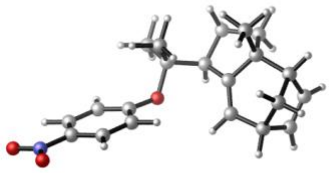

8a

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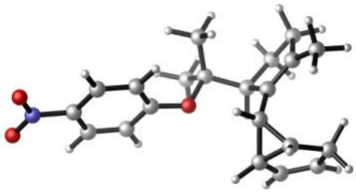
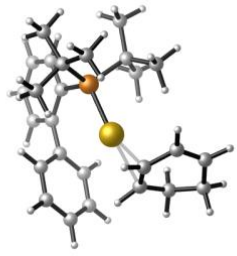
E (SP) = -1095.94314848 Hartrees

Ch calculations



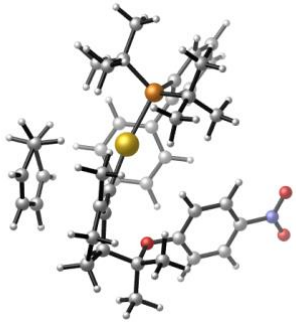
8a

E (opt) = -1095.64910218 Hartrees
G (opt) = -1095.281881 Hartrees
E (SP) = -1095.92754044 Hartrees



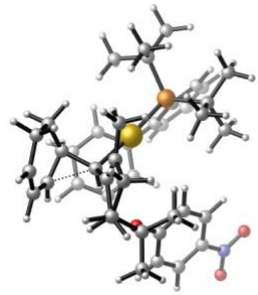
Ch-Au

E (opt) = -1488.698727 Hartrees
G (opt) = -1488.215512 Hartrees
E (SP) = -1488.961729 Hartrees



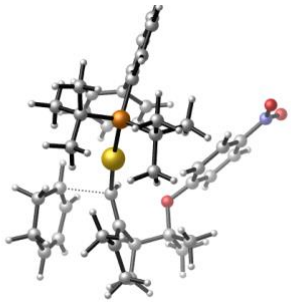
XIII

E (opt) = -2390.20660479 Hartrees
G (opt) = -2389.421790 Hartrees
E (SP) = -2390.703351 Hartrees



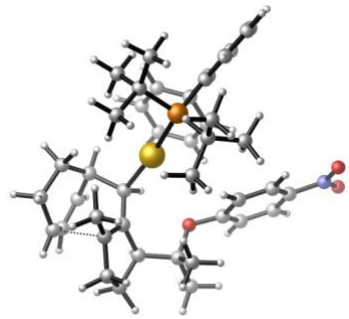
$TS_{XIVb\text{-}XVb}$

E (opt) = -2390.21564270 Hartrees
G (opt) = -2389.426048 Hartrees
E (SP) = -2390.706967 Hartrees



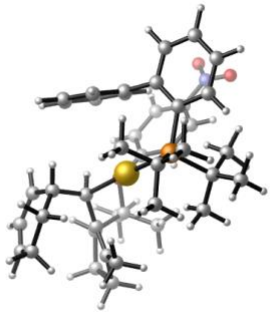
$TS_{XIII\text{-}XIVb}$

E (opt) = -2390.20335557 Hartrees
G (opt) = -2389.414465 Hartrees
E (SP) = -2390.698032 Hartrees



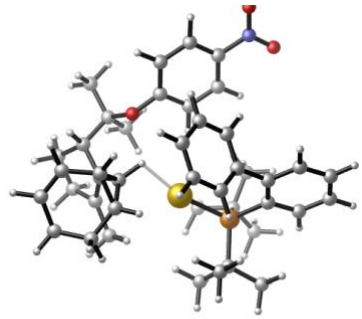
$TS_{XIVb\text{-}XVIb}$

E (opt) = -2390.21266218 Hartrees
G (opt) = -2389.417793Hartrees
E (SP) = -2390.703149 Hartrees



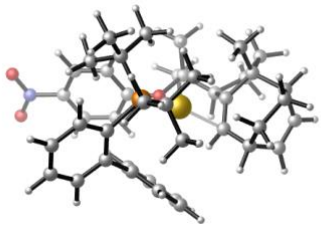
XIVb

E (opt) = -2390.21567887 Hartrees
G (opt) = -2389.427602 Hartrees
E (SP) = -2390.707092 Hartrees



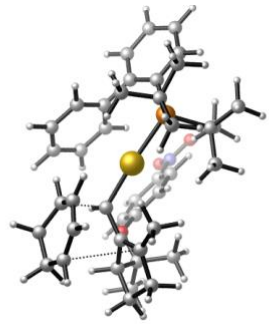
XVb

E (opt) = -2390.22501755 Hartrees
G (opt) = -2389.431700 Hartrees
E (SP) = -2390.715140 Hartrees



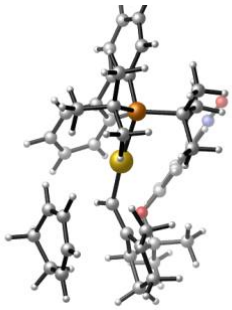
XVIb

E (opt) = -2390.25168581 Hartrees
G (opt) = -2389.453933 Hartrees
E (SP) = -2390.740709 Hartrees



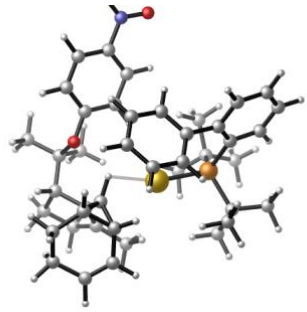
$TS_{XIIIa-XVIa}$

E (opt) = -2390.20085149 Hartrees
G (opt) = -2389.412762 Hartrees
E (SP) = -2390.694552 Hartrees



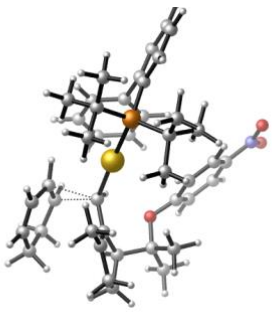
XIIIa

E (opt) = -2390.20515974 Hartrees
G (opt) = -2389.421267 Hartrees
E (SP) = -2390.701266 Hartrees



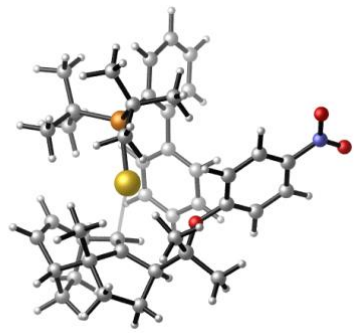
XVa

E (opt) = -2390.22451268 Hartrees
G (opt) = -2389.436808 Hartrees
E (SP) = -2390.714453 Hartrees



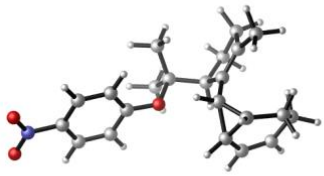
$TS_{XIIIa-XVa}$

E (opt) = -2390.19702047 Hartrees
G (opt) = -2389.408475 Hartrees
E (SP) = -2390.690848 Hartrees



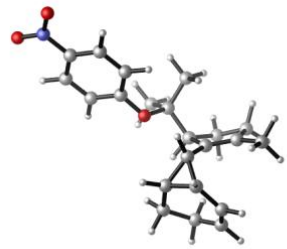
XVIa

E (opt) = -2390.25621811 Hartrees
G (opt) = -2389.456761 Hartrees
E (SP) = -2390.744754 Hartrees



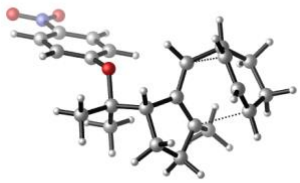
8d

E (opt) = -1134.975498 Hartrees
G (opt) = -1134.579427 Hartrees
E (SP) = -1135.261775 Hartrees



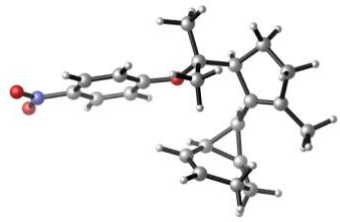
8d'

E (opt) = -1134.97594026 Hartrees
G (opt) = -1134.580069 Hartrees
E (SP) = -1135.262474 Hartrees



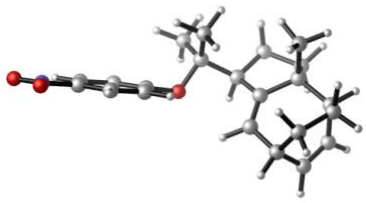
TS_{8d-7d}

E (opt) = -1134.925696 Hartrees
G (opt) = -1134.528794 Hartrees
E (SP) = -1135.213379 Hartrees



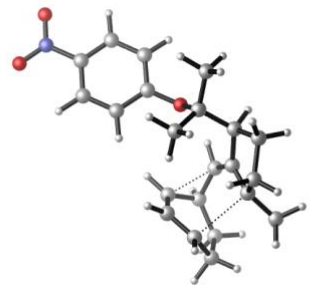
8d' turned

E (opt) = -1134.968263 Hartrees
G (opt) = -1134.571247 Hartrees
E (SP) = -1135.254333 Hartrees



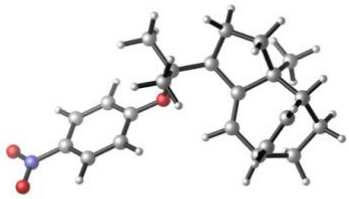
7d

E (opt) = -1134.988980 Hartrees
G (opt) = -1134.587503 Hartrees
E (SP) = -1135.275066 Hartrees



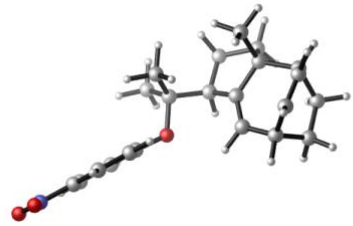
$TS_{8d'-7d'}$

E (opt) = -1134.918364 Hartrees
G (opt) = -1134.520180 Hartrees
E (SP) = -1135.205987 Hartrees



7d'

E (opt) = -1134.988160 Hartrees
G (opt) = -1134.586868 Hartrees
E (SP) = -1135.274287 Hartrees



7d''

E (opt) = -1134.99104826 Hartrees
G (opt) = -1134.588898 Hartrees
E (SP) = -1135.27683610 Hartrees

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GOLD(I)-CATALYZED CYCLOADDITIONS AND THEIR APPLICATION IN THE SYNTHESIS OF NATURAL PRODUCTS
Helena Armengol i Relats

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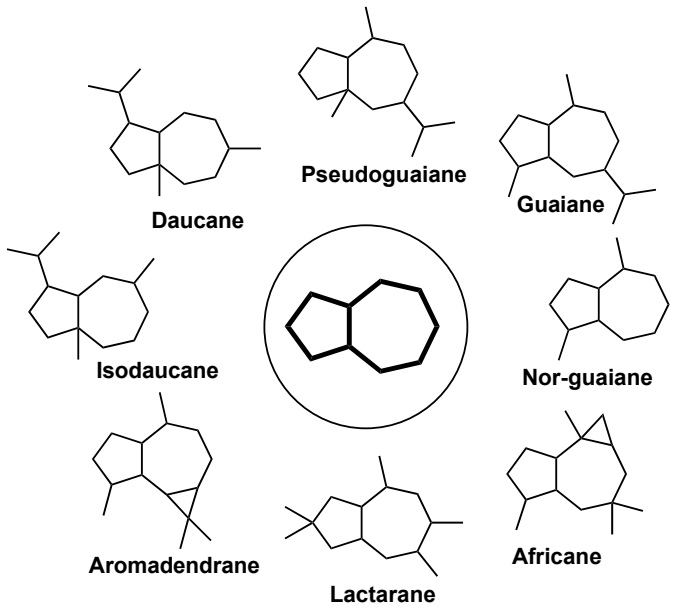
Chapter 3.
Towards the Total Synthesis of Aspterric Acid

UNIVERSITAT ROVIRA I VIRGILI
GOLD(I)-CATALYZED CYCLOADDITIONS AND THEIR APPLICATION IN THE SYNTHESIS OF NATURAL PRODUCTS
Helena Armengol i Relats

Introduction

Daucane family of natural products

The daucane family of sesquiterpenes is a relatively small group of compounds which, for a long time, seemed to be restricted to members isolated from of the plant Umbelliferae.[134] They belong to the class of natural products containing a bicyclo[5.3.0]decane skeleton (scheme 67).[135]

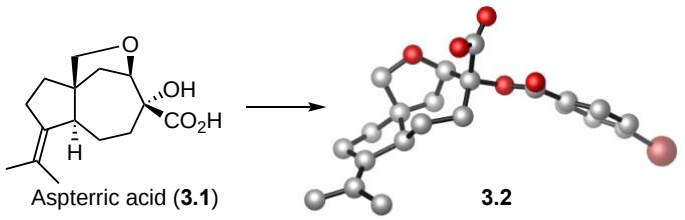


Scheme 67. Families of natural products containing a bicyclo[5.3.0]decane skeleton.

134. E. L. Ghisalberti, *Phytochemistry* **1994**, *37*, 597 – 623.
135. D. A. Foley, A. R. Maguire, *Tetrahedron* **2010**, *66*, 1131 – 1175.

Aspterric acid

Aspterric acid (**3.1**) (scheme 68) is a carotene-type sesquiterpenoid which was first isolated in 1978 from *Aspergillus terreus* IFO-6123,[136] a species of fungus found worldwide in warm arable soil. It was the first example of a carotane sesquiterpenoid obtained from a fungal origin. Its structure and absolute configuration were determined by chemical manipulation and X-ray diffraction of its *para*-bromobenzoate derivative **3.2**.[137]

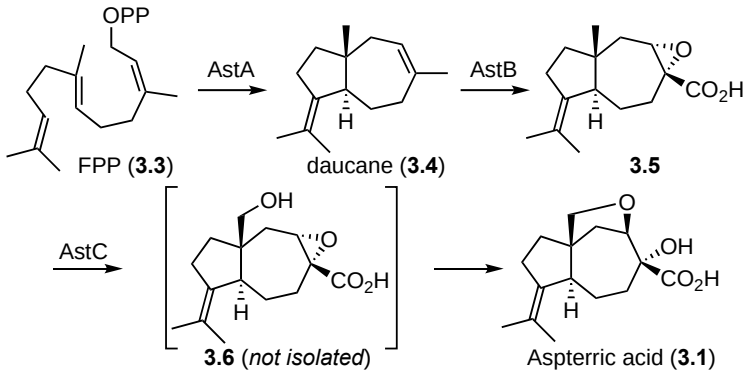


Scheme 68. Aspterric acid (**3.1**) and *para*-bromobenzoate **3.2**.

The biological proprieties of this natural product have been widely explored since its discovery. More recently, it became a compound of interest because it was found to be a very potent naturally-occuring herbicide with a new mode of action.[138]

The biosynthesis of aspterric acid was experimentally elucidated by sequential gene expression of genes astA-C in a species of yeast as the host (scheme 69).[138] After cyclization of farnesyl diphosphate (**3.3**) promoted by AstA to give daucane (**3.4**), AstB catalyzes the oxidation of **3.4** into epoxide **3.5**, which was isolated and fully characterized. Further oxidation by AstC produces alcohol **3.6**, which undergoes an intramolecular epoxide opening leading to aspterric acid (**3.1**).

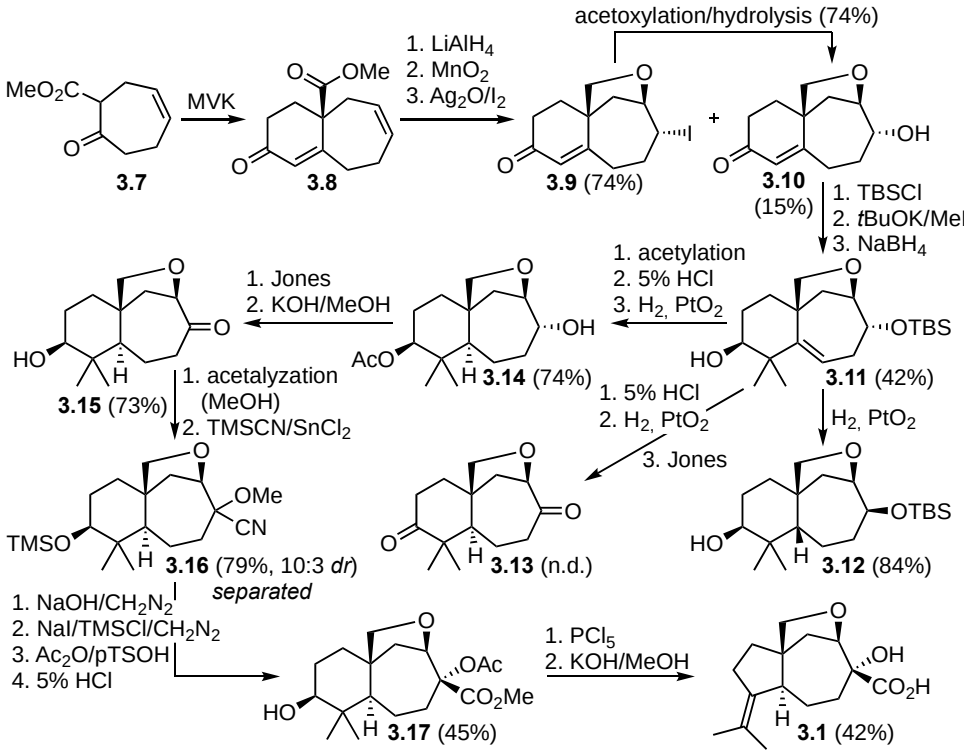
136. Y. Tsuda, M. Kaneda, A. Tada, K. Nitta, Y. Yamamoto, Y. Iitaka, *J. Chem. Soc. Chem. Commun.* **1978**, 160 – 161.
137 The crystal structure was downloaded from CCDC webpage deposit asociated to the isolation publication by Tsuda *et al.* and represented by CYLView. The H atoms were not resolved in the reported structure.
138. Y. Yan, Q. Liu, X. Zang, S. Yuan, U. Bat-Erdene, C. Nguyen, J. Gan, J. Zhou, S. E. Jacobsen, Y. Tang, *Nature* **2018**, *559*, 415 – 418.



Scheme 69. Biosynthesis of aspterric acid (**x**).

Previous synthetic report

Shortly after its isolation, in 1983, Harayama and Inubishi reported the first total synthesis of aspterric acid (scheme 70).[139] Their synthetic approach started by a Robinson annulation of cycloheptenone **3.7** and methyl vinyl ketone to form bicyclic product **3.8**. Reduction of the ketone and ester moieties followed by reoxidation with manganese oxide and treatment with silver oxide and iodine delivered a mixture of **3.9** and **3.10** (74% and 15% yield over 4 steps, respectively). Iodoether **3.9** could be converted into **3.10** by acetoxylation and hydrolysis, in 74% yield (conditions were not described). TBS protection, *alpha*-dimethylation and reduction afforded alcohol **3.11** in 42% yield over three steps. Hydrogenation of **3.11** in the presence of catalytic platinum oxide provided product **3.12** in 84% yield, presenting a *cis*-ring fusion. Alternatively, hydrogenation after acidic deprotection of the silyl group afforded the desired *trans* stereochemistry. This was confirmed by characterization of diketone **3.13**, obtained after oxidation with Jones reagent.



Scheme 70. Harayama's synthesis of aspterric acid.

Taking into account the effect of the neighboring free/protected secondary alcohol group, **3.11** was acetylated, desilylated and hydrogenated giving rise to **3.14** in good yield,

139. T. Harayama, K. Sakurai, K. Tanaka, Y. Hashimoto, H. Fukushi, Y. Inubushi, *Tetrahedron Letters* **1983**, *24*, 5241 – 5244.

presenting the desired *trans*-ring junction. Oxidation and hydrolysis of **3.14** provided ketone **3.15**, which was converted into the corresponding dimethyl acetal and treated with TMSCN in the presence of tin(II) chloride to yield **3.16**, as a 10:3 mixture of diastereomers. These were separated and submitted to the same steps to provide aspterric acid (**3.1**) and the corresponding diastereomer. A four-step sequence provided acetate **3.17** in 45% yield, which was transformed into the natural product by ring contraction and saponification (42% yield over two steps).

This synthesis afforded aspterric acid in 1.2% overall yield as a racemic product. It could probably be easily extrapolated to the corresponding enantioselective version, by performing the Robinson annulation in the presence of a chiral catalyst. The same group reported a very similar version of this synthesis in 1987,[140] also as a racemic approach.

Penigrisacid A

Aspterric acid has been isolated from other natural sources, including marine *Penicillium* fungi. For instance, the groups of Afiyatullov and Zhuravleva collected tricyclic compounds **3.18**-**3.20** (figure 11) from cultures of *Penicillium piltunense* KMM 4668.[141] Although aspterric acid was not isolated in this case, it appears to be biosynthetically related to these carboxylic acids. Additionally, very recently the group of Yang was able to obtain **3.1** from *Penicillium griseofulvum*,[142] together with products **3.21**-**3.23**, including penigrisacid A. These later compounds were tested for anti-food allergic activity and subjected to a cytotoxicity assay against five different cancer cells, but no significant effect was found in any of the cases. Nevertheless, these products have been only isolated two years ago, so its biological testing has been yet rather scarce. These natural products were found appealing for us since they are structurally very similar to aspterric acid and thus they might exhibit similar or even enhanced herbicide (or other) activities and they can be rapidly accessed synthetically from common chemical intermediates.

Among these compounds, we turned our attention to penigrisacid A (**3.21**), which presents an oxygen-bridged skeleton and is a chemical isomer of apsterric acid. No total synthesis of this natural product has been reported to date.

140 T. Harayama, K. Sakurai, K. Tanaka, Y. Hashimoto, H. Fukushi, Y. Inubushi, *Chem. Pharm. Bull.* **1987**, *35*, 1434 – 1442.
141. S. S. Afiyatullov, O. I. Zhuravleva *et al*, *Mar. Drugs* **2019**, *17*, 647, 1 – 12.
142. C.-P. Xing, C.-L. Xie, J.-M. Xia, Q.-M. Liu, W.-X. Lin, D.-Z. Ye, G.-M. Liu, X.-W. Yang, *Mar. Drugs* **2019**, *17*, 507, 1 – 8.

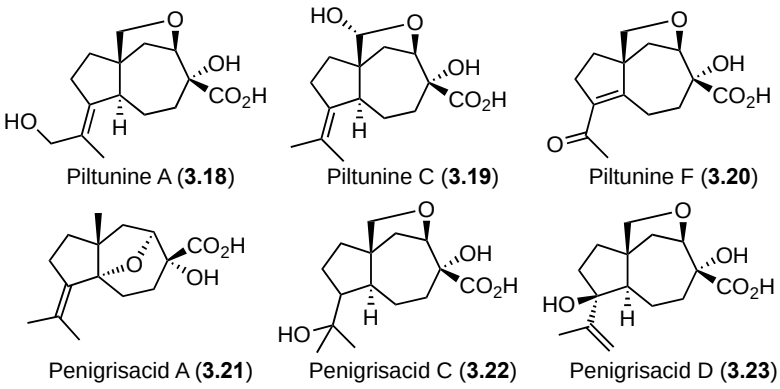


Figure 11. Examples of piltunines and penigrisacids.

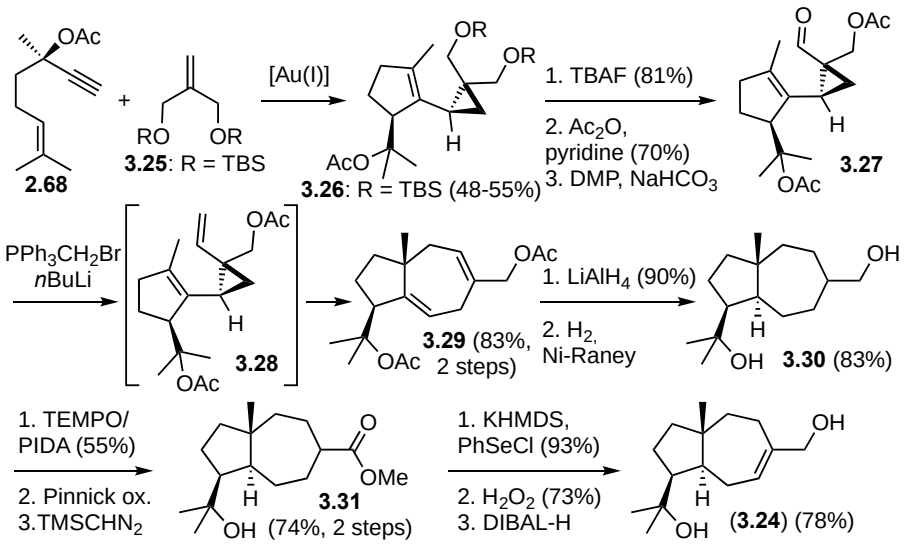
Schisanwilsonene A

Among the carotene-like natural products, schisanwilsonene A (**3.24**)[143] also presents interesting biological proprieties. This naturally-occurring compound was first isolated in 2009 from *Schisandra wilsoniana* by the group of Chen. It was found to have strong antiviral activity inhibiting HBsAg and HBeAg at 50 μg/mL. It is related to aspterric acid, as they are both carotene-like sesquiterpenoids and resemble oxidized daucane products.

Previous synthetic reports

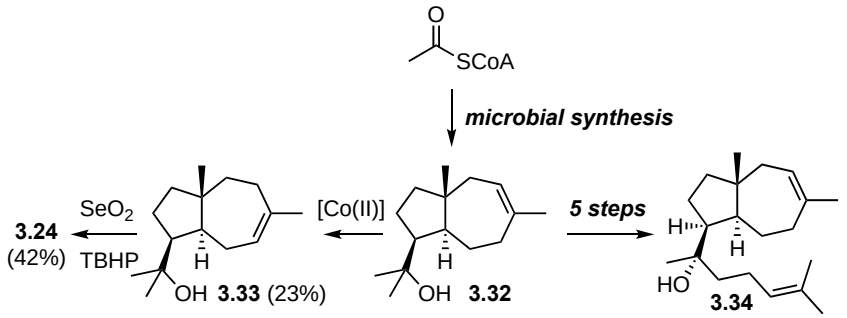
The first total synthesis of schisanwilsonene A was reported by our group in 2013, relying on a gold(I) catalysis as the key step (scheme 71).[144] Starting from enantioenriched enyne **2.68**, gold(I)-catalyzed cycloisomerization/cyclopropanation afforded cyclopentene **3.26** in moderate yield. Double desilylation with TBAF, monoacetylation and oxidation with Dess-Martin periodinane afforded aldehyde **3.27**. This was subsequently submitted to Wittig olefination to provide divinylcyclopropane **3.28**, which rearranged into cycloheptadiene **3.29** under the same reaction conditions. Reduction and hydrogenation afforded diol **3.30** in good yield as a mixture of epimers. Diol **3.30** is a hydrogenated analogue of the natural product. Introduction of the double bond found in the natural product proved to be challenging and required multiple steps: starting with a two-step oxidation/methylation to yield ester **3.31**, followed by a two-step oxidation to the obtain the corresponding α,β-unsaturated ester and finally selective reduction to deliver the natural product in good yield. Its absolute configuration was determined by x-ray diffraction of crystalline synthetic **3.24**.

143. W.-H. Ma, H. Huang, P. Zhou, D.-F. Chen, *J. Nat. Prod.* **2009**, *72*, 676 – 678.
144. M. Gaydou, R. E. Miller, N. Delpont, J. Ceccon, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 6396 –6399.



Scheme 71. Echavarren's synthesis of schisanwilsonene A (**3.24**).

Very recently the group of Xiang developed an alternative synthetic approach to schisanwilsonene A (**3.24**) involving the microbial synthesis of intermediate **3.32** and the subsequent chemical manipulation to get the natural product (scheme 72).[145] This second stage consisted in cobalt(II)-catalyzed double bond isomerization to compound **3.33** in 23% yield (+ 43% of recovered **3.32**) and an allylic oxidation to get **3.24** in moderate yield. Intermediate **3.32** was also employed for the synthesis of tormesol (**3.34**), in 5 chemical steps.

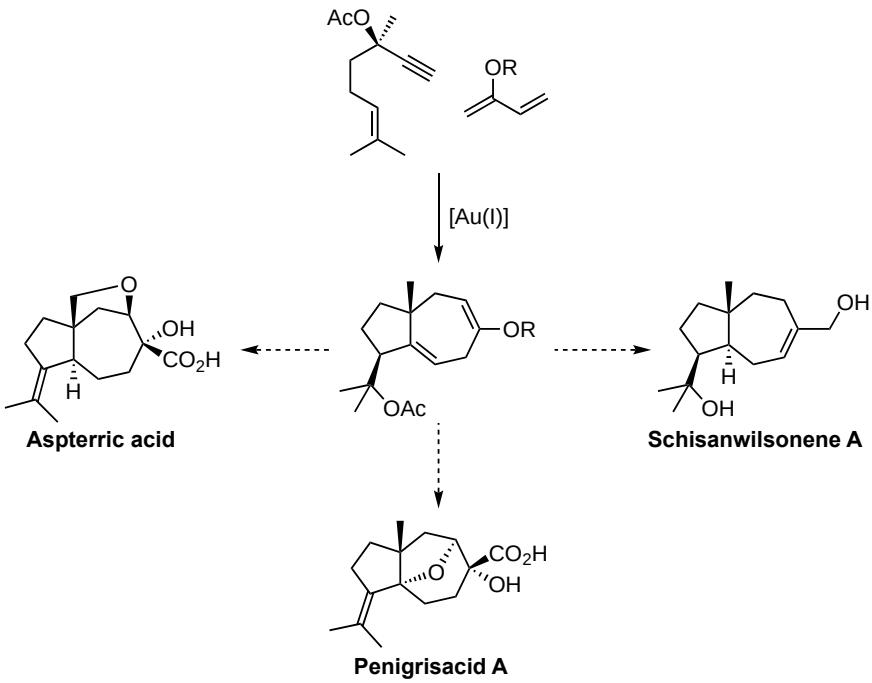


Scheme 72. Xiang's synthesis of **3.24** and **3.34**.

145. S.-B Mou, W. Xiao, H.-Q. Wang, K.-Y. Chen, Z. Xiang, *Org. Lett.* **2021**, *23*, 400 – 404.

Objectives

As mentioned in the General Introduction, gold(I) catalysis has been repeatedly used in natural product total synthesis. Thus, the objective of this Chapter is to apply our newly developed gold(I)-catalyzed reaction for the synthesis of complex hydroazulenes (described in Chapter 2) to the total synthesis of aspterric acid and structurally similar natural products (scheme 73). The gold(I)-catalyzed cycloisomerization/cycloaddition cascade would afford the 5/7-bicyclic skeleton in a common intermediate which would be latter converted into different naturally-occurring compounds.



Scheme 73. Divergent total syntheses of carotene-type sesquiterpenoids.

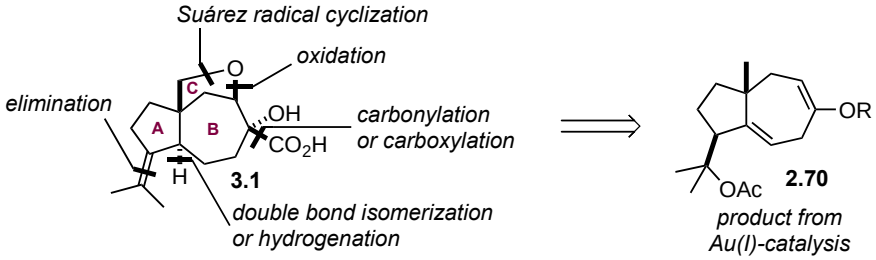
Results and Discussion

As the optimization of the gold(I)-catalyzed cascade reaction was already described in Chapter 2, this chapter will focus on the derivatization of enol ether **2.70** towards the different naturally occurring compounds presented in the introduction.

Towards the Total Synthesis of Aspterric Acid

Our strategy towards aspterric acid (**3.1**) from product **2.70** consisted essentially in 5 synthetic steps, whose order and reaction conditions would need to be addressed (scheme 74). These are collected in the following list:

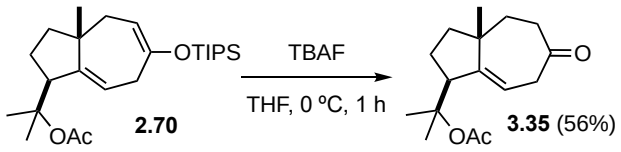
- a double bond isomerization or hydrogenation to afford the desired *trans*-ring junction between rings A and B,
- an oxidation of the enol ether to install the oxygen atom found in ring C,
- a Suárez radical cyclization to close ring C,
- the elimination of the acetate group to afford the tetrasubstituted exocyclic double bond
- and the introduction of the carboxylic acid moiety by a carbonylation or carboxylation reaction.



Scheme 74. Retrosynthetic analysis of aspterric acid (**3.1**) from **2.70**.

Initial attempts

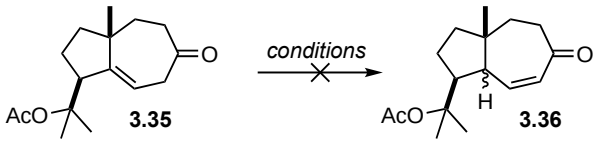
As first derivatization, TIPS enol ether **2.70** was treated with TBAF to afford ketone **3.35** in moderate yield (scheme 75).



Scheme 75. Treatment of **2.70** with TBAF.

Isomerization of ketone **3.35** to conjugated enone **3.36** was attempted under different conditions (table 22). However, we were not able to obtain the desired product under any of the conditions we used.

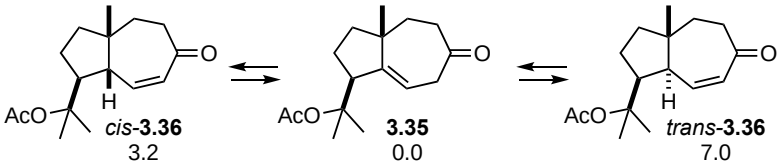
Table 22. Attempts on the double bond isomerization of **3.35**, all leading to no reaction.



Entry	Conditions
1	$RhCl_3$
2	*p*TSOH
3	HCl (conc.) /THF
4	DBU

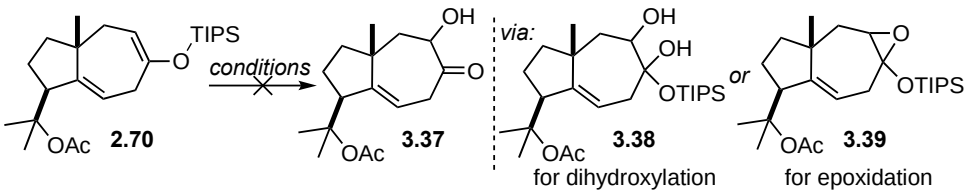
[a.] n.d = not determined.

We performed basic DFT calculations and found that indeed the thermodynamic product is non-conjugated **3.35** (scheme 76). According to the calculated relative energy values, the less stable isomer is *trans*-**3.36**, with a relative ground state energy of 7.0 kcal/mol, which would have been the desired product, as it presents the *trans*-ring fusion observed in the natural product.



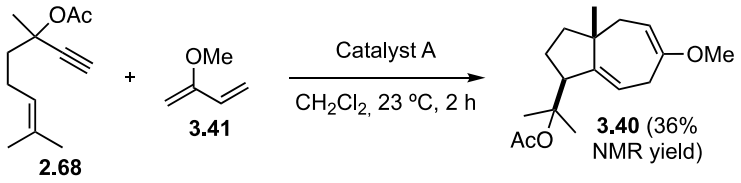
Scheme 76. Ground state relative energy values of **3.35**, *cis*-**3.36** and *trans*-**3.36**, found by DFT calculations. Energies in kcal/mol, at 25 ºC and 1 atm, in solution.

In a parallel approach we tried to take advantage of the already set enol ether to selectively functionalize the desired *alpha*-position with respect to the carbonyl carbon (scheme 77). We tried several oxidative conditions such as epoxidation with *m*CPBA or dihydroxylation with AD-mix but we found little to no conversion towards desired α-hydroxyketone **3.37**.



Scheme 77. Attempts to obtain **3.37** by oxidation of **2.70**.

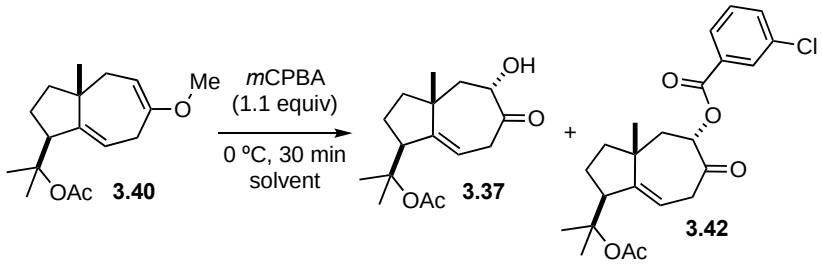
We hypothesized that the TIPS group was too bulky and it was preventing the oxidation to occur. Thus, we decided to prepare methyl enol ether analogue **3.40**, by reaction of enyne **2.68** with 2-methoxy-1,3-butadiene (**3.41**). We were pleased to find that the gold catalysis proceeded with similar moderate yield (scheme 78).



Scheme 78. Gold(I) catalysis with 2-methoxy-1,3-diene (**x**).

For the subsequent oxidation with *m*CPBA, we did a brief solvent screening and found that depending on the solvent of choice and on the addition of base, the main product obtained was desired α-hydroxyketone **3.37** or *meta*-chlorobenzoate adduct **3.42** (table 23).

Table 23. Solvent screening for the reaction of **3.40** with *m*CPBA



Entry	Solvent	Additive	NMR ratio 3.37:3.42	Isolated yield
1	hexanes	-	1:1	n.d.[a]
2	CH_2Cl_2	-	1:0	n.d.[a,b]
3	Et_2O	-	1:0	47% (**x**)
4	CH_2Cl_2	Na_2HPO_4 (1.1 equiv)	0:1	36% (**x**)

[a.] n.d. = not determined. [b.] Many byproducts observed by crude ^{1}H-NMR.

The relative configuration of **3.37** and **3.42** was found to be the same, according to ^{1}H-NOE experiments. We could obtain crystals of **3.42** and confirm its relative configuration by X-ray diffraction analysis (figure 12).

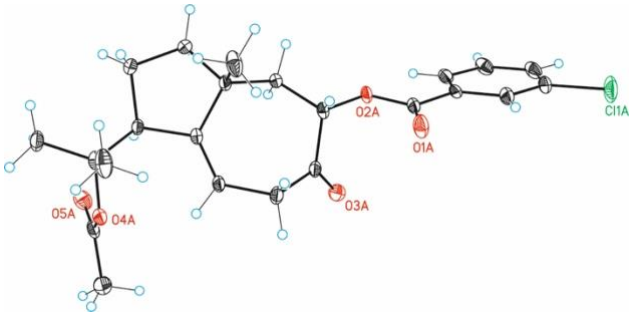
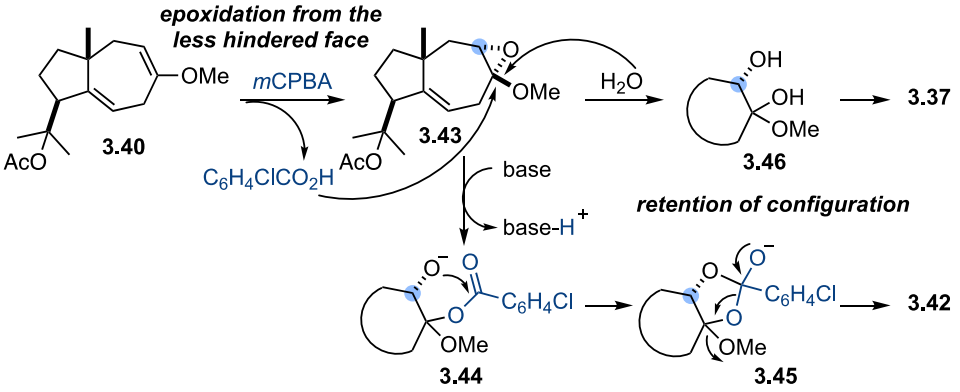


Figure 12. X-ray structure of **3.42**.

These *m*CBA adducts such as **3.42** have been observed before in similar Rubbottom-type oxidations, depending on the solvent of choice.[146] Similarly to the explanation that Boeckman proposed for silyl enol ethers, we proposed a mechanism for the two products to have the same relative stereochemistry (scheme 79). In our proposal, under basic conditions, intermediate **3.43** is trapped by deprotonated *m*CBA to afford benzoate **3.44**. The alkoxide moiety in **3.44** attacks the neighboring benzoate forming 5-membered ring intermediate **3.45**, which upon elimination of methoxide provides product **3.42**. Under acidic conditions, intermediate **3.43** reacts with water to afford hemiacetal **3.46**, that finally leads to hydroxyketone **3.37**.

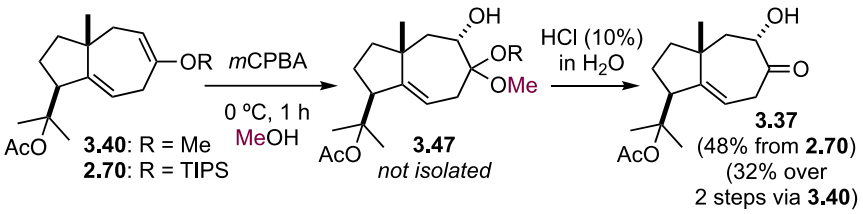


Scheme 79. Mechanism for the formation of **3.37** and **3.42**.

Later, we found that performing the oxidation of **3.40** in methanol provided **3.37** in slightly higher yields and with better reproducibility, probably due to the better solubility of *m*CPBA in this solvent (scheme 80). We attempted the oxidation of **2.70** under these new

146. R. K. Boeckman Jr., M. Ramaiah, *J. Org. Chem.* **1977**, *42*, 1581–1586.

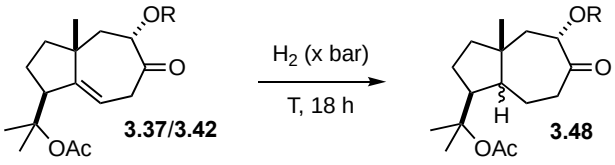
conditions and we were pleased to see that the same product was obtained, in similar yield. Interestingly, we could confirm by ^{1}H-NMR that prior to the acidic aqueous work up, **3.37** was not present in the crude mixture, while it was the only product after treatment with aqueous HCl (10%). Thus, we hypothesized that acetal **3.47** is an intermediate of the reaction, which gets hydrolyzed under acidic conditions to give **3.37**.



Scheme 80. Rubbottom oxidation of **3.40** and **2.70** in methanol. The yield from **3.40** is calculated over two steps: gold catalysis + *m*CPBA oxidation, due to the difficulties in getting **3.40** clean in the first step.

With products **3.37** and **3.42** in hand, we attempted the hydrogenation of the double bond (table 24). Unfortunately, with none of the conditions we tried we were able to obtain the desired reduced product **3.48**. Most of them provided no reaction while Rh/C and PtO_2 reduced the ketone moiety to a secondary alcohol, leaving the double bond untouched (entries 15, 18 and 19).

Table 24. Attempts on the hydrogenation of substrates **3.37** and **3.42**.

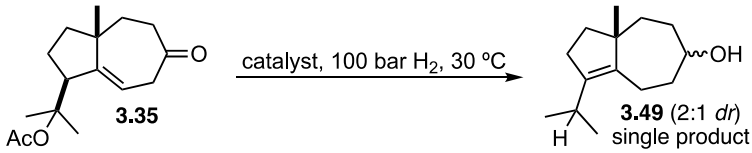


Entry	R	Solvent	Catalyst	H_2 pressure	T (ºC)	Outcome
1	$C(O)C_6H_4Cl$	EtOAc	Pd/C	1 atm	25	n.r.
2	$C(O)C_6H_4Cl$	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	1 atm	25	n.r.
3	$C(O)C_6H_4Cl$	EtOAc	Pd/C	5 bar	25	n.r.
4	$C(O)C_6H_4Cl$	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	5 bar	25	n.r.
5	$C(O)C_6H_4Cl$	EtOAc	Pd/C	20 bar	25	n.r.
6	$C(O)C_6H_4Cl$	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	20 bar	25	n.r.
7	$C(O)C_6H_4Cl$	EtOAc	Pd/C	20 bar	40	n.r.
8	$C(O)C_6H_4Cl$	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	20 bar	40	n.r.
9	H	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	1 atm	40	n.r.
10	H	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]BAr_4^F$	1 atm	40	n.r.
11	H	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	20 bar	40	n.r.
12	H	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]BAr_4^F$	20 bar	40	n.r.

13[b]	H	MeOH[a]	Pd/C	80 bar	40	n.r.
14[b]	H	MeOH[a]	$Pd(OH)_2/C$	80 bar	40	d.
15[b]	H	MeOH[a]	PtO_2	80 bar	40	side r.
16[b]	H	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	80 bar	40	n.r.
17[b]	H	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]BAr_4^F$	80 bar	40	n.r.
18[b]	H	MeOH[a]	Rh/Al_2O_3	80 bar	40	side r.
19[b]	H	MeOH[a]	$Rh(PPh_3)_4Cl_2$	80 bar	40	side r.

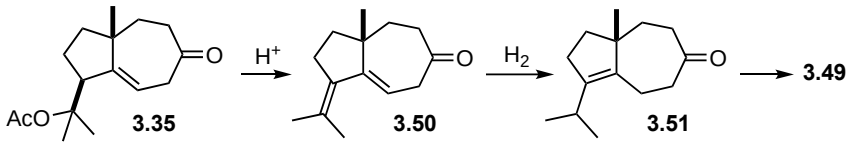
[a.] A 2:1 mixture of MeOH/THF was employed as the solvent; [b.] 68 h reaction time. n.r. = no reaction; d. = decomposition; side r. = side reaction: the double bond remained untouched but the ketone moiety was reduced to an alcohol.

In a collaboration with Jordi Faiges, from the group of Prof. Òscar Pàmies (URV), we attempted the reduction of simpler substrate **3.35**, with some iridium catalysts developed in their group (scheme 81). Compound **3.49** was formed as the only product. However, we were not able to fully characterize it and we could not reproduce the reaction at slightly larger scale.



Scheme 81. Iridium catalyzed hydrogenation on **3.35** using Pàmies' catalysts.

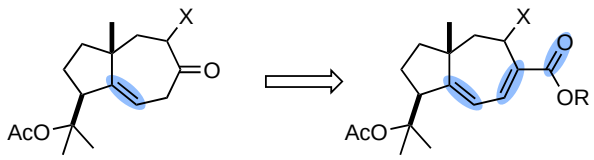
Presumably some traces of acid could have prompted the elimination of the acetate group in **3.35** forging conjugated diene **3.50** (explaining the irreproducibility of the reaction). Partial hydrogenation of **3.50** would afford product **3.51**. Parallelly, reduction of the carbonyl group would provide secondary alcohol **3.49** (scheme 82).



Scheme 82. Proposed mechanism for the formation of **3.49**.

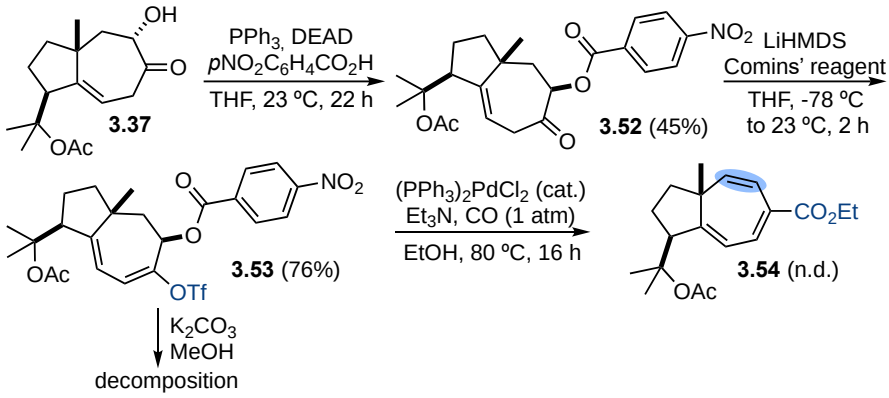
Diene-hydrogenation strategy

Discouraged with the difficulties to reduce the trisubstituted double bond at the ring fusion, we proposed an alternative approach. This consisted in the activation of the double bond by conjugation (scheme 83).



Scheme 83. Activation of the double bond by conjugation.

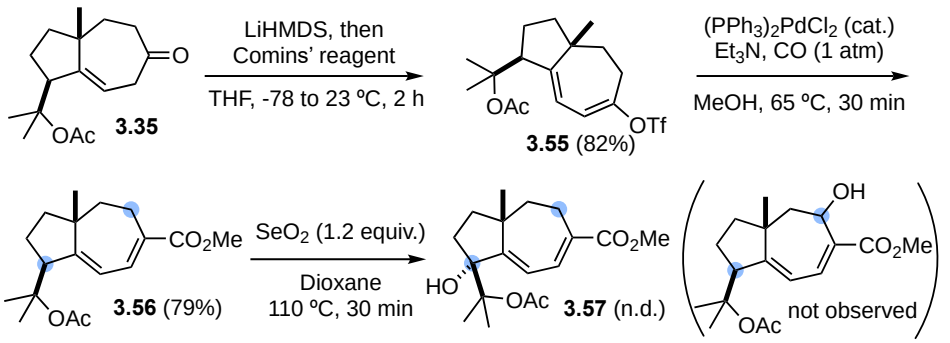
We started form substrate **3.37**, by concomitant inversion and protection of the hydroxy moiety, by Mitsunobu reaction (scheme 84). We confirmed the inversion of the *O*-stereocenter in product **3.52** by NMR and X-ray diffraction (although the crystals were not good enough for publication, thus we did not include them in this thesis). Then we attempted a two-step alkoxycarbonylation, via triflate **3.53**. Subsequent palladium-catalyzed alkoxycarbonylation of **3.53** with CO and ethanol provided the desired ester moiety but with concomitant elimination of the benzoate group, leading to product **3.54**. We tried to prevent the elimination reaction by lowering the temperature and changing the palladium source but we always observed the same outcome. Methanolysis of the benzoate moiety on substrate **3.53** afforded complete decomposition.



Scheme 84. Attempts for the two-step carbonylation of **3.52**.

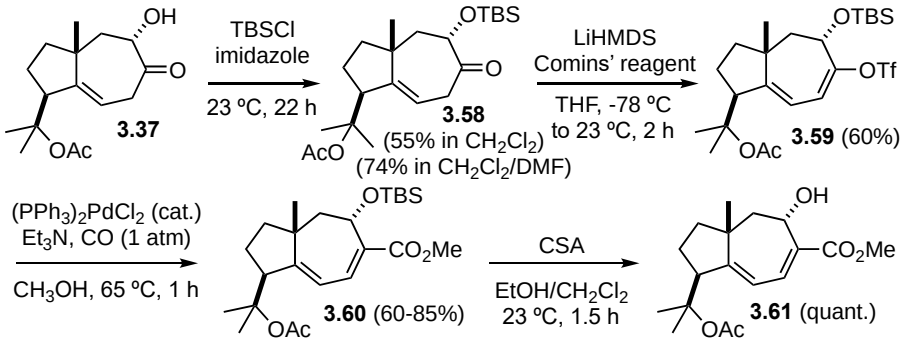
Parallelly, we tried the same sequence of steps for the synthesis from simpler substrate **3.35** (scheme 85). In this case, we were able to successfully obtain desired product **3.56** via triflate **3.55**. Next, we attempted an allylic oxidation, hoping that the most accessible secondary allylic position would get activated. Unfortunately, with one equivalent of SeO_2, we obtained product **3.57**, where the tertiary allylic position had got oxidized. Lower temperatures led to no reaction and excess of oxidant led to decomposition. Using other oxidants such as PCC or PIFA/TBHP/O_2[147] also decomposed the substrate to complex mixtures of products.

147 B. A. Sparling, D. C. Moebius, M. D. Shair, *J. Am. Chem. Soc.* **2013**, *135*, 644–647.



Scheme 85. Synthesis of **3.56** and attempt on its allylic oxidation.

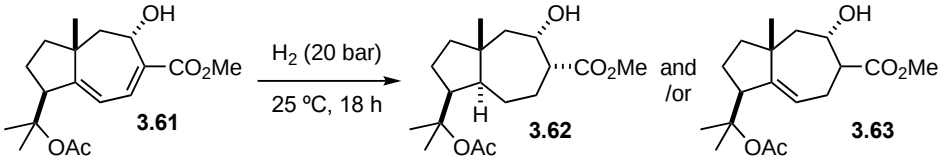
In a third attempt, we prepared substrate **3.58** by TBS-protection of hydroxyketone **3.37**. The protection yield could be slightly improved by using DMF as cosolvent. We were please to find that the two-step methoxycarbonylation sequence afforded product **3.60** in good yields, without products of elimination. We were able to deprotect the TBS group with CSA leading to **3.61** in quantitative yield (TBAF deprotection conditions were also successful but more byproducts were obtained).



Scheme 86. Synthesis of **3.61** by TBS protection/deprotection strategy.

With substrate **3.61** in hand, we attempted its hydrogenation (table 25). We were pleased to find that the desired product **3.62** was formed in moderate yield at room temperature and 20 bar of hydrogen, with Adam's pre-catalyst. We later found that the NMR-yield of the reaction was actually much higher than the isolated yield, so we concluded that **3.62** was decomposing in the purification, which was not essential for the subsequent steps. Iridium-based catalysts provided no reaction and Pd/C afforded partially reduced product **3.63**. Additionally, interestingly we found that TBS-ether **3.60** was not reactive under the same hydrogenation conditions.

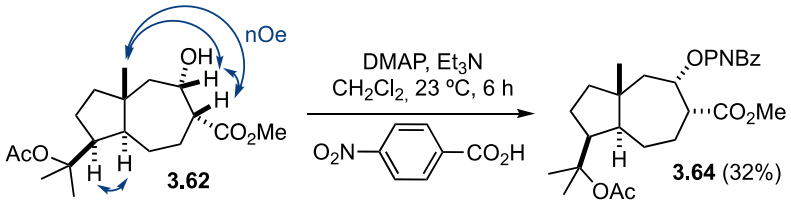
Table 25. Hydrogenation of substrate **3.61**.



Entry	Solvent	Catalyst	Conversion	Ratio 3.62:3.63[a]	Isolated yield
1	EtOAc	PtO_2	100%	6:1	32%
2	EtOAc	Pd/C	100%	0:1	-
3	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]PF_6$	0%	-	-
4	CH_2Cl_2	$[(PCy_3)(COD)(py)Ir]BAr_4^F$	0%	-	-

[a.] Determined by crude ^{1}H-NMR.

The relative configuration of the two newly formed stereocenters in **3.62** was determined by NOE ^{1}H-NMR and confirmed by X-ray analysis of crystalline **3.64**, which was prepared by reaction of **3.62** with *para*-nitrobenzoic acid (scheme 87 and figure 13).



Scheme 87. Assignment of the relative configuration of **3.62**.

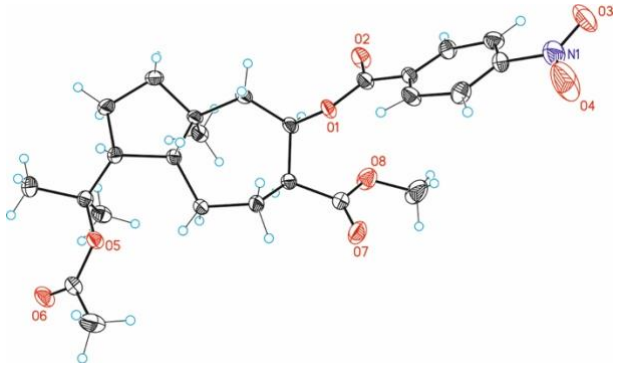
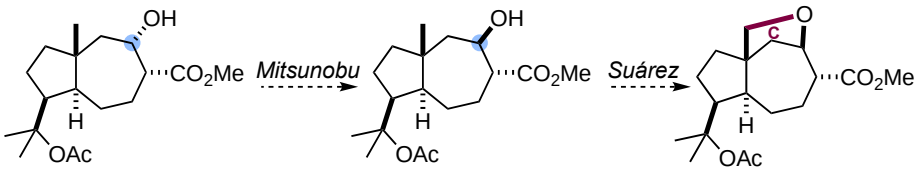


Figure 13. X-ray structure of **3.64**.

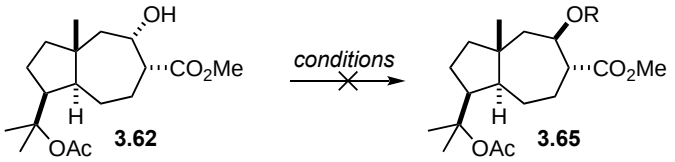
Attempts on the construction of ring C

At this point, we had achieved three of the key synthetic steps proposed for the synthesis of aspterric acid: the settlement of the *trans* ring fusion, and the introduction of a carboxylate group and the oxidation of the β–carbon with respect to the ester moiety (scheme 88). We then tackled the inversion of the secondary alcohol in order to set the desired stereochemistry, which would then enable the Suárez radical cyclization for the construction of ring C.



Scheme 88. Proposed route for the construction of ring C.

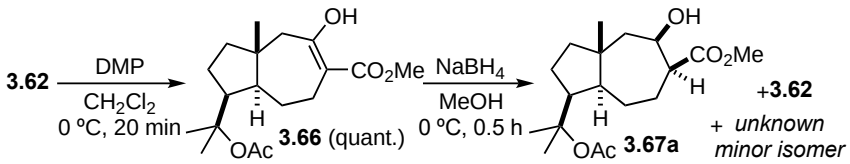
Initially, we submitted substrate **3.62** to Mitsunobu conditions in order to get inversion of configuration in a product such as **3.65** (scheme 89). Unfortunately, the reaction only led to decomposition products. Milder conditions such as the recently described catalytic version of the Mitsunobu reaction also afforded decomposition.[148]



Scheme 89. Attempts on the Mistunobu reaction on substrate **3.62**.

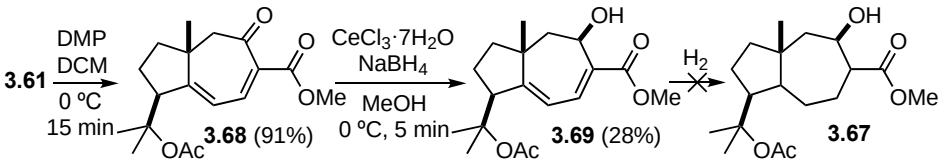
Thus, we thought of inverting the alcohol by a two-step oxidation/reduction strategy (scheme 90). Oxidation of **3.62** with DMP led to β-ketoester **3.66**, which was in equilibrium with its enol tautomer, with loss of the stereochemical information on the α-carbon. Subsequent treatment of **3.66** with $NaBH_4$ in methanol afforded the desired product **3.67** as a mixture of 3 isomers (**3.67a**, **3.62** and an uncharacterized product) in a 1.0:1.1:1.3 ratio. To improve the stereoselectivity of the reduction we used other reducing agents such as Super hydride or L-selectride. However, none of them provided selectively the desired isomer. Different hydrogenation catalysts ("Ir", Pd/C, PtO_2) with up to 20 bar of H_2 were also employed in an attempt to reduce enol **3.66**, affording no reaction.

148. Catalytic Mitsunobu



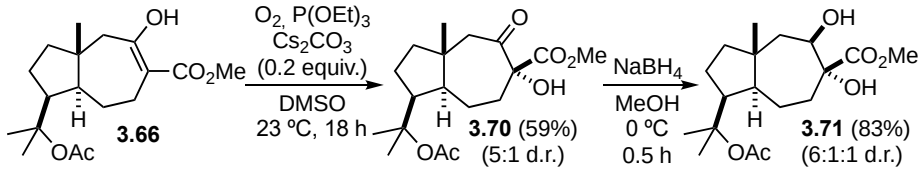
Scheme 90. Inversion of secondary alcohol **3.62** by a 2-step oxidation/reduction sequence.

To prevent epimerization of the stereocenter alpha to the ketone and ester moieties, we attempted the reduction of α,β,γ,δ-conjugated β-ketoester **3.68**, which was prepared by oxidation of **3.61** with DMP (scheme 91). Neither simple reaction with $NaBH_4$ nor Luche conditions led selectively to the desired product **3.69**, which was obtained in 28% yield as the minor product of the reaction. Attempts to fully hydrogenate **3.69** into **3.67** were not successful, delivering mainly products of partial reduction of the α,β-conjugated double bond.



Scheme 91. Oxidation/reduction sequence from **3.61**.

In order to reduce the number of isomers formed by the reduction of **3.66**, we decided to block the stereochemistry of the α-carbon by further oxidation (scheme 92). We first introduced a hydroxy group by reaction of **3.66** with oxygen and triethylphosphite in the presence of catalytic cesium carbonate.[149] Reduction of the resulting α-hydroxy-β-ketoester **3.70** with $NaBH_4$ afforded diol **3.71** in good yield and diastereoselectivity.



Scheme 92. Synthesis of diol **3.71**.

We were able to crystallize **3.71** and determine the relative configuration by X-ray diffraction analysis and NOE ^{1}H-NMR experiments (figure 14).

149. Alpha-hydroxylation with oxygen

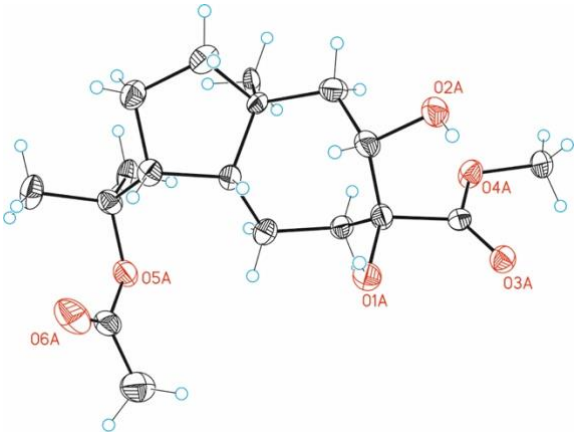
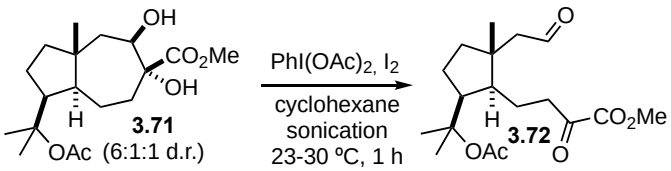


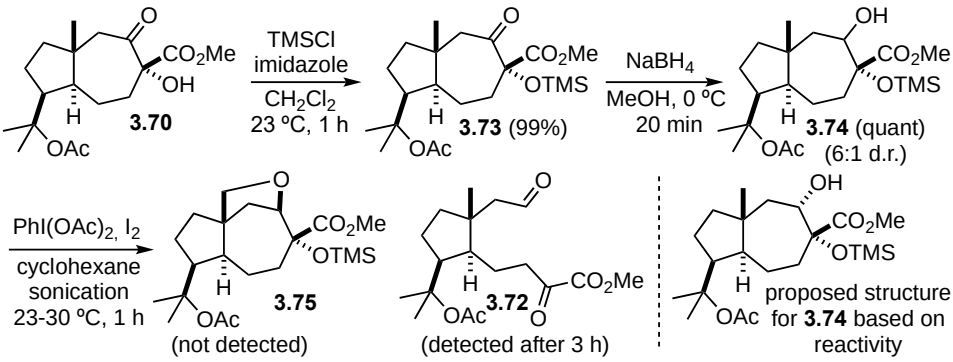
Figure 14. X-ray structure of **3.71**.

With substrate **3.71** in hand, we attempted the Suárez radical cyclization to form ring C (scheme 93). Unfortunately, under oxidative conditions, diol **3.71** underwent oxidative fragmentation leading to aldehyde **3.72**.



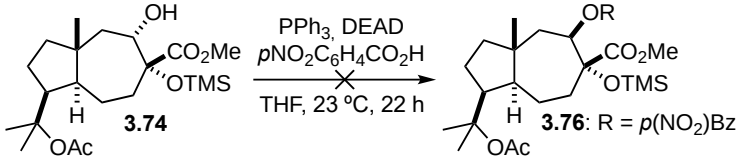
Scheme 93. Suárez reaction conditions on substrate **3.71**.

To avoid this fragmentation to occur, we had to protect the tertiary alcohol on **3.71**, in the presence of the secondary alcohol. We first introduced a TMS group on substrate **3.70** and then reduced ketone **3.73** to secondary alcohol **3.74** (scheme 94). We could not determine the relative configuration of the secondary alcohol moiety in **3.74** by ^{1}H-NMR. Thus, we decided to submit **3.74** to the Suárez radical cyclization conditions. We found that no reaction took place after 1 h. After longer reaction time, aldehyde **3.72** was detected. These results indicate that probably the OH-moiety was *trans* to the methyl group, and thus its activation by HAT could not occur. After longer reaction times, cleavage of the TMS group prompted the oxidative fragmentation of **3.71** into **3.72** (as found in scheme 93).



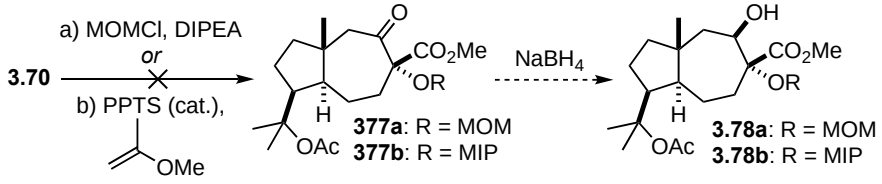
Scheme 94. TMS-protecting strategy.

We also tried to invert the secondary alcohol on product **3.74** by Mitsunobu reaction, which led to no reaction (scheme 95). Further screening of conditions for this transformation might lead to the desired product **3.76**, which after benzoate deprotection would be a suitable precursor for the Suárez radical cyclization.



Scheme 95. Attempt to invert the secondary alcohol on substrate **3.74**.

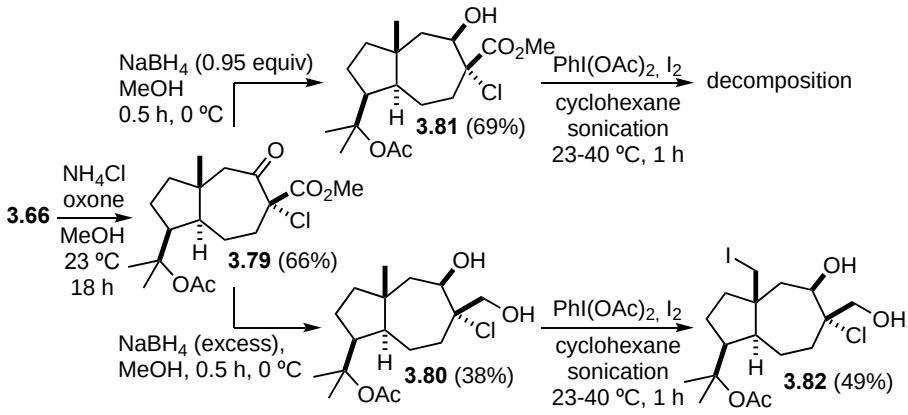
We envisioned that other protecting groups on the tertiary alcohol might be able to direct the ketone reduction leading to the desired diastereomer (scheme 96). We attempted to introduce a MOM group and its dimethyl analogue (MIP) in **3.70** to get to substrates **3.77a-b** but unfortunately both reactions led to complete decomposition.



Scheme 96. Attempts to introduce a MOM or MIP group on substrate **3.70**.

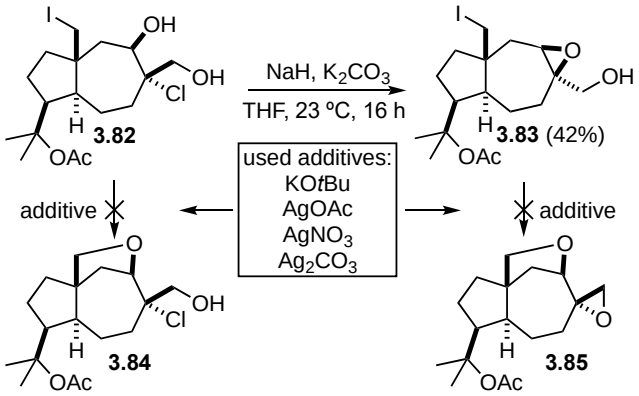
Since the directing strategies for the diastereoselective reduction of **3.66** were not successful, we decided to install a chlorine atom which would hopefully be small enough to provide a stereoselective reduction of the β-ketone (scheme 97). Reaction of **3.66** with ammonium chloride and oxone afforded alpha-chloro ketone **3.79** in 66% yield. Treatment of **3.79** with excess of $NaBH_4$ afforded diol **3.80** in moderate yield. When only 0.95 equiv. of $NaBH_4$ were used, alpha-chloro ester **3.81** was the main product obtained, in 69% yield. We subjected **3.80** and **3.81** to the Suárez radical cyclization conditions and we found that

diol **3.80** afforded alkyl iodide **3.82** in moderate yield, whereas **3.81** provided a complex mixture of products resembling decomposition.



Scheme 97. α-chloro strategy.

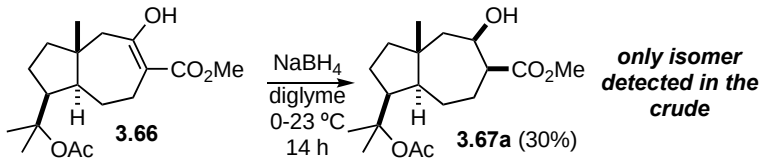
Product **3.82** is an intermediate of the Suárez radical cyclization, where the final alkylation has not taken place. We treated **3.82** with base in order to promote the cyclization but we obtained epoxide **3.83** instead (scheme 98). Attempts to convert **3.82** or **3.83** into the corresponding cyclized products **3.84** and **3.85** were not successful.



Scheme 98. Different attempts for the cyclization of **3.82**.

Thus, we decided to reconsider the stereoselective reduction of **3.66**. As reported by Brown, reduction with $NaBH_4$ can also take place in aprotic solvents such as diglyme.[150] The reaction in this solvent was much slower than in methanol but we found that **3.67a** was the only isomer detected by crude ^{1}H-NMR (scheme 99). Although the isolated yield was still low, this is a promising result for the stereoselective reduction of **3.66** and further optimization is needed for this step.

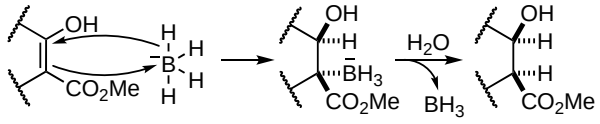
150. Reduction with NaBH4 in diglyme



Scheme 99. Stereoselective reduction of **3.66** in diglyme.

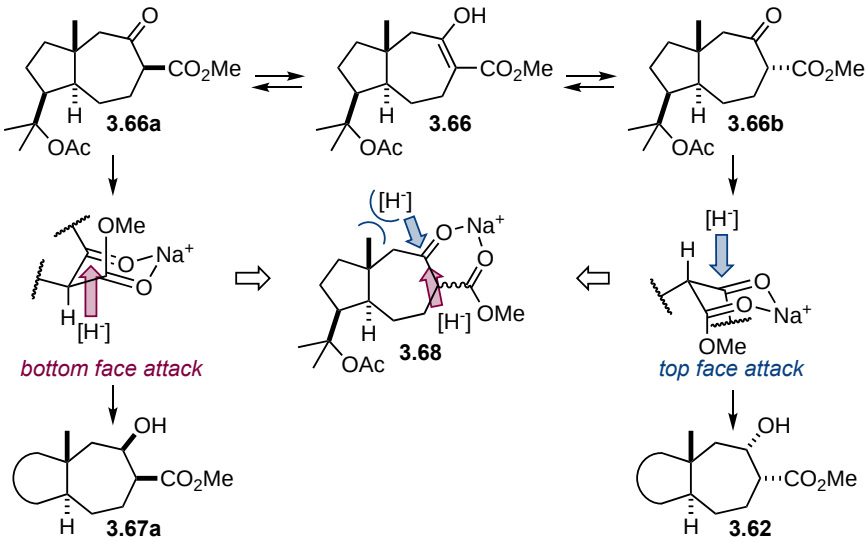
To explain the stereoselectivity of this reaction, we propose two possibilities:

In the first one, we hypothesized that the reduction of the enol tautomer would be favored (scheme 100). In this scenario, we proposed a very simplistic mechanism, where syn-addition of the borohydride anion to the double bond ans subsequent aqueous treatment would release borane and the corresponding β-hydroxy ester. Regarding the diastereoselectivity, given the planar character of the *trans*-bicyclic skeleton, the borohydride anion would set on the less hindered face of the substrate, thus attacking from the bottom and providing the secondary alcohol moiety with the desired stereochemistry.



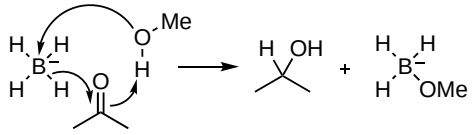
Scheme 100. Proposed mechanism for the syn formal H_2 addition.

In our second hypothesis, we propose that ketone tautomers **3.66a** and **3.66b** are the ones reacting (scheme 101). They are in equilibrium and thus the stereoselectivity of the reduction depends on the relative rate of reaction for each of them. For both **3.66a-b**, with a chelate model, we can predict that the hydride addition will take place from the same side as the axial hydrogen atom in the alpha carbon. And thus, the most favored pathway would lead to isomers **3.67a** and **3.62** from **3.66a** and **3.66b**, respectively. However, if we zoom out from the local chelate environment and consider the geometry of the whole molecule (**3.68**), the top face attack is hindered by the neighboring methyl group while there is no steric hindrance on the bottom face. This could explain a faster reaction profile for epimer **3.66a**, displacing the equilibrium of the starting materials towards **3.66a** and explaining the overall selectivity towards product **3.67a**.



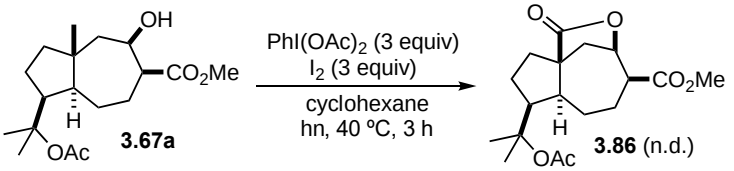
Scheme 101. Model to explain the stereoselectivity of the reduction of **3.66**.

In both proposed mechanisms, the difference in selectivity when performing the reaction in methanol or diglyme is attributed to a slower performance of the reducing agent, $NaBH_4$, in the latter. Although the precise role of methanol is difficult to define, it is accepted that it accelerates the reduction of carbonyl groups, for example, by concomitant protonation of the resulting alcohol moiety (scheme 102). Slower reaction with $NaBH_4$ allows isomers **3.66**, **3.66a** and **3.66b** to equilibrate while the most favored reduction takes place, providing higher stereoselectivity.



Scheme 102. Accelerating action of methanol in $NaBH_4$ reduction of carbonyl groups.

With **3.67a** in hand, we subjected it to Suárez radical cyclization excess of iodine and PIDA we found that the only product was **3.86** (scheme 103). The yield of the reaction was not determined due to the small scale of the reaction. However, we were able to crystallize **3.86** and analyze it by X-ray diffraction (figure 15).



Scheme 103. Over oxidizing Suárez radical cyclization of **3.67a**. n.d. = yield not determined.

We were very pleased to see that for the first time we were able to close ring C, although as a lactone instead of an ether.

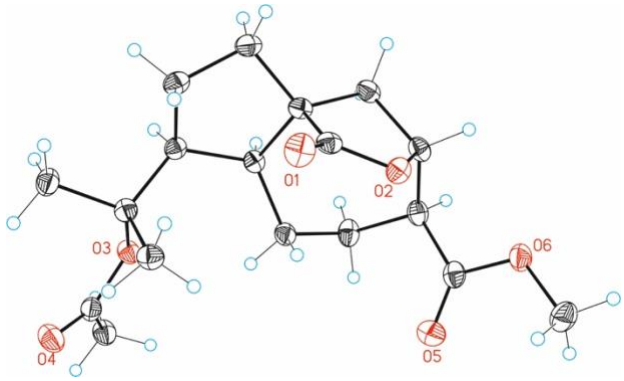
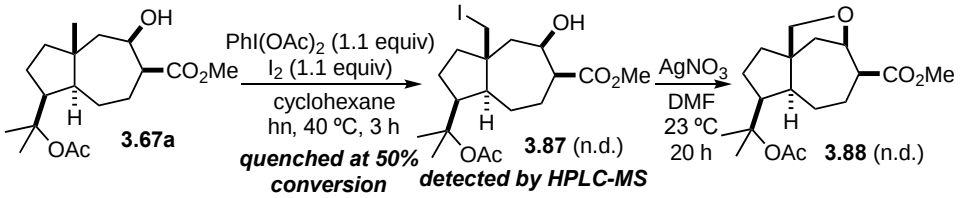


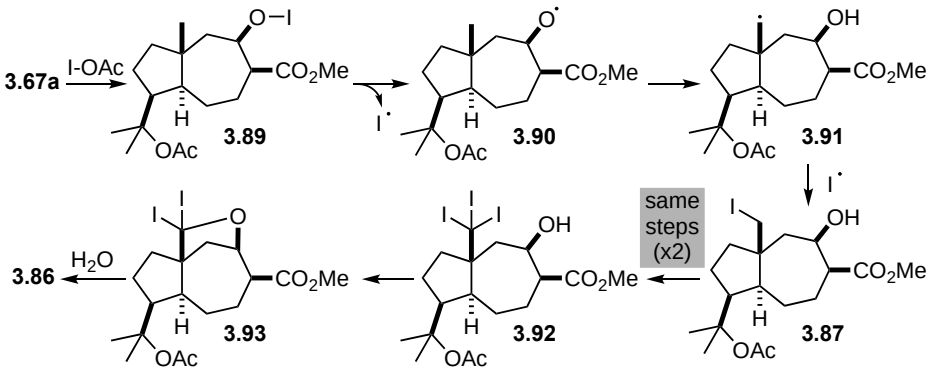
Figure 15. Representation of **3.86** obtained by x-ray diffraction analysis

When repeating the reaction with only one equivalent of iodine and PIDA (scheme 104), we detected the formation of intermediate **3.87** (by HPLC-MS and ^{1}H-NMR). However, after prolongation of time, **3.86** was starting to form, prior than full conversion of the starting material. Thus, we decided to stop the reaction at 50% conversion of **3.67a**, when only traces of **3.86** had been formed, and we treated the crude material with $AgNO_3$. We were able to isolate **3.88** and recovered starting material **3.67a**.



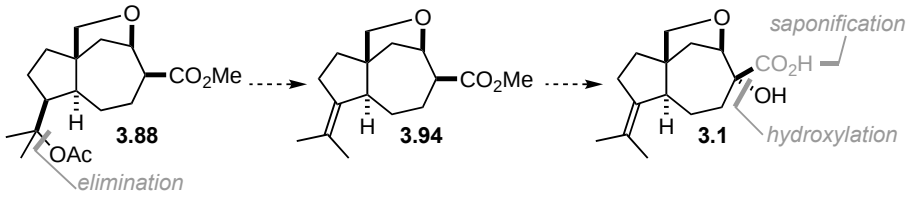
Scheme 104. Reaction of **3.67** with 1.1 equivalents of iodine and PIDA. n.d. = yield not determined.

Our hypothesis is that intermediate **3.87** can get iodinated again and suffer a second and a third HAT/iodination to form iodoform **3.92** (scheme 105). This very electrophilic carbon would then undergo intramolecular alkylation to form intermediate **3.93**, which would lead to lactone **3.86** by reaction with water.



Scheme 105. Proposed mechanism for the formation of **3.86** from **3.67a**.

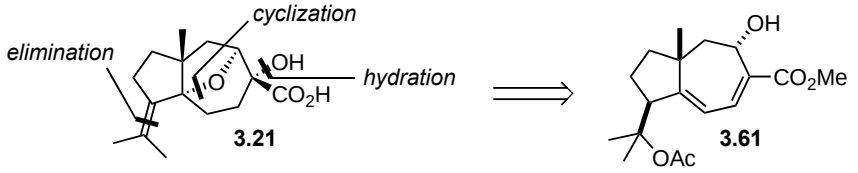
Further optimization of these steps is necessary in order to finish the synthesis of aspterric acid. However, we were able to obtain the tricyclic carbon skeleton of the natural product in compound **3.88**. From this synthetic intermediate, there are 3 conceptual steps left (scheme 106): elimination the acetate group, to give tetrasubstituted olefin **3.94**; hydroxylation at the alpha-position with respect to the methyl ester; and finally, saponification of the ester group to obtain the carboxylic acid-containing natural product (**3.1**).



Scheme 106. Missing steps for the synthesis of **3.1**.

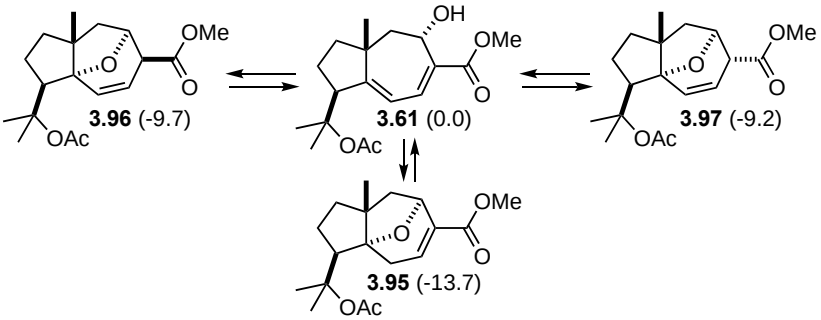
Towards the Total Synthesis of Penigrisacid A

In our studies towards aspterric acid, we came across structurally related sesquiterpenoid penigrisacid A (**3.21**). We proposed that its synthesis could be accomplished from product **3.61** (scheme 107), which is a synthetic intermediate on our approach towards aspterric acid.



Scheme 107. Proposed retrosynthesis of **3.21** from **3.61**.

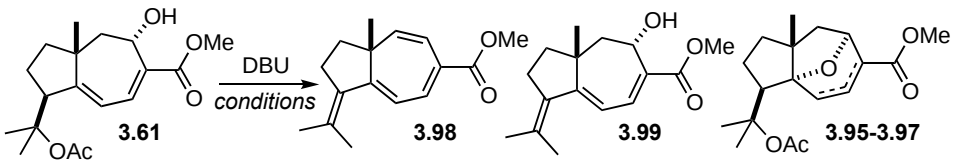
Our first strategy started with an intramolecular *oxa*-Michael addition to forge the oxygen bridged cycle (scheme 108). Based on ground state energy calculations, the thermodynamic product in an equilibrium environment would be tricyclic compound **3.95**, with a conjugated ester. The other two possible isomers **3.96** and **3.97**, containing the oxygen bridged system were at least 4 kcal/mol less stable, while open product **3.61** (the starting material) was more than 9 kcal/mol less stable than any of the tricyclic products.



Scheme 108. DFT calculations on the *oxa*-Michael cyclization of **3.61**. In brackets, energy values in kcal/mol at 25 ºC, 1 atm, in solution

Encouraged by the favoring energetic scenario found by DFT calculations, we performed the reaction in a basic media, with DBU, at different temperatures (table 26). While at room temperature no conversion was observed, elimination of the acetate group was achieved at higher temperatures (entries 2, 3), forming triene **3.99**, with concomitant elimination of the allylic alcohol moiety, leading to tetraene **3.98**. Weakly acidic conditions, such as wet TBAF or *p*TsOH, also lead to triene **3.99**.

Table 26. Attempts on the intramolecular *oxa*-Michael addition[a]

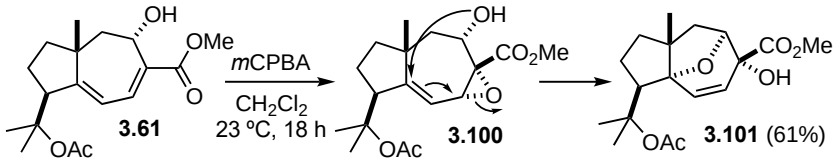


Entry	Temperature (ºC)	NMR ratio 3.61:3.98:3.99:3.95
1	23	1:0:0:0
2	80	0:1:2:0
4	100	0:1:0:0

[a.] The reactions were performed under argon, in dry toluene for 16 h.

Next we tried and epoxidation/S_N2' reaction sequence and we were pleased to find that **3.101** was formed in good yield (scheme 109). We found that this reaction was not reproducible, and depending on the batch we obtained mixtures of **3.101** with intermediate

epoxide **3.100**. Attempts to transform **3.100** into **3.101** under basic conditions failed so we moved to Bronsted-acidic conditions.[151]



Scheme 109. Tandem epoxidation/S_N2' reaction of **3.61**.

The structure and relative configuration of **3.101** was confirmed by X-ray diffraction analysis (figure 16).

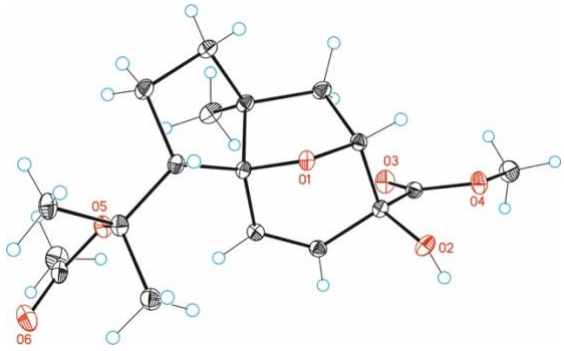
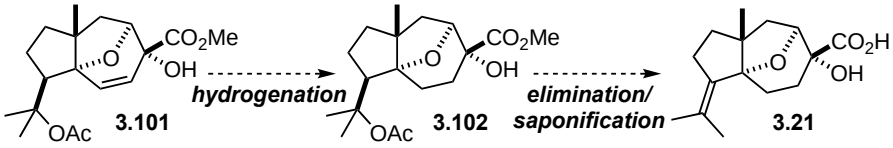


Figure 16. Representation of **3.101** obtained by x-ray diffraction analysis.

To accomplish the synthesis of penigrisacid A (**3.21**), we would need to reduce the double bond, to get to intermediate **3.102**, then eliminate the acetate group and saponificate the methyl ester to obtain the carboxylic acid moiety (scheme 110). The development of these steps is currently under study in our laboratories.

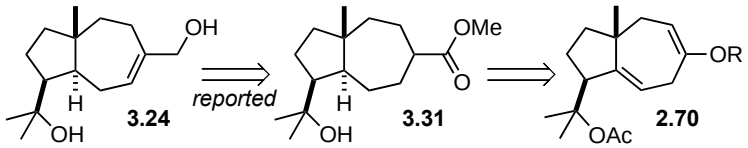


Scheme 110. Missing steps for the total synthesis of **3.21**.

151. The optimization of these conditions is currently under development in our laboratories by Dr. Anna Sadurní.

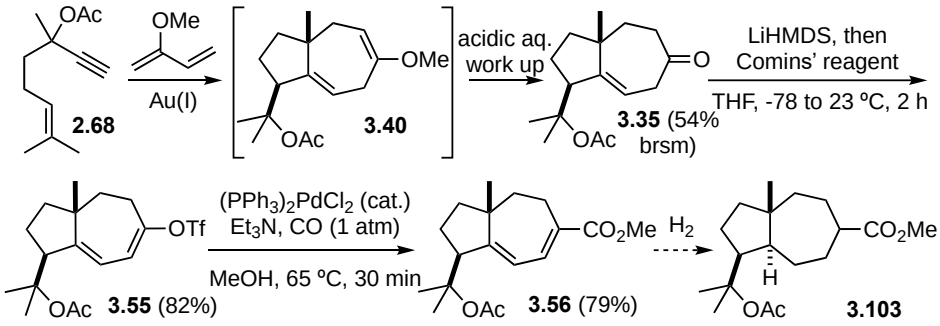
Towards the Formal Synthesis of Schisanwilsonene A

Lastly, we decided to apply our common strategy for a shorter synthesis of schisanwilsonene A (**3.24**), via reported intermediate **3.31** (scheme 111).



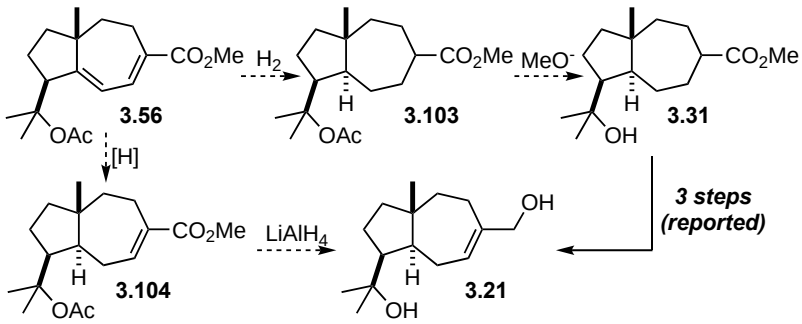
Scheme 111. Proposed retrosynthesis of **3.24** via **3.31**.

We started from ketone **3.35**, which can be obtained in moderate yield in a one pot strategy from the gold(I) catalysis step (scheme 112). Following the same strategy as for aspterric acid, we performed a two-step methoxycarbonylation to obtain **diene 3.56** from **3.35** in good yields. Preliminary results on the hydrogenation of **3.56** are promising and **3.103** could be detected as a ca 1:1 mixture of diastereomers. Further optimization on this step is still required and currently ongoing in our laboratories.



Scheme 112. Synthesis of **3.103** from **3.35**.

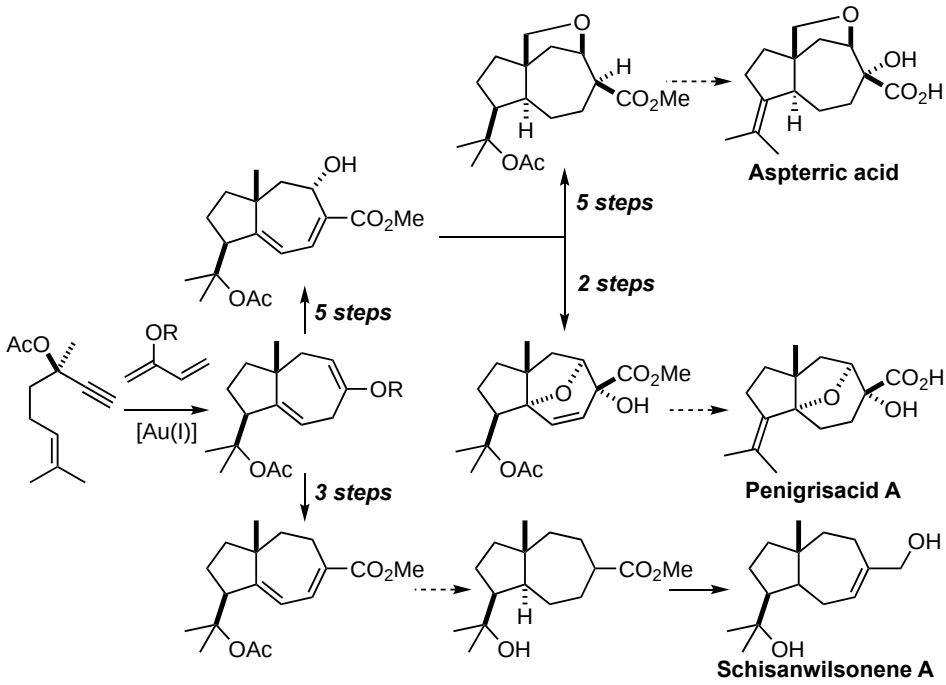
Reported compound **3.31** could be obtained from **3.56** after hydrogenation and acetate deprotection (scheme 113). In an alternative approach, partial reduction of diene **3.56** would provide product **3.104**, which after reduction of the two ester moieties would directly provide the diol natural product **3.21**. These two strategies are currently under study in our group.



Scheme 113. Future steps for the synthesis of schisanwilsonene A (**3.24**).

Conclusions

In this Chapter, we have applied our gold(I)-catalyzed cycloisomerization/(4+3)-cycloaddition methodology to a common strategy towards the syntheses of aspterric acid, penigrisacid A and schisanwilsonene A (scheme 114). The culmination of the three syntheses is currently under study in our laboratories.



Scheme 114. Summary of our advances towards the syntheses of different naturally-occurring daucanes.

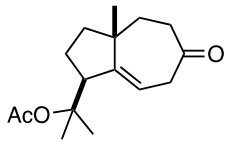
Experimental Section

Please refer to the experimental section of Chapter 1 for general information about the experimental procedures.

Synthetic Procedures and Characterization of Compounds

Towards the Total Synthesis of Aspterric Acid and Schisanwilsonene A

2-((1*S*,3a*R*)-3a-methyl-6-oxo-1,2,3,3a,4,5,6,7-octahydroazulen-1-yl)propan-2-yl acetate HA-6-064



To a solution of TIPS-enolate **2.70** (20 mg, 0.048 mmol) in THF (0.95 mL) at 0 ºC was added a solution of TBAF (95 μL, 1.0 M, 0.095 mmol, 2 equiv.) dropwise. The mixture was monitored by TLC and quenched with a saturated solution of $NaHCO_3$. The aqueous phase was extracted with EtOAc (x3) and the organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1) delivered the title compound (7.0 mg, 56% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (td, *J* = 6.1, 2.3 Hz, 1H), 3.32 – 3.19 (m, 2H), 3.11 – 3.03 (m, 1H), 2.67 – 2.53 (m, 2H), 1.97 (s, 3H), 1.93 – 1.80 (m, 2H), 1.79 – 1.72 (m, 1H), 1.52 – 1.48 (m, 3H), 1.48 (s, 3H), 1.41 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.2, 170.6, 151.7, 115.4, 85.1, 53.2, 46.3, 43.4, 40.9, 40.8, 35.8, 25.5, 25.2, 22.8 (2C), 22.7. **HRMS** (ESI+): m/z calc. for $[C_{16}H_{24}NaO_3]^+$: 287.1618, found: 287.1616.

The title compound was also prepared in a one-pot procedure from enyne **2.68** and diene **3.41**:

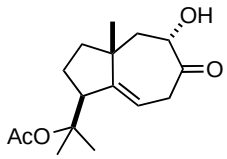
To a solution of complex **A** (25 mg, 0.032 mmol, 0.01 equiv.) and diene **3.41** (970 mg, 70%, 8.08 mmol, 2.5 equiv.) in anhydrous DCM (4.5 mL) at 0 ºC, was added enyne **2.68** (628 mg, 3.23 mmol) as a solution in DCM (2.0 mL), over 20 minutes. After the addition finished, it was stirred for 10 more minutes at 0 ºC, quenched with one drop of Et_3N and concentrated under reduced pressure to remove the excess of diene (note that with this procedure the conversion was <50%, so if repeating, longer reaction times and warming up to room temperature would be recommended, to achieve full conversion). The crude material was redissolved in DCM and transferred to a separatory funnel with an equal volume of aqueous HCl 10%, where it was vigorously agitated for 5 minutes (note a change of color). The layers were separated and the aqueous phase was extracted with DCM. The organic extracts were collected, washed with saturated aqueous $NaHCO_3$ (note a second change of color), dried over Na_2SO_4 and concentrated under reduced pressure. Purification

by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1) delivered the title compound (226 mg, 27% yield, 54% brsm) as a pale-yellow oil.

General procedure for the optimization of the oxidation of 2.70 and 3.40

To a solution of **2.70** or **3.40** in the corresponding solvent at 0 ºC was added *m*CPBA (1.1 equiv., >77% pure) as a solid. The resulting suspension was vigorously stirred at this temperature for 0.5-1 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$. The layers were separated, the aqueous phase was extracted with DCM or Et_2O (depending on the reaction solvent, x2) and the organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was analyzed by ^{1}H-NMR.

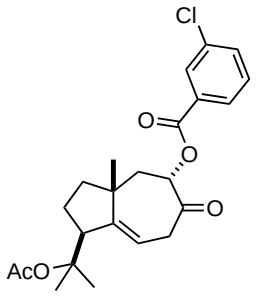
2-((1S,3aR,5S)-5-hydroxy-3a-methyl-6-oxo-1,2,3,3a,4,5,6,7-octahydroazulen-1-yl)propan-2-yl acetate (x)



From enyne **2.68** and diene **2.69**, large scale procedure: To a solution of diene **2.69** (17.9 g, 79 mmol, 2.5 equiv.) and complex **A** (0.155 g, 0.131 mmol, 0.004 mmol) in DCM (32 mL, 1.0 M) at room temperature, was added enyne **2.68** (6.15 g, 31.7 mmol), slowly (over 5 minutes). The reaction progress was monitored by GC-MS. After 2 h, since the progress was slower than usual, the reaction was cooled down to 0 ºC and complex **A** (0.101 g, 0.131 mmol, 0.004 mmol) was added carefully (note that the addition of catalyst is exothermic, so especial precaution may be taken to prevent the reacting solution from boiling out of the flask). After 5 minutes, the reaction was warmed up to room temperature again. This second addition of a gold (I) catalyst can be skipped if the reaction is progressing well, usually at least 50% conversion should be observed in the first 2 hours. After additional 2 h, the reaction was quenched by addition of 0.5 mL of TEA and concentrated under reduced pressure. The crude material was partially purified by column chromatography on silica gel (eluting first with 100% cyclohexane, to recover diene **2.69**, and then 30:1 cylohexane/EtOAc slowly increasing to 20:1). Unpure intermediate **2.70** was dissolved in methanol (130 mL) and cooled to 0 ºC in an ice bath. *m*CPBA (8.02 g, 1.1 equiv based on **2.68**) was added as a solid and the reaction was slowly warmed up to room temperature. The resulting solution was stirred for 1 to 3 h at this temperature and quenched by addition of saturated aqueous $Na_2S_2O_3$. The mixture was extracted with Et_2O (x3), and the organic extracts were collected, treated with aqueous 10 HCl% and washed with saturated aqueous $NaHCO_3$ (x2) or aqueous 10% NaOH. The last basic washings are to remove the excess of *meta*-chlorobenzoic acid present in the crude mixture. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 4:1) delivered the title compound (2.81 g, 32% yield) as a pale-yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dt, *J* = 10.0, 2.9 Hz, 1H), 4.52 (dd, *J* = 12.3, 5.6 Hz, 1H), 3.76 – 3.55 (m, 1H), 3.42 (dddd, *J* = 13.5, 4.0, 3.2, 0.7 Hz, 1H), 3.35 (s, 1H), 3.06 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.16 (dd, *J* = 13.3, 5.6 Hz, 1H), 2.06 – 1.99 (m, 1H), 1.98 (s, 3H), 1.81 – 1.72 (m, 1H), 1.71 – 1.62 (m, 1H), 1.51 (s, 3H), 1.50 – 1.40 (m, 2H), 1.39 (s, 3H), 1.29 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.2, 170.4, 153.7, 112.5, 85.0, 75.1, 53.4, 48.5, 43.8, 42.0, 39.7, 29.8, 26.0, 25.8, 21.7, 20.6 **HRMS** (ESI+): m/z calc. for $[C_{16}H_{24}NaO_4]^+$: 303.1567, found: 303.1580.

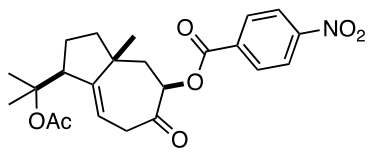
(1S,3aR,5S)-1-(2-acetoxypropan-2-yl)-3a-methyl-6-oxo-1,2,3,3a,4,5,6,7-octahydroazulen-5-yl 3-chlorobenzoate (HA-6-114)



To a suspension of Na_2HPO_4 (48 mg, 0.34 mmol, 1.1 equiv.) and methyl enol ether **3.40** (100 mg, 0.31 mmol, 85% pure) in dichloromethane (0.5 mL, HPLC grade) at 0 °C, was added dropwise a solution of *m*CPBA (58 mg, 0.34 mmol, 1.1 equiv., >77% pure) in dichloromethane (0.3 mL). The resulting solution was stirred for 15 min allowing it to warm to room temperature. The reaction was quenched with aqueous 10% NaOH and the layers were separated. The aqueous phase was extracted with EtOAc and the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1) delivered the title compound (46 mg, 36% yield) as a white solid. Single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation on DMC/hexane, at 4 ºC.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (t, *J* = 1.9 Hz, 1H), 7.96 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.54 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 5.80 (dt, *J* = 10.1, 3.0 Hz, 1H), 5.65 (dd, *J* = 12.9, 4.8 Hz, 1H), 3.51 (dt, *J* = 13.3, 3.8 Hz, 1H), 3.44 – 3.35 (m, 1H), 3.03 (dd, *J* = 13.4, 10.0 Hz, 1H), 2.19 (dd, *J* = 13.0, 4.7 Hz, 1H), 1.98 (s, 3H), 1.96 (d, *J* = 13.0 Hz, 1H), 1.84 – 1.77 (m, 1H), 1.75 – 1.69 (m, 1H), 1.61 – 1.54 (m, 1H), 1.52 (s, 3H), 1.51 – 1.46 (m, 1H), 1.40 (s, 3H), 1.36 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.6, 170.4, 164.6, 152.5, 134.7, 133.4, 131.5, 130.0, 129.9, 128.2, 113.6, 84.9, 77.6, 53.3, 44.4, 43.8, 42.1, 40.2, 26.1, 25.8, 22.9, 21.7, 21.1. **HRMS** (ESI+): m/z calc. for $[C_{23}H_{27}ClNaO_5]^+$: 441.1439, found: 441.1447.

(1S,3aR,5R)-1-(2-acetoxypropan-2-yl)-3a-methyl-6-oxo-1,2,3,3a,4,5,6,7-octahydroazulen-5-yl 4-nitrobenzoate (HA-6-154)

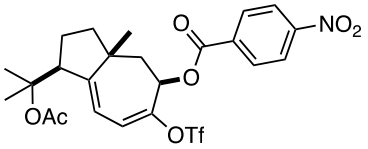


To a suspension of triphenylphosphine (210 mg, 0.803 mmol, 1.5 equiv.), *para*-nitrobenzoic acid (98 mg, 0.589 mmol, 1.1 equiv.) and **3.37** (150 mg, 0.535 mmol) in anhydrous THF (5.4 mL), under argon atmosphere and at 23 ºC, was added DEAD (318 μL, 0.803 mmol, 1.5 equiv., 40% pure)

dropwise. The reaction was stirred for 22 h at this temperature. The reaction was quenched by addition of water and extracted with Et_2O (x3). The organic extracts were collected, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1 to 5:1) delivered the title compound (103 mg, 45% yield) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 – 8.28 (m, 2H), 8.25 – 8.20 (m, 2H), 5.77 (dd, *J* = 6.4, 5.6 Hz, 1H), 5.69 (td, *J* = 5.8, 2.2 Hz, 1H), 3.37 – 3.27 (m, 3H), 2.38 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.24 (dd, *J* = 14.9, 6.5 Hz, 1H), 2.00 (s, 3H), 1.86 – 1.77 (m, 1H), 1.66 – 1.56 (m, 3H), 1.51 (s, 3H), 1.44 (s, 3H), 1.18 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.9, 170.5, 163.9, 151.4, 150.9, 135.3, 131.1, 123.7, 115.9, 84.9, 77.6, 53.2, 45.6, 41.3, 41.3, 40.8, 25.4, 25.2, 24.4, 22.9, 22.8. **HRMS** (ESI+): m/z calc. for $[C_{23}H_{27}NNaO_7]^+$: 452.1680, found: 452.1690. **Melting point** (EtOAc): 98-101 ºC.

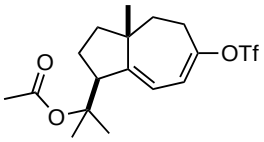
(1S,3aR,5R)-1-(2-acetoxypropan-2-yl)-3a-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,4,5-hexahydroazulen-5-yl 4-nitrobenzoate HA-6-155



To a solution of HMDS (18 μL, 0.084 mmol, 1.2 equiv.) in anhydrous THF (0.3 mL), under argon, at 0 ºC, in a Schlenk tube, was added nBuLi (34 μL, 0.084 mmol, 1.2 equiv.) dropwise. The solution was stirred for 5 minutes at room temperature and then cooled down to -78 ºC. Under argon, in a separate flask, **3.52** (30.0 mg, 0.070 mmol) was dissolved in 0.5 mL of anhydrous THF and the resulting solution was added to the lithiated species dropwise. The substrate's flask was rinsed with 0.2 mL of anhydrous THF and this solution was also added to the Schlenk tube. The resulting mixture was stirred at -78 ºC for 30 min. After this time, a solution of Comins' reagent (28.8 mg, 0.073 mmol, 1.05 equiv.) in anhydrous THF (0.4 mL + 0.1 mL for washing) was added dropwise. The mixture was stirred at -78 ºC for 20 minutes and then warmed up to room temperature and further stirred for 1 h. The reaction was quenched with water and extracted with Et_2O (x2). The organic extracts were collected, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 15:1 to 10:1) delivered the title compound (29.7 mg, 76% yield) as a pale-yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 – 8.29 (m, 2H), 8.27 – 8.22 (m, 2H), 6.29 (d, *J* = 8.7 Hz, 1H), 6.13 – 6.05 (m, 1H), 5.95 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.62 (t, *J* = 9.0 Hz, 1H), 2.30 (dd, *J* = 16.0, 2.5 Hz, 1H), 2.08 – 2.02 (m, 1H), 2.03 (s, 3H), 1.88 – 1.81 (m, 1H), 1.66 – 1.58 (m, 1H), 1.55 (s, 3H), 1.54 – 1.51 (m, 1H), 1.43 (s, 3H), 1.23 (s, 3H). **^{19}F NMR** (471 MHz, $CDCl_3$) δ -74.8. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.4, 163.6, 163.1, 150.9, 146.2, 134.9, 131.3, 123.8, 122.7, 112.0, 84.8, 71.8, 53.4, 46.6, 41.3, 40.7, 26.1, 25.7, 22.7, 22.0, 19.4 (missing *C*F_3). **HRMS** (ESI+): m/z calc. for $[C_{24}H_{26}F_3NNaO_9S]^+$: 584.1173, found: 584.1178. **Melting point** (EtOAc): 140-142 ºC.

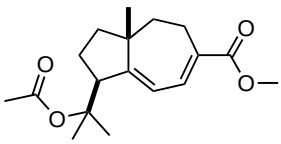
2-((1*S*,3a*R*)-3a-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,4,5-hexahydroazulen-1-yl)propan-2-yl acetate HA-6-390



In a Schlenk tube, HMDS (19 μL, 0.091 mmol, 1.2 equiv.) was dissolved in dry THF (0.3 mL), under argon. The solution was cooled to 0 ºC and *n*BuLi (36 μL, 2.5 M, 0.091 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred for 5 minutes at this temperature and then cooled to -78 ºC. In a separate flask, under argon, **3.35** (20 mg, 0.076 mmol) was dissolved in dry THF (0.5 mL) and the resulting solution was added to the freshly prepared LiHMDS dropwise. Additional THF (0.2 mL) was used to wash the substrate flask and this solution was also added to the LiHMDS mixture. The reaction was stirred for 30 min at -78 ºC. After this time, Comins' reagent (31 mg, 0.079 mmol, 1.05 equiv.) in anhydrous THF (0.4 mL + 0.1 mL for washing) was added dropwise. The mixture was stirred at -78 ºC for 20 minutes and then warmed up to room temperature and further stirred for 1 h. The reaction was quenched with water/brine 1:1 and extracted with Et_2O (x3). The organic extracts were collected, dried over Na_2SO_4 and concentrated. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 20:1) delivered the title compound (24.5 mg, 82% yield) as a pale-yellow oil. The product was used immediately in the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.79 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.53 – 3.41 (m, 1H), 2.83 – 2.67 (m, 1H), 2.62 (d, *J* = 19.4 Hz, 1H), 2.01 (s, 3H), 1.86 – 1.75 (m, 1H), 1.68 (ddd, *J* = 13.9, 5.9, 3.0 Hz, 1H), 1.61 – 1.55 (m, 2H), 1.55 – 1.48 (m, 4H), 1.39 (s, 3H), 0.94 (s, 3H).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.80. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.5, 159.8, 151.4, 117.8, 112.2, 85.1, 53.3, 46.4, 40.5, 33.1, 30.2, 26.3, 25.6, 22.9, 22.1, 20.1, (missing *C*F_3).

methyl (1*S*,3a*R*)-1-(2-acetoxypropan-2-yl)-3a-methyl-1,2,3,3a,4,5-hexahydroazulene-6-carboxylate HA-6-435/HA-6-439-b (sm)

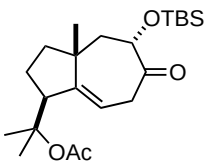


To a solution of trifluoromethanesulfonate **3.55** (24.5 mg, 0.062 mmol) in methanol (0.6 mL, HPLC grade), under air, at room temperatura, was added TEA (10 μL, 0.074 mmol, 1.2 equiv.) and $PdCl_2(PPh_3)_2$ (4.3 mg, 0.006 mmol, 0.1 equiv.). The flask was connected to a reflux condenser and the atmosphere was changed to CO (1 atm, balloon). The solution was heated to 65 ºC for 30 min then was cooled to room temperature and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 20:1) delivered the title compound (14.9 mg, 79% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (ddt, *J* = 8.3, 2.8, 0.9 Hz, 1H), 6.04 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.74 (s, 3H), 3.50 (t, *J* = 9.6 Hz, 1H), 2.77 (d, *J* = 20.4 Hz, 1H), 2.58 – 2.43 (m,

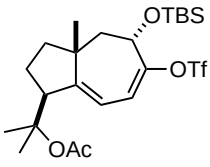
1H), 2.00 (s, 3H), 1.85 – 1.76 (m, 1H), 1.73 (ddd, *J* = 13.6, 5.2, 3.3 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.51 (s, 3H), 1.50 – 1.41 (m, 2H), 1.39 (s, 3H), 0.90 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.5, 169.5, 164.4, 133.2, 131.5, 116.6, 85.1, 53.6, 52.0, 47.5, 40.5, 35.1, 26.6, 26.6, 25.5, 22.9, 22.4, 21.4. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{26}NaO_4]^+$: 329.1723, found: 329.1716.

2-((1S,3aR,5S)-5-((tert-butyldimethylsilyl)oxy)-3a-methyl-6-oxo-1,2,3,3a,4,5,6,7-octahydroazulen-1-yl)propan-2-yl acetate HA-6-178 / 214 for NMR



To a solution of **3.37** (641 mg, 2.29 mmol) in a mixture of anhydrous DCM (10 mL) and DMF (1 mL) at 0 ºC, under argon, was added imidazole (202 mg, 2.97 mmol, 1.3 equiv.) and TBSCl (448 mg, 2.97 mmol, 1.3 equiv.), both as solids. The resulting mixture was allowed to warm up to room temperature and it was stirred for 18 – 24 h. The reaction was quenched by addition of saturated aqueous NH4Cl and extracted with DCM (x3). The organic extracts were collected, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 20:1) delivered the title compound (665 mg, 74% yield) as a colorless oil (note that in the fridge it can become a solid with low melting point).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (ddd, *J* = 7.6, 5.1, 2.5 Hz, 1H), 4.45 (dd, *J* = 11.4, 5.6 Hz, 1H), 3.33 – 3.21 (m, 1H), 3.20 – 3.05 (m, 2H), 2.00 (dd, *J* = 13.5, 5.6 Hz, 1H), 1.97 (s, 3H), 1.79 – 1.67 (m, 2H), 1.64 – 1.55 (m, 1H), 1.48 (s, 3H), 1.47 – 1.44 (m, 2H), 1.39 (s, 3H), 1.17 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 206.3, 170.4, 151.9, 115.0, 85.0, 76.7, 53.3, 48.3, 44.4, 42.1, 40.0, 25.9 (x3*C*), 25.7, 25.5, 22.9, 22.1, 21.3, 18.6, -4.5, -5.0. **HRMS** (ESI+): m/z calc. for $[C_{22}H_{38}NaO_4Si]^+$: 417.2432, found: 417.2428.

2-((1S,3aR,5S)-5-((tert-butyldimethylsilyl)oxy)-3a-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-1,2,3,3a,4,5-hexahydroazulen-1-yl)propan-2-yl acetate HA-6-179

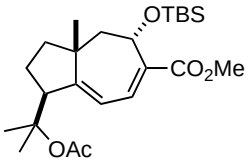


To a solution of HMDS (128 µL, 0.610 mmol, 1.2 equiv.) in dry THF (2.0 mL), under argon, at 0 ºC, was added *n*BuLi (0.24 mL, 2.5 M, 0.610 mmol, 1.2 equiv.) and the mixture was stirred for 10 minutes at this temperature. Then it was cooled to -78 ºC and a solution of **3.58** (200.5 mg, 0.508 mmol) in anhydrous THF (2.0 mL + 0.5 mL (x2) as washing solutions) was added dropwise. The resulting solution was stirred for 30 min at -78ºC, after which time a solution of Comins' reagent (209 mg, 0.533 mmol, 1.05 equiv.) in THF (2.0 mL + 0.5 mL (x2) as washing solutions) was added dropwise. The mixture was stirred for 30 min at -78ºC then slowly warmed up to 23 ºC over 1 h. The reaction was quenched with a mixture of water/brine (1:1) and extracted with Et_2O (x3).

The organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 50:1) delivered the title compound (159.5 mg, 60% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (d, *J* = 8.5 Hz, 1H), 5.76 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.59 (dd, *J* = 10.9, 7.1 Hz, 1H), 3.47 (br t, *J* = 9.1 Hz, 1H), 2.00 (s, 3H), 1.94 – 1.77 (m, 3H), 1.62 – 1.58 (m, 1H), 1.51 (s, 3H), 1.49 – 1.43 (m, 2H), 1.37 (s, 3H), 1.03 (s, 3H), 0.90 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -73.5. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 160.9, 151.1, 118.1, 112.4, 84.8, 69.2, 53.0, 44.0, 43.8, 40.7, 26.0, 25.9, 25.6, 22.8, 22.1, 19.2, 18.2, -4.3, -4.4. **HRMS** (ESI+): m/z calc. for $[C_{23}H_{37}F_3NaO_6SSi]^+$: 549.1924, found: 549.1940.

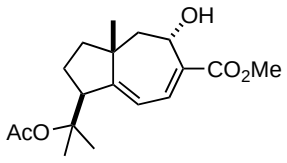
Methyl (1S,3aR,5S)-1-(2-acetoxypropan-2-yl)-5-((tert-butyldimethylsilyl)oxy)-3a-methyl-1,2,3,3a,4,5-hexahydroazulene-6-carboxylate



Trifluoromethanesulfonate **3.59** (39 mg, 0.074 mmol) was dissolved in methanol (0.7 mL, HPLC grade), under air, at room temperature. TEA (12 μL, 0.089 mmol, 1.2 equiv.) and $PdCl_2(PPh_3)_2$ (5.2 mg, 7.4 μmol, 0.1 equiv.) were added and the atmosphere was changed to CO (1 atm, balloon). The resulting solution was heated to 65 ºC (reflux) for 30 min, then it was cooled to room temperature and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 30:1) delivered the title compound (28 mg, 85% yield) as a pale-yellow solid. (Note: 0.05 equiv. of catalyst can be used, extending the reaction time to 1 h.)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (dt, *J* = 8.0, 1.2 Hz, 1H), 5.91 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.91 (dd, *J* = 11.3, 6.7 Hz, 1H), 3.72 (s, 3H), 3.48 (t, *J* = 8.9 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.99 (s, 3H), 1.90 (dd, *J* = 13.4, 6.8 Hz, 1H), 1.56 – 1.42 (m, 4H), 1.50 (s, 3H), 1.36 (s, 3H), 1.02 (s, 3H), 0.84 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 169.5, 163.3, 136.1, 130.6, 116.3, 84.8, 68.2, 53.2, 51.8, 46.4, 43.9, 40.8, 26.3, 26.0, 25.5, 22.8, 22.2, 19.3, 18.2, -4.1, -4.6. **HRMS** (ESI+): m/z calc. for $[C_{24}H_{40}NaO_5Si]^+$: 459.2537, found: 459.2540. **Melting point** (EtOAc): 87-89 ºC.

Methyl (1S,3aR,5S)-1-(2-acetoxypropan-2-yl)-5-hydroxy-3a-methyl-1,2,3,3a,4,5-hexahydroazulene-6-carboxylate

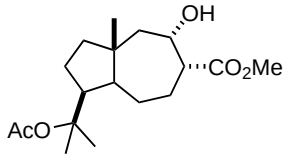


Silyl ether **3.60** (210 mg, 0.481 mmol) was dissolved in a mixture of DCM/methanol (9.6 mL, 1:1, both HPLC grade), at room temperature, under air. CSA (123 mg, 0.529 mmol, 1.1 equiv.) was added as a solid and the mixture was stirred for 1.5 h at this temperature. The progress was monitored by TLC (SiO_2, 5:1 cyclohexane/EtOAc). After this time, the reaction was quenched by addition of a saturated solution of $NaHCO_3$ and extracted with DCM (x3). The organic extracts were collected, dried over Na_2SO_4 and

concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 4:1 to 3:1) delivered the title compound (150.9 mg, 97% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.3 Hz, 1H), 5.99 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.78 (dd, *J* = 11.7, 6.1 Hz, 1H), 3.79 (s, 3H), 3.51 (t, *J* = 9.1 Hz, 1H), 2.04 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.01 (s, 3H), 1.93 (dd, *J* = 13.4, 11.7 Hz, 1H), 1.88 – 1.81 (m, 1H), 1.59 (dt, *J* = 8.6, 4.1 Hz, 1H), 1.53 – 1.48 (m, 2H), 1.51 (s, 3 H), 1.38 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.4, 169.6, 166.6, 133.9, 132.1, 116.4, 84.8, 66.9, 53.6, 52.2, 44.5, 43.8, 40.5, 26.2, 25.5, 22.8, 22.3, 20.2. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{26}NaO_5]^+$: 345.1672, found: 345.1681.

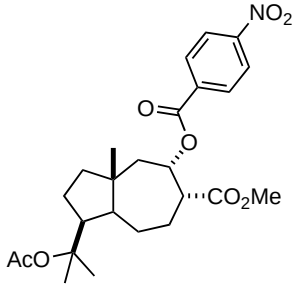
methyl (1S,3aR,5S,6R)-1-(2-acetoxypropan-2-yl)-5-hydroxy-3a-methyldecahydroazulene-6-carboxylate HA-6-183-A 238 for NMR



To an autoclave reactor was added a solution of diene **3.61** (196 mg, 0.608 mmol) in EtOAc (7.0 mL, HPLC grade) and PtO_2 (6.9 mg, 0.030 mmol, 0.05 equiv.), under air. The reactor was sealed, the atmosphere was changed to 20 bar of hydrogen and the mixture was stirred at 800 rpm, at 25 ºC, during 16 h. After this time, the solution was filtered through Celite and concentrated under reduced pressure. The internal standard, trichloroethene (82.4 mg, 0.627 mmol, 1.03 equiv.) was added and the mixture was dissolved in $CDCl_3$ to measure the NMR yield: full conversion, 78 % NMR yield of the desired product + 6% of side product (presumably a partially hydrogenated product). The product was used without further purification because we found that the isolated yield was much lower, indicating it decomposed or got stuck in the column.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (ddd, *J* = 10.5, 5.7, 3.9 Hz, 1H), 3.74 (s, 3H), 2.98 – 2.90 (m, 1H), 2.60 (td, *J* = 11.1, 8.4 Hz, 1H), 2.20 – 2.02 (m, 3H), 1.97 (s, 3H), 1.88 – 1.73 (m, 2H), 1.71 – 1.60 (m, 2H), 1.58 – 1.50 (m, 5H), 1.46 (s, 3H), 1.45 – 1.42 (m, 1H), 1.30 (td, *J* = 12.7, 6.8 Hz, 1H), 0.97 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.6, 170.4, 85.1, 71.3, 52.0, 51.8, 49.5, 49.3, 48.6, 43.0, 42.9, 27.5, 26.9, 25.5, 24.8, 24.6, 22.9, 20.0. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{30}NaO_5]^+$: 349.1985, found: 349.1970.

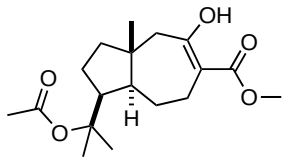
methyl (1S,3aR,5S,6R)-1-(2-acetoxypropan-2-yl)-3a-methyl-5-((4-nitrobenzoyl)oxy)decahydroazulene-6-carboxylate HA-6-189



To a solution of **3.62** (7.0 mg, 0.021 mmol), DMAP (0.8 mg, 0.006 mmol, 0.3 equiv.) and TEA (8.7 mg, 0.086 mmol, 4.0 equiv.) in anhydrous DCM (0.42 mL), under argon, at room temperature, was added 4-nitrobenzoyl chloride (8.0 mg, 0.043 mmol, 2.0 equiv.). The reaction was stirred at room temperature for 6 h and quenched by addition of water. The layers were separated and the aqueous phase was extracted with DCM (x2). The organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 4:1 to 3:1) delivered the title compound (3.2 mg, 32% yield) as a yellow solid. Slow evaporation from cyclohexane/acetonitrile afforded crystals suitable for single crystal X-ray diffraction analysis.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 – 8.24 (m, 2H), 8.18 – 8.13 (m, 2H), 5.59 (ddd, *J* = 9.8, 6.7, 4.8 Hz, 1H), 3.58 (s, 3H), 3.09 (ddd, *J* = 10.1, 4.8, 1.7 Hz, 1H), 2.66 (q, *J* = 10.1 Hz, 1H), 2.37 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.19 – 2.11 (m, 1H), 1.99 (s, 3H), 1.98 – 1.91 (m, 2H), 1.79 – 1.68 (m, 2H), 1.65 – 1.56 (m, 2H), 1.54 (s, 3H), 1.52 – 1.42 (m, 2H), 1.48 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.1, 170.4, 163.8, 150.8, 135.9, 130.9, 123.7, 85.2, 74.7, 52.9, 51.9, 51.4, 48.1, 45.3, 43.1, 42.6, 27.3, 26.7, 26.1, 25.7, 25.3, 22.9, 19.7.

methyl (3S,3aS,8aR)-3-(2-acetoxypropan-2-yl)-7-hydroxy-8a-methyl-1,2,3,3a,4,5,8,8a-octahydroazulene-6-carboxylate HA-6-233/468

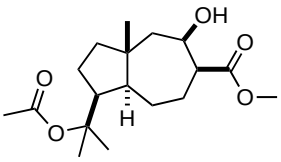


To a solution of **3.62** (13 mg, 0.040 mmol) in DCM (0.4 mL, HPLC grade), under air, at 0 ºC, was added DMP (20 mg, 0.048 mmol, 1.2 equiv.). The mixture was stirred at this temperature for 15 minutes and the reaction was quenched by addition of an aqueous solution of NaOH 10%. The layers were separated and the aqueous phase was extracted with DCM (x2). The organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure, to yield the title compound (13 mg, 100% yield) as a colorless oil. The product was used in latter steps without further purification nor characterization. In $CDCl_3$, at 25 ºC, it was a mixture of tautomers in a 6:2.5:1 ratio, being enol **3.66** the main component and ketones **3.66a** and **3.66b** the other isomers, according to ^{1}H-NMR and. Some ^{1}H NMR signals of the different isomers could be assigned.

^{1}H NMR (500 MHz, $CDCl_3$) δ 12.82 (s, 1H, **enol**), 3.76 (s, 3H, **enol**), 3.71 (s, 3H **3.66a** or **3.66b** minor isomer), 3.71 (s, 3H, **3.66a** or **3.66b**, major isomer), 3.49 (dd, *J* = 9.8, 3.4 Hz, 1H, **3.66a** or **3.66b**, minor isomer), 3.43 (dd, *J* = 12.4, 3.1 Hz, 1H, **3.66a** or **3.66b**, major isomer), 2.95 (ddd, *J* = 15.4, 6.7, 1.7 Hz, 1H, **enol**), 2.77 – 2.68 (m, 1H, overlap), 2.64 –

2.57 (m, 1H, overlap), 2.42 – 2.33 (m, 2H, overlap), 2.17 (dt, *J* = 6.6, 2.5 Hz, 1H, , **3.66a** or **3.66b**, minor isomer), 2.16 – 2.13 (m, 1H, , **3.66a** or **3.66b**, minor isomer), 2.09 (ddd, *J* = 7.0, 3.0, 1.9 Hz, 1H, **3.66a** or **3.66b**, major isomer), 2.06 (dt, *J* = 4.5, 2.0 Hz, 1H, **3.66a** or **3.66b**, major isomer), 2.05 – 2.00 (m, 2H, overlap), 1.98 (s, 3H, **3.66a** or **3.66b**, minor isomer), 1.97 (s, 3H, **3.66a** or **3.66b**, major isomer), 1.96 (s, 3H, **enol**), 1.88 – 1.80 (m, 2H, overlap), 1.80 – 1.74 (m, 2H, overlap), 1.72 – 1.63 (m, 1H, overlap), 1.55 (s, 3H, **3.66a** or **3.66b**, minor isomer), 1.54 (s, 3H, **3.66a** or **3.66b**, major isomer), 1.50 (s, 3H, **enol**), 1.48 (s, 3H, **3.66a** or **3.66b**, minor isomer), 1.47 (s, 3H, **3.66a** or **3.66b**, major isomer), 1.43 (s, 3H, **enol**), 1.42 – 1.35 (m, 2H, overlap), 1.03 (s, 3H, **3.66a** or **3.66b**, minor isomer), 0.97 (s, 3H, **3.66a** or **3.66b**, major isomer), 0.90 (s, 3H, **enol**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.1, 207.1, 177.3, 173.6, 171.4, 170.5, 170.4, 100.3, 85.5, 85.2, 84.8, 59.9, 57.6, 57.5, 56.7, 56.4, 54.9, 52.4, 52.4, 51.7, 51.1, 51.0, 49.7, 48.9, 42.7, 41.7, 41.6, 41.6, 40.9, 40.5, 29.8, 27.2, 27.0, 27.0, 26.9, 26.3, 26.2, 26.1, 25.2, 25.2, 24.9, 23.4, 23.0, 22.9, 22.9, 20.8, 20.5, 18.2.

methyl (1*S*,3a*R*,5*R*,6*S*,8a*S*)-1-(2-acetoxypropan-2-yl)-5-hydroxy-3a-methyldecahydroazulene-6-carboxylate HA-6-234-Col1/HA-6-497



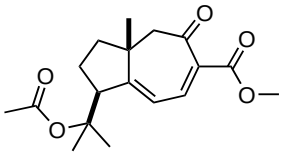
To a solution of **3.66** (13 mg, 0.040 mmol) in methanol (0.8 mL, HPLC grade), at 0 ºC, under air, was added $NaBH_4$ (3.0 mg, 0.080 mmol, 2.0 equiv.). The mixture was stirred for 20 minutes at 0 ºC and 20 more minutes at room temperature. After this time, the reaction was diluted with water/brine 1:1, quenched with a drop of acetone and extracted with DCM (x3). The organic extracts were collected, dried over Na_2SO_4, and concentrated under reduced pressure. By crude NMR we could determine a 1.0:1.1:1.3 ratio of isomers **3.67a**/**3.62**/unknown. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 3:1) delivered the title compound (1,6 mg, 12% yield) as a colorless oil (first fraction) and a mixture of **3.62** and the unknown isomer (second fraction). The relative configuration of the title compound was assigned by ^{1}H-NOE experiments and by comparison with its isomer **3.62**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (br s, 1H), 3.70 (s, 3H), 2.70 (dt, *J* = 11.2, 1.3 Hz, 1H), 2.61 (tt, *J* = 10.8, 8.6 Hz, 1H), 2.46 – 2.30 (m, 1H), 2.10 (dd, *J* = 14.7, 3.1 Hz, 1H), 2.07 – 2.00 (m, 1H), 1.99 (s, 3H), 1.92 – 1.79 (m, 1H), 1.74 – 1.57 (m, 4H), 1.56 (s, 3H), 1.49 (s, 3H), 1.45 (dd, *J* = 10.9, 4.8 Hz, 1H), 1.27 (dd, *J* = 14.4, 4.5 Hz, 1H), 1.22 (s, 1H), 1.13 (s, 3H). MASS UPLC

The title compound could also be prepared in a diastereoselective manner, following a similar procedure: To a solution of **3.66** (24.2 mg, 0.0746 mmol) in diglyme (0.75 mL, HPLC grade), at 0 ºC, under air, was added $NaBH_4$ (2.9 mg, 0.077 mmol, 1.0 equiv.). The mixture was stirred for 10 minutes at 0 ºC and warmed up to room temperature. The reaction was stirred overnight. After this time, the reaction was carefully quenched with acetone and

diluted with water. Then it was extracted with EtOAc (x3) and the organic extracts were collected, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 3:1) delivered the title compound (7.2 mg, 30% yield) as a colorless oil, as a single diastereomer.

methyl (1S,3aR)-1-(2-acetoxypropan-2-yl)-3a-methyl-5-oxo-1,2,3,3a,4,5-hexahydroazulene-6-carboxylate HA-6-221

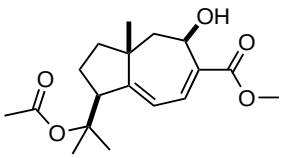


To a solution of **3.61** (60 mg, 0.19 mmol) in DCM (1.9 mL, HPLC grade), under air, at 0 ºC, was added DMP (95 mg, 0.22 mmol, 1.2 equiv.). The mixture was stirred at this temperature for 15 minutes and the reaction was quenched by addition of an aqueous solution of NaOH 10%. The layers were separated and the aqueous phase was extracted with DCM (x2). The organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure, to yield the title compound (54 mg, 91% yield) as a bright-yellow solid. The product was used in latter steps without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.6, 0.9 Hz, 1H), 6.28 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.81 (s, 3H), 3.66 (t, *J* = 8.9 Hz, 1H), 2.79 (d, *J* = 13.3 Hz, 1H), 2.56 (d, *J* = 13.3 Hz, 1H), 2.03 (s, 3H), 1.99 – 1.89 (m, 1H), 1.72 – 1.58 (m, 3H), 1.55 (s, 3H), 1.40 (s, 3H), 0.97 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.4, 172.2, 170.4, 167.5, 141.4, 131.7, 117.6, 84.5, 53.9, 52.5, 51.6, 43.6, 39.6, 26.2, 25.6, 22.8, 22.5, 18.8. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{24}NaO_5]^+$: 343.1516, found: 343.1512.

methyl (1*S*,3a*R*,5*R*)-1-(2-acetoxypropan-2-yl)-5-hydroxy-3a-methyl-1,2,3,3a,4,5-hexahydroazulene-6-carboxylate

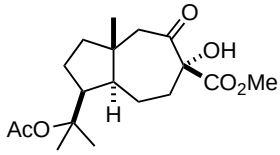
To a solution of **3.68** (20 mg, 0.062 mmol) in methanol (1.2 mL, HPLC grade) at room temperature was added $CeCl_3 \cdot 7H_2O$ (26 mg, 0.069 mmol, 1.1 equiv.). The mixture was cooled down to 0 ºC and $NaBH_4$ added as a solid. After 5 minutes, the reaction was quenched with water and extracted with DCM (x2). The organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 4:1) delivered the title compound (5.6 mg, 28% yield) as a pale-yellow oil. The product was characterized by NMR and its relative configuration was assigned by comparison. The other fractions of the column contained **3.61** and other over-reduced products.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dt, *J* = 8.3, 0.7 Hz, 1H), 6.06 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.74 (s, 1H), 3.80 (s, 3H), 3.59 (t, *J* = 9.2 Hz, 1H), 2.27 (dd, *J* = 15.0, 2.4 Hz, 1H), 2.01 (s, 3H), 1.85 – 1.79 (m, 1H), 1.79 (dd, *J* = 14.9, 4.8 Hz, 1H), 1.65 (q, *J* = 4.8 Hz, 1H), 1.61 – 1.50 (m, 2H), 1.53 (s, 3H), 1.40 (s, 3H), 1.15 (s, 3H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ 170.4, 169.8, 168.2, 134.7, 132.5, 116.0, 85.0, 68.1, 53.8, 52.2, 47.9, 44.0, 41.0, 26.5, 25.7, 22.8, 22.2, 20.2.

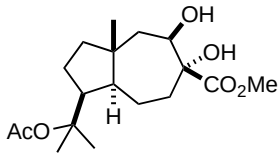
methyl (1*S*,3a*R*,6*R*,8a*S*)-1-(2-acetoxypropan-2-yl)-6-hydroxy-3a-methyl-5-oxodecahydroazulene-6-carboxylate HA-6-248/HA-6-376 check



In a conical MW vial were placed Cs_2CO_3 (5.3 mg, 0.016 mmol, 0.2 equiv.), $P(OEt)_3$ (27.2 mg, 0.164 mmol, 2.0 equiv.) and **3.66** (26.6 mg, 0.082 mmol), under air. DMSO (0.4 mL, HPLC grade) was added and the vial was sealed. The atmosphere was changed to O_2 (1 atm, balloon) and the mixture was vigorously stirred for 18 h – 24 h. After this time, the solution was then diluted with ethyl acetate and washed with brine. The aqueous phase was extracted with ethyl acetate (x2) and the organic extracts were collected, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 4:1 to 3:1) delivered the title compound (16.4 mg, 59% yield, 5:1 *dr*) as a colorless oil. The signals of the major isomer could be assigned by ^{1}H and ^{13}C-NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (br s, 1H), 3.75 (s, 3H), 2.99 (d, J = 12.6 Hz, 1H), 2.67 – 2.56 (m, 2H), 2.39 (q, J = 9.7, 9.3 Hz, 1H), 2.23 – 2.14 (m, 1H), 2.07 (ddd, J = 15.0, 6.1, 2.3 Hz, 1H), 1.98 (s, 3H), 1.93 (dd, J = 10.7, 4.3 Hz, 1H), 1.88 (ddd, J = 13.0, 5.6, 2.3 Hz, 1H), 1.79 – 1.73 (m, 1H), 1.55 (s, 3H), 1.55 – 1.49 (m, 3H), 1.47 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.5, 171.7, 170.3, 84.4, 81.7, 53.4, 51.5, 50.7, 46.4, 42.9, 41.4, 31.5, 27.0, 26.6, 25.3, 22.8, 22.2, 21.9. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{28}NaO_6]^+$: 363.1778, found: 363.1780.

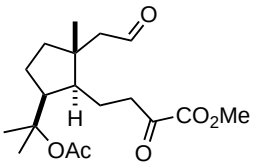
methyl (1S,3aR,5R,6R,8aS)-1-(2-acetoxypropan-2-yl)-5,6-dihydroxy-3a-methyldecahydroazulene-6-carboxylate HA-6-377



To a solution of **3.70** (16 mg, 0.047 mmol) in methanol (1.0 mL, HPLC grade), at 0 ºC, under air, was added $NaBH_4$ (3.6 mg, 0.094 mmol, 2.0 equiv.). The mixture was stirred for 20 minutes at 0 ºC. After this time, the reaction was diluted with water/brine 1:1, quenched with a drop of acetone and extracted with DCM (x3). The organic extracts were collected, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 2:1) delivered the title compound (13 mg, 83% yield, 6:1:1 *dr*) as a colorless gum. Single crystals suitable for X-ray diffraction analysis were obtained by diffusion of pentane into a solution in ethyl acetate, at room temperature. The signals of the major isomer could be assigned by ^{1}H and ^{13}C-NMR. The relative configuration was initially assigned by ^{1}H-NOE and confirmed by X-ray.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (br s, 1H), 3.82 (s, 3H), 3.39 (s, 1H, O*H*), 2.61 – 2.47 (m, 2H), 2.43 – 2.34 (m, 1H), 2.31 (dd, *J* = 11.9, 5.6 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.97 (s, 3H), 1.86 – 1.80 (m, 2H), 1.76 – 1.60 (m, 2H), 1.58 – 1.43 (m, 3H, overlapping with methyl s signals) 1.55 (s, 3H), 1.48 (s, 3H), 1.08 (s, 3H), (missing one O*H* signal). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5, 170.5, 85.0, 80.4, 75.5, 53.1, 51.3, 46.0, 45.3, 43.3, 43.0, 31.1, 30.8, 27.1, 25.3, 22.9, 22.3, 22.3. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{30}NaO_6]^+$: 365.1935, found: 365.1934.

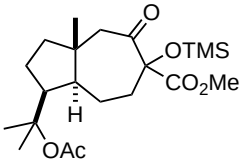
methyl 4-((1*S*,2*R*,5*S*)-5-(2-acetoxypropan-2-yl)-2-methyl-2-(2-oxoethyl)cyclopentyl)-2-oxobutanoate HA-6-257



To a solution of **3.71** (5.0 mg, 0.015 mmol) in cyclohexane (1.5 mL, HPLC grade, degassed with argon) at room temperature, were added iodine (3.9 mg, 0.015 mmol, 1.05 equiv.) and PIDA (5.2 mg, 0.016 mmol, 1.1 equiv.) as solids. The mixture was sonicated for 1 h at room temperature (the flask gets gradually warmed up due to the sonication: from 23 to 41 ºC). After this time, it was cooled to room temperature, diluted with Et_2O and quenched with water. The layers were separated and the organic phase was washed with a saturated solution of $Na_2S_2O_3$ (note the change of color to a clear colorless solution, by reduction of the iodine), dried over Na_2SO_4 and concentrated under reduced pressure to get the title compound (yield not determined) as the only product, as a colorless oil. The product could be partially characterized by crude NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (dd, *J* = 3.2, 2.3 Hz, 1H), 3.87 (s, 3H), 3.02 (ddd, *J* = 18.6, 10.3, 5.4 Hz, 1H), 2.88 (ddd, *J* = 18.6, 9.7, 5.5 Hz, 1H), 2.50 (dd, *J* = 15.4, 3.2 Hz, 1H), 2.35 (dd, *J* = 15.4, 2.3 Hz, 1H), 2.30 – 2.15 (m, 2H), 1.98 (s, 3H), 1.83 – 1.72 (m, 3H), 1.71 – 1.59 (m, 3H), 1.58 (s, 3H), 1.51 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.8, 196.6, 83.2, 55.7, 53.1, 53.1, 48.3, 44.7, 40.3, 37.3, 26.0, 25.8, 23.6, 23.3, 22.8, 19.1 (missing the two *C*O_2R signals).

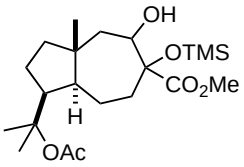
methyl (1*S*,3a*R*,8a*S*)-1-(2-acetoxypropan-2-yl)-3a-methyl-5-oxo-6-((trimethylsilyl)oxy)decahydroazulene-6-carboxylate HA-6-456



To a solution of **3.70** (36.0 mg, 0.106 mmol) in dry DCM (1.1 mL) at room temperature, under argon, was added imidazole (18.0 mg, 0.264 mmol, 2.5 equiv.). After 5 minutes, TMSCl (28 μL, 0.219 mmol, 2.1 equiv.) was added dropwise (Hamilton syringe) and the mixture is stirred at room temperature for 1 h. The reaction was quenched by addition of $NaHCO_3$ sat and extracted with DCM (x3). The organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc/TEA 10:2:0.1) delivered the title compound (43.2 mg, 99% yield, 5.5:1 *dr*) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 2.79 (d, *J* = 12.4 Hz, 1H), 2.64 (d, *J* = 12.4 Hz, 1H), 2.52 – 2.30 (m, 2H), 2.20 – 2.07 (m, 2H), 2.07 – 1.99 (m, 1H), 1.97 (s, 3H), 1.88 – 1.70 (m, 2H), 1.56 (s, 3H), 1.55 – 1.49 (m, 3H), 1.46 (s, 3H), 1.09 (s, 3H), 0.16 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.9, 172.5, 170.3, 84.6, 84.3, 52.8, 52.6, 50.7, 46.2, 42.9, 41.3, 34.3, 27.1, 26.9, 25.3, 22.8, 21.9, 21.6, 2.0 (x3*C*). **HRMS** (ESI+): m/z calc. for $[C_{21}H_{36}NaO_6Si]^+$: 435.2173, found: 435.2181.

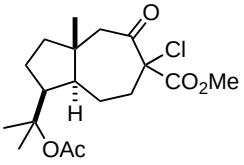
methyl (1*S*,3a*R*,8a*S*)-1-(2-acetoxypropan-2-yl)-5-hydroxy-3a-methyl-6-((trimethylsilyl)oxy)decahydroazulene-6-carboxylate



To a solution of **3.73** (33 mg, 0.079 mmol) in methanol (1.5 mL, HPLC grade), at 0 ºC, under air, was added $NaBH_4$ (4.5 mg, 0.118 mmol, 1.5 equiv.). The mixture was stirred for 20 minutes at 0 ºC. After this time, the reaction was quenched with one drop of acetone and diluted with DCM and water/$NaHCO_3$ (sat.). The layers were separated and the water phase was extracted with DCM (x3). The organic extracts were collected, dried over Na_2SO_4, and concentrated under reduced pressure to get the title compound (36 mg, 100% yield, 6:1 *dr*) as a colorless oil. The product was used without further purification

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 10.3, 3.3 Hz, 1H), 3.74 (s, 3H), 3.52 (s, 1H), 2.44 (q, *J* = 9.9 Hz, 1H), 2.31 (ddd, *J* = 14.8, 12.1, 6.8 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.01 (q, *J* = 6.5 Hz, 1H), 1.96 (s, 3H), 1.82 (dd, *J* = 14.5, 10.2 Hz, 1H), 1.78 – 1.69 (m, 2H), 1.70 – 1.60 (m, 3H), 1.56 (s, 3H), 1.48 (s, 3H), 1.42 – 1.35 (m, 2H), 1.06 (s, 3H), 0.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.6, 170.6, 84.7, 82.2, 77.3, 52.7, 50.9, 45.9, 45.4, 42.5, 42.4, 30.5, 26.9 (x2*C*), 25.4, 22.8, 22.5, 22.5, 0.1 (x3*C*). **HRMS** (ESI+): m/z calc. for $[C_{21}H_{38}NaO_6Si]^+$: 437.2330, found: 437.2335.

methyl (1*S*,3a*R*,8a*S*)-1-(2-acetoxypropan-2-yl)-6-chloro-3a-methyl-5-oxodecahydroazulene-6-carboxylate HA-6-289

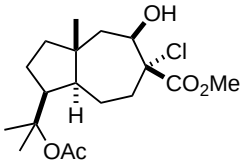


To a solution of **3.66** (41.9 mg, 0.129 mmol) in methanol (0.65 mL, HPLC grade), under air, were added Oxone (95.2 mg, 0.155 mmol, 1.2 equiv.) and NH4Cl (13.8 mg, 0.258 mmol, 2.0 equiv.). The mixture was stirred at room temperature for 16 h and then quenched by addition of water, extracted with EtOAc (x2), dried over Na2SO4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 6:1) delivered the title compound (30.6 mg, 66% yield, >10:1 *dr*) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 2.87 – 2.70 (m, 3H), 2.48 (q, *J* = 9.6 Hz, 1H), 2.34 – 2.23 (m, 2H), 2.09 – 2.01 (m, 1H), 2.01 – 1.94 (m, 1H , overlapping with methyl s), 1.98 (s, 3H), 1.83 – 1.76 (m, 1H), 1.56 (s, 3H), 1.55 – 1.49 (m, 3H), 1.47 (s, 3H), 1.11 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.0, 170.3, 168.7, 84.5, 74.6, 54.0, 52.9, 50.7, 48.5,

43.0, 41.1, 36.7, 27.0, 26.8, 25.2, 22.8, 22.6, 21.4. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{27}ClNaO_5]^+$: 381.1439, found: 381.1431.

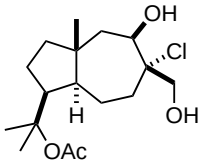
methyl (1*S*,3a*R*,5*R*,6*R*,8a*S*)-1-(2-acetoxypropan-2-yl)-6-chloro-5-hydroxy-3a-methyldecahydroazulene-6-carboxylate HA-6-294 for NMR



To a solution of **3.79** (60 mg, 0.167 mmol) in methanol (3.3 mL, HPLC grade), at 0 ºC, under air, was added $NaBH_4$ (6.0 mg, 0.159 mmol, 0.95 equiv.). The mixture was stirred for 15 minutes at 0 ºC. After this time, the reaction was diluted with water/brine 1:1, quickly quenched with a drop of acetone and extracted with EtOAc (x3). The organic extracts were collected, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 6:1) delivered the title compound (41.8 mg, 69% yield, >20:1 *dr*) as a colorless oil. The relative configuration was assigned by analogy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (td, *J* = 4.2, 1.2 Hz, 1H), 3.80 (s, 3H), 2.64 (ddd, *J* = 15.2, 10.3, 7.4 Hz, 1H), 2.57 – 2.49 (m, 1H), 2.49 – 2.42 (m, 1H), 2.33 (ddt, *J* = 15.5, 7.7, 1.7 Hz, 1H), 2.12 (dtd, *J* = 14.2, 7.1, 2.7 Hz, 1H), 2.03 – 1.97 (m, 1H, overlapping with methyl s), 1.98 (s, 3H), 1.97 – 1.92 (m, 1H, overlapping with methyl s), 1.88 (dd, *J* = 15.1, 3.9 Hz, 1H), 1.70 (dt, *J* = 12.8, 7.7 Hz, 1H), 1.61 (ddt, *J* = 12.6, 6.4, 3.0 Hz, 1H), 1.58 (s, 3H), 1.50 (s, 3H), 1.45 (dd, *J* = 11.7, 6.7 Hz, 1H), 1.32 (td, *J* = 12.6, 7.1 Hz, 1H), 1.13 (s, 3H) (missing O*H* signal). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.4, 170.5, 84.8, 75.4, 73.2, 53.5, 51.9, 46.1, 45.6, 44.5, 43.2, 28.4, 27.2, 26.7, 25.5, 23.2, 22.9, 21.0. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{29}ClNaO_5]^+$: 383.1596, found: 383.1589.

2-((1*S*,3a*R*,5*R*,6*S*,8a*S*)-6-chloro-5-hydroxy-6-(hydroxymethyl)-3a-methyldecahydroazulen-1-yl)propan-2-yl acetate HA-6-425 for NMR

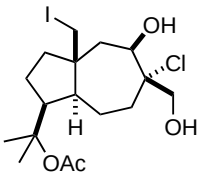


To a solution of **3.79** (30 mg, 0.084 mmol) in methanol (1.6 mL, HPLC grade), at 0 ºC, under air, was added $NaBH_4$ (16 mg, 0.42 mmol, 5.0 equiv.). The mixture was stirred for 5 minutes at 0 ºC and then 20 minutes at room temperature. After this time, the reaction was diluted with water/brine 1:1, quenched with a drop of acetone and extracted with EtOAc (x3). The organic extracts were collected, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 2:1) delivered the title compound (10.5 mg, 38% yield, >20:1 *dr*) as a colorless oil. Its relative configuration was assigned based on its reactivity.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 4.23 – 4.17 (m, 1H), 3.76 (d, *J* = 12.0 Hz, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 2.61 – 2.38 (m, 3H), 2.15 – 2.02 (m, 1H), 1.99 – 1.92 (m, 2H, overlapping with methyl s), 1.95 (s, 3H), 1.88 (dd, *J* = 9.0, 4.0 Hz, 2H), 1.76 – 1.59 (m, 4H), 1.56 (s, 3H), 1.48 (s, 3H), 1.47 – 1.39 (m, 2H), 1.37 – 1.30 (m, 1H), 1.15 (s, 3H). **^{13}C NMR** (126

MHz, CH_2Cl_2) δ 170.6, 84.8, 78.8, 75.6, 71.8, 52.4, 47.6, 46.7, 45.0, 43.5, 28.7, 27.2, 26.8, 25.7, 23.8, 22.9, 21.2. **HRMS** (ESI+): m/z calc. for $[C_{17}H_{29}ClNaO_4]^+$: 355.1647, found: 355.1641.

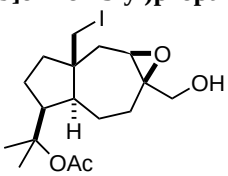
2-((1*S*,3a*S*,5*R*,6*S*,8a*S*)-6-chloro-5-hydroxy-6-(hydroxymethyl)-3a-(iodomethyl)decahydroazulen-1-yl)propan-2-yl acetate HA-6-426



To a solution of **3.80** (30 mg, 0.090 mmol) in cyclohexane (9.0 mL, HPLC grade, degassed with argon) at room temperature, were added iodine (24 mg, 0.095 mmol, 1.05 equiv.) and PIDA (32 mg, 0.099 mmol, 1.1 equiv.) as solids. The mixture was sonicated for 1 h at room temperature (the flask gets gradually warmed up due to the sonication: from 23 to 41 ºC). After this time, it was cooled to room temperature, diluted with Et_2O and quenched with water. The layers were separated and the organic phase was washed with a saturated solution of $Na_2S_2O_3$ (note the change of color to a clear colorless solution, by reduction of the iodine), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 2:1 to 1:1) delivered the title compound (20.3 mg, 49% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (br s, 1H), 3.91 (dd, *J* = 9.9, 2.2 Hz, 1H), 3.78 (dd, *J* = 11.7, 8.6 Hz, 1H), 3.72 (dd, *J* = 9.8, 1.9 Hz, 1H), 3.68 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.05 (td, *J* = 12.2, 7.6 Hz, 1H), 2.45 (ddd, *J* = 15.3, 10.5, 8.1 Hz, 1H), 2.41 – 2.34 (m, 1H), 2.31 (dd, *J* = 15.8, 3.8 Hz, 1H), 2.26 (d, *J* = 2.7 Hz, 1H), 2.14 – 2.08 (m, 1H), 1.98 (s, 3H), 1.92 (dd, *J* = 12.5, 6.2 Hz, 1H), 1.86 (dd, *J* = 15.3, 8.4 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.63 (s, 3H), 1.59 – 1.53 (m, 1H, overlaps with water), 1.50 (s, 3H). 1.33 – 1.27 (m, 1H, overlaps with grease) (missing the two O*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.1, 84.2, 74.9, 71.9, 52.3, 48.9, 44.9, 43.2, 41.2, 29.9, 27.8, 27.1, 26.3, 25.8, 23.5, 22.8, 18.8. **HRMS** (ESI+): m/z calc. for $[C_{17}H_{28}ClINaO_4]^+$: 481.0613, found: 481.0607.

2-((1a*R*,2a*S*,5*S*,5a*S*,7a*R*)-7a-(hydroxymethyl)-2a-(iodomethyl)decahydroazuleno[5,6-*b*]oxiren-5-yl)propan-2-yl acetate HA-6-292

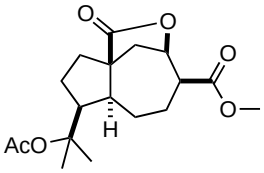


To a solution of **3.82** (20 mg, 0.044 mmol) in dry THF (0.8 mL) under argon at room temperature was added K_2CO_3 (10 mg, 0.072 mmol, 1.7 equiv.). After 1 h, NaH (3.5 mg, 60% dispersion in molecular oil, 0.088 mmol, 2.0 equiv.) was added. The mixture was stirred at room temperature for 2 h. Then it was quenched by addition of brine, extracted with DCM (x3), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 2:1 to 1:1) delivered the title compound (7.7 mg, 42% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, *J* = 9.7, 2.1 Hz, 1H), 3.60 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.52 (dd, *J* = 12.1, 7.7 Hz, 1H), 3.30 (dd, *J* = 9.6, 2.1 Hz, 1H), 3.22 (d, *J* = 5.6 Hz, 1H),

2.75 (dd, *J* = 15.8, 5.7 Hz, 1H), 2.69 (td, *J* = 11.2, 8.7 Hz, 1H), 2.24 – 2.18 (m, 1H), 2.14 – 2.08 (m, 1H), 2.08 – 2.01 (m, 1H), 1.99 – 1.93 (m, 1H, overlapping with methyl s), 1.96 (s, 3H), 1.81 – 1.74 (m, 1H), 1.74 – 1.69 (m, 1H), 1.67 – 1.62 (m, 1H), 1.53 (s, 3H), 1.51 – 1.46 (m, 1H), 1.43 (s, 3H), 1.40 – 1.33 (m, 1H), 1.14 (dddd, *J* = 13.6, 12.4, 6.8, 2.1 Hz, 1H) (missing O*H* signal). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.3, 85.3, 66.3, 63.9, 59.1, 50.9, 50.6, 47.2, 40.5, 37.6, 30.4, 27.3, 26.5, 24.7, 22.9, 20.5, 18.3. **HRMS** (ESI+): m/z calc. for $[C_{17}H_{27}INaO_4]^+$: 445.0846, found: 445.0840.

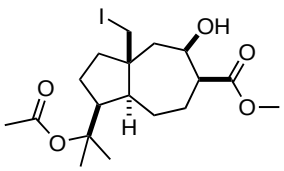
methyl (3*R*,4*S*,6a*S*,7*S*,9a*S*)-7-(2-acetoxypropan-2-yl)-1-oxooctahydro-1*H*-3,9a-methanocyclopenta[*c*]oxocine-4-carboxylate HA-6-493



To a degassed solution of **3.67a** (4.0 mg, 0.012 mmol) in cyclohexane (1.2 mL, HPLC grade) under argon, at room temperature, were added iodine (3.3 mg, 0.013 mmol, 1.1 equiv.) and PIDA (4.3 mg, 0.013 mmol, 1.1 equiv.) as solids. The mixture was irradiated with a desk lamp, warmed up to 40 ºC in a water bath and stirred for 1 h. After this time, the progress was checked by NMR, showing <20% conversion. Thus, the crude product was resubmitted to the same reaction conditions with additional iodine (6.6 mg, 0.026 mmol, 2.2 equiv.) and PIDA (8.6 mg, 0.026 mmol, 2.2 equiv.). Again, the mixture was irradiated with a desk lamp, warmed up to 40 ºC in a water bath and stirred for 3 h. The reaction was diluted with Et_2O, quenched with a saturated solution of Na_2SO_3, extracted with Et_2O (x3) and concentrated under reduced pressure. Crude NMR revealed full conversion. The reaction can also be monitored by UPLC-MS. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 1:1) delivered the title compound (yield not determined) as a colorless gum. Single crystals suitable for X-ray diffraction analysis could be obtained by slow evaporation in DCM/heptane at room temperature.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 (dd, *J* = 8.6, 4.9 Hz, 1H), 3.75 (s, 3H), 3.09 (td, *J* = 11.3, 8.5 Hz, 1H), 2.88 (t, *J* = 5.8 Hz, 1H), 2.62 (dd, *J* = 13.0, 8.5 Hz, 1H), 2.51 (ddd, *J* = 15.3, 7.6, 1.2 Hz, 1H), 2.31 (dd, *J* = 14.6, 7.6 Hz, 1H), 2.28 – 2.18 (m, 1H), 2.17 – 2.11 (m, 1H), 1.97 (s, 3H), 1.97 (d, *J* = 13.0 Hz, 1H), 1.92 (dd, *J* = 12.4, 6.8 Hz, 1H), 1.84 (dt, *J* = 12.7, 7.9 Hz, 1H), 1.75 – 1.66 (m, 1H), 1.63 (td, *J* = 12.8, 7.3 Hz, 1H), 1.54 – 1.49 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.3, 172.4, 170.6, 86.2, 77.2 (overlapping with *C*DCl_3 signal), 57.5, 53.8, 52.3, 49.7, 47.2, 37.8, 33.5, 28.3, 27.4, 27.2, 24.2, 24.0, 23.1. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{26}NaO_6]^+$: 361.1622, found: 361.1626.

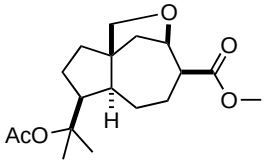
methyl (1*S*,3a*S*,5*R*,6*S*,8a*S*)-1-(2-acetoxypropan-2-yl)-5-hydroxy-3a-(iodomethyl)decahydroazulene-6-carboxylate



To a degassed solution of **3.67a** (3.1 mg, 0.010 mmol) in cyclohexane (1.0 mL, HPLC grade) under argon, at room temperature, were added iodine (2.5 mg, 0.010 mmol, 1.1 equiv.) and PIDA (3.7 mg, 0.011 mmol, 1.1 equiv.) as solids. The mixture was irradiated with a desk lamp, warmed up to 40 ºC in a water bath and stirred for 10 minutes. After this time, $CaCO_3$ (1.5 mg, 0.015 mmol, 1.6 equiv.) was added and the suspension was irradiated and stirred for 3 h at 40 ºC. The progress was monitored by UPLC-MS. After this time, we observed a 1:1 ratio of product/starting material and we could already detect traces of **3.86** by UPLC-MS. Thus, the reaction was diluted with Et_2O, quenched with a saturated solution of Na_2SO_3, extracted with Et_2O (x3) and concentrated under reduced pressure. Crude NMR confirmed *ca* 50% conversion and the presence of a characteristic C_qCH_2I signal: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.01 (dd, *J* = 9.6, 1.9 Hz, 1H), 3.56 (dd, *J* = 9.7, 2.2 Hz, 1H). **MS** (APCI+) m/z calc. for $[C_{16}H_{26}IO_3]^+ = [M - AcO^-]^+$: 393.09, found . MASS UPLC

Compounds **3.67a** and **3.87** had the same R_f by TLC so we submitted the crude material to the next step without separating them.

methyl (3*R*,4*S*,6a*S*,7*S*,9a*S*)-7-(2-acetoxypropan-2-yl)octahydro-1*H*-3,9a-methanocyclopenta[*c*]oxocine-4-carboxylate



The crude mixture of **3.67a** and **3.87** obtained in the previous step was dissolved in DMF (0.4 mL, HPLC grade) and $AgNO_3$ (3.1 mg, 0.018 mmol, 4.0 equiv. based on calculated **3.87**) was added. The slurry mixture was stirred at room temperature, protected from the light with aluminum foil. The progress of the reaction was monitored by UPLC. After 20 h, the reaction was quenched by addition of brine and Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O (x3). The organic extracts were washed with water and concentrated under reduced pressure. Crude NMR confirmed full conversion of **3.87** and unreacted **3.67a**. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 4:1 to 1:1) delivered the title compound (yield not determined) as a colorless oil, and **3.67a** (yield not determined) in a separate fraction.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (dd, *J* = 8.7, 4.3 Hz, 1H), 4.06 (d, *J* = 8.1 Hz, 1H), 3.72 (s, 3H), 3.31 (d, *J* = 8.2 Hz, 1H), 2.71 (q, *J* = 10.2 Hz, 1H), 2.68 – 2.62 (m, 1H), 2.34 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.25 (dd, *J* = 12.7, 8.7 Hz, 1H), 2.14 (dd, *J* = 11.4, 7.7 Hz, 1H), 2.00 (s, 3H), 1.98 (d, *J* = 11.6 Hz, 1H), 1.93 – 1.84 (m, 3H), 1.84 – 1.76 (m, 1H), 1.71 – 1.62 (m, 2H), 1.55 (s, 3H), 1.48 (s, 3H), 1.46 – 1.38 (m, 1H). **MS** (APCI+) m/z calc. for $[C_{16}H_{25}O_3]^+ = [M - AcO^-]^+$: 265.18, found 265. CONFIRM MASS UPLC

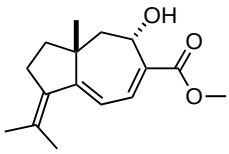
The title compound decomposed during the ^{13}C-NMR measuring so we cannot report it.

Towards the Total Synthesis of Penigrisacid A

General procedure for the attempts on the oxa-Michael addition:

To a solution of **3.61** in the solvent of choice (0.01 M, dry), under argon, was added DBU, KO*t*Bu, *p*TSOH, CSA (typically 5 equiv.). The mixture was stirred at the desired temperature and analyzed by TLC (cyclohexane/EtOAc 4:1) and ^{1}H-NMR.

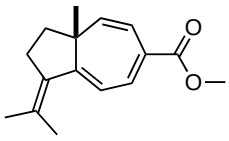
methyl (3a*R*,5*S*)-5-hydroxy-3a-methyl-1-(propan-2-ylidene)-1,2,3,3a,4,5-hexahydroazulene-6-carboxylate HA-6-444 or HA-6-181-Col



The title compound was obtained following the general procedure for the oxa-Michael addition. It could also be prepared using the following procedure: To a solution of **3.61** (15 mg, 0.034 mmol) in dry THF (1.0 mL) under argon, at 0 ºC was added TBAF (0.20 mL, 1.0 M in THF, 0.200 mmol, 5.8 equiv.) dropwise. The resulting solution was warmed up to room temperature and monitored by TLC (cyclohexane/EtOAc 4:1). The reaction was stirred for 7 h, then quenched by addition of a saturated solution of NH_4Cl and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 10:1) delivered the title compound (4.7 mg, 52% yield) as a pale-yellow oil.

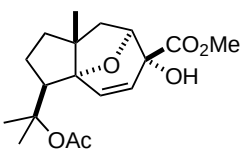
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.8, 1.5 Hz, 1H), 5.98 (d, *J* = 8.8 Hz, 1H), 4.80 (dd, *J* = 10.9, 5.9 Hz, 1H), 4.21 (br s, 1H, O*H*), 3.79 (s, 3H), 2.50 – 2.38 (m, 2H), 2.11 – 2.00 (m, 2H), 1.98 (t, *J* = 1.6 Hz, 3H), 1.85 (s, 3H), 1.68 – 1.61 (m, 2H), 1.02 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7, 163.4, 135.3, 134.7, 134.3, 131.2, 115.7, 66.8, 52.1, 45.0, 43.7, 39.8, 29.4, 25.4, 23.6, 21.8. **HRMS** (ESI+): m/z calc. for $[C_{16}H_{22}NaO_3]^+$: 285.1461, found: 285.1454.

methyl (*R*)-3a-methyl-1-(propan-2-ylidene)-1,2,3,3a-tetrahydroazulene-6-carboxylate



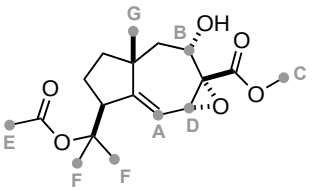
The title compound was obtained as a side product, following the general procedure for the oxa-Michael addition. It was partially characterized by crude NMR. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 10.4 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 5.31 (d, *J* = 10.3 Hz, 1H), 3.82 (s, 3H), 2.07 – 1.98 (m, 2H), 1.98 (s, 3H), 1.87 (s, 3H), 1.85 – 1.80 (m, 2H), 0.70 (s, 3H).

methyl (3*R*,3a*R*,6*R*,7*S*,8a*R*)-3-(2-acetoxypropan-2-yl)-6-hydroxy-8a-methyl-2,3,6,7,8,8a-hexahydro-1*H*-3a,7-epoxyazulene-6-carboxylate HA-6-461 and methyl (1a*R*,3*S*,5a*R*,7*S*,7a*S*)-3-(2-acetoxypropan-2-yl)-7-hydroxy-5a-methyl-3,4,5,5a,6,7-hexahydroazuleno[5,6-*b*]oxirene-7a(1a*H*)-carboxylate HA-6-474



To a solution of **3.61** (30.0 mg, 0.093 mmol) in DCM (2.0 mL, HPLC grade) at room temperature, under air, was added *m*CPBA (32.0 mg, >75% purity, 0.140 mmol, 1.5 equiv.) as a solid. The reaction mixture was stirred at this temperature for 14 h and then quenched by addition of a saturated solution of Na_2SO_3. The layers were separated and the aqueous phase was extracted with DCM (x2). The organic extracts were collected, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane/EtOAc 3:1 to 2:1) delivered the title compound (19.4 mg, 95% purity, 59% yield) as a colorless gum. Single crystals suitable for X-ray diffraction analysis could be obtained by slow evaporation in DCM/heptane at room temperature.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 10.3 Hz, 1H), 5.91 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.44 (dt, *J* = 8.2, 1.9 Hz, 1H), 3.78 (s, 3H), 2.86 (s, 1H), 2.23 (t, *J* = 9.5 Hz, 1H), 2.14 (dd, *J* = 13.4, 8.2 Hz, 1H), 1.99 (s, 3H), 1.99 – 1.92 (m, 2H), 1.79 (dd, *J* = 12.3, 8.4 Hz, 1H), 1.68 (s, 3H), 1.61 – 1.56 (m, 1H), 1.50 (s, 3H), 1.47 – 1.43 (m, 1H), 1.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.8, 170.2, 136.1, 123.6, 92.6, 82.6, 82.0, 74.2, 58.1, 56.2, 52.7, 39.1, 38.8, 29.1, 25.7, 25.6, 22.6, 21.0. **HRMS** (ESI+): m/z calc. for $[C_{18}H_{26}NaO_6]^+$: 361.1622, found: 361.1617.

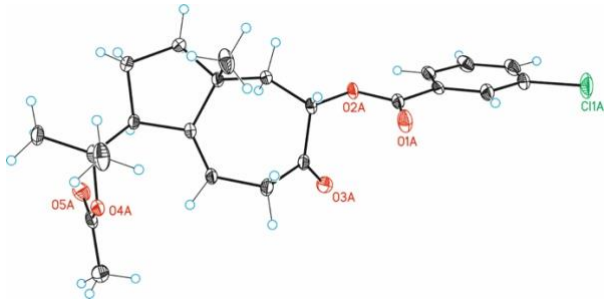


As mentioned in the main text of this Chapter, this procedure was not reproducible. In other batches we could obtain the intermediate epoxide **3.100**. This was partially characterized by crude NMR. It could not be isolated clean because it converted into **3.101** during chromatography on silica gel. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 5.2, 2.4 Hz, 1H, **A**), 5.02 (dd, *J* = 11.9, 4.7 Hz, 1H, **B**), 3.82 (s, 3H, **C**), 3.52 (d, *J* = 5.1 Hz, 1H, **D**), 2.00 (s, 3H, **E**), 1.51 (s, 3H, **F**), 1.39 (s, 3H, **F**), 1.09 (s, 3H, **G**).

We are currently working to develop a reproducible method for the synthesis of **3.101**.

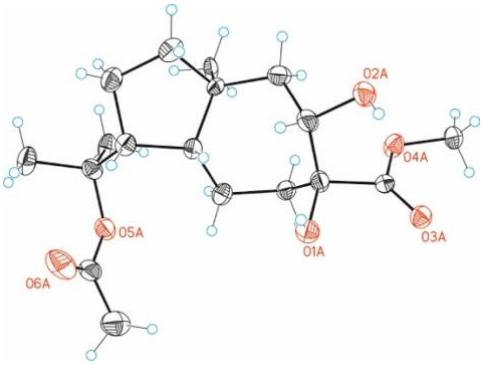
Crystal structures

Crystal data and structure refinement for mo_HA6091_0m.



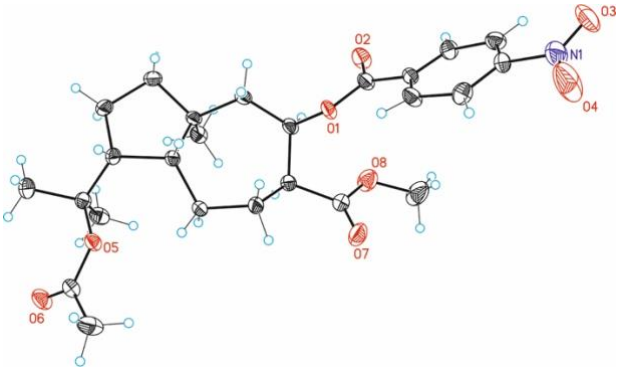
Identification code	mo_HA6091_0m	
Empirical formula	C23 H27 Cl O5	
Formula weight	418.89	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 14.9969(4)Å	a= 90°.
	b = 20.7903(5)Å	b = 118.4791(7)°.
	c = 15.4962(4)Å	g = 90°.
Volume	4246.90(19) $Å^3$	
Z	8	
Density (calculated)	1.310 Mg/m^3	
Absorption coefficient	0.211 mm^{-1}	
F(000)	1776	
Crystal size	0.200 x 0.200 x 0.200 mm^3	
Theta range for data collection	1.787 to 31.594°.	
Index ranges	-20<=h<=22,-30<=k<=30,-18<=l<=22	
Reflections collected	56067	
Independent reflections	14136[R(int) = 0.0363]	
Completeness to theta =31.594°	99.2%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.69	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	14136/ 0/ 531	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0453, wR2 = 0.1110	
R indices (all data)	R1 = 0.0648, wR2 = 0.1221	
Largest diff. peak and hole	0.794 and -0.634 e.$Å^{-3}$	

Crystal data and structure refinement for HA-6-256-P32.



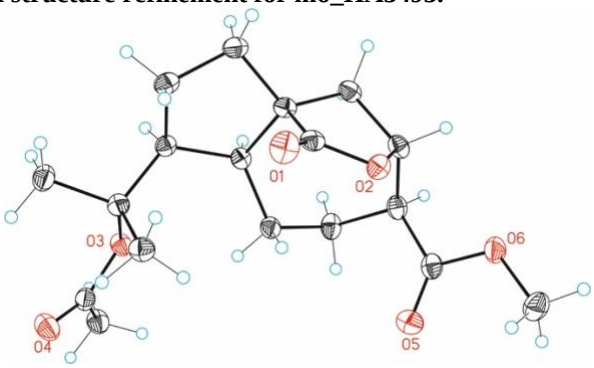
Identification code	HA-6-256-P32	
Empirical formula	C13.50 H22.50 O4.50	
Formula weight	256.81	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	trigonal	
Space group	P 32	
Unit cell dimensions	a = 26.5204(7)Å	a= 90°.
	b = 26.5204(7)Å	b = 90°.
	c = 6.8493(2)Å	g = 120°.
Volume	4171.9(3) $Å^3$	
Z	12	
Density (calculated)	1.227 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	1674	
Crystal size	0.100 x 0.100 x 0.020 mm^3	
Theta range for data collection	2.346 to 29.084°.	
Index ranges	-35<=h<=35,-35<=k<=35,-8<=l<=9	
Reflections collected	28716	
Independent reflections	13104[R(int) = 0.0485]	
Completeness to theta =29.084°	92.9%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.72	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	13104/ 1/ 671	
Goodness-of-fit on F^2	0.951	
Final R indices [I>2sigma(I)]	R1 = 0.0522, wR2 = 0.0922	
R indices (all data)	R1 = 0.1061, wR2 = 0.1103	
Largest diff. peak and hole	0.264 and -0.245 $e.Å^{-3}$	

Crystal data and structure refinement for ha-6-189.



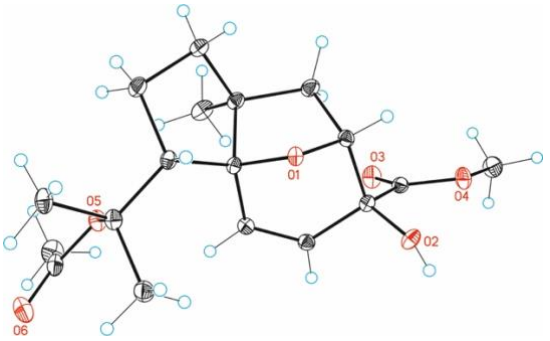
Identification code	ha-6-189	
Empirical formula	C25 H33 N O8	
Formula weight	475.52	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 12.4021(2)Å	a= 90°.
	b = 10.9094(2)Å	b = 93.8260(10)°.
	c = 17.7814(3)Å	g = 90°.
Volume	2400.45(7) $Å^3$	
Z	4	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	1016	
Crystal size	0.250 x 0.150 x 0.120 mm^3	
Theta range for data collection	2.296 to 29.896°.	
Index ranges	-17<=h<=16,-15<=k<=15,-24<=l<=24	
Reflections collected	68018	
Independent reflections	6501[R(int) = 0.0323]	
Completeness to theta =29.896°	93.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.89	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6501/ 317/ 427	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1195	
R indices (all data)	R1 = 0.0580, wR2 = 0.1257	
Largest diff. peak and hole	0.474 and -0.216 $e.Å^{-3}$	

Crystal data and structure refinement for mo_HA3493.



Identification code	mo_HA3493	
Empirical formula	C18 H26 O6	
Formula weight	338.39	
Temperature	99(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 21.3340(16)Å	a= 90°.
	b = 6.1120(4)Å	b = 105.126(3)°.
	c = 13.2811(11)Å	g = 90°.
Volume	1671.8(2) $Å^3$	
Z	4	
Density (calculated)	1.344 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	728	
Crystal size	0.300 x 0.200 x 0.010 mm^3	
Theta range for data collection	1.978 to 27.127°.	
Index ranges	-26<=h<=27,-5<=k<=7,-16<=l<=17	
Reflections collected	18145	
Independent reflections	3685[R(int) = 0.0318]	
Completeness to theta =27.127°	99.7%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.74 and 0.69	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3685/ 0/ 221	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.1081	
R indices (all data)	R1 = 0.0582, wR2 = 0.1169	
Largest diff. peak and hole	0.623 and -0.248 e.$Å^{-3}$	

Crystal data and structure refinement for HA-6-461.



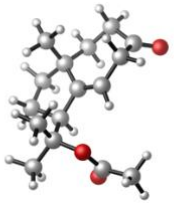
Identification code	HA-6-461	
Empirical formula	C18 H26 O6	
Formula weight	338.39	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.52365(10)Å	a= 90°.
	b = 11.23121(16)Å	b = 90°.
	c = 20.1534(3)Å	g = 90°.
Volume	1702.96(4) $Å^3$	
Z	4	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	728	
Crystal size	0.200 x 0.150 x 0.100 mm^3	
Theta range for data collection	2.716 to 31.983°.	
Index ranges	-11<=h<=11,-16<=k<=16,-29<=l<=29	
Reflections collected	28494	
Independent reflections	5592[R(int) = 0.0176]	
Completeness to theta =31.983°	96.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.70	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5592/ 0/ 223	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0259, wR2 = 0.0720	
R indices (all data)	R1 = 0.0266, wR2 = 0.0726	
Flack parameter	x =0.33(10)	
Largest diff. peak and hole	0.365 and -0.157 $e.Å^{-3}$	

DFT Calculations

Computational Methods

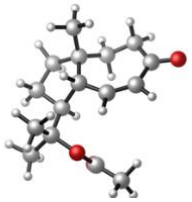
All DFT calculations were carried out with the Gaussian 09 package. Frequency calculations were analyzed to characterize the nature of the stationary points as minima (no imaginary frequency). The M06 functional was used for optimizations and frequency calculations together with the basis set 6-31G(d,p) for C, H and O atoms. Solvation Model Based (SMD) was used to simulate dichloromethane solvent. Unless otherwise stated, all the energies presented are potential (E) and free energies (G) in solution at 298.15 K and 1 atm in kcal/mol. Optimized geometries were visualized using CYLView.

Optimized Structures



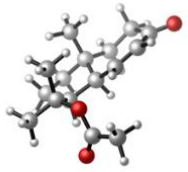
Non-conjugated enone x

E (opt) = -849.271512464 Hartrees
G (opt) = -848.943809 Hartrees



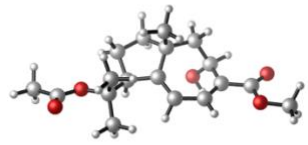
***Cis*-fused enone x**

E (opt) = -849.268703723 Hartrees
G (opt) = -848.938669 Hartrees



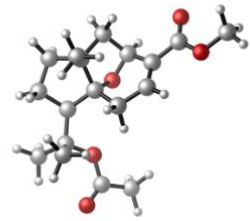
***Trans*-fused enone x**

E (opt) = -849.26092269 Hartrees
G (opt) = -848.932662 Hartrees



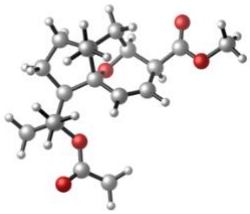
Open product x

E (opt) = -1.076.99795289 Hartrees
G (opt) = -1.076.633231 Hartrees



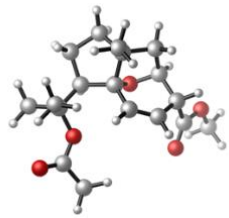
Cyclic product conj x

E (opt) = -1.077.02707915 Hartrees
G (opt) = -1.076.655139 Hartrees



Cyclic product nonconj x

E (opt) = -1.077.01921957 Hartrees
G (opt) = -1.076.648784 Hartrees

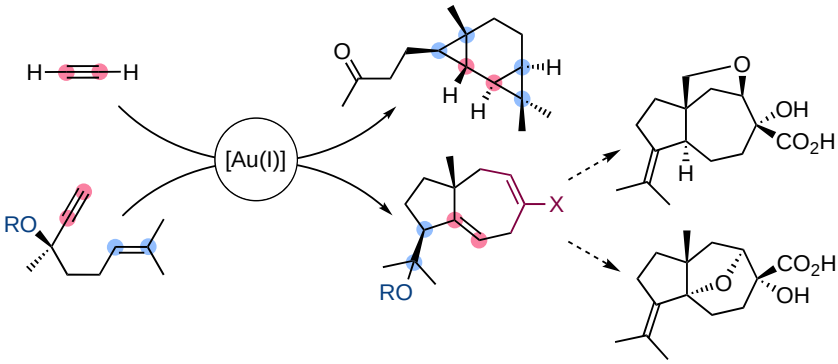


Cyclic product nonconj-b x

E (opt) = -1.077.01921957 Hartrees
G (opt) = -1.076.648784 Hartrees

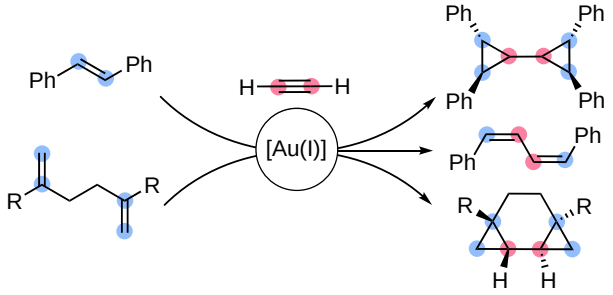
General Conclusions

This Doctoral Thesis exemplifies the potential of gold(I) catalysis for the synthesis of complex molecules. From acetylene activation to a cycloisomerization/cycloaddition cascade reaction, diverse gold(I)-catalyzed transformations were developed, studied both experimentally and computationally, and applied to different natural product syntheses (scheme 115).



Scheme 115. Summary of the newly developed gold(I)-catalyzed reactions in this thesis.

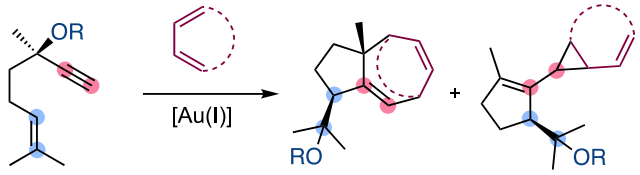
As first general conclusion, we found that acetylene serves as a dicarbene equivalent in its gold(I)-catalyzed reaction with stilbenes and 1,5-dienes providing *bis*-cyclopropanes and tricyclo[5.1.0.$0^{2,4}$]octanes, respectively. When a different gold(I) catalyst is employed, 1,3-dienes are obtained as the main product of the reaction, together with acetylene oligomers, with up to 4 units of the alkyne. DFT calculations were performed in order to explain the different reactivity of the two catalytic systems, providing no apparent energetic explanation.



Scheme 116. Acetylene gold(I)-catalyzed reactions with olefins and 1,5-dienes.

The reaction of acetylene with geranyl acetone under gold(I) catalysis yields waitziacuminone as a single isomer, forging 5 stereocenters and 4 new C-C bonds in one step.

Secondly, complex hydroazulenes can be obtained in moderate to good yields as the main product of the gold(I)-catalyzed reaction of 1,6-enynes bearing a propargyl ether and different 1,3-dienes (Scheme 117). Divinylcyclopropanes can be formed alternatively, depending on the catalyst of choice and on the nature of the diene partner. This latter case was studied computationally providing a rational for the different selectivity observed experimentally.



Scheme 117. Synthesis of hydroazulenes and divinylcyclopropanes by gold (I) catalysis.

Finally, this methodology was applied to access some advanced intermediates towards apsterric acid, penigrisacid A and schisanwilsonene A. These total syntheses are still under development in our laboratories.

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