GOLD CATALYSIS FOR THE SYNTHESIS OF PROTOILLUDANE SESQUITERPENES AND OTHER CYCLIC SYSTEMS

Anthony Pitaval

Dipòsit Legal: T 968-2014

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Gold Catalysis for the Synthesis of Protoilludane Sesquiterpenes and Other Cyclic Systems

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren
Institut Català d'Investigació Química (ICIQ)

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FAIG CONSTAR que aquest treball, titulat "Gold Catalysis for the Synthesis of Protoilludane Sesquiterpenes and Other Cyclic Systems", que presenta Anthony Pitaval per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Química Analítica i Química Orgànica d'aquesta Universitat i que acompleix els requeriments per poder optar a Menció Internacional.

Tarragona, 11 de Desembre de 2013

El Director de la Tesi Doctoral

Prof. Antonio M. Echavarren

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A toi Papa…

I liked science. I wasn't mathematically oriented,
so I became an organic chemist.

Koji Nakanishi
Organic and bioorganic chemist

Scientific work must not be considered
from the point of view of the direct usefulness of it.
It must be done for itself, for the beauty of science,
and then there is always the chance
that a scientific discovery may become like the radium, a benefit.

Marie Curie (1897 – 1934)
Nobel Prize in Physics (1903) and Chemistry (1911)

Acknowledgements – Agradecimientos – Remerciements

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I would like to thank the Ministerio de Educación y Ciencia for a FPU predoctoral fellowship (AP2009-0598), which funded this PhD (November 2009 – November 2013). Moreover, the Ministerio de Ciencia e Innovación (CTQ2010-16088/BQU), the AGAUR (Project 2009 SGR 47), the ERC (Advanced Grant No. 321066) and the ICIQ Foundation are also gratefully acknowledged for financial support to the group.

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At the moment of the writing of this thesis, the results presented herein had been published in:

A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren
Org. Lett., **2013**, *15*, 4580-4583.

A book chapter presenting the recent developments of the Stille cross-coupling reaction was also published:

A. Pitaval, A. M. Echavarren
Science of Synthesis: Cross-Coupling and Heck-Type Reactions, **2013**, *1*, 527-621.

Contents

This PhD thesis has been divided in six different parts:

- A summary in Spanish.
- A general introduction presenting some important aspects of gold catalysis.
- Three chapters presenting the research carried out during these four years.
- A general conclusion.

Each chapter is divided in six parts. First, a specific introduction on the topic investigated followed by a description of the objectives. Then, the results obtained will be presented. A part presenting the further developments carried out on the project is also included. A brief conclusion will summarize the outcomes of the research. Finally, an experimental section will describe the synthesis and the characterization of the compounds prepared and isolated.

The general introduction will discuss some important aspects of gold homogeneous catalysis. It will mainly focus on the activation of alkynes and the cycloisomerization of enynes.

The first chapter summarizes the work done on the cycloisomerization of alkyne-vinylcyclopropanes and the studies towards the synthesis of repraesentin F.

The second chapter presents the methodology developed for the access to the protoilludane core by gold(I)-catalyzed allene-vinylcyclopropane cycloisomerization.

The last chapter is completely independent and is devoted to the revisiting of the 1,5-migration mechanism. Surprising results were obtained and offer new perspectives for the synthesis of polycyclic molecules.

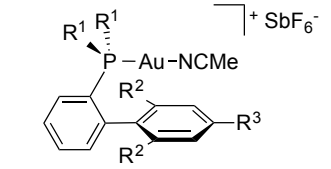
In this manuscript, the abbreviations and acronyms most commonly employed in organic and organometallic chemistry have been used following the recommendation found in the on-line "guidelines for authors" of *The Journal of Organic Chemistry*.

Additional abbreviations and acronyms used in this manuscript are referenced in the list below:

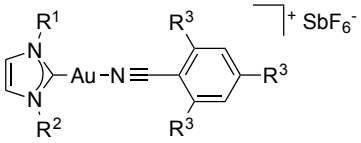
1,2-DCE	1,2-Dichloroethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DFT	Density functional theory
DMAP	4-(Dimethylamino)pyridine
DMP	Dess-Martin periodinane
Im	Imidazole
IPr	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
JohnPhos	(2-Biphenyl)di-tert-butylphosphine
L	Ligand
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
Nu	Nucleophile
PNB	*para*-Nitrobenzoyl
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBS	*tert*-Butyldimethylsilyl

A bookmark is also provided with the structure of the catalysts used during theses investigations.

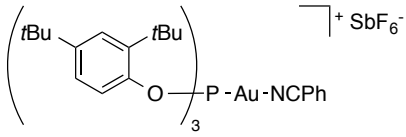
Several metal-catalysts were used during these investigations. The following naming applies to the whole manuscript.



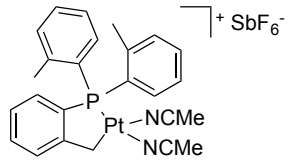
A, R^1 = *t*Bu, R^2 = R^3 = H
B, R^1 = *t*Bu, R^2 = R^3 = *i*Pr
C, R^1 = Cy, R^2 = R^3 = *i*Pr
D, R^1 = Cy, R^2 = OMe, R^3 = H



E, R^1 = Me, R^2 = Et, R^3 = OMe
F, R^1 = R^2 = Mes, R^3 = OMe
G, R^1 = R^2 = 2,6-*i*Pr$_2$C$_6$H$_3$, R^3 = H



H



I

J

Catalyst **A** was directly used as received from Sigma-Aldrich. Catalysts **B, C, D** bearing bulky phosphine ligands were synthesized according to reported procedures.[1] NHC-catalysts **E**[2] and **F**[3] were already reported. Catalysts **G** and **H** were prepared following a group procedure.[4] Platinacycle **I**[5] and silver complex **J**[6] were also prepared.

1. E. Herrero-Gómez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.

2. M. Raducan, PhD thesis, ICIQ, 2010.

3. C. Nieto-Oberhuber, P. Pérez-Galán, E. Herrero-Gómez, T. Lauterbach, C. Rodríguez, S. López, C. Bour, A. Rosellón, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2008**, *130*, 269-279.

4. C. H. M. Amijs, V. López-Carillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721-7730.

5. C. Ferrer, M. Raducan, C. Nevado, C. K. Claverie, A. M. Echavarren, *Tetrahedron* **2007**, *63*, 6306-6316.

6. M. Raducan, C. Rodríguez-Escrich, X. C. Cambeiro, E. C. Escudero-Adán, M. A. Pericàs, A. M. Echavarren, *Chem. Commun.* **2011**, *47*, 4893-4895.

Resumen de la Tesis

Los procesos catalizados por oro han emergido en las últimas dos décadas como una poderosa herramienta en síntesis orgánica.[7] Las reacciones más estudiadas son las cicloisomerizaciones de eninos,[8] que permiten acceder a una gran variedad de estructuras dependiendo del sustrato, así como del mecanismo de la reacción.[9]

Nuestro grupo de investigación ha participado activamente en el progreso de la catálisis con oro gracias al estudio de los mecanismos de reacción, la preparación de nuevos catalizadores y el desarrollo de nuevas reacciones. Estas nuevas metodologías han sido aplicadas en la síntesis total de sesquiterpenos naturales como *(+)-orientalol F*,[10] *(–)-englerins A* y *B*, [11] *(+)-schisanwilsonene A*,[12] y recientemente *epigolobulol* y *aromadendranediol*.[13]

En esta *Tesis Doctoral* presentamos el desarrollo de nuevas reacciones de cicloisomerización de eninos y enalenos, así como su aplicación en la síntesis de nuevos sesquiterpenos naturales.

El primer capítulo está dedicado al estudio de la ciclación intramolecular de vinilciclopropanos con alquinos sustituidos (**1**, Esquema 1) catalizada por complejos de oro(I). De acuerdo con el mecanismo esperado, se formarían productos tricíclicos del tipo **2**. El esqueleto de **2** está presente en la

7. M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448-2462.

8. E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350.

9. (a) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2013**, DOI: 10.1021/ar400174p; (b) C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16-28.

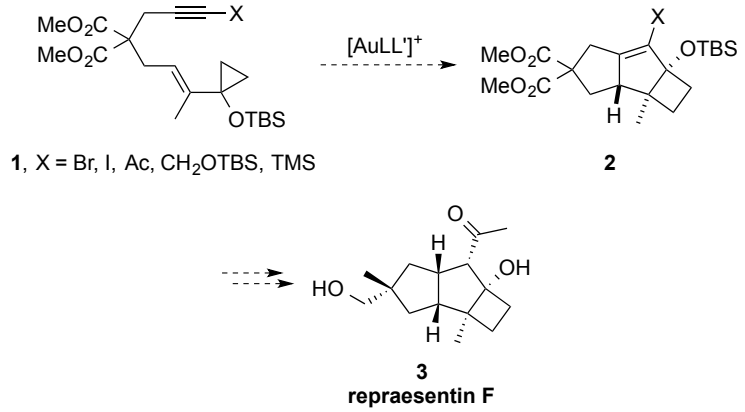
10. E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327-7329.

11. K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.

12. M. Gaydou, R. E. Miller, N. Delpont, J. Ceccon, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 6396-6399.

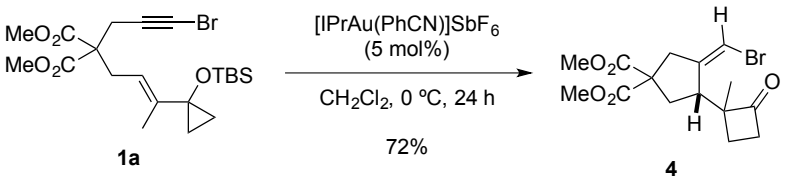
13. (a) Síntesis de *epiglobulol*: M. Livendahl, PhD thesis, ICIQ, 2013; (b) Síntesis estereoselectiva de *epiglobulol* y *aromadendranediol*: J. Carreras, P. McGonigal, resultados no publicados, ICIQ, 2012-2014.

estructura de *repraesentin F* (**3**), un sesquiterpeno de la familia de los *protoilludanes*, aislado en 2006 y que todavía no ha sido sintetizado.[14]



Esquema 1. Cicloisomerización de vinilciclopropanos con alquinos sustituidos

Al llevar a cabo la reacción con alquinos sustituidos, comprobamos que no se forma el producto tricíclico esperado, sino que se obtienen ciclobutanonas. En el caso de X = Br (Esquema 2), la reacción catalizada por el complejo catiónico [IPrAu(PhCN)]SbF_6 dio lugar a la ciclobutanona **4** con un buen rendimiento (72%).

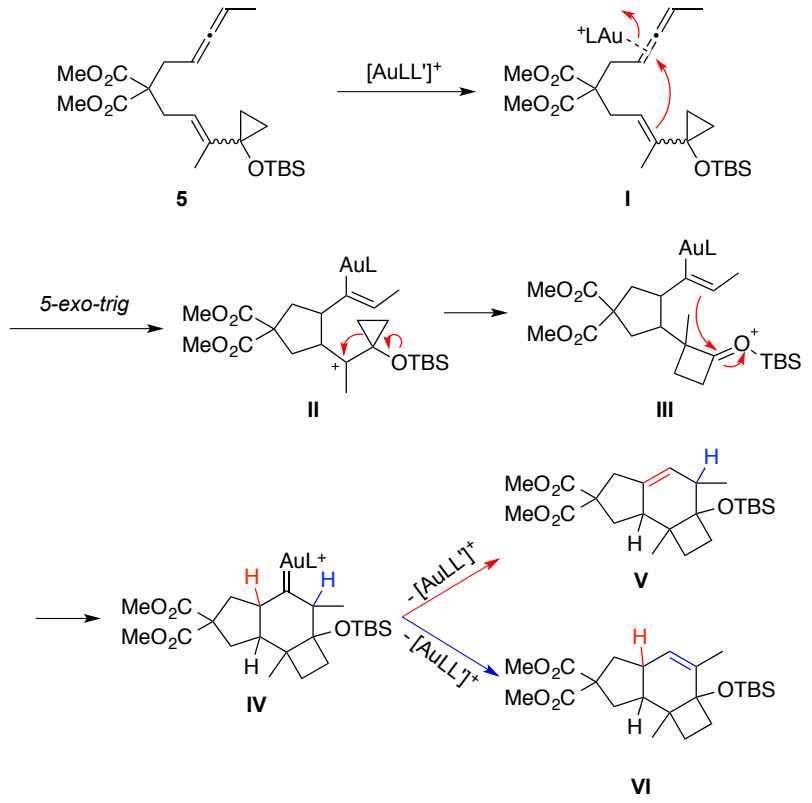


Esquema 2. Formación de la ciclobutanona 4

Desafortunadamente, todos los intentos para sintetizar compuestos tricíclicos a partir de **4** fallaron. Por ello, decidimos probar nuevos sustratos

14. M. Kashiwabara, T. Kamo, H. Makabe, H. Shibata, M. Hirota, *Biosci. Biotechnol. Biochem.* **2006**, *70*, 1502-1505.

conteniendo alenos en lugar de alquinos.[15] Desde un punto de vista mecanístico (Esquema 3), precursores tipo **5** deberían ciclarse mediante un camino de reacción tipo 5-*exo*-trig para dar lugar a **II**. Con la expansión del ciclopropano obtendríamos el intermedio oxonio **III**, el cual experimentaría una ciclación de tipo Prins para originar el carbeno de oro **IV**. La protodemetalación podría ocurrir de manera competitiva por ambos lados del carbeno, dando lugar a la posible formación de dos regioisomeros **V** y **VI**. Al igual que anteriormente, el esqueleto del compuesto final se puede encontrar en multitud de sesquiterpenoides de la familia de los *protoilludanes*.[16]



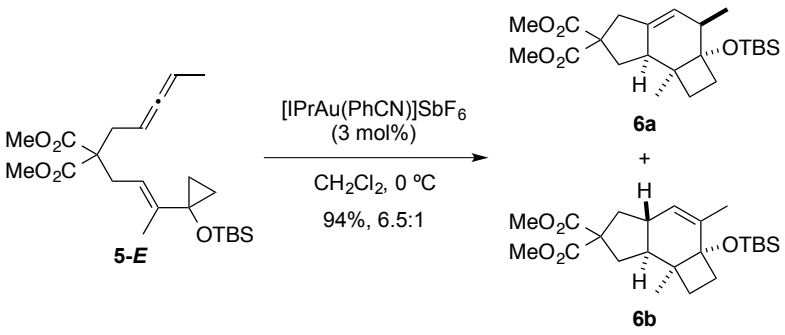
Esquema 3. Mecanismo propuesto para la ciclación de 5

15. A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 4580-4583.

16. P. Siengalewicz, J. Mulzer, U. Rinner, *Eur. J. Org. Chem.* **2011**, 7041-7055.

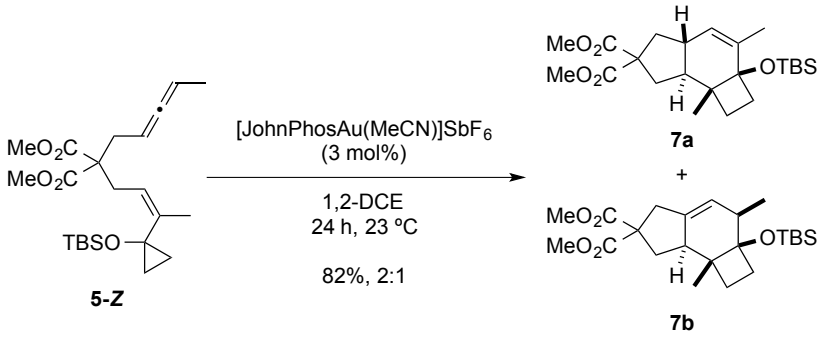
El segundo capitulo de esta *Tesis Doctoral* está dedicado a la síntesis de estos sustratos, así como las correspondientes reacciones de cicloisomerización catalizadas por oro.

En primer lugar, examinamos la reactividad de **5-*E*** en condiciones similares a las utilizadas para **1a** (Esquema 4). En este caso se obtuvieron productos tricíclicos **6a** y **6b**, confirmando el camino de reacción presentado previamente. La configuración relativa de estos compuestos fue determinada por análisis nOe y resultó ser la opuesta a la de los productos naturales.



Esquema 4. Ciclación de E-alenenos

Con el fin de resolver este problema, se llevó a cabo la reacción partiendo de **5-*Z*** y se obtuvo una mezcla de **7a** y **7b** (Esquema 5), que resultaron imposible de separar por cromatografía. No obstante, la separación fue posible transformando los grupos funcionales. Además, estas modificaciones dieron lugar a productos cristalinos que fueron analizados por difracción de rayos X. Las estructuras confirmaron la relación observada previamente por NMR.



Esquema 5. Ciclación de 5-Z

El esqueleto de **7a** es muy similar al producto natural *russujaponol D*, un sesquiterpenoide de la familia de los *protoilludanes* (Figura 1). La mayor diferencia entre estos compuestos es la fusión *cis* o *trans* entre los ciclos de 5 y de 6. Actualmente, se están ensayando nuevos catalizadores de oro(I) en nuestro grupo de investigación para obtener la fusión *cis*, así como la conversión estereoselectiva del dimetil malonato a la funcionalidad existente en el producto natural.

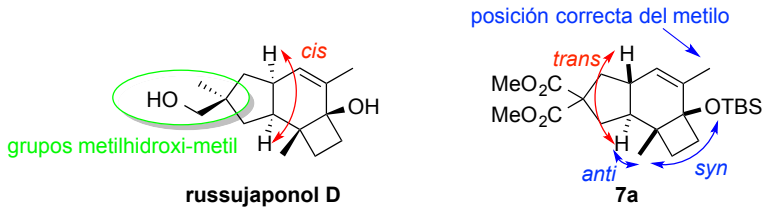
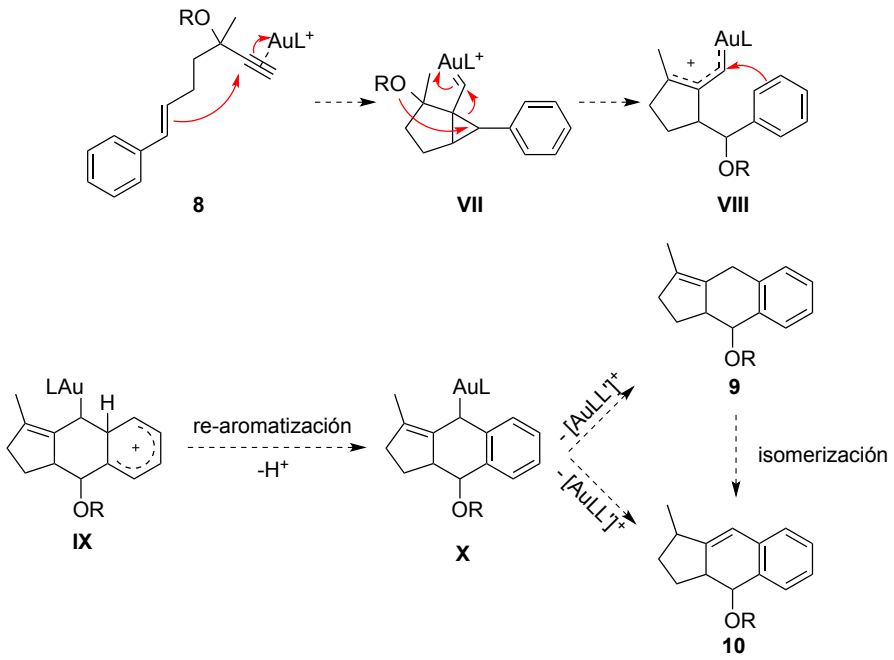


Figura 1. Comparaciones entre russujaponol D y 7a

En el último capítulo de esta *Tesis Doctoral* se aborda la síntesis de miembros de la familia de las *pycnanthuquinones*, gracias a una migración 1,5 de grupos OR.[17]

17. (a) D. M. Fort, R. P. Ubillas, C. D. Mendez, S. D. Jolad, W. D. Inman, J. R. Carney, J. L. Chen, T. T. Ianiro, C. Hasbun, R. C. Bruening, J. Luo, M. J. Reed, M. Iwu, T. J. Carlson, S. R. King, D. E. Bierer, R. Cooper, *J. Org. Chem.* **2000**, *65*, 6534-6539; (b) D. W. Laird, R. Poole, M. Wilkström, I. A. van Altena, *J. Nat. Prod.* **2007**, *70*, 671-674.

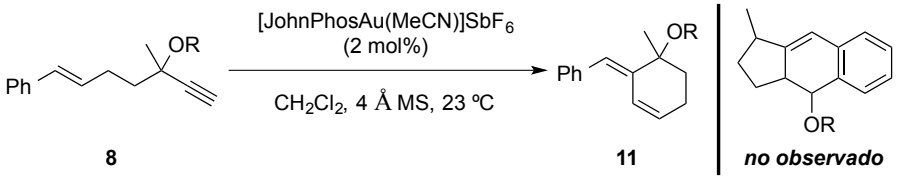
Inicialmente, pensábamos que el enino **8** podría ciclarse según un mecanismo de migración 1,5 del grupo OR propargílico (Esquema 6). El oro se coordinaría al alquino y el ataque nucleófilo del alqueno formaría el intermedio **VII**. El grupo OR podría migrar y abrir el ciclopropano produciendo un catión alílico del tipo **VIII**. Una reacción de tipo Friedel–Crafts causaría la formación del arenio **IX**, que podría rearomatizarse formando **X** mediante la pérdida de un protón. Finalmente, tras un proceso de protodemetalación se obtendrían compuestos tricíclicos **9** y/o **10**.



Esquema 6. Mecanismo propuesto para la ciclación del enino 8

Sin embargo, el producto **10** no se forma, obteniéndose únicamente **11** (Esquema 7). Este compuesto proviene de la ciclación de **8**, pero el

mecanismo es completamente diferente. Se trata en este caso de una transposición de tipo *endo*.[18]

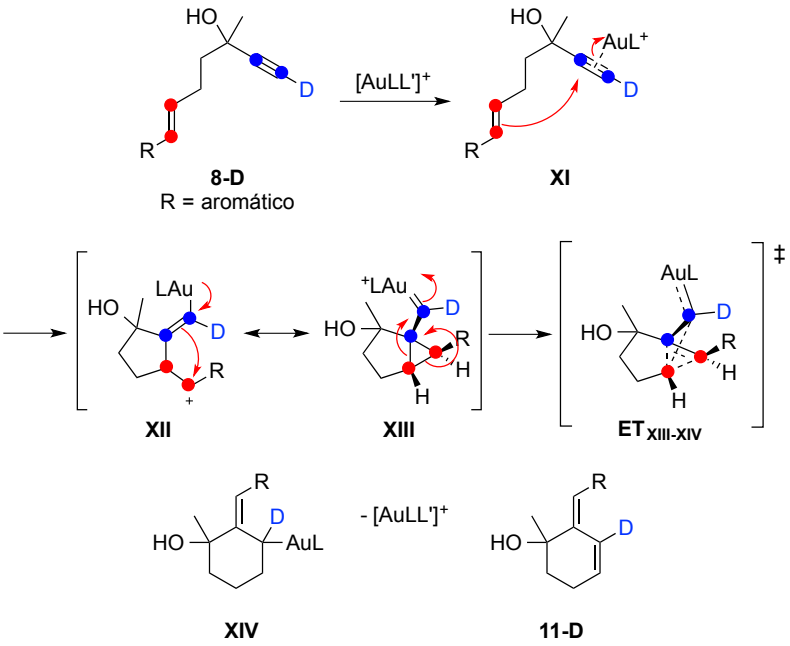


Esquema 7. Ciclación del enino 8 y formación del producto 11

La generalidad de la reacción fue estudiada con varios eninos. La reacción transcurrió con rendimientos excelentes con anillos aromáticos pobres en electrones, y con alcoholes terciarios o segundarios. Por el contrario, sustratos con arenos ricos en electrones se descompusieron durante el proceso y alquinos sustituidos no reaccionaron en estas condiciones.

El mecanismo de la reacción fue estudiado mediante deuteración del alquino (**8-D**, Esquema 8) y resultó ser una transposición de tipo *endo*. La coordinación del oro al alquino provoca el ataque nucleófilo del alqueno para formar el ciclopropil carbeno de oro **XIII**. Estudios teóricos por DFT propusieron el estado de transición $\mathbf{ET_{XIII\text{-}XIV}}$ para soportar la formación del intermedio **XIV**.[18] Finalmente, mediante un proceso de protodemetalación se obtiene el compuesto **11-D**.

18. N. Cabello, E. Jiménez-Núñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Eur. J. Org. Chem.* **2007**, 4217-4223.



Esquema 8. Mecanismo general de la transposición de tipo endo

General Introduction

Gold: from 5,000 years ago to present

Gold is a well-known transition metal, belonging to group 11, with the atomic number 79 (Figure 2). Its symbol, Au, comes from the Latin *aurum* ("shining dawn").

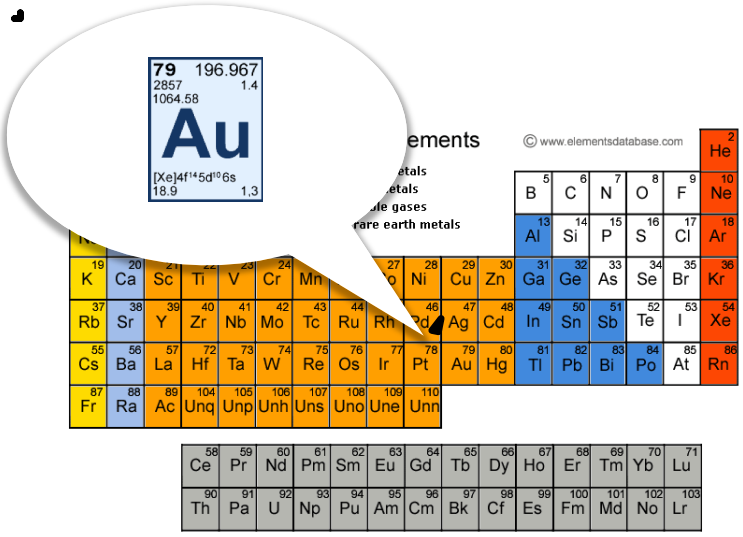


Figure 2. Gold in the periodic table of the elements

^{197}Au is the naturally occurring isotope of gold, although 36 radioisotopes have been synthesized.[19] Gold is a dense, soft, malleable and ductile metal that exhibits a high resistance to corrosion. Moreover, it has an excellent electrical conductivity and a reduced toxicity. It is important to mention that gold present several oxidation states. The most common ones are 0, +1 and +3, and less usual ones include −1, +2 and +5.[20]

Gold has also a long history and somehow have been part of mankind daily life. Indeed, examples of the use of gold in jewelry were found in Ancient

19. G. Audi, O. Bersillon, J. Blachot, A. H. Wapstra, *Nucl. Phys. A* **2003**, *729*, 3-128.

20. C. F. Shaw III, *Chem. Rev.* **1999**, *99*, 2589-2600.

Egypt about 3,000 – 5,000 years ago (Figure 3). Gold had a dramatic role in monetary exchanges as gold-made coins, struck approximately 600 BC, were found in Asia Minor. Nowadays, gold is used as an investment and speculation mean. In the medieval times, gold was also used as an additive in food and in medicine.

Figure 3. Funerary mask of Tutankhamen and the world's oldest gold-made coin

More recently, the interesting physical properties of gold were exploited in many industrial applications.[21] Thin layers of metallic gold are used as infrared protective faceplates in thermal protection suits and on astronauts' helmets (Figure 4). A more surprising function is the heat shielding of the engine compartment of the McLaren F1 racecars. Furthermore, gold is highly conductive to electricity so it is extensively employed in electronics for connections, soldering or coating.

Figure 4. Gold-covered astronaut helmet

21. For a review on optical constants of noble metals (Cu, Ag, Au), see: P. B. Johnson, R. W. Christy, *Phys. Rev. B* **1972**, *6*, 4370-4379.

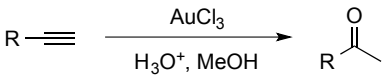
Moreover, gold salts play an important role in chemical industry. Gold cyanide solutions are used as electrolyte for the electroplating of gold onto metallic surfaces. Gold chloride and gold oxide are commonly used as additives in the manufacturing process of colored-glass.[22]

The first examples of gold-catalyzed reactions

Although gold has been known and used for centuries, its application in organic chemistry and catalysis is actually rather recent.

The very first report on the use of gold in organic transformations was the rearrangement of strained small ring hydrocarbons catalyzed by Au(III) salts.[23] Later, a chiral ferrocenylphosphine-gold(I) complex catalyzed an asymmetric aldol reaction of aldehydes with isocyanoacetates.[24]

In 1976, the first reaction in which alkynes are activated by gold(III) salts was reported by the group of Thomas (Scheme 9).[25] A similar study was published later in 1991 for the effective hydration of unactivated alkynes into ketones and the similar reaction with alcohols to form acetals.[26]



Scheme 9. First example of the use of gold(III) salts in catalysis

22. For a recent example of colouring crystals with gold nanoparticles, see: A. N. Kulak, P. Yang, Y.-Y. Kim, S. P. Armes, F. C. Meldrum, *Chem. Commun*. **2014**, *50*, 67-69.

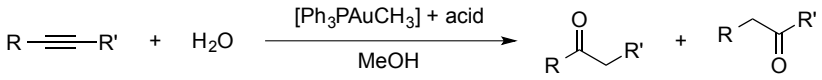
23. (a) P. G. Gassman, G. R. Meyer, F. J. Williams, *J. Am. Chem. Soc.* **1972**, *94*, 7741-7748; (b) L.-U. Meyer, A. de Meijere, *Tetrahedron Lett.* **1976**, *17*, 497-500.

24. Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.

25. R. O. C. Nomran, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983-1987.

26. Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729-3731.

In 1998, the seminal report presenting the use of cationic gold(I) complexes as catalysts for the hydration of alkynes was achieved by the group of Teles (Scheme 10).[27] Hayashi and Tanaka published an extended version of this investigation in 2002.[28]



Scheme 10. First example of the use of a cationic gold(I) complex as catalyst

The "gold rush"

From these examples, the interest in homogenous gold catalysis has grown exponentially,[29] leading to the so called *"catalysis gold rush"*[30] and opening new perspectives for the organic chemistry community.[31]

Both experimental and theoretical studies have been carried out to understand why gold(I) complexes exhibit such a reactivity.[32] Cationic gold(I) species present a strong Lewis acidity due to the relativistically contracted 6*s* orbitals of gold.[33] Interestingly, Au(I)-complexes exhibit a potential to stabilize cationic reaction intermediates because of the

27. J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415-1418.

28. E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem. Int. Ed.* **2002**, *41*, 4563-4565.

29. A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51-65.

30. A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2005**, *44*, 6990-6993.

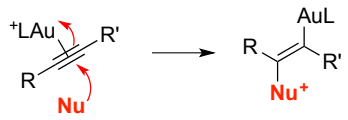
31. A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387-391.

32. (a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403; (b) M. Pernpointner, A. S. K. Hashmi, *J. Chem. Theory Comput.* **2009**, *5*, 2717-2725.

33. For more information on the relativistic effects, see: (a) K. S. Pitzer, *Acc. Chem. Res.* **1979**, *12*, 272-276; (b) P. Pyykkö, *Chem. Rev.* **1988**, *88*, 563-594; (c) L. J. Norrby, *J. Chem. Educ.* **1991**, *68*, 110-113.

relativistically expanded 5*d* orbitals. Although the 5*d* electrons remain too low in energy to be involved in a significant backbonding to anti-bonding orbitals, they are able to delocalize into lower-energy, empty, non-bonding orbitals.

The progresses made in the field of homogenous gold catalysis were accompanied by the development of new complexes. Simple chloride salts such as $AuCl_3$ or $NaAuCl_4$ proved to be carbophilic enough to activate alkynes towards nucleophilic attack (Scheme 11).[34] Moreover, AuCl also demonstrated to be catalytically active.[35] More recently, polynuclear gold complexes emerged and proved to be catalytically active.[36]



Scheme 11. Nucleophilic attack onto an alkyne activated by gold

It was demonstrated that the ligand chelating gold plays a dramatic role in the electrophilicity of the complex (Figure 5).[37] In other words, the reactivity of the complexes is easily tuned by playing with the donating properties of the ligand.

N-Heterocyclic carbenes (NHC) are highly donating ligands, rendering the corresponding gold(I) complexes less reactive, thus very selective.[38,39] More

34. See the first examples of reactions with gold catalysts.

35. N. Morita, N. Krause, *Angew. Chem. Int. Ed.* **2006**, *45*, 1897-1899.

36. E. S. Smirnova, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 9023-9026.

37. (a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378; (b) Y. W. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2013**, DOI: 10.1021/ar400188g.

38. For the synthesis of NHC Au(I) complexes, see: (a) P. De Frémont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics* **2005**, *24*, 2411-2418; (b) P. De Frémont, E. D. Stevens, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, S. P. Nolan, *Chem. Commun.* **2006**, 2045-2047.

electrophilic complexes are accessed with phosphine ligands, whereas the most electrophilic Au(I)-complexes bear phosphite ligands.

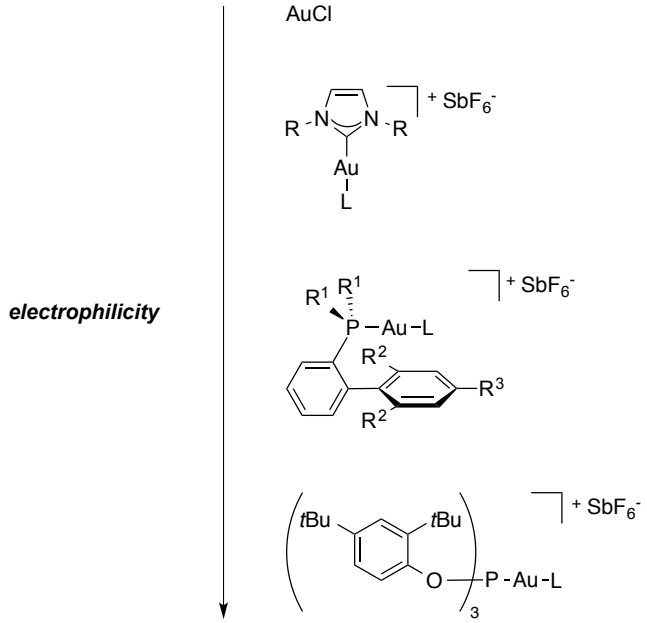


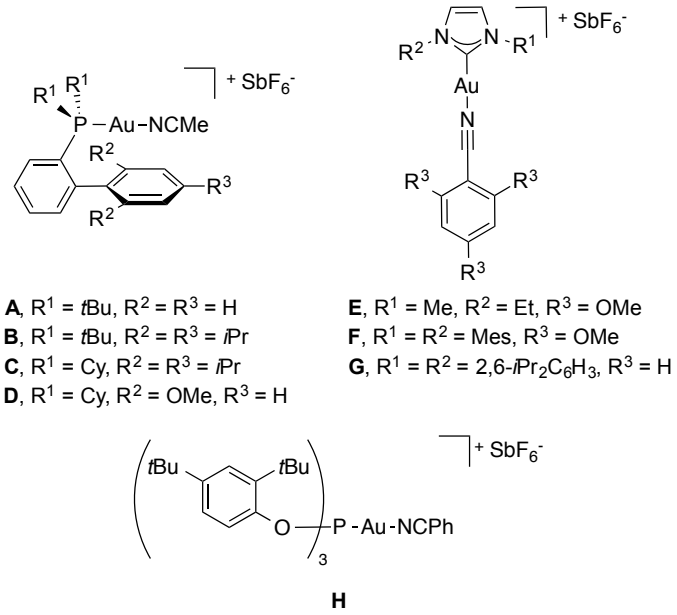
Figure 5. Electrophilicity of gold(I)-complexes depending on the ligand

Our group synthesized some complexes (both neutral and cationic) that are now commercially available and commonly used to perform Au(I)-mediated reactions (Figure 6).[40] Cationic phosphine-complexes[41] are rather active catalysts and really convenient to work with as they are crystalline, non-hygroscopic and stable under ambient conditions for an extended period of time.

39. For some applications of the NHC Au(I) complexes, see: (a) S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032; (b) X.-Y. Lin, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* **2007**, *9*, 2645-2648.

40. C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.

41. E. Herrero-Gómez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459.



A, R^1 = *t*Bu, R^2 = R^3 = H
B, R^1 = *t*Bu, R^2 = R^3 = *i*Pr
C, R^1 = Cy, R^2 = R^3 = *i*Pr
D, R^1 = Cy, R^2 = OMe, R^3 = H

E, R^1 = Me, R^2 = Et, R^3 = OMe
F, R^1 = R^2 = Mes, R^3 = OMe
G, R^1 = R^2 = 2,6-*i*Pr$_2$C$_6$H$_3$, R^3 = H

H

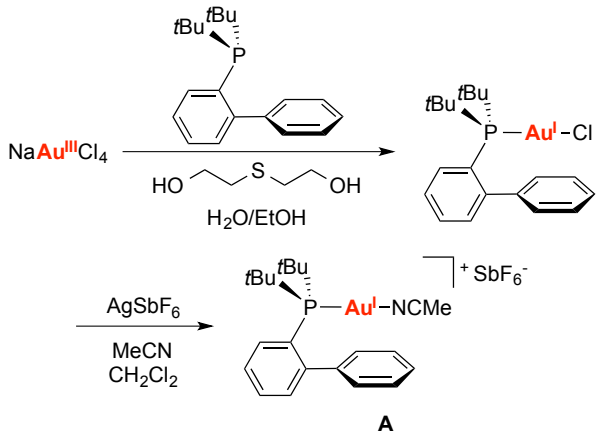
Figure 6. Selection of frequently used cationic Au(I)-complexes

It is important to mention that all the cationic complexes presented in Figure 6 arise from the corresponding neutral complex, in which the ligand is a chloride anion. Abstraction of the chloride by a Ag(I) salt (with a non-coordinating anion) in the presence of a labile ligand (often acetonitrile or benzonitrile) leads to the desired cationic complexes.

Catalyst **A** is widely used in the area of gold(I)-catalysis,[42] and its synthesis is presented in Scheme 12.[43]

42. M. Gaydou, A. M. Echavarren, *e-EROS Encyclopedia of Reagents For Organic Synthesis* **2011**, DOI: 10.1002/047084289X.rn01339.

43. For a synthesis of this complex, see: C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677-1693.



Scheme 12. Two-step synthesis of cationic JohnPhos catalyst A

The better understanding of the Au(I)-complexes properties led to the development of a multitude of new gold-catalyzed reactions. These advances have been extensively reviewed.[44] Gold complexes emerged as such a powerful tool and can promote so many different types of reactions that they were compared to *"a Swiss-army-knife catalyst"* in the toolbox of the modern organic chemist.[45] Gold encountered such a success because it enables reactions to proceed under very mild conditions whereas reactions catalyzed by other transition metals usually require harsher conditions.

44. (a) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333-346; (b) A. Fürstner, P. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449; (c) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180-3211; (d) N. Krause, V. Belting, C. Deutsch, J. Erdsack, H.-T. Fan, B. Gockel, A. Hoffmann-Röder, N. Morita, F. Volz, *Pure Appl. Chem.* **2008**, *80*, 1063-1069; (e) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239-3265; (f) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266-3325; (g) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395-3442; (h) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208-3221; (i) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675-691; (j) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657-1712.

45. H. A. Wegner, M. Auzias, *Angew. Chem. Int. Ed.* **2011**, *50*, 8236-8247.

Among all these transformations, cycloisomerizations of 1,*n*-enynes proceeded extremely well under gold-catalyzed conditions.[46, 47] Interestingly, 1,*n*-allenynes and –allenenes were also suitable substrates for gold(I)-catalyzed cycloisomerizations.

Gold-catalyzed cycloisomerization of 1,*n*-enynes

Cycloisomerization of 1,6-enynes

The mechanisms of the cycloisomerization of enynes are complex and advance through multistep pathways.[44,46] Isolation and even observation of intermediates proved to be rather difficult, forcing the assumption of the mechanistic pathway in many cases. Most of the proposed mechanisms actually rely on extensive study of the literature and analogy to other metal-catalyzed reactions.[48] However, a few intermediates could be observed by spectroscopic methods and characterized.[49] The recent studies (both

46. For some recent reviews on enantioselective cycloisomerization reactions, see: (a) I. D. G. Watson, F. D. Toste, *Chem. Sci.* **2012**, *3*, 2899-2919; (b) F. López, J. L. Mascareñas, *Beilstein J. Org. Chem.* **2013**, *9*, 2250-2264.

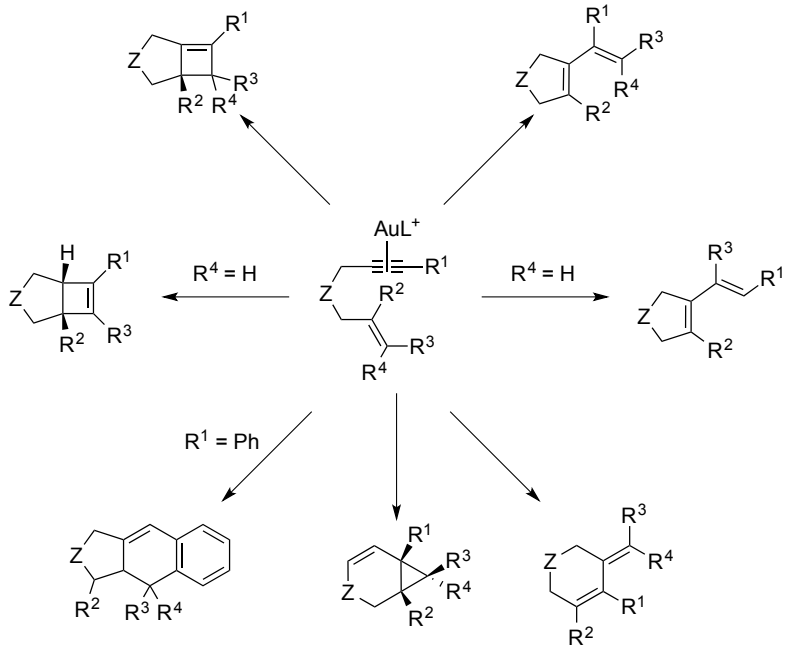
47. (a) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296; (b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350; (c) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.

48. For a recent comparison between gold and palladium in the regioselective cycloisomerization of aromatic enynes, see: J. Aziz, G. Frison, P. Le Menez, J.-D. Brion, A. Hamze, M. Alami, *Adv. Synth. Catal.* **2013**, *335*, 3425-3436.

49. (a) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232-5241; (b) R. E. M. Brooner, T. J. Brown, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2013**, *52*, 6259-6261.

experimental and theoretical)[50] on the gold(I)-catalyzed cycloisomerization of 1,6-enynes have been reviewed.[51]

In the absence of external nucleophiles, the gold(I)-catalyzed cycloisomerization of 1,6-enynes leads to the formation of many different compounds (Scheme 13). The formation of fused cyclobutenes was observed in some cases and their formation was studied by theoretical calculations.[52]



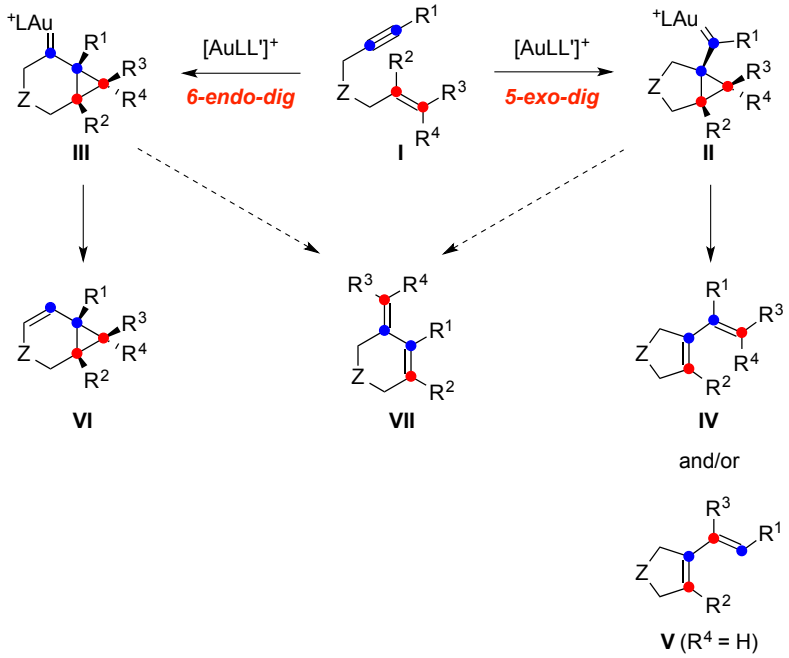
Scheme 13. Examples of products arising from the Au(I)-catalyzed cyclization of 1,6-enynes

50. (a) A. Homs, I. Escofet, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 5782-5785; (b) T. Zhou, L. Xu, Y. Xia, *Org. Lett.* **2013**, *15*, 6074-6077; (c) A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, *Adv. Synth. Catal.* **2014**, *356*, 221-228.

51. (a) H. G. Raubenheimer, H. Schmidbaur, *S. Afr. J. Sci.* **2011**, *107*, 31-34; (b) C. Obradors, A. M. Echavarren, *Chem. Commun.* **2014**, *50*, 16-28; (c) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2013**, DOI: 10.1021/ar400174p.

52. A. Escribano-Cuesta, P. Pérez-Galán, E. Herrero-Gómez, M. Sekine, A. A. C. Braga, F. Maseras, A. M. Echavarren, *Org. Biomol. Chem.* **2012**, *10*, 6105-6111.

Cycloisomerization reactions of 1,6-enynes such as **I** in the presence of gold(I)-complexes usually proceed *via* either a 5-*exo*-dig or a 6-*endo*-dig pathway leading to the formation of cyclopropyl gold carbenes **II** and **III** (Scheme 14). The most common pathway leads to the formation of 1,3-dienes such as **IV**, **V** and **VII** by respectively single cleavage, double cleavage and *endo*-cyclic rearrangement. Cyclopropanation products **VI** arise from a 6-*endo*-cyclization followed by proton elimination and protodeauration of intermediate **III**.[53]

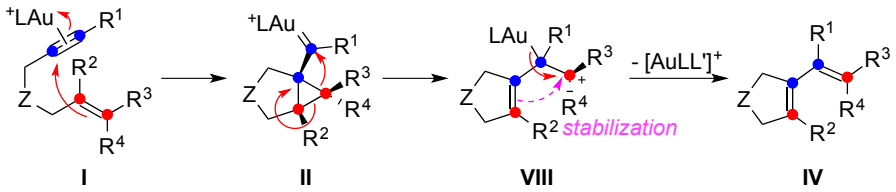


Scheme 14. General pathways for the Au(I)-catalyzed cyclization of 1,6-enynes

The formation of dienes **IV** proceeds through a single cleavage rearrangement (Scheme 15). Formally, the terminal carbon of the alkene migrates to the carbon-terminus of the alkyne. The main pathway proposes the conversion of intermediate **II** into stabilized carbocation **VIII** followed by deauration. This proposal was supported by DFT calculations, however

53. C.-M. Chao, D. Beltrami, P. Y. Toullec, V. Michelet, *Chem. Commun.* **2009**, 6988-6990.

this transformation may also occur by ring opening of a cyclobutene intermediate.[54]



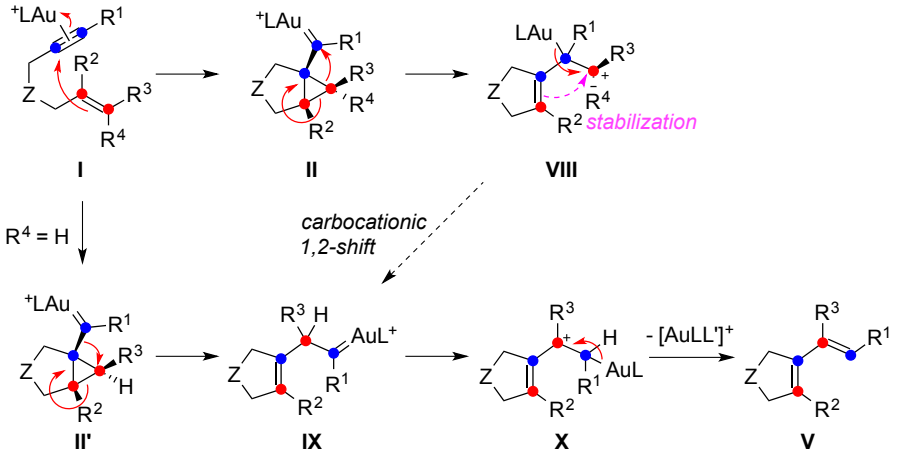
Scheme 15. Single cleavage rearrangement

The formation of dienes **V** arises from a double cleavage rearrangement in which both the alkene and the alkyne C-C multiple bonds are cleaved (Scheme 16). Cyclopropyl gold(I) carbene **II'** is either converted into diene **V** by a formal diatropic rearrangement from intermediate **IX**,[55] or by a carbocationic 1,2-shift of the cyclic alkenyl group in **VIII**.[40]

54. C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buñuel, C. Nevado, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2005**, *44*, 6146-6148.

55. For more information on the diatropic rearrangement, see: (a) M. T. Reetz, *Angew. Chem. Int. Ed.* **1972**, *11*, 129-130; (b) M. T. Reetz, *Angew. Chem. Int. Ed.* **1972**, *11*, 130-131.

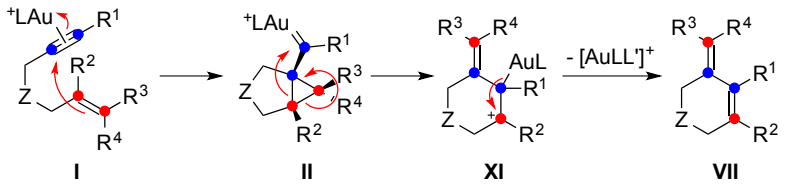
40. C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.



Scheme 16. Double cleavage rearrangement

In general, gold(I)-catalyzed cycloisomerization of 1,6-enynes bearing an electron-donating substituent at the alkyne tend to rearrange following a single cleavage pathway. On the contrary, substrates with electron-withdrawing substituents evolve selectively to double cleavage rearrangement.

Alternatively, six-membered dienes such as **VII** can be observed *via* the 5-*exo*-dig pathway. DFT studies suggest that their formation takes place by rearrangement of intermediate **II** to carbocation **XI**, followed by protodeauration.[56,57]



Scheme 17. Endo-cyclic skeletal rearrangement

56. N. Cabello, E. Jiménez-Núñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Eur. J. Org. Chem.* **2007**, 4217-4223.

57. See mechanistic investigations in chapter 3 for a case study.

As an extension of the 1,6-enyne cycloisomerization, our group reported the intramolecular cyclopropanation of dienynes.[58] The intermediate carbene was trapped by a pendant olefin, leading to cyclopropanation products. Both experimental and theoretical studies were carried out. An intermolecular version of this reaction was also published.[59]

Two other mechanisms of the Au(I)-catalyzed reaction of enynes were discovered in some particular cases and played an important role in total synthesis applications: the Prins cyclization,[60] and the so-called 1,5-migration.[61]

Cycloisomerization of 1,5-enynes

The cycloisomerization of 1,5-enynes has attracted much less attention; nevertheless their reactivity in gold catalysis has been examined comparably.[37]

Similarly to 1,6-enynes, the gold(I)-catalyzed cycloisomerization of 1,5-enynes also progresses *via* both single cleavage[62] and double cleavage

58. C. Nieto-Oberhuber, S. López, M. P. Muñoz, E. Jiménez-Nuñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1694-1702.

59. P. Pérez-Galán, E. Herrero-Gómez, D. T. Hog, N. J. A. Martin, F. Maseras, A. E. Echavarren, *Chem. Sci.* **2011**, *2*, 141-149.

60. See introduction of chapter 1 for a detailed presentation of the mechanism and applications in total synthesis.

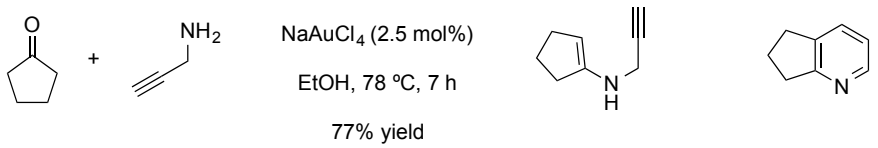
61. See introduction of chapter 3 for a detailed presentation of the mechanism and applications in total synthesis.

37. (a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378; (b) Y. W. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2013**, DOI: 10.1021/ar400188g.

62. F. Gagosz, *Org. Lett.* **2005**, *7*, 4129-4132.

rearrangements.[63] Theoretical studies to support the mechanistic proposals were carried out in our group.[64]

One of the first reports of *endo*-cyclization of 1,5-enynes was applied in a new synthesis of pyridines (Scheme 18).[65]



Scheme 18. Synthesis of pyridines by Au(III)-catalyzed cyclization of 1,5-enynes

Another example of Au(I)-catalyzed cycloisomerization of 1,5-enynes substituted at the alkyne terminus provided 1,3-di- and 1,2,3-trisubstituted naphthalenes. The reaction proceeded mainly *via* a 6-*endo*-dig pathway.[66] More recently, our group synthesized oxatricyclic derivatives by gold-catalyzed cyclization of oxo-1,5-enynes.[67]

Cycloisomerization of 1,*n*-enynes (*n*>6)

The cyclization of 1,7-enynes has also been studied,[68] however often being treated as a simple extension of the cyclization of 1,6-enynes. Nevertheless,

63. (a) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806-11807; (b) J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 9705-9710; (c) C. Li, Y. Zeng, H. Zhang, J. Feng, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 6413-6417.

64. V. López-Carillo, N. Huguet, Á. Mosquera, A. M. Echavarren, *Chem. Eur. J.* **2011**, *17*, 10972-10978.

65. G. Abbiati, A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, E. Rossi, *J. Org. Chem.* **2003**, *68*, 6959-6966.

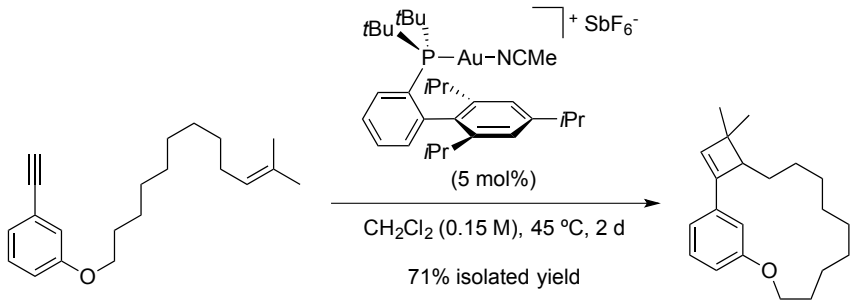
66. T. Shibata, Y. Ueno, K. Kanda, *Synlett* **2006**, *3*, 411-414.

67. N. Huguet, A. M. Echavarren, *Synlett* **2012**, *23*, 49-53.

68. N. Cabello, C. Rodríguez, A. M. Echavarren, *Synlett* **2007**, *11*, 1753-1758.

in comparison with other transition metals, gold allowed the use of reduced catalyst loading and milder reaction conditions.[69,70,71]

Reports accounting for the cycloisomerization of 1,8-[72] and 1,9-enynes are scarce.[73] Larger 1,*n*-enynes (*n* = 10-16) could also be cycloisomerized by gold-catalyzed reaction, forming macrocycles incorporating a cyclobutene moiety (Scheme 19).[74,75]



1,16-enyne

Scheme 19. Gold(I)-catalyzed cyclization of a 1,16-enyne to m-cyclophane

69. Some selected examples of 1,7-enyne cyclizations catalyzed by ruthenium complexes: (a) N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049-6050; (b) N. Chatani, K. Kataoka, S. Murai, N. Furukawa, Y. Seki, *J. Am. Chem. Soc.* **1998**, *120*, 9104-9105; (c) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 714-715.

70. For an example of 1,7-enyne cyclizations catalyzed by palladium complexes, see: M. Hatano, K. Mikami, *J. Am. Chem. Soc.* **2003**, *125*, 4704-4705.

71. For an example of 1,7-enyne cyclization catalyzed by $GaCl_3$ in the total synthesis of (±)-salviasperanol, see: E. M. Simmons, R. Sarpong, *Org. Lett.* **2006**, *8*, 2883-2886.

72. H. Ito, H. Ohmiya, M. Sawamura, *Org. Lett.* **2010**, *12*, 4380-4383.

73. E. Comer, E. Rohan, L. Deng, J. A. Porco Jr., *Org. Lett.* **2007**, *9*, 2123-2126.

74. C. Obradors, D. Leboeuf, J. Aydin, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 1576-1579.

75. Cyclobutenes were isolated in the Au(I)-catalyzed intermolecular [2+2] cycloaddition of alkynes with alkenes: V. López-Carillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292-9294.

Applications of gold(I)-catalysis in total synthesis

As demonstrated earlier, gold(I)-catalyzed reactions are perfectly suitable to construct easily and efficiently complex molecules. Therefore, many applications in total synthesis flourished in the literature over the past decade. Recent applications were reviewed in 2012 and some selected examples are presented in Figure 7.[76]

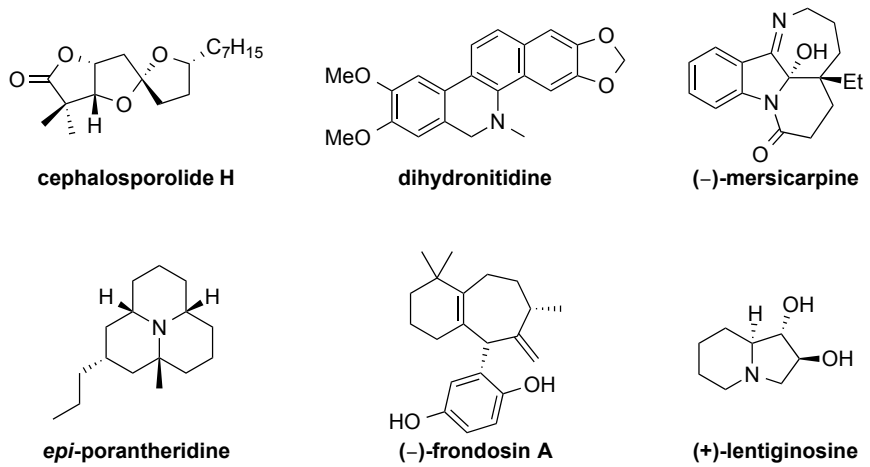


Figure 7. Selected examples of natural products synthesized using Au(I)-catalysis

Our group contributed actively to theses applications by reporting the total syntheses of several bioactive sesquiterpenes (Figure 8).

The first one, (+)-orientalol F,[77] was synthesized by a stereoselective gold(I)-catalyzed [2+2+2] cycloaddition of a ketoenyne substituted at the propargylic position. This methodology was later extended to the enantioselective synthesis of (–)-englerins A and B.[78] An intermolecular version of this reaction led to the formation of related oxabicycles.[79]

76. M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448-2462.

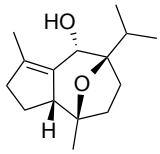
77. E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327-7329.

78. K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.

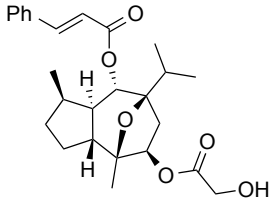
79. C. Obradors, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 3547-3551.

(+)-Schisanwilsonene A, a carotene-type sesquiterpenoid, was synthesized in 18 steps involving a complex gold(I)-catalyzed cyclization/1,5-migration/cyclopropanation as key step.[80]

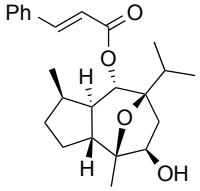
More recently, short syntheses of epiglobulol and aromadendranediol were completed in the group, relying on the 1,5-migration mechanism.[81]



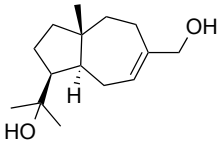
(+)-orientalol F



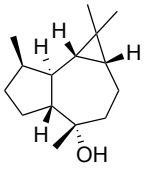
(–)-englerin A



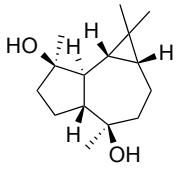
(–)-englerin B



(+)-schisanwilsonene A



epiglobulol



aromadendranediol

Figure 8. Molecules synthesized by the Echavarren group employing gold(I)-catalysis

80. M. Gaydou, R. E. Miller, N. Delpont, J. Ceccon, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 6396-6399.

81. (a) M. Livendahl, PhD thesis, ICIQ, 2013; (b) J. Carreras, P. McGonigal, unpublished results, ICIQ, 2012-2014.

Recent developments in the field of gold chemistry

Even though the field of gold catalysis has been intensively studied by both experimentation and theoretical calculations, it still continues its growth and represents one of the current *"hot topics"* in organic chemistry. Countless applications are published every week in the literature. We present hereafter a non-exhaustive selection of publications issued recently.[82]

Gold(I)-catalyzed reactions were applied in the synthesis of anthracenes,[83] and other polycyclic hydrocarbons.[84] Furthermore, homogeneous gold(I)-promoted transformations allowed the formation of a plethora of heterocycles such as quinolones,[85] azepinones,[86] indole-related molecules,[87] 1,4-dihydropyridines,[88] or indolequinones and pyrroles.[89] Oxygen-based heterocycles were also produced by gold(I)-catalysis.[90]

82. Published online between September 1st and November 8th 2013.

83. C. Shu, C.-B. Chen, W.-X. Chen, L.W. Ye, *Org. Lett.* **2013**, *15*, 5542-5545.

84. (a) A. M. Sanjuán, A. Martínez, P. García-García, M. A. Fernández-Rodríguez, R. Sanz, *Beilstein J. Org. Chem.* **2013**, *9*, 2242-2249; (b) R. J. F. Berger, M. Fuchter, I. Krossing, H. Rzepa, J. Schaefer, H. Scherer, *Chem. Commun.* **2014**, DOI: 10.1039/c3cc46986g.

85. S. Zhu, L. Wu, X. Huang, *J. Org. Chem.* **2013**, *78*, 9120-9126.

86. J. M. Fernández-García, P. García-García, M. A. Fernández-Rodríguez, A. Pérez-Anes, E. Aguilar, *Chem. Commun.* **2013**, *49*, 11185-11187.

87. (a) M. Chiarucci, R. Mocci, L. D. Syntrivanis, G. Cera, A. Mazzanti, M. Bandini, *Angew. Chem. Int. Ed.* **2013**, *52*, 10850-10853; (b) J. E. Perea-Buceta, T. Wirtanen, O.-V. Laukkanene, M. K. Mäkelä, M. Nieger, M. Melchionna, N. Huittinen, J. A. Lopez-Sanchez, J. Helaja, *Angew. Chem. Int. Ed.* **2013**, *52*, 11835-11839.

88. S. Wang, H. Chen, H. Zhao, H. Cao, Y. Li, Q. Liu, *Eur. J. Org. Chem.* **2013**, 7300-7304.

89. A. Abdukader, Q. Xue, A. Lin, M. Zhang, Y. Cheng, C. Zhu, *Tetrahedron Lett.* **2013**, *54*, 5898-5900.

90. (a) R. Quach, D. P. Furkert, M. A. Brimble, *Tetrahedron Lett.* **2013**, *54*, 5865-5868; (b) R. Guo, K.-N. Li, L.-Z. Gong, *Org. Biomol. Chem.* **2013**, *11*, 6707-6712; (c) C.-E. Kim, T. Ryu, S. Kim, K. Lee, C.-H. Lee, P. H. Lee, *Adv. Synth. Catal.* **2013**, *355*, 2873-2883.

The design of new catalysts and their applications is a very productive domain,[91] as well as the study of the mechanistic pathways behind gold-catalyzed transformations.[92] The development of tandem catalysis,[93] and enantioselective reactions with gold are also attracting the attention of the synthetic community.[46]

Gold(I)-catalyzed oxidative reactions (*i.e.* in the presence of an external oxidant) were utilized for the synthesis of indenones,[94] α-mesyloxy[95] and α-halomethyl ketones, [96] as well as quinolines [97] and indole-related heterocycles.[98] An example of construction of tetracyclic ketoethers under oxidative conditions, using $AuCl_3$ as catalyst, was also reported. [99]

91. (a) C. Dash, M. Yousufuddin, T. R. Cundari, H. V. R. Dias, *J. Am. Chem. Soc.* **2013**, *135*, 15479-15488; (b) G. Ung, G. Bertrand, *Angew. Chem. Int. Ed.* **2013**, *52*, 11388-11391; (c) A. Collado, A. Gómez-Suárez, Y. Oonishi, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2013**, *49*, 10745-10747; (d) S. Hase, Y. Kayaki, T. Ikariya, *Organometallics* **2013**, *32*, 5285-5288; (e) S. Dupuy, S. P. Nolan, *Chem. Eur. J.* **2013**, *19*, 14034-14038; (f) A. Gómez-Suárez, D. J. Nelson, D. G. Thompson, D. B. Cordes, D. Grahma, A. M. Z. Slawin, S. P. Nolan, *Beilstein J. Org. Chem.* **2013**, *9*, 2216-2223; (g) Y.-W. Sun, Q. Xu, M. Shi, *Beilstein J. Org. Chem.* **2013**, *9*, 2224-2232; (h) G. A. Frenánadez, A. S. Picco, M. R. Ceolín, A. B. Chopa, G. F. Silbestri, *Organometallics* **2013**, *32*, 6315-6323.

92. (a) S. Montserrat, H. Faustino, A. Lledós, J. L. Mascareñas, F. López, G. Ujaque, *Chem. Eur. J.* **2013**, *19*, 15248-15260; (b) M. M. Hansmann, M. Pernpointner, R. Döpp, A. S. K. Hashmi, *Chem. Eur. J.* **2013**, *19*, 15290-15303; (c) D.-H. Zhang, X.-Y. Tang, M. Shi, *Acc. Chem. Res.* **2013**, 10.1021/ar400159r; (d) B. Rubial, A. Ballesteros, J. M. González, *Adv. Synth. Catal.* **2013**, *355*, 3337-3343.

93. (a) A. W. Gregory, P. Jakubec, P. Turner, D. J. Dixon, *Org. Lett.* **2013**, *15*, 4330-4333; (b) F. Rodríguez, F. J. Fañanás, *Synlett* **2013**, *24*, 1757-1771.

94. P. Nösel, L. Nunes dos Santos Comprido, T. Lauterbach, M. Rudolph, F. Rominger, A. S. K. Hashmi, *J. Am. Chem. Soc.* **2013**, *135*, 15662-15666.

95. L. Xie, Z. Liang, D. Yan, W. He, J. Xiang, *Synlett* **2013**, *24*, 1809-1812.

96. L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang, W. He, *J. Org. Chem.* **2013**, *78*, 9190-9195.

97. D. B. Huple, S. Ghorpade, R.-S. Liu, *Chem. Eur. J.* **2013**, *19*, 12965-12969.

98. L. Wang, X. Xie, Y. Liu, *Angew. Chem. Int. Ed.* **2013**, *53*, 13302-13306.

99. T. Gross, P. Metz, *Chem. Eur. J.* **2013**, *19*, 14787-14790.

Chapter 1. Progress Towards the Synthesis of Repraesentin F

Introduction – the cycloisomerization of enynes *via* Prins-type reaction

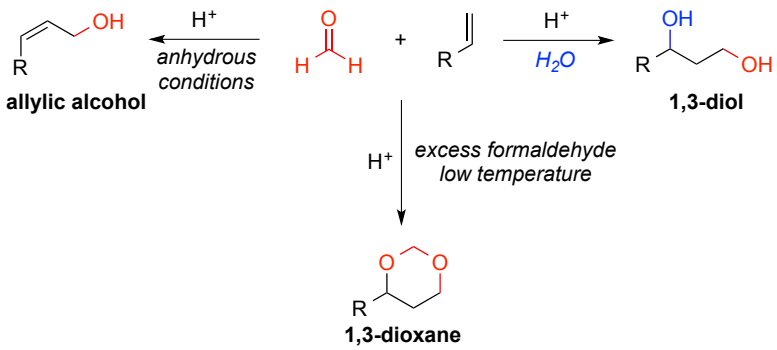
The Prins reaction – background

The Prins reaction is an electrophilic addition of a carbonyl compound (aldehyde or ketone) to an alkene or alkyne.[100,101] The outcome of the reaction is highly dependent on the conditions employed (Scheme 20).[102] The reaction of formaldehyde in water with a protic acid (sulfuric acid for instance) leads to the formation of a 1,3-diol. Under anhydrous conditions, an allylic alcohol can be isolated. With an excess of formaldehyde and a low reaction temperature the reaction product is a 1,3-dioxane. When water is replaced by acetic acid the corresponding esters are formed.

100. For a review with a detailed historical introduction, see: E. Arundale, L. A. Miseka, *Chem. Rev.* **1952**, *51*, 505-555;

101. For a recent update on the Prins reaction, see: I. M. Pastor, M. Yus, *Curr. Org. Chem.* **2012**, *16*, 1277-1312.

102. For some applications and developments, see: (a) T. Bach, J. Löbel, *Synthesis* **2002**, 2521-2526; (b) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, N. Niranjan, A. R. Prasad, *Eur. J. Org. Chem.* **2003**, 1779-1783; (c) J. S. Yadav, B. V. Subba Reddy, M. K. Gupta, S. K. Biswas, *Synthesis* **2004**, 2711-2715; (d) G.-Q. Tian, M. Shi, *Org. Lett.* **2007**, *9*, 2405-2408; (e) F. Liu, T.-P. Loh, *Org. Lett.* **2007**, *9*, 2063-2066; (f) V. Polshettiwar, R. S. Varma, *J. Org. Chem.* **2007**, *72*, 7420-7422; (g) J. S. Yadav, B. V. S. Reddy, G. G. K. S. N. Kumar, S. Aravind, *Synthesis* **2008**, 395-400; (h) K. Tadpetch, S. D. Rychnovsky, *Org. Lett.* **2008**, *10*, 4839-4842; (i) N. Chavre, H. Choo, J. K. Lee, A. N. Pae, Y. Kim, Y. S. Cho, *J. Org. Chem.* **2008**, *73*, 7467-7471.



Scheme 20. Example of Prins reactions

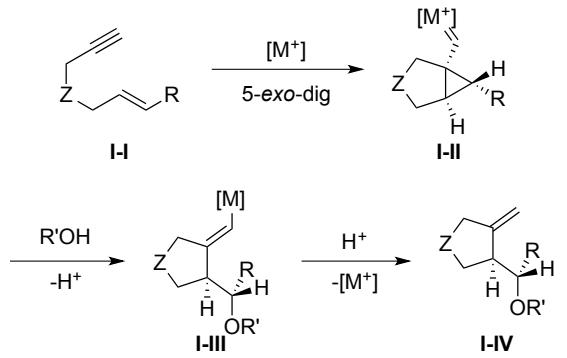
The Prins reaction was widely used as cyclization method in the context of many complex natural product syntheses.[103]

Preliminary studies on the cycloisomerization of enynes *via* Prins-type reaction

The hydroxy- or alkoxycyclization of enynes **I-I** catalyzed by electrophilic transition-metal complexes usually proceeds through cyclopropyl metal carbenes similar to **I-II** (Scheme 21). These carbenes can react with nucleophiles (such as R'OH) to give vinyl metal intermediates **I-III**. The reaction is then terminated by proto-demetalation of the alkenyl metal intermediate **I-III** to give cyclized products such as **I-IV**.[104]

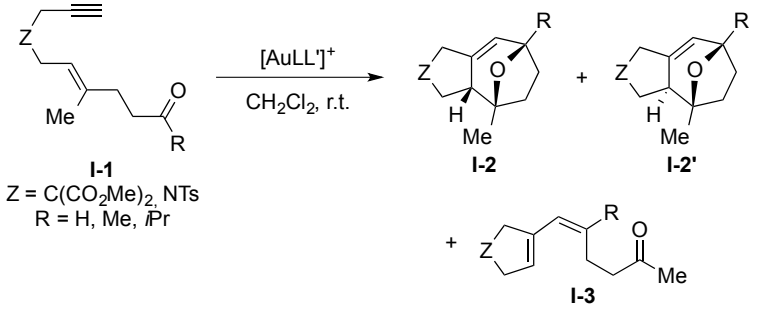
103. For recent reviews, see: (a) S. Yokoshima, *Chem. Pharm. Bull.* **2013**, *61*, 251-257; (b) X. Han, G. Peh, P. E. Floreancig, *Eur. J. Org. Chem.* **2013**, 1193-1208.

104. See general introduction for a full discussion on the mechanisms and the corresponding references.



Scheme 21. Mechanism for the hydroxy- and alkoxycyclization of enynes

In 2006, our group discovered that the alkenyl metal intermediate (**I-III** in Scheme 21) could be trapped with appropriate substituents in a Prins-type cyclization.[105] Enynes of type **I-1**, bearing a carbonyl group at the alkenyl side chain, reacted to form oxatricyclic derivatives **I-2** and **I-2'** and rearranged ketones **I-3** by using Au(I)-catalysts (Scheme 22).

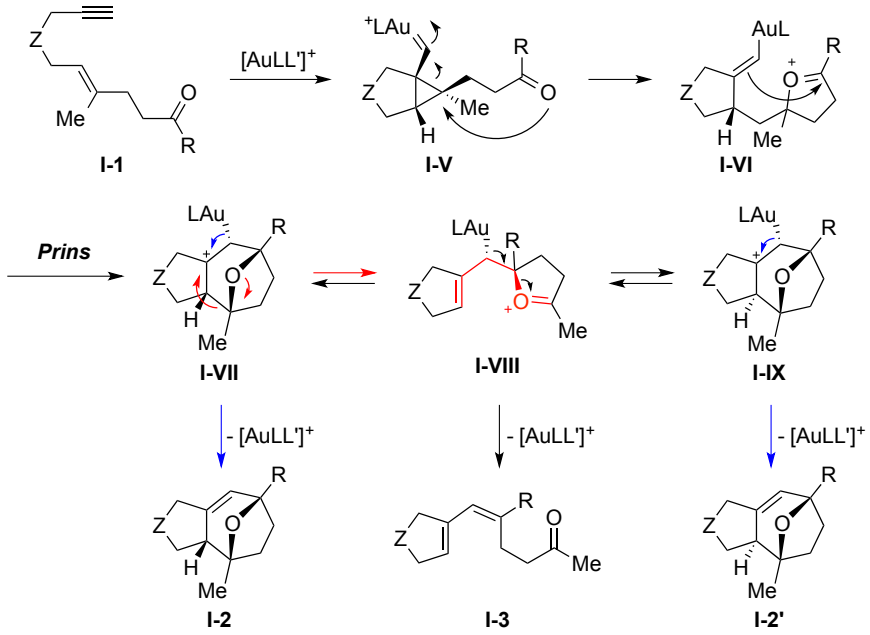


Scheme 22. Gold(I)-catalyzed cyclization of enynes I-1

The proposed mechanism for this transformation is presented in Scheme 23. The pendant carbonyl group acts as an internal nucleophile and attacks cyclopropyl gold-carbene **I-V**, thus forming oxonium cation **I-VI**.

105. E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455.

Subsequently, the Prins-type reaction takes place and **I-VII** is produced.[106] Intermediate **I-VII** is a substituted 4-tetrahydropyranyl cation,[107] which can evolve following two different pathways. Elimination of the metal fragment forms tricycles **I-2**. Alternatively, an elimination with fragmentation of the seven-membered ring via **I-VIII** leads to rearranged carbonyl compounds **I-3**. Minor epimers **I-2'** can arise by a competitive 2-oxonia-Cope rearrangement[108] through **I-VIII** and **I-IX**.



Scheme 23. Proposed mechanism for the cyclization of oxo-enynes via a Prins reaction.

106. (a) L. E. Overman, L. D. Pennington, *J. Org. Chem.* **2003**, *68*, 7143-7157; (b) R. Jasti, C. D. Anderson, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2005**, *127*, 9939-9945.

107. R. W. Lader, J. N. Harvey, M. T. Oakley, *J. Am. Chem. Soc.* **2002**, *124*, 4960-4961.

108. S. D. Rychnovsky, S. Marumoto, J. J. Jaber, *Org. Lett.* **2001**, *3*, 3815-3818.

This cascade reaction allows in one step the formation of tricyclic skeletons present in certain natural products such as β-kessyl ketone[109] and orientalol E[110] (Figure 9).

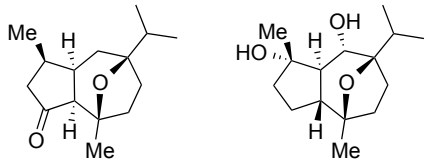


Figure 9. Structures of β-kessyl ketone and orientalol E

A related Prins-type cyclization was observed in the cyclization of enynes bearing a vinylcyclopropane (**I-4** type, Table 1).[105] These precursors formed tricyclic compounds with an octahydrocyclobuta[*a*]pentalene skeleton.[111,112,113]

109. H. Hikino, Y. Takeshita, H. Hikino, T. Takemoto, S. Ito, *Chem. Pharm. Bull.* **1967**, *15*, 485-489.

110. G.-P. Peng, G. Tian, X.-F. Huang, F.-C. Lou, *Phytochemistry* **2003**, *63*, 877-881.

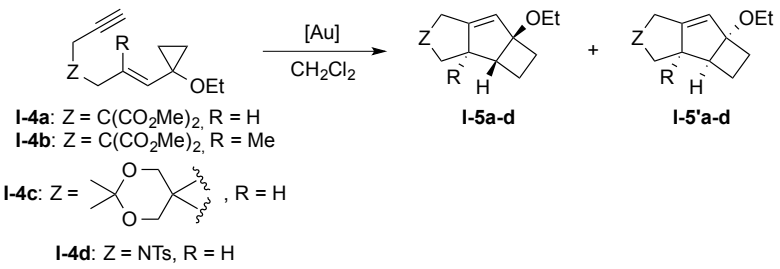
105. E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455.

111. Rh(I)-catalyzed reaction of cyclopropylenynes: (a) P. A. Wender, H. Takahashi, B. Witulski, *J. Am. Chem. Soc.* **1995**, *117*, 4720-4721; (b) Z.-X. Yu, P. A. Wender, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 9154-9155; and references therein.

112. Ru(II)-catalyzed reaction of cyclopropylenynes: (a) B. M. Trost, F. D. Toste, H. Shen, *J. Am. Chem. Soc.* **2000**, *122*, 2379-2380; (b) B. M. Trost, H. C. Shen, D. B. Horne, F. D. Toste, B. G. Steinmetz, C. Korandin, *Chem. Eur. J.* **2005**, *11*, 2577-2590.

113. Ni(I)-catalyzed cyclization of cyclopropylenynes: G. Zuo, J. Louie, *J. Am. Chem. Soc.* **2005**, *127*, 5798-5799.

Table 1. Prins-type reaction in the cyclization of alkyne vinylcyclopropanes I-4



I-4a: Z = $C(CO_2Me)_2$, R = H
I-4b: Z = $C(CO_2Me)_2$, R = Me
I-4c: Z = , R = H
I-4d: Z = NTs, R = H

I-5a-d **I-5'a-d**

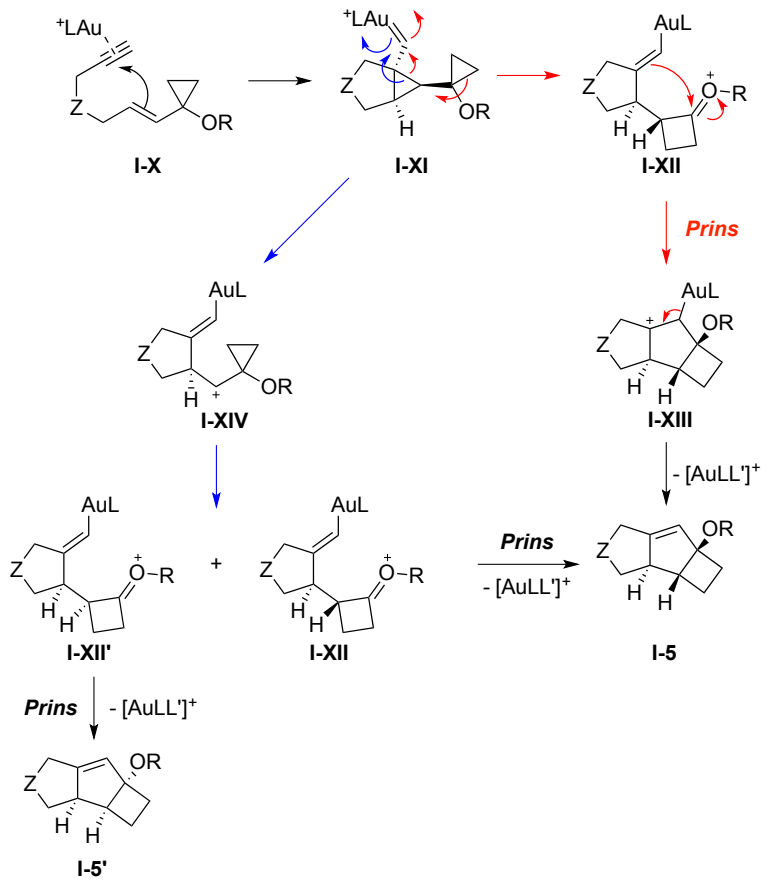
Entry	Enyne	[Au]	*t*	Product (ratio)	Yield (%)
1[a]	**I-4a**	**A**	5 min	**I-5a**/**I-5'a** (1:1)	88
2[b]	**I-4a**	**A**	5 min	**I-5a**/**I-5'a** (1:8)	81
3[b,c]	**I-4a**	**A**	5 min	**I-5a**/**I-5'a** (1:1)	93
4[b,d]	**I-4a**	AuCl	24 h	**I-5a**/**I-5'a** (30:1)[e]	80[e]
5[a,f]	**I-4b**	**A**	5 min	**I-5'b**	44
6[b,f]	**I-4b**	**A**	5 min	**I-5b**/**I-5'b** (2.5:1)	39
7[b,g]	**I-4c**	**A**	5 min	**I-5c**/**I-5'c** (3.2:1)	60
8[b,d,h]	**I-4c**	AuCl	2 h	**I-5c**/**I-5'c** (12:1)	91
9[b,g]	**I-4d**	cat[i]	5 min	**I-5d**/**I-5'd** (2:1)	60

[a] Reaction carried out in CH_2Cl_2 ($H_2O \approx 2$ ppm) with 3 mol% catalyst at r.t.
[b] Reaction with 3-5 mol% water.
[c] Reaction with NH_4Cl (2 equiv).
[d] Reaction at carried out at 0 ºC.
[e] Average of five runs and determined by ^1H NMR.
[f] *E*/*Z* ratio = 1:1.
[g] 2 mol% catalyst.
[h] 12 mol% catalyst.
[i] cat = $[Au(PPh_3)(MeCN)]SbF_6$

The following mechanism was proposed for the cyclization of substrates of type **I-4** (Scheme 24). Complex **I-X** is formed upon exposure of **I-4** to a gold(I) cationic catalyst. **I-X** cyclizes to cyclopropyl gold carbene **I-XI**, which ring-expands to alkenyl gold intermediate **I-XII**. Complex **I-XII** then

undergoes a Prins-type cyclization and evolves to tricyclic intermediate **I-XIII**, which upon protodemetalation forms tricycles **I-5**.

The concerted pathway (**I-XI** to **I-XII**) is probably preferred when AuCl is used as the catalyst. On the contrary, cationic Au(I)-complexes apparently favor a non-concerted reaction via cyclopropyl-stabilized cation **I-XIV**, which undergoes a non-stereospecific ring expansion to give mixtures of **I-5** and **I-5'**.

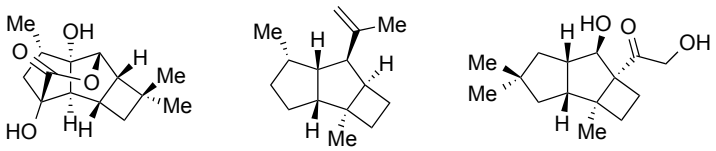


Scheme 24. Proposed mechanism for the cyclization of I-4 type substrates

The study of the reaction scope indicated that the stereochemical outcome of the reaction is closely related to the amount of water. This suggests a pathway in which water opens intermediate **I-XI** to form an alcohol,

followed by a pinacol-type expansion. This process would result in an overall retention of configuration to form **I-XII'**. It is important to mention that cyclobutanones were also formed as minor side products in these reactions.[114]

The tricyclic compounds isolated in this gold-catalyzed cyclization of alkyne vinylcyclopropanes are closely related to natural compounds such as fascicularone B,[115] kelsoene[116] and sulcatine G (Figure 10).[117]



fascicularone B **kelsoene** **sulcatine G**

Figure 10. Structures of fascicularone B, kelsoene and sulcatine G

In order to obtain the scaffolds related to the naturals products presented previously, the cyclization of substrates **I-4e** and **I-4f** was also examined using Au(I) and Pt(II) catalysts (Table 2).[118] The reactions proceeded with poor stereoselectivities and led to the formation of the undesired *syn-cis* diastereoisomers as major compound.

114. Ring expansion of alkynylcyclopropanols catalyzed by Au(I): J. P. Markham, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708-9709.

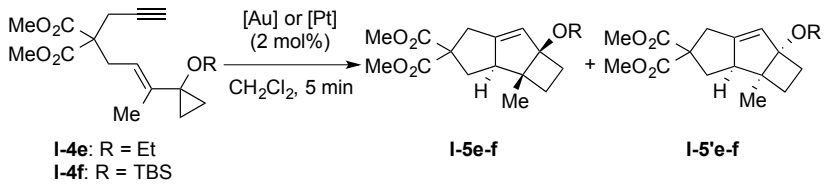
115. H. Akasaka, Y. Shiono, T. Murayama, M. Ikeda, *Helv. Chim. Acta* **2005**, *88*, 2944-2950.

116. L. Zhang, M. Koreeda, *Org. Lett.* **2002**, *4*, 3755-3758; T. Bach, A. Spiegel, *Synlett* **2002**, 1305-1307.

117. (a) E. Piers, A. Orellana, *Synthesis* **2001**, 2138-2142; (b) S. Fietz-Razavian, S. Schulz, I. Dix, P. G. Jones, *Chem. Commun.* **2001**, 2154-2155; (c) G. Mehta, K. Screenivas, *Tetrahedron Lett.* **2002**, *43*, 3319-3321; (d) D. G. Taber, K. J. Frankowski, *J. Org. Chem.* **2005**, *70*, 6417-6421.

118. C. K. Claverie, unpublished results, ICIQ, 2007.

Table 2. Prins-type reaction in the cyclization of alkyne vinylcyclopropanes I-4e and I-4f



I-4e: R = Et
I-4f: R = TBS

I-5e-f

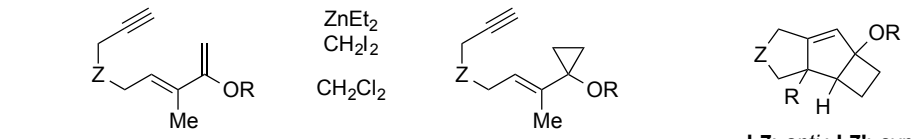
I-5'e-f

Entry	Enyne	Catalyst	Yield[a]	I-5/I-5'[b]
1[c]	**I-4e**	AuCl	85%	1:1
2[d]	**I-4e**	[Au(CyJohnPhos)(MeCN)]SbF_6	64%	1:4.9
3[d]	**I-4e**	$PtCl_2$/P(*o*-Tol)$_3$	88%	1:1
4[d]	**I-4e**	**I**	68%	1:2.7
5[c]	**I-4f**	AuCl	80%	1:3
6[d]	**I-4f**	[Au(CyJohnPhos)(MeCN)]SbF_6	57%	1:4

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Reaction carried out at 0 ºC.
[d] Reaction carried out at 23 ºC.

Interestingly, tricycles **I-7** and **I-7'** were directly obtained when the synthesis of **I-XV** was attempted by the cyclopropanation of dienynes **I-6** with the Furukawa reagent[119] (Scheme 25). This result is consistent with the mechanistic hypothesis of Scheme 24, in which the nonconcerted pathway is favored with Zn(II) through intermediates **I-XII'**, thus leading to the undesired *syn-cis* diastereomers **I-7'a** and **I-7'b** as major tricycles.

119. J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53-58.



I-6a Z = $C(CO_2Me)_2$, R = Et, 72%
I-6b Z = $C(CO_2Me)_2$, R = TBS, 80%

I-XV

I-7: *anti* ; **I-7'**: *syn*
I-7a/I-7'a 1:2.9
I-7b/I-7'b 1:2.5

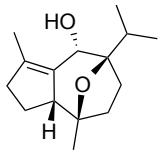
Scheme 25. Direct Zn(II)-promoted cyclopropanation/cyclization of enynes I-6

Application of the cycloisomerization of enynes *via* Prins-type reaction

The gold-catalyzed cycloaddition of functionalized ketoenynes was applied to the synthesis of (+)-orientalol F and later to the enantioselective synthesis of (–)-englerins A and B.

Application – synthesis of (+)-orientalol F

In 2009, our group published the synthesis of (+)-orientalol F **I-8** (Figure 11).[77] **I-8** is a guaiane-type sesquiterpenoid isolated from the rhizome of *Alisma orientalis*.[110]



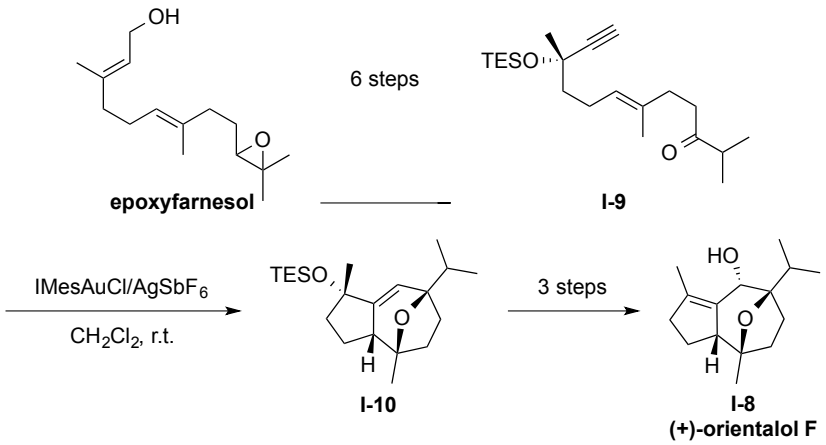
I-8
(+)-orientalol F

Figure 11. Structure of (+)-orientalol F

The synthesis of **I-8** was achieved in 10 steps in 18% overall yield from known epoxyfarnesol (Scheme 26).[120] Cyclization precursor **I-9** was

77. E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327-7329.
110. G.-P. Peng, G. Tian, X.-F. Huang, F.-C. Lou, *Phytochemistry* **2003**, *63*, 877-881.
120. R. P. Hanzlik, *Org. Synth.* **1977**, *56*, 112-117.

efficiently prepared in 6 steps and then cyclized to **I-10** in 65% yield. Three additional steps were required to complete the synthesis of **I-8**.

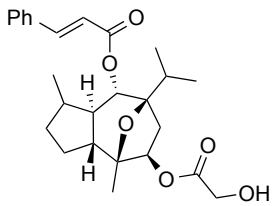


Scheme 26. Synthesis of (+)-orientalol F

Application – enantioselective synthesis of (–)-englerin A

Later in 2010, our group completed the enantioselective synthesis of (–)-englerin A **I-11** (Figure 12) along with englerin B, an intermediate of the synthesis.[78] **I-11** is a guaiane sesquiterpene diester isolated from the stem bark of the east African plant *Phylanthus engleri* that has been shown to selectively inhibit the growth of renal cancer cell lines at the nanomolar level.[121] **I-11** was found to be 1–2 orders of magnitude more potent than taxol against certain cancer cell lines.

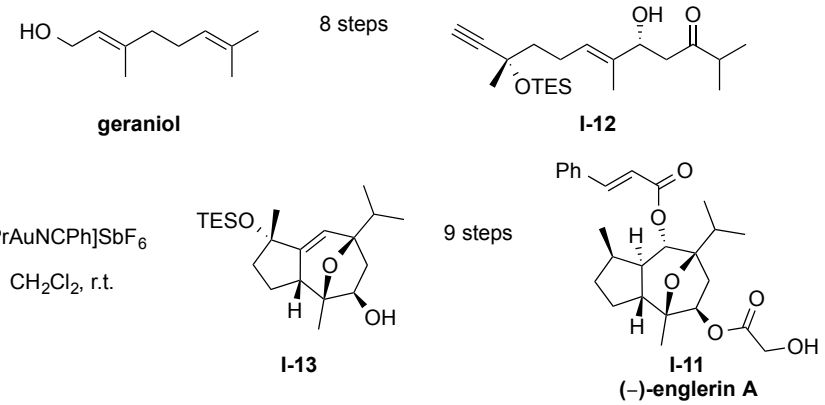
78. K. Molawi, N. Delpont, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.
121. R. Ratnayake, D. Covell, T. T. Ransom, K. R. Gustafson, J. A. Beutler, *Org. Lett.* **2009**, *11*, 57-60.



I-11
(–)-englerin A

Figure 12. Structure of (–)-englerin A

The total synthesis of **I-11** was achieved in 18 steps and 7% overall yield from geraniol (Scheme 27). Commercially available geraniol was converted through an eight-step sequence into precursor **I-12**, which underwent a gold-catalyzed cyclization to form tricycle **I-13**. A 9-step sequence completed the synthesis of **I-11**.



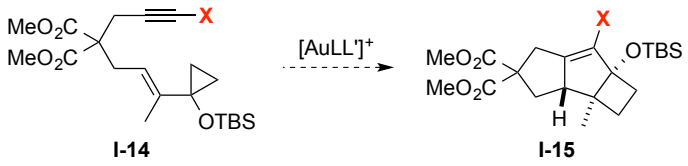
geraniol **I-12**

I-13 **I-11**
(–)-englerin A

Scheme 27. Synthesis of I-11

Objectives

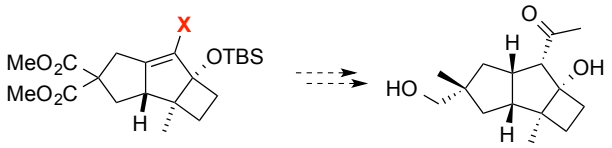
Based on the preliminary work presented earlier, we were interested in studying the gold(I)-catalyzed cyclization cascade of 1,6-enynes bearing a substituent at the alkyne terminus (**X** in **I-14**, Scheme 28). We expected the reaction to take place similarly to form **I-15**.



I-14 **I-15**

Scheme 28. Model reaction

I-15 can be considered as an intermediate platform in the synthesis of repraesentin F **I-16** (Scheme 29), using **X** as a functional group for further transformations. **I-16** is protoilludane sesquiterpene isolated in 2006, which has not been synthesized to date.[122]



I-15 **I-16**
repraesentin F

Scheme 29. Approach to repraesentin F

Therefore we envisioned synthesizing a set of precursors of type **I-14** bearing different groups at the alkyne terminus and studying their reactivity in the gold-catalyzed cyclization. The tricyclic products will be used to complete the synthesis of repraesentin F.

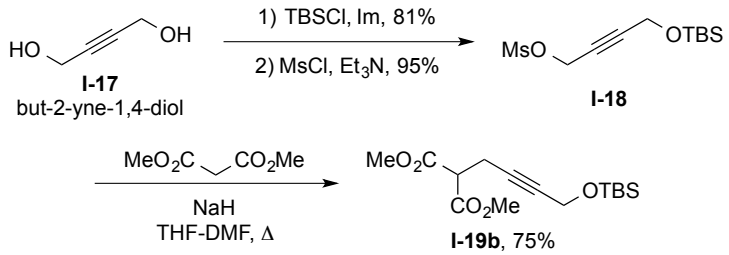
122. See introduction of chapter 2 for a detailed presentation of the protoilludane sesquiterpene family and their biosynthesis.

Results and discussion[123]

Synthesis of the cyclization precursors

A wide variety of enynes of type **I-14** (Scheme 28) bearing diverse substituents on the alkyne (X = H, Br, I, TMS, Ac, CH_2OTBS) were prepared. A common synthetic route was developed and is presented hereafter.

Firstly, malonate **I-19b** was synthesized in 3 steps from commercially available but-2-yne-1,4-diol **I-17** (Scheme 30). **I-17** was monoprotected with a TBS group and subsequent mesylation under standard conditions afforded mesylate **I-18** in 77% overall yield. Dimethylmalonate was alkylated with **I-18** under basic conditions to provide malonate **I-19b** in 75% yield.[124]



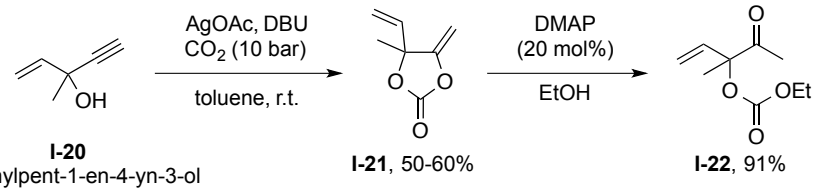
Scheme 30. 3-step synthesis of I-19b

Secondly, an other important building block, carbonate **I-22**, was prepared in two steps (Scheme 31). First, silver-catalyzed incorporation of CO_2 into commercially available 3-methylpent-1-en-4-yn-3-ol **I-20** afforded cyclic

123. In collaboration with Dr. Julien Ceccon and Dr. Tania Jiménez Trujillo.

124. N. E. Schore, S. D. Najdi, *J. Org. Chem.* **1987**, *52*, 5296-5298.

carbonate **I-21** in respectable yields.[125,126] Subsequent DMAP-promoted opening of **I-21** furnished allylic carbonate **I-22** in excellent yield. This transformation also proceeded in the presence of Et_3N, although with longer reaction times.[127]



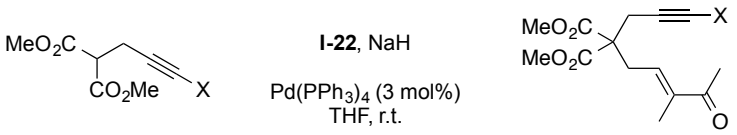
I-20
3-methylpent-1-en-4-yn-3-ol

I-21, 50-60%

I-22, 91%

Scheme 31. 2-step synthesis of carbonate I-22

Malonates **I-19** were coupled with allylic carbonate **I-22** by Pd-catalyzed Tsuji-Trost reaction[126] using $Pd(PPh_3)_4$ (3 mol%) as catalyst under basic conditions (Scheme 32). Enones **I-23** were isolated in excellent yields and excellent stereoselectivity (only *E*-isomer). Malonate **I-19c** was prepared from dimethylmalonate following a reported procedure.[128]



I-19a X = H
I-19b X = CH_2OTBS
I-19c X = TMS

I-23a, 96%
I-23b, 96%
I-23c, 93%

Scheme 32. Formation of enones I-23 by Tsuji-Trost reactions

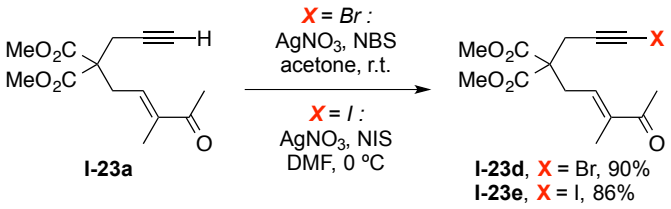
125. W. Yamada, Y. Sugawara, H. M. Cheng, T. Ikeno, T. Yamada, *Eur. J. Org. Chem.* **2007**, 2604-2607.

126. For other methods, see: (a) J.-M. Joumier, J. Fournier, C. Bruneau, P. H. Dixneuf, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3271-3274; (b) J.-M. Joumier, C. Bruneau, P. H. Dixneuf, *Synlett* **1992**, 453-454; (c) A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515-518.

127. The reaction was followed by GC. With DMAP (20 mol%), >99% conversion after 24 h. With Et_3N (20 mol%), >99% conversion after 36 h. With Et_3N (5 mol%), >98% conversion after 7 days.

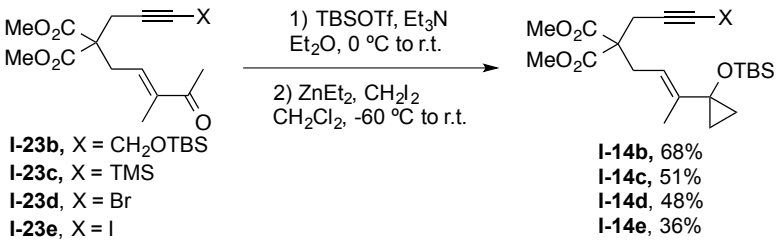
128. C. Fernández-Rivas, M. Méndez, C. Nieto-Oberhuber, A. M. Echavarren, *J. Org. Chem.* **2002**, *67*, 5197-5201.

In order to perform the gold(I)-cyclization on alkynyl halides, we synthesized bromoalkyne **I-23d** and iodoalkyne **I-23e** (Scheme 33). **I-23b** was obtained in 90% yield using standard bromination conditions,[129] whereas slightly unstable **I-23e** was isolated in 86% yield under optimized conditions.



Scheme 33. Halogenation of I-23a

Finally, cyclization precursors **I-14** were synthesized by a two-step sequence (Scheme 34). Enones **I-23** were converted into intermediate TBS-enol ethers under basic conditions. These intermediates proved to be stable enough to be purified by standard column chromatography on silica gel. Subsequent cyclopropanation afforded cyclization precursors **I-14** in reproducible yields.[130]

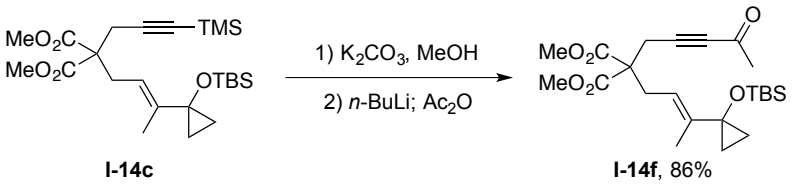


Scheme 34. 2-step sequence for the completion of the precursors synthesis

129. T. Miura, H. Murata, K. Kiyota, H. Kusama, N. Iwasawa, *J. Mol. Catal. A-Chem.* **2004**, *213*, 59-71.

130. L. Jiao, C. Yuan, Z.-X. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 4421-4430.

Acetylated alkyne **I-14f** was prepared in two steps from **I-14c** after cleavage of the TMS group under basic conditions. Subsequent treatment of the intermediate terminal alkyne with *n*-BuLi followed by Ac_2O led to **I-14f** in excellent overall yield (Scheme 35).



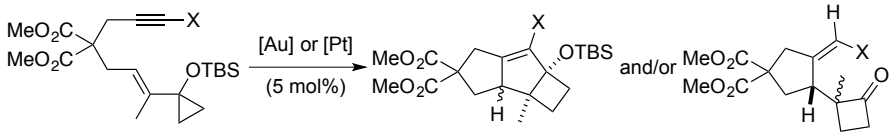
I-14c **I-14f**, 86%

Scheme 35. Two-step synthesis of acylated precursor I-14f

Metal-catalyzed cyclization cascades

Enynes **I-14** were submitted to cyclization conditions with various cationic gold(I) and platinum(II) catalysts. The results are presented in Table 3. Unless otherwise stated, the reactions were run for 24 h before being quenched (see experimental part for complete details of the reaction set-up).

Table 3. Metal-catalyzed cascade cyclization of enynes I-14



I-14b, X = CH_2OTBS
I-14d, X = Br
I-14e, X = I
I-14f, X = Ac

I-15b
I-15d
I-15e
I-15f

I-25b
I-25d
I-25e
I-25f

Entry	Enyne	Catalyst	Result (isolated yield)
1[a]	**I-14b**	AuCl	**I-14b**
2[b]	**I-14b**	**A**	decomp.
3[c]	**I-14b**	**A**	decomp.
4[c]	**I-14b**	**B**	**I-25b** (43%)
5[c]	**I-14b**	**E**	Mainly **I-14b**
6[c]	**I-14b**	**F**	Mainly **I-14b**
7[c,d]	**I-14b**	**H**	decomp.
8[c]	**I-14b**	**I**	**I-25b** (47%)
9[c]	**I-14d**	**A**	**I-25d** (68%)
10[c]	**I-14d**	**B**	**I-25d** (52%)
11[c]	**I-14d**	**E**	**I-14d** (51%), **I-25d** (15%)
12[c]	**I-14d**	**F**	**I-25d** (60%)
13[c]	**I-14d**	**G**	**I-25d** (72%)
14[e]	**I-14d**	**G**	**I-14d** (52%), **I-25d** (32%)
15[f]	**I-14d**	**G**	**I-14d** (54%), **I-25d** (36%)
16[c]	**I-14d**	**H**	**I-25d** (59%)
17[c]	**I-14d**	**I**	**I-25d** (<30%)
18[e]	**I-14e**	**G**	**I-14e** (52%)
19[b]	**I-14e**	**A**	decomp.
20[e]	**I-14f**	**G**	**I-14f** (61%)

[a] CH_2Cl_2, 0 ºC to r.t.
[b] CH_2Cl_2, r.t.
[c] CH_2Cl_2, 0 ºC.
[d] Reaction quenched after 12 h.
[e] CH_2Cl_2, 0 ºC, 4 Å MS.
[f] CH_2Cl_2, r.t., 4 Å MS.

First, we repeated the reported results with **I-14a** (X = H),[105] and used it as a reference for the other cyclizations.

With enyne **I-14b**, the desired tricyclic product **I-15b** was not observed in any experiments (entries 1-8). AuCl and cationic complexes **E** and **F** were unreactive and the starting material was recovered (entries 1 and 5-6). Catalyst **A** and the highly electrophilic complex **H** gave only decomposition (entries 2-3 and 7). Interestingly, a product identified as cyclobutanone **I-25b** was isolated when catalysts **B** and **I** were employed (entries 4 and 8).

Similarly, enyne **I-14c** was engaged in the metal-catalyzed reaction cascade. All the Au(I)-catalysts presented earlier gave complex mixtures or decomposition of the starting material. Platinacycle **I** did not change the outcome of the reaction. Ag(I) is also known to promote similar cyclization,[131,132] therefore we also screened catalyst **J** without any success.

The cyclization cascade of enyne **I-14d** was also examined (entries 9-17). In all the cases, cyclobutanone **I-25d** was isolated in variable amounts. With catalyst **G**, yields as high as 72% were achieved (entry 13).

In the case of precursor **I-14e**, only no reaction or decomposition was observed (entries 18-19). **I-14f** bearing an acetyl substitution of the alkyne did not react either (entry 20).

The formation of cyclobutanone **I-25d** could be due to the presence of residual water in the starting material. Thus, drying of the starting enynes by azeotropic evaporation with toluene was performed before their submission to the reaction conditions. The following series of reactions were carried out with 4 Å molecular sieves (entries 14-15 and 18-20), that partially shut down the cyclization, either at 0 ºC or room temperature.

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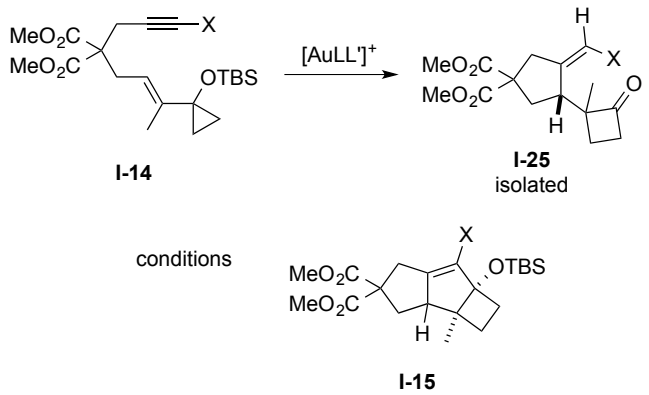
105. E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455.

131. C. Nevado, A. M. Echavarren, *Chem. Eur. J.* **2005**, *11*, 3155-3164.

132. For some reviews on the role of silver in catalysis see: (a) M. Naodovic, H. Yamamoto, *Chem. Rev.* **2008**, *108*, 3132-3148; (b) M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Chem. Rev.* **2008**, *108*, 3174-3198.

Further Developments

Guided by these somewhat surprising results, we changed our initial approach and sought a stepwise transformation of **I-14** into **I-15**, through isolation and reaction of the intermediate cyclobutanone **I-25** (Scheme 36).

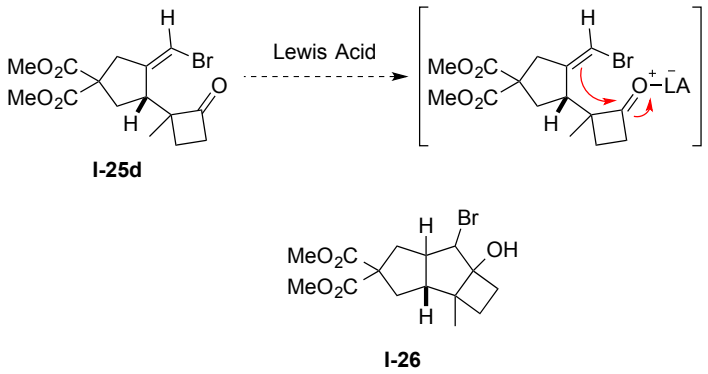


Scheme 36. Stepwise synthesis of I-15

We were particularly interested in carrying this stepwise approach with **I-14d** (X = Br) as it would allow us to use the resulting vinyl bromide of **I-15d** as a platform for final functionalization and approach the core of repraesentin F **I-16**.

Lewis acid-catalyzed Prins-type cyclization

First, we submitted cyclobutanone **I-25d** to several oxophilic Lewis acids expecting the acid to activate the carbonyl group towards subsequent nucleophilic attack of the alkene in a Prins-type cyclization (Scheme 37).

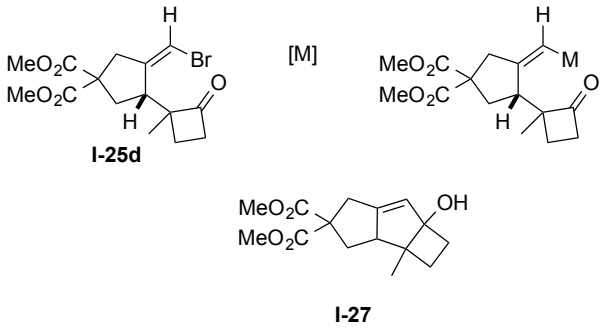


Scheme 37. Expected Prins cyclization under Lewis acid catalyzed conditions

$CeCl_3 \cdot 7H_2O$, TMSCl and $BF_3 \cdot Et_2O$ were used without any success. This might be due to the reduced nucleophilic character of the vinyl bromide.

Nucleophilic addition of organometallic species

We imagined another approach relying on the nucleophilic attack onto the ketone of an organometallic intermediate arising from **I-25d** (Scheme 38). This transformation would provide **I-27**.



Scheme 38. Proposed synthesis of I-27 via an organometallic intermediate

The organometallic intermediate could be generated by lithium halogen exchange with *n*-BuLi. Formation of the Grignard reagent by treatment with magnesium was another option.

The desired transformation might also be achieved by a Nozaki–Hiyama–Kishi reaction.[133] There are only few reports on the addition of organochromium species to ketones but cyclobutanones are rather reactive so this approach will be attempted on our substrate.[134] Preliminary experiments led to the formation of the desired **I-27**, although in low yield (about 30%).[135]

133. (a) Y. Okude, S. Hirano, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1977**, *99*, 3179-3181; (b) K. Takia, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050; (c) for a review on C-C bond formation with organochromium reagents, see: A. Fürstner, *Chem. Rev.* **1999**, *99*, 991-1045.

134. (a) B. M. Trost, A. B. Pinkerton, *Org. Lett.* **2000**, *2*, 1601-1603; (b) B. M. Trost, A. B. Pinkerton, *J. Am. Chem. Soc.* **2002**, *124*, 7376-7389; (c) K. Suzuki, H. Takayama, *Org. Lett.* **2006**, *8*, 4605-4608; (d) D. Xu, M. A. Drahl, L. J. Williams, *Beilstein J. Org. Chem.* **2011**, *7*, 937-943.

135. T. Jiménez-Trujillo, unpublished results, ICIQ, 2013.

Conclusions

We investigated the gold(I)-catalyzed cyclization cascade of cyclopropyl-substituted 1,6-enynes with a haloalkyne in order to approach the core of repraesentin F. A broad set of cyclization precursor was synthesized. Although the reaction did not furnish the expected tricyclic products, cyclobutanones were obtained in some cases by 1,6-enyne cyclization followed by cyclopropyl-ring expansion. These compounds are proposed intermediates in the mechanistic pathway of the reaction. Attempts to get the core of repraesentin F were unsuccessful but other methods are currently under investigation.

Experimental part

General information

Unless otherwise stated, reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv^{TM} solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF_{234}) using UV light as visualizing agent, and an acidic solution of vanillin in ethanol or a basic solution of potassium permanganate in water as stain solution. Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) or automated flash chromatographer CombiFlash Companion. Preparative TLC was performed on 20 cm x 20 cm silica gel plates (2.0 mm thick, catalogue number 02015, Analtech). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

NMR spectra were recorded at 298 K on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers.

Crystal structure determinations were carried out using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = −173 ºC). Full-sphere data collection was used with w and j scans. *Programs used:* Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. *Structure Solution and Refinement:* Crystal structure solution was achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located

from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

General procedures

General procedure for the mono-alkylation of dimethylmalonate

Dimethylmalonate (3.00 equiv) was added dropwise over 10 min to a suspension of NaH (60 wt% in mineral oil, 1.00 equiv), in a 2:1 mixture of anhydrous DMF and anhydrous THF. When the resulting mixture became homogeneous, a solution of the freshly prepared mesylate (1.00 equiv) in anhydrous THF was rapidly added and the resulting solution was refluxed for 6-7 h. After cooling down to room temperature, the reaction was quenched with brine and the aqueous layer was extracted with Et_2O (3 times). The combined organic layers were washed with brine (twice), dried over anhydrous $MgSO_4$, filtered and concentrated.

General procedure for the Pd-catalyzed Tsuji-Trost coupling with malonates

A solution of the mono-alkylated malonate (1.20 equiv) in anhydrous THF was added dropwise to a suspension of NaH (60 wt% in mineral oil, 1.20 equiv) in anhydrous THF. The intermediate malonate anion solution was added to $Pd(PPh_3)_4$ (3 mol%) in a dry Schlenk tube under argon. Then, a solution of the carbonate **I-22** (1.00 equiv) in anhydrous THF was added, and the resulting mixture was stirred at room temperature for 2.5 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with EtOAc (3 times). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated.

General procedure for the enolization of enones

Anhydrous Et_3N (2.50 equiv) and TBSOTf (1.50 equiv) were added dropwise to a solution of the enone (1.00 equiv) in anhydrous Et_2O at 0 ºC. The resulting mixture was stirred at room temperature for 4 h, then quenched with brine and extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated.

General procedure for the cyclopropanation of silyl enol ethers

CH_2I_2 was washed with saturated $NaSO_3$ (twice), dried over anhydrous $MgSO_4$, filtered and fractionally distilled over CaH_2 ($T°_{eb}$ = 54 ºC @ 10 mbar), then stored over 3 Å MS under an argon atmosphere.

CH_2I_2 (1.20 equiv) was added dropwise to a solution of $ZnEt_2$ (1 M in hexanes, 1.20 equiv) in anhydrous CH_2Cl_2 at −60 ºC. The resulting solution was warmed to 0 ºC until a white precipitate appeared, then cooled to −60 ºC, whereupon a solution of the intermediate enol ether (1.00 equiv) in anhydrous CH_2Cl_2 was added dropwise. The resulting mixture was stirred for 3 h at room temperature, then quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated.

General procedure for the metal-catalyzed cascade cyclizations

A dry flask under argon was charged with the gold(I) or platinum(II) catalyst (5 mol%), and, if needed, 4 Å molecular sieves. Then, a solution of the precursor of cyclization (1.00 equiv) in anhydrous CH_2Cl_2 (0.05 or 0.1 mol/L, depending on the scale) was added at the temperature shown in Table 3. The experiments were quenched with a few drops of Et_3N and filtered through a pad of SiO_2 (elution with EtOAc/hexane 50:50). Purifications were carried out by flash column chromatography (elution with EtOAc/hexane 5:95 to 50:50).

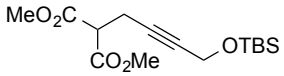
Synthesis of cyclization precursors

I-18

Imidazole (903 mg, 13.3 mmol) and TBSCl (1.00 g, 6.63 mmol) were successively added to a solution of diol **I-17** (2.23 g, 26.5 mmol) in anhydrous DMF (66 mL). The resulting solution was stirred for 18 h at 35 ºC, and then quenched with brine (80 mL). The aqueous phase was extracted with EtOAc (3 times) and the combined organic layers were washed with brine (twice), dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the residue by flash column chromatography (elution EtOAc/hexane 0:100 to 20:80) afforded the intermediate mono-protected alcohol as a colorless oil (1.08 g, 81% yield). Analytical data were in accordance with literature.[136]

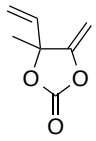
Triethylamine (1.60 mL, 11.3 mmol) and MsCl (0.66 mL, 8.49 mmol) were successively added to a solution of the intermediate mono-protected alcohol (1.13 g, 2.10 mmol) in anhydrous Et_2O (28 mL). The resulting mixture was stirred for 1 h, quenched with water, extracted with EtOAc (3 times) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude material was engaged in the subsequent step without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (t, J = 1.8 Hz, 2H), 4.37 (t, J = 1.8 Hz, 2H), 3.12 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H).

136. A. Padwa, H. Lipka, S. H. Watterson, S. S. Murphree, *J. Org. Chem.* **2003**, *68*, 6238-6250.



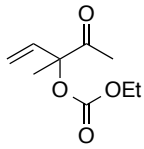
I-19b

I-19b was synthesized following the *general procedure for the mono-alkylation of dimethylmalonate* with mesylate **I-18** (736 mg crude). Purification of the crude material by flash column chromatography (elution EtOAc/hexane 5:95 to 15:85) afforded malonate **I-19b** as a colorless oil (625 mg, 75% yield). Analytical data were in accordance with literature.[137]



I-21

Cyclic carbonate **I-21** was prepared following the procedure described in reference 125. Analytical data were in accordance with literature.[126]



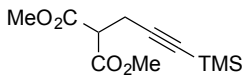
I-22

Allylic carbonate **I-22** was prepared following the procedure described in reference 126. Analytical data were in accordance with literature.[126]

137. A. Zawisza, B. Fenêt, D. Sinou, *Eur. J. Org. Chem.* **2007**, 2296-2309.

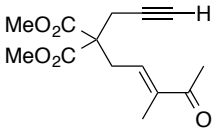
125. W. Yamada, Y. Sugawara, H. M. Cheng, T. Ikeno, T. Yamada, *Eur. J. Org. Chem.* **2007**, 2604-2607.

126. (a) J.-M. Joumier, J. Fournier, C. Bruneau, P. H. Dixneuf, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3271-3274; (b) J.-M. Joumier, C. Bruneau, P. H. Dixneuf, *Synlett* **1992**, 453-454; (c) A. Buzas, F. Gagosz, *Org. Lett.* **2006**, *8*, 515-518.



I-19c

Malonate **I-19c** was prepared following the procedure described in reference 128. Analytical data were in accordance with literature.[128,138]

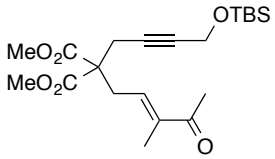


I-23a

I-23a was synthesized following the *general procedure for the Pd-catalyzed Tsuji-Trost coupling with malonates* with commercially available dimethyl propargylmalonate (561 mg, 3.30 mmol) and carbonate **I-22** (512 mg, 2.75 mmol). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane 10:90 to 30:70) afforded enone **I-23a** (703 mg, 96% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (tq, *J* = 7.5, 1.1 Hz, 1H), 3.77 (s, 6H), 3.02 (d, *J* = 7.5 Hz, 2H), 2.84 (d, *J* = 2.7 Hz, 2H), 2.29 (s, 3H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.82 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.51, 170.02, 141.11, 135.58, 78.53, 72.18, 56.76, 53.20, 32.16, 25.74, 23.59, 11.55.



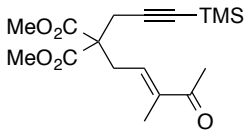
I-23b

I-23b was synthesized following the *general procedure for the Pd-catalyzed Tsuji-Trost coupling with malonates* with malonate **I-19b** (353 mg, 1.12 mmol) and carbonate **I-22** (174 mg, 0.94 mmol). Purification of

138 . See experimental part of reference 128: C. Fernández-Rivas, M. Méndez, C. Nieto-Oberhuber, A. M. Echavarren, *J. Org. Chem.* **2002**, *67*, 5197-5201.

the crude material by flash column chromatography (elution with EtOAc/hexane 5:95 to 20:80) afforded enone **I-23b** (369 mg, 96% yield) as a light yellow oil.

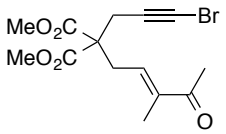
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (app. t, J = 7.0 Hz, 1H), 4.27 (t, J = 2.0 Hz, 2H), 3.75 (s, 6H), 3.00 (d, J = 7.4 Hz, 2H), 2.88 (t, J = 2.0 Hz, 2H), 2.28 (s, 3H), 1.81 (s, 3H), 0.89 (s, 9H), 0.09 (s, 6H).



I-23c

I-23c was synthesized following the *general procedure for the Pd-catalyzed Tsuji-Trost coupling with malonates* with malonate **I-19c** (540 mg, 2.23 mmol) and carbonate **I-22** (346 mg, 1.86 mmol). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane 5:95 to 20:80) afforded enone **I-23c** (369 mg, 96% yield) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (tq, J = 7.5, 1.2 Hz, 1H), 3.76 (s, 6H), 3.00 (d, J = 7.5 Hz, 2H), 2.83 (s, 2H), 2.28 (s, 3H), 1.82 (d, J = 1.2 Hz, 3H), 1.13 (s, 9H).

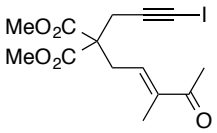


I-23d

$AgNO_3$ (13.1 mg, 0.08 mmol) and NBS (206 mg, 1.16 mmol) were added in one portion at room temperature to a solution of terminal alkyne **I-23a** (206 mg, 0.77 mmol) in degassed acetone (4 mL). The resulting mixture was protected from light and stirred for 1 h, then quenched with H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (elution with EtOAc/hexane 10:90 to 20:80) afforded bromoalkyne **I-23d** (241 mg, 90% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (tq, *J* = 7.5, 1.2 Hz, 1H), 3.77 (s, 6H), 2.99 (dd, *J* = 7.5, 0.6 Hz, 2H), 2.86 (s, 2H), 2.29 (s, 3H), 1.82 (d, *J* = 1.2 Hz, 3H).

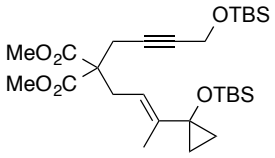
^{13}C NMR (100 MHz, $CDCl_3$) δ 199.51, 169.93, 141.11, 135.42, 100.13, 74.60, 56.70, 53.26, 42.49, 32.35, 25.77, 24.83, 11.58.



I-23e

$AgNO_3$ (6.30 mg, 0.04 mmol) and NIS (117 mg, 0.52 mmol) were added in one portion at 0 ºC to a solution of terminal alkyne **I-23a** (98.6 mg, 0.370 mmol) in anhydrous DMF (4 mL). The resulting mixture was protected from light and stirred for 2 h at 0 ºC, then quenched with brine and extracted with Et_2O. The combined organic extracts were washed with brine (twice), dried over anhydrous $MgSO_4$, filtered and concentrated. The reaction was not completed, as seen by NMR of the crude material, and was submitted to the same reaction conditions, with this time $AgNO_3$ (6.30 mg, 0.04 mmol), NIS (58.3 mg, 0.26 mmol) in DMF (4 mL). Purification by flash column chromatography (elution with EtOAc/hexane 10:90 to 20:80) afforded iodoalkyne **I-23e** (125 mg, 86% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (tq, *J* = 7.5, 1.3 Hz, 1H), 3.77 (s, 6H), 3.01-2.97 (m, 4H), 2.29 (s, 3H), 1.81 (s, 3H).



I-14b

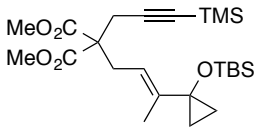
I-14b was synthesized following the *general procedure for the enolization of enones* with enone **I-23b** (207 mg, 0.51 mmol). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane/Et_3N

0:100:1 to 10:90:1) afforded the intermediate TBS-enol ether (204 mg, 77% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (app. t, *J* = 7.8 Hz, 1H), 4.43 (s, 1H), 4.29 – 4.23 (m, 3H), 3.72 (s, 6H), 2.91 (d, *J* = 7.8 Hz, 2H), 2.82 (t, *J* = 2.1 Hz, 2H), 1.80 (s, 3H), 0.95 (s, 9H), 0.89 (s, 9H), 0.15 (s, 6H), 0.09 (s, 6H).

The intermediate TBS-enol ether (204 mg, 0.39 mmol) was used following the *general procedure for the cyclopropanation of silyl enol ethers*. Purification of the crude material by flash column chromatography (elution with EtOAc/hexane 0:100 to 10:90) furnished the desired enyne **I-14b** (146 mg, 56% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (t, *J* = 7.1 Hz, 1H), 4.26 (t, *J* = 1.9 Hz, 2H), 3.71 (s, 6H), 2.81 – 2.77 (m, 4H), 1.72 (s, 3H), 0.89 (s, 9H), 0.83 (s, 9H), 0.80 – 0.76 (m, 2H), 0.69 – 0.65 (m, 2H), 0.09 (s, 6H), 0.04 (s, 6H).



I-14c

I-14c was synthesized following the *general procedure for the enolization of enones* with enone **I-23c** (160 mg, 0.47 mmol). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane/Et_3N 0:100:1 to 10:90:1) afforded the intermediate TBS-enol ether (174 mg, 81% yield) as a colorless oil.

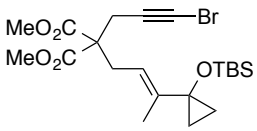
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (t, *J* = 7.8 Hz, 1H), 4.44 (d, *J* = 0.9 Hz, 1H), 4.28 (s, 1H), 3.72 (s, 6H), 2.93 (d, *J* = 7.8 Hz, 2H), 2.78 (s, 2H), 1.81 (s, 3H), 0.95 (s, 9H), 0.15 (s, 6H), 0.13 (s, 9H).

The intermediate TBS-enol ether (168 mg, 0.37 mmol) was used following the *general procedure for the cyclopropanation of silyl enol ethers*. Purification of the crude material by flash column chromatography (elution

with EtOAc/hexane 0:100 to 10:90) furnished the desired enyne **I-14c** (110 mg, 63% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (tq, *J* = 7.7, 1.3 Hz, 1H), 3.72 (s, 6H), 2.81 (d, *J* = 7.7 Hz, 2H), 2.76 (s, 2H), 1.73 (s, 3H), 0.84 (s, 9H), 0.79 (d, *J* = 7.6 Hz, 1H), 0.78 (d, *J* = 6.3 Hz, 1H), 0.69 (d, *J* = 6.3 Hz, 1H), 0.67 (d, *J* = 7.6 Hz, 1H), 0.13 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.49, 141.53, 117.08, 101.66, 88.29, 60.97, 57.36, 52.82, 30.56, 25.91, 24.14, 18.01, 14.16, 13.56, 0.07, -3.61.



I-14d

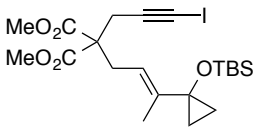
I-14d was synthesized following the *general procedure for the enolization of enones* with enone **I-23d** (229 mg, 0.66 mmol). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane/Et_3N 0:100:1 to 10:90:1) afforded the intermediate TBS-enol ether (259 mg, 85% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (t, *J* = 7.8 Hz, 1H), 4.45 (s, 1H), 4.28 (s, 1H), 3.73 (s, 6H), 2.92 (d, *J* = 7.8 Hz, 2H), 2.80 (s, 2H), 1.80 (s, 3H), 0.95 (s, 9H), 0.15 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.26, 156.85, 135.44, 120.47, 92.12, 75.20, 57.09, 53.02, 41.55, 31.35, 25.97, 24.14, 18.35, 13.53, -4.57.

The intermediate TBS-enol ether (254 mg, 0.55 mmol) was used following the *general procedure for the cyclopropanation of silyl enol ethers*. Purification of the crude material by flash column chromatography (elution with EtOAc/hexane 0:100 to 10:90) furnished the desired enyne **I-14d** (146 mg, 56% yield) as a colorless oil.

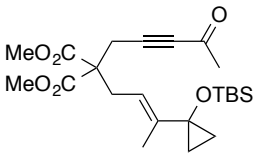
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (tq, *J* = 7.7, 1.4 Hz, 1H), 3.73 (s, 6H), 2.79 (d, *J* = 7.7 Hz, 2H), 2.78 (s, 2H), 1.72 (s, 3H), 0.84 (s, 9H), 0.81 – 0.77 (m, 2H), 0.70 – 0.67 (m, 2H), 0.04 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.37, 141.71, 116.69, 75.20, 60.93, 57.05, 52.96, 41.58, 30.76, 25.90, 24.10, 14.14, 13.57, -3.61.



I-14e

I-14e was synthesized following the *general procedure for the enolization of enones* with enone **I-23e** (119 mg, 0.30 mmol). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane/Et_3N 0:100:1 to 10:90:1) afforded the intermediate TBS-enol ether (135 mg, 88% yield) as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (t, *J* = 7.9 Hz, 1H), 4.45 (s, 1H), 4.28 (s, 1H), 3.73 (s, 6H), 2.94 (s, 2H), 2.92 (d, *J* = 7.9 Hz, 2H), 1.80 (s, 3H), 0.95 (d, J = 2.9, 10H), 0.15 (s, 6H).

The intermediate TBS-enol ether (128 mg, 0.25 mmol) was used following the *general procedure for the cyclopropanation of silyl enol ethers*. Purification of the crude material by flash column chromatography (elution with EtOAc/hexane 0:100 to 10:90) furnished the desired enyne **I-14e** (146 mg, 56% yield) as a colorless oil.
^{1}H NMR of this product was not pure enough for proper characterization.



I-14f

An error in the weight of either the starting material or the final product gave an erroneous yield for this reaction that was carried out only once.

K_2CO_3 (1.05 equiv) was added to a solution of vinylcyclopropane **I-14c** (1.00 equiv) in MeOH at room temperature. The resulting mixture was stirred for 2 h, then quenched with H_2O and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (elution EtOAc/hexane 0:100 to 15:85) afforded the expected terminal alkyne as a colorless oil which was directly engaged in the subsequent step.

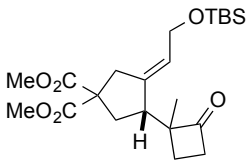
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (tq, *J* = 7.7, 1.3 Hz, 1H), 3.73 (s, 6H), 2.81 (d, *J* = 7.7 Hz, 2H), 2.76 (d, *J* = 2.7 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H), 1.73 (br. s, 3H), 0.84 (d, 9H), 0.79 (d, *J* = 7.6 Hz, 1H), 0.78 (d, *J* = 6.4 Hz, 1H), 0.69 (d, *J* = 6.4 Hz, 1H), 0.67 (d, *J* = 7.6 Hz, 1H), 0.04 (s, 6H).

n-BuLi (2.5 M in hexanes, 0.08 mL, 0.20 mmol) was added dropwise to a solution of the intermediate alkyne (60.0 mg, 0.15 mmol) in anhydrous THF (1.5 mL) at −78 ºC, then stirred for 15 min. Ac_2O (0.02 mL, 0.20 mmol) was added dropwise and the resulting mixture was stirred for 2 h at −78 ºC, then quenched with saturated NH_4Cl and warmed up to room temperature. The aqueous phase was extracted with EtOAc (3 times) and the combined organic layers were washed with H_2O, brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (elution EtOAc/hexane 0:100 to 10:90) furnished precursors **I-14g** (57.0 mg, 86% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (tq, *J* = 7.6, 1.4 Hz, 1H), 3.75 (s, 6H), 2.93 (s, 2H), 2.81 (d, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.72 (s, 3H), 0.84 (s,

9H), 0.81 (d, *J* = 7.5 Hz, 1H), 0.80 (d, *J* = 6.5 Hz, 1H), 0.70 (d, *J* = 6.5 Hz, 1H), 0.68 (d, *J* = 7.5 Hz, 1H), 0.04 (s, 6H).

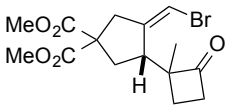
Metal-catalyzed cascade cyclizations



I-25b

I-25b was synthesized following the *general procedure for the metal-catalyzed cascade cyclizations* with precursor **I-14b** (15-20 mg scale) and different catalysts (Table 3). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane 0:100 to 10:90) afforded cyclobutanone **I-25b** (yield and d.r. depending on the catalyst, Table 3) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (td, *J* = 7.5, 1.6 Hz, 1H), 4.26 (t, *J* = 2.1 Hz, 2H), 3.75 (s, 6H), 2.99 (dd, *J* = 7.5, 1.2 Hz, 2H), 2.87 (t, *J* = 2.1 Hz, 2H), 2.64 (q, *J* = 7.3 Hz, 1H), 1.82 (d, *J* = 1.0 Hz, 2H), 1.08 (t, *J* = 7.3 Hz, 2H), 0.89 (s, 10H), 0.09 (s, 6H).



I-25d

I-25d was synthesized following the *general procedure for the metal-catalyzed cascade cyclizations* with precursor **I-14d** (15-20 mg scale) and different catalysts (Table 3). Purification of the crude material by flash column chromatography (elution with EtOAc/hexane 0:100 to 10:90) afforded cyclobutanone **I-25b** (yield and d.r. depending on the catalyst, Table 3) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 – 6.20 (m, 1H), 3.79 – 3.68 (m, 6H), 3.21 – 3.15 (m, 1H), 3.13 – 3.04 (m, 1H), 3.04 – 2.97 (m, 1H), 2.95 – 2.91 (m, 1H), 2.87 – 2.84 (m, 1H), 2.81 – 2.71 (m, 1H), 2.52 – 2.37 (m, 1H), 2.33 – 2.25 (m, 1H), 1.91 – 1.81 (m, 1H), 1.32 (s, 1H), 1.22 (s, 3H). The product tends to decompose and presents some aromatic signals.

^{13}C NMR of this product was not pure enough for proper characterization.

HRMS-ESI: *m/z* calculated for $C_{15}H_{19}O_5BrNa$ $[M+Na]^+$: 381.0308, found: 381.0305.

IR: The IR spectrum presented a strong C=O bond signal at 1770 cm^{-1}. The carbonyl signal of cyclobutanone is reported at 1775 cm^{-1}.[139]

139. E. Pretsch, P. Bühlmann, C. Affolter, A. Herrera, R. Martínez; In *Determinación estructural de compuestos orgánicos*; Elsevier Masson: Barcelona, 2002; Chapter 2, pp 288.

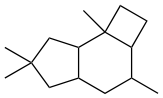
Chapter 2. A New Access to the Protoilludane Family

Introduction – sesquiterpenes and protoilludanes

The protoilludane family, biosynthesis and derivatives

Sesquiterpenes are a class of terpenes that consist of three isoprene units. They may be acyclic or (poly)cyclic, involving many unique combinations. Biochemical alterations such as oxidation or rearrangement produce the related sesquiterpenoids. Sesquiterpenes are ubiquitous in nature, especially in plants and insects. They often play the role of semiochemicals,[140] such as pheromones.[141]

Among the numerous classes of sesquiterpenes, the protoilludane family displays a characteristic tricyclic 5/6/4-framework (Figure 13).[142]



protoilludane

Figure 13. Framework of protoilludanes

The biosynthesis of this class of sesquiterpenes has been intensively studied and follows a well-defined cyclization pathway as highlighted in Scheme 39.[143] All the transformations are involving many enzymatic processes.

140. Semiochemical: *a pheromone or other chemical that conveys a signal from one organism to another so as to modify the behavior of the recipient organism*; from Oxford Dictionaries.

141. (a) B. M. Fraga, *Nat. Prod. Rep.* **2013**, *30*, 1226-1264; (b) B. M. Fraga, *Nat. Prod. Rep.* **2012**, *29*, 1334-1366; and previous editions of the review.

142. For a recent review of the protoilludanes and related compounds, see: P. Siengalewicz, J. Mulzer, U. Rinner, *Eur. J. Org. Chem.* **2011**, 7041-7055.

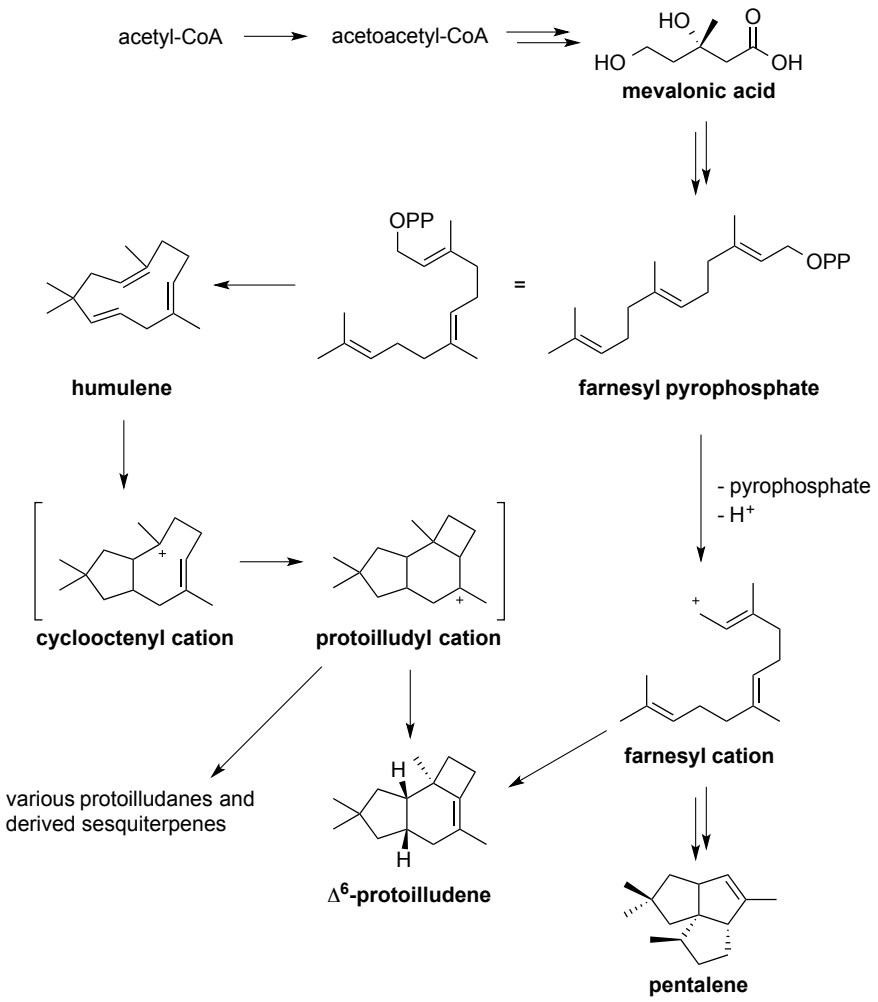
143. W. R. Abraham, *Curr. Med. Chem.* **2001**, *8*, 583-606.

Mevalonic acid derives from acetyl-CoA[144] and is converted into farnesyl pyrophosphate. It undergoes an enzymatic cyclization to provide humulene, a key intermediate in the biosynthesis of numerous sesquiterpenes.[143,145] Remarkably, humulene-related derivatives are rare in fungi because this intermediate is further elaborated mainly to bicyclic and tricyclic sesquiterpenes. However, some plants are known to contain humulene-derived sesquiterpenes. Although these compounds do not present biologically relevant properties, they often possess characteristic flavors and therefore serve as fragrances. Such compounds can be found in hops, being thus responsible for some of the flavors in beers.[146]

144. D. A. Bochar, J. Freisen, C. V. Stauffacher, V. W. Rodwell, *Comprehensive Natural Products Chemistry* **1999**, 15-44.

145. S. Nozoe, H. Kobayashi, S. Urano, J. Furukawa, *Tetrahedron Lett.* **1977**, *18*, 1381-1384.

146. (a) V. E. Peacock, M. L. Deinzer, L. A. McGill, R. E. Wrolstad, *J. Agric. Food Chem.* **1980**, *28*, 774-777; (b) V. E. Peacock, M. L. Deinzer, S. T. Linkens, G. B. Nickerson, L. A. McGill, *J. Agric. Food Chem.* **1981**, *29*, 1265-1269.



Scheme 39. Biosynthesis of protoilludanes and their derivatives

Humulene can be converted into various structurally complex polycyclic sesquiterpenes. The most important pathway generates the protoilludane skeleton through a cationic cyclization sequence as shown in Scheme 39.[147] This framework is prompt to be further transformed into related classes of sesquiterpenes with minimized ring strain of the cyclobutane moiety (Figure 14). Many different classes of sesquiterpenes can also be obtained

147. N. Morisaki, J. Furukawa, H. Kobayashi, S. Iwasaki, A. Itai, S. Nozoe, S. Okuda, *Chem. Pharm. Bull.* **1985**, *33*, 2783-2791.

by Wagner–Meerwein rearrangements.[148] The rearrangement of the intermediate cyclooctenyl cation[149] and some correlated oxygen-containing structures[147,150] have been deeply investigated.

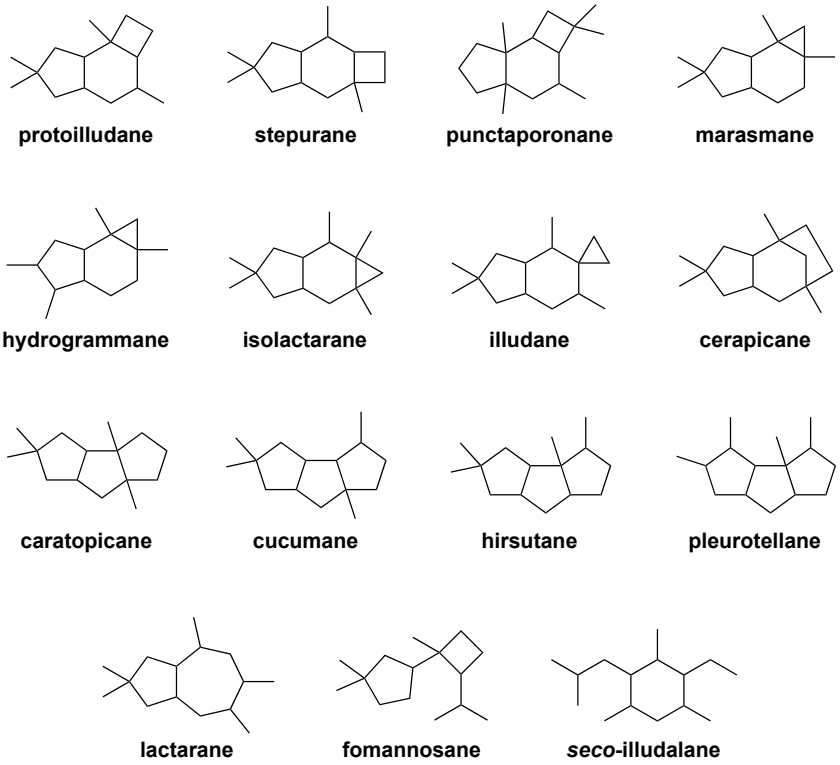


Figure 14. Protoilludane and related sesquiterpenes

148. (a) T. C. McMorris, M. Anchel, *J. Am. Chem. Soc.* **1965**, *87*, 1594-1600; (b) M. Anchel, T. C. McMorris, P. Singh, *Phytochemistry* **1970**, *9*, 2339-2343.

149. T. Takatsu, S. Ito, T. Kan, H. Shirahama, T. Matsumoto, *Synlett* **1989**, *1*, 40-42.

150. (a) N. Morisaki, J. Furukawa, H. Kobayashi, S. Iwasaki, A. Itai, S. Nozoe, S. Okuda, *Chem. Pharm. Bull.* **1985**, *33*, 2792-2797; (b) N. Morisaki, J. Furukawa, H. Kobayashi, S. Iwasaki, S. Nozoe, S. Okuda, *Tetrahedron Lett.* **1985**, *26*, 4755-4758; (c) N. Morisaki, J. Furukawa, H. Kobayashi, S. Iwasaki, S. Nozoe, S. Okuda, *Chem. Pharm. Bull.* **1987**, *35*, 2678-2685.

Numerous sesquiterpenes derive from protoilludane (Figure 14) and of course, plenty of natural compounds with relevant biological properties arise from these subclasses.

Illudins (categorized as a subclass of illudanes) are naturally occurring sesquiterpenes secondary metabolites of basidiomycetes.[151] From a biological standpoint, illudins and their acylfulvenes analogues (Figure 15) present interesting antitumor activity. Their chemistry, metabolism and biological activity have been recently reviewed.[152]

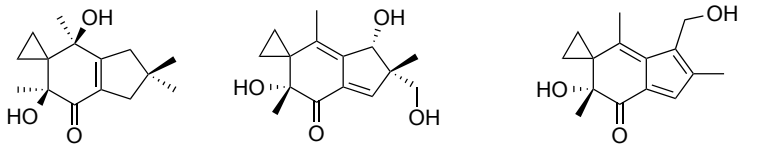


Figure 15. Structure of illudin A, illudin S and HMAF

Tremulane sesquiterpenes, that are isomeric to the lactarane skeleton, are a novel class of important biologically active molecules. In 2006, the enantioselective syntheses of tremulenediol A and tremulenolide A (Figure 16) was achieved relying on a series of efficient transition metal-catalyzed reactions (mainly with rhodium I and II).[153]

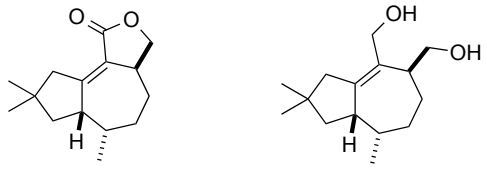


Figure 16. Structure of tremulenolide A and tremulenediol A

151. R. Schobert, S. Knauer, S. Seibt, B. Biersack, *Curr. Med. Chem.* **2011**, *18*, 790-807.

152. M. Tanasova, S. J. Sturla, *Chem. Rev.* **2012**, *112*, 3578-3610.

153. B. L. Ashfeld, S. F. Martin, *Tetrahedron* **2006**, *62*, 10497-10506.

The protoilludane framework can also be formed during the enzymatic transformation of farnesyl pyrophosphate to pentalene (Scheme 39).[154] Pentalene synthase plays an important role in the cyclization of farnesyl pyrophosphate to pentalene. This enzyme promotes the elimination of a diphosphate anion leading to farnesyl cation, which can evolve to pentalene or to Δ^6-protoilludene by divergent cationic rearrangements.[155]

The protoilludane family particularly interested us and we present thereafter a selection of members belonging to this family that have synthesized.

The protoilludanes – important members already synthesized

Over the last fifty years, several protoilludanes have been synthesized.[141] A selection of these natural compounds that were synthesized is presented in Figure 17. In some other cases, protoilludanes were used as synthetic intermediates.[142]

154. M. Seemann, G. Zhai, J.-W. De Kraker, C. M. Paschall, D. W. Christianson, D. E. Cane, *J. Am. Chem. Soc.* **2002**, *124*, 7681-7689.

155. (a) P. Gutta, D. J. Tantillo, *J. Am. Chem. Soc.* **2006**, *128*, 6172-6179; (b) L. Zu, M. Xu, M. W. Lodewyk, D. E. Cane, R. J. Peters, D. J. Tantillo, *J. Am. Chem. Soc.* **2012**, *134*, 11369-11371.

141. (a) B. M. Fraga, *Nat. Prod. Rep.* **2013**, *30*, 1226-1264; (b) B. M. Fraga, *Nat. Prod. Rep.* **2012**, *29*, 1334-1366; and previous editions of the review.

142. For a recent review of the protoilludanes and related compounds, see: P. Siengalewicz, J. Mulzer, U. Rinner, *Eur. J. Org. Chem.* **2011**, 7041-7055.

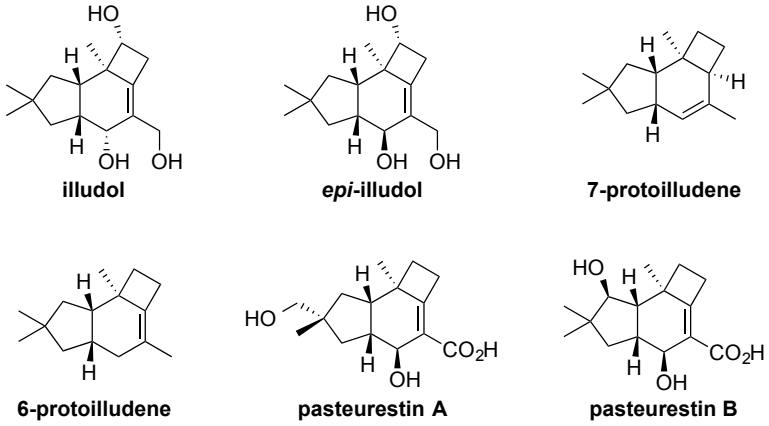


Figure 17. Important members of the protoilludanes family already synthesized

The fist member of the family to be synthesized was illudol in 1971 by the group of Matsumoto.[156] In 1980, Semmelhack reported another synthesis of this natural product,[157] and later in 1991 the group of Vollhardt published the third synthesis of this protoilludane.[158] In 1997, the group of Malacria synthesized *epi*-illudol.[159] The group of Takeshita reported the first synthesis of 7-protoilludene in 1979.[160] More recently (2003), the group of Stenstrøm reported a synthesis of this protoilludane.[161] The synthesis of related 6-protoilludene was also completed first by Furukawa in 1985,[162]

156. (a) S. Kagawa, S. Matsumoto, S. Nishida, S. Yu, J. Morita, A. Ichirara, H. Shiraham, T. Matsumoto, *Tetrahedron Lett.* **1969**, *10*, 3913-3916; (b) T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, J. Ogawa, A. Ichirara, *Tetrahedron Lett.* **1971**, *12*, 3521-3524.

157. (a) M. F. Semmelhack, S. Tomoda, K. M. Hurst, *J. Am. Chem. Soc.* **1980**, *102*, 7567-7568; (b) M. F. Semmelhack, S. Tomoda, H. Nagaoka, S. D. Boettger, K. M. Hurst, *J. Am. Chem. Soc.* **1982**, *104*, 747-759.

158. E. P. Johnson, K. P. C. Vollhart, *J. Am. Chem. Soc.* **1991**, *113*, 381-382.

159. M. R. Elliott, A. L. Dhimane, M. Malacria, *J. Am. Chem. Soc.* **1997**, *119*, 3427-3428.

160. (a) H. Takeshita, H. Iwabuchi, I. Kouno, M. Iino, D. Nomura, *Chem. Lett.* **1979**, 649-652; (b) H. Takeshita, I. Kouno, M. Iino, H. Iwabuchi, D. Nomura, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3641-3647.

161. T. V. Hansen, L. Skattebøl, Y. Stenstrøm, *Tetrahedron* **2003**, *59*, 3461-3466.

162. J. Furukawa, N. Morisaki, H. Kobayashi, S. Iwasaki, S. Nozoe, S. Okuda, *Chem. Pharm. Bull.* **1985**, *33*, 440-443.

and then by Oppolzer the same year.[163] More recently (2007), the group of Mulzer accomplished the synthesis of pasteurestins A and B.[164]

New challenges for the organic chemist

Among the recently isolated protoilludane sesquiterpenes, some remain a genuine challenge for the synthetic chemistry community. Hereafter, we highlight some families of isolated sesquiterpenoids that have not been synthesized to date and present attractive biological properties.

The plorantinones

In 1997, three new protoilludane sesquiterpenes were isolated from injured bodies of the basidiomycete *Russula delica* fungus,[165] namely plorantinone A, B and C (Figure 18). In 1998, these molecules could be identified among many others in the organic extract of both injured and intact fruit bodies of *Russula delica* fungus.[166]

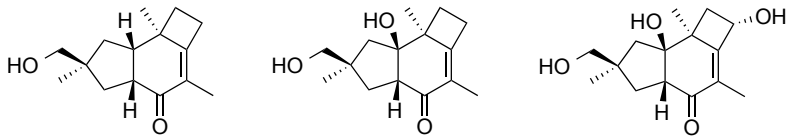


Figure 18. Structures of plorantinones A, B and C

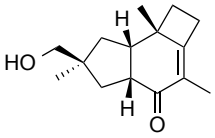
163. W. Oppolzer, A. Nakao, *Tetrahedron Lett.* **1986**, *27*, 5471-5474.

164. (a) M. Kögl, L. Brecker, R. Warrass, J. Mulzer, *Angew. Chem. Int. Ed.* **2007**, *46*, 9320-9322; (b) M. Kögl, L. Brecker, R. Warrass, J. Mulzer, *Eur. J. Org. Chem.* **2008**, 2714-2730.

165. M. Clericuzio, J. Fu, F. Pan, Z. Pang, O. Sterner, *Tetrahedron* **1997**, *53*, 9735-9740.

166. M. Clericuzio, F. Han, F. Pan, Z. Pang, O. Sterner, *Acta Chem. Scand.* **1998**, *52*, 1333-1337.

In 2003, isoplorantinone (Figure 19) was isolated along with several other sesquiterpenes from the ethanolic extract of *Lactarius piperatus* fungus.[167]



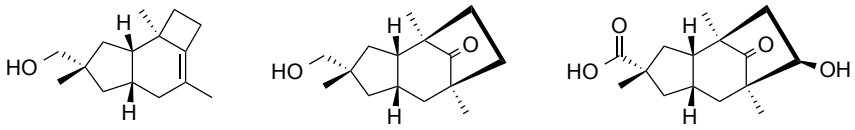
isoplorantinone

Figure 19. Structure of isoplorantinone II-42

The repraesentins

In 2003, three new plant growth regulatory sesquiterpenoids were isolated from the *Lactarius repraesentaneus* fungus (Figure 20).[168]

The structure of these newly identified compounds was elucidated by extensive NMR studies. Repraesentin A was identified as a protoilludane-type sesquiterpene whereas repraesentin B and C can be classified as cerapicane sesquiterpenes representatives (Figure 14).



repreasentin A **repreasentin B** **repreasentin C**

Figure 20. Structures of repraesentins A, B and C

These three new compounds showed promoting activities towards the radicle[169] elongation of lettuce seedling[170] by 136%, 118% and 184% at 67 ppm, respectively.

167. Y. Wang, S.-P. Yang, J. M. Yue, *Helv. Chim. Acta* **2003**, *86*, 2424-2433.

168. M. Hirota, Y. Shimizu, T. Kamo, H. Makabe, H. Shibata, *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1597-1600.

169. Radicle (botany): *the part of a plant embryo that develops into the primary root*; from Oxford Dictionaries.

In 2006, three new plant regulatory sesquiterpenes were isolated from the same *Lactarius repraesentaneus* fungus,[171] namely repraesentin D, E, and F (Figure 21). Repraesentin D and repraesentin E were elucidated to be lactarane sesquiterpenes whereas repraesentin F is related to the protoilludanes.

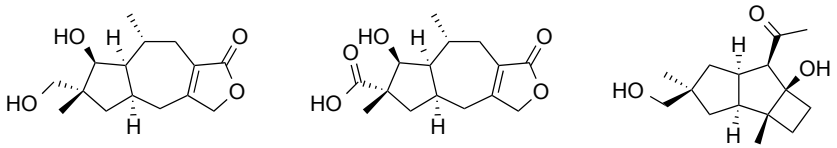


Figure 21. Structures of repraesentins D, E and F

All these compounds are active on the radicle elongation of lettuce seedlings, however repraesentin E showed the strongest promoting activity (164% at 3.6 μM).

The russujaponols

In 2006, a first set of six illudoid sesquiterpenes was isolated from the fruiting bodies of *Russula japonica* fungus and their cytotoxic activities against a disease-oriented panel of 39 human cancer cell lines were investigated.[172]

170. Seedling: *a young plant, especially one raised from seed and not from a cutting*; from Oxford Dictionaries.

171. M. Kashiwabara, T. Kamo, H. Makabe, H. Shibata, M. Hirota, *Biosci. Biotechnol. Biochem.* **2006**, *70*, 1502-1505.

172. K. Yoshikawa, A. Kaneko, Y. Matsumoto, H. Hama, S. Arihara, *J. Nat. Prod.* **2006**, *69*, 1267-1270.

Their structures (Figure 22) were established mainly by 2D NMR experiments. However, the scaffold of the main compound (russujaponol A) was confirmed by X-ray crystallographic analysis of its benzoate derivative.

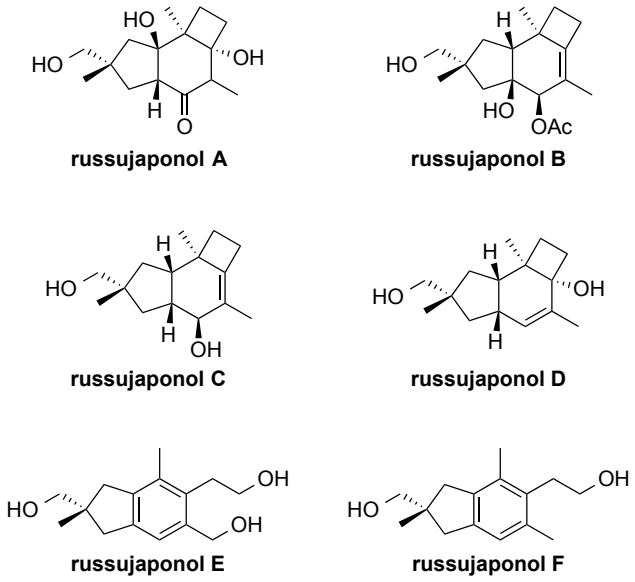


Figure 22. Structures of russujaponols A-F

Russujaponol A suppressed invasion of human fibrosarcoma (HT1080) cells into Matrigel in a concentration-dependent manner and caused 63% inhibition at 3.73 μM.

Later in 2009, a second set of 6 illudoid sesquiterpenes belonging to the same family, namely russujaponols G-L (Figure 23), was isolated from the fruit bodies of *Russula japonica*.[173] Their bioactivity was tested similarly.

173. K. Yoshiwaka, Y. Matsumoto, H. Hama, M. Tanaka, H. Zhai, Y. Fukuyama, S. Arihara, T. Hashimoto, *Chem. Pharm. Bull.* **2009**, *57*, 311-314.

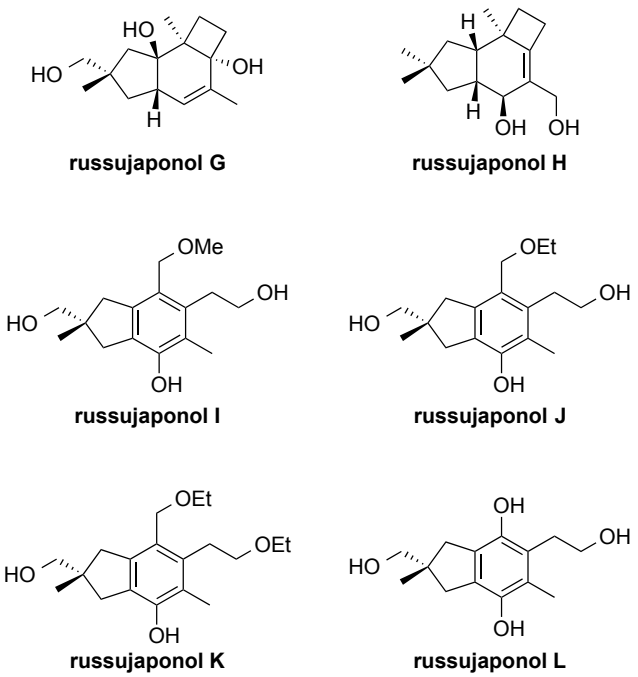
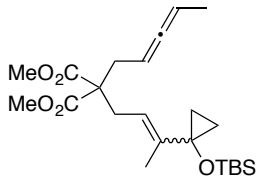


Figure 23. Structures of russujaponols G-L

Russujaponols I-L showed neurite outgrowth promoting activity in the primary cultured rat cortical neurons.

Objectives

The results obtained in previous chapter prompted us to test new substrates bearing allenes instead of alkynes. Allenes proved to be interesting functional groups in intramolecular cycloadditions catalyzed by Rh(I),[174] as well as cycloisomerizations catalyzed by transition metals and in particular gold.[175,176] In our particular context, we were especially interested in allene-vinylcyclopropane substrates such as **II-1** (Figure 24).



II-1

Figure 24. Model substrate II-1

From a mechanistic standpoint, this class of substrates could give us access to tricyclic structures as presented in Scheme 40.

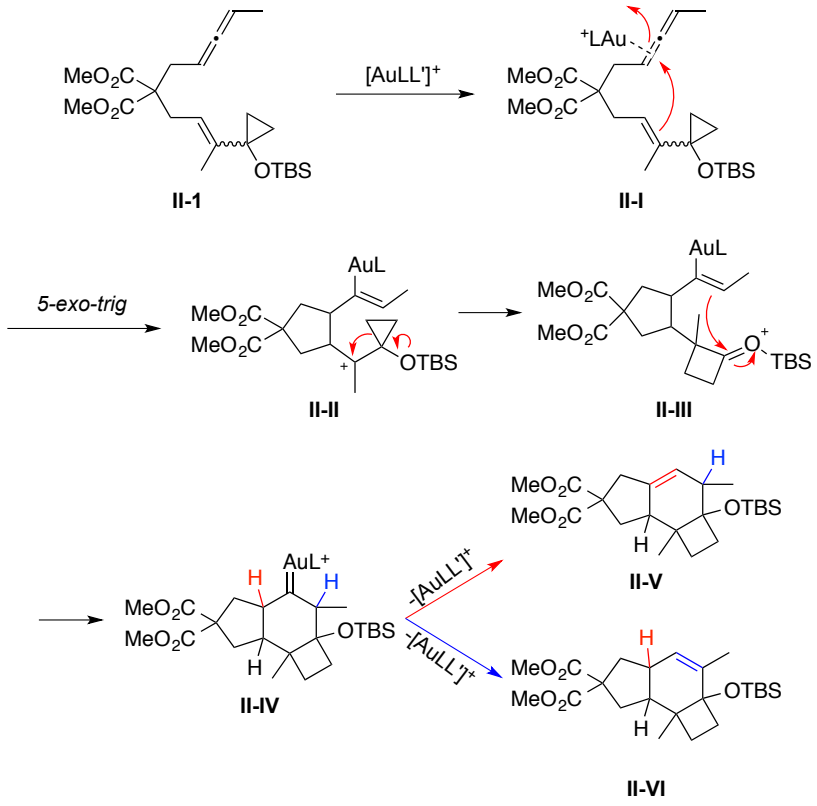
Coordination of gold to the allene (**II-I**) could trigger a 5-*exo*-trig cyclization to furnish cationic intermediate **II-II**, which could ring-expand to generate **II-III**. Upon attack of the vinyl gold on the oxonium cation in a

174. (a) P. A. Wender, A. G. Correa, Y. Sato, R. Sun, *J. Am. Chem. Soc.* **2000**, *122*, 7815-7816; (b) P. A. Wender, M. P. Croatt, N. M. Deschamps, *Angew. Chem. Int. Ed.* **2006**, *45*, 2459-2462.

175. The transition metal (including gold) catalyzed cycloisomerizations of enallenes and allenynes were recently reviewed, including the mechanistic studies: C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954-1993.

176. For an application of the gold-catalyzed cyclization of functionalized allenes for the synthesis of carbo- and heterocycles, see: M. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994-2009.

Prins-type cyclization,[105,177] gold carbene **II-IV** would be formed. Finally, proton elimination followed by a protodeauration would provide access to **II-V** and/or its regioisomer **II-VI**.[175,176]



Scheme 40. Proposed mechanism for the cyclization of allene-vinylcyclopropanes

Regarding the relative configuration of intermediates **II-II**, both *cis*- or *trans*-configurations have been obtained in gold(I)-catalyzed cycloisomerizations of enallenes.[178]

105. E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2006**, *45*, 5452-5455.

177. For a review on the synthetic applications of gold-catalyzed ring expansions, see: D. Garayalde, C. Nevado, *Beilstein J. Org. Chem.* **2011**, *7*, 767-780.

The structures formed according to this mechanism would allow us to approach the framework of the protoilludane sesquiterpenes family (Figure 13). After minor modification of the cyclized product, we may be able to access molecules related to 7-protoilludene (Figure 25), such as russujaponol D. More complex transformations would give an entry to the molecules related to 6-protoilludene, repraesentin A and plorantinone A for instance.

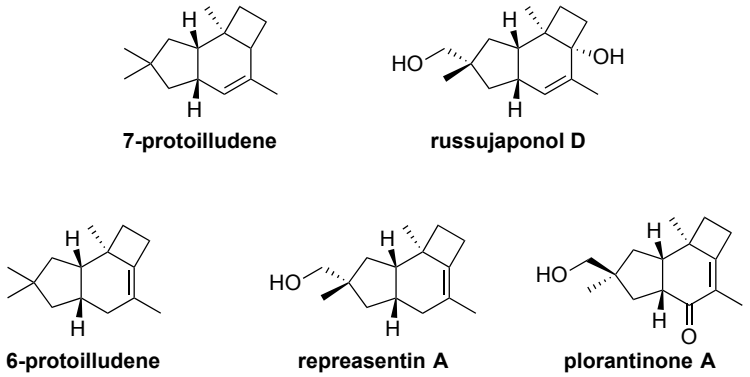


Figure 25. Potential targets accessible by the cyclization of allene-vinylcyclopropanes

We envisioned preparing cyclization precursors such as **II-1** (Figure 24) bearing a malonate tether and a TBS-protecting group, as they would form tricyclic structures related to the protoilludanes sesquiterpenes.[179] Both **II-1-*E*** and **II-1-*Z*** will be synthesized to gain better insight into the mechanism and the stereocontrol of the reaction.

178. (a) M. R. Luzung, P. Mauleón, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402-12403; (b) P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6348-6349.

179. The skeleton of illudanes and protoilludanes was also obtained by ring contration of fused cyclobutanols: K. Takasu, Y. Magamoto, Y. Takemoto, *Chem. Eur. J.* **2010**, *16*, 8427-8432.

Results and discussion[180,181]

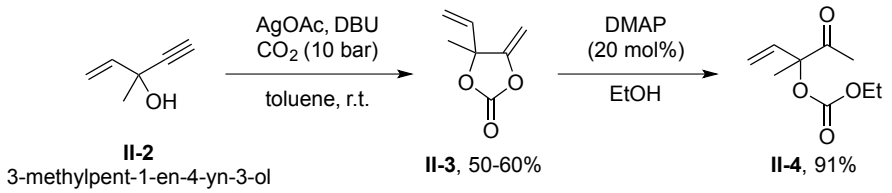
Allene *E*-vinylcyclopropane

Initially, we investigated the reactivity of allene-vinylcyclopropane **II-1-*E*** with a *E*-geometry around the alkene. The synthesis of this precursor and its reactivity is described hereafter.

*Synthesis of the cyclization precursor **II-1-E***

The synthesis of precursor **II-1-*E*** requires the preparation of two building blocks that will be tethered to dimethylmalonate.

On one hand and similarly to the synthesis of the precursors in chapter 1, carbonate **II-4** was synthesized in two steps from commercially available 3-methylpent-1-en-4-yn-3-ol **II-2** (Scheme 41).[182]



II-2
3-methylpent-1-en-4-yn-3-ol

II-3, 50-60%

II-4, 91%

Scheme 41. Two-step synthesis of carbonate II-4

On the other hand, mesylate **II-5** was prepared in three steps from THP-protected propargylic alcohol **II-6** (Scheme 42).[183] Hydroxymethylation of

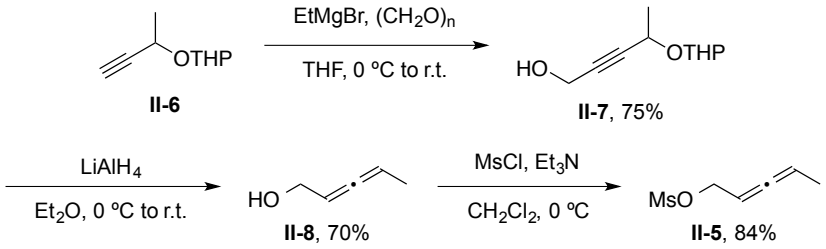
180. In collaboration with Dr. Julien Ceccon and Dr. David Leboeuf.

181. A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 4580-4583.

182. See Scheme 31 in chapter 1 and the discussion presenting its synthesis.

183. THP-protected propargylic alcohol **II-7** was synthesized according to the procedure reported in P. D. Landor, S. R. Landor, E. S. Pepper, *J. Chem. Soc. (C)* **1967**, 185-189.

II-66 afforded propargylic alcohol **II-7**,[184] which underwent SN_2' reduction mediated by $LiAlH_4$ leading to allenic alcohol **II-8**.[185] Final mesylation under standard conditions provided the desired building block **II-5**. Similarly, enantioenriched **II-5** was obtained through the same synthetic route, starting from enantiopure **II-6**.[186]



Scheme 42. Three-step synthesis of mesylate II-5

Finally, **II-4** and **II-5** were engaged in the construction of precursor **II-1-*E*** (Scheme 43). Dimethylmalonate was alkylated with mesylate **II-5** under basic conditions to give substituted-allene **II-9**.[187] Fomation of enone **II-10** was achieved by Tsuji-Trost reaction in excellent yield and outstanding stereoselectivity (exclusively *E*-isomer).[188] Enone **II-10** was efficiently converted into TBS-enol ether **II-11** and final Simmons-Smith cyclopropanation reaction completed the synthesis of precursor **II-1-*E*** in excellent yield.

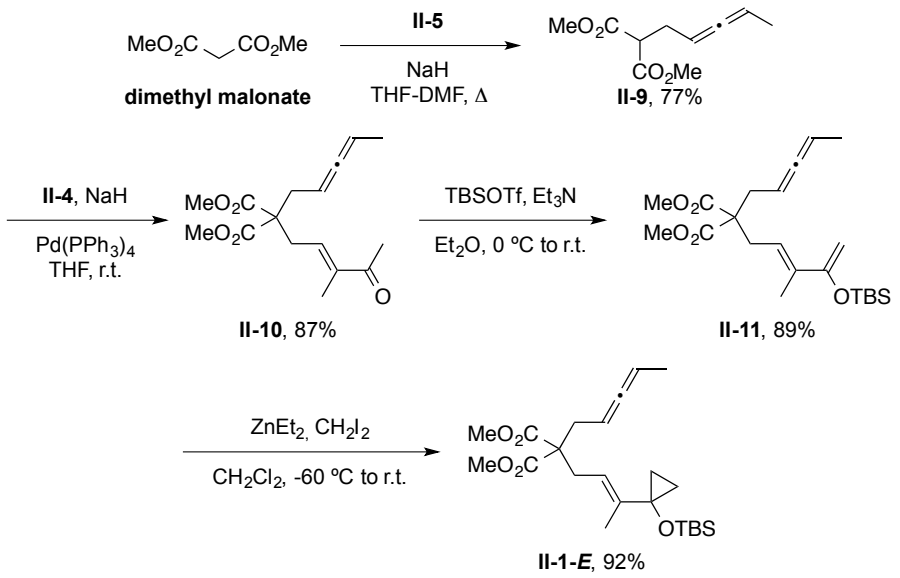
184. P. Wipf, L. T. Rahman, S. R. Rector, *J. Org. Chem.* **1998,** *63*, 7132-7133.

185. D. Djahanbini, B. Cazes, J. Gore, *Tetrahedron* **1984,** *40*, 3645-3655.

186. R. A. Smith, R. L. White, A. Krantz, *J. Med. Chem.* **1988,** *31*, 1558-1566.

187. P. Cérat, P. J. Gritsch, S. R. Goudreau, A. B. Charette, *Org. Lett.* **2010,** *12*, 564-567.

188. The conditions employed were identical to the ones in chapter 1.

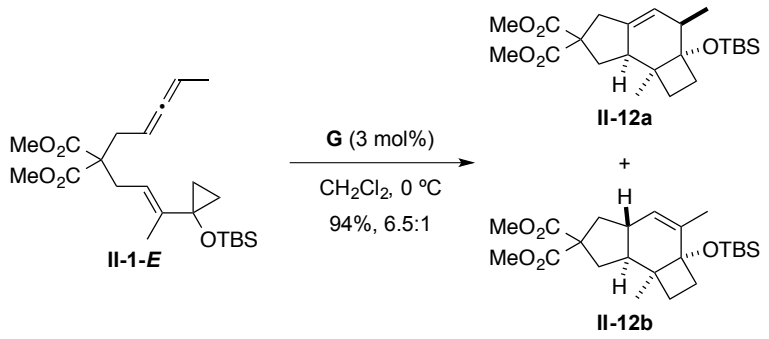


Scheme 43. Synthesis of cyclization precursor II-1-E

*Gold(I)-cyclization of precursor **II-1-E***

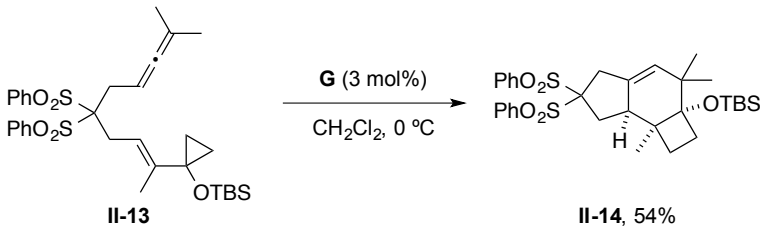
The gold(I)-catalyzed cyclization of allene-vinylcyclopropane **II-1-*E*** was investigated (Scheme 44). The transformation was carried out satisfactorily using [IPrAu(NCPh)]SbF_6 catalyst (**G**, 3 mol%) in CH_2Cl_2 at 0 ºC to provide tricyclic compounds **II-12** in 94% yield as a 6.5:1 mixture of two alkene regioisomers.[189]

189. The minor isomer **II-12b** could not be isolated, and its structure was tentatively assigned as a derivative of 3,7b-dimethyl-1,2,4a,5,6,7,7a,7b-octahydro-2a*H*-cyclobuta[*e*]inden-2a-ol (stereoisomer of **II-21a**, Table 4), with the *trans*-configuration between the five- and six-membered rings.



Scheme 44. Gold-catalyzed cyclization of II-1-E

Similarly, cyclization of substrate **II-13**[190] with two methyls at the allene terminus furnished tricyclic compound **II-14** in 54% yield as only product (Scheme 45).



Scheme 45. Gold-catalyzed cyclization of II-13

From a mechanistic point-of-view, the presence of the *gem*-dimethyl allene terminus prevents the competitive proton elimination (intermediate **II-IV**, Scheme 40) and explains the formation of a single isomer.

Although the cyclization of **II-1-*E*** furnished **II-12** in excellent yield (Scheme 44), some contaminants could not be removed by any purification mean. Nevertheless we were able to observe interesting nOe correlations (Figure 26). The cyclization of precursor **II-13** led to a significantly purer

190. **II-13** and **II-14** were prepared by Dr. Julien Ceccon during the preliminary studies on this reaction. The synthetic scheme was identical to the one presented for **II-1-*E*** and both products were characterized.

product allowing the determination of the complete relative stereochemistry of the tricyclic compounds through NMR studies. Both **II-12** and **II-14** exhibited a *syn-cis* relationship between the ring junctions.

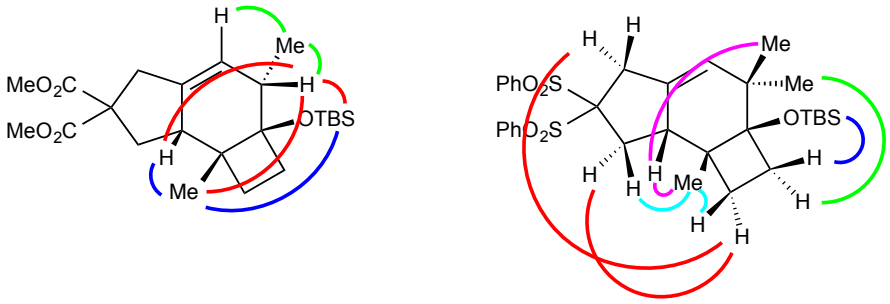


Figure 26. nOe correlations in II-12 and II-14

Pleasingly, the allene-vinylcyclopropane cyclization provided the desired tricyclic system as originally planned. However, the relative configuration of **II-12** and **II-14** was the opposite to that of the natural protoilludanes. This prompted us to investigate the reactivity of allene-vinylcyclopropanes bearing a *Z*-alkene.

Allene *Z*-vinylcyclopropane

Based on the promising results obtained earlier with the *E*-enallene precursors, the cyclization of *Z*-enallenes was then envisaged to appreciate whether this transformation is stereospecific with respect to the stereochemistry around the alkene.

A library of a dozen of precursors bearing different tethers and protecting groups was initially prepared. Only the results leading to structures closely related to the protoilludane sesquiterpene framework will be presented.[191]

191. J. Ceccon, A. Pitaval, unpublished results, ICIQ, 2008-2011.

*Synthesis of cyclization precursor **II-1-Z***

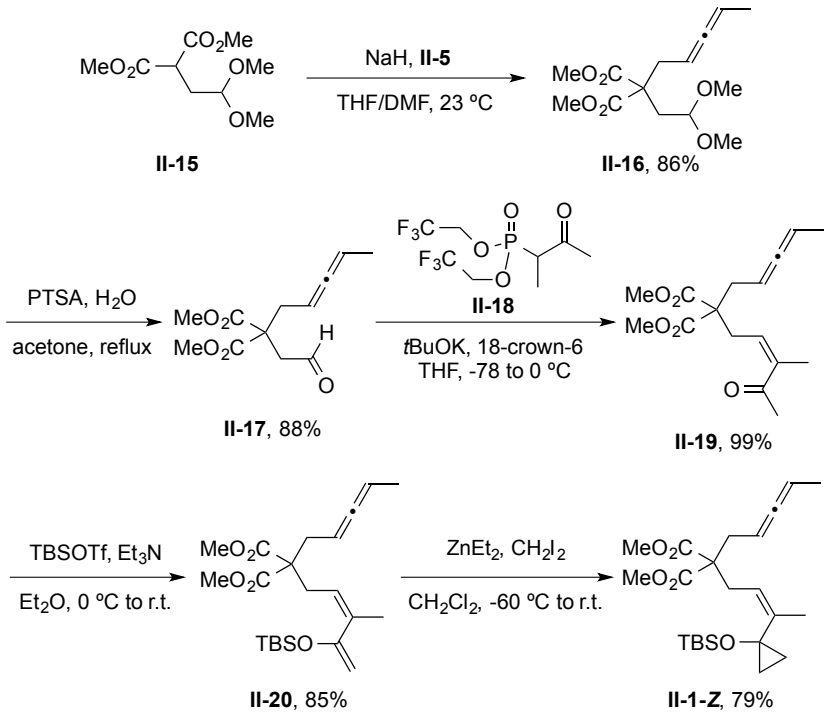
The methodology developed earlier for the synthesis of the *E*-precursors was not applicable. Therefore, a different approach was designed relying on the Still-Gennari modification of the Horner–Wadsworth–Emmons olefination reaction (Scheme 46).[192]

Thus, the anion of malonate **II-15**[193] was alkylated with mesylate **II-5** to give allenyl malonate **II-16** in 86% yield. The acetal was then efficiently hydrolyzed to furnish aldehyde **II-17** (88%), which was alkenylated with phosphonate **II-18** to yield enone **II-19** in almost quantitative yield with the desired *Z*-configuration.[130] Finally, formation of silylenol ether **II-20** with TBSOTf and Et_3N, followed by Simmons-Smith cyclopropanation led to **II-1-*Z*** (67% over two steps).[130]

192. W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

193. R. Shitani, K. Okamoto, Y. Otomaru, K. Ueyama, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 54-55.

130. L. Jiao, C. Yuan, Z.-X. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 4421-4430.



Scheme 46. Synthesis of cyclization precursor II-1-Z

Gold(I)-cyclization of enallene precursor ***II-1-Z***

Optimization of the reaction conditions was performed previously.[191] The influence of the solvent, temperature and other reaction parameters was screened.

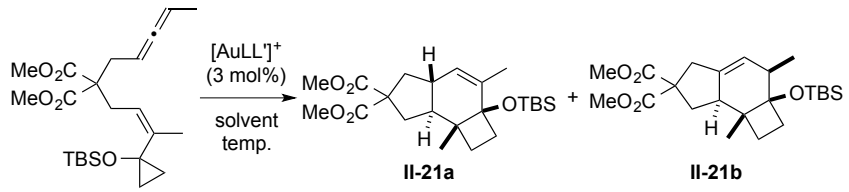
Reaction only occurred in chlorinated solvents. CH_2Cl_2 and 1,2-dichloroethane (1,2-DCE) gave the same results, whereas chloroform showed lower conversion and more decomposition. Performing the cyclization under microwave irradiation speeded up the reaction but additional by-products were observed. Moreover, slightly better results were obtained when 4 Å molecular sieves were used.

Catalysts screening

Based of the previous optimization, we then screened various catalysts for the cycloisomerization of **II-1-*Z*** (Table 4). Unless otherwise stated, the reactions were run for 24 h before being quenched.

The cyclization was best carried out in 1,2-dichloroethane at 23 ºC in the presence of catalyst **A** (3 mol%, entry 4). The reaction led to the formation of two major products **II-21a** and **II-21b** in a 2:1 ratio (82% NMR yield), which could not be separated by chromatography.

Table 4. Catalysts screening for the cyclization of II-1-Z



II-1-*Z* **II-21a** **II-21b**

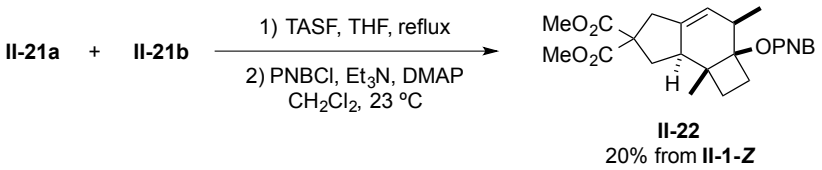
Entry	Catalyst	Solvent	T (ºC)	Yield II-21a:II-21b[a] (%)
1	**A**	CH_2Cl_2	0	36 (4:1)
2	**A**	CH_2Cl_2	23	69 (3.3:1)
3	**A**	1,2-DCE	23	73 (2.3:1)
4	**A**	1,2-DCE[b]	23	82 (2:1)
5	**G**	CH_2Cl_2	0	71 (3.5:1)
6	**G**	CH_2Cl_2	23	35 (2:1)
7	**B**	CH_2Cl_2	0	traces[c]
8	**B**	CH_2Cl_2	23	50 (3:1)
9	**F**	CH_2Cl_2	0	traces[d]
10	**F**	CH_2Cl_2	23	traces[d]
11	**H**	CH_2Cl_2	0	30[e] (1:10)
12	**H**	CH_2Cl_2	23	31[e] (1:10)

[a] Yields determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard. Complete conversion was observed.
[b] 4 Å molecular sieves added.
[c] Starting material recovered.
[d] Starting material + decomposition.
[e] Product contaminated by decomposed starting material.

Structure assignment

The structure of **II-21a** and **II-21b** was assigned by transformation into their crystalline derivatives.

The mixture of both cyclization products was engaged in a two-step sequence to prepare *p*-nitrobenzoate derivative **II-22** (Scheme 47). The TBS-protecting group was cleaved with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and the resulting tertiary alcohol was converted into **II-22**.



Scheme 47. Two-step synthesis of II-22

Final recrystallization provided crystalline **II-22** (20% yield from **II-1-*Z***). The crystals obtained were suitable for X-ray diffraction analysis (Figure 27).[194]

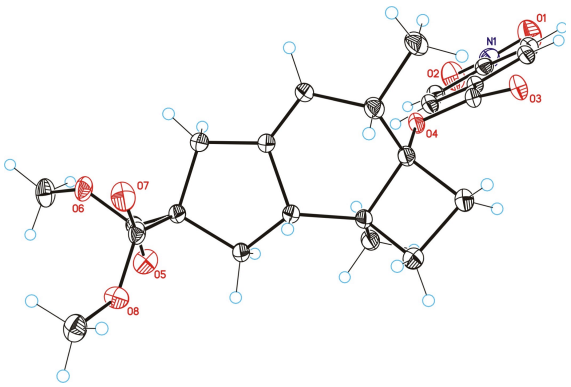
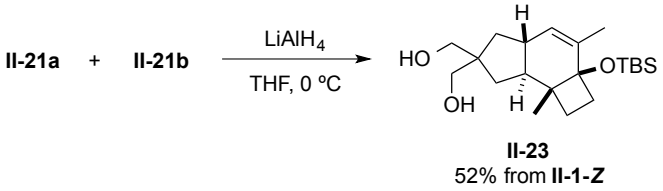


Figure 27. ORTEP drawing of II-22

194. CCDC 953503

The mixture of both cyclization products was treated with $LiAlH_4$ in THF (Scheme 48) and diol **II-23** was isolated (52% yield from **II-1-*Z***).



II-23
52% from **II-1-*Z***

Scheme 48. One-step synthesis of II-23

X-ray diffraction confirmed the *trans* configuration at the junction between the 5- and 6-membered rings observed by NMR (Figure 28).[195]

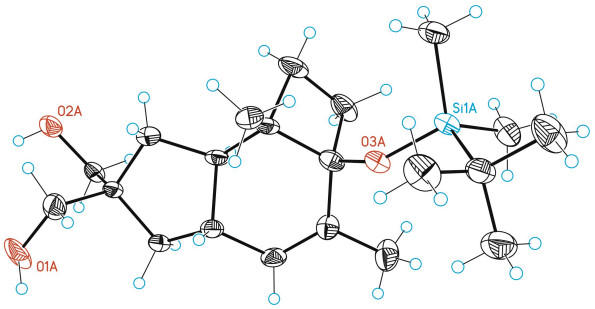
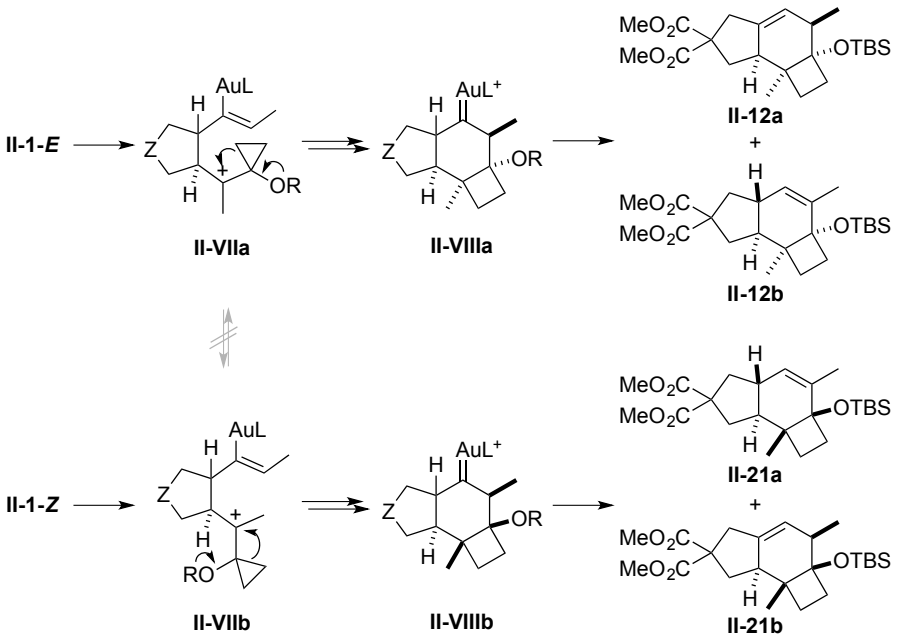


Figure 28. ORTEP drawing of II-23

Mechanistic considerations

Our results demonstrate that intermediates **II-VIIa** and **II-VIIb** do not undergo equilibration (Scheme 49), and that the cyclopropylcarbenium to cyclobutane ring expansion occurs with complete stereoselectivity to form **II-VIIIa** or **II-VIIIb** by intramolecular Prins-type reaction.

195. CCDC 953502



Scheme 49. Stereospecific cyclization of II-1-E and II-1-Z

II-21a was observed as the major product in the cyclization of **II-1-*Z***. This suggests that the gold(I) catalyzed allene-vinylcyclopropane cycloisomerization leads to intermediates **II-VIII** with the *trans*-relative configuration. However, compounds **II-12b** and **II-21b** could either arise from *trans*- or *cis*-configured intermediates.

Further Developments

Towards russujaponol D

We demonstrated before that precursor **II-1-*Z*** readily cyclized to afford products **II-21a** and **II-21b** in a 2:1 ratio (82% NMR yield, Table 4), which could not be separated by chromatography. Nevertheless, reduction of the malonate to diol **II-23** (Scheme 48) allowed the separation of the two regiosiomers.

The structure of **II-21a** is closely related to the one of russujaponol D (Figure 29). The 5/6/4-tricyclic framework is correctly assembled and the alkene and hydroxyl group are properly placed. However, the 5- and 6-membered ring fusion is *trans* instead of *cis*.

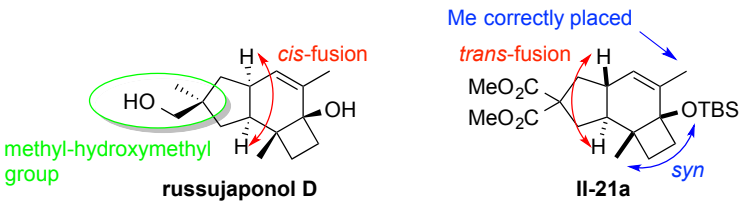
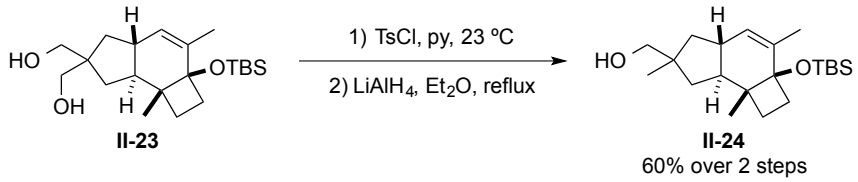


Figure 29. Comparison between the structure of russujaponol D and II-21a

Even though the ring fusion is not the correct one, we investigated the reduction of the malonate to the methyl-hydroxymethyl group present in most of the targeted natural compounds (Scheme 50). To do so, diol **II-23** was monotosylated and the resulting hydroxy-tosylate treated with $LiAlH_4$ in refluxing ether. Mono-reduced product **II-24** was isolated as 1:1 mixture of diastereoisomers. This indicates that this chiral center should be installed earlier in the synthesis, probably before the gold-cyclization step and protected orthogonally all along the synthesis to be released at the end of the synthesis.

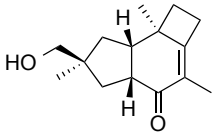


II-23 **II-24**
60% over 2 steps

Scheme 50. Mono-reduction of diol II-24

Towards plorantinone A and other related structures

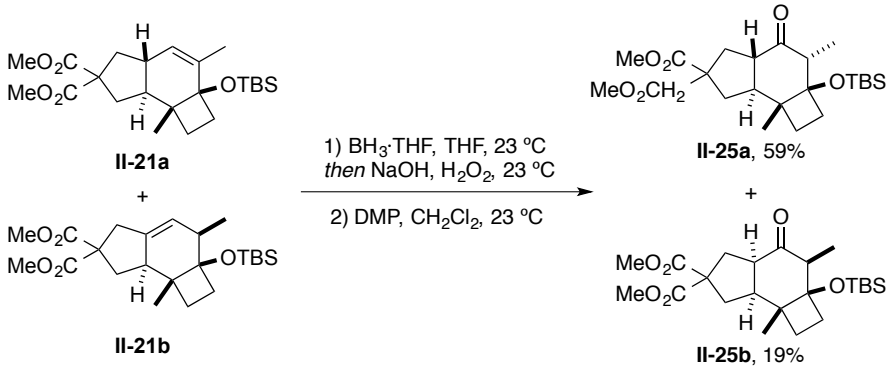
In order to approach plorantinone A (Figure 30), we also explored the introduction of an oxygen functionality on the 6-membered ring by a Brown hydroboration.



plorantinone A

Figure 30. Structure of plorantinone A

The mixture of both cyclization products **II-21a** and **II-21b** was treated with $BH_3 \cdot THF$ complex followed by oxidation with H_2O_2 (Scheme 51). The reaction led to a mixture of several diastereoisomeric alcohols, which could not be separated by chromatography. However, treatment of this mixture with Dess-Martin periodinane provided ketones **II-25a** and **II-25b** in 59% and 19% yield respectively.



Scheme 51. Two-step sequence to ketones II-25

After separation of these two compounds, we were able to establish their relative configuration by nOe experiments (Figure 31). The major compound (**II-25a**) displayed a *trans*-fusion between the 5- and 6-membered rings whereas the minor one (**II-25b**) presented a *cis*-fusion.

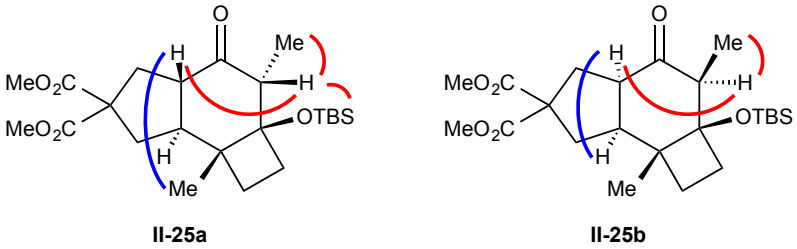
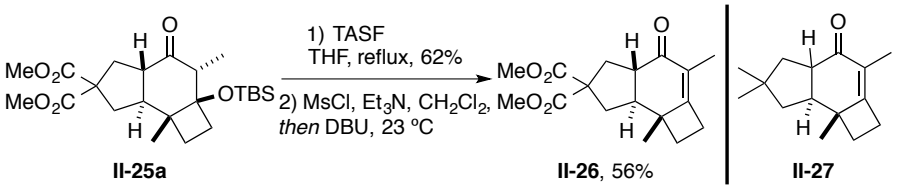


Figure 31. nOe correlations in II-25a and II-25b

The TBS group of the major compound **II-25a** was cleaved with TASF, and the resulting alcohol was converted into an unstable mesylate intermediate (Scheme 52). This intermediate was not isolated and the mesylate was directly eliminated with DBU to furnish enone **II-26**. No epimerization was observed under these conditions leading to the corresponding *cis*-stereoisomer.[196]

196. DFT calculations (B3LYP, 6-21G*) on model *cis*- and *trans*-**II-27** proved that the *trans*-isomer is the most stable ($\Delta\Delta H^{o}$ = 2.5 kcal.mol^{-1}).



Scheme 52. Synthesis of enone II-26

Even though the ring fusion is not correct, enone **II-26** can also be considered as an intermediate platform to reach epimers of many other natural compounds coming from the reduction of the carbonyl group such as russujaponol C (Figure 32). Russujaponol H and pasteurestin A display a higher oxidation state at the *exo*-cyclic methyl that could be introduced by allylic oxidation.

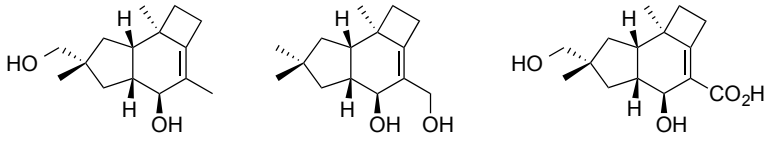


Figure 32. Structures of russujaponol C, russujaponol H and pasteurestin A

Conclusions

A new intramolecular gold(I)-catalyzed cycloisomerization of allene-vinylcyclopropanes leading to the formation of tricyclic molecules was developed. These molecules display the framework of protoilludanes, an important class of sesquiterpenes.

We were able to synthesize efficiently and selectively both *E*- and *Z*-enallene precursors by two different synthetic routes. The cyclization proceeded in excellent yields, although as a mixture of regioisomers. Further transformation of the cyclized compounds gave crystalline materials that supported their structures. The cyclization is stereospecific as different diastereoisomers can be specifically obtained depending on the geometry around the starting double bond.

The cyclization of the *Z*-enallene precursor provided a major cycloisomerized product bearing the skeleton of russujaponol D, yet with the opposite ring fusion. Attempts to install oxygen-functionalities were successful and pave the way to the access of many other related sesquiterpenes.

Ongoing work focuses on developing asymmetric syntheses of these natural compounds,[197] and exploring new routes to access the desired *cis*-fusion by screening new gold(I) catalysts. Even though the mechanism is entirely different, rhodium(I) catalysts could be also tested in order to obtain the desired ring fusion.[198]

197. T. Jiménez-Trujillo, unpublished results, ICIQ, 2013-2014.

198. Rh(I)-complexes were used by the group of Wender in related intramolecular cyclizations of allene-vinylcyclopropanes and the desired *cis*-fusion was observed: (a) P. A. Wender, F. Glorius, C. O. Husfeld, E. Langkopf, J. A. Love, *J. Am. Chem. Soc.* **1999**, *121*,

Experimental part

General information

Unless otherwise stated, reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF_{234}) using UV light as visualizing agent, and an acidic solution of vanillin in ethanol or a basic solution of potassium permanganate in water as stain solutions. Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 mm) or automated flash chromatographer CombiFlash Companion. Preparative TLC was performed on 20 cm x 20 cm silica gel plates (2.0 mm thick, catalogue number 02015, Analtech). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

NMR spectra were recorded at 298 K on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

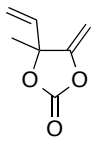
Crystal structure determinations were carried out using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = −173 ºC). Full-sphere data collection was used with w and j scans. *Programs used:* Data collection

5348-5349; (b) P. A. Wender, F. C. Bi, G. G. Gamber, F. Gosselin, R. D. Hubbard, M. J. C. Scanio, R. Sun, T. J. Williams, L. Zhang, *Pure Appl. Chem.* **2002**, *74*, 25-31.

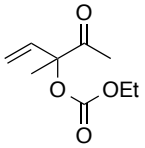
APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. *Structure Solution and Refinement:* Crystal structure solution was achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

Allene *E*-vinylcyclopropane

*Synthesis of the cyclization precursor **II-60-E***

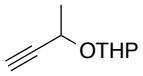


II-3



II-4

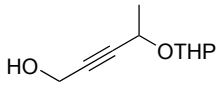
Cyclic carbonate **II-3** and allylic carbonate **II-4** were prepared following the same procedure described in the experimental part of the first chapter of this manuscript.



II-6

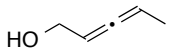
THP-protected propargylic alcohol **II-6** was prepared following the procedure described in reference 183. Analytical data were in accordance with literature.[183,199]

199. See experimental part of reference 183: P. D. Landor, S. R. Landor, E. S. Pepper, *J. Chem. Soc. (C)* **1967**, 185-189.



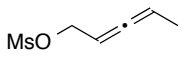
II-7

Propargylic alcohol **II-7** was prepared following the procedure described in references 183 and 184. Analytical data were in accordance with literature.[199,200]



II-8

Allenic alcohol **II-8** was prepared following the procedure described in references 183 and 184. Analytical data were in accordance with literature.[201]

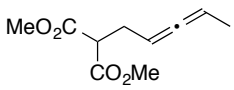


II-5

Anhydrous Et_3N (7.30 mL, 52.6 mmol) and MsCl (3.10 mL, 39.5 mmol) were added successively added over 5 min to a solution of the allenic alcohol **II-8** (2.21 g, 26.3 mmol) in anhydrous CH_2Cl_2 (130 mL) at 0 ºC. The resulting mixture was stirred for 1 h at 0 ºC, then quenched with water and extracted with Et_2O (3 times). The combined organic layers were washed with aqueous HCl 5% (twice), brine, dried over anhydrous $MgSO_4$, filtered and concentrated (max. 25 ºC and 150 mbar when evaporating the solvents) to afford crude mesylate **II-5** (3.59 g crude) as a colorless oil. The crude material was engaged in the subsequent step without further purification.

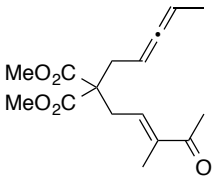
200. See experimental part in reference 184: P. Wipf, L. T. Rahman, S. R. Rector, *J. Org. Chem.* **1998,** *63*, 7132-7133.

201. See experimental part in reference 185: D. Djahanbini, B. Cazes, J. Gore, *Tetrahedron* **1984,** *40*, 3645-3655.



II-9

Malonate **II-9** was prepared following the procedure described in reference 202 (mesylate was used as leaving instead of tosylate). Analytical data were in accordance with literature.[187,202]



II-10

A solution of malonate **II-9** (1.17 g, 5.91 mmol) in THF (10 mL) was added to a suspension of NaH (60 wt% in mineral oil, 258 mg, 6.44 mmol) in THF (20 mL), and the resulting mixture was stirred for 30 min at room temperature. Then, the solution was transferred via cannula to a solution of $Pd(PPh_3)_4$ (186 mg, 0.16 mmol, 3 mol%) in THF (10 mL). Finally, solution of carbonate **II-4** (1.00 g, 5.37 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 3 h at room temperature, then quenched with saturated $NaHCO_3$ and extracted with Et_2O (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/cyclohexane 0:100 to 1:10) to afford enone **II-10** (1.43 g, 90% yield) as a colorless oil.

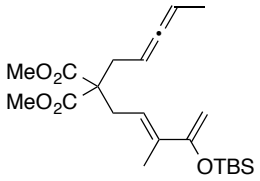
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (tq, J = 7.4, 1.4 Hz, 1H), 5.12 – 5.02 (m, 1H), 4.88 (tdd, J = 7.7, 6.3, 3.1 Hz, 1H), 3.73 (2 s, 6H), 2.88 (dt, J = 7.3, 1.1 Hz, 2H), 2.62 (dd, J = 7.7, 2.3 Hz, 2H), 2.28 (s, 3H), 1.77 (d, J = 1.2 Hz, 2H), 1.62 (dd, J = 7.0, 3.2 Hz, 3H).

202. M. Li, S. Datta, D. M. Barber, D. D. Dixon, *Org. Lett.* **2012**, *14*, 6350-6353.

187. P. Cérat, P. J. Gritsch, S. R. Goudreau, A. B. Charette, *Org. Lett.* **2010,** *12*, 564-567.

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 199.6, 171.1, 171.0, 140.3, 136.7, 86.2, 84.1, 57.6, 52.9, 52.8, 33.5, 32.3, 25.6, 14.3, 11.5.

HRMS-ESI: *m/z* calculated for $C_{16}H_{22}O_5Na$ $[M+Na]^+$: 317.1359, found: 317.1364.



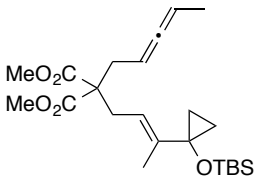
II-11

Anhydrous Et_3N (142 μL, 1.02 mmol) and TBSOTf (117 μL, 0.51 mmol) were added dropwise to a solution of enone **II-10** (100 mg, 0.34 mmol) in anhydrous Et_2O (10 mL) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with brine and extracted with Et_2O (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/hexane/Et_3N 0:100:1 to 10:90:1) to afford silylenol ether **II-11** (124 mg, 89% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.82 (m, 1H), 5.08 – 4.98 (m, 1H), 4.88 (m, 1H), 4.42 (dd, *J* = 1.4, 0.6 Hz, 1H), 4.28 – 4.20 (m, 1H), 3.70 (s, 6H), 2.85 – 2.77 (m, 2H), 2.57 (dd, *J* = 7.8, 2.3 Hz, 2H), 1.77 (d, *J* = 1.1 Hz, 3H), 1.61 (dd, *J* = 7.0, 3.2 Hz, 3H), 0.96 (s, 9H), 0.15 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 171.4, 157.1, 134.4, 121.3, 91.8, 85.8, 84.5, 58.0, 52.6, 52.5, 14.4, 13.5, -4.6.

HRMS-ESI: *m/z* calculated for $C_{22}H_{37}O_5Si$ $[M+H]^+$: 409.2405, found: 409.2402.



II-1-*E*

CH_2I_2 was washed with saturated aqueous Na_2SO_3 (twice), dried over anhydrous $MgSO_4$, filtered and fractionally distilled over CaH_2 (T^o_{eb} = 54ºC @ 10 mbar), then stored over 3 Å MS under an argon atmosphere.

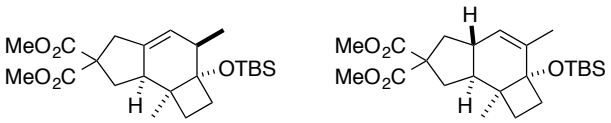
CH_2I_2 (270 µL, 3.35 mmol) was added dropwise to a solution of $ZnEt_2$ (1 M in hexanes, 3.3 mL, 3.30 mmol) in anhydrous CH_2Cl_2 (20 mL) at −60 ºC. The resulting solution was warmed up to 0 ºC until a white precipitate appeared, then cooled down to −60 ºC, whereupon a solution of the silylenol ether **II-11** (1.14 g, 2.79 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was then quenched with saturated NH_4Cl and extracted with Et_2O (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/hexane 0:100 to 10:90) to afford substrate **II-1-*E*** (1.09 g, 92% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 – 5.21 (m, 1H), 5.08 – 4.99 (m, 1H), 4.90 – 4.82 (m, 1H), 3.69 (s, 6H), 2.67 (d, *J* = 7.4 Hz, 2H), 2.54 (dd, *J* = 7.7, 2.4 Hz, 2H), 1.70 (s, 3H), 1.61 (dd, *J* = 7.0, 3.2 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.83 (s, 9H), 0.79 – 0.75 (m, 2H), 0.67 – 0.63 (m, 2H), 0.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 171.3, 171.2, 140.4, 117.5, 85.6, 84.3, 60.9, 57.8, 52.4, 52.3, 32.5, 30.5, 25.7, 17.8, 14.3, 14.0, 13.4, -3.8.

HRMS-ESI: *m/z* calculated for $C_{23}H_{38}O_5SiNa$ $[M+Na]^+$: 445.2381, found: 445.2371.

*Gold(I)-cyclization of precursor **II-1-E***



II-12a:II-12b (6.5:1)

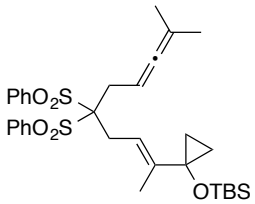
A dry flask under argon was charged with catalyst **B** (6.20 mg, 0.01 mmol). Then, a solution of precursor **II-1-*E*** (95.0 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (2.2 mL) was added at 0 ºC. After completion of the reaction (2 h), the solution was quenched with a few drops of Et_3N and filtered through a pad of SiO_2 (elution with EtOAc/hexane 50:50). After removal of the solvent, the crude product was purified by flash column chromatography over silica gel (eluent pentane/EtOAc 98:2) to afford a mixture of **II-12a** and **II-12b** as a pale yellow oil (89.0 mg, 94% yield) in a ratio 6.5:1 (corrected yield for **II-12a**: 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 – 5.33 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.10 – 3.03 (m, 1H), 2.84 – 2.75 (m, 1H), 2.48 – 2.33 (m, 2H), 2.15 – 2.10 (m, 1H), 1.91 – 1.82 (m, 2H), 1.70 – 1.63 (m, 2H), 1.25 – 1.21 (m, 1H), 1.11 (s, 3H), 0.99 (d, J = 7.1 Hz, 3H), 0.86 (s, 9H), 0.16 (s, 3H), 0.05 (s, 3H). NOESY experiments were carried out to assign the relative configuration of the cyclized compounds.[203]

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 172.1, 142.6, 123.3, 81.9, 59.9, 52.8, 52.7, 47.8, 47.7, 39.8, 39.3, 35.3, 27.2, 26.0, 25.9, 22.6, 21.5, 18.4, 14.9, –1.8, –1.9.

HRMS-ESI: *m/z* calculated for $C_{23}H_{38}O_5SiNa$ $[M+Na]^+$: 445.2381, found: 445.2366.

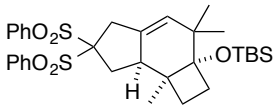
203. See experimental part in reference 181: A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 4580-4583.



II-13

Cyclization precursor **II-13** was prepared according to the same procedure used for compound **II-1-*E***.[204]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.03 (m, 4H), 7.72 – 7.68 (m, 2H), 7.59 – 7.54 (m, 4H), 5.58 (dt, *J* = 6.1, 1.1 Hz, 1H), 5.11 – 5.04 (m, 1H), 2.98 (d, *J* = 6.3 Hz, 2H), 2.95 (d, *J* = 7.2 Hz, 2H), 1.71 (s, 3H), 1.70 (s, 3H), 1.65 (br s, 3H), 0.84 (s, 9H), 0.81 (d, *J* = 7.5 Hz, 1H), 0.80 (d, *J* = 6.6 Hz, 1H), 0.69 (d, *J* = 6.6 Hz, 1H), 0.67 (d, *J* = 7.5 Hz, 1H), 0.07 (s, 6H).



II-14

Tricyclic product **II-14** was prepared following the same procedure used for compound **II-12**. Starting from precursor **II-13** (102 mg, 0.17 mmol), cyclized product **II-14** (54.7 mg, 53% yield) was isolated as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.06 (m, 2H), 8.00–7.97 (m, 2H), 7.75 – 7.67 (m, 2H), 7.64–7.54 (m, 4H), 5.45 (q, *J* = 2.2 Hz, 1H), 3.55 (dt, *J* = 19.5, 2.1 Hz, 1H), 3.27 (d, *J* = 19.5 Hz, 1H), 2.53 – 2.42 (m, 2H), 1.92 (ddd, *J* = 13.5, 11.4, 6.0 Hz, 1H), 1.79 (ddd, *J* = 13.5, 11.1, 7.2 Hz, 1H), 1.46 – 1.37 (m, 1H), 1.33 – 1.24 (m, 1H), 0.98 (s, 3H), 0.91 (s, 9H), 0.87 (s, 3H), 0.72 (s, 3H), 0.23 (s, 3H), 0.08 (s, 3H).

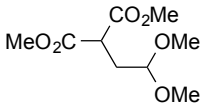
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 137.4, 136.4, 134.6, 134.5, 131.0(1), 130.9(7), 130.3, 128.9, 128.7, 100.0, 93.3, 83.8, 48.2, 47.9, 41.3, 36.8, 33.4, 28.8, 26.9, 26.1, 23.9, 23.4, 23.3, 21.1, 18.8, –1.5, –2.1.

204. **II-13** and **II-14** were prepared by Dr. Julien Ceccon during the preliminary studies on this reaction; J. Ceccon, A. Pitaval, unpublished results, ICIQ, 2008-2011.

HRMS-ESI: *m/z* calculated for $C_{32}H_{44}O_5S_2SiNa$ $[M+Na]^+$: 623.2292, found: 623.2232.

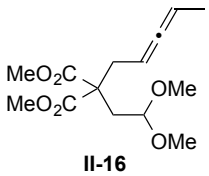
Allene *Z*-vinylcyclopropane

*Synthesis of cyclization precursor **II-1-Z***



II-15

Malonate **II-15** was prepared following the procedure described in reference 193. Analytical data were in accordance with literature.[205]



II-16

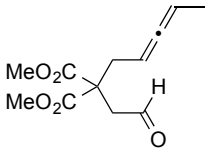
A solution of acetal **II-15** (2.23 g, 10.1 mmol) in anhydrous THF (17 mL) was added dropwise to a suspension of NaH (60 wt% in mineral oil, 900 mg, 22.5 mmol) in a mixture of anhydrous THF (34 mL) and anhydrous DMF (34 mL) at 0 ºC. The resulting mixture was stirred until a homogeneous solution was obtained (ca. 10-15 min). A solution of freshly prepared mesylate **II-5** (1.81 g, 11.1 mmol) in anhydrous THF (17 mL) was added dropwise and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then quenched with saturated NH_4Cl and extracted with Et_2O (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash

205. See expererimental part in reference 193: R. Shitani, K. Okamoto, Y. Otomaru, K. Ueyama, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 54-55.

column chromatography (eluent EtOAc/hexane 5:95 to 20:80) to afford acetal **II-16** (2.47 g, 86% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (m, 1H), 4.86 (tdq, *J* = 7.7, 6.3, 3.2 Hz, 1H), 4.45 (t, *J* = 5.6 Hz, 1H), 3.70 (s, 6H), 3.30 (s, 3H), 3.29 (s, 3H), 2.63 (ddd, *J* = 7.9, 2.2, 0.7 Hz, 2H), 2.27 (d, *J* = 5.6 Hz, 2H), 1.62 (dd, *J* = 7.0, 3.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 171.4, 102.1, 85.9, 84.3, 55.6, 53.8, 53.7, 52.6, 52.5, 35.8, 33.4, 14.4.



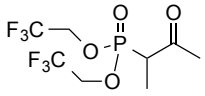
II-17

PTSA (monohydrate, 276 mg, 1.45 mmol) was added to a solution of the dimethylacetal **II-16** (4.15 g, 14.5 mmol) in a mixture of acetone (66 mL) and water (6.6 mL). The resulting mixture was refluxed for 5 h, then cooled down to room temperature and diluted with hexane. The solution was partially concentrated to remove the acetone, and then diluted with EtOAc, washed with water, brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/hexane 20:80) to afford aldehyde **II-17** (3.06 g, 88% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.4 Hz, 1H), 5.07 (qt, *J* = 7.1, 2.2 Hz, 1H), 4.89 (tdq, *J* = 7.8, 6.3, 3.2 Hz, 1H), 3.75 (s, 6H), 3.04 (d, *J* = 1.4 Hz, 2H), 2.70 (dd, *J* = 7.8, 2.2 Hz, 2H), 1.62 (dd, *J* = 7.1, 3.2 Hz, 3H).

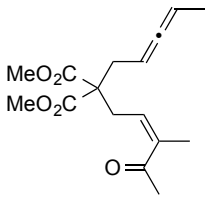
^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 198.9, 170.5, 86.2, 84.3, 55.2, 53.1, 53.0, 46.2, 34.2, 14.3.

HRMS-ESI: *m/z* calculated for $C_{12}H_{16}O_5Na$ $[M+Na]^+$: 263.0890, found: 263.0896.



II-18

Phosphonate **II-18** was prepared following the procedure described in reference 206. Analytical data were in accordance with literature.[206]



II-19

In order to perform this reaction and obtain optimal results, several considerations should be followed cautiously. First, the monomethylated phosphonate used in that reaction contains trace amounts of the dimethylated product. The weight purity should be determined by NMR to include it in the stoichiometry. The second recommendation is a direct consequence of the contamination of the monomethylphosphonate: the base (KOtBu) should ALWAYS be used in slight default compared to the phosphonate. Finally, freshly sublimated KOtBu and recrystallized 18-crown-6 should be used.[207]

A freshly prepared solution of KO*t*Bu (1.49 g, 13.3 mmol) in anhydrous THF (13 mL) was added dropwise over 20 min to a suspension of the phosphonate **II-18** (85 wt%, 4.95 g, 13.3 mmol) and 18-crown-6 (4.47 g, 16.9 mmol) in anhydrous THF (160 mL) at −78 ºC. The resulting mixture was stirred for 20 min at −78 ºC, whereupon a solution of the aldehyde **II-14** (2.91 g, 12.1 mmol) in anhydrous THF (40 mL) was added dropwise over 20 min. The resulting solution was stirred for 1 h at −78 ºC, then

206. W. Yu, M. Su, Z. Jin, *Tetrahedron Lett.* **1999**, *40*, 6725-6728.

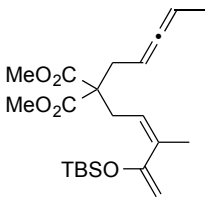
207. G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris F. L. Cook, *Org. Synth.* **1977**, *57*, 30-32.

warmed up to 0 ºC over 3 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/hexane 10:90 to 20:80) to afford enone **II-19** (3.53 g, 99% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (tq, *J* = 7.4, 1.4 Hz, 1H), 5.08 – 4.99 (m, 1H), 4.93 – 4.85 (m, 1H), 3.72 (s, 6H), 2.97 – 2.93 (m, 2H), 2.57 (dd, *J* = 7.7, 2.3 Hz, 2H), 2.24 (s, 3H), 1.93 (q, *J* = 1.4 Hz, 3H), 1.61 (dd, *J* = 7.0, 3.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 202.8, 171.2, 171.1, 138.6, 131.2, 85.9, 84.3, 58.0, 52.7, 52.60, 33.4, 32.5, 30.0, 21.3, 14.4.

HRMS-ESI: *m/z* calculated for $C_{16}H_{22}O_5Na$ $[M+Na]^+$: 317.1359, found: 317.1357.



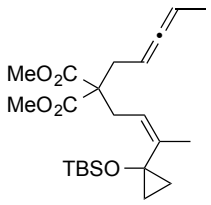
II-20

Anhydrous Et_3N (1.20 mL, 8.45 mmol) and TBSOTf (1.20 mL, 5.07 mmol) were added dropwise to a solution of the enone **II-19** (994 mg, 3.38 mmol) in anhydrous Et_2O (34 mL) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/hexane/Et_3N 0:100:1 to 10:90:1) to afford silylenol ether **II-20** (1.17 g, 85% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (dt, *J* = 7.1, 1.4 Hz, 1H), 5.06 – 4.97 (m, 1H), 4.94 – 4.86 (m, 1H), 4.34 (d, *J* = 1.0 Hz, 1H), 4.20 (d, *J* = 1.0 Hz, 1H), 3.70 (s, 6H), 2.95 – 2.88 (m, 2H), 2.56 (dd, *J* = 7.8, 2.3 Hz, 2H), 1.80 (q, *J* = 1.4 Hz, 3H), 1.60 (dd, *J* = 7.0, 3.2 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 171.6, 171.5, 156.2, 137.2, 122.3, 94.1, 85.5, 84.6, 58.1, 52.5, 52.4, 33.0, 32.4, 25.9, 25.8, 22.8, 18.3, 14.4, −4.5.

HRMS-ESI: *m/z* calculated for $C_{22}H_{37}O_5SiNa$ $[M+Na]^+$: 409.2405, found: 409.2406.



II-1-*Z*

CH_2I_2 was washed with saturated aqueous Na_2SO_3 (twice), dried over anhydrous $MgSO_4$, filtered and fractionally distilled over CaH_2 (T^o_{eb} = 54ºC @ 10 mbar), then stored over 3 Å MS under an argon atmosphere.

CH_2I_2 (275 µL, 3.41 mmol) was added dropwise to a solution of $ZnEt_2$ (1 M in hexanes, 3.40 mL, 3.41 mmol) in anhydrous CH_2Cl_2 (9.5 mL) at −60 ºC. The resulting solution was warmed up to 0 ºC until a white precipitate appeared, then cooled down to −60 ºC, whereupon a solution of the silylenol ether **II-20** (1.16 g, 2.84 mmol) in anhydrous CH_2Cl_2 (8 mL) was added dropwise. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was then quenched with saturated NH_4Cl and phases were separated. The aqueous layer was extracted with Et_2O (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent

EtOAc/hexane 0:100 to 10:90) to afford substrate **II-1-*Z*** (953 mg, 79% yield) as a colorless oil.

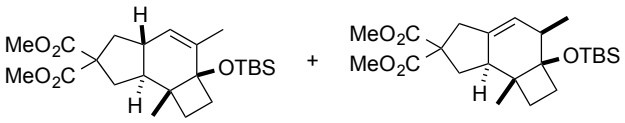
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (dt, *J* = 6.9, 1.3 Hz, 1H), 5.05 – 4.94 (m, 2H), 3.73 (s, 6H), 3.02 – 2.92 (m, 2H), 2.61 (dd, *J* = 7.7, 2.4 Hz, 2H), 1.76 (d, *J* = 1.3 Hz, 3H), 1.64 (d, *J* = 6.9, 3.2 Hz, 3H), 0.88 – 0.83 (m, 2H), 0.82 (s, 9H), 0.62 – 0.60 (m, 2H), 0.08 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 171.7, 171.6, 136.2, 123.6, 85.8, 84.7, 57.9, 55.9, 52.5, 52.4, 33.4, 31.9, 25.8, 22.6, 17.9, 14.5, 14.4, 14.3, -3.66.

HRMS-ESI: *m/z* calculated for $C_{23}H_{38}O_5SiNa$ $[M+Na]^+$: 445.2381, found: 445.2381.

*Gold(I)-cyclization of enallene precursor **II-1-Z***

Catalysts screening

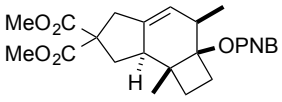


II-21a **II-21b**

A solution of precursor **II-1-*Z*** (942 mg, 2.23 mmol) in anhydrous 1,2-DCE (22 mL) was added to a dry flask under argon charged with catalyst **A** (51.6 mg, 0.10 mmol) and activated 4 Å molecular sieves (balls, 3.37 g) at room temperature. The resulting mixture was stirred for 24 h at room temperature, then quenched with a few drop of Et_3N, and filtered through a short pad of SiO_2 (elution EtOAc/hexane 50:50). The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/hexane 0:100 to 10:90) to afford a mixture of compounds **II-21a** and **II-21b** contaminated by a side-product (936 mg, 99% yield). The yields of both compounds were determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard (Table 4). Extensive

purification did not provide a sample with an appropriate purity for complete characterization. Thus, the mixture was engaged in the next steps to obtain a full characterization of the products.

Structure assignment



II-22

A solution of compounds **II-21a** and **II-21b** (50.0 mg, 0.118 mmol) in anhydrous THF (1 mL) was added to TASF (65.0 mg, 0.236 mmol), and the resulting mixture was refluxed for 3 h, then cooled down to room temperature and diluted with EtOAc and water. Layers were separated and the organic phase was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed by rotary evaporation, and the crude tertiary alcohol was engaged in the next step without further purification.

DMAP (43.3 mg, 0.354 mmol) was added to a solution of the intermediate alcohol in anhydrous CH_2Cl_2 (2 mL) at room temperature. Et_3N (0.05 mL, 0.354 mmol) and *p*-$NO_2C_6H_4COCl$ (65.7 mg, 0.354 mmol) were successively added and the resulting solution was stirred at room temperature for 24 h, then quenched with water and diluted with CH_2Cl_2. The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/pentane 10:90) to give a mixture of esters. Recrystallization by slow diffusion (CH_2Cl_2/pentane) afforded PNB-ester **II-22** as white crystals (10.8 mg, 20% yield).[194,208]

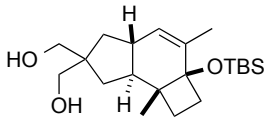
194. CCDC 953503

mp = 58 – 62 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.26 (m, 2H), 8.20 – 8.16 (m, 2H), 5.45 – 5.42 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.27 – 3.23 (m, 1H), 3.21 – 3.15 (m, 1H), 2.94 – 2.79 (m, 2H), 2.53 – 2.48 (m, 1H), 2.28 – 2.20 (m, 1H), 2.11 – 2.04 (m, 1H), 1.75 – 1.69 (m, 1H), 1.41 – 1.35 (m, 1H), 1.22 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 172.0, 163.8, 150.4, 143.3, 136.5, 130.5, 123.5, 122.4, 89.9, 59.8, 52.9, 52.8, 47.8, 47.5, 39.3, 35.1, 33.6, 24.7, 23.1, 20.7, 14.3.

HRMS-ESI: *m/z* calculated for $C_{24}H_{27}NO_8Na$ $[M+Na]^+$: 480.1629, found: 480.1624.



II-23

A solution of compounds **II-21a** and **II-21b** (200 mg, 0.473 mmol) in anhydrous Et_2O (2 mL) was added dropwise to a suspension of $LiAlH_4$ (37.7 mg, 0.994 mmol) in anhydrous Et_2O (2 mL) at 0 ºC. The resulting suspension was stirred for 1 h at 0 ºC, then cautiously quenched with aqueous NaOH (1 M). The resulting mixture was vigorously stirred until a white precipitate appeared, then filtered through Celite (eluent EtOAc). The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography (eluent EtOAc/pentane 25:75) to afford diol **II-23** (90.0 mg, 52% yield over two steps) as white crystals.[195,208]

mp = 68 – 70 ºC.

208. See experimental part in reference 181: A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 4580-4583.

195. CCDC 953502

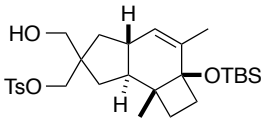
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 – 5.42 (m, 1H), 3.63 – 3.55 (m, 4H), 2.61 (bs, 2H), 2.18 – 2.03 (m, 4H), 1.87 – 1.72 (m, 4H), 1.57 – 1.53 (m, 5H), 0.93 (s, 3H), 0.89 (s, 9H), 0.21 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 126.7, 82.0, 71.0, 70.9, 53.3, 46.2, 44.9, 37.3, 36.3, 31.9, 30.8, 28.7, 26.0, 18.7, 17.6, 15.3, –1.8, –2.3.

HRMS-ESI: *m/z* calculated for $C_{21}H_{38}O_3SiNa$ $[M+Na]^+$: 389.2482, found: 389.2488.

Further Developments

Towards russujaponol D



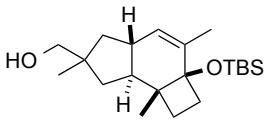
1:1

((2a*R,4a*R**,7a*S**,7b*R**)-2a-((*tert*-butyldimethylsilyl)oxy)-6-(hydroxymethyl)-3,7b-dimethyl-2,2a,4a,5,6,7,7a,7b-octahydro-1*H*-cyclobuta[*e*]inden-6-yl)methyl 4-methylbenzenesulfonate**

To a solution of diol **II-23** (40.0 mg, 0.109 mmol) in CH_2Cl_2 (0.5 mL) were added pyridine (0.10 mL) and TsCl (22.9 mg, 0.12 mmol). The reaction mixture was stirred at room temperature overnight. Then, the solution was quenched with saturated NH_4Cl and extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/pentane 30:70) to afford the corresponding mono-tosylate (39.0 mg, 68% yield) as a colorless oil. The product was directly engaged in the subsequent step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.79 (m, 2H), 7.36 – 7.34 (m, 2H), 5.39 – 5.36 (m, 1H), 3.98 – 3.94 (m, 1H), 3.90 – 3.85 (m, 1H), 3.51 – 3.47

(m, 1H), 3.44 – 3.39 (m, 1H), 2.45 (s, 3H), 2.15 – 1.95 (m, 3H), 1.83 – 1.70 (m, 4H), 1.56 – 1.44 (m, 5H), 1.16 – 0.94 (m, 2H), 0.89 (s, 1.5H), 0.88 (s, 4.5H), 0.87 (s, 4.5H), 0.84 (s, 1.5H), 0.20 (s, 3H), 0.14 (s, 1.5H), 0.13 (s, 1.5H).



II-24

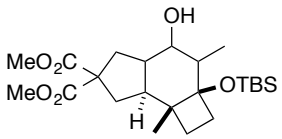
A solution of the previous tosylate (35.0 mg, 0.067 mmol) in anhydrous Et_2O (1 mL) was added dropwise to a suspension of $LiAlH_4$ (7.70 mg, 0.202 mmol) in anhydrous Et_2O (1 mL) at 0 ºC. The resulting suspension was stirred for 1 h under reflux. Then, the reaction mixture was cooled down to room temperature, and cautiously quenched with aqueous NaOH (1 M). The resulting mixture was vigorously stirred until a white precipitate appeared, then filtered through Celite (eluent EtOAc). The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (eluent EtOAc/pentane 4:96) to afford mono-reduced product **II-24** (21.0 mg, 89% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 – 5.42 (m, 1H), 3.40 – 3.34 (m, 2H), 2.21 – 2.01 (m, 3H), 1.87 – 1.74 (m, 3H), 1.66 – 1.58 (m, 1H), 1.57 – 1.51 (m, 5H), 1.34 – 1.31 (m, 1H), 1.15 – 1.11 (m, 1H), 1.07 (s, 1.5H), 1.05 (s, 1.5H), 0.94 (s, 1.5H), 0.92 (s, 1.5H), 0.90 (s, 4.5H), 0.89 (s, 4.5H), 0.21 (s, 3H), 0.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 127.3, 127.2, 82.2, 82.1, 72.3, 72.2, 54.7, 53.6, 45.0, 42.1, 41.9, 41.6, 37.7, 36.7, 36.6, 36.2, 30.9, 30.8, 28.8, 28.7, 26.7, 26.5, 26.0, 18.7, 17.6, 15.3, 15.2, –1.8, –2.4.

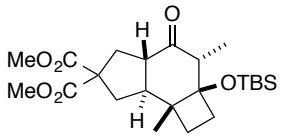
HRMS-ESI: *m/z* calculated for $C_{21}H_{38}O_2SiNa$ $[M+Na]^+$: 373.2534, found: 373.2539.

Towards plorantinone A and other related structures

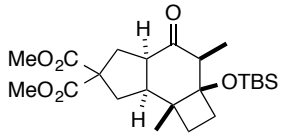


Dimethyl (2a*R*,7a*S***,7b*R***)-2a-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3,7b-dimethyldecahydro-6*H*-cyclobuta[*e*]indene-6,6-dicarboxylate**

$BH_3 \cdot THF$ (1 M in THF, 2.00 mL, 2.00 mmol) was added to a solution of **II-21a** and **II-21b** (196 mg, 0.47 mmol) in THF (5 mL). The mixture was stirred at room temperature overnight and NaOH (10 wt%, 5 mL) followed by H_2O_2 (30 wt%, 5 mL) were added. The resulting mixture was stirred at room temperature for 2 h. EtOAc was added and phases were separated. The aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent EtOAc/cyclohexane 85:15) to afford the intermediate secondary alcohol as a mixture of diastereoisomers not separable by column chromatography. Thus, the alcohol was engaged in the subsequent step.



II-25a



II-25b

Dess-Martin periodinane (171 mg, 0.40 mmol) was added in one portion to a solution of the previous mixture of alcohols (89.0 mg, 0.20 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 3 h, and a 1:1 solution of saturated $NaHCO_3$ and saturated Na_2SO_3 was added. The resulting biphasic mixture was stirred until it became clear and phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 times).

The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent EtOAc/pentane 1:15) to afford ketones **II-25a** (70.0 mg, 59% yield) and **II-25b** (22.0 mg, 19% yield).

*Ketone **II-25a***

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (2 s, 6H), 2.60 – 2.69 (m, 1H), 2.54 – 2.41 (m, 3H), 2.35 (qd, *J* = 7.0, 1.1 Hz, 1H), 2.12 – 1.74 (m, 5H), 1.53 – 1.45 (m, 1H), 1.12 – 1.03 (m, 5H), 0.90 (s, 9H), 0.19 (s, 3H), 0.13 (s, 3H). NOESY experiments were carried out to assign the relative configuration of the cyclized compounds.[209]

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 173.0, 172.8, 87.7, 58.4, 54.0, 53.0, 52.9, 52.3, 50.0, 46.5, 36.2, 32.0, 28.7, 28.4, 26.0, 18.7, 14.9, 9.5, −1.8, −2.1.

HRMS-ESI: *m/z* calculated for $C_{23}H_{38}O_6SiNa$ $[M+Na]^+$: 461.2330, found: 461.2320.

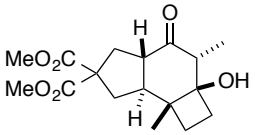
*Ketone **II-25b***

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.70 (s, 3H), 3.01 – 3.07 (m, 1H), 2.92 (dd, *J* = 14.2, 2.2 Hz, 1H), 2.87 (tt, *J* = 6.7, 1.3 Hz, 1H), 2.47 (ddd, *J* = 13.7, 7.9, 6.2 Hz, 1H), 2.31 (dd, *J* = 14.2, 7.4 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.16 – 2.08 (m, 1H), 2.02 – 1.93 (m, 3H), 1.65 – 1.48 (m, 1H), 1.15 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.15 (s, 3H), 0.04 (s, 3H). NOESY experiments were carried out to assign the relative configuration of the cyclized compounds.[209]

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 173.8, 172.0, 84.8, 57.6, 53.0, 52.8, 52.7, 50.4, 50.0, 45.3, 36.8, 33.2, 32.2, 28.1, 26.1, 22.6, 18.6, 8.6, −1.2, −1.9.

HRMS-ESI: *m/z* calculated for $C_{23}H_{38}O_6SiNa$ $[M+Na]^+$: 461.2330, found: 461.2325.

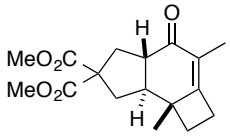
209. See experimental part in reference 181: A. Pitaval, D. Leboeuf, J. Ceccon, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 4580-4583.



Dimethyl (2a*R*,3*R***,4a*S***,7a*S***,7b*R***)-2a-hydroxy-3,7b-dimethyl-4-oxodecahydro-6*H*-cyclobuta[*e*]indene-6,6-dicarboxylate**

A solution of ketone **II-25a** (70.0 mg, 0.16 mmol) in THF (3 mL) was added to TASF (88.0 mg, 0.32 mmol) and the mixture was refluxed for 2 h. The reaction mixture was cooled down to room temperature. Water followed by EtOAc were added and phases were separated. The aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent EtOAc/cyclohexane 10:90) to afford the intermediate ketoalcohol (32 mg, 62% yield) as a colorless oil. The product was directly engaged in the formation of the enone.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.70 (s, 3H), 3.14 – 3.01 (m, 1H), 2.78 – 2.66 (m, 2H), 2.56 (ddd, *J* = 13.3, 11.0, 7.8 Hz, 1H), 2.40 (dd, *J* = 12.9, 6.5 Hz, 1H), 2.33 – 2.08 (m, 2H), 1.98 – 1.83 (m, 3H), 1.60 (d, *J* = 1.5 Hz, 3H), 1.32 (d, *J* = 0.7 Hz, 3H).



II-26

Et_3N (0.10 mL, 0.72 mmol), followed by MsCl (0.05 mL, 0.65 mmol) were added to a solution of the previous crude ketoalcohol (32 mg) in CH_2Cl_2 (2 mL) at 0 ºC. The mixture was stirred for 1 h, and then DBU (0.20 mL, 1.33 mmol) was added. The reaction mixture was allowed to warm up to room temperature, stirred overnight and quenched with saturated $NaHCO_3$. Phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluent EtOAc/cyclohexane 1:9) to afford enone **II-26** (17.0 mg, 34% yield over 2 steps) as a colorless oil. A pure analytical fraction was obtained by HPLC isolation.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.71 (s, 3H), 3.09 (dddd, *J* = 15.3, 11.3, 7.8, 1.7 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.57 (ddd, *J* = 13.3, 11.0, 7.8 Hz, 1H), 2.41 (dd, *J* = 12.9, 6.5 Hz, 1H), 2.27 (ddd, *J* = 13.3, 12.2, 6.5 Hz, 1H), 2.17 (dd, *J* = 14.1, 11.0 Hz, 1H), 2.01 – 1.81 (m, 3H), 1.61 (d, *J* = 1.5 Hz, 3H), 1.33 (d, *J* = 0.7 Hz, 3H).

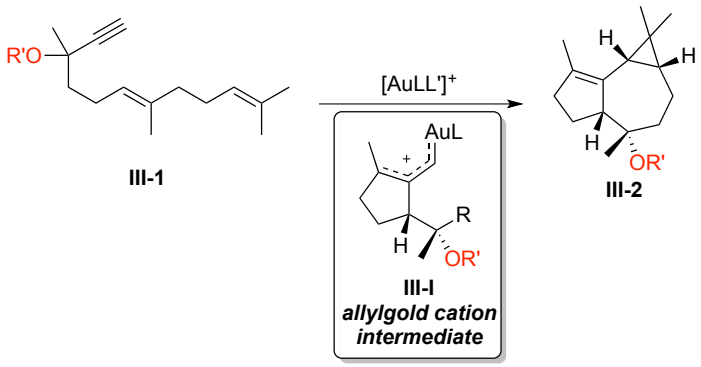
^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 172.9, 172.8, 169.2, 125.4, 57.8, 54.7, 52.9, 52.8, 49.1, 48.6, 35.3, 33.8, 33.0, 30.4, 16.1, 9.4.

HRMS-ESI: *m/z* calculated for $C_{17}H_{22}O_5Na$ $[M+Na]^+$: 329.1359, found: 329.1357.

Chapter 3. Revisiting the 1,5-Migration

Introduction – the cycloisomerization of enynes *via* a 1,5-migration mechanism

The gold(I)-catalyzed cycloisomerization of 1,6-enynes have been intensively studied and numerous applications in total synthesis were published.[47b] From a mechanistic point-of-view, 1,6-enynes bearing propargylic OR group proved to cyclize by a 1,5-migration pathway, forming an allylgold cation intermediate (Scheme 53).[210]



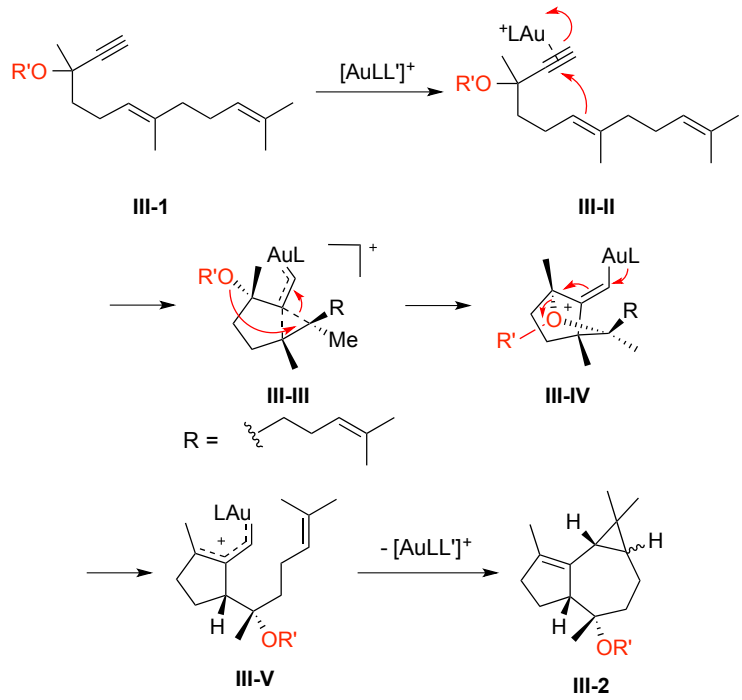
Scheme 53. 1,5-migration of OR' groups in the gold(I)-catalyzed cycloisomerization of 1,6-enynes

Mechanistic studies demonstrated that the 1,5-migration proceeds through an intramolecular pathway (Scheme 54). Gold(I)-complex coordinates to the alkyne moiety of dienyne **III-1** and cyclopropyl gold carbene **III-III** is formed by 5-*exo*-dig cyclization. At this stage, the OR' group attacks the cyclopropyl to form oxonium cation **III-IV**. Opening of this oxonium leads to allylgold cation **III-V**, resulting in a 1,5-migration of the OR' group.

47. (b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350.

210. E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.

Allyl cation **III-V** is trapped by the pendant alkene in an intramolecular cyclopropanation yielding to tricycle **III-2**.

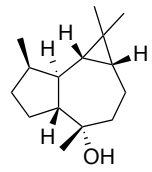


Scheme 54. Mechanistic proposal for the 1,5-migration

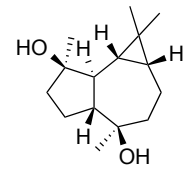
The migration of the OR' group is faster than the direct cyclopropanation by the pendant alkene of cyclopropyl gold(I)-carbene. The final cyclopropane was obtained as separable mixture of diastereoisomers. The *cis*-cyclopropane was highly favored (*cis*:*trans* > 8:1). Interestingly, a somewhat similar 1,6-migration was observed in the cyclization of 1,7-enynes.[211]

211. W. Yang, Y. Yu, T. Zhang, M. M. Hansmann, D. Pflästerer, A. S. K. Hashmi, *Adv. Synth. Catal.* **2013**, *355*, 2037-2043.

Recently, our group applied a similar methodology to the total synthesis of two sesquiterpenoids: (±)-epiglobulol [212] and (±)-aromadendranediol [213] (Figure 33).[81]



(–)-epiglobulol



aromadendranediol

Figure 33. Structure of (–)-epiglobulol and aromadendranediol

When the propargylic alcohol is protected as a carboxylate (acetate, pivalate, benzoate…), two competing mechanistic pathways can interfere *i.e.* the 1,2-acyloxy shift or the 1,3-carboxylate shift also named 3,3-rearrangement (Scheme 55).[214,215,216]

212. D. S. Caine, J. T. Gupton, *J. Org. Chem.* **1975**, *40*, 809-810.

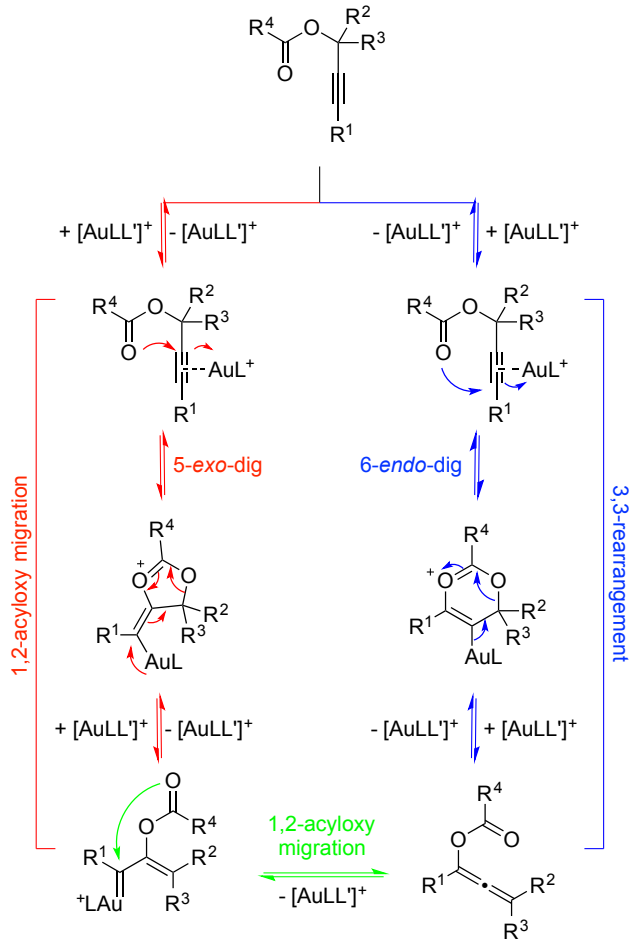
213. I. C. Moreira, J. H. G. Lago, M. C. M. Young, N. F. Roque, *J. Braz. Chem. Soc.* **2003**, *14*, 828-831.

81. M. Livendahl, PhD thesis, ICIQ, 2013; J. Carreras, P. McGonigal, unpublished results, 2012-2014.

214. For a recent review see: S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, *5*, 692-706.

215. For some applications to the synthesis of polycyclic molecules see: (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) Y. Harrak, M. Makhlouf, S. Azzaro, E. Mainetti, J. M. López-Romero, K. Cariou, V. Gandon, J.-P. Goddard, M. Malacria, L. Fensterbank, *J. Organomet. Chem.* **2011**, *696*, 388-399.

216. For an extensive experimental and theoretical study, see: N. Marion, G. Lemière, A. Correa, C. Costabile, R. S. Ramón, 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.



Scheme 55. Possible mechanisms for the Au-catalyzed reaction of propargylic carboxylates

Remarkably, similar reactivity was observed when rhodium(I) is used instead of gold in the catalytic process.[217]

The rearrangement reactions of propargyl acetates were applied in the context of the total syntheses of tricyclic sesquiterpenes from the cubebane family, such as (–)-α-cubebene and (–)-cubebol (Figure 34).[218]

217. X.-Z. Shu, D. Shu, C. M. Schienebeck, W. Tang, *Chem. Soc. Rev.* **2012**, *41*, 7698-7711.
218. A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006-3019.

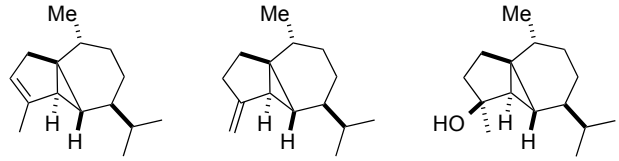


Figure 34. Representative members of the cubebane family

More recently, our group completed the total synthesis of (+)-schisanwilsonene A (Figure 35) in which the competition between the 1,5-migration and the 1,2-acetate shift was crucial for the reaction outcome.[219] In this case, the key step is a complex tandem cyclization/1,5-migration/cyclopropanation.

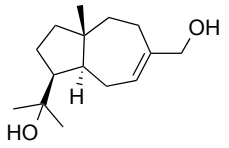
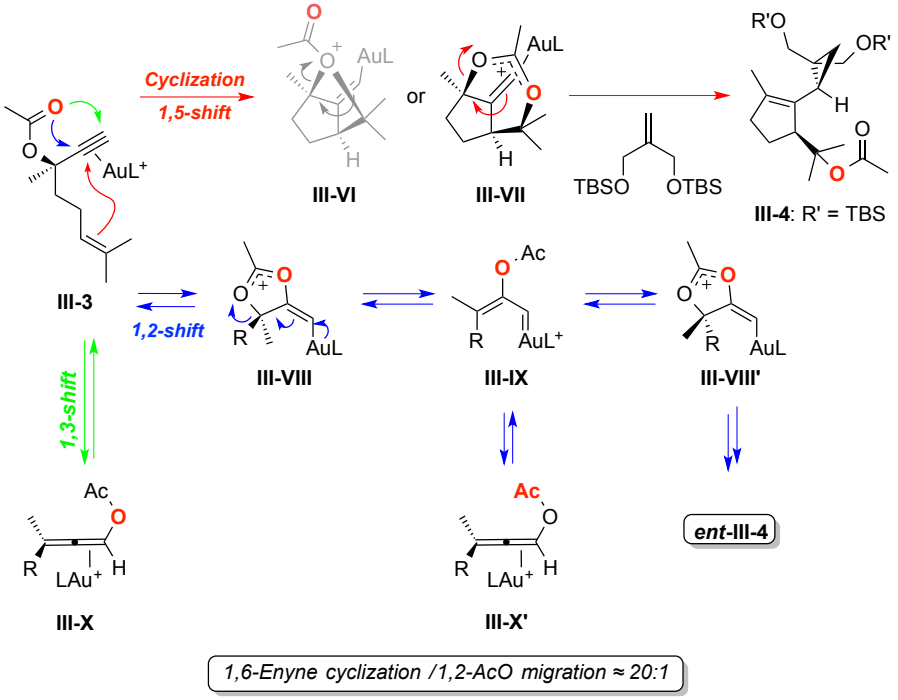


Figure 35. Structure of (+)-schisanwilsonene A

The mechanism of the key step is presented in Scheme 56, along with the competing migration pathways. Starting propargylic acetate **III-3** cyclizes upon treatment with gold(I) catalyst following a 1,5-shift pathway. The resulting intermediate **III-VII** traps the di-TBS protected alkene in a cyclopropanation reaction leading to vinyl cyclopropyl **III-4**. It is worth mentioning that the cyclization of 1,6-enyne is considerably faster than the 1,2-acetate migration therefore only **III-4** was observed.[210]

219. For a complete discussion on the mechanism of the key step, see reference 80: M. Gaydou, R. E. Miller, N. Delpont, J. Ceccon, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2013**, *52*, 6396-6399.

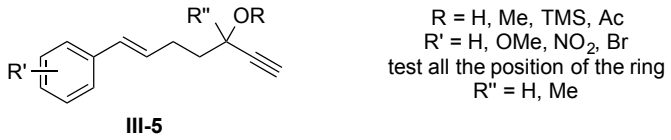


Scheme 56. Key step in the synthesis of schisanwilsonene A

In order to determine which of the five- (**III-VI**) or seven-membered ring (**III-VII**) intermediate is preferentially formed, ^{18}O labeling of **III-3** at the carbonyl group was performed. The mass spectral data of the hydrolysis product revealed that the ^{18}O had been transferred as the alcohol oxygen atom (95% incorporation).

Objectives

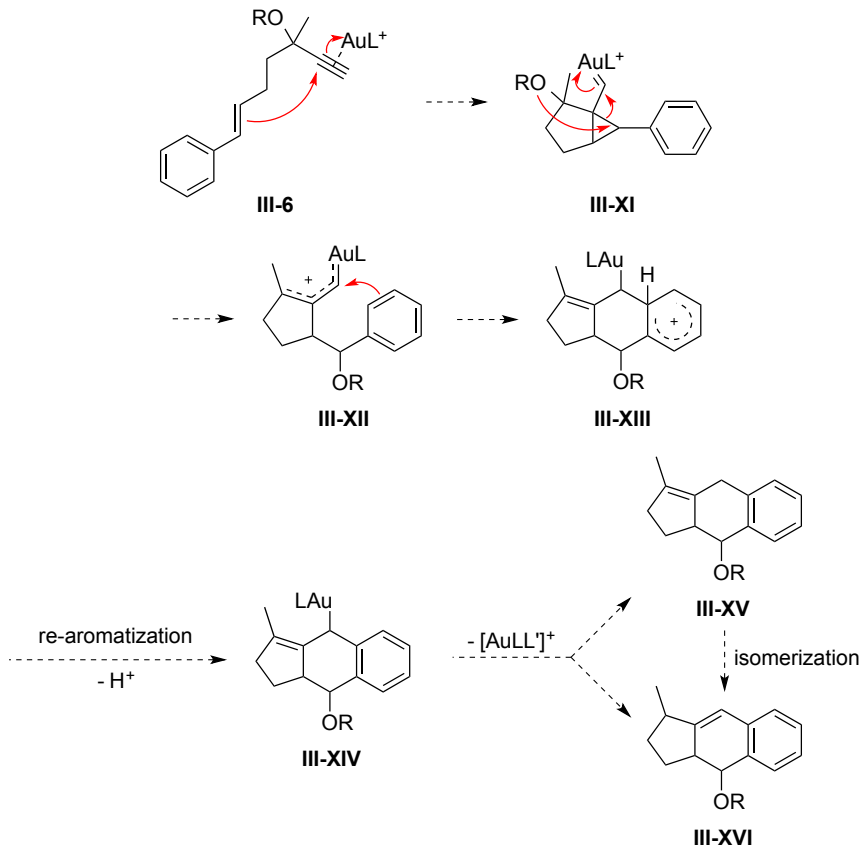
In order to re-visit the gold(I)-catalyzed cycloisomerization of 1,6-enynes proceeding with a 1,5-migration, we decided to prepare a set of molecules such as **III-5** (Figure 36), bearing an unsubstituted alkyne terminus and an *E*-alkene moiety substituted with an aryl group.



III-5

Figure 36. New class of substrates to be tested

From a mechanistic standpoint, if the 1,5-migration takes place as expected, these substrates would allow the formation of tricyclic molecules (Scheme 57). Gold would coordinate to the alkyne part of **III-6** and cyclopropyl gold carbene **III-XI** might be formed by nucleophilic attack of the alkene. Then the OR group would migrate, which would open the cyclopropyl leading to the formation of open allyl cation **III-XII**. This cation would undergo nucleophilic attack of the aromatic ring in a Friedel–Crafts type reaction providing arenium ion **III-XIII**. Subsequent rearomatization would lead to **III-XIV** that would eventually undergo, protodeauration to **III-XV** and/or **III-XVI**.



Scheme 57. Plausible mechanism and expected products

This methodology could pave the way to tricyclic products that display the carbon backbone of the pycnanthuquinone family (Figure 37),[220] a class of natural compounds that is currently under investigation in our group.[221] To date, only one synthesis has been published by the group of Trauner, employing a biomimetic approach.[222]

220. (a) D. M. Fort, R. P. Ubillas, C. D. Mendez, S. D. Jolad, W. D. Inman, J. R. Carney, J. L. Chen, T. T. Ianiro, C. Hasbun, R. C. Bruening, J. Luo, M. J. Reed, M. Iwu, T. J. Carlson, S. R. King, D. E. Bierer, R. Cooper, *J. Org. Chem.* **2000**, *65*, 6534-6539; (b) D. W. Laird, R. Poole, M. Wilkström, I. A. van Altena, *J. Nat. Prod.* **2007**, *70*, 671-674.

221. P. Pérez-Galán, T. Lauterbach, N. Huguet, unpublished results, ICIQ, 2007-2012.

222. F. Löbermann, P. Mayer, D. Trauner, *Angew. Chem. Int. Ed.* **2010**, *49*, 6199-6202.

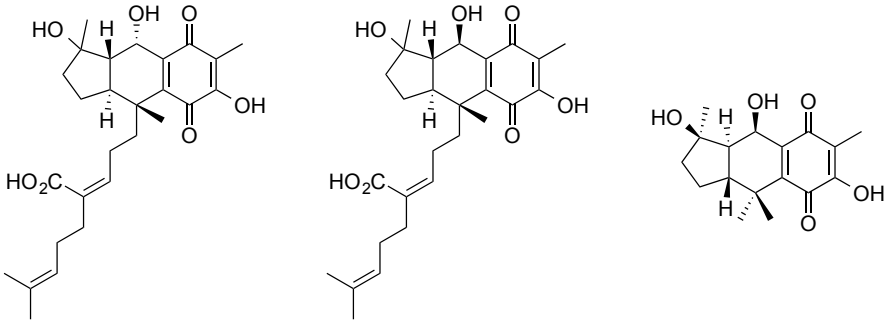


Figure 37. The pycnanthuquinone family

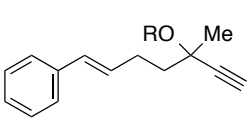
Results and discussion

A set of substrates bearing different substitution patterns on the aromatic ring as well as various protections on the propargylic alcohol was synthesized. This would allow us to inspect and compare their reactivity in gold(I)-catalyzed reactions to prove the possibility of accessing the tricyclic molecules presented earlier.

Preliminary study[223]

Synthesis of model substrates

Firstly, model substrates **III-6** (Figure 38), without any substituent on the aryl ring were prepared. Their synthesis is rather straightforward and was performed in 4 steps.



III-6

III-6a R = H

III-6b R = Me

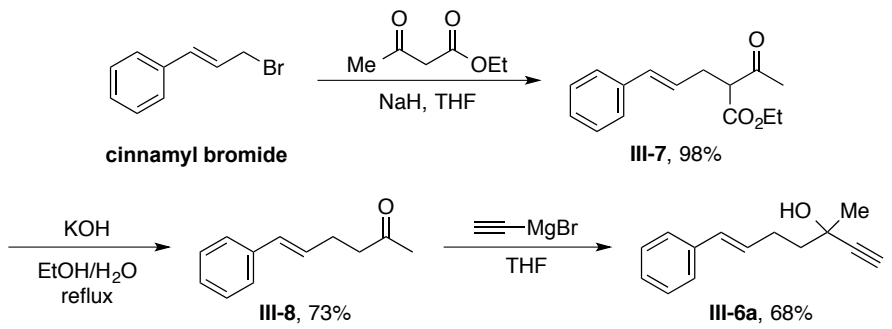
III-6c R = TMS

III-6d R = Ac

Figure 38. Model substrates for the preliminary study

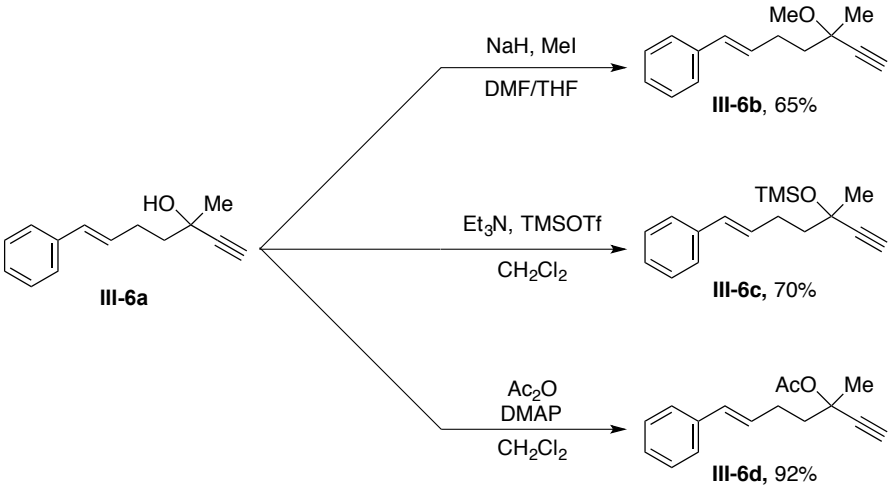
III-6a was synthesized in 3 steps from commercially available cinnamyl bromide (Scheme 58). First, nucleophilic substitution of the bromide by the anion of ethyl 3-oxobutanoate led to *β*-ketoester **III-7**. Subsequent decarboxylation provided ketone **III-8** that reacted with ethynylmagnesium bromide to afford propargylic alcohol **III-6a** in good overall yield (49% over 3 steps).

223. In collaboration with Dr. María Moreno and Pilar Calleja.



Scheme 58. Synthesis of model substrate III-6a

In order to evaluate the migration potential of the oxygenated groups at the propargylic position, **III-6a** was then protected as methyl ether **III-6b**, TMS ether **III-6c** and acetate **III-6d** in good yields (65%, 70% and 92% respectively, Scheme 59).[224,210]



Scheme 59. Protection of III-6a as propargylic methyl ether, TMS ether and acetate

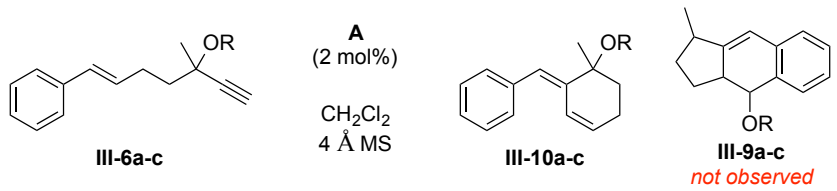
224. Free propargylic alcohols migrate really poorly and propargylic TMS ethers slightly better. Propargylic acetates migrate readily and methyl ethers tend to migrate comparably.

210. E. Jiménez-Núñez, M. Raducan, T. Lauterbach, K. Molawi, C. R. Solorio, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155

Test of model substrates in catalysis

Model substrates **III-6** were then reacted with gold catalyst **A** (2 mol%) in CH_2Cl_2, expecting to get tricyclic products of type **III-9** (Scheme 60). The reaction proceeded rapidly but the formation of expected **III-9** was not observed in any of the cases.

With substrates **III-6a-c**, compounds **III-10a-c** were identified, arising from a completely different pathway (see mechanistic study section).



Scheme 60. Surprising cyclization of substrates III-6a-c

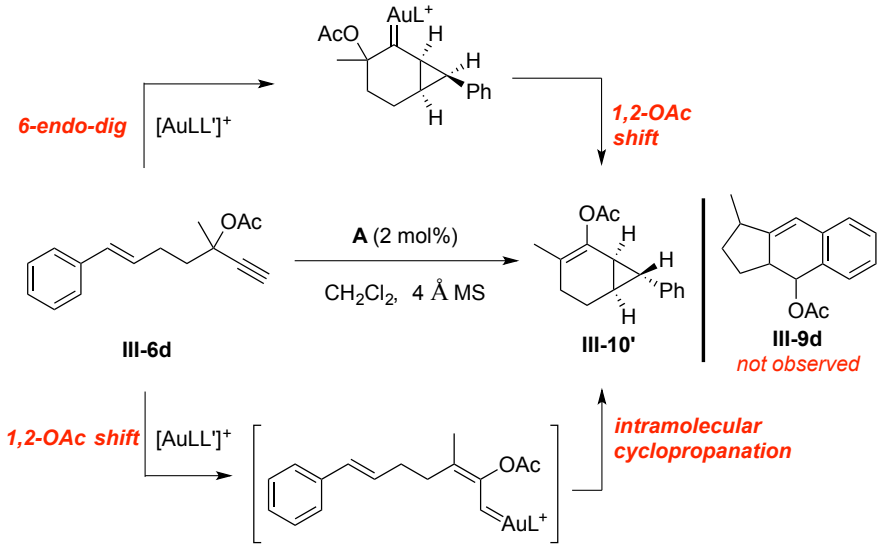
We expected the migration of the propargylic acetate to take place with precursor **III-6d**. However, the formation of **III-9d** was not observed, and bicycle **III-10'** was isolated, although in low yield (10%, Scheme 61).[225]

A 6-*endo*-dig cyclization could lead to the intermediate cyclopropylgold carbene. Subsequent 1,2-OAc could occur to provide the isolated fused bicyle.[226] Alternatively, a 1,2-shift of the acetate and then trapping of the gold carbene by the pendant alkene can explain the formation of this type of bicycle.[218]

225. A. Pitaval, M. Moreno, P. Calleja, unpublished results, ICIQ, 2013.

226. For mechanistic studies on this type of transformation, see: (a) E. Soriano, J. Marco-Contelles, *J. Org. Chem.* **2007**, *72*, 2651-2654; (b) E. Soriano, J. Marco-Contelles, *Chem. Eur. J.* **2008**, *14*, 6771-6779.

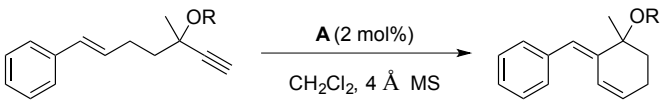
218. A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006-3019



Scheme 61. Cyclization of substrates III-6d

The results of this preliminary study with precursors **III-6a-c** are presented in Table 5.

Table 5. Cyclization of model substrates III-6



III-6a R = H
III-6b R = Me
III-6c R = TMS

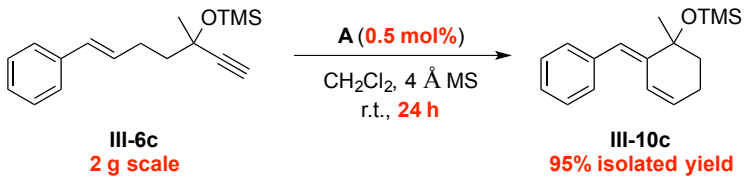
III-10a-c

Entry	Precursor	Reaction time	Products	Isolated yield (%)
1	**III-6a**	10 min	**III-10a**	52
2	**III-6b**	25 min	**III-10b**	14
3	**III-6c**	5 min	**III-10c**	95

In the case of free propargylic alcohol **III-6a** (entry 1) and methyl ether **III-6b** (entry 2), moderate and low yields were obtained (52% and 14% respectively). In the case of the TMS ether **III-6c**, excellent yield (entry 3,

95%) was achieved. It is important to mention that only products of type **III-10** were observed.

The cleanliness and the reaction rate prompted us to scale-up the reaction (Scheme 62). In the case of **III-6c**, the catalyst loading could be lowered to 0.5 mol%. Identical yield was obtained on 2 g scale of starting material. The only limitation is the extended reaction time (24 h) to reach completion.



Scheme 62. Scale-up of the model reaction

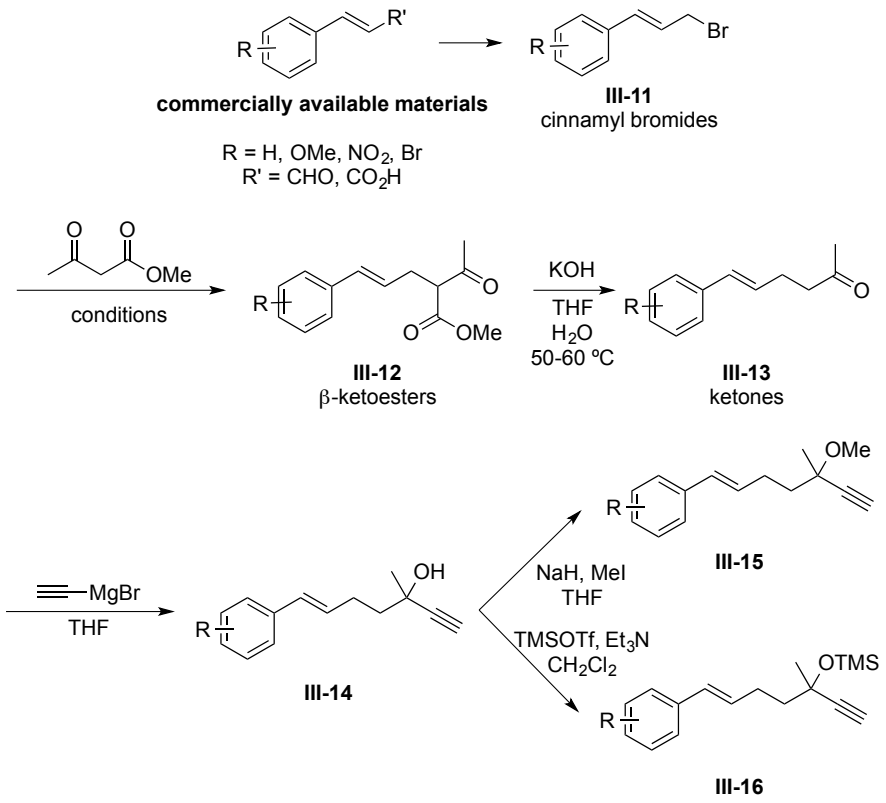
With these encouraging results in hand, new substrates were prepared in order to study the scope of the reaction. For practical reasons, 2 mol% of catalyst were used because of the relatively small scale of the reaction carried out.

Scope of the reaction with tertiary propargylic alcohols

General synthetic route of the tertiary propargylic alcohols

The synthesis of the cyclization precursors followed the route developed for model substrates **III-6** (Scheme 63). Commercially available reagents were converted into the corresponding cinnamyl bromides **III-11**. β-Ketoesters **III-12** were synthesized either by displacement of the leaving group by S_N2 reaction of the anion methyl acetoacetate or by Tsuji-Trost cross-coupling. Subsequent decarboxylation under basic conditions provided ketones **III-13**. Finally, addition of ethynylmagnesium bromide delivered propargylic

alcohols **III-14**. These free alcohols were finally protected either as methyl ethers **III-15** or TMS ethers **III-16**.



Scheme 63. General synthetic route

This synthetic route allowed us to prepare a large set of precursors on relatively large scale. The detailed synthesis of each precursor and the characterization of the new compounds are presented in the experimental part.

In order to gain more insight into the substitution influence on the aromatic ring, substrates with electron-withdrawing group and electron-donating groups were prepared (Figure 39). Two internal alkynes were also synthesized (**III-14f** and **III-14g**). Substitution on the alkene was also introduced (**III-14h**, **III-15h** and **III-16h**).

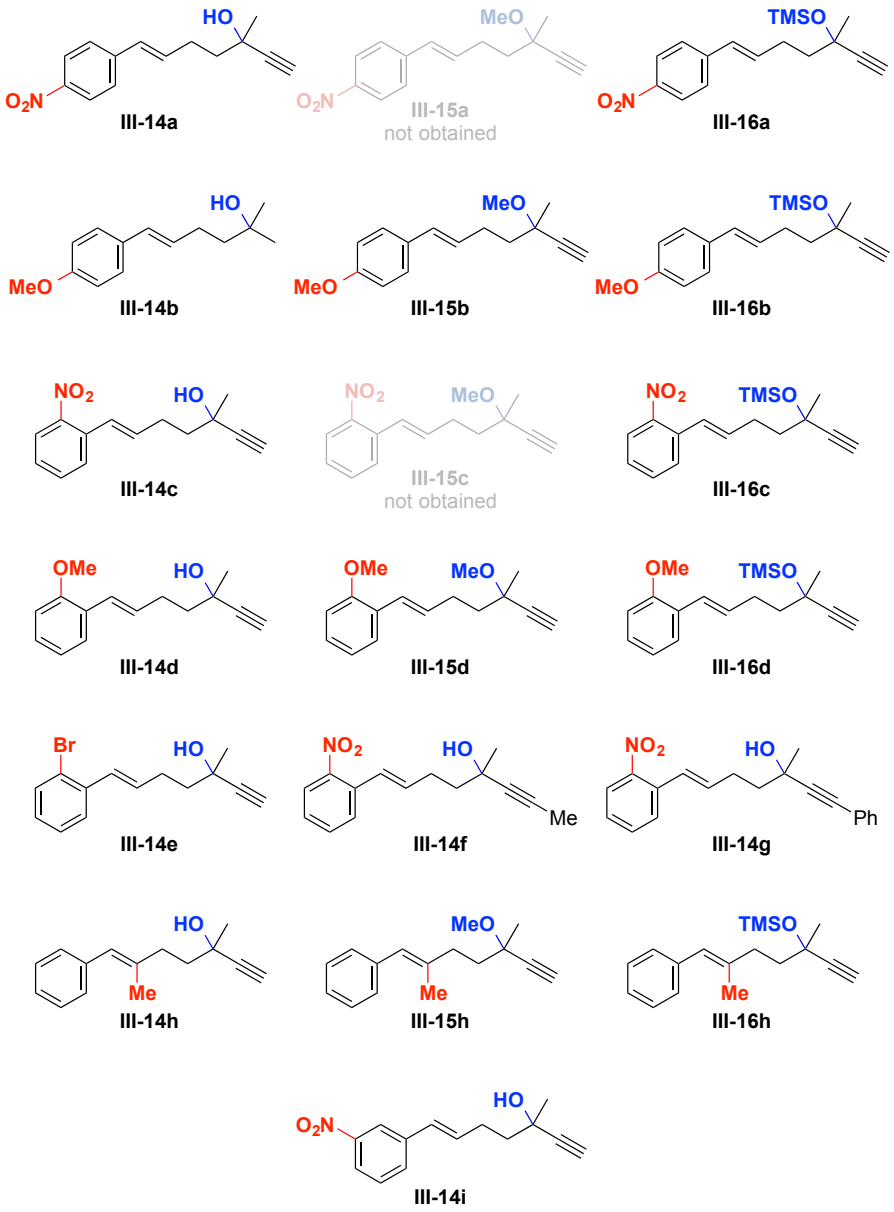


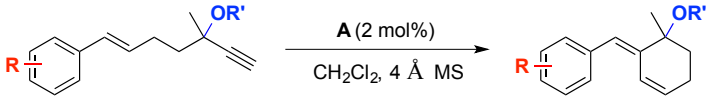
Figure 39. List of tertiary alcohols precursors prepared

Surprisingly, nitrophenyls could not be protected as the propargylic methyl ether as the starting material decomposed during the course of the reaction.

Gold-catalyzed cyclization of tertiary propargylic alcohols

All the substrates prepared previously were then tested under the same reaction conditions (CH_2Cl_2 at 23 ºC, 2 mol% of catalyst **A**). The results are presented in Table 6. Unless otherwise stated, the reactions were run on 100 mg of precursor.

Table 6. Gold-catalyzed reaction of tertiary propargylic alcohols



III-14, R' = H
III-15, R' = Me
III-16, R' = TMS

III-17, R' = H
III-18, R' = Me
III-19, R' = TMS

Entry	Precursor	Product	Isolated yield (%)	Remarks
1	**III-14a**	**III-17a**	88	-
2	**III-16a**	**III-19a**	72	-
3	**III-14b**	-	decomp.	-
4	**III-15b**	-	decomp.	-
5	**III-16b**	-	decomp.	-
6	**III-14c**	**III-17c**	92 96 98	100 mg scale 600 mg scale 800 mg scale
7	**III-16c**	**III-19c**	91	-
8	**III-14d**	-	decomp.	-
9	**III-15d**	-	decomp.	-
10	**III-16d**	-	complex mixture	non-separable

11	**III-14e**	**III-17e**	74 84 80	100 mg scale 140 mg scale 500 mg scale
12	**III-14f**	-	n.r.	-
13	**III-14g**	-	n.r.	-
14	**III-14h**	-	decomp.	-
15	**III-15h**	-	decomp.	-
16	**III-16h**	-	decomp.	-
17	**III-14i**	**III-17i**	97	-

Substrates bearing nitro group on the aromatic ring (entries 1-2, 6-7 and 17) reacted in good to excellent yields even on larger scale (98% isolated yield on 800 mg). Interestingly, *o*-bromo derivative **III-14e** gave alsogood yields (entry 11).

On the contrary, substrates substituted with a methoxy group on the aromatic ring led to decomposition or mixtures of inseparable products (entries 3-5 and 8-10).

Internal alkynes (entries 12-13) did not react under the tested conditions, most probably because of electronic effects.

Substrates bearing substitution on the alkene (entries 14-16) decomposed under the reaction conditions.

As a general comment, we can highlight that electron-poor aromatic rings cyclize satisfactorily, regardless of the substitution pattern, whereas electron-rich substrates tend to decompose under the reaction conditions.[227]

227. See mechanistic study for a potential explanation of this outcome.

Structure assignment

The structure of the cyclization products was unambiguously assigned by comprehensive NMR study and by X-ray diffraction of crystalline compounds.

Cyclization product **III-17e** (bearing a *o*-Br substituent) gave crystalline material without further chemical transformation (Figure 40).[228]

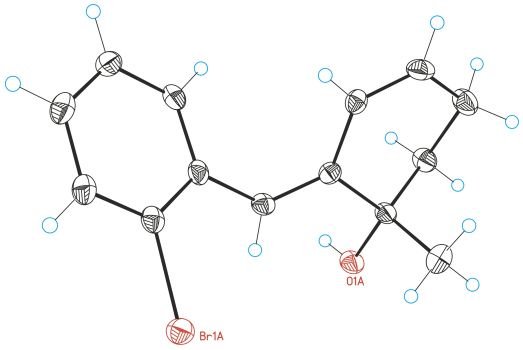


Figure 40. X-ray structure of III-17e

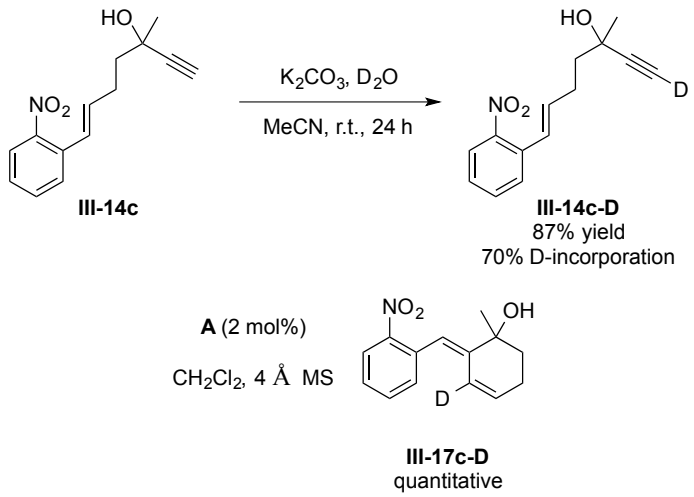
Mechanistic study

We were also intrigued by the mechanism of the reaction. Therefore, deuteration of precursor **III-14c** was performed under the reported conditions although with longer reaction time (Scheme 64).[229] The use of strong bases (LDA, *n*-BuLi) and quenching with D_2O did not give satisfactory deuterium incorporation. Deuterated derivative **III-14c-D** was then reacted under the standard reaction conditions leading to **III-17c-D**.[230]

228 . Another crystalline compound with this carbon skeleton was obtained by functionalizing tertiary alcohol **III-17c** to the corresponding *p*-nitrobenzoate derivative. See experimental part for its synthesis and crystallographic data.

229. S. P. Bew, G. D. Hiatt-Gipson, J. A. Lovell, C. Poullain, *Org. Lett.* **2012**, *14*, 456-459.

230. See experimental part for mono and bidimensional ^{1}H NMR spectra.

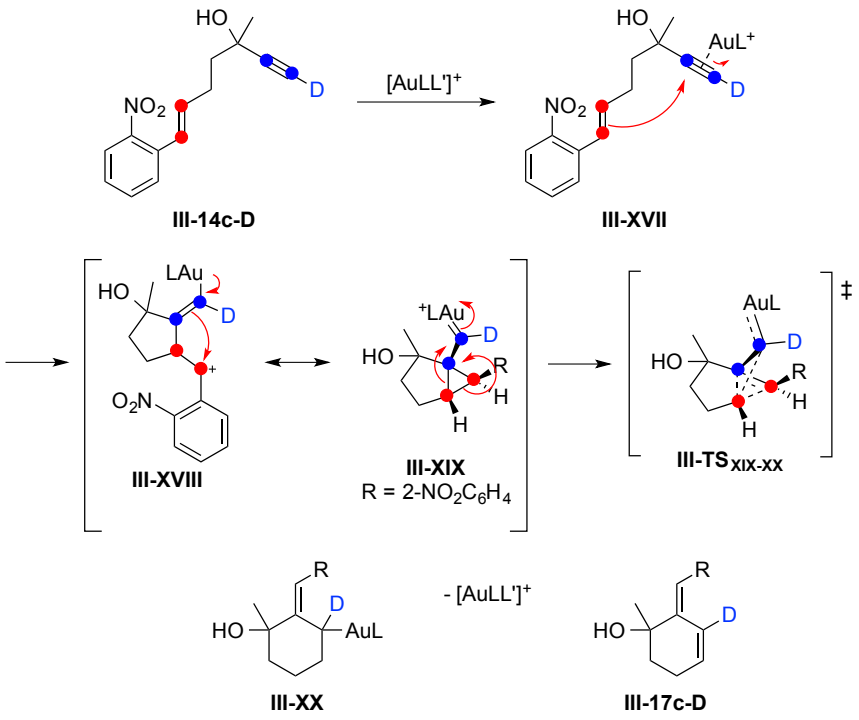


Scheme 64. Deuteration of III-14c and cyclization

This outcome suggests that the reaction proceeds through an *endo*-type single cleavage mechanism (Scheme 65). Although this reaction is known,[231] only a few examples had been reported.

Gold(I) coordinates to the alkyne moiety of **III-14c-D** to form **III-XVII** *via* ligand exchange. Then, nucleophilic attack of the alkene onto the alkyne occurs leading to cyclopropyl gold carbene **III-XIX**. This intermediate is proposed to advance towards secondary carbocation **III-XX** through transition state **III-TS$_{XIX-XX}$** (based on DFT calculations).[231] In this step, the cleavage of the endocyclic cyclopropane bond furnishes the final six-membered ring of **III-XX**. Final protodemetalation yields **III-17c-D.**

231. For a theoretical study of this transformation, see reference 56: N. Cabello, E. Jiménez-Núñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Eur. J. Org. Chem.* **2007**, 4217-4223.



Scheme 65. Proposed endo-type single cleavage mechanism

The reason why substrates with electron-withdrawing groups cyclize readily in excellent yields whereas precursors bearing electron-donating substituents decompose is not evident.

In the case of electron-donating substituents, benzylic carbocation **III-XVIII** is more stabilized, making it less reactive towards the nucleophilic attack of the alkenyl-gold. Being less reactive, this intermediate might evolve by other reaction pathways.

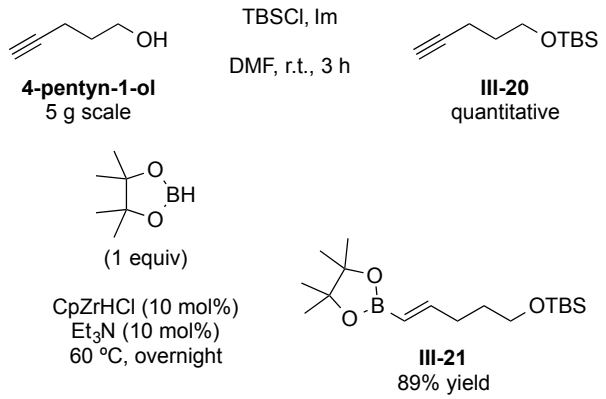
DFT calculations could be useful to compare the energy profiles depending on the substitution pattern. This would help us fully understand why electron-poor substrates react nearly quantitatively whereas electron-rich substrates do not. Besides, theses calculations might help us to rationalize why the 1,5-migration does not take place in this context.

Expanding the reaction scope to secondary propargylic alcohols

A new set of substrates bearing a secondary propargylic alcohol was prepared. These precursors were prepared following a common synthetic pathway, involving a Suzuki cross-coupling as key step. The detailed synthesis of the precursors and the characterization of the new compounds are presented in the experimental part.

Synthesis of secondary propargylic alcohols

The cyclization precursors were prepared by Suzuki cross-coupling of the corresponding bromoraryls with common boronate **III-21**, that was prepared in two steps (Scheme 66).[232] Commercially available 4-pentynol was quantitatively protected as TBS ether **III-20**.[233] Subsequently, a zirconium-mediated hydroborationprovided **III-21** in excellent yield even on large scale (11 g isolated).[234]



Scheme 66. Preparation of vinylpinacolborane III-21

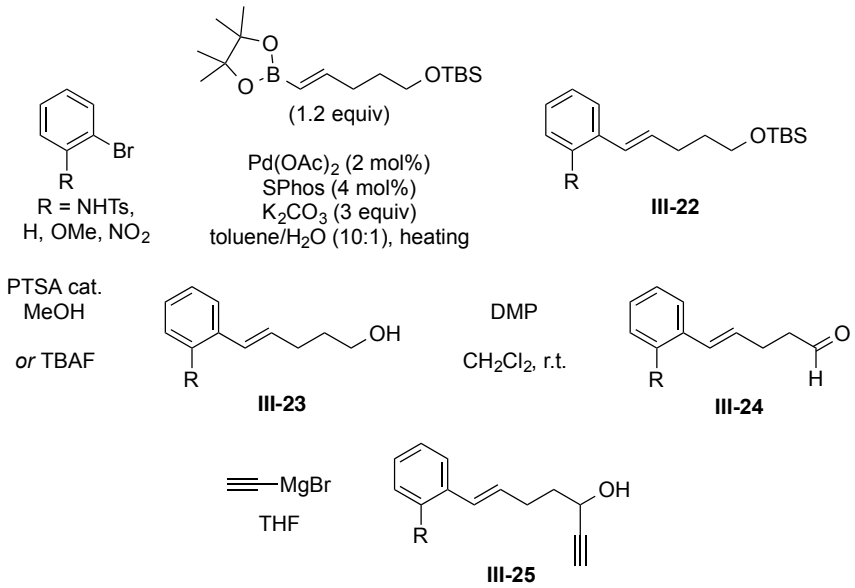
232. D. J. St. Jean Jr., S. F. Poon, J. L. Schwarzbach, *Org. Lett.* **2007**, *9*, 4893-4896.

233. H. Guo, G. A. O'Doherty, *Org. Lett.* **2005**, *7*, 3921-3924.

234. Y. D. Wang, G. Kimball, A. S. Prashad, Y. Wang, *Tetrahedron Lett.* **2005**, *46*, 8777-8780.

The Suzuki coupling (Scheme 67) afforded the desired coupled-products in good to excellent yields even if some impurities remained after purification (excess of boronate). These contaminants could be removed later in the synthesis. Other Pd-catalysts ($Pd(PPh_3)_4$, $Pd_2dba_3 \cdot CHCl_3$, $Pd(OAc)_2/PPh_3$) were also screened but the reaction was usually slower and less clean.

The coupling furnished TBS-protected alcohols **III-22** that were efficiently deprotected by treatment with PTSA in MeOH. TBAF was used in the case of R = H. Primary alcohols **III-23** were then oxidized with Dess-Martin periodinane to aldehydes **III-24**. Eventually, addition of ethynylmagnesium bromide provided the desired secondary propargylic alcohols **III-25**.



Scheme 67. Synthesis of precursors III-25 via Suzuki cross-coupling

Precursors of type **III-25** (Figure 41) were engaged in the gold-catalyzed cyclization without any protecting group on the propargylic alcohol.

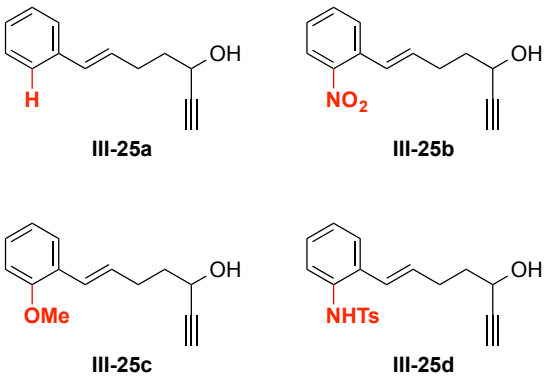
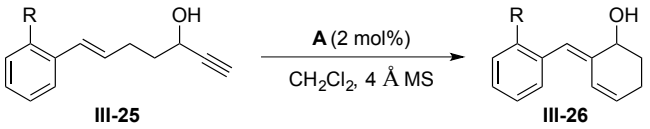


Figure 41. Secondary propargylic alcohols synthesized

Gold-catalyzed cyclization of secondary propargylic alcohols

Secondary alcohols **III-25** were also reacted under the standard reaction conditions presented previously for the cyclization of tertiary alcohols. Results are presented in Table 7. Unless otherwise stated, reactions were run on 100 mg scale.

Table 7. Gold-catalyzed reaction of secondary propargylic alcohols



III-25 **III-26**

Entry	Precursor	Product	Isolated yield (%)	Remarks
1	**III-25a**	**III-26a**	64	-
2	**III-25b**	**III-26b**	84	100 mg scale
			81	240 mg scale
			90	1 g scale
3	**III-25c**	**III-26c**	49	-
4	**III-25d**	**-**	n.r.	-
			decomp.	5 mol% catalyst reflux overnight

Non-substituted **III-25a** gave only moderate yield (entry 1, 64%). The cyclization of **III-25b** bearing a nitro group took place in excellent yields even on large scale (entry 2, up to 90%). Interestingly, precursor **III-25c** with a methoxy substituent did cyclize although in moderate yield (entry 3, 49%). Precursor **III-25d** (entry 4) did not react under the standard conditions. Increasing the amount of catalyst to 5 mol% and refluxing the reaction mixture overnight led to decomposition of the starting material.

Further Developments

We also envisioned applying the methodology developed previously to the synthesis of polycyclic molecules.

Intramolecular Heck reaction

The Heck reaction has been extensively studied over the past decades as it gives access to numerous families of compounds and it demonstrated its synthetic utility in dozens of natural product syntheses.[235] More precisely, the intramolecular version has been considerably investigated[236] and applied in several syntheses of natural compounds[237,238,239] and biologically active molecules.[240]

235. (a) J. T. Link, *Org. Reactions* **2002**, *6*0, 157-534; (b) S. Bräse, A. de Meijere, *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002**, *1*, 1223-1254.

236. (a) J.-M. Gaudin, *Tetrahedron Lett.* **1991**, *32*, 6113-6116; (b) S. E. Gibson, R. J. Middleton, *Contemp. Org. Synth.* **1996**, *3*, 447-471; (c) P. Vital, P.-O. Norrby, D. Tanner, *Synlett* **2006**, *18*, 3140-3144.

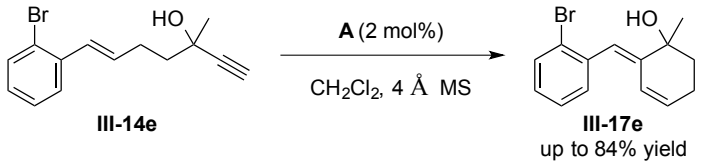
237. For a review on the application of the intramolecular Heck reaction in natural product total synthesis, see: A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945-2963.

238. For some reviews on the synthesis of heterocycles by intramolecular Heck reaction, see: (a) M. Ikeda, S. A. A. El Bialy, T. Yakura, *Heterocycles* **1999**, *51*, 1957-1970; (b) M. M. Heravi, A. Fazeli, *Heterocycles* **2010**, *81*, 1979-2026.

239. For some recent applications of the intramolecular Heck reaction in total synthesis, see: (a) K. C. Majumdar, I. Ansary, B. Sinha, B. Chattopadhyay, *Synthesis*, **2009**, *21*, 3593-3602; (b) J. Choi, H. Kim, S. Park, J. Tae, *Synlett* **2013**, *24*, 379-382; (c) M. Ozeki, M. Satake, T. Toizume, S. Fukutome, K. Arimitsu, S. Hosoi, T. Kajimoto, H. Iwasaki, N. Kojima, M. Node, M. Yamashita, *Tetrahedron* **2013**, *69*, 3841-3846.

240. (a) O. Cornec, B. Joseph, J.-Y. Mérour, *Tetrahedron Lett.* **1995**, *36*, 8587-8590; (b) L. F. Tietze, I. K. Krimmelbein, *Chem. Eur. J.* **2008**, *14*, 1541-1551.

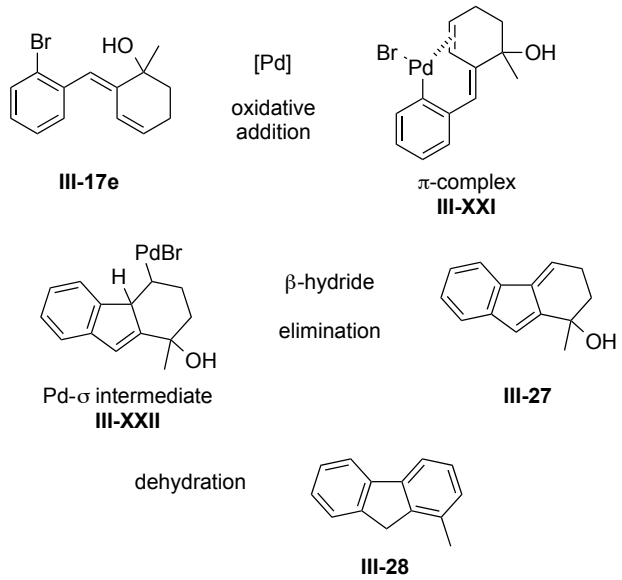
Our methodology provided substrate **III-17e** (Scheme 68) in good yields (up to 84%, Table 6, entry 11). **III-17e** can be considered an interesting candidate for an intramolecular Heck reaction.



Scheme 68. Cyclization of III-14e to III-17e

If the mechanism of the intramolecular Heck reaction were applied to **III-17e**, the outcome of the transformation would give access to tricyclic molecules related to fluorene (Scheme 69).

Oxidative addition of palladium into the C–Br bond of **III-17e** would furnish π-complex **III-XXI** that would further evolve to σ-complex **III-XXII**. β-Hydride elimination would provide tricyclic compound **III-27**, which could dehydrate to afford fluorene-related compounds such as **III-28**.

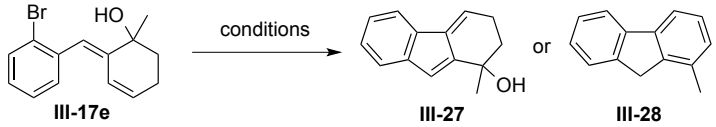


Scheme 69. Plausible mechanism of the intramolecular Heck reaction of III-17e

Some typical conditions for the intramolecular Heck reaction of **III-17e** were screened (Table 8). $Pd(OAc)_2$ was chosen as the palladium source and K_2CO_3 as base. The influence of the ligand (PPh_3 or dppe) and the solvent (DMF or CH_3CN) were inspected. Additionally, the reaction was also performed in pure Et_3N.

In most of the cases, a complex mixture was obtained. Nevertheless, the formation of **III-27** could be observed (entry 2), although in low yield. When neat Et_3N was used (entry 5), palladium black was produced rapidly.

Table 8. Intramolecular Heck reaction trials



III-17e **III-27** **III-28**

Entry	Conditions	Product	Remarks
1	$Pd(OAc)_2$ (10 mol%) PPh_3 (20 mol%) K_2CO_3 (5 equiv) DMF, 80 ºC	complex mixture	-
2	$Pd(OAc)_2$ (10 mol%) dppe (20 mol%) K_2CO_3 (5 equiv) DMF, 80 ºC	**III-27**	low yield (30-40%) isolated compound unpure
3	$Pd(OAc)_2$ (10 mol%) PPh_3 (20 mol%) K_2CO_3 (5 equiv) CH_3CN, 80 ºC	complex mixture	-
4	$Pd(OAc)_2$ (10 mol%) dppe (20 mol%) K_2CO_3 (5 equiv) CH_3CN, 80 ºC	complex mixture	-
5	$Pd(OAc)_2$ (10 mol%) PPh_3 (20 mol%) Et_3N, 80 ºC	complex mixture	rapid catalyst decomposition

Towards the acridine family

Acridine and its derivatives have been known for decades (Figure 42).[241] They were initially used as pigments and dyes[242] but found many other applications especially in catalysis as ligand.[243] From a biological perspective, this class of compounds displayed interesting activites. Applications were found as antibacterial,[244] antiparasitic,[245] antitumor,[246] or DNA-intercalating agents.[247] Recently, acridine derivatives were used in the treatment of Creutzfeldt-Jakob[248] and Alzheimer's diseases.[249]

241. A. Labert, *The Acridines*, 2nd ed; Edward Arnold Ltd: London, 1966.

242. For recent publications on the application of acridine derivatives in dyes see: (a) R. Mosurkal, L. Hoke, S. A. Fossey, L. A. Samuelson, J. Kuma, D. Waller, R. A. Gaudiana, *J. Macromol. Sci. A* **2006**, *43*, 1907-1922; (b) D. Zhang, X. Jiang, H. Yang, A. Martinez, M. Feng, Z. Dong, G. Gao, *Org. Biomol. Chem.* **2013**, *11*, 3375-3381.

243. (a) C. Gunanathan, B. Gnanaprakasam, M. A. Iron, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2010**, *132*, 14763-14765; (b) A. K. Cook, M. H. Emmert, M. S. Sanford, *Org. Lett.* **2013**, 5428-5431.

244. (a) M. Wainwright, *J. Antimicrob. Chemother.* **2001**, *47*, 1-13; (b) M. Demeuncynck, F. Charmantray, A. Martelli, *Curr. Pharm. Design* **2001**, *7*, 1703-1724.

245. (a) L. Guetzoyan, F. Ramiandrasoa, H. Dorizon, C. Desprez, A. Bridoux, C. Rogier, B. Pradines, M. Perrée-Fauvet, *Bioorg. Med. Chem.* **2007**, *15*, 3278-3289; (b) P. R. Carlier, E. S.-H. Chow, Y. Han, J. Liu, J. El Yazal, Y.-P. Pang, *J. Med. Chem.* **1999**, *42*, 4225-4231.

246. (a) H. H. Lee, W. R. Wilson, D. M. Ferry, P. Van Zijl, S. M. Pullen, W. A. Denny, *J. Med. Chem.* **1996**, *39*, 2508-2517; (b) W. Denny, *Curr. Med. Chem.* **2002**, *9*, 1655-1665.

247. (a) I. Antonini, P. Polucci, A. Magnano, D. Cacciamani, M. T. Konieczny, J. P. Lukowicz, S. Martelli, *Bioorg. Med. Chem.* **2003**, *11*, 399-405; (b) J. Joseph, E. Kuruvilla, A. T. Achuthan, D. Ramaiah, G. B. Schuster, *Bioconjugate Chem.* **2004**, *15*, 1230-1235; (c) S. Badr, M. M. El-Kerdawy, F. A. Taniuos, W. D. Wilson, D. W. Boykin, *Heterocyclic Commun.* **2008**, *14*, 15-20.

248. H. T. Nguyen Thi, C.-Y. Lee, K. Teruya, W.-Y. Ong, K. Doh-ura, M.-L. Go, *Bioorg. Med. Chem.* **2008**, *16*, 6737-6746.

249. Y. Wang, C. Chen, S. Zhang, Z. Lou, X. Su, L. Wen, M. Li, *Org. Lett.* **2013**, *15*, 4794-4797.

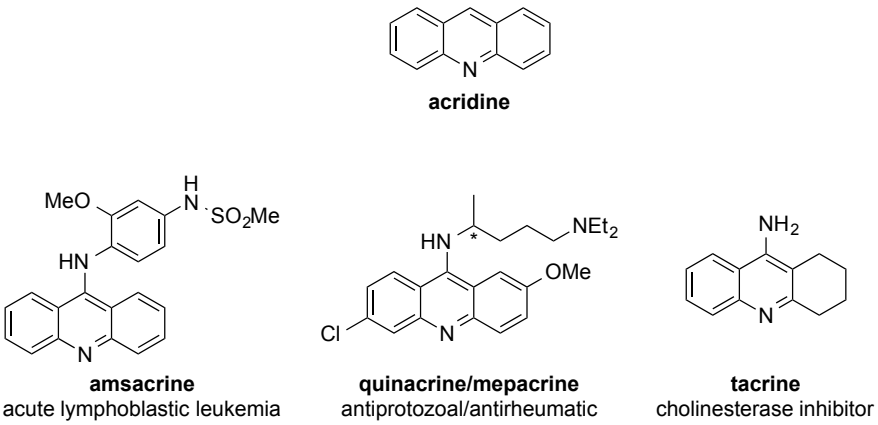
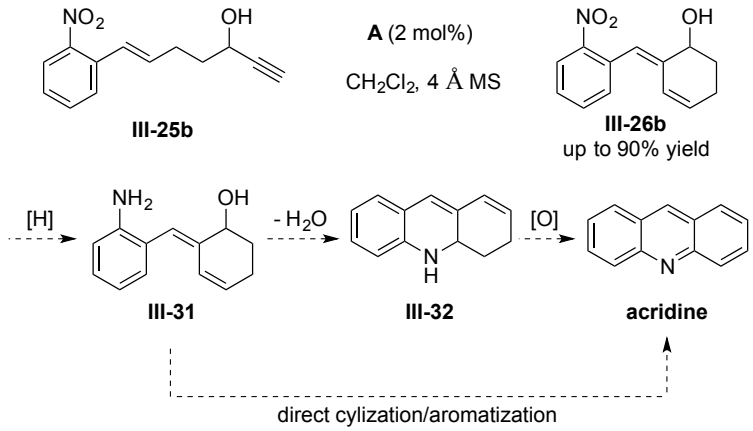


Figure 42. Structure of acridine and examples of bioactive acridine derivatives

From an organic synthesis standpoint, acridine and its derivatives have attracted the attention of many research groups and numerous methodologies had been developed to synthesize this important class of molecules.[250]

Our methodology could possibly be applied as a new method to access this family of compounds (Scheme 70). As demonstrated earlier, **III-25b** was cyclized efficiently to **III-26b** (Table 7, entry 2) under the developed conditions. The nitrophenyl could be easily reduced to aniline **III-31**, which can undergo a dehydration and aromatization to acridine. Depending on the conditions employed, a direct cyclization/aromatization might occur.

250. (a) T. Horaguchi, T. Oyanagi, E. Cuevas Creencia, K. Tanemura, T. Suzuki, *J. Heterocyclic Chem.* **2004**, *41*, 1-6; (b) P. Belmont, J.-C. Andrez, C. S. M. Allan, *Tetrahedron Lett.* **2004**, *45*, 2783-2786; (c) N. Desbois, A. Szollosi, A. Maisonial, V. Weber, E. Moreau, J.-C. Teulade, O. Chavignon, Y. Blache, J. M. Chezal, *Tetrahedron Lett.* **2009**, *50*, 6894-6896; (d) D. C. Rogness, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 2289-2295; (d) R. Ghorbani-Vaghei, S. M. Malaekehpoor, *J. Iran. Chem. Soc.* **2010**, *7*, 957-964; (e) B. Zhang, Y. Cui, N. Jiao, *Chem. Commun.* **2012**, *48*, 4498-4500; (f) J. Yu, H. Yang, Y. Jiang, H. Fu, *Chem. Eur. J.* **2013**, *19*, 4271-4277.



Scheme 70. Possible synthesis of acridine from III-25b

Conclusions

We developed a new gold(I)-catalyzed cycloisomerization of 1,6-enynes in which the expected 1,5-migration does not take place. The structure of the new compounds was unambiguously assigned by X-ray diffraction of some crystalline substrates and derivatives.

The mechanism was investigated by deuteration of the terminus alkyne and occurs through an *endo*-type single cleavage pathway.

The reaction proceeds in good to excellent yields with electron-poor aromatic rings but decomposition is frequently observed in the case of electron-rich substrates. The cycloisomerization is neither sensitive to substitution pattern of the aryl nor the protection of the tertiary alcohol. The transformation was performed on large scale (up to 2 g of substrate) with lowered catalyst loading (0.5 mol%) without decrease in the chemical yield.

Experimental part

General information

Unless otherwise stated, all the compounds were obtained as oils and the reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv^{TM} solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF_{234}) using UV light as visualizing agent, and an acidic solution of vanillin in ethanol or a basic solution of potassium permanganate in water as stain solutions. Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) or automated flash chromatographer CombiFlash Companion. Preparative TLC was performed on 20 cm x 20 cm silica gel plates (2.0 mm thick, catalogue number 02015, Analtech). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

NMR spectra were recorded at 298 K on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

Crystal structure determinations were carried out using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = −173 ºC). Full-sphere data collection was used with w and j scans. *Programs used:* Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. *Structure Solution and Refinement:* Crystal structure solution

was achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

General procedures

Bromination with PBr_3

PBr_3 was added dropwise to a solution of the cinnamyl alcohol in CH_2Cl_2 (0.1 M) at 0 ºC. The reaction mixture was stirred for 30 min at 0 ºC and carefully quenched with saturated $NaHCO_3$ at 0 ºC. The resulting mixture was allowed to warm up to r.t. and phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were washed with NaOH 10%, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

*Formation of the β-ketoesters **III-12***

Ethyl or methyl 3-oxobutanoate was added dropwise to a suspension of NaH (60 wt% in mineral oil) in THF at 0 ºC. The resulting mixture was allowed to warm up to r.t. and stirred for 30 min. Then a solution of cinnamyl bromide **III-11** in THF (0.1 M) was added dropwise and the reaction mixture was stirred at r.t. overnight for convenience. The reaction was quenched with saturated NH_4Cl. EtOAc was added and phases were separated. The aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Decarboxylation in EtOH/water

A solution of β-ketoester **III-12** in EtOH was added to a solution of KOH (0.5 M) in EtOH/water. The reaction mixture was refluxed overnight, cooled to r.t. and extracted with EtOAc (3 times). The combined organic extracts were washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Decarboxylation in THF/water

To a solution of β-ketoester **III-12** in THF (0.2 M) was added KOH and water. The reaction mixture was stirred at 50-60 ºC for 4-5 h (TLC monitoring) and then cooled down to r.t. EtOAc was added and phases were separated. The aqueous layer was extracted with EtOAc (3 times) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Addition of ethynylmagnesium bromide

Ethynylmagnesium bromide (0.5 M in THF) was added dropwise to a solution of ketones **III-13** or aldehydes **III-24** in THF (0.1 M) at −10 ºC. The mixture was allowed to warm up to r.t. and was stirred overnight for convenience. The reaction was quenched with saturated NH_4Cl and EtOAc was added. Phases were separated and the aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

Protection as methyl ether

A solution of alcohol **III-14** in THF was added dropwise to a suspension of NaH (60 wt% in mineral oil) in THF at 0 ºC. After 30 min, MeI was added dropwise. The resulting mixture was allowed to warm up to r.t. and stirred overnight for convenience. The reaction was quenched with saturated

NH_4Cl and EtOAc was added. Phases were separated and the aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

Protection as TMS ether

TMSOTf was added dropwise to a solution of alcohol **III-14** and Et_3N in CH_2Cl_2 (0.1 M) at 0 ºC. The resulting mixture was allowed to warm up to r.t. and was stirred overnight for convenience. The solvent was removed under reduced pressure and the residue was purified by flash chromatography over silica gel.

Gold-catalyzed cyclization of precursors

Gold catalyst **A** (2 mol%) was added to a solution of the precursor in CH_2Cl_2 (0.1 M) with activated powdered 4 Å MS. The reaction mixture was stirred at r.t. for 4 h and quenched with Et_3N. The solution was filtered through a short pad of silica (elution EtOAc) and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

*Suzuki cross-coupling of **III-21** with aryl bromides*

A flask was charged with the aryl bromide, K_2CO_3, $Pd(OAc)_2$ and SPhos. A solution of boronate **III-21** in toluene was added followed by water. The reaction mixture was stirred vigorously under reflux overnight for convenience, cooled down to r.t. and then filtered through silica (elution EtOAc). The filtrate was concentrated under reduced pressure and the crude material was engaged in the subsequent step without further purification.

*Deprotection of protected primary alcohols **III-22** with PTSA/MeOH*

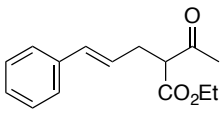
PTSA (monohydrate, 30 mol%) was added to a solution of crude TBS-protected primary alcohols **III-22** in MeOH (0.2 M). The reaction mixture was stirred overnight at r.t. for convenience and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel.

*Oxidation of primary alcohols **III-23** to aldehydes*

Dess-Martin Periodinane was added to a solution of primary alcohols **III-23** in CH_2Cl_2 (0.1 M). The reaction mixture was stirred at r.t. for the required time (TLC monitoring) and a 1:1 mixture of saturated $NaHCO_3$ and saturated Na_2SO_3 was added. The biphasic mixture was stirred until it became clear and phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

Preliminary study

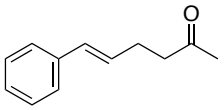
Synthesis of model substrates



III-7

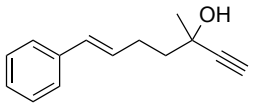
β-Ketoester **II-7** was prepared following the procedure described in reference 251. Analytical data were in accordance with previous reports.[251]

251. J. Tummatorn, S. Ruchiwarat, P. Ploypradith, *Chem. Eur. J.* **2010**, *16*, 1445-1448.



III-8

Ketone **II-8** was prepared following the procedure described in reference 251. Analytical data were in accordance with previous reports.[251]



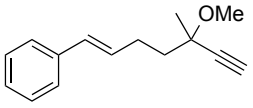
III-6a

III-6a was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-8** (191 mg, 1.00 equiv) and ethynylmagnesium bromide (3.30 mL, 1.50 equiv) The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-6a** (150 mg, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H), 7.22 – 7.18 (m, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.8, 6.9 Hz, 1H), 2.55 – 2.41 (m, 3H), 1.89 – 1.83 (m, 2H), 1.55 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.59, 130.39, 129.95, 128.50, 126.99, 125.96, 87.35, 71.78, 67.99, 42.81, 29.98, 28.38.

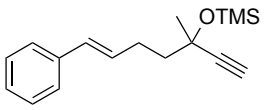
HRMS-ESI: *m/z* calculated for $C_{14}H_{16}ONa$ $[M+Na]^+$: 223.1099, found: 223.1094.



III-6b

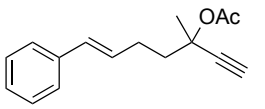
III-6b was prepared following the procedure for the *protection as methyl ether* with **III-6a** (100 mg, 1.00 equiv), NaH (60 wt% in mineral oil, 24.0 mg, 1.20 equiv) and MeI (37.0 μL, 1.20 equiv) The crude material was purified by flash chromatography over silica gel (pure hexane) to afford **III-6b** (88.0 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H), 7.21 – 7.17 (m, 1H), 6.45 – 6.39 (m, 1H), 6.24 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.39 (s, 3H), 2.48 (s, 1H), 2.45 – 2.31 (m, 2H), 1.93 – 1.78 (m, 2H), 1.45 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.91, 130.36, 130.17, 128.63, 127.02, 126.08, 84.79, 73.61, 73.30, 51.62, 40.92, 27.99, 25.73.
HRMS-ESI: *m/z* calculated for $C_{15}H_{19}O$ $[M+H]^+$: 215.1436, found: 215.1435.



III-6c

III-6c was prepared following the procedure for the *protection as TMS ether* with TMSOTf (54.0 µL, 1.50 equiv), **III-6a** (34.0 mg, 1.00 equiv) and Et_3N (50.0 µL, 1.80 equiv). The crude material was purified by flash chromatography over silica gel (pure hexane, 1% Et_3N) to afford **III-6c** (30.0 mg, 65% yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 6.6, 5.0 Hz, 2H), 6.86 – 6.81 (m, 2H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.11 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.80 (s, 3H), 2.47 (s, 1H), 2.38 (dt, *J* = 10.9, 5.8 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.50 (s, 3H), 0.20 (d, *J* = 3.0 Hz, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.62, 130.74, 129.14, 128.41, 126.96, 113.90, 87.86, 72.50, 69.06, 55.28, 44.67, 31.22, 28.25, 1.93.
HRMS-ESI: *m/z* calculated for $C_{17}H_{25}OSi$ $[M+H]^+$: 273.1675, found: 273.1682.



III-6d

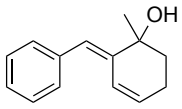
DMAP (419 mg, 3.43 mmol) and acetic anhydride (0.30 mL, 3.12 mmol) were added in that order to a solution of **III-6a** (313 mg, 1.56 mmol) in

CH_2Cl_2 (30 mL). The reaction mixture was stirred for 12 h at r.t. and quenched with saturated $NaHCO_3$. Phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 3:1) to afford **III-6d** (348 mg, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 − 7.32 (m, 2H), 7.29 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.22 − 7.18 (m, 1H), 6.43 (dt, *J* = 15.7, 1.5 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.8 Hz, 1H), 2.59 (s, 1H), 2.43 (dddd, *J* = 14.3, 10.2, 7.1, 1.7 Hz, 2H), 2.14 (ddd, *J* = 13.6, 10.5, 5.9 Hz, 1H), 2.04 (s, 2H), 1.98 (ddd, *J* = 13.6, 10.8, 5.7 Hz, 1H), 1.73 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.51, 137.73, 130.53, 129.61, 128.66, 127.15, 126.08, 83.73, 74.67, 73.74, 41.09, 27.96, 26.68, 22.07.

Test of model substrates in catalysis



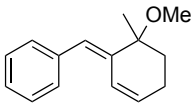
III-10a

III-6a was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (5.40 mg, 2 mol%) and **III-6a** (70.0 mg, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-10a** (36.0 mg, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 12.9, 7.6 Hz, 4H), 7.21 (d, *J* = 6.7 Hz, 1H), 6.80 (s, 1H), 6.53 (d, *J* = 9.9 Hz, 1H), 5.88 – 5.81 (m, 1H), 2.33 – 2.26 (m, 2H), 1.89 – 1.80 (m, 2H), 1.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.83, 137.43, 129.73, 129.33, 128.07, 126.53, 124.05, 122.04, 71.21, 37.75, 26.68, 24.87.

HRMS-ESI: *m/z* calculated for $C_{14}H_{15}$ $[M\text{-}OH]^-$: 183.1174, found: 183.1174.

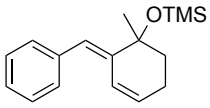


III-10b

III-6b was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (9.1 mg, 3 mol%) and **III-6b** (84.0 mg, 1.00 equiv). The crude material was purified by preparative TLC (pentane/Et_2O 10:1) to afford **III-10b** (12.0 mg, 14% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 − 7.28 (m, 4H), 7.22 (td, *J* = 6.4, 5.9, 2.6 Hz, 1H), 6.62 (s, 1H), 6.54 (dt, *J* = 9.9, 2.4 Hz, 1H), 5.89 − 5.81 (m, 1H), 3.24 (s, 3H), 2.40 (dd, *J* = 18.7, 5.3 Hz, 1H), 2.27 − 2.13 (m, 1H), 2.05 (ddd, *J* = 13.5, 8.0, 5.7 Hz, 1H), 1.73 (dt, *J* = 12.7, 5.4 Hz, 1H), 1.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.02, 137.64, 130.33, 129.52, 128.21, 126.65, 124.44, 124.04, 75.48, 49.96, 32.78, 24.91, 24.28.



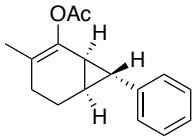
III-10c

III-6c was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (3.10 mg, 2 mol%) and **III-6c** (54.0 mg, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-10c** (51.0 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.23 (dd, *J* = 9.7, 4.3 Hz, 1H), 6.74 (s, 1H), 6.51 (d, *J* = 10.0 Hz, 1H), 5.84 – 5.78 (m, 1H), 2.39 – 2.22 (m, 2H), 1.98 – 1.83 (m, 2H), 1.42 (s, 3H), 0.18 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.46, 129.32, 129.23, 128.00, 126.28, 124.18, 122.81, 74.08, 37.60, 28.37, 24.93, 2.60.

HRMS-ESI: *m/z* calculated for $C_{17}H_{25}OSi$ $[M+H]^+$: 273.1596, found: 273.1598.



III-10'

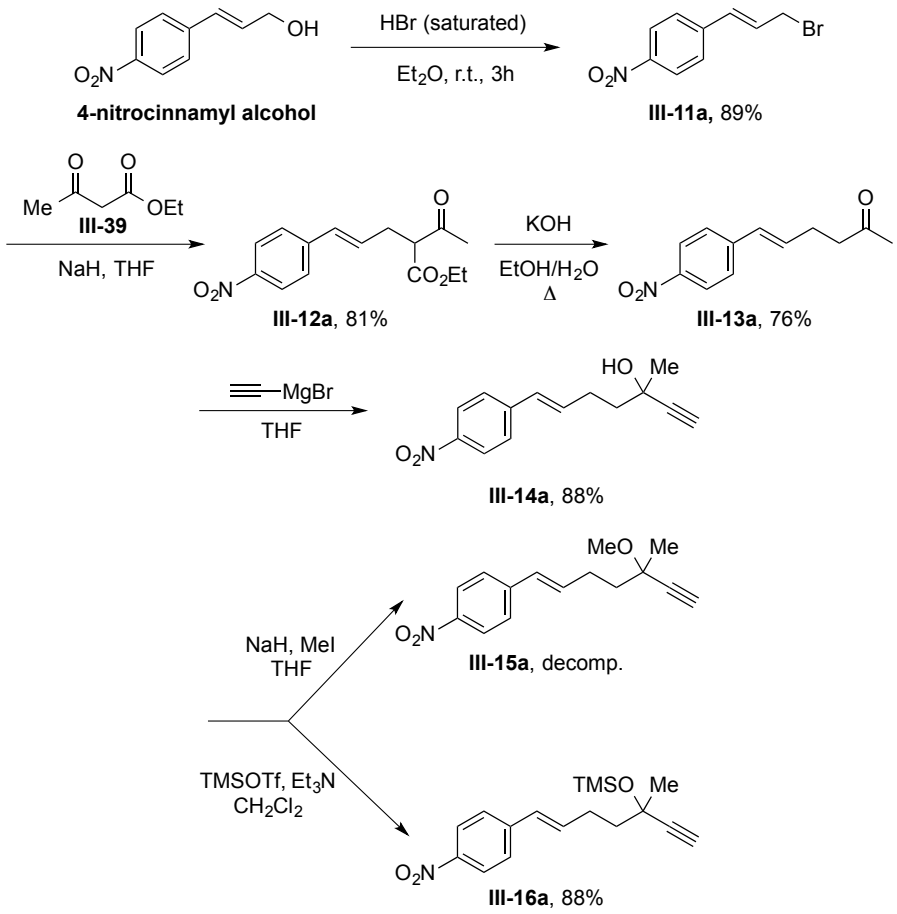
III-6d was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (9.5 mg, 3 mol%) and **III-6d** (100 mg, 1.00 equiv). The crude material was purified by preparative TLC (pentane/Et_2O 15:1) to afford **III-10'** (10.0 mg, 10% yield).

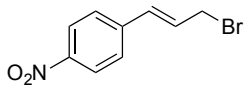
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 − 7.23 (m, 2H), 7.16 − 7.12 (m, 2H), 7.07 − 7.04 (m, 1H), 2.17 (dd, *J* = 5.0, 3.9 Hz, 1H), 2.15 (s, 3H), 2.08 − 2.03 (m, 2H), 2.03 − 2.00 (m, 1H), 1.92 − 1.80 (m, 2H), 1.56 (s, *J* = 0.9 Hz, 3H), 1.52 (dd, *J* = 8.7, 3.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.30, 142.20, 142.04, 128.47, 125.78, 125.74, 115.99, 28.46, 26.50, 25.05, 24.42, 20.92, 19.18, 16.40.

Reaction scope with tertiary propargylic alcohols

*Synthesis of precursors **III-14a** and **III-16a***

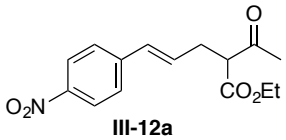




III-11a

A solution of 4-nitrocinnamyl alcohol (300 mg, 1.67 mmol) in Et_2O (5.6 mL) was saturated with HBr (48 wt% in water, roughly 2 mL) and stirred for 3 h at r.t. After that period of time, TLC control showed incomplete conversion so more HBr (5 mL) was added. The resulting mixture was stirred overnight at r.t., dried over Na_2SO_4, filtered and concentrated under

reduced pressure. The residue was purified by flash chromatography over silica gel (hexane/EtOAc 85:15) to afford **III-11a** (361 mg, 89% yield). Analytical data were in accordance with previous reports.[252]

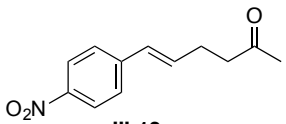


III-12a

III-12a was prepared following the procedure for the *formation of β-ketoesters* with ethyl 3-oxobutanoate **III-39** (0.33 mL, 1.00 equiv), NaH (60 wt % in mineral oil, 109 mg, 1.05 equiv) and **III-11a** (625 mg, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (hexane/EtOAc 9:1) to afford **III-12a** (675 mg, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.10 (m, 2H), 7.49 – 7.40 (m, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.41 – 6.26 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.61 (t, *J* = 7.2 Hz, 1H), 2.79 (td, *J* = 7.2, 1.3 Hz, 2H), 2.27 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.83, 168.94, 146.84, 143.34, 131.11, 130.87, 126.66, 123.99, 61.69, 59.05, 31.42, 29.24, 14.14.



III-13a

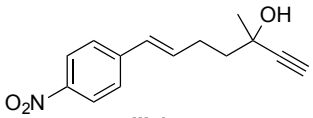
III-13a was prepared following the procedure for the *decarboxylation in EtOH/water* with **III-12a** (670 mg, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (hexane/EtOAc 9:1) to afford **III-16** (407 mg, 81% yield).

252. Y. Sonoda, M. Goto, S. Tsuzuki, N. Tamaoki, *J. Phys. Chem. A* **2006**, *110*, 13379-13387.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 2H), 7.47 – 7.39 (m, 2H), 6.51 – 6.35 (m, 2H), 2.66 (dd, *J* = 10.8, 3.7 Hz, 2H), 2.53 (dt, *J* = 8.2, 3.9 Hz, 2H), 2.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.36, 146.63, 143.88, 134.24, 129.07, 126.48, 123.97, 42.57, 30.03, 27.08.

HRMS-ESI: *m/z* calculated for $C_{12}H_{13}NO_3Na$ $[M+Na]^+$: 242.0793, found: 242.0797.



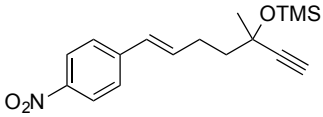
III-14a

III-14a was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13a** (185 mg, 1.00 equiv) and ethynylmagnesium bromide (2.50 mL, 1.50 equiv) The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-14a** (182 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 9.1, 2.0 Hz, 2H), 7.48 – 7.41 (m, 2H), 6.55 – 6.42 (m, 2H), 2.61 – 2.45 (m, 3H), 1.90 – 1.78 (m, 2H), 1.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.57, 144.13, 135.45, 128.57, 126.40, 124.00, 87.12, 72.00, 67.78, 42.32, 30.14, 28.53.

HRMS-ESI: *m/z* calculated for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1130, found: 246.1140.



III-16a

III-16a was prepared following the procedure for the *protection as TMS ether* with TMSOTf (59.0 µL, 1.50 equiv), **III-4a** (53.0 mg, 1.00 equiv) and Et_3N (54.0 µL, 1.80 equiv). The crude material was purified by flash

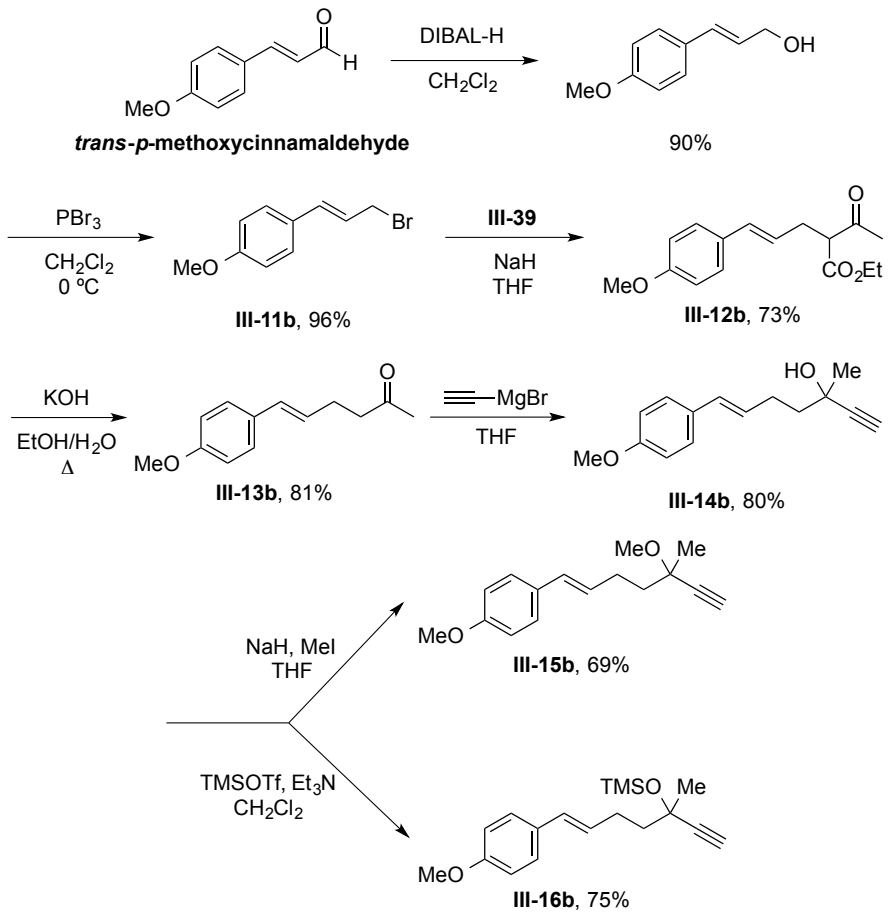
chromatography over silica gel (pure hexane, 1% Et_3N) to afford **III-16a** (60.0 mg, 88% yield).

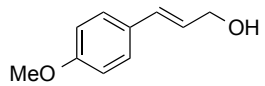
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.2 Hz, 2H), 7.45 (m, *J* = 7.2 Hz, 2H), 6.50 – 6.46 (m, 2H), 2.51 – 2.44 (m, 2H), 2.48 (s, 1H), 1.85 – 1.76 (m, 3H), 1.51 (s, 3H), 0.20 (m, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.45, 144.40, 136.19, 128.12, 126.33, 123.99, 99.99, 87.56, 72.76, 68.91, 44.08, 28.55, 1.87.

HRMS-ESI: *m/z* calculated for $C_{17}H_{24}NO_3Si$ $[M+H]^+$: 318.1525, found: 318.1530.

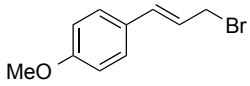
*Synthesis of precursors **III-14b**, **III-15b** and **III-16b***





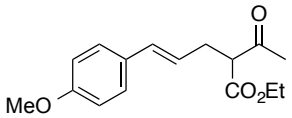
(*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol

(*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol was prepared by modifying the general procedure reported in reference 261, using *trans-p*-methoxycinnamaldehyde as starting material, DIBAL-H (1 M in CH_2Cl_2) and CH_2Cl_2 as solvent. The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 7:3) to afford (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (585 mg, 96% yield). Analytical data were in accordance with previous reports.[253]



III-11b

III-11b was prepared following the procedure for the *bromination with PBr_3* with (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (753 mg, 1.00 equiv) and PBr_3 (0.47 mL, 1.10 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 10:1) to afford **III-11b** (626 mg, 69% yield). Analytical data were in accordance with previous reports.[254]



III-12b

III-12b was prepared following the procedure for the *formation of β-ketoesters* with ethyl 3-oxobutanoate **III-39** (0.39 mL, 1.00 equiv), NaH (60 wt% in mineral oil, 78.0 mg, 1.05 equiv) and **III-11b** (311 mg, 1.00 equiv).

261. E. Kim, M. Koh, B. J. Lim, S. B. Park, *J. Am. Chem. Soc.* **2011**, *133*, 6642-6649.

253. B. Schmidt, F. Hölter, A. Kelling, U. Schilde, *J. Org. Chem.* **2011**, *76*, 3357-3365.

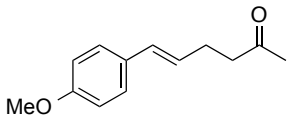
254. T. Janecki, A. Albrecht, E. Warzycha, K. Studzian, A. Jannecka, U. Krajewska, M. Rózalski, *Chem. Biodiversity* **2005**, *2*, 1256-1265.

The crude material was purified by flash chromatography over silica gel (hexane/EtOAc 9:1) to afford **III-11b** (349 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dt, *J* = 9.6, 2.5 Hz, 2H), 6.85 – 6.79 (m, 2H), 6.39 (d, *J* = 15.8 Hz, 1H), 5.96 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.23 – 4.16 (m, 2H), 3.79 (s, 3H), 3.57 (t, *J* = 7.4 Hz, 1H), 2.72 (t, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.26 (dd, *J* = 8.6, 5.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.56, 169.28, 159.07, 132.10, 129.82, 127.29, 123.42, 113.93, 61.45, 59.76, 55.29, 31.58, 29.23, 14.14.

HRMS-ESI: *m/z* calculated for $C_{16}H_{20}O_4Na$ $[M+Na]^+$: 299.1259, found: 299.1252.



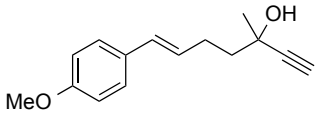
III-13b

III-13b was prepared following the procedure for the *decarboxylation in EtOH/water* with **III-12b** (1.05 g, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (hexane/EtOAc 10:1) to afford **III-13b** (731 mg, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 6.86 – 6.80 (m, 2H), 6.35 (d, *J* = 15.8 Hz, 1H), 6.04 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.79 (d, *J* = 5.9 Hz, 3H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.48 – 2.42 (m, 2H), 2.16 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.20, 158.84, 130.23, 130.11, 127.10, 126.59, 113.93, 55.28, 43.38, 30.03, 27.14.

HRMS-ESI: *m/z* calculated for $C_{13}H_{16}O_2Na$ $[M+Na]^+$: 227.1048, found: 227.1050.



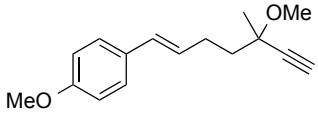
III-14b

III-14b was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13b** (372 mg, 1.00 equiv) and ethynylmagnesium bromide (5.10 mL, 1.50 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-14b** (358 mg, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 6.85 – 6.81 (m, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.11 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.80 (s, 3H), 2.49 (s, 1H), 2.47 – 2.36 (m, 2H), 1.88 – 1.80 (m, 2H), 1.54 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.79, 130.44, 129.79, 127.76, 127.06, 113.95, 87.40, 71.72, 68.03, 55.29, 42.95, 29.95, 28.35.

HRMS-ESI: *m/z* calculated for $C_{15}H_{19}O_2$ $[M+H]^+$: 231.1385, found: 231.1380.



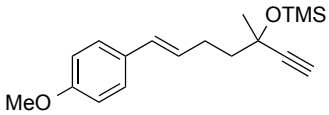
III-15b

III-15b was prepared following the procedure for the *protection as methyl ether* with **III-14b** (62.0 mg, 1.00 equiv), NaH (60 wt% in mineral oil, 13.0 mg, 1.20 equiv) and MeI (37.0 μL, 1.20 equiv) The crude material was purified by flash chromatography over silica gel (hexane/EtOAc 95:5) to afford **III-15b** (45.0 mg, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 6.87 – 6.80 (m, 2H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.09 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.80 (s, 3H), 3.38 (s, 3H), 2.48 (s, 1H), 2.44 – 2.29 (m, 2H), 1.90 – 1.77 (m, 2H), 1.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.69, 130.61, 129.36, 128.01, 127.00, 113.91, 84.70, 73.41, 73.17, 55.28, 51.46, 40.88, 27.80, 25.59.

HRMS-ESI: *m/z* calculated for $C_{16}H_{21}O_2$ $[M+H]^+$: 245.1542, found: 245.1554.



III-16b

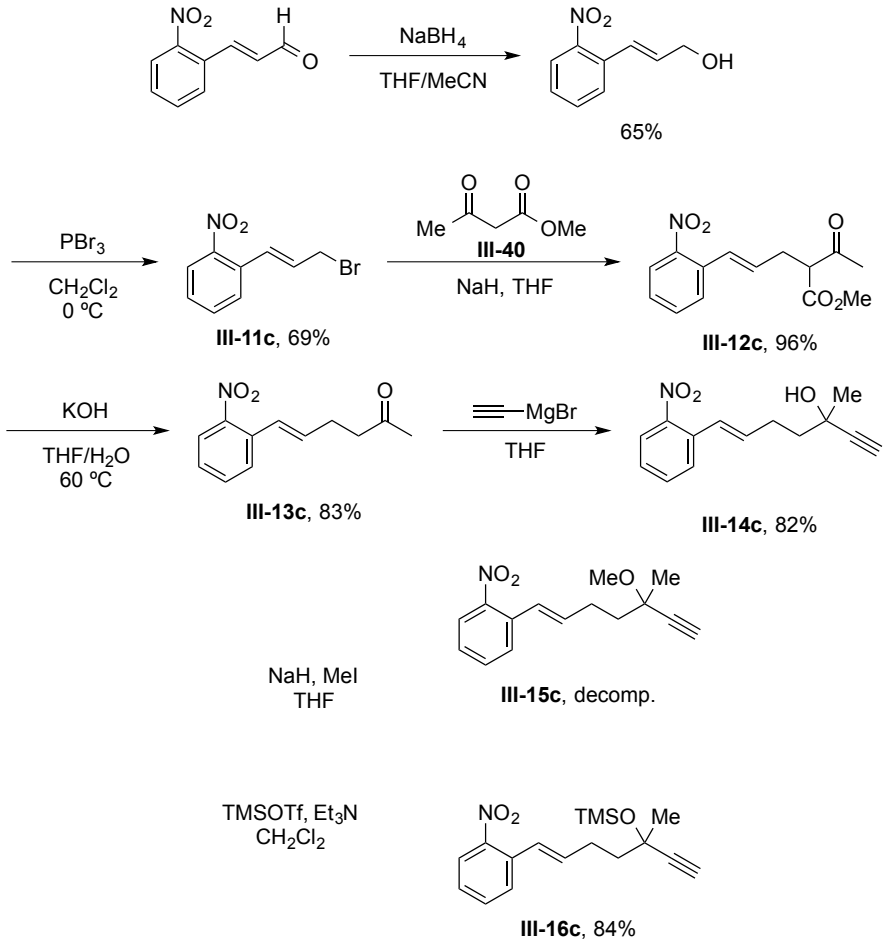
III-16b was prepared following the procedure for the *protection as TMS ether* with TMSOTf (120 µL, 1.50 equiv), **III-14b** (100 mg, 1.00 equiv) and Et_3N (110 µL, 1.80 equiv). The crude material was purified by flash chromatography over silica gel (hexane/EtOAc 95:5, 1% Et_3N) to afford **III-16b** (85.0 mg, 75% yield).

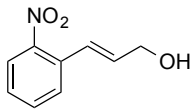
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 6.6, 5.0 Hz, 2H), 6.86 – 6.81 (m, 2H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.11 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.80 (s, 3H), 2.47 (s, 1H), 2.38 (dt, *J* = 10.9, 5.8 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.50 (s, 3H), 0.20 (d, *J* = 3.0 Hz, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.62, 130.74, 129.14, 128.41, 126.96, 113.90, 87.86, 72.50, 69.06, 55.28, 44.67, 31.22, 28.25, 1.93.

HRMS-ESI: *m/z* calculated for $C_{18}H_{27}O_2Si$ $[M+H]^+$: 303.1780, found: 303.1782.

*Synthesis of precursors **III-14c**, **III-15c** and **III-16c***

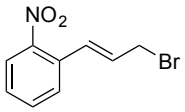




(*E*)-3-(2-nitrophenyl)prop-2-en-1-ol

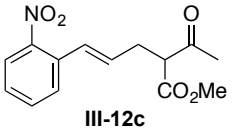
trans-2-Nitrocinnaldehyde (1.00 g, 5.64 mmol, 1.00 equiv) was added to a suspension of $NaBH_4$ (500 mg, 13.22 mmol, 2.30 equiv) in THF (50 mL) at 0 ºC. MeCN (10 mL) was used to rinse the inner walls of the flask and help dissolution. The mixture was allowed to warm up to r.t. and was stirred for 3 h. The reaction was carefully quenched with HCl 10% at 0 ºC and the

resulting mixture was diluted with EtOAc. Phases were separated and the aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude (*E*)-3-(2-nitrophenyl)prop-2-en-1-ol was engaged in the subsequent step without further purification (1.04 g, 90% pure, 93% yield). Analytical data were in accordance with previous reports.[255]



III-11c

III-11c was prepared following the procedure for the *bromination with PBr_3* with (*E*)-3-(2-nitrophenyl)prop-2-en-1-ol (670 mg, 1.00 equiv) and PBr_3 (1.50 mL, 4.20 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 10:1) to afford **III-11c** (626 mg, 69% yield). Analytical data were in accordance with previous reports.[256]



III-12c

III-12c was prepared following the procedure for the *formation of β-ketoesters* with methyl 3-oxobutanoate **III-40** (0.35 mL, 1.25 equiv), NaH (60 wt% in mineral oil, 109 mg, 1.05 equiv) and **III-23** (625 mg, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 7:3) to afford **III-12c** (688 mg, 96% yield).

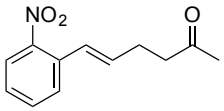
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 1H), 7.55 – 7.49 (m, 2H), 7.40 – 7.34 (m, 1H), 6.91 (dt, *J* = 15.5, 1.4 Hz, 1H), 6.12 (dt, *J* = 15.6, 7.1

255. C. Morrill, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 2842-2843.

256. P. Magnus, T. Rainey, *Tetrahedron* **2001**, *57*, 8647-8651.

Hz, 1H), 3.77 (s, 3H), 3.65 (dd, *J* = 7.6, 6.9 Hz, 1H), 2.80 (tdd, *J* = 7.0, 3.0, 1.5 Hz, 2H), 2.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.12, 169.63, 147.73, 133.21, 132.88, 131.47, 128.94, 128.24, 128.15, 124.60, 59.14, 52.77, 31.50, 29.32.

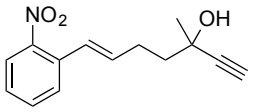


III-13c

III-13c was prepared following the procedure for the *decarboxylation in THF/water* with **III-12c** (688 g, 1.00 equiv), KOH (418 mg, 3.00 equiv) and water (10 mL). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-13c** (445 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 1H), 7.57 – 7.50 (m, 2H), 7.35 (ddd, *J* = 8.5, 7.0, 1.8 Hz, 1H), 6.86 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.22 (dt, *J* = 15.7, 6.7 Hz, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.56 – 2.50 (m, 2H), 2.19 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.75, 147.81, 134.71, 133.15, 133.06, 128.67, 127.80, 126.02, 124.56, 42.79, 30.14, 27.19.



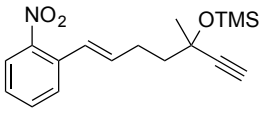
III-14c

III-14c was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13c** (1.94 g, 1.00 equiv) and ethynylmagnesium bromide (30.0 mL, 1.70 equiv) The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-14c** (1.79 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 1.2, 8.3 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.36 – 7.32 (m, 1H), 6.90 (d, *J* = 16.1 Hz, 1H), 6.27 (dt, *J* = 6.8,

15.5 Hz, 1H), 2.60 – 2.50 (m, 2H), 2.50 (s, 1H), 2.07 (s, 1H), 1.93 – 1.83 (m, 2H), 1.55 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.82, 135.92, 133.31, 133.01, 128.61, 127.67, 125.58, 124.53, 87.31, 72.12, 67.99, 42.47, 30.20, 28.70.



III-16c

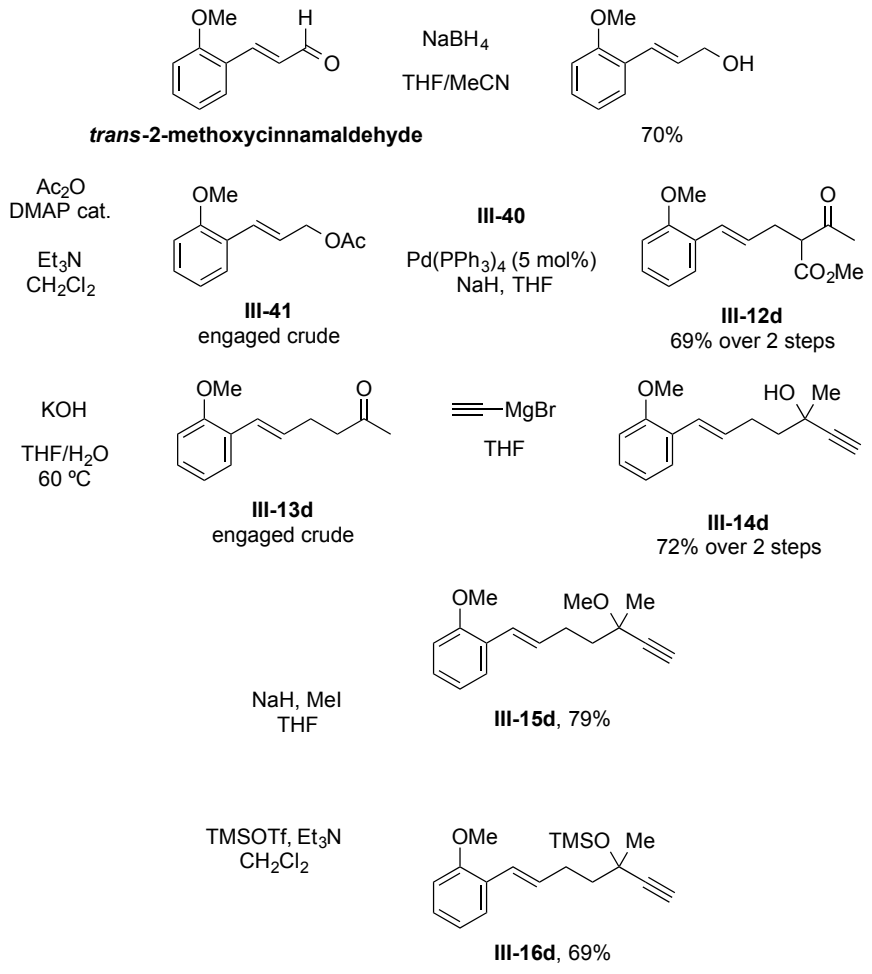
III-16c was prepared following the procedure for the *protection as TMS ether* with TMSOTf (0.15 mL, 2.00 equiv), **III-14c** (100 mg, 1.00 equiv) and Et_3N (0.20 mL, 3.50 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 10:1, 1% Et_3N) to afford **III-16c** (104 mg, 84% yield).

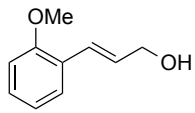
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 1.0, 8.4 Hz, 1H), 7.6 – 7.5 (m, 2H), 7.33 (dt *J* = 1.6, 7.8 Hz, 1H), 6.86 (d, *J* = 15.7 Hz, 1H), 6.28 (dt, *J* = 6.7, 15.7 Hz, 1H), 2.50 – 2.44 (m, 3H), 1.89 – 1.74 (m, 2H), 1.51 (s, 3H), 0.20 (s, 9H).

*Synthesis of precursors **III-14d, III-15d** and **III-16d***

In the case of the *o*-methoxy precursor **III-14d**, the cinnamyl bromide intermediate could not be obtained by bromination of the allylic alcohol. Therefore, the corresponding allylic acetate **III-41** was prepared and engaged in a Tsuji-Trost cross-coupling in good yield.[257]

257. B. M. Trost, L. Weber, P. Strege, T. J. Fullerton, T. J. Dietsche, *J. Am. Chem. Soc.* **1978**, *100*, 3426-3435.

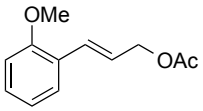




(*E*)-3-(2-methoxyphenyl)prop-2-en-1-ol

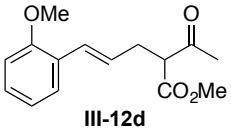
(*E*)-3-(2-methoxyphenyl)prop-2-en-1-ol was prepared following the same procedure as the one employed for the synthesis of (*E*)-3-(2-nitrophenyl)prop-2-en-1-ol, using *trans*-2-methoxycinnaldehyde (10.0 g scale) as starting material and rinsing the inner wall of the flask with acetonitrile. The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 7:3) to afford (*E*)-3-(2-methoxyphenyl)prop-

2-en-1-ol (7.09 g, 70% yield). Analytical data were in accordance with previous reports.[258]



III-41

Et_3N (10.0 mL, 71.7 mmol), DMAP (539 mg, 4.41 mmol) and Ac_2O (5.00 mL, 53.0 mmol) were added in that order to a solution of (*E*)-3-(2-methoxyphenyl)prop-2-en-1-ol (7.09 g, 43.2 mmol) in CH_2Cl_2 (100 mL) at 0 ºC. The reaction mixture was allowed to warm up to r.t. and stirred overnight for convenience. The reaction was quenched with saturated $NaHCO_3$ and phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude **III-41** was engaged in the subsequent step without further purification (7.61 g crude). Analytical data were in accordance with previous reports.[259]



III-12d

Methyl 3-oxobutanoate **III-40** (5.00 mL, 46.3 mmol) was added dropwise to a suspension of NaH (60 wt % in mineral oil, 1.80 g, 45.0 mmol) in THF (50 mL). The resulting mixture was stirred for 30 min and this solution was added to a solution of $Pd(PPh_3)_4$ (2.13 g, 1.84 mmol) in THF (30 mL). Then, a solution of **III-41** (7.61 g crude) in THF (20 mL) was added and the reaction mixture was stirred at r.t. overnight for convenience. The reaction was quenched with saturated $NaHCO_3$. EtOAc was added and phases were

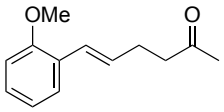
258. D. J. Vyas, M. Oestreich, *Chem. Commun.* **2010**, *46*, 568-570.

259. J. Wang, Z. Cui, Y. Zhang, H. Li, L.-M. Wu, Z. Liu, *Org. Biomol. Chem.* **2011**, *9*, 663-666.

separated. The aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-12d** (5.84 g, 84% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 6.92 – 6.88 (m, 1H), 6.84 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.78 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.11 (dt, *J* = 15.9, 7.2 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.62 (t, *J* = 7.4 Hz, 1H), 2.77 (tdd, *J* = 7.3, 2.2, 1.5 Hz, 2H), 2.26 (s, 3H).

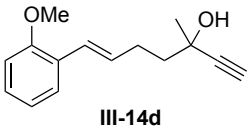
^{13}C NMR (125 MHz, $CDCl_3$) δ 202.66, 169.89, 156.59, 128.59, 127.67, 126.81, 126.33, 126.20, 120.74, 110.94, 59.74, 55.56, 52.56, 32.17, 29.42.



III-13d

III-13d was prepared following the procedure for the *decarboxylation in THF/water* with **III-12d** (5.84 g, 1.00 equiv), KOH (3.75 g, 3.00 equiv) and water (70 mL). The crude **III-13d** was engaged in the subsequent step without further purification (4.67 g crude).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 6.93 – 6.88 (m, 1H), 6.85 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.73 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.19 (dt, *J* = 16.0, 6.8 Hz, 1H), 3.84 (s, 3H), 2.62 (dd, *J* = 7.7, 6.5 Hz, 2H), 2.53 – 2.47 (m, 2H), 2.17 (s, 3H).



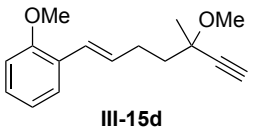
III-14d

III-14d was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13d** (4.67 g crude) and ethynylmagnesium bromide (70.0 mL, 1.50 equiv). The crude material was

purified by flash chromatography over silica gel (cyclohexane/EtOAc 85:15) to afford **III-14d** (3.81 g, 72% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 6.94 – 6.89 (m, 1H), 6.88 – 6.84 (m, 1H), 6.78 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.26 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.84 (s, 3H), 2.55 – 2.40 (m, 2H), 2.49 (s, 1H), 2.10 (s, 1H), 1.93 – 1.82 (m, 2H), 1.54 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.45, 130.83, 128.14, 126.81, 126.64, 125.20, 120.78, 110.93, 87.57, 71.84, 68.17, 55.58, 43.05, 30.05, 28.95.

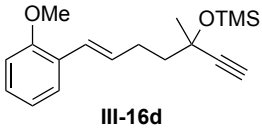


III-15d

III-15d was prepared following the procedure for the *protection as methyl ether* with **III-14d** (1.00 g, 1.00 equiv), NaH (60 wt% in mineral oil, 347 mg, 2.00 equiv) and MeI (0.60 mL, 2.20 equiv) The crude material was purified by flash chromatography over silica gel (pentane/Et_2O 10:1) to afford **III-15d** (840 mg, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.18 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 6.93 – 6.88 (m, 1H), 6.85 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.75 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.23 (dt, *J* = 16.0, 6.8 Hz, 1H), 3.84 (s, 3H), 3.39 (s, 3H), 2.48 (s, 1H), 2.45 – 2.35 (m, 2H), 1.94 – 1.78 (m, 2H), 1.46 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.42, 131.00, 128.03, 126.97, 126.56, 124.74, 120.78, 110.93, 84.88, 73.53, 73.34, 55.58, 51.60, 40.89, 28.40, 25.74.



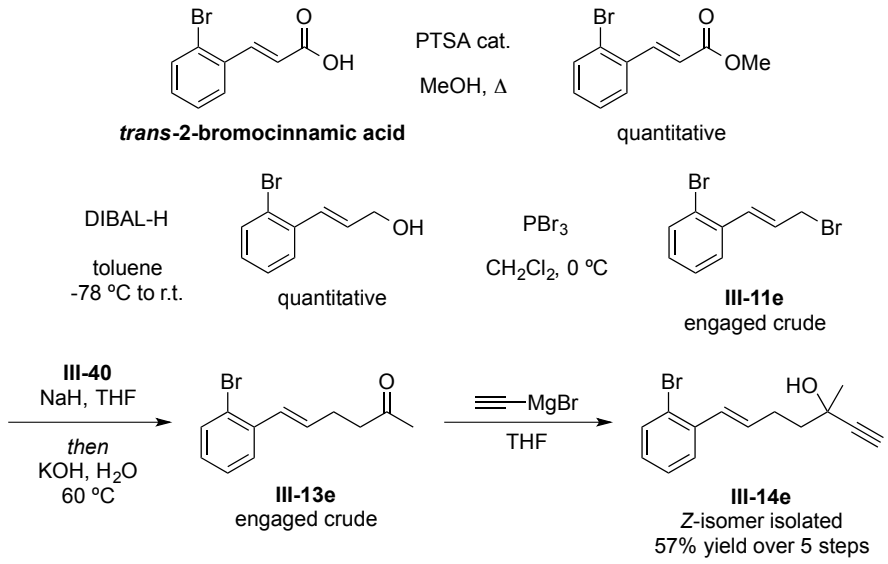
III-16d

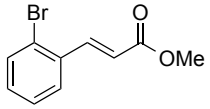
III-16d was prepared following the procedure for the *protection as TMS ether* with TMSOTf (0.15 mL, 1.90 equiv), **III-14d** (100 mg, 1.00 equiv)

and Et_3N (0.20 mL, 3.30 equiv). The crude material was purified by flash chromatography over silica gel (pentane/Et_2O 10:1, 1% Et_3N) to afford **III-16d** (90 mg, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.18 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 6.94 – 6.88 (m, 1H), 6.85 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.73 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.24 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.84 (s, 3H), 2.47 (s, 1H), 2.46 – 2.39 (m, 2H), 1.88 – 1.74 (m, 2H), 1.50 (s, 3H), 0.21 (s, 9H).

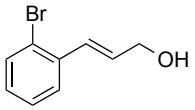
*Synthesis of precursor **III-14e***





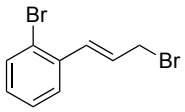
Methyl (*E*)-3-(2-bromophenyl)acrylate

Methyl (*E*)-3-(2-bromophenyl)acrylate was prepared following the procedure described in reference 263, using *trans*-2-bromocinnamic acid was starting material and PTSA monohydrate as acid source. The crude material was engaged in the subsequent step without further purification. Analytical data were in accordance with previous reports.[260]



(*E*)-3-(2-bromophenyl)prop-2-en-1-ol

(*E*)-3-(2-bromophenyl)prop-2-en-1-ol was prepared by modifying the general procedure reported in reference 261, using methyl (*E*)-3-(2-bromophenyl)acrylate as starting material, DIBAL-H (1 M in toluene) and toluene as solvent. The crude material was engaged in the subsequent step without further purification. Analytical data were in accordance with previous reports.[261]



III-11e

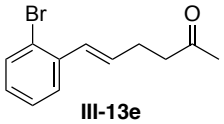
III-11e was prepared following the procedure for the *bromination with PBr_3* with (*E*)-3-(2-bromophenyl)prop-2-en-1-ol (2.82 g, 1.00 equiv) and PBr_3 (2.00 mL, 1.60 equiv). Crude **III-11e** was engaged in the subsequent

263. C. O. Sánchez, F. R. Díaz, N. Gatica, C. Bustos, K. Espiñeira, D. Huaquimilla, *Polym. Bull.* **2011**, *67*, 29-43.

260. P. A. Byrne, D. G. Gilheany, *J. Am. Chem. Soc.* **2012**, *134*, 9225-9239.

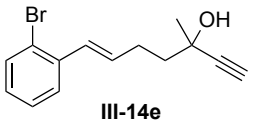
261. E. Kim, M. Koh, B. J. Lim, S. B. Park, *J. Am. Chem. Soc.* **2011**, *133*, 6642-6649.

step without further purification (3.50 g crude). Analytical data were in accordance with previous reports.[262]



III-13e

III-13e was prepared following the procedure for the *formation of β-ketoesters* with methyl 3-oxobutanoate (1.70 mL, 1.25 equiv), NaH (60 wt% in mineral oil, 582 mg, 1.05 equiv) and (*E*)-1-bromo-2-(3-bromoprop-1-en-1-yl)benzene (5.84 g, 1.00 equiv). Decarboxylation following the procedure for the *decarboxylation in THF/water* was performed subsequently in one-pot with KOH (3.70 g, 5.00 equiv) and water (50 mL). Crude **III-13e** was directly engaged in the subsequent step without further purification (4.67 g crude).



III-14e

III-14e was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13e** (1.19 g crude) and ethynylmagnesium bromide (11.0 mL, 1.20 equiv) The crude material was purified by flash chromatography over silica gel (pentane/EtOAc 10:1) and then re-purified by flash chromatography over silica gel (pentane/Et_2O 15:1) to afford **III-14e** (730 mg, 57% yield over 5 steps).

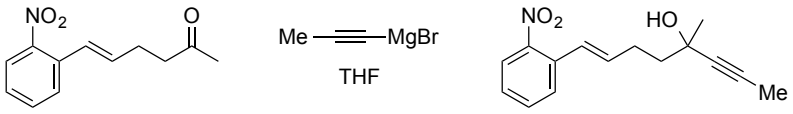
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.06 (ddd, *J* = 7.9, 7.3, 1.7 Hz, 1H), 6.78 (dt, *J* = 15.7, 1.7 Hz, 1H), 6.21 (dt, *J* = 15.7, 6.9 Hz, 1H), 2.59 – 2.43 (m, 3H), 2.04 – 2.00 (m, 1H), 1.95 – 1.82 (m, 2H), 1.56 (s, 3H).

262. M. L. Hammond, R. A. Zambias, M. N. Chang, N. P. Jensen, J. McDonald, K. Thompson, D. A. Boulton, I. E. Kopka, K. M. Hand, E. E. Opas, S. Luell, T. Bach, P. Davies, D. E. MacIntyre, R. J. Bonney, J. L. Humes, *J. Med. Chem.* **1990**, *33*, 908-918.

^{13}C NMR (125 MHz, $CDCl_3$) δ 137.59, 133.29, 132.98, 129.37, 128.45, 127.55, 127.02, 123.33, 87.43, 72.03, 68.08, 42.76, 30.17, 28.62.

HRMS-ESI: *m/z* calculated for $C_{14}H_{16}BrO$ $[M+H]^+$: 279.0379, found: 279.0368; *m/z* calculated for $C_{14}H_{14}Br$ $[M-OH]^+$: 261.0273, found: 261.0273.

Synthesis of precursor ***III-14f***



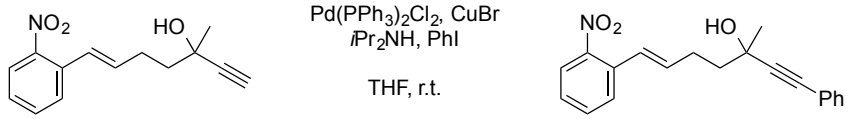
III-13c **III-14f**, 90%

III-14f was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13c** (500 mg, 1.00 equiv) and prop-1-yn-1-ylmagnesium bromide (0.5 M in THF, 9.00 mL, 2.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-14f** (531 mg, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.60 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.40 – 7.35 (m, 1H), 6.92 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.31 (dt, *J* = 15.7, 6.8 Hz, 1H), 2.58 – 2.48 (m, 2H), 1.88 (s, 3H), 1.87 – 1.82 (m, 2H), 1.53 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.85, 136.38, 133.39, 132.96, 128.57, 127.59, 125.29, 124.52, 82.81, 80.13, 68.24, 42.90, 30.55, 28.95, 3.66 .

*Synthesis of precursor **III-14g***



III-14c **III-14g**, 81%

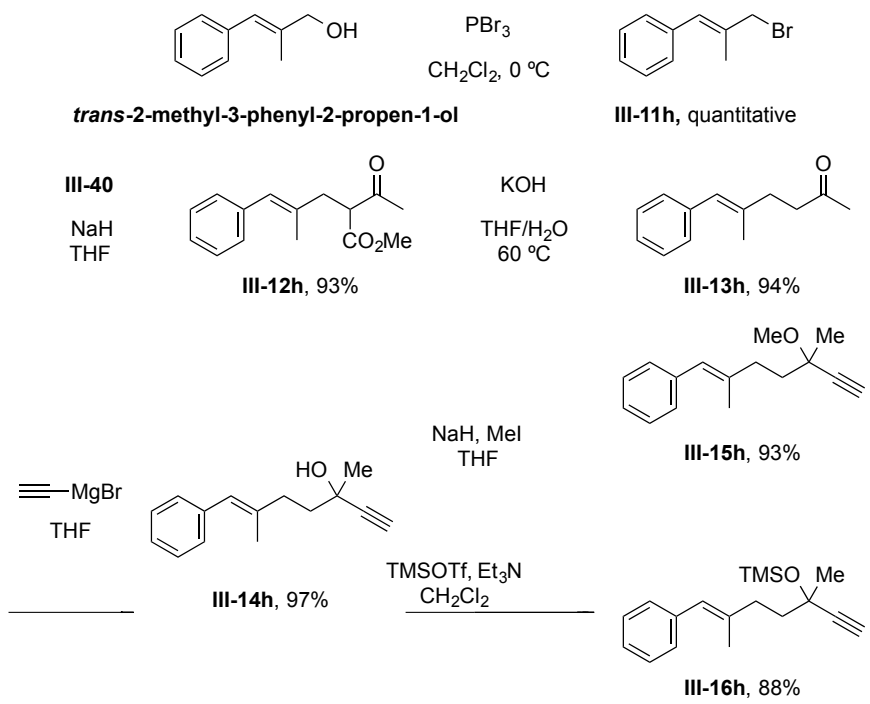
A dry flask was charged with a solution of **III-14c** (187 mg, 0.76 mmol) in THF (8 mL), *i*Pr_2NH (0.50 mL, 3.57 mmol), $PdCl_2(PPh_3)_2$ (53.3 mg, 0.076 mmol), CuBr (55.0 mg, 0.38 mmol) and PhI (0.12 mL, 1.07 mmol). The reaction mixture was stirred overnight at r.t. for convenience and quenched with saturated NH_4Cl. EtOAc was added and phases were separated. The aqueous layer was extracted with EtOAc (3 times) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-14g** (198 mg, 81% yield).

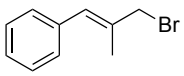
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.55 – 7.45 (m, 1H), 7.45 – 7.41 (m, 2H), 7.38 – 7.28 (m, 4H), 6.92 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.32 (dt, *J* = 15.7, 6.9 Hz, 1H), 2.65 – 2.57 (m, 2H), 1.97 (ddd, *J* = 9.4, 6.8, 2.2 Hz, 2H), 1.64 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.92, 136.27, 133.48, 133.09, 131.92, 128.76, 128.63, 128.53, 127.74, 125.64, 124.64, 122.78, 92.54, 84.28, 68.66, 42.91, 30.49, 29.09.

HRMS-ESI: *m/z* calculated for $C_{20}H_{19}NO_3Na$ $[M+Na]^+$: 344.1257, found: 344.1250.

*Synthesis of precursors **III-14h**, **III-15h** and **III-16h***

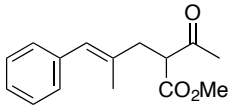




III-11h

III-11h was prepared following the procedure for the *bromination with PBr_3* with *trans*-2-methyl-3-phenyl-2-propen-1-ol (5.00 mL, 1.00 equiv) and PBr_3 (10.0 mL, 3.00 equiv). Crude **III-11h** was engaged in the subsequent step without further purification (7.37 g crude).

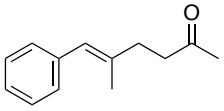
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.30 – 7.22 (m, 3H), 6.65 (s, 1H), 4.14 (d, J = 0.8 Hz, 2H), 2.02 (d, J = 1.4 Hz, 3H).



III-12h

III-12h was prepared following the procedure for the *formation of β-ketoesters* with methyl 3-oxobutanoate **III-40** (5.00 mL, 1.30 equiv), NaH (60 wt% in mineral oil, 1.47 g, 1.05 equiv) and **III-11h** (7.37 g crude). Crude **III-12h** was engaged in the subsequent step without further purification (10.8 g crude).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.23 – 7.15 (m, 3H), 6.31 (d, *J* = 1.8 Hz, 1H), 3.79 – 3.72 (m, 4H), 2.76 – 2.68 (m, 2H), 2.27 (s, 3H), 1.86 (d, *J* = 1.4 Hz, 3H).

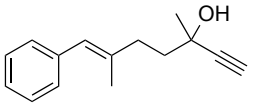


III-13h

III-13h was prepared following the procedure for the *decarboxylation in THF/water* with **III-12h** (10.8 g crude), KOH (7.50 g, 3.00 equiv) and water (75 mL). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-13h** (5.78 g, 88% yield over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.24 – 7.16 (m, 3H), 6.30 – 6.26 (m, 1H), 2.69 – 2.61 (m, 2H), 2.48 – 2.42 (m, 2H), 2.19 (s, 3H), 1.86 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.44, 138.29, 137.50, 128.93, 128.18, 126.20, 125.55, 42.43, 34.57, 30.13, 17.96.

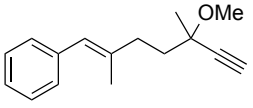


III-14h

III-14h was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13h** (5.78 g, 1.00 equiv) and ethynylmagnesium bromide (92.0 mL, 1.50 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-14h** (6.38 g, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 8.1, 7.2 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.21 – 7.17 (m, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 2.50 (s, 1H), 2.49 – 2.36 (m, 2H), 1.97 – 1.91 (m, 1H), 1.90 (d, *J* = 1.4 Hz, 3H), 1.89 – 1.83 (m, 1H), 1.56 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.66, 138.48, 128.92, 128.18, 126.11, 125.49, 87.52, 71.91, 68.29, 41.81, 35.95, 30.10, 18.10.

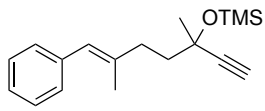


III-15h

III-15h was prepared following the procedure for the *protection as methyl ether* with **III-14h** (1.00 g, 1.00 equiv), NaH (60 wt% in mineral oil, 373 mg, 2.00 equiv) and MeI (0.60 mL, 2.00 equiv). The crude material was purified by flash chromatography over silica gel (pentane/Et_2O 10:1) to afford **III-15h** (991 mg, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.1, 7.2 Hz, 2H), 7.24 – 7.21 (m, 2H), 7.21 – 7.15 (m, 1H), 6.31 (d, *J* = 2.0 Hz, 1H), 3.40 (s, 3H), 2.49 (s, 1H), 2.40 – 2.30 (m, 2H), 1.97 – 1.84 (m, 5H), 1.47 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.74, 138.67, 128.93, 128.15, 126.00, 125.02, 84.85, 73.58, 73.41, 51.62, 39.93, 35.33, 25.70, 18.18.

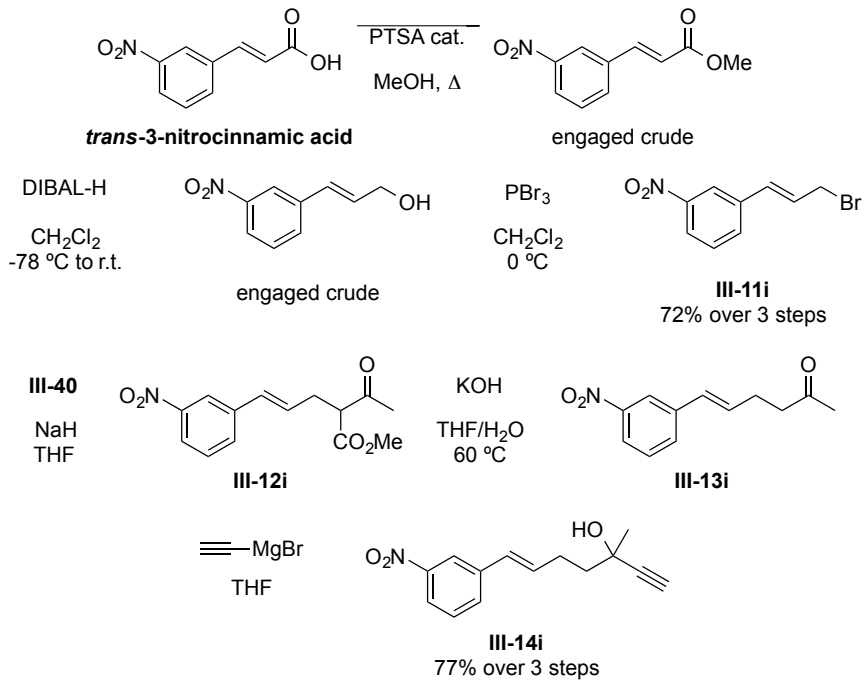


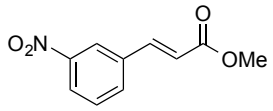
III-16h

III-16h was prepared following the procedure for the *protection as TMS ether* with TMSOTf (1.50 mL, 1.80 equiv), **III-14h** (1.00 g, 1.00 equiv) and Et_3N (2.00 mL, 3.00 equiv). The crude material was purified by flash chromatography over silica gel (pentane/Et_2O 10:1, 1% Et_3N) to afford **III-16h** (1.33 g, quantitative).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (tt, J = 7.8, 1.7 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.21 – 7.16 (m, 1H), 6.31 (d, J = 1.8 Hz, 1H), 2.49 (s, 1H), 2.40 – 2.30 (m, 2H), 1.93 – 1.77 (m, 5H), 1.53 (s, 3H), 0.22 (s, 9H).

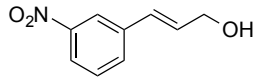
*Synthesis of precursor **III-14i***





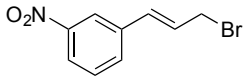
Methyl (*E*)-3-(3-nitrophenyl)acrylate

Methyl (*E*)-3-(3-nitrophenyl)acrylate was prepared following the procedure described in reference 263, using PTSA monohydrate as acid source. The crude material was engaged in the subsequent step without further purification. Analytical data were in accordance with previous reports.[263]



(*E*)-3-(3-nitrophenyl)prop-2-en-1-ol

(*E*)-3-(3-nitrophenyl)prop-2-en-1-ol was prepared by modifying the general procedure reported in reference 261, using methyl (*E*)-3-(3-nitrophenyl)acrylate as starting material, DIBAL-H (1 M in hexanes) and CH_2Cl_2 as solvent. The crude material was engaged in the subsequent step without further purification.[264]



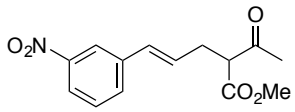
III-11i

III-11i was prepared following the procedure for the *bromination with PBr_3* with (*E*)-3-(3-nitrophenyl)prop-2-en-1-ol (996 mg crude) and PBr_3 (2.00 mL, 4.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-11i** (841 mg, 67% yield over 3 steps).

263. C. O. Sánchez, F. R. Díaz, N. Gatica, C. Bustos, K. Espiñeira, D. Huaquimilla, *Polym. Bull.* **2011**, *67*, 29-43.

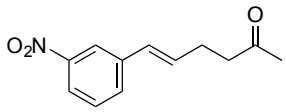
264. A. Bouziane, M. Hélou, B. Carboni, F. Carreaux, B. Demerseman, C. Bruneau, J.-L. Renaud, *Chem. Eur. J.* **2008**, *14*, 5630-5637.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.22 (m, 1H), 8.15 – 8.10 (m, 1H), 7.69 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 15.6 Hz, 1H), 6.54 (dt, *J* = 15.5, 7.6 Hz, 1H), 4.16 (dd, *J* = 7.6, 1.0 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$) δ 148.76, 137.75, 132.59, 132.08, 129.77, 128.62, 122.98, 121.46, 32.09.



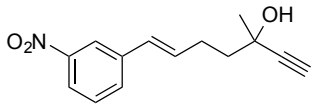
III-12i

III-12i was prepared following the procedure for the *formation of β-ketoesters* with methyl 3-oxobutanoate **III-40** (0.50 mL, 1.30 equiv), NaH (60 wt% in mineral oil, 146 mg, 1.05 equiv) and **III-11i** (841 mg, 1.00 equiv). Crude **III-12i** was engaged in the subsequent step without further purification (1.28 g crude).



III-13i

III-13i was prepared following the procedure for the *decarboxylation in THF/water* with **III-12i** (1.28 g crude), KOH (688 mg, 3.00 equiv) and water (20 mL). Crude **III-13i** was engaged in the subsequent step without further purification (786 mg crude).



III-14i

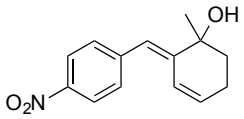
III-14i was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-13i** (786 mg crude) and ethynylmagnesium bromide (15.0 mL, 2.20 equiv). The crude material was

purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-14i** (655 mg, 77% yield over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, *J* = 2.0 Hz, 1H), 8.05 – 8.03 (m, 1H), 7.62 (d, *J* = 7.9, 1H), 7.45 (t, *J* = 8.2 Hz, 1H), 6.51 – 6.39 (m, 2H), 2.56 – 2.46 (m, 3H), 2.05 (s, 1H), 1.90 – 1.83 (m, 2H), 1.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.75, 139.55, 133.71, 131.98, 129.49, 128.33, 121.70, 120.66, 87.32, 72.10, 67.94, 42.60, 30.25, 28.47.

Gold-catalyzed cyclization of tertiary propargylic alcohols



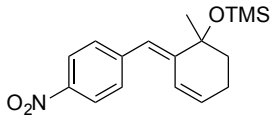
III-17a

III-14a (70.0 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (3.60 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-17a** (50.0 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.13 (m, 2H), 7.50 – 7.35 (m, 2H), 6.83 (s, 1H), 6.47 – 6.43 (m, 1H), 6.00 – 5.94 (m, 1H), 2.47 – 2.26 (m, 2H), 1.97 – 1.79 (m, 2H), 1.59 (s, 1H), 1.40 (d, *J* = 0.6 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 146.11, 144.67, 132.29, 129.90, 123.43, 123.22, 119.95, 77.27, 76.76, 71.27, 37.62, 26.68, 25.14.

HRMS-ESI: *m/z* calculated for $C_{14}H_{16}NO_3$ $[M+H]^+$: 245.1052, found: 245.1060.



III-19a

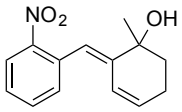
III-16a (48.0 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (2.30 mg, 2 mol%).

The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-19a** (38.0 mg, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.74 (s, 1H), 6.42 (d, *J* = 10.0 Hz, 1H), 5.95 – 5.88 (m, 1H), 2.32 – 2.20 (m, 2H), 1.97 – 1.85 (m, 2H), 1.40 (s, 3H), 0.18 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.46, 145.97, 145.19, 131.79, 129.90, 123.37, 123.28, 120.53, 74.17, 37.31, 28.12, 25.20, 2.62.

HRMS-ESI: *m/z* calculated for $C_{17}H_{24}NO_3Si$ $[M+H]^+$: 318.1525, found: 318.1522.



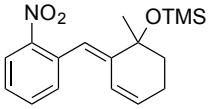
III-17c

III-14c (800 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (51.0 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-17c** (743 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1H), 7.45 – 7.34 (m, 2H), 7.03 (s, 1H), 6.14 – 6.10 (m, 1H), 5.87 – 5.81 (m, 1H), 2.42 – 2.22 (m, 2H), 1.93 – 1.81 (m, 2H), 1.71 (s, 1H), 1.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.50, 144.45, 132.94, 132.66, 131.28, 127.74, 124.83, 123.41, 118.83, 71.34, 37.42, 26.91, 25.04.

HRMS-ESI: *m/z* calculated for $C_{14}H_{15}NNaO_3$ $[M+Na]^+$: 268.0944, found: 268.0943.

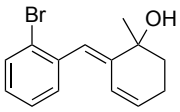


III-19c

III-16c (88.0 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (5.10 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 10:1, 1% Et_3N) to afford **III-19c** (80.0 mg, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.40 – 7.30 (m, 2H), 6.98 (d, *J* = 1.7 Hz, 1H), 6.15 – 6.10 (m, 1H), 5.82 – 5.75 (m, 1H), 2.37 – 2.29 (m, 1H), 2.26 – 2.16 (m, 1H), 2.02 – 1.90 (m, 1H), 1.88 – 1.75 (m, 1H), 1.42 (d, *J* = 0.6 Hz, 3H), 0.18 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.47, 144.71, 133.72, 133.07, 132.47, 130.72, 127.44, 124.73, 123.61, 119.13, 74.28, 37.40, 28.12, 25.24, 2.73.



III-17e

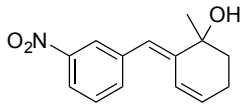
III-14e (100 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (6.00 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 10:1) to afford **III-17e** as a whitish solid (74.0 mg, 74% yield) that crystalized upon drying under high vacuum (see crystallographic data).

mp: 77 – 80 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 1H), 7.32 – 7.27 (m, 2H), 7.16 – 7.08 (m, 1H), 6.82 – 6.75 (m, 1H), 6.35 – 6.25 (m, 1H), 5.90 – 5.80 (m, 1H), 2.43 – 2.22 (m, 2H), 1.94 – 1.85 (m, 2H), 1.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.88, 137.58, 132.67, 131.63, 130.50, 128.33, 126.84, 124.58, 123.93, 122.18, 71.38, 37.62, 27.07, 25.01.

HRMS-ESI: *m/z* calculated for $C_{14}H_{14}Br$ $[M\text{-}OH]^+$: 261.0273, found: 261.0286.



III-17i

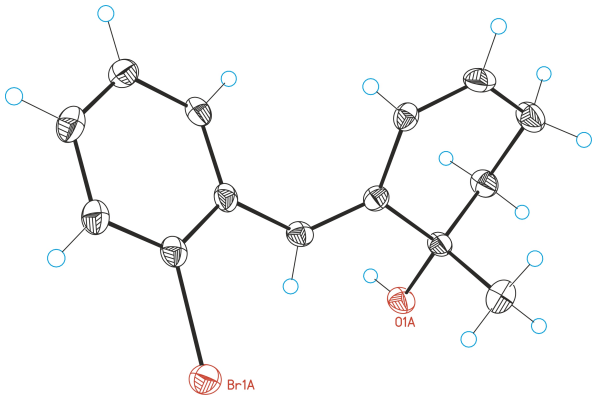
III-14i (100 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (7.00 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-17i** (97.0 mg, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.07 (br d, *J* = 8.09 Hz, 1H), 7.59 (d, *J* = 7.81 Hz, 1H), 7.49 (t, *J* = 8.22 Hz, 1H), 6.82 (s, 1H), 6.43 (br d, *J* = 10.20 Hz, 1H), 5.99 – 5.92 (m, 1H), 2.45 – 2.25 (m, 2H), 1.95 – 1.80 (m, 2H), 1.59 (s, 1H), 1.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.36, 145.58, 139.45, 135.43, 132.06, 129.11, 124.08, 123.11, 121.42, 119.68, 71.36, 37.77, 26.85, 25.21.

Structure assignment and crystallographic data

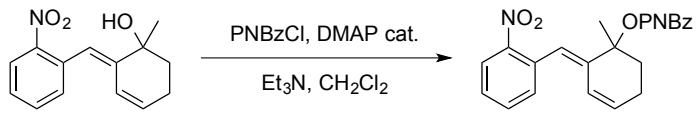
*X-ray structure of **III-17e***



Empirical formula	C14 H15 Br O
Formula weight	279.17
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.6576(3) Å a= 95.5550(10) °. b = 12.5297(4) Å b = 94.2200(10) °. c = 13.4288(5) Å g = 102.6250(10) °.
Volume	1245.43(8) $Å^3$
Z	4
Density (calculated)	1.489 Mg/m^3
Absorption coefficient	3.277 mm^{-1}
F(000)	568
Crystal size	0.10 x 0.10 x 0.06 mm^3
Theta range for data collection	2.14 to 28.15 °.
Index ranges	-10<=h<=6, -16<=k<=14,-17<=l<=17

Reflections collected	9522
Independent reflections	5910 [R(int) = 0.0275]
Completeness to theta =28.15 °	97.0%
Absorption correction	Empirical
Max. and min. transmission	0.8276 and 0.7353
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5910 / 0 / 293
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0469, wR2 = 0.0987
R indices (all data)	R1 = 0.0790, wR2 = 0.1106
Largest diff. peak and hole	1.512 and -1.243 e.$Å^{-3}$

*Synthesis and X-ray structure of the p-nitrobenzoate derivative of **III-17c***



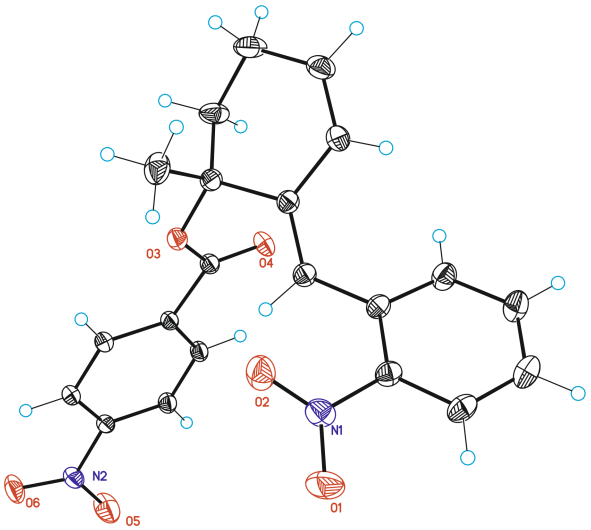
III-17c **III-17c-PNB**, 62%

Et_3N (0.10 mL, 0.72 mmol), DMAP (20 mg, 0.16 mmol) and 4-nitrobenzoyl chloride (50.0 mg, 0.27 mmol) were added in that order to a solution of **III-17c** (20 mg crude) in CH_2Cl_2 (5 mL). The reaction mixture was stirred 4 days at r.t. for convenience and quenched with saturated $NaHCO_3$. Phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-17c-PNB** (20.0 mg, 62% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 8.30 – 8.26 (m, 2H), 8.24 – 8.20 (m, 2H), 8.08 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.60 (td, *J* = 7.5, 1.3 Hz, 1H), 7.48 – 7.40 (m,

2H), 6.99 (s, 1H), 6.25 – 6.17 (m, 1H), 5.95 – 5.88 (m, 1H), 2.61 – 2.51 (m, 1H), 2.45 – 2.24 (m, 3H), 1.87 (s, 3H).

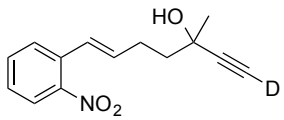
Some crystals suitable for X-ray diffraction were obtained by diffusion: a concentrated solution of **III-17c-PNB** in CH_2Cl_2 was placed in a vial. That vial was placed in a larger container with pentane. The container was stoppered and after a few days, the crystals had formed.



Empirical formula	C21 H18 N2 O6	
Formula weight	394.37	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6848(4) Å	a= 99.246(2) °.
	b = 10.1210(6) Å	b = 95.931(2) °.
	c = 12.5425(7) Å	g = 99.563(2) °.
Volume	940.96(9) $Å^3$	
Z	2	

Density (calculated)	1.392 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	412
Crystal size	0.32 x 0.12 x 0.10 mm^3
Theta range for data collection	2.07 to 35.42 °.
Index ranges	-12<=h<=12, -16<=k<=16, -20<=l<=20
Reflections collected	28662
Independent reflections	8462 [R(int) = 0.0252]
Completeness to theta =35.42 °	98.799995%
Absorption correction	Empirical
Max. and min. transmission	0.9897 and 0.9676
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8462 / 0 / 263
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1378
R indices (all data)	R1 = 0.0548, wR2 = 0.1454
Largest diff. peak and hole	0.653 and -0.369 $e.Å^{-3}$

Mechanistic study



III-14c-D

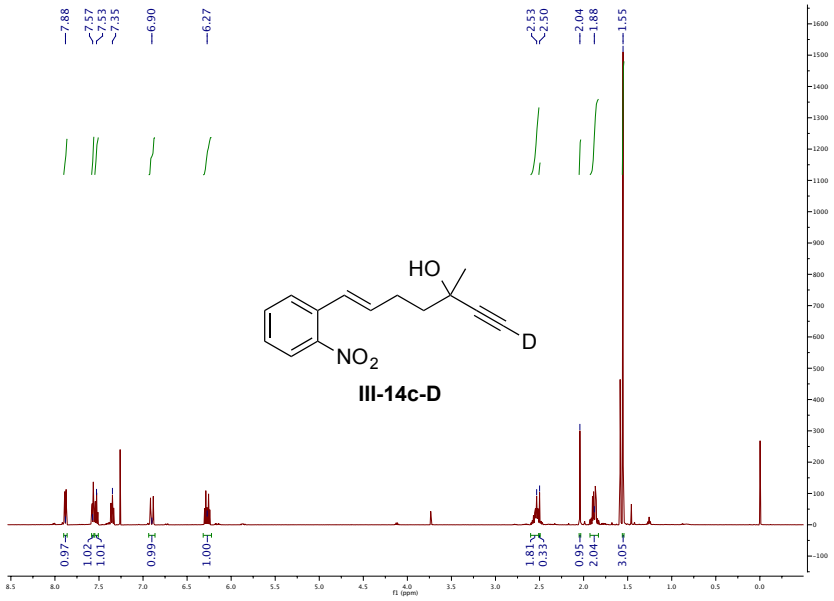
To a solution of **III-26** (482 mg, 1.97 mmol) in acetonitrile (20 mL) was added K_2CO_3 (543 mg, 3.93 mmol) in one portion. The mixture was stirred for 30 min at r.t. and D_2O (1.00 mL, 55.3 mmol) was added. The reaction mixture was stirred at r.t. for 24 h (for convenience) and quenched with saturated NH_4Cl. EtOAc was added and phases were separated. The aqueous layer was extracted with EtOAc (3 times) and the combined

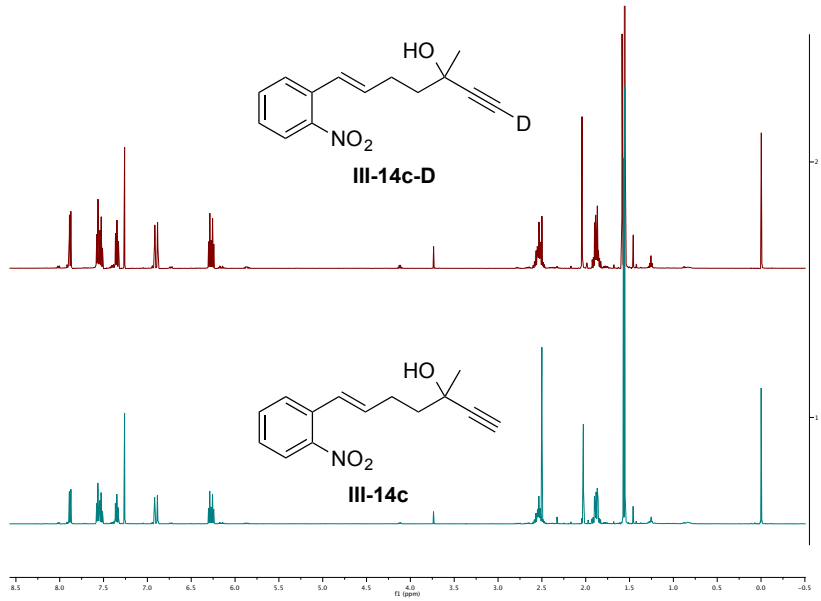
organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-26-D** (425 mg, 88% yield, 70% of deuterium incorporation).

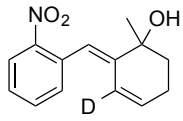
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 1H), 7.57 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.38 – 7.30 (m, 1H), 6.90 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.27 (dt, *J* = 15.6, 6.8 Hz, 1H), 2.60 -2.51 (m, 2H), 2.05 (s, 1H), 1.91 – 1.85 (m, 2H), 1.55 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.70, 135.79, 133.18, 132.87, 128.48, 127.53, 125.46, 124.40, 99.99, 67.84, 42.34, 30.07, 28.57.

HRMS-ESI: *m/z* calculated for $C_{14}H_{14}DNO_3Na$ $[M+Na]^+$: 269.1007, found: 269.1003.







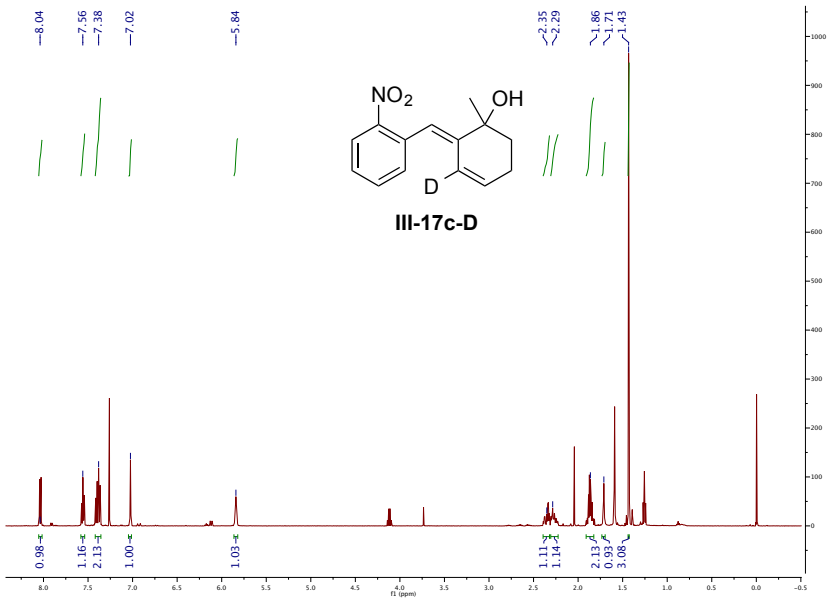
III-17c-D

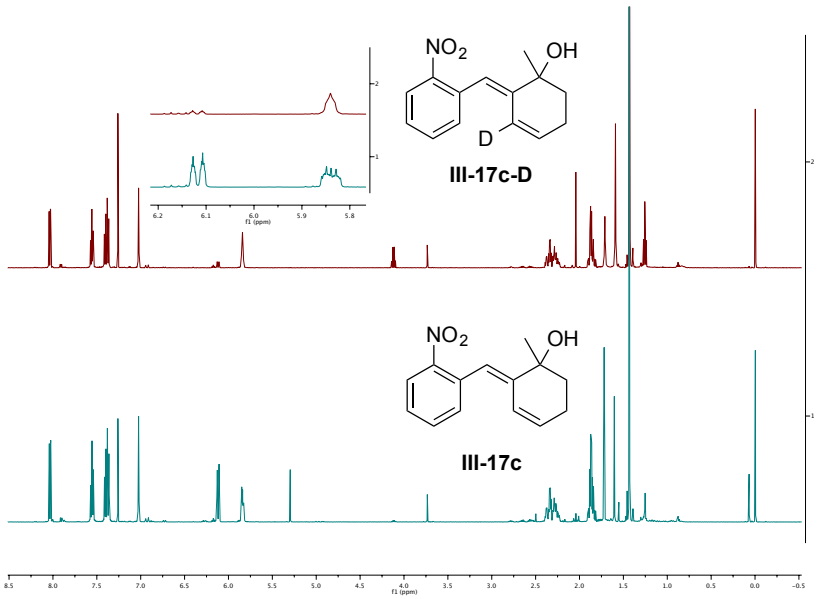
III-26-D (100 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (6.60 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-46c-D** (99.0 mg, quantitative).

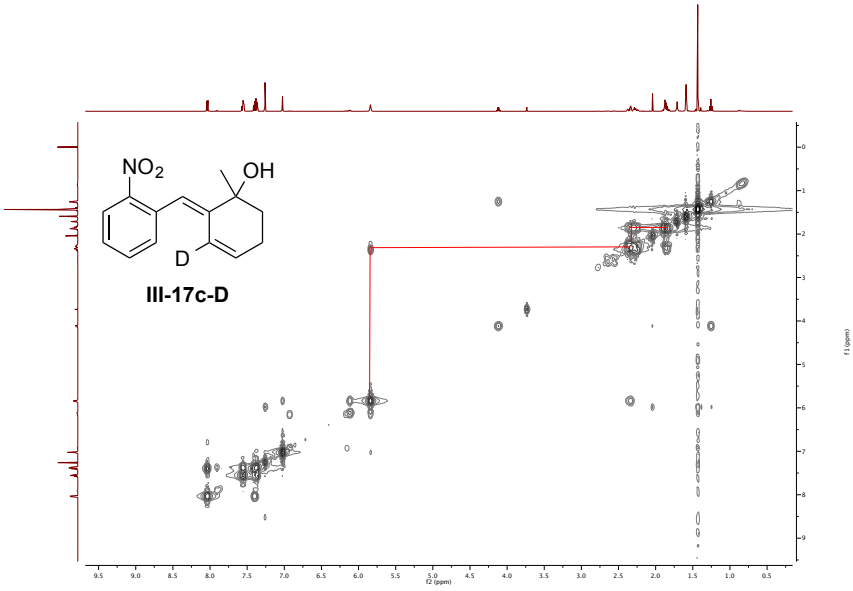
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.43 – 7.34 (m, 2H), 7.02 (d, *J* = 1.6 Hz, 1H), 5.93 – 5.54 (m, 1H), 2.40 – 2.32 (m, 1H), 2.31 – 2.21 (m, 1H), 1.92 – 1.81 (m, 2H), 1.71 (s, 1H), 1.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.52, 144.42, 133.34, 132.93, 132.67, 131.16, 127.74, 124.84, 123.42, 118.80, 71.32, 37.44, 26.92, 25.00.

HRMS-ESI: *m/z* calculated for $C_{14}H_{14}DNO_3Na$ $[M+Na]^+$: 269.1007, found: 269.1016.

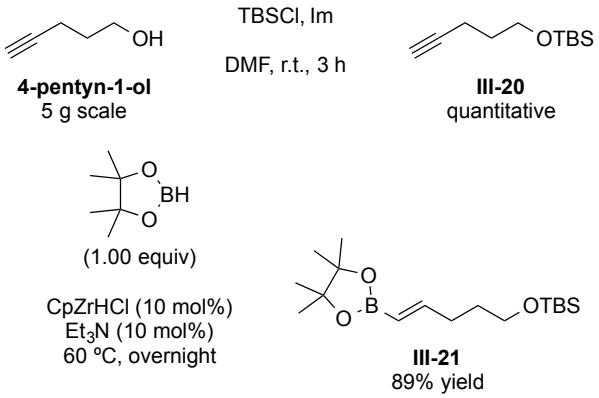


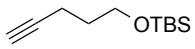




Expanding the reaction scope to secondary propargylic alcohols

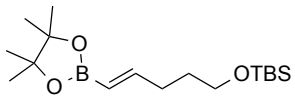
Synthesis of common vinylpinacolborane ***III-21***





III-20

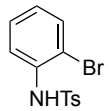
III-20 was prepared following the procedure described in reference 265. Analytical data were in accordance with previous reports.[265]



III-21

III-21 was prepared following the representative procedure described in reference 234 with **III-20** as starting material. Analytical data were in accordance with previous reports.[266]

Synthesis of N-(2-bromophenyl)-4-methylbenzenesulfonamide



***N*-(2-bromophenyl)-4-methylbenzenesulfonamide**

TsCl (1.05 g, 5.52 mmol) was added to a solution of 2-bromoaniline (1.00 g, 5.81 mmol) and pyridine (1.50 mL, 18.55 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred overnight for convenience and quenched with HCl 10%. Phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (pentane/EtOAc 9:1) to afford *N*-(2-bromophenyl)-4-methylbenzenesulfonamide (1.76 g, 93% yield). Analytical data were in accordance with previous reports.[267]

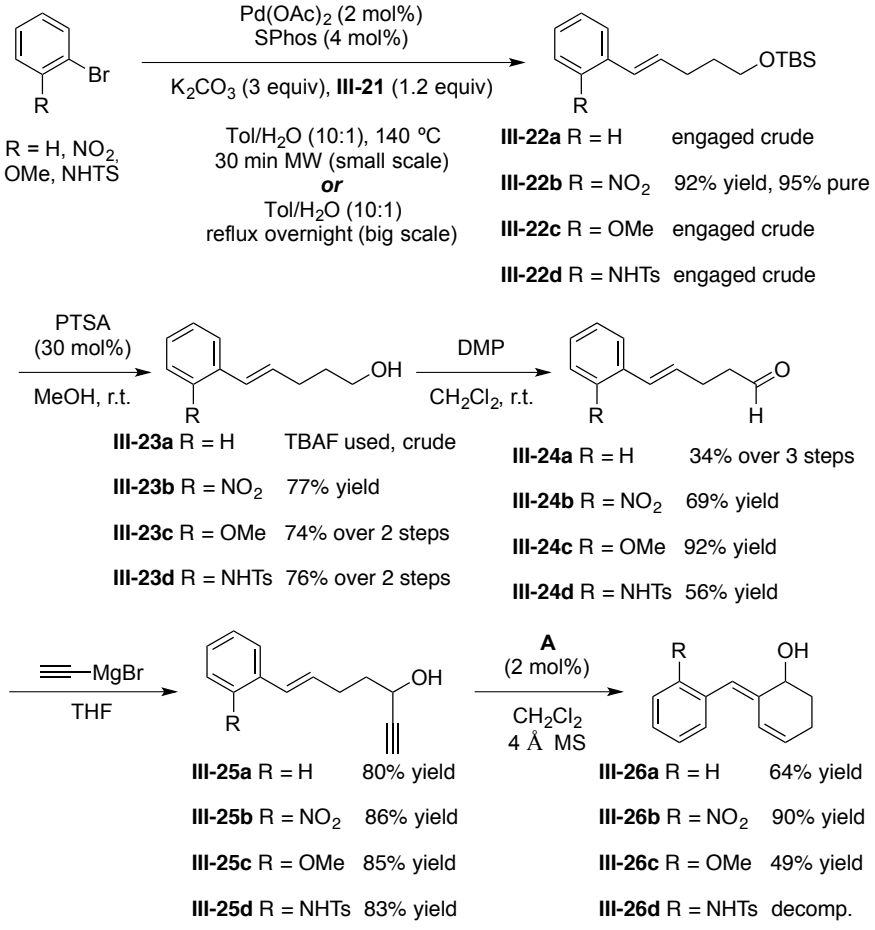
265. I. Ooi, T. Sakurai, J. T., N. Iwasawa, *Chem. Eur. J.* **2012**, *18*, 14618-14621.

234. Y. D. Wang, G. Kimball, A. S. Prashad, Y. Wang, *Tetrahedron Lett.* **2005**, *46*, 8777-8780.

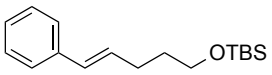
266. G. N. Varseev, M. E. Maier, *Angew. Chem. Int. Ed.* **2006**, *45*, 4767-4771.

267. O. René, D. Lapointe, K. Fagnou, *Org. Lett.* **2009**, *11*, 4560-4563.

*Synthesis of secondary propargylic alcohol precursors **III-26***



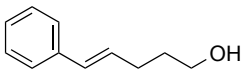
*Synthesis of precursor **III-26a***



III-22a

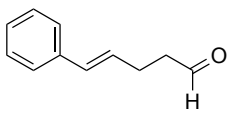
III-22a was prepared following the procedure for the *Suzuki cross-coupling of **III-21** with aryl bromides* with bromobenzene (1.00 mL, 1.00 equiv), K_2CO_3 (3.94 g, 3.00 equiv), $Pd(OAc)_2$ (43.0 mg, 2 mol%), SPhos (156 mg, 4 mol%), a solution of **III-21** (3.70 g, 1.20 equiv) in toluene (20 mL) and

water (2 mL). The crude material was engaged in the subsequent step without further purification. Analytical data were in accordance with previous reports.[268]



III-23a

TBAF (1 M in THF, 20.0 mL, 20.0 mmol) was added to a solution of crude **III-22a** in THF (40 mL). The reaction mixture was stirred overnight at r.t. for convenience and was quenched with NaOH 10%. EtOAc was added and phases were separated. The aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 7:3) to afford **III-23a** (1.10 g, 85% yield over 2 steps). Analytical data were in accordance with previous reports.[269]



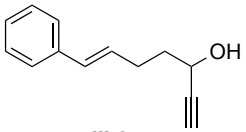
III-24a

III-24a was prepared following the procedure for the *oxidation of primary alcohols to aldehydes* with Dess-Martin Periodinane (3.45 g, 1.30 equiv) and **III-23a** (1.10 g, 95% pure, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-24a** (519 mg, 48% yield). Analytical data were in accordance with previous reports.[270]

268. J. R. Seiders II, L. Wang, P. E. Floreancig, *J. Am. Chem. Soc.* **2003**, *125*, 2406–2407.

269. K. P. Kornecki, J. F. Berry, *Chem. Commun.* **2012**, *48*, 12097-12099.

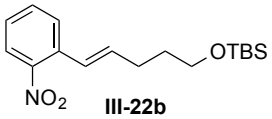
270. A. J. Bunt, C. D. Bailey, B. D. Cons, S. J. Edwards, J. D. Elsworth, T. Pheko, C. L. Willis, *Angew. Chem. Int. Ed.* **2012**, *51*, 3901-3903.



III-25a

III-25a was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-24a** (519 mg, 1.00 equiv) and ethynylmagnesium bromide (8.00 mL, 1.20 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-25a** (482 mg, 80% yield). Analytical data were in accordance with previous reports.[271]

*Synthesis of precursor **III-26b***



III-22b

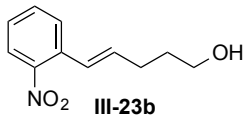
III-22b was prepared following the procedure for the *Suzuki cross-coupling of **III-21** with aryl bromides* with 2-nitrobromobenzene (5.00 g, 1.00 equiv), K_2CO_3 (10.3 g, 3.00 equiv), $Pd(OAc)_2$ (111 mg, 2 mol%), SPhos (406 mg, 4 mol%), a solution of **III-21** (8.89 g, 1.20 equiv) in toluene (100 mL) and water (10 mL). The crude material was engaged in the subsequent step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.38 – 7.32 (m, 1H), 6.85 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.25 (dt, *J* = 15.6, 6.9 Hz, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 2.34 (dtd, *J* = 8.3, 7.0, 1.6 Hz, 2H), 1.72 (ddt, *J* = 8.4, 7.3, 6.3 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.56, 133.46, 132.91, 128.55, 127.51, 125.26, 124.51, 62.59, 32.24, 29.76, 26.12, 18.50, -5.13.

271. See experimental part of reference 77: E. Jiménez-Núñez, K. Molawi, A. M. Echavarren, *Chem. Commun.* **2009**, 7327-7329.

HRMS-ESI: *m/z* calculated for $C_{17}H_{27}NO_3SiNa$ $[M+Na]^+$: 344.1652, found: 344.1656.



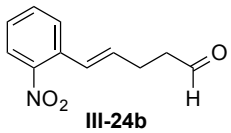
III-23b

III-23b was prepared following the procedure for the *deprotection of primary alcohols with PTSA/MeOH* with PTSA monohydrate (1.15 g, 0.30 equiv) and **III-22b**. The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-23b** (3.05 g, 95% pure, 56% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 1H), 7.61 – 7.49 (m, 2H), 7.38 – 7.30 (m, 1H), 6.87 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.24 (dt, *J* = 15.6, 6.9 Hz, 1H), 3.73 (t, *J* = 6.4 Hz, 2H), 2.44 – 2.32 (m, 2H), 1.84 – 1.74 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.82, 135.93, 133.38, 133.02, 128.65, 127.66, 125.77, 124.54, 62.38, 31.95, 29.66.

HRMS-ESI: *m/z* calculated for $C_{11}H_{14}NO_3$ $[M+H]^+$: 208.0968, found: 208.0968.

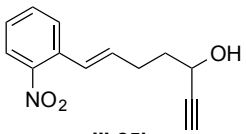


III-24b

III-24b was prepared following the procedure for the *oxidation of primary alcohols to aldehydes* with Dess-Martin Periodinane (5.00 g, 1.30 equiv) and **III-23b** (2.00 g, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-24b** (1.36 g, 95% pure, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, *J* = 1.3 Hz, 1H), 7.98 – 7.84 (m, 1H), 7.56 – 7.52 (m, 2H), 7.39 – 7.33 (m, 1H), 6.90 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.21 (dt, *J* = 15.6, 6.6 Hz, 1H), 2.72 – 2.66 (m, 2H), 2.64 – 2.58 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.34, 147.81, 133.95, 133.11, 133.01, 128.71, 127.95, 126.57, 124.60, 43.09, 25.68.



III-25b

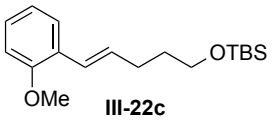
III-25b was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-24b** (348 mg, 1.00 equiv) and ethynylmagnesium bromide (5.00 mL, 1.50 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-25b** (338 mg, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.79 (m, 1H), 7.59 – 7.51 (m, 2H), 7.38 – 7.34 (m, 1H), 6.90 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.22 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.47 (qd, *J* = 4.5, 3.0 Hz, 1H), 2.51 (d, *J* = 2.1 Hz, 1H), 2.47 (dt, *J* = 7.7, 1.2 Hz, 1H), 1.99 – 1.89 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.82, 135.12, 133.28, 133.05, 128.67, 127.76, 126.23, 124.56, 84.60, 73.61, 61.74, 36.76, 28.83.

HRMS-ESI: *m/z* calculated for $C_{13}H_{13}NO_3Na$ $[M+Na]^+$: 254.0788, found: 254.0794.

*Synthesis of precursor **III-26c***



III-22c

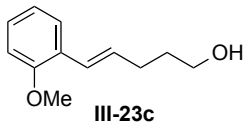
III-22c was prepared following the procedure for the *Suzuki cross-coupling of **III-21** with aryl bromides* with 2-methoxybromobenzene (1.00 mL, 1.00 equiv), K_2CO_3 (3.33 g, 3.00 equiv), $Pd(OAc)_2$ (36.0 mg, 2 mol%), SPhos (132 mg, 4 mol%), a solution of **III-21** (3.14 g, 1.20 equiv) in toluene (20

mL) and water (2 mL). The crude material was engaged in the subsequent step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.18 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H), 6.94 – 6.88 (m, 1H), 6.85 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.72 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.84 (s, 3H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.29 (qd, *J* = 7.0, 1.6 Hz, 2H), 1.74 – 1.68 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.42, 131.38, 127.95, 127.10, 126.55, 124.78, 120.77, 110.93, 100.14, 62.78, 55.58, 32.70, 29.89, 26.14, 18.53, -5.11.

HRMS-ESI: *m/z* calculated for $C_{18}H_{30}O_2SiNa$ $[M+Na]^+$: 329.1907, found: 329.1909.



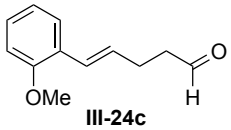
III-23c

III-23c was prepared following the procedure for the *deprotection of primary alcohols with PTSA/MeOH* with PTSA monohydrate (506 mg) and **III-22c**. The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 7:3) to afford **III-23c** (1.27 g, 82% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.22 – 7.16 (m, 1H), 6.93 – 6.88 (m, 1H), 6.86 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.74 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.23 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.84 (s, 3H), 3.71 (t, *J* = 6.5 Hz, 2H), 2.33 (qd, *J* = 7.2, 1.6 Hz, 2H), 1.86 – 1.66 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.43, 130.93, 128.11, 126.83, 126.59, 125.15, 120.78, 110.94, 62.71, 55.59, 32.53, 29.95.

HRMS-ESI: *m/z* calculated for $C_{12}H_{16}O_2Na$ $[M+Na]^+$: 215.1043, found: 215.1042.

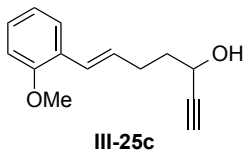


III-24c

III-24c was prepared following the procedure for the *oxidation of primary alcohols to aldehydes* with Dess-Martin Periodinane (2.90 g, 1.20 equiv) and **III-23c** (1.10 g, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-24c** (1.00 g, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (t, *J* = 1.6 Hz, 1H), 7.39 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 6.94 – 6.88 (m, 1H), 6.86 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.76 (dt, *J* = 16.0, 1.5 Hz, 1H), 6.20 (dt, *J* = 15.9, 6.6 Hz, 1H), 3.84 (s, 3H), 2.66 – 2.61 (m, 2H), 2.60 – 2.54 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 202.16, 156.50, 128.91, 128.40, 126.68, 126.40, 125.95, 120.79, 110.95, 55.58, 43.60, 26.14.



III-25c

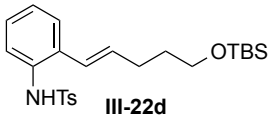
III-25c was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-24c** (1.00 g, 1.00 equiv) and ethynylmagnesium bromide (15.00 mL, 1.50 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-25c** (971 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.22 – 7.17 (m, 1H), 6.94 – 6.88 (m, 1H), 6.86 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.77 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.22 (dt, *J* = 15.9, 7.0 Hz, 1H), 4.45 (dt, *J* = 6.5, 4.3 Hz, 1H), 3.84 (s, 3H), 2.50 (d, *J* = 2.1 Hz, 1H), 2.43 (tdt, *J* = 6.8, 5.4, 1.6 Hz, 2H), 1.98 – 1.88 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.47, 130.11, 128.20, 126.72, 126.65, 125.65, 120.78, 110.96, 84.88, 73.33, 61.97, 55.59, 37.37, 29.12.

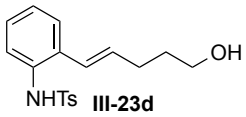
HRMS-ESI: *m/z* calculated for $C_{14}H_{16}O_2Na$ $[M+Na]^+$: 239.1041, found: 239.1043.

*Synthesis of precursor **III-26d***



III-22d

A 20 mL microwave vial was charged with *N*-(2-bromophenyl)-4-methylbenzenesulfonamide (300 mg, 0.92 mmol), K_2CO_3 (381 mg, 2.76 mmol), $Pd(OAc)_2$ (4.00 mg, 20 μmol), SPhos (15.0 mg, 0.04 mmol). The vial was sealed and a solution of boronate **III-21** (360 mg, 1.10 mmol, 1.20 equiv) in toluene (8 mL) was added, followed by water (0.8 mL). The reaction mixture was irradiated in the microwave oven (140 ºC, 30 min) and filtered through silica (elution EtOAc). The filtrate was concentrated under reduced pressure and crude **III-22d** was directly engaged in the subsequent step without further purification.

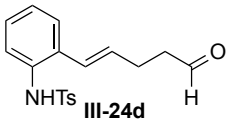


III-23d

III-23d was prepared following the procedure for the *deprotection of primary alcohols with PTSA/MeOH* with PTSA monohydrate (74.0 mg) and crude **III-22d**. The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 7:3) to afford **III-23d** (230 mg, 76% yield over 2 steps).

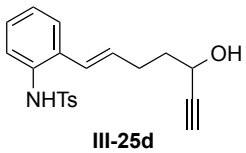
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.32 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H), 7.09 (td, *J* = 7.5, 1.4 Hz, 1H), 6.86 (s, 1H), 6.18 (dt, *J* = 15.8, 1.6 Hz, 1H), 5.93 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.71 (t, *J* = 6.1 Hz, 2H), 2.38 (s, 3H), 2.23 (qd, *J* = 7.1, 1.5 Hz, 2H), 1.69 (tt, *J* = 7.2, 6.1 Hz, 2H), 1.61 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.90, 136.76, 135.58, 133.31, 132.38, 129.72, 127.97, 127.51, 126.10, 124.80, 124.20, 62.61, 31.89, 30.26, 21.69.
HRMS-ESI: *m/z* calculated for $C_{18}H_{21}NO_3SNa$ $[M+Na]^+$: 354.1134, found: 354.1141.



III-24d

III-24d was prepared following the procedure for the *oxidation of primary alcohols to aldehydes* with Dess-Martin Periodinane (455 mg, 1.50 equiv) and **III-23c** (237 mg, 1.00 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-24d** (131 mg, 56% yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.21 (m, 2H), 7.20 – 7.12 (m, 2H), 6.37 (s, 1H), 6.21 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.93 (dt, *J* = 15.7, 6.7 Hz, 1H), 2.60 – 2.53 (m, 2H), 2.44 (ddt, *J* = 8.1, 7.0, 1.0 Hz, 2H), 2.39 (s, 3H).



III-25d

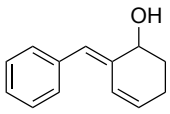
III-25d was prepared following the procedure for the *addition of ethynylmagnesium bromide* with **III-24d** (170 mg, 1.00 equiv) and ethynylmagnesium bromide (3.00 mL, 2.90 equiv). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 8:2) to afford **III-25d** (98 mg, 53% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 2H), 7.34 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H), 7.10 (td, *J* = 7.5, 1.3 Hz, 1H), 6.71 (s, 1H), 6.18 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.91 (dt, *J* =

15.7, 6.9 Hz, 1H), 4.44 (td, *J* = 6.2, 2.2 Hz, 1H), 2.54 (d, *J* = 2.1 Hz, 1H), 2.39 (s, 3H), 2.36 – 2.27 (m, 2H), 1.86 – 1.81 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.94, 136.68, 134.67, 133.26, 132.34, 129.74, 128.08, 127.45, 127.38, 126.21, 125.26, 124.43, 84.63, 73.66, 61.87, 36.55, 29.04, 21.70.

HRMS-ESI: *m/z* calculated for $C_{20}H_{21}NO_3SNa$ $[M+Na]^+$: 378.1134, found: 378.1133.

Gold-catalyzed cyclization of secondary propargylic alcohols



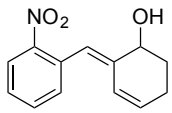
III-26a

III-25a (100 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (8.80 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 10:1) to afford **III-26a** (64.0 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.26 – 7.20 (m, 1H), 6.59 – 6.54 (m, 2H), 5.94 (dtd, *J* = 9.8, 4.0, 1.4 Hz, 1H), 4.42 (dd, *J* = 6.9, 3.8 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.32 – 2.22 (m, 1H), 2.00 – 1.92 (m, 2H), 1.62 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.09, 137.14, 131.61, 129.40, 128.29, 126.91, 125.16, 123.38, 70.97, 30.90, 23.10.

HRMS-ESI: *m/z* calculated for $C_{13}H_{13}$ $[M-OH]^+$: 169.1012, found: 169.1011.



III-26b

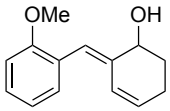
III-25b (1.05 g, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (74.0 mg, 2 mol%).

The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9:1) to afford **III-26b** (950 mg, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.50 – 7.34 (m, 2H), 6.83 (s, 1H), 6.23 – 6.09 (m, 1H), 6.02 – 5.83 (m, 1H), 4.49 (dt, *J* = 5.5, 2.7 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.32 – 2.22 (m, 1H), 2.04 – 1.89 (m, 2H), 1.76 (d, *J* = 5.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.49, 140.10, 133.05, 132.90, 132.74, 132.68, 127.94, 124.88, 122.74, 120.79, 100.14, 70.35, 30.78, 23.42.

HRMS-ESI: *m/z* calculated for $C_{13}H_{13}NO_3Na$ $[M+Na]^+$: 254.0788, found: 254.0792.



III-26c

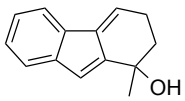
III-25c (100 mg, 1.00 equiv) was cyclized following the procedure for the g*old-catalyzed cyclization of precursors* with catalyst **A** (7.60 mg, 2 mol%). The crude material was purified by flash chromatography over silica gel (cyclohexane/EtOAc 10:1) to afford **III-26c** (49.0 mg, 49% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 1H), 7.25 – 7.21 (m, 1H), 6.96 – 6.90 (m, 1H), 6.87 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.65 (s, 1H), 6.52 – 6.45 (m, 1H), 5.90 (dtd, *J* = 9.9, 4.0, 1.7 Hz, 1H), 4.46 (t, *J* = 5.3 Hz, 1H), 3.82 (s, 3H), 2.46 – 2.35 (m, 1H), 2.28 – 2.20 (m, 1H), 2.03 (s, 1H), 2.00 – 1.90 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.41, 137.94, 131.03, 131.01, 128.41, 125.85, 123.67, 120.96, 120.09, 110.45, 70.86, 55.48, 30.63, 22.98.

HRMS-ESI: *m/z* calculated for $C_{14}H_{16}NaO_2$ $[M+Na]^+$: 239.1043, found: 239.1051.

Further Developments, intramolecular Heck reaction



III-27

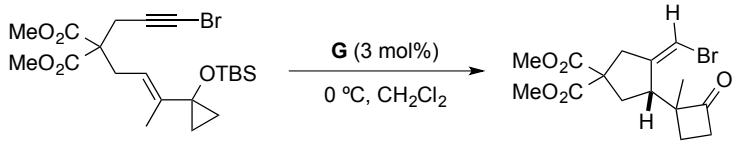
III-17e (100 mg, 0.36 mmol), $Pd(OAc)_2$ (8.00 mg, 36.0 µmol), dppe (29.0 mg, 0.07 mmol), K_2CO_3 (248 mg, 1.79 mmol) and DMF (5 mL) were charged in a dry vial under argon atmosphere. The resulting mixture was stirred at 80 ºC for 4 h (TLC monitoring) before being cooled down to r.t. and filtered through a short pad of Celite (elution EtOAc). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (pentane/EtOAc 10:1) to afford **III-27** (isolated product unpure, 30-40% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 1H), 7.29 – 7.26 (m, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.10 (m, 1H), 6.92 – 6.85 (m, 1H), 6.79 – 6.70 (m, 1H), 2.79 – 2.69 (m, 1H), 2.57 – 2.46 (m, 1H), 2.00 – 1.96 (m, 1H), 1.94 – 1.91 (m, 1H), 1.56 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.62, 142.65, 139.36, 134.83, 129.37, 127.82, 125.08, 123.04, 121.17, 119.85, 69.11, 39.19, 27.80, 27.17, 24.92.

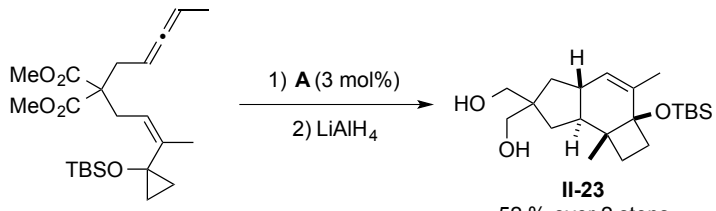
General Conclusions

• In the first chapter of this *Doctoral Thesis*, we summarized our investigations on the gold(I)-catalyzed cyclization cascade of cyclopropyl-substituted 1,6-enynes bearing a substituent at the alkyne terminus in order to approach the core of repraesentin F. The reaction did not provide the expected product but led to the formation of cyclobutanones, some proposed intermediates of the mechanism. Attempts to get the core of repraesentin F were unsuccessful but other methods are currently under investigation.

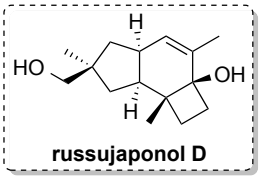


I-14d **I-25d**
72% yield

• Based on the results obtained in the previous part, the second chapter reports the development of a new intramolecular gold(I)-catalyzed cycloisomerization of allene-vinylcyclopropanes. Tricyclic molecules displaying the framework of protoilludanes were isolated. The cyclization is stereospecific as different diastereoisomers can be specifically obtained depending on the geometry around the starting double bond. This methodology paves the way to access more elaborated sesquiterpenes.

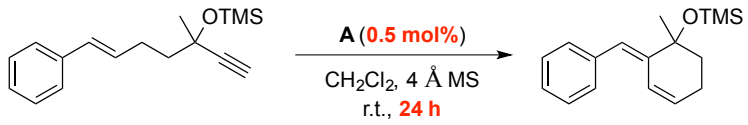


II-1-*Z* **II-23**
52 % over 2 steps



russujaponol D

- In the last chapter of this *Doctoral Thesis*, we presented a new gold(I)-catalyzed cycloisomerization of 1,6-enynes proceeding by a *endo*-type single cleavage pathway (determined by deuteration). The structure of the isolated compounds was unambiguously assigned by X-ray diffraction of some crystalline substrates and derivatives. Further developments to access tricyclic molecules (fluorene and acridine type) are under investigation.



III-6c
2 g scale

III-10c
95% isolated yield

Notes

Notes

Notes

Notes